# FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF MOSAPRIDE CITRATE.

Dissertation Submitted to

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**MASTER OF PHARMACY**

**IN**

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Submitted by

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**Under the guidance of**

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# EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF MOSAPRIDE CITRATE"** submitted by the student bearing **Reg. No: 26103015** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfilment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on ……

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# DECLARATION

I hereby declare that the dissertation work entitled **"FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF MOSAPRIDE"** is based on the original work carried out by me under the guidance of **Dr. V. Venu, M.pharm, Ph.D**., for submission to The Tamil Nadu Dr. M.G.R Medical University, Chennai, in the partial fulfillment of the requirement for the award of **Degree of Master of Pharmacy** in Pharmaceutics. The work is original and has not been submitted in part or full for the award of any other Diploma or Degree of this or any other University. The information furnished in this dissertation is genuine to the best of my knowledge and belief.

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**Tanushree Adhikary**

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# CONTENTS

# ABBREVIATIONS

| | | |
|---|---|---|
| mg | - | Milligram |
| Kg | - | Kilogram |
| % | - | Percentage |
| gm | - | Gram |
| ml | - | Milliliter |
| µg/ml | - | Microgram per ml |
| SR | - | Sustained release. |
| GERD | - | Gastro Esophageal Reflux Diseases |
| NDDS | - | Novel Drug Delivery System |
| SMP | - | Standard Manufacturing Procedure |
| IP | - | Indian Pharmacopoeia |
| BP | - | British Pharmacopoeia |
| HPMC | - | Hydroxy Propyl Methyl Cellulose |
| $F_1$ | - | Matrix tablets using HPMC K4M 10mg. |
| $F_2$ | - | Matrix tablets using HPMC K4M 15mg. |

$F_3$ - Matrix tablets using HPMC K15M 10mg.

$F_4$ - Matrix tablets using HPMC K4M 10mg and HPMC K15M 10mg.

$F_5$ - Matrix tablets using HPMC K4M 15mg and HPMC K15M 10mg.

$F_6$ - Matrix tablets using HPMC K4M 18mg and HPMC K15M 10mg.

$F_7$ - Matrix tablets using HPMC K4M 16mg and HPMC K15M 15mg.

$F_8$ - Matrix tablets using HPMC K4M 20mg and HPMC K15M 20mg.

$F_9$ - Matrix tablets using HPMC K4M 20mg and HPMC K15M 25mg.

S.C.P. - Standard Compression Procedures

S.O.P. - Standard Operating Procedures

ORML - Operating Raw Material List

M/C - Machine

UP - Upper Punch

LP - Lower Punch

NMT - Not More Than

NLT - Not Less Than

rpm - Revolution Per Minute

H.R - Hausner's Ratio

# 1. INTRODUCTION

## 1.1 Oral drug delivery

Drugs are most frequently administered by oral route. Although a few drugs taken orally are intended to be dissolved in the mouth, nearly all drugs taken orally are swallowed. Of these, most are taken for the systemic drugs effects that result after absorption from the various surfaces along the gastrointestinal tracts. A few drugs such as antacids are swallowed for their local action in the gastrointestinal tracts.[1]

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, cost-effective manufacturing process and flexibility in dosage form.[7] Oral sustained release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects.[8] The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu.[9]

## 1.2 Historical perspective of sustained drug delivery

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced from 1938 patent of Israel Lipowski. This work involved coated pellets for prolong release of drug and was presumably the forerunner to the development of the coated particle approach to sustained drug delivery that was introduced in the early 1950's. There has been 40 years of research and development experience in the sustained release area since that patent, and a number of strategies have been developed to prolong drug levels in the body. These range from the very simple, slowly dissolving pellets or tablets to the technologically sophisticated controlled drug-release systems which have been recently started to appear in the market and in pharmaceutical literature.[20]

Over past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled-release drug-delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease state, a substantial number of therapeutically effective compounds already exists. The effectiveness of drug however is often limited by side effects or the necessity to administer the compounds in clinical setting.[3]

Successful fabrication of sustained release products is usually difficult & and involves consideration of physicochemical properties of drug, pharmacokinetic behavior of drug, route of administration, disease state to be treated and, most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug.[3]

The reasons behind the increase in the interest in new system are firstly reorganization of the possibility of repeating successful drugs by applying the concepts and techniques of controlled release drug delivery systems, coupled with the increasing expense in bringing new drug entities to market, has encouraged the development of new delivery system and secondly new systems are needed to deliver the novel, genetically engineered pharmaceuticals for example- peptides & proteins to their site of action without incurring significant immunogenicity or biological inactivation.[3]

## 1.3 Sustained Release Concept[3]

A sustained release product may be considered one in which a drug is initially made available to the body in an amount sufficient to cause the desired pharmacological response as rapidly as is consistent with the properties of the drug determining its intrinsic availability for absorption; and one which provides for maintenance of activity at the initial level for a desirable number of hours in excess of the activity resulting from the usual single dose of drug.[5]

For the pharmaceutical industry sustained release dosage forms provide multiple commercial benefits. Reduced dosing frequency improves patient compliance. Better therapeutic outcomes due to improved efficacy and improved tolerability can lead to fewer medication switches and greater physician loyalty.[53] For any drug therapy to be successful, the drug must reach the target tissue or systemic circulation in optimum concentration which should be maintained for desired time. In recent years, attention has been focused on the development of new drug delivery system rather than invention of new molecules. Because the development cost for new drug molecule is very high.[26] Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effects by continuously releasing medication over an extended period of time after administration of single dose.

Sustained release and controlled release will represent separate delivery processes; sustained release constitutes any dosage from that provides medication over an extended period of time. Controlled release however, denotes that, system is able to provide same actual therapeutic control, whether this is temporal nature, spatial nature, or both. In other words, the system attempts to control drug concentration in target tissue. This correctly suggests that there are sustained-release systems that cannot be considered as controlled release.

In general, the goal of a sustained release dosage form is to maintain therapeutic blood level or tissue level of the drug for extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constitutes of the amount of drug in the delivery system (a constant release rate). Sustained release systems generally do not attain this type of release and usually try to minis zero order release by providing drug in a slow first order fashion (concentration-dependent).

Oral ingestion has been the most convenient and commonly employed route of drug delivery. Indeed, for sustained – release systems, the oral route of administration has received the most attention with respect to research on physiological and drug constraints as well as designing and testing of products.

With most of orally administered drugs targeting is not primary concern, and it is usually intended for drugs to permeate to the general circulation and perfuse to other body tissues (the obvious exception being medication intended for local gastrointestinal tissue treatment), for this reason, most systems employed are of the sustained-release variety. It is assumed that increasing concentration at the absorption site will increase the rate of absorption and, therefore, increase circulating blood levels, which in turn promotes greater concentrations of the drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion.[24]

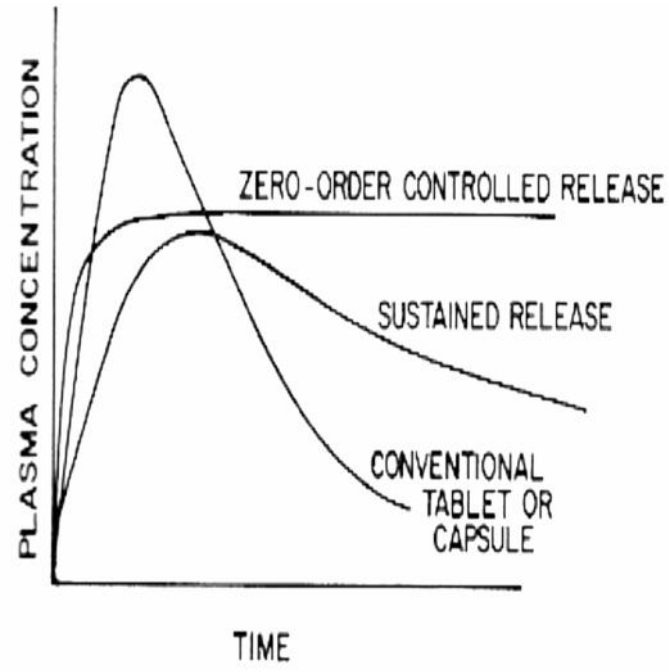



Fig. 1 Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero-order controlled release formulation.

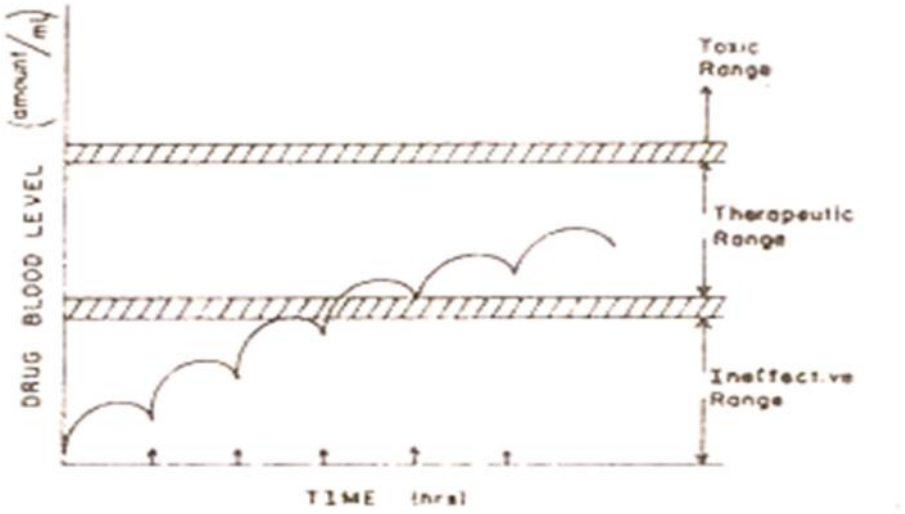



**Figure 2, typical drug blood level versus time profiles following oral multiple dose therapy[6].**

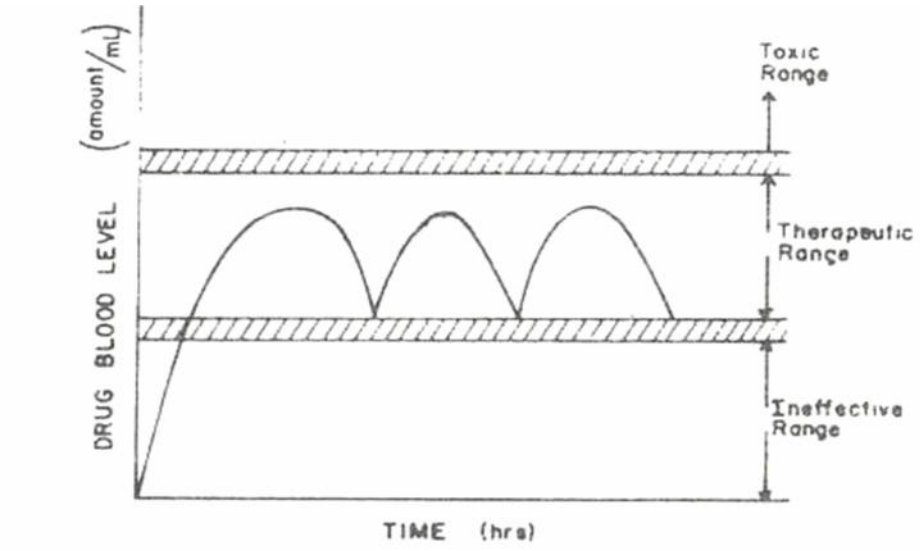



**Figure 3, typical drug-blood level versus time profile for delayed release drug delivery by repeat action dosage form[6].**

An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. This is shown in Figure **2** for the oral route. In this case the drug blood level reached and time required to reach that level depend on the dose and dosing interval. There are several potential problems inherent in multiple-dose therapy. If the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys in the drug blood level may result. For example, drug with short half-life requires frequent dosing to maintain constant therapeutic levels. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease state. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

### 1.4 Rationale of sustained drug delivery[3]

The basic rationale for sustained drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a design property of a sustained dosage form and less or not at all a property of the drug molecules inherent kinetic properties. Thus optional design of sustained release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs.[22] The aim of sustained drug delivery is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side-effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route[7].

There are certain considerations for the formation of sustained release formulations: If the active compound has a long half-life (over six hours), it is sustained on its own. If the pharmacological activity of the active compound is not related to its blood levels, time releasing than has no purpose. If the absorption of

the active component involves an active transport, the development of a time-release product may be problematic. Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unworthy to take and another mode of administration would be recommended.[24]

As mentioned earlier, primary objectives of controlled drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and frequent dosing. For conventional dosage forms, only the dose (D) and dosing interval (C) can vary and, for each drug, there exists a therapeutic window of plasma concentration, below which therapeutic effect is insufficient, and above which toxic side effects are elicited. This is often defined as the ratio of median lethal dose ($LD_{50}$) to median effective dose ($ED_{50}$).

**1.5 Potential advantages of sustained drug therapy[6].**

1) Improved patient convenience and compliance due to less frequent drug dosing.

    - Employs minimum drug.
    - Minimizes or eliminates local and systemic side effects.
    - Obtain less potentiating or deduction in drug activity with chronic use.
    - Avoidance of night time dosing.

2) Reduction in fluctuation in steady-state levels and therefore-

    - Better control of disease condition, and
    - Reduced intensity of local or systemic side-effects.
    - It minimizes drug accumulation with chronic dosing.

3) Improves efficacy in treatment.

    - Cure or control confirm more promptly.

- Improve control of condition thereby reducing fluctuation in circulating drug level.
- Improve bioavailability of some drugs.
- Make use of special effects, example- sustained release aspect for morning.
- More uniform effect.

4) Reduction in health care costs through-

- Improved therapy.
- Shorter treatment period.
- Lower frequency of dosing.
- Reduction in personnel time to dispense, administer and monitor patients.

5) Improved therapy-

- Sustained blood level- The dosage form provides uniform drug availability/blood levels unlike peak and valley pattern obtained by intermittent administration.
- Attenuation of adverse effects- The incidence and intensity of undesirable side effects caused by excessively high peak drug concentration resulting from the administration of conventional dosage form is reduced.
- It is seldom that a dose is missed because of non-compliance by the patient.

6) Increased safety margin of high potency drugs due to better control of plasma levels.
7) Maximum utilization of drug enabling reduction in total amount of drug administered.

## 1.6 Disadvantages of sustained release dosage forms[7].

- They are costly.
- Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.
- Poor systemic availability in general.
- Effective drug release period is influenced and limited by GI residence time.

## 1.7 Factors governing the design of sustained/controlled release dosage form[6].

### A) Drug related Factors

- Molecular size and diffusivity
- Aqueous solubility and pKa.
- Partition coefficient.
- Molecular size.
- Drug stability.
- Protein binding.

### B) Biological factors

- Absorption.
- Distribution.
- Metabolism.
- Elimination.
- Elimination half-life.
- Therapeutic Index.
- Dose size.
- Duration of action.
- Plasma concentration response.
- Margin of safety.
- Side effects.

- Diseased state.

### 1.7.1 Physicochemical Factors[6,7,34].

#### 1) Molecular size and diffusivity

A drug must diffuse through a variety of biological membranes during its time course in the body. In addition to these, drugs in many sustained release systems must diffuse through a rate controlling polymer membrane or matrix. The ability of a drug to diffuse in polymer, is so called diffusivity (diffusion coefficient D) is a function of its molecular size (or molecular weight). For most polymers it is possible to relate log D empirically to some function of molecular size as,

$$\textbf{Log D = - Sv log V + Kv = - Sm logM + Km}$$

Where, V = molecular volume.

M = molecular weight.

Sv, Sm, Kv, Km = constant.

The value of 'D' thus is related to the size and shape of the cavities as well as size and shape of drugs. Generally, values of the diffusion coefficient for drugs of intermediate molecular weight (i.e150 to 400 Daltons), through flexible polymers, range from $10^{-6}$ to $10^{-9}$ $cm^2$/sec, with values in the order of $10^{-8}$ being most common. A value of approximately $10^{-6}$ is typical for these drugs through water as the medium.

For drugs with molecular weight greater than 500 Da, their diffusion coefficients in many polymers are frequently are so small that they are difficult to quantify, (i.e., less than $10^{-12}$ $cm^2$/sec). Thus, high molecular weight drugs and /or polymeric drugs should be expected to display very slow release kinetics in extended-release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.

#### 2) Aqueous solubility and pKa

Solubility is defined as the amount of material that remains in solution in a given volume of solvent containing undissolved material. It is the thermodynamic property of a compound. The fraction of drug absorbed into the portal blood is a function of the amount of drug in the solution in the G.I tract, i.e. the intrinsic permeability of the drug.

