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MESSAGE

Over the past three decades Chaitanya Institutions have made steady and phenomenal progress in imparting quality education with several awards and accolades. Our vision is to take Chaitanya Deemed University (CDU) to greater heights with good digital governance and sound academic standards. Eventually, we want to make CDU a Center of Academic Excellence with creativity, productivity and accountability for knowledge society.

Our proposed Atal Chaitanya Incubation and Innovation Centre involves Engineering, Pharmacy, and other departments in thrust areas of farming, app development, manufacturing, etc. We are planning for BIRAC under Bio-Nest in collaboration with the University of Hyderabad involving the departments of Biotechnology, Microbiology, Biochemistry, Chemistry, Mathematics, Computer Science, Engineering Pharmacy, in thrust areas of agriculture, poultry, animal husbandry, food processing and value addition, biomedical engineering, etc. We were shortlisted for the DBT Skill Vigyan Program monitored by TSCOST. We have submitted the DBT Builder Program for financial assistance involving all the departments of science. We have also submitted proposals for CRG, Startup Grants and Matrix under SERB-DST. Departments of Engineering, Pharmacy, Computer Science, Commerce and Business Management have submitted Research Project Scheme (RPS) under AICTE Program.

We have instituted the *Chaitanyam* to encourage high impact factor papers with original ideas and patent holders, and to promote serious and sustained academic work. Prof. M. Sunder Ram (from Maths), Dr. T. Narasimha Swamy and Prof. M. Ravindar (both from Chemistry), Dr. G. Kumara Swamy and Prof. V. Mallikarjun (both from Pharmacy) received Chaithanyam-2021 Awards (with a gold medal and a certificate). We hope these awards will create healthy competition promoting serious and sustained academic work on our campus.

Earn-While-You-Learn Program is our latest initiative. Interested PG first year students can register to work in the Softpath Company established at our university. The beginning salary is Rs 12,000 per month and it goes up based on the merit and work of the candidates. Aspiring students can email their bio-data to placements@cdu.ac.in.

Faculty-wise research journals are planned under the guidance of our Vice-Chancellor. *Current English Review* (CER), edited by Prof. G. Damodar and Prof. M. Rajeshwar as Editors and Dr. D. Vidyanath as Assistant Editor, was launched in September 2021. It covers 18 critical and creative write-ups and reviews. We have applied for ISSN for the journal. *The Journal of Bioscientia* edited by Prof. BS Anuradha and Prof. S. Jeevan Chandra was launched on January 26, 2022. *Cosmopolitan Journal of Innovations in Engineering and Technology,* edited by Prof. G. Shankar Lingam, and Dr. N. Sateesh Kumar and the latest issue of *Prakarsha, Journal of Management and Research* edited by Prof. P. Krishnamachary, Prof. Ch. Rajesham and Prof. P. Rajendar will be out shortly. *Journal of Pharmacy and Drug Research*, edited Dr. G. Kumara Swamy, is in the pipeline.

We have beyond classroom solutions. We want to go for futuristic solutions to facilitate our students to access our content anytime, anywhere, improve satisfaction and personalized learning outcomes, and give them the opportunity to learn with others. A Centre for Volunteerism as a step towards inclusiveness is being planned. All our M. Sc. students undertake Community Service and Project work as the part of the curriculum. They spend five days in rural areas, render community services and collect samples pertinent to agriculture, water, soil and community health. After thorough research, they submit the project reports to the departments concerned for evaluation. The paper/ poster presentation in the conferences is a part of the curriculum for the PG students.

There is commendable participation of our students in extracurricular activities. Martyrs Day was observed on March 23, 2021 in the Engineering Department with a skit in the open theater. We inculcate competitive spirit among students by recognizing the first five class-wise toppers. There are regular interactive sessions with students and class representatives. NSS Unit is for beyond classroom experience, service and social education under the leadership of Program Coordinator, Dr D. Gopinath and Program Officer, Dr. Aravind. As part of *Azaadi ka Amrit Mahotsav*, our University is conducting nine events such as (a) GK Test using Google Forms / Zoho (b) Essay writing on "Freedom Struggle Movements"," (c) Elocution on "India's Progress in 75 Years" (d) Painting depicting "Pandemic Crisis" (e) Poetry on "Contemporary Issues" (f) Songs on "Patriotism" (g) Debate on "Our Progress in 75 years (For and Against) (h) Short Concept Videos on Social Issues (i) Poster Designing showcasing "India in 75 Years". Events commence online from July 19, 2021 onwards. Prizes with certificates will be given on 75th Independence Day. Responding to the call by the Centre, our NSS Unit conducted various events as part of *Azadika Amruth Mahostav.* SamvidaanDiwas, Vaccination Drive four times, Voter Awareness, International Yoga Day, National Youth Day were observed. Our NSS volunteers took part in Swachh Bharat activities at Kazipet, distributed 150 bed sheets to the homeless people and organized some awareness programs in villages.

Our Mechanical Engineering faculty, Dr Srinivas Naik, Mr Harish and Mr Santhosh, have converted a petrol engine car into a battery operated eco-friendly electric car without gears. A motor of 48 volts, 700 watts and 500 rpm has been replaced with an

engine of a Maruti 800 car. The weight of the engine was reduced by removing the gearboxes. The motor is connected to the drive shaft by a chain. The vehicle runs at a speed of 60 kmph. The car is economical and it costs just 20 paise per km. The conversion of the car costs two lakh rupees.

Coming to other innovations, a unique Chaitanya App was designed for teachers by Prof. G. Shankar Lingam and Mr. K. Praveen in 2020 for attendance, results, timetables and general information. Our mechanical branch staff members have designed a solar bike (see photo 4) and agri-cultivators. A cost-effective electronic bike has been designed by Mr G. Sagar. A digital electronic clock was designed by Dr Santhosh Reddy of ECE. The wing of ECE has also designed a Digital Display Board and devised Easy Vehicle Lifting Mechanism. The process of making transparent mementoes with a special material is in the pipeline.

We impart quality education by reviewing the impact of the existing programs and their relevance, restructuring of a few courses, consolidation of existing teaching programs, strengthening the learning process, strict adherence to the academic schedule, researching monitoring and assistance, encouraging national and international seminars, webinars, workshops, refresher courses, exhibitions, placement sessions, etc. Our pedagogy calls for hands-on experience, extensive laboratory and workshop exposure to link students to real world problems and situations. Students become industry-ready with good life and employability skills.

We have so far conducted 21 national and international webinars/ seminars on various topics. In addition to these, 60 standard online quizzes were conducted, and a hundred video lessons for YouTube Channel covering all branches were made available. All our 297 research scholars of two batches are enthusiastic to pursue their research seriously from the date of joining their research program due to our good research facilities, weekly / fortnightly Regular Review Meetings (RRMs) and monthly and yearly reports by the scholars. The snapshots of RRMs have to be uploaded to the Chaitanya Research Group as a proof. Within ten months of joining the Ph.D program, our 139 research scholars of the first batch published 54 Research Papers in refereed journals during 2020-21.

Chaitanya has created a benchmark in Upgradation of Knowledge Through Interaction (UKTI) sessions to update the skills of teachers of various subjects. We have so far conducted 45 sessions and are now producing video lessons, making them available online for the benefit of all. To update the skills of teachers of various subjects, a daily interactive session was launched on April 27, 2020. All senior teachers have conducted the sessions with impressive PPTs. The Facultylnduction Program (Guru Dakshta) is done at the beginning of academic year. FDPs and Workshops are conducted to update their skills. We have initiated these UKTI sessions for the staff through Whatsapp for focus, clarity and readability. These sessions have exposed the teachers to the use of ICT and online teaching tools for better instruction.

Our university has developed adequate infrastructural facilities for the already existing and newly introduced academic programs during the past five years. Our laboratories are very well equipped and not short of anything. The teachers are at liberty to go in for any equipment that is useful for their laboratories. The University is equipped with HPLC, FTIR, IPR Spectrophotometer, U.V. Spectrophotometer, PCR, Fermenter, Gel documentation system etc. The purpose of these instruments is to familiarize the students with the latest equipment so that they are not at sea when they encounter such instruments in industries or research institutions later.

Our university has been rated as one of the most sought-after colleges for the students of this region with the result that there has been considerable pressure on student admissions for all the courses. In view of the large number of academic programs, courses and course combinations and ever-increasing intake, the college has to live up to the expectations of the parents. A lot of emphasis has been placed on teaching, learning and evaluation.

I congratulate the Pharmacy Department on bringing out this maiden research journal.

Prof. G. Damodar
Vice-Chancellor
Chaitanya (Deemed to be University)
Kishanpura, Hanamkonda, Warangal

MESSAGE

Pleased to know that the Faculty of Pharmacy is bringing out this journal titled *Journal of Pharmacy and Drug Research,* edited Dr. G. Kumara Swamy. The Faculty of Engineering brought out *Cosmopolitan Journal of Innovations in Engineering and Technology,* edited by Prof. G. Shankar Lingam, and Dr. N. Sateesh Kumar. I brought out *Current English Review,* a peer-reviewed and refereed journal of critical and creative writings and reviews, and it was launched in September 2021. Life Sciences brought out *The Journal of Bioscientia* edited by Prof. BS Anuradha and Prof. S. Jeevan Chandraon January 26, 2022. The latest issue of *Prakarsha, Journal of Management and Research* edited by Prof. P. Krishnamachary, Prof. Ch. Rajesham and Prof. P. Rajendar will be out shortly.

In addition to the above research journals, a novel research-oriented initiative calledChaitanyam was instituted at our university to encourage high impact factor papers with original ideas and patents, and to promote serious and sustained academic work by the staff and research scholars. Universities are expected to undertake research related activities seriously and we understand them and implement them in the right earnest.

Ever since we got deemed to be university status in November 2019, we have been striving hard to take Chaitanya to greater heights. Our healthy practices so far include Academic Interphase Programs with TCS and IBM, good practices appreciated by AICTE, At-Home-Exam™ announcing the results on time, Best Paper and Patent Publication Awards, Beyond Classroom Solutions, *Vidyanjali,* a Centre for Volunteerism, unique Chaitanya App, Chaitanya At-Home-Library, Community Service and Rural Based Projects, Free-ships worth 1.10 crores last year, Implementation of some provisions of NEP 2020, Internationalisation of Higher Education, eight Inventions and Innovations including the battery-operated car, the introduction of latest courses including Agriculture and Nursing, Life Skills, DBT Skill Vigyan Program, NCC as a General Generic Elective, Interactive Sessions as *Deeksharambh,* Regular Research Review Meetings with Ph.D. scholars, State-of-Art Labs, Study Tours of *Ek Bharat Shreshtha Bharath,* Sustainable Campus as SATAT, UKTI Sessions under *Guru Dakshta,* making video lessons available on YouTube, conducting online quizzes, Earn-

While-You-Learn Schemes, University Social Responsibility Initiatives, encouraging patents, a proposal for Atal Chaitanya Incubation and Innovation Center, BIRAC under Bio-Nest in collaboration with University of Hyderabad, etc.

We have initiated a positive action to encourage research in post graduate courses project work is now included as a part of curriculum. Sectoral specializations like Tourism and Hospitality, Health Care Management for MBA, Net Programming, Multimedia Applications, Cloud Computing for MCA as in-house projects were introduced. Efforts are being made to have a much more and rigorous University-Industry nexus so that the batches of students get industrial experience along with academic programs by conducting meetings with the entrepreneurs in the region to impress upon the need to support the students' training programs in their establishments so that they and others can employ them after completion of their courses.

Ten PhD courses in the Faculty of Science, Commerce and Business Management (1) Biochemistry, (2) Bio-technology, (3) Chemistry, (4) Commerce & Business Management, (5) Computer Science, (6) English, (7) Mathematics, (8) Microbiology, (9) Physics, (10) Statistics; Five PhD courses in the Faculty of Engineering (1) CS & Engg (2) ECE (3) EEE (4) ME (5) CE; Seven PhD courses in the Faculty of Pharmacy (1) Pharmaceutics (2) Pharmaceutical Analysis (3) Pharmacology (4) Pharmacy Practice (5) Pharmaceutical Chemistry (6) Pharmacognosy (7) Phytochemistry are offered at our university.

We have introduced the latest and emerging papers in subjects like Creativity and Innovation, Business Analytics, Business Informatics, Infrastructure Management, Data Base Management, Programming and Problem Solving Using Python, Ethical Hacking, E-Commerce, Web Programming, Immunology, Bioinformatics, Data Analysis, .Net Prog, Cryptography, Network Security, Software Testing, Artificial Intelligence, Research Methodology (in BBA), OOD in UML (in BCA), Heritage and Culture, Business Economics, Discrete Mathematics, Visual Data Base Application, CRBI (in B.Com.), Web Programming, Prog Concepts (Using C), Human Values and Ethics, Cell Biology, Genetics, Biodiversity, Plant Biotechnology, Animal Biotechnology, Enzymology, Concepts of Clinical Research, Advanced Programming in J2EE, Scripting Language, Mobile Application Development, ERP 7 Supply Chain Management, Design Patterns, Machine Language, Mobile Computing, Communicative English, Bacteriology, Virology, Cell Biology, Classical Mechanics, Programming in C & MAT Lab, Indian Constitution and Human Rights (in Int. M.Sc. Chemistry), Internet Technologies, Personality Development (in M.Sc. Courses), Nano Technology, Environmental Studies, Event Management (in BBA), Food & Beverage Mgt, Health Care Technology, Industrial Relations, Science and Civilization, Managerial Economics, Foreign Trade, Prog in C++, MIS, Office Automation, Operation research (in BCA), Digital Marketing, etc.

We have introduced Open electives like Food Technology, Nanotechnology, Biosafety, IPR, Tourism and Hospitality Management, Health Care Management, Fundamentals of Electronics, E-commerce, Computer Applications and Airline Management. These courses can be taken up by all the students of post-graduation to have an insight of

the different fields which might help them in enriching their career prospects. We started offering B.Sc. Agriculture from the current academic year. We have got permission to start B.Sc. Nursing Course next year. Currently, we have about 6000+ students who belong to 14+ countries including India.

All our M.Sc. students undertake Community Service and Project work as the part of the curriculum. They spend five days in rural areas, render community services and collect samples pertinent to agriculture, water, soil and community health. After thorough research, they submit the project reports to the departments concerned for evaluation. The paper/poster presentation in the conferences is a part of the curriculum for the PG students.

Our library is well-equipped to meet the ever-growing needs of the teachers and learners right from internet support to audio-visual services with N-List, IEEE Gogotal, ALM, Sage DELNET Membership providing online access to the staff and students. Latest books are acquired from time to time from all sources. Students have access to massive open online courses in MP3 format based on MHRD model MOOCS, Commonwealth Education Services, cec.nic.in for all lessons. As students do not have access to the physical library during Pandemic, a Digital Library called "Chaitanya At-Home-Library" was launched. It is a new initiative with all prescribed e-books made available with the efforts of the Faculty on our University Website and on Chaitanya App.

We are committed and dedicated to our vision and mission and constantly evolve ourselves to the future needs and impart education that makes the world a better place to live in. The pillar of our strength is innovative teaching and learning experiences offered by experienced faculty backed with high quality resources. We offer academic ambience, fruitful interaction and friendly support with excellent placements making life a celebration for every student. Our syllabus is skill-based and industry focused with contemporary curriculum, choice-based credit system (CBCS) and continuous assessment and grading pattern (CAGP). Social outreach programs, eco-friendly environment, diversified student community, education scholarships for deserving and meritorious students, internal quality assurance, enriching projects and internships, corporate linkages, global alumni network, learning management system, highly accomplished faculty members and levitating research culture are some of our salient features.

We always remember our core vision of empowering our future generations to be morally, ethically and intellectually strong with LOCF and following some provisions of National Education Policy 2020. To be with our university is an exciting and rewarding experience with opportunities for nurturing abilities, challenging cognizance and gaining competence.

I compliment the Faculty of Pharmacy, particularly Prof. V. Mallikarjun and Dr. G. Kumara Swamy for bringing out this maiden journal with ten research articles contributed by subject experts and research scholars on emerging topics that require further research.

JOURNAL OF PHARMACY AND DRUG RESEARCH (JPDAR)

Instructions to the Authors

JPADR accepts review and research article in the field of Life Science and Pharmaceutical Science.

The preferred format of all manuscripts are in MS Office (2003 or above). Manuscript should be concisely typewritten in 1.5 spaces in A4 sized sheets. Manuscript can be submitted through online submission process, In case of any problem through the online submission, submit manuscripts to our email: editorjpadr@chaitanya.edu.in

Research articles should be divided into the following sections:

1. **TITLE:** The title should be as short as possible on the first page and provide precise information about the contents. The title should be followed by full names of author (s), affiliations of author (s) and institutional addresses.
2. **ABSTRACT:** The abstract of the manuscript should not exceed 300 words. The abstract should include 3-6 Keywords.
3. **TEXT:** Text type should be 12 point Times Roman. Text should be single spaced. First line of all paragraphs should be indented and there should be one line gap between consecutive paragraphs.
4. **INTRODUCTION:** A brief introduction about the manuscript within 600 words.
5. **MATERIALS AND METHODS:** This section must contain specific details about the materials studied, instruments used, specialized chemicals source and related experimental details. Levels of subheadings should be easily distinguishable from each other with the use of numbers. There should be one line space before each subheading and one line space after each subheading. Examples of Subheading Style:

   FIRST LEVEL HEADING (12 point, bold, caps, Times Roman font, numbered)

   1.1. Second Level Subheading (12 point bold, Title case, Times New Roman, numbered)

   1.1.1. Third level subheading (12 point bold, Title case, numbered)
6. **RESULTS AND DISCUSSIONS:** The results should be concisely presented. Results and discussion may be separate or combined based on the author requirement.
7. **CONCLUSIONS:** A brief conclusion about the manuscript within 300 words.
8. **ACKNOWLEDGEMENTS:** The acknowledgments of those who do not qualify for authorship or to acknowledge finding, donated resources of significant contribution to the research
9. **REFERENCES:** a) In the text: Our Journal recommends and adheres to Vancouver style for Reference listing For the complete guide to the Vancouver Style, please consult this online book: Citing Medicine, 2nd ed. http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=citmed.TOC&depth=2

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CONTENTS

FORMULATION AND EVALUATION OF GALANTAMINE EXTENDED-RELEASE PELLETS

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ABSTRACT

The main objective of the present study is to prepare a robust and stable formulation and evaluation of extended-release Galantamine capsules. Galantamine is a sparingly soluble drug, so it is suitable to develop an extended-release dosage form. Short biological half-life (7hrs), 60% bio availability and dosage frequency more than once a day(50mgt.i.d.) make the Galantamine an ideal candidate for the controlled drug delivery systems. Galantamine hydro bromide extended-release pellets were formulated using a Fluidized Bed Processor (FBP) by Wurster technique (bottom spray). The formulation of Galantamine HBr extended-release pellets comprises three separate layers: a) The drug layer b) The barrier layer c) The extended-release layer, coated on to the Inert core pellets. Finally, the functional coating was performed using various concentrations of Ethyl cellulose polymers retarding material. The concentration of the polymer was optimized based on dissolution studies. Different properties such as bulk & tapped density, Hausner's ratio, compressibility index & moisture content were also studied in all formulations. The formulated pellets were analyzed for in-vitro release studies. (Fourier Transform - infrared spectroscopy) analyses were performed to know the compatibility of the drug with various excipients. The comparisons between the optimized formulation and innovator formulation done by *in-vitro* release studies. Three-month stability conducted at accelerated conditions showed the optimized formulation to be stable.

Keywords: Galantamine HBr, Extended-release, Ethyl cellulose, Polymer, Pellets, Wurster technique

INTRODUCTION

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Drug release occurs only after the administration or for a prolonged period or to a specific target in the body. Modifications in drug release are often desirable to increase the drug's stability,

safety, and efficacy, improve the therapeutic outcome of the drug treatment, and increase patient compliance and convenience of administration. This type of oral drug delivery system allows the drug to be released over prolonged periods. By extending the release profile of a drug, the frequency of dosing can be reduced. Extended-release can be achieved using sustained or controlled-release dosage forms[1].Today's most commonly used pharmaceutical sustained-release solid oral dosage forms include tablets, capsules, granules, and pellets. Pelletsare defined as multiple unit dosage forms that are small (0.5mm to 1.5mm), free-flowing, and spherical particulates formed by agglomeration of powders or granules of drug substances and excipients using appropriate processing equipment. Pellets are also used to describe small rods with an aspect ratio close to unity[2].

Galantamine hydro bromide (GHBr) is a sparingly soluble drug, so it is suitable to develop an extended release dosage form. Short biological half-life (7 hrs), 60% bioavailability and dosage frequency more than once a day (50mgt. i.d.) make the GHBr ideal for the controlled drug delivery systems. GHBr is a para sympatho mimetic, specifically, a reversible choline sterase inhibitor[3]. It is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. A nearly patho physiological feature of Alzheimer's disease associated with memory loss and cognitive deficits are a deficiency of acetylcholine due to selective loss of cholinergic neurons. In the Cerebral cortex, nucleus basalis, and hippocampus. GHBr is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetyl cholinesterase[4].

The main aim of the present study is to extend the release of Galantamine capsules by 16 hours release to reduce the dosing frequency compared with the IR tablet for treating Alzheimer.

MATERIALS AND METHODS

Materials

GHBr was obtained as a gift sample from Aurobindo Pharma; Hyderabad, PEG6000, Hydroxy propylmethyl cellulose (HPMCE5), Ethyl cellulose (EC), isopropyl alcohol (IPA) were obtained from SARC labs, Hyderabad.

1. Preformulation Studies

(a) Identification of drug

Solubility: The solubility of GHBr was tested in various solvents such as water, sodium hydroxide Solution, ether, alcohol and methylene chloride.

Melting point determination: A small extent of GHBr in a capillary tube closed at one end and was placed in its melting point apparatus, and the temperature at which the drug melts was noted. The average of triplicate readings was reported[5].

Infrared absorption spectrum (FTIR): FTIR of GHBr was detailed with a KBr discover wave no.4000 to 400cm-16.

Sieve Analysis: Sieve analysis aim is to determine the different size of drug particles present. A series of sieves are arranged to decrease pore diameter (increasing sieve number), such as sieve number 20, 30, 40, 60,100 and 200.100 grams of drug is weighed accurately and transferred to sieve number 20, kept on top. The sieves are shaken for about 5-10 minutes[6]. Then the drug retained one a sieve is taken, weighed separately, and the amount retained is expressed in percentage.

(b) Analytical method development

Preparation of standard curve of GHBr: 100mg of GHBr was dissolved in 100ml calibrated volumetric flask and completed to volume with PH6. 5 phosphate Buffer. This 10ml pipette out in100ml, calibrated volumetric flask and dilution was made with PH6.5phosphate Buffer[7]. From this solution, 2ml, 4ml, 6ml, 8ml…upto10ml was pipette out in different 10ml volumetric flask, and this was finally diluted with PH6. 5 Phosphate Buffer to10ml. The absorbance was noted λ_{max} of 289nm.

Flow Properties of GHBr[8]

Bulk Density (BD): Bulk density = Weight of powder / Bulk volume

Tapped density (TD): Tapped Density = Weight of powder / Tapped volume

Carr's Index: It is as impletes to evaluate the BD and TD of a powder and the formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = [(TD-BD) \times 100]/TD$$

Hausner's Ratio: The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material, and their standard values are given in Table-1.

Hausner's Ratio = TD / BD

TABLE-1
Effect of Carr's Index and Hausner's Ratio and Angle of repose on flow property

Flow Character	Carr's Index (%)	Hausner's Ratio	Angle of repose
Excellent	≤10	1.00-1.11	<20
Good	11-15	1.12-1.18	20-30
Fair	16-20	1.19-1.25	—
Passable	21-25	1.26-1.34	30-34
Poor	26-31	1.35-1.45	—
Very poor	32-27	1.46-1.59	>35
Very very poor	>38	>1.6	—

Compatibility Studies

The compatibility studies are carried out by taking a mixture of drug and excipients at the ratio in which they are expected to be present in the innovator product. A part of the mixture can be exposed to different storage conditions like 40 °C±2°C/ 75% RH±5% RH and control samples kept at 2-8 °C. They are tested concerning their physical and chemical aspects[9].

Method of Manufacture

Fluidized Bed Processing (FBP): It involves drying, cooling, agglomeration, granulation and coating of particulates materials.

Coating Solution Preparation: HPMCE5 is dissolved in a specific quantity of water. All other ingredients and drugs are added to it, which are stirred under a mechanical stirrer at 1600-1900 RPM. The above two solutions are mixed by stirring[10].

Filtration: The solution is filtered through #80 mesh to remove any lumps or visible particles.

Drug Loading: Accurately weighed sugar spheres (cores) are transferred into FBP; these cores are coated with drug solution uniformly[11].

Sieving: Finally, these dried pellets are sieved to obtain pellets of uniformity with the required size.

Barrier Coating: HPMCE5 is dissolved in a specific quantity of water. PEG-6000 is added to it, which is stirred under a mechanical stirrer at 1600-1900 RPM. Transfer the drug-loaded pellets to FBP for Barrier coating[12].

Extended-Release Coating: Ethyl Cellulose N_{50} is dissolved in a specific quantity of IPA, PEG-6000 are added to water, which is stirred under mechanical stirrer at1600-1900 RPM. The above two solutions are mixed by stirring. Transfer the barrier Coated pellets to FBP for ER coating[13].

Sieving and Drying: Finally, these dried pellets are sieved to obtain pellets of uniformity with the required size and dried.

Capsule Filling: The weight of pellets equivalent to 24mg Galantamine is filled into hard gelatin capsules of size 1 by capsule filling machine.

Process Control Parameters:

Spray Gun; needle; spray type; bottom spray; spray rate: 5ml/min; spray pump RPM: 2-6 RPM; inlet temperature: 39°C; bed temperature: 37°C; out let temperature: 31-33°C; air pressure: 1Kg/cm2.

2. Formulation Development

GHBr extended-release capsules were prepared. The process was displayed in the below flowchart as Figure-1.

Formulation Trails: Formulation studies GHBr extended-release capsules are based on pre-formulation data of various excipients were selected, and their compilation was shown in the Table-2. Pellets were evaluated for physical parameters like like bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose, sieve analysis and chemical parameters, like assay.

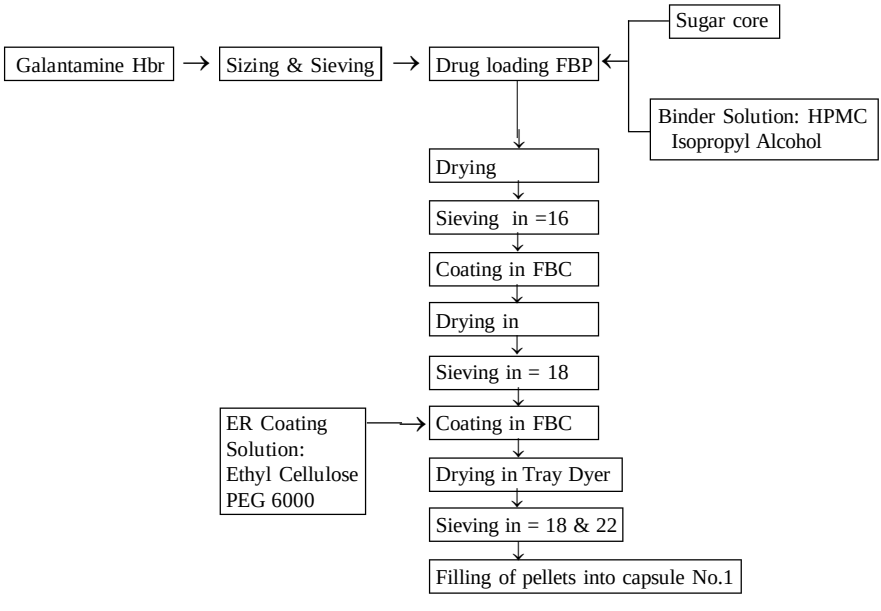
TABLE-2

Formulas and their quantities as per w/w: 350 gms Batch

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	GHBr	35.87	35.87	35.87	35.87	35.87	35.87	35.87	35.87	**35.87**
2.	Sugar Pellets (18 ≠ 22)	273.2	273.2	273.2	273.2	273.2	273.2	273.2	273.2	**273.2**
3.	HPMC E5	8	9	10	11	12	16	15	14.5	**14**
4.	Water	478.2	478.2	478.2	478.2	478.2	478.2	478.2	478.2	**478.2**
Barrier Coating										
5.	HPMC E5	15	12	14	10	14	14	14	14	**14**
6.	P.E.G-6000	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	**1.4**
7.	Purified Water	260	260	260	260	260	260	260	260	**260**
ER Coating										
10	Ethylcellulose	17.5	16.5	15.5	8	8	12	9.5	10	**10.5**
11	P.E.G-6000	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	**1.4**
12	I.P.A	493.5	493.5	493.5	493.5	493.5	493.5	493.5	493.5	**493.5**
13	Purified Water	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	**10.0**

Figure-1

Manufacturing flow chart for extended-release capsules



Loading of GHBr Pellets in Capsules: To prepare Galantamine capsules 24mg by taking GHBr pellets 24mg from the formulation F9 is carried and filled. Size '1' blue colour capsules were selected for capsule formulation[14] with an Automatic capsule filling machine. Coated pellets were transferred into capsules by spreading them into equal quantities equivalent to 24mg GHBr.

