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05/06/2018

To

The Principal,
JKK Munirajah Institute of Health Sciences College of Pharmacy,
TN Palayam.

Sub: Request for Funding for Research Project – Reg.

Dear Sir,

Greetings. I am writing to express our strong interest in initiating a research collaboration with JKK Munirajah Institute of Health Sciences College of Pharmacy, a respected institution known for its contributions to pharmaceutical research and education.

At Medreich Limited., we are committed to advancing knowledge and innovation in the field of pharmaceuticals. We believe that collaborative research with your institution presents a valuable opportunity to leverage your expertise and resources for a mutually beneficial project.

We are particularly interested in exploring a research project in the area of an Evaluation of Clopidogrel Bisulphate, which aligns with our strategic goals and has the potential to bring meaningful contributions to the pharmaceutical industry. We are confident that the combined efforts of our organization and your esteemed institution can lead to significant advancements in this field.

To facilitate this collaboration, we kindly request your consideration for a research partnership and potential financial support for the proposed project. We are fully committed to providing the necessary financial resources and any additional support required to ensure the successful execution of the research endeavor.

Understanding that every collaboration comes with unique terms and conditions, we are open to discussing and accommodating any specific requirements or standards set by JKK Munirajah Institute of Health Sciences College of Pharmacy. Additionally, we commit to adhering to all reporting and accountability guidelines throughout the research process.

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

JKK Munirajah Institutes of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt.

Medreich Limited
Phone: +91 80 4048 7100 Fax: +91 80 2547 4741
Bangalore Rural Dist. 562 114, INDIA. Phone: ++91 80 4048 7395 / 4048 7396
E-mail: info@medreich.com, Website: www.medreich.com

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Enclosed with this letter is a comprehensive project proposal that outlines the project's objectives, methodologies, expected outcomes, and budget requirements. We kindly ask for your review of the proposal, and we would greatly appreciate the opportunity to engage in further discussions about the project's implementation.

We genuinely believe that a collaborative effort between our organization and your institution has the potential to drive impactful change in the pharmaceutical landscape. We are excited about the prospect of working closely with JKK Munirajah Institute of Health Sciences College of Pharmacy and contributing to the advancement of pharmaceutical research.

To further our discussions and provide clarity for project planning, we kindly request the following details:

Budget Details: We would appreciate a comprehensive breakdown of the estimated budget required for the proposed research project. This should include expenses for equipment, materials, personnel, and any other relevant costs.

Faculty Details: Information regarding the faculty members who will be involved in the project, including their qualifications, expertise, and experience in related fields. We are particularly interested in identifying the Principal Investigator for this project.

Understanding that every collaboration may have unique terms and conditions, we are open to discussing and adhering to any specific requirements or standards set by JKK Munirajah Institute of Health Sciences College of Pharmacy. Additionally, we reiterate our pledge to maintain the highest standards of reporting and accountability throughout the research process.

Thank you for considering our proposal, and we eagerly await your response. Please feel free to reach out to us at your convenience to initiate discussions and explore the potential of this partnership.

Thanking you

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

JKK Munirajah Institutes of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt.

Sincerely,

05/06/18

JKK MUNIRAJAHH INSTITUTE OF HEALTH SCIENCES
COLLEGE OF PHARMACY

(Approved by AICTE & Pharmacy Council of India - New Delhi, Affiliated to The Tamilnadu Dr. M.G.R.Medical University, Chennai)

Thookanaickenpalayam (PO), Gobichettipalayam (TK), Erode (DT) - 638506, Tamilnadu.

Dr. J.K.K.MUNIRAJAH, M.Tech.,(Bolton)
Chairman & Managing Trustee

Dr. P. MOHANRAJ, M.Pharm.,Ph.D.,
Principal

08.06.2018

To

Medreich Limited,
12/8, Saraswati Ammal Street,
Maruthi Sevanagar,
Bangalore - 560 033.

Subject: Response to Your Request for a Second Research Project Collaboration – Reg.

Dear Sir/Madam,

Warm Greetings. On behalf of JKK Munirajah Institute of Health Sciences College of Pharmacy, I extend my warm greetings and express our sincere appreciation for your continued interest in collaborating on research initiatives with our institution.

We are delighted to receive your request for a second research project, and I would like to convey our enthusiasm for the prospect of furthering our fruitful collaboration. It is heartening to know that our previous joint research efforts have yielded positive outcomes and left a lasting impression on your esteemed organization.

The proposal for the proposed second research project has been received with great interest, and we are excited about the possibility of embarking on another impactful research journey together. As we begin our discussions and preparations for this endeavour, please accept our gratitude for your willingness to support this initiative.

In response to your request for budget and faculty details, we are committed to providing the necessary information promptly. We understand the importance of clarity and transparency in project planning and will ensure that you receive a comprehensive breakdown of the estimated budget and details regarding the faculty members, including the Principal Investigator, who will be involved in this project.

Our team at JKK Munirajah Institute of Health Sciences College of Pharmacy is dedicated to making this collaboration a success. We are confident that by working closely together and combining our expertise and resources, we can achieve remarkable outcomes in this research project.

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (TK), Erode (Dt) - 638 506

JKK Munirajah Institutes of Health Sciences College of Pharmacy T.N.Palayam Erode Dt.

04285 - 262220 jkkmihscp@gmail.com www.jkkmihscp.org

JKK MUNIRAJAHH INSTITUTE OF HEALTH SCIENCES
COLLEGE OF PHARMACY

(Approved by AICTE & Pharmacy Council of India - New Delhi, Affiliated to The Tamilnadu Dr. M.G.R.Medical University, Chennai)

Thookanaickenpalayam (PO), Gobichettipalayam (TK), Erode (DT) - 638506, Tamilnadu.

Dr. J.K.K.MUNIRAJAH, M.Tech.,(Bolton)
Chairman & Managing Trustee

Dr. P. MOHANRAJ, M.Pharm.,Ph.D.,
Principal

I propose that we schedule a meeting at your earliest convenience to discuss the specifics of the project, including budget details, faculty involvement, project timelines, and any other relevant aspects. Your insights and contributions will be invaluable as we move forward.

Once again, thank you for your continued interest in collaborating with us. We look forward to a productive and mutually beneficial research endeavour and are excited about the opportunity to contribute to the advancement of knowledge in our field.

Please feel free to contact me directly at **principal@jkkmihscp.org** to coordinate our meeting or to address any further inquiries you may have.

BUDGET AND FACULTY DETAILS

Project Title: Formulation and Evaluation of Clopidogrel Bisulphate loaded Ethylcellulose Microspheres

Project Duration: 6 months

Project Budget Estimation:

S. No	Detail of Expenditure	Amount in lakhs
1.	Laboratory Equipment and Supplies (Glassware, Instruments)	0.25
2.	Raw Materials (Clopidogrel Bisulphate)	0.35
3.	Research Personnel (Salaries, Stipends)	0.40
4.	Chemicals and Reagents	0.20
5.	Data Analysis Software and Tools	0.20
6.	Miscellaneous Expenses	0.10
	Total Budget (Including Buffer)	**1.5 lakhs**

T.N.Palayam Erode Dt.

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

JKK MUNIRAJAHH INSTITUTE OF HEALTH SCIENCES
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Thookanaickenpalayam (PO), Gobichettipalayam (TK), Erode (DT) - 638506, Tamilnadu.

Dr. J.K.K.MUNIRAJAH, M.Tech.,(Bolton)
Chairman & Managing Trustee

Dr. P. MOHANRAJ, M.Pharm.,Ph.D.,
Principal

Details of the Project Team:

Principal Investigator (PI):	Mr. S. SELVARAJ Associate Professor, Department of Pharmaceutics, JKKMIHSCP.
Co-Investigators:	Mrs. K. ANUSUYA Assistant Professor, Department of Pharmaceutics, JKKMIHSCP. Mrs. M. ABIRAMI Assistant Professor, Department of Pharmaceutics, JKKMIHSCP.

Kindly permit the above faculty members to execute the above research work. We are expecting a positive reply from your end.

Thank you

Yours Sincerely,

Principal
JKK Munirajah Institute of Health Science
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

JKK Munirajah Institutes of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt.

SANCTION ORDER

Date: 14.06.2018

Medreich Limited is operating a programme for supporting research projects in Colleges and University Departments. MR. S. SELVARAJ, Associate Professor, Department of Pharmaceutics, JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N Palayam, Erode, has submitted a research project with Mrs. K. ANUSUYA, Assistant Professor, Department of Pharmaceutics, and Mrs. M. ABIRAMI, Assistant Professor, Department of Pharmaceutics, as co-investigator for project assistance.

Medreich Limited has sanctioned **Rs. 1,50,000/-** (Rupees One lakh fifty thousand only) for the conduct of the above said project. The PI has submitted the final report and financial statements after completion of the project.

Medreich Limited has verified the submitted documents and is pleased to accord sanction for the release of Rs. 1,50,000 /- (Rupees One lakh fifty thousand only) towards financial assistance for the research project titled "Formulation and Evaluation of Clopidogrel Bisulphate loadded Ethylcellulose Microspheres" submitted by MR. S. SELVARAJ, Associate professor, Department of Pharmaceutics, JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N Palayam.

