FORMULATION AND EVALUATION OF EPALRESTAT MICROSPHERES

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY

(PHARMACEUTICS)

By

(REG.NO:261310401)

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APRIL – 2015

CERTIFICATE

This is to certify that the investigation described in the dissertationentitle**"FORMULATION AND EVALUATION OF EPALRISTAT MICROSPHERES"** submitted by **Reg.No:261310401**was carried out in the **Department of Pharmaceutics,** *ArulmiguKalasalingam College of Pharmacy, Anand Nagar, Krishnankoil-626 126,*which is affiliated to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** under my supervision and guidance for the partial fulfillment of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS.**

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EVALUATION CERTIFICATE

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Date:

Examiners:

1.

2.

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"Success is how high you bounce when you hit bottom"

"If you can dream it, you can do it"

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Affectionately dedicated to

My beloved Family

INDEX

CHAPTER 1

INTRODUCTION :

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, Patient's compliance, least sterility constraints and flexible design of dosage form. Time release technology, also known as sustained release (SR), sustained-action (SA), extended-release (ER, XR or XL), time release or timed release, Controlled release (CR), modified release (MR) or continuous release (CR) is a mechanism used in pill tablets or capsules to dissolve slowly and release a drug over a prolonged period of time. Different polymers are employed due to their In situ gel forming characteristics and their ability to release entrapped drug in the specific medium by swelling and cross linking.

Usually conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems. Sustained release drug delivery system works on many different mechanisms to control the release rate of drugs. Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches. The present article contains brief review on various formulation approaches for Sustained release drug delivery system.

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of Sustained drug delivery, greater attention is being paid on development of oral sustained release drug delivery systems.

The goal in designing sustained release drug delivery system is to reduce the frequency of the dosing, reducing the dose & providing uniform drug delivery. So, Sustained release dosage form

is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ [1-3].

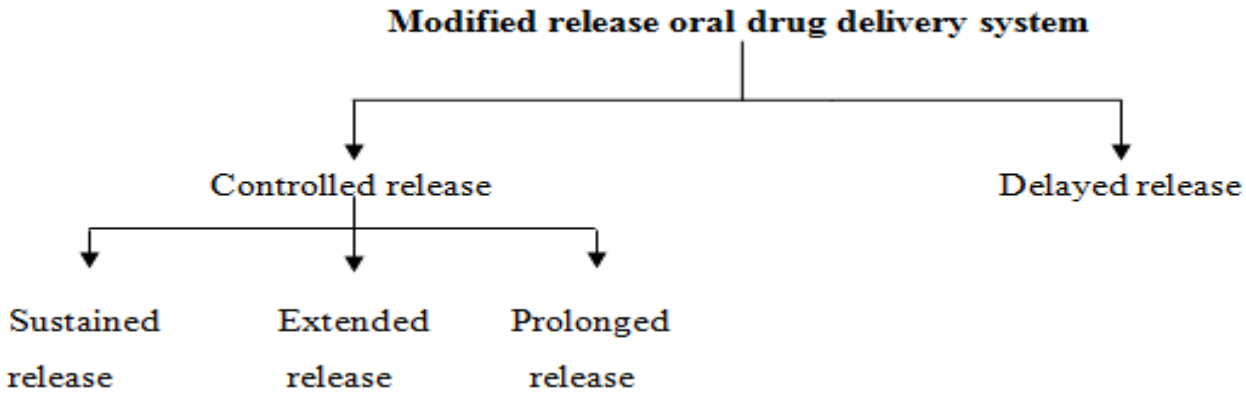
Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. The modified release oral delivery system classification is shown in (**Figure 1**) [3-4]

Terminology Sustained release drug delivery system [2-4]

It includes any drug delivery system achieves release of drug over an extended period of time, which not depend on time. Hydrophilic polymer matrix is widely used for formulating an Sustained dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in blood plasma.

Classification of Modified Release Drug Delivery System

The IR drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral Sustained drug delivery has some potential advantage like Sustained release rate & dose maintenance in plasma. The SR formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate.



Classification of Modified Release Drug Delivery System

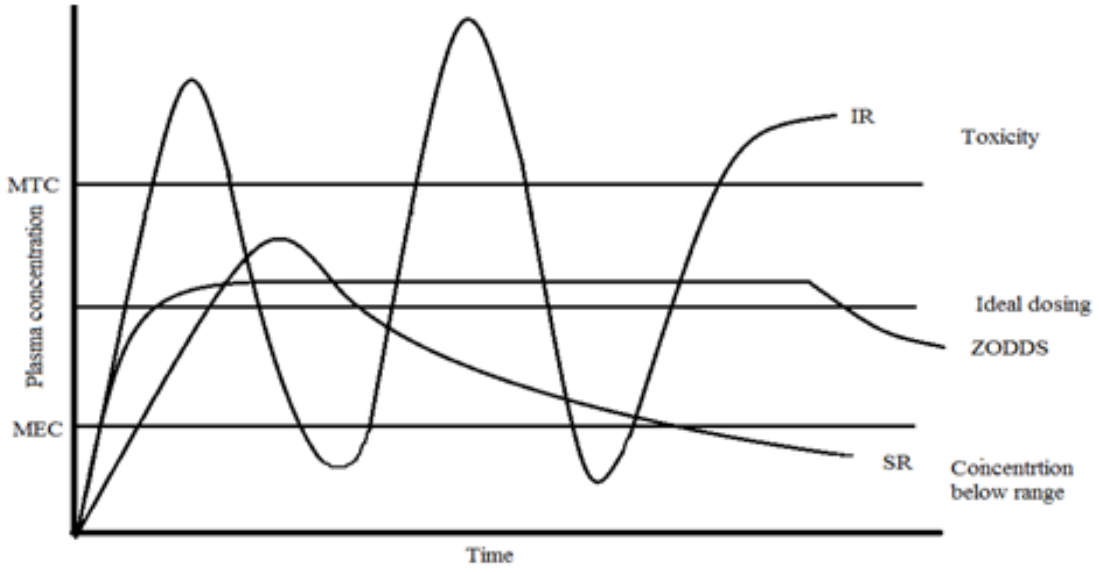


Figure 1.1: Ideal Plasma Concentration Curves For Immediate Release, Zero Order Release, Sustained Release

Advantages of Sustained/Controlled release drug delivery system over the conventional dosage form [4] :

- Reduced dosing frequency.
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided.

Controlled release :

It includes any drug delivery system which releases the drug pre determined rate over an extended period time.

Limitation of oral conventional dosage form [2-3] :

- Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.

- The unavoidable fluctuations of drug concentration may lead to under medication or over medication in narrow therapeutic index drug.

Factors affecting the formulation of oral Sustained release drug delivery system :

1) Physicochemical factors [2-5] :

1.1) Aqueous Solubility:

Most of the drugs are weak acids or weak bases Drugs with low water solubility will be difficult to incorporate into sustained release mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or gastrointestinal fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate a highly water soluble drug in the dosage form and retard the drug release especially when the dose is high. The pH dependent solubility particularly in the physiological pH range would be another problem for Sustained release formulation because of the variation in the pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral absorption.

Class III (High solubility- Low permeability) & Class IV (Low solubility- Low permeability) drugs are poor candidates for Sustained release dosage form compound with solubility < 0.1 mg/ml face significant solubilisation obstacles and often compounds with solubility 10 mg/ml present difficulties to solubilisation dosing formulation. In general, highly soluble drugs are undesirable for formulation in to a Sustained release product.

1.2) Partition coefficient (P (o/w)):

Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that passes though biological membrane, if partition co-efficient of drug influences shows very much bioavailability because lipophillic nature of biological membrane. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have higher partition co-efficient are also not suitable for oral SR drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane [5].

1.3) Drug pK_a and ionization at physiological pH:

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3 to 4 times less than that of the unionized drug. The pK_a range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and pK_a range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0% [2].

1.4) Drug stability:

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. If the drug in the solid state the degradation will occur in reduced rate, for the drugs that are unstable in stomach that prolong delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. This occurs due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation [8-10].

1.5) Molecular size and diffusivity[7] :

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10-6-10-9 cm2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm^2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

2) Biological factor[2]:

The aim of formulating Sustained release product is to place a control on the delivery system. It is essential that the rate of release is much slower than the rate of absorption. If we assume the transit time of dosage forms in the absorptive areas of GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours. Otherwise the dosage form will pass out of absorptive regions before drug release is complete. Therefore, the compounds with lower absorption rate constants are poor candidates. Some possible reasons for low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis and metabolism or its site

of absorption. The distribution of drugs in tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can

be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug are poor candidate for oral SR drug delivery system.

For design of sustained release products, formulation scientist must have information on disposition of the drug. A drug which extensively metabolizes is not suitable for SR drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is poor candidate for SR delivery, as it could be difficult to maintain constant blood level.

2.1) Half-life:

The half-life of a drug is an index of its residence time in the body. If the drug has short half life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of 8 hours or more are sufficiently controlled in the body, when administered in conventional dosage from and Sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of 3 to 4 hours for formulation of drug delivery system [2-5].

2.2) Therapeutic index:

Drugs with low therapeutic index are unsuitable for incorporation in Sustained release formulations. If the system fails in the body, dose dumping may occur, which leads to toxicity [5].

2.3) Size of dose:

If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for SRDDS. This is because the size of a unit dose Sustained release oral formulation would become too big to administer without difficulty [6].

2.4) Absorption window:

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the ‘absorption window’. These candidates are also not suitable for SRDDS [7].

2.5) Plasma concentration response relationship:

Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral SR drug delivery system [6].

2.6) Concentration dependency on transfer of drug:

Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidate for oral SR delivery system. It should be of first order kinetics [7].

The (**Figure 3**) represents various formulation strategies for oral Sustained release drug delivery system.

I) Diffusion sustained system: Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration.

(a).Diffusion reservoir system:

In this system, a water insoluble polymeric material covers a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The drug release takes place by diffusion mechanism. The diffusion type reservoir system is shown in (**Figure 1.2**)

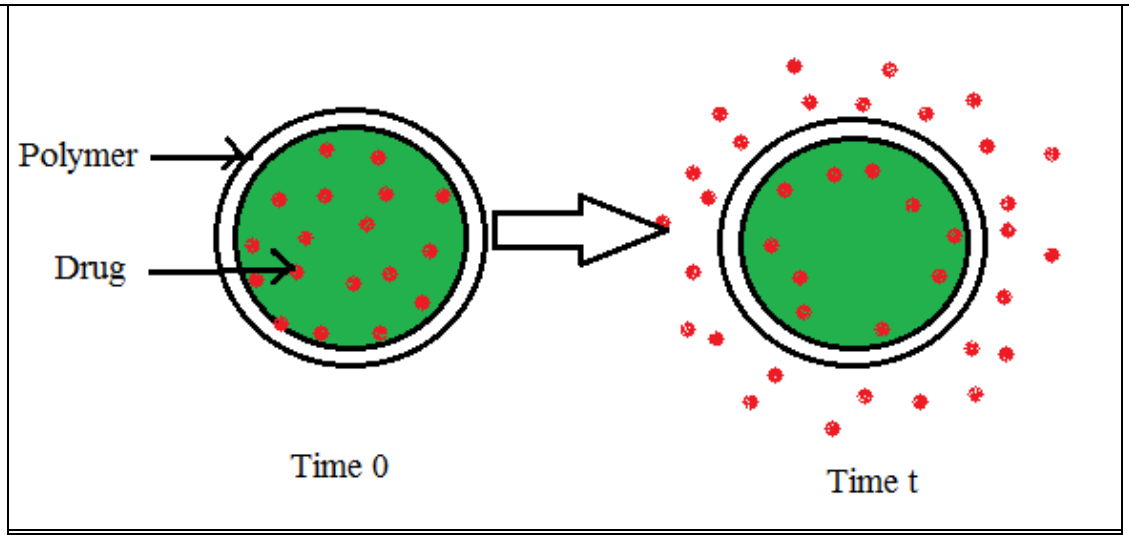


Figure 1.2: Schematic Representation of Diffusion Type Reservoir System

Advantages:

- ❖ Zero order delivery is possible.
- ❖ Release rates can be modified with polymer type & concentration.

Disadvantages:

- ▪ Difficult to deliver high molecular weight compound.
- ▪ Generally increased cost per dosage unit.
- ▪ Potential toxicity if dose dumping occurs.

(b). Diffusion matrix system:

The matrix system is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Matrix systems are widely used for sustaining the release rate. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed [7,18]. A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. The diffusion type matrix system is shown in (**Figure 1.3**)

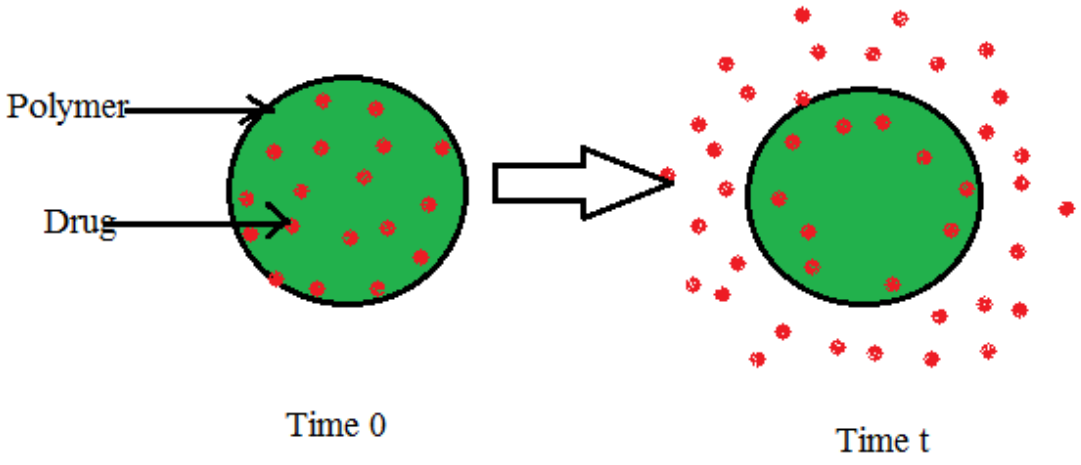


Figure (1.3): Schematic Representation of Diffusion Type Matrix System

Advantages:

- ❖ Easier to produce than reservoir or encapsulated devices.
- ❖ Versatile, effective and low cost.

- ❖ Possible to formulate high molecular weight compounds.
- ❖ Increased the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.

Disadvantages:

- The ghost matrix must be removed after the drug has been released.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- Cannot provide pure zero order release.

Types of diffusion matrix system [11]

The matrix system can be divided into two categories depending on the types of retarding agents or polymeric materials.

(b) i) Hydrophobic matrix system [11]

ii) Hydrophilic matrix system [18-20]

iii) Fat-wax matrix system [12-13]

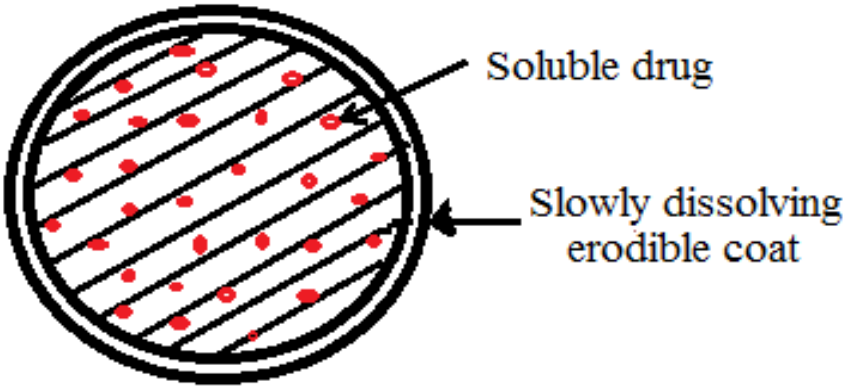
II) Dissolution sustained systems [13-14] :

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the dosage form until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

a) Soluble reservoir system:

In this system drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract by alternating layers of drug with the rate controlling coats as shown in (**Figure 1.4**).

Figure (1.4): Schematic Representation of Dissolution of Reservoir System



3) Dissolution- sustained pulsed delivery system [16-17] :

Amongst Sustained release formulations hydrophilic matrix technology is the most widely used due to its following **advantages.**

- ❖ Provide desired release profile for a wide therapeutic drug category, drug and solubility.
- ❖ Simple and cost effective manufacturing and robust.
- ❖ Patient acceptance.
- ❖ Ease of drug modulation through level, choice of polymeric systems & function coating.

A hydrophilic matrix tablet consists of mixture of drug, polymer &excipient (filler/diluents as well as other excipient) prepared by hydrophilic polymer in the matrix. Formulators often choose from a range of hydrophilic polymer as stand alone or in combination with different polymers for release rate control.

III) Ion exchange resins sustained release [27] :

Ion exchange resins are cross-linked water-insoluble polymers carrying ion sable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrant, because of their swelling ability. It forms irreversible complex with ionisable drugs upon prolonged exposure of the drug to the resin. A resin bound drug is removed

when appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway and the amount of cross-linked polymer in the resin moiety governs the rate of drug release. Sriwongjanya et al. has found the effect of ion exchange resin with drug containing opposite charge in matrix system. After this investigation they concluded that the release of drug containing opposite charge retarded by the addition of ion exchange resin to HPMC-matrices due to formation of complex between drug and resin.

IV) Methods using osmotic pressure [28-29] :

In this method, the release controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. This technology provides zero order release used for hydrophilic drugs. Drug may be osmotically active or combine with osmotically active salt e.g.Nacl. Osmotic pressure is the hydrostatic pressure produced by a solution in a space divided by a semi permeable membrane due to difference in concentration of solutes. Osmosis is the diffusion of fluid through a semi permeable membrane from a solution with a low solute concentration to a solution with a higher solute concentration until there is an equal concentration of fluid on both sides of the membrane. A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating. The osmotic systems are classified in major two types, i.e. type-A & type-B.

- In type-A system, the core contains both, the drug and electrolytes. The electrolytes provide osmotic pressure and maintain the rate of drug release.
- In type-B system, the drug solution is present in a semi permeable membrane surrounded by the electrolytes. Both the systems are shown in (**Figure 8 & 9**) respectively.

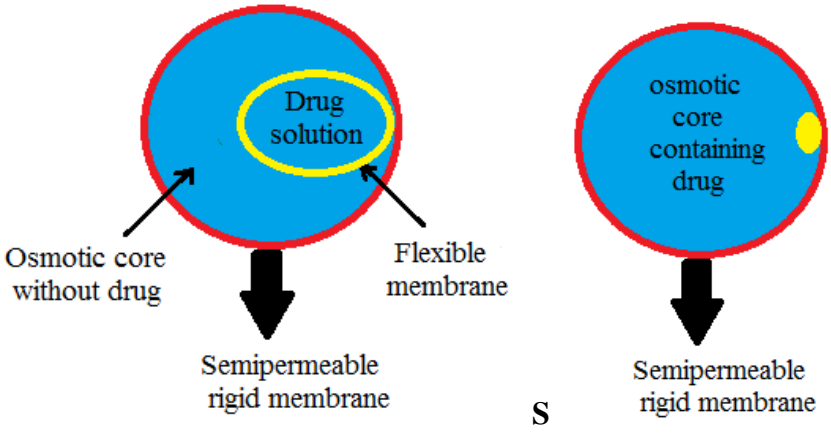
The ODDS can be conveniently classified in to following types: [22-24]

A) Single chamber osmotic pump

B) Multi chamber osmotic pump

C) Specific types

Figure (1.5): Type-A osmotic system



S

V) pH Independent formulations [25-26] :

Most drugs are either weak acids or weak bases. The release from Sustained release formulations is pH dependent. However; buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation to help to maintain a constant pH thereby rendering pH independent drug release.

VI) Altered density formulations [21-22]:

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract. The delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released. In high density approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4g/cm3. In low density approach, the globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose. This system is generally used when, the single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension is required. All sustained release technologies and their some example shown in (**Table 1**).

Table (1.1)

S.No	Technoloy		Brandname	Drug	Manufacturer
1	Diffusion controlled release		Welbutrin XL	Bupropin	GlaxoSmithKline
2	Matrix system tablet		Ambient CR	ZolpidemTartarate	Sanofi-Aventis
3	Method using ion Exchange		TussionexPennkinetic ER suspension	Hydrocodone Polistirex&Chlor-pheneraminePolistirex	UCB Inc
4	Methods using osmotic pressure	Elementary Osmotic Pump	Efidac 24®	Chlorpheniramine Maleate	Novartis
		Push-Pull Osmotic Systems	Glucotrol XL®	Glipizide	Pfizer Inc.
5	pH independent formulation		Inderal® LA	Propranolol HCl	Wyeth Inc.
6	Altered density formulation		Modapar	Levodopa &Bense-razide	Roche Products, USA

The Sustained release drug delivery system is very helpful in increasing the efficiency of the dose, safety of dose as well as the patient compliance. Nowadays, the oral route of administration for Sustained release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance.

Rationale for selection of micro spheres:

Most of the research effort in developing novel drug delivery systems has been focused on oral controlled release dosage forms. Among them, in the last decade, multiple unit dosage forms, such as micro spheres or micro particles. Have gained in popularity for different reasons when compared to non-disintegrating single unit dosage forms. They distribute more uniformly in the gastro intestinal tract, resulting in more uniform and reduce local irritation, and also avoid the unwanted intestinal retention.

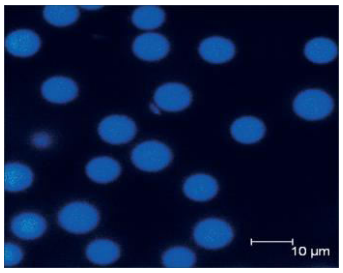
Micro particles:

These are particles with size more than '1' um, containing the polymer. At present, there is no universally accepted size range that particles must have in order to be classified as micro spheres .however, may workers classify the particles smaller than ' 1 ' um, as Nanoparticles as and those more than 1000 um, as micro spheres or micro particles.

MICROSPHERES:

[30] Micro spheres as drug carriers have the advantages of both easier administration via injection in suspension without surgical implantation and the potential for administration of multiple drug in a single injection.Microspheres are solid, spherical particles containing dispersed drug molecules, either in solution or crystalline form, among the polymer molecule.

