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IN SITU GEL FORMING TABLET

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ABSTRACT

Drug delivery systems (DDS) have become an integral part of the development of new medicines. There are numerous elements that enable drug delivery to the correct site at a desirable rate and time of release .There is need for an evolution of such systems, in particular those for oral administration, in order to obtain a site specific delivery. The ultimate aim of such systems is tailoring of the drug formulation to individual requirements under the control of pathophysiological or *in vivo* conditions rather than *in vitro* characteristics. The majority of oral DDS are matrix-based systems. Swellable matrices are monolithic systems prepared by compression of a powdered mixture of a hydrophilic polymer and a drug. Their success is linked to the established tabletting technology of manufacturing. During drug delivery, the gel layer is exposed to continuous changes in its structure and thickness. The gel layer is a hydrophilic barrier that controls water penetration and drug diffusion. It begins when the polymer becomes hydrated and swells. Here, the polymer chains are strongly entangled and the gel layer is highly resistant. However, moving away from this swelling position, the gel layer becomes progressively hydrated and, when sufficient water has accumulated, the chains disen-tangle and the polymer dissolve.

Keywords: *In-situ*, Swellable matrix, Drug diffusion.

INTRODUCTION

Controlled drug delivery technology has progressed over the last six decades. In 1952, the first sustained release formulation was introduced. The 1st generation of drug delivery (1950-1980) focused on developing oral and transdermal sustained release systems and establishing controlled release mechanisms. The 2nd generation (1980-2010) was dedicated to the development of zero-order release systems, self –regulated drug delivery systems, long term depot formulations and nano technology based delivery systems. The latter part of the 2nd generation was largely focused on studying nano particle formulations [1-3].

Controlled release dosage form provides continuous release of their active ingredients at a predetermined rate and for a predetermined time.Oral Sustained release (SR) / Controlled release (CR) products provide and advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance [4-5].

Advantages of Controlled Release Dosage Forms

- Avoid patient compliance problems
- Employ less total drug
- Minimization or elimination of local or systemic side effects.
- Minimal drug accumulation on chronic usage.
- Improve efficiency of treatment.
- Cure or control the condition more promptly.
- Reduce the fluctuation in drug level.
- Improves the bioavailability of some drugs.
- Make use of special effects.

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Disadvantages

- The physician has less flexibility in adjusting the dosage regimen. This is fixed by dosage form design.
- Careful calculation necessary to prevent overdosing
- Drug goes to non-target cells and can cause damage
- Low concentrations can be ineffective
- High systemic concentrations can be toxic, causing side effects or damage to organs
- Expensive (using more drugs than necessary)
- Drugs like Riboflavin and ferrous salt,which are not effectively absorbedinlower intestine are poor candidates.
- Drugs which are having very short half life (<1 hour) e.g.: Penicillin

Oral drug delivery system

Oral controlled release products refer to those formulations in which a "controlling technology or component" is incorporated that is critical to modulate the drug release pattern in predictable fashion or that controls the timing and subsequently the location of drug release within GIT. All the pharmaceutical products formulated for systemic delivery via oral route of administration, irrespective of the mode of delivery – (immediate, sustained or controlled release) and the design of dosage forms (either solid, liquid or dispersion) must be developed within the intrinsic characters of GI physiology. The performance of a drug presented as a controlled release system depends upon [6-7].

- Release from the formulation
- Movement within the body during its passage to the site of action.

The scientific frame work required for the successful development of an oral delivery system consist of basic understanding of following 3 aspects:

1. Physiochemical, pharmacokinetic and pharmacodynamic characteristic of the drug.
2. The anatomic and physiologic characters of GIT (surface area, length and transit time).
3. Physiochemical characteristics and drug delivery mode of dosage form design. Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit.

Terminology

- Controlled drug delivery or modified release delivery
- systems may be defined as follows:-

Controlled release formulation

The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. An ideal Controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systematically, for a specific period of time.

Repeat action preparations

A dose of the drug initially is released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period of time, a second single dose is released. In some preparation, a third single dose is released after a certain time has elapsed, following the second dose.

Advantage: It provides the convenience of supplying additional dose or doses without the need of re administration.

Disadvantage: The blood levels still exhibit the "Peak and valley" characteristic of conventional intermittent drug therapy [8].

Extended-Release formulation

Extended-Release formulations are usually designed to reduce dose frequency and maintain relatively constant or flat plasma drug concentration. This helps avoid the side effects associated with high concentration.

