A STUDY OF EFFECT OF DIFFERENT CELLULOSIC POLYMERS ON SUSTAINED RELEASE DOSAGE FORM- EPLERENONE AS MODEL DRUG

Dissertation

Submitted to

The Tamil Nadu Dr.M.G.R Medical University, Chennai

In partial fulfillment for the award of degree of

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in

PHARMACEUTICS

by

26113301

DEPARTMENT OF PHARMACEUTICS

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OCTOBER-2013

DECLARATION

I hereby declare that this thesis work entitled**" A STUDY OF EFFECT OF DIFFERENT CELLULOSIC POLYMERS ON SUSTAINED RELEASE DOSAGE FORM- EPLERENONE AS MODEL DRUG"** Submitted to The Tamilnadu Dr.M.G.R Medical university, Chennai was carried out by me in the Department of Pharmaceutics, Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Mrs.PREETHA.S.PANICKER, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, Ultra college of Pharmacy, Madurai during the academic year Nov 2012- Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not formed the basis for the award of any degree, diploma, and associateship, fellowship of any other university or institution.

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CERTIFICATE

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EXAMINERS:

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2

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INTRODUCTION

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 controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments etc. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factors as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Several types of modified-release drug products are recognized (Leon Shargel et al., 2004).

Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

Delayed-release drug products: A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

Targeted-release drug products. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery.

1.1. Conventional Drug Delivery System

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption (Robinson, 1987).

As can be seen in the graph (Figure 1), administration of the conventional dosage form by extra vascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

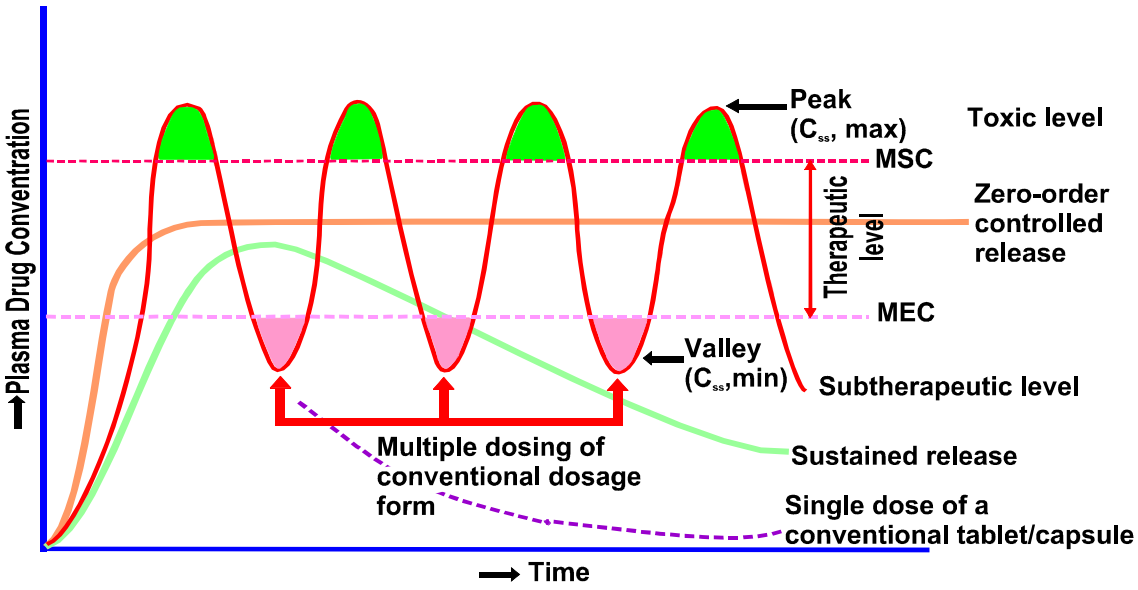


Fig. 1. A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

The conventional dosage forms like solution; suspension, capsule, tablets and suppository etc. have some limitations such as

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.
3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits (Chien, 1992).

1.2. Controlled Release Drug Delivery Systems (CRDDS)

More precisely, controlled delivery can be defined as

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

4) Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics.

Advantages of Controlled Drug Delivery System

1. Overcome patient compliance problems.
2. Employ less total drug
    a) Minimize or eliminate local side effects
    b) Minimize or eliminate systemic side effects
    c) Obtain less potentiation or reduction in drug activity with chronic use.
    d) Minimize drug accumulation with chronic dosing.
3. Improve efficiency in treatment
    a) Cures or controls condition more promptly.
    b) Improves control of condition i.e., reduced fluctuation in drug level.
    c) Improves bioavailability of some drugs.
    d) Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.
4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2) Poor in vitro – in vivo correlation.
3) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
4) Reduced potential for dose adjustment of drugs normally administered in varying strengths (Hoffman, 1998).

1.3. Oral Controlled Drug Delivery Systems

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action (Vora et al., 1996).

Classification of Oral Controlled Release Systems

A) Diffusion Controlled Systems

I. Reservoir Devices.

A core of drug (the reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release.

The characteristics of reservoir diffusion systems are

1. Zero order drug release is possible.
2. The drug release rate is dependent on the type of polymer.
3. High molecular weight compounds are difficult to deliver through the device. Coating and microencapsulation technique can be used to prepare sub devices.

II. Matrix Devices.

It consists of drug dispersed homogeneously in a matrix. The characteristics of the matrix diffusion system is

1. Zero order release cannot be obtained.
2. Easy to produce than reservoir devices.
3. High molecule weight compounds are delivered through the devices.

B) Dissolution controlled systems

I. Matrix Dissolution Controlled System

Aqueous dispersions, congealing, spherical agglomeration etc. can be used.

II. Encapsulation Dissolution Control

Particles, seeds or granules can be coated by technique such as microencapsulation. Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing spherical or semispherical solid units typically from about 0.5-1.5mm.

These are intended usually for oral administration.

Advantages of pellets

- Pellets are non dusting.
- Dose uniformity and accurate release profile
- Takes up less space because they are compressed.
- The ingredients that make up a pellet do not separate during transit and storage.
- Pellets also allow the separation of incompatible ingredients with in different layers of the pellet body.

Theory of pellet formation and growth (James Swarbick et al., 1993)

- Nucleation
- Coalescence
- Layering
- Abrasion transfer.

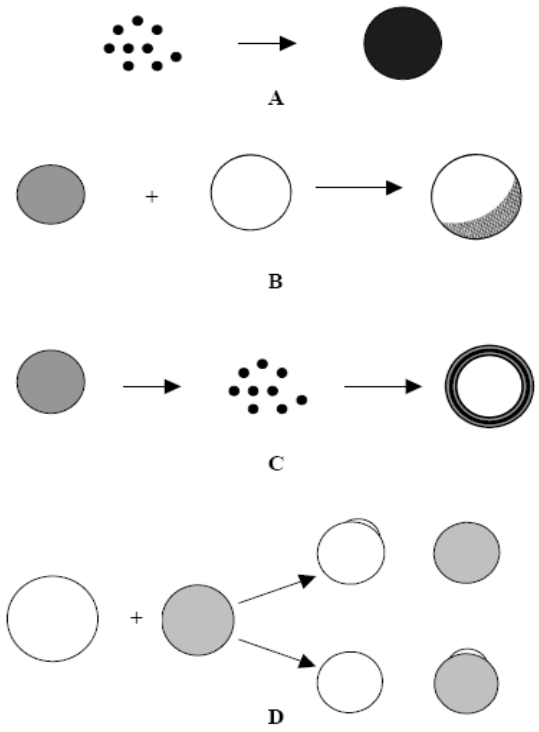


Fig 2. Pellet growth mechanism. (A) Nucleation, (B) coalescence, (C) layering and (D) abrasion transfer

Methods of preparation of pellets

1. Drug layering.
2. Extrusion and Spheronization.
3. Other pelletization methods

Globulation

Agitation

Compaction.

Compaction and drug layering are the most widely used pelletization techniques in pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipments, eg: High-shear mixer. Other methods of

pelletization such as globulation, balling and compression are also used in development of pharmaceutical pellets but in a limited scale.

1. Pelletization by Drug Layering (Olsen, K., Ghebre-Sellassie, I 1989)

Pelletization by layering is nothing but pellet build-up, layer by layer, around a given starting core. Pellet diameter may be between 0.6mm and 2.5mm.

Two types of layering are

a. Powder layering

b. Suspension layering

a. Powder layering

Powder layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders, hence it requires specialized equipments like spheronizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked off by the wet mass of pellets that is being layered.

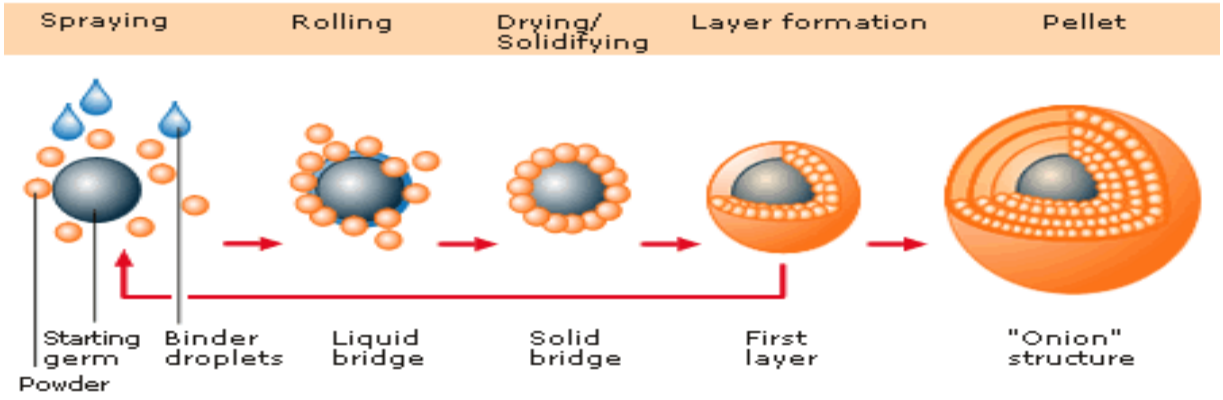


Figure 3. Powder layering process

b. Suspension layering

Solution layering involves the deposition of successive layers of solution and/or suspensions of drug substances and binder over the starter non-pareal seeds, which is an inert material or crystals or granules of the same drug. In fact the coating process involved in general is applicable

to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used.

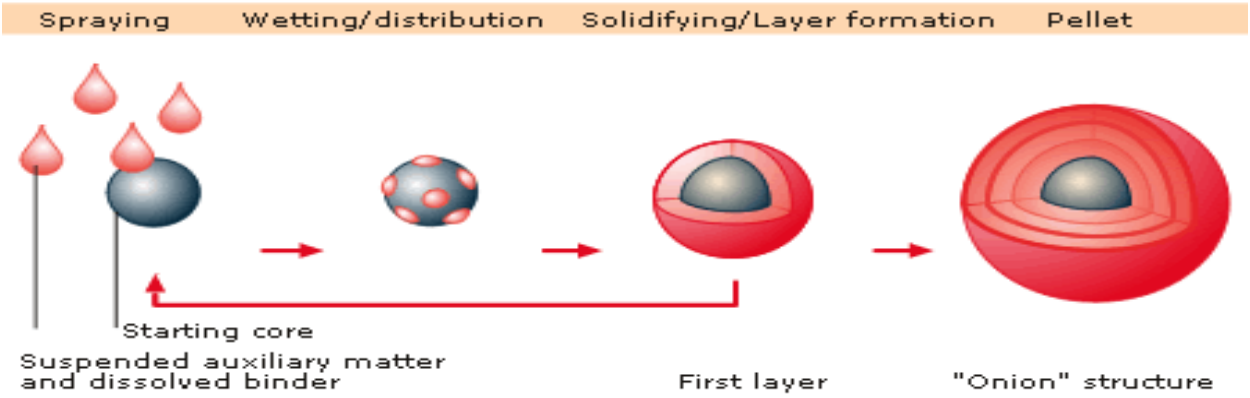


Figure 4. Suspension or Solution layering process

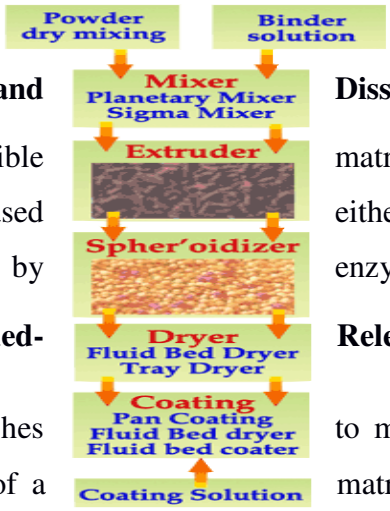
With suitable additives pellets can be made into tablets or used to fill capsules. The round shape is ideal for uniform coating. Pellets are good for automatic dosing.

2. Pelletization by Extrusion and Spheronization (Fu Jijun et al., 2011 PornsakSriamornsak., et al., 1997)

The process involves first making the extrudes from the powder material and then converting the extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc). A diagrammatic representation of the entire process is explained in figure No.5.

Fig 5. Pelletization by Extrusion and Spheronization.

C) Diffusion and Dissolution Controlled System.



In a bioerodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack.

1.4. Types of Extended-Release Products

General approaches to manufacturing an extended-release drug product include the use of a matrix structure in which the drug is suspended or dissolved, the use of a rate-controlling membrane through which the drug diffuses, or a combination of both. Among the many types of commercial preparations available, none works by a single drug-release mechanism. Most extended-release products release drug by a combination of processes involving dissolution, permeation, and diffusion. The single most important factor is water permeation, without which none of the product release mechanisms would operate. Controlling the rate of water influx into the product generally dictates the rate at which the drug dissolves. Once the drug is dissolved, the rate of drug diffusion may be further controlled to a desirable rate. Table 1 shows some common extended-release product examples and the mechanisms for controlling drug release, and lists the compositions for some drugs (Leon Shargel, 2004).

Table 1. Examples of Oral Extended-Release Products

Type	Trade Name	Rationale
Erosion tablet	Constant-T	Theophylline
	Tenuate Dospan	Diethylpropion HCl dispersed in hydrophilic matrix
	Tedral SA	Combination product with a slow-erosion component (theophylline, ephedrine HCl) and an initial-release component theophylline, ephedrine HCl, phenobarbital)
Waxy matrix tablet	Kaon Cl	Slow release of potassium chloride to reduce GI

		irritation
Coated pellets in capsule	Ornade spansule	Combination phenylpropanolamine HCl and chlorpheniramine with initial- and extended-release component
Pellets in tablet	Theo-Dur	Theophylline
Leaching	Ferro-Gradumet (Abbott)	Ferrous sulfate in a porous plastic matrix that is excreted in the stool; slow release of iron decreases GI irritation
	Desoxyn gradumet tablet (Abbott)	Methamphetamine methylacrylate methylmethacrylate copolymer, povidone, magnesium stearate; the plastic matrix is porous
Coated ion exchange	Tussionex	Cation ion-exchange resin complex of hydrocodone and phenyltoloxamine
Flotation–diffusion	Valrelease	Diazapam
Osmotic delivery	Acutrim	Phenylpropanolamine HCl (Oros delivery system)
	Procardia-XL	GITS—gastrointestinal therapeutic system with NaCl-driven (osmotic pressure) delivery system for nifedipine
Microencapsulation	Bayer timed-release	Aspirin
	Nitrospan	Microencapsulated nitroglycerin
	Micro-K Extencaps	Potassium chloride microencapsulated particles

1.5. Factors Influencing the Design and Performance of Sustained Release Products

The type of delivery system and route of administration of the drug presented in sustained drug delivery system may depend upon two properties (Bramhankar and Jaiswal, 1995). They are

I. Physicochemical Properties of drugs

II. Biological Factors.

I. Physicochemical Properties of Drugs

1. Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to 1gm is considered maximum (Nicholas et al., 1987).