Figure (1.6):



Method of Micro sphere preparation[31]:

1)coacervation- phase separation

2)Interfacial polymerization

3)In-situ polymerization

4)Solvent evaporation

5)co acervation induced by temperature change method

6)solvent extraction

7)Spray drying

8)Fluidized bed coating

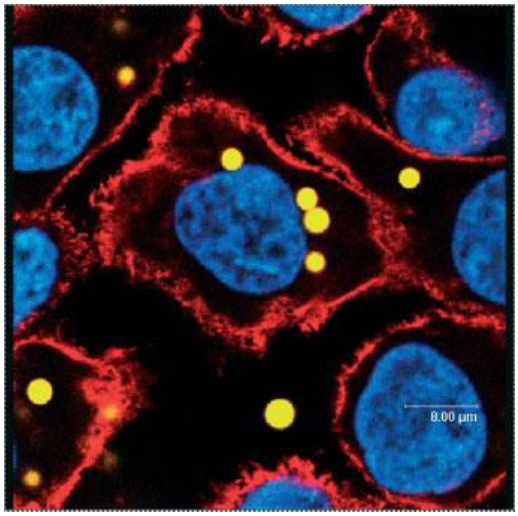
9)Multiorifice centrifugal process

10)Pan coating

1. Coacervation-Phase separation[32]: Coacervation is a colloid phenomenon. If one starts with a solution of a colloid in an appropriate solvent, then according to the nature of colloid, various changes can bring about a reduction of the solubility of the colloid. As a result of this reduction a large part of colloid can be separated out into a new phase. The original one phase becomes two phases. One is rich and other is poor in colloid concentration. The colloid rich phase in a dispersed state appears as amorphous liquid droplets called coacervate droplets. Upon standing these coalesce into one clear homogenous colloid-rich liquid layer, known as coacervate layer which can be deposited so as to produce the wall material of the resultant particles.

2. Simple coacervation: Simpleco acervation involves the use of either a second more-water soluble polymer or an aqueous non-solvent for the gelatin. This produces the partial dehydration/desolvation of the gelatin molecules at a room temperature above the gelling point. This results in the separation of a liquid gelatin-rich phase in association with an equilibrium liquid (gelatin-poor) which under optimum separation conditions can be almost completely devoid of gelatin. Simple co acervation can be effected either by induced by adding a strongly hydrophilic substance such as alcohol or sodium sulfate[33] .

Figure (1.7):



2. Interfacial polymerization(If p): In this method the particle shell is formed at or in the surface of a droplet by polymerization of reactive monomers. If the micro particulate core is water-immiscible liquid then a multifunctional monomers dissolved in the core material. This solution is dispersed in an aqueous phase containing dispersing agent. A co-reactant is then added to the aqueous phase. This produce a rapid polymerization reaction at the interface which generates the micro particles shell.

Advantage:

- It is a versatile technology able to micro particles a wide range of core material, including aqueous solutions, water immiscible liquids and solids.

Disadvantage:

- Because one of the reactants used to create the micro particles shell is dissolved in the core material and is free to react with any groups located on core material molecules to create new molecules.
- particle shell is not uniformly deposited around the core..

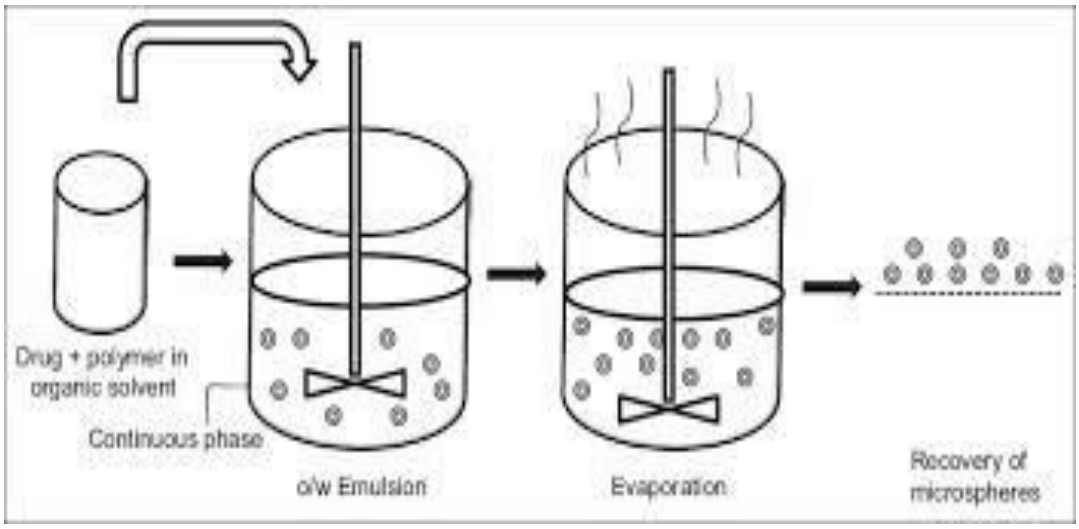
3. In situ polymerization: In a few processes, the direct polymerization of a single monomer is carried out on the particle surface. In one process, e.g. cellulose fibers are covered in poly ethylene while immersed in try toluene. Usual deposition rates are about 0.5µm/min. Coating thickness range 0.2-75µm. The coating is uniform, even over sharp projections[35].

4. Solvent Evaporation Technique[36,37]:

(Emulsification-Evaporation Method)

This technique is based on the evaporation of the internal phase of an emulsion by agitation. Initially, The coating polymeric material is dissolved in a volatile organic solvent. The core to be covered then dispersed in the coating polymer solution to form a suspension or emulsion. In the next step, this organic solution is emulsified under agitation in dispersing phase, which is immiscible with the organic solvent, which contains the emulsifier. Once the emulsion is stabilized, agitation is maintained and the solvent evaporates after diffusing through the continuous phase. This result in the formation of micro spheres. On the completion of the process, the micro spheres held in the continuous phase are recovered by filtration or centrifugation and are washed and dried.

Figure (1.8):



Types of solvent evaporation techniques:

a. Oil in water emulsion.

b. Water in oil emulsion.

c. Multiple emulsion, w/o/w:

Advantages:

This process is more effective when the water solubility of the drug is high and partitioning between the organic phases is dis favourable.

Mechanism of solvent evaporation:

This system is characterized by the existence of several interfaces through which mass transfer occurs during particle formation, as shown in the below figure;

Organic solvent of the dispersed phase of the emulsion is eliminated in two stages:

1. Diffusion of the solvent in the dispersing phase.

2.Elimination of the solvent at dispersing phase -air interface.

The formation of solid micro spheres is brought about by the evaporation of the volatile solvent L_1 at interface L_2/G. During the course of solvent evaporation, a partitioning is produced across the interface L_1/L_2 from the dispersed phase to continuous phase leading to the formation of solid micro spheres.

5. Solvent Extraction Method: As mentioned in the previous method ,the organic solvent of the dispersed phase of the emulsion is eliminated in two stages i.e.

1. Diffusion into continuous phase&
2. Elimination of solvent at continuous phase-air interface.

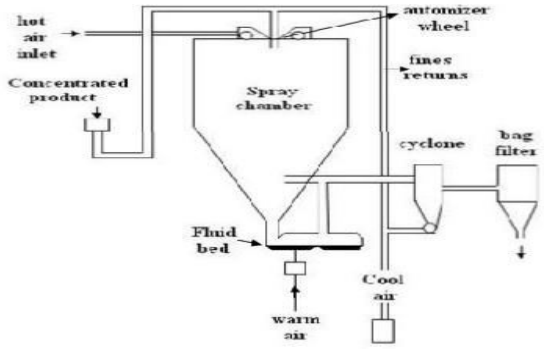
If one uses a continuous phase which will immediately extract the solvent of the dispersed phase, the evaporation stage is no longer necessary in microencapsulation.

6. Co accervation Induced By Temperature Change Method: This process involves dissolving ethyl cellulose in the non-ideal solvent cyclohexane at 80°c and gradually cooling the solution so that the polymer separates as a liquid co acerbate and encloses particles of core material that are dispersed by various agitation in the system. The deposited wall material may be hardened by continuing to lower the temperature while maintaining vigorous agitation to prevent coalescence of microspheres. When the system reaches 20 to 25°c, the microspheres can be filtered and dried.

7. Spray Drying: Spray drying serves as a microencapsulation technique when an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. Coating solidification in the case of spray drying is effected by rapid evaporation of solvent in which the coating material is dissolved. Coating solidification in spray congealing methods, however, is accomplished by thermally congealing a molten coating material or by solidifying a dissolved coating by introducing the coating -core material mixture into a non solvent. Removal of the non solvent or solvent from the coated product is then accomplished by sorption, extraction, or evaporation techniques. In practice, Micro spheres formation by spray drying is conducted by dispersing core material in coating solution, in which the coating

substance is dissolved and in which the core material is insoluble, and then by atomizing the mixture into air stream. The air, usually heated , supplies the latent heat of vaporization required to remove the solvent from the coating material , thus forming the micro sphere product[38]. Micro sphere formation by spray congealing can be accomplished with spray drying equipment when the protective coating is applied as amelt. Coating solidification is accomplished by spraying the hot mixture into a cool air stream. waxes, fatty acids and alcohols, polymers and sugar, which are solids at room temperature but melt able at reasonable temperature, are applicable to spray congealing techniques. Typically, the particle size of spray congealed products can be accurately controlled when spray drying equipment is used, and has been found to be a function of the feed rate, the atomizing wheel velocity, dispersion of feed material viscosity, and variables[(39)].

Figure (1.9): Spray dryer



Advantage:

Low cost of method and able to produce large amount of micro spheres.

Disadvantages:

This process is limited to coating material soluble in water, but the list of water soluble coating material are limited.

8. Fluidized bed coating (Water Air Suspension): It consists of the dispersing of solid core material in a supporting air steam and then spray coating of the air suspended particles.

Advantage:

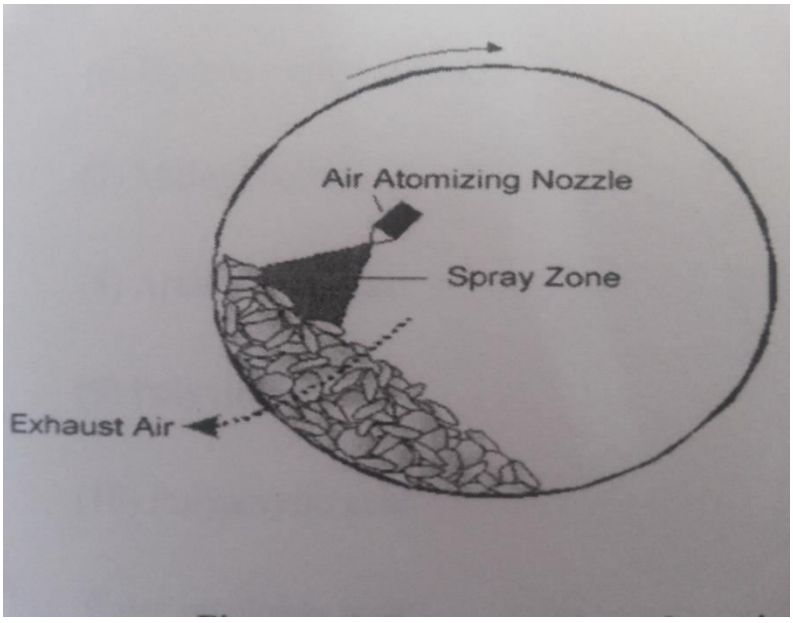
Able to handle an extremely wide range of coating formulations.

9. Multiorifice-Centrifugal processes: In this process it utilizes centrifugal forces to hurl a core material particle through an enveloping micro particles membrane, there by effecting mechanical micro sphere formation.

10. Pan coating:

In this pan coating the particles are tumbled in a pan or other device while the coating material is applied slowly[40] with respect to micro sphere formation, solid particles greater than 600 μ in size are generally considered essential for effective coating, and the process has been extensively employed for the preparation of controlled-release beads. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds, and then coated with protective layers of various polymers.Usually to remove the coating solvent, warm air is passed over the coated materials as the coating are being applied in the coating pans. in some cases, final solvent removals accomplished in a drying oven[41].

Figure(1.10)



Application of Micro sphere formation[42,43]:

- To mask the bitter taste of drug like Paracetamol etc
- Many drugs have been micro sphere formation to reduce gastric and other G.I.tract irritation. Sustained release Aspirin preparations have been reported to cause significantly less G.I. bleeding then conventional preparations.
- A liquid can be converted to a pseudo-solid for easy handling and storage. e.g.Eprazinone
- Hygroscopic properties of core materials may be reduced by micro particles formation. e.g. Sodium chloride.
- Carbon tetra chlorides and a number of other substances have been micro sphere formulated to reduce their odor and volatility.
- Micro spheres formation has been employed to provide protection to the core materials against atmospheric effects, e.g. vitamin A.
- Separation of incompatible substance has been achieved by micro particles formation.
- Cell immobilization: In plant cell cultures, Human tissue is turned into bio-artificial organs, in continuous fermentation processes.
- Protection of molecules from other compounds.
- Drug delivery: Controlled release delivery systems.
- Quality and safety in food, agricultural & environmental sectors.
- Beverages production, soil inoculation.
- In textiles: means of imparting finishes.
- Protection of liquid crystals.

[44] Micro spheres for medicinal purpose consist of solid, liquid or gaseous drug enveloped within a coating or shell. The coating cane be an organic polymer, a hydro colloid, a sugar, a wax , a fat, a metal or an inorganic oxide. Depending on the manufacturing process various structure are possible within the capsule.

[45] Number of different polymers biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres.These polymers are natural and synthetic origin and also modified natural substance. Synthetic polymers employed as carrier materials are methyl methacrylate, acrolein, lactide, glycolide, and their co-polymers, ethylene vinyl acetate co-polymer, poly anhydride etc.

POLYMERS USED:

Synthetic polymers:

Non- biodegradable:

- Acrolein
- Glycidyl methacrylate
- Epoxy polymers
- Biodegradable
- Lactide and glycilides and their co polymers
- Polyalkyl cyano acrylates
- Poly anhydrides

Natural materials:

- Proteins
- Albumins
- Gelatin
- Collagen
- Carbohydrates
- Starch
- Agarose
- Carrageen
- Chitosan

Chemically modified carbohydrates

- Poly(acryl)dextran
- Poly(acryl)starch

Release mechanisms [46,47&48]

1. Degradation controlled monolithic system:

The drug is dissolved in matrix and is distributed uniformly throughout. The drug is strongly attached to the matrix and is released on degradation of the matrix. The diffusion of the drug is slow as compared with degradation of the matrix.

2. Diffusion controlled monolithic system:

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Rate of release also depend upon where the polymer degrades by homogeneous mechanism.

3. Diffusion controlled reservoir system:

Here the active agent is covered by a rate controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix.

4. Erosion:

Erosion of the coat due to pH and enzymatic hydrolysis cures drug release with certain coat material like glyceryl mono stearate, beeswax and steryl alcohol etc.

Diabetic neuropathy[57]

Diabetic neuropathy is one of the most common long-term complications in patients with diabetes mellitus, with a prevalence of 60-70% in the United States. Treatment options include antidepressants, anticonvulsants, tramadol, and capsaicin. These agents are modestly effectivefor symptomatic relief, but they do not affect the underlying pathology nor do they slow progression of the disease. Epalrestat is an aldose reductase inhibitor that is approved in Japan for the improvement of subjective neuropathy symptoms, abnormality of vibration sense, and abnormal changes in heart beat associated with diabetic peripheral neuropath. Unlike the current

treatment options for diabetic neuropathy, Epalrestat may affect or delay progression of the underlying disease process. Data from experimental studies indicate that Epalrestat reduces

sorbitol accumulation in the sciatic nerve, erythrocytes, and ocular tissues in animals, and in erythrocytes in humans. Data from six clinical trials were evaluated, and it was determined that Epalrestat 50 mg 3 times/day may improve motor and sensory nerve conduction velocity and subjective neuropathy symptoms as compared with baseline and placebo.

EPALRESTAT

Epalrestat is Oral anti diabetic agent, Aldose reductase inhibitor which is a carboxylic acid derivative which inhibits aldose reductase, an enzyme of the sorbitol (polyol) pathway. Under hyperglycemic conditions Epalrestat reduces intracellular sorbitol accumulation, which has been implicated in the pathogenesis of late-onset complications of diabetes mellitus. Epalrestat150 mg/day for 12 weeks improved motor and sensory nerve conduction velocity, and vibration threshold compared with baseline and placebo in patients with diabetic neuropathy. Subjective symptoms including pain, numbness, hyperesthesia, coldness in the extremities, muscular weakness, dizziness, and orthostatic fainting were also improved. Similar benefits wereseen in a comparison with historical controls. Epalrestat 300 mg/day for 1 or 3 years was also significantly superior to placebo or no treatment in improving electroretinogram parameters and photo stress recovery time in patients with diabetic retinopathy. Improvements were also documented by funduscopy and fluorescein angiography.Epalrestat appeared most effective in patients with less severe diabetes mellitus and more recent. Long-term treatment with Epalrestat is well tolerated and can effectively delay the progression of diabetic neuropathy and ameliorate the associated symptoms of the disease, particularly in subjects with good glycemic control and limited microangiopathy. Natural sources reported to inhibit aldose reductase include spinach, cumin seeds, fennel seeds, basil leaves, lemon, black pepper, orange, curry leaves, and cinnamon. Chemical name of Epalrestat is C15-H13-N-O3-S2 (5-[(Z, E)-β- ethylcinnamylidene]- 4-oxo-2-thioxo-3-thiazolidineacetic acid) andits molecular weight is 319[49].

Aldose Reductase Inhibitors

Aldose reductase (E.C.1.1.1.21), a ubiquitous enzyme which has been identified in brain, kidney, liver, lensand skeletal muscle tissue, is an aldo-keto reductase that catalyzes the NADPH-dependent reduction ofglucose into sorbitol in the first step of the polyol pathway. In turn,

sorbitol is converted into fructose bysorbitol dehydrogenase through an NAD+-dependent reaction. Although not determinant, the osmotic stress generated by sorbitol accumulation has been proposed as contributing to the development of tissue damage above all in the lens.[50]Moreover, the increase in the NADH/NAD+ ratio promotes the activation of PKC isoforms which are found to be crucial mediators of biochemical and functional alterations triggered by hyperglycemia. Thus, the oxidative stress triggered by the glucose-oxidation process and upheld by increased ALR2 activity is rightly considered to be a major and unifying mechanism responsible for the onset of diabetic complications[51]. Over the last three decades, numerous ALR2 inhibitors(ARIs) have been identified; most of them belong to either carboxylic acid (such as Epalrestat) or hydantoin (such as sorbinil, fidarestat) classes of compounds[51-56]. However, many of the clinically tested ARIs proved to be inadequate as drug candidates because of adverse pharmacokinetics, toxic side effects or low efficacy. At present, Epalrestat is the only ARI available on the market.

CHAPTER 2

LITERATURE SURVEY

S.B.Jayasural et al.,[58] worked on sustained release captopril micro spheres by spherical crystallization technique using acrylic polymers [Eudragit RL 100 & Eudragit RS 100] and ethyl cellulose as the matrix. The effect of drug to the polymer ratio and stirring rate on the drug release rate was investigated. It was reported that increase in the concentration of the polymer decreases the drug release rate significantly.

Sanjay K .Jain, Subhash pande and S.P. Vyaset al.,[59]worked on slow release micro spheres of propanolol hydro chloride by an emulsion solvent evaporation technique using Eudragit RS 100 and RL 100.The effect of polymer - solvent ratio, drug polymer ratio, stirring rate and evaporation temperature were evaluated.

Biswanath sa et al.,[60] worked on sulphamethizole loaded Eudragit RL 100 micro spheres by emulsion-solvent evaporation technique with a view to characterize the factors influencing in-vitro drug release. It was reported that the cross flow of solvent and solute inside the micro spheres did not influence the drug release which however was strongly dependent on pH of the dissolution media.

A Nokhodchi et al.,[61] worked on the effect of thermal treating on the tensile strength of tablets and release of indomethacin from Eudragit RS &RL matrices

Stephan Gibaud et al.,[62] worked on Eudragit RS micro spheres containing 3,4- diamino pyridine by a solvent-evaporation technique using light mineral oil as continuous phase.

Khanfar ms and Salem M.S et al.,[63]worked on kinetics of the release of indomethacin from Eudragit RS polymers

K.N. Shobha Rani et al.,[64] worked on microencapsulated Diclofenac sodium by using different polymeric materials viz. albumin, ethyl cellulose, gelatin, calcium alginate and waxes and reported that the release of drug from the micro spheres of gelatin and ethyl cellulose was significantly retarded.

K.P.R. Chowdary et al.,[65]worked on ethyl cellulose micro spheres of Glipizide by an industrially feasible emulsion solvent evaporation technique and also evaluated in vitro-in vivo performance. It was reported that the micro spheres was suitable for parental controlled release.

Uzunkaya.G, Bergisadi.N et al.,[66] formulated sustained release suppositories containing indomethacin micro spheres prepared by solvent evaporation method using ethyl cellulose polymer. Drug release results were evaluated for kinetic parameters.

Kruba.R et al.,[67] formulated and evaluated the micro capsules of Amindarone by solvent evaporation method using ethyl cellulose polymer. The formulation method was based on drug polymer ratio. It was concluded that the ethyl cellulose(drug: polymer 1:1) desired controlled release a drug.

S.Madhusudhan et al.,[68] worked on developed sustained release formulations of glipizide by microencapsulation techniques using rate retarding polymer ethyl cellulose to promote better diabetic therapy.

R.Sathiyasundar et al.,[69] worked on Flurbiprofen microspheres by emulsion solvent evaporation technique using ethyl cellulose as the polymer drug content and drug entrappingefficiency of microspheres, were also studied.

Giovanni F.Palmieri et al.,[70] worked on ketoproton microspheres by emulsion solvent evaporation technique at 15^0 and 60^0 and then micro encapsulated using different polymer such as ethyl cellulose, cellulose acetate, Eudragit RS. The compressibility measurement indicated that the microcapsule showed better compaction than the microcapsule showed better compaction that corresponding physical mixture and so were easily transformed into tablets.

Dilip G. Maheshwari and Keval l. Chaudhari et al.,[71]worked on Development and Validation of UV SpectrophotometricMethod for Simultaneous estimation of Epalrestat and Methylcobalamine in the Pharmaceutical Dosage Form A new sensitive, simple, rapid and precise spectrophotometric method has been developed forsimultaneous estimation of Epalrestat (EPAL) and Methylcobalamine (MEC) in pharmaceutical dosage form.This method was based on UVspectrophotometric determination of two drugs, using simultaneous equation

method. It involves measurement of absorbance's at two wavelengths 390nm (λ max of Epalrestat (EPAL)) and 354nm (λ max of Methylcobalamine (MEC)) in methanol for the simultaneous quantitative determination of Epalrestat and Methylcobalamine in the binary mixture without previous separation. The linearity was observedin the concentration range of 3 – 15 μg/ml for Epalrestat and 15-35 μg/ml for Methylcobalamine. The accuracyand precision of the method was determined and validated statically. The method showed good reproducibility and recovery with % RSD less than 2. Method was found to be rapid, specific, precise and accurate, can besuccessfully applied for the routine analysis of Epalrestat and Methylcobalamine in combined dosage formwithout any interference by the excipient.