Thanking you

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

Sincerely

14/06/18

Copy to:

Principal,
JKK Munirajah Institute of Health Sciences College of Pharmacy,
T.N. Palayam.

JKK MUNIRAJAHH INSTITUTE OF HEALTH SCIENCES
COLLEGE OF PHARMACY

(Approved by AICTE & Pharmacy Council of India - New Delhi, Affiliated to The Tamilnadu Dr. M.G.R.Medical University, Chennai)

Thookanaickenpalayam (PO), Gobichettipalayam (TK), Erode (DT) - 638506, Tamilnadu.

Dr. J.K.K.MUNIRAJAH, M.Tech.,(Bolton)
Chairman & Managing Trustee

Dr. P. MOHANRAJ, M.Pharm.,Ph.D.,
Principal

PROJECT COMPLETION REPORT

Date: 17/12/2018

To

Medreich Limited,
12/8, Saraswati Ammal Street,
Maruthi Sevanagar,
Bangalore - 560 033.

Subject: Research Project Completion Report – Reg.

Respected Sir/Madam,

With respect to the above-mentioned subject I, MR. S. SELVARAJ, Principal Investigator, have completed research project, sanctioned under Student Project Scheme for the year 2018-2019.

The audit for the research project has been completed. The details of the completed research project are as follows:

Title of the project: Formulation and Evaluation of Clopidogrel Bisulphate loaded Ethylcellulose Microspheres.

Project Duration: 14.06.2018 – 14.12.2018

Thanking You

Yours sincerely,

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

JKK Munirajah Institutes of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt.

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

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Date: 03.01.2019

To

The Principal,
JKK Munirajah Institute of Health Sciences College of Pharmacy,
T.N. Palayam.

LETTER OF APPRECIATION

Dear Sir,

We would like to take opportunity to thank you for your time spending and valuable Research work to our organization. Once again, we extend our sincere gratitude to you and your team for your efforts in making the "Formulation and Evaluation of Clopidogrel Bisulphate loadded Ethylcellulose Microspheres" a resounding success.

We look forward to the continuation of our successful partnership and to exploring new opportunities for collaboration.

Thank you

JKK Munirajah Institute of Health Sciences College of Pharmacy T.N.Palayam Erode Dt.

Principal
JKK Munirajah Institute of Health Science
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

Sincerely,

03/01/19

JKK MUNIRAJAHH INSTITUTE OF HEALTH SCIENCES
COLLEGE OF PHARMACY

(Approved by AICTE & Pharmacy Council of India - New Delhi, Affiliated to The Tamilnadu Dr. M.G.R.Medical University, Chennai)

Thookanaickenpalayam (PO), Gobichettipalayam (TK), Erode (DT) - 638506, Tamilnadu.

Dr. J.K.K.MUNIRAJAH, M.Tech.,(Bolton)
Chairman & Managing Trustee

Dr. P. MOHANRAJ, M.Pharm.,Ph.D.,
Principal

UTILIZATION CERTIFICATE

Certified that the grant of Rs. 1,50,000 /- (Rupees One lakh fifty thousand only) received from the Medreich Limited, Bangalore, under the scheme of support for Research Project entitled "Formulation and Evaluation of Clopidogrel Bisulphate loaded Ethylcellulose Microspheres" dated 14 June 2018 has been fully utilized for the purpose for which it was sanctioned and in accordance with the terms and conditions laid down by the Medreich Limited, Bangalore.

Date: 14/12/2018

Place: T.N. palayam

Name and Signature of Principal

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

(S. SELVARAJ)

Name and Signature of Principal investigator

JKK Munirajah Institutes of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt.

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

FORMULATION AND EVALUATION OF CLOPIDOGREL BISULPHATE LOADED ETHYLCELLULOSE MICROSPHERES

PRINCIPAL INVESTIGATOR

Mr. S. SELVARAJ, M. Pharm.,

Associate Professor

Department of Pharamaceutics

CO-INVESTIGATORS

Mrs. K. ANUSUYA, M. Pharm.,

Assistant Professor,

Department of Pharmaceutics

Mrs. M. ABIRAMI, M. Pharm.,

Assistant Professor,

Department of Pharmaceutics

T.N.Palayam Erode Dt

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

DECEMBER 2018

JKK MUNIRAJAH INSTITUTE OF HEALTH SCIENCES COLLEGE OF PHARMACY, T.N- PALAYAM-638506, GOBI (TK), ERODE (DT),TAMILNADU.

CERTIFICATE

This is to certify that the Research entitled **"FORMULATION AND EVALUATION OF CLOPIDOGREL BISULPHATE LOADED ETHYLCELLULOSE MICROSPHERES"** submitted to The **Medreich Limited, Bangalore,** is the bonafide project work carried out in the Department of Pharmaceutics , JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N-Palayam, Gobi, Erode, Under the guidance of **Mr. S. SELVARAJ, M. Pharm., Associate Professor, Department of Pharmaceutics,** JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N Palayam,Gobi, Erode. During the academic year 2018-2019.

Place: T.N-Palayam

Date: 14/12/2018

DR. P. MOHANRAJ, M. Pharm, Ph. D.,

PRINCIPAL

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

T.N.Palayam
Erode Dt.

DECLARATION

This is to certify that the Research entitled **"FORMULATION AND EVALUATION OF CLOPIDOGREL BISULPHATE LOADED ETHYLCELLULOSE MICROSPHERES"** submitted to The **Medreich Limited, Bangalore,** is the bonafide project work carried out in the Department of Pharmaceutics , JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N-Palayam, Gobi, Erode, Under the guidance of **Mr. S. SELVARAJ, M. Pharm., Associate Professor, Department of Pharmaceutics,** JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N Palayam, Gobi, Erode. During the academic year 2018-2019.

Place: T.N-Palayam
Date: 14/12/2018

Mr. S. SELVARAJ, M. Pharm.,
Principal Investigator

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

Mrs. K. ANUSUYA, M. Pharm.,
Co-Investigator

JKK Munirajah Institute of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt.

Mrs. M. ABIRAMI, M. Pharm.,
Co-Investigator

DECLARATION

The research work emboided in this work entitled "Formulation and Evaluation of Clopidogrel Bisulphate Loaded Ethylcellulose Microspheres" was carried out by us under the direct supervision of Mr. S. Selvaraj, M. Pharm., Associate Professor, Department of Pharmaceutics, JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N Palayam, Gobi.

The Project submitted to the **Medreich Limited, Bangalore,** during the academic year 2018-2019.

JKK Munirajah Institutes of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

ACKNOWLEDGEMENT

First and for most we express our heartful sense of gratitude and faithfulnessto God 'grace and our family members, which has enabled us to finish our project work successfully.

With the blessing of our Founder chairman Dr. J.K.K Munirajah, M.Tech, (Bolton). D.Litt., and Secretary Mrs. Kasthuripriya Kirupakarmurali, M.B.A.,

J.K.K Munirajah Institute of Health Sciences College of Pharmacy, T.N-Palayam, Gobi, Erode for providing all the facilities to carry out this work.

Our sincere gratitude to our beloved sir, DR. P. MOHANRAJ, M. Pharm, Ph.D.,Principal and Head of the Department of Pharmaceutical Chemistry, J.K.K Munirajah Institute of Health Sciences College of Pharmacy, T.N Palayam, Gobi, Erode for his kindly support for our project work and for his encouragement and alsoproviding all facilities in this Institute to the fullest possible extent enabling us to complete this work.

With the immense pleasure and pride, we would to take opportunity in expressing our deep sense of gratitude to our beloved guide Mr. S. SELVARAJ, M. Pharm., Associate Professor, Department of Pharamaceutics J.K.K Munirajah Institute of Health Sciences College of Pharmacy, T.N Palayam, Gobi, Erode under whose active guidance, innovate ideas, constant inspiration and encouragement of the work entitled "Formulation and Evaluation of Clopidogrel Bisulphate Loaded Ethylcellulose Microspheres" has been carried out.

We also express our grateful thanks to all the teaching and non-teaching staff members of J.K.K Munirajah Institute of Health Sciences College of Pharmacy for their valuable advice and cooperation.

We express our heartful gratitude to the algmighty, for giving us the right way to achieve the best of our project.

We would like to give sincere thanks to our classmates for their timely help and co-operation.

JKK Munirajah Institute of Health Sciences College of Pharmacy T.N.Palayam Erode Dt.

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

We also extend our thanks to all staff members of Department of Pharmaceutical Biotechnology, Pharmaceutical Chemistry, Pharmacognosy, Pharmaceutics and Pharmacology for their co-operation.

We would like to Thank, Medreich Limited, Bangalore to give a Financial and moral support to completion of the project being a successful manner on the duration 2018-2019.

Finally yet importantly, great thanks from the heart to our beloved MOTHER and FATHER. They are our living god, as who guided us in the rightful way to achieve all our activities. They gave the incredible effort to become a successful for bright future in this world. Thanks a lot, to my parents.