Delayed release preparations

The drug is released at a later time after administration. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as the formaldehyde treatment of soft and hard gelatin capsules. The purposes of such preparations are to prevent side effects related to the drug presence in the stomach, protect the drug from degradation in the highly acidic pH of the gastric fluid.

Site specific targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue [9].

Receptor targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug with in organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems. The controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the

scale of side effects increases as we approach the maximum safe concentration.

Drugs having following characteristics are not suitable for sustained release systems

- Those which are not effectively absorbed in the lower intestine
- Those having short biological half-lives (<1hr) e.g.Furosemide
- Those having long biological half-lives (>12hrs) e.g.diazepam
- Those for whom large dose is required e.g. sulphonamides
- Those with low therapeutic indices e.g.Phenobarbital
- Those for which no clear advantage of sustained release system e.g. griseofulvin.
- Those with extensive first pass metabolism.
- Those candidates with low solubility and/or active absorption

Different types of sustained release systems

There are several types of sustained release systems that are designed and categorised according to the mechanism they employ. These include diffusion controlled, dissolution controlled, erosion controlled, ion exchange controlled and transport control also known as osmotic pump systems

Matrix systems

Diffusion controlled systems also known as matrix systems are very popular for sustained release formulation. The can be divided up into different types of mechanisms by which they prolong drug release, these includes reservoir matrix systems, monolithic matrix systems and osmotic pump systems

Reservoir matrix systems

This system involves a membrane which controls the release of drugs from the matrix system. The drug will eventually diffuse through the membrane and its release is kept constant by the diffusion distance that the drug particles have to cover (Fig. 1).

Osmotic pump systems

Osmotic systems operate on osmotic pressure. They contain a core tablet that is surrounded by a semi permeable membrane coating which has an orifice. The core tablet has two layers to it, one containing the active ingredient/drug known as the active layer and the second containing the osmotic agent which is also known as the push layer . Water enters the tablet through the semi permeable membrane causing the drug to dissolve and suspend. The increase in osmotic pressure causes the dissolved/suspended drug to be pumped out of the delivery orifice. The rate of drug delivery can be changed by altering the size of the delivery orifice and the thickness of the semipermeable membrane

Monolithic matrix systems

These systems involve drug to be encapsulated or dispersed in a matrix. These systems can be employed by forming hydrophobic matrices and/or hydrophilic matrices to allow for control or prediction of drug release. They can be divided into soluble/hydrophilic matrix systems which swell on hydration and dissolve to release drug and insoluble/hydrophobic matrix systems which release drug after being dissolved by a solvent (Fig. 2).

Hydrophobic matrix systems are formulated by waxes mainly and can be suitable for drugs which have a high solubility. Wax based matrices have been investigated to ascertain the factors that would affect the release of drug. Drug release has been successfully modulated in hydrophobic matrices however, in a study it was found that matrices which are based on waxes can modify release rate by increasing the amount of drug or wax concentration, as well as incorporating hydrophilic polymers which would enhance the release. Even though the hydrophobic matrix was able to modulate drug release, the processes that had to be carried out such as hot fusion and thermal treatment highlighted the length of the process that would be required to form such tablets. This can potentially be a deterrent for manufacturing companies who would prefer a more economical method of producing sustained release formulations.

Hydrophilic matrix systems tend to be more popular in tablet manufacture for controlled release drug delivery systems due to their low manufacturing cost. On contact with water a hydrophilic matrix increases in size due to the entry of the solvent. This then allows the polymer to swell up forming a barrier to drug release. The drug particles would then move through this gel layer via diffusion or erosion of the gel eventually allowing drug to be released. There has been a lot of research into the mechanisms of drug release from hydrophilic matrices and the critical factors that influence the release rate [9-11].

These swellable matrices have more than one ‘front’ as a part of its release mechanism. This has been shown in Fig. 3.

The area of dissolved drug and un-dissolved drug are separated by two types of “fronts” from the swollen gel region. They have a diffusion front which is located in between the swelling and erosion front . Drug release can occur by many mechanisms such as erosion, diffusion, polymer relaxation or a combination. Modulation of drug release from geomatrix multi-layered tablets was proposed by Conti and Maggi (1996) and they found that a swellable barrier around an active core provides greater modulation for soluble drugs.