Evaluation of Capsules

Weight variation test: Individual weights of 20 capsules weretaken, and the average weight was calculated using the following formula. Weight variation should not be more than 5 %.

$$\text{Weight variation} = \frac{(\text{Weight of capsule} - \text{Average weight})}{\text{Average weight of capsules}} \times 100$$

Disintegration time: The capsules are placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37ºC + 2ºC and observed over the time described in the individual monograph. The capsules disintegrate completely into a soft mass to fully satisfy the test, having no probably firm core and only some fragments of the gelatin shell[15].

Moisture permeation test: The USP requires determination of the moisture permeation characteristics of single unit and unit dose containers to assure their suitability for packing capsules. The degree and rate of moisture penetration are determined by filling the dosage unit to gether with a color revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for color change (indicating desiccating absorption of moisture) and comparing the pre and post weight of the packaged unit and also by the Karl Fisher titration equipment[16].

***In vitro* Dissolution**[17]

For capsules, place 500ml of dissolution medium in each vessel and allow the medium to equilibrate to a temperature of 37±0.5ºC, place one capsule in each of the paddle and operate the apparatus at 50rpm for a specifictime. Withdraw10ml of the solution from each vessel and replace it with an equal volume of fresh dissolution medium at particular time intervals. Filter the solution through a 0.45 microns membrane filter and discard the first few ml of the filtrate. Dissolution study was carried out in pH 6.5 buffer for 0^{th}, 2^{nd}, 6^{th},12^{th} and 16^{th} hours was done by using USP dissolution test apparatus type II (paddle type)[17]. The dissolution profile of the prepared GHBr extended-release capsules was compared with that of Reminyl extended-release capsules (Razadyne ER) of the product.

Stability Study

Specification, which is a list of tests, references the analytical procedures and proposed acceptance criteria, including the concept of different acceptance criteria

for release and shelf-life specifications, is addressed in ICHCSL6AS and IS6B[18]. The formula of F9 was optimized and selected for evaluation studies. Further stability study was done for F9.

RESULTS AND DISCUSSION

Preformulation Studies

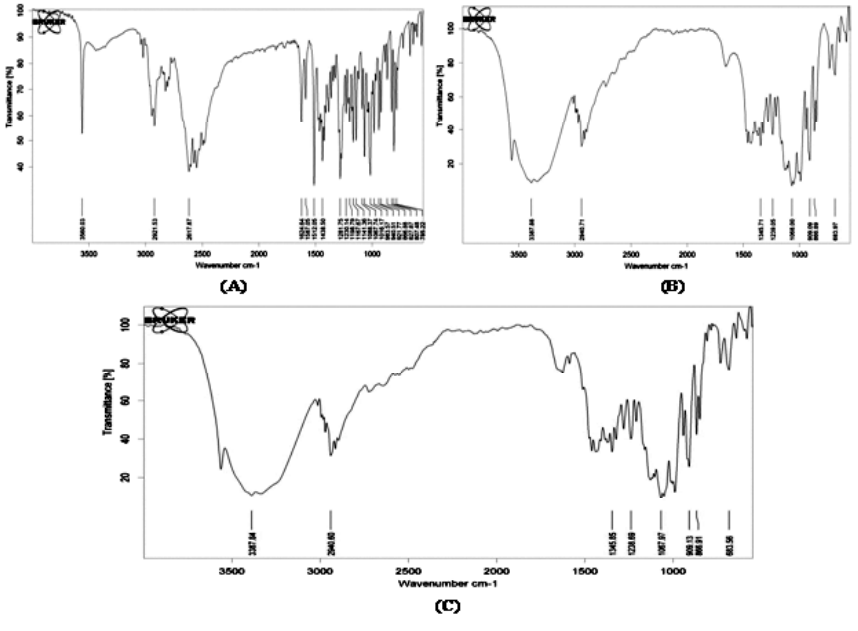
Solubility: GHBr was slightly soluble in water, freely soluble in Sodium hydroxide Solution, Insoluble in ether, alcohol and methylene chloride.

Melting Point Determination

The melting point of GHBr was found to be 270°C, which complied with Pharma Euro standards, indicating the purity of the drug sample.

Infrared absorption spectrum (FTIR): The FTIR of GHBr was carried out using various excipients mentioned above. It was observed that no physical and chemical incompatibility was observed amid drug and excipients as shown from Figure-3.

Figure-1
FT-R Spectrum of (A) Pure Drug, (B) Placebo Pellets, (C) Finished Product



Sieve Analysis: Through this sieve analysis, we realized that a large quantity of powder was retained on sieve no.200, indicating an inadequate flow of the drug, as displayed in Table-3. Flow property and particle size are inversely proportional to each other as GHBr has a fine grade of particles, it has poor flow. Hence the GHBr has insufficient flow property.

TABLE-3

Sieve Analysis Values of GHBr Drug

Sieve No.	Empty sieve (gm)	Sample sieve (gm)	Difference (gm)	% Retained	%Cumulative retained
#20	321.4	321.4	0	0	0
#30	328.6	328.8	0.2	0.2	0.2
#40	299.0	300.0	1.0	1.0	1.2
#60	287.2	297.4	10.2	10.2	11.4
#80	245.0	268.2	23.2	23.2	34.6
#100	274.0	299.0	25.0	25.0	59.6
#200	270.0	310.0	40.0	40.0	99.6
Receiver	348.8	349.0	0.2	0.2	99.8

(b) Analytical method development Preparation of standard curve of GHBr:

Standard curve of GHBr was determined by plotting absorbance V/s concentration at 289 nm, and it follows Beer's law as displayed in Figure-2. The results were shown in Table-4, and the R2 value is 0.9994, and the slope is 0.0267.

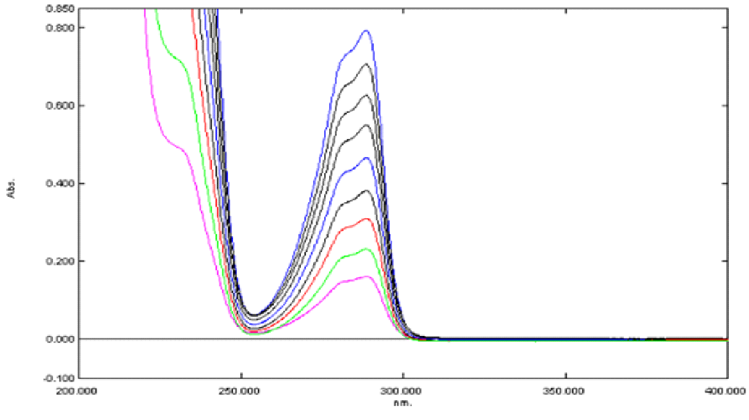
TABLE-4

Standard Curve Values of Galantamine Hbr

S.No.	Concentration µg/ml	Absorbance at 289 nm
0	0	0.00
1	2	0.06
2	4	0.132
3	6	0.212
4	8	0.268
5	10	0.327

Figure-1

An Overlain UV Spectra of Galantamine Hydrobromide



Flow Properties of GHBr

The bulking properties of a powder with powder flow influenced by the Inter-particulate interactions. A comparison of the bulk density and tapped density can measure the relative importance of this inter action in a given powder; such a comparison is often used as an index of the ability of the powder to flow. The bulk density and tapped density was found to be 0.248g/ml and 0.328g/ml, respectively.

The application of a compressibility index gives a simple indication of the ease with which a material can be induced to flow. The value for compressibility index of GHBr was 24.39% that reflects the poor flow property of Galantamine Hbr, which was supported by the Hausner ratio of 1.322. The physical characterization of the polymer was done by evaluating them for physical characteristics such as bulk density, tapped density, compressibility index, and Hauser's ratio and angle of repose.

Compatibility Studies

The compatibility studies were carried out at 25°C / 60% RH and 40°C/75% RH for 0,2 and 4 weeks. They were tested concerning physical and chemical aspects, and there are no drug-excipients interactions observed, as shown in Table-5. This indicates that the drug was compatible with the formulation components. The spectrum for the formulation is also shown in Figure-3.

TABLE-5

Standard Curve Values of Galantamine Hbr

S.No.	Drug and Excipients	Initial Physical Description	25°C / 60% RH & 40°C / 75% RH		
			1st Week	2nd Week	3rd Week
1.	Galantamine hbr	White crystalline powder	*	*	*
2.	Galantamine hbr + Sugar spheres	Off-white powder contain spherical pellets	* *	* *	* *
3.	Galantamine hbr + Ethylcellulose N-50	Off-white powder			
4.	Galantamine hbr + Polyethene glycol 6000	white powder contain crystalline material	*	*	*
5.	Galantamine hbr + HPMC E_5	Off-white powder	*	*	*
6.	Galantamine hbr + Isopropyl alcohol	Off-white thick mass	*	*	*
7.	Galantamine hbr + Purified Water	Off-white thick mass.	*	*	*
8.	Galantamine hbr + Sugar spheres + Ethyl cellulose N-50 +HPMC + Polyethyleneglycol-6000 +Isopropylalcohol + Purified Water.	Off-white powder containing lumps	*	*	*

Evaluation of Capsules

Weight Variation: The uniformity of dosage units may be demonstrated by determining weight variation or content uniformity. The amount of active ingredient determined by assay is within the range of 85% to 115% of the label claim for 9 of 10 dosage units assayed with no unit outside the range of 70% to 125% of label claim as displayed in Table-6. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes, and all the capsules are within the range of USP.

Disintegration test: The disintegrating value of F9 is found to be 4.25±0.59 min. the disintegrating values of all the remaining formulations are found to be within the range as shown in Table-6.

TABLE-6
Evaluation of Capsules

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Weight variation	275.7 ±1.01	288.4 ± 1.26	324.2 ± 2.02	252.4 ± 1.91	261.2 ± 1.85	292.4 ± 2.21	299.6 ±2.18	298.4 ±1.79	300.6 ±2.14
2	Strength 200mg (%)	109.9 ±1.59	108.7 ± 1.32	105.0 ± 1.28	102.5 ± 1.37	104.2 ± 1.14	95.7 ±1.43	100.6 ±1.29	98.9 ±1.41	99.0 ± 1.35
3	Disintegration time in min.	4.30 ±0.71	4.50 ±0.54	4.40 ± 0.82	5.10 ± 0.79	4.50 ± 0.76	4.50 ±0.48	4.55 ± 0.75	5.05 ±0.67	4.25 ± 0.59
4	Moisture content (%)	3.2± 0.41	2.9± 0.24	3.2 ± 0.18	3.6 ± 0.11	3.3 ± 0.20	2.9 ±0.48	2.3 ± 0.32	1.8 ±0.28	1.75 ± 0.32

Each value is the mean ± SD (n=3)

Moisture Permeation Test: The USP requires determination of the moisture permeation characteristics of single unit and unit dose containers to assure their suitability for packing capsules.

Dissolution Studies: The size and strength of the pellets are good, and the coating margins around 17% is there for further development and to increase the HPMC ratio drug loading from F1 formulation as displayed in Table-7 and Figure-4. From F2, the Ethylcellulose N50 and HPMC concentration increase to attain the desired drug release. From F3, the Ethylcellulose N50 and HPMC concentration are reduced for achieving expected drug release. From F4, it is evident that coat only with Ethyl cellulose N50 with decreasing HPM Cleve to get the more release in the final hour. From F5, the concentration of Ethyl cellulose N50 has to be increased to get the desired release. From F6, the starting release in a lower limit, so the concentration of the HPMC is high, reducing which retorts the release. From F7, the ethyl cellulose N50 concentration has to be increased. From F8, we have to increase ethyl cellulose concentration; but the shape, size and strength of the pellets are good. From F9, the release, shape, size and strength of the pellets is good, and we got reproducible results.

TABLE-7

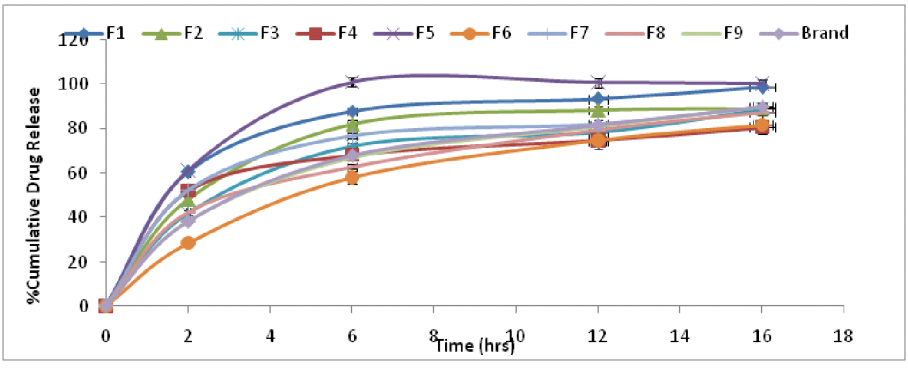
***In-vitro* Dissolution Studies**

Time (Hrs)	Percentage of Drug release									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**Razadyne ER (Brand)**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	60.49 ±1.02	48.17 ±1.11	42.17 ±1.32	52.04 ±1.20	61.01 ±1.73	28.61 ±1.59	52.39 ±1.41	42.28 ±1.45	38.25 ±1.18	38.35 ±1.84
6	87.88 ±1.01	82.12 ±1.23	72.12 ±1.02	68.12 ±1.11	101.01 ±1.02	57.86 ±1.08	76.82 ±1.06	62.85 ±1.31	66.94 ±1.42	67.72 ±1.04
12	93.24 ±0.71	88.33 ±0.54	78.33 ±0.82	74.60 ±0.79	100.08 ±0.48	74.58 ±0.83	82.06 ±0.75	79.34 ±0.67	80.97 ±0.74	81.35 ±0.59
16	98.65 ±0.81	89.04 ±0.52	89.04 ±0.41	80.62 ±0.78	100.10 ±0.58	81.77 ±0.47	89.62 ±0.82	87.23 ±0.52	91.68 ±0.48	90.09 ±0.72

Each value is the mean ± SD (n=3)

Figure-4

***In-vitro* Dissolution Studies**



Stability Studies

Stability studies are to be carried out as per ICH guidelines for the F9 batch of this product at long term, Intermediate and Accelerated storage conditions, as shown in Table-8.

TABLE-8

Stability Studies of Formulation F9

S.No	Parameter	Stability Conditions at		
		25±2°C/60± 5% RH	**30±2°C/65± 5% RH**	**40±2°C/75± 5% RH**
1.	Assay (%)	100.13±0.41	100.05±0.52	100.10±0.24
2.	Moisture content (%)	1.72 ±0.18	1.75±0.11	1.85 ±0.20
3.	Disintegration time (min.)	4.30±0.31	4.25±1.42	4.20±1.37

Each value is the mean ± SD (n=3)

CONCLUSION

The active pharmaceutical ingredient GHBr was subjected to a pre formulation study, which encompasses the "Accelerated drug excipient compatibility study". The results obtained with selected excipients showed good compatibility with GHBr drug. GHBr coated pellets were formulated using commercially available sugar pellets, and GHBr coated capsules were filled by an automatic capsule filling machine with various excipients. The optimization procedure said edin stabilizing the formula and in the formulation of the GHBr Extended-release capsules. The stability of the capsules and pellet was determined by conducting "Accelerated stability testing" in 40°C ± 2°C/75%±5% RH and 25ºC±2ºC/60%±5% RH, 30ºC±2ºC/65±5% RH conditions for 3months as per ICH guidelines. Finally, after the duration, the product was analyzed for content uniformity, assay, disintegration and dissolution studies. The stability studies formulated GHBr extended-release capsules and pellets tobestablethroughout the storage. The GHBr extended-release pellets were loaded in size1 hard gelatin capsules. It showed promising results in the formulation of stable dosage. The dissolution profile of the prepared GHBr extended-release capsules was compared with that of Reminyl extended-release capsules (Razadyne ER) of the product. The release was found nearer in the case of pellets loaded in capsules. And dissolution profile of GHBr extended-release capsules was compared with that of the innovator (Razadyne ER). The prepared product was said to be equivalent to an innovator, when coated pellets in capsule, the dosage form extended-release showed better drug release. Extended-release pellets have minimum volume in size, greater surface area and more surface activity. The drug-loaded pellets release rate area was also more. There was no need for disintegration time for pellets in capsules because small size pellets enter the systemic circulation very fast. Moreover, there was no accumulation of the drug in the body. The drug release rate was more when compared with the innovator (Razadyne ER) sample. The release in the starting hours is controlled by increasing the concentration of Ethylcellulose N-50 in the F9 formula and HPMC formulations. Even though GHBr tablets and capsules, gels available in the market, the formulation of F9 show better results with innovator product and the formulation process will be easy, safe, andeffective.

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A NOVEL APPROACHE FOR ENHANCEMENT OF DISSOLUTION RATE AND BIOAVAILABILITY OF SOME INSOLUBLE DRUGS: REVIEW ON IMMEDIATE RELEASE DOSAGE FORM

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ABSTRACT

Immediately bioavailable dosage forms dissolve rapidly after administration, with an increased rate of dissolution, compared to conventional dosage forms. Using superdisintegrates such as linked polyvinylpyrrolidine or crospovidone sodium starch glycolate carboxymethylcellulose, for example, is the fundamental approach employed in the development of development tablets. Following administration in the stomach, this pill causes instantaneous disintegration of the tablet in the stomach. being able to increase patient compliance Moreover, they serve as a tool for expanding marketing, extending product life cycles, and creating new opportunities. It has a number of advantages over other types of medication delivery systems. It is the purpose of this article to provide a comprehensive account of the significance of super disintegrants in the preparation of immediate-release tablets, as well as the mechanism of disintegration, as well as various conventional techniques and novel granulation technology, which are used to prepare immediate-release tablets.This review also includes some of the most recent research on immediate releasereleasedoage forms that have been done in recent years.

Keywords: Immediate release tablets, superdisintegrants, polyvinylpyrrolidone, sodium starch glycolate, carboxymethyl-cellulose.

1. INTRODUCTION

At the moment, novel drug delivery systems are being developed with the goal of expanding markets/indications, lengthening product life cycles, and creating new opportunities. The most frequently used route of administration for systemic effects

is ingestion due to its ease of ingestion, discomfort avoidance, variety, and most significantly, patient compliance. These solid formulations do not require sterile conditions, which makes manufacturing them less expensive. The oral route of administration continues to be the optimal method for the administration of therapeutic drugs due to its low cost, convenience of manufacture, and ease of administration, which results in high levels of patient compliance (Rathod VG et.al.). Numerous patients require rapid start of action for specific therapeutic conditions, necessitating the prompt release of medication. This condition is believed to afflict 50% of the population, resulting in a high rate of unsuccessful therapy. Immediate release drug delivery systems are comprised of a single or multiple-unit reservoir or matrix system that is meant to dispense drug at a rapid rate. Immediate release is preferred for medications with a lengthy biological half life, a high bioavailability, a low clearance rate, and a low elimination half life. However, the primary condition for a rapid release dosage form is the medicine's poor solubility and the need for the drug to act immediately to treat an undesired defect or disease (Pavuluri P et al). Rapid or slow dissolving rates are used to classify immediate release solid oral dose formulations. The term "immediate release" refers to dose formulations in which 85% of the labelled amount dissolves within 30 minutes. (Pande V et.al.).

1.1. Disintegrants

It is common for disintegrants to be added to tablet and some encapsulated formulations in order to break down the tablet and capsule "slug," increasing the surface area of the "slug" and facilitating a faster release of the medicine. As a rule, super disintegrants are employed at a modest percentage of the total weight of the dose unit, typically 1% to 10%. All kinds of classifications In order to circumvent the limits of standard tablet dosage forms, superdisintegrants such as synthetic, semi-synthetic and natural and co-processed blends have been used (Jadhav SB et.al). Moisture penetration and pill dispersion are facilitated by them. The importance of tablet breakdown in achieving rapid medication release has been well-documented. The primary role of disintegrants is to counteract the effectiveness of the tablet binder and the physical forces that act during compression to form the tablet. For a tablet to release its drug, dissolving agents must be equally effective as the binder (Patel N et.al.). Tablets should disintegrate into both granules from which they were compacted, and powder particles from which they were made, in order to be effective. The most frequent pills are those that are meant to be ingested whole and breakdown quickly in the gastrointestinal tract, releasing their medication (GIT). Choosing the right disintegrant and ensuring that it performs consistently are important to the creation of these tablets (Pande V et.al.). Recently, considerable focus has been made to producing fast-dissolving orally disintegrating tablets that dissolve and/or disintegrate swiftly in the mouth, rather than swallowed pills. A majority of earlier studies have concentrated on the functional qualities of super disintegrants, with a particular emphasis on linking these functional properties to disintegrant efficiency and drug release rate, as well.

1.2. Mechanism of Disintegration by Super Disintegrants

There are five major mechanisms for tablet disintegration as follows:

- Swelling
- Porosity and Capillary Action (Wicking)
- Deformation
- Due to disintegrating particle / particle repulsive forces
- Enzymatic reaction

1.2.1. Swelling

Swelling is thought to be a mechanism by which certain disintegrating substances (such as starch) convey their effect. When a tablet comes into touch with water, the adhesiveness of the other ingredients is overcome, causing the tablet to disintegrate. For example, sodium starch glycolate. (Rajni D et.al.)

1.2.2. Porosity and Capillary Action (Wicking)

Porous and capillary disintegrants, which don't swell, are thought to be responsible for their dissolving properties. Tablet porosity creates passageways for fluids to pass through. The disintegrant particles (which have a poor cohesion and compressibility) inherently promote porosity and provide these paths into the tablet itself. These routes are "wicked" by capillary action, which causes the interparticle connections to be ruptured, causing the tablet to disintegrate by Crospovidone and Cross carmillose. (Jampala Rajkumar et.al.)

1.2.3. Deformation

It is widely accepted that starch granules are "elastic" in nature, which means they return to their former shape after being distorted by pressure. These grains are said to be "energy rich" because of the compressive forces involved in tableting, and this energy is released when they come into contact with water. As a result, starch granules that have been deformed under pressure are more likely to swell than starch grains that have not been distorted (Patil N et.al.).

1.2.4. Due to disintegrating particle / particle repulsive forces

Tablets produced with "nonswellable" disintegrants may be swelled due to another process of breakdown. Based on the discovery that nonswelling particles similarly disintegrate tablets, Guyot-Hermann proposed a particle repulsion theory. In order for disintegration to occur, water must be present in order for it to occur. Research has shown that wicking is more important than repulsion. Most disintegrants are thought to have a variety of mechanisms at work. However, it is most likely the outcome of interactions between these primary systems (Jampala Rajkumar et.al.).

1.2.5. By Enzymatic Reaction

Enzymes present in the body also act as disintegrants.These enzymes enhance the binding action of binder and helps in disintegration. Due to swelling,pressure is exerted in the outer direction that causes the tablet to burst or the accelerated

absorption of water leads to an enormous increase in the volume of granules to promote disintegrationrevealed that Saikh MAA research work.

1.3. Super Disintegrants

Crospovidone, croscarmellose sodium, and sodium starch glycolate are the three most frequent superdisintegrants. Even though they differ in chemistry and particle structure, disintegrants are able to break down both wet and dry granulations and direct compression tablet techniques. Since the material is made up of extremely porous particles, it has a very large surface area. Unlike disintegrant methods now in use, poorly soluble medicines have greater surface area and unique chemistry that enhances interfacial activity. Consideration is being given to the use of superdisintegrants in the dissolving process.The selection of a superdisintegrant and the use level plays a key role in determining the drug release of finished formulations. (Sisodiya MH et.al.).

1.3.1. Selection of Super Disintegrants

In order to be utilised as an excipient in the tablet formulation, superdisintegrant must meet a number of conditions in addition to its swelling capabilities. It is essential that the requirements put on the tablet disintegrant are well established. The perfect disintegrants should possess the following characteristics.

- Insufficiency of solubility
- Inadequate gel formation
- Sufficient hydration capacity
- Excellent moulding and flow characteristics
- There is no tendency for the medications to develop complexes with one another
- Excellent mouth feel.(Mahida MV et.al.).

In addition to this, it should be compatible with the other excipients and possess desirable tableting qualities.Compounds that expand to many times their original size when introduced in water have been developed in three major classes. Superdisintagrants include:

1.3.1.1. Modified Starches

Sodium Carboxymethyl Starch(Chemically treated Potato Starch) i.e. Sodium Starch Glycolate (Explotab, Primogel).The way it works: It causes a lot of swelling quickly, but there isn't a lot of gel. Effective concentration: 4% to 6%. Above 8%, the time it takes to break down may actually get longer because of gelling and the viscosity it makes.

1.3.1.2. Cross-linked Polyvinylpyrrolidone

water insoluble and strongly hydrophiliccrospovidone (Polyplasdone XL, Kollidon CL). Mechanism of Action: Water wicking, swelling, and maybe even some deformation recovery. Effective Concentration: 2-4%

1.3.1.3. Modified Cellulose

Form of sodium carboxymethyl cellulose that has been internally cross-linked. i.e. Ac-Di-Sol (Accelerates Dissolution), Nymcel.

Mechanism of Action: Because of the fibre nature, wicking occurs, as does swelling with minimal gelling. Concentrations that are effective: 1-3% (Direct Compression), 2-4%(Wet Granulation)

1.3.2. Method of Blending for selective super disintegrants

Disintegrating agents can be incorporated into fabrication of immediate release doage form as follows. (Sood R et.al.).

1.3.2.1. Internal Addition

The disintegrant is added to the other excipients before the powder is wetted with the granulating fluid in the wet granulation process. The disintegrant is integrated into the granules as a result of this method. The disintegrant is added to the other excipients before the powder is compressed between the rollers in the dry granulation process. Croscarmellose sodium, a disintegrant, was studied in a computer-optimized experiment to see if it had any influence on the dissolution of a weakly soluble medicine when it was included intragranularly, extragranularly, or equally between the two phases of a tablet. The results of the general quadratic response surface model imply that the super disintegrant is incorporated intragranularly, tablets with the same total concentration of crosscarmellose sodium dissolve more quickly. Using a disintegrant does not influence tablet friability. (Verma K et.al.).

1.3.2.2. External Addition

The superdisintegrant is added to the granules prior to compression in both the wet and dry granulation methods. Croscarmellose sodium, sodium starch glycolate, and crospovidone were used as superdisintegrants in the wet granulation of tablet formulations of three model pharmaceuticals with varied water solubility (carbamazepine, acetaminophen, and cetrizine HCl). Extra granular form of addition appears to be the optimal mode of inclusion, regardless of the solubility of the main tablet component, as it has been proven that crospovidone is effective in enhancing drug dissolving. (Shilpa S et.al.).

1.3.2.3. Internal and External Addition

The disintegrant is split into two parts in this manner. Prior to compression, one component is added to the granules, and the remaining amount is added to the granules with mixing. This strategy is more effective. Extragranular methods split the tablet into granules, and the granules are further disintegrated by intragranular methods to release the medicinal component into solution when both methods are used. As a result, intra-granular disintegrant in wet granulation processes (as opposed to extra-granular disintegrant in dry granulation processes) is usually less

effective since it is subjected to wetting and drying (which diminishes activity of the disintegrant). The intragranular disintegrant retains itsdisintegration activity since the compaction process does not expose it to wetting and drying. (Rajni D et.al).