JKK Munirajah Institutes of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt.

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

INTRODUCTION

Drug delivery system target the specific body site which having enormous impact on the healthcare system. The ideal drug delivery system delivers the drug at rate decided by need of body throughout the period of treatment therefore carrier technology find out the intelligent approach for drug delivery by coupling the drug to carrier particles example ,microspheres, nanoparticles and liposomes. Oral route of drug administration is most preferable route for taking medication. Microspheres are small spherical particles which having diameter lum to 100um.they are free flowing particles which are consisting of proteins or synthetic polymers this are biodegradable in nature.

There are two types of microspheres

1) Microcapsule-entrapped substance distinctly surrounded by distinct capsule wall.

2) Micromatricess-entrapped substance is dispersed throughout the matrix.

Controlled drug delivery system overcome the problems of conventional therapy andenhance therapeutic efficacy of given drug to obtain maximum therapeutic efficacy it becomesnecessary to deliver the agent. Microspheres are used in development of new drug deliverysystem for controlled release of drug

Advantages of microspheres

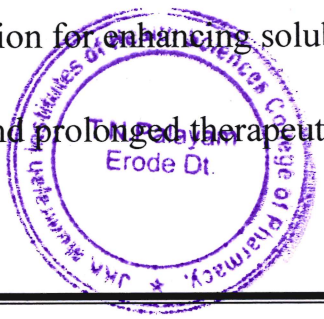
1. They provide protection before after administration for unstable drug.

2. They reduced concentration of drug at site other than the tissue or the target organ.

3. Decrease dose and toxicity.

4. Particle size reduction for enhancing solubility of poorly soluble drugs.

5. Provide constant and prolonged therapeutic effect.



Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

Types of microspheres

1. Bioadhesive microspheres

2. Magnetic microspheres

3. Floating microspheres

4. Radioactive microspheres

5. Polymeric microspheres

i) Biodegradable polymeric microspheres

ii) Synthetic polymeric microspheres

1. Bioadhesive microspheres

The sticking of drug to membrane by using the sticking property can be defined Adhesion of water-soluble polymers. This type of microspheres exhibit a prolonged residence time at the site of application. Adhesion of the drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc.,

2. Magnetic microspheres

This type of delivery system is very much important for localizes the drug to the disease site, site. In which larger amount of freely circulating drug can be replaced by small amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field.

3. Floating microspheres

In floating microspheres, the bulk density is less than the gastric fluid therefore it remains buoyant in stomach without affecting on gastric emptying rate. Drug is released

T.N.Palayam Erode Dt.
Principal
JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N.Palayam, Kavuthipalayam (Pk), Erode (Dt) - 638 506

slowly at the desired rate of the site. It also reduces chances of striking and dose dumping Produces.

4. Radioactive microspheres

Radio emobilisation therapy microspheres having sized 10-30 nm are of larger than capillaries. They are injected to arteries, which lead to tumor of interest. These radioactive microspheres deliver high radiation dose to targeted areas without damaging the normal tissues. Different types of radioactive microspheres are a emitters, B emitters, y emitters".

6. Polymeric microspheres

The different types of polymeric microspheres classified as

i) Biodegradable polymeric microspheres

Natural polymers such as starch are used as concept that they are biodegradable,biocompatible and also bioadhesive in nature. This polymer prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium, results get gel formation".

ii) Synthetic polymeric microspheres

Synthetic polymeric microspheres are widely used in clinical application, that are alsoused as bulk- ing agent, fillers, embolic particles and drug delivery vehicles etc. and proved tobe safe and biocompatible but the disadvantage of these kind of microspheres are tend to migrate away from injection site and lead to potential risk, embolism, further organ damage

Method of prepration of microspheres

1. Spray Drying

2. Solvent Evaporation

3. Single emulsion technique

Munirajah Institutes of Health Sciences College of Pharmacy
T.N.Palayam
Erode Dt.

Principal
IKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

4. Double emulsion technique

5. Phase separation concervation technique

6. Spray drying and spray congealing

7. Solvent extraction

8. Quassi emulsion solvent diffusion:

1. Spray Drying

In Spray Drying technique, polymer is first dissolved in volatile organic solvent such as dichloromethane, acetone, etc. The drug in solid form is then dispersed in to polymeric solution with the high-speed homogenization. This dispersion is then atomized in hot air stream. The atomization leads to the form the small droplets from which the solvent evaporates instantly leads the formation of the microspheres in the size range 1-100um. Micro particles are separated from hot air by the cyclone separator while the trace of solvent is removed by vacuum drying. The major advantages of this process is feasibility of operation under aseptic conditions.

2. Solvent Evaporation

This process is carried out in vehicle phase of liquid manufacturing. The microcapsule coating is dispersed in the volatile solvent which immiscible with the vehicle phase of liquid manufacturing A core material which is microencapsulated is dissolved in the coating polymer solution. Agitation With the core material mixture is dissolved in the liquid manufacturing vehicle phase to obtain appropriate size microcapsule. Then the mixture is heated if necessary to evaporate and the solvent for the polymer of the core material are dissolved in the polymer solution, around the core polymer shrinks. If core material is dissolve in the coating polymer solution, matrix type microcapsules are formed. The core materials are either water soluble or soluble materials".

T.N.Palayam
Erode Dt.

Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt)

3. Single emulsion technique

The micro particulate carriers of the natural polymers i.e. proteins and carbohydrates are prepared by the single emulsion technique. Natural polymers are dissolved in aqueous medium which is followed by the dispersion in non-aqueous medium like oil. In next step, the cross linking of dispersed globule is carried out. The cross linking can be achieved by the heat or by using the chemical cross linkers. T chemical cross linking agents used are glutaraldehyde, formaldehyde, acid chloride. Heat denaturation is not suitable for the hermolabile substance. Chemical cross linking having the disadvantage of excessive exposure of active ingredient to chemicals if added at time of preparation and then subjected to centrifugation, washing, separation nature of the surfactants used to stabilize the emulsion phases can greatly influence by the size, size distribution, surface morphology and loading drug release, and bio per- formance of the final multiparticulate product.

4. Double emulsion technique

This method of microspheres preparation involves formation of multiple emulsions or double emulsion of type w/o/w and is best suited to the water soluble drugs, peptides, proteins and vaccines. This method can be used with the both natural as well as synthetic polymers.The aqueous protein solution is dispersed in the lipophilic organic continuous phase. This protein solution may contain the active constituents.

5. Phase separation coacervation technique

This process is based on the principle of the decreasing the solubility of polymer in organic phase which affect the formation of polymer rich phase called the coacervates. In this method, drug particles are dispersed in a solution of polymer and an incompatible polymer is added to system which makes first polymer for the phase separation'.

T.N.Palayam
Erode Dt.
Principal
JKK Munirajah Institute of Health Sciences
College of Pharmacy, T.N.Palayam,
Gobi (Tk), Erode (Dt) - 638 506

6. Spray drying and spray congealing

These methods are based on the drying of the mist of polymer and drug in the air. Depending upon removal of the solvent or cooling of the solution, this two processes are named spray drying and spray congealing

7. Solvent extraction

Solvent evaporation method is used for the manufacturing of microparticles and involves removal of the organic phase by extraction of the non-aqueous solvent. This method involves the water miscible organic solvent which is isopropanol[1].

8. Quassi emulsion solvent diffusion

A novel quasi-emulsion solvent diffusion method used for the manufacturing of the controlled release microspheres of drugs with acrylic polymers has been reported in the literature, Microsponges can be manufactured by the quassi emulsion solvent diffusion method by using extemal phase which contains distilled water and polyvinyl alcohol. The internal phase consists of the drug, ethanol and polymers. Firstly the internal phase is manufactured at 60°C and after then added to the external phase at room temperature. Then emulsification the mixture is continuously stirred for 2 hours. Then the mixture can be filtered for separate the microsponges

PHYSICOCHEMICAL EVALUATION OF MICROSPHERES

1.Particle size and shape

The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM

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provides higher resolution in contrast to the LM. SEM allows investigations of the microspheres surfaces and after particles are cross-sectioned

2.Fourier transform infrared spectroscopy

Drug polymer interaction and degradation of microspheres can be assessed by FTIR

3.Drug entrapment efficiency

Weighed amount of microsphere are taken and crushed. Then dissolved in buffer. solution with the help of stirrer and filtered. The filtrate is assayed by UV spectrophotometer at particular wavelength by using calibration curve.

Drug Entrapment efficiency weight of microspheres/actual weight 100

4. Percentage yield

It is calculated as the weight of microspheres obtained from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100.

5. In vitro Drug release

In vitro drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from physic-chemically and hydro dynamically defined conditions are necessary. however no standard in vitro method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions depending on the shape and application of the dosage form developed,

CORONARY ARTERY DISEASE

Coronary artery disease (CAD) (or atherosclerotic heart disease) is the end result of the accumulation of atheromatous plaques within the walls of the arteries that supply the myocardium (the muscle of the heart) with oxygen and nutrients. It is sometimes also called

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coronary heart disease (CHD), but although CAD is the most common cause of CHD, it is not the only cause.