P. S.GOUDANAVAR, R.S.BAGALI, CHANDRASHEKHARA.S ANDS. M.PATIL et al.,[72]worked on Design and Characterization of Dichlofenac sodium micro beads by Ion tropic gelation techniques.Sustained release oral product of Diclofenac sodium prepared by ionotropicgelation technique using Sodium alginate alone and combination with Hydroxypropyl methyl cellulose,Chitosan, Pectin as release rate modifiers, and investigated for flow behavior, particle size, swellingproperties, surface study by SEM, and in vitro drug release potential. While increase in theconcentration of sodium alginate and other polymer dispersions increased sphericity, size distribution,mean particle size. Drug entrapment efficiency approached nearly 95%. Increasing calcium chlorideconcentration decreases the mean diameter of the microbeads, no appreciable change in morphology,and drug release behaviors. In vitro drug release was dependent on the pH of the medium andconcentration of polymer dispersions. Among the nine formulation batches F5, F7 and F9 were found toshow optimum sustained effect. The mechanism of drug release from the microbeads was found to be followed super case-II transport.

Thulasi V Menon, C.I.Sajeeth et al.,[73]worked on Formulation And Evaluation Of Sustained Release Sodium Alginate Micro beads Of Carvedilolto formulate Carvedilol loaded micro beads of sodium alginate using gelatin and pectin as release modifiers by ionotropic gelation method. The microbeads were prepared byvarying the concentration of sodium alginate, gelatin and pectin. The drug-polymer compatibility was studied byFTIR studies.The prepared microbeads were evaluated for swelling ratio, particle size, drug entrapment,Scanning electron microscopy

(SEM), bio adhesion study and in-vitrorelease study. Particle size distribution ofboth placebo and drug loaded formulations were measured by an optical microscope and particle size of optimized beads was determined by SEM. No significant drug-polymer interactions were observed in FT-IRstudies. In-vitrodrug release profile of Carvedilol micro beads was examined in pH 1.2 N Hydrochloric acid forfirst 2 hours followed by phosphate buffer pH 7.4 for

remaining time.The in vitro wash-off test indicated thatthe sodium alginate micro beads had good mucoadhesive properties. The formulated beads had shown higherentrapment efficiency, drug loading, low particle size and moisture content. The formulation F3 released Carvedilol for longer duration (24 hours) and showed better mucoadhesion.

E. Chandra Sekhar1, K. Madhusudana Rao2 et al.,[74]worked on Development of Sodium Alginate/(Lignosulfonicacid -g- Acrylamide) IPN Micro Beads for Controlled Release of an Anti-Malarial Drug. NaAlg/(LSA-g-Am) interpenetrating polymeric network micro beads were developed by graft polymerization using calcium chloride as crosslinker. Pyronaridine drug was loaded into these microbeads via blending method. Various formulations were prepared by varying the ratios of LSA/AAm/NaAlg, crosslinker and % of pyronaridine loading. Micro beads were characterized by Fourier transforms infrared spectroscopy (FTIR), differential scanning calorimetric (DSC), X-ray diffraction (X-RD) and Scanning electron microscopy (SEM). DSC and X-RD studies were performed to understand the crystalline nature of drug after encapsulation into semi IPN micro beads. SEM images gave the beads with smooth surface. FT-IR spectroscopy of microbeads confirms the formation of co-polymerization and grafting of the polymers. The encapsulation efficiency was found up to 68 %. Drug release profiles of the IPN micro beads at pH 7.4 confirmed that micro beads formed are pH-sensitive, resulting controlled release of drug during in vitro dissolution experiments. Both encapsulation efficiency and release patterns are found to be dependent on the nature of the cross-linking agent, amount of drug loading and % of LSA/Am/NaAlg The release was extended up to 12h and release rates were fitted to an empirical equation to compute the diffusion parameters, which indicated non-Fickian or anomalous trend release of pyronaridine.

Sharath Chandra. Seelam, Dhanalakshmi.K, Nagarjuna reddy et al.,[75] worked on A simple, efficient and reproducible derivative spectrophotometric method was developed for the drug Epalrestat in bulk and tablet dosage forms. First derivative spectrophotometric estimation is use for the elimination of irrelevant absorption. Epalrestat wasdetermined at 388 nm, 366nm for zero, and first order derivatives respectively using methanol as solvent. Linearity was obtained within the range of 1-7 μg/ml with correlation coefficient of 0.999, and 0.998 for zero and first order derivatives. The %recovery forthe proposed method was found to be 100.04-131.06, 102.31-129.34% indicating no interferences from the tablet excipient. Theresult of analysis was validated statistically and recovery studies confirmed the accuracy and precision of the proposed method.

VM. Sherina, K. Santhi and C.I. Sajeeth et al.,[76] worked an Formulation and Evaluation of Sodium Alginate Microbeads as a Carrier for the Controlled Release of Nifedipine. The objective of the current investigation is to reduce dosing frequency and improve patient compliance by designing and systematically evaluating sustained release micro beads of Nifedipine. Frequent administration and variable low bioavailability (40-50%) after oral administration are problems of conventional dosage forms of Nifedipine can be attenuated by designing it in the form of mucoadhesive microbeads which would prolong the residence time at the absorption site to facilitate intimate contact with the absorption surface and thereby improve and enhance the bioavailability. Nifedipine-loaded mucoadhesive micro beads were successfully prepared by ionotropic gelation and cross linking technique by using sodium alginate as the hydrophilic carrier in combination with HPMC and chitosan polymers as drug release modifiers. Prepared beads were evaluated for particle size, swelling ratio, drying rate, drug entrapment, bio adhesion study, in-vitrorelease, release kinetic and stability study. Particle size distribution of both placebo and drug loaded formulations were measured by an optical microscope and particle size of optimized beads was determined by SEM. No significant drug-polymer interactions were observed in FT-IR studies.In-vitrodrug release profile of Nifedipine micro beads was examined in phosphate buffer pH 6.8 and exhibited zero order kinetic followed bysuper caseII-transport.

Gayathri S et al.,[77] worked on formulation and Evaluation of Sustained Release Alginate microbeads enclosed Gabapentin The objective of the present study was to develop sustained release beads of gabapentin by ion tropicgelation technique by using different proportions of sodium alginate, HPMC- E15, K4M, Sodium carboxyl methyl cellulose and pectin. The drug-polymer compatibility was studied by FTIR and DSC. The obtained microbeads were characterized for particle size determination, swelling ratio, drug entrapment, scanning electron microscopy (SEM), drug content, *in-vitro* release, kinetic models and stability studies. The prepared beads were found to be optimal in terms of particle size and entrapment efficacy. There was no compatibility issues was found to be in prepared microbeads, which were confirmed by FTIR and DSC studies. *In-vitro* drug release profile of microbeads coated with sodium alginate and pectin was examined 98.3% of drug release with in 12h. The release data from all the formulation was found to fit higuchi model. The release kinetics data indicated that the drug release from microbeads was diffusion-controlled and the microbeads were stable in nature. From this study, it was concluded that the micro beads of gabapentin could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and sustained release characteristics.

P. Janaki Pathi1*, N. Appala Raju et al.,[78]Formulation of the Estimation of Epalrestat in Tablet Dosage Form by RP-HPLC. A simple, precise, rapid and accurate reverse phase HPLC method was developed for the estimation of Epalrestat in tablet dosage form. An XTerra(R) C18 analytical column (250x4.6 mm, 5 µm particle size) with mobile phase consisting of mixture of buffer (0.03M Potassium Dihydrogen phosphate in water at pH 3.2 with ortho-phosphoric acid) and acetonitrile in the gradient program was used. The flow rate was 1.0 ml/min and the effluents were monitored at 294 nm. The retention time was 15.9 min. The detector response was linear in the concentration of 20- 120 mcg/ml. The respective linear regression equation being y= 3818.8x-3819. The limit of detection and limit of quantification was 0.005mcg/ml and 0.015mcg/ml respectively. The percentage assay of Epalrestat was 99.3%. The method was validated by determining its accuracy, precision and system suitability.

Swapon Kumar Birwa's, Sujit Birwa's et al.,[79]worked an Formulation Development and Physico-Chemical Study of Epalrestat Tablet with Improved Bioavailability in Terms ofDisintegration and Dissolution Epalrestat is available in tablet dosage form by some local manufacturers of Bangladesh. This proposed formulation will provide better efficacy with low

price due to cost effective measures have been taken during every steps of development. It is also noted by the performance of improved bioavailability specially parameter like lower Disintegration Time and greater Dissolution Rate. Other quality control tests (e.g. Thickness, Hardness, Friability, Individual Weight and content of active ingredients) were also performed to ensure its better tablet properties. The most amazing and attractive thing of my study is that the price will be cheaper than local manufacturer of Bangladesh absolutely with better quality because of using some cheap but effective excipient which will help greatly for the poor in our country.

By Wei Wei, Lian-Yan Wang, Lan Yuan, et al.,[80]worked on Preparation and Application of Novel Microspheres Possessing Autofluorescent PropertiesFluorescent microspheres are widely used as biological tracers. In this study, uniformly sized chitosan microspheres crosslinked with glutaraldehyde (CG microspheres) and formaldehyde (CF microspheres) are successfully prepared by the Shiras Porous Glass (SPG) membrane emulsification technique. Selectively reduced CG microspheres (SRCG microspheres) are obtained by NaBH4 reduction. These chitosan microspheres are found to exhibit fluorescent properties without conjugation to any fluorescent agent. The fluorescence color varies with different crosslinkers and can be modulated by further chemical reduction, whereas the fluorescence intensity can be controlled by tuning the particle size and degree of crosslinking. The autofluorescence of the microspheres is applied to study the phagocytosis of HepG2 cells using the microspheres as novel tracers.
Quantitative and qualitative evaluations show that these chitosan microspheres serve as bright, inert, durable, and extremely photostable tracers.
Nurten O¨ zdemir,1,* Sefika Ordu,et al., [81]worked on Studies of Floating Dosage Forms of Furosemide In Vitro and In Vivo Evaluations of Bilayer Tablet Formulations. the design of dosage form, bilayer floating tablets were prepared. After dissolution rate studies were performed usingthe continuous flow-through cell method, the formulation that provided delivery of active material near the target profile was given to six healthy male volunteer subjects, and in vivo tests were performed. It was determined by radiographs that floating tablets prepared by adding BaSO4 stayed in the stomach for 6 hr. Further, values of the area under the plasma concentration-time curve (AUC) obtained with the floating dosage form were about 1.8 times

those of the conventional FR tablet in blood analyses; maximum and minimum plasma concentrations were also found to be between the desired limits. In urine analyses, the peak diuretic effect seen in classical preparations was decreased and prolonged in floating dosage forms. Also, a considerably significant correlation was detected between in vivo results and in vitro data ofthe dissolution rate, and it was concluded that the modified continuous flow-through cell method is usable for in vitro dissolution rate tests of floating dosage forms.

CHAPTER 3

OBJECTIVE OF THE RESEARCH WORK

Epalrestat is an effective diabetic neuropathy drug used for reliving nerve pain. Because of relatively short biological half life, it needs frequent administration to the patient. Hence controlled release of this drug is highly desirable. Epalrestat when formulated as microspheres eliminate the disadvantages of the controlled release tablets such as Absorption of drug irrespective of the feeding state, Minimal potential for dose dumping, shorter lag time and lower variability. Selection of right excipient is crucial and important during the development of matrix system because there is a chance of drug dumping. Hence different polymers were used to control the drug release from the matrix system. In the present study different polymer were used.

The present study was aimed to prepare the micro spheres of Epalrestat using various Eudragit and Ethyl cellulose polymer at different drug to polymer concentrations.Eudragit RL 100 and Eudragit RS 100 are two copolymers synthesized from acrylic and methacrylic acid esters, containing a low level of quaternary ammonium groups. Eudragit RS 100 has a lower content of charged groups (4.5–6.8%), and it is considered less permeable to water with respect to the more readily permeable Eudragit RL 100 (8.8–12% ammonium groups). Higher permeability of Eudragit RL 100 is due to maximum number of quaternary ammonium substitution present in the structure of Eudragit RL 100 compared to RS 100 which affects the release behaviour of the drug. Ethyl cellulose is hydrophobic in nature; thus, the hydrophobic polymer encapsulates larger amount of the drug and hence was used in combination with Eudragit RL and RS 100 to increase the encapsulation efficiency and for a better controlled release. Eudragit S- 100 being a pH dependent polymer may reduce the impermeability of Ethyl cellulose by the formation of pores in the matrix. Hence the study was aimed to study the controlling effect of Epalrestat using the aforementioned polymers in the microspheres. The micro spheres prepared were evaluated for assay encapsulation efficiency, average particle size, in vitro drug release kinetics. The micro spheres were evaluated for drug excipient compatibility studies by FT-IR.

PLAN OF RESEARCH WORK

Construction of standard calibration curves:

The standard calibration curve of Epalrestat was prepared by methanol & water.

Preparation of micro spheres:

Micro spheres were prepared by using solvent evaporation method.

Formulation of Epalrestat Micro spheres with Ethyl cellulose, Eudragit L 100, Eudragit RS 100, Eudragit RL 100 in the ratio of 1:2 drug and polymer. In this same time the three different polymer only changing ratio of 1:1.2:0.8, 1:1.4:0.6, 1:1.6:0.4 & 1:1.8:0.2.

In vitro drug release studies of prepared micro spheres:

The in vitro dissolution studies were performed for the prepared micro spheres using dissolution apparatus (LABINDIA, DS 8000, Mumbai, India).

Kinetic analysis of dissolution data;

The release rate and mechanism of drug release from the prepared formulations were analyzed by fitting the dissolution data into various release models such as :

a. zero order

b. First order

c. Higuchi model

d. Peppas equation

Encapsulation efficiency (EE):

The percentage entrapment was calculated by using following formula.

$$\% \text{ of EE} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) \times 100$$

Flow property studies:

The flow properties of micro spheres which were prepared are studied by

angle of repose.

Particle size distribution of micro spheres:

Particle size analysis of the micro spheres was done by using optical micro spheres was done by using optical microscopy method.

Scanning electronic microscopy (SEM):

Morphological characterization of the microcapsules was done by using scanning electron microscope.

Fourier transforms infrared radiation measurement (FT-IR):

The FT-IR spectrums of pure drug, initial formulation were determined

CHAPTER 4

DRUG & POLYMER PROFILE

Drug profile of epalrestat[82]

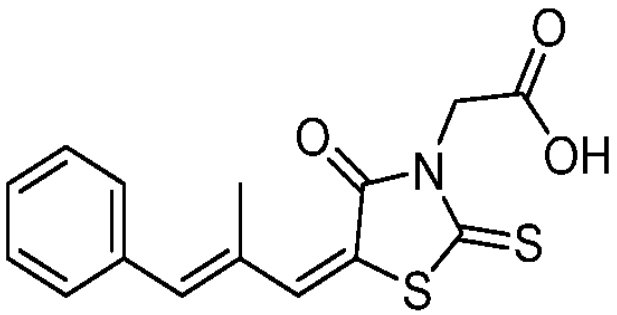
Epalrestat is a carboxylic acid derivative which inhibits aldose reductase, an enzyme of the sorbitol (polyol) pathway. Under hyperglycemic conditions Epalrestat reduces intracellular sorbitol accumulation, which has been implicated in the pathogenesis of late-onset complications of diabetes mellitus.

Chemical name: 3-Thiazolidineacetic acid, 5-(2-methyl-3-phenyl-2-propenylidene)-4-oxo-2-thioxo-,(E,E)-5-((1Z,2E)-2-Methyl-3-phenylpropenylidene)-4-oxo-2-thioxo-3-thiazolidineacetic acid

Molecular formula: C15H13NO3S2

Molecular Weight: 319.41
Solubility: Soluble in organic solvent of di chloro methane
State: orange Red colour
Melting Point: 210-217 ^{o}C
Mechanism of action: aldose reductase inhibitor used for treatment of diabeticnephropathy. Epalrestat suppresses accumulation of sorbitol in nerve by inhibiting aldose reductase, and relieves numbness/pain of the hands and feet and leg cramp, etc.,
Marketed products: Kineda

Figure (4.1):



EPALRESTAT

Product Description:

Epalrestat is an Aldose Reductase Inhibitor. Aldose Reductase is an enzyme which converts excess glucose in to sorbitol which may lead to Neuropath

Mechanism of Action:

Epalrestat (5-2-methyl-3-phenylpropenylidene]- 4-oxo-2-thioxo-3-thiazolidineacetic acid) is a noncompetitive, reversible inhibitor of aldose reductase, an enzyme of the polyol pathway.

PHSICOCHEMICAL PROFILE

Pharmacokinetics[83]

Indications

A peak plasma concentration of 3.9 μg/ml is reached approximately 1 hour after administration.

Distribution

Epalrestat is highly protein bound, with a protein binding rate of 90.1%.

Metabolism

Metabolism occurs in the liver by phase 1 and phases 2 reactions. During phase 1 metabolism, Epalrestat is metabolized through hydroxylation into two metabolites, monohydroxy and dihydroxy compounds. The enzyme responsible for phase 1 metabolism is unknown. These compounds are further metabolized by a phase 2 reaction to produce glucuronide and sulfate conjugates.

Pharmacology

The sorbitol (polyol) metabolic pathway, an alternative glucose reduction pathway involving the enzymes aldose reductase and sorbitol dehydrogenase, is thought to be activated by

hyperglycemic conditions. Intracellular accumulation of sorbitol during hyperglycemia is considered to be at least partially responsible for the pathogenesis of late-onset complications of diabetes mellitus. Epalrestat, an uncompetitive aldose reductase inhibitor, significantly reduces intracellular sorbitol accumulation in sciatic nerve, erythrocytes and ocular tissues from animal models, and in erythrocytes in humans, with diabetes mellitus, without affecting glucose levels. Epalrestat also increased sodium-dependent myoinositol uptake into sciatic nerve tissue in rats and skin fibroblasts from patients with diabetes, and attenuated nerve conduction velocity and retinal changes commonly seen in patients with diabetic neuropathy and retinopathy, respectively.

In healthy volunteers, distribution of Epalrestat is rapid and peak plasma concentrations are reached 1 to 2 hours after oral doses of 50 to 200mg. The elimination half-life is about 1 hour, and unchanged Epalrestat and sulphate conjugates of the mono- and dihydroxyphenyl metabolites are found in the urine.

- **Excretion**

  The unchanged parent drug is excreted in the urine, as are sulfate conjugates of the two metabolites.

  Indications

  To reduce the symptoms of Diabetic Peripheral Neuropathy(DPN) such as numbness, tingling and burning sensation of the feet and arms.

  Contraindications

  Hypersensitivity to any component of the drug & in severe hepatic insufficiency.

  Drug Interactions

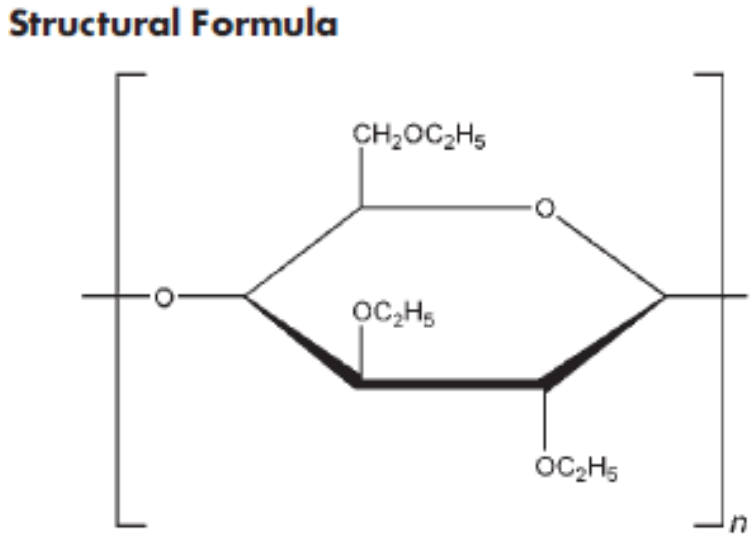
  No established drug interaction.

POLYMER PROFILE:

A polymer, natural or synthetic is a substance that is combined with a drug or other active agent to release drug in a pre-designed manner1. The development of NDDS has been made possible by the various compatible polymers to modify the release pattern of drug[84, 85]. Choice of polymers always suffering from the problems of non-biocompatible, non-biodegradable and expensive and this problem can solve with a polymer of different properties. The basic objective of controlled drug release is to achieve more effective therapies by eliminating the potential for both under- and overdosing. Other advantages administrations, optimal drug use and increased patient complia[86].

ETHYL CELLULOSE [87]

Figure (4.2)



1. Synonyms

Aqua coat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosum;

2.Chemical Name and CAS Registry Number

Cellulose ethyl ether [9004-57-3]

3. Empirical Formula and Molecular Weight

Ethyl cellulose is partially ethoxylated. Ethyl cellulose with completeethoxyl substitution (DS = 3) isC12H23O6(C12H22O5)nC12H23O5 where n can vary to provide awide variety of molecular weights. Ethyl cellulose, an ethyl ether ofcellulose, is a long-chain polymer of b-an hydro glucose units joinedtogether by acetyl linkages.

4.Functional Category

Coating agent; flavoring agent; tablet binder; tablet filler; viscosity increasing agent.

5.Applications in Pharmaceutical Formulation orTechnology

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations; see Table I. The main use of Ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl `cellulose 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 are coated with Ethyl cellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using Ethyl cellulose as a matrix former. Ethyl cellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity Ethyl cellulose grades tend to produce stronger and more durable films. Ethyl cellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer.

An aqueous polymer dispersion(or latex) of Ethyl cellulose such as Aqua coat ECD (FMC Biopolymer) or Sure lease (Colorcon) may also be used to produce Ethyl cellulose films without the need for organic solvents. Drug release through ethyl cellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous Ethyl cellulose dispersions are generally used to coat granules or pellets. Ethyl cellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression. High-viscosity grades of ethyl

cellulose are used in drug microencapsulation. Release of a drug from an ethyl cellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethyl cellulose may additionally be employed as a binder, the ethyl cellulose being blended dry or wet granulated with a solvent such as ethanol (95%). Ethyl cellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethyl cellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances. In topical formulations, ethyl cellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethyl cellulose has been studied as a stabilizer for emulsions. Ethyl cellulose is additionally used in cosmetics and food products.