Effects of system parameters

- Polymer solubility
- Solution solubility
- Partition coefficient
- Polymer diffusivity
- Solution diffusivity
- Thickness of polymer diffusional path
- Thickness of hydrodynamic diffusion layer
- Drug loading dose
- Surface area

Polymer solubility

Drug particles are not released until they dissociate from their crystal lattice structure, dissolve or partition into surrounding polymer. Solubility of drug in polymer membrane or matrix plays important role in it's release from a polymeric device. For a drug to release at an appropriate rate the drug should have adequate polymer solubility.The rate of drug release is directly proportional to magnitude of polymer solubility [11].

Solution solubility

Aqueous solubility varies from one drug to another. The difference in aqueous solubility is depend on the difference in their chemical structure, types & physicochemical nature of functional groups & the variations in their stereo chemical configurations .By using a water – miscible co-solvent as a solubilizer & addition of the co-solvent into the elution solution to increase the solution solubility of drugs. Solubilization of poorly soluble drug in aqueous solution can be accomplished by using multiple co-solvent system.The drug release increases with increase in solution solubility of drug.

Partition coefficient

Partition co-efficient, K of a drug for it's interfacial partitioning from the surface of a drug delivery device towards an elution medium as given :

$$K = C_s/C_p$$

where,

C_s = conc. Of drug at the solution/polymer interface

C_p= solubility of drug in the polymer phase

Ratio of drug solubility in the elution solution C_s over its solubility in polymer composition C_p of device.Any variation in either C_s or C_p result in increase or decrease in magnitude of 'K' value. Rate of drug release increase with increase in partition coefficient.

Polymer diffusivity (D_p)

The diffusion of small molecules in a polymer structure is an energy activated process in which the diffusant molecules move to a successive series of equilibrium positions when a sufficient amount of energy of activation for diffusion E_d, has been acquired by the diffusant& it's surrounding polymer matrix.

This energy- activated diffusion process is frequently described by the following Arrhenius relationship :

$$D_p = D_0\, e^{-(Ed/RT)}$$

The bulkier the functional group attached to polymer chain lower the polymer diffusivity. Magnitude of polymer diffusivity is dependent upon type of functional group and type of stereo chemical position in diffusant molecule [12].

Solution diffusivity (D_s)

The diffusion of solute molecules in solution medium is a result of the random motion of molecules. Under concentration gradient molecule diffuse spontaneously from higher concentration to lower concentration.

When solution diffusivity are compared on bases of molecular volume, alkanes are most rapidly diffusing chemicals.

The relative rates of diffusion of various chemical classes are as follows :

Alkane > alcohol > amides > acids > amino acids >dicarboxylic acid

Diffusivity of solute molecule in aqueous solution usually decreases as its concentration increases [12].

Thickness of polymer diffusional path (h_p)

Control release of drug species from both polymer membrane & polymer matrix controlled drug delivery system is governed by,

The solute diffusion coefficient in the membrane lipid and the thickness of the membrane.

h_p value for polymer membrane controlled reservoir devices, which are fabricated from non biodegradable and non swollen polymer, the value is defined by polymer wall with constant thickness that is invariable with time span.In polymer matrix controlled reservoir devices, which are fabricated from non biodegradable polymers, the thickness of diffusional path is defined as drug depletion zone progressively in proportion to the square root of time.The rate of growth in the $h_p$value can be defined mathematically by,

$$(HD)\ nr = (\Pi\, Ds)1/2\ t1/2$$

where,

nr = refers to stationary (non rotationary) state

C_p= solubility of drug in the polymer phase

D_p= diffusivity of drug in the polymer matrix

A = loading dose of a drug

Thickness of hydrodynamic diffusion layer (h_d)

The hydrodynamic diffusion layer has a rate limiting role on controlled release dosage form. Magnitude of drug release value decreases as the thickness of hydrodynamic diffusion layer is increased.

Drug loading dose

In preparation of the device varying loading doses of drugs are incorporated, as required for different length of treatment.

Variation in the loading doses results only in the change in duration of action with constant drug release profile.

Surface Area

Both the in-vivo& in-vitro rates of drug release dependant on the surface area of the drug delivery device. Greater the surface area greater will be the rate of drug release

Factor Influencing The Design And Performance Of Controlled Drug Delivery System

1. Biopharmaceutic characteristic of the drug

a) Molecular weight of the drug
b) Aqueous solubility of the drug
c) Apparent partition coefficient
d) Drug pKa and ionization physiological pH
e) Drug stability
f) Mechanism and site of absorption
g) Route of administration.