TABLE-1

A Model Formula for fabrication of Immediate Release dosage form (Tablets)

Ingredient	Amount Per Tablet (25mg)	Amount per Tablet (50mg)
Metronidazole	25	50
Microcrystalline cellulose	743	743
Crosscarmellose sodium	24	24
Magnisum stearate	8	8

1.3.3. Requirements for Immediate Release

The basic requirements are consider for designing the Immediate release dosage forms as followos below:

- Disintegrates in a short period of time
- Is not sensitive to changes in humidity or temperature
- Quick commencement of action is a plus
- There is no residue left behind
- Suitable for use with taste masking agents

1.3.3.1. Advantageof Immediate Release Drug Delivery System

- Better compliance, solubility, stability, and bioavailability
- Allows for high drug loading and is cost-effective
- The ability to give the benefits of liquid medicine in a form that can be taken in a solid form. (Shaik A, et. al.)
- It can be used with existing processing and packaging machines so it can be used.

1.3.3.2. Disadvantages

- A drug with a short half-life needs to be taken a lot
- Drugs that are released all at once may have a high concentration in the blood, which could be harmful.

1.4 A Model Conventional Techniques Used for Preparation of Immediate Release Tablets

Numerous technologies exist for the manufacturing of immediate-release tablets. Molding, lyophilization or freeze drying, direct compression, spray drying, and sublimation are the most frequently used preparation procedures. (Patil N et.al.).

1.4.1. Tablet Molding Technique

Water-soluble chemicals are included into this technology to accelerate the disintegration and dissolution of the tablet. Hydroalcoholic solvents are added to a wet powder blend, and the tablet is moulded using a compression pressure that is lower than that used for traditional tablets. After that, the solvent is removed via air drying. The porous structure of moulded tablets aids in dissolution. (Rathod VG et.al.).

1.4.2. Direct Compression

Direct compression is a method of making tablets from a powder mixture of excipients and API. No pretreatment of blended powder by dry or wet granulation is required. Its benefits include faster manufacturing, less machinery, less staff, fewer unit operations, less processing time, and better product stability.

1.4.3. Granulation Technique

It is a process in which small particles are transformed into larger agglomerates, resulting in a material that is more durable. Improve powder flow and handling and reduce dustiness by preventing product constituents from becoming separated. (Shilpa S et.al.).

1.4.3.1. A Traditional model techniques for Granulation

1.4.3.1.1 Wet Granulation:

Using the wet granulation technique, fine particles can be easily fed into the manufacture of severe-feed drugs with ease. An aqueous solution of a binding polymer is usually added to the fine particles accumulation of an immediate release formulation. Binder polymer solution added to granular composition for controlled release. (Ahmed JA et.al.).

1.4.3.1.2. Dry Granulation

The powder combination is compacted in a dry granulation process without the use of heat or solvent. The first step is to compress the material into a solid mass, and the second is to mill the solid mass into granules. Dry granulation can be done in two ways.

1.4.3.1.3. Mass-Extrusion

In this method, the active drug mixture is softened using water-soluble solvent methanol, polyethylene glycol, and softened mass before being extruded into a cylinder shape and segmented with a heated blade to produce dosage forms in the form of pills.

1.4.3.1.4. Solid Dispersions

Products with at least two separate components, mainly hydrophilic matrix and hydrophobic medication, are called solid products. There are two types of matrix:

crystalline and amorphous. While the matrix and medication are often weakly miscible, this approach aims to overcome this problem by combining them at the molecular level. An increase in the quantity of dispersion in an instant release solid dosage form for oral administration to an environment such as a human's gastrointestinal tract is frequently desired. (Shaik A et.al.).

1.4.3.1.5. Lyophilization

Sublimation is the underlying principle. During sublimation, a substance is transformed from a solid to a gaseous state without affecting its liquid state. At temperatures and pressures below the triple point, lyophilization is carried out. Vacuum drying is ideal for drying thermolabile substances because the procedure is carried out at low temperatures and pressures.

1.4.3.2. Novel Granulation Technologies

1.4.3.2.1. Pneumatic Dry Granulation (PDG)

Granules are formed using an automated or semi-automatic process in this new dry method approach. It has superior qualities to dry granulation, direct compression, wet granulation, and granules are demonstrating great compressibility and flowability in comparison. The end result can be achieved without the use of expensive and unusual resources.

1.4.3.2.2. Freeze Granulation Technology (FGT)

One of Integrated Biosystems' unique freeze GTs (California, USA) results in perfectly round, free-flowing, homogeneous pellets. Freeze drying is required to produce dry, finely dispersed particles from a mixture of powder and liquid nitrogen, which is then atomized and frozen into granules from the studies were made by (Sisodiya MH).

1.4.3.2.3. Spray Drying Granulation

Compared to wet massed products, this approach enhanced flow, even distribution of colours, and required less lubricant. To improve the bioavailability and dissolving rate of many pharmacological products, an active pharmaceutical ingredient can be co-precipitated with a suitable polymer. (JampalaRajkumar et.al.).

1.4.3.2.4. TOPO (TOPO Granulator) Technology

Hermes Pharma has developed a unique single pot granulation method that requires only a minimal amount of liquid to start the chain reaction. Water or ethanol blends are used. A solid crystalline, an organic acid, and an alkaline earth metal carbonate that combines with the organic acid in water solution to create carbon dioxide are used to make TOPO tablet granules. Soluble final goods and granules offer exceptional hardness and stability. It was used to make effervescent tablets using Hermes Pharma's TOPO vacuum granulation technology. To avoid uncontrolled chain reactions, granulation is required.

1.4.3.2.5. Moisture Activated Dry Granulation (MADG):

Using moisture to stimulate granule production eliminates the requirement for heat to dry the granules. MADG 26 has two main stages.

1.4.3.2.6. Continuous Flow Technology

Chain reaction preceded by liquid does not occur in this method.

1.4.3.2.7. Thermal Adhesion Granulation Process

An alternative to moist granulation, it uses only a tiny amount of liquid and heat to create agglomeration. In addition, the use of heat speeds up the granulation process. Excipient and API combination is heated in a closed chamber with a tumble rotation at 30 to 130 degrees Celsius to generate agglomeration of the powder particle. Because less liquid is utilised and that is wasted during agglomeration of powder particles, this method ends the drying process. Granules of the desired particle size can be obtained after chilling and sifting. (Buwade P et.al.).

1.4.3.2.8. Granurex Technology:

When it comes to the powder stacking procedures, including single and multiple layering, this technology is consistently and accurately able to provide the desired results.

1.4.3.2.9. Foamed Binder Technologies:

It helps improve wet granulation by employing methocel polymers and homogenising the binder solution and drug mixture. It saves water and ensures reproducibility.

1.5. Recent Developments in Immediate ReleaseTablets

1.5.1. Miniaturized Approach for Excipient Selection

An excipient is a substance other than an API that is used in a drug delivery system to help process, protect, support, improve stability, patient compliance and bioavailability, or assist in product identification and safety and effectiveness during storage or use. Excipients are chosen for their functioning, material consistency, regulatory approval, cost, availability, and sources.

1.5.2. Meticulous Research Experiments on Super-disintegrants

It took 15 minutes for croscar-mellose sodium superdisintegrants to release 100% of the norfloxacin medication at a 6% concentration in a study employing fast dissolving norfloxacin tablets. Croscarmellose's fibrous character is more apparent at lower concentrations, although it gradually smooths out over time. Wicking and swelling occur simultaneously at high concentrations, resulting in a reduction in disintegration time due to a reduction in pore size. Tablets containing crospovidone, croscarmellose, and sodium starch glycolate show complete drug release within 20 minutes and quick dissolving when compared to other formulations.(Neeraj B et.al.).

CONCLUSION

As a result, many patients are unable to adhere to standard pharmacological therapy, which has a negative impact on treatment outcomes. Instant-release tablets are designed to deliver the medication at a quicker rate. Improving manufacturing procedures for immediate-release pharmaceutical forms that are mechanically strong, allowing for ease of handling and packing, and at a cost comparable to regular tablets is an unmet requirement in the existing technologies. Additional market exclusivity, which can be offered by an immediate release dosage form, leads to increased earnings and the treatment of underserved populations. Immediate-release pharmacological forms have been developed that combine the comfort of dosing with ease of dosing in a current dose structure. These pills are designed to release more potent medicines from the dosage form, making them more effective. Formulators have spent a lot of time and effort inventing a new type of tablet dosage form that dissolves and dissolves quickly with increased dissolving in order to meet these medical needs.

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DEVELOPMENT AND EVALUATION OF OSMOTIC PUMP TABLETS OF ACECLOFENAC

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ABSTRACT

The aim of the work is to develop & evaluate bilayer-core osmotic pump tablet by wet granulation method, using Aceclofenac as model drug. The prepared bilayer- core osmotic pump tablet will be evaluated for influence of sodium chloride, PEO (WSR Coagulant) and PEG level on drug release profile, etc. The granules of drug layer and push layer were prepared separately by wet granulation method using isopropyl alcohol. The prepared osmotic tablet of Aceclofenac was coated using ethyl cellulose as semi permeable membrane and PEG 400 as pore forming agent, the prepared tablets were evaluated for bulk density, tapped density, compressibility index, angle of repose, weight variation test, hardness, friability, content uniformity and In vitro drug release studied using USP XXIX Paddle method; formulated tablets were also evaluated for effect of pH, effect of agitation, FTIR, the results of IR study showed that there is no interaction between osmo agent, and pure drug.

Results showed that as the concentration of the sodium chloride and PEO (WSR Coagulant) increases it affects the in vitro drug release. Formulation F6 prepared with sodium chloride 65mg, PEO (WSR Coagulant) 37.5mg which exhibited excellent micro meritic properties, percentage yield, and percentage drug release 84.089 % for a period of 12 hrs. Osmotic tablets of Aceclofenac may be an effective alternative to conventional dosage form, which can be effectively used in the treatment of Rheumatoid arthritis.

Keywords: Osmogent, Osmotic pump tablets, Aceclofenac, disintegration time.

1. INTRODUCTION

Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner.

Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi-permeable membrane coat.

Osmotically Controlled Drug Delivery System

Osmosis[1,2]

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device.

Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogent. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic dispensing devices is dependent on the solubility and molecular weight and activity coefficient of the solute (osmogent).

Basic Components of Osmotic Systems[1,2]

1. Drug:

Which have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems. Various drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide, etc are formulated as osmotic delivery.

2. Osmotic Agent:

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Different magnesium chloride or sulfate; lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate; water-soluble salts of organic acids like sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate; Carbohydrates like mannose, sucrose, etc.

3. Semi Permeable Membrane:

An important part of the osmotic drug delivery system is the SPM housing. Therefore, the polymeric membrane selection is key to osmotic delivery formulation. The membrane must possess certain performance criteria such as:

- Sufficient wet strength and water permeability
- Should be biocompatible
- Rigid and non-swelling
- Should be sufficient thick to withstand the pressure within the device.

Example: Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits.

4. Plasticizers:[2]

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Example: Polyethylene glycols, castor oil.

Objectives

Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systemic effect. Such as patient acceptance, convenience in administration and cost effective manufacturing process. Thus wide variety of approaches of drug delivery system have been investigated for oral application.[3] Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken or applied to reduced inflammation and as an analgesic reducing pain in certain conditions.[4] Osmotic pump tablet systems offer potential clinical benefits. Such as being potentially able to mitigate the food effect increase patient compliance and treatment tolerance. Specially designed to deliver the poorly soluble drugs.[5] Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drugs.[6] Osmotic pump tablets reduce risk of adverse reactions, improving compliance of Patients. Its release rate will much more closer to zero - order.[7]

The aim of the work is to develop and evaluate bilayer-core osmotic pump tablet by wet granulation method, using Aceclofenac as model drug. The prepared bilayer-core osmotic pump table will be evaluated for influence of sodium chloride, PEO (WSR Coagulant) and PEO (N80) on drug release profile, influence of PEG 400 level on drug release profile, etc.

Plan of Work

1. Formulation of the osmotic pump tablets of Aceclofenac using different concentration of sodium chloride and polyethylene oxide (WSR coagulant).
2. Coating of the osmotic pump tablets using ethyl cellulose as semi permeable membrane and PEG 400 as pore forming agent in different concentration.
3. *In vitro* dissolution studies.
4. Effect of pH on drug release.
5. Effect of agitational intensity.
6. Stability studies.

Materials and Methods: Aceclofenac was bought from Hetro Laboratories Hyderabad, ethyl cellulose, sodium choride, Polyethylene oxide, poly vinyl pyrolidne, Sodium choride, isopropyl alcohol, lactose, magnesium stearate, was procured from S.D. Fine Chem. Pvt. Ltd in Mumbai.

EVALUATION OF ACECLOFENAC[8]

Standard calibration curve for Aceclofenac in pH 7.4 phosphate buffer:

Stock Solution:

Accurately weighed quantity of 100 mg Aceclofenac was dissolved in few ml of ethanol in 100 ml volumetric flask and volume was made up to 100 ml with phosphate buffer pH 7.4 to produce 1 mg/ml of solution.

Sub-Stock Solution:

From the above stock solution a series of dilution viz., 2, 4, 6, 8,10,12,14 µg/ml were prepared respectively. The absorbance was measured at 276 nm using PG instrument T_{80} model UV/VIS spectrophotometer against reagent blank and graph was plotted as shown in table-3.

FORMULATION OF ACECLOFENAC OSMOTIC PUMP TABLETS[9]

Core tablets of Aceclofenac were prepared by wet granulation method. The composition of the core tablets are given in Table-4,5. Aceclofenac was mixed with Nacl, lactose, PEO (N80) and passed through 30 mesh screen. The blend was mixed for 10 mins and the mixture was granulated with PVP k-30 in isopropyl alcohol. The resulting wet mass passed through 18# sieve. The granules were dried at 50oC in hot air oven for 30 mins after which they were passed through 22# sieve. These sized granules were then blended with magnesium stearate.

Push Layer: The push layer comprise of PEO (WSR Cogulant), NaCl, Lactose and Magnesium stearate. All the ingredients were weighed accurately and blend mixed for 10 mins, the mixture was granulated with PVP k-30 in isopropyl alcohol. The resulting wet mass was passed through 18 # sieve. The granules were dried at 50oC in hot air oven for 30 mins after which they were passed through 22 # sieve. These sized granules were then blended with magnesium stearate.

Finally osmotic tablet was compressed using 9mm concave punch (Karnavati press) firstly the push layer were laid into the die cavity and pre-compressed then the drug layer granules were loaded on it and the tablet was compressed.

An indentation at diameter and depth of 1.0 mm was produced at the center of drug layer surface using mechanical drill.

TABLE-1

Formulation table of Aceclofenac Osmotic tablets F1 to F3

FORMULATION CODE	**F-1**	**F-2**	**F-3**
DRUG LAYER			
ACECLOFENAC (mg)	100	100	100
PEO(WSR N80) (mg)	15	15	15
SODIUM CHLORIDE (mg)	-	-	-
PVP K30 (mg)	4.5	4.5	4.5
LACTOSE (mg)	29	29	29
MAGNESIUM STEARATE (mg)	1.5	1.5	1.5
PUSH LAYER			
PEO (WSR COAGULANT) (mg)	22.5	30	37.5
SODIUM CHLORIDE (mg)	15	30	45
PVP K30 (mg)	4.5	4.5	4.5
LACTOSE (mg)	106.5	84	61.5
MAGNESIUM STEARATE (mg)	1.5	1.5	1.5
TOTAL WEIGHT(mg)	**300**	**300**	**300**
COATING			
ETHYL CELLULOSE (%W/V)	2	2	2
PEG 400 (%W/V)	20	25	30

TABLE-2

Formulation table of Aceclofenac osmotic tablets F4 to F 12

FORMULATION CODE	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**	**F-10**	**F-11**	**F-12**
DRUG LAYER									
ACECLOFENAC (mg)	100	100	100	100	100	100	100	100	100
PEO(WSR N80) (mg)	15	15	15	15	15	15	15	15	15
SODIUM CHLORIDE (mg)	15	15	15	15	15	15	15	15	15
PVP K30 (mg)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
LACTOSE (mg)	14	14	14	14	14	14	14	14	14
MAGNESIUM STEARATE (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PUSH LAYER									
PEO (WSR COAGULANT) (mg)	22.5	30	37.5	22.5	30	37.5	22.5	30	37.5
SODIUM CHLORIDE (mg)	15	30	45	15	30	45	15	30	45
PVP K30 (mg)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
LACTOSE (mg)	106.5	84	61.5	106.5	84	61.5	106.5	84	61.5
MAGNESIUM STEARATE (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
TOTAL WEIGHT(mg)	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
COATING									
ETHYL CELLULOSE (%W/V)	2	2	2	2	2	2	2	2	2
PEG 400 (%W/V)	20	25	30	25	30	20	30	20	25

Coating of the osmotic pump tablets[10]

The core tablets of Aceclofenac were coated with ethyl cellulose in an coating pan (Swastic, Hyderabad, India). The compositions of the coating solution used for coating tablets are given in Table-1,2. The rotating speed of the pan was kept 20 rev/min. The coating was performed using sprayer and the spray rate of 3-5 ml/ min. Coating was continued until desired weight gain (10%) was obtained on the active tablets. In all the cases, active tablets were dried at 50°C for 10 h before further evaluation.

EVALUATION FOR PRE-COMPRESSIVE PARAMETER

Micromeritic Properties[11,12]

Prior to the compression, the Aceclofenac powder blends were evaluated for micromeritic properties such as bulk density, tapped density, compressibility index, Hausners ratio and angle of repose.

Bulk Density

Loose bulk Density: An accurately weighed (2.5G) quantity of powder was transferred to a 10ml measuring cylinder and the volume occupied by the powder in terms of ml was recorded.

$$\text{Loose bulk Density (L.B.D)} = \frac{\text{Weight of powder in gm.}}{\text{Volume of packing in ml}}$$

Tapped bulk Density: The loosely packed powder in the measuring cylinder was to tapping 100 times on a plane hard wooden surface and volume occupied in ml was noted.

$$\text{Tapped bulk Density (T.B.D)} = \frac{\text{Weight of powder in gm}}{\text{Tapped volume in ml}}$$

% Compressibility index

Compressibility index was determined by using the following formula:

$$\text{Compressibility index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's factor:

Hausner found that the ratio D F / D O was related to interparticle friction and, as such, could be used to predict powder flow properties.

$$\text{Hausner's factor} = \frac{\text{Tapped bulk density}}{\text{Poured bulk density}}$$

Carr's Compressibility Index:

$$\text{Percent Carr's Index} = \frac{\text{TBD - LBD}}{\text{TBD}} \times 100$$

Angle of repose

Angle of repose (θ) of the powder blend, which measures the resistance to particle flow, was determined by a fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed powder blend were allowed to pass through the funnel freely on to the surface.

The height and radius of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} h / r$$

Where,

θ - Angle of repose
h - Height of granules above the flat surface
r - Radius of the circle formed by the granule heap.

EVALUATION FOR POST COMPRESSIVE PARAMETERS[13,14,15]

Uniformity of thickness

Thickness and diameter of both core tablets and coated tablets were measured using a Vernier calliper. Three tablets of each formulation were picked randomly and dimensions is determined. It is expressed in mm and standard deviation was also calculated.

Weight variation test

The average weight of core tablets and coated tablets were determined using a digital weighing balance. Ten tablets were selected randomly from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this, percentage weight difference was calculated and then checked for USP specifications.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of both core and coated tablets were determined using a Monsanto hardness tester. It is expressed in kg/cm^2. Ten tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated.

Friability test

The friability of core tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty core tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again (W_{final}). The % friability was then calculated.

Content uniformity test

The Aceclofenac core tablets were tested for their drug content. Five tablets were finely powdered; quantities of the powder equivalent to 100 mg of Aceclofenac

were accurately weighed and transferred to a 100-ml of volumetric flask containing 20ml of ethanol, the solution was made up to volume using phosphate buffer pH 7.4 and filtered The solutions was filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbance of solutions were determined at 276 nm by UV spectrophotometer.

IN-VITRO DISSOLUTION STUDY:[16]

In vitro dissolution of Aceclofenac osmotic tablets was determined in a USP dissolution apparatus by using paddle method, under stirring at 100 rpm. The dissolution media consisted of 900 ml of phosphate buffer (pH 7.4) at 37±0.5 °C. Dissolution study was carried out for 12 hrs. Samples were withdrawn every 1 hrs and analyzed at 276 nm for Aceclofenac by using a PG instrument T-80 UV-spectrophotometer. An equivalent volume of phosphate buffer was replaced with fresh buffer into the dissolution bath following the removal of each sample.

Dissolution test were performed in triplicate.

Kinetic values obtained from Aceclofenac from in vitro release profile 1. Zero order, 2. First order and 3. Higuchi model

EFFECT OF CONCENTRATION OF PORE FORMER ON DRUG RELEASE[17]

In order to assess the effect of concentration of pore former on In Vitro drug release, formulations were coated with a ethyl cellulose as semi permeable membrane with varying amount of poreformer (PEG 400) i.e. 20%, 25% and 30% as per the procedure described earlier. The effect of increasing concentration of pore former on in vitro drug release was studied.

EFFECT OF PH ON DRUG RELEASE[17]

To study the effect of pH on In Vitro drug release and to assure a reliable performance of the developed formulations independent of pH release studies of the optimized formulations were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) phosphate buffer pH 4.5 acetate buffer and pH 7.4 phosphate buffer. The samples were withdrawn at predetermined intervals and analyzed spectrophotometrically.

EFFECT OF AGITATIONAL INTENSITY[17]

In order to study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution was carried at 50, 75 and 100 rpm in 900 ml of phosphate buffer pH 7.4 maintained at 37 ± 0.5 °C in the dissolution medium.

STABILITY STUDIES[18]

The optimized formulation of Aceclofenac osmotic tablets (F6) was packed in strips of thick aluminum foil and these packed formulations were used to carry out

stability studies as per ICH guidelines using certified stability chambers (Thermal instrument and equipment, Hyderabad) at room temp 20°C and 40°C and 60% and 75% RH for 3 months The samples were withdrawn periodically and evaluated for their hardness, content uniformity and for in vitro drug release.

FOURIER-TRANSFORMER INFRARED (FTIR) SPECTROSCOPY

Infrared spectra of pure drug and excipient are carried out by using KBR pellet technique and were recorded on a Shimadzu FTIR spectrophotometer.

Results:

TABLE-3

Standard Calibration Data of Aceclofenac phosphate buffer pH 7.4 (λmax=276nm)

S.No.	Concentration	Absorbance
1.	0	0
2.	2	0.121
3.	4	0.224
4.	6	0.292
5.	8	0.378
6.	10	0.447
7.	12	0.596
8.	14	0.712

Figure-1

Standard Calibration Curve of Aceclofenac in phosphate buffer pH7.4 (λmax=276nm)

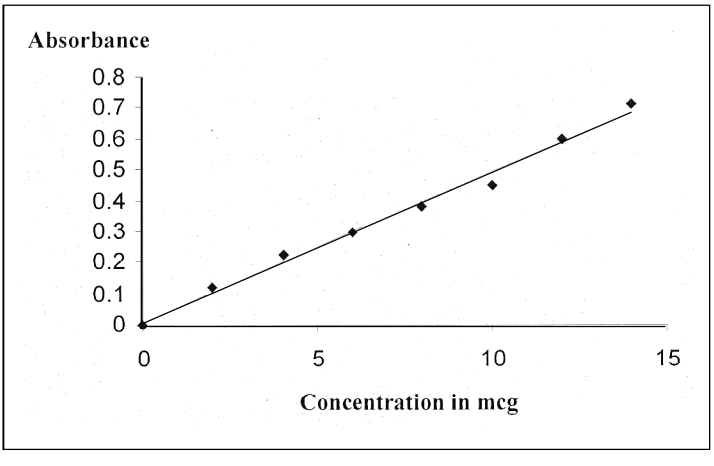

TABLE-4

Micromeritic properties of Aceclofenac osmotic tablets

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausners Ratio	Carr's Index	Angle of Repose
F 1	0.704±0.04	0.770±0.02	1.10±0.07	12.17±1.3	17.18±1.13
F 2	0.714±0.02	0.782±0.03	1.13±0.09	13.33±1.4	23.14±2.42
F 3	0.704±0.04	0.801±0.02	1.15±0.07	13.99±2.2	22.53±1.95
F 4	0.766±0.05	0.822±0.04	1.14±0.02	15.11±09	16.88±1.57
F 5	0.755±0.03	0.811±0.02	1.17±0.09	11.58±1.2	19.24±2.32
F 6	0.741±0.06	0.789±0.08	1.15±0.05	14.11±1.4	21.35±1.49
F 7	0.801±0.03	0.867±0.03	1.17±0.04	14.78±2.2	19.35±2.42
F 8	0.804±0.02	0.871±0.02	1.19±0.08	16.14±1.5	20.38±1.85
F 9	0.815±0.03	0.881±0.03	1.14±0.06	15.77±1.2	18.28±2.4
F 10	0.799±0.03	0.848±0.02	1.17±0.03	16.45±1.9	16.96±1.48
F 11	0.784±0.04	0.851±0.03	1.16±0.06	14.24±1.8	15.1.2±1.56
F 12	0.802±0.02	0.874±0.04	1.13±0.09	13.33±1.7	17.44±1.87

All values are represented as mean ± standard deviation (n=3)

TABLE-5

Evaluation of thickness, weight, hardness, friability and contain uniformity of Aceclofenac osmotic tablets

Formulation Code	Thickness Nm (N=3)		Average Weight Mg (N=10)		Hardness (N=10)		Friability (N=10)	Content Uniformity (N=10)
	Before Coating	After Coating	Before Coating	After Coating	Before Coating	After Coating		
F 1	4.13	4.48	302.2	342.2	6.6	8	0.052	102
F 2	4.16	4.43	303.3	344.6	6.4	7.7	0.056	103
F 3	4.12	4.45	301.3	339.3	6.8	7.8	0.065	101
F 4	4.09	4.39	300.2	335.2	6.4	7.6	0.067	102
F 5	4.13	4.48	298.9	339.8	6.7	8	0.054	99
F 6	4.16	4.51	300.4	339.9	6.9	8.4	0.059	101
F 7	4.11	4.42	303.3	339.4	6.6	8	0.059	98
F 8	4.12	4.43	297.9	336.9	6.5	8.2	0.065	103
F 9	4.15	4.44	298.8	340.9	6.8	8.4	0.062	101
F 10	4.13	4.45	301.2	342.3	6.4	7.5	0.059	98
F 11	4.14	4.47	299.5	345.6	6.6	8.3	0.066	97
F 12	4.10	4.46	304.2	345.3	6.3	7.9	0.064	101

TABLE-6

***In-vitro* Drug Release from formulation F 1 to F 6**

Time (hr)	F 1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	4.00 ± 0.12	4.00 ± 0.21	4.14 ± 0.36	4.07±0.33	4.07±0.41	4.38 ± 0.30
2	7.60 ± 0.32	7.79 ± 0.33	8.07 ± 0.41	8.17±0.42	7.67±0.55	8.38 ± 0.56
3	14.30 ± 0.36	15.08 ± 0.39	15.41 ± 0.45	14.78±0.51	13.40±0.69	15.65 ± 0.41
4	20.65 ± 0.56	21.10 ± 0.41	21.29 ± 0.66	21.03±0.66	20.77±0.91	23.54 ± 0.66
5	27.47 ± 0.91	27.07 ± 0.42	29.36 ± 0.61	28.65±0.91	27.94±0.93	33.39 ± 0.75
6	35.76 ± 0.84	36.47 ± 0.45	36.07 ± 0.81	38.13±1.02	35.76±1.32	39.07 ± 0.65
7	39.78 ± 1.04	41.44 ± 0.49	43.57 ± 0.89	45.47±0.88	41.02±1.01	50.68 ± 0.81
8	47.60 ± 1.64	52.10 ± 0.53	49.97 ± 0.91	54.23±0.67	50.92±1.41	58.02 ± 0.91
9	56.84 ± 1.66	58.97 ± 0.75	57.78 ± 0.97	60.68±0.84	65.52±0.87	64.89 ± 0.67
10	58.05 ± 1.84	62.07 ± 0.86	60.84 ± 1.10	67.60±0.81	69.81±0.99	72.23 ± 0.99
11	60.05 ± 1.91	64.76 ± 0.91	64.42 ± 1.31	69.76±0.99	70.73±1.32	77.68 ± 1.23
12	62.00 ± 1.97	67.02 ± 1.23	65.81 ± 1.56	71.68±1.36	72.78±1.33	84.78 ± 1.41

