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(RESEARCH ARTICLE)

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A Research on: Formulation and Evaluation of Sustained Release matrix Tablets

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Abstract

The study focused on developing a sustained release matrix tablet of Mosapride Citrate to achieve prolonged therapeutic effects, reduce side effects, and improve patient compliance by minimizing dosing frequency. Mosapride Citrate, with a half-life of 2-3 hours, was used as a model drug. Matrix tablets were prepared using different viscosity grades of Eudragit through direct compression and evaluated. Results indicated that polymer matrices alone were insufficient for 8-hour sustained release, whereas a combination of Eudragit RS 100, Eudragit RL 100, and Eudragit E 100 provided effective sustained release, primarily through diffusion. The study also aimed to identify and rectify manufacturing defects. Mosapride Citrate tablets displayed good dissolution and tableting behavior. Preformulation studies evaluated physical properties like bulk and tapped density, angle of repose, compressibility, and Housner's ratio. Tablet formulations underwent evaluations for thickness, hardness, friability, weight variation, assay, dissolution, and stability, with optimized formulations compared to marketed samples.

Keywords: Sustained Release; Mosapride; Matrix System; Eudragit; Long Acting

1. Introduction

The sustained release drug delivery consists of the utility of physical and polymer chemistry. Those polymers slowly release the drug in bio-system and maintain drug blood stage inside therapeutic range for longer length. Some of the products signify the drug permeation through the precise biological membrane and any first pass metabolic consequences previous to the access of drug into systemic circulation. The fact that the absorption and release rate of the drug from the dosage form, is one of the exciting and maximum latest improvement in pharmaceutical discipline [1].

There are numerous definitions of sustained release but the only definition is "Any drug or dosage form or remedy that prolongs the healing activity of drug''. The general goal is that, as soon as the drug-carrier material has been injected or otherwise implanted or taken orally into the body, the drug is released at a predetermined price for some favored time frame. Controlled release generation is tremendously new discipline and hence, studies on this field has been extremely fertile and has produced many discoveries.

Several terms had been used to explain the diverse kinds and modes of action meant to offer long length of drug activity. Sadly, the phrases have been implemented loosely and are interchanged perpetually so that nowadays there's no steady nomenclature for the extended action products available in the market. Several nomenclatures had been applied synonymously to explain sustained launch medicinal drugs. Some of those are: continuous release (CR), depot release (DR), slow release (SR), long acting (la), durable (LL), long term release (LTR), extended action (PA), managed release (CR), extended release (ER), gradual release (GR) etc. However, the recent literature survey suggests the ones as on today the most widely used terms are sustained release and controlled release. [1]

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1.1. Rationale of Sustained and Controlled Drug Delivery [2,3]

1.1.1. Controlled release drugs delivery system

The fundamental rational for controlled drug delivery is to modify the pharmacokinetic and pharmacodynamic of pharmacological energetic moieties by way of the usage of novel drug delivery gadget or by using modifying the molecular structure and pharmacological parameters inherent inside the selected route of administration. It is ideal that the duration of drug action turns into greater a needing belongings of rate controlled dosage form and less or in no way a property of the drug molecule inherent kinetics properties. Thus optionally available design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamic of the medication.

1.1.2. Sustained Drug delivery system

Over the past 30 years, because the fee and hardship involved in marketing, new entities have expanded with concomitant popularity of the therapeutics advantages of controlled drug delivery, more attention has been targeted on improvement of sustained or controlled drug delivery system. Sustained release technology is rather new field and for this reason, studies within the field has been extremely fertile and has produced many discoveries. With many drugs, the primary aim is to acquire a consistent state blood level this is therapeutically effective and non-poisonous for an prolonged time period. The design of right dosage form is an important detail to accomplish this purpose. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are time period used to identify drug delivery device which can be designed to achieve extended healing effect by means of continuously liberating medicinal drug over an prolonged period of time after administration of a unit dose.

The blood stage oscillation traits of multiple dosing form of traditional dosage form is decreased, because extra even blood stage is maintained inside the design of sustained release dosage form. The overall quantity of drug administered, accordingly maximum availability with a minimum dose. Similarly, the protection margin of high efficiency drug can be expanded and the occurrence of each local and systemic adverse consequences can be reduced in sensitive sufferers. General, multiplied management of sustained launch dosage form gives increased reliability.

Oral extended release drug transport device becomes a completely promising approach for those drugs that are given orally but having the shorter half of-lifestyles and excessive dosing frequency. Prolonged-launch drug-delivery device reduces the dosing frequency of certain tablets by means of liberating the drug slowly over an extended period of time Matrix tablets can be formulated by way of moist granulation or direct compression methods by dispersing strong 7particles inside a porous matrix formed of hydrophilic and hydrophobic polymers. The use of various classes of polymers in controlling the discharge of drugs has come to be the maximum crucial aspect inside the components of matrix tablets. The drug release in matrix drug delivery structures by way of both dissolution- characteristic of the drug for the sustained release dosage form are drug should have a shorter half of-lifestyles as drug with a longer half-lifestyles are inherently long controlled in addition to diffusion controlled mechanisms.

Not all the medication are the perfect candidates for the sustained release dosage form. Perfect characteristic of the drug for the sustained release dosage form are:

- Drug should have a shorter half of lifestyles are inherently long acting drugs.
- Drug should be absorbed form large portion of gastrointestinal tract, when you consider that absorption have to occur through the gut.
- Drug should be having a great solubility profile to be a very good candidate for sustained launch dosage form.
- Dose of the drug have to now not be too large, as a larger dose is to be included into sustained release dosage form.

2. Classification: [7,8,9]

- Diffusion sustained system
- Reservoir type
- Matrix type
- Dissolution sustained system
    - Reservoir type
    - Matrix type
- Methods using Ion-exchange

- Methods using osmotic pressure
- pH-independent formulation
- Altered density formulation

2.1. Diffusion Sustained System

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Basically, diffusion process shows the movement of drug molecules from a region of a higher concentration to one of the lower concentration. The flux of the drug J (in amount/area–time), across a membrane in the direction of decreasing concentration is given by Fick's law.

J= -Ddc

dxL

D = diffusion coefficient in area/time

Dc/dx = change of concentration "c" with distance "x"

2.1.1. Reservoirs type

In the system, water insoluble polymeric material encases a core of drug. The drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Drug core surrounded by polymer membrane that controls release rate [27].

- **Advantages**
- Zero-order delivery is possible.
- Release rate variable with polymer type.
- **Disadvantages**
- System must be physically removed from implants site.
- Difficult to deliver high molecular weight compound.
- Potential toxicity, if the system fails.
    - **Matrix types**

In a matrix system, the drug is dispersed as solid particles within a porous matrix formed of a water-insoluble polymer. The drug particles located at the surface of the release unit will be dissolved first and drug release rapidly.

    - **Advantages**
- Easier to produce than reservoir devices
- Can deliver high molecular weight compounds.
    - **Disadvantages**
- Cannot obtain zero-order release
- Removal of remaining matrix is necessary for implanted system.

2.2. Dissolution Sustained System

A drug with a slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. SR preparation of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include preparing appropriate salts or derivatives, coating the drugs with slowly dissolving materials. [30]

2.2.1. Reservoir type

The drug is coated with a given thickness coating, which is slowly dissolved in the contents of GI tract. By alternating layers of the drug with the rate controlling coats, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug.

2.2.2. Matrix type

The more common type of dissolution sustained dosage form as it can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

2.3. Methods Using Ion-Exchange [8]

Ion-exchange systems generally use resins composed of water-insoluble cross-linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups. For the better release in this system is to coat the ion-exchange resin with hydrophobic rate-limiting polymer.

- **Advantages**
- Suitable for the drugs that are highly susceptible to degradation by enzymatic processes.
- **Disadvantages**
- The release rate is proportional to the concentration of the ions present in the area of administration, and the release rate of a drug can be affected by variability in diet, water intake, and individual intestinal content.

2.3.1. SR Formulation Based On Osmotic Pressure [6]

In this system, the flow of liquid into the release unit driven by a difference in osmotic pressure between the inside and the outside of the release unit is used as the release-controlling process. In osmosis SR system, the following sequences of steps are involved in the release process:

- Osmotic transport of liquid into the release unit.
- Dissolution of the drug within the release unit.
- Convection transport of a saturated drug solution by pumping of the solution through a single orifice or through pores in the semi-permeable membrane.
  - Description [9]
  - Drug surrounded by semi-permeable membrane and release governed by osmotic pressure.
  - Advantages [9]
  - Zero-order release obtainable.
  - Reformulation not required for different drugs.
  - The release of a drug independent of the environment of the system.
  - Disadvantages [9]
  - The system can be much more expensive than the conventional counterpart.
  - Quality control more extensive than most conventional tablets.
  - Independent Formulation[27]

Since most drugs are either weak acids or weak bases, the release from SR formulations is pH-dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid, phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH-independent drug release. A buffered SR formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with GI fluid permeable film forming a polymer.

2.3.2. Altered Density Formulations [6,11]

It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of DDS in the GI tract.

Criteria to be met by Drug Proposed to be Formulated in Sustained Release Dosage Forms. [5,13]

- Desirable half-life.
- Small dose
- Desirable absorption and solubility characteristics.
- Desirable absorption window.
- First past clearance.
- **Desirable half-life:** The half-life of a drug is an index of its residence time in the body. If the drug has a short half life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug.
- **High therapeutic index:** Drugs with low therapeutic index are unsuitable for incorporation in sustained release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities eg. Digitoxin.
- **Small dose:** If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for sustained release is seriously undetermined.

- **Desirable absorption and solubility characteristics:** Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such Compounds into sustained release formulations.
- **Desirable absorption window:** Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the 'absorption window'. Drugs exhibiting an Absorption window like fluorouracil, thiazide diuretics, if formulated as sustained release dosage forms are unsuitable.
- **First pass clearance:**As discussed earlier in disadvantages of sustained delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in sustained release forms.

Potential Advantage Of Sustained Release Dosage Form:

- Avoid patient's compliance trouble because of reduced frequency of dosing.
- Hire a less total drug.
- Put off local or systemic side outcomes.
- Limit drug accumulation with chronic dosing.
- Acquired much less capability of reduction in drug activity with chronic use.
- Stepped forward efficiency in treatment.
- Treatment or manage situation more promptly.
- Improved control of circumstance i.e. Reduced fluctuation in drug level.
- Improved bioavailability of a few drugs.
- Make a use of special effects, e.g sustained release thing for comfort of arthritis with the aid of economy.