2. Ionization, P^{Ka} & Aqueous Solubility

The pH Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between the P^{Ka} of the compound and its absorptive environment. For many compounds, the site of maximum absorption will also be the area in which the drug is least soluble.

For conventional dosage forms the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine. For sustained release formulations much of the drug will arrive in the small intestine in solid form. This means that the solubility of the drug is likely to change several orders of magnitude during its release.

Compounds with very low solubility are inherently controlled, since their release over the time course of a dosage form in the GIT will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1mg/mL (Fincher et al., 1968). Thus for slightly soluble drugs, diffusional systems will be poor choice, since the concentration in solution will be low.

For example Tetracycline has maximum solubility in the stomach and least solubility in the intestine where it is maximally absorbed. Other examples of drugs whose incorporation into sustained release systems are limited because of their poor aqueous solubility and slow dissolution rate are digoxin, warfarrin, griseofulvin and salicylamide. Very soluble drugs are also good candidates for the sustained release dosage forms.

3. Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore partitioning effects apply equally to diffusion through polymer membranes.

4. Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be detrimental for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anticholinergic drugs from controlled /sustained release formulation. In general the drugs, which are unstable in GIT environment poor candidates for oral sustained release forms.

5. Protein Binding

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are mostly recirculated and not eliminated. Drug protein binding can serve as depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

II. Biological Factors

1. Biological Half-Life

Therapeutic compounds with half-life less than 8 hrs are excellent candidates for sustained release preparations. Drugs with very short half-life (less than 2 hrs) will require excessively large amounts of drug in each dosage unit to maintain controlled effects. Thus forcing the dosage form itself to become too large to be administered. Compounds with relatively long half-lives, generally greater than 8 hrs are not used in the sustained release dosage forms, since their effect is already sustained and also GI transit time is 8-12 hrs (Jantzen et al., 1996). So the drugs, which have long -half life and short half- life, are poor candidates for sustained release dosage forms.

Some examples of drug with half-lives of less than 2 hours are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G and propylthiouracil. Examples of those with

half-lives of greater than 8 hours are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin and warfarin.

2. Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of the gastrointestinal tract (Absorption Window) are poor candidates for sustained release products.

3. Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant(s) for the process (es) are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Examples of drugs that are subject to intestinal metabolism upon oral dosing are hydralazine, salicylamide, nitroglycerine, isoproterenol, chlorpromazine and levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetine, propranolol and lidocaine.

Drugs that are significantly metabolized especially in the region of the small intestine can show decreased bioavailability from slower releasing dosage forms. This is due to saturation of intestinal wall enzyme systems. The drugs should not have intestinal first pass effect and should not induce (or) inhibit metabolism are good candidates for sustained release dosage forms. Various technologies used for controlled release drug delivery systems were given in Table 2 (Chien et al., 1990).

Table 2. Technologies used for CRDDS

S.NO.	DESIGN OR TYPE OF THE SYSTEM	RELEASE MECHANISM
1	**Dissolution Controlled CR systems** • Encapsulation (including Micro encapsulation) - Barrier coating - Embedment into a matrix of fatty materials) - Repeat action coatings - Coated plastic materials or hydrophilic materials • Matrix Dissolution Control	The dissolution of drug from system
2	**Diffusion Controlled CR systems** • Reservoir Devices (Fatty	The diffusion of the drug solution through a water - insoluble, permeable polymeric

	polymer coated systems) • Matrix Devices (Fatty polymer dispersed systems)	film
3	**Dissolution and Diffusion Controlled CR systems** • Non disintegrating polymeric matrix • Hydrophilic matrices	Diffusion of a drug solution through a porous matrix
4	**Ion- Exchange Resin CR Systems**	Ion- Exchange between the resin - drug complex and ions in the GI tract
5	**pH - Independent formulations**	Influenced by change in pH and ionic permeability of the membrane coating
6	**Osmotically Controlled CR systems**	They contain the buffering agents in a system which maintains constant pH throughout the GIT, so the drug release from the device is not affected by variable pH of GIT. Water entering by Osmosis dissolves the drug, and the drug solution is forced out through a laser drilled orifice
7	**Altered - Density systems**	Diffusion from high - density pellets or from floating

1.6. Monolithic Matrix System

In pharmaceutical CRDDS, matrix based systems are the most commonly used type of release controlling methodology owing to their simple manufacturing process. The preparation of

a tablet with the matrix involves the direct compression of the blends of drug, release retardant and other additives, in which the drug is uniformly distribute throughout the matrix core of the release retardant. Alternatively, drug-release retardant blends may be granulated to make the mix suitable for the preparation of tablets by wet granulation or beads (Colombo et al., 1993).

To characterize and define the matrix systems the following properties of the matrix are considered.

1. Chemical nature of the support.
2. The physical state of the drug.
3. The matrix and alteration in volume as the function of the time.
4. The routes of administration.
5. The release kinetics model (in accordance with Higuchi's equation, these system considered to release the drug as a function of square root of time).

The classification of the matrix-based systems is based on the following criteria.

- Matrix structure
- Release kinetics
- Controlled release properties (diffusion, erosion and swelling).
- Chemical nature and the properties of the applied release retardant(s).

Based on the chemical nature of the release retardant(s), the matrix systems are classified as given in Table 3.\

Table 3. Classification of Matrix Systems.

Type of the Matrix System	Mechanism
Hydrophilic	- Unlimited swelling delivery by diffusion - Limited swelling controlled delivery eg: Hydroxyethylcellulose, Hydroxypropylmethyl cellulose
Inert	- Inert in nature - Controlled delivery by diffusion eg: Ethylcellulose
Lipidic	- Delivery by diffusion & erosion eg: Carnauba wax.
Biodegradable	- Non lipidic nature - Controlled delivery by surface erosion
Resin Matrices	- Drug release from drug-resin complex eg: Ion exchange resins

1.7. Mechanism of Drug Release from Matrix Tablets

. As shown in Figure 2, in erodible matrices, polymer erosion from the surface of the matrix determines the drug release; whilst in hydrophilic matrices, formation of the gel layer and its dynamics as a function of time determines the drug release. Gel layer thickness, which determines the diffusion path length of the drug, corresponds to the distance between the diffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate.

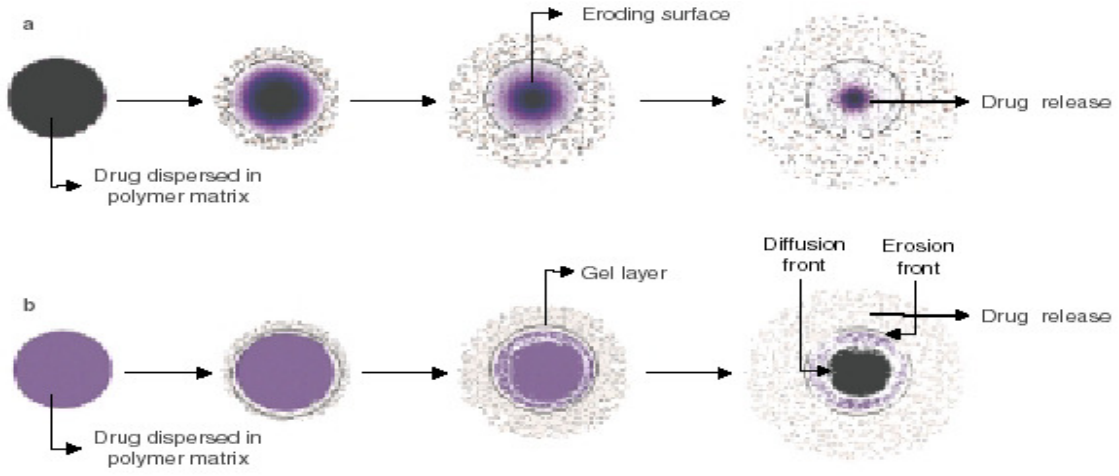


Fig.6. Schematic drug release from matrix diffusion controlled-release drug delivery systems with the drug homogenously dispersed in: (a) an erodible polymer matrix; and (b) a hydrophilic, sellable polymer matrix.

1.8. Drug Release Kinetics -Model Fitting of the Dissolution Data

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q=f(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Hixson–Crowell, Higuchi, Korsmeyer–Peppas

models. (Mulye and Turco, 1995; Colombo et al., 1999; Kim et al., 1997; Manthena et al., 2004; Desai et al., 1996; Higuchi et al., 1963).Different models expressing drug release kinetics were given in Table 4

Zero order kinetics

$Q_1 = Q_0 + K_0 t$

where Q_1 is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0=0$) and K_0 is the zero order release constant.

$f_t = K_0 t$

where $f_t = 1-(W_t/W_0)$ and f_t represents the fraction of drug dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled.

Use: This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First order kinetics

Kinetic equation for the first order release is as follows

$\text{Log } Q_t = \log Q_0 + K_1 t/2.303$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

$$f_t = K_H t^{1/2}$$

Where K_H is the Higuchi dissolution constant treated sometimes in a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water-soluble drugs.

Hixson–Crowell model

Hixson and Crowell (1931) recognizing that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and K_s is a constant incorporating the surface–volume relation. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

A graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution.

Mechanism of Drug Release

To find out the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix, first 60% drug release data can be fitted in

Korsmeyer–Peppas model which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved (Korsmeyer et al., 1983).

$$\text{Log } (M_t / M_\infty) = \text{Log } K_{KP} + n \text{ Log } t$$

where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time, K_{KP} is a release rate constant incorporating structural and geometrical characteristics of the tablet, and n is the release exponent indicative of the mechanism of drug release.

Table 4. Drug Release Kinetics

Kinetic Model	**Relation**	**Systems Following the Model**
First order	$\ln Q_t = \ln Q_o + K_t$ (release is proportional to amount of drug remaining)	Water-soluble drugs in porous matrix
Zero order	$f_t = K_o t$ (independent of drug concentration)	Transdermal systems Osmotic systems
Higuchi	$f_t = K_H t^{1/2}$ (proportional to square root of time)	Matrix formulations
Hixson-Crowell	$W_o^{1/3} - W_t^{1/3} = K_s t$	Erodible isometric matrices

f_t = fraction of dose release at time 't';

K_H, K_o, and K_s = release rate constants characteristic to respective models;

Q_o = the drug amounts remaining to be released at zero hour;

Q_t = the drug amounts remaining to be released at time 't';

W_o = initial amount of drug present in the matrix;

W_t = amount of drug released at time 't'.

1.9. Introduction to Hypertension

Blood pressure is the force of blood pushing against blood vessel walls. The heart pumps blood into the arteries (blood vessels), which carry the blood throughout the body. High blood pressure, also called hypertension, is dangerous because it makes the heart work harder to pump blood to the body and it contributes to hardening of the arteries or atherosclerosis and the development of heart failure.

Hypertension, also referred to as high blood pressure, HTN or HPN, is a medical condition in which the blood pressure is chronically elevated.

There are several categories of blood pressure, including

- Normal: 120/80 mm of Hg
- Prehypertension: 120-139/80-89 mm of Hg
- Stage 1 hypertension: 140-159/90-99 mm of Hg
- Stage 2 hypertension: 160 and above/100 and above

Hypertension can be classified either **essential** (primary) or **secondary**.
Essential hypertension indicates that no specific medical cause can be found to explain a patient's condition. Secondary hypertension indicates that the high blood pressure is a result of (i.e., secondary to) another condition, such as kidney disease or tumors.

The mechanisms and causes of hypertension

The direct mechanisms causing hypertension is one or more of these factors

- An increased tension  in the blood vessel walls.

- An increased blood volume caused by elevated levels of salt and lipids  in the blood holding back water.
- Hardened and inelastic  blood vessels caused by arteriosclerosis.
- The primary causes behind these mechanisms are not fully understood, but these factors contribute to causing hypertension
- A high consume of salt
- A high fat consume.
- Stress at work and in the daily life.
- Smoking.
- Over-weight
- Lack of exercise.
- Kidney failure.

Lifestyle measures to prevent and treat hypertension

Lifestyle measures shall always be a component of the hypertension treatment. Sometimes such measures are enough to cure the condition. Those measures are

- Reducing salt consume.
- Reduction of fat consume, and especially of saturated fat consume.
- Weight reduction.
- Relaxing and stress reduction techniques, for example meditation and autogenic training.

- Regular exercise.

Special food types that reduce the blood pressure

Research projects suggest that the following food types reduce blood pressure.

- Fish oil and fat fish. The working substances seem to be the omega-3 unsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The effect from fish oil seems to cease when the fish oil supplements are stopped.
- Olive oil, especially olive oil of the quality extra virgin.

Natural supplements to help against hypertension

Natural supplements to treat hypertension exist. These supplements reduce blood pressure by lowering the cholesterol and lipid content in the blood, by preventing oxidation of tissue components by free radicals, and by helping damaged blood vessels to heal. Examples of ingredients having these effects are vitamin B3, inositol, turmenic extract and gum extract.

They may also contain Ingredients giving a direct anti-hypertensive effect, like potassium, magnesium, calcium, vitamin C and fatty acids from marine sources.

Medical treatment of hypertension

When lifestyle measures and supplements are not enough to cure the condition, medical treatment must be applied. Many different types of drugs are used, alone or in combination with other drugs, to treat high blood pressure. The major categories are

- **Angiotensin-converting Enzyme (ACE) Inhibitors:** ACE inhibitors work by preventing a chemical in the blood, angiotensin I, from being converted into a substance that increases salt and water retention in the body. These drugs also make blood vessels relax, which further reduces blood pressure.

- **Angiotensin II Receptor Antagonists:** These drugs act at a later step in the same process that ACE inhibitors affect. Like ACE inhibitors, they lower blood pressure by relaxing blood vessels.

- **Beta blockers:** Beta blockers affect the body's response to certain nerve impulses. This, in turn, decreases the force and rate of the heart's contractions, which lowers blood pressure.

- **Blood Vessel Dilators (Vasodilators):** These drugs lower blood pressure by relaxing muscles in the blood vessel walls.

- **Calcium Channel Blockers:** Drugs in this group slow the movement of calcium into the cells of blood vessels. This relaxes the blood vessels and lowers blood pressure.

- **Diuretics:** These drugs control blood pressure by eliminating excess salt and water from the body.

- **Nerve Blockers**: These drugs control nerve impulses along certain nerve pathways. This allows blood vessels to relax and lowers blood pressure.

