FORMULATION AND EVALUATION OF SERRATIOPEPTIDASE TABLETS

Dissertation Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment of the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

SANTHOSH KUMAR.R **(REG. NO: 26119209)**

Under the guidance of

Mrs.C.Kalaiselvi., M.Pharm.,

Assistant Professor, Department of Pharmaceutics.

DEPARTMENT OF PHARMACEUTICS
PGP COLLEGE OF PHARMACEUTICAL SCIENCE AND RESEARCH INSTITIUTE
NH-7, Karur Main Road, NAMAKKAL - 637207

OCT– 2013

Prof. Dr. G. ARUNACHALAM. M. Pharm., Ph.D. FIC.,
Principal
PGP College of Pharmaceutical Science and
Research Institute, Namakkal-637207.

CERTIFICATE

This is to certify that the dissertation entitled ***"FORMULATION AND EVALUATION OF SERRATIOPEPTIDASE TABLETS "***was carried out by **SANTHOSH KUMAR.R** (Reg. No: 26119209), under the guidance of **Mrs.C.Kalaiselvi., M.Pharm., Assistant Professor** in the Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal, Affiliated to The Tamilnadu Dr. M.G.R Medical University, Chennai - 32.

Prof.Dr. G. ARUNACHALAM

Place: Namakkal

Date:

Mrs. C.Kalaiselvi., M.Pharm.,

Assistant Professor

Department of Pharmaceutics

PGP College of Pharmaceutical Science and

Research Institute, Namakkal-637207.

CERTIFICATE

This is to certify that the dissertation entitled ***"FORMULATION AND EVALUATION OF SERRATIOPEPTIDASE TABLETS"*** was carried out by **SANTHOSH KUMAR.R (Reg. No: 26119209)** in the **Department of Pharmaceutics, PGP College of Pharmaceutical Science and Research Institute, Namakkal, Affiliated to The Tamilnadu Dr. M.G.R Medical University, Chennai - 32** under my direct supervision and guidance to my fullest satisfaction.

Mrs.C.KALAISELVI

Place: Namakkal

Date:

DECLARATION

I hereby declare that the matter embodied in the dissertation entitled ***"FORMULATION AND EVALUATION OF SERRATIOPEPTIDASE TABLETS*** "is a bonafide and genuine research work carried by us under the guidance of **Mrs.C.KALAISELVI, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, PGP College of Pharmaceutical Science & Research Institute, NH-7, Karur Main Road, Namakkal.

R.SANTHOSH KUMAR **REG. NO: (26119209)_____**

Place: Namakkal

Date:

.

ACKNOWLEDGEMENT

We extend all glory and honour to our almighty god by whose grace we were to complete work and also course successfully.

We would like to express our sincere thanks to orchid health care ltd, Chennai for providing all facilities and support through out our project work.

We are profoundly grateful to our principal Dr.G. Arunachalam M.Pharm.,Ph.D.,AIC.,

For constant help and encouragement through out the course of this investigation.

We express our profound sense of gratitude to Mr.D.Sakthivel., M.Pharm.,Ph.D., Assistant professor, department of pharmaceutics pgp college of pharmaceutical sciences and research institute namakkal, for his valuable help regarding our project work.

A special word of thanks to Assistant professor cum guide Mrs.C.Kalaiselvi., M.Pharm., department of pharmaceutics pgp college of pharmaceutical sciences and research institute namakkal, For a valuable guidance rendered to this project work.

We extend our sincere thanks to Assistant professor Mr. Suresh., M.Pharm., for helping our project and literature work.

We whish to express our heartful thank to all the teaching & non-teaching staffs members of Pgp college of pharmaceutical science and research institute namakkal, for their valuable help in all aspects.

Finally we would like to present this project work as a tribute to our loving parents.

BY

R.SANTHOSH KUMAR

REG.NO. 26119209

INTRODUCTION

Tablet[1] is defined as a solid pharmaceutical dosage form containing drug substance with or without suitable diluents and prepared by either compression or molding methods. They have been widely used since the later part of the 19th century and their popularity still continues. Tablets remain poplar as a dosage from because of the advantages afforded both to the manufacture (e.g. simplicity and economy of the preparation, stability and convenience in packing, shipping and dispensing) and the patient (e.g.accuaracy of dosage, compactness, portability of taste and ease of administration.

Although the basic medicinal approach for their manufacture has remained the same tablet technology has undergone great improvement. Feecets are being made continually to understand more clearly the physical characteristics of powder compaction and the factors affecting the availability of the drug substance from the dosage form after oral administration. There has been a continued interest to improve the tableting equipment by increasing the production speed and uniformity of the compressed tablets.

Although tablets frequently are discoid in shape they may also be round oval oblong cylindrical or triangular. They may differ greatly in size and weight depending on the amount of the dug substance resent and the intended method of administration. They are divided into two general classes by whether they are made by compression or molding, compressed tablets usually are prepared by large scale production methods while molded tablets generally involve small scale operation.

Tablet formulation and design may be described as the process where by the formulator ensures that the current amount of the drug in the right form is delivered at or over the proper time rate and in the desired location. While having its chemical integrity protected to that point. Most recently, neq concepts and federal regulations being made

on bioavailability and bioequivalence and on validation are impacting on tablet formulation design and manufacture.

ADVANTAGE OF TABLETS

- They are solid unit dosage forms and they offer greatest capabilities of all oral dosage forms for the greatest dosage precision and the least content variability.
- Their cost is lowest of all the dosage forms.
- They are the lightest and most compact of all the dosage forms.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.
- They may provide the greatest ease of swallowing with the least tendency for "hang –up" above the stomach especially when coated, provided that tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile riducts such as enteric or delayed release products.
- They are better suited to large scale production than the other unit oral forms.
- They have the best combined properties of chemical mechanical and microbiologucal stability of all the oral forms.

DISADVANTAGE OF TABLETS

- Some drugs resist compression into dense particles, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting slow dissolution properties intermediate to large dosages high optimum absorption in the GIT, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet.
- Bitter tasting drugs with an objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression.

TYPES OF TABLETS

1. Compressed tablets (CT)
2. Multiple compressed tablets
3. Layered tablets
4. Compression coated tablets
5. Repeat action tablets
6. Delayed action and enteric coated tablets
7. Sugar coated tablets
8. Chewable tablets
9. Buccal tablets
10. Sublingual tablets
11. Troches and Lozenges
12. Dental cones
13. Implantation tablets
14. Vaginal tablets
15. Effervescent tablets
16. Dispensing tablets
17. Hypodermic tablets.

TABLET PROCESSING

Pharmaceutical products are process all over the world using the direct compression, wet granulation or dry granulation methods. . Method[2] is chosen depending on the ingredients individual characteristics like flow property, compressibility, etc choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients and how they work with each other. Then the proper granulation process cab be applied.

Direct Compression

Direct compression name implies compressing tablets directly form powdered materials without modifying the physical nature of the materials itself. Direct compression is generally done for the crystalline materials having good physical properties required for formation of good physical properties required for formation of good tablets. Main advantage of direct compression like wet granulation.

TYPES OF GRANULATION

1.Wet Granulation

The most widely used and the most general method or tablet preparation is by wet granulation method. Wet granulation forms the granules by binding the powders together with an adhesion instead of by compaction. The wet granulation technique is done by adding a solute, suspension or slurry containing binder. This can be aqueous or non aqueous which is added to the dry mix powder. In general, the mass should be moist rather than wet or paste merely. The surface tension forces and capiliary pressure are primarily responsible for intital granules formation. The main disadvantage is that it requires many steps in the process, which is time consuming.

2.Dry Granulation

The dry granulation process is used to form granules without using a liquid solution. This type of process is recommended for products which are sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be done on a tablet press using slugging tooling. On large scale roller compactor commonly referred to as a chilsonator is used. The compacted mass is called slug and the process in known as slugging. The slugs are then screened or milled to produce a granular form of tablet materials, which have good flow properties than the original mixture. The main advantage of dry granulation is that it requires less equipment and eliminates the addition of moisture and the application of heat as found in wet massing and drying steps of the wet granulation method.

Enteric coatings

Enteric coating are those which remain intact in the stomach but will dissolve and release the contents once is reaches the small intestine. Their prime intension is to delay the release or drugs which are inactivated by the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa.

Cracking[3] of the film either during application or on storage will result in a loss of enteric properties. Therefore consideration must be given to the mechanical properties of the applied film. Cracking problems can be effectively overcome by plasticization. Plasticizer can also be used to reduce the permeability of the polymer film to water vapor. The choice of suitable plastizer is restricted to non water soluble material because these are likely to be most effective.

An evaluation in made of the solubility parameters of species together with an assessment of the intrinsic viscosity of dilute solutions of the polymer on the plasticzers. This determines the maximum interaction between polymer and plasticizer and indicates which plasticizer is likely to be most effective.

A general rule to follow is to use 1 part plasticizer to 10 parts polymer one should also consider viscosity of the plasticizer its influence on the final coating solution its effect on film permeability tackiness flexibility solubility and taste and its toxicity compatibility with other coating solution components and stability of the film and the final coated product.

Important reasons for enteric Coating are as follows

- To protect acid liable drugs form the gastric fluid
- To protect gastric distress or nausea due to irritation form drug
- To deliver drugs intended for local action in the intestines
- To deliver drug that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
- To provide a delayed release component to repeat actions

- Protect the drugs from harmful effect of the gastric contents: some if the drugs are prone to be hydrolyzed in acid media (E.G. Esomeprazole, Omeprazole, Pantaprazole)

Ideal Enteric Coating materials should have the following properties:

- Resistance to gastric fluids
- Ready susceptibility to or permeability to intestinal fluids
- Compatibility with most coating solution components and the drug substrates
- The film should not change on aging
- Formation of continuous film
- Non- toxicity
- Low cost
- Ease of application.

ENTERIC COATING MATERIALS:

Enteric coatings work because they are selectively insoluble substances they won't dissolve in the acidic juices of the stomach, but they will when they reach the higher pH of the small intestine.

Most enteric coatings won't dissolve in solutions with a pH lower than 5.5 commonly used enteric coating may be made form:

- Methacrylic acid copolymer
- Cellulose acetate (and its succinate and phthalate version)
- Polymethacrylic acid /acrylic acid copolymer
- Hydroxypropyl methyl cellulose phthalate
- Cellulose acetate tetrahydrophtalate
- Acrylic resin
- Shellac

The earliest enteric coatings utilized formalized gelatin, this was unreliable because of the polymerization of gelatin could not be accurately controlled. Another was shellac disadvantage was polymerization with time resulting in poor dissolution of the coating.

The most extensively used polymer are CAP, PVAP, the most recently used polymer are HPMCP, Methacrylic acid copolymer.

Cellulose Acetate Phthalate (CAP):

Effective enteric coating it only dissolves above pH 6 and may delay drug release longer than desired. It is permeable to moisture and simulated gastric fluid in comparison with other enteric polymers and it is susceptible to hydrolytic breakdown on storage.

Poly Vinyl Acetate Phthalate (PVAP)

Less permeable to moisture and simulated gastric juice it is more stable to hydrolysis on storage enteric dosage forms coated with PVAP disintegrates at pH5.

Hydroxy Propyl Methyl Cellulose Phthalate (HPMCP):

- It is available in two grades HP50 and HP55.
- HP55 Solutions are more viscous than HP50.
- HP50 disintegrates at pH5 and HP 55 disintegrates at pH5.5

It has stability similar to that of PVAP and dissolves in the same pH range. The advantage is that it does not require plasticizer.

Methacrylic acid copolymer:

Two grades are available A and B which differs in the ration of free carboxyl to ester groups therefore.

Type A has a ration of 1:1 and disintegrates at pH6

Type B has a ration of 1:2 and disintegrates at pH7.

Available under the trade names Eufragit L and S correspond to NF types A &B.