TABLE-7

***In-vitro* Drug Release from formulation F 7 to F 12**

Time (hr)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	4.19 ± 0.41	4.90 ± 0.64	4.31 ± 0.55	4.35 ± 0.32	4.239 ± 0.66	4.42 ± 0.32
2	8.14 ± 0.44	9.09 ± 0.66	8.00 ± 0.31	9.09 ± 0.91	8.052 ± 0.81	8.17 ± 0.51
3	15.25 ± 0.35	16.00 ± 0.84	15.51 ± 0.81	16.29 ± 0.82	15.51 ± 0.89	15.72 ± 0.66
4	21.48 ± 0.86	23.30 ± 0.89	21.57 ± 1.21	23.06 ± 0.77	21.45 ± 0.99	23.23 ± 0.81
5	28.65 ± 0.91	32.68 ± 0.91	28.65 ± 0.94	31.73 ± 1.31	29.84 ± 1.61	31.00 ± 0.92
6	37.42 ± 1.32	40.26 ± 0.99	35.76 ± 0.81	39.78 ± 1.10	38.84 ± 1.66	40.00 ± 1.32
7	45.94 ± 1.52	48.55 ± 1.21	44.52 ± 1.33	46.18 ± 1.35	44.28 ± 1.87	47.13 ± 1.36
8	54.23 ± 1.21	56.84 ± 1.32	52.34 ± 1.46	51.63 ± 0.81	52.34 ± 0.94	55.42 ± 1.21
9	61.34 ± 1.38	62.28 ± 1.41	61.81 ± 1.81	60.86 ± 0.66	59.92 ± 1.65	63.07 ± 1.66
10	67.26 ± 1.67	69.39 ± 1.63	69.15 ± 1.66	67.97 ± 0.91	68.02 ± 1.22	68.92 ± 1.87
11	72.23 ± 1.95	75.03 ± 1.21	78.15 ± 1.98	75.78 ± 1.32	73.65 ± 1.34	77.68 ± 1.99
12	76.73 ± 1.61	80.28 ± 1.44	82.02 ± 1.06	82.55 ± 1.84	79.10 ± 1.71	83.36 ± 1.32

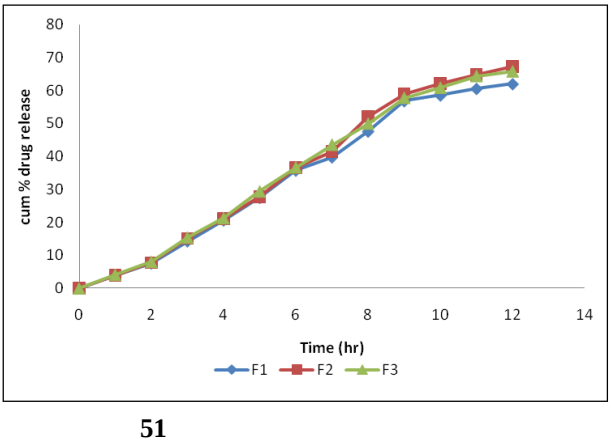

Figure-2
Cumulative percentage drug release of Aceclofenac from formulation F1 to F3

Figure-3

First order plots of Aceclofenac formulation F 1 to F 3

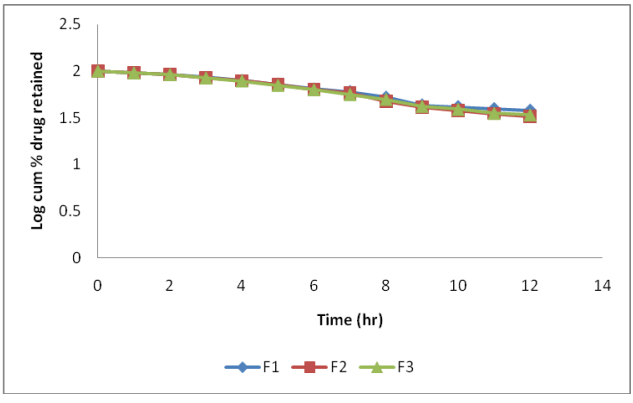

Figure-4

Higuchi order plots of Aceclofenac formulation F 1 to F 3

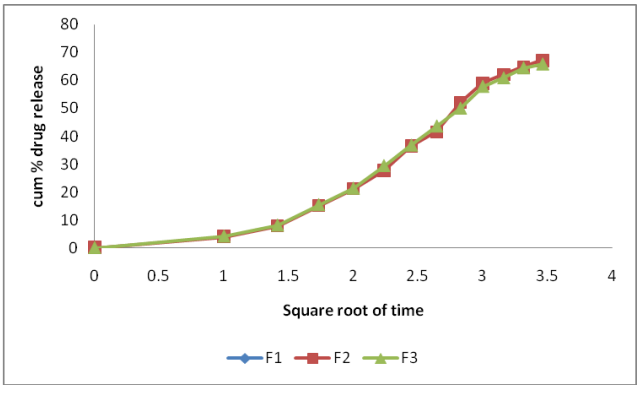

Figure-5

Cumulative percentage drug release of Aceclofenac from formulation F4 to F 6

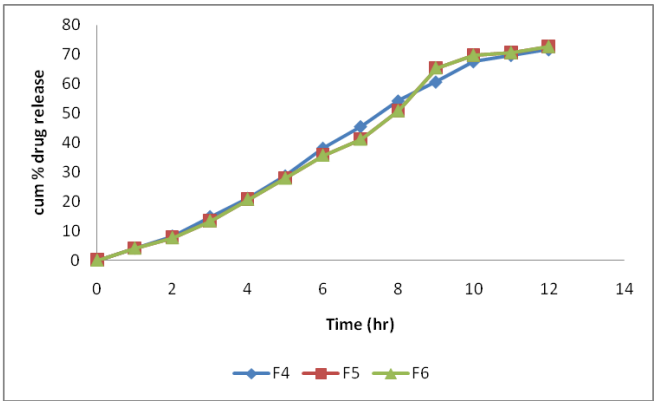

Figure-6

First order plots of Aceclofenac formulation F 4 to F 6

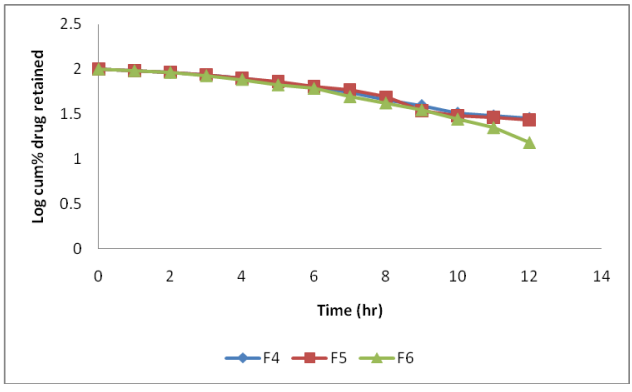

Figure-7

Higuchi order plots of Aceclofenac formulation F 4 to F 6

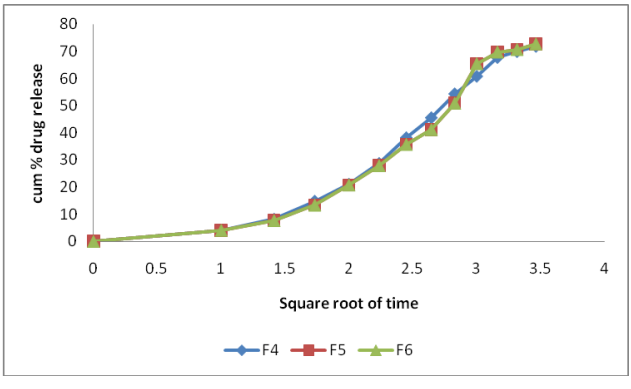

Figure-8

Cumulative percentage drug release of Aceclofenac from Formulation F 7 to F 9

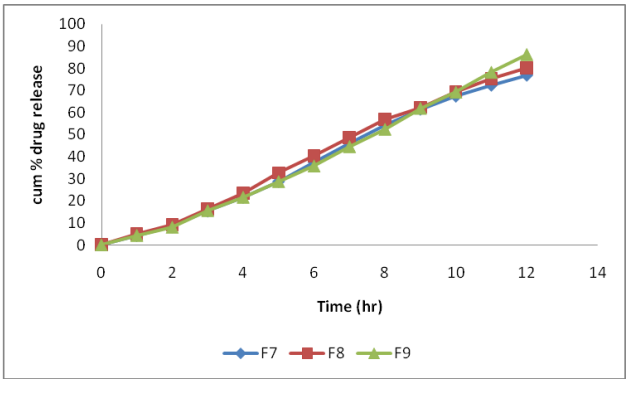

Figure-9

First order plots of Aceclofenac formulation F 7 to F 9

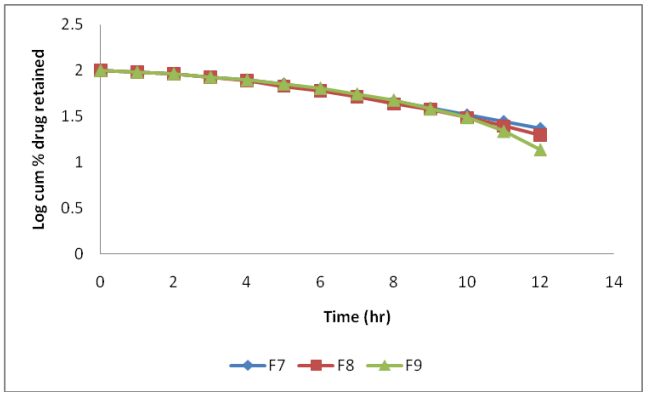

Figure-10

Higuchi order plots of Aceclofenac formulation F 7 to F 9

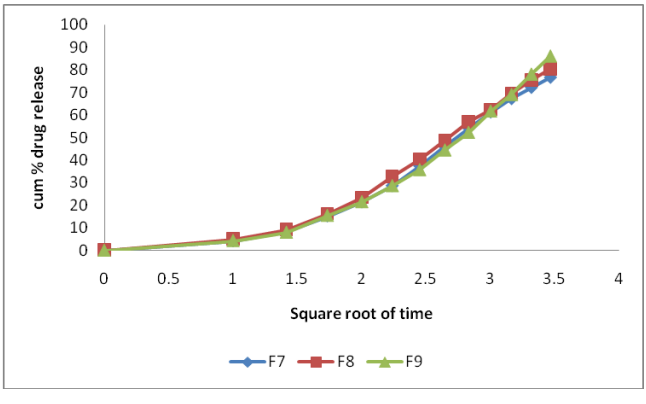

Figure-11

Cumulative percentage drug release of Aceclofenac From Formulation F 10 to F 12

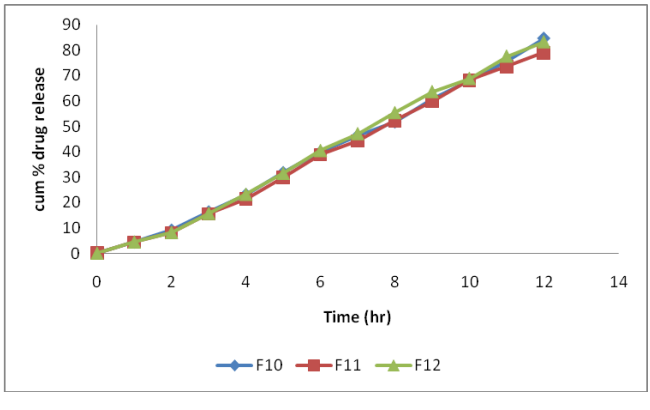

Figure-12

First order plots of Aceclofenac formulation F 10 to F 12

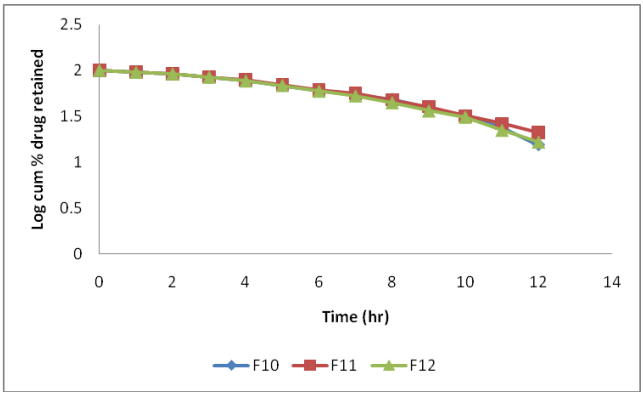

Figure-13

Higuchi order plots of Aceclofenac formulation F 10 to F 12

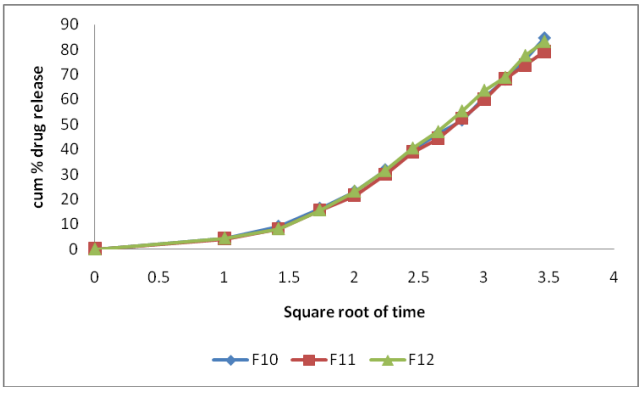

TABLE-8

Kinetic values obtained from in-vitro release profile of osmotic tablets of Aceclofenac

Formulation Code	Zero order kinetic data	First order kinetic data	Higuchi Matrix kinetic data
	Regression coefficient (r)	Regression coefficient (r)	Regression coefficient (r)
F 1	0.9994	-0.1922	0.9672
F 2	0.9989	-0.1133	0.9729
F 3	0.9984	-0.1526	0.9591
F 4	0.9965	-0.1144	0.9749
F 5	0.9975	-0.1658	0.9781
F 6	0.9985	-0.2462	0.9274
F 7	0.9993	-0.1196	0.9693
F 8	0.9976	-0.1588	0.9719
F 9	0.9994	-0.2163	0.9731
F 10	0.9999	-0.1571	0.9685
F 11	0.9993	-0.2624	0.9615
F 12	0.9997	-0.2184	0.9704

TABLE-9

Effect of pore former on *In Vitro* drug release study

Formulation	PEG 400% wt/ v		
	20%	**25%**	**30%**
1.	4.073	4.073	4.381
2.	8.171	7.673	8.384
3.	15.788	14.405	16.655
4.	22.031	21.771	24.542
5.	28.657	27.763	33.394
6.	38.131	41.021	39.078
7.	46.473	51.921	52.684
8.	54.236	65.526	58.026
9.	60.688	69.815	64.894
10.	67.605	70.736	72.236
11.	69.765	76.621	77.604
12.	75.684	81.709	86.589

Figure-14
Effect of pore former on in vitro drug release study

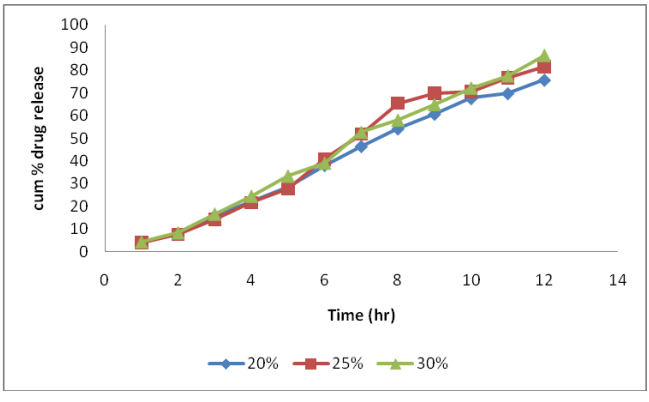

TABLE-10

Effect of pH on In vitro drug release from optimized formulation F6

Time (hrs)	Cumulative % drug released		
	pH 1.2	**pH 4.5**	**pH 7.4**
1.	1.99±0.38	2.01 1.32	2.14±1.23
2.	4.23±2.13	2.45 0.84	3.8±3.08
3.	9.28±3.10	6.74 2.02	8.89±2.33
4.	18.13±3.59	17.92 1.48	20.64±2.63
5.	25.22±2.46	26.44 2.50	27.29±2.79
6.	38.5±4.05	40.16 2.30	42.24±4.23
7.	50.78±1.53	51.76 1.22	53.52±5.62
8.	65.5±1.89	63.52 2.19	62.72±2.48
9.	72.16±2.04	71.60 3.05	70.06±1.74
10.	79.18±2.46	80.20 2.17	81.29±1.04
11.	80.28±3.02	81.47 1.89	82.94±3.18
12.	81.27±2.6	82.03 2.90	83.5±2.46

Figure-15

Effect of pH on in vitro drug release from optimized formulation F6

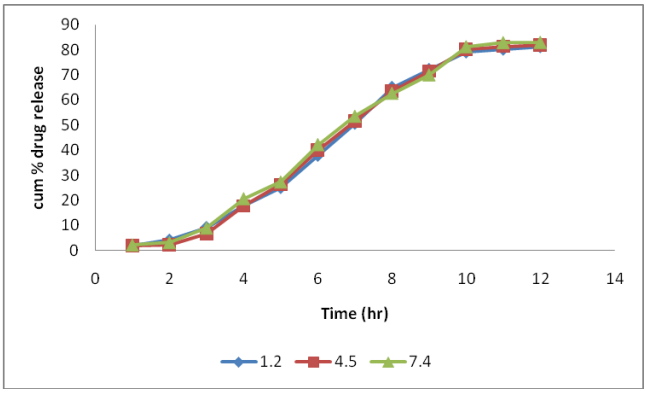

TABLE-11

Effect of Agitational on In vitro drug release from optimized formulation F6

Time (hrs)	Cumulative % drug released		
	50 rmp	75 rmp	100 rpm
1	1.85 ±5.25	2.14±1.28	2.93±0.29
2	6.05 ±1.55	8.64±2.07	10.4±1.25
3	14.34±3.88	24.29±3.28	26.37±2.59
4	33.15±2.85	35.16±3.46	39.85±2.29
5	42.27±4.36	44.06±4.25	53.43±2.36
6	54.23±3.59	56.24±1.48	66.77±4.59
7	66.22±3.48	67.52±2.78	70.43±2.48
8	73.95±1.38	72.72±4.49	75.74±1.27
9	76.29±3.19	73.06±2.68	76.87±3.46
10	77.8±2.08	77.29±3.63	79.64±1.34
11	82.73±3.68	80.94±3.44	82.48±2.94
12	83.39±2.55	84.50±1.39	86.23±1.2

Figure-16

Effect of agitational on in vitro drug release from optimized formulation F 6

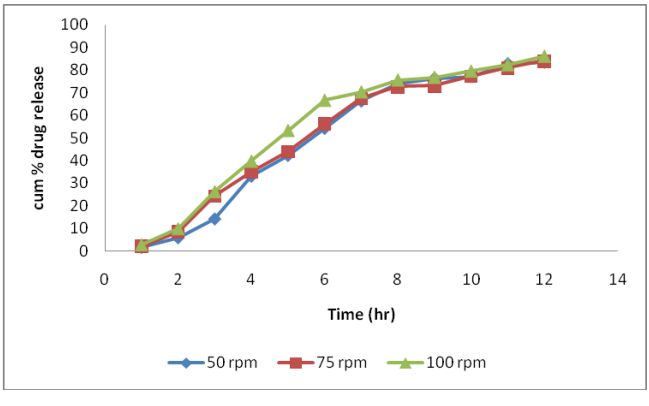

TABLE-12

Stability studies of formulation F6 at temp. 25°C, RH 60 %, & 40°C, RH 75 %

Formulation F 6	% Drug content At room temp. 25° C & Relative humidity 60 %				% Drug content At temp. 40° C & Relative humidity 75 %		
	1 st day	After 30 Days	After 60 Days	After 90 Days	After 30 Days	After 60 Days	After 90 Days
	92.46	92.46	92.4	92.31	92.43	92.4	92.3

In Vitro Release Profile of Best Formulation F 6								
Formulation F 6	Time (hr)	% Drug release				% Drug release		
	1	3.772	3.772	3.767	3.765	3.771	3.761	3.759
	12	94.079	94.079	94.076	94.069	94.076	94.069	94.056

DISCUSSION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systemic effect. Such as patient acceptance, convenience in administration and cost effective manufacturing process. Thus wide variety of approaches of drug delivery system have been investigated for oral application.

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken or applied to reduced inflammation and as an analgesic reducing pain in certain conditions.

Osmotic pump tablet systems offer potential clinical benefits. Such as being potentially able to mitigate the food effect increase patient compliance and treatment tolerance. Specially designed to deliver the poorly soluble drugs.

Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drugs. Osmotic pump tablets reduce risk of adverse reactions, improving compliance of Patients. It's release rate will much more closer to zero - order.

The aim of the work is to develop and evaluate bilayer-core osmotic pump tablet by wet granulation method, using Aceclofenac as model drug, sodium chloride, PEO (WSR Coagulant) & (N80), the prepared tablets will be coated with ethyle cellulose using PEG 400 as pore former agent.

PREFORMULATION METHOD

Calibration curve

In pre formulation studies it was found that, the estimation of Aceclofenac by spectrophotometric method at 276 nm had good reproducibility (as shown in Figure-1).

Micromeritic Properties

Bulk Density

The bulk density of the Formulation F 1 to F 3 ranges from 0.704±0.04gm/cm^3 to 0.714±0.02gm/cm^3, formulation F 4 to F 6 ranges from 0.741±0.06 gm/cm^3 to 0.766±0.05 gm/cm^3, formulation F 7 to F 9 ranges from 0.801±0.03 gm/cm^3 to 0.815±0.03 gm/cm^3, formulation F 10 To F 12 ranges from 0.799±0.03 gm/cm^3 to 0.802±0.02 gm/cm^3 respectively (as shown inTable-4).

Tapped Density

The tapped density of the formulation F 1 to F 3 varied from 0.770±0.02 to 0.801±0.02, formulation F 4 to F 6 varied from 0.789±0.08 to 0.822±0.04, formulation F 7 to F 9 varied from 0.867±0.3 to 0.881±0.03, formulation F 10 to F 12 varied from 0.848±0.02 to 0.874±0.04 respectively (as shown in Table-4).

Hausners Ratio

The hausners ratio of the entire formulation F 1 to F-12 were in the range of 1.10±0.07 to 1.19±0.08 (as shown in Table-4)

Carr's Index

The carr's index of entire formulation F 1 to F 12 were in range of 11.58±1.2 to 16.45±1.9 (as shown in Table-7) The Carr's compressibility index values showed up to 15% result in good to excellent flow properties.

Angle of Repose (θ)

The data obtained from angle of repose for formulations F 1 to F 3were found to be in the range of 17.18 1.13° θ to 23.14 2.42 ° θ. The angle of repose less than 30°, which reveals good flow property (as shown in Table-4).

POST FORMULATION METHOD

Thickness: The thickness of entire formulation F_1 to F_{12} were in range of before coating 4.09 to 4.16 and after coating 4.39 to 4.51 (as shown in Table-5).

Average Weight: The average weight of entire formulation F_1 to F_{12} were in range of before coating 297.9 to 304.2 after coating 335.2 to 345.6 (as shown in Table-5).

Hardness: The hardness of entire formulation F_1 to F_{12} were in range of before coating 6.3 to 6.9 and after coating 7.5 to 8.4 (as shown in Table-5).

Friability: The friability of entire formulation F_1 to F_{12} were in range of 0.052 to 0.067 (as shown in Table-5).

Content Uniformity: The content uniformity of entire formulation F_1 to F_{12} were in range of 97 to 103 (as shown in Table-5).

***IN VITRO* DRUG RELEASE**

In vitro drug release studies of Aceclofenac from osmotic tablets were performed in pH 7.4 for 12hrs. Using USP Type I dissolution test apparatus. It was found that in vitro drug release of formulation F1 to F 3 were in the range of 62.002±1.97 to 67.021±1.23.

Formulation F 4 to F 6 were in the range of 71.684±1.36 to 84.789±1.41. Formulation F 7 to F 9 were in the range of 76.736±1.61 to 82.021±1.06 and formulation F 10 to F 12 were in the range of 82.552±1.84 to 83.368±1.32. Among all formulations F6 was found to be the best formulation as it release Aceclofenac 84.789±1.41 % in a sustained manner with constant fashion over extended period of time (for 12 hr).

It was observed that the concentration of sodium chloride and PEO (WSR Cogulant) increased, percent of drug release of Aceclofenac increases. Higher the concentration of sodium chloride and PEO (WSR Coagulant) drug release was in a sustain manner.

The release rates obtained were subjected for Kinetic treatment to know the order of release. The 'r' values for zero order kinetics of formulation F 1 to F 12 are

0.9994, 0.9989, 0.9984, 0.9965, 0.9975, 0.9985, 0.9993, 0.9976, 0.9994, 0.9999, 0.9993 and 0.9997 respectively (as shown in Table-8). The 'r' values indicates that drug release of all formulation F 1 to F 12 follows zero order kinetics.

To ascertain the drug release mechanism, the in-vitro data were also subjected to Higuchi diffusion. The 'r' values of Higuchi diffusion was in the range of 0.9274 to 0.9781 of all formulation F 1 to F 12. It suggests that the Higuchi diffusion plots of all the formulations were fairly linear because 'r' values near about 1 in all the cases. So it confirms the drug release by Higuchi diffusion mechanism (as shown in Table-8).

Effect of poreformer on *In Vitro* drug release study:

The amount of PEG 400 (pore former) in the coating was verified and its effect on the drug release on formulations was evaluated. PEG 400 was used in three different concentrations 20, 25, and 30% w/w and ethyl cellulose 2% as semi permeable membrane. The in vitro release profile containing varying amount of PEG 400 in the coating are shown as in Table No.9 and in fig no. 14. Coating solution containing 20, 25 & 30% PEG 400 released 75.684, 81.709, 86.589% of drug after 12hrs. While highest release was obtained with 30%w/w of PEG 400 in the coating membrane with a cumulative release of 86.589% after 12hrs.

Increase of PEG 400 level led to an increase of drug release rate. As PEG is a pore forming agent, it could be leached easily and left behind porous structure, which enhanced the membrane permeability and drug release rate.

Effect of pH on *In Vitro* drug release:

In general, drug release from osmotic pumps, is pH independent. The effect of pH of dissolution media on drug release was evaluated by pH change method. Release studies of formulation F6 were conducted in phosphate buffer solution pH 1.2 and pH 4.5 acetate buffer and pH 7.4, drug release data of optimized formulation F6 are given as in table no.10 and Figure-15 there is no significant change in release.

Therefore, it was evident that pH of the dissolution media has no significant effect on the release of drug. So it can be expected that variations in pH of gastrointestinal tract may not affect the drug release from the core formulation.

Effect of agitational intensity on *In Vitro* drug release:

Drug release test under different agitation rates were also conducted at three different rpm (50, 75, and 100) in order to investigate the influence of agitation rate on drug release profiles. Formulation F6 was considered for this study. Dissolution studies were carried out using USP- Type I dissolution apparatus and results are given in the Table-11 and Figure-16. The cumulative percentage of drug released after 12 hrs, were 83.39±2.55, 84.50±1.39 and 86.23±1.2% respectively for 50, 75, and 100 rpm. The results indicate that drug release from controlled porosity osmotic pump is independent of agitation intensity.

Stability Study:

The promising formulations were subjected to short term stability study by storing the formulations at 25°C with relative humidity 60% and 40°C with relative humidity 75% showed the maximum stability. The values of drug content and in vitro drug release were close to initial data with only slight variations. Accelerated stability studies for 3 month revealed that the formulations were stable upto 40°C and 75% RH. It should be stored in a cool, dry place. Stability studies are shown in Table-12.

Infrared Spectroscopy (FTIR)

The prepared osmotic tablets were characterized by FTIR spectroscopy to find out any chemical interaction between Aceclofenac and polymers used.