For a drug to be absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and, hence, the driving force for diffusion across membranes. Dissolution rate is related to aqueous solubility as shown by the Noyes-Whitney equation that, under sink condition, is $\mathbf{dc/dt = K_D A.C_s}$

Where,

dc/dt = Dissolution rate

$K_D$ = Dissolution rate constant

A = Total surface area of the drug particles.

Cs = Aqueous saturation solubility of the drug.

The dissolution rate is constant only if surface areas (A) remain constant, but, as the initial rate is directly proportional to aqueous solubility (Cs). Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems.

The aqueous solubility of weak acids or bases is governed by the pKa of the compound and pH of the medium.

For weak acids,

$$\mathbf{St = S_0 (1+Ka/ [H^+]) = S_0 (1+10^{pH-pKa})} \ldots\ldots\ldots\ldots \mathbf{(1)}$$

Where,

St = Total solubility (both ionized and un-ionized forms) of the weak acid

$S_0$ = Solubility of the un-ionized form

Ka= Acid dissociation constant

$H^+$= Hydrogen ion concentration of the medium

Equation (1) predicts that the total solubility, St, of a weak acid with a given pKa can be affected by the pH of the medium.

For a weak base,

$$\mathbf{St = S0\ (1+\ [H^+]/Ka) = S0\ (1+10^{pKa-pH})\ldots\ldots\ (2)}$$

Where,

St = Total solubility (both conjugate acid and free base forms) of the weak base.

$S_0$ = Solubility of the free base form.

Ka = Acid dissociation constant of the conjugate acid

So, total solubility (St), of a weak base with a given pKa can be affected by the pH of the medium.

Extremes in the aqueous solubility of a drug are undesirable for formulation into controlled release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. Formulation of such a drug into a controlled-release system may not provide considerable benefits over conventional dosage forms.

Any system relying upon diffusion of drug through a polymer as the rate-limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is the concentration of drug in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it often is quite difficult to decrease its dissolution rate and slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is, however, one possible method for preparing controlled release dosage forms.

**pKa- Ionization Constant**

The pKa is a measure of the strength of an acid or a base. The pKa allows us to determine the charge on a drug molecule at any given pH. Drug molecules are active in only the undissociated state and also unionized molecules cross these lipoidal membranes much more rapidly than the ionized species.

**3) Partition Coefficient**

Partition coefficient influences not only the permeation of drug across the biological membranes but also diffusion across the rate controlling membrane or matrix.

Between the time when a drug is administered and when it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid-like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes (i.e, its membrane permeability) in its apparent oil/water partition coefficient, defined as

$$\mathbf{K=C_0/Cw}$$

Where,

$C_0$ = Equilibrium concentration of all forms of the drug e.g., ionized and unionized in an organic phase at equilibrium.

Cw = Equilibrium concentration of all forms in aqueous phase.

Drugs with large values of 'K' are very oil-soluble and will partition into membrane quite readily. The relationship between tissue permeation and partition coefficient for the drug generally is defined by the Hansch correlation, which describes a parabolic relationship between the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient.

The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. The more effectively a drug crosses membranes, the greater its activity.

There is also an optimum partition coefficient, value below which results in decreased lipid solubility, and the drug will remain localized in the first aqueous phase it contacts. Values larger than the optimum result in poorer aqueous solubility but enhanced lipid solubility, and the drug will not partition out of the lipid membrane once it gets in. The value of K at which optimum activity is observed is approximately 1000/1 in n-octanol/water. Drugs with a partition coefficient that is higher or lower than the optimum are, in general, poorer candidates for formulation into extended-release dosage forms.

**4) Drug stability**

One important factor for the loss of drug is through acid hydrolysis and/or metabolism in the GIT when administered orally. It is possible to significantly improve the relative bioavailability of a drug that is unstable in GI tract by placing it in a slowly available controlled release form. For those drugs that are unstable in the stomach, the most appropriate controlling unit would be one that releases its content only in the intestine. The release in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus, the protein binding nature of a drug plays significant role in its duration of therapeutic effect. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a

controlled–release dosage form. Drugs sometimes may bind to biopolymers in the GI tract, which could have an influence on controlled-drug delivery.

**Pharmacokinetic and Pharmacodynamic Considerations**

### 1.7.2 Biological Properties[6].

#### 1) Absorption

It is the process by which a drug proceeds from the site of administration to the site of measurement within the body. Since the drug cannot be generally measured directly at the site of action, its concentration is measured at the alternative site, the plasma. The concentration of drug in plasma also reflects the concentration of drug at the site of action. The rate of absorption is then measured as the rate of disappearance of drug in the plasma.m[jain]The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into an extended-release system. The most critical case of oral administration is $K_r<<<K_a$. Assuming that the transit time of drug through the absorptive area of GIT is between 9-12 hours, the maximum absorption half-life should be 3-4 hours. This corresponds to a minimum absorption rate constant $K_a$ value of 0.17-0.23/hr necessary for about 80-95% absorption over a 9-12hr transit time.

For a drug with a very slow rate of absorption ($K_a<<0.17$/hr), the first order release rate constant $K_r$ less than 0.17/hr results is unacceptably poor bioavailability in many patients. Therefore slowly absorbed drug will be difficult to be formulated into extended release systems where the criterion $K_r<<<K_a$ must be met. If the drug were erratically absorbed because of variable absorptive surface of GIT, design of the sustained release product would be more difficult or prohibitive.

#### 2) Distribution

It refers to the reversible transfer of drugs from one location to another within the body. Distribution occurs at various rates and to various extents. Several factors determine the distribution pattern of a drug. They include-

- rate of delivery of a drug to the tissues by the circulation.
- the ability of a drug to pass through tissue membranes.
- the binding affinity of drug to plasma proteins, erythrocytes, and tissues.

The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in its overall elimination kinetics. Apparent volume of distribution and the ratio of drug in tissue to plasma T/P concentration are used to describe the distribution characteristics of a drug.

For drugs which have apparent volume of distribution higher than real volume of distribution i.e., drugs which are extensively bound to extra vascular tissues, the elimination half life is decreased i.e., the drug leaves the body gradually provided drug elimination rate is limited by the release of drug from tissue binding sites and that drug is released from the tissues to give concentrations exceeding the threshold level or within the therapeutic range, one can assume that such drugs are inherently sustained. The larger the volume of distribution, the more the drug is concentrated in the tissues compared with the blood. It is the drug in the blood that is exposed to hepatic or renal clearance, so that when the distribution volume is large these mechanisms have fewer drugs to work on. By contrast, if the volume of distribution is small, most of the drug in the body is in the blood and is accessible to the elimination process.

**3) Metabolism**

The metabolism of a drug can either inactivate or active drug or convert an inactive drug to active metabolite. Complex metabolic patterns would make the sustained release design much more difficult particularly when biological activity is wholly or partly due to a metabolite.

There are two areas of concern related to metabolism that significantly restrict sustained release product design. First, if a drug upon chronic administration is capable of either inducing or inhibiting enzyme synthesis, it will be a poor candidate for a sustained release product because of the difficulty of maintaining

uniform blood levels of a drug. Second, if there is a variable blood level of a drug through either intestinal (or tissue) metabolism or through first pass effect, this also will make sustained release dosage form difficult, since most of the process are saturable, the fraction of the drug loss would be dose dependent and that would result in significant reduction in bioavailability if the drug is slowly released over a extended period of time.

**4) Elimination**

The process of elimination mainly comprises of-

- biotransformation or metabolism of the drug primarily by the liver, and
- renal excretion of both the unchanged drug and its metabolites.
- Metabolism by the gut, epithelium, lungs, blood, kidneys, and other organs and tissues, biliary excretion and excretion through sweat, saliva and breast milk are some of the other modes of elimination.

**5) Elimination Half Life**

Half life is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half and is determined by both clearance (Cl) and volume of distribution (Vd).

$$\mathbf{t_{1/2}=0.693.Vd/Cl}$$

Half life is increased by increasing in volume of distribution or a decrease in clearance, and vice-versa. The larger the volume of distribution the more the drug is concentrated in the tissues compared with the blood. If the volume of distribution is small, most of the drug in the body is in the blood and is accelerated to the elimination process.

For drugs that follow linear kinetics, the elimination half-life is constant and does not change with dose or drug concentration. For drugs that follow non-linear kinetics, the elimination half-life and drug clearance both change with dose or drug concentration. Drugs with short half-lives (<2hrs) and high dose impose a constraint on formulation into sustained release systems because of the necessary dose size and drugs with long half-lives (>8hrs) are inherently sustained. Sustained release products for drugs with intrinsically long biological half-lives are available. As expected, little or no therapeutic advantages have been demonstrated in these products over conventional dosage forms.

**6) Therapeutic Index**

It is most widely used to measure the margin of safety of a drug.

**TI = TD 50 / ED50**

Where,

TD50 = median toxic dose
ED50 = median effective dose

For potent drugs, the value of TI is small. Larger the value of TI, safer is the drug. Drugs with very small value of TI are poor candidates for formulation into controlled-release product. A drug is considered to be relatively safe if its TI value exceeds 10.

**7) Dose Size**

Generally, controlled-release systems will contain greater amount of drug than a corresponding conventional dosage form. For those drugs requiring large conventional doses, the volume of the sustained dose may be so large as to be impractical or unacceptable. The same may be true for drugs that require a large release rate from the controlled-release system, e.g., drugs with shorter half-life.

**8) Duration of Action**

It is the time period for which the blood levels remain above the MEC and below the MSC levels (or) more specifically within the therapeutic window. Drugs acting for long duration are unsuitable candidates for formulation into sustained release forms.

The long duration of action of few drugs is determined by plasma half-life and the affinity of binding to tissue. Drugs with short plasma half-life but high binding tissue may remain active for 24 hours. In contrast few drugs which has relatively shorter duration of action has weaker tissue binding and short plasma half life. Receptor occupation, tissue binding, half life, metabolism, partition coefficient, irreversible binding to cells are some parameters which are responsible for long duration of action of drugs.

**9) Plasma concentration-response**

Drugs whose pharmacological activity is independent of its concentration are poor candidates for sustained release systems.

### 1.8 Classification of Oral sustained release systems[7].

**1) Continuous release systems**

a) Dissolution controlled release systems.
   - Matrix type.
   - Reservoir type.

b) Diffusion controlled release systems.
   - Matrix type.
   - Reservoir type.

c) Dissolution and diffusion controlled release systems.
d) Ion exchange resin drug complexes.
e) Slow dissolving salts and complexes.
f) pH dependent formulations.
g) Osmotic pressure controlled systems.
h) Hydrodynamic pressure controlled systems.

**2) Delayed transit and continuous release systems**

Altered density systems.

- High density.
- Low density.
- Floating.
- Mucoadhesive systems.
- Size based systems.

**3) Delayed release systems**

- Intestinal release systems
- Colonic release systems

## 1.9 Matrix devices[6].

Historically, the most popular drug delivery system has been the matrix because of its low cost and eases of fabrication. Matrix devices consist of drug dispersed homogenously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. Methods of altering the kinetics of drug release from the inherent first order behavior especially to achieve a constant rate of drug release from matrix devices have involved several factors[24].

This process continues with the interface between the bathing solution and the solid drug moving toward the interior. For this system, rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

- A pseudo steady state is maintained during drug release.

- The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.
- The bathing solution provides sink conditions at all times.
- The diffusion coefficient of drug in the matrix remains constant i.e. no change occurs in the characteristics of the polymer matrix.

*Higuchi* has derived the appropriate equation for drug release for this system-

**dM = Codh-(Cs/2) dh ……..... (1)**

Where,

dM = Change in the amount of drug released per unit area.

dh = Change in the thickness of the zone of matrix that has been depleted of drug.

$C_0$ = Total amount of drug in a unit volume of the matrix.

Cs = Saturated concentration of the drug within the matrix.

From diffusion theory,

**dM = (DmCs/h).dt ……. (2)**

Where,

Dm = diffusion coefficient in the matrix.

Equation (1) and (2) integrating and solving for 'h' gives,

$M= [CsDm (2Co-Cs) t]^{1/2}$…… (3)

When amount of drug is in excess of the saturation concentration, that is $C_0$>>Cs,

**$M= [2 Cs Dm C_0 t]^{1/2}$…… (4)**

Equation (4) indicates that the amount of drug released is a function of the square root of time.

The drug release from a porous or granular matrix can be described by

$$M= (Ds.Ca.\{P/T\}.[2C_0-PCa]t)^{1/2}$$

Where

P = Porosity of the matrix.

T = Tortuosity.

Ca= Solubility of the drug in the release medium.

Ds= Diffusion coefficient in the release medium.

The system is slightly different from the previous matrix system in that the drug is able to pass out of the matrix through fluid filled channels and does not pass through the polymer directly. Thus diffusion sustained products are based on two approaches. The first approach entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid[24.]

### 1.9.1 Requirements of matrix materials

The matrix materials must comply with the following conditions,

- They must be completely inert and non-reactive with the drug and additives in the tablet.
- They must be able to form stable and strong matrices when compressed either directly or more often as granules prepared by the addition of a binding agent.

- They must be non-toxic.

### 1.9.2 Advantages of Matrix Diffusion System

A hydrophilic matrix system essentially consists of a drug dispersed in water swelling viscous polymer. These systems offer a number of advantages over other sustained release technologies namely-

- Unlike reservoir devices, products can be manufactured using conventional processes and equipments.
- Can deliver high molecular weight compounds.
- Development cost and time associated with matrix system are viewed as variables, and no additional capital investment is required.
- Simplicity of formulation.
- The system has usually a rate controlling agent GRAS (generally accepted as safe) food polysaccharides.
- The systems are eroded as they pass the GIT thus there is no accumulation of "Ghosts" or empty shells.
- As system depends on both diffusion and erosion for drug release, release is not totally dependent on gastro intestinal motility.
- It is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.
- Number of matrix former is available allowing development of formulations that meet special needs and avoid patient infringement.
- Lastly, it offers easy scalability and process validation due to simple manufacturing processes.

### 1.9.3 Disadvantages of Matrix Diffusion System

- Cannot obtain zero order release.
- Removal of remaining matrix is necessary for implanted systems.

### 1.10 Matrix tablet

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant material, and additives to form a tablet in which drug is embedded in a matrix core of retardant. Sustained-release matrix tablets are formulated so that the active ingredient is embedded in a matrix of insoluble substance so that the dissolving drug has to find its way out through the holes in the matrix. In some sustained release formulations the matrix physically swells up to form a gel, so that the drug first has to dissolve in the matrix, then exit through the outer surface[24]. The adjustment of the polymer concentration, the viscosity grades and addition of different types and levels of excipients to the polymer matrix can modify the drug release rate[23].

### 1.10.1 Materials used as retardants in matrix tablet formulations.

There must be sufficient polymer content in a matrix system to form a uniform barrier. The barrier protects the drug from immediately releasing into the dissolution medium. If the polymer level is too low, a complete gel layer may not form. In most studies, increased polymer level in the formulation results in decreased drug-release rates. There are three classes of materials used as retardants in matrix tablet formulations viz:

**1) Insoluble, inert polymers**

Tablets prepared from these materials are designed to be egested intact and not break apart in GI tract. Egested tablets contain unreleased drug in the core.

**Examples-** Polyethylene
Poly vinyl chloride
Methyl acrylate – methacrylate copolymer
Ethyl cellulose

**2) Insoluble, erodible polymers**

These form matrices that control release through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to the totally insoluble polymer matrix. Total release of drug from

wax-lipid matrices is not possible, since a certain fraction of the dose is coated with impermeable wax films.

**Examples-** Carnauba wax in combination with stearic acid, steryl alcohol
Castor wax
Triglycerides
Poly ethylene glycol
Polyethylene glycol mono stearate

**3) Hydrophilic polymers**

This group represents non-digestible materials that form gels in situ. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion of the gelled layer. The extent to which diffusion or erosion controls release depends on the polymer selected for formulation as well as on drug: polymer ratio.