COATING EQUIPMENT:

Most of the coating processes use one of three general types of equipment

1. The standard coating pan
2. The perforated coating pan
3. The Fluidized bed coater.

CONVENTIONAL PAN SYSTEM:

The standard[4] coating pan system consists of a circular metal pan mounted some what angularly on a stand the pan is rotated on its horizontal axis by a motor the hor air is directed into the pa and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied by spraying the materials on the bed surface.

THE PERFORATED COATING PAN:

Neocota is an automatic coating system for tablets and pellets. Neocota is a completely updated automatic coating system having a batch capacity of 500 got 1 kg. this model efficiently carries out the following operations. Aqueous film coating of tablets /pellets: Non –aqueous organic solvent based film coating of tablets/ pellets; and enteric film coating of tablets/ pellets.

The basic units of the system are coating pan has perforations along its cylindrical portion. It is driven by a variable speed drive with a flame proof motor, supply of hot air and exhaust of drying air are arranged to facilitate the coating system through stainless steel plenums positioned on both sides of the perforated coating pan. The pan is enclosed in a cylindrical airtight housing provided with a suitable door and front glass window. This housing of pan with drive is a stainless steel basinet accommodating the gearbox, AC variable drive power panel hot air unit ex- haust unit and an air fitter.

Liquid spray system is complete with stainless steel liquid storage vessel, variable flow rate liquid dosing pump automatic spray gun and inter connecting flexible hoses.

The Fluidized bed coater:

The fluid Bed technology offers a very efficient coating technique.

The major advantage of the fluid Bed systems is that it is as per GMP standards it is a closed system.

The second advantage of the fluid Bed Systems is that not only coating but granulation and pellet formation is also possible in the same machine.

Fluidized bed coating is a process that takes place inside a fluidized bed whereby a coat is introduced to cover the intended objective in order to protect it or modify its behavior particulate coating is a form of fluidized bed coating involving the coating of solid.

Particles by spraying with a solution of the coating material. The fluidizing gas is also use to dry the deposited solution to form a coat on the surface of the particle.

There is considerable diversity in methods of using fluidized bed technology. For e.g liquids can be applied to fluidized particles in a variety of ways, including top bottom and tangential spraying. For a given product each method can offer markedly different finished product characteristics.

Fluidized beds are used for coating because of their high energy and mass transfer fluidized beds for film coating can be divided into there groups.

- Top Spray
- Tangential Spray
- Bottom Spray equipment

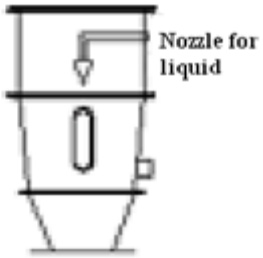
Top Spry

The expansion chamber is lengthened to allow powder to remain fluidized linger and to move with a higher velocity so that agglomerations is minimized. The expansion chamber is conically shaped to allow uniform deceleration of air stream.

The filter housing is larger and designed to shake the fines back into the bed interrupting fluidization this reduces agglomeration tendencies.

The nozzle is positioned low in the expansion chamber so that coating materials impinge on the fluidized particle a short distance form the nozzle : this reduces droplet spray drying and provides for longer subsequent drying of the coated particles.

The top spray coater has been used to apply aqueous and organic solvent based film coating controlled release coatings.

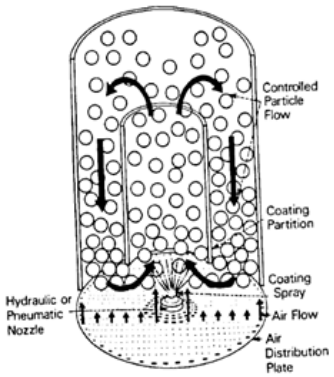


TOP SPRAY

Bottom spray coating 10 (Wurster process, Make- GLATT)

The wurster machine employs a cylindrical product container with a perforated plate. Inside the container is a second cylinder (coating partition) with is raised slightly above the perforated plate, centered in the plate below this partition is a spray nozzle used to dispense the coating solution. The perforated plated is designed with large holes in the area under the coating partition and smaller holes in the remainder of the plate, except for one ring of large holes at the perimeter. The design allows the substrate particles to be pneumatically transported upward through the coating partition and downward outside this partition. Material passing through coating partition receives a layer of coating materials dries in the expansion chamber and falls back in a semi fluidized state. Materials circulates rapidly in this fashion and receives layer of coating materials dries in the expansion chamber and falls back in a semi fluidized state materials circulates repaid in this fashion and receives a layer of coating on each pass through the coating partition.

The ring of large holes on the periphery of perforated plate prevents the accumulation of materials at the container wall. It has been for coating small particles pellets and tablets.



Wurster coating chamber

Parameters Used in Bottom Spray Equipment

Inlet temperature	38-42°C
Product temperature	32-36°C
Exhaust temperature	32-38°C
Spray rate	8-12mg/min
Peristaltic pump	12-18 rpm

FLUID END COATING

Particles smaller than approx.2mm should be coated in fluid equipments because with decreasing particle diameter the specific surface area of a substrate increase dramatically thus the required coating weight gain is much higher than tablet coating processes. In order to achieve acceptable process times the high efficiency of fluid bed compared to pan coating equipment shows clear advantages in particles coating processes.

SHAPE- in order to achieve good flow properties spherical particles with smooth surfaces are preferred, while needle shaped particles show poor flow properties and tend to form lumps. Another advantage of the latter is the increased risk of breakage during the coating process creating un coated spaces and leading to an increased coating weight gain besides crystals and pellets granules can be used as substrates as a disadvantages we may have uneven surfaces and often increased abrasion compared to the shapes

mentioned first which can also lead to increased surface areas which requires higher amounts of coating.

SIZE –Usual particle sizes are in arrange of 0.2-1.2 mm. smaller particles may have problematic flow properties in higher scale and may tend to break if the length /diameter ratio is 2. Smaller particle size are required if particles are administered form sachets or incorporated into chewable tablets in order to avoid damage by chewing the coated particles should have a maximum size of 0.4mm smaller end products may given a better mouth felling but increasing specific surface areas requires higher coating amounts.

TOP/BOTTOM/TANGENTAL SPRAY

The top spray method is known and used for particle coating and granulation processes. Compared to other fluid bed coating technologies the top spray method is susceptible for porous film structure especially if organic coating formulations are processed. Bottom spraying (wurster process) is the usual method in particle compared to the top spray method and the required polymer weight gain for a certain functions usually lower to some extent. A disadvantage is that in case of nozzle can blockage during the coating process, the product must be discharged before the nozzle can be cleaned. Tangential spraying system which is commonly fitted with a rotating bottom plate, can achieve film quantities nearly as good as bottom spraying system. The rotation of the plate nicely supports product movement so that the required air amount is mainly used for drying process and only to a smaller degree for the product movement.

NOZZLES FOR THE PARTICLE COATING

Common spray gun are air borne with a round spray pattern. Some equipment is fitted with a double air supply which is used for common atomizing air and extra microclimate air, which surrounds the spray pattern preventing over wetting of the products and reducing spray drying effects.

PUMP SYSTEM.

Peristaltic pumps fitted with silicon tubing are standard. Tubing cab be selected in a wide range of internal diameters in order to keep the flow speed high and hence to prevent sedimentation therefore the use of tubing with small internal diameters recommended alternative pump systems include gear pump and piston pump

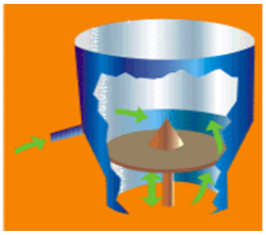
ROATING DISK GRANULATION

Granulation techniques utilizing centrifugal fluidizing drive have been studied only recently. These techniques have been extended to coating operations and combined with an expansion chamber to form the rotation disk granulator and coater fluid bed device. The basic design employs a rotating disk in the product container.

The disk can be moved up or down to create a variable slit opening between the outer perimeter of the disk and the sidewall of the container. Air is drawn into the product container through the slit under negative pressure. This fluidizes the materials along the circumferential surface of the product container. At the same time the disk rotates at varying speeds and moves the products by the centrifugal force to the outer portions where it is lifted by the fluidizing air stream into the expansion chamber. As the material decelerates, it descends to the center of the disk and repeats the same sequence.

The fluidization pattern is often described as a spiraling helix or rope like pattern around the inside of the rotor chamber.

Spray nozzles can be immersed in the bed of fluidized materials and spray applied in tangential fashion with respect to the particle flow.



ROTATING DISK GRANULATOR

LITERATURE REVIEW

1. **Manish Maheswari et al[5] (2006)** The developed Tetra cycline Serratiopeptidase contain periodontal gel by reducing polymer concentration and to obtain reasonable viscosity at lower concentration by addition of viscosity.

2. **TH All Khateeb et al[6] (2007)** The aim of the study was to investigate the ability of Serratiopeptidase to reduce post operative swelling , pain after 3rd molar surgery

3. **Deependra Singha et al[7]** Serratiopeptidase loaded poly (D,L lactic-co-glycolic acid) Microspheres were prepared using the modified double emulsion method the effect of polymer concentration and external aqeous phase volume on microsphere size and entrapment efficient was studied by 32 full factorial experiment .

4. **Sandhya KV et al[8] (2007)** The developed liposomal formulation of Serratiopeptidase on caoco-2 cell permeability and oral bio availability liposomes Serratiopeptidase was formulated by standard lipid film hydration method with drug in hydration medium

5. **Rajvaidya et al (2007)[9]** The present study aimed to prepare and characterize serratiopeptidase bearing multivesicular liposomes for sustained delivery of serratiopeptidase. Multivesicular liposomes (MVLs) bearing serratiopeptidase were prepared using the double emulsification technique using amphipathic lipid, cholesterol, neutral oil and negatively charged lipid and characterized for their shape, size, drug entrapment and in vitro drug release. In vivo performance of multivesicular liposomes bearing serratiopeptidase was evaluated by assessing anti-inflammatory activity using the carrageenan-induced rat paw edema volume method and the cotton pellet granuloma method. The results thus obtained were compared with those of conventional drug solution and conventional liposomes containing serratiopeptidase in equal amounts.

6. **Sumit Chakraborty et al [10](2009)** Pantoprazole 5-(difluoromethoxy)- 2-[(3,4-imethoxypyridin-2-yl) methylsulfinyl]- 3H-benzoimidazole is proton pump inhibitor belongs to group of benzimidazole . This compound inhabits gastric acid formation and there by it is very efficient for the treatment of gastric and duodenum ulcers. In aqueous media more acidicthan pH 4 it suffers a practically complete decomposition within a period shorter than 10 minutes. Even in solid state it is sensitive to heat, humidity, light and especially to substances containing an acidic group. Pantoprazole which have an irritant effect on the stomach can be coated with a substance that will only dissolve in the small intestine. For such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment (intestines pH 5.5 and above) where they do not degrade, and give their desired action.

7. **Murat Tu¨rkog˘lu et al[11] (2003**) In this study, fluidized-bed manufactured enteric-coated omeprazole pellets were compressed into tablets. The stability of the pellets and those of compressed tablets were evaluated for remaining omeprazole and for degradation products under an accelerated stability protocol.the data were analyzed using the artificial neural network (ANN) and analysis of variance (ANOVA). It was found that enteric-coatedomeprazole pellets could be compressed into quickly disintegrating tablets using microcrystalline cellulose granules as the pressureabsorbing matrix.

8. **Michael J. Story et al [12](1976)** The advantages of encapsulated enteric-coated pellets as dosage forms are discussed theoretically and compared to enteric-coated tablets. An enteric-coated tablet may take from approximately 0.5 to more than 8 hr to pass from the stomach to the duodenum. On the other hand, enteric-coated pellets are subjected to dispersion in the stomach, but they pass through the pyloric sphincter after a mean residence time in the stomach that would not be different from that exhibited by a suspension dosage form. The dispersion effect causes a

theoretical reduction in peak blood level over that of an enteric-coated tablet of equivalent potency while maintaining bioavailability. It is hypothesized that enteric-coated pellets will reduce intestinal side effects that may occur with enteric-coated tablet preparations.