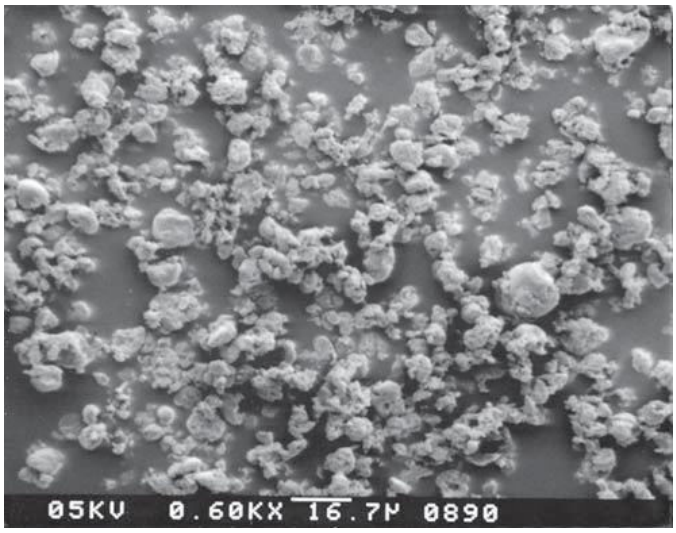
Table I: Uses of ethyl cellulose.

Use	Concentration (%)
➢ Microencapsulation	10.0–20.0
➢ Sustained-release tablet coating	3.0–20.0
➢ Tablet coating	1.0–3.0
➢ Tablet granulation	1.0–3.0

6. Description

Ethyl cellulose is a tasteless, free-flowing, white to light tan-colored powder.

Figure (4.3)



7. Typical Properties

Density (bulk)0.4 g/cm3

Glass transition temperature 129–1338C

Moisture content Ethyl cellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Solubility

Ethyl cellulose is practically insoluble in glycerin, propylene glycol, and water. Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform,
methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethyl cellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol,
and toluene.

8.Safety

Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethyl cellulose is not metabolized following oral consumption and is therefore a no calorific substance. Because ethyl cellulose is not metabolized it is not recommended for parenteral products. parenteral use may be harmful to the kidneys. Ethyl cellulose is generally regarded as a nontoxic, nonallergenic, and nonirritating material. As ethyl cellulose is not considered to be a health hazard, the WHO has not specified an acceptable daily intake. The highest reported level used in an oral product is 308.8 mg in an oral
sustained release tablet.

9. Stability and Storage Conditions

Ethyl cellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340nm range. Ethyl cellulose should be stored at a temperature not exceeding 328C (908F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

10. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

11. Related Substances

Hydroxyethyl cellulose; hydroxyethylmethyl cellulose; mEthyl cellulose.

EUDRAGIT:

Eudragit is trademark of Rohm GmbH & Co. KG. Darmstadt in Germany, firstmarketed in 1950s. Eudragit prepared by the polymerization of acrylic and Methacrylicacids or their esters, e.g., butyl ester or Dimethylaminoethyl ester. Eudragit introduced inUSPNF, BP, PhEur, Hand book of pharmaceutical excipients[88]. The Eudragit acrylicpolymers have a long history of use, the individual types and grades being introduced in the following chronological order:year of introduction;

1972 Eudragit RS PO

Eudragit RL PO

Glass transition temperature (Tg):

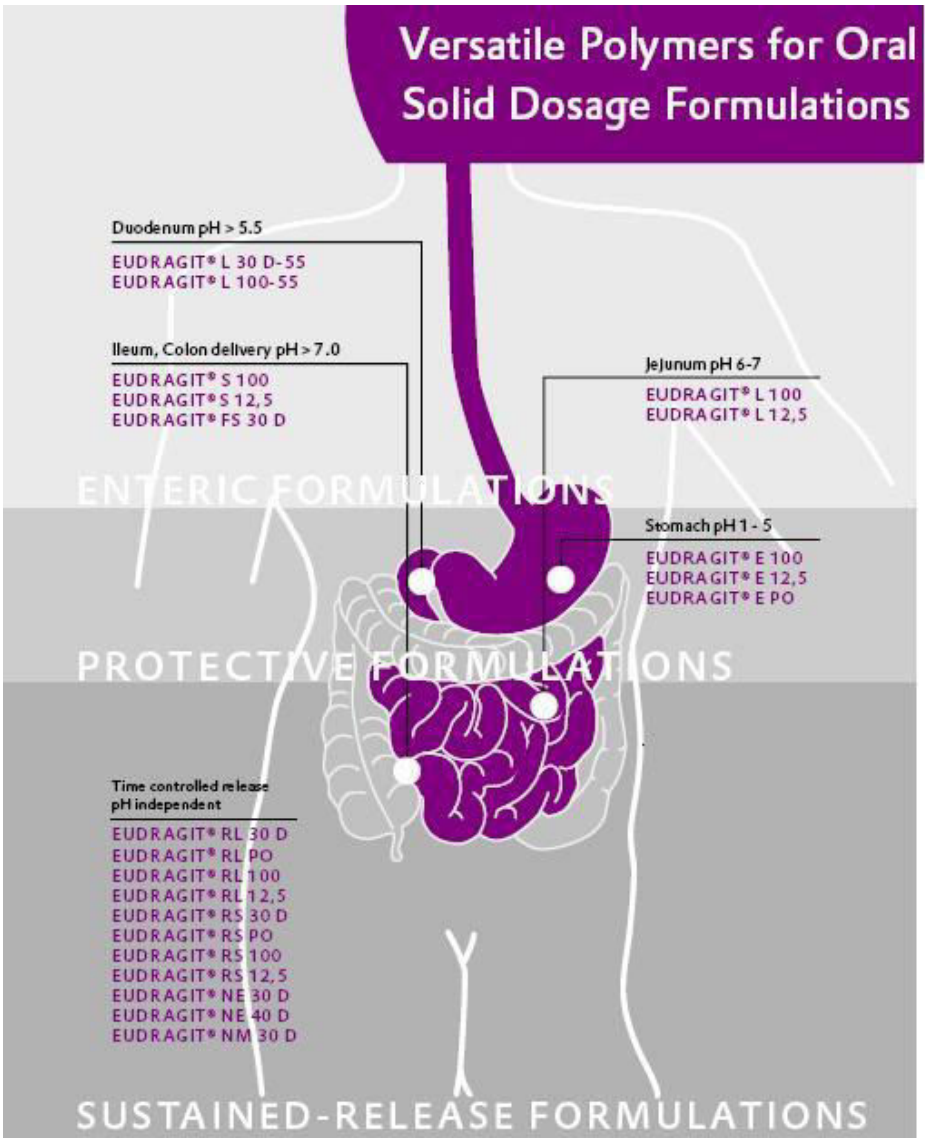
The glass transition temperature is an important factor for describing the physicalproperties of polymers. On a macroscopic level it describes the solidification of ananisotropic polymer melt. The glass transition temperature has far-reaching consequences,e.g. for film formation, melt processing and storage of finished pharmaceutical dosageforms. Plasticizers, solvents or residual solvents (including water) that act as plasticizersusually cause a reduction in glass transition temperature, which is specifically exploited inapplication formulations. Most common plasticizer for EUDRAGIT polymers is triethylcitrate (TEC).

Physical and chemical properties;

S. No	Trade name	Solubility	Description	Applications
1	Eudragit S 100	Soluble in intestinal-fluid from pH 7	Anionic, white free flowing powders[5]	Enteric coatings
2	Eudragit RL PO	High permeability	Cationic, nonbiodegradable[89]	Sustained release
3	Eudragit RS PO	Low permeability	Cationic, nonbiodegradable[89]	Sustained release

Figure (4.4):

Different grades of Eudragit in oral solid dosage formulation



Drug Release Mechanism:

Oral preparation for controlled release can be sub divided in systems where drug release from the dosage form is governed by the following principles:

A. Dissolution
B. Diffusion
C. Osmotic Pressure
D. Ion-Exchang
E. Other Principle[90]

Dissolution controlled dosage forms can be divided into reservoir and matrix system. Reservoir principle is given by a controlled release formulation comprising 400mg 5-ASA within an acrylic resin coat, Eudragit S[91].

Eudragit RS PO release the Carbamazepine drug by complex mixture of diffusion and Erosion mechanism[92]**.**

Applications of Eudragit polymers:

- Ophthalmic Drug Delivery
- Buccal and Sublingual Drug Delivery
- Gastrointestinal Drug Delivery
- Intestinal Drug Delivery
- Colon Drug Delivery
- Transdermal Drug Delivery
- Vaginal Drug Delivery
- Gene Delivery
- Vaccine Delivery

CHAPTER 5

MATERIALS AND METHODS:

Table (5.1)

S.No	Name of the material	Source/supplier/manufacturer
1.	Epalrestat	Gift sampled from EXCELTIS
2.	Ethyl cellulose	S d fine-CHEM LiMiTEd
3.	Eudragit	Gift sampled from PHARMAFABRIKAN
4.	PVA	CHEMICO LABORATORIES (P) LTD. MUMBAI
5.	Stearic acid	HIMEDIA MUMBAI
6.	Methanol	CHANGSHU Yangquan chemical CHINA
7.	SLS	s d fine-CHEM Limited
8.	Chloroform	HIMEDIA MUMBAI
9.	Di Chloro Methane	CENTRAL DRUG HOUSE (P) LTD
10.	Sodium hydroxide	Rankem Laboratory Ambattur
11.	Potassium Di hydrogen Ortho phosphate	FISCHER CHEMIC Ltd Chennai

List of equipments used in the present study:

Table (5.2)

Instruments	Manufacturer
Electronic weighing balance	AUX 220 Shimadzu corporation, Japan.
Magnetic stirrer	Remi motors.
Dissolution apparatus	DISSO 2000, LABINDIA, Mumbai, India.
UV-VIS Spectrophotometer	SHIMAZHU UV-1700 pharma spec
Hot air oven	Micro Technik, Model-JEQ-3A, Amble, India.
Rotary shaker	RS-12,Remi equipments Ltd, Mumbai, India.
Sonicater	ELECTROSONIC INDUSTRIES.

Construction of standard calibration curves[94]:

A standard calibration curve was plotted in methanol and water. accurately weighed 20 mg of drug was transferred in to a 10 ml volumetric flask and this solution diluted in 100 ml distilled water. Taken 5 ml of in this solution and make up to 10 ml with distilled water. This gives a solution having concentration of 10µg/ml, of stock Epalrestat solution. From this primary stock solution 1ml was transferred into 10ml volumetric flask and made up to 10ml with distilled water to produce 1,2,3,4,5,6,7,8,9 &10 µg/ml solution respectively. The absorbance was measured at ƛ max 389 nm using UV spectrophotometer.

Preparation Methods of Micro spheres:

Emulsion solvent evaporation technique[93]:

Micro spheres were prepared by Solvent evaporation method.

Micro spheres were prepared by solvent evaporation method. Accurately weighed , different quantities of polymer were dissolved in 10 ml of chloroform and DiChloromethane by using a stirrer. The drug was mixed with the polymer solution followed by stirring for 10 min.

The resulting dispersion was then poured in to 500 ml beaker containing the mixture of 200 ml poly vinyl alcohol (as continuous phase). and 2% of Sodium Lauryl Sulphate(SLS). A mechanical stirrer with a three bladed paddle was used for stirring (at 1000 RPM) and it was continued for 2-3 hours, until complete evaporation of chloroform. After evaporation of chloroform , the micro spheres formed were filtered using filter paper and washed with water. The micro spheres were dried at room temperature for 24 hours and kept for further evaluations study. The prepared micro spheres were spherical and free flowing. The prepared micro spheres were analyzed for various Physico chemical properties such as entrapment efficiency, particle size distribution, in vitro dissolution studies, FT-IR and SEM.

Table (5.3)

FORMULATION COMPONENTS OF THE PREPARED EPALRESTAT MICRO SPHERES:

Formulation	Drug (mg)	Ethyl cellulose (mg)	Eudragit S-100 (mg)	Eudragit RS 100(mg)	Eudragit RL 100(mg)	Amount of chloroform & DCM (ml)	SLS (%)
F1	500	600	400	-	-	5:5	2
F2	500	700	300	-	-	5:5	2
F3	500	800	200	-	-	5:5	2
F4	500	900	100	-	-	5:5	2
F5	500	600	-	400	-	5:5	2
F6	500	700	-	300	-	5:5	2
F7	500	800	-	200	-	5:5	2
F8	500	900	-	100	-	5:5	2
F9	500	600	-	-	400	5:5	2
F10	500	700	-	-	300	5:5	2
F11	500	800	-	-	200	5:5	2
F12	500	900	-	-	100	5:5	2

Fourier Transforms Infrared Spectroscopy (FT-IR)[99]:

The FT-IR spectrum of pure drug and the formulation were determined.

The FT-IR was used for the analysis in the frequency between 4000-400cm^{-1} and 4cm^{-1} resolutions the reagent were the means of six determinations. The quality equivalent 2mg of pure drug was used for the study.

Determination of Encapsulation efficiency (EE)[94]:

The encapsulation efficiency of the prepared micro spheres was determined by performing assay / drug content in the prepared microspheres. The microspheres from each batch were taken. The microspheres were first crushed in a mortar and pestle and then 25 mg equivalent of the powder was taken in to the 10 ml volumetric flask. The volumetric flask then filled with methanol and Sonication for 1 min. And finally make up the volume. Further dilution made by 100 % encapsulation efficiency. The samples were analyzed using UV-visible spectrophotometer at 389 nm. The Values are given in the table 6.2.

The percent entrapment was calculated by using the following formula;

$$\% \text{ of EE} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) \times 100$$

In vitro drug release studies of prepared microspheres[95]:

The in vitro dissolution studies were performed for the prepared microspheres using USP dissolution apparatus(apparatus 1),LABINDIA,DS-2000,Mumbai,India). The micro spheres were kept in the bowel of the dissolution medium. The dissolution medium consisted of 0.1N Hcl (900ml) for 2 hrs. Later the dissolution medium was replaced with 7.4 ph phosphate buffer(900 ml) at 100 rpm speed, maintained at 37.5°C. An aliquot (2ml) was withdrawn at specific time interval and filter through 0.45µ(Millipore)filter. After appropriate dilution the samples were analyzed and cumulative% of the drug release was calculated.

Kinetic analysis of dissolution data[96]:

Drug release kinetics and mechanism:

To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches were fitted to zero order, 1st order , Higuchi and Peppas models to ascertain the kinetic modeling of drug release.

Zero order:

In many of the modified release dosage form particularly controlled or sustained dosage forms(those dosage forms that release the drug in planned, predictable and slower than normal manner) is zero order kinetics

$$Q = k_o t$$

where, Q is the amount of drug release at time, t & k_o is the release rate constant.

First order:

The dissolution data was fitted to first order equation

$$\ln(100-Q) = \ln 100 = k_1 t$$

where k_1 is the release rate constant

Higuchi equation:

A large number of modified released dosage form contain some sort of matrix system is such instances the drug dissolves from this matrix. The dissolution pattern of the drug is dictated by water penetration rate(diffusion control) and thus the following relationship applies.

$$Q = k_2 t^{1/2}$$

where Q is the % of drug release at time t & k2 is the diffusion rate constant.

Peppas equation:

The Peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation shown as equation ;

$$Mt/M\infty = kt^n$$

Where $Mt/M\infty$ is the fraction of drug released 'k' is the release constant, t is the release time.

n is diffusion exponent, if n= 0.89, the release rate is zero order. If n = 0.45 the release is best explained by Fickian diffusion and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non Fickian diffusion(swellable and cylindrical matrix). In this model a plot of log ($Mt/M\infty$) Vs log (time is linear).

Table (5.4)

Release exponent	**Drug transport mechanism**	**Rate as a function of time**
0.5	Fickian diffusion	t-0.5
S0.5< n < 1.0	Anomalous diffusion	tn^{-1}
1.0	Case II transport	Zero order release
Higher than 1.0	Super Case II transport	tn^{-1}

Particle distribution of microspheres[97,98]:

Particle size analysis of microspheres was done by optical microscopy method by using a calibrated stage micrometer. Particle size was calculated by using equation

$$X_g = 10 \text{ x } [(n_i x \log X_i)/N]$$

where, X_g is geometric mean diameter n_i is number particle in range, X_i is the midpoint range

and N is total number of particles.

Scanning Electron Microscopy (SEM):

Morphological characterization of the micro spheres was done by using scanning electron microscope.

Flow property studies:

Angle of repose and compressibility index methods were carried out for studying flow properties of microspheres which were prepared.

Angle of repose[100]:

Fixed funnel method was selected to find the angle of repose which employ a funnel that is secured with its tip at a given height (h), above a plain of paper that is placed on a flat horizontal surface. Microspheres of different batches were carefully poured separately through the funnel until the apex of the conical pile just touches the tip of the funnel, 'r' being the radius of the base of the conical pile. Angle of repose was found out by using the formula given below:

$$\tan \theta = h/r$$

$$\theta = \tan\text{-}1(h/r)$$

Stability study[101]:

Formulation were stored at 4°C in freeze, room temperature and at 60°c in hot air oven. After 30 days of storage, the formulation were observed physically and no color change and hardness was perceptible. the content of Epalrestat in all formulations at various intervals of 10, 20 and 30 days calculated.

CHAPTER 6

RESULT AND DISCUSSION'S:

Standard calibration curve for Epalrestat:

The standard calibration curve of Epalrestat was developed in media such as methanol and water and the water measured at 389 nm. Standard graph of Epalrestat shows linearity in the concentration range of 1-10 µg/ml with correlation coefficient of 0.999.

Table (6.1)

Concentration (µg/ml)	Absorbance
0	0
1	0.105
2	0.167
3	0.227
4	0.287
5	0.347
6	0.404
7	0.465
8	0.523
9	0.587
10	0.646

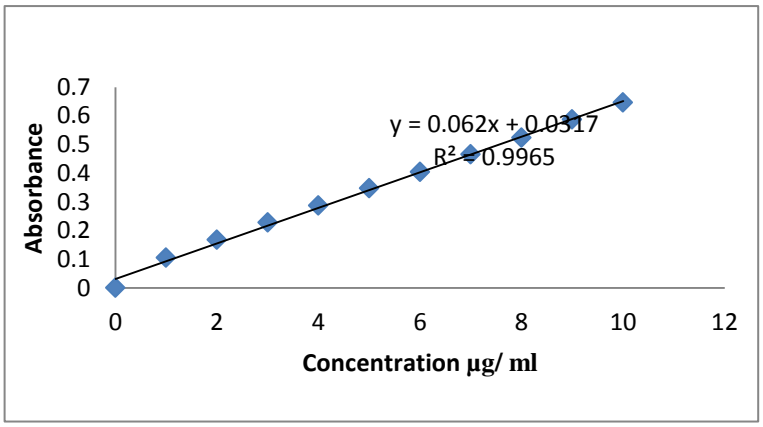


Figure (6.1)

Table(6.2)

Determination of Encapsulation efficiency (EE):

Formulation	Drug content in 100 mg of micro spheres	Encapsulation Efficiency (%)
F1	10.4	52
F2	13.8	69
F3	16	80
F4	16.2	81
F5	15.4	77
F6	16.2	81
F7	18.3	94
F8	18.9	94.5
F9	14.1	70.5
F10	15.6	78
F11	16.8	84
F12	19.2	96

The drug content was determined and finally encapsulation efficiency was calculated. The encapsulation efficiency for the microspheres prepared with Eudragit S 100 (F1to F4)was in the range of 52 to 81%. The encapsulation efficiency for the microspheres prepared with Eudragit RS 100 (F5 to F8) was in the range of 77 to 94.5%. The microspheres prepared with Eudragit RL 100 (F9 to F12) was in the range of 70.5 to 96%.Highest entrapment was observed in the microspheres prepared with Eudragit RL 100. However the particle size also changed with polymer might be due to change in the droplet formation in the emulsification process. The average particle size distribution of microspheres was given in the Table 6.27.

In vitro drug release studies:

The in vitro dissolution studies were performed for the prepared microspheres using dissolution apparatus (LABINDIA,DS 2000, Mumbai, India). The microspheres were kept in the bowel of the dissolution medium. The dissolution medium consisted of 0.1 N Hcl (900 ml) for 12 hours at 100 rpm speed, maintained at 37+5°c. The microspheres were weighed as per drug content estimated earlier of this chapter and subjected for the dissolution study.

Table: 6.3 summarize the practical amount of microspheres taken for the dissolution study.

In vitro dissolution of formulation prepared with Eudragit S 100:

The drug release from the microspheres prepared with Eudragit S 100 (F1) was found between 1 to 8 hours. The drug release for the microspheres prepared at (F2) to (F4) was found more than 12 hours. This may be the reason due to Eudragit S 100 being a more soluble polymer in the pH above 7 has with stand the acid pH but have dissolved in the alkaline pH. Due to this the microspheres have resulted in the formation of many pores in the matrix resulting in the leeching of much drug along with the dissolution medium which has much more space to enter into the matrix. In vitro dissolution showed that the drug release mainly depends upon the polymer concentration. As the Ethyl Cellulose polymer proportion increases in the microspheres the release rate was delayed. The in vitro drug release was fitted to the various kinetic models. The drug release kinetics showed that the release was followed zero order.