Principle of Sustained Release Drug Delivery [18]

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme. The absorption pool represents a solution of the drug at the site of absorption, and the term Kr, Ka and Ke are first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. Alternatively speaking the absorption of drug across a biological membrane is the rate-limiting step. For non immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. Essentially, the absorptive phase of the kinetic scheme become insignificant compared to the drug release phase. It means that the drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

Kr° = Rate In = Rate Out = Ke Cd Vd

Where,

Kr°: Zero-order rate constant for drug release-Amount/time
Ke: First-order rate constant for overall drug elimination-time-1
Cd: Desired drug level in the body – Amount/volume, and
Vd: Volume space in which the drug is distributed-Liter

Physicochemical Factors[4, 8,12]

- Aqueous solubility
- Partition coefficient (P [O/W])
- Drug pKa and ionization at physiological pH
- Drug stability
- Molecular weight and diffusivity
- Protein binding
- Dose size.

MATRIX system [5,18,19]

The matrix system is most customarily used for a drug-controlled release from a pharmaceutical dosage form. Many of the innumerable method utilized in controlled release drug from pharmaceutical dosage form, the matrix system is the maximum often carried out; it's release system for put off and control of the release of the drug this is dissolved or dispersed in a resistant helps to disintegration. To outline matrix, it is vital to recognise the characters that differentiate it from different controlled release dosage forms. As a result the subsequent must be taken into consideration:

- The chemical nature of support (generally, the support are formed by way of polymeric net)
- The physical state of drug (dispersed below molecular or particulate form or both)
- The matrix shape and alteration in quantity as a characteristic of time.
- The direction of management (oral administration stays the maximum broadly used but other route are adaptable)
- The release kinetic model.

Advantages of Matrix Tablet:

- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.

Disadvantages Of Matrix Tablet:

The rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusion resistance and a decrease in effective area at the diffusion front.

Classification of matrix tablets [14]

Hydrophobic Matrices (Plastic matrices): The idea of the usage of hydrophobic or inert substances as matrix materials became first introduced in 1959. In this method of acquiring sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer after which compressed in to a tablet. Sustained release is produced due to the reality that the dissolving drug has diffused

Via a community of channels that exist between compacted polymer particles. Examples of substances which have been used as inert hydrophobic matrices consist of polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.

Lipid Matrices: Those matrices prepared by means of the lipid waxes and related substances. Drug release from such matrices takes place through each pore diffusion and erosion. Release characteristics are consequently greater sensitive to digestive fluid composition than to absolutely insoluble polymer matrix. Carnauba wax in mixture with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release system.

Hydrophilic Matrices: Hydrophilic polymer matrix systems are extensively utilized in oral controlled drug delivery because of their flexibility to attain a suitable drug release profile, cost effectiveness, and large regulatory recognition.

Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxy ethylcellulose; Hydroxy propylmethylcellulose (EUDRAGIT) 25, 100, 4000 and 15000cPs; and Sodium carboxy methylcellulose.

Non cellulose natural or semisynthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and changed starches.

Polymers of acrylic acid: Carbopol-934, the most used range.

Polymers Used In Matrix Tablet:

- Hydrogels:Cross-linked polyvinyl alcohol (PVA), Cross-linked polyviny pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)

- Soluble polymers: Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (EUDRAGIT)
- Biodegradable polymers:Polylactic acid (PLA), Polyglycolic acid (PGA)
- Non-biodegradable polymers:Polyethylene vinyl acetate (PVA), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)
- Mucoadhesive polymers: Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin
- Natural gums:Xanthan gum, Guar gum, Karaya gum

Factors Influencing the Drug Release from Matrix:

- Choice of matrix material.
- Amount of drug incorporated in the matrix.
- Viscosity of the hydrophilic material in aqueous system at a fixed concentration.
- Tablet hardness, porosity and density variation.
- Entrapped air in tablets.
- Tablet shape and size.
- Drug particle size.
- Solubility of drug in aqueous phase
- Surfactants and other additives

2.4. Review of literature

- **Joshny Joseph et al. (2012),** Tamarind seed polysaccharide: A promising atural excipient for pharmaceuticals. This review focuses on the possibilities of using this polysaccharide in industries, with particular reference to its physical, chemical properties for the formation of new drug delivery systems. All these research studies conclude that Tamarind seed polysaccharide has a wide range of applications and ensure it as a promising component for the pharmaceutical industries and food industries.
- **Anil kumar et al. (2012)** Prepared antihypertensive sustained release matrix tablets of valsartan, using natural polymers as the matrix material in different proportion by direct compression method. In vitro dissolution studies indicate that guar gum significantly reduced the rate of drug release compared to other formulations.
- **Kulkarni et al. (2011)** Studied binding property of the polysaccharide extracted from the seeds of Tamarindus indica was investigated in tablets using ibuprofen as model drug. The tablets exhibited satisfactory properties, which were comparable with corn starch. However, the tablets prepared with tamarind seed polysaccharide exhibited slow dissolution profiles.
- **S. Bharath et al. (2012)** Studied and evaluate aloe vera gel powder as an extended drug releasing agent. Tablets were formulated using different ratios of Aloe veragel powder were prepared. The dissolution study showed a drug release retarding efficiency with the linear increase polymer concentration in the formulation.
- **Prakash Pawan et al. (2013)** Matrix tablets of diclofenac sodium were prepared using natural mucilage of Hibiscus rosa-sinensis and Abelmoschus esculentus as a release retardant. The matrix tablet prepared by Abelmoschus esculentus mucilage provide better zero order release kinetics compared to marketed tablet Voveran SR 50mg.
- **R. Malviya et al. (2010)** Prepared sustained release matrix tablets of Diclofenac sodium using gum acacia and tamarind gum as release modifier. A better sustained drug release was obtained with the matrix tablet of the tamarind gum. Results showed that the drug release from matrix tablets prepared by using natural polymers can be sustained for more than 12 hrs and the drug release vary with concentration of polymer in matrix tablets.
- **Deepthi B.et al. (2012)** Prepared matrix tablets of quetiapine fumarate using natural polymers (Aloe vera gel, Gum Karaya, Xanthum Gum) alone and in combination. Matrix tablets of quetiapine fumarate were produced by wet granulation method. The in vitro drug release studies were shows the extended release for more than 10 hours in most of the formulations.
- **V. N. Deshmukh et al. (2009)** Studied the drug release retardant effect of natural hydrophilic gums such as karaya gum and xanthan gum. Prepared sustained release tablets of Metoprolol succinate using natural hydrophilic gums alone and in combination. Among the formulations studied, formulation containing cobination of KG and XG showed sustained release of drug.
- **U. K. Patil et al. (2008)** Sustained release tablets of furosemide, were fabricated using pectin, guar gum and xanthan gum. The tablet with guar gum exhibited greater swelling index than those with pectin and xanthan gum. A better controlled drug release was obtained with the matrix tablet made-up of the guar gum than with the pectin and xanthan gum.

2.5. Aim and Objectives

Aim: To study the release retardant effect of polymers on release pattern of model drug by formulating matrix tablet.

Objectives–

The present study was aimed towards the formulation and evaluation of sustained the drug release matrix tablet. To achieve the mentioned aim of the study various objectives are planned as below:

- To study the effect of concentration of various natural polymers on drug release pattern.
- To find out the best combination of different polymers ratio for constant and controlled drug release.
- To achieve a stable and cost effective tablet formulation.
- To compare the prepared tablets parameters with marketed tablets to evaluate rectified parameters.

Plan of work:

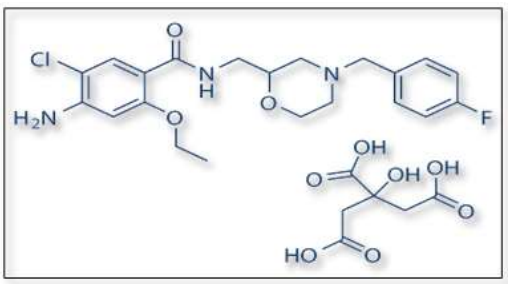
- Literature survey
- Selection of drug and polymer.
- Procurement of drug and polymer.
- Drug polymer compatibility study.
- Preliminary study of drug and polymer.
- Physical characterization-
  - Bulk density.
  - Tapped density.
  - Angle of repose.
  - Hausner ratio.
  - Percent compressibility (carrs index).
- Formulation and compression of tablets.
- Evaluation of prepared tablets.
  - Hardness.
  - Friability.
  - Thickness.
  - Weight variation.
  - Disintegration.
  - Content uniformity.
  - Swelling behaviour of tablets.
  - *In-vitro* drug release study.
  - Stability study

3. Drug and excipients profile

3.1. MOSAPRIDE [32,33,34]

Mosapride is known as Gasmotin® and Mosapride stimulates serotonin-5-HT4 receptors in the gastrointestinal nerve plexus, which increases the release of acetylcholine, resulting in enhanced gastrointestinal motility and gastric emptying.

Structure:



Generic name: Mosapride citrate hydrate

Chemical name: (±)-4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2 morphonyl]methyl]benzamide citrate dihydrate

Molecular formula: C21H25ClFN3O3·C6H8O7·2H2O

Molecular weight: 650.05

Partition coefficient: 9.1 x 102 (Chloroform/water based solvent; pH 7.0; room temperature)

Therapeutic uses: potent anti-histaminic drug.

Description: Mosapride citrate occurs as a white to yellowish white crystalline powder. It has no odor and a slightly bitter taste.

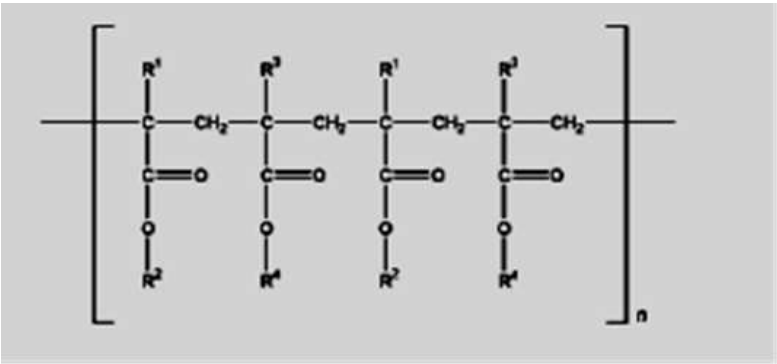
Solubility: It is freely soluble in N,N-dimethylformamide, pyridine, and acetic acid (100), sparingly soluble in methanol, slightly soluble in ethanol (95) and anhydrous acetic acid.and practically insoluble in water and diethyl ether.

Storage: Store at room temperature in tight containers. See the outer packaging for the expiration date.