9. **J. G. HARDY et al[13] (1990)** In this study enteric coated formulation of naproxen has been evaluated using 8 healthy subjects and identified that small intestinal transit of enteric coated formulation before and after the break fast.
10. **Gonzales, Gilbert et al[14] (Application Number: 10/154629) (2003)** an enteric-coated caffeine delivery system includes a caffeine-containing core and an enteric coating made of methacrylic acid copolymer. The caffeine delivery system may also include a sub coating. The caffeine delivery system resists disintegration and release of the caffeine at a pH less than 5, but disintegrates rapidly to release the caffeine at a pH greater than about 6.

11. **Kim, Sang Min et al** [15]United States Patent Application 20080292696 The invention relates to an enteric, sustained-release tablet comprising paroxetine or a hydrates or anhydrides of a pharmaceutically acceptable salt thereof as active substance, more particularly to a tablet prepared by coating a sustained-release tablet core containing paroxetine with an enteric polymer, wherein the interaction between the tablet core and the enteric coating layer is minimized to enable constant drug release without regard to the residence time of the tablet in the stomach.

12. **Raghavan, Vineeth et al[16]** WIPO Patent Application WO/2004/058228. An enteric coated composition of fluoxetine (N-metthyl- (p-trifluoromethylphenoxy)-3-phenylpropylamine) in the form of coated tablets and pellets providing gastric pH resistance but disintegrating rapidly in intestinal. The composition is suitable for oral administration comprising a core consisting of the active fluoxetine and/or its pharmaceutically acceptable acid addition salts along with one or more

pharmaceutically acceptable excipients with a selective seal coat on said core and an enteric coat over said seal coated core. A seal coat of polyvinyl alcohol is proposed over which an enteric coat of methacrylic acid copolymer is provided. The above enteric coated formulations of fluoxetine involve a cheaper, commercially available, easier to apply enteric polymer wherein smaller quantities of polymer are required to achieve the desired results. It would provide enteric coated formulation of fluoxetine requiring smaller quantities of polymer and yet achieve the desired characteristics of gastric pH resistant to release and rapidly disintegrating release profile in intestine pH.

13. **Curatolo, William J. et al** [17] United States Patent Application 20080199527 A pharmaceutical composition is disclosed which comprises multiparticulates wherein said multiparticulates further comprise an azithromycin core and an enteric coating disposed upon said azithromycin core.
14. **Kanazawa, Hashime et al**[18] United States Patent 6326360 The invention is to obtain an oral glycyrrhizin preparation not only manufacturable by a simple method but also having an excellent property of being absorbed from the digestive tract. In the present invention, such oral preparations are made into enteric forms wherein glycyrrhizin is admixed with an effervescent agent in combination with an absorption enhancer such as a medium-chain fatty acid or a salt thereof. In the preparation of the present invention, it is now possible to achieve an excellent absorption of glycyrrhizin from the digestive tract by addition of an effervescent agent and, moreover, the preparation can be manufactured by a simple, convenient method without special steps.

15. **Chen, Chih-ming et al** [19]United States Patent 5830503 A once-a-day diltiazem dosage form which comprises: (a) a core element which is a compressed tablet which contains a therapeutic dose of diltiazem and an amount of a solubility modulating substance that controls the release of said diltiazem in order to provide a therapeutic level over a period of about 24 hours; and (b) on the outer surface of

the core element, a sufficient amount of an enteric coating that causes the diltiazem to release at a rate that permits the use of once-a-day dosing to maintain steady state therapeutic levels of diltiazem.

16. **Deshmukh, Abhijit Mukund et al,**[20] United States Patent Application 20040170688 An industrially advantageous enteric formulation of Fluoxetin without the use of hydroxyl propyl methylcellulose acetate succinate and sucrose is covered by this invention. The present invention also covers said enteric formulations of Fluoxetin in the form of tablets or capsules with an optional separating layer. When in the form of capsules, the separating layer is capsule shell itself thus reducing processing step of said enteric formulations. The formulation of the present invention along with Fluoxetin or its pharmaceutically accepted salts, solvates, enantiomers or mixtures thereof including racemic mixture is also contemplated to be within the scope of present invention

17. **Wendsj, Stig et al,**[21] WIPO Patent Application WO/1998/040054 An enteric coated oral dosage form comprising sodium amoxycillin, wherein the dosage form is a single unit tableted dosage form or a multiple unit tableted dosage form is claimed. Processes for the manufacture of the dosage forms as well as the formulations, use in the treatment of $i(Helicobacter pylori) infections are claimed.
18. **Ikemoto, et** al [22] Japanese Patent JP2004175768 To provide a method for producing a stabilized omeprazole enteric coated tablet by coating a core tablet containing the omeplazole with an intermediate coating layer on the surface of the core tablet, then coating an enteric coating layer on the intermediate coated layer in this order without containing any alkali reactive compound in the core tablet and in the intermediate coated layer.
19. **Ullah, Ismat et al**'[23] WIPO Patent Application WO/2006/055740 Disclosed is an enteric coated bead comprising Ixabepilone, a compound having a structure: (A). Also disclosed is a capsule comprising a multitude of the enteric coated beads.

Further, a method of preparing the enteric coated bead and a method of treating cancer or other proliferative diseases using the enteric coated bead are disclosed

20. **Sugita, Katsuji et al**[24] United States Patent Application 20030175350 The invention provides enteric coated preparation excellent in absorbability, containing thyrotropin-releasing hormone (TRH) or derivatives thereof as a medicinally active ingredient
21. **Kelm, Gary Robert et al** [25]WIPO Patent Application WO/1998/022096 The present invention relates to a pharmaceutical composition in a unit dosage form for per oral administration in a human or lower animal, having a gastrointestinal tract comprising a small intestine and a colon with a lumen there through having an inlet to the colon from the small intestine, comprising: a) a safe and effective amount of a therapeutically active agent incorporated into or coated on the surface of a dosage form selected from the group consisting of a spherical substrate, an elliptical substrate, a hard capsule, or a compressed tablet, with a maximum diameter of about 3 mm to about 10 mm; and b) an enteric polymer coating material comprising at least one inner coating layer and one outer coating layer; wherein the dosage form has a smooth surface free from edges or sharp curves; the elliptical substrate and the hard capsule have a ratio of the long to short diameters of no greater than about 1.5; the therapeutically active agent is released at a point near the inlet to, or within the colon; each of the inner coating layer(s) is an enteric polymer that begins to dissolve in an aqueous media at a pH between about 5 to about 6.3; and the outer coating layer is an enteric polymer that begins to dissolve in an aqueous media at a pH between about 6.8 to about 7.2.
22. **Eiji Fukui et al (May 2000)**[26] As a new oral drug delivery system for colon targeting, enteric coated timed-release press-coated tablets (ETP tablets) were developed by coating enteric polymer on timed-release press-coated tablets composed of an outer shell of hydroxypropylcellulose and core tablet containing diltiazem hydrochloride (DIL) as a model drug. The results of the in vitro dissolution tests in JP 1st fluid (pH 1.2) and JP 2nd fluid (pH 6.8) indicated that these tablets showed both acid resistance and timed-release. The gastric emptying

time and lag time after gastric emptying were evaluated by determining the times at which PPA and DIL first appeared in the plasma (TFAPPA and TFADIL, respectively). TFAPPA and TFADIL were about 4 and 7 h, respectively. This value of TFAPPA indicated that ETP tablets displayed acid resistance in the stomach as well as in JP 1st fluid. Subtraction of TFAPPA from TFADIL gave a value of about 3 h which agreed well with the lag time determined by in vitro dissolution test in JP 2nd fluid.

23. **Ann Debunne et al (March 2004)**[27] the aim of this study was to investigate the influence of formulation and compression parameters on the properties of tablets, containing enteric-coated pellets, and on the integrity of the enteric polymer of the individual pellets after compression. In addition the piroxicam plasma concentrations were determined after single and multiple oral administrations of powder, pellet and tablet formulations at a dose of 0.3 mg piroxicam/kg bodyweight to dogs. Tablets consisted of enteric-coated pellets (containing 2.5% (w/w) piroxicam in combination with microcrystalline cellulose and sodium carboxymethylcellulose (using Avicel® PH 101 and Avicel® CL 611 in a ratio of 1–3)), cushioning waxy pellets and 10% Kollidon® CL (as an external disintegrator).

24. **M. Marvola et al (June 1998)**[28] the aim of this study was to develop a multiple-unit, site-specific drug formulation allowing targeting of drug release in the colon. Initially, characteristics of matrix pellets containing various enteric polymers as binders were tested. An enteric coating was then added to the formulations. Ibuprofen and furosemide were used as model drugs. The former is absorbed throughout the gastrointestinal tract, the latter only from upper parts. Methacrylate copolymers, hydroxypropyl methylcellulose acetate succinates and cellulose acetate phthalate were used as enteric polymers. The properties of the products were initially tested via dissolution studies at different pHs, then via bioavailability studies in healthy volunteers. The main conclusion was that drug

release can be targeted on the distal part of the small intestine and the colon by preparing film-coated matrix pellets in which enteric polymers dissolving at pHø7 have been used both as binders in the pellets and as coating material.

25. **Ehab A.Hosny et al[29] (December 1995)** Polycarbophil containing diclofenac sodium tablets were formulated using two different size of granules. The granules were obtained by evaporation under reduced pressure of polycarbophil particles loaded with alcoholic solution of the drug. The in-vitro release of these bioadhesive containing tablets was evaluated together with that of Ciba-Geigy commercially available enteric coated tablets 'Voltaren' in simulated gastric fluid for 2 h followed by another 2 h in simulated intestinal fluid. The Voltaren tablets released no drug in simulated gastric fluid but released all their drug contents within 1 h in simulated intestinal fluid. The tablets formulated using polycarbophil granules of smaller size (0.18-0.313 mm) released about 13% of their drug contents in simulated gastric fluid and released the remaining drug in simulated intestinal fluid within 0.5 h of dissolution, while tablets formulated with larger granules size (0.5-0.8 mm) released 10% of their drug contents in the first medium and released the remaining drug within 2 h in the second. The results also indicated the effect of bioadhesive granules size on rate and extent of absorption where tablets formulated with smaller granules size showed higher C .... shorter Tma~, larger AUC and higher relative bioavailability compared with those tablets formulated with larger granules size.

26. **L. Diane Bruce et al [30](July 2003)** the influence of sub coat application and micro-environmental pH on the dissolution properties of enteric coated sodium valproate pellets was investigated. The pellets were prepared by solution-layering or wet-mass extrusion-spheronization methods. In order to pass the USP enteric test, the solution-layered and wet-mass extruded pellets required 35 and 25% weight gain of Eudragit® L 30D-55, respectively. The application of a sub coat of either Methocel®-E5 (HPMC) or Opadry® AMB to the pellets

resulted in a delay in sodium valproate release in 0.1N HCl. Further delay in drug release was observed when citric acid was present in a HPMC sub coat or when added to the core pellet formulation. The amount of drug released from coated pellets was a function of the level of citric acid in the pellet core or sub coat and subsequent micro-environmental pH of the pellets.

27. **W.Y. Donga et al (September 2006)**[31] The objective of the study was to prepare and evaluate carbamazepine-loaded enteric micro particles produced by a novel coacervation method. An aqueous polymeric stabilizer solution was added to an organic carbamazepine/Eudragit® L100-55 solution. Water, which is a non-solvent for the drug and the enteric polymer, caused phase separation and the formation of coacervate droplets. These droplets hardened into micro particles upon further addition of the aqueous phase. The micro particles were characterized with respect to particle size distribution, morphology, encapsulation efficiency, yield, physical state and physical stability of the drug, wettability, in vitro release and in vivo bioavailability. The drug was in a non-crystalline state in the matrix and physically stable for 5 months at room temperature.