Table (6.3)

Cumulative % drug release of the Epalrestat micro spheres prepared with Eudragit S100 (F1):

Reagents	Time (Hrs)	% Drug release (F1)
0.1N Hcl	0	0
	60	9.98
	120	20.21
	180	39.83
	240	42.02
7.4 pH Phosphate buffer	300	54.54
	360	60.98
	420	73.31
	480	81.84
	540	92.97
	600	93.28
	660	93.87
	720	94.42

Table (6.4)

Kinetic analysis of dissolution data for formulation (F1):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F1	0.999	0.943	0.921	0.998	1.031

Table (6.5)

Cumulative % drug release of the Epalrestat micro spheres prepared with Eudragit S 100 (F2):

Reagents	Time Hrs)	% Drug release (F2)
0.1 N Hcl	0	0
	60	7.58
	120	14.16
	180	23.74
	240	29.32
7.4 pH Phosphate buffer	300	38.90
	360	44.84
	420	55.60
	480	60.74
	540	67.89
	600	76.90
	660	82.83
	720	91.08

Table (6.6)

Kinetic analysis of dissolution data for formulation (F2):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F2	0.999	0.953	0.916	0.997	1.018

Table (6.7)

Cumulative % Drug release of the Epalrestat micro spheres prepared with Eudragit S 100 (F3):

Reagents	Time (Hrs)	% Drug release (F3)
0.1 N Hcl	0	0
	60	7.25
	120	13.80
	180	22.01
	240	28.03
7.4 pH Phosphate buffer	300	36.55
	360	43.08
	420	51.92
	480	57.30
	540	65.43
	600	70.89
	660	78.02
	720	86.83

Table (6.8)

Kinetic analysis of dissolution data for formulation (F3):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F3	0.998	0.971	0.919	0.998	1.008

Table (6.9)

Cumulative % Drug release of the Epalrestat micro spheres prepared with Eudragit S 100 (F4):

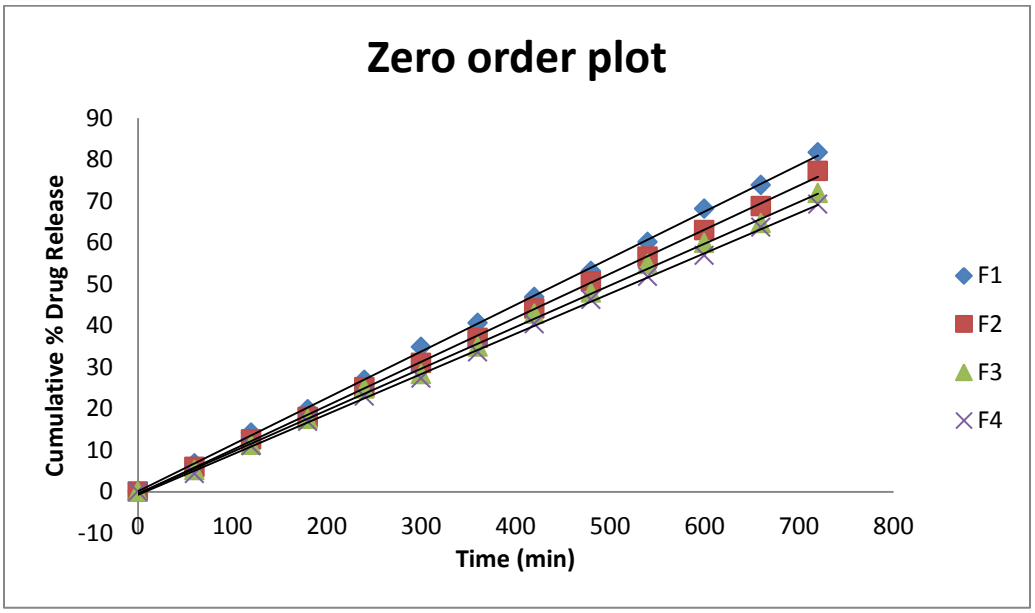
Reagents	Time (Hrs)	% Drug release (F4)
0.1 N Hcl	0	0
	60	7.08
	120	13.16
	180	22.21
	240	29.32
7.4 pH Phosphate buffer	300	36.40
	360	40.48
	420	49.86
	480	55.64
	540	63.02
	600	64.80
	660	75.87
	720	83.09

Table (6.10)

Kinetic analysis of dissolution data for formulation (F4):

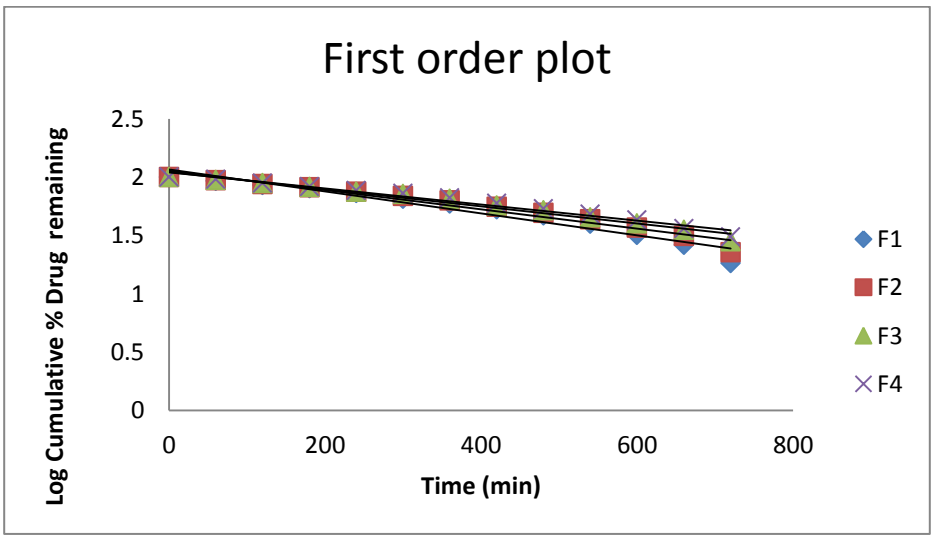
Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F4	0.999	0.972	0.916	0.997	1.002

Figure (6.2)



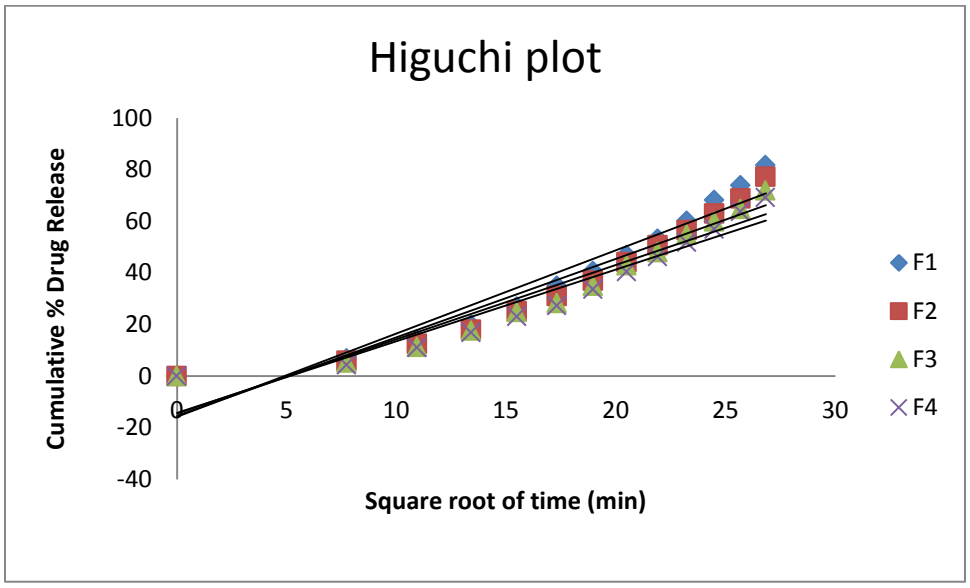
Cumulative % Drug release (vs) Time plot of the Epalrestat microspheres prepared with Eudragit S 100

Figure (6.3)



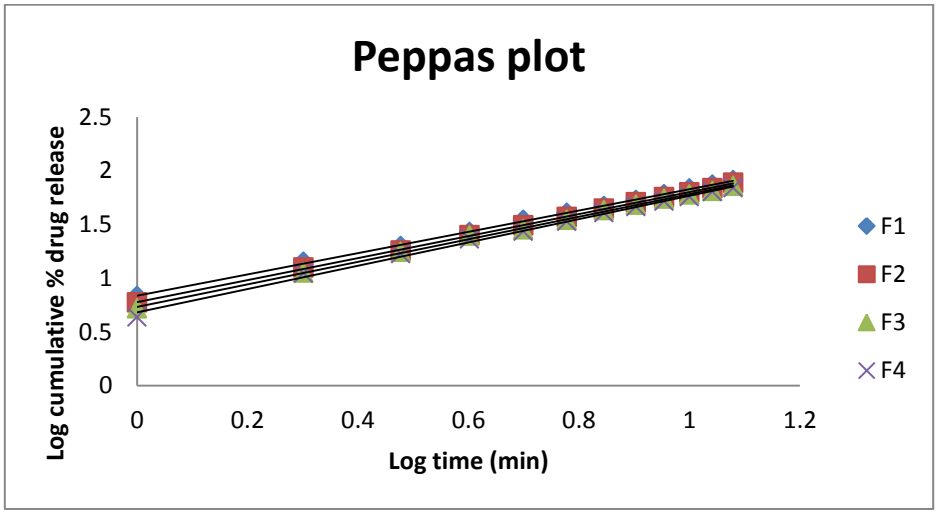
Log % Drug remaining (vs) Time plot of the Epalrestat microspheres prepared with Eudragit S 100.

Figure(6.4)



Cumulative % Drug release (vs) Square root of time plot of the Epalrestat microspheres prepared with Eudragit S 100

Figure(6.5)



Log cumulative % Drug release vs. Log time plot of the Epalrestat microspheres prepared with Eudragit S 100

In vitro dissolution of formulation prepared with Eudragit RS 100:

The drug release from the micro spheres prepared with Eudragit S 100 was found between 1 to 10 hours for the micro spheres prepared at (F5). The drug release for the micro spheres prepared at (f6) to (F8) was found more than 12 hours. This may be the reason due to Eudragit RS 100 has with stand the acid pH as well as alkali pH. Because this polymer have pH independent property. Due to this the microspheres have resulted in the formation of much pores in the matrix resulting in the leeching of much drug along with the dissolution medium which has much more space to enter into the matrix. In vitro dissolution showed that the drug release mainly depends upon the polymer concentration. As the Ethyl cellulose polymer concentration increase the release rate was decreases. The in vitro drug release was fitted to the various kinetic models. The drug release kinetics showed that the release was followed zero order. The kinetics were best fitted to the Peppas order clearly indicates that the drug release was surface erosion mechanism.

Table (6.11)

Cumulative % Drug release of the Epalrestat microspheres prepared with Eudragit RS 100 (F5):

Reagents	Time (Hrs)	% Drug release (F5)
0.1N Hcl	0	0
	60	8.71
	120	17.04
	180	26.89
	240	33.91
7.4 pH Phosphate buffer	300	43
	360	53.87
	420	64.02
	480	74.07
	540	83.27
	600	91.87
	660	92.09
	720	92.89

Table (6.12)

Kinetic analysis of dissolution data for formulation (F5):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F5	0.983	0.929	0.927	0.998	1.018

Table (6.13)

Cumulative % Drug release of the Epalrestat micro spheres prepared with Eudragit RS 100 (F6):

Reagents	Time (Hrs)	% Drug release (F6)
0.1 N Hcl	0	0
	60	6.92
	120	15.2
	180	22.07
	240	28.81
7.4 pH phosphate buffer	300	35.62
	360	44.10
	420	52.22
	480	58.81
	540	64.94
	600	74.27
	660	80.92
	720	86.92

Table (6.14)

Kinetic analysis of dissolution data for formulation (F6):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F6	0.999	0.931	0.921	0.998	1.017

Table (6.15)

Cumulative % Drug release of the Epalrestat microspheres prepared with Eudragit RS 100 (F7):

Reagents	Time (Hrs)	% Drug release (F7)
0.1 N Hcl	0	0
	60	6.54
	120	13.92
	180	21.63
	240	26.91
7.4 pH Phosphate buffer	300	33.63
	360	41.98
	420	48.12
	480	53.97
	540	64.01
	600	69.86
	660	75.92
	720	83.78

Table (6.16)

Kinetic analysis of dissolution data for formulation (F7):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F7	0.999	0.938	0.918	0.998	1.015

Table (6.17)

Cumulative % Drug release of the Epalrestat microspheres prepared with Eudragit RS 100 (F8):

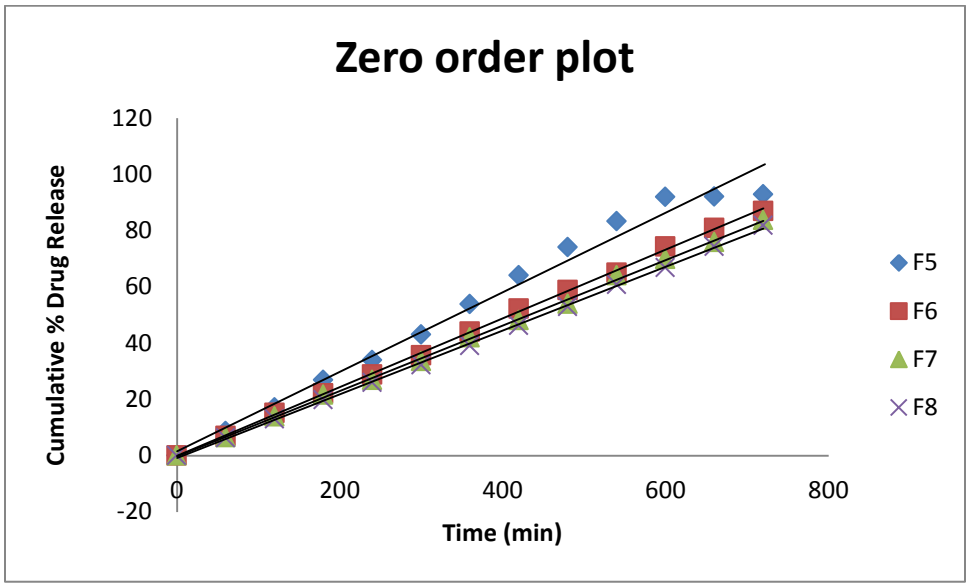
Reagents	Time (Hrs)	% Drug release (F8)
0.1 N Hcl	0	0
	60	6.24
	120	13.05
	180	19.87
	240	25.98
7.4 pH phosphate buffer	300	32.21
	360	39.04
	420	46.25
	480	52.89
	540	60.73
	600	66.84
	660	74.25
	720	81.78

Table (6.18)

Kinetic analysis of dissolution data for formulation (F8):

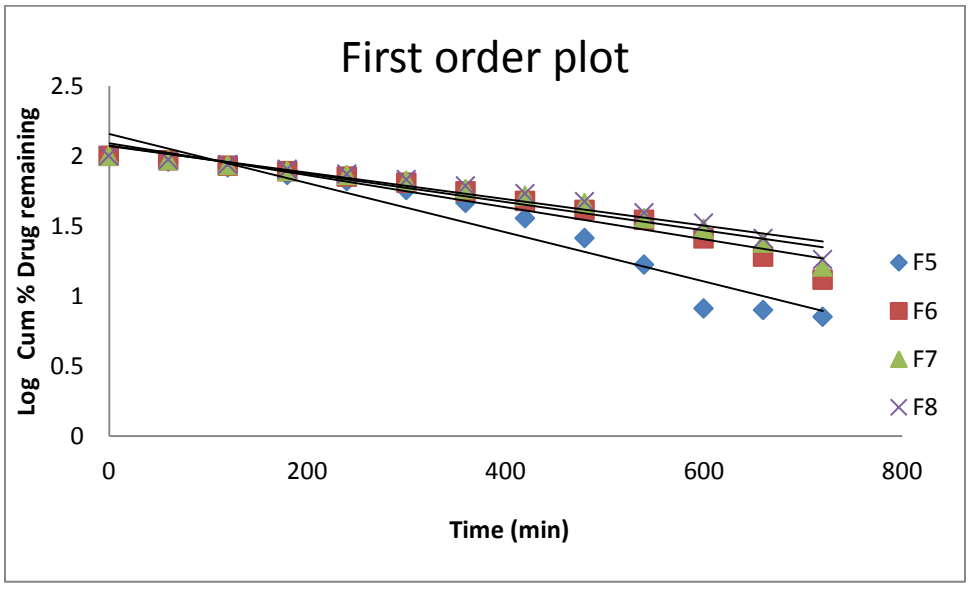
Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F8	0.999	0.938	0.912	0.999	1.023

Figure (6.6)



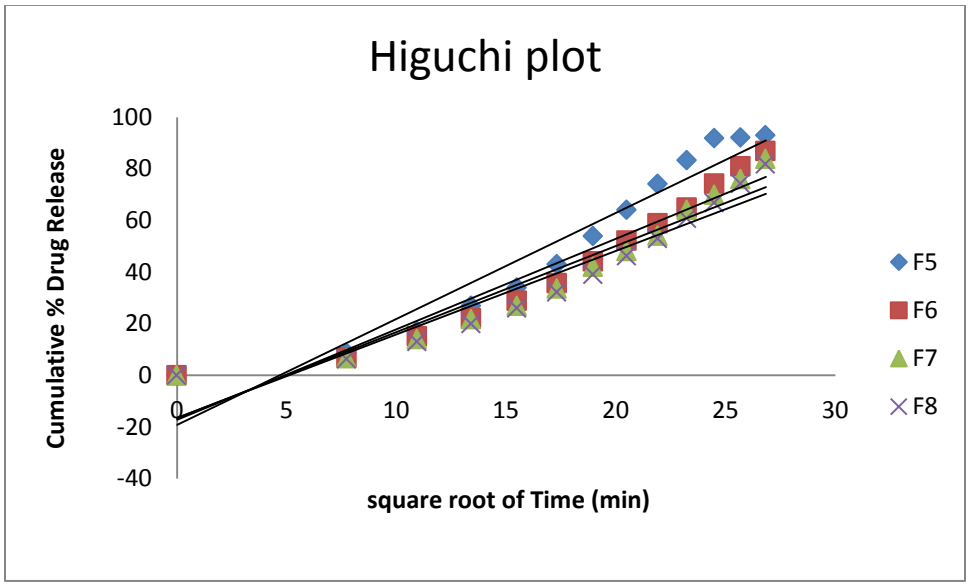
Cumulative % Drug release (vs) Time plot of the Epalrestat micro spheres prepared with Eudragit RS 100

Figure (6.7)



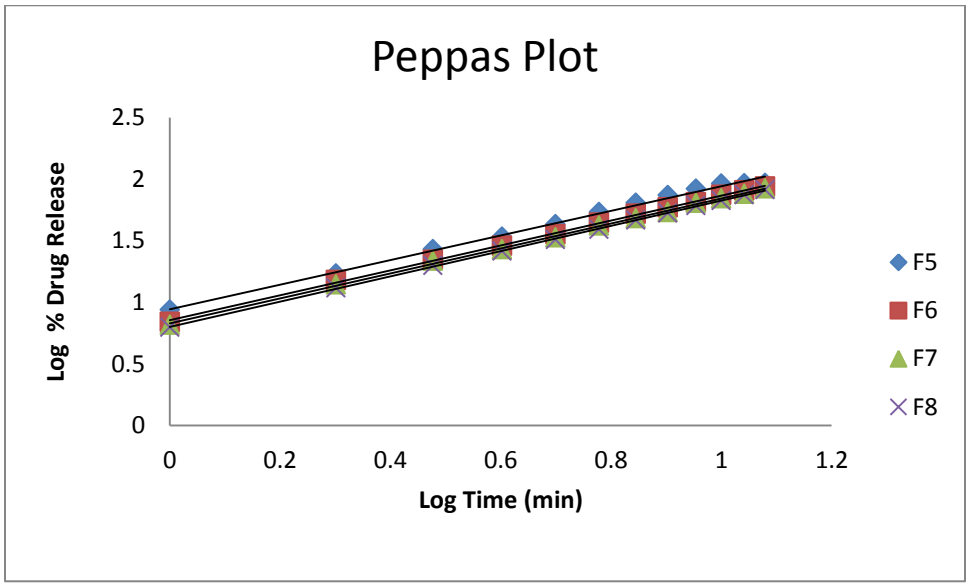
Log Cumulative % Drug remaining (vs) Time plot of the Epalrestat microspheres prepared with Eudragit RS 100.

Figure (6.8)



Cumulative % Drug release (vs) Square root of time plot of the Epalrestat microspheres prepared with Eudragit RS 100.

Figure (6.9)



Log cumulative % release (vs) Log time plot of the Epalrestat micro spheres prepared with Eudragit RS 100

In vitro dissolution of formulation prepared with Eudragit RL 100 :

The drug release from the micro spheres prepared with Eudragit RL 100 was found between 1 to 12 hours for the micro spheres prepared at F(9). The drug release for the micro spheres prepared at (F10) to (F12) was found more than 12 hours. This may be the reason due to Eudragit RS 100 has withstand the acid pH as well as alkali pH. Because this polymer have pH independent property. Due to this the microspheres have resulted in the formation of much pores in the matrix resulting in the leeching of much drug along with the dissolution medium which has much more space to enter into the matrix. In vitro dissolution showed that the drug release mainly depends upon the polymer concentration. As the Ethyl cellulose polymer concentration increase the release rate was decreased. The in vitro drug release was fitted to the various kinetic models. The drug release kinetics showed that the release was followed zero order. The kinetics were best fitted to the peppas order clearly indicates that the drug release was surface erosion mechanism.