REVIEW OF LITERATURE

Madhusudan Rao Yamsani et al., (2011) studied the effect of hydrophilic cellulosic polymers to control the release profile of the Eplerenone and he was the first one who studied the prolonged drug release profile of Eplerenone. He has prepared matrix mini tablets containing cellulose polymers like HPMC K4M, HPMC K15M, were prepared by wet granulation technique using PVP K60 as a tablet binder. The optimized formulation contains 1: 1 ratio (drug to HPMC K4M ratio) and contains 1:0.7 ratio (drug and HPMC K15M) respectively. The in vitro release kinetic studies of prepared matrix mini tablets with both the polymers revealed that the amount of Eplerenone released from the matrix mini tablets at different time intervals were matched with theoretical release profile of drug for a period of 12 h.

Hiremath and Saha (2008) have formulated hydrophilic controlled release matrix tablets of rifampicin, a poorly soluble drug, using hydroxypropyl methylcellulose (HPMC) polymer (low, medium, and high viscosity) by direct compression method. Influence of formulation variables and process parameters such as drug : HPMC ratio, viscosity grade of HPMC, drug particle size, and compression force on the formulation characters and drug release has been studied. Their results indicated that the release rate of the drug and the mechanism of release from the HPMC matrices are mainly controlled by the drug:HPMC ratio and viscosity grade of the HPMC. In general, decrease in the drug particle size decreased the drug release. Lower viscosity HPMC polymer was found to be more sensitive to the effect of compression force than the higher viscosity.

Ravi et al., (2008) have designed oral controlled release (CR) matrix tablets of zidovudine (AZT) using HPMC, EC and cabopol-971P (CP) and studied the effect of various formulation factors on in vitro drug release. . Release rate decreased with increase in polymer proportion and compression force. The release rate was lesser in formulations prepared using CP (20%) as compared to HPMC (20%) as compared to EC (20%). No significant difference was observed in the effect of pH of dissolution media on drug release from formulations prepared using HPMC or EC, but significant difference was observed in CP based formulations. Decrease in agitation speed from 100 to 50 rpm decreased release rate from HPMC and CP formulations but no significant difference was observed in EC formulations. Mechanism of release was found to be dependent predominantly on diffusion of drug through the matrix than polymer relaxation incase of HPMC and EC formulations, while polymer relaxation had a dominating influence on drug release than diffusion incase of CP formulations. Designed CR tablets have shown an initial release of 17-25% in first hour and extending the release up to 16-20 hours.

Roberts et al., (2007) have studied the release profiles of aspirin from hypromellose matrices in hydro-ethanolic media. Percent aspirin released increased with increasing levels of ethanol in the dissolution media, correlating with the drug's solubility, however, dose dumping of aspirin did not occur. An initial rapid release was observed in media comprising 40% ethanol. Release in these conditions was considered to be both erosion and diffusion-mediated, in contrast

to the release in 0, 10, 20 and 30% ethanol media, where erosion-controlled release dominated. Image analysis of matrix swelling indicated a slower initial interaction between ethanol and Hypromellose accounting for the initial rapid release. Cloud point studies suggested that ethanol retarded hydration of the polymer.

Sinju et al., (2004) have described the effects of temperature and humidity on tablets containing kollidon® SR using diphenhydramine HCl as a model drug. Exposure of tablets to accelerated stability condition (40°C/75%RH) in an open dish resulted in rapid increases in tablet hardness, accompanied by step-wise decreases in dissolution rate. But exposure to 25°C/60%RH similarly resulted in increases in tablet hardness, although with minimal impact on dissolution. Exposure of kollidon® SR tablets to the aqueous coating process indeed resulted in noticeable changes in both hardness and dissolution. Application of the opadry solution appears to affect tablet behavior to a lesser degree, compared to water, most likely due to protection via formed barrier film. Therefore the authors concluded that attention needs to be paid to the extreme sensitivity of kollidon® SR matrix tablets to temperature and moisture during product development.

Ghali, Gazzaniga et al. (1998) Extrusion-spheronisation is a multiple-step compaction process comprising dry mixingof the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into the spheroniser to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution The granulation step can be performed both in batch-type processors, including a conventional planetary mixer, and in vertical or horizontal high-shear and sigma-blade mixers and in continuous mixers, such as Nica M6 instant (Hellén 1992), and high-shear twin-screw mixer-extruders

Jackson, Mohammed Nastruzzi et al., (1989). The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid. In powder layering, complete dissolution does not occur, due to low liquid saturation, irrespective of the solubility of

the active agent in the binding liquid. In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the addition of powder Conventional pan coaters have been used from the very beginning of the history of drug layering pelletization. From the economic point of view, however, use of conventional pan coaters is not very reasonable due to the higher labor costs and time consumption, and lower yield

Sastry and Fuerstenau (1972) In order to judiciously select and optimise any pelletization/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are confined to visual observations. Results obtained from the experiments with some form of tracer technique are regarded as acceptable and convincing. As the conventional granulation the most thoroughly studied, most classified pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consequtive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.

Scope of Work

Eplerenone is a highly selective aldosterone receptor antagonist (SARA) to effectively block aldosterone at receptor sites in body tissues (Spertus J.A.et al., 2002). Aldosterone plays an important role in chronic heart failure, even when other rennin–angiotensin–aldosterone system (RAAS)-inhibiting agents are used (Stier C.T, 2002, Staessen S.,1981). Eplerenone is used for treatment of hypertension and heart failure. Eplerenone is a steroid nucleus- based antimineral corticoid that is chemically and enzymatically interconvertible to an open lactone ring form. It is rapidly and nearly completely absorbed from the gastrointestinal tract (GIT) following oral ingestion, showing 69% bioavailability. Detectable plasma levels occur within one-half hour and

peak plasma levels occur in about 1-2 hours and the plasma half-life is 4 hours. In the treatment of hypertension the usual initial dosage is 25 mg once daily, whether used alone or added to diuretic therapy. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 50-100 mg per day.

Although conventional tablets of Epelerenone are available in the market commercially, no study has been done so far for preparing the Epelerenone sustained-release tablets. To improve the oral bioavailability and to reduce the dose dependent toxicity there is a need for the development of sustained-release formulations (Gregory et al., 2004; Mandana et al., 2000).

The most commonly used method of modulating the drug release is to include it in a matrix system (Salsa et al., 1997).An effort was therefore made to develop simple and effective sustained-release Epelerenone tablets using a polymer matrix system in multi unit particles. The drug is slightly soluble in water and hence judicious selection of matrix layer formation over a dump mass of the drug is essential for achieving constant release. HPMC is the most commonly and successfully used hydrophilic binding agent, pore forming agent along with hydrophobic polymer system for the preparation of oral controlled drug delivery systems (Colombo et al,, 1993).Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly (Siepmann et al., 1999). The pores formed in the matrix layer acting as a barrier to both the influx of water and the efflux of the drug in solution (Colombo et al., 2000; Kiil and Dam. 2003). As the proportion of the hydrophobic polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix (Ford et al., 1985). The dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer erosion and pore formation in the release retarding layer as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading (Narasimhan and Peppas.,1997). However, the use of hydrophilic pore former alone for sustaining drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network but for the drugs like Eplerenone we can use as it is or in combination with hydrophobic polymers (Liu et al., 2001).

Hence, in the present study, an attempt has been made to develop the sustained-release multi unit particles in tablets of Eplerenone using hydrophobic ethyl cellulose and two other commercial aqueous dispersions of ethyl cellulose, and the sustained pattern of Eplerenone was evaluated by in-vitro drug release for 12 hours. The drug release data were plotted using various kinetic equations (zero-order, first-order, Higuchi's kinetics, Korsmeyer's equation, and Hixson-Crowell cube root law) to evaluate the drug release mechanism and kinetics. In-vivo drug release, biopharmaceutical evaluation, and in-vitro/in-vivo correlations were beyond the scope of this study and will be considered in future work.

Objective

- The present work is aimed at preparing and evaluating sustained-release tablets (MUPS) of Eplerenone using different cellulosic polymers

- To study the effect of nature of different cellulosic polymers in different concentrations on the rate of drug release.

Plan of Work

- Construction of the calibration curve for Epelerenone in 0.1N HCl and 6.8 pH phosphate buffer.

- Calculation of the dose and to construct theoretical release profile of Eplerenone from sustained –release formulations.

Preparation of Sustained release pellets using different cellulosic polymers,

a) Ethyl cellulose
b) Surelease
c) Aquacoat ARC

- Evaluation of prepared pellets and Precompression blend and prepared tablets.
- Selection of the best batch of tablets based on the in-vitro release studies.

- Preparation of tablets by direct compression method using the final selected batch of pellets and evaluation of the tablets.

- To perform swelling and erosion studies, FTIR studies, and stability studies for the optimized tablet formulation.

Drug profile

1. Description

Nomenclature

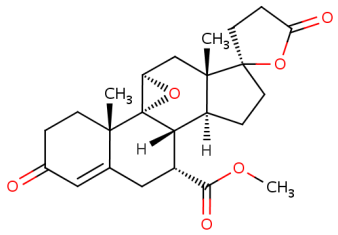
Generic Name **:** Eplerenone

Chemical name : Methyl hydrogen 9, 11- epoxy-17- hydroxy-3- xopregn-4-ene-7, 21-dicarboxylate, γ-lactone

Formula

Empirical formula : $C_{24}H_{30}O_6$

Chemical structure :



Physical and Chemical Properties

Molecular weight : 414.49

Description : Eplerenone is an odorless, white to off-white crystalline Powder

Melting point : 241-243°C

Solubility : It is very slightly soluble in water, with its Solubility essentially pH independent.

2. Pharmacokinetics

Bioavailability : 69%

Half-life : 4-6 hrs

Apparent Volume of distribution : 66.5 L

BCS Class : Class II

Clearance : 10 L/hr.

Partition coefficient : 7.1 at pH 7.0.

Calculated dose : 70mg

3. Pharmacology

i) Indications and Dosage

For improvement of survival of stable patients with left ventricular systolic dysfunction (ejection fraction <40%) and clinical evidence of congestive heart failure after an acute myocardial infarction. The usual initial dosage of Eplerenone is 25 mg once a day. Dosage may be increased or decreased depending on heart rate and blood pressure response.

iii) Mechanism of Action

Eplerenone binds to the mineralocorticoid receptor and thereby blocks the binding of aldosterone (component of the renin-angiotensin-aldosterone-system, or RAAS). Aldosterone synthesis, which occurs primarily in the adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms.

iv) Drug Interactions

Eplerenone has some interactions with the drugs like itraconazole, the concomitant use of the CYP3A4 potent inhibitors ketoconazoleand itraconazole is contraindicated

v) Adverse Effects

Common adverse drug reactions (ADRs) associated with the use of eplerenone include: hyperkalaemia, hypotension, dizziness, altered renal function, and increased creatinine concentration (Rossi S, 2006). Eplerenone, may have a lower incidence of sexual side effects such as feminization, gynecomastia, impotence, low sex drive and reduction of size of male genitalia. (Craft, Jennifer, 2004)

vi) Toxicity

The most likely symptoms of human overdosage would be anticipated to be hypotension or hyperkalemia. However, no cases of human overdosage with eplerenone have been reported.

4. Pharmacodynamics

Eplerenone, an aldosterone receptor antagonist similar to spironolactone, has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effects of eplerenone. Eplerenone selectively binds to recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

5. Method of analysis

- Spectroscopy like-IR, NMR, Mass and UV-Visible Spectroscopy.
- Thin Layer Chromatography
- High Performance Liquid Chromatography

6. Storage

Store at USP control room temperature 20° to 25°C (68° to 77°F) & protected from light. Dispense in a well-closed, light-resistant container.

Excipients Profile

1. Hypromellose

Hypromellose is a partly O-methylated and O-(2- hydroxypropylated) cellulose.

Synonyms : Benecel MHPC; Hydroxypropylmethylcellulose (HPMC); Methocel; Metolose; Tylopur.

Description : Odorless and tasteless, white or creamy-white fibrous or granular powder.

Grades : Methocel 5cps, Methocel 6cps, Methocel K100 Premium LVEP, Methocel K4M, K15M, K100M, Metolose 60SH, 65SH, 90SH.

Stability : Stable material, although it is hygroscopic after drying.

Acidity/alkalinity : pH = 5.5–8.0 for a 1% w/w aqueous solution

Density (true) : 1.326 g/cm^3.

Melting point : Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

Viscosity : Ranges from 3-100000 mPa s.
Methocel K100M (100000 mPa s),
Methocel K15M (15000 mPa s),
Methocel K4M (4000 mPa s).

Safety : Non-toxic and non-irritant material, although excessive oral consumption may have a laxative effect.

Uses : As a binder (2% - 5% w/w),
Matrix former (10% - 80% w/w),
Thickening agent (0.45% - 1% w/w),

It is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

2. Ethylcellulose

Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages.

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

Description : It is a tasteless, free-flowing, and white to light tan-colored powder.

Functional Category : Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

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

Density (bulk) : 0.4 g/cm^3

Viscosity : 7 to 100 mPa s

Stability and Storage : It is a stable, slightly hygroscopic material. It should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Safety : It is generally regarded as a nontoxic, nonallergenic, and nonirritating material. It is not metabolized following oral consumption and is therefore a noncalorific substance.

Uses : It is used in the microencapsulation (10-20% w/w).
As a sustained-release tablet coating (3-20% w/w).
It can be used for tablet coating and tablet granulation (1- 3% w/w).

3. Microcrystalline cellulose

Microcrystalline cellulose is purified, partially depolymerized cellulose.

Synonyms : Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Description : It occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Grades : Avicel PH-101, PH-102, PH-103; Emcocel 50M, 90M; Vivapur 101, 102.

Functional Category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant & Cushioning agent.

Solubility : Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Melting point : Chars at 260-270°C.

Stability and Storage : It is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Safety : It is a relatively nontoxic and nonirritant material.

Uses : It is widely used as a diluent (20 – 90 %w/w).
As a tablet disintegrant (5-15% w/w).
It can be used as an adsorbent, antiadherent (20- 90%w/w).

4. Talc

Talc is a purified, hydrated, magnesium silicate.

Synonyms : Altalc; E553b; Hydrous magnesium calcium silicate; Hydrous magnesium silicate; Luzenac Pharma; Magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; Powdered talc; Purified French chalk; Purtalc; Soapstone; Steatite; Superiore.

Description : Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional Category: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Solubility : Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Stability and Storage : Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene

oxide or gamma irradiation. It should be stored in a well-closed container in a cool, dry place.

Safety **:** Talc is used mainly in tablet and capsule formulations. It is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc

causes irritation and may cause severe respiratory distress in infants.

Incompatibilities **:** Incompatible with quaternary ammonium compounds.

Uses **:** Talc can be used in oral solid dosage formulations as a lubricant and diluent. However, it is widely used as a dissolution retardant in the development of controlled-release products. It is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

5.Magnesium Stearate

Synonyms : Magnesium octadecanoate; Octadecanoic acid, magnesium salt; Stearic acid, magnesium salt.

Functional Category : Tablet and capsule lubricant.

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

Flowability : Poorly flowing, cohesive powder.

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

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

Stability and Storage : It is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities : Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. It cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety : Nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

Uses : It is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at

concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

6. Colloidal Silicon Dioxide

Nonproprietary Names

• BP: Colloidal anhydrous silica
• PhEur: Silica colloidalis anhydrica
• USPNF: Colloidal silicon dioxide

Synonyms: Colloidal silica; fumed silica; light anhydrous silicicacid; silicic anhydride; silicondioxide fumed.Wacker HDK. Aerosil; Cab-O-Sil; Cab-O-Sil M-5P;
Chemical Name and CAS Registry Number: Silica

Structural Formula: SiO2

Uses: Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Table 2.6: Uses of colloidal silicondioxide.