2. Pharmacokinetic characteristic of the drug

a) Absorption rate
b) Elimination half life
c) Rate of metabolism
d) Dosage form index

3. Pharmacodynamic characteristic of the drug

a) Therapeutic range
b) Therapeutic index
c) Plasma–concentration–response relationship

1.Biopharmaceutical characterization of drug

For designing a controlled drug delivery system the following biopharmaceutic properties of drugs must be included [13-16]

a) **Molecular weight of the drug**

Lower the molecular weight, faster and more complete the absorption. About 95% of the drugs are absorbed by passive diffusion. Diffusivity is defined as the ability of a drug to diffuse through the membrane is inversely related to the molecular size. Thus drugs with large molecular weight are poor candidates for oral controlled release systems.

b) **Aqueous solubility of the drug**

A drug with good aqueous solubility, especially if pH independent, serves as a good candidate for oral controlled release dosage form. Solubility of drug can limit the choice of mechanism to be employed for CRDDS, for example the diffusional systems are not suitable for poorly soluble drugs. Absorption of poorly soluble drugs is dissolution rate-limited hence control release device does not control the absorption process, so they are poor candidates.

c) **Apparent partition coefficient**:

Greater the apparent partition coefficient of a drug, greater its lipophilicity and thus greater is its rate and extend of absorption. These types of drugs even cross the highly selective blood brain barrier. This parameter is also important in deciding the release rate of a drug from lipophilic matrix or device.

d) **Drug pKa and ionization at physiological pH**:

For optimum passive absorption, the drugs should be non ionised at that site for an extend of 0.1-5%. Drugs that are existing largely in ionosed forms are poor candidates for controlled delivery systems eg: hexamethonium.

e) **Drug stability**

Drugs that are unstable in the GI environment are not suitable candidates for controlled release systems. Drugs that are unstable in gastric pH can be designed to release in intestine with limited or no release in stomach and vice versa.

f) **Mechanism and site of absorption**

Drugs that are absorbed by carrier mediated transport process or through a window are poor candidates for controlled release systems, eg:Vitamin B.

g) **Route of administration**

For controlled release oral and parenteral routes are the most prefered which is the followed by transdermal.

i. Oral route: the drug should have following properties to be a succesfull candidate

- ❖ It must get absorbed through the entire length of GIT.
- ❖ Main limitation is transit time (mean of14 hours), which can be extended for 12-24 hours.
- ❖ Dose as high as 1000mg can be given through this route.

ii.Intramuscular/subcutaneous route:

This route is preferred because

- ❖ The action is to be prolonged for 24hours to 12 months.
- ❖ Small amount of drug is administered (2ml/2gm).
- ❖ Factors important are solubility of drug in surrounding tissue, molecular weight, partition coefficient and pKa of drug.

iii. Transdermal route:

This route is selected for drugs which show extensive first pass metabolism upon oral administration or drugs with low dose. Important factors to be considered are partition coefficient of drugs, contact area, skin condition, skin permeability of drug, skin perfusion rate, etc.

2.Pharmacokinetic characteristic of a drug

a) **Absorption rate**

A drug which is fabricated into a controlled release system its absorption must be efficient since the desired rate limiting step is rate of drug release. A drug with slow absorption is is a poor candidate for such dosage forms, as continuous release will result in a pool of unabsorbed drug. If a drug is absorbed by active transport, or transport is limited to a specific region of intestine, sustained-release preparations may be disadvantageous to absorption.

b) **Biological half life**

An ideal CRDDS is one in which the rate of drug absorption is equal the rate of drug elimination. If the t1/2 is smaller (less than 2 hours) for a given drug then more amount of drug is to be incorporated into the controlled release dosage form. Drugs having t1/2 in the range of 2-4 hours are ideal candidates for controlled release system. Drugs with long half life need not be formulated into such formulations.

c) **Metabolism**

Drug selected for controlled release system should be completely metabolized but the rate of metabolism should not be too rapid. A drug which induces and inhibits metabolism is a poor candidate because steady states are difficult to achieve.

d) Protein Binding Drug

The drug can bind to components like blood cells and plasma proteins and also to tissue proteins and macromolecules. Drug protein binding is a reversible process. As the free drug concentration in the blood decreases, the drug-protein complex dissociates to liberate the free drug and maintain equilibrium. A protein bound drug due to its high molecular size is unable to enter into hepatocytes, resulting in reduced metabolism. The bound drug is not available as a substrate for liver enzymes there by further reducing the rate of metabolism. The glomerular capillaries do not permit the passage of plasma-protein and drug protein complexes. Hence only unbound drug is eliminated. The elimination half-life of drugs generally increases when the percent of bound drug to plasma increases. Such drugs need not be formulated into sustained/controlled release formulations.

e) **Dosage form index**

It is defined as the ratio of Css, max to Css, min. Its value must be close to as possible as one.