CAD is the leading cause of death worldwide. While the symptoms and signs of coronary artery disease are noted in the advanced state of disease, most individuals with coronary artery disease show no evidence of disease for decades as the disease progresses before the first onset of symptoms, often a "sudden" heart attack finally arises. After decades of progression, some of these athermanous plaques may rupture and (along with the activation of the blood clotting system) start limiting blood flow to the heart muscle. The disease is the most common cause of sudden death, and is also the most common reason for death of men and women over 20 years of age.

Symptoms

Cardiac Syndrome X often is a diagnosis of exclusion where the presence of typical chest pains is not accompanied by coronary artery narrowing on angiography. In considering Syndrome-X. it is important to understand that about 80% of chest pains have nothing to do with the heart. Therefore, the characteristics of typical chest pains must be carefully documented to avoid unnecessary labelling patients with heart disease:

Chest pain or Angina with physical stress, the pain may spread to the left arm or the neck. back, throat, or jaw. There might be present a numbness (paresthesia) or a loss of feeling in the arms, shoulders, or wrists.

1. Coronary angiography demonstrates "normal" coronary arteries, i, e.
2. No blockages or stenoses can be detected in the larger epicardial vessels.
3. No inducible coronary artery spasm present during cardiac catheterization
4. Characteristic ischemic ECG changes during exercise testing

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5. ST segment depression and angina in the presence of left ventricular wall perfusion abnormalities during thalliam or other stress perfusion test.

6. Consistent response to sublingual nitrates

7. Postmenopausal or menopausal status

The diagnosis of "Cardiac Syndrome X" the rare coronary artery disease that is more common in women, as mentioned, an "exclusion diagnosis. Therefore, usually the same tests are used as in any patient with the suspicion of coronary artery disease

1. Baseline ECG

2. Exercise ECG-Stress test

3. Exercise radioisotope test (nuclear stress test, myocardial scintigraphy).

4. Echocardiography (including stress echocardiography).

5. Coronary angiography

6. Intravascular ultrasound.

7. MRI scan

Treatment

Variety of drugs are used in the attempt to treat the Syndrome-X coronary artery disease: nitrates, calcium channel antagonists, ACI-inhibitors, statins, imipramin (analgesia). aminophylline, hormone replacement therapy (oestrogen), even electrical spinal cord stimulation are tried to overcome the symptomatology -all with mixed results. Quite often the quality of life for these women remains poor.

While not enough is known about Syndrome-X coronary artery disease to list specific prevention techniques, adopting heart-healthy habits can be a good start. These include

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monitoring cholesterol and blood pressure levels, maintaining a low-fat diet, exercising regularly, quitting smoking, avoiding recreational drugs, and moderating alcohol intake, However, there might be a new option for women suffering from "Cardiac Syndrome X" Protein based Angiogenesis. This new protein-based angiogenic therapy using fibroblast growth factor 1 (FGF-1)- might be used as sole therapy as well as adjunct to bypass surgery- thus overcoming the limitations of conventional bypass surgery. Neo-angiogenesis in a woman's heart after FGF-1 treatment.

Beyond drug therapy, interventional procedures, and coronary artery bypass grafting. angiogenesis now offers a new, specific and so far as we know from three human clinical trials-effective treatment targeted for women's coronary artery disease.

Risk factor

The following are confirmed independent risk factors for the development of CAD

1. Hypercholesterolemia (specifically, serum LDL concentration)
2. Smoking
3. Hypertension (high systolic pressure seems to be most significant in this regard)
4. Hyperglycemia (due to diabetes mellitus or otherwise)
5. Type A Behavioural Patterns, TABP Added in 1981 as an independent risk factor after a majority of research into the field discovered that TABP's were twice as likely to exhibit CAD than any other personality type [cestation needed]
6. Hemostatic Factors: High levels of fibrinogen and coagulation factor VII are associated with an increased risk of CAD. Factor VII levels are higher in individuals with a high intake of dietary fat. Decreased fibrinolytic activity has been reported in patients with coronary atherosclerosis

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7. Hereditary differences in wach diverse aspects as lipoprotein structure and that of their associated receptors, bomocysteine processing/metabolism, etc.

Prevention

Coronary artery disease is the most common form of heart disease in the Western world, Prevention centers on the modifiable risk factors, which include decreasing cholesterol levels, addressing obesity and hypertension, avoiding a sedentary lifestyle, making healthy dietary choices, and stopping smoking. There is some evidence that lowering homocysteine levels may contribute to more heart attacks (NORVIT trial). In diabetes mellitus, there is little evidence that very tight blood vagar control actually improves cardiac risk although improved war control appears to decrease other undesirable problems like kidney failure and blindness Some recommend a diet rich in omega-3 fatty acids and vitamin C. The World Health Organization (WHO) recommends "low to moderate alcohol intake to reduce risk of coronary artery disease although this remains without scientific cause and effect proof.

An increasingly growing number of other physiological markers and bomeostatic mechanisms are currently under scientific investigation. Patients with CAD and those trying to prevent CAD are advised to avoid fats that are readily oxidized (eg, saturated fats and tram-fan limit carbohydrates and processed sagars to reloce production of low-density lipoproteins, triacylglycerol and apolipoprotein-B. It is also important to keep blood pressure normal, exercise and stop smoking. These measures reduce the development of heart attacks. Recent studies have shown that dramatic reduction in LDL levels can cause regression of coronary artery disease in as many as 2/3 of patients after just one year of sustained treatment. Menaquinone (Vitamin K2), but not phylloquinone (Vitamin K1), intake is associated with reduced risk of CAD mortality, all-cause mortality and severe aortic calcification

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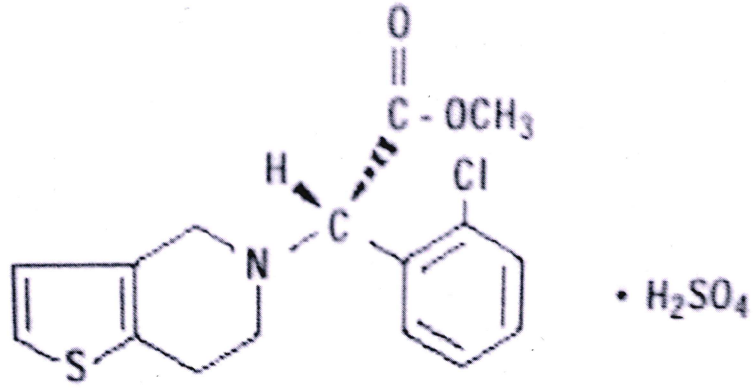
ANTI- PLATELET THERAPY

A meta-analysis of randomized controlled trials by the international Cochrane Collaboration found "that the use of clopidogrel plus aspirin is associated with a reduction in the risk of cardiovascular events compared with aspirin alone in patients with acute non-ST coronary syndrome. In patients at high risk of cardiovascular disease but not presenting acutely, there is only weak evidence of benefit and hazards of treatment almost match any benefit obtained.

DRUG PROFILE

Drug : Clopidogrel bisulphate

Structure:



Chemical Name: Methyl(+)-(S)-a-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)acetate Sulfate (1:1)

Molecular formula : C16H16CINO2S-H2SO4

Molecular Weight : 419.9

Appearance : White to off-white crystalline powder.

Melting point : 149-150°C

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SOLUBILTY :

Practically insoluble in water at neutral pH, but freely soluble at pH 1: freely soluble in methanol, sparingly soluble in methylene chloride, and practically insoluble in ethyl ether.

Packaging and Storage

Store in airtight containers & protected from light

Pharmacology:

Clopidogrel is an inhibitor of platelet aggregation. Varieties of drugs that inhibit platelet function have been shown to decrease morbid events in people with established cardiovascular atherosclerotic disease as evidenced by stroke or transient ischemic attacks. myocardial infarction, unstable angina or the need for vascular bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate

The mechanism of action of Clopidogrel is an irreversible blockade of the adenosine diphosphate (ADP) receptor on platelet cell membranes. This part of this receptor that it binds to is named P2Y 12 and is important in platelet aggregation, the cross-linking of platelets byfibrin. The blockade of this receptor inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway. The IIb/Illa complex functions as a receptor mainly for fibrinogen and vitronectin but also for fibronectin and von Willebrand factor. Activation of this receptor complex is the "final common for platelet aggregation and is important in platelet aggregation, the cross-linking of platelets by fibrin.

Pharmacokinetics:

Clopidogrel is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is highly protein bound (94-96%). Administration of clopidogrel bisulfate with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating

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metabolite. Clopidogrel is a pro-drug, which requires metabolism by the liver for its activation. The active metabolite has an elimination half-life of about 8 hours and acts by forming a disulfide bridge with the platelet ADP receptor.