Table (6.19)

Cumulative % Drug release of the Epalrestat microspheres prepared with Eudragit RL 100 (F9):

Reagents	Time (Hrs)	% Drug release (F9)
0.1N Hcl	0	0
	60	6.8
	120	14.21
	180	19.84
	240	26.92
7.4 pH phosphate buffer	300	34.87
	360	40.58
	420	46.89
	480	53.71
	540	60.13
	600	68.1
	660	73.80
	720	81.69

Table (6.20)

Kinetic analysis of dissolution data for Formulation (F9):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F9	0.959	0.941	0.943	0.999	0.986

Table (6.21)

Cumulative % Drug release of the Epalrestat microspheres prepared with Eudragit RL 100 (F10):

Reagents	Time (Hrs)	% Drug release (F10)
0.1 N Hcl	0	0
	60	5.94
	120	12.54
	180	17.98
	240	25.11
	300	30.93
7.4 pH phosphate buffer	360	36.97
	420	44.12
	480	50.62
	540	56.54
	600	62.97
	660	68.72
	720	77.21

Table (6.22)

Kinetic analysis of dissolution data for formulation (F10):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F10	0.998	0.905	0.922	0.999	1.022

Table (6.23)

Cumulative % Drug release of the Epalrestat microspheres prepared with Eudragit RL 100 (F11):

Reagents	Time (Hrs)	% Drug release (F11)
0.1 N Hcl	0	0
	60	5.20
	120	11.24
	180	17.52
	240	24.81
7.4 pH phosphate buffer	300	28.27
	360	34.91
	420	42.86
	480	47.92
	540	54.80
	600	59.91
	660	64.63
	720	71.89

Table (6.24)

Kinetic analysis of dissolution data for Formulation (F11):

Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F11	0.999	0.926	0.922	0.998	1.048

Table (6.25)

Cumulative % Drug release of the Epalrestat microspheres prepared with Eudragit RL 100 (F12):

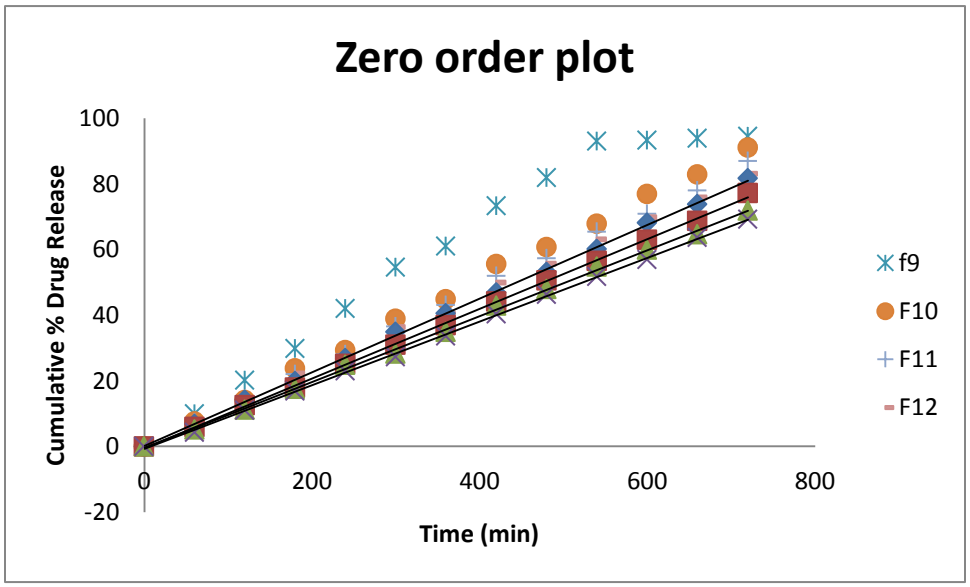
Reagents	Time (Hrs)	% Drug release (F12)
0.1 N Hcl	0	0
	60	4.32
	120	11.05
	180	16.89
	240	23.00
	300	27.25
7.4 pH phosphate buffer	360	33.63
	420	40.35
	480	46.27
	540	51.75
	600	56.89
	660	63.64
	720	69.21

Table (6.26)

Kinetic analysis of dissolution data for Formulation (F12):

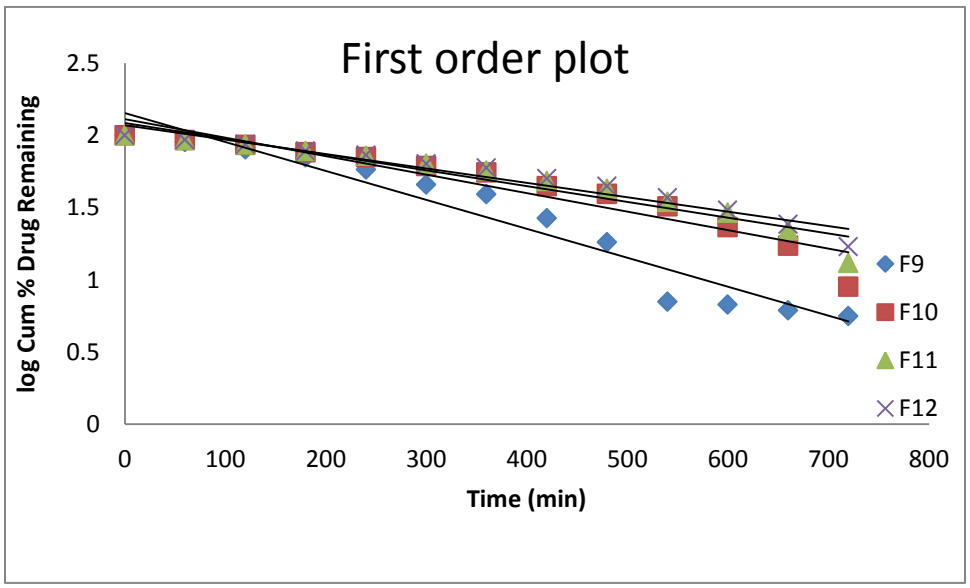
Formulation	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F12	0.999	0.947	0.924	0.999	1.089

Figure (6.10)



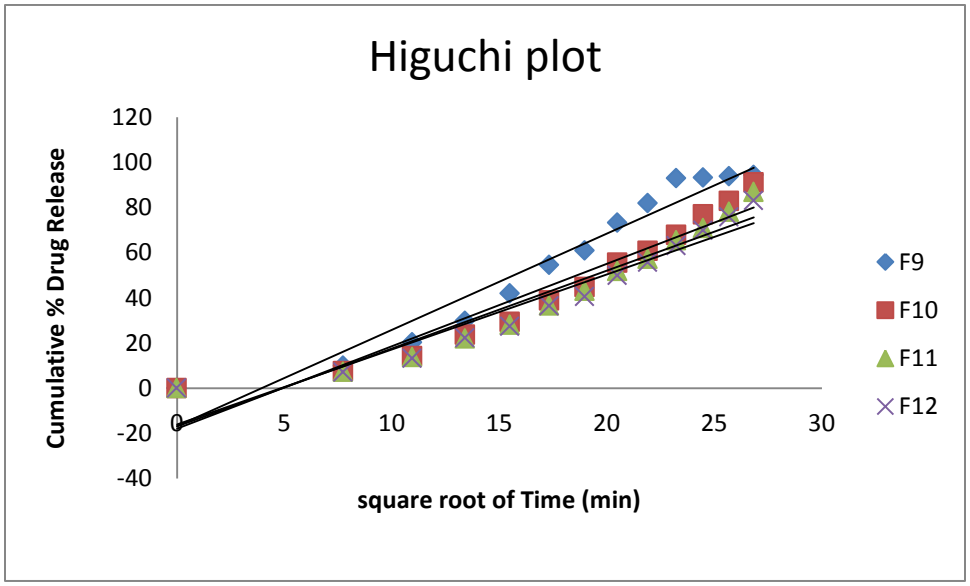
Cumulative % Drug release (vs) Time plot of the Epalrestat microspheres prepared with Eudragit RL 100

Figure (6.11)



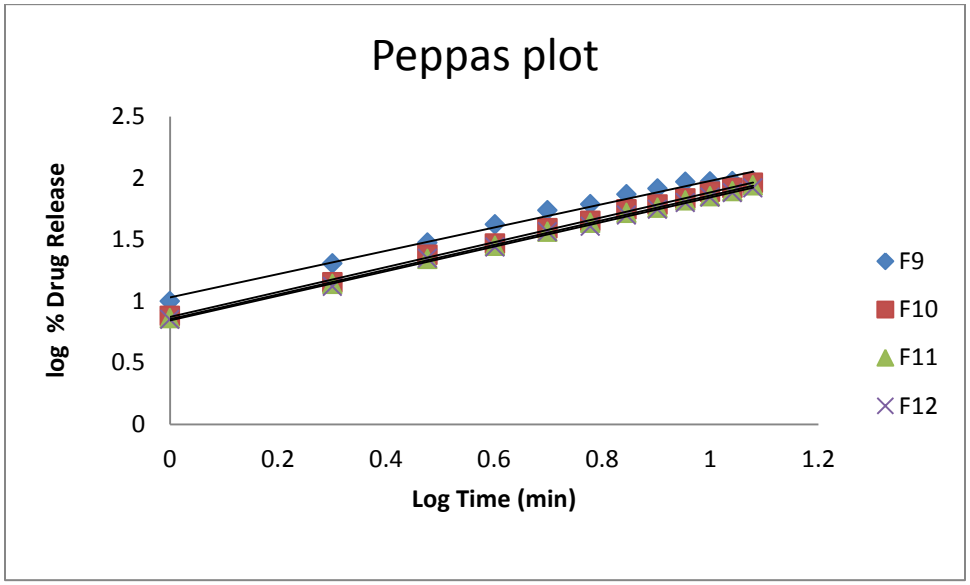
Log % Drug remaining (vs) Time plot of the Epalrestat microspheres prepared with Eudragit RL 100

Figure (6.12)



Cumulative % Drug release (vs) Square root of time plot of the Epalrestat microspheres prepared with Eudragit RL 100

Figure (6.13)



Log cumulative % Dug release (vs) Log time plot of the Epalrestat microspheres prepared with Eudragit RL 100

Table (6.27)

Time taken for 30%, 50% & 70% Drug release for various Formulation's:

Formulations	$t_{30\%}$ values	$t_{50\%}$ values	$t_{70\%}$values
F1	209.79	349.65	489.51
F2	238.09	398.82	555.55
F3	252.1	420.16	588.23
F4	260.86	437.78	608.69
F5	212.76	354.6	496.45
F6	245.9	409.83	573.77
F7	258.62	431.03	603.44
F8	265.48	442.47	619.46
F9	267.857	446.428	625
F10	283.0188	471.698	660.377
F11	300	500	700
F12	309.27	515.46	721.64

From the above result, Eudragit RL 100 formulation (F9- F12) time taken for drug release (30%,50%,70%) were comparable to greater than Eudragit S 100 (F1- F4), Eudragit RS 100 (F5-F8) formulation's.

In-vitro drug release kinetics:

The results of the in vitro drug release study obtained from various batches were plotted using model dependent kinetic models such as Zero-order kinetics, first-order kinetics, Higuchi's matrix and Korsmeyer Peppas model to evaluate the release mechanism from Epalrestat microspheres. The kinetic model showing highest correlation coefficient was considered as the most appropriate model for the dissolution data. The best fit with the highest correlation coefficient was observed in the Korsmeyers-peppas model and zero-order release kinetics followed by Higuchi model, as given in the previous tables. The 'n' value of formulation was found to be 0.986 to 1.089 for the various batches indicating that the drug release was followed by anomalous (non-fickian) case 2 or super case 2 diffusion. According to the relative rates of diffusion (Rdiff) and polymer relaxation (Rrelax) three classes of diffusion can be distinguished. If the value of n = 0.5 it indicates a Fickian diffusion mechanism (Case I) in which the rate of diffusion is much smaller than the rate of relaxation (Rdiff« Rrelax), system controlled by diffusion), ii) n = 1.0 indicates Case II, where the diffusion process is much faster than the relaxation process (Rdiff» Rrelax, system controlled by relaxation), iii) $0.5 < n < 1.0$ indicates non-Fickian (anomalous) diffusion mechanism, which describes those cases where the diffusion and relaxation rates are comparable (Rdiff≈ Rrelax). If the values of $n > 1$have been observed, which are regarded as Super Case II kinetics.

Determination of particle size by sieving method:

The weighed amount of prepared twelve batches of micro spheres were passed through the four sets of sieves of constant mesh size of 60/80, 80/100, 100/140,and 140/200. The weight, percentage recovery and particle size of micro spheres are tabulated in table.

Table (6.28)

Particle size determination of Epalrestat micro spheres by sieving method:

S .No	Formulation	Particle size(µm)
1	F1	171
2	F2	165
3	F3	153
4	F4	167
5	F5	135
6	F6	122
7	F7	119
8	F8	105
9	F9	98
10	F10	83
11	F11	75
12	F12	50

Particle size analysis of different formulations of Epalrestat Microsphere was carried out using digital micrometer. Data is given in table 6.27. By increasing the concentration of Ethyl cellulose, the mean particle size of microspheres increased. From results it can be seen that larger microspheres were obtained by increasing the concentration of Ethyl cellulose. As the concentration of the Ethyl cellulose increases the particle size increases.

stability study:

Table (6.29)

Stability studies of the Epalrestat micro spheres prepared with Eudragit S 100:

Formulation	Temperature (0°C)	% of Epalrestat			
		0 days	10 days	20 Days	30 Days
F1	4	52	51.19	51.17	51.17
	Room temp	52	52	52	52
	60	52	51.16	51.12	51
F2	4	69	68.95	68.74	68.63
	Room temp	69	69	69	69
	60	69	68.25	67.56	65.23
F3	4	80	79.69	79.25	79.10
	Room temp	80	80	80	80
	60	80	78.23	77.36	76.85
F4	4	81	80.96	80	79.85
	Room temp	81	81	81	81
	60	81	80.25	79.56	78.21

Table (6.30)

Stability study of the Epalrestat micro spheres prepared with Eudragit RS 100:

Formulation	**Temperature 0°C**	**% of Epalrestat**			
		0 Days	**10 Days**	**20 Days**	**30 Days**
F5	4	77	76.95	76	75.89
	Room temp	77	77	77	77
	60	77	75.6	74.3	73.6
F6	4	81	80.95	80	79.56
	Room temp	81	81	81	81
	60	81	79.5	78.5	77.2
F7	4	94	93.69	93	92.56
	Room temp	94	94	94	94
	60	94	92.5	91.5	90.23
F8	4	94.5	94	93.35	93.12
	Room temp	94.5	94.5	94.5	94.5
	60	94.5	92.45	90.23	89.47

Table (6.31)

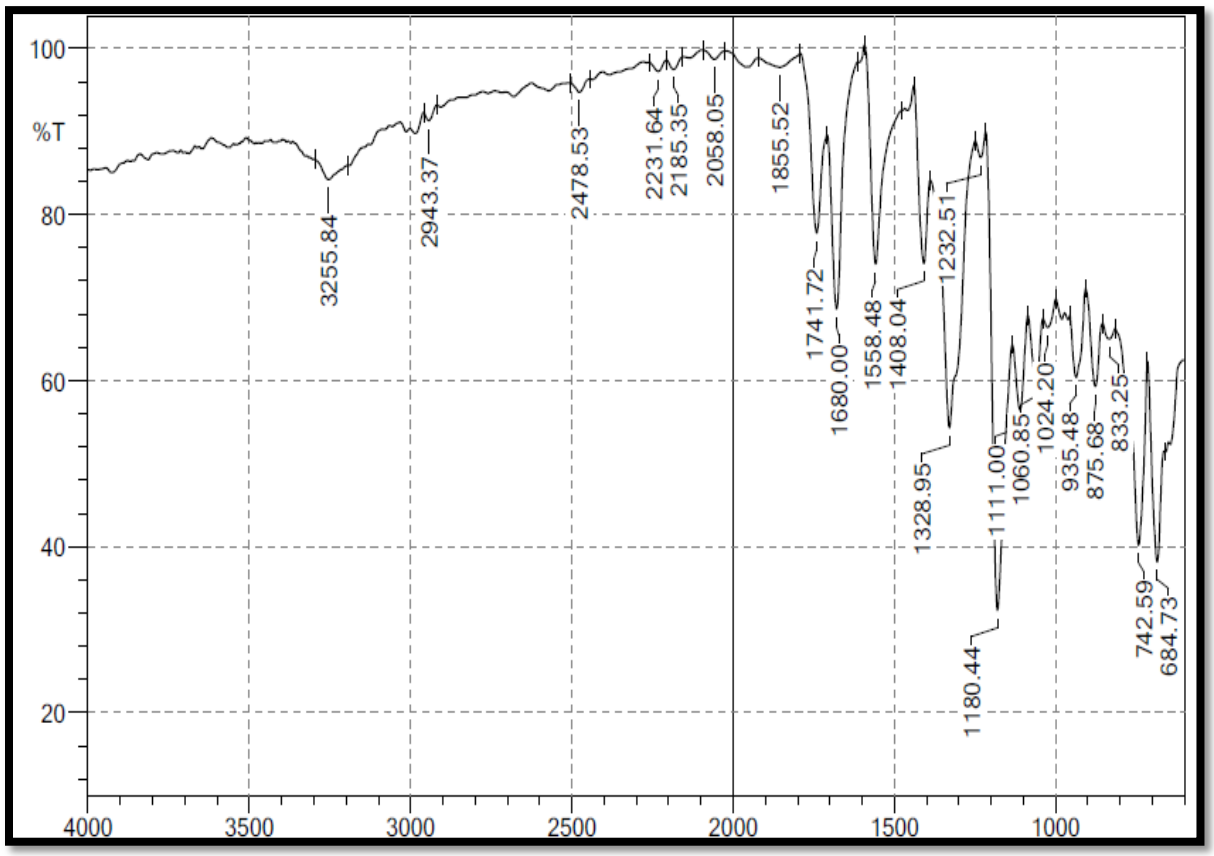
Stability studies of the Epalrestat microspheres prepared with Eudragit RL 100:

Formulation	Temperature 0°C	% of Epalrestat			
		0 Days	10 days	20 Days	30 Days
sF9	4	70.5	69.56	69	68.32
	Room temp	70.5	70.5	70.5	70.5
	60	70.5	69.32	68.21	67.23
F10	4	78	77.98	77	76.23
	Room temp	78	78	78	78
	60	78	77.51	76.25	75.62
F11	4	84	83.69	83	82.95
	Room temp	84	84	84	84
	60	84	83.25	82.45	81.45
F12	4	96	95.78	94.52	93.15
	Room temp	96	96	96	96
	60	96	95.68	94.12	93.65

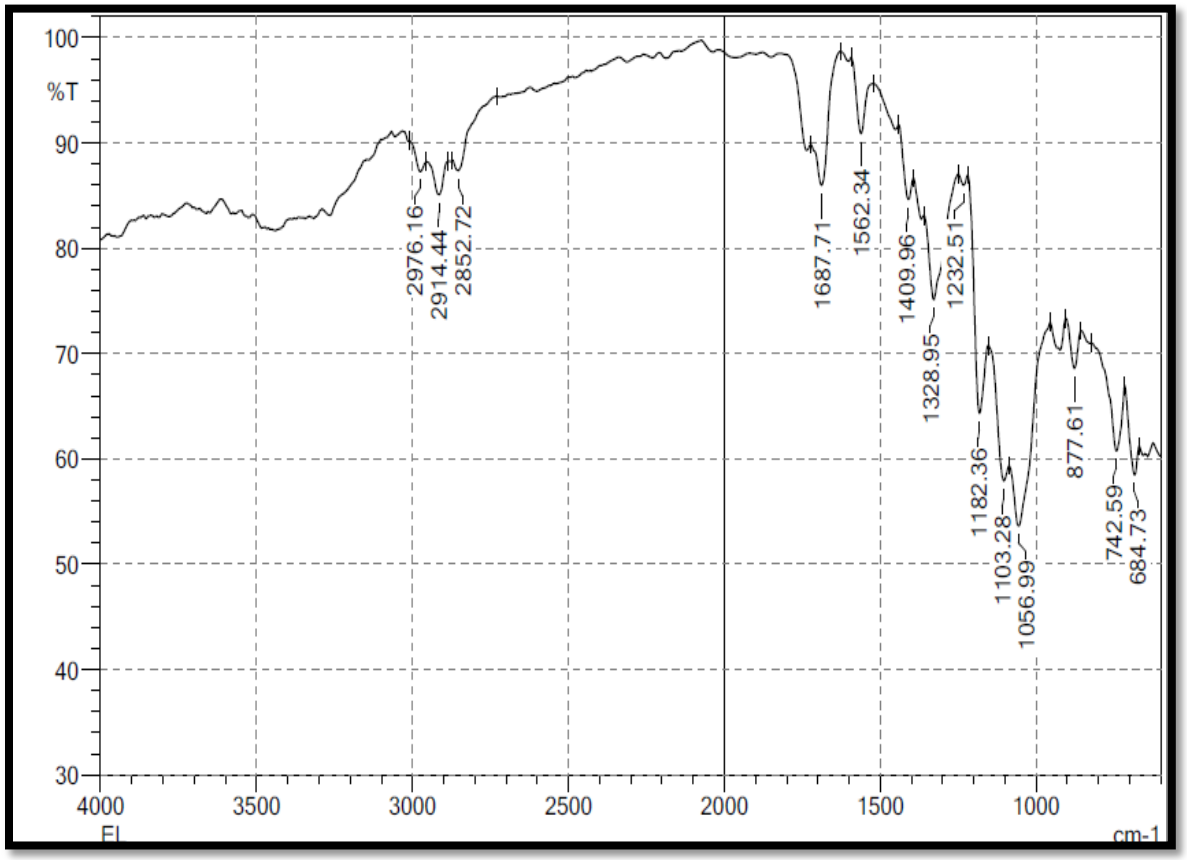
Formulation were stored at 4°C in freeze, room temperature and at 60°c in hot air oven. After 30 days of storage, the formulation were observed physically and no color change and hardness was perceptible. the content of Epalrestat in all formulations at various intervals of 10, 20 and 30 days calculated. The result provide that the percentage of Epalrestat was not less than 4-6 % in all the formulations after storing different temperatures, as shown in table.

It reveals that there was no degradation of Epalrestat in all formulations when stored under room and freeze temperature but at elevated temperature, the little degradation was found.