3.Pharmacodynamic characteristics of the drug

a) **Therapeutic range**

A candidate drug for controlled release drug delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in concentration beyond this level.

b)**Therapeutic index**:

It is most widely used to measure the margin of safety of a drug. TI = TD50 /ED50 .The longer the value of T.I the safer is the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its T.I value is greater than 10.

c) **Plasma concentration-response relationship**

Drugs such as reserpine whose pharmacological activity is independent of its concentration are poor candidates for controlled-release system.

Drug properties influencing the dosage form

The design of a controlled release system depends on various factors such as the route of delivery, the type of drug delivery system, the disease being treated, the length of therapy, and the properties of the drug. Most important factor is properties of the drug that are as follows [17-20].

A] Physicochemical properties

1] Aqueous solubility and pKa

Absorption of poorly soluble drugs is often dissolution rate-limited. Such drugs do not require any further control over their dissolution rate and thus may not seem to be good candidates for oral controlled release formulations. Controlled release formulations of such drugs may be aimed at making their dissolution more uniform rather than reducing it.

2] Partition coefficient

Drugs that are very lipid soluble or very water-soluble i.e., extremes in partition coefficient, will demonstrate either low flux into the tissues or rapid flux followed by accumulation in tissues. Both cases are undesirable for sustained release system.

3] Stability of the drug

Since most oral controlled release systems are designed to release their contents over much of the length of GI tract, drugs that are unstable in the environment of theintestine might be difficult to formulate into prolonged release system.

***4*] Size of the dose**

For drugs with an elimination half-life of less than 2 hours as well as those administered in large dosages, a controlled release dosage form may need to carry a prohibitively large quantity of drug.

5] Molecular size and diffusivity

In addition to diffusion through a variety of biological membranes, drugs in many sustained release

systems must diffuse through a rate controlling membrane or matrix. The ability of drug to pass through membranes, its so called diffusivity, is a function of its molecular size (or molecular weight). An important influence upon the value of diffusivity, D, in polymers is the molecular size of the diffusing species. The value of D
thus is related to the size and shape of the cavities as well as size and shape of the drugs. Generally, the values of diffusion coefficient for intermediate molecular weight drugs i.e., 150-400, through flexible polymers range from 10-6 to 10-9 cm2/sec, with values on the order of 10-8 being most common. For drugs with molecular weight greater than 500, the diffusion coefficients in many polymers frequently are so small that they are difficult to quantify, i.e., less than 10-12 cm2/sec. Thus high molecular weight of drug should be expected to display very slow release kinetics in sustained release devices where diffusion through polymeric membrane or matrix is the release mechanism [21-22].

B] Biological properties

***1*] Absorption**

Slowly absorbed drugs or the drugs absorbed with a variable absorption rate are poor candidates for a controlled release system. Water-soluble but poorly absorbed potent drugs and those absorbed by carrier mediated transport processes or absorbed through window are poor candidates for controlled release system.

2] Metabolism

Drug metabolism can result in either inactivation of an active drug or conversion of an inactive drug to an active metabolite. The process of metabolism can take place in variety of tissues but the organ mainly responsible for metabolism is liver as it contains variety of enzyme systems and thus greatest metabolic alteration of a drug takes place after its absorption into the systemic circulation. Thus the metabolic pattern of a drug may influence the choice of the route of administration. There are two factors associated with metabolism that significantly limit controlled release product design. First, if a drug is capable of either inducing or inhibiting enzyme synthesis it will be difficult to maintain uniform blood levels of drug upon chronic administration. Second, if the drug undergoes intestinal (or other tissue) metabolism or hepatic first pass metabolism, this also will result in fluctuating drug blood levels

3] Elimination or Biological half-life

The rate of elimination of drug is described quantitatively by its biological half- life. The biological half-life and hence the duration of action of a drug plays
a major role in considering a drug for controlled release systems. Drugs with short half-life and high dose impose a constraint because of the dose size needed and those with long half-lives are inherently controlled.