A characteristic IR spectra of Aceclofenac showed at 1573 cm^{-1} for C C, 1089 cm^{-1} for C-N str, 3867 cm^{-1} for N-H str, 1279 cm^{-1} for C-C str, 952 cm^{-1} for C-O, 2879 cm^{-1} for O-H. All these prominent peaks of drug is observed in formulation F6. Thus, indicating the compatibility of drug with polymers and excipient used. Here, the FT-IR Spectrum of Aceclofenac and "F 6" are matching with each other. So there is no interaction take place in optimized formulation as shown in Table-13.

CONCLUSION

The data obtained from the study of "Development and evaluation of osmotic pump tablets of Aceclofenac" reveals following conclusion.

The present study has been satisfactory attempt to formulate osmotic tablets of an NSAID drug Aceclofenac with a view of improving its bioavailability and giving controlled release of drug. From the experimental results it can be concluded that:

Biocompatible polymers like PEO (WSR Coagulant), PEO WSR (N80), ethyle cellulose, PEG 400 and osmotic agent sodium chloride can be used to formulate osmotic tablets.

The flow properties of all the prepared powder blends were good as indicated by low angle of repose (□□ < 40º) and low compressibility index (I < 25). The good flow properties suggested that the powder blends produced were non aggregated.

In vitro release of Aceclofenac was found to be in following order. F 6 > F 12 > F 10 > F 9 > F 8 > F 11 > F 7 > F 5 > F 4 > F 2 > F 3 > F 1. Among all formulations, F 6 prepared using 37% of PEO (WSR Coagulant), 45% sodium chloride and coated with 30% PEG 400 (poreformer) was found to be the best formulation as it release Aceclofenac 84.789% in a sustained manner with constant fashion over extended period of time (after 12 hr).

In vitro release data fitted into various kinetic models suggest that the release obeyed zero order kinetic, higuchi diffusion mechanism.

Hence, finally it was concluded that the prepared osmotic tablets of Aceclofenac may prove to be potential candidate for safe and effective sustained drug delivery over an extended period of time which can reduce dosing frequency.

Summary

Osmotically controlled oral drug delivery systems utilize osmotic pressure as the energy source for the controlled delivery of drug. Drug release from there systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.

In the present study, osmotic tablets of Aceclofenac were prepared using different polymers like ethyl cellulose, PEO (WSR Coagulant), PEO (WSR N80) PVP K-30, PEG-400 as (pore forming agent), Nacl, Lactose and magnesium strearate by wet granulation method.

The objective of the study is presented in chapter-2. Initially, an extensive literature survey was done for the collection of theoretical and technical data. The review of literature, drug profile and excipient profiles, are presented in chapter-3. This was followed by procurement and characterization of raw materials used in the study.

The prepared osmotic tablets also characterized by FTIR spectroscopy to find out any chemical interaction between Aceclofenac and polymers used. The prepared osmotic tablets were evaluated for micromeritic properties (like bulk density, tapped density, hausners ratio, angle of repose, compressibility index) in vitro drug release study.

Osmotic tablets improved the in vitro drug release using Nacl, PEO (WSR coagulant) and pore former PEG 400 in varying drug to excipient ratio, which suggest that in future they could be easily and successfully developed into drug delivery system.

Thus the prepared osmotic tablets proved to be a potential candidate as a sustained release drug delivery device.

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IMPROVE THE DISSOLUTION RATE OF DOLUTEGRAVIR TABLETS BY SOLID DISPERSION METHOD

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ABSTRACT

The present study was carried out on Dolutegravir by employing solid dispersion technique. The λ_{max} of phosphate buffer pH 6.8 of Dolutegravir were found to be at 334 nm. The pure drug the optimized Solid dispersion formulations were subjected to Fourier transforms infrared studies. The results were showed that there is no interaction between the drug and excipients. Angle of repose was less than 28^0, Carr's index values were 10 to 17 for the pre-compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.2 for all the batches indicating good flow properties. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2 to 3 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.1 to 3.8 mm. All the formulations satisfied the content of the drug as they contained 96-100% of Dolutegravir and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.The dissolution profile of Dolutegravir tablets were compared between solid dispersion tablets. The Dolutegravir solid dispersion tablets showed better release in phosphate buffer pH 6.8, in that F2 showed good drug release i.e., 99.89 at 15 minutes. F2 formulation was taken as optimized formulation.

Key words: Dolutegravir, solid dispersion tablets, dissolution, FTIR , fair flowability and compressibility.

1. INTRODUCTION

From the last few years, the pharmaceutical scientists were working to develop patient compliance and safe dosage forms due to enhanced demand in the market

for them. As a result developing the new technologies has been increasing annually because the development of new drug molecule requires high cost rather than new technology. So the current trend in most of pharmaceutical industries is development of dosage form with new formulation technology using old drug molecules to improve safety, efficacy and patient compliance.

Oral drug delivery is still preferred way of administration for most of the active drug molecules due to its several advantages were greater flexibility in design and high patient compliance. Because of greater stability, accuracy in dose, easy of production, formulation of tablets is preferred oral dosage form. But the poor dissolution of water insoluble drugs is the major problem for pharmaceutical formulators to prepare in the form of tablets. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption. Since they exhibit poor and erratic dissolution profiles, most water-insoluble drugs are included by the FDA in the list of drugs having a high risk for therapeutic in equivalence due to differences and inconsistencies in bio-availability.

Bio-pharmaceutical Classification System

Class I: High Solubility - High Permeability,
Class II: Low Solubility - High Permeability,
Class III: High Solubility - Low Permeability and
Class IV: Low Solubility - Low Permeability.

2. Material

S.No.	Materials	Supplied by
1.	Dolutegravir	Procured from Aurobindo Pharma,
		Provided by **Sura Labs**
2.	PEG 4000	Nihar Traders Pvt. Ltd.
3.	Polaxomer	Nihar Traders Pvt. Ltd.
4.	Camphor	Nihar Traders Pvt. Ltd
5.	Magnesium Stearate	Himedia Laboratories
6.	SSG	Nice Chemicals Ltd.
7.	Mannitol	Nihar Traders Pvt. Ltd.
8.	Talc	S.D. Fine Chemical Pvt. Ltd, Mumbai
9.	Explotab	Himedia Laboratories
10.	Polyplasdone XL	Finer Chemicals Ltd.

2.1.Methods

2.1.1.Determination of Wavelength:

10 mg of pure drug was dissolved in 10 ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml

volumetric flask and made it up to 10ml with the media (Secondary stock solution - 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

2.1.2. Determination of Calibration Curve:

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution - 100µg/ ml). From secondary stock solution required concentrations were prepared (shown in Table) and those concentrations absorbance were found out at required wavelength.

2.1.3. Fourier Transform Infrared (FTIR) spectroscopy:

The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FTIR analysis of the Pure drug and optimised formulation were carried out using an FTIR spectrophotometer (Bruker FT-IR - GERMANY).

3. Formulation development for solid dispersion:

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Dolutegravir and Water soluble polymers such as Polaxomer and PEG 4000 were selected as carriers. Drug and polymers were taken in 1:1 ratio stated in the formulation chart . The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dipersions were mixed with required quantities of super disintegrants, diluent, lubricant and glidant . The blend was evaluated for precompression parameters.

3.1 Formulation of solid dispersion showing various compositions (Ratios only)

	SD1	SD2	SD3	SD4	SD5
Drug	1	1	1	1	1
Polaxomer	1	2	--	--	1
PEG 4000	—	—	1	2	1

3.2 Formulation of fast dissolving tablet by using solid dispersion

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Equivalent to 50mg	SD1 (100mg)	SD2 (150mg)	SD3 (100mg)	SD4 (150mg)	SD5 (150mg)	SD1 (100mg)	SD2 (150mg)	SD3 (100mg)	SD4 (150mg)	SD5 (150mg)
Explotab/sodium starch glycolate	15	15	15	15	15	-	-	-	-	-
Crosspovidone	-	-	-	-	-	15	15	15	15	15
Mg.stearate	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5
Mannitol	175	125	175	125	125	175	125	175	125	125
Total weight	300	300	300	300	300	300	300	300	300	300

4. RESULTS AND DISCUSSION

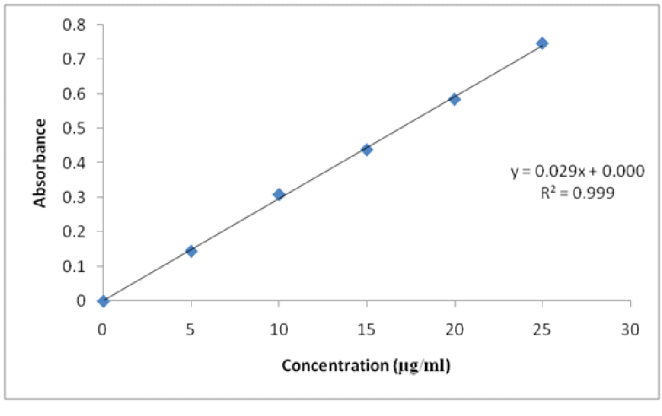
4.1. Analytical Method Development Construction of calibration curve for Dolutegravir:

The λ_{max} of phosphate buffer pH 6.8 of Dolutegravir were found to be at 334nm. Standard graphs of Dolutegravir in phosphate buffer pH 6.8 were shown in Table 7.1. Good linearity was observed with concentration verses absorbance. Its R^2 value in 0.1N HCl and phosphate buffer pH 6.8 was0.999 which were very nearer to '1' and so obeys "Beer -Lambert" law.

4.2. Calibration Curve of Dolutegravir in Phosphate Buffer pH 6.8

Concentration(µg/ml)	Absorbance
0	0
5	0.145
10	0.309
15	0.439
20	0.585
25	0.747

4.3 Calibration curve of Dolutegravir in phosphate buffer pH 6.8

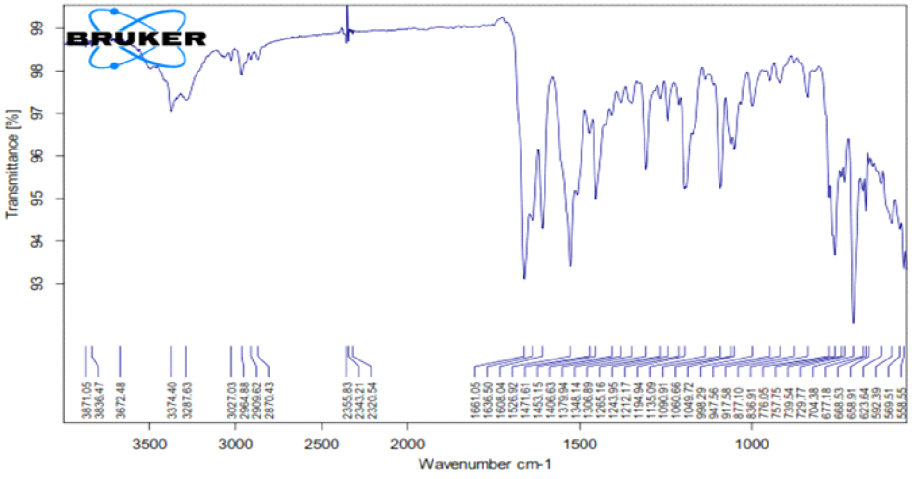


5. Drug Excipient Interactions

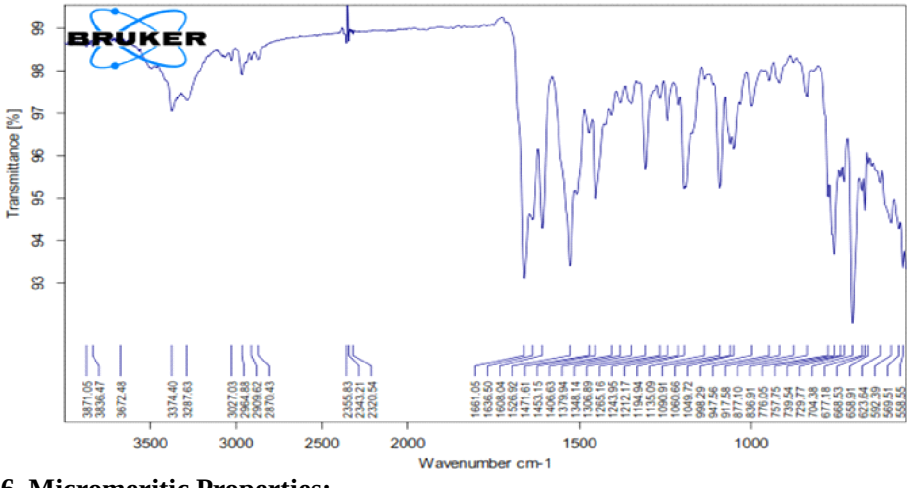
5.1 Fourier transform infrared (FTIR) spectroscopy studies:

The pure drug and the optimised formulation (F2) were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients.

FT-IR Spectrum of Dolutegravir pure drug



5.2 FT-IR Spectrum of Optimised Formulation (F2)



6. Micromeritic Properties:

TABLE-6.1

Evaluation of pre compression parameters of solid dispersion blend

Formulation Code	Angle of repose(θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner ratio
F1	25.74	0.39	0.48	18.75	1.23
F2	26.03	0.32	0.38	15.78	1.18
F3	25.73	0.35	0.42	16.66	1.20
F4	27.14	0.36	0.43	16.27	1.19
F5	24.63	0.38	0.46	17.39	1.21
F6	24.74	0.32	0.41	12.12	1.25
F7	26.03	0.33	0.41	15.5	1.24
F8	25.73	0.35	0.40	22.2	1.14
F9	26.63	0.35	0.41	13.19	1.17
F10	25.31	0.56	0.62	9.67	1.2

The micrometric properties of blend of Dolutegravir soild dispersion were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 28^0, Carr's index values were 10 to 17 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.2 for all the batches indicating good flow properties.

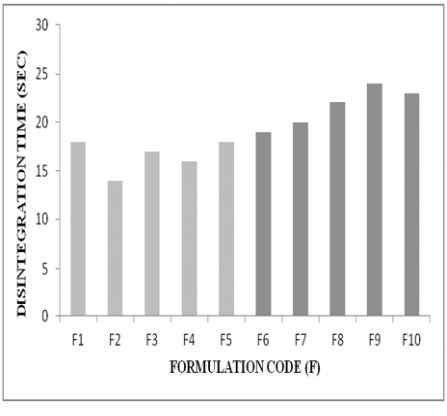
6.2 Post Compression Parameters:

The results of the weight variation, hardness, thickness, friability, and drug content of the soliddispersion tablets were given in Table. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2 to 3 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.1 to 3.8 mm. All the formulations satisfied the content of the drug as they contained 96-100% of Dolutegravir and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

TABLE-6.2

Evaluation of Post Compression Parameters of Solid Dispersion Tablets

Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%loss)	Disinte-gration time (sec)	Content uniformity (%)
F1	298	3.2	2.5	0.39	18	96.31
F2	299	3.1	2.1	0.29	14	98.34
F3	301	3.4	2.7	0.32	17	97.36
F4	296	3.6	2.4	0.41	16	96.42
F5	302	3.8	2.6	0.26	18	96.59
F6	301	3.3	2.7	0.28	19	99.33
F7	300	3.5	2.2	0.37	20	99.45
F8	303	3.2	2.3	0.48	22	99.56
F9	304	3.2	2.8	0.54	24	98.96
F10	301	3.4	2.2	0.65	23	98.78



From the above pre and post compression of solid dispersion tablets of all the required evaluation tests were found to be within limit. Less disintegration time is F2 formulation i.e., 14 seconds.

6.3 *In vitro* Dissolution Studies

All the solid dispersion formulations of Dolutegravir were subjected to In vitro dissolution studies, these studies were carried out using phosphate buffer pH 6.8 by using dissolution apparatus type II.

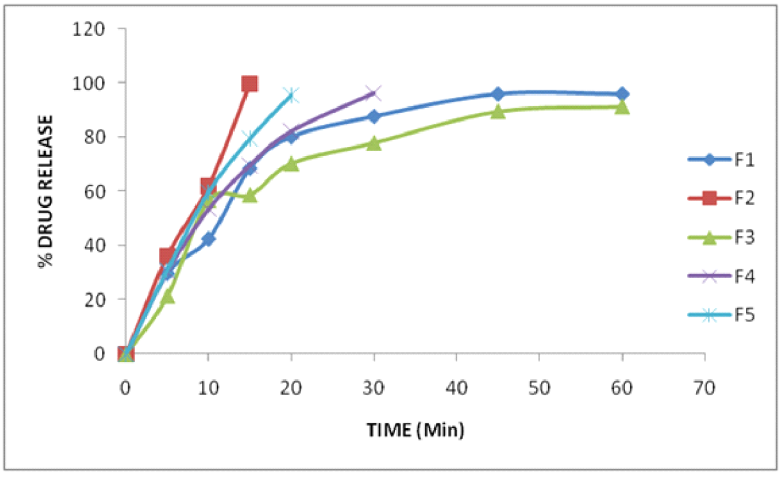
The dissolution profile of Dolutegravir tablets were compared between solid dispersion tablets. The Dolutegravir solid dispersion tablets showed better release in phosphate buffer pH 6, in that F2 showed good drug release i.e., 99.89 at 15 minutes.

In vitro dissolution studies of formulated solid dispersion tablets by using Explotab/sodium starch glycolate as super disintegrant

Time (min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	29.86	36.33	21.5	30.48	31.06
10	42.72	62.18	56.8	53.61	59.88
15	68.75	99.89	58.75	69.83	79.52
20	80.35		70.35	82.41	95.64
30	87.94		77.94	96.54	
45	96.24		89.5		
60	96.24		91.3		

Figure

In vitro dissolution studies of formulated solid dispersion tablets by using Explotab/sodium starch glycolate as super disintegrant

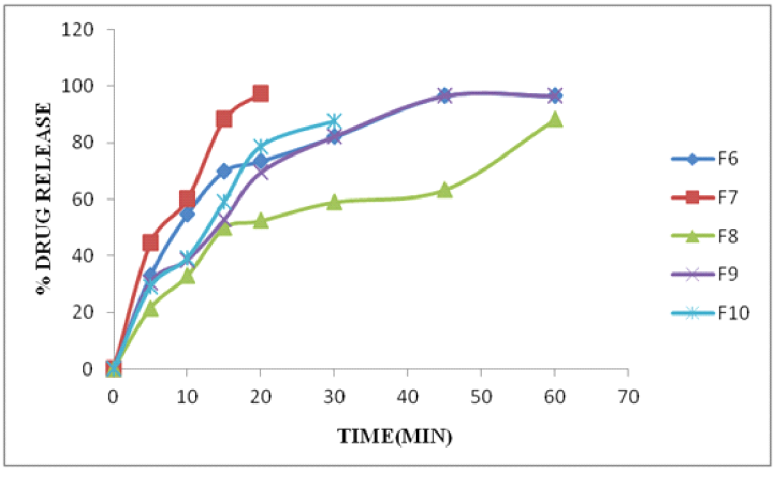


***In vitro* dissolution studies of formulated solid dispersion tablets by using Crosspovidone as super disintegrant**

Time (min)	F6	F7	F8	F9	F10
0	0	0	0	0	0
5	32.86	44.33	21.5	30.47	28.96
10	54.56	59.89	32.8	38.48	39.16
15	69.75	88.2	49.75	52.68	58.97
20	73.34	97.2	52.32	69.46	78.65
30	81.94		58.94	82.17	87.53
45	96.5		63.28	96.58	
60	96.5		88.14	96.58	

Figure

***In vitro* dissolution studies of formulated solid dispersion tablets by using Crosspovidone as super disintegrant**



From the above graphs it was revealed that F2 formulation was optimised formulation. Why because in that F2 showed good drug release i.e., 99.89% at 15 minutes. and less disintegration time is F2 formulation i.e., 14 seconds. Hence F2 formulation considered as optimised formulation.

7. Conclusion

The present study was carried out on dolutegravir by employing solid dispersion technique. The ?max of phosphate buffer pH 6.8 of Dolutegravir were found to be at 334 nm. Standard graph of Dolutegravir in phosphate buffer pH 6.8 was plotted. Good linearity was observed with concentration verses absorbance. Its R2 value in 0.1N HCL and phosphate buffer pH 6.8 was0.999 which were very nearer to '1' and so obeys "Beer -Lambert" law.

The pure drug the optimized Solid dispersion formulations were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients. The micrometric properties indicating good to fair flowability and compressibility. properties.

All the solid dispersion formulations of Dolutegravir were subjected to in vitro dissolution studies, these studies were carried out using phosphate buffer pH 6.8 by using dissolution apparatus type II. The dissolution profile of Dolutegravir tablets were compared between solid dispersion tablets. The Dolutegravir solid dispersion tablets showed better release in phosphate buffer pH 6.8, in that F2 showed good drug release i.e., 99.89 at 15 minutes. F2 formulation was taken as optimised formulation.

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ROLE OF HYPOMAGNESEMIA AS A RISK FACTOR IN CORONARY ARTERY DISEASE - STUDY FROM A TERTIARY CARE HOSPITAL IN NORTHERN TELANGANA

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ABSTRACT

Background & Objectives: Magnesium is an essential ion that regulates numerous biological activities in the human body. Many epidemiological, experimental and clinical studies revealed the pathological role of magnesium in the development of major coronary risk factors. Serum magnesium has been linked with hypertension, atherosclerosis and myocardial infarction. The study focused to measure serum magnesium levels in patient with coronary artery disease (CAD) and control group; and to identify its association with CAD in patients admitted to a tertiary care hospital. Methods: A prospective observational study was conducted in 100 subjects for a period of 8 month, where 50 are CAD patients & 50 controls. All the medical records were assessed and serum magnesium levels were measured by colorimetric assay. A p-value of <0.05 was considered to be statistically significant. Results: The mean age of CAD group was found to be 50.08±11.83 years in males and 49.25±10.43 years in females respectively. The study results show a significant difference in serum magnesium between CAD (1.517±0.04840 mg/dL) and control group control (1.821±0.07827 mg/dL). In addition, a positive association between serum magnesium in CAD patients was observed. Low serum levels of magnesium were found in CAD patients who are diabetic, hypertensive and alcoholic. Interpretation & Conclusion: The results indicate that assessment of this serum magnesium should be undertaken as it may be a good predictor of mortality. Effective treatment & appropriate life style changes can be implemented early to prevent morbidity and mortality.

Key words: Hypomagnesaemia, CAD, morbidity, mortality

INTRODUCTION

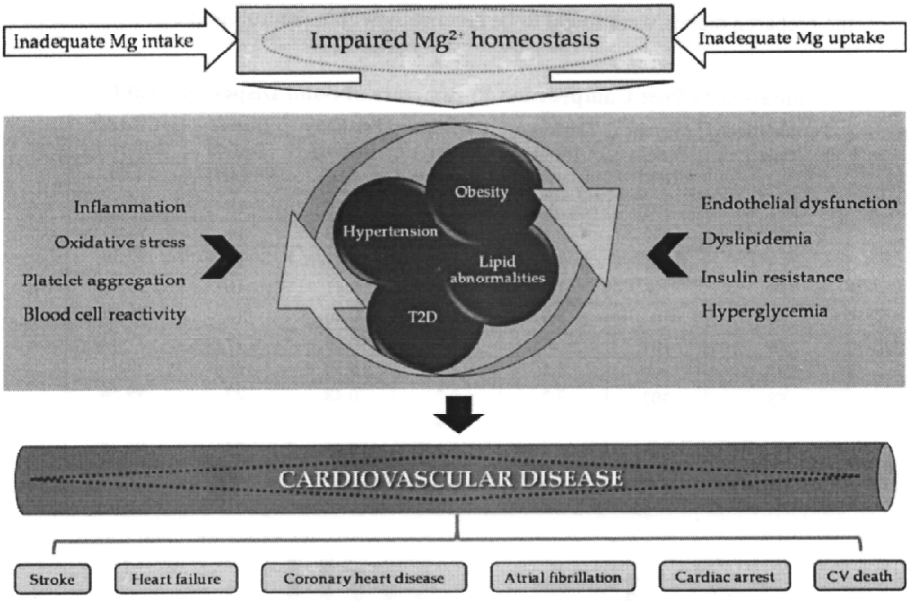
Magnesium is an essential mineral that has abundant biological functions in the cardiovascular system. Serum magnesium has been associated with atherosclerosis, myocardial infarction, hypertension and heart failure [1] but was not an independent risk factor for cardiovascular mortality[2]. Many studies have established the correlation between magnesium and risk factors in animal models[3-7], whereas very few suggested that low magnesium may contribute to atherosclerosis, HTN, DM in human[8-10].

In India, the prevalence of hypomagnesaemia increased from 0.2-2.5% among urban residents and from 0.2-1.5% among rural residents in the past six decades. According to Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, the overall prevalence of hypomagnesaemia will be 15.9/1000 population by 2020 due to contributing factors like urbanization and lifestyle changes.

A low dietary intake of magnesium is strongly related to cardiovascular disease and develops complications among known subjects with coronary artery disease [Figure-1].

Figure-1

Role of magnesium in the development of CVD



Hence, this study was undertaken to assess the prevalence and association of serum magnesium with traditional cardiovascular risk factors like hypertension and hyperlipidemia among subjects with established coronary artery disease where target therapy with magnesium supplementation may reduce the worsening of cardiovascular disease and thus reduce the risk of mortality.

MATERIALS AND METHODS

The study was conducted in 100 subjects (50 CAD group and 50= Control group) for a period of eight months in Mahatma Gandhi Memorial Hospital, a teaching hospital. Serum magnesium was measured using Calmagite method (normal range 1.6- 2.6mg/ dL), lipid profile (triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol) was measured using standard validated methods and data of other biochemical routines were obtained from medical records. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Socio-Demography of study subjects

Among total subjects, 50 are control group with 58% males & 42% females) and 50 are CAD group with 52% males & 48% females). The mean age of CAD patients was found to be 50.08±11.83 years in males and 49.25±10.43 years in females respectively.

Socio-demographic data of study population is presented in table 1 where among CAD group majority are farmers, house wives, labors and most of them are alcoholic and smokers.

TABLE-1

Socio-Demography of the Study Population

Variable	Control		CAD	
	N	%	N	%
No. of Population	50	100%	50	100%
Farmer	4	8%	15	30%
Business	3	6%	10	20%
Housewife	4	8%	10	20%
Labor	19	38%	9	18%
Teacher	20	40%	6	12%
Married	44	88%	6	12%
Unmarried	40	80%	10	20%
Smoking	7	14%	7	14%
Alcohol consumption	8	16%	9	18%
Smoking & Alcohol consumption	5	10%	8	16%
No Smoking and alcohol	30	60%	26	52%

Baseline Characteristics in CAD group

The mean values of baseline characteristics in CAD patients like age, length of stay, random blood sugar, CPK-MB, troponin-T, serum creatinine, blood urea, total cholesterol, LDL, HDL, triglycerides, ejection fraction and serum magnesium, ejection fraction, troponin-T, systolic and diastolic blood pressure are presented in table 2, showing comparison between males and females.

TABLE-2

Baseline Characteristics of CAD Patients

Variable	Mean ± SD		
	Total	Male	Female
Age in years	49.68±11.07***	50.08±11.83	49.25±10.43
Length of Stay	7.460±1.644***	7.192±1.297	7.750±1.939
Random Blood Sugar (mg/dL)	147.1±50.72***	150.1 ± 55.20	143.8 ± 46.35
Creatine Phosphokinase-MB (IU/l)	115.8±86.73***	122.3 ±91.77	108.8 ±82.30
Creatinine (mg/dL)	0.13±0.50***	0.835 ± 0.188	0.950 ±0.2226
Blood Urea (mg/dL)	28.10±10.79***	29.04 ±10.63	27.08 ±11.10
Cholesterol (mg/dL)	156±35.46***	154.4 ±33.37	157.7 ±38.25
LDL-C (mg/dL)	75.34±31.63***	75.54 ±23.17	77.92 ±38.12
HDL-C (mg/dL)	39.08±5.903***	39.73 ±5.008	38.38 ±6.781
Triglycerides (mg/dL)	149.3±93.09***	132.9 ±64.30	167 ±115.5
Magnesium (mg/dL)	1.517±0.3422***	1.490 ±0.3284	1.547 ±0.3613
Ejection Fraction (%)	45.3±14.88***	0.491 ±0.127	0.412 ±0.162
Troponin-T (ng/mL)	0.4364 ±1.537*	0.4434 ±1.573	0.4067 ±0.538
Systolic BP (mm of Hg)	129.8 ± 28.13**	127.5± 20.13	115.8± 15.19
Diastolic BP (mm of Hg)	82.38 ± 16.19**	90.38 ± 12.14	84.38 ± 10.1

**p= <0.005, **p= <0.001, ***p=<0.0001 when compared between males and females*

The levels of cholesterol, triglycerides and LDL-C are found higher in females than males. This may be an issue of concern where low levels of cholesterol induce physical and mental disturbances, which may be one of the reasons for hospital admissions, predominantly males.