Applications

- Mosapride is currently approved in the Far East for treatment of gastrointestinal symptoms associated with chronic gastritis including heartburn; nausea; vomiting; and gastroesophageal reflux disease (GERD).
- Mosapride is also in Phase II clinical trials for the treatment of GI dumping syndrome or post-gastrectomy syndrome.
- Additional clinical studies have been initiated using mosapride for treating constipation in patients with Parkinson's disease.
- Treating patients with type-2 diabetes mellitus in order to improve insulin action.
- Treating patients with gastroparesis; and treatment of patients with opiate-induced respiratory depression. Despite the beneficial activities of mosapride, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

3.2. EUDRAGIT RS 100:



Structural Formula[35]

R1, R3 = H, CH3

R2, R4 = CH3, CH2CH2N (CH3)3Cl

Profile of Eudragit RS 100[35]

Description

Chemical name:Poly(ethyl acrylate, methyl methacrylate)2: 1

It is aqueous dispersions of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

CAS No. 9010-88-2

Molecular weight. Greater than 1, 00,000.

Functional Categories. Film former, tablet binder, tablet diluent

Density (bulk). 0.390 g/cm 3

Uses. Used to form water-insoluble film coats for sustained-release products. For sustained release or slow release enteric film coating of tablet, pellets, granules, pills, powder etc. Used to form water-insoluble film coats for sustained-release products. For sustained release or slow release enteric film coating of tablet, pellets, granules, pills, powder etc.

Solubility.: Water, Isopropyl alcohol and acetone.

Stability Stability. Sensitive to extreme temperatures and phase separation occurs below 0°C, stored at temperatures between 5 and 25°C and are stable for at least 18 months.

Incompatibilities. Occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. Occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent.

Safety. A daily intake of 2mg/kg body-weight of Eudragit (Equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

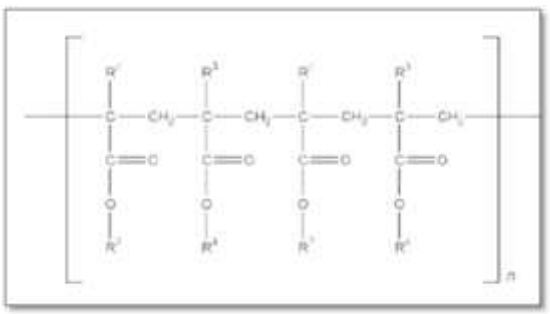
Application in pharmaceutical formulation and technology [35'36]

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced; Eudragit RS 100 is used to form water-insoluble film coats for sustained-release products. Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct compression processes in quantities of 10–50%. Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.

3.3. Eudragit L 100 (Polymethacrylate)

Description: Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylate's, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60: 40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent.

Structural Formula [37]



Eudragit L - 100 is white free-flowing powders with at least 95% of dry polymers.

Chemical name: Poly (methacrylic acid, methyl methacrylate) 1: 1 Eudragit RL 100 Evonik Industries.

CAS No.: 25806-15-1.

Molecular weight: Greater than 5100 000.

Functional Categories: Film-forming agent; tablet binder; tablet diluent.

Density (bulk): 0.390 g/cm 3

- Uses: Used to form water-insoluble film coats for sustained-release products. For sustained release or slow release enteric film coating of tablet, pellets, granules, pills, powder etc.
- Solubility: Soluble in Acetone and alcohols and also in1N NaOH, insoluble or immiscible in Dichloromethane, Ethyl acetate, Petroleum ether and Water.
- Stability: Dry powder polymer forms are stable at temperatures less than 308C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can be readily broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 308C.
- Incompatibilities: Incompatibilities occur with certain Polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature.

Application in pharmaceutical formulation and technology [35,37]

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Eudragit L types are used as enteric coating agents because they are resistant to gastric fluid. Eudragit L films are more permeable than those of Eudragit S, and films of varying permeability can be obtained by mixing the two types together.

Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.

3.4. EUDRAGIT E 100

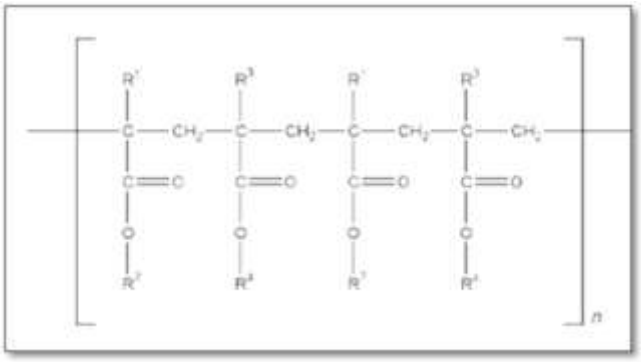
Uses: Used to form water-insoluble film coats for sustained-release products.

Solubility: Soluble in Acetone and alcohols and also in1N NaOH, insoluble or immiscible in Dichloromethane

Stability: Dry powder polymer forms are stable at temperatures less than 308C.

Incompatibilities: Incompatibilities occur with certain Polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent

Structure:

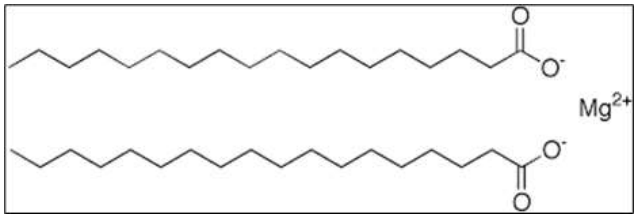


Application in pharmaceutical formulation and technology [35,37]

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Eudragit L types are used as enteric coating agents because they are resistant to gastric fluid. Eudragit L films are more permeable than those of Eudragit E.

3.5. Magnesium Stearate[43]

Structure of Magnesium stearate:



Chemical name: Octadecanoic acid magnesium salt

chemical formula:Mg (C18H35O2)2.

It is the salt containing two equivalents of stearate (the anion of stearic acid) and one magnesium cation (Mg++).

CAS registry number: [557-04-0]

Molecular weight: 591.24

Melting point: at about 88oC.

insoluble in water and is generally considered safe for human consumption at levels below 2500 mg/kg.

Functional category: Tablet and capsule lubricant.

Applications: Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. Magnesium stearate is used as a diluent in the manufacture of tablets, capsules and powders. It has lubricating properties, preventing ingredients from sticking to manufacturing equipment during compression into solid tablets. Studies have shown that that magnesium stearate may affect the release time of the active ingredients in the tablets. Magnesium stearate is manufactured from both animals and vegetables. Used in cosmetics.

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

Bulk density: 0.159 g/cm3

Tapped density: 0.286 g/cm3

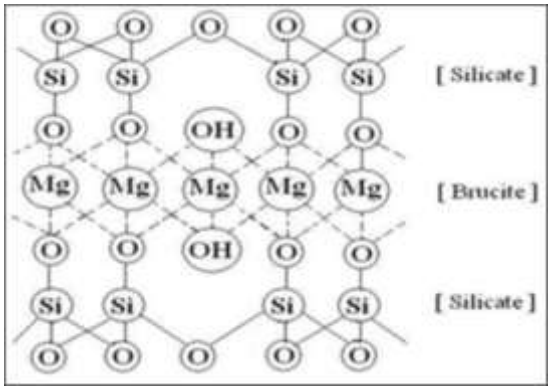
Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm water.

Storage conditions: Magnesium state is stable and should be stored in a well closed container in a cool, dry.

Incompabilities: Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing mater. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety: Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being non toxic following oral administration. However, oral consumption of large quantities may produce a laxative effect.

3.6. Talc[43]



Structure of talc

Talc derived from the Persian 'talc' is a mineral composed of hydrated magnesium silicate with

chemical formula: H2Mg3(SiO3)4.

Chemical Name and CAS Registry Number: Talc [14807-96-6]

Functional Category:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant

Properties:

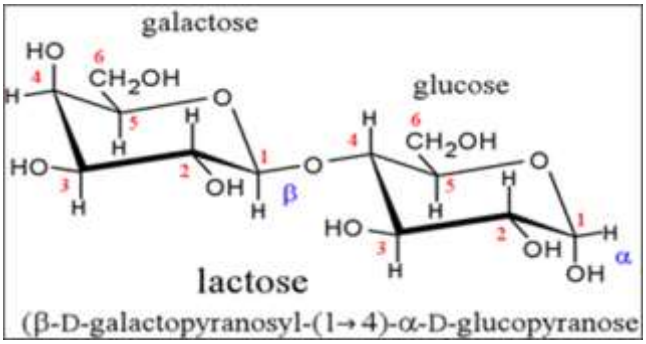
It is a very fine, white to grayish-white, odorless, oily, crystalline powder used as both lubricant and glidant. It was purchased from S.D. Fine

Applications in Pharmaceutical Formulation or Technology

- Talc was once widely used in oral solid dosage formulations as a lubricant and diluents.
- It is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is also used as a lubricant in tablet formulations.
- As an adsorbant 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

3.7. Lactose[43]

Chemical structure



Synonyms: Milk sugar; (beta)-Lactose; Lactose, monohydrate

Molecular Weight: 360.32

Chemical Formula: C12H22O11.H2O

Chemical Name and CAS Registry Number O-b-D-Galactopyranosyl-(1!4)-b-D-glucopyranose [63-42-3]

Description

Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b-lactose and anhydrous a-lactose. Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose. White crystals or white powder.

Functional Category

Directly compressible tablet excipient; dry powder inhaler carrier; lyophilization aid; tablet and capsule diluent; tablet and capsule filler.

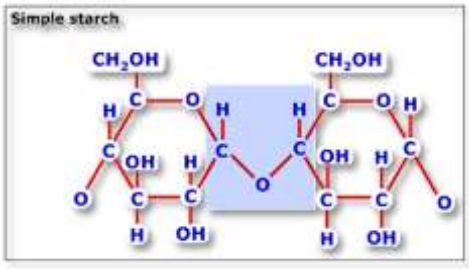
Applications in Pharmaceutical Formulation or Technology

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

Solubility: Soluble in water.

Density: 20C

3.8. Starch[29,43]



Structure of starch:

Chemical Name and CAS Registry Number: Starch [9005-25-8]

Empirical Formula and Molecular Weight:(C6H10O5)n where n = 300–1000.

Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.

Applications in Pharmaceutical Formulation or Technology

- Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.
- As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations.
- Starch quantities of 3–10% w/w can act as an antiadherent and lubricant in tableting and capsule filling.
- In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation.

- The required binder ratio should be determined by optimization studies, using parameters such as tablet friability and hardness, disintegration time, and drug dissolution rate.
- Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w;(2–7) a typical concentration is 15%.
- starch in direct compression, improving the tableting process and
- the disintegration time of the tablets.
- Balancing the elastic properties of starch with adapted excipients has been shown to improve the compaction properties in tableting.
- Starch, particularly rice starch, has also been used in the treatment of children's diarrheal diseases.