SCOPE AND OBJECTIVE

The aim and objective of this work is to develop small intestine targeting tablets of Serratiopeptidase enteric coated tablets-conventional standard coated technique.The present study is to develop a pharmaceutically stable, cost effective and quality improved formulation of Serratiopeptidase enteric coated tablets.

OBJECTIVES OF THE STUDY:

The objectives of the present study are:

- To formulate Serratiopeptidase encapsulated tablets.
- To evaluate the hardness, friability and in vitro release of Serratiopeptidase.

PLAN OF WORK

1. Extensive literature survey.
2. Procurement of Excipients.
3. Procurement of drug (Serratiopeptidase)
4. Preformulation Studies
   a. Tapped density
   b. Bulk density
   c. Angle of repose
   d. Car's index
5. Formulation of Serratiopeptidase enteric coated tablets.
6. Evaluation of Serratiopeptidase enteric coated tablets.
   a) Hardness
   b) Friability
   c) Disintegration
   d) In- vitro drug release.
7. Selection of best formulation on the basis of In-vitro drug release

DRUG PROFILE

Synonym : Shara Bacilli (serratias.p.e 15)[32]

Description : Serratiopeptidase is an enzyme derived from bacteria belongs to genus Serratia. Serratiopeptidase is a protolytic or protein digestive enzyme.

Molecular Weight : 60k Dalton

Characteristic : Fine dry powder

Description : off white light brown

Solubility : Readily soluble in water

Odour : Free of Offensive Odour

Drug Category : Analgesics, Anti-Inflammatory

Indication : Trauma Surgery: In sports injuries, fractures, dislocatiand Osteoarthritis etc, Serratiopeptidase reduces inflammation and helps in faster healing and repair.

Optimum P^H : 8.5-9.5

P^H stability : 5-6

Optimal temperature: 37℃

Mode of action: Serratiopeptidase is a proteolytic enzyme available for clinical use more than a decade. Serratiopeptidase binds to alpha -2-macroglobulin in the blood in the ratio of 1:1, which helps to mask its antigenicity but retains its enzymatic activity and is slowly, transferred to site of inflammation. Serratiopeptidase hydrolyses bradykinin, histamine and serotonin responsible for oedematic status. Serratiopeptidase reduces swelling improves microcirculation and expectoration of sputum etc. Thus it can be concluded that Serratiopeptidase has anti-inflammatory, anti-oedemic and fibrinolytic activity and acts rapidly on localized inflammation.Serratiopeptidase when consumed in unprotected form is destroyed by acid ion the stomach. However, enteric coated of tablet enable the enzyme to pass through the stomach unchanged and absorb in the intestine.

Pharmacological action: Anti-inflammatory and anti-edematous actions: Serratiopeptidase causes fibrin and bradykinin hydrolysis, without affecting human proteins such as albumin and
Alpha- or gamma-globulins.

Pharmacodynamics: enzymetherapy with anti-inflammatory, anti-edematous and Fluidifying action on the locomotive and respiratory systems.

Pharmacokinetics: Following oral administration to experimental animal, peak plasma Concentrations were achieved within less than one hour, the highest concentrations being found in the lymph. All of the substance was absorbed by the lymph within 6 hours following administration and increased in a dose-dependent fashion.

Dosage: Therapy for adults only: The usual recommended dose is one tablet taken By mouth 3 times daily with meals. This dose may be increased according to the Severity of the condition.

Dosage forms : Capsule and Tablet.

Applications:

Surgery: Serratiopeptidase reduces post operative Edema at injection sites. Serratiopeptidase reduces internal tissue edema and inflammation caused at post-operative handling. Reduction in edema reduces chances of rupture at tissue as well as risk of in case of plastic surgery graft rejection.

Respiratory Medicine: Serratiopeptidase breaks down complex sputum molecules into smaller peptidase of lower viscosity, helping in expectorating them more easily. Reduced viscosity of secretion helps in better antibiotic penetration to enable control over stubborn infections like bronchitis,lungabscess.

ENT: Serratiopeptidase has Mucolytic activity in sinuses, ear cavities and anti – inflammatory activity in upper respiratory tract organs help in faster resolution, better

antibiotic bioavailability and fastercurerates.

Dermatology: Serratiopeptidase is used in acute painful inflamed dermatitis.

Dentistry: Serratiopeptidase helps in better control over dental infections and inflammation.

Obstetrics & Gynecology: The anti-inflammatory activity of Serratiopeptidase helps in resolution of post-partum haematomas, breast engorgements and pregnancy related thrombophlebitis.

Male Genital Infection: Serratiopeptidase restores microcirculation and augments antibiotic penetration in these organs which are known to produce poor antibiotic availability.

Storage: In sealed container under cool and dry condition.

EXCIPIENTS PROFILE

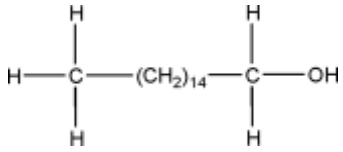
Cetyl Alcohol [33,34,35]

Synonyms: Avol; Cachalot; Crodacol C70; Crodacol C90; Crodacol C95; ethal; ethol; 1-hexadecanol; n-hexadecyl alcohol; Rita CA; Tego Alkanol 16.

Chemical Name: Hexadecan-1-ol

Empirical Formula: C16H34O 242.44 (for pure material)

Structural Formula:



Functional Category: Coating agent; emulsifying agent; stiffening agent

Applications in Pharmaceutical Formulation or Technology:

- Cetyl alcohol is widely used in cosmetics and pharmaceutical formulations such as suppositories, modified-release solid dosage forms, emulsions, lotions, creams, and ointments.
- In suppositories cetyl alcohol is used to raise the melting point of the base, and in modified-release dosage forms it may be used to form a permeable barrier coating.
- Cetyl alcohol is also used for its water absorption properties in water-in-oil emulsions.

Description: Cetyl alcohol occurs as waxy, white flakes, granules, cubes, or castings. It has a faint characteristic odor and bland taste.

Solubility: Freely soluble in ethanol (95%) and ether, solubility increasing with increasing temperature; practically insoluble in water.

Stability and Storage Conditions

Cetyl alcohol is stable in the presence of acids, alkalis, light, and air; it does not become rancid. It should be stored in a well-closed container in a cool, dry place.

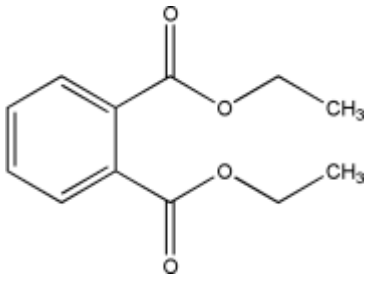
Diethyl Phthalate

Synonyms: DEP; ethyl benzene-1,2-dicarboxylate; ethyl phthalate; Kodaflex DEP; phthalic acid diethyl ester.

Chemical Name: 1,2-Benzenedicarboxylic acid, diethyl ester

Empirical Formula: C12H14O4 222.24

Structural Formula:



Functional Category: Film-former; plasticizer; solvent.

Applications in Pharmaceutical Formulation or Technology:

- Diethyl phthalate is used as a plasticizer for film coatings on tablets, beads, and granules at concentrations of 10–30% by weight of polymer.
- Diethyl phthalate is also used as an alcohol denaturant and as a solvent for cellulose acetate in the manufacture of varnishes and dopes.

Description: Diethyl phthalate is a clear, colorless, oily liquid. It is practically odorless, or with a very slight aromatic odor and a bitter, disagreeable taste.

Solubility: Miscible with ethanol (95%), ether, and many other organic solvents Practically insoluble in water.

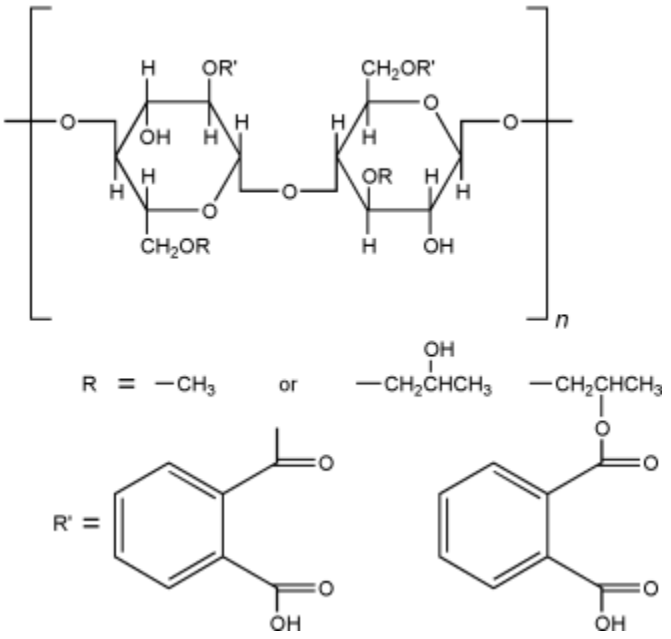
Stability and Storage Conditions: Diethyl phthalate is stable when stored in a well-closed container in a cool, dry place.

Hypromellose Phthalate

Synonyms: Cellulose phthalate hydroxypropyl methyl ether; HPMCP; hydroxypropyl methylcellulose benzene-1,2-dicarboxylate; 2-hydroxypropyl methylcellulose phthalate; methylhydroxypropylcellulose phthalate.

Chemical Name: Cellulose, hydrogen 1,2-benzenedicarboxylate, 2-hydroxypropyl methyl ether

Structural Formula:



Functional Category: Coating agent.

Applications in Pharmaceutical Formulation or Technology:

- Hypromellose phthalate is widely used in oral pharmaceutical formulations as an enteric coating material for tablets or granules.
- Hypromellose phthalate can be applied to tablet surfaces using a dispersion of the micronized hypromellose phthalate powder in an aqueous dispersion of a suitable plasticizer such as triacetin, triethyl citrate, or diethyl tartrate along with a wetting agent.
- Hypromellose phthalate may be used alone or in combination with other soluble or insoluble binders in the preparation of granules with sustained drug-release properties.

Description: Hypromellose phthalate occurs as white to slightly off-white, free-flowing flakes or as a granular powder. It is odorless or with a slightly acidic odor and has a barely detectable taste.

Solubility:

Readily soluble in a mixture of acetone and methyl or ethyl alcohol (1 : 1), in a mixture of methyl alcohol and dichloromethane (1 : 1), and in aqueous alkali.

Practically insoluble in water and dehydrated alcohol and very slightly soluble in acetone.

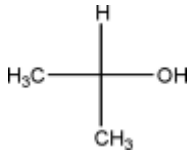
Isopropyl Alcohol

Synonyms: Dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec-propyl alcohol.

Chemical Name: Propan-2-ol

Empirical Formula: C3H8O 60.1

Structural Formula:



Functional Category: Disinfectant; solvent.

Applications in Pharmaceutical Formulation or Technology:

- Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations primarily as a solvent in topical formulations.
- Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation.
- Isopropyl alcohol has some antimicrobial activity.

Description:

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

Solubility:

- Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water.
- Soluble in acetone;
- Insoluble in salt solutions.

Stability and Storage Conditions

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

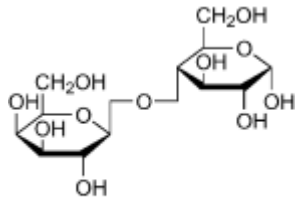
Lactose, Anhydrous

Synonyms: Anhydrous Lactose NF 60M; Anhydrous Lactose NF Direct Tableting; lactosum; lattioso; milk sugar; Pharmatose DCL 21; Pharmatose DCL 22; saccharum lactis; Super-Tab Anhydrous.

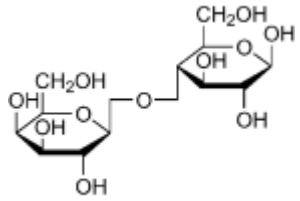
Chemical Name: O-β-d-galactopyranosyl-(1→4)-β-d-glucopyranose

Empirical Formula: $C_{12}H_{22}O_{11}$

Structural Formula:



Anhydrous α-lactose



Anhydrous β-lactose

Functional Category: Binding agent; directly compressible tableting excipient; lyophilization aid; tablet and capsule filler.