**Examples-** Methyl cellulose
Hydroxy Ethyl cellulose
Hydroxy propyl methyl cellulose
Sodium alginate.
Sodium carboxy methyl cellulose
Poly ethylene oxide
Poly vinyl alcohol
Galacto mannose
Carbopol
Hydroxy propyl cellulose
Guar gum
Alginic acid
Chitosan
Pectin

**1.10.2 Types of Matrix Tablets[21].**

There are 3 Types of Matrix Tablets

- Hydrophilic matrices
- Fat wax matrices
- Plastic matrices

**1) Hydrophilic Matrix Tablet**

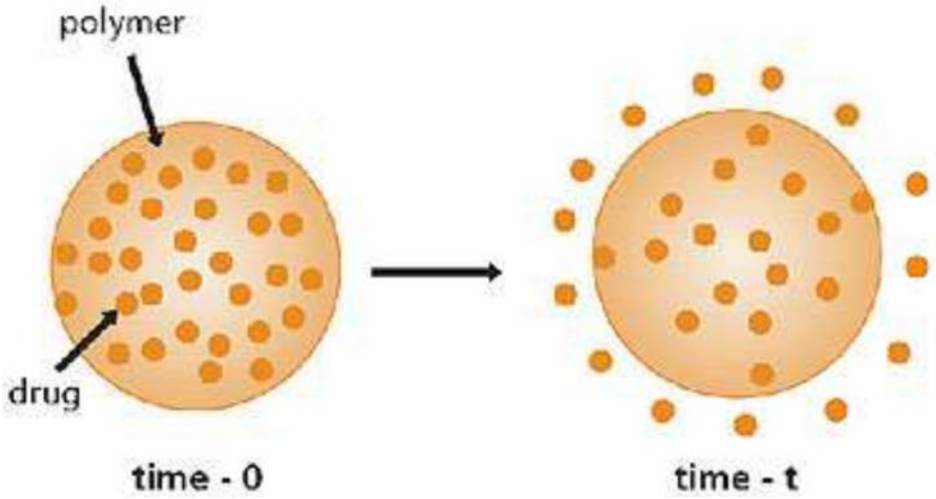
Hydrophilic matrix is the one where the release-retarding material is water-swellable or swellable cum erodible hydrocolloid such as high molecular weight. Hydrophilic matrices containing swellable polymers are referred to as swellable sustained release systems or hydrophilic matrix tablets. A number of polymers have been investigated to develop in situ gel-forming systems, due to the ability of these matrices to release an entrapped drug in aqueous medium and to regulate release of such drug by control of swelling and cross linking.[rupali kale] hydroxypropyl methylcellulose (HPMC), Eudragit, Sodium alginate and Guar gum are the polymers most widely used as gel-forming agents in the formulation of solid sustained release dosage forms. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from these dosage forms are controlled by the hydration of polymer, which forms a gel barrier through which the drug diffuses[23].

**Examples-**

Sodium Carboxy Methylcellulose, Methyl Cellulose, Hydroxy propyl Methyl Cellulose, Hydroxyl Ethyl cellulose, Polyethylene Oxide, Poly Vinyl Pyrrolidine, Poly Vinyl Acetate, Gelatin, Natural Gums.

Several commercial patented hydrophilic matrix systems are currently in use, such as synchron technology and hydrodynamically balanced system.

**Fig.4 Schematic representation of diffusion sustained drug release: matrix system.**




**Advantages**

- Ease of manufacture.
- Excellent uniformity of matrix tablet.

**2) Fat wax matrix tablet**

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactants and spray drying techniques.

**Examples-** Polyethylene, Ethyl cellulose, Glyceryl esters of hydrogenated resins have been added to modify the drug release pattern.

**3) Plastic matrix tablets**

With plastic materials, tablets can be easily prepared by direct compression of drug provided the plastic material can be communited or granulated to desired particle size to facilitate mixing with drug particles.

**Examples-**

Polyvinyl chloride, Polyethylene, Vinyl acetate, Vinyl chloride copolymer, Vinyllidine chloride, Acrylate (or) Methyl methacrylate copolymer, Ethyl cellulo se, Cellulose acetate, Polystyrene.

## 1.11 Dry Granulation [8]

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, pre-compression, or the double-compression method. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication and compression. The active ingredient, diluents (if one is required), and part of the lubricant are blended. One of the constituents, either the active ingredient or the diluents, must have cohesive properties. Powdered material contains a considerable amount of air; under pressure this air is expelled and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug.

When slugging is used, large tablets are made as slugs because fine powders flow better into large cavities. The punches should be flat-faced. The compressed slugs are comminuted through the desirable mesh screen either by hand, or for larger quantities through the Fitzpatrick or similar comminuting mill. The lubricant remaining is added to the granulation, blended gently, and the material is compressed into tablets[4]. Compression granulation has been used for many years, and is a valuable technique in situations where the effective dose of drug is too high for direct compaction, and the drug is sensitive to heat and moisture or both, which precludes wet granulation. Many drugs such as Aspirin and vitamin formulations are prepared for tabletting by compression granulation. Other drugs are aspirin combinations, acetophenetidin, thiamine hydrochloride, ascorbic acid, magnesium hydroxide, and other antacid compounds.

Compression granulation involves the compaction of components tablet formulation by means of a tablet press or specially designed machinery, followed by

milling screening, prior to final compression into tablet. When the initial blend of powder is forced into the dies of large capacity tablet press and is compacted by means of flat punches, the compacted masses are called ***slugs,*** and process is referred to as ***slugging*****. [**Usually, extra large tablet punches are used to form compressed slugs of the powder material. This procedure is usually slow because the inherently poor compressibility of the powders requires slower press speeds to provide the extended compression dwell time under load needed to hold the compacted material together[9]. After compression, the slugs are broken down using a hammer mill or an oscillating granulator to obtain a granulation with a suitable particle size distribution. It is then screened or milled to produce a granular form of a tabletting material, which now flows more uniformly than the original powder mixture. When a single slugging process is insufficient to confer the desired granular properties to the material, the slugs are sometimes screened, slugged again, and screened once more.

Slugging is just an elaborate method of subjecting a material to increased compression time. The act of slugging followed by screening and subsequent compression of the particles is roughly equivalent to an extended dwell time during compression in tablet machine. The two or more times that the material is subjected to compaction pressers causes a strengthening of the bonds that holds the tablet together. The resultant granules increased the fluidity of the powder mixtures, which by themselves do not flow well enough to fill the dies satisfactorily.

**Table No 1 Processing steps involved in tablet granulation technique.[7]**

| Processing step | Wet granulation | Dry granulation |
|---|---|---|
| Raw material | Yes | Yes |
| Weigh | Yes | Yes |
| Screen | Yes | Yes |
| Mix | Yes | Yes |
| Compress(slug) | No | Yes |
| Wet mass | Yes | No |
| Mill | Yes | No |
| Dry | Yes | No |
| Mill | Yes | Yes |
| Mix | Yes | Yes |
| Compress | Yes | Yes |

### 1.11.1 Advantages of Dry Granulation over Wet Granulation[8].

- The compression granulation (dry) requires less equipment and steps than wet granulation.
- Dry granulation technique eliminates the addition of moisture and application of heat and thus useful for moisture and heat sensitive drugs.
- Dry granulation technique is less time consuming and labour requirement is less.
- Dry granulation is an economical technique.
- Fewer manufacturing steps.

## 1.12 DISEASE PROFILE

Gastro-esophageal reflux disease or (GERD) is defined as a collection of symptoms that occur when stomach acid and other irritating substances move from the stomach into the esophagus.

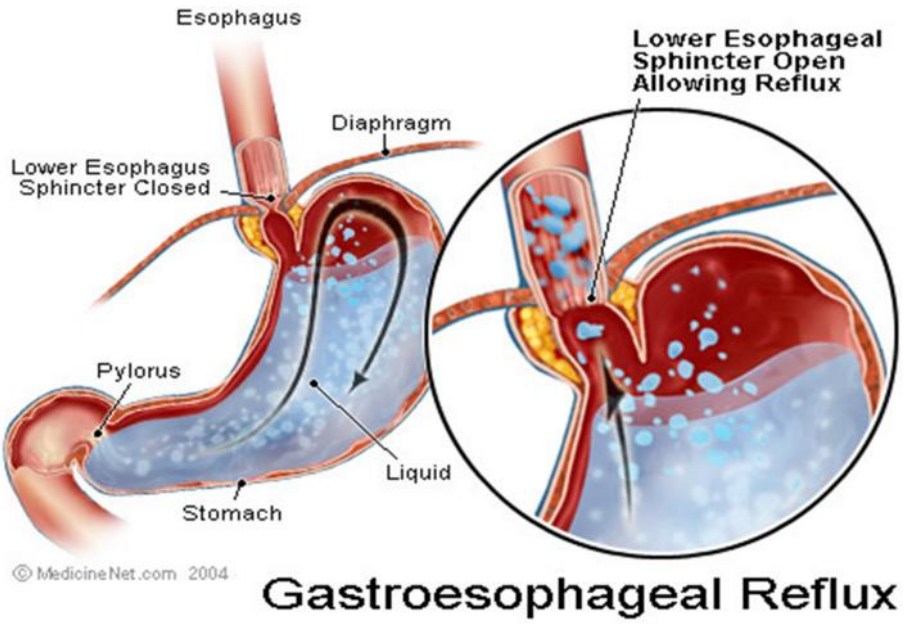



**Fig.5 Gastroesophageal reflux**

**Symptoms of GERD**

The symptoms of GERD may include persistent heartburn, acid regurgitation, and nausea. Some people have GERD without heartburn. Instead they experience pain in the chest that can be severe enough to mimic the pain of a heart attack, hoarseness in the morning, or trouble swallowing. Some people also feel like they have food stuck in their throat or like they are choking. GERD can also cause a dry cough and a bad breath[64]. Other common symptoms are belching and hyper-salivation. Some uncommon symptoms of GERD that would require further evaluation include cough, asthma, hoarseness and dental erosion. Since the

symptoms of GERD mimic those of other conditions, it is important to see a physician for proper diagnosis[65].

**Causes of GERD**

Physical causes of GERD can include a malfunctioning or abnormal lower esophageal sphincter muscle (LES), hiatal hernia, abnormal esophageal contractions, and slow emptying of the stomach. Lifestyle factors that contribute to GERD include- alcohol use, obesity, pregnancy and smoking. Certain foods can also contribute to GERD such as citrus fruits, chocolate, caffeinated drinks, fatty and fried foods, garlic and onions, mint flavorings (especially peppermint), spicy foods, tomato based foods[64].There are few medications that may lower LES pressure which are: Anticholinergics- amitriptyline, nortriptyline; Barbiturates- Phenobarbital; Benzodiazepines- diazepam, alprazolam; Estrogen- premarin; NSAID- ibuprofen, naproxen; Progesterone- medroxyprogesterone, Narcotics- morphine[36].

**Prevention of GERD**

Avoiding alcohol, loss of weight, quit smoking, limited intake of caffeine, carbonated drink, chocolate, peppermint, tomato and citrus foods, spicy foods, fatty and fried food, wearing loose clothes around the waist, eating small meals and slowly, eating last meal of the day three hours before going to bed[64].

**Diagnosis of GERD**

GERD can be diagnosed or evaluated by clinical observation and the patient's response to a trial of treatment with medication. In some cases other tests may be needed including: an endoscopic examination (a long tube with a camera inserted into the esophagus), biopsy, x-ray, examination of the throat and larynx, 24 hour esophageal acid testing, esophageal motility testing (manometry), emptying studies of the stomach and esophageal acid perfusion (Bernstein test). Endoscopic examination, biopsy and assay may be performed as an outpatient in a hospital setting. Light sedation may be used for endoscopic examination.

**Treatment of GERD**

Lifestyle changes are the first-line treatment for patients suffering from mild GERD. These behavioral changes can be initiated alone or in combination with OTC medicines (Antacids). If patients do not respond to lifestyle changes or OTC medicines after two weeks, the next phase of treatment is generally the introduction of acid-suppressing therapy.

The backbone of acid-suppression therapy centers around the use of H2 receptor antagonists (H2RA's) and proton pump inhibitors (PPI's). H2RA's work by blocking histamine receptors on gastric parietal cells which helps reduce gastric acid secretion. 5H2RA's are generally most effective in mild cases of GERD, but may lose effectiveness over time since several studies has shown that people may develop a tolerance to the medication's side-effects. Members of this medication class include Axid (nizatidine), Pepcid (famotidine), Tagamet (cimetidine), and Zantac (ranitidine).

PPI's show superior effect in the treatment of moderate to severe GERD. PPI's work to inhibit acid secretion at the level of acid pump which represents the final step of acid output in the stomach. It is best to take a PPI thirty minutes to one hour before first meal so the drug can dissolve and take effect. Members of this medication class include Aciphex (rebeprazole), Nexium (esomeprazole), Prevacid (lansoprazole), Prilosec (omeprazole), and Protonix (pantoprazole).

**Complications of GERD**

GERD is rarely a life-threatening condition, but left untreated it can lead to some serious consequences. Untreated GERD can b ulcerations, stricture, hemorrhage, pulmonary aspiration, perforation, and Barrett's esophagus. Barret's esophagus is a pre-malignant change in the lining of the esophagus, which is the result of long-term contact of stomach acid with the esophagus. Patients who develop Barret's esophagus have a 30 to 60 times higher rate of esophageal cancer compared to the general population.

## FUNCTIONAL DYSPEPSIA[67]

### What is functional dyspepsia?

Dyspepsia refers to group of upper gastrointestinal symptoms that occur mainly in adults. Dyspepsia is known to result from organic causes, but the majority of patients suffer from non-ulcer or functional dyspepsia. The generally accepted definition by most clinicians includes the presence of upper abdominal pain or discomfort with or without other upper gastrointestinal symptoms, such as nausea, belching, vomiting, etc. []Functional dyspepsia is sometimes called 'non-ulcer' dyspepsia. It means that no known cause can be found for the symptoms. That is, other causes for dyspepsia such as duodenal ulcer, stomach ulcer, acid reflux, inflamed oesophagus (oesophagitis), gastritis, etc, are not the cause. The inside of your gut looks normal (if you have an endoscopy - see below). It is the most common cause of dyspepsia. About 6 in 10 people who have recurring bouts of dyspepsia have functional dyspepsia.

### Causes of functional dyspepsia.

The latest definition of this includes the presence of chronic or recurrent pain or discomfort centered in the upper abdomen in the absence of any known structural cause and without any features of irritable bowel syndrome. The precise pathophysiology of this condition remains unclear, but it is thought to result from a combination of visceral hypersensitivity, gastric motor dysfunction and psychological changes. The symptoms seem to come from the upper gut, but the cause is not known. If you have tests, nothing abnormal is found inside your gut. The lining inside your gut looks normal and is not inflamed. The amount of acid in the stomach is normal.

The following are some theories as to possible causes-

- Sensation in the stomach or duodenum may be altered in some way - an 'irritable stomach'. About 1 in 3 people with functional dyspepsia also have 'irritable bowel syndrome' and have additional symptoms of lower abdominal

pains, erratic bowel movements, etc. The cause of irritable bowel syndrome is not known.

- A delay in emptying the stomach contents into the duodenum may be a factor in some cases. The muscles in the stomach wall may not work as well as they should.
- Infection with a bacterium (germ) called *Helicobacter pylori* may cause some cases. This bacterium is found in the stomach in some people with functional dyspepsia. However, many people are 'carriers' of this bacterium, and it causes no symptoms in most people. The role of *Helicobacter pylori* is controversial in functional dyspepsia (although it is the main cause of duodenal and stomach ulcers). However, getting rid of *Helicobacter pylori* infection helps in some cases.
- Some people feel that certain foods and drinks may cause the symptoms or make them worse. It is difficult to prove this. Food is not thought to be a major factor in most cases.
- Anxiety, depression, or stresses are thought to make symptoms worse in some cases.
- A side-effect of some medicines can cause dyspepsia. The most common culprits are anti-inflammatory medicines. Various other medicines which sometimes cause dyspepsia, or make dyspepsia worse, include: digoxin, some antibiotics, steroids, iron, calcium antagonists, nitrates, theophyllines, and bisphosphonates.