4] Safety considerations and Side effects

For certain drugs the incidence of side effects is believed to be a function of plasma concentration. A controlled release system can, at times, minimize side effects for a particular drug by controlling its plasma concentration and using less total drug over the time course of therapy. The most widely used measure of the margin of safety of a drug is its therapeutic index (TI), which is defined as

TI = TD50/ED50

Where TD50 is median toxic dose ED50 is median effective dose

In general, larger the value of TI, safer is the drug. Drugs with very small values of TI usually are poor candidates for formulation into CR productsprimarily because of technological limitations of precise control over release rates. A drug is considered to be relatively safe if its TI value exceeds 10.

5] Protein binding

The characteristics of protein binding by a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. 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 sustained release dosage form.

6] Disease state

Disease state is an important factor in considering a drug for controlled release system. In some instances better management of the disease can be achieved by formulating the drug as controlled release system.

7] Circadian rhythm

Many biological parameters like liver enzyme activity, blood pressure, intraocular pressure and some disease states like asthma, acute myocardial insufficiency, and epileptic seizures have been shown to be influenced by circadian rhythm. Hence the response to certain drugs like digitalis glycosides, diuretics, amphetamines, barbiturates, carbamazepine, ethyl alcohol, and chlordiazepoxide display time dependent nature.

Factors influencing drug release

Various factors could be accounted for the drug release mechanism from hydrophilic matrices. These factors include; geometry of matrix, particle size of polymers , matrix swelling ratio (which depend on polymer type and controls water and drug diffusion coefficients),polymer and drug concentration , chain length and degree of substitution on HPMC as well as drug characteristics.The study of the drug release from the hydrophilic matrices requires knowledge of properties and interaction of the polymers used as the binder [23].

1. Polymer hydration

Dissolution of a polymer includes absorption/adsorption of water in more accessible place, rapture of polymer-polymer linking with the simultaneous forming of water- polymer linkage, separation of polymeric chain, swelling and finally dispersion of polymeric chain in the dissolution medium. The Methocel K polymer, because of low content of methoxy groups, hydrate quickly, which justifies its application in the controlled release matrices. Larger sized fraction of HPMC can hydrates more rapidly than smaller fraction. The first minutes of hydration are the most important because they correspond to the time when the protective gel coat is formed around matrices containing HPMC.

2. Polymer composition

The complex composition of polymer cellulose ether precedes several reactions, as hydroxyl groups, that can be reacting covalently with many species. Both mono and poly functional, in order to stabilize and insolubilize their structure. The intermolecular interaction include the formation of acetal with non-functional aldehydes, formation of hemeacetal or acetal with dialdehyde, formation of ether or methylene link with reagent containing methyl groups and formation of ether links with epoxies, ethylene imines derivatives, ethylene imine derivatives, sulfones, and labile chlorine compounds.

3. Polymer viscosity

With cellulose ether, polymer viscosity is used as an indication of the matrix weight.Increasing the molecular weight or viscosity of the polymers in the matrix formulation increasing the gel layer viscosity and thus slows the drug dissolution. Also the greater dilution and erosion thus control the drug dissolution. Viscosity of the gelling agent retards orhastens the initial process of hydration (without altering the release rate). Works applying DSC allows conclusion that temperature affect HPMC hydration. With increase of gel temperature, the HPMC looses hydration water fallowed by decrease in relative viscosity.

4. Drug solubility

Absorption of poorly soluble drugsis often dissolution rate limited. Such drug does not require any further control over their dissolution rate; during the Pre-formulation phase it is necessary to determine drug solubility not only in water but also at various pH values. The aqueous and pH dependent solubility is of important for drug release. The hydro solubility of drug play an important role in drug release mechanism, soluble drugs are generally released by diffusion mechanism while insoluble drugs are release by erosion mechanism.

5. Polymer drug proportion

Studies completed by Salomen, E. Docker demonstrated that the release rate increase for lower amount of HPMC with slightly soluble drug, the proportion is dependent on gel consistency, since it is affected by gel proportion.

6. Polymer: drug interaction

The evaluation of water concentration profile was calculated from HPMC matrices with different molecular Weights. The Thermal analysis of cellulose ether polymer demonstrated that the drug polymer interaction occurs at hydrated gel layer around the matrix tablet and is partially responsible for the drug release modulation.