Dosage/Monitoring:

The recommended daily oral dose of clopidogrel is 75 mg. A dose adjustment is not needed for age, sex, or weight. Clopidogrel can be taken with or without food. An I.V. form of the drug is not currently available. Patients with renal impairment may use the drug without risk. Patients with active peptic ulcer or intracranial bleeding should not use the drug. Because clopidogrel has not been shown to cause neutropenia or routine hematologic monitoring is not required.

Drug Interactions:

Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by clopidogrel. Clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel and aspirin have been administered together for up to one year. Heparin: In a study in healthy volunteers, Clopdogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by clopidogrel.Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of Clopidogrel was associated with increased occult gastrointestinal blood loss. NSAIDS and Clopidogrel should be coadministered with caution.

1. Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with Clopidogrel should be undertaken with caution.

2. Other Concomitant Therapy: No clinically significant pharmacodynamic interaction were observed when Clopidogrel was coadministered with atenolol, nifedipine, or both atenolol

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and nifedipine. The pharmacodynamic activity of Clopidogrel was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen.

3.The pharmacokinetics of digoxin or theophylline was not modified by thecoadministration of clopidogrel bisulfate.

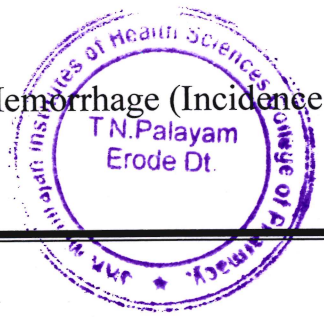
4. At high concentrations in vitro, clopidogrel inhibits P450 (209). Accordingly. Clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with Clopidogrel.

In addition to the above specific interaction studies, patients entered into clinical trials with Clopidogrel received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), thrombolytics, heparins (unfractionated and LMWH), GPIIb/lla antagonists, antiepileptic agents and hormone replacement therapy without evidence of clinically significant adverse interactions.

Adverse Drug Reaction:

Clopidogrel is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system. Serious adverse drug reactions associated with clopidogrel

1. therapy include: Severe neutropenia 1/2,000)
2. Thrombotic thrombocytopenic purpura (TTP) (Incidence: 4/1,000,000 patients treated) Hemorrhage - The incidence of hemorrhage may be increased by the co-administration of aspirin .
3. Gastrointestinal Hemorrhage (Incidence: 2.0%)



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4. Cerebral Hemorrhage (Incidence: 0.1 to 0.4%)

5. Use of non-steroidal anti-inflammatory drugs is discouraged in those taking clopidogrel due to risk of digestive tract haemorrhage

6. Other adverse effect, which is not common such as dizziness (1%), vertigo (0.3%), and rare cases: par aesthesia and tremor.

INDICATION

Clopidogrel bisulfate is indicated for the reduction of atherothrombotic events as follows:

1. Recent MI, Recent Stroke or Established Peripheral Arterial Disease

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Clopidogrel has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death .

2. Acute Coronary Syndrome

For patients with non-ST-segment elevation acute coronary syndrome (unstableangina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, Clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

For patients with ST-segment elevation acute myocardial infarction, Clopidogrel has been shown to reduce the rate of death from any cause and the rate ofa combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplastyl.

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3. Other adverse effect, which is not common such as dizziness (1%), vertigo (0.3%), andrare cases par aesthesta and tremor

Indication

Clopidogrel bisulfate is indicated for the reduction of atherothrombotic events as follows

- Recent MI, Recent Stroke or Established Peripheral Arterial Disease

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Clopidogrel has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fata) or not), and other vascular death

- **Acute Coronary Syndrome**

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, Clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia

- **For patients with ST-segment elevation acute myocardial infarction.**

Clopidogrel has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke This benefit is not known to pertain to patients who receive primary angioplasty.

POLYMER PROFILE

Polymer: Ethylcellulose

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1. Nonproprietary Names -

BP: Ethylcellulose

PhEur Ethylcellulosum USPNE

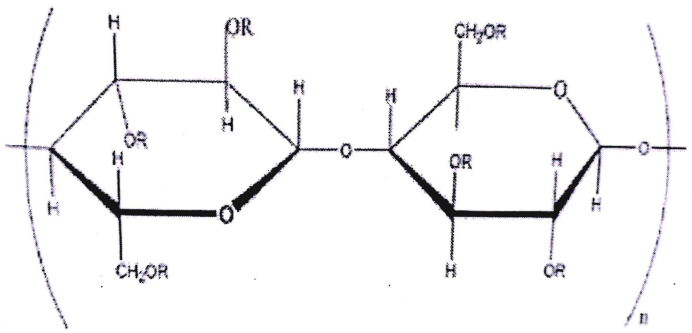
Ethylcellulose

2. Synonyms :Aquacoat ECD, Aqualon; E462, Ethocel, Surelease

3. Chemical Name and CAS Registry Number

Cellulose ethyl ether [9004-57-31 4 Empirical Formula and Molecular Weight Ethylcellulose with complete ethoxyl substitution (DS-3) is C12H2306(C12H2205)nC12H2305 where n can vary to provide a wide variety of molecular weights Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of b-anhydroglucose units joined together by acetal linkages

4. Structural formula



5. Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations, The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules (1-8) Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation, for example, where granules

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are coated with ethylcellulose to inhibit oxidation Modifiedrelease tablet formulations may also be produced using ethylcellulose as a matrix, former Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films

Higher-viscosity ethylcellulose grades tend to produce stronger and more durable filmsEthylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer

An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents

High-viscosity grades of ethylcellulose are used in drug microencapsulation

Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet-granulated with a solvent such as ethanol (95%):

Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e g dental) appliances In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels. provided an appropriate solvent is used Ethylcellulose has been studied as a stabilizer for emulsions. Ethylcellulose is additionally used in cosmetics and food products

6. Description

Ethylcellulose is a tasteless, free-flowing, white to light tancolored powder

7. Solubility: ethylcellulose is practically insoluble in glycerin, propylene glycol, and water Ethylcellulose that contains less than 46 5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons

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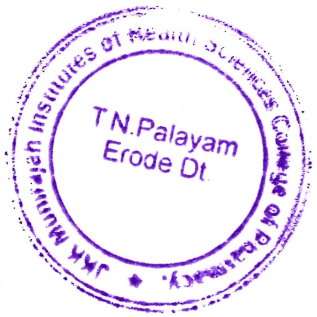
with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

8. Specific gravity: 1.12-1.15 g/cm3

9. Viscosity:

the viscosity of ethylcellulose is measured typically at 258C using 5% ethylcellulose dissolved in a solvent blend of 80% toluene 20% ethanol (w/w).w/v



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AIM AND OBJECTIVE OF THE STUDY

Coronary heart disease (CHD) is a major cause of mortality and morbidity all over the word. According to a report of World Health Organization (WHO) in 2005, cardiovascular disease (CVD) caused 17.5 million (30%) of the 58 million deaths that occurred worldwide**. Clopidogrel bisulfate is an oral, thienopyridine class antiplateletagent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Clopidogrel is a prodrug of carboxyl clopidogrel activated in the liver by cytochrome P450 and CYP2C19 enzyme. The active metabolite has an elimination half-life of about 7-8 hrs and acts by forming a disulfide bridge with the platelet ADP".

Clopidogrel bisulphate shows bioavailability of about only 50% due to poor water solubility and first pass metabolism to large portion of inactive metabolite. The main side effect of the drug is gastric bleeding. A sustained release microparticle of clopidogrel bisulphate formulation may be preferred over conventional film coated tablet for improving the bioavailability, to minimize gastric bleeding and better patient compliance"®.

The main objective is to prepare the sustained release microspheres of clopidogrel bisulphate using ethylcellulose natural polymer achieving a sustained release for 24 h to target the stomach.

Based on these considerations, the present study is proposed to develop formulation and evaluation of microparticulate drug delivery system for clopidogrel bi sulphate an antiplatlate drug using ethylcellose polymer.

The present study was formulated with the following objectives:

- To conduct compatibility study of the drug and carrier polymer.
- Estimation and construction of linearity chart for clopidogerl bisulphate by UV spectrophotometry.

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- Preparation of clopidogrel bisulphate loaded ethylcellulose microspheres by solvent evaporation method.
- Characterization and evaluation of clopidogrel bisulphate loaded ethylcellulose microspheres.
- In-vitro evaluation of clopidogrel bisulphate loaded ethylcellulose microspheres.
- Stability study of optimized clopidogrel bisulphate loaded ethylcellulose microspheres as per the ICH guidelines.