# 2. LITERATURE REVIEW

**M Sakashita* *et.al.,* (1993):** studied the effect of pharmacokinetics of the gastrokinetic agent mosapride citrate after single and multiple oral administrations in healthy subjects. The pharmacokinetics and dose proportionality of mosapride citrate (±) 4-amino-5-chloro-2-ethoxy-N-[[4- (4-fluorobenzyl)-2-morpholinyl] methyl] benzamide citrate dihydrate, were investigated in healthy male volunteers. The subjects were given a single oral dose (5, 10, 20 and 40 mg, each of 5 subjects) and a multiple oral dose (20 mg t.i.d. for one day, and 10 and 20 mg t.i.d. for 8 days, each of 5 subjects). Food effect on the pharmacokinetics of mosapride was also evaluated after a single oral 10 mg dose by an open, two-way crossover method. Mean plasma levels of mosapride reached a peak 0.5-1 h after single dosing of 5, 10, 20 and 40 mg. The peaks were dose-related with values of 25.1, 51.2, 157.8 and 280.6 mg/ml, respectively, and were followed by a first-order decrease with apparent half-lives of 1.4-2.0 hours. The $C_{max}$ and AUC increased in proportion to the dose, indicating linear pharmacokinetics of mosapride up to 40 mg. The $C_{max}$ of M-1, a des-4-fluorobenzyl metabolite, was 1/6 of that of the unchanged drug. Urinary excretion of the unchanged mosapride and M-1 during 48 h after single dosing accounted for 0.1-0.4% and 7.0-11.0% of the dose, respectively. There were no significant changes in the plasma concentration-time profiles and urinary excretions between single and multiple doses, indicating that the pharmacokinetics of mosapride in man was not altered by its multiple administrations. Plasma levels of Mosapride reached steady state on day 2 of multiple administrations.[16]

**Anroop B. Nair * *et.al.,* (2010):** formulated controlled release matrix uncoated tablets of Enalapril Maleate using HPMC alone. Direct compression technique was used to prepare the tablets, and these tablets were evaluated for physical properties, drug content, in vitro release and drug release kinetics as well. All the formulations demonstrated good physical integrity and the drug content were in the official limits. The formulations with HPMC K 100 (25mg/tablet) and K4M (15mg/tablet) have been found to release the required amount of drug (2.97mg/h) throughout the study period (14h). The calculated regression coefficients showed higher $r^2$ value with Higuchi model and zero order kinetics. Given the excellent release profile, the study

concluded that HPMC in different grades with low concentration alone can control the enalapril maleate release over a period of 14hours.

**Bhupendra G. Prajapati* *et.al.*, (2010):** developed matrix sustained release tablets of water soluble prokinetic agent which is itoporide Hydrochloride. Two polymer grades of HPMC-K4M and K100M along with ethyl cellulose and pregelatinised starch were used in different batches of formulations. The release rates of drug from individual as well as combined polymers were studied. The optimized formulation was found to be the one in which a combination of polymers of HPMC K4M and HPMC K100M were used i.e F11. It was found that the drug was completely released from the optimum formulation and the drug release was also extended to 12 hours. This study indicates that by using the combination of these polymers we can obtain good control on the release profile of water soluble drug and sustained release can be obtained.

**Deepak Kumar Mourya* *et.al.*, (2010):** studied the formulation and release characteristics of novel monolithic HPMC matrix tablets containing metronidazole. The excipients used were HPMC, Starch 1500, sodium lauryl sulphate, microcrystalline cellulose, and sodium dihydrogen phosphate. The tablets contained 500mg metronidazole and different drug polymer ratios of HPMC. The m- HPMC tablets were prepared using a wet granulation method followed by direct compression. Sustained released matrix tablets were found to be highly influenced by amounts of m-HPMC polymer polymer incorporated. Results showed that granules can be used to prepare in terms of micromeritic properties and flow behaviour. Findings of the results showed that batchF1 have maximum drug release while F6 have minimum drug release. It can be concluded from the obtained results that as the concentration of HPMC increases, % drug release decreases.

**Syed Namath Ulla* *et.al.*, (2011):** formulated matrix sustained release tablets of lornoxicam by using different viscosity grades of HPMC polymers namely HPMC K4M, HPMC K15M, HPMC K100M. A total number of nine formulations were prepared by direct compression technique using 6mm flat punches to an average weight of 120 mg. The optimum formulation was found to be F1 which comprises of HPMC K4M alone. A sustained release pattern was obtained for 12 hours from the

optimum formulation F1. The hydrophilic matrix of HPMC controlled the Lornoxicam release effectively. The order of drug release from the selected polymers were found to decrease in the following order HPMC K4M> HPMC K15M> HPMCK100M.

**Dr. Ritesh Patel* *et.al.*, (2009):** studied the optimization of propranolol hydrochloride controlled release matrix tablet using factorial design. Direct compression technique was involved. HPMC K15M and Carbopol 934P were used in formulating the matrix tablets. A 32 full factorial design were applied for systemic studies. The blending ratio of HPMC K15M and Carbopol 934P (X1) and polymer concentrations (X2) were the independent variables. The times required for 50% (t50) and 80% (t80) drug release were selected as dependent variables. The results indicated that the values of t50, t80, f2 and MDT are strongly dependent on the independent variables. in vitro drug release profile of all batches of factorial design was compared with theoretical drug release profile. The results indicated that batch F7 showed the highest value among all the batches, and it also shows similarity in t50 and t80 values. The f2 value (74) of batch F7 indicates less than 5% difference in *in vitro* drug release profile with theoretical release profile.

**Margret Chandira* *et.al.*, (2009):** formulated sustained release matrix tablets of Zidovudine by using two different grades of HPMC polymers- HPMC K15M and HPMC K100M. A total of eight formulations were prepared. The first 3 formulations were made by direct compression technique and the rest of the formulations were prepared by wet granulation technique. The formulation B8 had given the optimum release till 12 hours which includes HPMCK100 alone as polymer and so this was taken as the optimized formulation and coating was done.

**N. N. Rajendran* *et.al.*, (2010):** formulated and evaluated sustained release bilayer tablets of metformin hydrochloride and pioglitazone hydrochloride. Sustained layer were prepared by wet granulation method using different viscosity grade of hydroxypropyl methyl cellulose (HPMC K4M and HPMC K100M) as polymers and immediate release layer were prepared by direct compression method using superdisintegrants such as sodium starch glycolate and crosscarmellose sodium. The tablets were evaluated for physicochemical properties. The values were found within

the limits. In vitro release studies were carried out by USP type-2 paddle apparatus. The result showed that combinations of polymers namely HPMC K4M and HPMC K100M in sustained layer can control the release of drug. The in vitro release profiles of drug from sustained release layer could be best expressed by Higuchi's equation as the plots showed high linearity ($R^2$>0.988) and diffusion was the dominant mechanism of drug release. The formulations (P6M7) having immediate release layer produces immediate effect within 54 seconds followed by sustained release (97.35%) at 8 hours and it is comparable with the innovator's brand. The present study concluded that bilayer tablets of these drugs can serve as an alternative to the conventional dosage form.

**Anna Korner* *et.al.*, (2009):** studied the effect of three different types of polymer chain structures on the polymer release from hydrophilic matrix tablets by comparing a synthetic semi-crystalline linear polymer (PEO), a branched amorphous polysaccharide (dextran) and an amorphous substituted cellulose derivative (HPMC). The results showed that independent of polymer type plots of the release versus time had similar shapes, the release of long and short polymer chains was equal and no fractionation occurred during the release and the release rate could be related to the average intrinsic viscosity of the polymer mixtures. This confirms the hypothesis that the release rate can be related to a constant viscosity on the surface of the hydrophilic matrix tablet and that it is valid for all the investigated polymers.

**Subramaniam Kannan* *et.al.*, (2010):** formulated and evaluated sustained release tablets of aceclofenac using hydrophilic matrix system. A once daily sustained release tablets of aceclofenac (200mg) were prepared by wet granulation technique and using hydrophilic polymer like hydroxypropyl methyl cellulose k-100. The tablets were subjected to physicochemical studies, in-vitro drug release, kinetic studies and stability studies. The drug release from optimized formulations was extended for a period of 24 hours. The kinetic treatment of selected formulation (F8) showed that the release of drug follows zero order models. Stability studies were also carried out. Results of the present study indicated the suitability of hydrophilic polymers in the preparation of matrix based sustained release formulation of aceclofenac.

**Dinanath Gaikwad* *et.al;* (2011):** formulated and evaluated sustained release tablet of aceclofenac by film coating. The drug has a short half life so it was film coated with HPMC (E5 LV). The incorporation of aceclofenac was performed in inert HPMC. This polymer was used in different concentrations to achieve sustained release kinetics for the drug. From the dissolution studies, it was observed that all batches gave the release by diffusion-dissolution controlled mechanism. The dispersion of the drug in the polymer network altered its dissolution profile at pH 6.8, thus making it possible to obtain a gradual and prolonged release, and to modulate the release pattern. Optimized batches show similarity with market product and give sustained release till 12 hours.

**Rupali Kale* *et.al.,* (2010):** developed matrix diffusion controlled drug delivery system of pentoxifylline. HPMC formulations showed very high dissolution rate releasing 70% of drug within two hours but its combination formulation with eudragit showed low dissolution rate of 0.14 $hour^{-1}$. Sodium alginate used did not show controlled drug release pattern. Eudragit and Guar gum formulations showed low dissolution rates indicating controlled release pattern of drug but their combination formulation showed high dissolution rate of 0.73 $hour^{-1}$.

**Tapan Kumar pal* *et. al.,* (2007):** formulated and optimized sustained release matrix tablets of metformin hydrochloride 500mg using response surface methodology. Tablets were prepared by non-aqueous wet granulation method using HPMC K 15M as matrix forming polymer. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile. HPMC K 15M ($X_1$) and PVP K 30 ($X_2$) were taken as the independent variables. The dependent variables were percentage of drug released in one hour ($rel_{1\ hour}$), percentage of drug released in 8 hours ($rel_{8\ hours}$) and time to 50% drug release ($t_{50\%}$). Contour plots were drawn, and optimum formulations were selected by feasibility and grid searches. The formulated tablets followed Higuchi drug release kinetics and diffusion was the dominant mechanism of drug release, resulting in regulated and complete release within 8 hours. The polymer (HPMC K 15M) and binder (PVP K 30) had significant effect on the drug release from the tablets ($p<0.05$). Validation of optimization studies were performed using 8 confirmatory runs, indicated very high degree of prognostic ability of response surface methodology, with mean percentage

error (±S.D) 0.0437±0.3285. Besides unravelling the effect of the 2 factors on the in vivo drug release, the study helped in finding the optimum formulation with sustained drug release.

**Saravanan M*, Nataraj K S, Ganesh K S *et.al.*, (2003):** studied hydroxypropyl methylcellulose based cephalexin extended release tablets: Influence of tablet formulation, hardness and storage on in vitro release kinetics. The object of this study was to develop hydroxypropyl methylcellulose (HPMC) based cephalexin extended release tablet, which can release the drug for six hours in predetermined rate. The influences of HPMC, microcrystalline cellulose powder (MCCP), granulation technique, wetting agent and tablet hardness on cephalexin release from HPMC based extended release tablets were studied. The dissolution results showed that a higher amount of HPMC in tablet composition resulted in reduced drug release Tablets prepared by dry granulation was released the drug slowly than the same prepared with a wet granulation technique. Addition of wetting agent in the tablets prepared with dry granulation technique showed slower release. An increase in tablet hardness resulted in faster drug release. The in vitro release data was well fit in to Higuchi and Korsmeyer-Peppas model. Physical and chemical parameters of all formulated tablets were within acceptable limits[22]

**Anthon smith* *et.al.*, (2009):** developed sustained release matrix tablets of ondasetron hydrochloride by employing HPMC K4M, HPMC K15M and HPMC K100M polymers and sustained release behaviour of the tablet was investigated. Tablets were prepared by wet granulation technique.

**Marina Levina, *et al.*, (2004):** Studied influence on drug release from HPMC matrix system. The influence of commonly used excipients such as spray dried lactose, microcrystalline cellulose and partially pregelatinized maize starch on drug release from HPMC matrix system has been investigated, model formulation contained 30% w/w drug, 20%w/w HPMC ,0.5%w/w fumed silica, 0.25%w/w magnesium stearate and 49.25%w/w filler. Chlorphenaramine maleate and theophyline were used freely (1in 4) and slightly (1in 120) water soluble drugs, respectively. It was found that for both the drug addition of 20-49.2%w/w starch 1500 resulted in significant reduction in drug release rate compared to when MCC

and lactose was used. The studies showed that using lactose or MCC in the formulation resulted in faster drug release profiles.[23]

**European Patent EP0895780 (2002):** this invention relates to pseudo ephedrine hydrochloride extended-release tablets which comprise a sustained release hydroxypropyl methylcellulose matrix, a microcrystalline cellulose disintegrant, and a filler and which are formed by a dry granulation, direct compression method. A method for forming these caplets is al so disclosed.[50]

**Md. Selim Reza, *et al.*, (2002):** developed sustained release theophyllin matrix tablets kollidon SR. Four matrix formulations were prepared by dry blending and direct compression method by varying proportion of HPMC, with fixed percentage of theophyline. Tablets containing ingredient demonstrated a rapid rate of drug release with an initial burst effect. Incorporation of HPMC-15cps, in the drug with subsequent minimization of burst effect as confirmed by mean dissolution time, a direct relationship was obtained between release rate and percentage of HPMC-15cps profile was obtained with the matrix tablets containing 30% HPMC-15cps, and 20% kollidon SR. It was found that, fickian release is predominant in tablets.[29]

**Outi Honkanen**. ***et. al.*, (2002):** studied the Bioavailability and in vitro esophageal sticking tendency of hydroxypropyl methylcellulose capsule formulations and corresponding gelatin capsule formulations in the present study was to widen our knowledge about the biopharmaceutical behavior of novel hydroxypropyl methylcellulose (HPMC)-based two-piece capsules by comparing them with the classic hard gelatin capsules. Firstly, the tendency of the HPMC capsules to stick to isolated porcine esophageal preparation was evaluated. The force needed to detach the HPMC capsules from the esophagus was significantly lower than that for the gelatin capsules ($P<0.001$), which is evidently an advantage of this new dosage form. The second aim was to investigate the possibility of preparing sustained-release capsules using different powdered HPMC as diluents (K100, K4M and K15M) and the effect of the molecular weight of HPMC powder on the in vitro and in vivo behavior of the capsules. Using different viscosity grades of HPMC powders as diluents it was possible to control the absorption rate of the model drug both from gelatin and HPMC capsules as far as the oral route was concerned.[13]

**Yan G. *et al*., (2000):** Prepared and evaluated sustained release tablets of nifedipine by using HPMC as polymer. A nifedipine, polyethylene glycol solid dispersion was prepared; using solid dispersion method. Both the high viscosity grade HPMC K-15M and low viscosity grade viscosity were applied in the tablet to form the matrix. The dissolution stand the absorption of nifedipine from the tablet was evaluated as the formulation that has sustained release over 24 hours. Hixon-Crowell equation and Higuchi equation were used to investigate the dissolution and the erosion and diffusion co dependent mechanism was established.[45]

**M. Victoria Velasco*, *et. al*., (1999):** studied the influence of drug: hydroxypropyl methyl cellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. This study evaluates the relationship and influence of formulation and technological factors such as drug: hydroxypropyl methyl cellulose (HPMC) ratio, particle size of the drug, particle size of HPMC and compression force, on drug release from matrices containing HPMC and diclofenac sodium as a model drug. The influence of these variables was assessed by multi-way analysis of variance. The results of the present study point out that the rate and mechanism of diclofenac sodium release from HPMC K15M matrices are mainly controlled by the drug: HPMC ratio. The drug and HPMC particle size also influence the drug release parameters, although to a lesser extent. Finally, the independence of the drug release from matrix tablets with respect to the compression force is reported.[11]

**Naoyuki Yoshida* *et.al*., (1999):** studied the pharmacological effects of mosapride Citrate, and reported that mosapride dose- dependently enhanced gastric emptying of a liquid or solid meal in rats with potency equal to that of cisapride and more potent than that of metaclopramide. In rats mosapride improved the gastric emptying delayed by gastro duodenal surgical invention, mosapride had no affinity for dopamine $D_2$ receptors, where as metaclopramide and cisapride had high affinity for dopamine $D_2$ receptor. In conclusion, mosapride is a selective and potent 5HT4 receptor agonist and improves gastrointestinal symptoms in a patients with non-ulcer dyspepsia without causing extra pyramidal syndrome associated with dopamine $D_2$-receptor blockage and adverse cardiovascular effects such as torsadose de points.[17]

# 3. AIM AND OBJECTIVE

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained-release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products.

The aim of the present study was to formulate and evaluate sustained release matrix tablets of mosapride citrate using hydrophilic polymer hydroxypropyl methylcellulose (HPMC) alone, of two different viscosity grades of hydroxypropyl methylcellulose (HPMC K4M & HPMC K15M.).

Mosapride citrate has a short half life 1.4 -2.0 hours and usual oral dosage regimen of 5 mg 3-4 times daily. And thus the objective was to reduce the frequency of administration and to improve patient compliance; a once-daily sustained release formulation of mosapride citrate was formulated.

The most commonly used method of modulating the drug release is to include it in a matrix system. Hydrophilic polymer matrix systems were widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug-release profile, they are cost effective and they have US Food and Drug Administration acceptance.

The viscosity of hydroxypropyl methylcellulose polymer influences the erosion rate of matrix tablet. In other words, the rate of tablet erosion can be adjusted by the choice of hydroxypropyl methylcellulose polymer viscosity or by mixing hydroxypropyl methylcellulose polymer of varying viscosities. So, in order to study the effect of viscosity of polymer on erosion of matrix tablet, two different viscosity grades of hydroxypropyl methylcellulose were used.