Use	**Concentration (%)**
Aerosols	0.5 - 2.0
Emulsion stabilizer	1.0 – 5.0
Glidant	0.1 - 0.5
Suspending and thickening agent	2.0 – 10.0

Description: Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.
Physical Properties:

Flowability: 35.52% (Carr compressibility index) pH (4% w/v dispersion) 3.5–5.5

Specific surface area: 200–400 m2/g (Stroehlein apparatus, single point); 50–380 m2/g (BET method).

Stability and Storage conditions: Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. The bulk material should be stored in a well-closed in a cool, dry place.

Incompatibilities: Incompatible with diethylstilbestrol preparations.

7. Stearic acid

Nonproprietary Names

BP: Stearic acid

JP: Stearic acid

PhEur: Acidum stearicum

USPNF: Stearic acid

Synonyms

Cetylacetic acid; Crodacid; E570; Edenor; Emersol; Hystrene; Industrene; Kortacid 1895; Pearl Steric; Pristerene; stereophonic acid; Tegostearic.

Chemical Name and CAS Registry Number

Octadecanoic acid

Empirical Formula and Molecular Weight

$C_{18}H_{36}O_2$ 284.47 (for pure material)

The USPNF 23 describe stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$). In the USPNF 23, the content of stearic acid is not less than 40.0% and the sum of the two acids is not less than 90.0%. The USPNF 23 also contains a monograph for purified stearic acid. The PhEur 2005 contains a single monograph for stearic acid but defines stearic acid

50, stearic acid 70, and stearic acid 95 as containing specific amounts of stearic acid ($C_{18}H_{36}O_2$);

Functional Category Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant, although it may also be used as a binder or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used as a sustained-release drug carrier. In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams. The partially neutralized stearic acid forms acreamy base when mixed with 5–15 times its own weight ofaqueous liquid; the appearance and plasticity of the cream being determined by the proportion of alkali used. Stearic acid is used as the hardening agent in glycerin suppositories. Stearic acid is also widely used in cosmetics and food products.

Description

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor and taste suggesting tallow.

Stability and Storage Conditions

Stearic acid is a stable material; an antioxidant may also be added to it. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Stearic acid is incompatible with most metal hydroxides and may be incompatible with oxidizing agents. Insoluble stearates are formed with many metals; ointment bases made with stearic acid

may show evidence of drying out or lumpiness due to such a reaction when compounded with zinc or calcium salts. A number of differential scanning calorimetry studies have investigated the compatibility of stearic acid with drugs. Although such laboratory studies have suggested incompatibilities, e.g. with naproxen, they may not necessarily be applicable to formulated products. Stearic acid has been reported to cause pitting in the film coating of tablets coated using an aqueous film-coating technique; the pitting was found to be a function of the melting point of the stearic acid.

Safety

Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. Stearic acid is generally regarded as a nontoxic and nonirritant material. However, consumption of excessive amounts may be harmful.

LD50 (mouse, IV): 23 mg/kg

LD50 (rat, IV): 21.5 mg/kg

8. Polyethylene Glycol

Nonproprietary Names

BP: Macrogols

JP: Macrogol 400

Macrogol 1500

Macrogol 4000

Macrogol 6000

Macrogol 20000

PhEur: Macrogola

USPNF: Polyethylene glycol

Synonyms

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

Chemical Name and CAS Registry Number

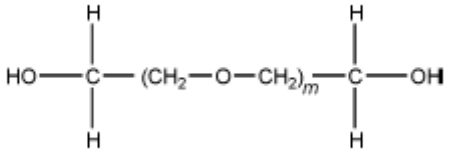
a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

Empirical Formula and Molecular Weight

HOCH2(CH2OCH2)mCH2OH where m represents the average number of oxyethylene groups.

Alternatively, the general formula

Structural Formula



Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases. Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol. Mixtures of polyethylene glycols can be used as suppository bases, for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats. Aqueous polyethylene glycol solutions can be used either as suspending agents or to

adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell. In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms. In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules. However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations, a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes paste like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required. Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps. In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers. The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating. Polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents. It has also been used in insulin-loaded microparticles for the oral delivery of insulin, it has been used in inhalation preparations to improve aerosolization, polyethylene glycol nano particles have been used to improve the oral bioavailability of cyclosporine, it has been

used in self assembled polymeric nano particles as a drug carrier, and copolymer networks of polyethylene glycol grafted with poly(methacrylic acid) have been used as bioadhesive controlled drug delivery formulations.

9. Hydrogenated Vegetable Oil

Non proprietary names:

BP: Hydrogenated vegetable oil

JP: Hydrogenated oil

USPNF: Hydrogenated vegetable oil

Synonyms:

Hydrogenated cottonseed oil: Akofine; Lubritab; Sterotex.

Hydrogenated palm oil: Softisan 154.

Hydrogenated soybean oil: Lipovol HS-K; Sterotex HM

Chemical name and CAS registry no:

Hydrogenated vegetable oil [68334-00-9]

Empirical formulae:

R1COOCH2—CH(OOCR2)—CH2OOCR3

where R1, R2, and R3 are mainly C15 and C17.

Functional category:

Tablet and capsule lubricant; tablet binder

Description:

Hydrogenated vegetable oil is a mixture of triglycerides of fattyacids. The two types that are defined in the USPNF 23 are characterized by their physical properties; Hydrogenated vegetable oil type I occurs in various forms,e.g. fine powder, flakes, or pellets. The color of the materialdepends on the manufacturing process and the form. In general,the material is white to yellowish-white with the powder gradesappearing more white-colored than the coarser grades.

Typical properties:

Density (tapped): 0.57 g/cm3

Melting point: 61–668C

Particle size distribution: 85% < 177 mm, 25% < 74 mm in size

Average particle size is 104 mm.

Solubility: soluble in chloroform, petroleum spirit, and hot propan-2-ol; practically insoluble in water.

Stability and Storage Conditions:

Hydrogenated vegetable oil type I is a stable material; typically it is assigned a 2-year shelf-life. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with strong oxidizing agents.

Safety:

Hydrogenated vegetable oil type I is used in food products and oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant excipient.

Applications:

- Hydrogenated vegetable oil type 1 is used as a lubricant in tablet and capsule formulations. It is used at concentrations of 1–6% w/w, usually in combination with talc.
- It may also be used as an auxiliary binder in tablet formulations.
- Hydrogenated vegetable oil type I is additionally used as the matrix-forming material in lipophilic-based controlled-release formulations;
- It may also be used as a coating aid in controlled-release formulations.
- Hydrogenated vegetable oil type I is used as a viscosity modifier in the preparation of oil-based liquid and semisolid formulations
- In the preparation of suppositories, to reduce the sedimentation of suspended components and to improve the solidification process
- In the formulation of liquid and semisolid fills for hard gelatin capsules.

Table 5 : Instruments Used

Instrument Name	Manufacturer	Model
Weighing balance	Sartorius	CP225D
Analytical balance	Essae DS-852	DS-852
Tray dryer	Millennium equipments Pvt Ltd	METD-6G
Tablet compression machine	Rimek (Karnavathi)	D tooling
Friablitor	Electrolab	EF-2(USP)
Hardness tester	Electrolab	EH01
Dissolution test system	Electrolab	TDT-14L
Mechanical stirrer	Vision labs	NA
Coating pan	Bectochem	GMP4938
HPLC	Schimadzu	LC2010CHT

The total dose of Eplerenone for biphasic delivery was calculated with available pharmacokinetic data. (Martin J., 2001)As per the zero order release principle, the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. The release from the dosage form should follow zero-order kinetics, as shown by the equation. (Robinson and Eriksen, 1966)

$\mathbf{K^0_r}$ = Rate in= Rate out = ke×Cd×Vd. Eq. (1)

Where $\mathbf{K^0_r}$ is the zero-order rate constant for drug release (amount per time), ke is the first order rate constant of overall drug elimination (per hour), Cd is the desired drug level in the body

(amount per volume), and Vd is the volume in which the drug is distributed. The elimination half-life of Eplerenone is 4 h (ke= 0.693/4=0.173h-1)

The loading dose is required to give initial rapid burst of dose so as to attain therapeutic range immediately after dosing

Loading dose (DL) = Css avg×Vd / F = (0.2495×66.5) / 0.69 = 24mg Eq. (2)

Where DL = Loading Dose,
Css avg = Average Steady State Concentration (0.2495 mg/ml),
Vd = Apparent Volume of Distribution (66.5 l),
F = Fraction of Dose Absorbed (0.69).

The maintenance dose was (DM) = K0 r× H, Eq. (3)

H = Total desired time for sustained action in hours,
Drug availability rate (Rate of drug input) K0 r= Ke× DL Eq. (4)
Ke is the overall elimination rate constant (per hour),
K0 r= 0.1732 ×12 = 2.0784 mg / h.
Thus K0 r (Rate of drug input) is 4.158 mg / h, which should also have been equal to the elimination constant so as to maintain the steady state condition. For a system in which the maintenance dose releases drug by a zero order p7rocess for a specified time, the total dose is as follows:

Total dose = DT = DL*+DM, Eq. (5)
DL *is corrected loading dose
DM = K0 r×H= 2.0784 ×12 = 24.94 mg

If the maintenance dose begins the release of the drug at the time of dosing, it will add to that which is provided by the initial dose, thus increasing the initial drug level. In this case, a correction factor is needed (K0 r× TP) to account for the added drug from the maintenance dose.

This correction factor is the amount of drug provided during the period from t=0 to the time of the peak drug level, TP.

If DL is 24mg, K0 r is 4.158 mg/h, and TP is 1.5h, then the corrected loading dose
(DL*)= DL- (K0 r×TP) = 2.0784 ×1.5= 20.88 Thus,

The total dose required (DT) =DL*+DM=20.88 +49.89= 70.77 mg

The total dose of Eplerenone rounded off to 70 mg (which is equivalent to 74 mg of Eplerenone with 24 mg loading dose and 49.89 mg maintenance dose)(Madhusudan Rao Y. et al., 2011)

Construction of Standard Graph of Eplerenone

Accurately weighed amount of 120 mg Eplerenone was transferred into a 100ml volumetric flask. 20 mL of 0.1N hydrochloric acid (HCl) was added to dissolve the drug and volume was made up to 100 mL with the same HCl. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 mL with 0.1N HCl which has given the solution having the concentration of 120 mcg/mL. Necessary dilutions were made by using this second solution to give the different concentrations of Eplerenone (80 to 120mcg/mL) solutions.

Similarly, standard graph was plotted with 6.8 pH phosphate buffer.

PREFORMULATION STUDIES:

Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

Drug-Excipients Compatibility studies:

Eplerenone was mixed with all excipients, used in the formulation in different ratios and subjected to Physical observation.

Drug-Excipient Compatibility study (Physical Observation): Eplerenone was mixed with different proportions with all excipients which were used in the formulation, in different ratios and kept at 40ºC/75%RH conditions for one month. The physical properties (Color change) were monitored regularly. The change in color of any mixture was considered as incompatibility and the excipient blend was discarded from stud

Table 6:

S.No	Drug excipients blend	Ratio	Condition: 40°C ± 2°C / 75% ± 5%			
			Initial	1 week	2 weeks	4 weeks
1	Eplerenone + sucrose	1:1	White to Off white crystalline powder			
2	Eplerenone+hypromellose	1:1	White to Off white powder			
3	Eplerenone + Aqua coat ARC	1:1	White to Off white powder			
4	Eplerenone+Ethyl cellulose	1:1	White to Off white powder			
5	Eplerenone + Surelease	1:1	White to Off white powder			
6	Eplerenone + MCC	1:1	White to Off white powder			
7	Eplerenone + Mg.stearate.	1:1	White to Off white powder			
8	Eplerenone + Lubritab	1:1	White to Off white powder			
9	Eplerenone + Talc	1:1	White to Off white powder			
10	Eplerenone + Stearic acid	1:1	White to Off white powder			
11	Eplerenone + PEG 6000	1:1	White to Off white powder			
12	Eplerenone+ sucrose+ hypromellose+ Aqua coat ARC+ Ethyl cellulose + Surelease+ MCC+ Mg.stearate+ Lubritab + Talc+ Stearic acid+ PEG 6000	1:1:1:1 :1:1:1: 1:1:1:1 :1	White to Off white crystalline powder			
13	Sucrose+ hypromellose+ Aqua coat ARC+ Ethyl cellulose + Surelease+	1:1:1:1 :1:1:1: 1:1:1:1	White to Off white crystalline powder			

	MCC+ Mg.stearate+ Lubritab + Talc+ Stearic acid+ PEG 6000					

Preparation of Eplerenone sustained release Tablets (MUPS):

Table 7: Composition of Pellet formulations:

Ingredients						
Drug loading	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
Eplerenone	50	50	50	50	50	50
Sugar spheres (#35 - #40)	29	29	28	29	29	29
Aerosil	0.7	0.7	0.7	0.7	0.7	0.7
Sucrose	0	4	4.8	7.05	10.3	7.7
Binder solution						
Sugar	10	5	2	2	2	2
HPMC E5	3	1.5	0.6	0.6	0.6	0.6
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Coating						
Ethyl cellulose	No Coating has been done bcz of the pellets were not good enough (physical properties)	No Coating has been done bcz of the pellets were not good enough (physical properties)	10	7.5	5	0
Surelease			0	0	0	10
Stearic acid (20% of EC)			2	1.5	1	0
PEG 6000 (10% of EC)			1	0.75	0.5	0
Talc			0.9	0.9	0.9	0
IPA			Nil	Nil	Nil	Nil
Purified water			Q.S	Q.S	Q.S	Q.S

Table 8: Composition of Pellet formulations:

Drug loading	Trial 7	Trial 8	Trial 9	Trial 10	Trial 11
Eplerenone	50	50	50	50	50
Sugar spheres (#35 - #40)	29	29	29	29	29

Aerosil	0.7	0.7	0.7	0.7	0.7
Sucrose	10.2	12.7	3.8	7.05	10.3
Binder solution					
Sugar	2	2	2	2	2
HPMC E5	0.6	0.6	0.6	0.6	0.6
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S
Coating					
Surelease	7.5	5	0	0	0
Aqua coat ARC	0	0	10	7.5	5
Stearic acid(20% of EC)	0	0	2	1.5	1
PEG 6000(10% of EC)	0	0	1	0.75	0.5
Talc	0	0	0.9	0.9	0.9
IPA	Nil	Nil	Q.S	Q.S	Q.S
Purified water	Q.S	Q.S	Q.S	Q.S	Q.S

Table 9: Composition of Tablet formulations

Ingredients	F 1	F 2	F 3	F 4
Compression				
Eplerenone Pellets 50% w/w	140.00	140.00	140.00	140.00
MCC pH 102	244.00	234.00	229.00	224.00
Aerosil	2.00	2.00	2.00	2.00
Lubritab	0.00	10.00	15.00	20.00
Magnesium stearate	2.00	2.00	2.00	2.00
Film Coating				
Opadry white	12.00	12.00	12.00	12.00
Purified water	Q.S	Q.S	Q.S	Q.S

The selected manufacturing process for the preparation of Eplerenone Sustained release tablets given below,

DRUG LAYERING

1. **Sifting:**
   Sift Eplerenone & sucrose through #100 in Vibro Sifter and collect in pre-labeled double lined polythene bag in HDPE Containers
2. **Blending:**
   Transfer the sifted materials to Conta blender and blend for about 15 minutes at 12 RPM. After completion of the blending unload the material into pre-labeled double lined polythene bag HDPE Containers

3. **Binder solution preparation:**
   Take the Purified water in SS container. Add Hypromellose, Sucrose (Syrup grade) in purified water under continuous stirring till the clear solution is obtained Filter the clear solution through #200 nylon cloth into a cleaned SS container.
4. **Pellatization:**
   Load the Sugar spheres (#35-#40) in to coating pan and start the coating pan and allow the spheres to rotate. Adjust the spray gun atomization air pressure to 1.0-2.0 kg/sq cm. Start the peristaltic pump and adjust to 5 - 15 RPM. Start spraying the syrup solution by adjusting the gun distance (30-40 cm). Continue spraying till the spheres become wet. Add drug blend in small quantities to the wet pellets in the coating pan until the spheres are free flowing. Adjust the Peristaltic pump 15- 30 RPM and continue the spraying of syrup solution and powder addition till the complete drug blend is exhausted After completion of the process unload the wet drug pellets into trays in equal quantities and keep for drying.
5. **Drying:**
   Load the wet drug coated pellets into Tray drier trays and load the trays into Tray Drier.
   Set the inlet temperature at **45±3°C** and maintain the bed temperature between **42°- 48°**C.