7. Tablet hardness and density

Tablet hardness did not show marked difference in as evaluated by an invitro method. Ladipus et al utilized to compression forces and observed no significant difference in drug release patterns from tablets of different densities. Valasco MV et al evaluated effect of compression force on drug release from HPMC matrices and reported independence of drug release with compression force.

8. Effect of diluents

The inclusion of water soluble diluents (lactose) and water insoluble diluents (tribasiccalcium phosphate) in matrix tablets showed divergence in the release profile of drug, because of the difference in the solubility of the diluents and their subsequent effect on the tortuosity factor. As the water soluble diluents dissolves, they diffuse outward and decrease the tortuosity of the diffusion path of the drug. But tricalcium phosphate does not diffuse outward, but rather get entrapped within the matrix and bring about an increase in the release of the drug by the fact that its presence necessarily decreases the gum concentration.

Preformulation testing

It is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

a) Determination of Melting Point

Melting point of drug was determined by capillary method. Fine powder of drug was filled in a glass capillary tube (previously sealed at one end). The capillary tube is tied to thermometer and the thermometer was placed in the This tube and this tube is placed on fire. The powder at what temperature it will melt was noticed.

b) Solubility

Solubility of drug was determined in pH 1.2 and pH 6.8 buffers. Solubility Studies were performed by taking excess amount of drug in beakers containing the Solvents.

The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions are analyzed spectrophotometrically at 260.5nm as pH 1.2 as blank and 262.4nm as pH 6.8 as blank.

c) Compatibility Studies

Compatibility study with excipients was carried out by FTIR. The pure drug and its formulations along with excipients were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

d) Identification of Drug

Weigh accurately about 0.25 gm, dissolve in 50 ml of carbon dioxide-free water and titrate with 0.1 M sodium hydroxide using phenol red solution as indicator. Repeat the operation without the substance under examination. The difference between the titrations represents the amount of sodium hydroxide required.

Evaluation Parameters

1) Pre Compression Parameters

A. Bulk density (Db)

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

Db = M / Vo

Where, Db = Bulk density (gm/cc)

M is the mass of powder (g)

Vo is the bulk volume of powder (cc)

B. Tapped density (Dt)

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

Dt = M / Vt

Where, Dt = Tapped density (gm/cc)

M is the mass of powder (g)

Vt is the tapped volume of powder (cc)

C. Compressibility index

The compressibility of the powder was determined by the Carr's compressibility index.

Carr's index (%) = = b=(v/b) X100

D. Hausner ratio

Hausner ratio = tapped density/ bulk density

Values of Hausner ratio; < 1.25: good flow,>1.25: poor flow If Hausner ratio is between 1.25-1.5, flow can be improved by addition of glidants.

E. Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

Tanθ =h/r

θ = tan-1(h/r)

where, θ = angle of repose,

h = height of pile,

r = radius of the base of the pile.

F. Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (Vbulk) and the true volume of the powder blend (The space occupied by the powder exclusive of

spaces greater than the intermolecular spaces, V).

Porosity (%) =Vbulk-V/Vbulkx 100

G. Flow rate

Flow rate of granules influences the filling of die cavity and directly affects the weight of the tablets produced.

2. Post Compression Parameters

A. Thickness and diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm2.

C. Friability (F)

Tablet strength was tested by Friabilator USP. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

Percentage friability (F) = (initial weight (W1)- final weight/Initial weight $\times$100

D. Weight variation test

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount

of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

Average weight of tablet	Percentage difference
123 or <	10
125-250	7.5
>250	5

E. Uniformity of drug content

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at suitable wave length after suitable dilution using a UV/Visible Spectrophotometer (UV-1800) [22].

***In vitro* release kinetics**

The quantity of drug released from matrix tablets is often analyzed as a function of the square root of time; this is typical for systems where drug release is governed by pure diffusion. However, the use of this relationship in swellable systems is not completely justified, as such systems can be erodible and the contribution of the relaxation of polymeric chains to drug transport has to be taken into account. Therefore, analysis of drug release from swellable matrices must be performed with a flexible model that can identify the different contribution to overall kinetics.An empirical equation (Eqn 2), proposed by Ritger and Peppas, rapidly gained popularity for the analysis of release data in these systems. The equation is a power law in which the fraction released is linearly related to the time raised to an exponent n, whose values can range between 0.43 and 1.00, according to the geometry, and the prevalence of the Fickian or the Case II (relaxation) transport [23].

$$\frac{M_t}{M_\infty} = kt^n \qquad (2)$$

where M_t is the drug released at time t, M_∞ is the quantity of drug released at infinite time, k is the kinetics constant and n is the diffusional exponent.