Hence, in present work, an attempt has been made to develop once-daily sustained release matrix tablets of mosapride citrate using hydrophilic matrix materials such as hydroxypropyl methylcellulose with two different viscosity grades ( HPMC K4M & HPMC K15M).The lower viscosity grade of hydroxypropyl methylcellulose (HPMC K4M) sustain the drug release up to 12 hrs, for further

sustaining the release of drug up to 24 hours from matrix of the tablet, the higher viscosity grade of hydroxypropyl methylcellulose (HPMCK15M) is useful. So in present study the combination of two different viscosity grades of hydroxypropyl methylcellulose were used.

In present study sustained release matrix tablets of mosapride citrate was compressed by using dry granulation/slugging technique. The dry granulation / roller compaction technique is especially useful for the drugs that are sensitive for heat, moisture. Mosapride citrate is moisture, heat sensitive drug hence the dry granulation / roller compaction technique is useful.

# 4. PLAN OF WORK

The present work was carried out to formulate and evaluate the sustained release matrix tablets of mosapride citrate using polymers like HPMC (K4M & K15M). This work was carried out as outlined below.

Stage1 : Procurement of drug and raw materials.

Stage2 : Preformulation studies by using Fourier Transform Infra red spectrometer (FTIR)

Stage3 : Preparation of Mosapride citrate matrix tablets by dry granulation method.

Stage4 : Standard Graph of Mosapride citrate in Acetate Buffer pH 4.0

Stage5 : Characterization of physical mixture / granules

- Bulk density
- Tapped density
- Angle of repose
- Carr's index
- Hausner's ratio

Stage6 : Characterization of granules prepared matrix tablets.

- Uniformity of weight.
- Thickness variation test
- Hardness test.
- Friability test.
- In vitro dissolution study.

Stage7 : Kinetics studies.

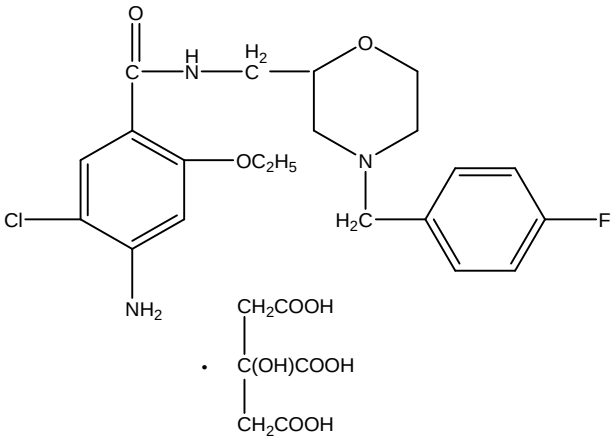
Stage 8 : Stability studies.

# 5. THEORETICAL BACKGROUND[17,29, 39, 51,68,69,70]

## 5.1 Drug Profile

**Mosapride citrate**

**Structure:**




**Chemical name:** (±)-4-Amino-5chloro-2-ethoxy-N-[[4-(4-flurobenzyl)-2-2morpholinyl] methyl] benzamide citrate.

**Description:** an off white crystalline powder.

**Physical properties-**

**Solubility:** soluble in DMF.

**Residue on ignition:** not more than 0.1w/w.

**Molecular formula:** $C_{21}H_{25}ClFN_3O_3.C_6H_8O_7.2H_2O$.

**Molecular weight:** 650.50

**Melting point:** 110-113°C

**Pharmacokinetics-**

**Absorption:** Mosapride is quickly absorbed after oral ingestion. Absorption is unaffected by the presence of food.

**Distribution:** Mosapride is 93-99% bound to plasma protein, including albumin and alpha-1- acid glycoprotein. The drug is distributed to most body tissues, more to the gastrointestinal tract than to the brain. Mosapride achieves high levels in milk and crosses the placenta.

**Half life:** 1.4-2.0 hours.

**Metabolism:** Most drugs are metabolized and negligible amount of unchanged drug is appeared in urine. The drug is degraded in the liver by cytocrome P-450(3A4) pathway. Only 0.1 to 4% is excreted in the urine. M-1 is a des-4-flurobezyl metabolite and is the cheep degradation product of mosapride. M-2 is another metabolite, and is very little activity. The metabolites thus contribute very little to the gastro-prokinetic activity of Mosapride. However M-1 is a 5HT-3 antagonist with significant potency.

**Mechanism of action:** Mosapride is an agonist of 5HT-4 receptor. 5HT-4 receptors are present in the gut in the myenteric plexus, in the neurons of the longitudinal and circular muscles, and in the gut interneuron's. On stimulation the receptors result in neuronal release acetylcholine, which causes increased motility and hyper secretion. Mosapride increases gastric emptying. Mosapride has affinity only for receptors located in the foregut, and does not stimulate colonic receptors, and therefore rarely causes diarrhoea. In contrast, Cisapride and tegaserod increases colonic motility and result in diarrhoea.

The specificity extends to a lack of affinity to D2 receptors in the brain, in comparison to other prokinetic agents. Mosapride does not influence the QT interval even at higher doses.

**Adverse effects:** Abdominal cramps, headache, dry mouth, nausea.

**Interactions:** Mosapride's major degradation is the cytocrome P-450 (3A4) system. However, electrophysiological study show that the co administration of drugs that

inhibits the CYP3A4 enzymes, (Erythromycin, ketoconazole, flucanazole, etc.) Have no effect on mosapride indicating that the satisfactory safety margin exists in relation to rhythm abnormalities, unlike that which occurs with Cisapride.

**Indications:** Gastro-esophageal reflux diseases (GERD).

Functional dyspepsia.

Diabetic gastropathy.

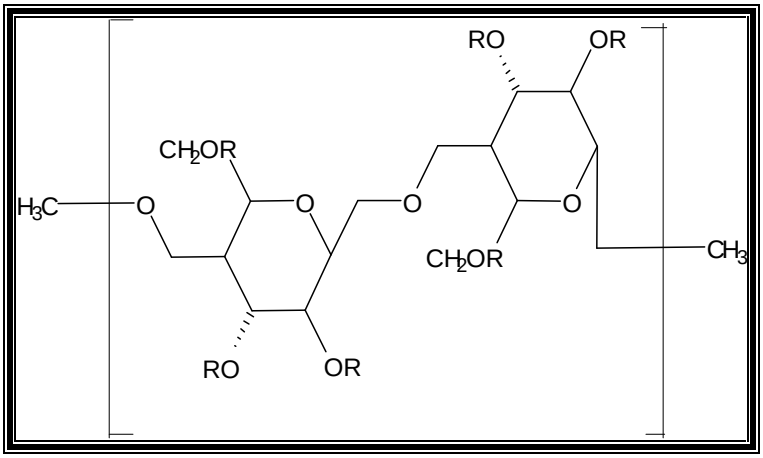
Disorders associated with decreased gastric motility.

**Dosage:** Oral 5 mg three times a day.

**Storage:** Store at 15-30°C in tightly closed container, protect from heat and light. Keep out of reach of children.

## 5.2 EXCIPIENTS PROFILE[10]

### HYDROXY PROPYL METHYL CELLULOSE (HPMC)




R=H, $CH_3$ or $CH_3CH$ (OH)

**Chemical Name:** Cellulose 2-hydroxyl Propyl methyl ether

**Nonproprietary names:** Cellulose, Hypromellose, 2-Hydroxypropyl methyl ether, Methyl Hydroxy Propyl cellulose, Hypromellosum (ph Eur), Methocel, Pharmacoat, Metolose.

**Synonym:** Benecel MHPC, e464, Methylcellulose propylene glycol ether, Pharmacoat, Tylopur, Tylose MO.

**Molecular Weight:** 10000-1500000

**Description:** Hypromellose is an odorless and tasteless white or creamy white fibrous or granular free flowing powder.

**Physical properties-**

**Solubility:** Soluble in cold water, forming a colloidal solution; practically insoluble in hot water, dehydrated alcohol, chloroform and ether. It undergoes reversible transformation from solution to gel on heating and cooling respectively.

**pH:** A 1%w/w solution has a pH of 5.5-8.0.

**Melting Point:** Browns at 190-200$^0$C; chars at 225-230$^0$C; Tg is at 170-180$^0$C.

**Auto ignition Temperature:** 360$^0$C

**Bulk Density:** 0.341 gm/cm$^3$

**Tapped Density:** 0.557 gm/cm$^3$

**Gel Formation:** Undergoes a reversible transformation from solution to gel upon heating and cooling respectively.

**Gel point:** 50-900$^0$C

**Storage:** Stored in well closed containers.

**Table No 2: Various grades of Hypromellose varying in viscosity and extent of substitution.**

| **Methocel Grade** | **Nominal** | **Viscosity (mPas)** |
|---|---|---|
| K100LVP | 100 | 80-120 |
| K4M | 4000 | 3000-5600 |
| K15M | 15000 | 12000-21000 |
| K100MP | 100000 | 80000-120000 |
| E4MP | 4000 | 3500-5600 |
| E10MP CR | 10000 | 8000-13000 |
| E3 PREM. LV | - | 2.4-3.6 |
| E5PREM. LV | - | 4-6 |
| E6PREM.LV | - | 5-7 |
| E15PREM.LV | - | 12-18 |
| E50PREM.LV | - | 40-60 |
| K3PRem.LV | - | 2.4-3.6 |

**Note:** HPMC is prepared by reacting alkali-treated cellulose first with methyl chloride to introduce methoxy groups and then with propylene oxide to introduce propylene glycol ether groups.[4]

**Applications in pharmaceutical formulation and Technology:**

Widely used in oral and topical pharmaceutical formulations.

Concentrations between 2% and 5% w/w may be used as a binder in either wet or dry granulation processes.

High viscosity grades may be used to retard the release of drugs from the matrix at levels of 10-80% w/w in tablets and capsules.

Low viscosity grades are used in aqueous film coating.

Useful as a dispersing and thickening agent.

In ophthalmic solutions to provide demulcent action[4].

**MAGNESIUM STEARATE**

**Nonproprietary Names:** Magnesium stearate (BP), Magnesium stearate (JP), Magnesium stearas (PhEur), Magnesium stearate (USPNF)

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

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

**Chemical Name and CAS Registry Number:** Octadecanoic acid magnesium salt [557-04-0]

**Empirical Formula and Molecular Weight:** $C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

**Structural Formula:** $[CH_3 (CH_2)_{16}COO]_{2Mg}$

**Functional Category:** Tablet and capsule lubricant.

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

**TALC**

**Synonyms:** Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; powdered talc.

**Chemical Name:** Talc

**Nonproprietary Names:** Purified talc (BP), Talc (JP), Talcum (PhEur), Talc (USP).

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

**Description:** Talc is a very fine, white to grayish- white.

**Properties:**

**Density (bulk):** 0.159 g/cm$^3$

**Density (tapped):**0. 286 g/cm$^3$

**Density (true):** 1.092 g/cm$^3$

**Melting range:** 117-150$^0$C (commercial samples)

126-130$^0$C (highly pure)

**LACTOSE, ANHYDROUS**

**Nonproprietary Names:** Anhydrous lactose (BP), Anhydrous lactose (JP), Lactosum anhydricum (PhEur), Anhydrous lactose (USPNF)

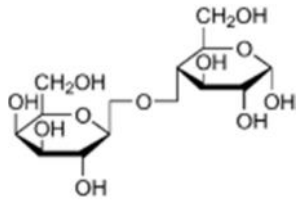
**Synonyms:** Anhydrous Lactose NF 60M; Anhydrous Lactose NF Direct Tabletting; Lactopress Anhydrous; lactosum; lattioso; milk sugar; Pharmatose DCL 21; Pharmatose DCL 22; saccharum lactis; Super-Tab Anhydrous.

**Chemical Name and CAS Registry Number:** O-β-d-galactopyranosyl-(1→4)-β-d-glucopyranose [63-42-3]

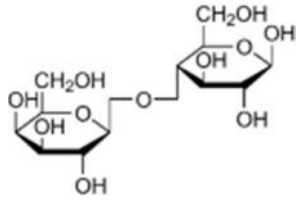
**Empirical Formula and Molecular Weight:** $C_{12}H_{22}O_{11}$ 342.30

**Description:** white or creamy white, hard, crystalline masses or powder;odourless, and has a faintly sweet taste; stable in air, but readily absorbs odors.

**Structural Formula:**




Anhydrous α-lactose




Anhydrous β-lactose

**Melting point:** 223.0°C for anhydrous α-lactose;

252.2°C for anhydrous β-lactose;

232.0°C (typical) for commercial anhydrous lactose.

**Solubility:** 1g in 5ml water and 2.6 ml boiling water. Sparingly soluble in ethanol (95%) and insoluble in chloroform and ether.

**Functional Category:** Binding agent, directly compressible tabletting excipients, lyophilization aid, tablet and capsule filler.

**Applications in Pharmaceutical Formulation or Technology:**

Anhydrous lactose is widely used in direct compression tabletting 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. Lactose occurs as white to off-white crystalline particles or powder. Several different brands of

anhydrous lactose are commercially available which contain anhydrous β-lactose and anhydrous α-lactose. Anhydrous lactose typically contains 70–80% anhydrous β-lactose and 20–30% anhydrous α-lactose.used as a diluent in medicine and pharmacy. It is generally an ingredient of the medium used in penicillin production. It is extensively used as an addition to milk for infant feeding.remington-1262

**Incompatibilities:** Lactose anhydrous is incompatible with strong oxidizers. When mixtures containing a hydrophobic Leukotriene antagonist and anhydrous lactose or lactose monohydrate were stored for six weeks at 40°C and 75% RH, the mixture containing anhydrous lactose showed greater moisture uptake and drug degradation.

**Note:** It is prepared from skim milk, to which is added dilute hydrochloric acid to precipitate the casein. After removal of the casein by filtration, the reaction of the whey is adjusted to ph 6.2 by adding lime and remaining albuminous matter is coagulated by heating. This is filtered and liquid set aside to crystallize. Animal charcoal is used to decolorize the solution.

**COLLOIDAL SILICON DIOXIDE**

**Nonproprietary Names:** Colloidal anhydrous silica (BP), Silica colloidalis anhydrica (PhEur), Colloidal silicon dioxide (USPNF).

**Synonyms:** Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed; Wacker HDK.

**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, non-gritty amorphous powder.

**Chemical Name and CAS Registry Number:** Silica [7631-86-9]

**Empirical Formula and Molecular Weight:** $SiO_2$ 60.08

**Structural Formula:** $SiO_2$

**Functional Category:** Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer and viscosity-increasing agent.

**Applications in Pharmaceutical Formulation or Technology:**

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products; its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tabletting. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than non-polar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity.

**Solubility:** Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide forms a colloidal dispersion with water.

**Stability and Storage Conditions:** Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container.

Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

**Incompatibilities:** Incompatible with diethylstilbestrol preparations.

# 6. MATERIALS AND EQUIPMENTS

| Material | Company Name |
|---|---|
| 1. Mosapride Citrate | DR. Reddy's Holdings limited, Hyderabad. |
| 2. HPMC K15M | Colourcon Asia Pvt. limited, Mumbai |
| 3. HPMC K4M | Colourcon Asia Pvt. limited, Mumbai |
| 4. Lactose | Concept pharmaceuticals limited, Aurangabad. |
| 5. Magnesium stearate | Concept pharmaceuticals limited, Aurangabad |
| 6. Aerosil 200 | Concept pharmaceuticals limited, Aurangabad |
| 7. Talcum | Concept pharmaceuticals limited, Aurangabad |

**EQUIPMENTS**

| | |
|---|---|
| 11. Single punch tablet rotary machine | Cadmach |
| 12. Dissolution apparatus | Electro lab (Model: TDT-06P, Aurangabad). |
| 13. UV Visible spectrophotometer | Shimadzu (UV 1700) |
| 14. Hardness tester | Monsanto |
| 15. Friabilator | Electro lab |
| 16. Vernier caliper | Baker |
| 17. pH meter | Control Dynamic |
| 18. FTIR | Shimadzu |

# METHODOLOGY

## PREFORMULATION STUDIES

Prior to development of any dosage form, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. This information will dictate many of subsequent events and possible approaches in formulation development. This first learning phase is called as preformulation.[71]

### Bulk Density[12]

It is the ratio of a given mass of a powder and its bulk volume.

### Procedure:

Bulk density (gm/ml) is determined by pouring presieved (40-mesh) bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight[9].

$$\text{Bulk Density} = \frac{\text{Mass of powder}}{\text{Bulk Volume of the powder}}$$

### Tapped Density[12]

Tapped density is the ratio of mass of powder to that of tapped volume of the powder.