   NOTE: i) Record the drying parameters every one hour.
   ii) Rake the pellets at every 1 hour.
   iii) Drug pellets drying up to Moisture Content should be below 2.0%.
6. **Sifting:**

   Check the integrity of the sieve/screen before and after sifting. Record the observations and action taken in case of damage if any. Sift the dried pellets through #25 and collect 30# retains and passing separately into double lined polythene bag HDPE containers. Sift #25 passing pellets through #30and collect retains and passing separately into double lined polythene bag HDPE containers. The sifted pellets are colleted into HDPE containers lined with double polythene bags. Wear latex hand gloves during operations

COATING PROCESS:

1. **Preparation of coating solution:**
   a) Ethyl Cellulose solution: Pass the Isopropyl Alcohol through #200 Nylon cloths into SS container. Dissolve the in half quantity of Isopropyl Alcohol with continuous stirring. Dissolve the PEG 6000 in purified water with continuous stirring in a separate container. Mix the above prepared Magnesium stearate and PEG 6000

solution to Ethyl Cellulose. Solution with continues stirring for 15 minuties. After stirring, filter the solution through #200 Nylon cloths into separate SS containers.

b) Surelease solution: Add Surelease to purified water with continuous stirring to prepare the dispersion of 15% solid content.
c) Aquacoat ARC: Add Aquacoat ARC to purified water with continuous stirring to prepare the dispersion of 15% solid content.

2. **Coating process:**
   Load the Drug coated pellets into the product bowl and carry out the operation as Per Standard Operating Procedures. Set the inlet temperature to 45°-60°C & maintain the bed temperature between 38°-44°c for Ethyl cellulose coating and 40°-50°c for Surelease and Aquacoat ARC coating by adjusting the Inlet set temperature. Coat the drug pellets by bottom spray Wurster at peristaltic pump rpm of 2 to 20 and atomizing air pressure of 0.5 - 2.0 Kg/cm^2 till the coating solution is completed. After completion of solution, dry the pellets in FBC for about 15 minutes at given bed temperature & Atomization air pressure 2.0kgs/cm^2. After drying, unload the pellets into pre-labeled HDPE containers with double lined polythene bags. If there is any breakage or lumps were observed during the coating, sift the pellets through suitable sieve to remove them.

3. **Sifting:**
   Sift the coated pellets through # 25 and collect # 30 retains and passing separately into double lined Polythene bag HDPE containers. Collect the filled capsules in to IPC lined with virgin double polythene bags. Store the pellets below 25 ° C.

COMPRESSION

Sift all the excipients through the sieve no #40 add the pellets to this dry blend and blend well in the blender for 5 min.

Compress the lubricated blend with the following specifications

Compression specifications:

Table 10:

Description	White colored round shaped tablets
Tooling	12 mm round shape
Hardness	60-75N
Thickness	3.40-4.20mm
Friability	NMT 1% w/w
Uniformity of Weight	± 5% of average weight

FILM COATING

Prepare the film coating solution with opadry white. Add slowly opadry to the water stir well until the uniform dispersion formed. Coat the tablets until the coating weight buildup is reached

Evaluation of Pre-compression Blend

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced.

The various characteristics of blends tested are as given below:

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

$$\mathbf{Tan\ \theta = h/r}$$

Where; θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Angle of repose less than 30^0 shows the free flowing of the material.

Bulk density

Density is defined as weight per unit volume. Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

About 30 g powder blend was introduced into a dry 100 mL cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated using the formula:

$$\mathbf{\rho_b = M / Vo}$$

Where ρ_b = Apparent Bulk Density

M = weight of sample

V = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provided

a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement was less than 2 % and then tapped volume, V_f was measured, to the nearest graduated unit. The tapped density was calculated, in gm per mL, using the formula:

$$\boldsymbol{\rho_{tap} = M / V_f}$$

Where ρ_{tap} = Tapped Density

M = Weight of sample & V_f = Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measure of relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formula:

$$Carr's Index = \left[\frac{\left(\rho_{tap} - \rho_b\right)}{\rho_{tap}}\right] 100$$

Where $\boldsymbol{\rho_b}$ = Bulk Density

$\boldsymbol{\rho_{tap}}$ = Tapped Density

Table 11: Carr's Index Values

S. No.	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Evaluation of pellets

During the drug layering process

i) Size of the pellets

Sift the pellets through specified sieve #25-#30 not more than 10% the pellets retain on the sieve no#25 and not more than 10 % pellets pass through the sieve no #30

ii) Assay

The drug content of the pellets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 100mg contain 50mg and lies within the range of 95% to 105% of the standard amount.

Pellets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 100 mg of Eplerenone was transferred to a 100 mL volumetric flask containing 70 mL of 0.1N HCl. It was shaken by mechanical means for 1h.Then it was filtered through a Whatman filter paper (No. 1) and diluted to 100 mL with 0.1N HCl. From this resulted solution 1 mL was taken, diluted to 50 mL with 0.1N HCl and absorbance was measured at 240 nm.

After coating

i) Size of the pellets

Sift the pellets through specified sieve #25-#30 not more than 10% the pellets retain on the sieve no#25 and not more than 10 % pellets pass through the sieve no #30

ii) Assay

The drug content of the pellets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 100mg pellets contains 50mg and lies within the range of 95% to 105% of the standard amount.

Pellets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 100 mg of Eplerenone was transferred to a 100 mL volumetric flask containing 70 mL of 0.1N HCl. It was shaken by mechanical means for 1h.Then it was filtered through a Whatman filter paper (No. 1) and diluted to 100 mL with 0.1N HCl. From this resulted solution 1 mL was taken, diluted to 50 mL with 0.1N HCl and absorbance was measured at 240 nm.

iii) Dissolution

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type I dissolution apparatus at 50 rpm in 900 mL of 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by HPLC with UV-visible detector at 240 nm.

6.6. Evaluation of Tablets (MUPS)

i) Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

ii) Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

iii) Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were

observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

where W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

iv) Weight Variation Test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100/ W_A$$

As the total tablet weight was 120 mg, according to IP 1996, out of twenty tablets ±7.5 % variation can be allowed for not more than two tablets.

According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

v) Drug Content (Assay)

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 95% to 105% of the standard amount.

Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 100 mg of Eplerenone was transferred to a 100 mL volumetric flask containing 70 mL of 0.1N HCl. It was shaken by mechanical means for 1h.Then it was filtered through a Whatman filter paper (No. 1) and diluted to 100 mL with 0.1N HCl. From this resulted solution 1 mL was taken, diluted to 50 mL with 0.1N HCl and absorbance was measured at 240 nm.

vi) Content uniformity (Assay)

Select not fewer than 30 units, and proceed as follows for the dosage form designated

Assay 10 units individually using assay method has said previously. Calculate the acceptance criteria value by the formula

$$\left|M - \overline{X}\right| + ks$$

X= Mean of individual contents (x_1,x_2,..x n), expressed as a percentage of the label claim

n= Sample size (number of units in asample)

k= Acceptability constant, If n = 10, then k =2.4

k= Acceptability constant, If n = 10, then k =2.0

M value calculation is given in the below table

Table 12

M (case 1) to be applied when T ≤101.5	Reference value	If 98.5% ≤$\overline{X}$ ≤101.5%, then	M = $\overline{X}$ (AV = ks)
		If $\overline{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\overline{X}$ + ks)
		If $\overline{X}$ >101.5%, then	M = 101.5% (AV = $\overline{X}$ – 101.5 + ks)
M (case 2) to be applied when T >101.5	Reference value	If 98.5 ≤$\overline{X}$ ≤T, then	M = $\overline{X}$ (AV = ks)
		If $\overline{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\overline{X}$ + ks)
		If $\overline{X}$ >T, then	M = T% (AV = $\overline{X}$ – T + ks)
Acceptance value (AV)			general formula: $\left\|M - \overline{X}\right\| + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		L1 = 15.0 unless otherwise specified

vii) In -Vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type I dissolution apparatus at 50 rpm in 900 mL of 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by HPLC with UV-visible detector at 240 nm.

viii) Kinetic Analysis of Dissolution Data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou *et al*., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \qquad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - K_1 t / 2.303 \qquad (2)$$

where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \qquad (3)$$

where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t \qquad (4)$$

where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model);
Log cumulative of % drug remaining vs. time (First order kinetic model);
Cumulative % drug release vs. square root of time (Higuchi model);
And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

viii) Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \qquad (5)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table16, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

Table 13: Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
$0.45 < n < 0.89$	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
$n > 0.89$	Super case-II transport

ix) In vitro drug release studies

Dissolution

Apparatus **:** Dissolution test as per USP, apparatus I

Dissolution medium : pH 1.2 buffer for 2 hours and 6.8 phosphate buffer for 10 hrs

Volume (ml) : 900 mL

Rpm : 50

Temperature : 37.5+0.5ºC

Time : 2, 4, 6, 9 and 12hrs

Wavelength (nm) : 240nm

Procedure: Weighed the pellets equivalent to 100 mg of Eplerenone transfer individually to six dissolution bowls having 900ml pH 1.2 buffer equilibrated to 37.0±0.5°C taking care to exclude air bubbles from the surface of the pellets and start apparatus for 2 hrs. then transfer the the pellets after 2 hrs in to 900 mL of 6.8 Phosphate buffer carefully using a filter, follow the same procedure and same parameters continued for this media also.

Samples will be taken for specified time points

HPLC Conditions:

A. Chromatographic conditions

Samples were assayed for Eplerenone using a sensitive HPLC method with UV-detection. Chromatography was performed on A Stainless steel column (inertsil ODS 3 V 250mm, 4.6mm, 5µ ID) 250mm long, 4.6mm internal diameter filled with octadecylsilance chemically bonded with silica gel particles of 5 µm diameter. The mobile-phase consisted of acetonitrile and pH 2.0 buffer (30:70, v/v), The flow rate was 1.5ml/ min. Ultraviolet detection was set at wavelength of 240nm and the column temperature was kept at 40ºC.(Madhusudan Rao Y. et al., 2011)

Preparation of pH 6.8 phosphate buffer : Accurately measured 50 mL of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200mL volumetric flask and 22.4 mL of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 mL with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide or 0.2 M othophosphoric acid.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Preparation of mobile phase:

Mobile phase is a mixed buffer of pH 3.2 (potassium dihydrogen orthophosphate) and organic mixture (Acetonitrile and Methanol in the ratio of 90:10.) (V/V) in the ratio of 50:50 and filtered through 0.45 µ and degassed.

Preparation of acid stage medium:

Dissolve 2.0 g of sodium chloride in 5.7 ml of HCl, and add water to makeup to 1000ml.

Preparation of standard solution (Acid stage):

Weigh accurately about 50 mg of working reference standard of Eplerenone exactly weighed and transfer to 100 ml volumetric flask add 70 ml of diluents, sonicate to dissolve the content and makeup to the mark with diluents. Transfer 2 ml of this solution, transfer into a 50 ml volumetric flask and dilute with buffer (pH1.2) and mix well. Filter the solution through0.45µ membrane filter.

Preparation of sample solution:

Weigh the tablets first and take as accurate as possible to formulation weight of the tablet and transfer individually to six dissolution bowls having 500ml pH 1.2 buffer equilibrated to 37.0±0.5°C taking care to exclude air bubbles from the surface of the tablet and run apparatus. After completion of 2 hrs with drawn 15ml of sample solution from each bowl and filter through 0.45µ filter. Samples will be taken for specified time points

Procedure:

Separately inject 100 µl of dissolution media, five replicate injections of standard solution and single injection of sample solution in to the chromatograph, record the chromatograms and measure the peak responses**.**

System suitability:

Chromatograph the standard preparation and sample preparation record the peak responses. The relative standard deviations for five replicate standard solution injections is not more than 2.0%.

The tailing factor of peak should be not more than 2.0 and the theoretical plates of peak should be not less than 2000.

Calculation:

Calculate the amount of drug substance released in pH 1.2 buffers in specified time intervals by using this following formula.

$$\frac{At}{As} \times \frac{Ws}{100} \times \frac{2}{50} \times \frac{2}{50} \times \frac{500}{1} \times \frac{P}{Lable claim \in mg}$$

Where,

At= The area of the Eplerenone peak in sample solution.

A_S= The average area of the Eplerenone peak in sample standard solution.

Ws= Weight of the Eplerenone working standard taken in mg.

Wt= Weight of sample in mg.

P= Potency of the Eplerenone working standard.

Preparation of 0.5N Hydrochloric acid solution:

Mix 41.5 ml of Hydrochloric acid (35%) in 1000ml of water.

Preparation of standard solution (buffer stage):

Weigh accurately about 50 mg of working reference standard of Eplerenone exactly weighed and transfer to 100 ml volumetric flask add 70 ml of diluents, sonicate to dissolve the content and makeup to the mark with diluents. Transfer 2 ml of this solution, transfer into a 50 ml volumetric flask and dilute with buffer (pH 6.8) and mix well. Filter the solution through 0.45 µ membrane filter.

Transfer 2 ml of this solution, transfer into a 50 ml volumetric flask and dilute with buffer (pH 6.8) and mix well. Filter the solution through 0.45 µ membrane filter.

Transfer the 10 ml of above solution into a test tube contains 1.0 ml of 0.5 N HCl and mix well. Filter the solution through 0.45µ nylon filter.