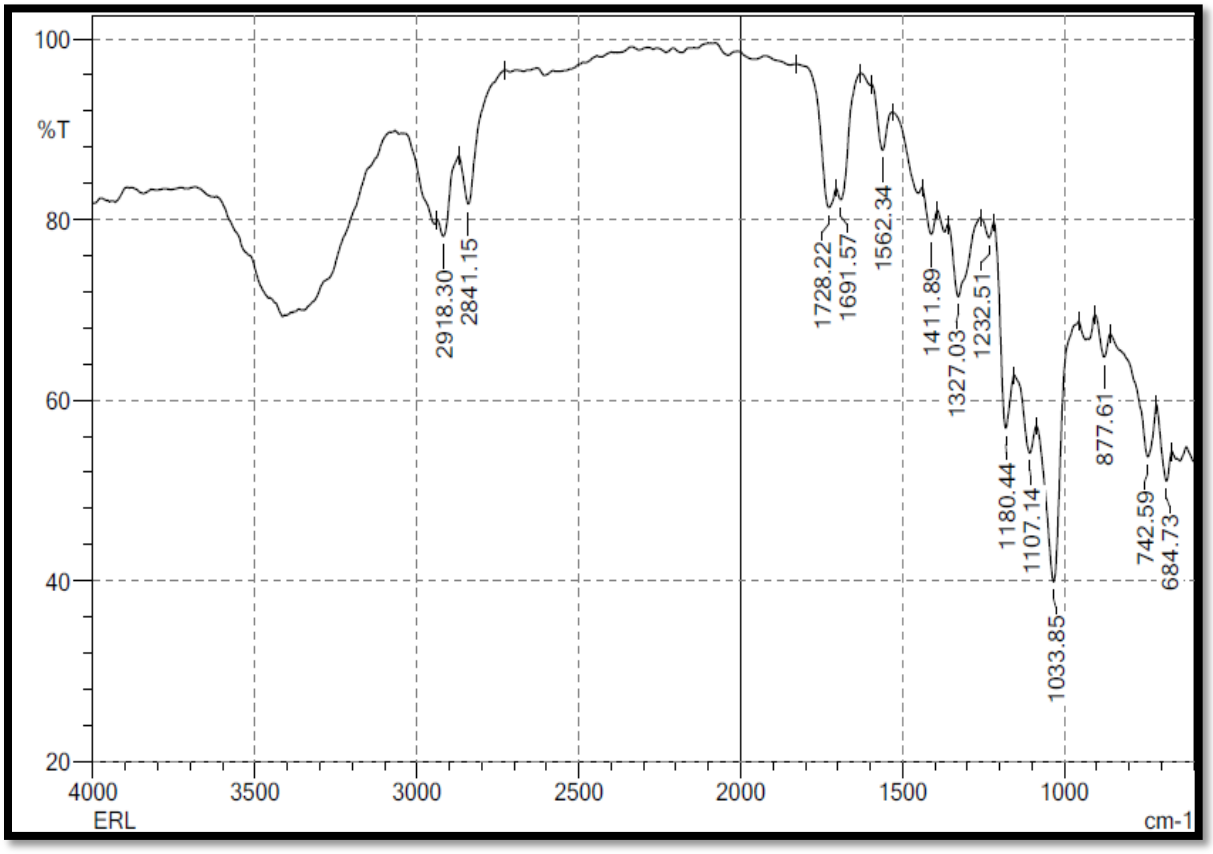
Fourier Transforms Infrared Radiation measurement(FT-IR)



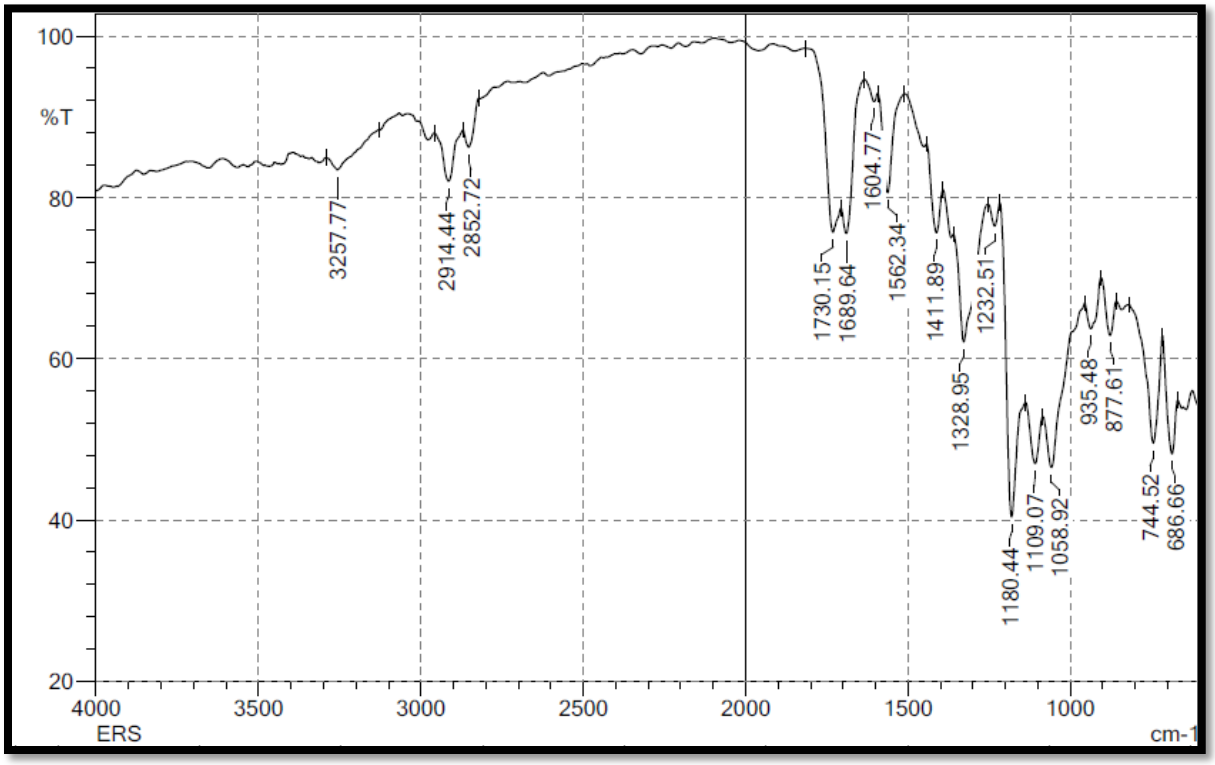
FT-IR spectrum of pure Epalrestat drug



FT-IR Spectrum of Drug with Eudragit S 100



FT-IR Spectrum of Drug with Eudragit RL 100



FT-IR Spectrum of Drug with Eudragit Rs 100

FT-IR study on the selected formulation prepared with different polymer combinations such as ethyl cellulose Eudragit S 100, Eudragit RS 100 & Eudragit RL 100. The spectrum peak point of the formulation were similar with that of the pure Epalrestat, this clearly indicating that there is no polymer interaction.

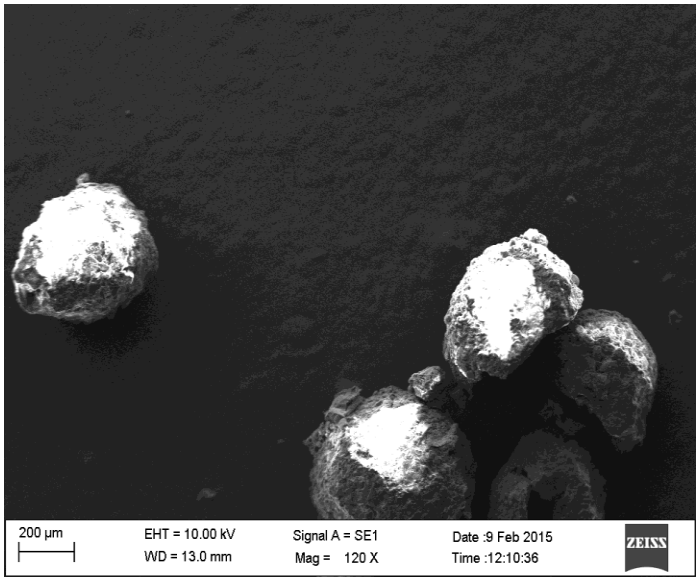
Flow property study:

Angle of repose:

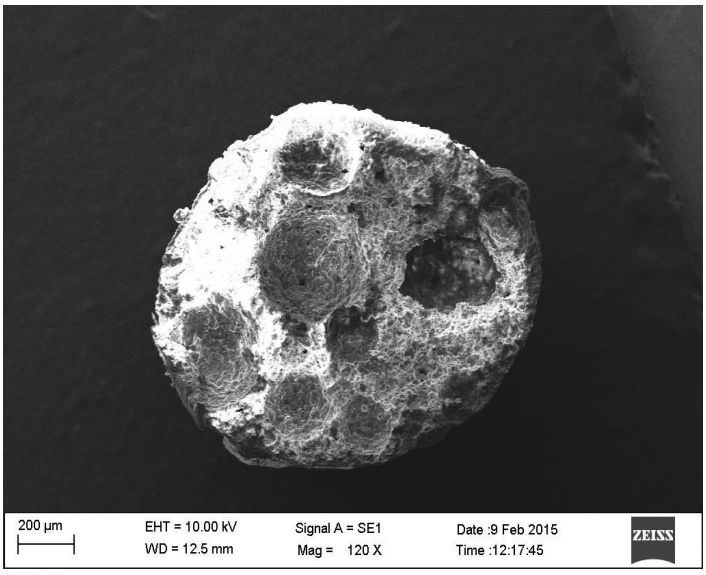
S. No	Batch of microspheres	Angle of Repose
1	Pure drug	43.56°
2	D:Ec:Eu S 100 (F1)	30.50°
3	D:Ec:Eu S 100 (F2)	29.41°
4	D:Ec:Eu S 100 (F3)	30.21°
5	D:Ec:Eu S 100 (F4)	28.45°
6	D:Ec:Eu RS 100 (F5)	32.14°
7	D:Ec:Eu RS 100 (F6)	30.15°
8	D:Ec:Eu RS 100 (F7)	25.23°
9	D:Ec:Eu RS 100 (F8)	23.22°
10	D:Ec:Eu RL 100 (F9)	30.44°
11	D:Ec:Eu RL 100 (F10)	29.65°
12	D:Ec:Eu RL 100 (F11)	25.32°
13	D:Ec:Eu RL 100 (F12)	20.65°

Batches { D:Ec:Eu S 100 (F1-F4), D:EC:Eu RS 100 (F5-F8), D:EC:Eu RL 100 (F9-F12) }were found to give the values given in the table. °value less than 30 is considered to give good flow property. So the Batch F5 formulations were gave poor flow property.

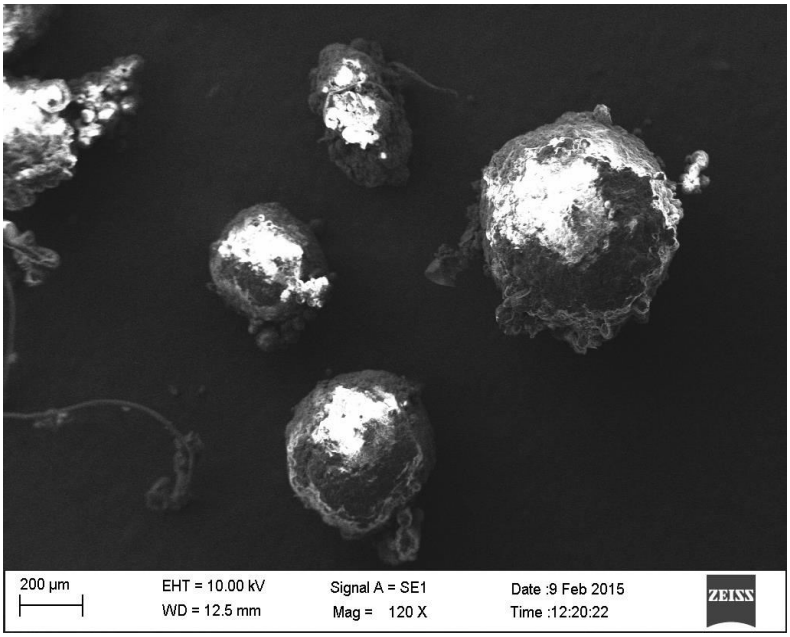
Scanning electronic microscopy (SEM):



Scanning electronic microscopic photograph of the microspheres prepared with Eudragit S 100 (F1)



Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit S 100(F1)



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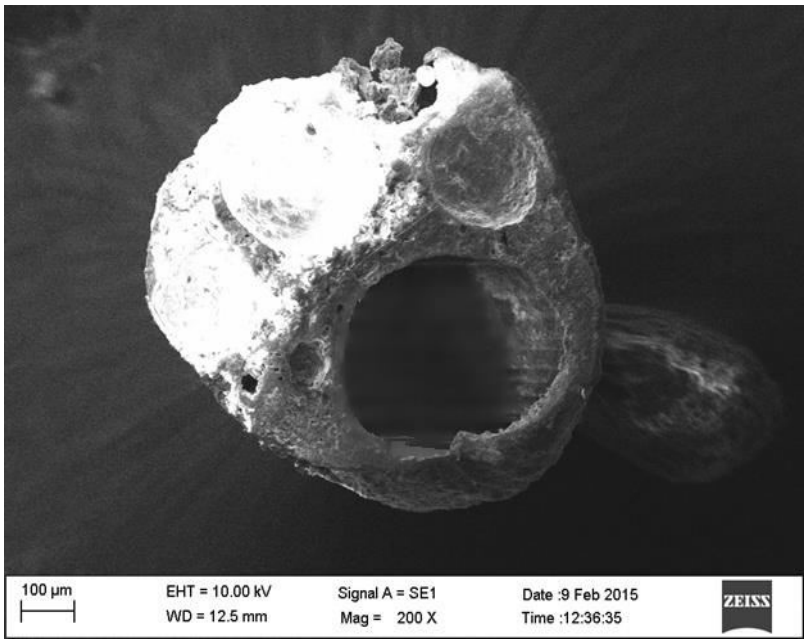
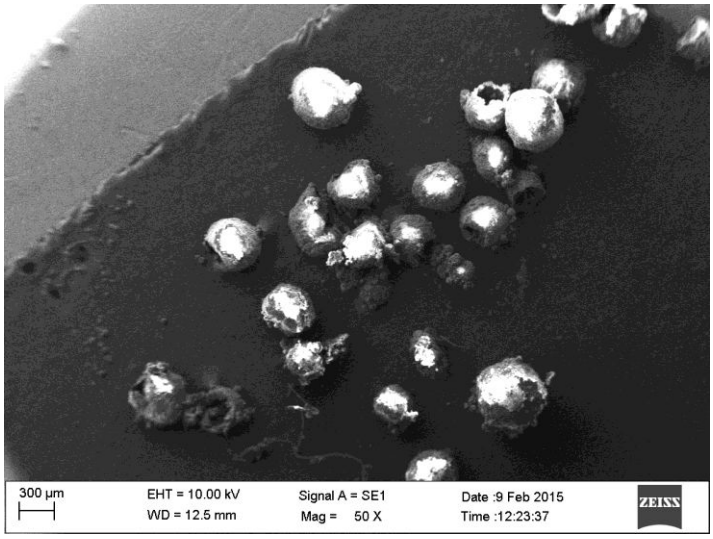
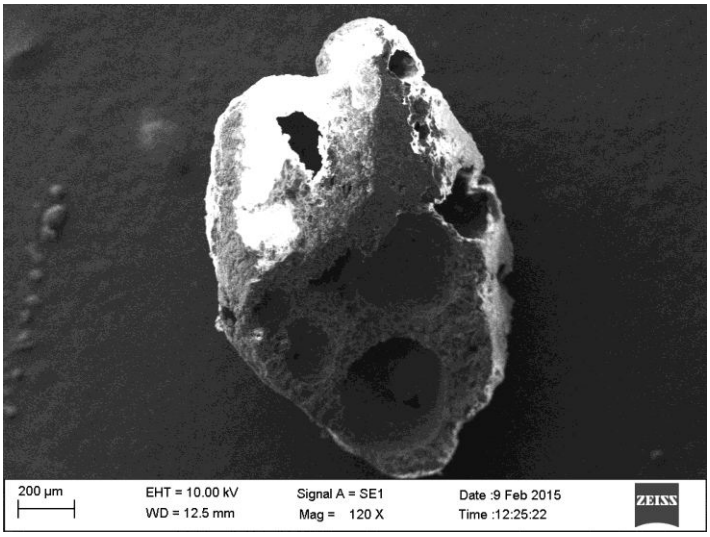


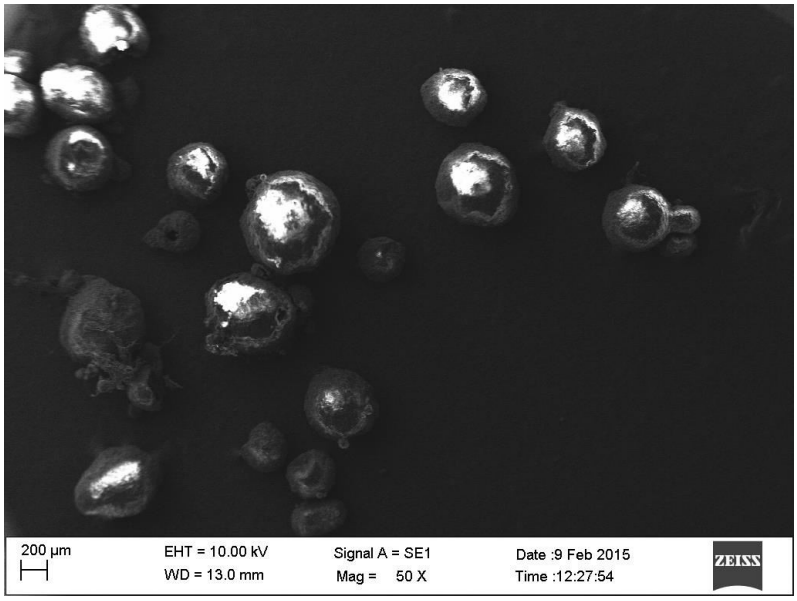
Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit S 100 (F2)



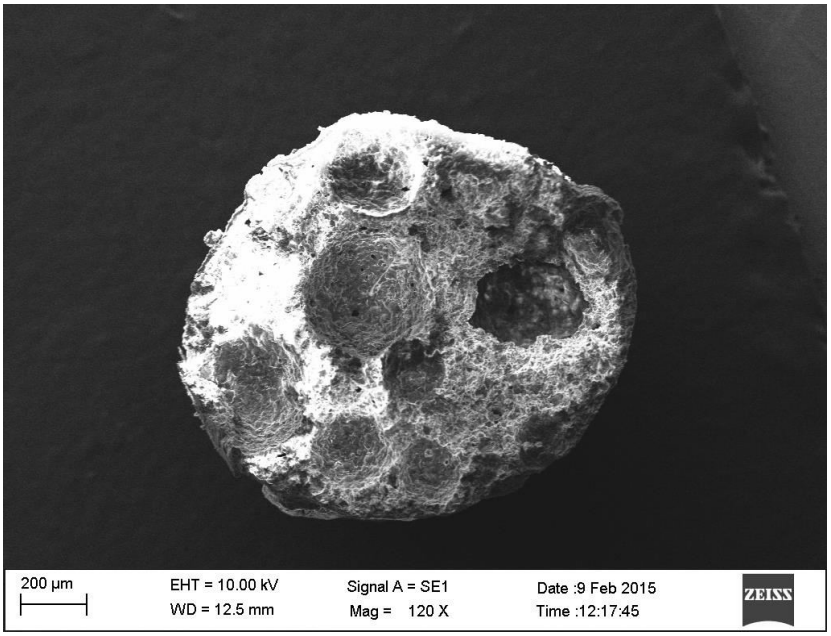
Scanning electronic microscopic photograph of the microspheres prepared with Eudragit S 100 (F3)



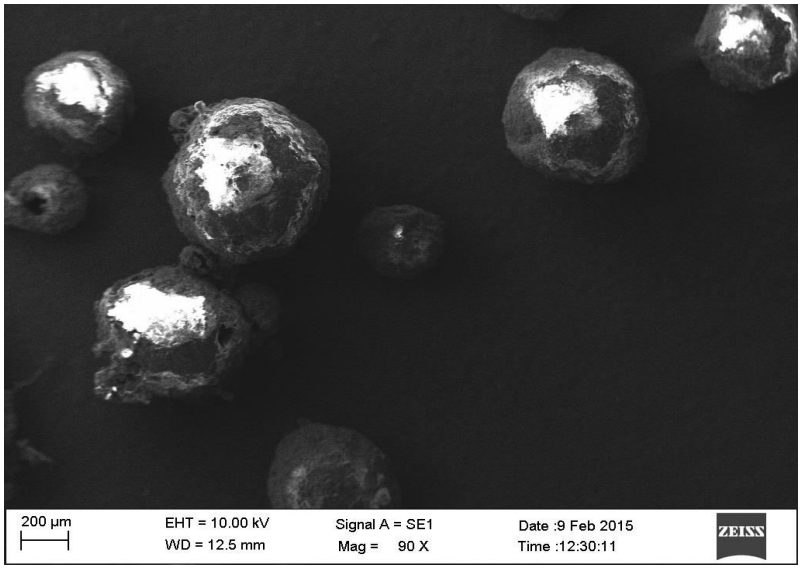
Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit S 100 (F3)



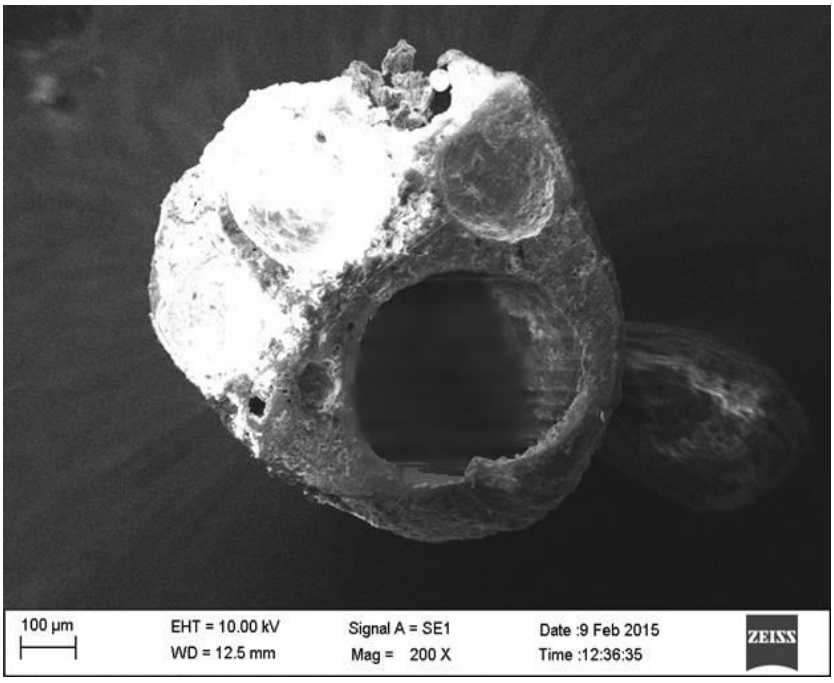
Scanning electronic microscopic photograph of the microspheres prepared with Eudragit S 100 (F4)



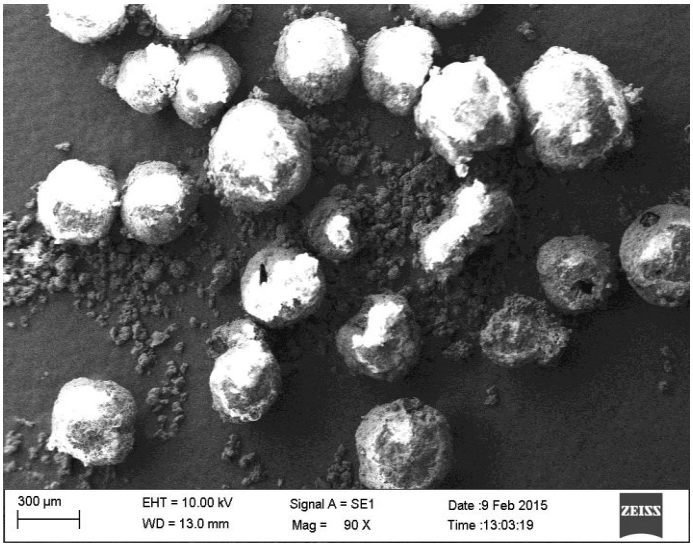
Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit S 100 (F4)



Scanning electronic microscopic photograph of the microspheres prepared with Eudragit RS 100 (F5)