4. Methods

4.1. Preparation of Tablets

The mosapride citrate matrix tablets were prepared by direct compression method. were 100mg tablets prepared containing 15mg of Mosapride Citrate and different proportions of Lactose, Eudragit RS,. Eudragit RL, Eudragit E 100. Lubricants were added prior to compression. Talc was used as an adsorbent. Half the quantity of lubricants was added and. The punch size was 7mm. method. Lactose was used as diluent.. Talc and magnesium Stearate were used as lubricants. Drug, polymers and lubricants were blended and sifted through different sieves. Then mixed and blended the ingredients to form a dry mixture. Compression of formulation blend were done using tablet Minirotary machine (Dynamic machine, Aurangabad, India).

4.2. Evaluation of Preformulation Parameters

4.2.1. Friability

Friability is the measure of tablet strength. Roche Friabilator was used for testing rin the plastic chamber that revolves at 25 rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined. % loss = Initial wt. of tablets - Final wt. of tablets x 100 Initial wt. of tablets.

4.2.2. Dissolution studies

The release rate of Mosapride citrate from sustained matrix tablets were determined using USP dissolution testing apparatus II (paddle type) at 50 rpm. The dissolution test was performed using 900ml of pH 6.8 Phosphate buffer for 2 h at 37 ± 0.5 °C. Dissolution The temperature of the dissolution medium is maintained at 37±0.5°C. 5 ml of the sample was withdrawn at regular intervals and replaced with the same volume pre-warmed with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug. Wavelength used was 274 nm.

4.2.3. Loose bulk Density

The loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm3. The 10 gm sample was carefully introduced into a 25 ml graduated cylinder. The volume occupied by the powder was recorded and bulk density then calculated.. It was calculated by using equation given below:

$$Df = M / Vp$$

Where,

Df = Loose bulk density
M = Weight of samples in grams
Vp = Final volumes of granules in cm3

4.2.4. Tapped bulk density

The tapped bulk density was obtained by dividing the mass of a powder by the tapped volume in cm3. The 10 gm sample was carefully introduced into a 25 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface 100 times from a height of 1 inch. The tapped bulk density of each formulation was then obtained by

dividing the weight of sample in grams by the final tapped volume in cm3 of the sample contained in the cylinder. It was calculated by using equation given below:

Do = M / Vp

Where,

Do = Tapped bulk density.
M = Weight of samples in grams.
Vp = Final tapped volumes of granules in cm3

The results were illustrated in table. No.15.

Compressibility Index and Hausner ratio

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the Hausner ratio are determined by measuring both the bulk density and the tapped density of a powder.

Compressibility Index $=\frac{Tapped\ density - Bulk\ density}{Tapped\ density}$

Hausner Ratio $=\frac{Tapped\ \ Bulk\ density}{loose\ Bulk\ density}$

Table 1 Relationship between % compressibility and flowability:

Compressibility Index (%)	Flow properties	Hausner Ratio
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.17
16-20	Fair	1.19-1.25
21-25	Passable	1.26-135
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>37	Very very poor	>1.60

4.2.5. Angle of repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

tan = h / r

= tan –1 h / r

Where,

= Angle of repose.

h = Height.

r = Radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed. Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

Table 2 Relationship between angle of repose (θ) and flowability**:**

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

4.3. Evaluation of prepared tablets

4.3.1. Hardness

Although hardness test is not an official, tablet should have sufficient handling during packing and transportation. Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying the force. The hardness of 6 tablets, from each batch was determined and means hardness was taken into account, which was expressed in kg/cm2.

4.3.2. Weight variation test

Table 3 Weight variation tolerance for uncoated tablets

Average Weight of Tablet (Mg)	Maximum % Deviation Allowed
30mg or less	10%
30mg to 100mg	7.5%
More than 100 mg	5%

Weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average USP weight variation test. The table No.7 given below shows the weight variation tolerance for uncoated tablets.

4.3.3. Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$\% F = \{1-(Wo/W)\} \times 100$

Where,

% F = friability in percentage

Wo= Initial weight of tablet
W= weight of tablets after revolution

4.3.4. Content Uniformity

For this at least 30 tablets were randomly selected. Out of 30 tablets, 10 tablets were crushed into fine powder and assayed individually; the tablet should be within 75% to 115% of the labeled claim.

4.3.5. Thickness:

The thickness of the tablet was measured using Vernier caliper. Thickness of five tablets from each batch was measured and mean was calculated.

4.3.6. In- Vitro Release Profile of Formulated Tablets:

The drug release rate from matrix tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. Then it was placed in the dissolution apparatus. The dissolution medium was 900 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 274nm.

Table 4 Parameter of dissolution studies

Speed of rotation	50rpm
No. of tablets tested	4 tablets
Temperature	37^{o}C ± 0.5^{o}C
Time	7 hours
Test Medium	6.7 Phosphate Buffer
Volume of test medium	900 ml in each vessel for 7 hrs.
Sampling time	2,3,4,5,…up to 7hours

- FTIR Analysis

- Small quantity of Mosapride 1mg was placed in diamond ATR crystal then it was scanned between 4000-5000 cm-1
- Model fitting
- The model fitting for percent cumulative release was done using PCP Disso software to find the best fitted kinetic equation for the dissolution profile.
- Stability Studies of Eudragit Matrix Tablets:
- In any rationale design and evaluation of dosage forms, the stability of the active component must be major criteria in determining their acceptance or rejection.

5. Result and Discussion

5.1. Characterization of Mosapride

Table 5 Organoleptic characterization and Melting point determination of drug

Test	**Observation**
Colour	White,crystalline powder
Odour	Odorless
Test	Bitter
Melting point	142-145c

5.2. Solubility Analysis

Table 6 Solubility profile of Mosapride.

Sr.No	Solvent	Solubility
1.	Distilled water	Soluble
2.	NaOH	Insoluble
3.	Water	Low solubility
4.	DMSO	Soluble

UV Spectra of Mosapride Citrate is shown in

- Calibration curve was drawn in Phosphate buffer of pH 6.8, which follows beer's Lambert law.
- IR Spectra of Mosapride Citrate

Table 7 Calibration graph values of Mosapride Citrate in pH 6.8 phosphate buffer.

S. No	Concentration (µg/mL)	Absorbance
1	0	0
2	10	0.4376
3	20	0.6493
4	30	0.9193
5	40	1.3057
6	50	1.5383

5.3. Calibration curve of Mosapride citrate

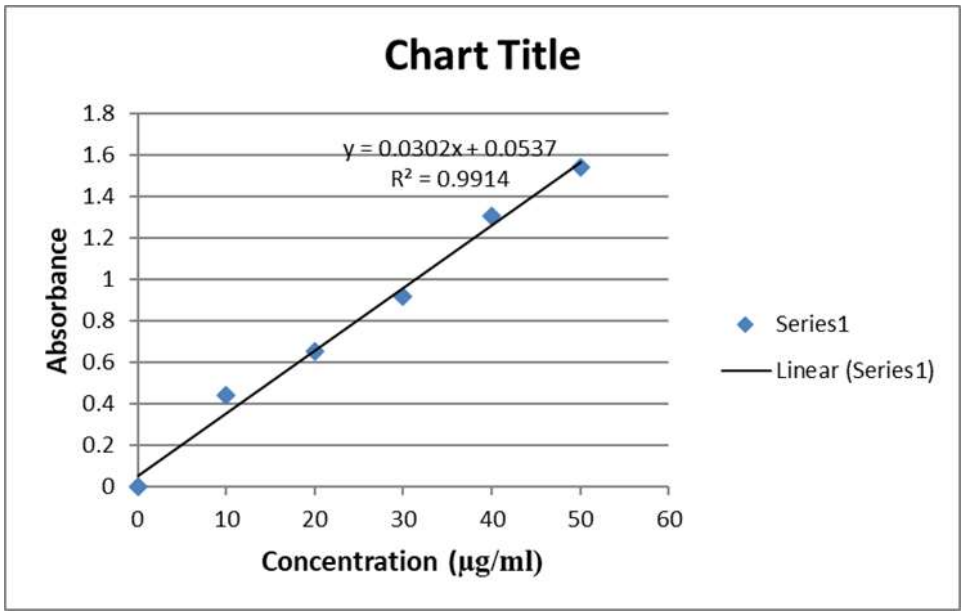


Figure 1 Calibration curve of Mosapride citrate

5.4. FTIR Results

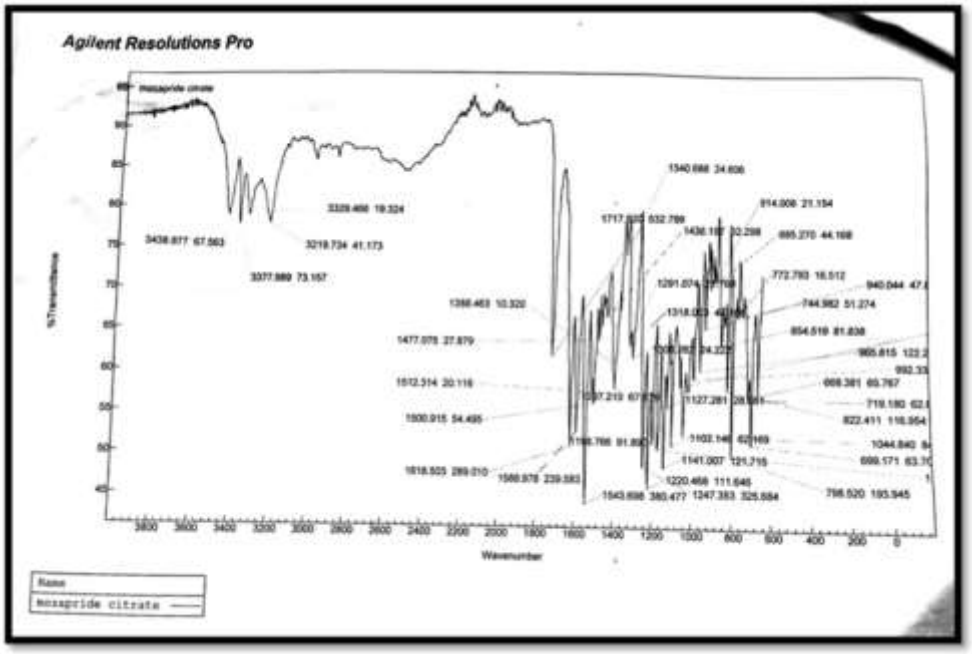


Figure 2 FTIR studies of pure drug Mosapride Citrate.