Applications in Pharmaceutical Formulation or Technology:

Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content.

Description: Lactose occurs as white to off-white crystalline particles or powder.

Solubility: Soluble in water; sparingly soluble in ethanol (95%) and ether.

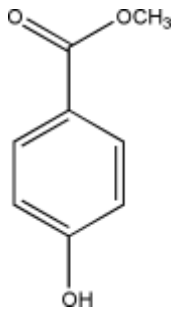
Methylparaben

Synonyms: 4-hydroxybenzoic acid methyl ester; methyl p-hydroxybenzoate; Nipagin M

Chemical Name: Methyl-4-hydroxybenzoate

Empirical Formula: C8H8O3

Structural Formula:



Functional Category: Antimicrobial preservative.

Applications in Pharmaceutical Formulation or Technology:

- Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations
- Owing to the poor solubility of the parabens, paraben salts (particularly the sodium salt) are more frequently used in formulations. However, this raises the pH of poorly buffered formulations.
- Methylparaben (0.18%) together with propylparaben (0.02%) has been used for the preservation of various parenteral pharmaceutical formulations.

Description: Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

Titanium Dioxide

Synonyms: Anatase titanium dioxide; brookite titanium dioxide.

Chemical Name: Titanium oxide

Empirical Formula: TiO_2

Structural Formula: TiO_2

Functional Category: Coating agent; opacifier; pigment.

Applications in Pharmaceutical Formulation or Technology:

- Titanium dioxide is widely used in confectionery, cosmetics, and foods, in the plastics industry, and in topical and oral pharmaceutical formulations as a white pigment.
- Owing to its high refractive index, titanium dioxide has light-scattering properties that may be exploited in its use as a white pigment and opacifier.
- Titanium dioxide is also used in dermatological preparations and cosmetics, such as sunscreens.

Description: White, amorphous, odorless, and tasteless nonhygroscopic powder.

Solubility:

- Practically insoluble in dilute sulfuric acid, hydrochloric acid, nitric acid, organic solvents, and water.
- Soluble in hydrofluoric acid and hot concentrated sulfuric acid.

Magnesium Stearate

Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

Chemical Name: Octadecanoic acid magnesium salt

Empirical Formula: C36H70MgO4

Structural Formula: [CH3(CH2)16COO]2Mg

Functional Category: Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Typical Properties

Crystalline forms: High-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): 0.159 g/cm3

Density (tapped): 0.286 g/cm3

Density (true): 1.092 g/cm3

Flash point: 250°C

Flowability: poorly flowing, cohesive powder.

Melting range:

- 117–150°C (commercial samples);
- 126–130°C (high purity magnesium stearate).

Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

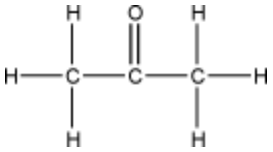
Acetone

Synonyms: Dimethylformaldehyde; dimethyl ketone; β-ketopropane; pyroacetic ether.

Chemical Name: 2-Propanone

Empirical Formula: C3H6O

Structural Formula:



Functional Category: Solvent.

Applications in Pharmaceutical Formulation or Technology: Acetone is used as a solvent or cosolvent in topical preparations, and as an aid in wet granulation. It has also been used when formulating tablets with water-sensitive active ingredients, or to solvate poorly water-soluble binders in a wet granulation process. Acetone has also been used in the formulation of microspheres to enhance drug release.Owing to its low boiling point, acetone has been used to extract thermolabile substances from crude drugs.

Description: Acetone is a colorless volatile, flammable, transparent liquid, with a sweetish odor and pungent sweetish taste.

Typical Properties:

Boiling point: 56.2°C

Flash point: –20°C

Melting point: 94.3°C

Refractive index: n20D = 1.359

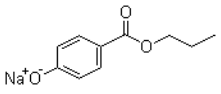
Solubility: soluble in water; freely soluble in ethanol (95%)

Vapor pressure: 185 mmHg at 20°C

Stability and Storage Conditions: Acetone should be stored in a cool, dry, well-ventilated place out of direct sunlight.

Propyl paraben sodium

Chemical Name: sodium propyl p-hydroxybenzoate
Trade Name: propyl paraben sodium
Molecular Formula: C10H11O3Na
MolecularWeight: 202.2
Physical and Chemical Properties: This chemical is white hygroscopic crystalline powder. It is easily dissolved in water and alkaline
Synonyms: Sodium propyl p-hydroxybenzoate; 4-Hydroxybenzoic acid propyl ester sodium salt

Molecular Structure: 

Molecular Formula: C10H11NaO3

Molecular Weight: 202.18

MATERIALS

S.NO	Materials	Use
1.	Lactose	Diluent
2.	Maize starch	Disintegrating agent/ Binding agent
3.	Methyl paraben sodium	Preservative
4.	Propile paraben sodium	Preservative
5.	Magnesium sterate	Anti adherent
6.	HPMC 15 cps	Polymer
7.	HPMC pthalate	Polymer
8.	Propyline glycol	Plastecizer
9.	Isopropile Alcohol	Solvent
10.	Iron red oxide	Coloring agent

EQUIPMENTS

S. No.	Instruments	Used in section
1.	Weighing Balance	Store In process
2.	DM Water plant	All processing areas
3.	Mass mixers	Granulation
4.	Mechanical vibrating shifter	Granulation
5.	Fluid bed drier	Granulation
6.	Multy mill	Granulation
7.	Tablet compression machine	Compression
8.	Coating machine	Coating
9.	Sieves	Granulation

METHADOLOGY

STEP 1:DISPENSING AND RECEIPT OF RAW MATERIALS

1, Dispensing and receipt operation is to be carried as per the sop.

2. Dispense the materials as per the raw materials requisition and duly

3. Weigh the raw materials in double poly-linedHDPE container and affix materials issue slips with all details

4. Dispense the purified water in SS vessels

STEP 2: SIFTING OF MATERIALS

Sift the following materials using mechanical vibrating sifter in to individual poly-lined HDPE DRUMS, tie properly and affix container label with details

S.NO	MATERIALS	MESH NO
1	Lactose	20
2	Maize Starch	40
3	Magnesium Stearate	40

STEP3: BINDING AGENT PREPARATION

1. Dissolve methyl paraben sodium ip and propyl paraben sodium ip in boiling purified water

2 disperse maize starch ip in cold purified water in a separate SS vessel to form starch slurry and filter through 100#

3. Add above starch slurry to boiling water (stage 1) under continuous stirring

4. mix thoroughly, weigh and adjust the weight with purified water (if necessary) allow it to cool 600c

STEP4: MIXING

1. load the sifted lactose and maize starch in mass mixer slowly so that no spillage of material occur and close the lid .switch on the mixer and run for 30 minutes

STEP5: GRANULATION (WET MIXING)

1. Open the lid mixture, add the entire quantity of starch at a time, and the close the lid properly.

2. Switch on the mixture run for 2 min, switch off the mixer wipe the paddles and shaft of the mixture to remove the wet mass adhered

3. switch on the mass mixture and run for 2 min more to form wet granular mass as per the requirement

4. Un load the wet material in plastic tube and mill the wet mass through multi mill fitted with 8 mm mesh

STEP6: DRYING

1. Place the bowl of FBD below the discharge chute of the multi mill and collect the wet granules in to the bowl of sufficient quantity for drying.

2. Place the bowl of FBD in operating position set the temperature at 650c and switch on the FBD.

3 dry the materials to the required moisture content1.9 to2.4%

4 unload the dried material in to poly-lined HDPE containers and label accordingly

5 the drying again loads wet mass or granules of this batch and repeat the drying operation.

6 if tray dryer is to be used for drying place the wet granules in trays and keep in tray dryer.

7. Set the temperature at 65oc and switch on the tray dryer and run for5to6 hours or to attain required moisture content in granules.

8 unload the dried granules in poly-lined HDPE container and label accordingly

STEP 7: SIFTING AND MILLING

1 sifts the dried materials through20# by operating mechanical vibrating sifter and collect in poly bags

2. Mill the retains (coarse granules) which are left on sieve, through multi mill fitted with 2mm screen

3. Resift the milled material through 20# and add to sifted granules

STEP8 BLENDING

1. Load the sifted and milled granules in mass mixer

2. Add serratiopeptidase to mass mixer and mix for 10 min

3. To this add the weighed quantities of lubricating material of magnesium stearate and maize starch in to the mass mixer

4. Operate the mass mixer for 5min

5. Transfer the blended granules in to poly ethylene bags lined containers with proper label

6. Weigh, record and store the granules in the quarantine

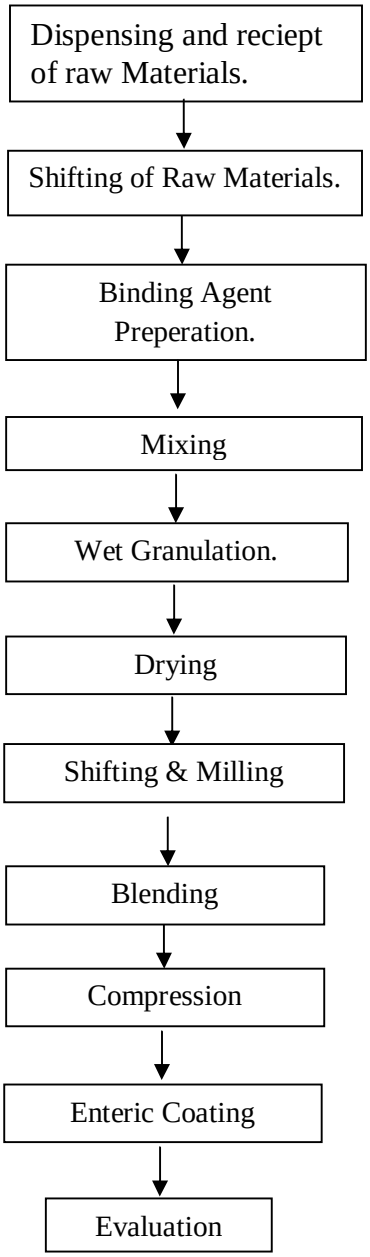
7. Send requisition to QC to collect samples of blend.

STEP9: COMPRESSION

Set the compression machine with 7.0mm size, round and normal concave shape upper and lower punches and dies. Load the blended granules in to the hopper and start compression.

Process Flow Chart

.



PREFORMULATION STUDIES

Preformulation[36] activities range from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage form. Critical information provided during preformulation can enhance the rapid and successful introduction of new therapeutics entities for humans. Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage form.

Objective

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailability. Further the use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like physical appearance, solubility, bulk density, tapped density, compressibility, melting point, molecular weight, sieve analysis.

A.P.I CHARACTERISATION:

1. Physical appearance
2. Solubility
3. Determination of bulk density and tapped density
4. compressibility index
5. Loss on drying
6. Angle of repose

1. Physical appearance: A small quantity of serratiopeptidase powder was taken in butter paper and viewed in well illuminated place. Finally the colour, odour and texture were observed.

2. Solubility: A semi-quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system vigorously shaken and examined visually for any undissolved solute particles. The solubility was expressed in terms of ratio of solute and solvent.

3. Determination of bulk density and tapped density:

It refers to a measurement to describe packing of particles and also used to determine the amount of drug that occupies the volume in mg/ml before tapping and after tapping an accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (Vo) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density and tapped density were calculated using the following formula:

$$\textbf{Bulk density} = W / V_o$$

$$\textbf{Tapped density} = W / V_f$$

Where,

W = weight of the powder,

VO = initial volume,

VF = final volume

4. Loss on drying: This is employed in EP, BP and USP. Although, the loss in weight in the samples so tested, principally is due to water, small amount of other volatile materials will a contribute to the weight loss. The moisture balance combines both the drying process and weight recording, it is suitable where large numbers of samples are handled and where a continuous record of loss in weight with time is required. The results were given in Table No: 21.(LIMIT: Not more than 0.5% W/W).