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PLAN OF WORK

1. Compatibility studies

- Determination of melting point
- Solubilty
- Drug and carrier interaction by FT-IR spectroscopy

2. Estimation and construction of calibration curve of clopidogrel bisulphate in phosphate buffer (pH7.4) by UV spectrophotometry

3. Preparation of clopidogrel bisulphate loaded ethylcellulose microspheres by solvent evaporation method.

4. Characterization and evaluation of clopidogrel bisulphate loaded ethylcellulose microspheres.

a) Flow properties and Micromeritics parameters

b) Particle size analysis

c) Surface characteristic by Scanning Electron Microscopy (SEM)

d) Percentage yield

e) Drug loading and entrapment efficiency

f) In-vitro drug release of clopidogrel bisulphate from the microspheres.

g) Release kinetics

h) Stability studies

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MATERIALS

The drug and chemicals required for the work was procured from reputed firm. The details are furnished below:

Drug and Chemicals	Supplier/ Manufacturer
Clopidogrel bisulphate	Micro labs Pvt.Ltd. Hosur.
Ethyicellulose	Colorcon Asia pvt. Lid.
Sodium Hydroxide	Spectrum Reagents & Chemicals, Cochin
Potassium Dihydrogen Phosphate	Spectrum Reagents & Chemicals,
Liquid paraffin	Loba chemicals, Mumbai.
N Hexane	S.D Fine chem. Ltd, Mumbai
Ethanol	S .D Fine chem. Ltd, Mumbai

Instruments	Model/ Manufacturer
Particle size analyser	Nano plus DLS, Japan
FT-IR spectrophotometer	Perkin Elmer Spectrum RX 1
UV-Visible Spectrophotometer	Perkin Elmer Lambda 25
Scanning Electron Microscopy	Carel Zeiss EVO18 SE , Germany
Single pan digital balance	Shimadzu BL220H
Digital pH meter	Hanna instruments, Italy HI98
Magnetic stirrer	Eltek MS 2012.
Tablet Dissolution Tester (USPXX III)	Veego Labs, Chennai

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METHODS

- Preformulation Studies

It is one of the important prerequisite in development of any drug delivery system. reformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

A. Determination of melting point

Melting point of Clopidogrel bisulphate was determined by capillary method.

B . Solubility:

Solubility of Clopidogrel bisulphate was determined in water, 0.1N HCl, practically insoluble in water and freely soluble in acetone, soluble in alcohol.

C. Compatibility Studies

Before formulation of drug substances into a dosage form, it is essential that the drug and polymer should be chemically and physically characterized. Compatibility studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipient in the fabrication of a dosage form

Fourier Transform InfraRed Spectroscopy (FTIR)

Compatibility study of pure clopidogrel bisulphate, ethylcellose polymer, clopidogrel bisulphate with ethyl cellulose polymer and clopidogrel bisulphate loaded ethylcellose (F-3) were determined by FTIR Spectroscopy using Perkin Elmer RX1. The pellets were prepared by gently mixing sample with potassium bromide at high pressure. The scanning range used is 450 to 4000 cm. The pellets thus prepared were examined and the spectra of drug and the polymer in the formulations were compared with that of pure drug and polymer spectra.

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Preparation of Standard Calibration Curve of Clopidogrel bisulphate"®

Method

Clopidogrel bisulphate can be estimated spectrophotometrically at 240 nm.

Preparation of 0.1 N HCl

Dilute 8.5 ml conc. Hydrochloric acid with water to produce 1000 ml.

preparation of Standard Drug Solution:

Stock Solution

100 mg of Clopidogrel bisulphate was dissolved in 100 ml of 0.1 N HCL, so as to get a stock solution of 1000 pg/ml concentration.

Standard Solution

4 ml of stock solution was made to 100 ml with 0.1N HCI, thus giving a concentration of 40 yg /ml. Aliquot of standard drug solution ranging from | to 10m! were transferred in to 10 ml volumetric flask and were diluted up to the mark with 0.1N HCl. Thus the final concentration ranges from 4-40 ug/ml. Absorbance of each solution was measured at 240.0 nm against 0.1N HCl as a blank. A plot of concentrations of drug versus absorbance was plotted.

Preparation of microspheres

Controlled release microspheres of clopidogrel bisulphate were prepared by nonaqueous solvent evaporation method using ethylcelluose natural polymer. Take 100 ml of beaker add 10 ml of alcohol; place magnetic beads on a magnetic stirrer at 400 rpm—500 rpm. Following the solvent mix, add polymer and the drug as core material to dissolve in it. Then add the above-prepared solution to the beaker undergoing homogenization process containing 90 ml of liquid paraffin with mechanical stirring at 700 rpm. The spheres are

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formed and the Solvent is removed from the spheres for 3-4 h then the spheres are filtered and washed with 50 ml of n-hexane for 3—4 times to get microspheres hardened and then kept 24 h for drying at room temperature30,31, The concentrations and amounts applied are summarized in Table-1.

FORMULATION CODE	DRUG (mg)	POLYMER (mg)	DRUG POLYMER RATIO (mg)
F-1	300	100	3:1
F-2	300	200	3:2
F-3	300	300	3:3
F-4	300	400	3:4
F-5	300	500	3:5

Evaluation of clopidogrel bisulphate loaded ethylcellulose microspheres

1. Flow properties and micromeritic properties

Flow characteristics such as angle of repose (©) of the microspheres, which measures the resistance to particle flow was determined by the fixed funnel method using the following equation.

Angle of repose = tan-1 (h/r)

Where "h" is the height of the pile, "r" is the radius of the base pile on the graph paper.

The prepared microspheres were characterized for their micromeritic properties such as bulk density, tapped density, and % Carr's index. The tapping method was used to calculate tapped densities and % Carr's Index.

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$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

$$\%\ \text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Particle size analysis

The prepared clopidogrel bisulphate loaded ethylcellulose microspheres were evaluated for their particle size by zeta potential analyzer Zetasizer 3000 HS (Malvern instrument.UK). The formulations were diluted to 1:1000 with the aqueous phase of the formulation to get a suitable kilo counts per second. Analysis was carried out at 25°C with an angle of detection of 90 degrees™.

3. Surface morphology by Scanning Electron Microscopy

The morphology of the clopidogrel bisulphate loaded ethylcellulose microspheres were analyzed by scanning electron microscope. The instrument used for this determination was JEOL MODEL JSM 6400 scanning electron microscope. The microspheres were mounted directly on the SEM stub, using double sided, sticking tape and coated with platinum and scanned in a high vacuum chamber with a focused electron beam. Secondary were detected and the image formed*»,

4.Determination of percentage yield

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres*®

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$$\text{Percentage Yield} = \frac{\text{Weight of microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

5. Encapsulation efficiency and loading capacity of the microspheres

An accurately weighed quantity of the microspheres was extracted with pH 1.2 for 24h, centrifuged at 6000 rpm for 30 min and filtered (Hitachi Centrifuge USA). The dispersion was filtered and the absorbance of the filtrate was measured at 240 nm after appropriate dilution in a UV-visible spectrophotometer (Perkin Elmer Lambda 25). The drug content was estimated in triplicate using a calibration curve constructed in the same solvent. Polymers did not interfere with the assay at this wavelength. The amount of clopidogrel bisulphate encapsulated in to the microspheres is determined by using the formula.

The clopidogrel bisulphate encapsulation efficiency (EE) and loadw g capes (4 of the microspheres was calculated as follows.

$$\text{Encapsulation efficiency} = \frac{\text{Total amount of drug — Free drug}}{\text{Weight of microspheres}} \times 100$$

$$\text{Loading capacity} = \frac{\text{Total amount of drug — Free drug}}{\text{Total amount of drug}} \times 100$$

6. In-vitro Drug release studies

The drug release studies were carried out using six-basket dissolution apparatus LSP type I. The microspheres were placed in a non-reacting mesh that had a smaller mesh suze than the microspheres. The dissolution medium used was 900ml of 0.1N HCI at 37°C. At speerfic time intervals, 1 ml aliquots were withdrawn and analyzed by UV

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spectrophotomeser at the respective Amax value 240 nm after suitable dilution against suitable blank. The wwhdraee volume was replaced with an equal volume of fresh 0.1N HCP".

7. Kinetics of drug release

In order to understand the mechanism and kinetic of drug release, the drug release data of the in-vitro diffusion study were analyzed with various kinetic models like zero ander. first Order, Higuchi's and Peppa's. Coefficient of correlation (r) values were calculated for the linear curves by regression analysis 7°?

8. Stability Studies

The short term stability study was carried out as pet ICH gurichnes wang the Optimized formulation F-9. Formulation F-9 was divided into 3 sets of samples and sored at *'C in refrigerator, room temperature 37°C and at ambient temperature, dy wire release study of formulation F-9 was carried out after 90 days of storage*®.

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RESULTS

1. Preformulation Studies

a.) Melting point determination

Melting point of Clopidogrel bisulphate was found to be in the range 184 °c-194 °C, which womphied with J. P standards, indicating purity of the drug sample.

b) Solubility:

Clopidogrel bisulphate is highly soluble in 0.1 N HCI. Practically insoluble in water at neutral pH, but freely soluble in methanol, sparingly soluble in methylene chloride, and insoluble in ethyl ether.

c) Compatibility Studies

Fourier Transform Infra Red Spectroscopy (FTIR)

There was no appearance or disappearance of any characteristics peaks of pure drug or of polymer in the physical mixture and clopidogrel bisulphate loaded microspheres, thus indicating absence of any physical interaction between the drug and polymer. The results show that the incorporation of the drug into the polymer did not change the characteristics of the drug. Observations of compatibility studies of infrared spectra for the pure drug, the mixture of clopidogrel bisulphate with ethylcellulose and clopidogrel bisulphate loaded microspheres are shown in Table-2. The IR spectra of ethylcellulose, mixture of clopidogrel bisulphate with ethylcellulose and clopidogrel bisulphate loaded microspheres (F-3) are shown in Fig1A, 1B and IC.