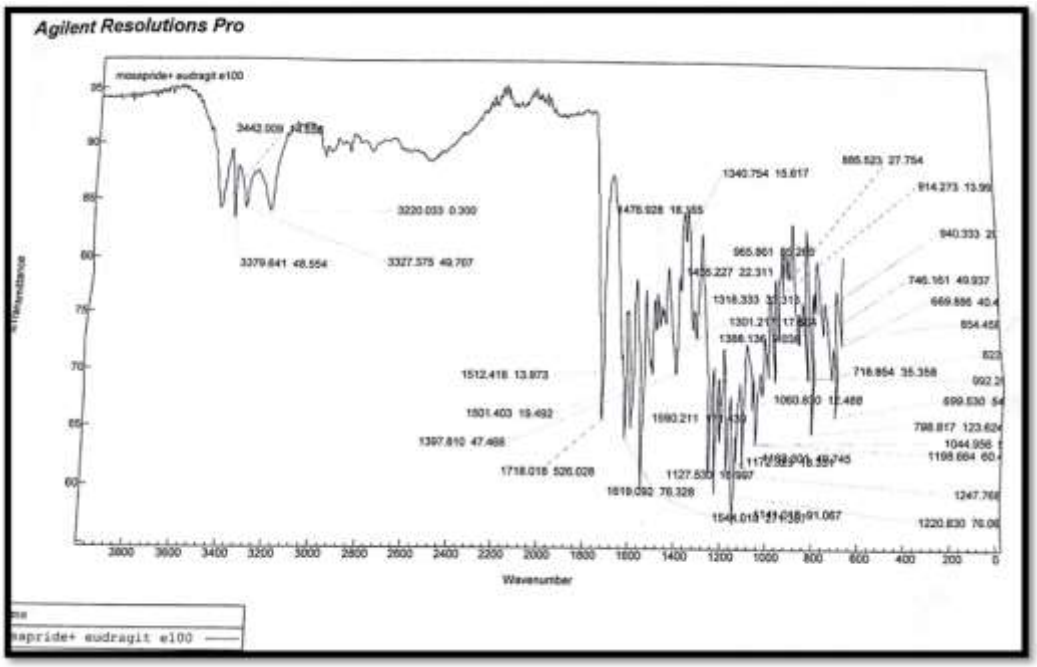


Figure 3 FTIR studies of Mosapride Citrate+ Eudragit E 100

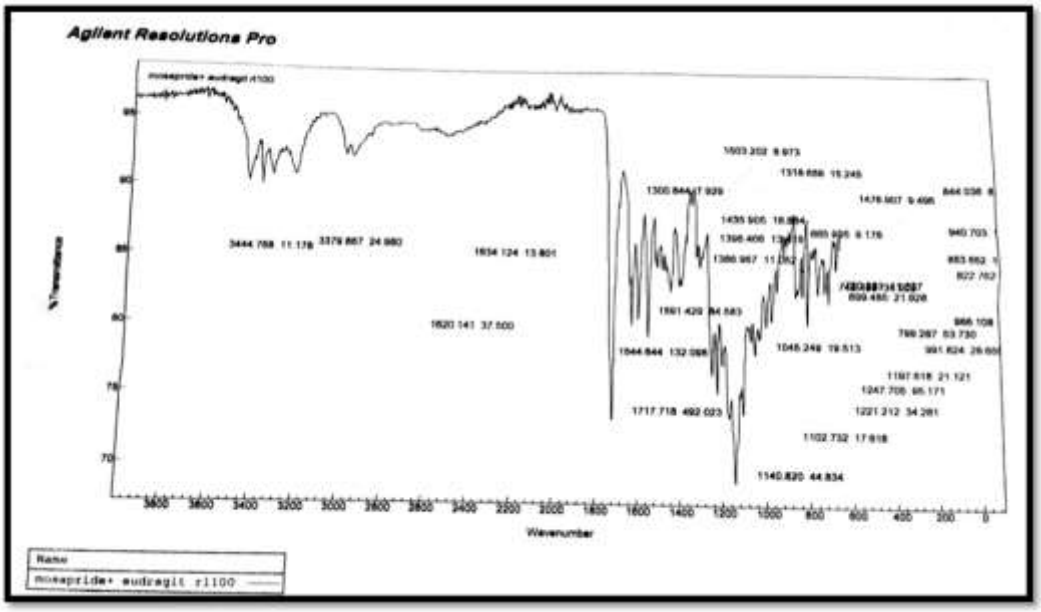


Figure 4 FTIR studies of Mosapride Citrate+ Eudragit RL 100

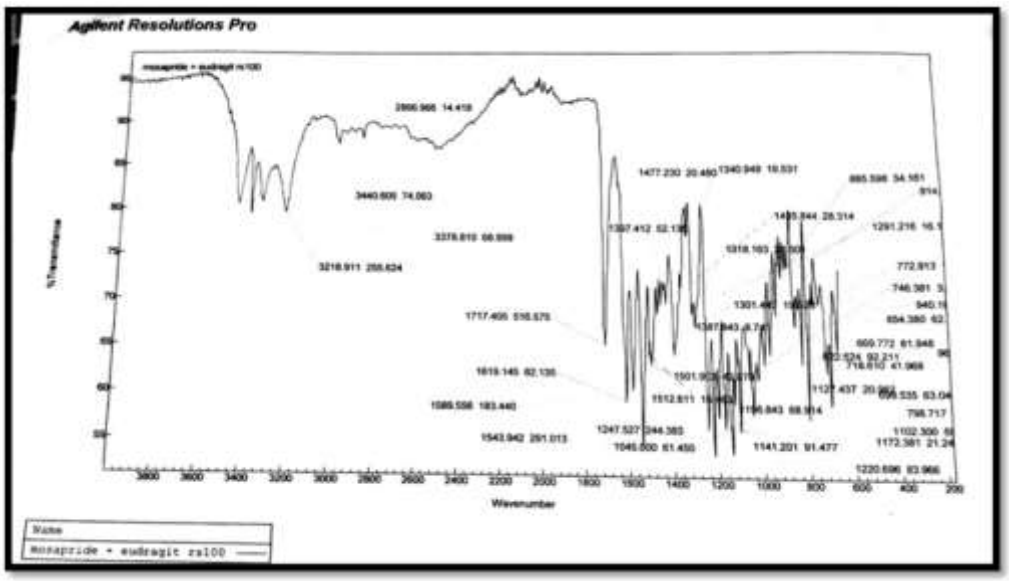


Figure 5 FTIR studies of Mosapride Citrate+ Eudragit RS 100.

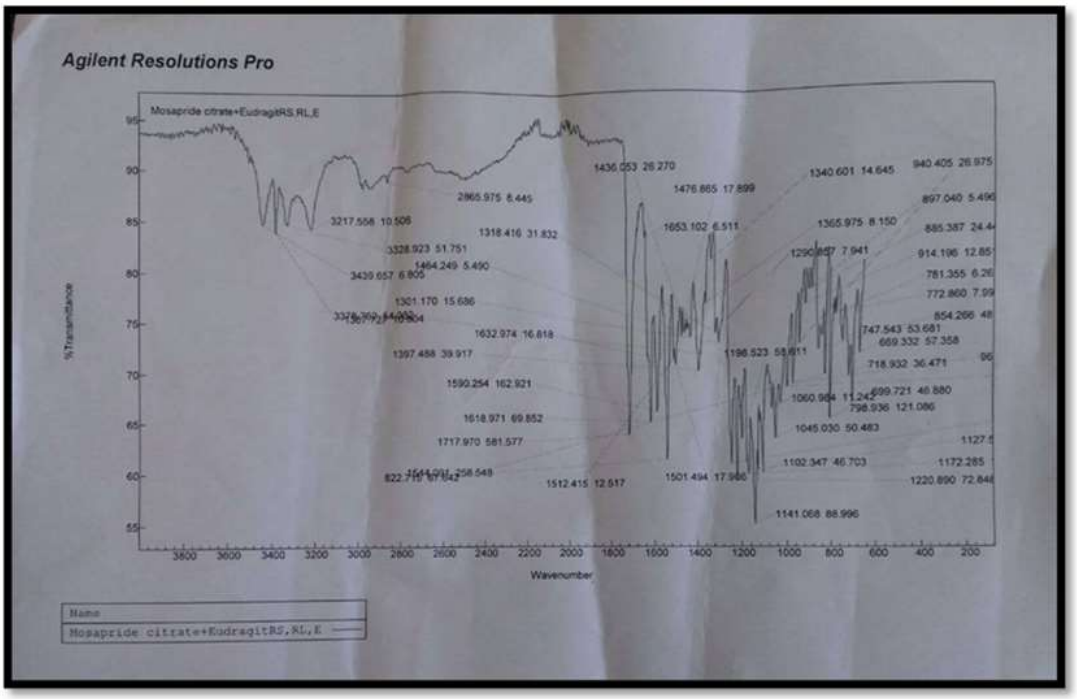


Figure 6 FTIR studies of Mosapride Citrate+ Eudragit RS 100+ Eudragit RL 100+ Eudragit RE 100

5.5. *In- Vitro* Release Profile of Formulated Tablets:

The drug release rate from matrix tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. Then it was placed in the dissolution apparatus. The dissolution medium was 900 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 274nm.

Table 8 Formulation chart of sustained release matrix tablets of Mosapride Citrate

Time in hour	**In average % drug release**				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	19.96%	21.92%	25.62%	23.43%	25.63%
2	20.28%	37.36%	39.48%	30.52%	41.24%
3	32%	39.88%	43.27%	46.71%	51.02%
4	36.84%	51.64%	56.16%	51.64%	56.73%
5	40.84%	61.24%	68.32%	67.59%	62.97%
6	57.52%	79.72%	73.75%	70.06%	73.42%
7	69.12%	79.6%	82.91%	82.54%	85.93%
8	83.64%	89.08%	94.09%	86.48%	91.92%

Time in hour	In average % drug release				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	37.48%	39.68%	28.43%	35.96%	21.13%

2	49.56%	45.16%	39.08%	43%	49.20%
3	54.64%	58.88%	57.8%	52.02%	43.01%
4	69.84%	69.68%	61.4%	67.52%	51.89%
5	75.36%	79.72%	79.28	74.31%	65.33%
6	81.12%	81.44%	83.36%	81.12%	72.34%
7	92%	85.08%	90.02%	91.92%	86.39%
8	95.92%	96.76%	97.76%	99.01%	98.82%

Table 9 Peak of functional groups

IR Spectra	**Peak of functional groups {wave length(cm-1)**			
	C=O	C=F	C=C	N-H
Drug	1717.92	1618.50	1340.68	3438.87
Drug+ EUDRAGIT RS 100	1717.40	1619.14	2866.96	3378.81
Drug + EUDRAGIT RL 100	1717.71	1620.14	1591.42	3444.76
Drug + EUDRAGIT E100	1718.08	1619.09	1544.010	3379.64
Optimized formulation	1717.23	1620.87	1341.21	3470.38

5.6. Interpretation

The result shows that there was no incompatibility seen in between drug Mosapride Citrate and polymer used, as there was no significant change in the pattern of peaks of pure drug and formulations. All principle peaks were present in the IR spectra of drug also present in the IR spectra of formulations and there were no extra peaks in the IR of formulations. Hence the formula for preparing Mosapride citrate microcapsules can be reproduced in the industrial scale without any apprehension of possible drug-polymer interaction. IR of optimized batch F9.