Comparison of serum magnesium in two groups of study population

It was found that serum magnesium level in CAD (1.517±0.04840 mg/dL) is less than control (1.821±0.07827 mg/dL) at significantly difference of p= 0.0013 (i.e., p<0.05) which indicates that hypomagnesaemia was observed in CAD group.

Comparison of serum magnesium among different conditions in CAD

Magnesium levels in serum was interpreted in CAD group and found that patient with co morbidities like diabetes, hypertension significantly showed lower serum magnesium than patients without diabetic and hypertension. It shows that patients with only diabetes and hypertension may develop CAD if they have low serum magnesium levels. CAD group with social habits like smoking, alcohol, and both had significant lower serum magnesium level compared to non smokers and non alcoholics. Mostly in patients with high LDL-C, serum magnesium was found less than other lipids [Table-3].

TABLE-3

Comparison of Serum Magnesium (mg/dL) among different risk factors

Risk factors	Serum Magnesium (mean ± SD)
Control	1.821±0.5534
Coronary Artery Disease	1.517±0.3422
Diabetes	1.348±0.2109
No Diabetes	1.549±0.3546
Hypertension	1.410±0.2829
No Hypertension	1.528±0.3492
Smoking	1.469±0.2524
Alcoholic	1.378±0.1652
Both	1.446±0.2840
No	1.600±0.4081
Cholesterol >200mg/dl	1.527±0.3011
LDL >180mg/dl	1.140±0.3012
TG >160mg/dl	1.391±0.2204
HDL <40mg/dl	1.53±0.3123

Drug Utilization

In CAD patients the majorly utilized cardiac drugs are aspirin (100%), sorbitrate (100%), atorvastatin (98%), low molecular weight heparin (82%) and clopidogrel (80%) followed by metaprolol (46%), Ivabradin (44%) and streptokinase (40%).

DISCUSSION

Most of the cardiovascular events occur in individuals aged at 60 years or more[11]. But among the study population it was observed that more number of cardiovascular events developed in 35-55 years of age. Some studies reviewed that patient with hypomagnesaemia reported high blood pressure[8,9,12], but some[13] doesn't support to this observation. The present study findings showed that magnesium levels are found less in patients with elevated blood pressure. Hence it was identified that hypomagnesaemia may develop hypertension.

All patients with CAD had normal random blood sugar, serum creatinine, blood urea whereas, abnormality was observed in lipid profile, serum magnesium, left ventricular ejection fraction, creatine phosphokinase-MB, and troponin-T.

Hyperlipidemia and reduced HDL-C is associated with magnesium deficiency[8,10,12]. Similarly the study stated that CAD patients with hyperlipidemia were observed with low level of serum magnesium. Hypomagnesaemia is strongly related to cardiovascular risk factor among known subjects with CAD[14]. Similarly the study shows that patients with CAD were reported with low level of serum magnesium when compared with controls and are significant different. Therefore a strong

relationship exists between hypomagnesaemia and CAD, and it appears to be a marker of vascular disease indicative of an incremental risk for cardiovascular mortality. Thus, magnesium supplementation may help in reducing development of cardiovascular disease as well as mortality associated with it.

CONCLUSION

More than half of the CAD patients have hypomagnesaemia and a positive relationship was observed between hypertension and lipid levels with serum magnesium. Therefore, hypomagnesaemia can be corrected by intake of dietary magnesium and administration of magnesium during hospitalization which may reduce the risk of cardiovascular disease and associated mortality.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

All authors declared no conflicts of interest.

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IMPLEMENTATION OF ARTIFICIAL INTELLIGENCE IN PHARMA INDUSTRY

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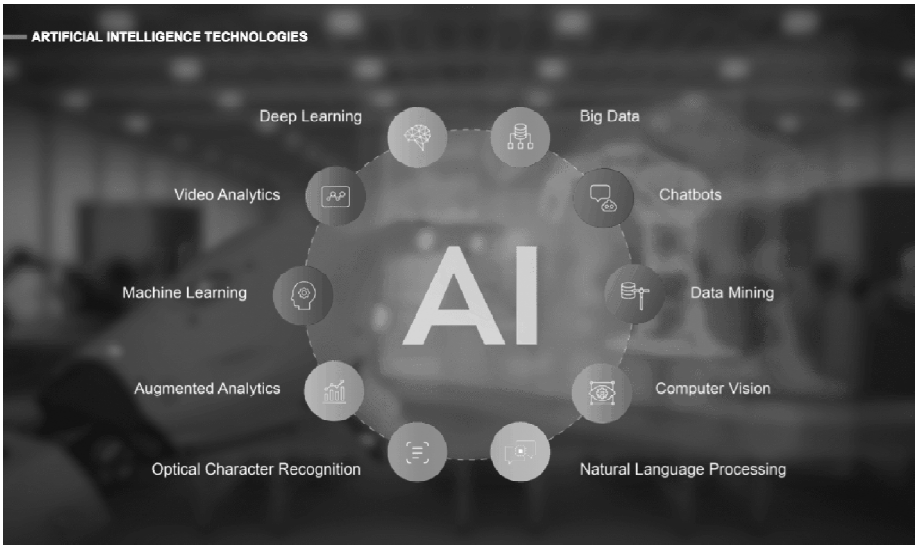
INTRODUCTION:

According to father of artificial intelligence[1-3] [AI], "John Mc Carty", it is "the science and engineering of making Intelligent Machines."Artificial Intelligence refers to the ability of a computer or a computer enable robotics system to process information and procedure outcomes in a manner similar to the thoughts process of human in learning, decision making and solving problems.

The goals of AI system[4-5] is to develop system capable of taking complex problems in ways similar to human logic reasoning.



Artificial Intelligence[6-9] is nothing but a computer programme using artificial intelligence machines learns from the surrounding and thinks on their own. It is not like writing a program and getting an output.

Nearly 50% of global health care companies will implement artificial intelligence strategies and by 2025 and some experts believe it is crucial for how businesses operate down the line.

OBJECTIVES[10-12]:

1. AI Solves Problems:

When it comes to artificial intelligence there is a frankestinian urge to create AI programs that look, act, and feel like real humans many computes scientists now understand that the real goal is not to make a human like robot.

2. AI Completes Multiple Tasks:

Completing multiple tasks in another aims and objectives of artificial intelligence. One of the largest difficulties to overcome has been making it possible for an AI program or a "robot" to do more than one task. For instance, it can bring an item from point A to point B.

3. AI shapes the future of every company:

AI is quickly becoming a crucial tool for all companies. They are using this technology to streamline their processes, such as using "chatbot software for customer operations". It's no secret that the goal is to continue this trend for as many low level tasks as possible.

It ultimately saves the companies' many in the long run, and it allows them to up productivity in other areas.

4. AI prepare for a boom in big data:

"Big data has already taken the world by storm".

Big data is the large - scale, and sometimes even random collection of data about peoples, habits conversation and more. AI will be able to do much more for the analysis of this data than humans ever did, so data driven research, advertisements, and content are going to explode.

5. AI creates synergy between humans and AI:

One of the key goals in AI is to develop a strong synergy between AI and humans, so that they can work together to enhance the capabilities of both.

6. AI is good at problem-solving:

AI is unable to employ advanced problem solving abilities that is,it can tell you a factual answer but cannot analyse a specific situation and make a decision based on the very specific context of that situation.

7. AI helps with planning:

One of the most human traits in existence is the ability to plan make goals and subsequently accomplish them and one of the goals for AI is to have AI be able to do these things.

8. AI performs more complex tasks:

The key goal is this to develop AI programs that can complete more and more complex tasks. Already the abilities are shocking, although not yet widespread.

Innovations in medical and biological engineering:

*** 1950**

- Artificial kidney
- X- ray
- Electrocardiogram
- Cardiac pacemaker
- Cardiopulmonary by pass
- Antibiotic production technology
- Defibrillator

*** 1960**

- Heart valve replacement
- Intraocular lens
- Vascular grafts
- Blood analysis and processing

*** 1970**

- Computer assisted tomography
- Artificial hip and knee replacements
- Endoscopy
- Biological plant food engineering

*** 1980**

- Magnetic resonance imaging
- Laser surgery
- Vascular grafts
- Recombinant therapy

Definition of Artificial Intelligence

AI is a branch of computer science that aim to create intelligent machines.

Artificial intelligence is based on studying human behavior such as how human brain thinks. How humans learn, how human solve an issue, how they take decisions and so on. This machine can also be called as expert system.

Use of a computer to model intelligent behavior with minimal human intervention.

* Machines and computer programs are cable of problem solving and learning, like a human brain.

* Natural language processing [NLP] and translation.

* Pattern recognition.

* Visual perception

* Decision making

♦ Machines teach [ML] one of the most exiting areas for development of computational approaches to automatically make sense of data.

Advantages of Machine:

- can retain information
- becomes smarter over time
- machine is not susceptible to sleep deprivation distractions ,information overload and short term memory loss.

AI in Pharma

- Pharmaceutical industry can accelerate innovation by Using technological advancements
  - The recent technological advancement that comes to mind would "recognition, decision making" and translation between languages.
  - An estimate by IBM shows that entire healthcare domain has approx.161 billion GB of data as of 2011.
  - With humongous data available in this domain AI can be of real help in analyzing the data and presenting results that would help out in decision making, saving human effort, time, money and thus help save lives.

Artificial Intelligence in Medicine

The future of 'standard' medical practice might be here sooner than anticipated, where a patient could see a computer before seeing a doctor. Through advances in artificial intelligence [AI], it appears possible for the days of misdiagnosis and treating disease symptoms rather than their root cause to move behind us. The accumulating data generated in clinics through common tests and medical imaging allows for more applications of artificial intelligence and high performance data - driven medicine. These applications have changed and will continue to change the way both doctors and researchers approach clinical problem-solving.

However, while some algorithms can compete with and sometimes outperform clinicians in a variety of tasks, they have yet to be fully integrated into day-to-day medical practice. Why because even though these algorithms can meaningfully impact medicine and bolster the power of medical intervention, there are numerous regulatory concerns that need addressing first.

Recent Applications of AI in Medicine:

- Advances in computational power paired with massive amounts of data generated in healthcare system make many clinical problems ripe for AI applications. Below are two recent applications of accurate and clinically relevant algorithms that can benefit both patients and doctors through making diagnosis more straightforward.
- One of the most promising areas of health innovation is the application of artificial intelligence [AI .Machine / deep learning" and analyses the integration of AI into radiology.

- Over 10 years, publications on AI in radiology have increased from 100 - 150 per year to 700 - 800 per year.
- Magnetic resonance imaging and computed tomography are the most involved techniques.
- Radiologists, the physicians who were on the forefront of the digital era in medicine, can now guide the introduction of AI in healthcare.

The Virtual Branch:

The virtual component is represented by machine learning [also called deep learning]- mathematical algorithms that improve learning through experience.

Three types of machine learning algorithms:

1 . Unsupervised [ability to find patterns]
2. Supervised
3. Reinforcement learning.

The Physical Branch:

- Physical objects
- Medical devices
- Sophisticated Robots for delivery / robots for surgery.

Growth drivers of AI in health care:

- Increasing individual health care expenses
- Large geriatric population
- Imbalance between health work force and patients
- Increasing global health care expenditure
- Continuous shortage of nursing and technician staff. The number of vacancies for nurse will be 1.2 million by 2020.
- AI is and will help medical practitioners efficiently achieve their tasks with minimal human intervention, a critical factor in meeting increasing patient demand.

Benefits of Artificial Intelligence

- AI can definitely assist physician.
- Clinical decision making - better clinical decisions..
- Replace human judgment in certain functional area of health care [e.g.: radiology].
- Up to date medical information from journals, text books and clinical practices.
- 24×7 Availability of expert.
- Early diagnosis.
- Prediction of outcome of the disease as well as treatment.

- ♦ Feed back on treatment.
- ♦ Reinforce non pharmacological management.
- ♦ Reduce diagnostic and therapeutic errors.
- ♦ Increased patient safety and huge cost savings associated with use of AI.
- ♦ AI system extracts useful information from a large patient population.
- ♦ Assist making real -time inferences foe health risk alert and health outcome prediction.
- ♦ Learning and self - correcting abilities to improve its accuracy based on feedback.

Future Indian Scenario:

- Collaboration between medical and technical institutions
- Remove firewalls of clinical load and hope of IPR
- Government funding- more intelligent and result oriented rather than you pat-I pat
- Scientific mafia or scientist mafia

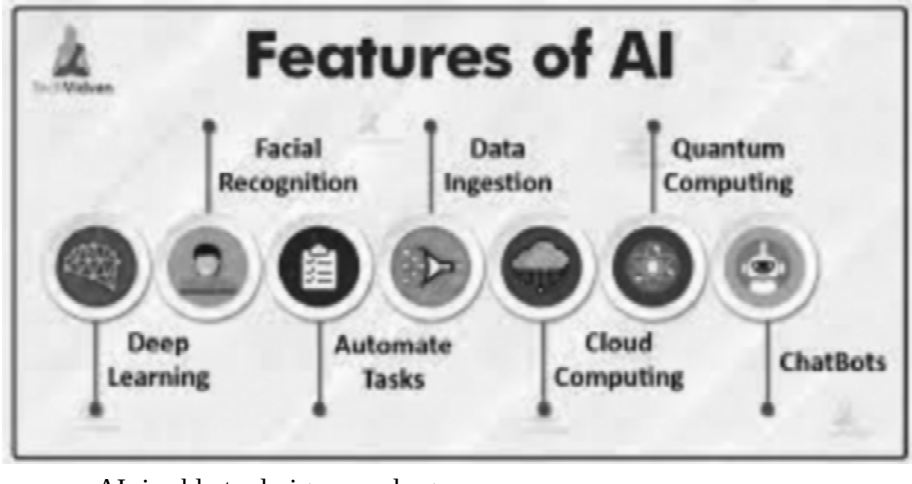
Current Status of Medical Records:

- Data need to be captured in real time, and institutions should promote their transformation into intelligible process.
- Simplification, read ability and clinical utility of data sets

Electronic Medical or Health Records:

- Are essential tool for personalized medicine.
- Early detection and targeted prevention again

Future of AI:



- AI is able to design new drugs
- Find new drug combination

- Deliver clinical trials within minutes
- Robots help in the manufacturing of medication as well as their distribution
- Counter feinting drugs become almost impossible.

Most popular presentation on AI and machine learning

- **AI and low overview**

  AI is abroad branch of computers science that is focused on a machines capability to produce rational behavior from external inputs. The goal of AI is to create system that can perform tasks that would otherwise require human intelligence.
- Artificial intelligence aims to develop machines that can accomplish what a human can in terms of reasoning.
- Artificial intelligence now affects productivity, employment and competitive behavior in significant ways.

AI Tutorial for Beginners

This tutorial provides introductory knowledge on artificial intelligence. It would come to a great help if you are about to select artificial intelligence as a course subject. You can briefly know about the areas of AI in which research prospering.

The basic knowledge of computers science is mandatory. The knowledge of mathematics, languages, science, mechanical or electrical engineering is a plus.

This artificial intelligence tutorial provides basic and intermediate information on concepts of artificial intelligence. It is designed to help students and working professionals who are complete beginners. In this tutorial, our focus will be on artificial intelligence, through the course of this artificial intelligence tutorial, we will look at various concepts such as the meaning of artificial intelligence, the levels of AI, WHY AI is important, its various applications, the future of artificial intelligence, and more.

AI Future Communication

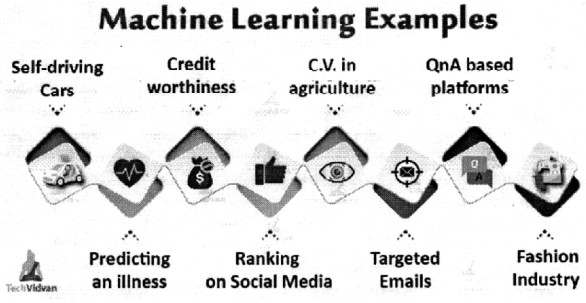
Social media, chat bots, are the future of communication an exciting application of AI can be found in chat bots. Here, the limitless scope of chat bots. The various milestones reached by leading players in boot technology such as face book, Skype and kick are enumerated. The evaluation of chat bots and its and its absorption of more AI in the future is also looked into E- commerce is touted as the biggest beneficiary of the advancement in chat bots and that boot technology will owe its rise to service and commerce.

AI AND THE FUTURE OF WORK

The subjects of self - learning of robots and machines is explored here, fictional Babel fish, it is suggested that the advancements in technology leading to improved learning and translations by machines made the Babel fish a near- real entity.

New 'power' values such as speed, net worked governance, collaboration and transparency among others, have been put forth and juxtaposed against older ones that are not fully technology driven.

AI and Machine Learning Demystified



In this presentation, carol smith establishes that AI cannot replace humans. Smith conveys that AI can serve the purpose of enabling human beings in making better decision

Asians Artificial Intelligence Agenda

The global absorption of AI being sped up by ASIAN countries. It suggests that Asia will not only benefit greatly from the rise in AI technology.

The data collected for the review has been summarized in the form of simple info-graphics. They are a adoption of AI across different industries hoe it could possibly impact human capital. The review also suggests that while there is awareness about AI in Asia only a small percentage of companies are investing in it.

Pointers for business leaders in Asia to capitalize on ASIA is offered in the graphic timeline of the history of AI.

How is "AI "currently being applied in the Pharmaceutical industry

- **Disease identification:**
  * 2015_ report by "pharmaceutical research and manufactures of America"_ more than 800 drugs and vaccines are in trial phase to treat cancer.
  * googles "deep mind health " , announced multiple partnerships including some EYE hospitals in which they are developing technology to address macular degeneration in aging eyes.
  * "oxfords pivotal predicting response to depression treatment" [PReDicT]. Project is aiming to produce commercially available emotional test battery for use in clinical setting.
- Berg, on innovative us bio-pharma company, is using AI to research and develop diagnostics and therapeutics in the fields of oncology, endocrinology, and neurology.
  * it can range from oncology to copied to degeneration in the eyes.

* Their unique AI - based interrogative biology platform combines patient biology and AI- based analytics to identify difference between healthy and disease environments

- **Radiology and radiotherapy:**

  This is an area which AI has been speculated to play a major role in the future.

  * Presently, googles deep mind health is working on machine learning algorithms to detect difference between healthy and cancerous tissues.
  * The goal is to improve the accuracy of radiotherapy planning while minimizing damage to healthy organs at risk.

- **Personalized medicine and rare disease**
- **Identification:**
  * Using AI, body scans can detect cancer and other diseases early, as well as predict health issues people might face based on their genetics.
  * Although far from perfect, IBM Watson for oncology in currently the leader in AI for personalized treatment decisions in the oncology space. It uses each patients medical information and history to optimize the treatment decision - making. recently, Watson correctly diagnosed a rare form of leukemia, it reportedly examined millions of oncology research papers in 10 minutes after which it successfully diagnosed the patient and recommended a personalized treatment plan.
  * this can be effectively used to assist and identify individuals to provide early insight into the condition- such as gum condition, accurately classify cutaneous skin disorders, suggest primary treatment option with over the - counter medication, and serve as an ancillary tool to enhance the diagnostic accuracy of clinicians, or improve educational and clinical decisions made by your Childs teacher, or your mental health professional or even your medical doctor.

Drug Discovery and Manufacturing:

* A study published by the Massachusetts Institute of Technology [MIT] has found that only 13.8% of drugs successfully pass clinical trials. Furthermore a company to 2 billion dollars for any drug to complete the entire clinical trials process and get FDA approval.
* It helps in the initial screening of drug compounds to the predicted success rate based on biological factors . Measuring RNA, DNA quickly, precision medicine or next-generation sequencing helps in the faster discovery of drugs and tailored medication for individual patients. With this in mind, pharma businesses are using AI to increase the success rates of new drugs while decreasing operational costs at the same time.

* Ideally, would also translate to lower drug costs for patients, all while offering them more treatment choices.

Predictive Forecasting:

We have popular seasonal brands in the allergens and cold and flu category. The business use case is to have a predictive model that predicts how the upcoming season for allergy or cold and flu would shape up in different regions, and when are the predicted peaks and troughs.

- **Sensory models:**

  Humans react differently, to taste size, texture, color, and sensory AI models help in a holistic way of understanding, predicting, and optimizing consumer preference.

  We use multiple parameters such as taste, texture, color, and MI models, to understand the relationship between the consumer and the desired product experience .our brands ofter gummies, tablets, and liquids for our over the counter products and these models are beneficial.

- **AI in eye- tracking:**

  * Consumers and retail terms with consent in our labs wear eye- tracking glasses and look at the products on shelf or online during this process, images are captured and analyzed using AI . The analysis includes areas of interest [AOI] metrics; including the time to first fixation and time spent, gaze plots, heat maps, and video replays.

    This helps in better product placement, improves our art and labeling, and helps us understand consumer.

- **Clinical Trials:**

  Identifying the right candidate for the trial based on history and disease conditions, and additional attributes, overlaying with infection rates, demographics, and to represent the most impacted apart from the health care conditions we see many AI ML usage in digital transformation areas for pharma and health care companies such as mar tech, ad tech, supply chain, sales, and service.

  * Advanced predictive analytics can analyze genetic information to identify the appropriate patient population for a trial.
  * AI can also determine the optimal sample sizes for increased efficiency and reduce data errors such as duplicate entries.

Challenges to AI adoption at larger organization

- **Data challenges**

  Quality and Quantity of data as for any machine learning model to work efficiently, a training data set with a minimum of 2 to 3 years of historical data is critical this is the most critical challenge we see in large

organizations due to mergers and acquisitions or prior data management or prior source of data being unavailable.

- **Skills challenges**

  Getting the right resource and with the right back ground is very challenging we have a limited data science skilled pool in the marked , delays hiring and getting them up to speed and scale multiple AI projects.

Business Value

Larger organizations are struggling to prove the business value for AI projects.

- Potential challenges
- Development costs
- Integration issues
  * ethical issues
  * reluctance among medical practitioners to adopt AI
  * Fear of replacing humans
- Data privacy and security
  * mobile health applications and devices that use AI
  * Lack of interoperability between AI solutions.
- Data exchange
  * need for continuous training by data from clinical studies
  * incentives for sharing data on the system for further development and improvement of the system
- State and federal regulations.

Industry Challenges

- High initial capital requirement
- Potential for increased un employment
- Difficulty in deployment
- Reluctance among medical practitioners to adopt AI
- Ambiguous regulatory guidelines for medical software
- Lack of created health care data
- Concern regarding privacy and security
- Lack of interoperability between AI solutions
- State and federal regulations.

Recent AI adoption

1. **Novartis**: uses AI to predict untested components researchers should explore to find new cures.
2. **IBM Watson:** helps match patients with the right drug trials
3. *Verge Genomics:* uses AI to predict the effect of new treatment for patients suffering from ALS and Alzheimer's.

4. **Bayer and Merck and Co:** Uses AI algorithms to identify pulmonary hypertension.
5. **Tencent Holdings:** leverages AI to remotely monitor patients with Parkinson's.
6. **Mission Therapeutics:** Uses AI to develop treatment for Alzheimer's
7. **Healx :** Uses AI to helps biotech companies find treatments for rare diseases
8. **AiCure and Abb Vie:** use image recognition to improve drug adherence
9. **Santen and two XAR:** are using AI to develop drugs for glaucoma
10. **AstraZeneca and Alibaba:** Build AI to help patients with automated diagnostics
11. **Apple:** use AI to screen children for autism
12. **GNS Healthcare and Genentech:** Use AI to develop new cancer therapies
13. **Deep 6:** uses AI to proactively find drug trial candidates.

The process of AI adoption in the pharma sector can be made easy by taking these steps:

- Partnering and collaborating with academic institutions that specialize in AI R & D to guide pharma
- Collaborate with companies that specialize in AI driven medicine discovery to reap the benefits of expert assistance ,advanced tools, and industry experience
- Train R & D manufacturing teams to use and implement AI tools and techniques in the proper way for optimal productivity.

Applications of AI

Drug Discovery:

The use of AI in drug discovery can expedite the overall process. Applied intelligence can improve drug discovery success rates by 8-10% resulting in saving worth billions of dollars for the industry finding drug discovery compounds and precision medicine are the major trending applications over other pharma - based AI applications.

AI also helps in better understanding the diseases' mechanisms for instance astellar pharma has leveraged an AI instilled image analysis solution known as IMAC lab from LPIXEL, Aa leader in image. Analysis and life sciences technology they are working on cell selection and management process involced in researching regenerative medicine and cell therapy.

Drug Development:

Drug development through clinical trials runs a high risk of failure due to human errors in data processing and candidate monitoring. The time line of clinical trials also runs longer , which ultimately delays it's commercialization.

AI system and algorithms process vast amounts of information quickes and with precision, maintain proper records and ensure transparency when it comes to clinical trail data through its data driven decision making, AI not only reduces the entire timeline of drug development, but its accuracy also ultimately improves drug approval and minimizes loss. It can be used to optimize the entire trial process, including trial designing and site solution.

Disease Prevention:

Pharma companies can use AI to develop cures for both known disease like alzheimers and Parkinsons and diseases.

Generally pharmaceutical companies do not spend their time and resources on finding treatments for rare diseases sinces the ROI is very low compared to the time and cost it takes to develop drugs for treating rare diseases.

According to "global genes".nearly 95% of rare diseases don't have FDA approved treatments or cures.

Epidemic Prediction:

AI and ML are already used by many pharma companies and healthcare providers to monitor and forecast epidemic out breaks across the globe these technologies feed on the data gathered from disparate sources in the web, study the connection of various geological, environmental, and biological factors on the health of the populations of different geographical locations, and try to connect the dots between these factors and previous epidemic outbreaks.

Such AI/MI models become especially useful for under developed economics that lack the medical infrastructure and financial frame work to deal with an epidemic outbreak

Examples: AI application is the ML -based "Malaria outbreak prediction model " that functions as a warning tool predicting any possible malaria outbreak and aid healthcare provides in taking the but course of action to combat it.

Remote Monitoring:

Remote monitoring is a breakthrough in the pharma and healthcare sectors. Many pharma companies have already developed wearables powered by AI algorithms that can remotely monitor patients suffering from life threatening disease.

For instance "tencent holdings" has collaborated with "medopad" to develop an AI technology that can remotely monitor patients with Parkinson's disease and reducing the time taken to perform a motor function assessment from 30 minutes to 3 minutes. by integrating this AI technology with Smartphone apps, it is possible to monitor the opening and closing motions of the hands of a patient from a remove location.

On detecting hand movement, the Smartphone camera will capture it to determine the severity of the symptoms [Parkinsons] the frequency and amplitude of the

movement will determine the severity score of the patients conditions there by allowing doctors to change the drug as well as the drug doses remotely.

Manufacturing:

Pharma companies can implement AI in the manufacturing process for higher productivity, improved efficiency, and faster production of life- saving drugs. AI can be used to manage and improve all aspects of the manufacturing,

Process including:

- Quality control
- Predictive maintenance
- Waste reduction
- Design optimization
- Process outomation

AI can replace the time - consuming conventional manufacturing techniques, thereby helping pharma companies to launch drugs in the market much faster and at cheaper rates as well. Apart from increasing their ROI substantially by limiting the human intervention in the manufacturing process, AI would also eliminate any scope for human error.

AI can be used for pharma quality control, reducing design time, inventory management, predictive maintenance, demand forecasting, logistics optimization and end to end visibility, has developed an AI powered process that has greatly enhanced its ability to find patterns in manufacturing deviation and to prevent their recurrence

AI also makes the entire manufacturing process more accurate through proper planning of the supply chain.

Marketing:

Given the fact that the pharmaceutical industry is a sale - driven sector, AI can be a handy tool in pharma marketing. With AI, pharma companies can explore and develop unique marketing strategies that promise high revenues and brand awareness.