FTIR Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION

Construction of Standard Graph of Eplerenone

Table 14:Standard graph in pH 6.8 Phosphate buffer

Concentration (µg/ml)	Peak Area
0	0
80	106795
90	119831
100	128817
110	141632
120	154964

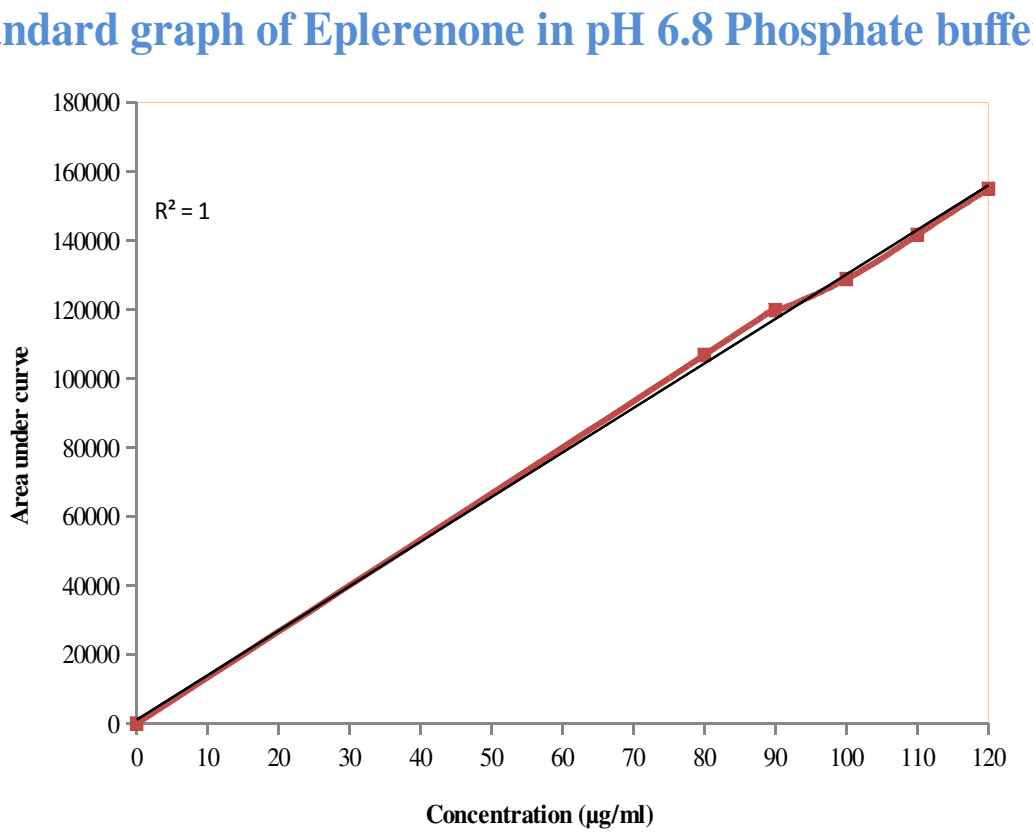


Fig 7: Standard graph in pH 6.8 Phosphate buffer

Table 15: Standard graph in 0.1N HCl

Concentration (µg/ml)	Peak Area
0	0
80	95968

90	109458
100	112856
110	138562
120	145268

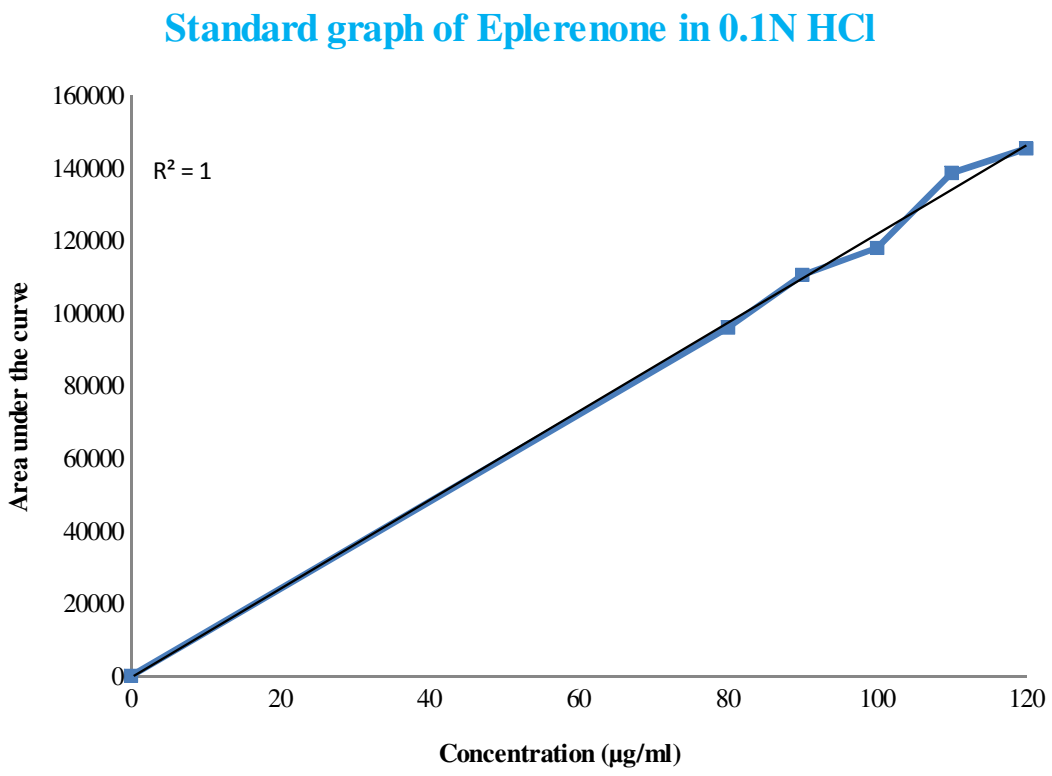


Fig 8: Standard graph in 0.1N HCl

Table 16: Preformulation Study results

S.No	Drug excipients blend	Ratio	Condition: 40°C ± 2°C / 75% ± 5%			
			Initial	1 week	2 weeks	4 weeks

1	Eplerenone + sucrose	1:1	White to Off white crystalline powder	*	*	*
2	Eplerenone + hypromellose	1:1	White to Off white powder	*	*	*
3	Eplerenone +Aqua coat ARC	1:1	White to Off white powder	*	*	*
4	Eplerenone + Ethyl cellulose	1:1	White to Off white powder	*	*	*
5	Eplerenone + Surelease	1:1	White to Off white powder	*	*	*
6	Eplerenone + MCC	1:1	White to Off white powder	*	*	*
7	Eplerenone + Mg.stearate.	1:1	White to Off white powder	*	*	*
8	Eplerenone + Lubritab	1:1	White to Off white powder	*	*	*
9	Eplerenone + Talc	1:1	White to Off white powder	*	*	*
10	Eplerenone + Stearic acid	1:1	White to Off white powder	*	*	*
11	Eplerenone + PEG 6000	1:1	White to Off white powder	*	*	*
12	Eplerenone+ sucrose+ hypromellose+ Aqua coat ARC+ Ethyl cellulose + Surelease+MCC+Mg.stearate+ Lubritab + Talc+ Stearic acid+ PEG 6000	1:1:1:1:1:1:1:1:1:1:1	White to Off white crystalline powder	*	*	*
13	Sucrose+ hypromellose+ Aqua coat ARC+ Ethyl cellulose + Surelease+ MCC+Mg.stearate+ Lubritab + Talc+ Stearic acid+ PEG 6000	1:1:1:1:1:1:1:1:1:1:1	White to Off white crystalline powder	*	*	*

Note: * indicates there is no change in the physical appearance of the blend

Table 17: Assay results of the pellet formulations

S.No	Trial no	Assay (95%-105%)
1.	Trial 3	102.3
2.	Trial 4	99.6
3.	Trial 5	100.6
4.	Trial 6	102.5
5.	Trial 7	99.6
6.	Trial 8	101.0
7.	Trial 9	101.4
8.	Trial 10	100.8
9.	Trial 11	101.1

Apparatus: Basket, **Medium:** pH 1.2 acid buffer for 2hrs & pH 6.8 phosphate buffer for 10 hrs, **Volume:** 900ml, **RPM:** 50

Table 18: Comparative Drug release profiles of the trial batches from Trial 3 to Trial 6

	Trial 3	Trial 4	Trial 5	Trial 6
Dissolution: HPLC				
2hr (NMT 25%)	0.6	3.9	7.1	4
4hr (20-40%)	16.5	20.1	23.6	20.2
6hr (40-60%)	33.5	42.1	50.6	36.7
9hr (60-80%)	55.2	62.1	68.9	60.4
12hr (NLT 85%)	67.8	80.0	92.1	73.5

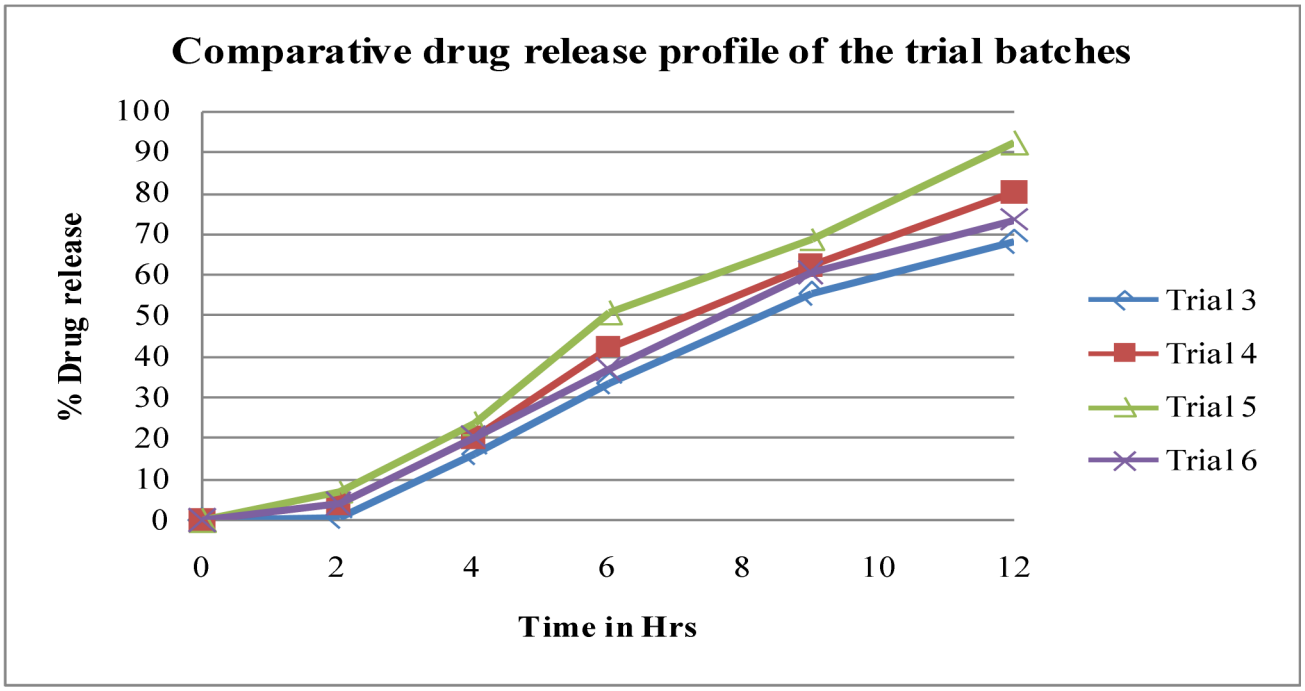


Fig 9: Comparative Drug release profiles of the trial batches from Trial 3 to Trial 6

Table19: Comparative Drug release profiles of the trial batches from Trial 7 to Trial 11

	Trial 7	Trial 8	Trial 9	Trial 10	Trial 11
Dissolution: HPLC					
2hr (NMT 25%)	2.2	12	2	5.8	9.4

4hr (20-40%)	23.9	28.2	17.4	22.0	25.4
6hr (40-60%)	46.1	55.1	35	44.0	52.9
9hr (60-80%)	67	74.6	57.4	64.2	71.2
12hr (NLT 85%)	85.3	96	69.2	82.2	94.4

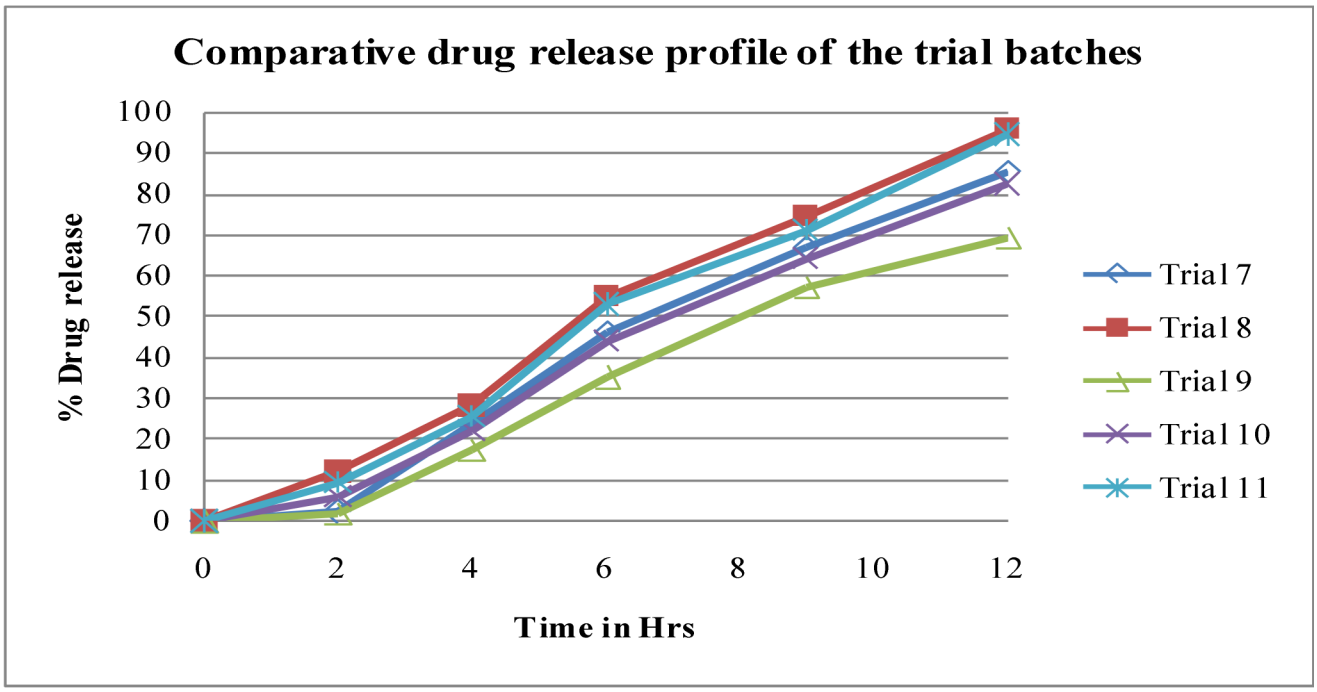


Fig 10: Comparative Drug release profiles of the trial batches from Trial 7 to Trial 11

Trial 1

In the first trial we have planned on the basis of literature to get the good drug layered pellets using coating pan with powder dusting process. The prepared pellets found to be inconsistent in shape and size. Since the pellets were not good to proceed further we have not performed coating for this batch.

Trial 2

In order to get uniform size and shaped spheres we have decided to reduce the concentration of binder (both Sugar and HPMC) and compensated with the sugar powder addition as diluent in this trial. Even though there is an improvement in the size and shape of the pellets it was not found to be meeting our requirement as our target was to get the pellets with uniform shape and

size without any doublets or triplets in order to get the coating efficiency on sustained release coating part.