5.7. Physical properties of Mosapride tablet

Table 10 Physical properties of Mosapride tablet

Formulation Code	**Angle of repose (Θ)**	**Bulk density (gm/cm3)**	**Tapped density (gm/cm3)**	**Carr's Index (%)**	**Hausner's ratio**
F1	105±3	2.81±0.04	3.8±0.4	0.482	99±0.60
F2	97±3	2.74±0.05	4.4±0.6	0.513	99±0.40
F3	99±1	2.76±0.03	5.0±0.1	0.412	98±0.90
F4	100±2	2.71±0.04	4.6±0.2	0.432	99±0.10
F5	98±3	2.73±0.03	4.0±0.3	0.512	100±0.10
F6	99±1	2.79±0.04	4.0±0.3	0.459	99±0.80
F7	100±1	2.81±0.04	5.6±0.2	0.464	99±0.84
F8	98±2	2.63±0.04	4.6±0.2	0.443	99±0.91
F9	107±4	2.89±0.04	6.6±0.2	0.582	99±0.98
F10	102±3	2.76±0.04	4.7±0.2	0.410	99±0.56

The Physical parameters like angle of repose and bulk density of all the microspheres confirms better flow properties. Thus the Mosapride citrate matrix tablet requires less amount of lubricants and ensures low production cost leading to its feasibility for large scale production. The mean particle size data indicates that the amount of polymer affected the particle size. An increase in amount of polymer resulted in an increase in viscosity, which in turn resulted in increased in result

5.8. Evaluation of Preformulation Parameters

Table 11 Physical evaluation of Mosapride Citrate tablet:

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Content uniformity (%)
F1	102±1	2.72±0.01	4.5±0.7	0.420	99±0.12
F2	104±2	2.70±0.04	4.2±0.5	0.341	99±0.30
F3	100±1	2.71±0.01	3.6±0.6	0.363	100±0.10
F4	101±2	2.80±0.06	4.8±0.5	0.561	100±0.30
F5	105±3	2.81±0.04	5.8±0.4	0.482	99±0.60
F6	97±3	2.90±0.05	4.4±0.6	0.513	99±0.40
F7	99±1	2.76±0.03	5.0±0.1	0.412	98±0.90
F8	100±2	2.71±0.04	4.6±0.2	0.432	99±0.10
F9	101±3	2.92±0.03	5.1±0.3	0.512	100±0.10
F10	103±2	2.95±0.02	4.2±0.6	0.523	99±0.30

5.9. *In-vitro* drug release study

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Mosapride Citrate from different formulations varies with characteristics and composition of matrix forming polymers as shown in graph

Table 12 *In-vitro* dissolution data of F1,F2, and F3 formulation;

Time (hrs)	% Cumulative drug release		
	F1	F2	F23
0	0	0	0
1	19.96±0.97	21.92±0.81	20.62 ±1
2	20.28±0.96	28.36±1	39.48 ± 0.88
3	32±0.150	37.88± 0.96	43.27 ±1.031
4	36.84 ± 0.82	39.64± 1	56.16 ±0.92
5	40.84±0.98	51.24±0.98	68.32 ± 0.84
6	57.52±1	61.72±0.99	73.75 ±0.97
7	69.12± 0.99	79.6± 0.72	82.91 ±1
8	83.64±0.82	89.08±1.04	94.09 ±0.95

*All the value are represents as Mean ± S.D.(standard deviation) (n=3)

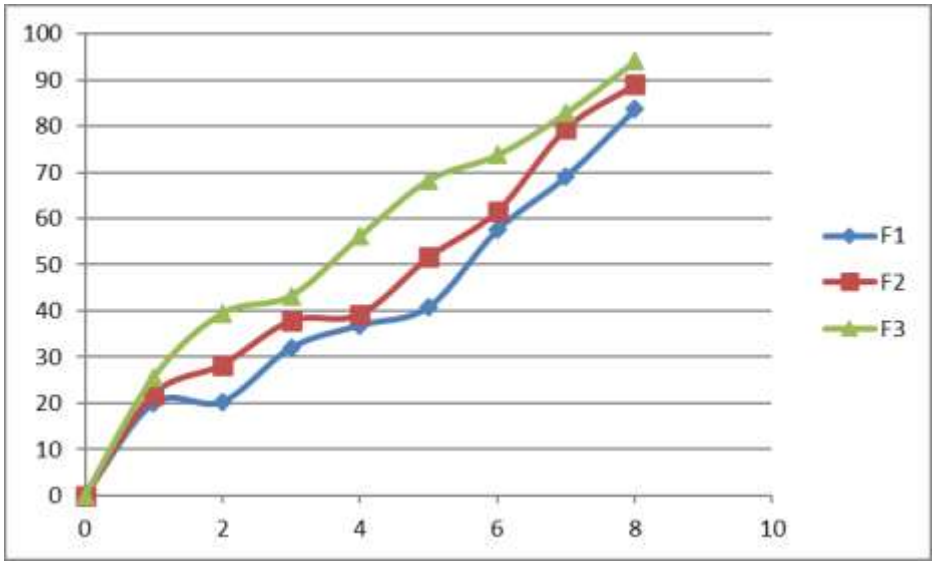


Figure 7 *In-vitro* dissolution profile of F1,F2, and F3 formulation

From the above graphs it was evident that Eudragit E in the concentration of 1:2 drug with other two ratios 1:1, 1:3 drug polymer ratios. In case of F2 and F3 formulation the polymer quantity was in sufficient to produce the required1 retarding nature upto 8 hrs, maximum drug release was occured in 6 hrs only, where as in F1 formulation the quantity of polymer was because high hence it showed more drug retardation with less drug release that is 83.64 % in 8 hrs.

Table 13 *In-vitro* dissolution data of F4,F5, and F6 formulation

Time (hrs)	**% Cumulative drug release**		
	F4	F5	F6
0	0	0	0
1	23.43 ±0.98	25.63 ± 1.01	37.48 ±1.24
2	30.52± 0.99	41.24 ± 0.92	49.56 ±1.05
3	46.71 ± 1.53	51.02 ± 0.99	54.64 ±1.31
4	51.64 ± 1.52	56.73 ± 0.98	69.84 ±1.44
5	67.59 ± 1.04	62.97 ± 0.97	75.36 ±1.52
6	70.06 ± 1.030	73.42 ±1	81.12 ±1.58
7	82.54 ± 0.98	85.93 ±1.10	92 ± 1
8	86.48 ±1.40	91.92 ±1.52	95.92 ±1.48

*All the value are represents as Mean ± S.D.(standard deviation) (n=3)

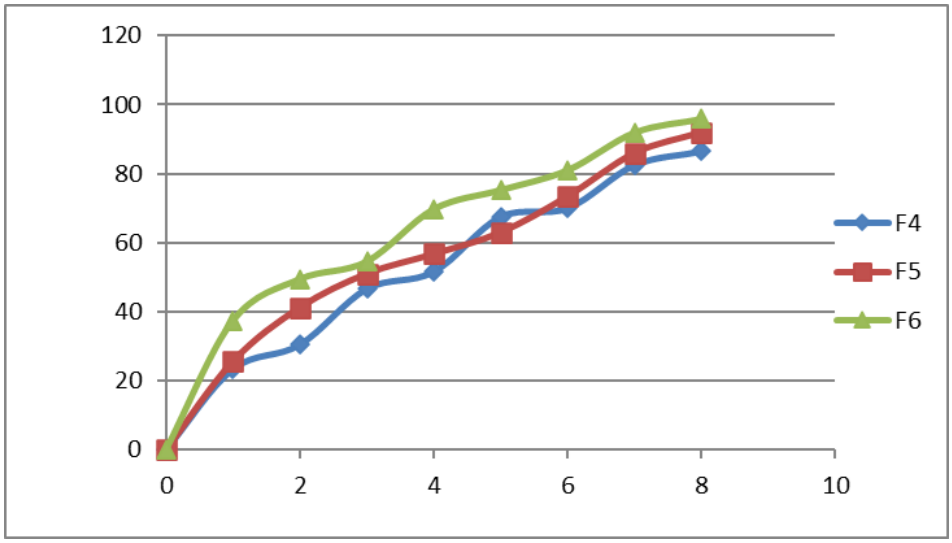


Figure 8 *In-vitro* dissolution profile of F4,F5, and F6 formulation.

From the above graphs it was evident that Eudragit Rl in the concentration of 1:2 (F6), drug to polymer ratio, is showing better result 95.92 % drug release when compared with other two ratios 1:1, 1:3 drug polymer ratios. As the concentration of polymer increases the retarding of drug release also increased. Hence they were not considered.