5.Angle of repose:

This is the maximum angle possible between the surface pile of powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the co-efficient friction (μ) between the particles. Hence the rougher & more irregular the surface of particles the greater will be angle of repose.

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

Where,

h = height of the pile

r = radius of the pile

Angle of repose

S. No.	Angle of repose (degrees)	Powder flow
1.	25-30	Excellent
2.	31-35	Good
3.	36-40	Fair
4.	41-45	passable
5.	46-55	Poor
6.	56-65	Very Poor
7.	>66	Extremely poor

6. Compressibility Index:

The compressibility index is indirectly related to relative flow rate, cohesiveness and particle size of the powder. The compressibility index of material can be estimated from the tapped and bulk density of power.

%Compressibility index = [(T.D – B.D) / T.D] x 100

Where T.D and B.D are bulk density and tap density respectively.

Compressibility Index

S.No	% Comp. Index	Powder flow
1.	<10	Excellent
2.	11-15	Good
3.	16-20	Fair
4.	21-25	passable
5.	26-31	Poor
6.	32-37	Very Poor
7.	>38	Extremely poor

7. Moisture Content (Or) Water by Kf:

Take around 50ml of methanol in titration vessel of Karl Fischer titrator and titrate with Karl Fischer reagent to end point. In a dry mortar grind the pellets to fine powder .Weigh accurately about 0.5 g of the sample, transfer quickly to the titration vessel, stirr to dissolve and titrate with Karl Fischer reagent to end point.

Calculation:

$$\textbf{Moisture content} = \frac{\textbf{V X F X 100}}{\textbf{Weight of Sample in Mg}}$$

Where,

F= factor of Karl Fischer reagent.

V= volume in ml of Karl Fischer reagent consumed for sample titration.

8. Chemical Evaluation:

Assay:

Standard preparation:

Standard serratiopeptdise 100mg into 50ml volumetric flask. Make up the volume with 0.1 NaoH. From this solution take 25ml into 50ml volumetric flask and make up the volume with 5N Hcl.

Sample Preparation:

100mg serratiopeptdise into 50ml volumetric flask and make up the volume with 0.1N NaoH. Take 25ml into 50ml volumetric flask and make up the volume with 5N Hcl.

Procedure:

Take 10ml sample and standard to 50ml volumetric flask + 5ml 20% NaoH cool on ice for 10min + 5ml 5% Na2co3 + 2ml folins reagent(folins reagent dilution 1ml to 10ml with water).Measure the obsorbants of both the solutions at 660nm.

Calculation:

$$A = \frac{A_T}{A_S} \times \frac{W_S}{100} \times \frac{2}{100} \times \frac{100}{W_T} \times \frac{100}{2} \times P$$

AT = Absorbance of the sample preparation.

AS = Absorbance of the standard preparation.

WS = Weight of the standard taken in mg

WT = Weight of the sample taken in mg

P = Purity of the standard

EVALUATION OF TABLETS

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made.

The important parameters in the evaluation of tablets can be divided into physical and chemical parameters.

Physical parameters

General appearance:

The general appearance of tablets its visual identity and over all elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color presence or absence of odor, taste, surface texture and consistency of any identification marks.

Tablet size and thickness:

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

Average weight of Tablets:

Take randomly 20 tablets and weigh accurately 20 tablets and calculate the average weight.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Weight variation test:

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits:

±10% for tablets weighing 130mg or less

±7.5% for tablets weighing 130mg-324mg

±5% for tablets weighing more than 324mg

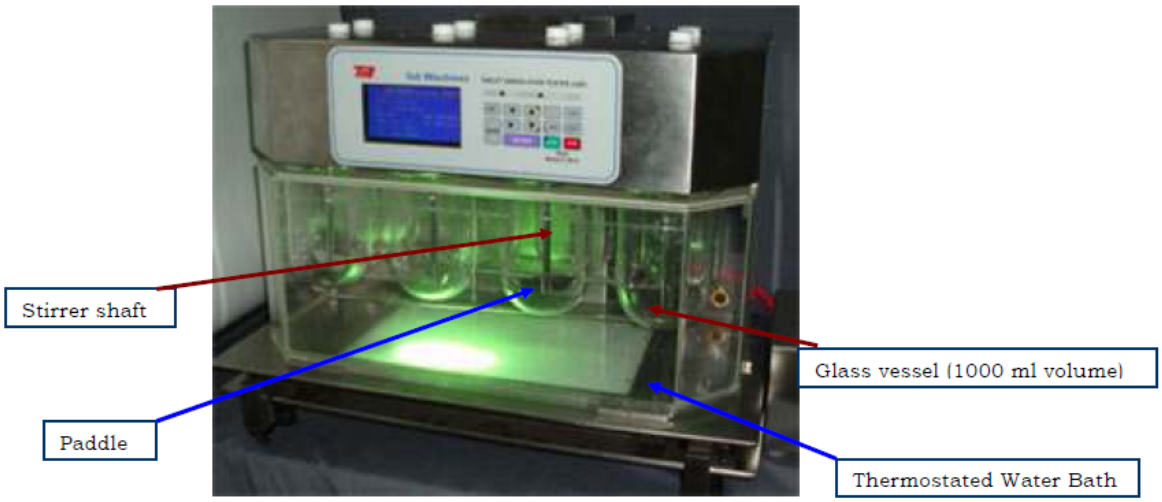
The test is considered correct if not more than two tablets fall outside this range. If 20 tablets are taken for the test and not more than 1 tablet fall outside this range if only 10 tablets are taken for the test. The difference of weight in tablets can lead to variation in doses. For carrying out this test 20 tablets at random are taken and weighed. The weights of individual tablets are then compared to equal to average weight.

Friability:

This test is performed to evaluate the ability to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. the difference in the weight is noted and expressed as %. It should be preferably between 0.5 to 1.0%.

DISSOLUTION:

Dissolution test apparatus



(USP apparatus II)

.

Dissolution by UV VISIBLE SPECTROSCOPY:

Dissolution Parameters:

Type of apparatus: U.S.P. Type II (paddle)

Medium: 0.1N HCL for 2Hrs,Phosphate buffer pH 6.8 for 45 min.

RPM: 100

Volume of Medium:900mL

Sampling intervals:10min,20min,30min,45min,60min

Sampling volume : 10mL

Method of analysis: UV Spectrometric

Wave length:660nm.

Procedure:

The in-vitro dissolution study was carried out with the USP dissolution test apparatus.900ml of dissolution medium (6.8 phosphate buffer) was taken in covered vessel and the temperature was maintain at 37 ± 0.5^{o}C.The speed of the paddle was set at 100rpm.Sampling was done every 10min interval. For each sample 10ml of dissolution medium was withdrawn and the same amount of dissolution medium at 37^{o}C was replaced. The sample withdrawn was filtered with what man filter paper and diluted with 6.8 phosphate buffer and then analyzed in the UV-spectrophotometer. The absorbance was measured at 660nm and percentage drug release was calculated.

Hardness test:-

This is to force required to break a tablet in diametric compression. Hard ness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauze in the barrel which the tablet fractures. Hardness of 5 kg considered as suitable for handing the tablet.

Disintegration test:

For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type sustained release tablets are tested for disintegrating time.

RESULTS AND DISCUSSION

FORMULATION TABLE

S.No	INGREDIENTS (kgs)	F1	F2	F3	F4	F5	F6
	DUMMY GRANULES						
1.	LACTOSE	16.10	16.10	16.10	16.10	16.10	16.10
2.	MAIZE STARCH	4.21	4.21	4.21	4.21	4.21	4.21
3.	METHYL PARABEEN SODIUM	0.03	0.03	0.03	0.03	0.03	0.03
4.	PROPYL PARABEEN SODIUM	0.01	0.01	0.01	0.01	0.01	0.01
5.	PURIFIED WATER(Lit)	5.50	5.50	5.50	5.50	5.50	5.50
6.	SERRATIOPEPTIDASE	2.00	2.00	4.00	6.00	4.00	2.00
7.	MAGNESIUM STEARATE	0.35	0.35	0.35	0.35	0.35	0.35
	SUB COATING MATERIALS						
8.	HPMC 15cps	0.45	0.45	0.45	0.45	0.45	0.45
9.	PROPYLENE GLYCOL	0.12	0.12	0.12	0.12	0.12	0.12
10.	METHYLENE CHLORIDE(Lit)	7.80	7.80	7.80	7.80	7.80	7.80

ENTERIC COATING MATERIAL

S.No	INGREDIENTS (kgs)	F1	F2	F3	F4	F5	F6
11.	HPMC PTHALATE	1.83	3.66	1.83	3.66	5.49	5.49
12.	CETYL ALCOHOL	0.12	0.24	0.12	0.24	0.36	0.36
13.	DIETHYL PTHALATE	0.035	0.070	0.035	0.070	0.105	0.105
14.	IRON RED OXIDE(gm)	22.3	22.3	22.3	22.3	22.3	22.3
15.	TITANIUM DIOXIDE	0.035	0.070	0.035	0.070	0.105	0.105
16.	ACETONE(lit)	27.0	27.0	27.0	27.0	27.0	27.0
17.	ISOPROPYL (lit)ALCOHOL	6	6	6	6	6	6

Coating parameters:

Pan Rpm: 11-12

Inlet temperature:50-60^{o}C

Outlet temperature:45-55^{o}C

Air pressure:3-4kg/sqcm

Preformulation Characteristics of All Formulations:

Precompressional parameters:

The value of precompressional parameters were found to be within the prescribed limits and indicated good free flowing property and the results were given in the table.

S.No	Formulations	Angle of Repose (º)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Moisture Content (%)
1	F1	25.4	0.55	0.69	20.0	2.1
2	F2	26.4	0.53	0.67	21.0	2.2
3	F3	28.2	0.57	0.59	23.0	2.4
4	F4	28.4	0.55	0.64	19.0	2.2
5	F5	23.2	0.53	0.62	23.0	2.1
6	F6	29.6	0.56	0.68	26.0	2.4

Chemical Evaluation:

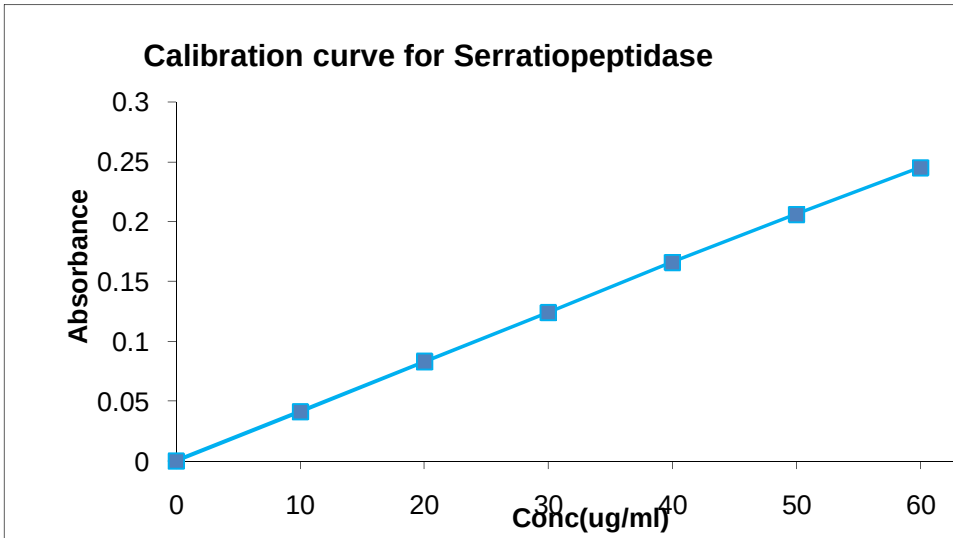
The assay of all formulations are found to be between 90% - 114%.