'**Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit RS 100 (F5)**



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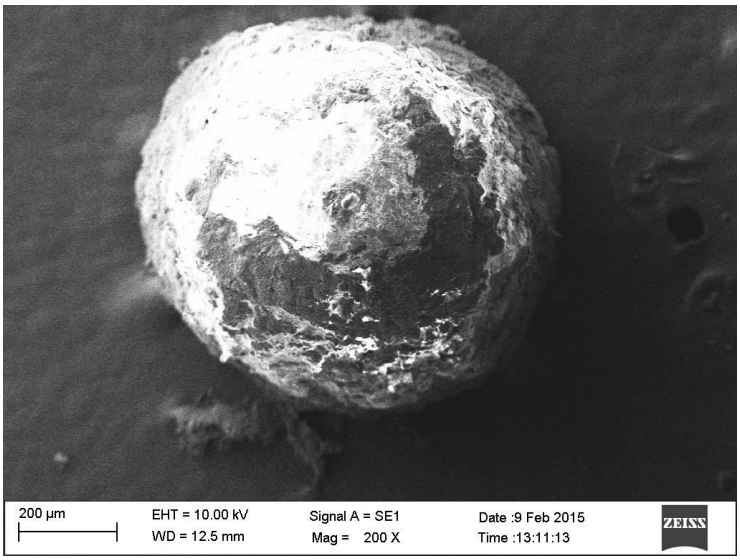
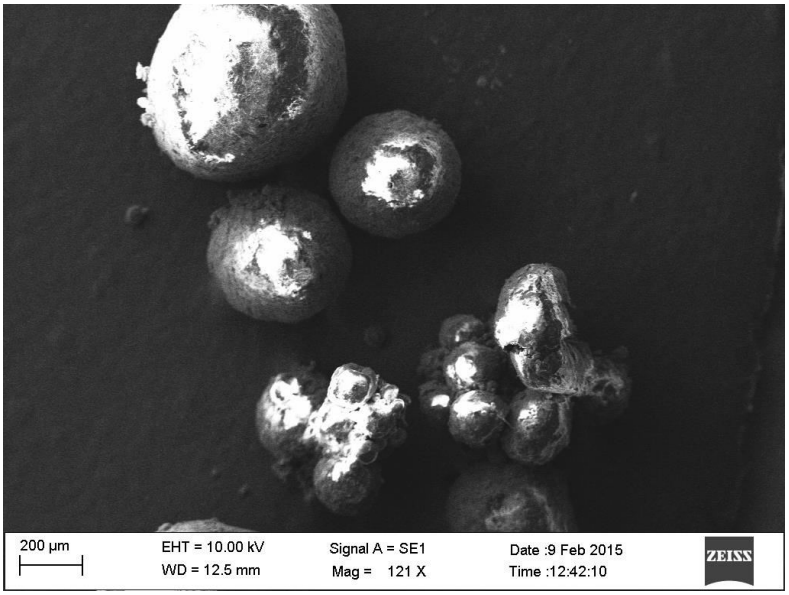
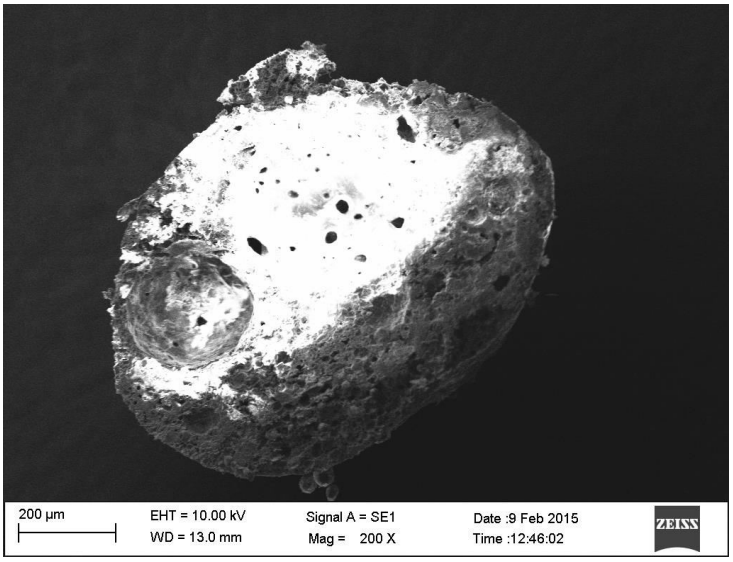


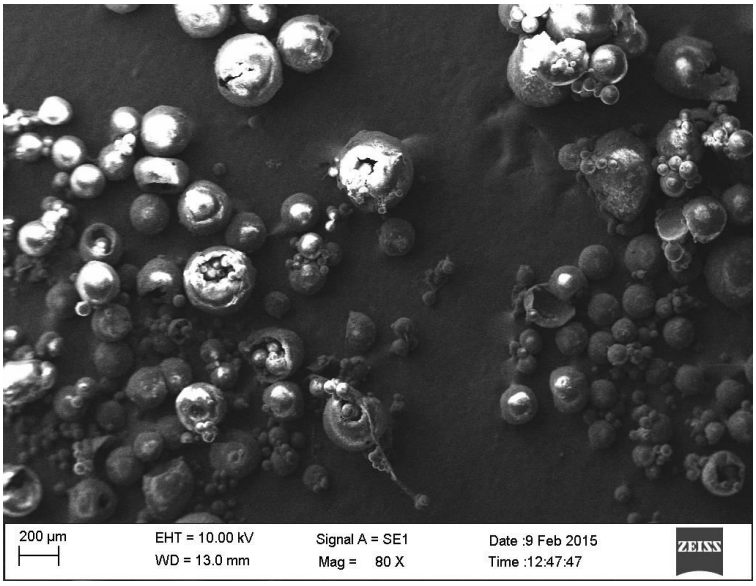
Scanning electronic microscopic photograph of the microspheres prepared with Eudragit RS 100 (F6)



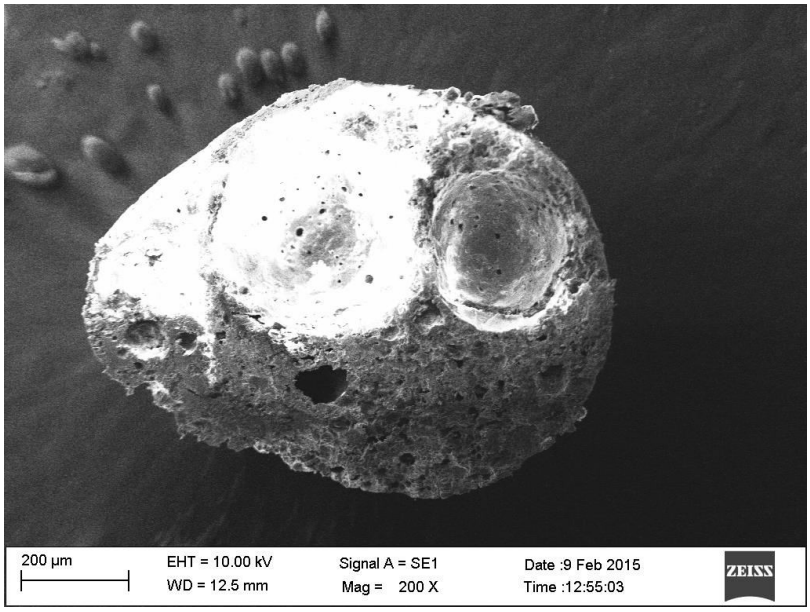
Scanning electronic microscopic photograph of the microspheres prepared with Eudragit RS 100 (F7)



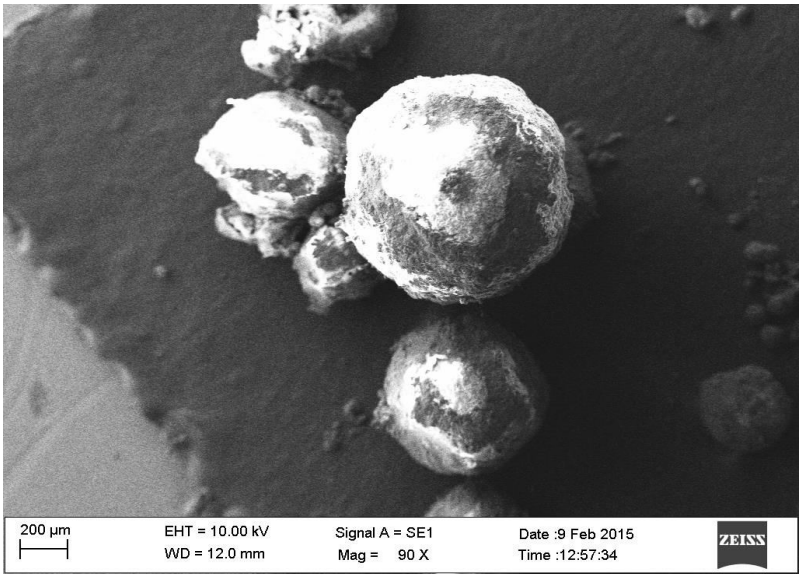
Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit RS 100 (F7)



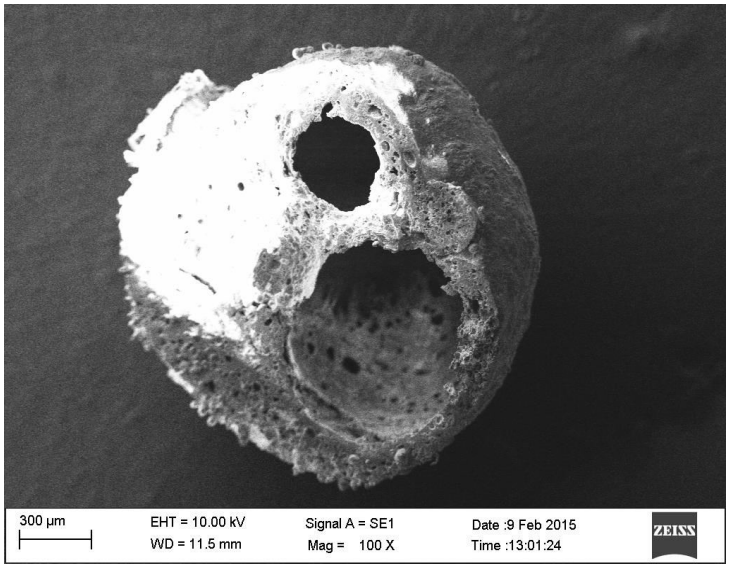
Scanning electronic microscopic photograph of the microspheres prepared with Eudragit RS 100 (F8)



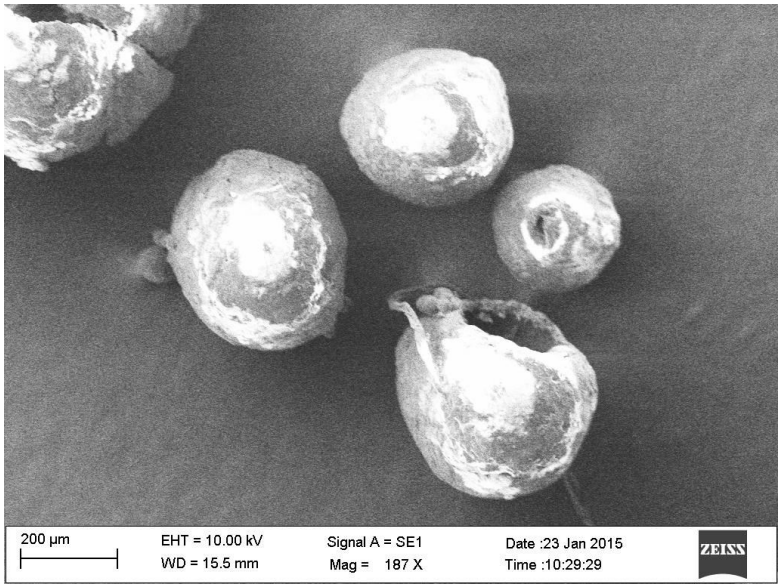
Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit RS100 (F8)



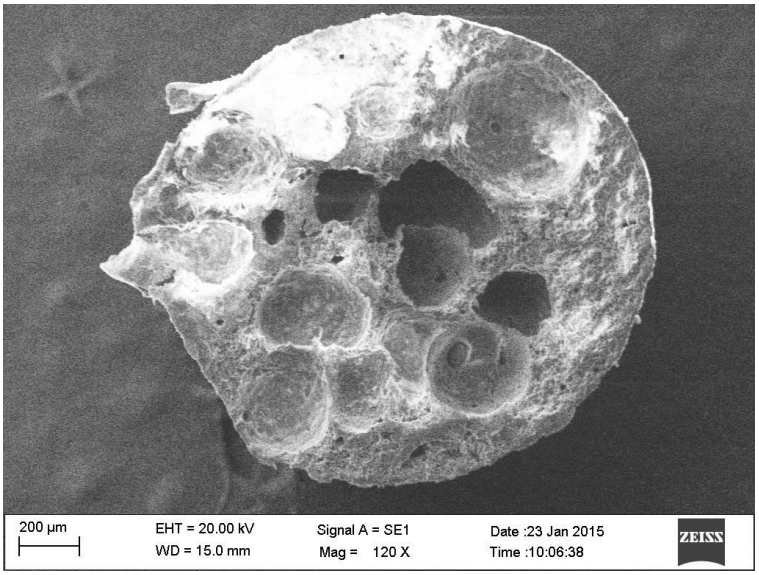
Scanning electronic microscopic photograph of the microspheres prepared with Eudragit RL 100 (F9)



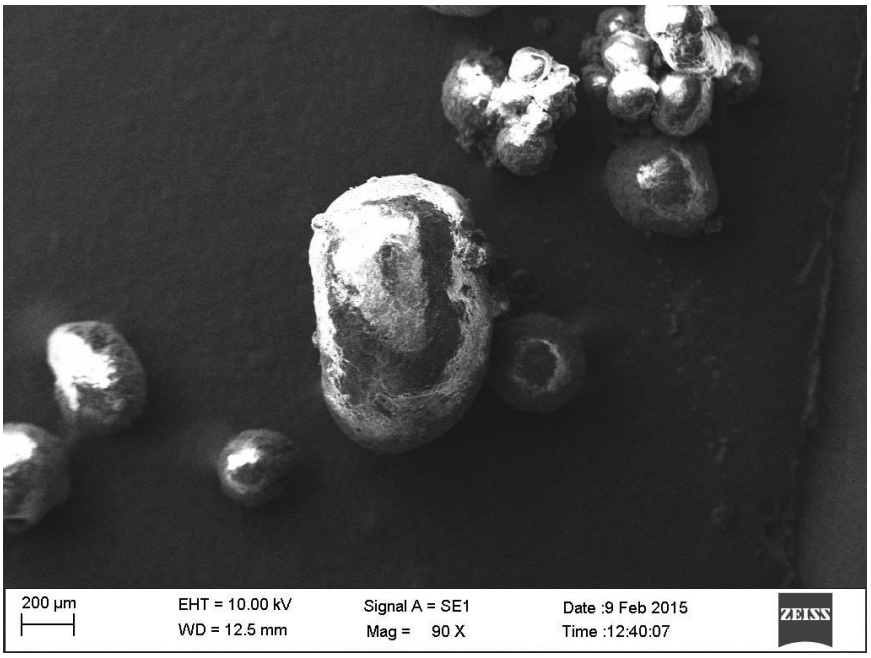
Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit RL 100 (F9)



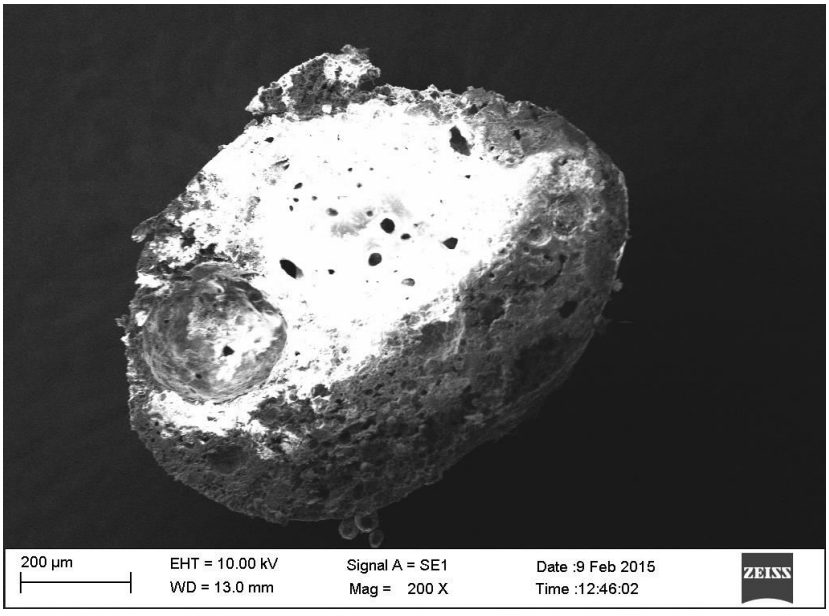
Scanning electronic microscopic photograph of the microspheres prepared with Eudragit RL 100 (F10)



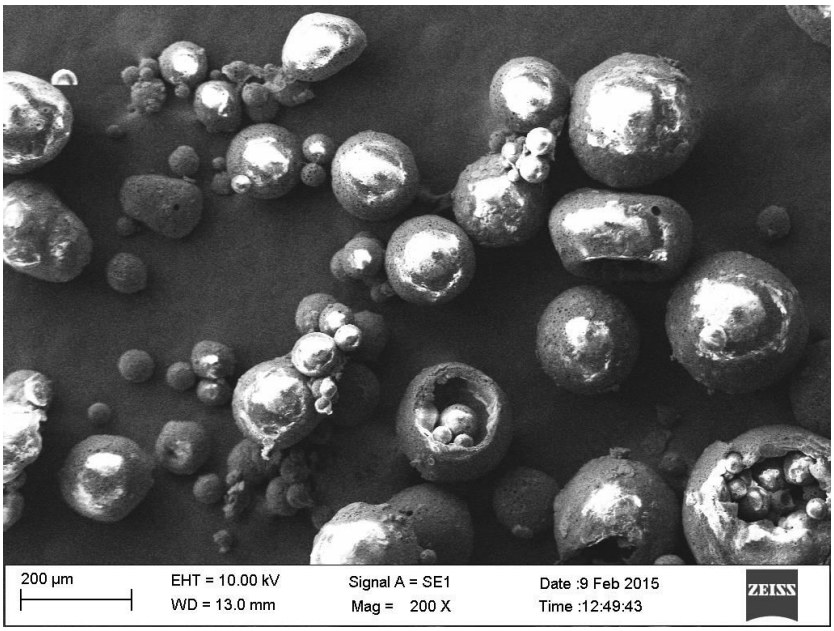
Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit RL 100 (F10)



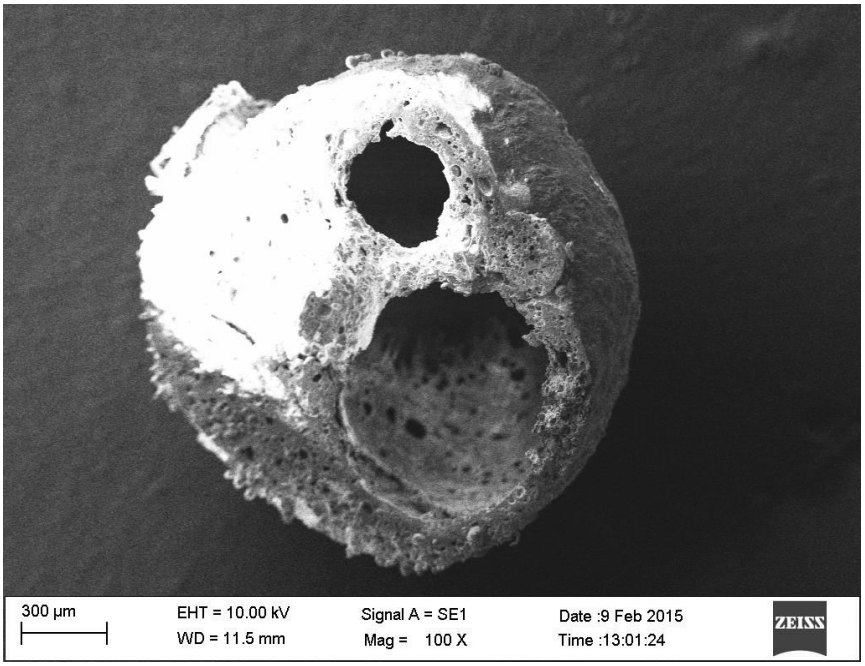
Scanning electronic microscopic photograph of the microspheres prepared with Eudragit RL 100 (F11)



Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit RL 100 (F11)



Scanning electronic microscopic photograph of the microspheres prepared with Eudragit RL 100 (F12)



Scanning electronic microscopic photograph of the prepared cross section microspheres with Eudragit RL 100 (F12)

Micro spheres before dissolution study were only subjected to SEM study. The surface topography of the prepared micro spheres was investigated by SEM. The prepared micro spheres were found to be spherical with smooth surface.

SUMMARY

- The prepared microspheres were analyzed for various Physico chemical properties such as entrapment efficacy, particle size , in-vitro dissolution studies, FT-IR, SEM.
- The entrapment efficacy can be varied to the changing the different kinds of polymers. The entrapment efficacy depends upon the some factors such as, nature of the polymer, RPM of the propeller, solubility of the drug , and concentration of surfactant.
- Highest proportion of the microspheres was obtained in the range of 389 nm for all the formulations. The average percent of microspheres obtained at 389 nm not varied with the type of polymer used.
- The drug release from the F1 formulation microspheres releases the more amount of drug in phosphate buffer solution.
- The kinetics showed that the release was followed Zero order and it was best fitted koresmeyer - Peppas model clearly indicates that the mechanism was erosion mechanism.
- The drug release from the micro spheres prepared with Eudragit S 100 was found between 1 to 8 hours for the micro spheres prepared at (F1). The drug release for the micro spheres prepared at (f2) to (F4) was found more than 12 hours.
- The drug release from the micro spheres prepared with Eudragit RS 100 was found between 1 to 10 hours for the micro spheres prepared at (F5). The drug release for the micro spheres prepared at (f6) to (F8) was found more than 12 hours.
- The drug release from the micro spheres prepared with Eudragit RL 100 was found between 1 to 12 hours for the micro spheres prepared at F(9). The drug release for the micro spheres prepared at (F10) to (F12) was found more than 12 hours.
- FT-IR Study on the selected formulations prepared with different polymers such as Ethyl cellulose , Eudragit S 100, Eudragit R 100 and Eudragit RL 100. The Spectrum peak points of the formulation were similar with that of pure Epalrestat, this clearly indicating that there is no drug polymer interaction.
- In the SEM photograph , the microspheres prepared with different polymers found spherical/round. The surface of the microspheres was rough and observed some particles.

CONCLUSION

Epalrestat microspheres were prepared using Ethyl cellulose, Eudragit S 100 & Eudragit RL 100. The result of drug release kinetics show zero order with erosion mechanism.

From the FTIR study, it is observed that there was no interaction between the drug and polymers.

Dissolution studied study showed that all the polymer combinations gave sustained release. Maximum drug release was from the formulation (Drug: Ethyl cellulose: Eudragit S 100) (F1).

From the SEM, the morphological characterization of the microspheres was studied .

The prepared microspheres were spherical and free flowing by flow property studies and particle size distribution.

The research work gives some preliminary idea about the release of Epalrestat embedded in the core system of microspheres.

CHAPTER 09

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