Table 14 *In-vitro* dissolution data of F7,F8,F9 and F10 formulation

Time (hrs)	**% Cumulative drug release**			
	F7	F8	F9	F10
0	0	0	0	0
1	39.68 ± 1.31	28.43 ± 1.72	35.96 ± 1.05	21.13±1.00
2	45.16±1.05	39.08 ± 1	43 ± 1	36 ±1.10
3	58.88±1.42	57.8 ± 1.52	57.02±1.52	49.01 ± 1
4	69.68±1.35	61.4 ± 1.02	67.52 ± 1.27	51.89±1.04
5	75.72±0.99	79.28 ± 0.96	74.31 ±1.50	65.33±1.15
6	83.44±1.29	83.36 ±1.18	81.12 ±1.05	72.34±1.50
7	85.08 ±1.53	90.02 ±0.99	91.92 ± 1.04	86.39 ± 1.20
8	96.76±1.37	97.76 ±1.92	99.01 ± 1	98.82 ±0.99

*All the value are represents as Mean ± S.D.(standard deviation) (n=3)

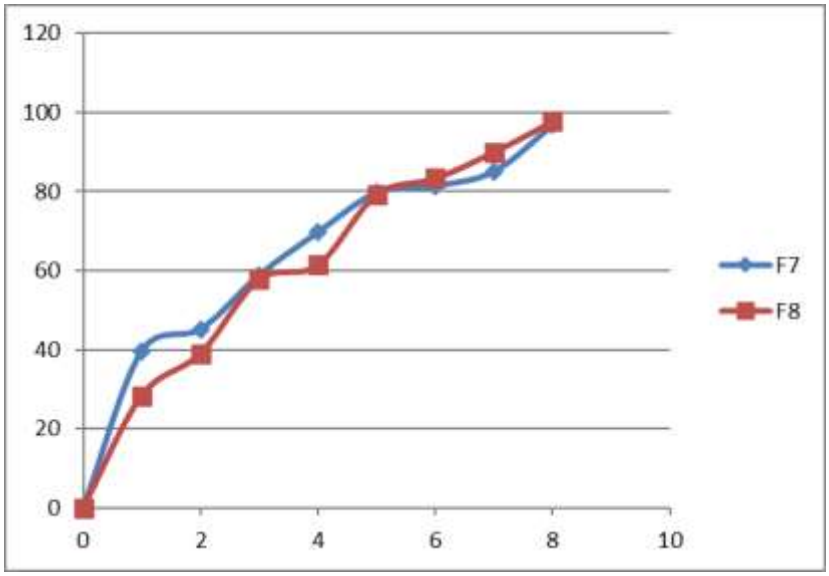


Figure 9 *In-vitro* dissolution profile of F7,F8 formulation**.**

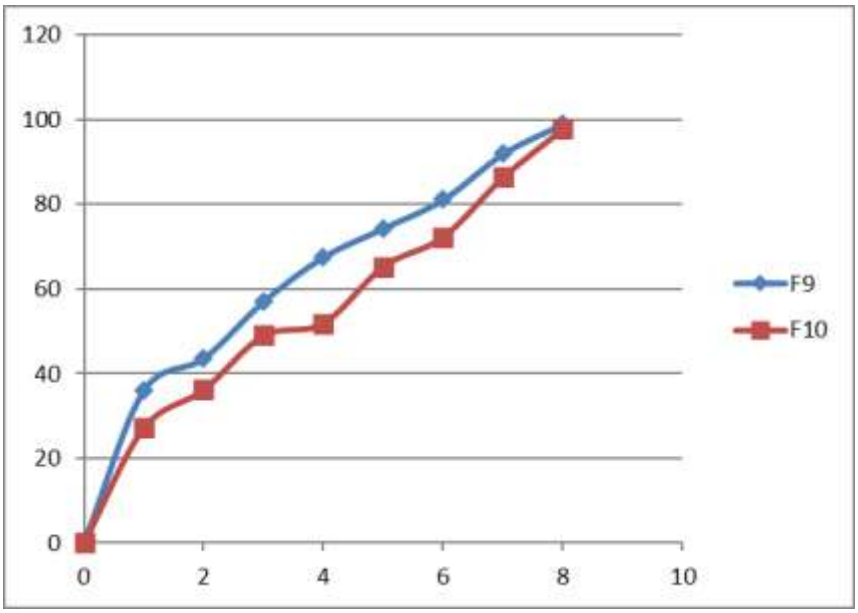


Figure 10 *In-vitro* dissolution profile of F9 and F10 formulation**.**

From the above graphs it was evident that Eudragit Rs 100 shows the better results as compare to last batches. F9 batch to polymer ratio, is showing better result 99.01 % drug release when compared with other three batches. In case of F7 formulation the polymer was insufficient to produce required bioadhesion strength and the maximum drug was released in 6 hrs only where as in F7 and F8 formulation the concentration become high and the drug release was retarded more than 8 hrs, hence it was not taken in to consideration.

All the formulations were subjected to *In-vitro* dissolution studies and results are shown in tables and Fig. The results release profile of matrix tablet of Mosapride citrate containing varying proportion of Eudragits E polymer i.e. batch F1,F2,F3 showed drug release as 83.64%,89.08%,94.09 for 8 hrs respectively. The release profile of matrix tablet of Mosapride containing varying proportion of Eudragit Rl i.e. batch F4,F5,F6 showed drug release as 86.48%, 91.92 %, 95.92%. for 8 hours respectively.

The results release profile of matrix tablet of Mosapride citrate containing varying proportion of Eudragits RS polymer i.e. batch F7,F8,F9 showed drug release as 96.76%, 97.76%, and 99.01% for 8 hours respectively. The release profile of matrix tablet of Mosapride containing varying proportion combinations of Eudragit polymer i.e. RL,RS and E in batch

F10 showed drug release as 98.82%. for 8 hours respectively. *In-vitro* drug release study of all formulations (F1-F10) were also compared and evaluate. The result showed that the drug release profile of formulation F9,F8 containing Eudragit RS 100 and formulation F10 containing combination of Eudragit RS, RL and E 100 resembles formulation was all batches gives the good results. The F9 batch gives the very good results and hence it is consider as optimized batch and used for further studied.

Table 15 Drug release kinetics for the various formulations of Mosapride citrate

Batch Code	R^2 Value				Release exponent 'n'		Mechanism of release
	Zero order	First order	Higuchi model	KMP	HXC		
F1	0.898	0.9726	0.9343	0.882	0.9548	0.940	Super case II transport
F2	0.9456	0.9818	0.9967	0.9909	0.9883	0.6100	Non fickian
F3	0.9571	0.9732	0.9828	0.940	0.992	1.010	Super case II transport
F4	0.950	0.9747	0.9780	0.9763	0.9936	0.755	Non fickian
F5	0.920	0.9747	0.9640	0.9303	0.9842	0.876	Non fickian
F6	0.978	0.9414	0.9780	0.973	0.9844	0.891	Case II transport
F7	0.9456	0.9818	0.9967	0.9909	0.9883	0.6100	Non fickian
F8	0.9571	0.9732	0.9828	0.940	0.992	9.010	Non fickian
F9	0.9581	0.9532	0.9738	0.9758	0.09519	1.4505	Super case II transport
F10	0.8808	0.9312	0.9691	0.9622	0.08386	0.927	Non fickian

*KMP = KorsmeyerPeppas mode; *HXC = Hixson Crowell model.