### Procedure:

Tapped density is determined by placing a graduated cylinder containing a known mass of the drug or formulation on a mechanical tapper apparatus, which is operated for a fixed number of taps (~1000) until the powder bed volume has reached a minimum. Using the weight of drug in the cylinder and this minimum volume, the tapped density may be computed.

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume of the powder}}$$ [9]

**Carr's Index**[8]

A simple indication of the ease with which a material can be induced to flow is given by application of a compressibility index (I), given by the equation

I= [1- Tapped density / Bulk density] x 100.

Values of I below 15% usually give rise to good flow characteristics, but readings above 25% indicate poor flow ability[9].

**Table No.3 Standard range of Carr's Index.**

| Carr's Index | Type of flow |
|---|---|
| 5-15 | Excellent |
| 12-18 | Good |
| 18-23 | Fair to passable |
| 23-35 | Poor |
| 35-38 | Very poor |
| Above 40 | Extremely poor |

**Hausner's Ratio**[71]

Hausner's ratio is defined as the ratio of tapped density to poured density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Poured Density}}$$

Values less than 1.25 (= 25% Carr's index) indicates good flow, while greater than 1.25 indicates poor flow (= 33% Carr's index). Between 1.25 and 1.5 added glidants normally improves flow.

**Table No.4 Standard range of Hausner's Ratio.**

| Hausner's Ratio | Type of flow |
|---|---|
| 1.00 - 1.11 | Excellent |
| 1.12 - 1.18 | Good |
| 1.19 - 1.25 | Fair |
| 1.26 - 1.34 | Passable |
| 1.35 – 1.45 | Poor |
| 1.46 – 1.59 | Very poor |
| Above 1.60 | Extremely poor |

**Angle of repose** [8]

Angle of repose is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane.

**Procedure:**

It was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\Theta = \tan^{-1} (h/r)$$

Where, h= Height of pile

r= Radius of pile

Θ= Angle of repose

**Table No.5 Standard range of Angle of Repose.**

| Angle of repose | Type of flow |
|---|---|
| 25 – 30 | Excellent |
| 31 – 35 | Good |
| 36 – 40 | Fair |
| 41 – 45 | Passable |
| 46 – 55 | Poor |
| 56 – 65 | Very poor |
| Above 66 | Extremely poor |

## DRUG EXCIPIENT COMPATABILITY STUDY BY FTIR SPECTROSCOPY

The FTIR spectra of pure mosapride citrate, mosapride citrate with HPMC K4M, HPMC K15M and mosapride citrate with HPMC K4M, HPMC K15M, Lactose, Magnesium stearate, Talc, Aerosil were analyzed for compatibility study.

**Procedure:**

Drug and excipients were analysed by infra red spectral studies by using potassium bromide pellet technique. In this method, the drug and potassium bromide were mixed at the ratio of 1:100. Then these mixtures were pressed in to a pellet. The FTIR spectra were recorded using potassium bromide pellet method. Spectra were recorded for pure drug, pure excipients and drug with excipients (tablet). The instrument was operated under dry air purge and the scans were collected at scanning speed 2mm/sec with resolution of 4cm-1 over the region 4000-400cm-1. The scans were evaluated for the presence of principle of peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction. The FT-IR spectra of pure Mosapride citrate, are shown in Fig. no-6.

## PREPARATION OF STANDARD CALIBRATION CURVE OF MOSAPRIDE CITRATE.

**Method:**

100 mg of mosapride citrate was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and diluted to volume with purified water to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with purified water to get 10ug/ml of mosapride citrate. The λmax was found to be 274 nm using UV Spectrophotometer. The absorbance values were plotted against concentration (µg/ml).

## FORMULATION DEVELOPMENT OF MOSAPRIDE CITRATE.

**Step 1**: Weigh the raw materials as per ORML, check control number and record them.

**Step 2: Sifting**

Check the integrity of the sieves being used for sifter as per SOP & first sift the material dry mixing and then shift material required for dry lubrication as per the specified sieve for each material.

**Table No.6 Materials used for Dry granulation**

| Materials | Actual Quantity (gm/1000 tablets) | Sieve no |
|---|---|---|
| **Materials for dry mixing** | | |
| Mosapride Citrate | 10.77 | 24# |
| Lactose IP/BP | 37.05 | 24# |

| | | |
|---|---|---|
| HPMC K4M | 20.00 | 24# |
| HPMCK15M | 25.00 | 24# |
| Talcum | 0.50 | 40# |
| Magnesium Stearate IP/BP | 0.50 | 40# |
| Aerosil IP/USP | 0.10 | 40# |
| **Materials for dry lubrication** | | |
| Mosapride Citrate | 4.23 | 24# |
| Talcum | 0.50 | 40# |
| Magnesium Stearate IP/BP | 0.50 | 40# |
| Aerosil IP/USP | 0.10 | 40# |

**Step 3**: **Dry Mixing**

Blend of Mosapride Citrate with Polymer (HPMC) & lactose mix slowly in polybag for 15 minutes. Add half quantity of lubricants & reblend for 5-6 minutes. Now blend is ready for slug formation.

**Step 4**: **Slugging**

Slugging is a method of subjecting a material to increased compression time. When the initial blend of powders is forced into the dies of a large-capacity tablet press and is compacted by means of flat-faced punches the compacted masses are called slugs, and the process is referred to as slugging[9.] Clean & operate the M/C as per S.C.P. & S.O.P for Slugging.

**Parameters for Slugging:**

| | |
|---|---|
| Punch size | 16 mm |
| Average Weight | 900 mg/slug |
| Hardness | NLT 10 Kg/cm$^2$ |

**Step 5**: **Deslugging**

Deslug the above slug, and screen it through 2 mm screen slowly. Pass the final granules through #30.

**Step 6**: **Dry Lubrication**

Mix final granules & remaining mosapride citrate slowly in polybag for 15 minutes. Add remaining half quantity of lubricants slowly for 10 minutes. Record the total weight of granules. Now blend is ready for compression.

**Step 7: Compression**

Clean & operate the machine as per S.C.P. ensure blend release before taking for compression. Check batch details on the label & total weight of granules.

**Parameters for compression**

| | |
|---|---|
| 1.Punch | UP: Plain SC, LP: Plain SC. |
| 2.Dimensions | 6.00 mm |
| 3.Diameter | 6.00 mm (± 0.05) |
| 4.Theoretical Weight to Tablet | 94mg / Tab |
| 5.Weight of two Tablets | 188mg (±2%) |
| 6.Weight variation (of actual average weight) | ± 7.5% |
| 7.Hardness of Tablet | NLT 4.0 $Kg/cm^2$ |
| 8.Friability | NMT 1.0% |
| 9.Thickness | 3.0 (± 0.2) mm |
| 10.Appearance of tablet. | White to off-white, biconvex. |

## Formulation variables for mosapride citrate matrix tablets.

**Table No.7. Formulation ingredients.**

| Ingredients | F1 (mg) | $F_2$ (mg) | $F_3$ (mg) | $F_4$ (mg) | $F_5$ (mg) | $F_6$ (mg) | F7 (mg) | F8 (mg) | F9 (mg) |
|---|---|---|---|---|---|---|---|---|---|
| Mosapride citrate | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| HPMCK4M | 10 | 15 | - | 10 | 15 | 18 | 16 | 20 | 20 |
| HPMC K15 M | - | - | 10 | 10 | 10 | 10 | 15 | 20 | 25 |
| Lactose | 73 | 68 | 73 | 62 | 58 | 55 | 52 | 43 | 38 |
| Talcum | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Magnesium Stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Colloidal silicon dioxide(Aerosil) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |

## PHYSICOCHEMICAL EVALUATION OF TABLET

## Post compression parameters:

- **Shape of tablet:**

The compressed tablets were examined under the magnifying lens for the shape of tablet.

- **Uniformity of weight[13]:**

The USP weight variation test was carried out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight. The tablet meet USP test if no tablet differs by more than two times of percentage deviation.

**Table No.8 Standard range of weight of tablets.**

| Sl.no | Average weight of tablets (mg) | Minimumm percentage difference allowed |
|---|---|---|
| 1 | 130 or less | 10 |
| 2 | 130-324 | 7.5 |
| 3 | More than 324 | 5 |

- **Tablet thickness:**

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulation were taken randomly and thickness was measured individually.

- **Hardness test:**

Hardness of the tablet was determined by using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it[9]. The hardness was measured in terms of $Kg/cm^2$

- **Friability test:**

The most popular and commercially available friability apparatus is the Roche Friabilator, in which approximately 6g ($w_o$) of dedusted tablets are subjected to 100 free falls i.e the apparatus revolves at 25rpm dropping the tablets through a distance of 6 inches in a rotating drum and are then reweighed (w). the friability,f, is given by:

$$\mathbf{f = 100.\ (1-w_o/w)}$$

Values of f from 0.8 to 1.0% are regarded as the upper limit of acceptability[9].

## IN VITRO DRUG RELEASE STUDY

### DISSOLUTION [14, 72]

| | | |
|---|---|---|
| Medium | - | Acetate buffer pH – 4.0 |
| Apparatus | - | USP (Type II) paddle type. |
| Medium volume | - | 900.0 ml |
| Speed | - | 100 rpm |
| Temperature | - | 37°C [± 0.5°C] |
| Wavelength | - | 274 nm |
| Sample Withdrawal | - | At the end of $1^{st}$, $4^{th}$, $7^{th}$, $12^{th}$, $16^{th}$ and $24^{th}$ hours |
| Sample volume | - | 5 ml |

**Procedure:**

Tablets of all preliminary batches were subjected to dissolution rate studies. In vitro dissolution were carried out on dissolution apparatus (model) to determined the drug release from various formulations.1000ml of acetate buffer was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Studies were carried out in 900 ml of acetate buffer ph4 upto 24hrs at 100 rpm. The dosage form was allowed to sink to the bottom of the flask before stirring. dosage forms may have a small loose piece of nonreactive material such as not more than few turns of wire helix attached to prevent them from floating. The apparatus was operated for 24 hours and then the medium was taken and process was continued from 0 to 24 hrs at 100 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 274 nm using UV-spectrophotometer.

**Standard Dissolution Profile:**

**Table No.9 Standard dissolution profile.**

| Dissolution | Sustained release profile |
|---|---|
| After 1st hour | NMT – 30% |
| After 4th hour | 30 -50% |
| After 7th hour | 50 – 65% |
| After 12th hour | 70-75% |
| After 16th hour | 75-85% |
| After 24th hour | NLT 90% |

## DATA ANALYSIS

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Korsmeyer and Peppas and Hixson Crowell model using PSP-DISSO – v2 software. Based on the r-value, the best-fit model was selected.

**Zero order kinetics:**

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t \text{……..} (8.11)$$

Where,

**Q t** = amount of drug dissolved in time t.

**Q o** = initial amount of the drug in the solution and

**K o** = zero order release constant.

**First order kinetics:**

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

**Log Qt= log Qo+ K1t/2.303……..** (8.12)

Where,

**Qt**= the amount of drug released in time t,

**Qo**= the initial amount of drug in the solution

**K1** = the first order release constant.

**Higuchi model:**

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices.

Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

**Qt= KH ·t1/2……..** (8.13)

Where,

**Qt**= amount of drug released in time t,

**KH** = Higuchi dissolution constant.

**Korsmeyer and Peppas release model:**

To study this model the release rate data are fitted to the following equation,

**Mt / M ¥ = K · t n……** (8.14)

Where,

**Mt / M ¥** = the fraction of drug release,

**K** = the release constant,

**T** = the release time,

**N** = the diffusional coefficient for the drug release that is dependent on the shape of the matrix dosage form.

**Table No.10 Release Kinetics**

| **DIFFUSION EXPONENT Release Exponent(n)** | **OVERALL SOLUTE DIFFUSION MECHANISM Drug Transport Mechanism** |
|---|---|
| 0.45<br>0.5 | Fickian Diffusion<br>SLAB/CYLINDER |
| 0.45<n<0.89<br>0.5<n<1.0 | Anomalous (Non Fickian)Transport<br>SLAB/CYLINDER |
| 0.89<br>1.0 | Case II<br>SLAB/CYLINDER |
| n>0.89<br>n>1.0 | Super Case II Transport<br>SLAB/CYLINDER |

## STABILITY STUDY

Stability of a pharmaceutical preparation can be defined as 'the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf-life.' The purpose of stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

An ethical drug manufacturer is committed to provide to his consumers drug products, which are efficacious and safe. This can be ensured only by instituting a sound programmed to study the stability of a product during its various phases of

development and to arrive at the proper storage conditions and the expiry period under those conditions. This is a requirement in most of the countries and is stipulated by the regulatory agencies of those countries. These studies would very quickly identify the need, if any, to stabilize the active substance or the formulation, and save invaluable time and effort from being spend on an unmarketable formulation. With the recent trend towards globalization of manufacturing operation, it is imperative that the final product be sufficiently rugged for marketing worldwide under various climatic conditions including tropical, subtropical and temperate.

**Long term testing:** 25ºC±2 ºC/60% RH±5%RH for 12 months.

**Accelerated testing:** 40ºC±2 ºC/75% RH±5%RH for 6 months.

**Procedure:**

In the present study, stability studies were carried out at 40ºC and 75% RH for a specific time period upto 3 months for selected formulations. For stability study, the tablets were sealed in aluminium packaging coated inside with polyethylene. These sample containers were placed in dessicator maintained at 75% RH.

**Note:** Saturated solution of sodium chloride at 400 ºC yields a 75% relative humidity.

**Evaluation of samples:**

The samples were analyzed for the following parameters:

1. **Physical evaluation:**

**Appearance:** The samples were checked for any change in colour at every week.

**Hardness:** The samples were tested for hardness at every week.

**2. Chemical evaluation:**

**Drug release:** The samples were subjected to drug release studies.

## ANALYSIS OF REFERENCE / INNOVATOR PRODUCT

With the help of analysis of the innovator product we will be able to compare the results obtained of our formulated product.

Analysis of the innovator product was carried out for various physical parameters and *In-vitro* dissolution profile.

**Table No.11 Reference product physical characterization**

| GENERIC NAME | BRAND NAME | MANUFACTURED AND MARKETED BY | STRENGTH | DOSAGE FORM | THICKNESS |
|---|---|---|---|---|---|
| Mosapride Sustained Release Tablets | MOZA SR | Intas Pharmaceuticals | 5mg,10mg | Sustained release tablet | 3mm |

# RESULTS AND DISCUSSION

## PREFORMULATION STUDIES

### Precompression parameters

**Table No.12. Physical parameters of granules before dry granulation (slugging)**

| Physical Properties | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ |
|---|---|---|---|---|---|---|---|---|---|
| Bulk Density(gm/ml) | 0.434 | 0.435 | 0.433 | 0.431 | 0.435 | 0.439 | 0.428 | 0.422 | 0.438 |
| Tapped Density(gm/ml) | 0.625 | 0.626 | 0.631 | 0.628 | 0.630 | 0.634 | 0.623 | 0.615 | 0.632 |
| Compressibility Index | 31.45 | 32.60 | 31.02 | 31.36 | 30.95 | 30.75 | 31.30 | 31.38 | 30.69 |
| Hausner's Ratio(H.R.) | 1.39 | 1.40 | 1.44 | 1.45 | 1.448 | 1.444 | 1.46 | 1.467 | 1.452 |
| Angle of Repose | 34°33" | 34°18" | 32°64" | 33°75" | 32°42" | 32°05" | 31°47" | 32°55" | 33°32" |
| Observation | Poor flow | Poor flow | Poor flow | Poor flow | Poor flow | Poor flow | Poor flow | Poor flow | Poor flow |

### Physical parameters of granules after dry granulation (slugging)

For the granules of all the formulated batches, the results of the pre-compression parameters were found within their respective limits after carrying out dry granulation technique. The various parameters such as bulk density, tapped density, compressibility index, hausner's ratio and angle of repose were re-tested.

Compressibility index was found within the limits 5-40. Hausner's ratio was less than 1.25 for all batches indicating good flow properties. The angle of repose was also found to be in the range of 25° to 30°, thus indicating that the flow properties were good.