AI can help to map the customer journey; thereby allowing companies to see which marketing technique led visitors to their site [lead conversion] and ultimately pushed the converted visitors to purchases from them. In this way, pharma companies can focus more on those marketing strategies that lead to most conversions and increase revenues

AI tools can analyze past marketing campaigns and compare the results to identify which campaigns remained the most profitable. This allows companies to design the present marketing campaigns according, while also reducing time and saving money further more, AI system can even accurately predict the success or failure rate of marketing campaigns.

Although AI is rapidly finding applications in the pharma industry the process of transformation is not without challenges usually, the current IT infrastructure of most pharma companies is based on legacy system that are not optimized AI

Advantages:

- More powerful and more useful computers
- New and improved interfaces
- Solving new problems
- Better handling of information
- Relives information overload
- Conversion of information into knowledge
- Quick genetic improvement
- Control of venereal diseases
- Maximum possible use of best sires
- Quick progeny testing
- Economical
- Correct breeding records
- Quality of semen
- Overcome size difference of animal
- Overcome physical inability of bull
- Easy transportation
- Cryopreservation of semen
- Early detection of undesirable genetic traits in the progeny
- Good programme for small holding dairy farmers

Disadvantages of AI

Cost: relatively more expensive in beef herds C\F dairy herds *may also incure costs associate with synchronization it this is used to induce oestrus and ovulation

Requires good management: To facilitate the process and to ensure cows are in their optimum condition to maximize pregnancy rates

Requires skills: to achieve satisfactory pregnancy rates

Increase the frequency undesirable traits with in population

Inappropriate bull selection can lead to dystocia, and introduction of physical traits that are undesirable

Can reduce reproductive performance in same circumstances

Poor semen quality, semen handling or AI technique can lead to poor reproductive performance and delay conception. Increased pregnancy loss if pregnant cows are inseminated.

- Need well trained inseminators
- Handling of frozen semen which is legerities quicken spreading venereal disease

- Selection and recording less careful hence spreading of it is nature undesirable live stock easy to extend
- When is skill of inseminator of AI in detecting pregnant female less hence happened abortion?

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EVALUATION OF TECOMELLA UNDULATA AND ARISTOLOCHIA BRACTEOLATA FOR HEPATOPROTECTIVE ACTIVITY IN RATS BY INDUCING AZATHIOPRINE

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ABSTRACT

The present study has been designed to evaluate the hepatoprotective activity of *ME-TUAB* on Azathioprine induced oxidative stress in rats. On the basis of our findings, it may be worthy to suggest that *ME-MKAB* has hepatoprotective activity against Azathioprine induced oxidative stress in rats by decreasing the oxidative stress biomarkers serum AST, serum ALT in liver .*ME-TUAB* has antioxidant effect by measuring antioxidant enzymes. There is an increase in superoxide dismutase in liver tissue when Azathioprine induced oxidative stress in rats.

Key words: Hepatotoxicity, ME-TUAB , serum AST, serum ALT etc.

INTRODUCTION

Hepatotoxicity may be predictable or unpredictable. Predictable reactions typically are dose related and occur which are exposed shortly after some threshold for toxicity is reached. Chemicals such as carbon tetrachloride, phosphorus, and chloroform fairly predictable hepatotoxins that are no longer used as drugs. Unpredictable hepatotoxic reactions occur without warning and are unrelated to dose. They have variable latency periods ranging from a few days to 12 months. Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years and have served humans well as valuable components of medicines, seasonings, beverages, cosmetics and dyes. Herbal medicine is based on the premise that plants contain natural substances that can promote health and alleviate illness. Today, we are witnessing a great deal of public interest in the use of herbal remedies. Further more many western drugs had their origin in plant extract. There are many herbs, which are predominantly used to treat cardiovascular problems, liver disorders, central

nervous system, digestive and metabolic disorders. Given their potential to produce significant therapeutic effect, they can be useful as drug or supplement in the treatment / management of various diseases. Herbal drugs or medicinal plants, their extracts and their isolated compound(s) have demonstrated spectrum of biological activities.

Materials

Trichloroacetic acid (TCA), nitro blue tetrazolium (NBT), reduced nicotinamide adenine dinucleotide (NADH), phenazinemethosulfate (PMS), ferrozine, glutathione reduced, batho phenanthroline sulfonate disodium salt, Thiobarbituric acid (TBA), and 5,5?-dithiobis-2- nitrobenzoic acid (DTNB) were obtained from Sisco Research Laboratories Pvt. Ltd, Mumbai, India. Hydrogen peroxide, ammonium iron (II) sulfatehexahydrate [(NH4)2Fe(SO4)26H2O], 1-chloro-2,4-dinitrobenzene (CDNB), chloramine-T, hydroxylamine hydrochloride, Dimethyl-4-aminobenzaldehyde, and 2,4-dinitro phenylhydrazine (DNPH) were obtained from Merck, Mumbai, India.

Ferritin was purchased from MP Biomedicals, USA. Streptomycin sulphate was obtained from HiMedia Laboratories Pvt. Ltd, Mumbai, India.

The standard oral iron-chelating drug, desirox, was obtained from Cipla Ltd, Kolkata, India.

EXPERIMENTAL ANIMALS:

Healthy swiss rats (Wistar strain) weight about 25-35 g were kept in individual polyethylene cages and maintained standard condition (12 h dark and 12 h light circle; 25±5°C; 40-60% humidity), and the animals were fed ad libitum with normal laboratory chow standard pellet diet, purchased from the sanzyme pvt. Limited, Hyderabad, India. The animals were allowed to acclimatize for 5 days before commencing the experiments. All the studies were conducted in accordance with the Animal Ethical Committee.

Plant Material:

The whole plant of Tecomella Undulata and aristolochia bracteolate were collected and authenticated by Dr. K. Madhava Chetty, Department of Botany, Sri Venkateswara University, Tirupathi.

Extraction of Plant Material

The plant fruits are separated dried and then grinded in to a coarse powder with the help of suitable grinder.

In this work the cold extraction process was done with the help of Ethanol. About 200 gms of powdered material was taken in a clean, flat bottomed glass container and soaked in 750 ml of Ethanol. The container with its contents were sealed and kept for period of 7 days accompanied by continuous shaking with the shaker.

The whole mixture then went under a coarse filtration by a piece of a clean, white cotton wool.The filtrates (Ethanol extract) obtained were evaporated using Rotary evaporator in a porcelain dish. They rendered a gummy concentrate of greenish black. The extract was kept in vacuum desecrator for 7 days.

Preliminary phyto chemical screening tests:

Freshly prepared extracts of plants were tested for the presence of phytochemical constituents by using reported methods.

Acute toxicity studies

The Acute oral toxicity test of the extracts was determined prior to the experimentation on animals according to the OECD (Organisation for Economic Co-operation and Development) guidelines no 423. Female Albino swiss rats (25-35g) were taken for the study and dosed once with 2000 mg/kg. The treated animals were monitored for 14 days to observe general clinical signs and symptoms as well as mortality. No mortality was observed till the end of the study revealing the 2000 mg/kg dose to be safe. Thus, 1/10 and 1/20 doses of 2000 mg/kg i.e. 200 mg/kg and 100 mg/kg were chosen for subsequent experimentation.

Induction Procedure

Induction of oxidative stress:

3mg/ml of Azathioprine solution was given through oral to all the group of animals and the samples were collected from the animals through retro-orbital plexus root and the liver, kidney bio marker parameters were estimated like SGOT, SGPT.

Experimental design:

The animals were assigned to five groups, each group containing six rats:

Group I: Rats were orally administered with normal saline(1.2ml/day) for 21days as the normal control.

Group II: Rats were orally administered with Azathioprine (20mg/kg) for 21days.

Group III: Rats were treated with Azathioprine (20mg/kg) and treated with Tecomella Undulata and Aristolochia BRACTEOLATA (100 mg/kg) by oral for 21days.

Group IV: Rats were treated with Azathioprine (20mg/kg) and treated with Tecomella Undulata and Aristolochia BRACTEOLATA (200 mg/kg) by oral for 21days.

Group V: Rats were treated with Azathioprine (20mg/kg) and treated with Ascorbic acid (10mg/kg) by oral for 21days.

Collection of blood samples and organs: Blood samples were collected from all the groups of animals 24hours after the 21st day of treatment through puncture of retro orbital plexus and were centrifuged at 3000 revolutions per minute (RPM)

for 15 minutes. Serum was separated and stored at -20^{0}C and used for estimating SGOT, SGPT, levels. Rats were killed by over anaesthesia. A midline abdominal incision is made to open up the abdominal cavity and access the liver. The liver are removed rapidly and washed with saline. Then fixed quickly in formaldehyde. The liver were homogenized in 0.25 M cold sucrose solution and centrifuged at 5000 rpm for five minutes. The supernatant which is store at -20^{0}C used for the quantitative estimation of superoxide dismutase within 48hours by using U.V. Spectrophotometry.

Estimation of Biochemical Parameters:

The following are the biochemical parameters estimated to evaluate the effect of the test materials against the experimentally induced oxidative stress in rats. They are SOD, ALT (SGPT), AST (SGOT).

Estimation of Superoxide Dismutase (SOD)

Superoxide dismutases are the enzymes that catalyze the dismutation of superoxide into oxygen and hydrogen peroxide. As such, they are an important antioxidant defense in nearly all cells exposed to oxygen. The enzyme superoxide dismutase (SOD) was determined in erythrocytes using photo oxidation method.

Principle: In this assay free radicals are generated by photo-oxidation of o-dianisidine sensitized by riboflavin. The photo oxidation of O-dianisidine involves a complex series of free radical chain reactions involving the superoxide anion ($O2^{-}$) as the propagating series (Figure-5.1). A general free radical scavenging compound has a inhibitory effect on this reaction leading to a decrease in the oxidized dianisidine measurable by UV/visible spectrophotometer. In contrast, any compound which specifically scavenges $O2^{-}$ will remove the O^{-} from step 3 and 4 in Figure-5.1 thus increasing the amount of oxidized dianisidine and hence will have an augmentary effect in this reaction. This assay can thus be used to determine whether a compound is a general, free radical or a scavenger specific for the super oxide anion. A substance with no free radical scavenging activity.

Photo-oxidation of o-dianisidine

1. $Rb + h\nu \longrightarrow Rb$
2. $Rb + DH2 \longrightarrow RbH + DH$
3. $RbH + O2 \longrightarrow Rb + O2^{-} + H^{+}$
4. $DH + O2^{-} + H^{+} \longrightarrow DH2 + O2$
5. $DH + DH \longrightarrow D + DH2$
6. $O2^{-} + O2^{-} \xrightarrow{SOD} H2O2\ Rb =$

$H\nu$ = energy of photon light

Rb = exited riboflavin

DH2 = o-dianisidine

$O2^{\cdot-}$ = Superoxide anion

D = product formed by photo oxidation measured at 460nm

Reagents Preparation:

For SOD estimation, 0.01M phosphate buffer (pH 7.5) was prepared.

Preparation of riboflavin solution:

Riboflavin (5mg) was weighed, and dissolved in 1lit of potassium phosphate buffer, to attain concentration of 1.3*10-5 M.

Preparation of o-dianisidine solution:

O-dianisidine solution was prepared by weighing of 122mg and dissolved in 50ml of ethanol.

Extraction Procedure: 3ml of packed blood cells were lysed by the addition of equal volume of cold deionized water. Hemoglobin was then precipitated by the addition of chloroform: ethanol (1.5:1). This was diluted with 500µl of water and centrifuged for 15 minutes at 3000 rpm. The supernatant containing SOD was taken for the measurement of its activity.

Assay Procedure: 0.88ml of riboflavin solution (1.3×10^{-5} M in 0.01M potassium phosphate buffer, pH 7.5) was added to 60µl of O-dianisidine solution (10^{-2} M in ethanol) and to this 100µl of clear separated SOD was added and optical density was measured at 460nm. Then the cuvette containing reaction mixture was transferred to the illuminating box, illuminated for 4min., and optical density was remeasured against blank containing ethanol in place of enzyme. The change in the optical density was determined. The SOD content was determined from the standard graph prepared using pure bovine SOD.

Serum Glutamate Pyruvate Transaminase (SGPT) Clinical significance:

Alanine transaminase present large amounts in liver, kidney, heart and skeletal tissues. It is also present in spleen, lungs, pancreas, brain and erythrocytes at lower concentration. Primary to liver damages and secondary to other causes result in elevated levels of GPT.

Principle:

SGPT converts L- Alanine and α- ketoglutarate to pyruvate and Glutamate. The pyruvate formed reacts with 2,4, Dinitrophenyl hydrazine to procedure a hydrazone derivative, which in an alkaline medium produces a brown coloured complex whose intensity is measured. The reaction does not obey Beer's law and hence a calibration curve is plotted using a pyruvate standard. The activity of SGPT (ALAT) is read off this calibration curve (Excel Diagnostics Pvt. Ltd, Hyd, India).

Reagents:

Enzyme Reagent

Buffer Solution

Preparation and stability of working reagent: Reconstitute one vial of Enzyme reagent with 10 ML Buffer solution, this working reagent is stable upto 30 days at 2-8°C.

Sample: Serum free hemolysis. SGPT is reported to be stable in serum for 3days at 2-8°C

Procedure:

Assay Procedure for SGPT:

Working Reagent	1ml
Sample	0.1ml

Mix and after a 1minute incubation, measure the change of optical dencity per minute (ΔOD/min). During 3 minutes.

Normal range: <40U/L.

Wave length: 340nm.

Calculation:

Activity (U/L) = ΔOD/min × 1768

Serum Glutamate Oxaloacetic Transaminase (SGOT) Clinical significance:

Aspertate transaminase is present in all human tissues of the body. It also presents large amounts in liver, kidneys, heart and skeletal muscles. Elevated levels are associated with liver disease or damage, myocardial infraction, muscular dystrophy. In myocardial infraction GOT levels increase after 3-8 hours of onset of attack and returns to normal in 4-6 weeks. The duration and extent of increase in levels is proportional to the severity of attack.

Principle:

SGOT converts L- Aspartate and α- ketoglutarate and Glutamate. The oxaloacetate formed reacts with 2,4, Dinitrophenyl hydrazine to procedure a hydrazone derivative, which in an alkaline medium produces a brown coloured complex whose intensity is measured. The reaction does not obey Beer's law and hence a calibration curve is plotted using a pyruvate standard. The activityf SGOT (AST) is read off this calibration curve (Excel Diagnostics Pvt, Ltd, Hyd, India).

Reagents:

Enzyme reagent
Buffer reagent

Preparation and stability of working reagent :

Reconstitute one vial of Enzyme reagent with 10 ML Buffer solution, this working reagent is stable upto 30 days at 2-8°C.

Sample: Serum free hemolysis. SGOT is reported to be stable in serum for 3days at 2-8°C

Procedure:

Assay procedure for SGOT

Working Reagent	1ml
Sample	0.1ml

Mix and after 1 minute incubation, measure the change of optical dencity per minute (ΔOD/min). During 3 minutes.

Statistical Analysis:

All the values were expressed as mean ±standard deviation (S.D). Statistical comparisons between different groups will be done by using one way analysis of variance (ANOVA) followed by dunnett's test. P <0.05 will be considered as statistically significant.

Results and Discussion

Me-Tuab = Mixed Extract of Tecomella Undulata And Aristolochia Bracteolata

Results

% yield of ethanol extract=(weight of extract)/(powder taken for extraction)×100

= 20 / 200 ×100 = 10%.

% Yield of the ME-TUAB is found to be **10.0**

TABLE-1

Results of Phytochemical Analysis Ethanolic Extract of ME-TUAB

Name of the Phytochemical Constituents	Ethanol extract
Saponins	-
Alkaloid	+
Glycoside	_
Reducing Sugar	+
Tannin	+
Flavonoid	++
Steroid	_
Anthocyanin	_
Phenol	+
Amino acid	_
Protein	++

+: Indicates the presence and -: Indicates the absence of phytoconstituents

In Vivo Studies Superoxide Dismutase:

Superoxide dismutase is class of enzyme that catalyze the dismutation of superoxide into oxygen and hydrogen peroxide. It is an important antioxidant defence in

nearly all cells exposed to oxygen. Superoxide dismutase activity was estimated in tissue homogenate with help of pure bovine superoxide dismutase standard. The values were shown in below table, and figure.

TABLE-1

Standard graph values of superoxide dismutase

SOD(µU)	Absorbance
1000	0.015
3000	0.017
10000	0.039
30000	0.062
100000	0.16

Figure-1

Standard graph of superoxide dismutase

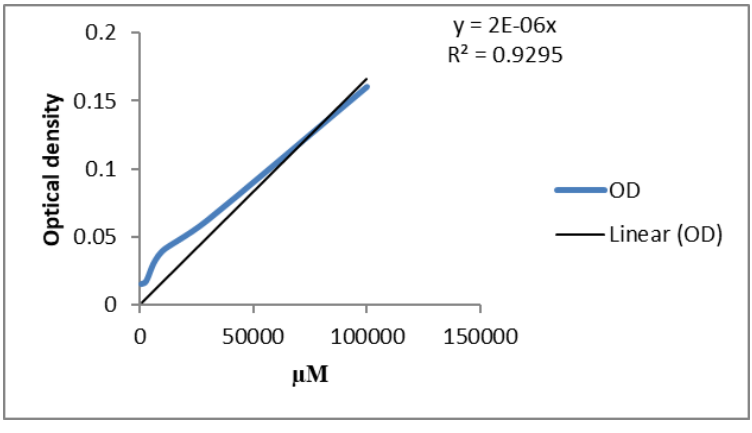

TABLE-2

Superoxide dismutase levels in liver tissue homogenate

Group	SOD(U/mg) in liver
Normal group	6.75±0.5
Toxic control (20mg/kg)	1.0±0.09
(ME-TUAB) low dose(100mg/kg)	3.1±0.3**
ME-TUAB high dose (200mg/kg)	4.3±0.31**
Standard ascorbic acid(10mg/kg)	5.4±0.21***

All the values are expressed as mean ±SD (n=6); ** indicates $p<0.001$, *** indicates $p<0.0001$ vs toxic control.

In this study, we found that 20mg/kg dose of azathioprine causes significant ($p<0.001$) decrease in superoxide dismutase levels. This reduction indicates that

oxidative stress and toxicity is produced with azathioprine. Post treatment with ME-TUAB at the dose of 100mg/kg and 200mg/kg after a 20mg/kg dose of azathioprine administration, shown a significant ($p<0.001$, $p<0.0001$) dose dependent increase in levels compared to toxic control group.

SERUM ALANINE AMINOTRANSFERASE (ALT):

TABLE-3

Effects of test compound on serum ALT levels in rats treated with Azathioprine

Group name	ALT (IU/L)
Normal group	132.65± 1.28
Toxic control (20mg/kg)	201.3± 22.5
ME-TUAB low dose(100mg/kg)	174.9± 9.71**
ME-TUAB high dose (200mg/kg)	150.2± 7.5***
Standard ascorbic acid(10mg/kg)	141.1 ± 8.8***

All the values of mean ±SD; (n= 6), ** indicates $p<0.001$, *** indicates $p<0.0001$ vs toxic control.

Azathioprine and test compound effects on ALT in rats from various groups shown in following figure. Measurements of ALT levels in AZP intoxicated female albino rats, and treated rats with ME-TUAB indicate the effect of treatment. The normal control group ALT level show 132.65±1.28IU/L. After AZP treatment, the ALT level is 201.3± 22.5IU/L. This AZP treated group ALT level was increased compared to the normal control group in 21days. After 21days treatment, the ME-TUAB low dose ALT level was (174.9± 9.71IU/L) decreased compared to the toxic control group has shown significance (**$p<0.001$) and at high dose ALT level was (150.2± 7.5IU/L) decreased compared to the toxic control group has shown significance (***$p<0.0001$). On treatment standard ascorbic acid serum ALT level 141.1 ± 8.8, has shown significant (***$p<0.0001$).

Serum Aspartate Aminotransferase (AST):

TABLE-4

Effects of test compound on serum AST levels in rats treated with Azathioprine

Group names	SAT(IU/L)
Normal group	140.7± 10.43
Toxic control (20mg/kg)	210.5± 11.5
ME-TUAB low dose(100mg/kg)	160.0± 10.3***
ME-TUAB high dose (200mg/kg)	150.3± 9.92***
Standard ascorbic acid(10mg/kg)	141.0± 8.06***

All the values of mean ±SD; n= 6, *** indicates $p<0.0001$ vs toxic control.

The above table shows the effect of test compound on serum AST levels in rats intoxicated with AZP. After 21days, the normal control group shows the AST level is 140.7±10.43IU/L. In AZP control group level is 210.5± 11.5IU/L, increased compared to the normal group. Treatment with ME-TUAB at low dose AST level was (160.0± 10.3IU/L) decreased compared to the toxic control group has shown significance (***p<0.0001) and at high dose AST level was (150.3± 9.92IU/L) decreased compared to the toxic control group has shown significance (***p<0.0001). On treatment standard ascorbic acid serum AST level 141.0± 8.06, has shown significant (***p<0.0001)

CONCLUSION

On the basis of our findings, it may be worthy to suggest that ME-TUAB has antioxidant activity against Azathioprine induced oxidative stress in rats by decreasing the oxidative stress biomarkers serum AST, serum ALT in liver ME-TUAB has antioxidant effect, elevated by measuring antioxidant enzymes. There is increase in superoxide dismutase in liver tissue in Azathioprine induced oxidative stress in rats.

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EVALUATION OF ANTIANXIETY AND ANTIDEPRESSANT ACTIVITY OF CASSIA OCCIDENTALIS LEAVES IN RODENT

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ABSTRACT

The present study has been designed to evaluate the antianxiety and antidepressant activity of the ethanolic and aqueous extract of cassia occidentalis leaves in rodents. The antianxiety activity in rodents was done by using elevated plus maze (EPM) and actophotometer and anti depressant activity by using FORCED swim test (FST) and tail suspension test on the basis of our findings, it may be worthy to suggest that the ethanolic extract of cassia occidentalis leaves possess more significant anti anxiety and anti depressant activity compared to aqueous extract.

Key words: EPM, FST, locomotor activity, ad libitium

INTRODUCTION

Depression is a heterogeneous disorder that affects person's mood, physical health and behavior. According to the world health report approximately 450 million people suffer from a mental or behavioral disorder, yet only a small minority of them receives even the most basic treatment, accounting for 12.3% of the global burden of the disease. it is expected to rise to 15% by 2020 in the search for new therapeutic products for the treatment of neurological disorders, medicinal plant research, worldwide, has progressed constantly, demonstrating the pharmacological effectiveness of different plant species in a variety of animal models. Patients with major depression have symptoms that reflect changes in their brain neurotransmitters, specifically nor epinephrine, serotonin and dopamine. a muscle relaxant is a drug which effects skeletal muscle function and decreases the muscle tone. the sedative action of a drug along with antidepressant action is useful in the treatment of depression associated with anxiety. Since all the synthetic drugs available for the treatment of depression have various adverse effects associated with problematic interactions, our aim was to explore the potential of plants in the management of depression.

MATERIALS AND METHODS:

Drugs and Chemicals: fluoxetine (crescent therapeutics limited, himachal pradesh), diazepam (ranbaxy laboratory limited.), ethanol (loba chemicals mumbai.).

Animals: Wistar rats (150-200 g) and swiss albino mice (18-22g) of either sex were procured from sainath agencies, uppal, hyderabad and acclimatized at the animal house of trinity college of pharmaceutical sciences, peddapalli. all the animals were maintained under standard conditions, that is room temperature 26 ± 1°c, relative humidity 45 - 55% and12:12 h light - dark cycle.

Plant Collection: The leaves of cassia occidentalis belonging to the family caesalpiniaceae were collected in the month of March 2020 from the local areas of peddapalli district, telangana, india.

Processing of sample leaves were dried in shade for 25 days and then powdered to get a coarse powder. This powder was stored in an air tight container and used for successive extraction.

Preparation of the extracts: Preparation of ethanolic extract of cassia occidentalis leaves the leaves of cassia occidentalis were shade dried and reduced to coarse powder. The standardized coarse powder was evenly packed in the soxhlet apparatus and subjected to ethanol extraction. The extract was filtered and filtrate was concentrated by vaccum distillation. Percentage yield of ethanolic extract was found to be 13.8%.

Preparation of aqueous extract of cassia occidentalis leaves the leaves of cassia occidentalis were powdered and extracted by maceration process by using 300ml of distilled water. In maceration procedure, total amount of 50g of powdered leaves were macerated for 3 days it was occasionally stirred at regular intervals of time. it was filtered and concentrated. Then it was dried by rotary evaporator. The percentage yield of aqueous extract was found to be 11.3%.

Phytochemical analysis both the ethanolic and aqueous extracts of cassia occidentalis were subjected to preliminary phytochemical screening.

Acute Toxicity Studies swiss albino mice of either sex (18-22 g weight) were used for acute oral toxicity study. The study was carried out as per the guidelines set by oecd and animals were observed for mortality and behavioral changes.

Antianxiety And Antidepressant Activity: The ethanolic and aqueous extracts of cassia occidentalis leaves were tested for antianxiety activity using elevated plus maze and actophotometer and antidepressant activity using FORCED swim test and tail suspension test.

Antianxiety Activity

Animals were divided into four (I - IV) groups.

Group I - control group received distilled water (1ml, p.o).

Group II - standard group received diazepam (5mg/kg i.p). Standard group received fluoxetine (10mg/kg i.p).

Group III - test group received ethanolic extract of cassia occidentalis (500mg/kg p.o).

Group IV - test group received aqueous extract of cassia occidentalis (500mg/kg p.o).

Antianxiety Activity

Elevated Plus Maze (EPM) Model

The apparatus comprises of two open arms (35x5cm) and two closed arms (30x5x15cm) that extend from a common central platform (5x5cm). The floor and walls of the closed arms are made of wood and painted black. The entire maze is elevated to a height of 50 cm above the ground level. Rats weighing (150 - 200gms) were housed in a pair of 10 days prior to the test in the apparatus. During this time the rats were handled by the investigator on alternate days to reduce stress. 30 min and 60min after oral administration of the drug treatment, each rat was placed in the center of the maze facing one of the enclosed arms. During five minutes session, number of entries into open arm and time spent in the open arm were noted. The procedure was conducted preferably in a sound attenuated environment.

Locomotor Activity

The locomotor activity can be easily studied with the help of actophotometer, the rats were grouped and treated with drugs. Each animal was placed individually in actophotometer and the basal activity score of all the animals were recorded for 10 mins after 30 and 60 min of drug treatment.

Antidepressant Activity

FORCED Swim Test Apparatus

For the determination of antidepressant activity, forced swim test (FST) protocol was employed. during the test, animals were individually placed in a glass cylinder (20 cm in height, 14 cm in diameter) filled with water up to a height of 10cm, at 25 ± 2°c. All animals were forced to swim for 5 min and the duration of immobility was observed and measured during the 5 min interval of the test. Immobility period was regarded as the time spent by the rats to float in water with no struggle and making only those movements necessary to keep its head above the water. in order to check the fitness level of each test animal, a pre-test was carried out 24 h before the FST by subjecting each test animal to a session of 15 min swimming.

Tail Suspension Test

Tail suspension test was performed based on the method prescribed. The mice were suspended 58cm above the floor by means of an adhesive tape, placed approximately 1cm from the tip of the tail. The total duration of immobility was

quantified during a test period of 5min. mice were considered immobile when they were completely remain motionless.

Statistical Analysis

The results were expressed as mean ± s.e.m. the differences were compared using one way analysis of variance (anova) and subsequently followed by bonferroni's test.

Results

Physical properties of the extracts

The colour, texture and the percentage yield of the ethanolic and aqueous extracts of leaves of cassia occidentalis were tabulated in table-1.

TABLE-1

Physical properties of cassia *occidentalis* leave extracts

plant part	type of extract	% yield	texture	colour
cassia occidentalis leaves	ethanolic extract	13.8	gummy	reddish brown
	aqueous extract	11.3	gummy	greenish

Phytochemical analysis after subjecting to screening, both the ethanolic and aqueous extracts of leaves of cassia occidentalis revealed the presence of flavonoids glycosides, tannins and saponins. The details of phytochemical constituents are given in table-2.