Figure 11 Zero order release F9

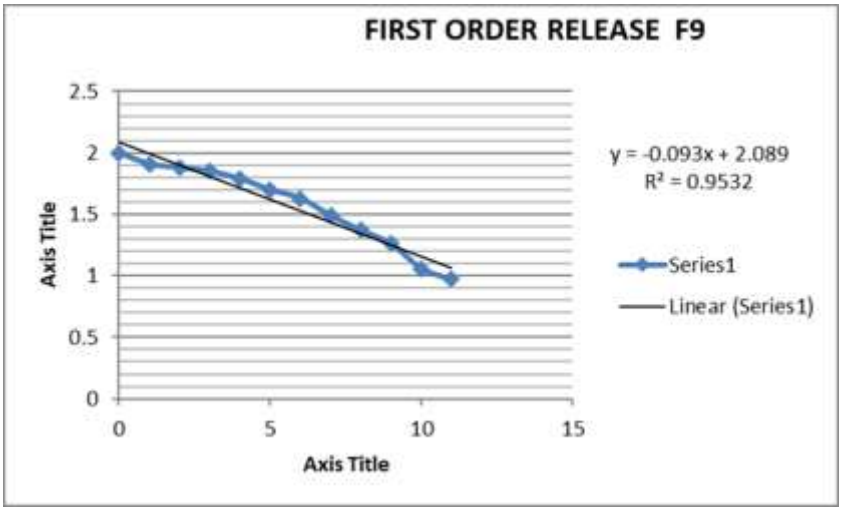


Figure 12 First Order Release F9

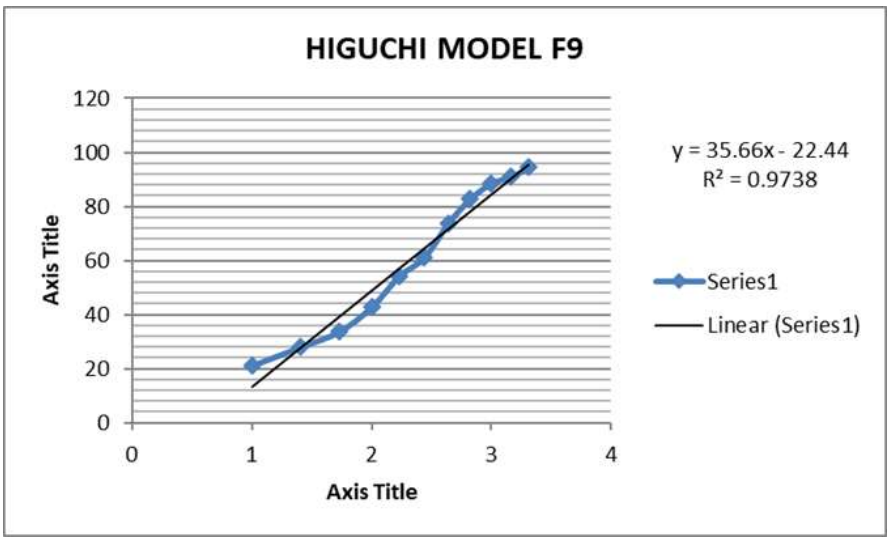


Figure 13 Higuchi Model F9

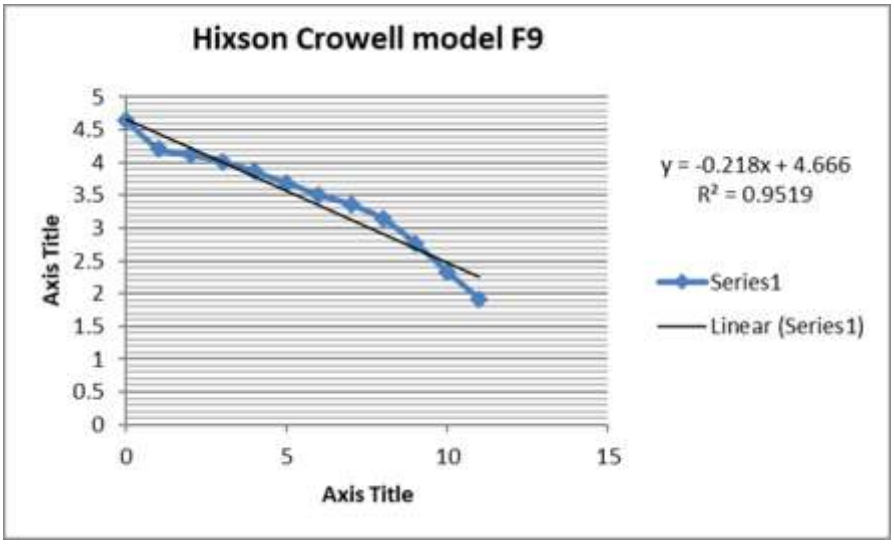


Figure 14 Hixson Crowell model F9

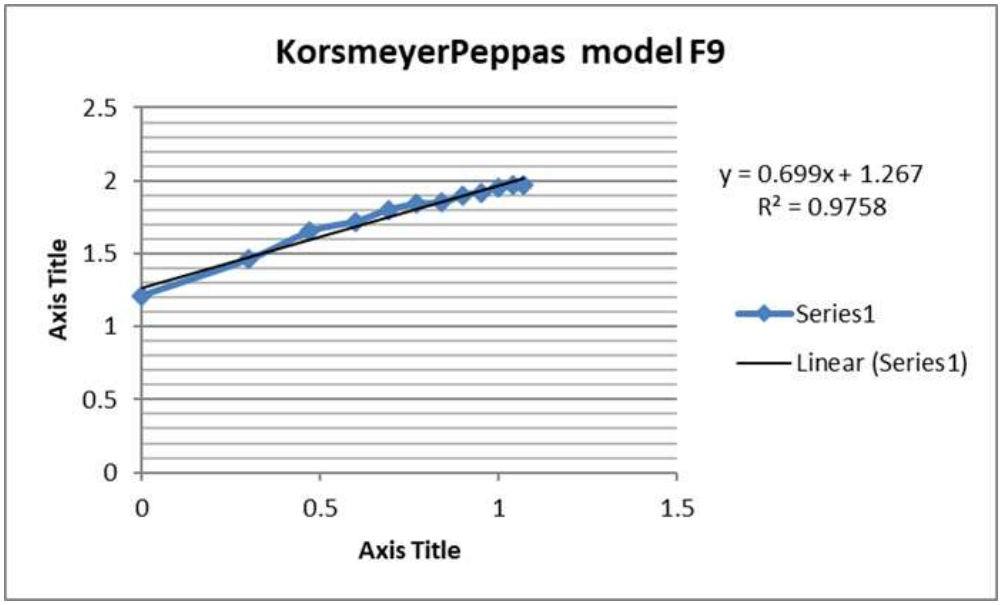


Figure 15 Korsmeyer Peppas Model F9.

6. Result

First order, Zero order, Korsmeyer's Peppas, Higuchi's equation, Hixson Crowell models were studied for diffusion coefficient. The optimized batch F9 follows first order release kinetics follows zero order release kinetics indicated by their r^2 values as shown in above table.The n' exponent value for batch F9 and F10 in Korsmeyer Peppas model showed Super case II transport and Case II transport respectively.

6.1. Stability studies

The optimized Matrix tablet (F8,F9 and F10) was selected for stability study on the basis of in vitro dissolution studies. The tablets were stored as per stress testing studies for 3 months. However there was slight variation in vitro release when it is stored at accelerated condition (40°C ± 2°C and 75% RH ± 5%) and there was no change in Thickness, drug content, hardness and release pattern when it is stored at controlled condition (25°C ± 2°C and 60% RH ± 5%). Hence, it is revealed the matrix tablets of batch (F8,F9 and F10) was found to be stable under the conditions mentioned before since there was no significant change in thickness, appearance, drug content, hardness, and *In-vitro* release.

Table 16 Parameters studied on F8, F9 and F10 Formulation Before and After study

Parameters	**Before Stability study**		
	F8	F9	F10
Thickness	3.67 ±0.012	3.63±0.033	3.65±0.001
Hardness	5.2±0.8	5.3±0.5	5.5±0.4
Drug content	97.59%	98.05%	97.08%
Parameters	After Stability study		
	F8	F9	F10
Thickness	3.67 ±0.012	3.63±0.033	3.65±0.001
Hardness	5.2±0.8	5.3±0.5	5.5±0.4
Drug content	97.08%	98.30%	97.68%

*All the value are represents as mean ± S.D. (n=3)

Table 17 Cumulative % drug released of optimized formulation F8, F9 and F10 before stability study.

Time (hrs)	**% Cumulative drug release**		
	Before Stability study		
	F8	F9	F10
0	0	0	0
1	28.43 ± 1.72	35.96± 1.05	21.13 ± 1.00
2	39.08 ± 1	43 ± 1	36 ±1.10
3	57.8 ± 1.52	57.02±1.52	49.01 ± 1
4	61.4 ± 1.02	67.52 ± 1.27	51.89 ±1.04
5	79.28 ± 0.96	74.31 ±1.50	65.33 ±1.15
6	83.36 ±1.18	81.12 ±1.05	72.34 ± 1.50
7	90.02 ±0.99	91.92 ± 1.04	86.39 ± 1.20
8	97.76 ±1.92	99.01 ± 1	98.82 ±0.99

Table 18 Cumulative % drug released of optimized formulation F8, F9 and F10 after stability study.

Time (hrs)	% Cumulative drug release		
	After Stability study		
	F8	F9	F10
0	0	0	0
1	28.43 ± 1.64	35.96± 1.20	21.13 ± 1.48
2	39.08 ± 1.5	43 ± 1.08	36 ±1.27
3	57.8 ± 1.32	57.02±1.42	49.01 ± 0.77
4	61.4 ± 1.20	67.52 ± 1.39	51.89 ±1.46
5	79.28 ± 0.88	74.31 ±1.28	65.33 ±1.32
6	83.36 ±1.30	81.12 ±1.10	72.34 ± 1.34
7	90.02 ±0.66	91.92 ± 1.12	86.39 ± 1.32
8	97.76 ±1.80	99.01 ± 0.89	98.82 ±0.86

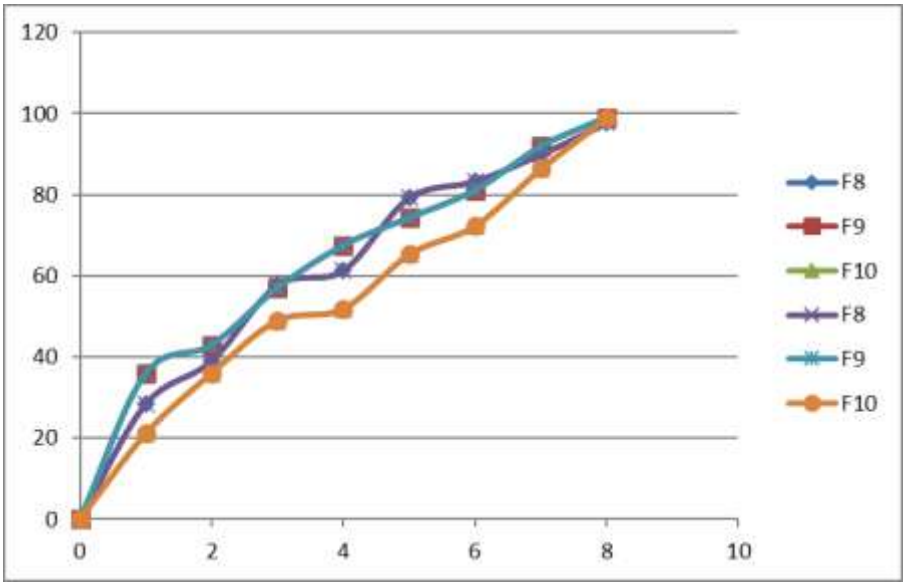


Figure 16 Dissolution profile of formulations F8,F9 and F10 before and after Stability study

There were no considerable change in physical parameter of tablet such as Thickness, Hardness, appearance and drug content of formulations F8,F9 and F10 before and after accelerated Stability study.

The physical parameter of formulations F8,F9 and F10 before and after accelerated Stability study is shown in table.

The percent cumulative drug release and plot of formulations F9 before and after accelerated Stability study is shown in table and figure respectively.

7. Discussion

- Sustain release drug delivery system of matrix tablet are designed to achieve a prolonged therapeutic effect by continuously releasing the medicament over an extended period of time. Such system extended the duration time of drug therapy, reduce side-effect and increases the safety and patient compliance by reducing frequency of dosing.
- In the present study was carried out to develop sustained release matrix tablets of mosapride citrate used as model drug as its half-life is 2-3hrs and use in low dose and to avoid various side effects. Matrix tablets of mosapride citrate with different viscosity grades of Eudragit were prepared by direct compression method and evaluated.
- The matrix of polymers alone could not give sustained release of mosapride citrate for 8 hrs. It is evident from results that matrix tablet prepared by direct compression technique using combination of polymers Eudragit RS 100, Eudragit RL 100, Eudragit E 100 is a better system for sustained release of mosapride citrate. Based on regression values, release of drug was found to be diffusion dominated.
- The present study was carried out to identify and rectify the manufacturing defects in Mosapride Citrate tablets. The Mosapride Citrate tablets were manufactured by Direct Compression Method and formula was optimised from method.
- The common antihypertensive drug Mosapride Citrate shows good dissolution and tableting behavior.
- Preformulation study of drug and excipients were done by visual inspection. Powders mixtures were evaluated for bulk density, tapped density, angle of repose and Compressibility and Housner's ratio.
- Mosapride Citrate tablet formulations were prepared and evaluated. Evaluations like thickness, hardness, friability, weight variation, assay, dissolution and accelerated stability study were performed. Optimized formulations were subjected to evaluations like thickness, hardness, friability, weight variation, assay, dissolution and compared with marketed sample.

8. Conclusion

- The present work showed that Mosapride Citrate tablets were successfully manufactured by Direct Compression.

- Mosapride Citrate tablet shows good dissolution, by using Eudragit used as polymers i.e. Eudragit Rs, Eudragit RL, Eudragit E. and hence all the formulations shows successful assay and dissolution.
- Since the Mosapride Citrate does not possess excellent fluidity and flow, Magnesium Stearate was selected as common lubricant, because of it, a uniform flow from hopper to die was possible. It prevents the adhesion of tablet material to the machine parts such as punches and dies, reduce inter particle friction and facilitates the ejection of tablets from the die cavity.
- In formulation F9, percentage of Eudragit was increased from 20% - 24.00% (in F9) while the percentage of Eudragit RS kept constant up to 20% and tablets of formulation F9 were evaluated for in vitro dissolution study. The matrix tablets of formulation F9 released the drug slowly as per standard dissolution profile up to 8 hours and total drug release from matrix tablet of formulation F9 at the end of 8th hours was 99.01% Hence, it can be concluded that once daily sustained release matrix tablet of mosapride citrate having short half life, was found to exert a satisfactory sustained release profile. which may provide an improved bioavailability, increased therapeutic efficacy and patient compliance.
- All batches give the better result of Mosapride citrate tablet, also the F9 batch gives the very good results. And hence it is consider as the optimize batch from formulations.
- Stability study for optimized trials were carried out and concluded that there was no much effect of the temperature and moisture on the various parameters of the tablet.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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