**Table No.13 Physical parameters of granules after dry granulation**

| Physical Properties | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ |
|---|---|---|---|---|---|---|---|---|---|
| Bulk Density(gm/ml) | 0.437 | 0.439 | 0.436 | 0.438 | 0.435 | 0.440 | 0.426 | 0.429 | 0.443 |
| Tapped Density(gm/ml) | 0.502 | 0.509 | 0.513 | 0.510 | 0.516 | 0.521 | 0.511 | 0.523 | 0.512 |
| Compressibility Index** | 15.35 | 15.22 | 14.29 | 14.15 | 15.69 | 15.54 | 16.63 | 17.01 | 15.10 |
| Hausner's Ratio(H.R.) | 1.17 | 1.15 | 1.18 | 1.16 | 1.18 | 1.18 | 1.19 | 1.21 | 1.18 |
| Angle of Repose | 24°12" | 23°21" | 23°44" | 24°32" | 24°51" | 25°32 " | 23°49" | 26°60" | 25°11 " |
| Observation | good flow | good flow | good flow | good flow | good flow | good flow | good flow | good flow | good flow |

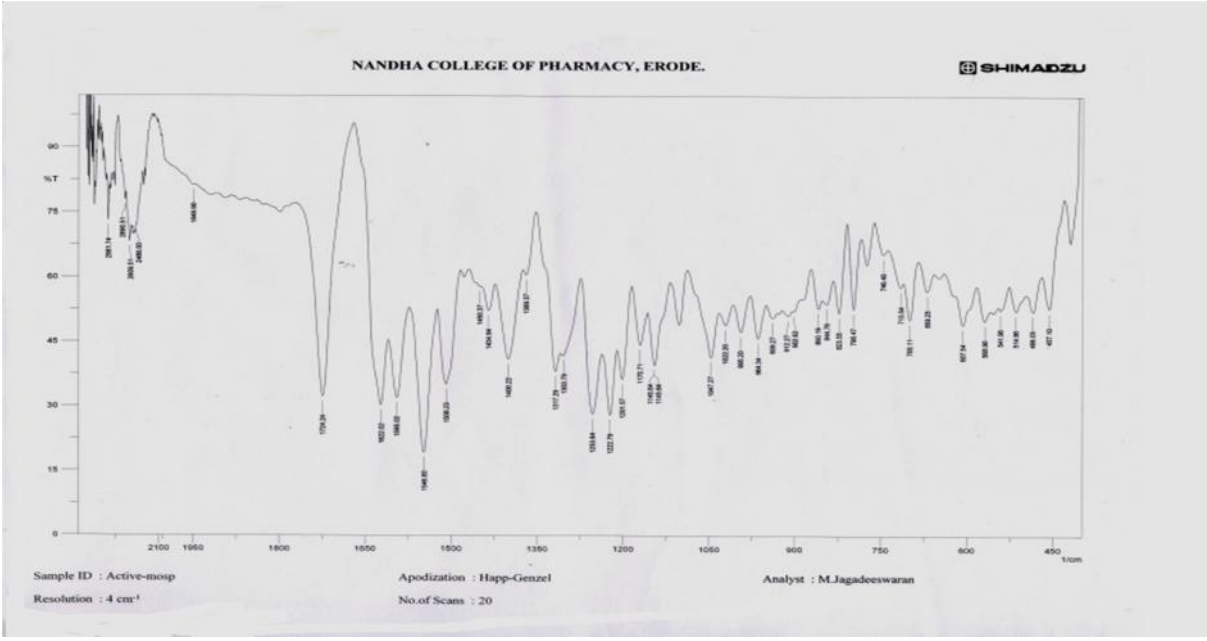



**Fig.6 FTIR Spectra of mosapride citrate**

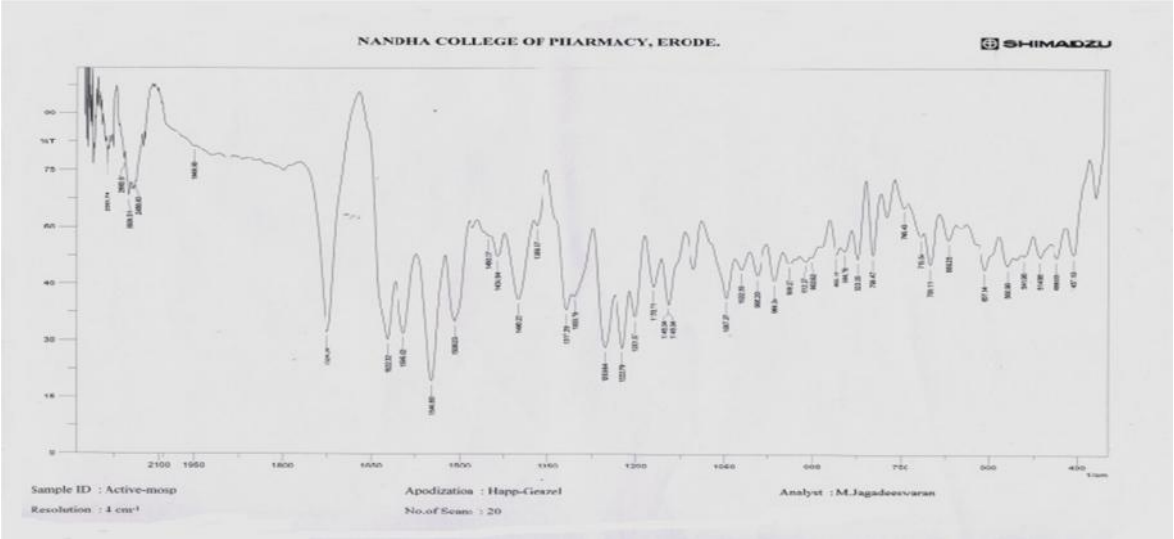



**Fig.7 FTIR Spectra of mosapride citrate with HPMC K4M and HPMC K15M**

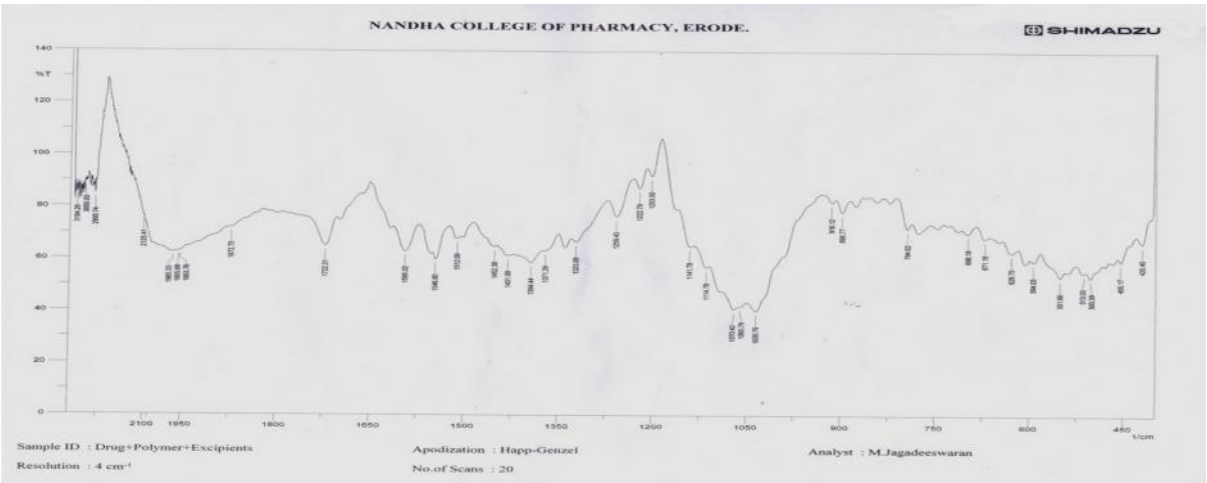



**Fig.8 FTIR Spectra of Mosapride citrate with two different grades of hydroxypropyl methyl cellulose polymer (HPMC K4M and HPMC K15M) and other excipients of formulations.**

**Table No.14 Interpretation of FTIR Spectra[15,16.]**

| Sr.No | Functional groups presents in mosapride citrate. | Standard FTIR range | Observed Peak |
|---|---|---|---|
| 1 | C=O (in ketone) | 1705-1725 | 1724.11 |
| 2 | C-N (vibrations) | 1000-1400 | 1400.20,1434.94,1450.37 |
| 3 | C-H | 700-850 | 607,669,700,715,746,798 |
| 4 | C-Cl | 800-600 | 700.11 |
| 5 | C-F | 1000-1400 | 1201.57 |

In FTIR study the characteristic peak due to pure mosapride has appeared in the spectra of formulation without any makeable changes in the position. This confirms the identity and compatibility among the drug mosapride citrate, the polymers used HPMC K4M, HPMC K15M and other excipients of the formulation.

**Standard Curve of Mosapride citrate in Acetate Buffer pH-4.0**

The calibration curve of mosapride citrate was prepared in acetate buffer ph4.0 following table no-15, shows the absorbance at ƛmax 274 nm and fig no-9 shows the calibration curve with regression coefficient 0.994, and the y intercept 0.022.

**Table No.15 Standard Curve of Mosapradi citrate.**

| Concentration In µg/ml | Absorbance at 274 nm in Acetate buffer pH- 4.0 |
|---|---|
| 0 | 0 ± 0 |
| 2 | 0.055 ± 0.0019 |
| 4 | 0.09 ±0.0016 |
| 6 | 0.137 ± 0.0021 |
| 8 | 0.172 ± 0.0013 |

| | |
|---|---|
| 10 | 0.202 ±0.0018 |
| 12 | 0.271 ±0.0013 |
| 14 | 0.325 ±0.0011 |
| 16 | 0.358 ±0.0019 |
| 18 | 0.428 ±0.0011 |
| 20 | 0.457 ±0.0014 |

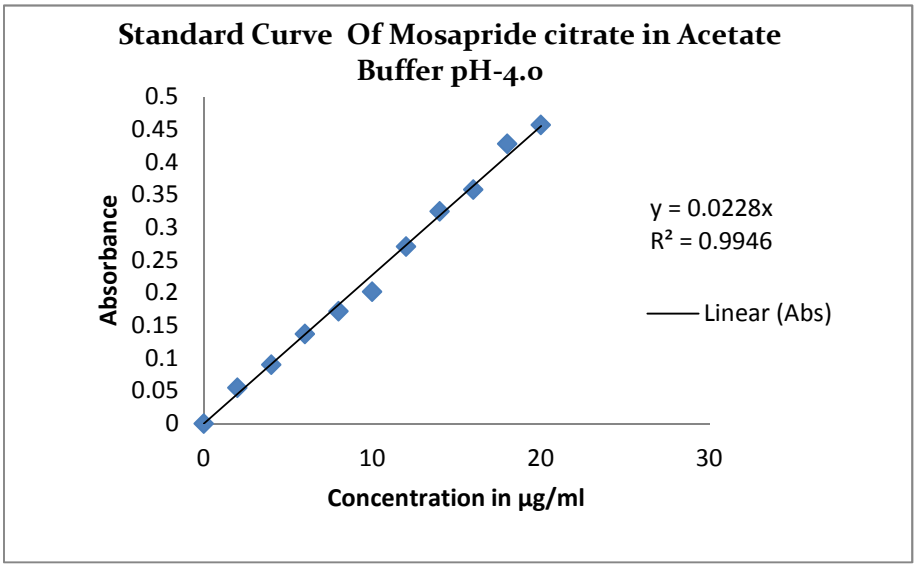



**Fig.9 Standard Curve of Mosapride citrate in Acetate Buffer pH-4.0**

## EVALUATION OF TABLETS

### Physical Parameters of Prepared Tablets-post compression parameters

The tablets from each batch of factorial design were evaluated for uniformity of weight, thickness, hardness, friability and the results were reported in table no --. The tablets showed good weight uniformity as indicated by the low value of Relative Standard Deviation (RSD<1%). The tablet thickness were found in the range of 3.90±0.01mm to 4.00±0.01mm. the tablet hardness varied from—to --. The tables pass the friability test, as all the batches were within the pharmacopoeial limit. (F<1%).

**Table No. 16 Post compression parameters of mosapride citrate.**

| Formulations | Uniformity in weight (mg) | Thickness variation (mm) | Hardness ($kg/cm^2$) | Friability (%) |
|---|---|---|---|---|
| **$F_1$** | 98.4 | 3.16 | 5.20 | 0.103 |
| **$F_2$** | 98.90 | 3.21 | 4.40 | 0.210 |
| **$F_3$** | 99.02 | 3.15 | 4.60 | 0.141 |
| **$F_4$** | 99.97 | 3.12 | 5.30 | 0.158 |
| **$F_5$** | 99.89 | 3.20 | 4.60 | 0.21 |
| **$F_6$** | 99.74 | 3.08 | 4.70 | 0.265 |
| **$F_7$** | 99.37 | 3.22 | 5.30 | 0.106 |
| **$F_8$** | 98.59 | 3.15 | 4.90 | 0.150 |
| **$F_9$** | 99.98 | 3.13 | 5.20 | 0.160 |

| Time (hrs) | Average percentage drug release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **$F_1$** | **$F_2$** | **$F_3$** | **$F_4$** | **$F_5$** | **$F_6$** | **$F_7$** | **$F_8$** | **$F_9$** |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 40.07 | 41.89 | 38.99 | 45.54 | 42.01 | 35.00 | 30.82 | 25.06 | 24.3 |
| 4 | 65.0 | 60.04 | 59.37 | 78.53 | 63.0 | 53.23 | 47.11 | 44.11 | 41.9 |
| 7 | 96.22 | 89.93 | 85.0 | 97.0 | 86.72 | 79.09 | 72.40 | 66.29 | 58.20 |
| 12 | -- | 97.02 | 98.89 | - | 98.58 | 97.66 | 84.21 | 79.56 | 74.10 |
| 16 | -- | -- | -- | - | - | - | 97.0 | 98.01 | 83.50 |
| 24 | -- | -- | -- | - | - | - | - | - | **98.6** |

**Table No.17 Dissolution Profiles of Formulation $F_1$-$F_9$.**

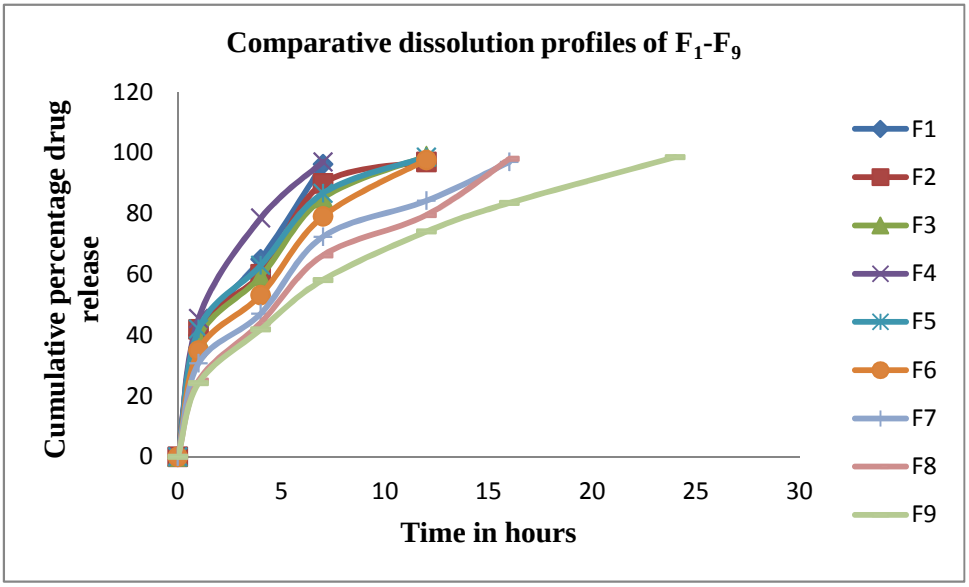



**Fig.10 Comparative dissolution profiles of F1-F9**

**Table No.18 Kinetic studies of optimum formulation $F_9$**

| S. No | Time in hours | Log time | Square root of time | Cumulative percentage drug release | Cumulative percentage drug remain | Log cumulative percentage drug release | Log cumulative percentage drug remain |
|---|---|---|---|---|---|---|---|
| 1 | 0 | - | 0 | 0 | 100 | - | 2 |
| 2 | 1 | 0 | 1 | 24.3 | 75.7 | 1.385 | 1.879 |
| 3 | 4 | 0.602 | 2 | 41.9 | 58.1 | 1.622 | 1.764 |
| 4 | 7 | 0.845 | 2.645 | 58.20 | 41.8 | 1.764 | 1.621 |
| 5 | 12 | 1.079 | 3.464 | 74.10 | 25.9 | 1.869 | 1.413 |
| 6 | 16 | 1.204 | 4 | 83.50 | 16.5 | 1.921 | 1.217 |
| 7 | 24 | 1.380 | 4.898 | 98.6 | 1.4 | 1.993 | 0.146 |