Physical parameter	F1	F2	F3	F4	F5	F6
Assay% (w/w)	114	99.03	96	95.01	96	92

STANDARD GRAPH OF SERRATIOPEPTIDASE:

Series of dilutions are made from standard working solution with 6.8 pH phosphate buffer to get concentrations ranges from 10 -60mcg and the absorbance was measured at 660nm and the values are listed below.

Concentration (µg/ml)	Absorbance
10	0.041
20	0.083
30	0.124
40	0.166
50	0.206
60	0.245



Physical Evaluation:

Postcompressional parameters:

The data obtained of postcompressional parameters such as weight variation, thickness, friability and hardness, disintegration time were shown in the table. Hardness was found to be the range of NLT 3.0kg/cm^2 in all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions were handling. In all the formulations the friability values NMT 1.0% giving an indication that the tablets formulated are mechanically stable. All the tablets passed weight variation test at the percentage weight variation was within the I.P limits. All the tablets passed disintegration test NMT 15min as per I.P limits.

S.NO	Physical Parameters	F1	F2	F3	F4	F5	F6
1	Weight Variation (mg)	0.12	0.11	0.12	0.13	0.13	0.11
2	Hardness (kg/cm^2)	3.2	3.1	3.4	3.2	3.5	3.2
3	Thickness (mm)	3.1	3.3	3.3	3.2	3.5	3.1
4	Friability (%)	0.25	0.32	0.22	0.45	0.35	0.47
5	Disintegration Time	4m20s	6m20s	3m20s	8m32s	10m40s	11m23s

SPECIFICATION OF SERRATIOPEPTIDASE

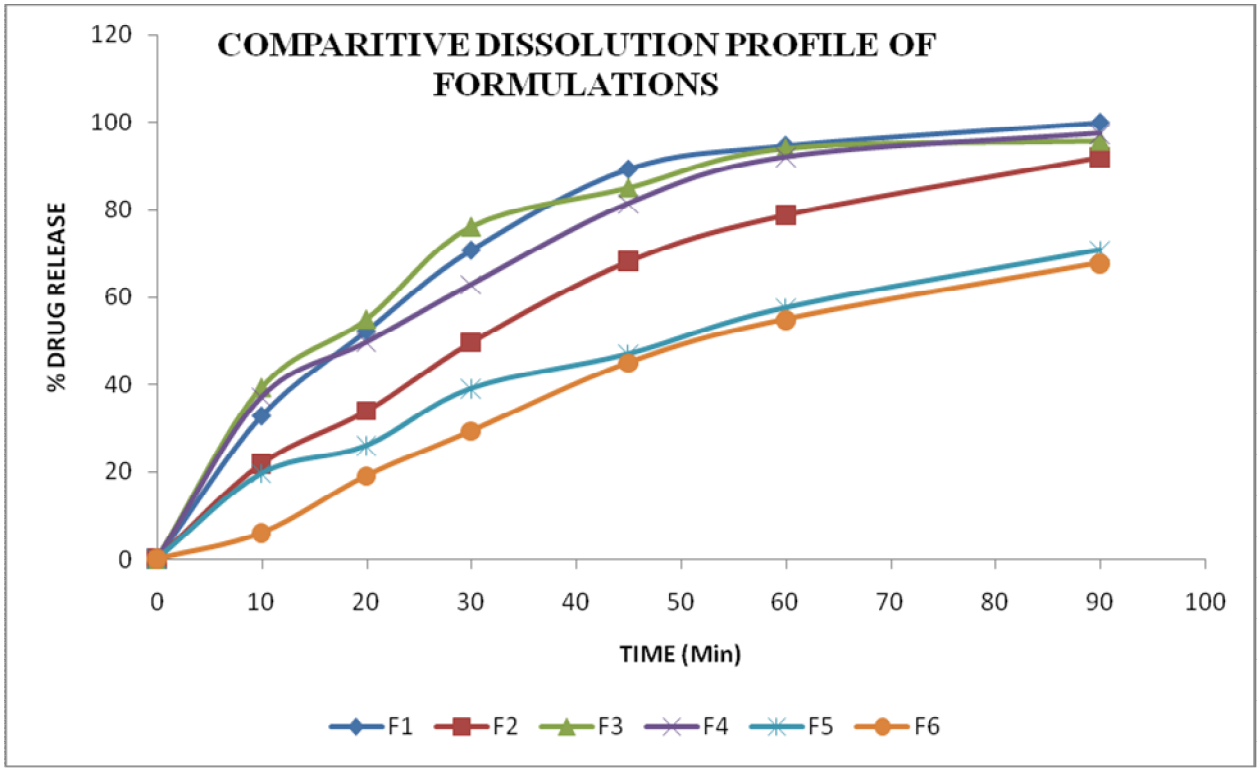
S. No	Tests	Results	Limits
1	Description	Off white powder	Off white to light brown color
2	Loss on drying	5.88%	NMT 7.00w/w
3	Heavy metal	<50ppm	NMT 50ppm
4	Arsenic	< 5ppm	NMT 5ppm
5	Enzyme activity	2.463u/mg	2, 200u/mg to 2, 600u/mg

Dissolution Studies of All Formulations:

By comparing the all formulations F1 formulation showed better percentage drug release.

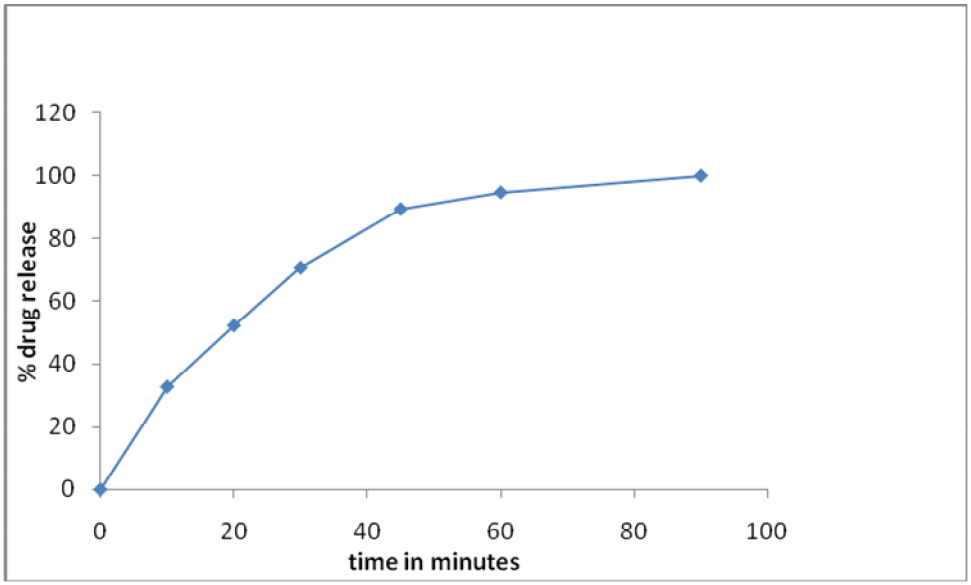
S.No	Dissolution time (min)	F1	F2	F3	F4	F5	F6
1	10	**32.71**	21.73	39.29	37.10	19.54	5.98
2	20	**52.27**	33.79	54.93	49.66	25.89	19.00
3	30	**70.79**	49.64	76.06	62.88	39.08	29.20
4	45	**89.30**	68.49	84.96	81.37	47.09	45.06
5	60	**94.66**	78.76	93.93	91.98	57.60	54.98
6	90	**99.94**	91.97	95.70	97.38	70.81	67.87

COMPARITIVE DISSOLUTION PROFILE OF FORMULATIONS:



Formulation 1(6.8 Phosphate buffer)

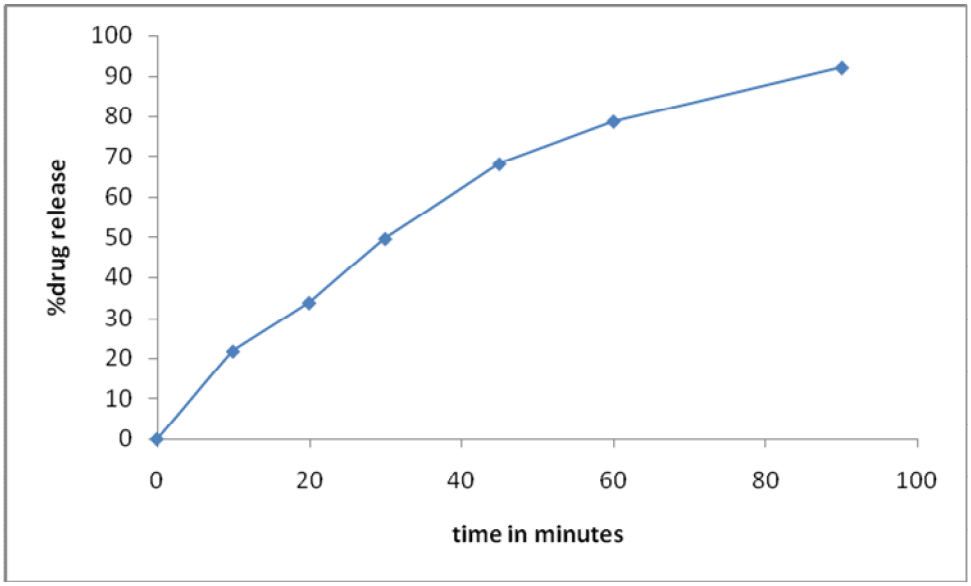
S.no	Time (min)	%drug release
1	10	32.71
2	20	52.27
3	30	70.79
4	45	89.30
5	60	94.66
6	90	99.94



DISSOLUTION PROFILE FOR SERRATIOPEPTIDASE TABLETS F1

Formulation 2 (6.8 Phosphate buffer)

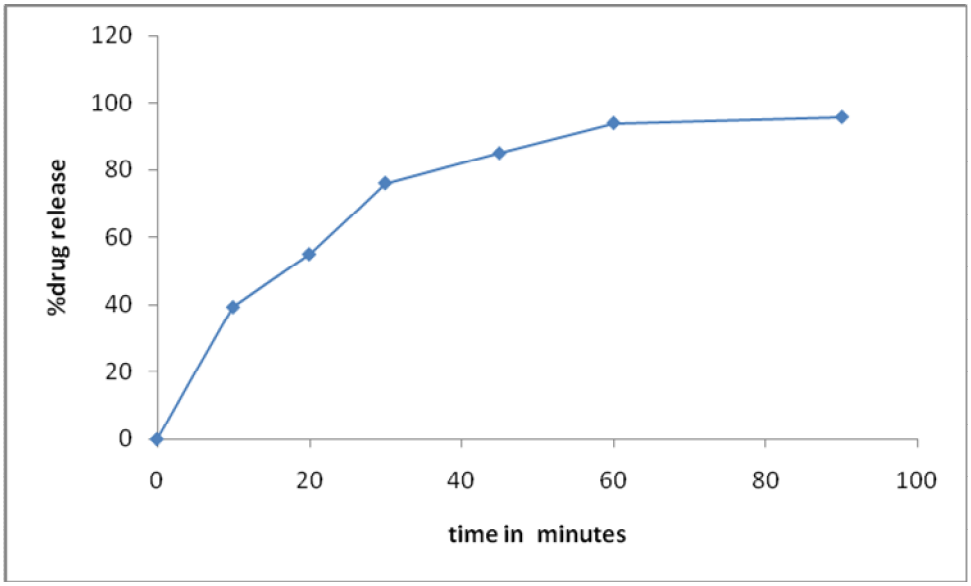
S.no	Time (min)	%drug release
1	10	21.73
2	20	33.79
3	30	49.64
4	45	68.49
5	60	78.76
6	90	91.97



DISSOLUTION PROFILE FOR SERRATIOPEPTIDASE TABLETS F2

Formulation 3 (6.8 Phosphate buffer)