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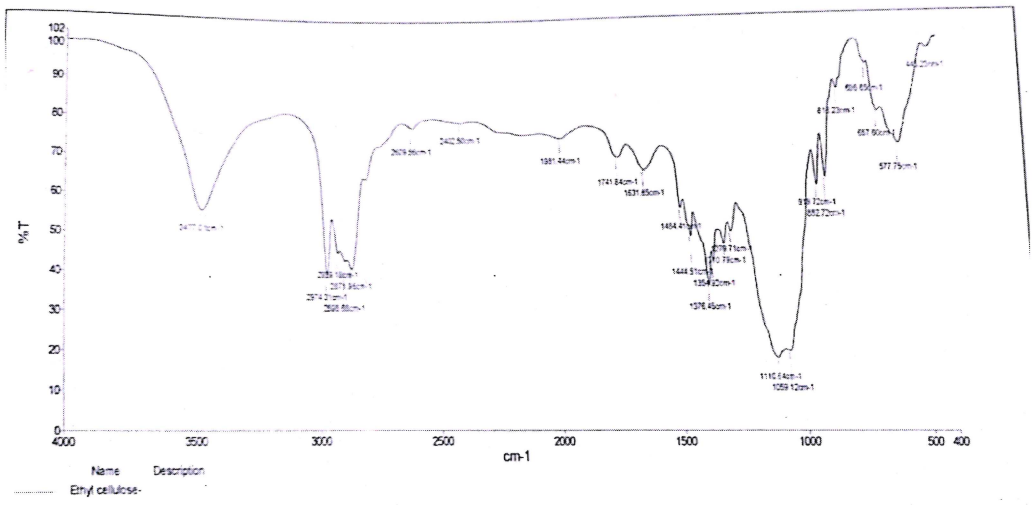
IR SPECTRUM	WAVE NUMBER in Cm	Groups	Stretching / Deformations
Ethylcellulose	3477..01	C-H Alkane	Stretching
	2898.68	C=O Ketone	Stretching
	1059.12	N-H2 Amine	Stretching
Clopidogrel bisulphate	2552.90	N-H3 Amine	Stretching
	1031.21	C-H Alkane	Stretching
	3058.30	C=O Ketone	Stretching
	1640.77	C=C Aromatic	Stretching
Clopidogrel bisulphate microspheres	3482.56	N-H3 Amine	Stretching
	2954.05	C-H Alkane	Stretching
	1031.21	C=O Ketone	Stretching
	1640.77	C=C Aromatic	Stretching



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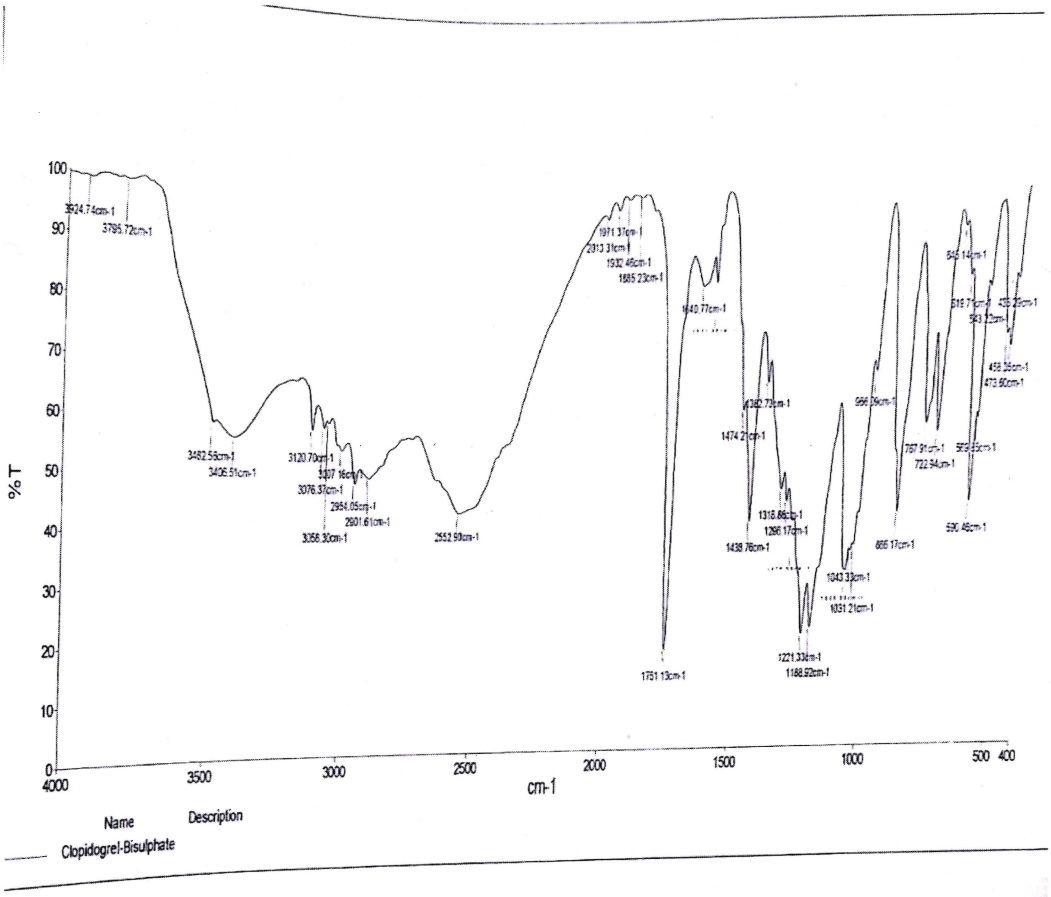

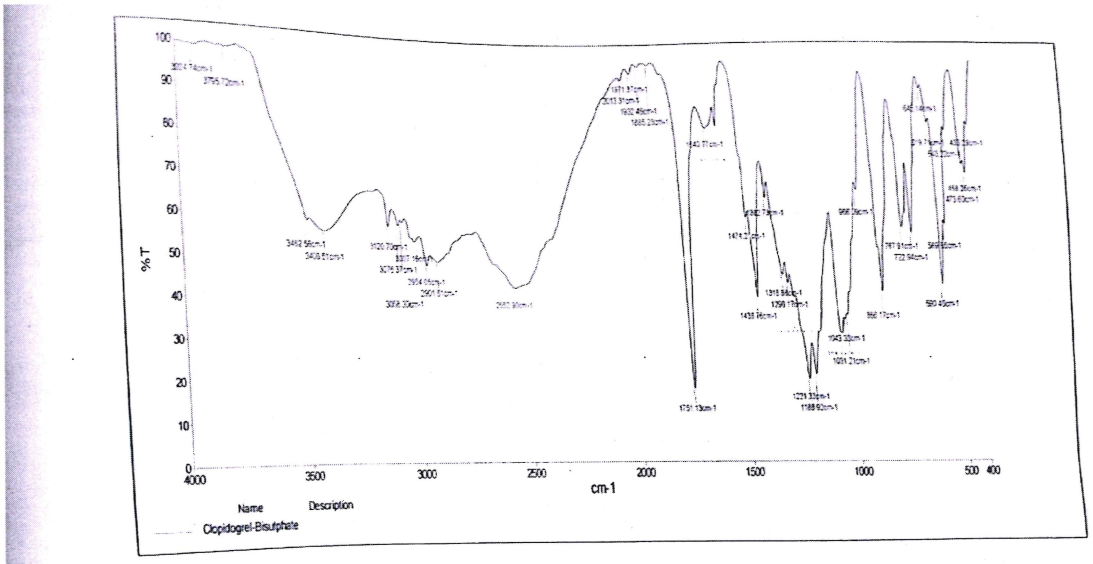

Fig-1C FTIR Spectrum of Clopidogrel Bisulphate with ethylcellulose

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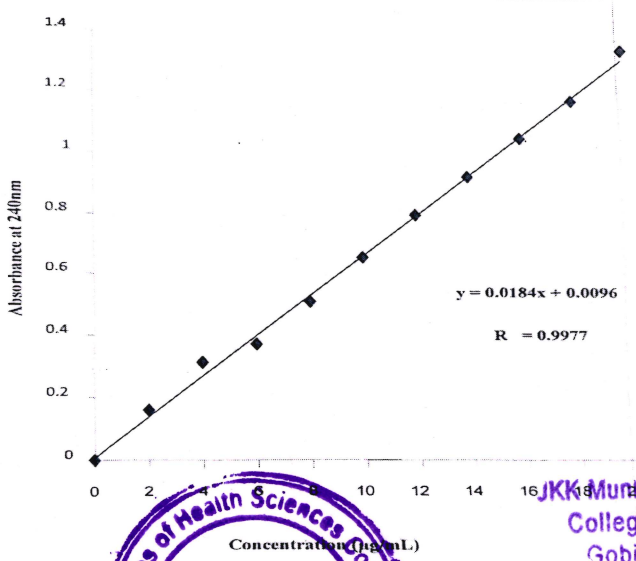
2. Estimation and construction of linearity chart for clopidogeral bisulphate

Standard calibration curve of clopidogrel bisulphate was determined by Plotting absorbance (nm) versus concentration (mcg/ml) at 240 nm and it was found to follow the Beer' s law in the range 4-40mcg / ml.