Trial 3

Hence it was further decided to reduce the concentration of binder (both sugar and HPMC) and compensate with sugar powder as diluent. The prepared pellets were found to be good in shape and size meeting our target. Further we have coated the prepared pellets using ethyl cellulose at different concentration (10, 7.5, 5%) trial 3, 4, 5 respectively. Ethyl cellulose at 5% concentration gave the dissolution profile meeting our target specification. Hence it was concluded that 5% concentration of Ethyl cellulose would be the ideal concentration.

Trial 6, 7 & 8

Since our objective was to study the different cellulosic polymers effect trial 6, 7 & 8 were prepared using Surelease polymer at 10%, 7.5% & 5% respectively. Surelease at 7.5% level was meeting the specification. However the release pattern was on the lower side. Surelease at 5% level found to be satisfactorily meeting our targeted specification.

Trial 9, 10 & 11

Trial 9,10 & 11 were prepared using Aquacoat ARC at 10%, 7.5% & 5% concentration and based on the results all three trails the batch with 7.5% coating was meeting the specification. However the release pattern was on the lower side. Trial 11 which contain 5% polymer showed good release profile matching to the targeted specification.

From the above studies the formulation which showed the release profile matching to the specification (Trial 5, 7, 8, 10 & 11) has been taken for conducting alcohol resistant study. Since concomitant consumption of alcoholic beverages along with the products might be expected to have the potential to induce dose dumping. Due to concerns of dose dumping from this drug product when taken with alcohol, we have studied additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus I @ 50 rpm, with and without the alcohol

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours.

Table 20: Comparative Drug release profiles of the selected trial batches in 0.1N HCl without alcohol

Without alcohol					
	Trial 5	Trial 7	Trial 8	Trial 10	Trial 11
Time in min					
15min	0.9	0.6	1.4	0.7	1.1
30 min	1.8	1.1	2.9	1.4	2.3
45 min	2.7	1.7	4.4	2.2	3.1
60 min	3.6	2.2	5.9	2.7	4.3
75 min	4.5	2.7	7.4	3.5	5.3
90 min	5.5	3.3	8.9	4	6.5
105 min	6.4	3.8	10.4	4.8	7.8
120 min	7.3	4.3	11.8	6	8.9

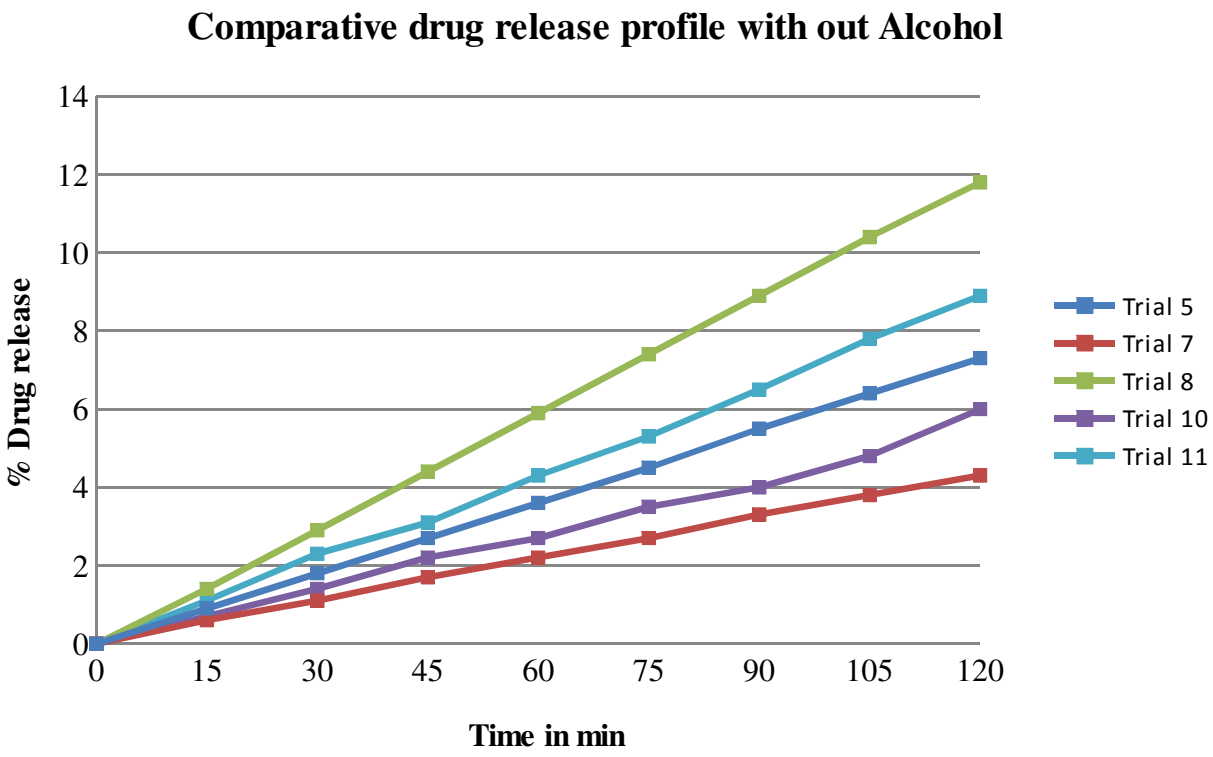


Fig 11: Comparative Drug release profiles of the selected trial batches in 0.1N HCl without alcohol

Test 2: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Table 21: Comparative Drug release profiles of the selected trial batches in 0.1N HCl with 20 % of alcohol

With 20% alcohol					
	Trial 5	Trial 7	Trial 8	Trial 10	Trial 11
Time in min					
15min	5.6	3.5	4.8	1.5	2.2
30 min	11.2	7.1	10.1	2.7	4.3
45 min	16.7	10.3	14.3	3.9	6.3
60 min	22.4	14.2	20.5	5.1	8.5
75 min	28.4	16.9	25.4	6.4	11.4
90 min	34.2	20.8	29.5	7.4	13.1
105 min	41.2	25.3	36.1	8.8	15.6
120 min	45.3	28.2	41.1	10	18

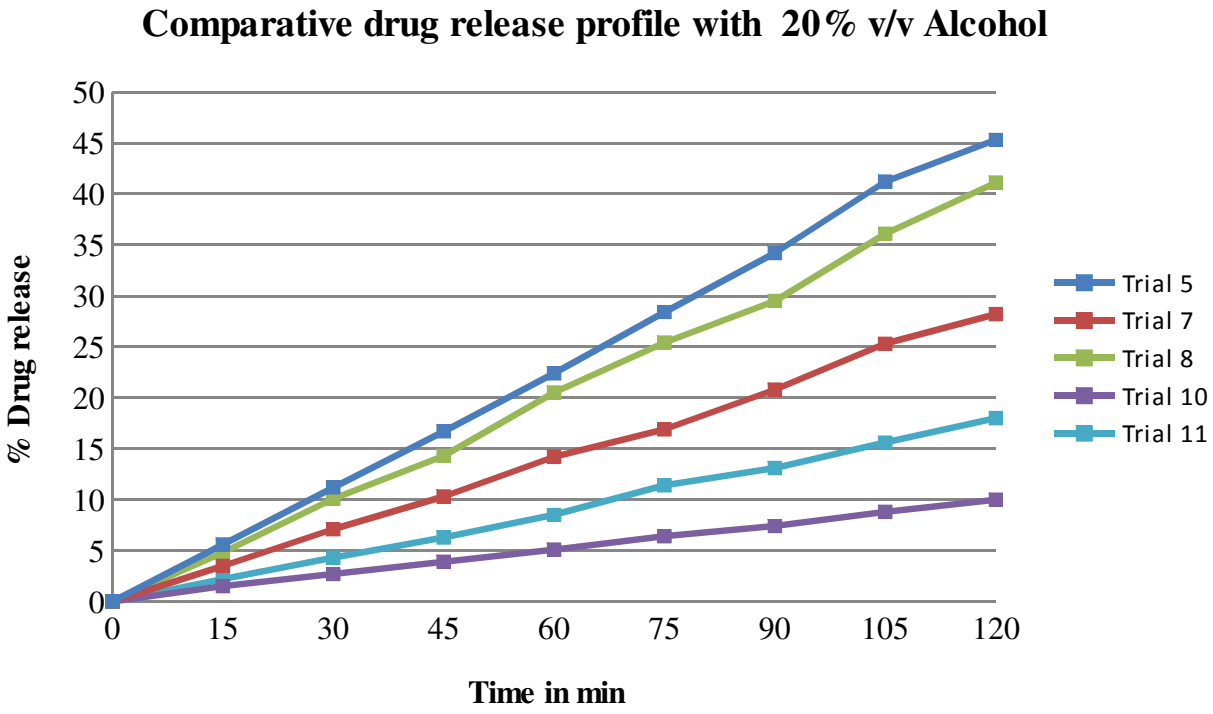


Fig 12: Comparative Drug release profiles of the selected trial batches in 0.1N HCl with 20 % of alcohol

Test 3: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours.

Table 22: Comparative Drug release profiles of the selected trial batches in 0.1N HCl with 40 % of alcohol

With 40% alcohol					
	Trial 5	Trial 7	Trial 8	Trial 10	Trial 11
Time in min					
15min	7.4	4.4	5.6	1.7	2.1
30 min	15.1	8.5	11.3	3	4.5
45 min	22.1	12.2	16.5	4.1	6.4
60 min	31.2	17.8	23.2	5.7	8.8
75 min	38.5	21.4	28.5	6.4	11.5
90 min	45.6	25.3	33.5	7.8	14
105 min	52.3	30.4	40.3	10.2	16.3

120 min	60.2	35.4	45.3	12	21.3

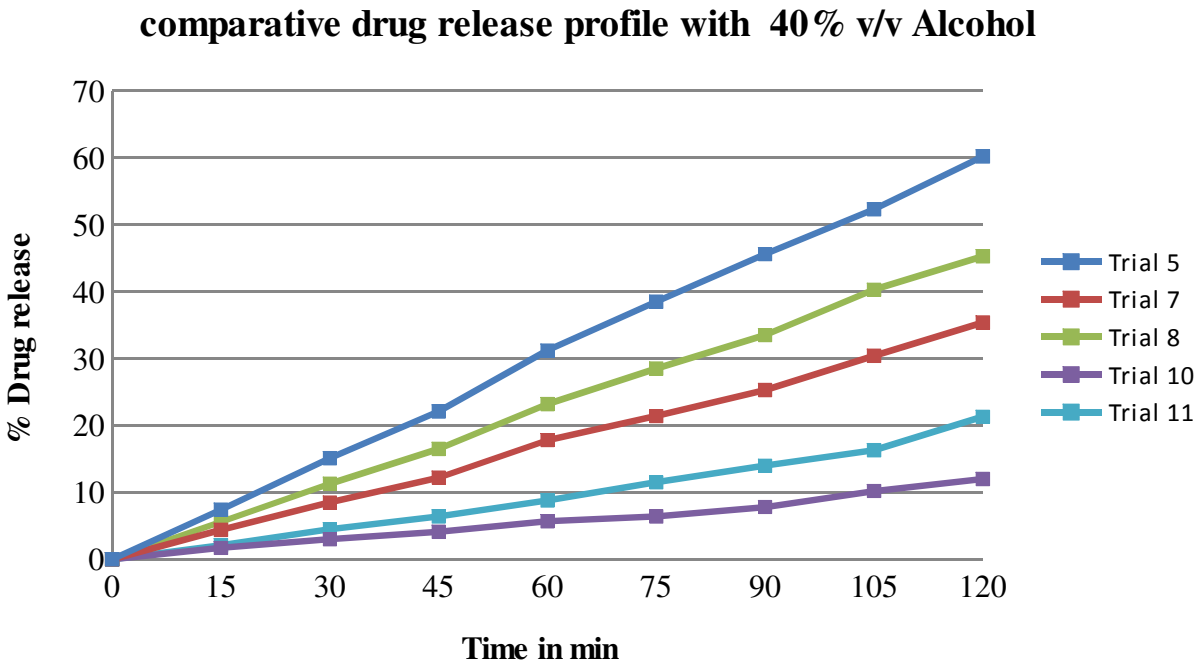


Fig 13: Comparative Drug release profiles of the selected trial batches in 0.1N HCl with 40 % of alcohol

From the above study formulation 10 found to be more ideal pellets formulation for next study. Hence the pellets prepared according to trial 10 were further compressed in to tablets using different concentration of cushioning agent Lubritab. The prepared tablet formulations were analyzed for content uniformity and the formulation F4 had shown good content uniformity with the L1 value less than 15 (n=10).

Table 23

s.no	Content uniformity L1 value	Assay	Hardness	Disintegration
F1	43	97.7	40-50 N	15-20 sec
F2	25	105.6	40-50 N	5 min
F3	19	102.3	40-50 N	7 min
F4	7.9	100.8	40-50 N	10 min

Table 24: Dissolution profile of the tablet formulation i.e., F4

	F4
Dissolution: HPLC	
0	0
2hr (NMT 25%)	8.5
4hr (20-40%)	23.8
6hr (40-60%)	54.8
9hr (60-80%)	75.6
12hr (NLT 85%)	92.4