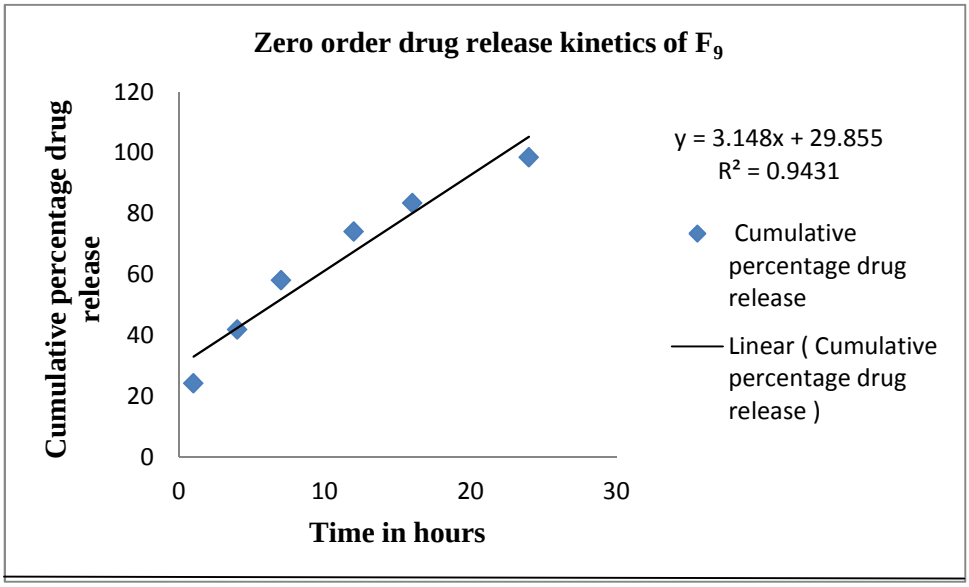



**Fig.11 Zero Order Drug Release Kinetics of $F_9$.**

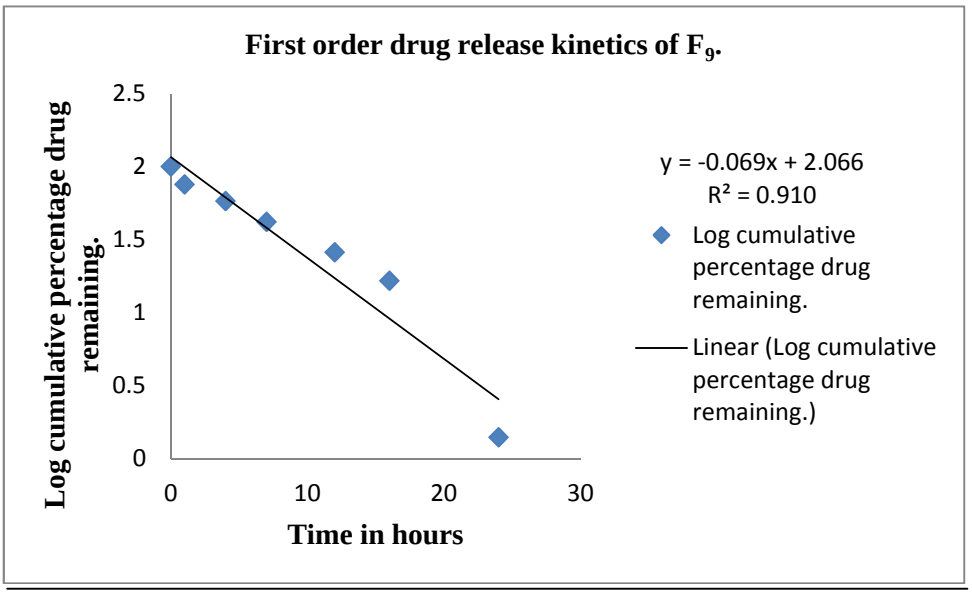



**Fig.12 First Order Drug Release Kinetics of $F_9$.**

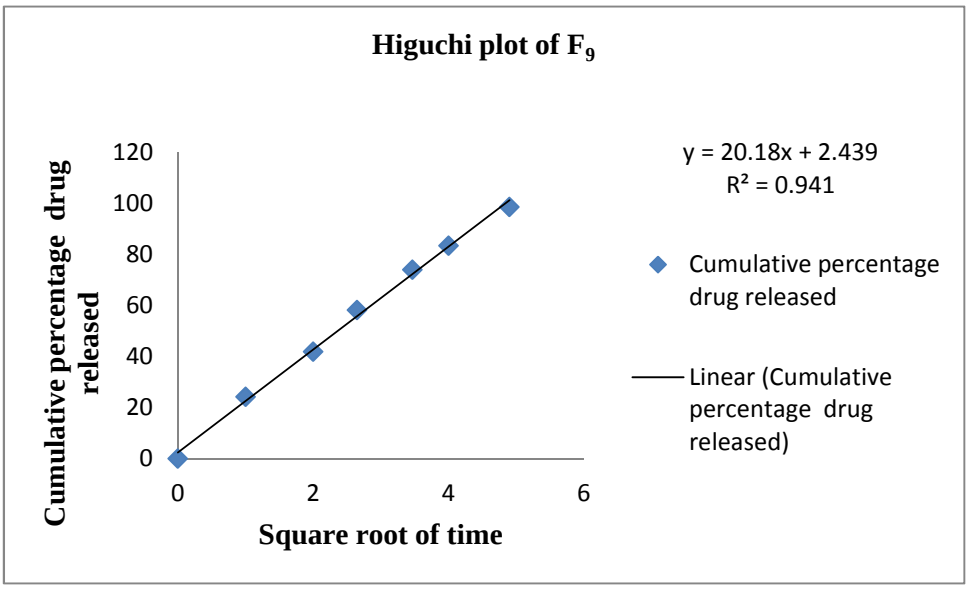



**Fig.13 Higuchi Model Of Drug Release Kinetics For $F_9$**

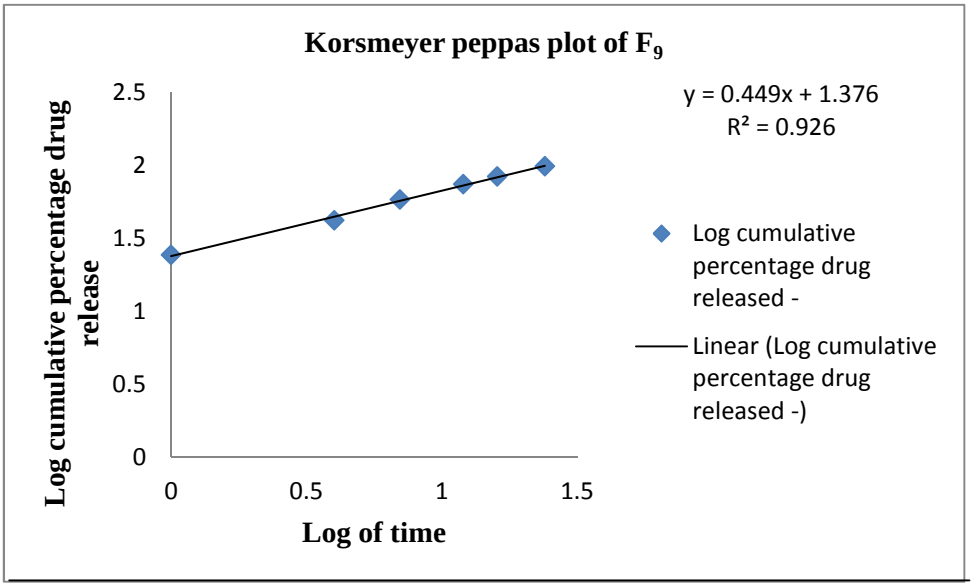



**Fig.14 Korsmeyer-Peppas Release Kinetics of $F_9$.**

**Table No.19 Kinetic values obtained from $F_9$ plot formulation of Mosapride citrate**

| Formulation | Zero order $R^2$ | First order $R^2$ | Higuchi $R^2$ | Korsmeyer – Peppas $R^2$ | N | Mechanism of drug release |
|---|---|---|---|---|---|---|
| F9 | 0.943 | 0.910 | 0.941 | 0.926 | 0.724 | Zero order Non Fickian diffusion |

**Mechanism of drug release**

In order to understand the complex mechanism of drug release from the matrix system, the in vitro release rate were fitted to korsmeyer peppas model and interpretation of release exponent value (n) enlighten in understanding the release mechanism from the dosage form. The release exponent value (n) thus obtained was 0.724. the $F_9$ formulation exhibited anomalous (non fickian) diffusion mechanism. The drug release was diffusion controlled as plot of Higuchi's model was found to be linear.

These formulations also showed higher $r^2$value of zero order release kinetics thereby indicating that the release of drug from the matrix system were both by diffusion and erosion.

**Stability studies as per ICH guidelines**

The optimized formulation $F_9$ of Mosapride citrate sustained release matrix tablets were evaluated for stability studies at $40^0$C $\pm 2^0$C/75 % RH±5% for 90 days. The product was evaluated for appearance and hardness for every 10 days. Drug release studies were conducted as per planned schedule. The stability details / results are presented as below.

Storage Condition- $40^0$C / 75 % RH
Pack- HDPE Container
Storage Period- 1 month, 2 months and 3 months.

**Table No. 20: Stability data**

| Duration | Hardness(kg/cm) | Friability (%) |
|---|---|---|
| After one month | 5.20 | 0.160 |
| After two months | 5.20 | 0.160 |
| After three months | 5.19 | 0.161 |

**Table No. 21: Stability data**

| Time in hours | Cumulative percentage drug release | | |
|---|---|---|---|
| | 1st month | 2nd month | 3rd month |
| 0 | 0 | 0 | 0 |
| 1 | 24.1 | 24.0 | 23.98 |
| 4 | 41.8 | 41.6 | 41.52 |
| 7 | 58.2 | 58 | 57.97 |
| 12 | 74 | 73.8 | 73.65 |
| 16 | 83.3 | 83 | 82.95 |
| 24 | 98.4 | 98.3 | 97.82 |

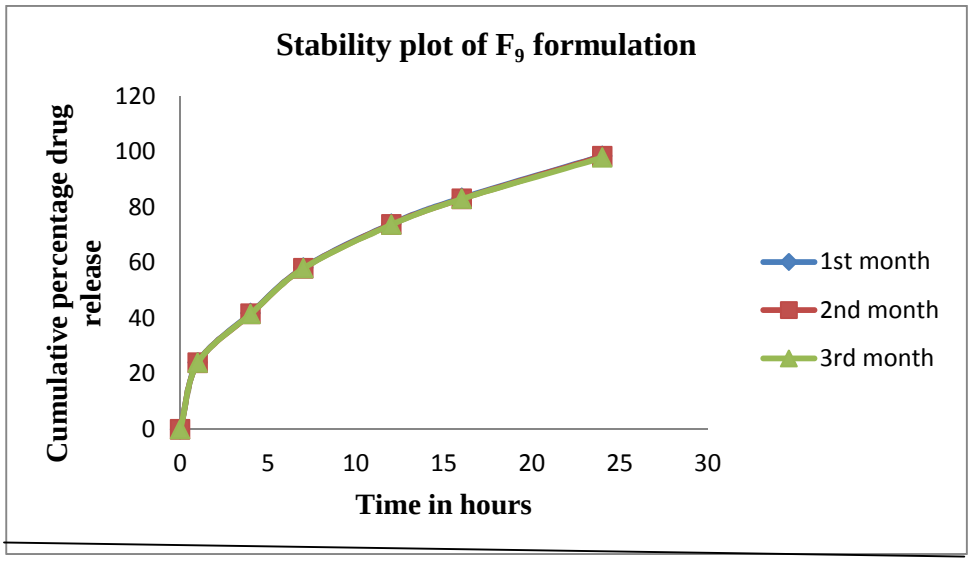



**Fig.No-15 Stability plot of F9 formulation**

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# 9. SUMMARY AND CONCLUSION

The present study was carried out to develop sustained release matrix tablets of mosapride citrate. Matrix tablets of mosapride citrate with two different viscosity grades of hydroxypropyl methylcellulose were prepared by dry granulation and direct compression method and evaluated.

The FTIR study was carried out to know the compatibility of the excipients with mosapride citrate dihydrate, the active constituent of the formulation. The FTIR spectrum of pure mosapride citrate, mixture of mosapride citrate with, HPMC K4M, HPMC K15M polymers and mixture of mosapride citrate, HPMC K15M, HPMC K4M with Lactose, talc, magnesium stearate, aerosil were analyzed for compatibility study. The study of FTIR spectrum confirms that mosapride citrate and excipients used in the formulation are compatible with each other.

The Sustained release Matrix tablets of mosapride citrate dihydrate were prepared by Dry granulation / roller compaction technique and Direct Compression Method. The angle of repose of the granules after slugging (dry granulation) was found to have 24° to 26°. The matrix tablets were compressed by applying optimum force of compression and the hardness of tablets was found to be in the range of 4.6 to 5.3kg/$cm^2$.

The flow property of the granules was good after slugging that was confirmed by the determination of angle of repose which indicates better uniformity of weight. Good hardness of the matrix tablets with less standard deviation indicated retardation in the release as observed in dissolution profile.

On performing the friability for all the formulations the % weight loss falls between the range 0.26% and 0.60% indicates that it falls within the limit showing good compressibility and non defective tabletting.

In first attempt of study, matrix tablets were prepared by using hydroxypropyl methylcellulose (HPMC) of lower viscosity alone i.e.HPMC K4M (10%). This formulation (i.e. $F_1$) failed to sustain the drug release for extended period of time and all most all the drug got released in $7^{th}$ hour. For sustaining the

drug release up to 24th hour the percentage of HPMC K4M in $F_2$ was increased (15%) but the formulation did not sustain the drug release more than 12th hour. It clearly indicates that the lower viscosity grade of hydroxypropyl methylcellulose (HPMC K4M) is able to sustain the drug release up 12th hour and for sustaining the drug release for extended period up to 24th hour, percentage of higher viscosity grade of hydroxypropyl methylcellulose (HPMC K15M) must be used.

In formulation $F_3$, HPMC K15M was used alone (i.e.10%) and the tablets were evaluated for in vitro dissolution study. The formulation failed to sustain the release up to extended period of time. In Formulation $F_4$ ( HPMC K4M 10%, and HPMC K15M 10%) sustained the drug release up to 7th hour, so in formulation $F_5$ the percentage of HPMC K15 was kept constant and the percentage of HPMC K4 was increased, this formulation released the drug in 12th hour. In formulation $F_6$ the percentage of HPMC K4M was further increased and the percentage of HPMC K15M was kept constant. This formulation also failed to sustain the drug release. F7 slowly released the drug, up to 16th hour. The total drug release from formulation $F_8$ was (98.01%) but it also failed to sustain the release up to 24 hour.

In formulation $F_9$, percentage of HPMC K15M was increased from 20% (in $F_8$) to 25mg (in $F_9$) while the percentage of HPMC K4M was kept constant up to 20 and tablets of formulation $F_9$ were evaluated for in vitro dissolution study. The matrix tablets of formulation $F_9$ released the drug slowly as per standard dissolution profile up to 24th hour and total drug release from matrix tablet of formulation $F_9$ at the end of 24th hour was 98.01%.

Hence the above study demonstrated that combination of HPMC K4M and HPMC K15M can be used to formulate sustained release matrix tablets of mosapride citrate. This can sustain the drug release up to 24 hours as per standard dissolution profile. This can be expected to reduce the frequency of administration and decrease the dose – dependent side effects associated with repeated administration of conventional mosapride citrate dihydrate tablets. The cumulative drug release of innovators brand (MOZA SR, Intas Pharmaceuticals) of sustained release tablet of mosapride citrate were compared for in vitro dissolution study. The formulation $F_9$ matrix tablet releases the drug appropriately in comparison of innovators brand. The

cumulative drug release at the end of 24$^{th}$ hour from formulation $F_9$ (98.01%) and the cumulative drug release at the end of 24$^{th}$ hour from innovators brand was (97.30%).

The in vitro drug release result indicates that formulation $F_9$ released more drug than innovators brand and hence more drug is available at the absorption site from formulation $F_9$ as compared to innovators brand, hence the formulation $F_9$ has better bioavailability than innovators brand of mosapride citrate sustained release matrix tablet and also the sustained release matrix tablet was found to be beneficial in terms of reduction in frequency of administration.

The formulation $F_9$ best suited with zero order release kinetics (corr. coefficient =0.943) than the first order release kinetics (corr. Coefficient = 0.910). The formulation $F_9$ follows Higuchi model of drug release kinetics (corr. coefficient=0.41).

The Koresmyer peppas drug release kinetics showed correlation coefficient (0.926) and release exponent (n) 0.724 which indicates that the drug release mechanism is non-fickanian diffusion.

Hence it can be concluded that once daily sustain 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.