S.NO	CONCENTRATION(mcg/ml)	ABSORBANCE
1	4	0.074
2	8	0.159
3	12	0.224
4	16	0.314
5	20	0.374
6	24	0.449
7	28	0.531
8	32	0.620
9	36	0.663
10	40	0.723
SLOPE		**0.0184**
REGRESSION		**0.9977**



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Evaluation of clopidogerl bisulphate loaded ethyl cellulose microspheres

1. Micromeritic properties

The microspheres were evaluated for process bulk density, compressibility index, Hausner's ratio and angle of repose and the results are shown in Table 4.

Table.3 Bulk density, compressibility index, Hausner's ratio and angle of repose

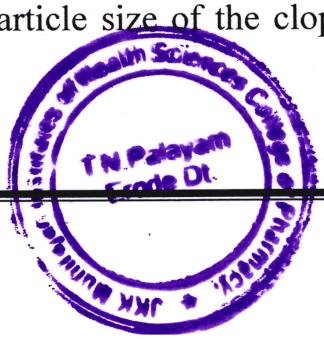
Formulation code	Bulk density	Carr" s Index	Hausner" ratio	Angle of repose
F-1	0.286±0.01	8.12±0.13	1.08±0.06	22.86±0.21
F-2	0.301±0.02	9.62±0.17	1.13±0.03	23.66±0.63
F-3	0.308±0.01	10.6±0.09	1.17±0.07	24.60±0.55
F-4	0.317±0.03	14.5±0.21	1.18±0.08	26.86±0.41
F-5	0.327±0.02	15.17±0.19	1.16±0.05	28.79±0.37

2. Particle size

Table 4 : Particle size of clopidogrel bisulphate loaded microspheres

Formulation code	Mean Particle size (µm)
F-1	6.54
F-2	7.30
F-3	8.00
F-4	9.21
F-5	9.67

The mean particle size of clopidogrel bisulphate loaded microspheres (F1-FS) wereshown in Table-3. The mean particle size of the clopidogrel bisulphate loaded microspheres(F1-FS)



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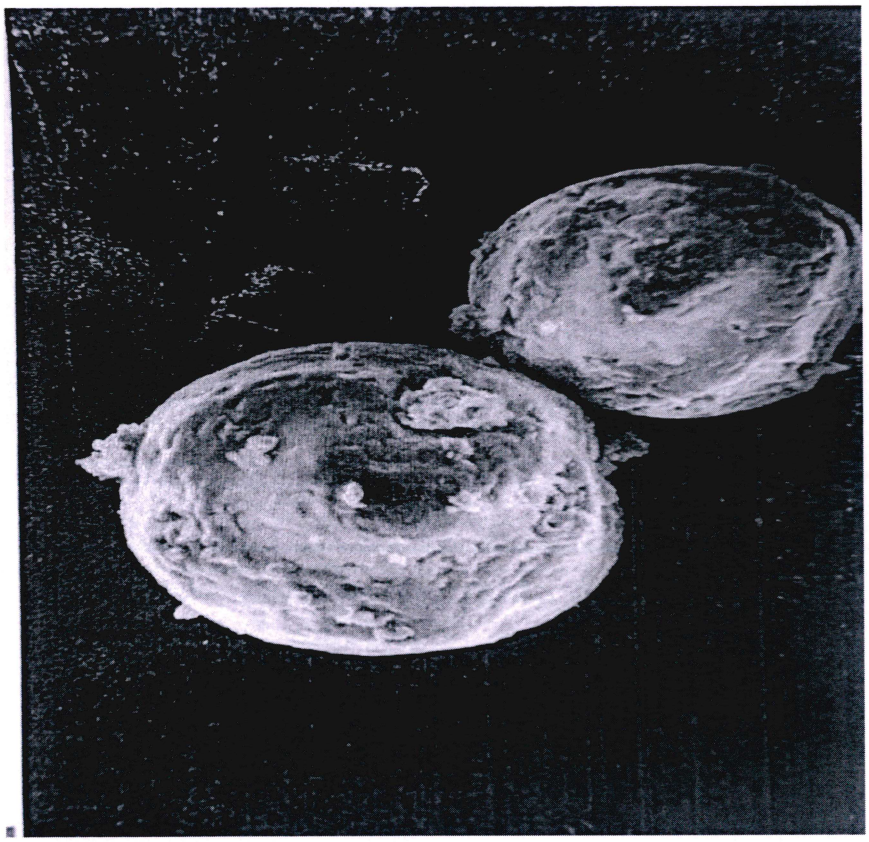
were increased by increasing the polymer concentration. The maximum size was found to be 967.32nm for F-5 and minimum size was 654.9nm for F-1 formulation.

Surface Morphology by scanning electron microscopy

According to morphological evaluation analysis by scanning electron microscopy all the prepared clopidogrel bisulphate loaded microspheres (F1-F5) seemed to have a similar spherical shape. The size of Microparticles of all the formulations were in micrometer. The morphological characters of clopidogrel bisulphate loaded microspheres (F3) are shown in Fig.3



Percentage of yield, encapsulation efficiency and loading capacity of microspheres

Percentage yield, the encapsulation efficiency and loading capacity of clopidogrel bisulphate loaded microspheres F1-F5 are shown in Table-4.

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Table.5 Percentage of yield, Encapsulation efficiency and Loading capacity of the clopidogrel bisulphate loaded microspheres

Formulation code	Percentage Yield(%)	Encapsulation Efficiency(%)	Loading capacity (%)
F-1	82.47	68.7	45.8
F-2	88.7	70.5	40.6
F-3	90.2	72.8	35.3
F-4	93.11	74.3	32.58
F-5	97.20	76.2	30.67

The percentage yield, the encapsulation efficiency was increased by increasing the concentration of polymer. The encapsulation efficiency ranged between 68.7 to 76.2%. The maximum entrapment was found in F-5 (76.2%) and lowest entrapment in F1 (68.7%).Conversely the loading capacity of the microspheres decreased as the concentration of polymer increased. The loading capacity ranged between 30.67 to 45.8% The results suggested that the encapsulation efficiency and loading capacity of the microspheres depend on the concentration of the polymer used in the preparation.

In-vitro drug release

Dissolution of clopidogrel bisulphate from the ethylcelluose microspheres, the drug leakage was monitored for 24 hrs as shown in Fig- 4. From the in-vitro drug release data for FI-FIS, it was observed that increase in the polymer concentration delays the drug release due to increased particle size and reduced surface area available for drug release. Based on this five formulations F-1, F-2, F3, F4 and F-5 were chosen for in-vitro drug release study. In the first hour, drug released was 12.0%, 12.5%, 12.8%, 13.8%, 14.71%, 16.62%, 14.56% and15.85% for F-1. F-2, F-3, F-4and F-5 respectively.

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The cumulative percentage of drug released for F1, F2, F3, F4 and 15 after 24 hrs was 76,14%, 85.38% 90 10 2.10% and80.40% respectively.

Maximum drug release was found in F-3 (90.19%) and muminum was found in 1-1(70.2%). Out of all the formulations F-3 was selected as optimized formulation doe desirable drug release in 24hrs. released for F1, F2, F3, F4 and 15 after 24 hrs was 76,14%, 85.38% 90 10 2.10% and 80.40% respectively

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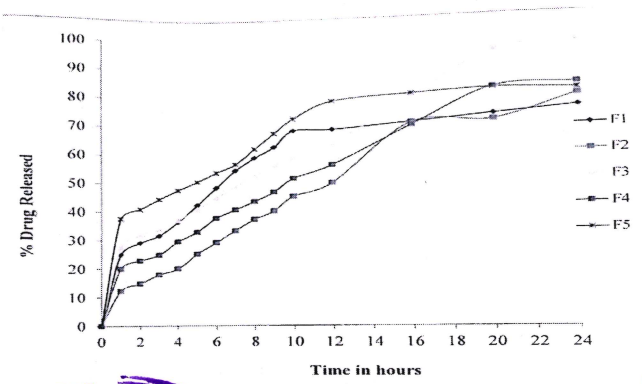

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CONCLUSION

From the present study, it can be considered that the diosgenin and diosgenin adjuvant therapy exhibited significant neruroprotective effect on rotenone model in Parkinson mouse. All the Parameters of diosgenin and diosgenin with standard treated group animals have shown better results when compared with Rotenone- induced group and the standard L-dopa treated group.

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