TABLE-2

Phytochemical analysis of cassia *occidentalis* leaves extracts.

phytochemicals	ethanolic extract	aqueous extract
flavonoids	+	+
glycosides	+	+
saponins	+	+
tannins	+	+
alkaloids	_	_

+ indicates presence; - indicates absence of the phytochemical constituents which were screened using various identification tests.

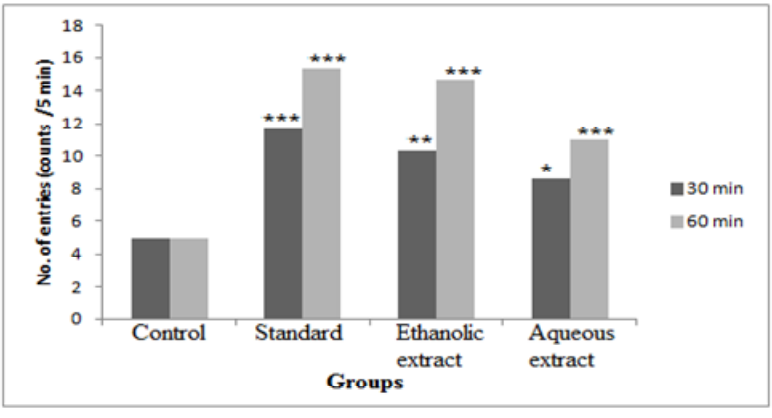
Acute toxicity: The acute toxicity study revealed the non toxic nature of all the extracts even at a higher dose of 4 g/kg body weight of mice for oral route of administration. for the present study the dose is being selected as 500mg/kg p.o.

Assessment of Antianxiety Activity

Elevated Plus-Maze Model

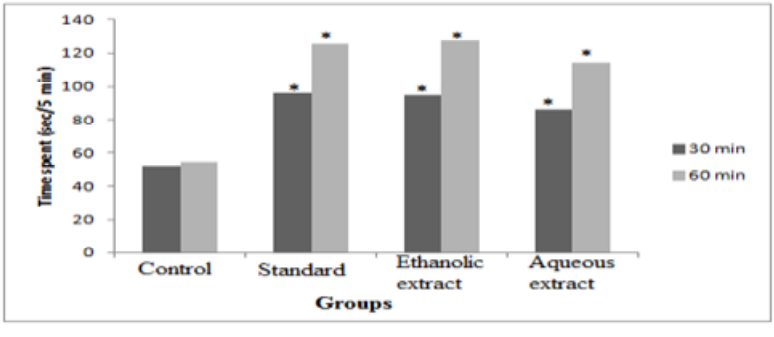
In elevated plus-maze test (EPM), the ethanolic and aqueous extracts of cassia occidentalis leaves at a dose of 500 mg/kg p.o. significantly increased the number

of entries and time spent into the open arm. The magnitude of the antianxiety effects 500mg/kg p.o. of ethanolic and aqueous extracts of cassia occidentalis was comparable to that of diazepam 5 mg/kg i.p. (Figure-1 and 2).



***p<0.001, **p<0.01 *p<0.1 when compared to control

Figure-1: Effect of ethanolic and aqueous extracts of *cassia occidentalis* leaves on number of entries (open arm) in elevated plus maze.



*p<0.001 when compared to control

Figure-2: Effect of ethanolic and aqueous extracts of cassia occidentalis leaves on time spent (open arm) in elevated plus maze.

Actophotometer

The average of basal activity scores in the control group after 30 and 60min of administration of ethanolic and aqueous extracts of cassia occidentalis leaves 500 mg/kg p.o. significantly reduced the locomotor activity. it may be due to the cns depressant property of the drug (table-3).

TABLE-3

effect of ethanolic and aqueous extracts of *cassia occidentalis* leaves on locomotor activity (actophotometer) in rats at different time intervals

group	treatment	photo cell count / 600 sec		% change in activity	
		30 min	60 min	30 min	60 min
i	Control (vehicle)	306±5.032	307.7±4.842	na	na
ii	diazepam (5mg/kg i.p.)	119*±1.528	84.67*±2.690	61.1(↓)	72.45(↓)
iii	ethanolic extract (500mg/kg p.o.)	145.7*±4.910	97.33*±1.856	52.4(↓)	68.35(↓)
iv	aqueous extract (500mg/kg p.o.)	167.3*±2.404	118.3*±1.453	45.32(↓)	61.53(↓)

Na- not applicable, *p<0.001 when compared to control

assessment of antidepressant activity

Forced Swim Test Apparatus

In Forced swim test apparatus, the ethanolic and aqueous extracts of leaves of cassia occidentalis at a dose of 500 mg/kg p.o. significantly decreased the immobility time. the magnitude of the antidepressant effects of 500 mg/kg p.o. of ethanolic and aqueous extracts of leaves of cassia occidentalis was comparable to that of fluoxetine 10 mg/kg i.p. (table-4).

Tail Suspension Test

In tail suspension test, the ethanolic and aqueous extracts of leaves of cassia occidentalis at a dose of 500 mg/kg p.o. significantly decreased the immobility time. the magnitude of the antidepressant effects of 500 mg/kg p.o. of ethanolic and aqueous leaves of cassia occidentalis was comparable to that of fluoxetine 10 mg/kg i.p. (table-5).

TABLE-4

effect of ethanolic and aqueous extracts of cassia occidentalis leaves on FORCED swim test in rats at different time intervals

group	treatment	duration of immobility sec / 5 min		% change in activity	
		30 min	60 min	30 min	60 min
i	control(vehicle)	186.7±4.410	188 ±4.583	na	na
ii	diazepam (5mg/kg i.p.)	88.33*±1.453	56.33*±1.453	52.6(↓)	70.0(↓)
iii	ethanolic extract (500mg/kg p.o.)	98.67*±2.082	68*±2.082	47.15(↓)	63.8(↓)
iv	aqueous extract (500mg/kg p.o.)	111.7*±3.383	83.3*±2.404	40.19(↓)	55.69(↓)

Na- not applicable, *p<0.001 when compared to control

TABLE-5

effect of ethanolic and aqueous extracts of cassia occidentalis leaves on tail suspension test in mice at different time intervals.

group	treatment	duration of immobility sec / 5 min		% change in activity	
		30 min	60 min	30 min	60 min
i	control(vehicle)	105.7±3.480	107.3 ±3.528	na	na
ii	diazepam (5mg/kg i.p.)	38.3*±1.764	36.6*±1.202	63.73(↓)	68.89(↓)
iii	ethanolic extract (500mg/kg p.o.)	35.33*±1.764	27.33*±2.906	66.57(↓)	74.55(↓)
iv	aqueous extract (500mg/kg p.o.)	58.67*±1.764	44.33*±2.33	44.50(↓)	58.99(↓)

Na- not applicable, *p<0.001 when compared to control

CONCLUSION:

From the results it was concluded that both ethanolic and aqueous extracts of leaves of *cassia occidentalis* showed antianxiety and anti-depressant activity. these findings suggest that the ethanolic extract of *cassia occidentalis* leaves posses more significant antianxiety and anti-depressant activity compared to aqueous extract.

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ASSESSMENT OF QUALITY OF LIFE IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

The present study is to assess the health related quality of life in chronic kidney disease patients in a tertiary care hospital using BI and SSQOL scales.The present study is a prospective observational study conducted for duration of 6 months at Chalmeda Institute of Medical Sciences. Data was collected from 110 participants using structured questionnaire. The patients were observed keenly during 3 visits, an additional 4th visit was done. The questionnaire was applied to all the participants on first visit.The Major objectiveof this study will be assessment of quality of life in CKD patient using BI and SSQOL scales. The Minor objective will be evaluation of factors leading for deterioration QOL and also to study the effect of patient counseling in improving their QOL in CKD patients. Based on the results obtained patients were counselled about lifestyle modifications and an attempt was made to improve the quality of life by reducing the misconceptions. On the 1st visit it was observed that 78% patients have worsened condition, 27% poor condition and only 5% good health condition. On 3rd visit, the QOL has drastically changes 54% patients were in good condition, 34% in poor and only 22% in worse condition. Results were obtained and analysed using Graphpad prism and MS Excel 2010.

INTRODUCTION

No factory can manufacture a product without generating any waste. This is true to our body which is a living cellular factory. Wastes are generated at regular intervals from the body. Kidneys are vital organs for survival, several factors like infections, injury, very high blood pressure, high blood sugar levels, restricted blood flow to kidneys or malfunctions lead to accumulation of waste, dangerous levels of fluids and electrolytes in the body, serious illness, or even death.Chronic kidney disease (CKD) is the intensifying and unalterable damage of the kidneys.

The term "chronic kidney disease" means subtle loss of kidney functions. It may lead to complications like hypertension, anemia, weak bones, poor nutritional health, and nerve damage. If the impairment is severe, the kidneys may stop working. This complication is known as kidney failure, or end-stage renal disease (ESRD). If kidneys fail to filter the blood, dialysis or a kidney transplant is required to survive.

Classification of CKD:

Chronic kidney failure refers to all or any 5 stages of kidney damage, from very mild damage in Stage 1 to complete renal failure in Stage 5. The stages of kidney disease are based on how well the kidneys can do their job to filter waste and additional fluid out of the blood. In the earlier stages of renal disease, kidneys are still able to filter out waste from the blood. Whereas in the later stages, kidneys may not be able to get rid of waste and may stop working altogether.

TABLE-1

STAGES OF CKD

CKD	**STAGE DESCRIPTION**	**eGFR (ml/min/1.73m2)**
STAGE 1	Kidney damage with normal renal functioning	90 or above
STAGE 2	Mild loss of renal functions	60-89
STAGE 3A	MILD TO MODERATE LOSS OF KIDNEY FUNCTIONING	45-59
STAGE 3B	Moderate to severe loss of renal functions	30-44
STAGE 4	Severe loss of renal functions	15-29
STAGE 5	Renal failure and need for kidney transplantation or dialysis	Below 15

METHODOLOGY

Study design: A prospective questionnaire based observational study.

Study population: 110

Study site: Chalmeda Anand Rao Institute of Medical Sciences in Karimnagar

Study period: 6 Months.

Inclusion Criteria:

- Patients who are willing to participate in the study.

- Patients diagnosed with CKD.
- Patients of age from 11 years to 90 years will be included.
- Patients of either gender.
- Patients with ESRD on maintenance hemodialysis.

Exclusion Criteria:

- Patients who are not willing to or unable to give consent to participate in study.
- Pregnant and pediatric patients.
- Patients with cancer and on chemotherapy, radiation therapy.

Data Sources:

- Patient case sheet
- Patient or representative interview form
- Data collection form

Data Collection:

- The study will be conducted at general medicine and nephrology inpatient departments by interviewing patients and/or their representatives according to the scales (BI and SSQOL) used.
- Patients data like demographic details, co-morbidities, stage of CKD, time taken to reach the hospital and physiotherapy management are obtained by direct patients interview and review of the patient medical records (case sheets) are documented in the data collection forms specially designed for the study.
- In this study QOL of inpatients diagnosed with CKD are assessed using the QOL scales and the patient's condition is followed up either by telephone contact or by direct contact in nephrology OP.
- Counseling will be given to the patient according to the patient data.

TABLE-2

By using Bi scale score patient will be interpreted as:

SCORE	INTERPRETATION
0-20	TOTAL DEPENDENCE/QOL
21-60	SEVERE DEPENDENCE/QOL
61-90	MODERATE DEPENDENCE/QOL
91-99	SLIGHT DEPENDENCE/QOL
100	INDEPENDENCE/QOL

SSQOL scale score represent patient's functionality, where high score represents high QOL and low score represents low QOL.

Study is divided into two phases:

PHASE-I:

In phase-I BI is applied and the patient's QOL score will be obtained which represents their dependency. Based on their knowledge about warning signs of CKD appropriate counseling will be given and based on patient's condition he/she is encouraged to continue medication or hemodialysis as prescribed. Each patient will be counseled in verbal form, in their native language Telugu and Hindi

PHASE-II:

In this phase, patients and/or their representatives will be interviewed by applying SSQOL and BI scales through telephonic contact after 3 months of discharge from the hospital. The obtained scores will be used to compare for changes on QOL with phase-I in case of BI and scores of both scales will be correlated in Phase-II.

STATISTICAL METHODS:

- MS Excel
- Graph Pad Prism-8
- One-way ANOVA followed by Tuckey's test.

RESULTS

A total of 110 CKD patients were screened during the study period out of which 78 were males and 32 were female patients.

Figure-1
GENDER DISTRIBUTION

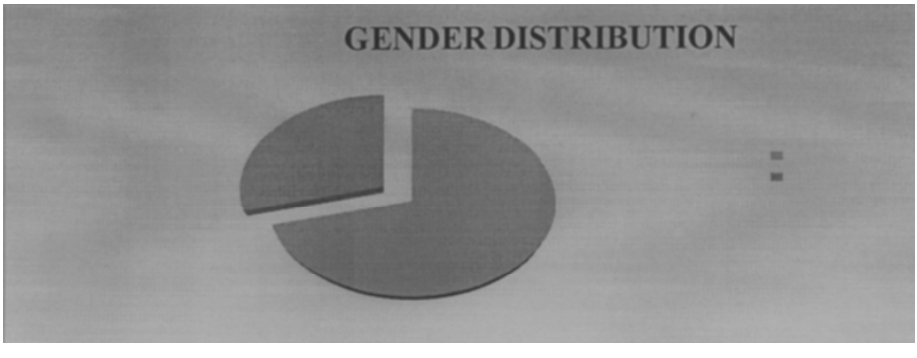


TABLE-3
AGE GROUP POPULATION

AGE	PATIENTS
11-30	14
31-50	51
51-70	38
71-90	7

Figure-2

AGE GROUP DISTRIBUTION

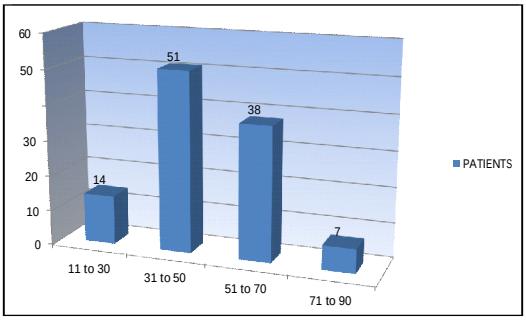


TABLE-4

QUALITY OF LIFE BASED ON VISITS

CONDITION	1ST VISIT	2ND VISIT	3RD VISIT
WORSEN	78	48	22
POOR	27	30	34
GOOD	5	32	54

Figure-3

QUALITY OF LIFE BASED ON VISITS

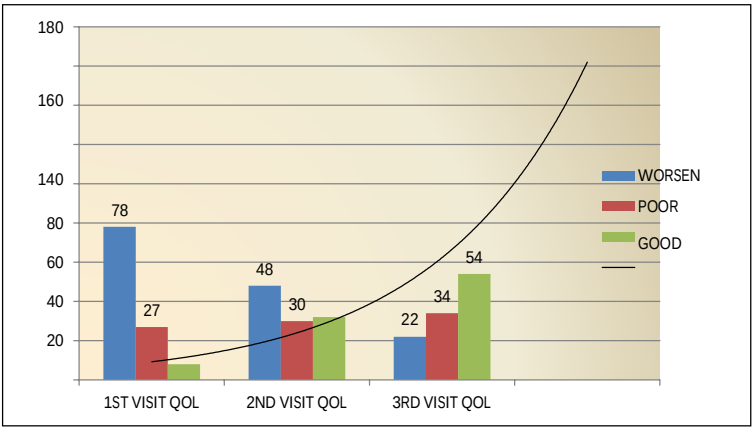


TABLE-5

4TH VISIT OF QOL

CONDITION	1ST VISIT
WORSEN	7
POOR	18
GOOD	31

Figure-4

4TH VISIT OF QOL

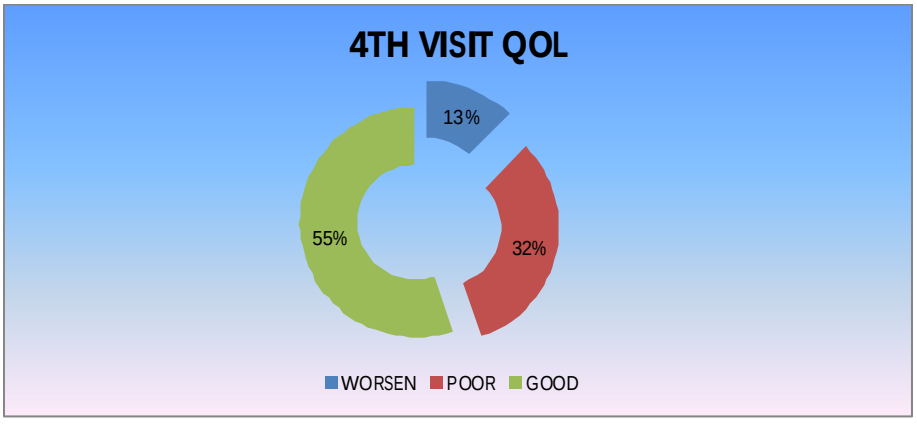


TABLE-6

AGE GROUP BASED ON COMORBIDITIES

AGE	HYPERTENSION	DIABETES MELLITUS	HTN+DM
11-30	6	0	0
31-50	20	1	6
51-70	12	1	11
71-90	1	0	3

Figure-5

AGE GROUP BASED ON COMORBIDITIES

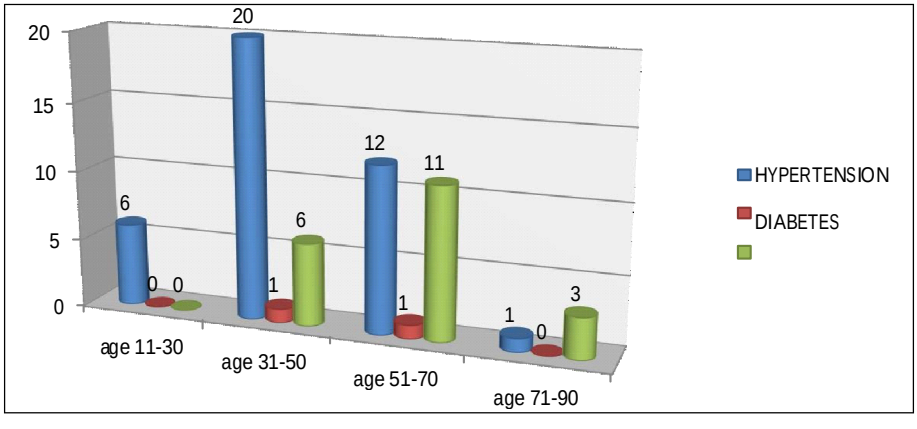


TABLE-7

BASED ON LITERACY

LITERATE	ILLITERATE
13	97

Figure-6

BASED ON LITERACY

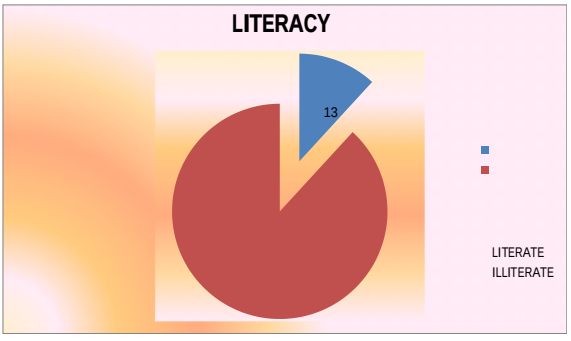


TABLE-8

COMPARISION OF LITERATE AND ILLITERATE BASED ON CONDITION AND VISITS

CONDITION	1ST LITERATE	1ST ILLITERATE	3RD LITERATE	3RD ILLITERATE
WORSEN	10	67	5****	18****
POOR	2	24	6****	28****
GOOD	1	6	2****	51****

In the above table P value is represented by ****

Figure-7

COMPARISION OF LITERATE AND ILLITERATE BASED ON CONDITION AND VISITS

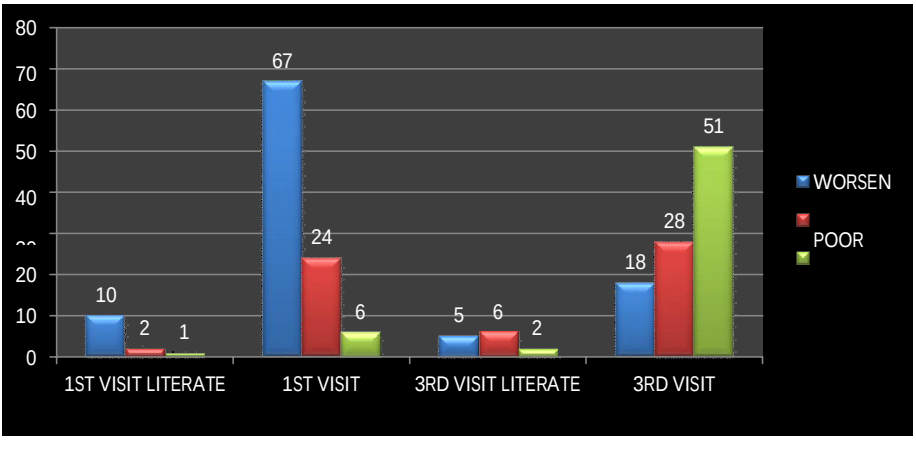


TABLE-9

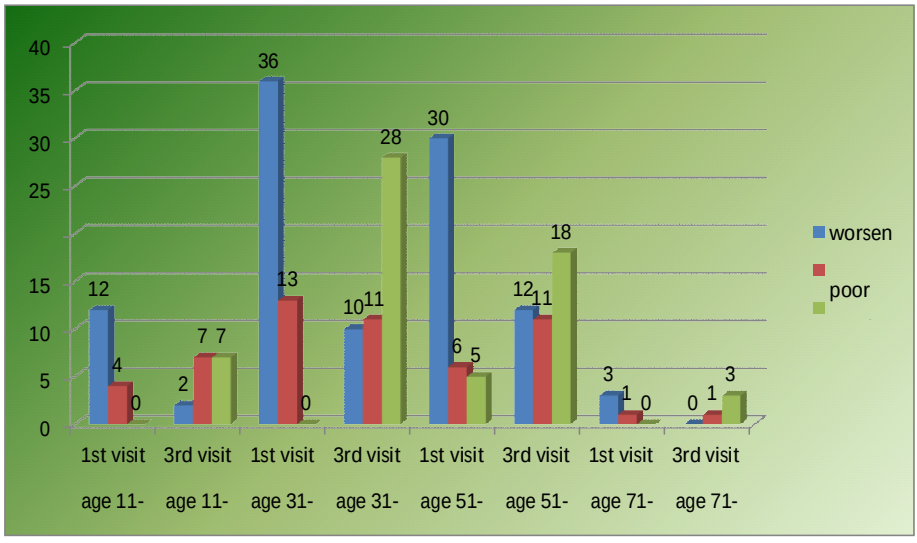
BASED ON AGE WISE IN 1ST AND 3RD VISIT

Condition	1st visit age group 11-30	3rd visit age group 11-30	1st visit age group 31-50	3rd visit age group 31-50	1st visit age group 51-70	3rd visit age group 51-70	1st visit age group 71-90	3rd visit age group 71-90
Worsen	12	2****	36	10****	30	12****	3	0****
Poor	4	7****	13	11****	6	11****	1	1****
Good	0	7****	0	28****	5	18****	0	3****

P Value is represented by ****

Figure-8

BASED ON AGE WISE IN 1ST AND 3RD VISIT



DISCUSSION

Chronic kidney disease is also known as chronic renal failure, where there is a gradual loss of kidney functions and degeneration of nephrons over a period of time. On reaching the end stage of CKD, the process of filtration is carried out by haemodialysis machine.

A total of 110 patients were included in the study, at nephrology ward who are in the last stages of CKD (i.e., hemodialysis patients).

This study includes 78 males and 32 females. The number of males is more when compared to females in this study.

In this study design, the patients of age 11-30 were 14, 31-50 years of age were 51, 51-70 years of age were 38 and older age i.e., was 7. Majority of patients were found to be between the ages of 31-50.

The study carried out by Mandoorah *et. al.,* co morbidity disease conditions had a negative effect, vascular diseases was associated with dyslipidemia and diabetes mellitus. In the present study, the past medical history of the hypertensive patients was found to be 38.4% in which 5.7% were between the age of 11-30 years, 20.2% from 31-50 years, 12.1% were of the age 51-70 and 0.4% was between 71-90 years of age. Out of 2.6% diabetic patients, 0.3% patients were of age between 11-30 years, 1.4% was of age from 31-50 years and 0.9% of patients were from 51-70 years. Patients with both diabetes and hypertension was found to be 19.3% of which 6.3%from 31-50 years of age, 10.7% of age between 51-70 years and 3.2% was from 71-90 years. The results obtained by the present study were similar to the results from the study of Mandoorah *et.al.*

The study of Abraham *et al.,* revealed remarkable difference in the QOL of hemodialysis patients in the test group during the 1st and 2nd visits whereas the control group showed no or slight change. There was an increase in the overall QOL of test group when compared to control group. During the current study 3 visits were done to determine the QOL of patients based on condition (worsen, poor and good). During the first visit of the study, the conditions of the patients were observed as worsen in 78 patients, poor in 27 patients and good in 5 patients. In second visit of the observational study, patient with worsen condition were 48 patients, poor in 30 patients and good in 32 patients. In the final visit the patients with worsen condition was found to be 22, poor in 34 patients and good in 54 patients. An additional visit was done in 56 patients, in which 7 patients were in worsen condition, followed by 18 patients in poor condition and 31 were in good condition. A good improvement was observed in the final of the study, which was similar to the observations of Abraham *et.al,* studies.

The present study was also carried out on the basis of literacy. 20.6% were literate and 79.4% were illiterate. The condition of patients was also calculated based on the literacy rate which was observed in 1st and 3rd visit. During first visit the patients, who are literate in which 10 patients in worsen condition, 2 in poor state and 1 patient was in good condition. Followed by illiterates, out of which 67 patients in worsen state, 24 in poor and 6 in good condition. During the 3rd visit of observational study who are literate 5 in worsen state, 6 poor and 2 in good condition, whereas illiterates in which 18 patients in worsen condition, 28 patients in poor and 51 patients in good conditions. The condition of patient was found improvement from 1st to 3rd visit in both literates and illiterates. According to Mandoorah *et. al.,* study suggests that age, gender, education and comorbidity conditions have poor impact on QOL in CKD patients.

With the observations during the study, the different age group considerations were taken to determine the condition of patients during the 1st and 3rd visits. In 1st visit patients with age of 11-30 years 12 were in worsen, 4 patients in poor and 0 in good condition. The patients with age of 31-50 years were 36 patients were in

worsen, 13 patients in poor, 0 patients in good condition. The patients of age group 51-70 years, 30 patients in worsen 6 patients in poor and 5 patients in good condition. The patients of age 71-90 were 3 patients in worsen, 1 patient in poor and 0 in good condition. During the 3rd visit, patients with age of 11-30 years 2 were in worsen 7 patients in poor and 7 in good condition. The patients with age of 31-50 years were 10 patients were in worsen, 11 patients in poor, 28 patients in good condition. The patients of age group 51-70 years, 12 patients in worsen 11 patients in poor and 18 patients in good condition. The patients of age 71-90 were 0 patients in worsen, 1 patient in poor and 3 in good condition.

CONCLUSION

The prevalence and incidence of CKD is increasing at fast pace throughout the world. Management of CKD is very demanding presently. The present study mainly focus on the improvement of quality of life in CKD patients. The core reason of the study is to decrease the disease burden and to address the rural and urban inequality among the literates and illiterates in CKD interventions.

In this study majority of the patients were of age group between 31-50 years (51 patients). Female patients were less than male patients. It was observed that Hypertension has severe and predominant effect on CKD. The quality of life has drastically improved from 1st visit to 3rd visit.

The condition based on literacy rate, different age group distribution was taken into consideration to state the condition of the patient.

Patient counselling must be done to improve the quality of life. The study suggests that, patient counselling has statistically and clinically improved the QOL in CKD patients. It also improves the awareness and removes the misconception about CKD.

CKD is a progressive and degenerative disease, upon negligence it may lead to death. Early detection, treatment and prevention are the only ways to improve the quality of life in chronic kidney disease patients.

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CHAITANYA

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