FTIR Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

Fig 14 : Eplerenone API FTIR graph

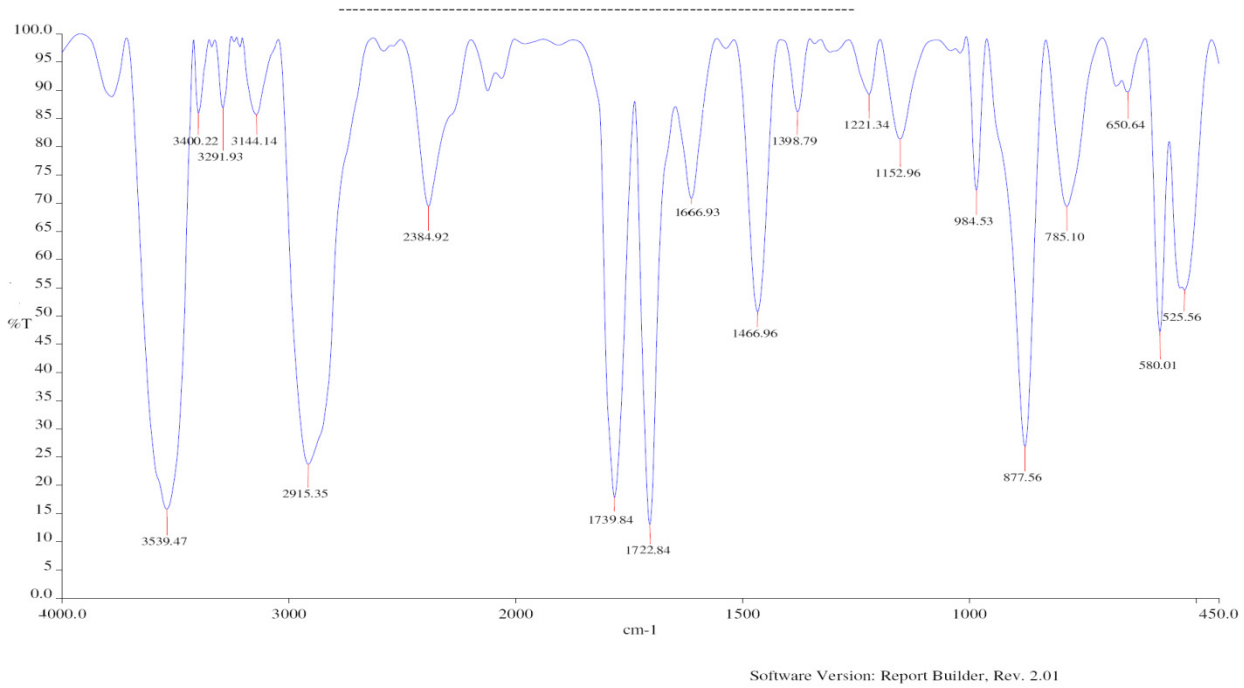


Fig 15 :Eplerenone optimized formulation (F4) FTIR graph

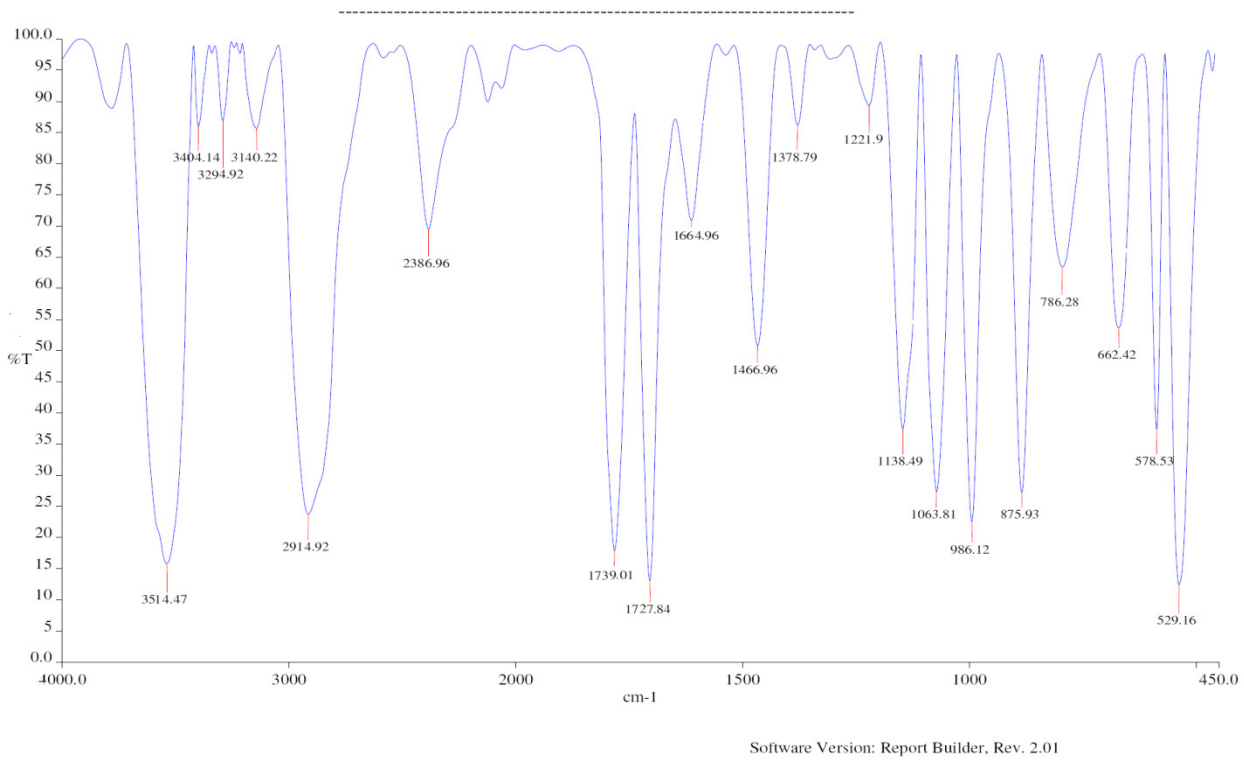
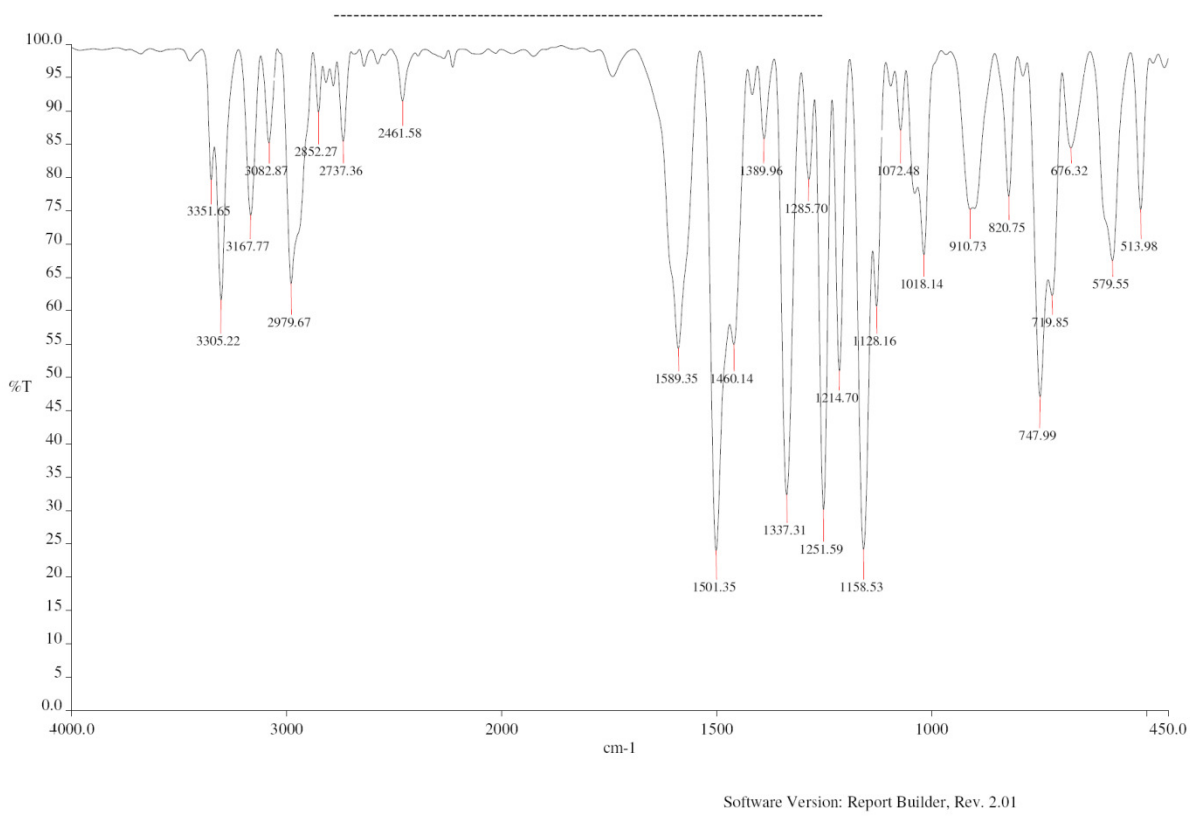


Fig 16: Eplerenone formulation Placebo FTIR graph



Eplerenone has an ester carbonyl stretch of approximately 1739 cm^{-1} methyl ethyl ketone solvate have the corresponding stretch at approximately 1724 and 1722 cm^{-1}, respectively. The ester carbonyl stretch occurs at approximately 1727 cm^{-1} the stretch of the ester of the conjugated ketone in the A-steroid ring shifts from approximately 1664-1667 cm^{-1}. The functional group responsible peaks were appearing in the API, Formulation FTIR graphs, so that we concluded that there is no change in the activity of the Eplerenone API.

Kinetic study the Final formulation

Kinetic profiles were calculated for the final formulation and the data presented below,

Zero	Higuchi	Peppas	n value	First	Hixson Crowell
0.938991	0.859135	0.97358	0.599	0.988	0.987

The above data shows that the formulation is following the first order kinetic and erosion mechanism with non-Fickian (Anomalous) release

Graphical representation of the kinetic study results

Fig 17: Zero order release kinetics of the optimized formulation

Fig 18 : First order release kinetics of the optimized formulation

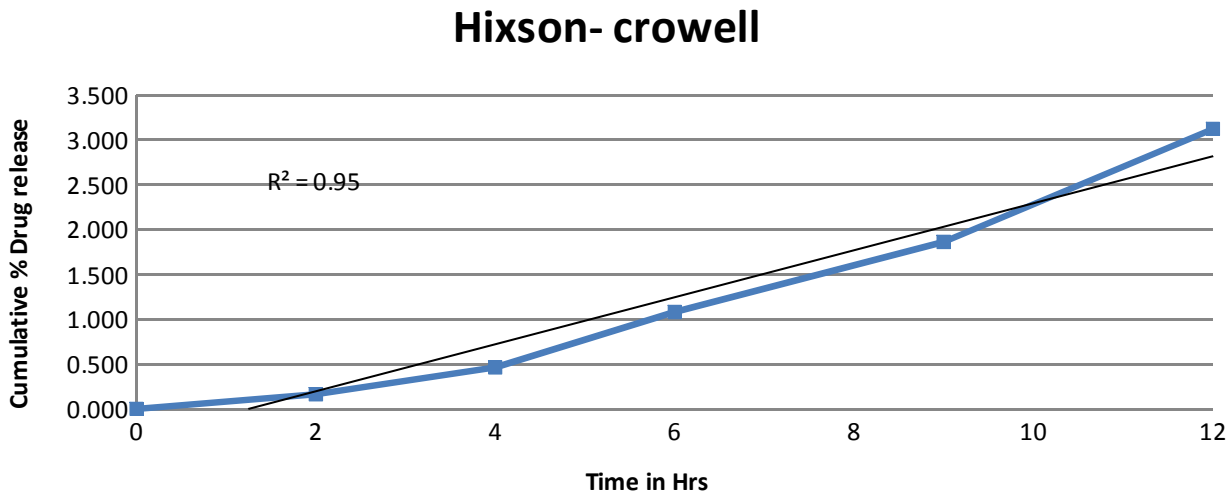


Fig 19: Hixson crowell model release kinetics of the optimized formulation

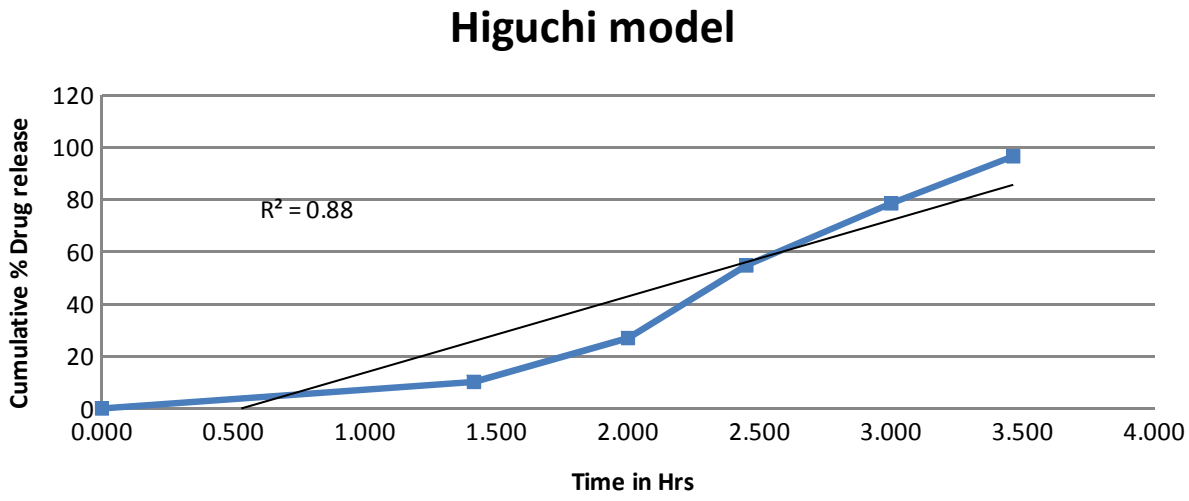


Fig 20: Higuchi model release kinetics of the optimized formulation

Summary and conclusion

Eplerenone is a highly selective aldosterone receptor antagonist (SARA) to effectively block aldosterone at receptor sites in body tissues (Spertus J.A.et al., 2002). Aldosterone plays an important role in chronic heart failure, even when other rennin–angiotensin–aldosterone system (RAAS)-inhibiting agents are used (Stier C.T, 2002, Staessen S.,1981). Eplerenone is used for treatment of hypertension and heart failure. Eplerenone is a steroid nucleus- based antimineral corticoid that is chemically and enzymatically interconvertible to an open lactone ring form. It is rapidly and nearly completely absorbed from the gastrointestinal tract (GIT) following oral ingestion, showing 69% bioavailability. Detectable plasma levels occur within one-half hour and peak plasma levels occur in about 1-2 hours. A plasma half-life is 4 hours. In the treatment of hypertension the usual initial dosage is 25 mg once daily, whether used alone or added to diuretic therapy. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 50-100 mg per day.

Although conventional tablets of Epelerenone are available in the market commercially, no study has been done so far for preparing the Epelerenone sustained-release tablets. To improve the oral bioavailability and to reduce the dose dependent toxicity there is a need for the development of sustained-release formulations (Gregory et al., 2004; Mandana et al., 2000)

The intention of present study was to adopt a novel approach in designing and characterize twice-daily sustained-release (MUPS) tablets of Eplerenone, using Cellulose polymers as release modifiers in the form of matrix layer spherical particles in the tablets. Multi unit particles in the tablets containing cellulose polymers like ethyl cellulose, Surelease and Aqua coat ARC, were prepared by drug layering and coating those particles in FBC with suspension layering technique using Hypromellose as a binder solution and the tabletting process was optimized for formation of uniform tablets in all respects.

In this study Eplerenone pellets are prepared using powder layering technique and coated using Fluid bed processor for the strength of 50% to achieve the final tablet formulation of 70mg dose. Eleven formulations of sustained release pellets are prepared by using different cellulosic polymers varying in their concentration (10%, 7.5% & 5%). Ethyl cellulose at 5% level gave the dissolution profile meeting the requirement. Further Surelease/ Aqua coat at 7.5% concentration gave the dissolution profile matching to the specification with the release at lower side of the

specification. At 5% level both Surelease and Aqua coat ARC gave acceptable dissolution profile matching to the specification. Since concomitant consumption of alcoholic beverages along with the products might be expected to have the potential to induce dose dumping. Due to concerns of dose dumping from this drug product when taken with alcohol, we have studied additional dissolution testing using various concentrations of ethanol in the dissolution medium for the batches which showed match in the dissolution profile. Based on the study it is further concluded that the pellets prepared using Aqua coat ARC at 7.5% concentration (Trial 10) was more identical and not showed any significant effect in the presence of alcohol. Further the final formulation trail 10 compressed in to tablets for 70mg dose and from the study it is concluded that the concentration of 10mg Lubritab found to be meeting in all respect. The prepared formulation studied for stability and the results were found to be satisfactory after one month accelerated condition (40ºC/ 75% RH).

The Optimized formulation shall be utilized for the development and other studies like bioequivalence for the successful launching of this product.

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