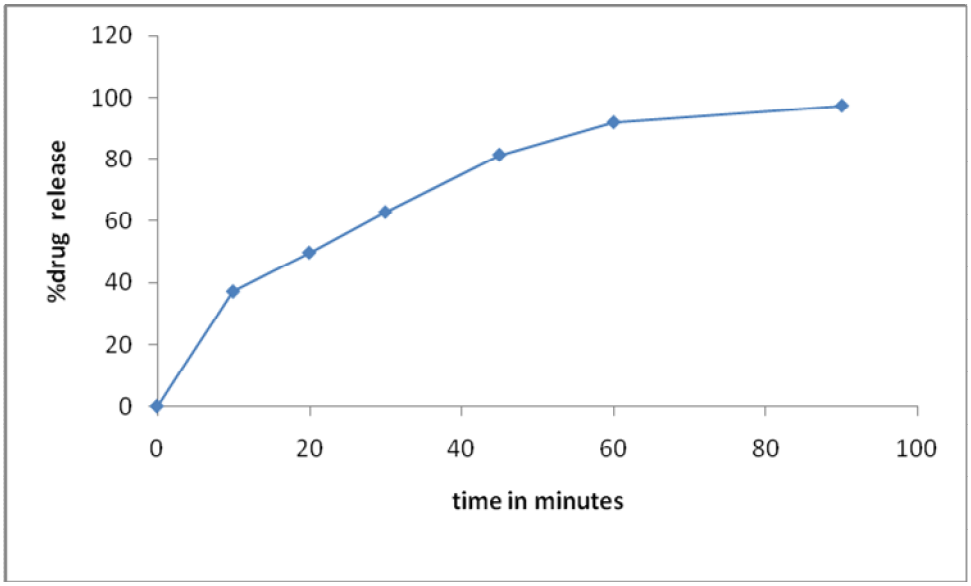
S.no	Time (min)	%drug release
1	10	39.29
2	20	54.93
3	30	76.06
4	45	84.96
5	60	93.93
6	90	95.70



DISSOLUTION PROFILE FOR SERRATIOPEPTIDASE TABLETS F3

Formulation 4 (6.8 Phosphate buffer)

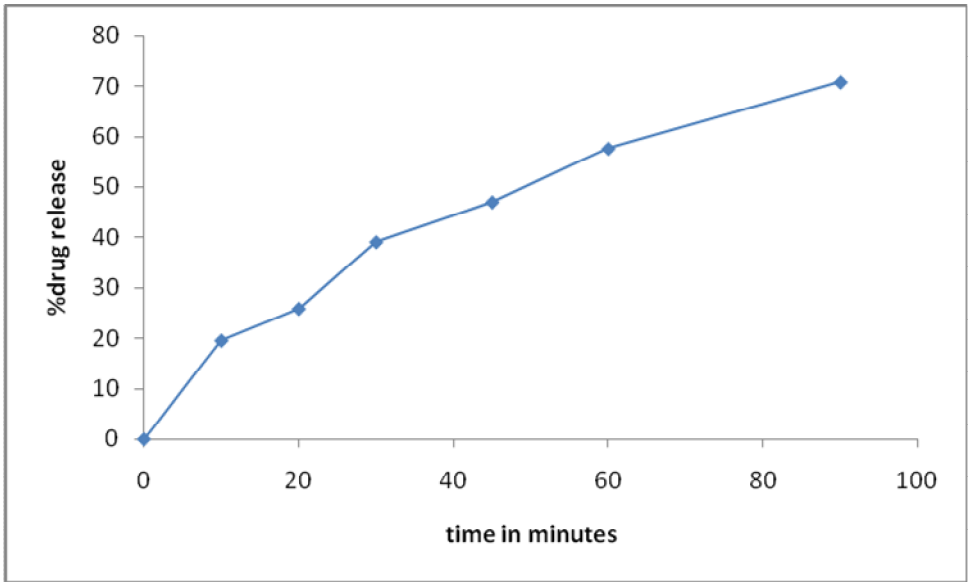
S.no	Time (min)	%drug release
1	10	37.10
2	20	49.66
3	30	62.88
4	45	81.37
5	60	91.98
6	90	97.38



DISSOLUTION PROFILE FOR SERRATIOPEPTIDASE TABLETS F4

Formulation 5 (6.8 Phosphate buffer)

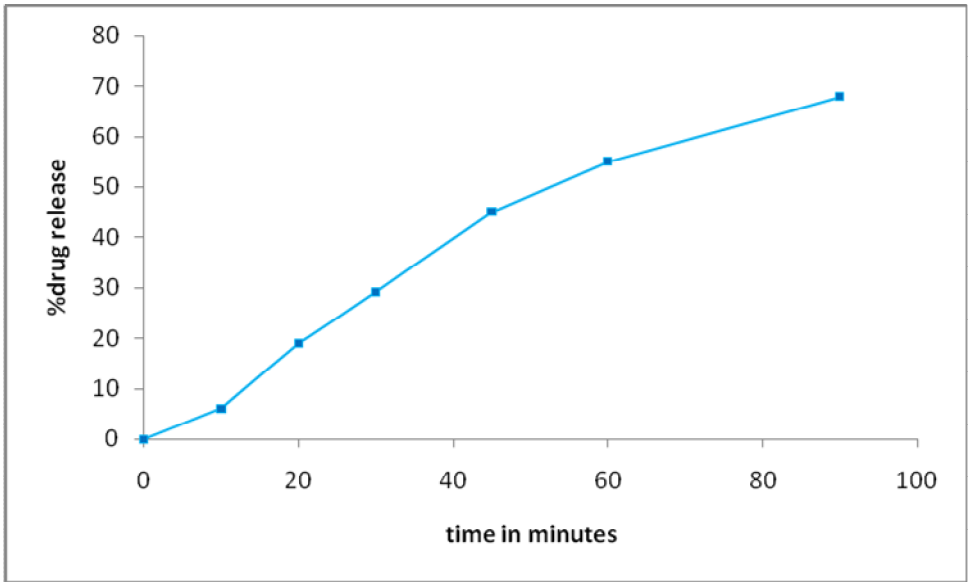
S.no	Time (min)	%drug release
1	10	19.54
2	20	25.89
3	30	39.08
4	45	47.09
5	60	57.60
6	90	70.81



DISSOLUTION PROFILE FOR SERRATIOPEPTIDASE TABLETS F5

Formulation 6 (6.8 Phosphate buffer)

S.no	Time (min)	%drug release
1	10	5.98
2	20	19.00
3	30	29.20
4	45	45.06
5	60	54.98
6	90	67.87



DISSOLUTION PROFILE FOR SERRATIOPEPTIDASE TABLETS F6

SUMMARY AND CONCLUSION

Serratiopeptidase is derived from bacteria belonging to genus Serratia. Serratiopeptidase tablets used in the treatment of viral diseases and hepatitis. In this study Serratiopeptidase enteric coated tablets were prepared by using HPMC phthalate, HPMC 15cps (Polymer).

Several formulations were made with varying the concentrations of drug polymer and enteric coating tablets were done by wet granulation method. They were tested for normal quality control tests like disintegration, weight variation, hardness and friability. The drug release study is carried out for 2hrs in 0.1N HCl and followed with 1hr in 6.8 phosphate buffer.

The present work of Serratiopeptidase was formulated as delayed release tablet which significantly increase the small intestinal absorption and the drug was targeted to small intestinal regions. This was achieved by enteric coating of tablets by simple standard pan coating method.

Serratiopeptidase were formulated using HPMC phthalate as enteric coating polymer in different concentrations to optimize delayed drug release profile and to target the drug release in the small intestine regions.

The present work was made to develop enteric coated tablets containing Serratiopeptidase tablets were made by direct compression method.

While concluding the best formulation among the six F1 formulation shows 99.94% drug release than the all other formulations.

References

1. Liberman, lachman and Joseph, Tablet in pharmaceutical dosage form, 2nd edn 2005, 2, 201-339.
2. M.E.Aulton, Tablet in the science of dosage form design, 2nd edn, 397-460.
3. Remington, The science and practice of pharmacy, 20th edition, 1, B.I publications Pvt.Ltd, Noida, 2000, 903-929.
4. Aulton ME, pharmaceutics- The sciences of dosages form design, 3rd edition, international student Edition, Churchill Living stone, 2007, 419-421.
5. Manish maheshwari, Development of tetracycline serratiopeptidase-containing gel: Formulation and preliminary clinical studies. AAPS pharm sci Tech, 2006, 76.
6. T.H. Al khateeb, Effect of the proteolytic enzyme serrapeptase on swelling pain and trismus after surgical extraction of mandibular third molar, International journal of oral and maxillofacial surgery, 2008, 37, 264-265.
7. Deependra singha, serratiopeptidase-loaded PLA microspheres using selected variables, Journal PDA (pharmaceutical science and technology), 2009.
8. K.V.Sandya, liposomal formulation of Serratiopeptidase – in vitro studies using PAMPA and CACO – to model, Molecular pharmaceutics book, 2008, 92-97.
9. Sumitchakraborty, Formulation development and evaluation of Pantoprazole enteric coated tablet, International Journal of chem tech Research, 2009, 1, 663-2666.
10. Murat – turkoglu, Tableting and stability evaluation of enteric coated omeprazole pellets, European Journal of pharmaceutics and Biopharmaceutics, 2004, 279-286.
11. J. Michael, Enteric coated pellets: theoretical analysis of effect of dispersion in the stomach on blood level profiles, 1976
12. J,G.Hardy, Evaluation of an enteric coated naproxen pellets formulation, 1990.
13. Gonzales, Gilbert) An enteric-coated caffeine delivery system(Application Number: 10/154629) et al (2003)

14. Kim, Sang Min et al an enteric, sustained-release tablet comprising paroxetine or a hydrates United States Patent Application 20080292696
15. Raghavan, Vineeth An enteric coated composition of fluoxetine (N-metthyl- (p-trifluoromethylphenoxy)-3-phenylpropylamine) in the form of coated tablets and pellets WIPO Patent Application WO/2004/058228
16. Curatolo, William J. A pharmaceutical composition is disclosed which comprises multiparticulates United States Patent Application 20080199527
17. Kanazawa, Hashime an oral glycyrrhizin enteric coated preparation United States Patent 6326360
18. Chen, Chih Deshmukh, Abhijit Mukund -ming an enteric coated diltiazem dosage form United States Patent 5830503
19. Deshmukh, Abhijit Mukund an enteric formulation of Fluoxetin United States Patent Application 20040170688
20. Wendsj, Stig An enteric coated oral dosage form of sodium amoxycillin, WIPO Patent Application WO/1998/040054\
21. Ikemoto, a stabilized omeprazole enteric coated tablet Japanese Patent JP2004175768
22Ullah, Ismat an enteric coated bead comprising Ixabepilone, WIPO Patent Application WO/2006/055740
23.Sugita, Katsuji enteric coated preparation containing thyrotropin-releasing hormone United States Patent Application 20030175350
24.Eiji Fukui Preparation of enteric coated timed-release press-coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting International Journal of Pharmaceutics 204 (2000) 7–15 May 2000
25.Ann Debunne Compaction of enteric-coated pellets: influence of formulation and process parameters on tablet properties and in vivo evaluation European Journal of Pharmaceutical Sciences 22 (2004) 305–314 March 2004
26.M. Marvola Enteric polymers as binders and coating materials in multiple-unit site-specific drug delivery systems European Journal of Pharmaceutical Sciences, 7 (1999) 259–267 June 1998

27.Enabhab A. Hosny Properties of enteric coated sodium valproate pellets H International Journal of Pharmaceutics 264 (2003) 85–96os July 2003

28.W.Y. Donga, In vitro and in vivo evaluation of carbamazepine-loaded enteric microparticles indian journal of pharmaceutics September 2006.

29.Chemyq.com

30.www.pcl.ox.ac.uk/MSDS/HY/ Hydroxy propyl _methyl_cellulose.html

31.pharmaceutical dosage and drug delivery system-ansel-8thedition 2005 186-226

32.C. Raymond, Rowe, Hand book of pharmaceutical excipients.230

33.British Pharmacopeia, 1, 2007, 113-114.