A binomial equation (Eqn 3), similar in meaning to Eqn 2, in which the contribution of the relaxation or erosion mechanism and of the diffusive mechanism can be quantified, was also proposed by Hopfenberg and adapted to pharmaceutical problems by Peppas and Sahlin:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \qquad (3)$$

where k_1 is the diffusional constant, k_2 is the relaxational constant and m is the diffusional exponent.

Analysis performed by different authors on various systems prepared from HPMC or PEO showed that the release was usually identified as anomalous, owing to the contribution of a mechanism other than diffusion to drug transport. In fact, published data for cylindrical matrices that contain these polymers showed that typical values of the exponent n were approximately 0.6 and 0.8, for HPMC and PEO, respectively. By contrast, when a soluble polymer was used, as in the case of the low-molecular weight polyvinyl alcohol (PVA), linear drug release was obtained and the value of the exponent n was very close to 1.0, implying an erosion-controlled mechanism [24].

The relative contributions of drug diffusion, polymer relaxation and matrix erosion to drug release in HPMC matrices, produce n values that range from 0.5 to 1.0.To shift release kinetics towards linearity, a matrix formulation can be created to facilitate one of the previously described contributions. Swellable matrices pre-pared to increase the susceptibility of cylindrical matrices to the chain relaxation or erosion, by a proper use of swellable excipients, including HPMC.

Improvement of linearity of release kinetics can also be obtained by mixing HPMC with other swellable polymers. HPMC matrices show an initial burst of drug release rate, owing to the time required for the formation of an efficient gel layer. This is particularly evident for highly soluble drugs. It was ob-served that sodium carboxymethyl cellulose matrices, because of its polymer swelling and dissolution properties, did not show initial burst release. Using optimized mixtures of HPMC and CMC, obtained zero-order release of β-adrenoceptor antagonists. The results were explained in terms of diffusional path length for drug diffusion remaining fairly constant. When the data were fitted to Eqn 2, the exponent n reached a value of 0.89.

Similarly, zero-order release kinetics can be obtained using a binary polymer matrix consisting of highly methoxylated pectin and HPMC, both in the case of soluble and poorly soluble drugs. With these matrices, the drug release rate can be modulated according to the pectin: HPMC ratio.

***In vivo* release behaviour**

Not many data are available in the literature showing the *in vivo* performance of swellable matrices. A series of bioavailability trials in human volunteers was conducted with the intent of correlating the *in vitro* release properties of swellable matrices with drug absorption. In these experiments, cylindrical matrices, containing diclofenac sodium and a soluble poly(vinyl alcohol) brand, were coated with a water-insoluble polymer on one base and lateral surface, to obtain a core-in-cup system with a constant delivery area. This system showed zero-order *in vitro* release, as the polymer used for the matrix preparation(low molecular weight and quite soluble)

enabled front movement synchronization. Moreover, the delivery rate could be easily manipulated by changing the area of the punches used.

Fig. 1. Schematic representation of Reservoir matrix systems

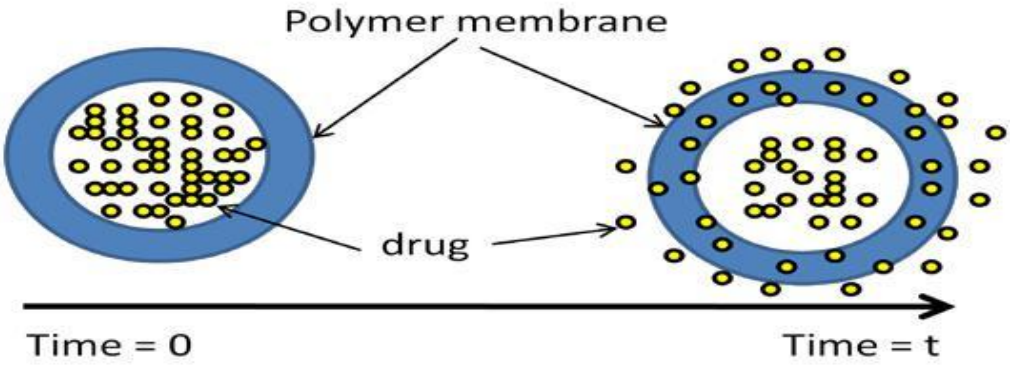

Fig 2. Schematic representation of drug release from different types of matrix tablets

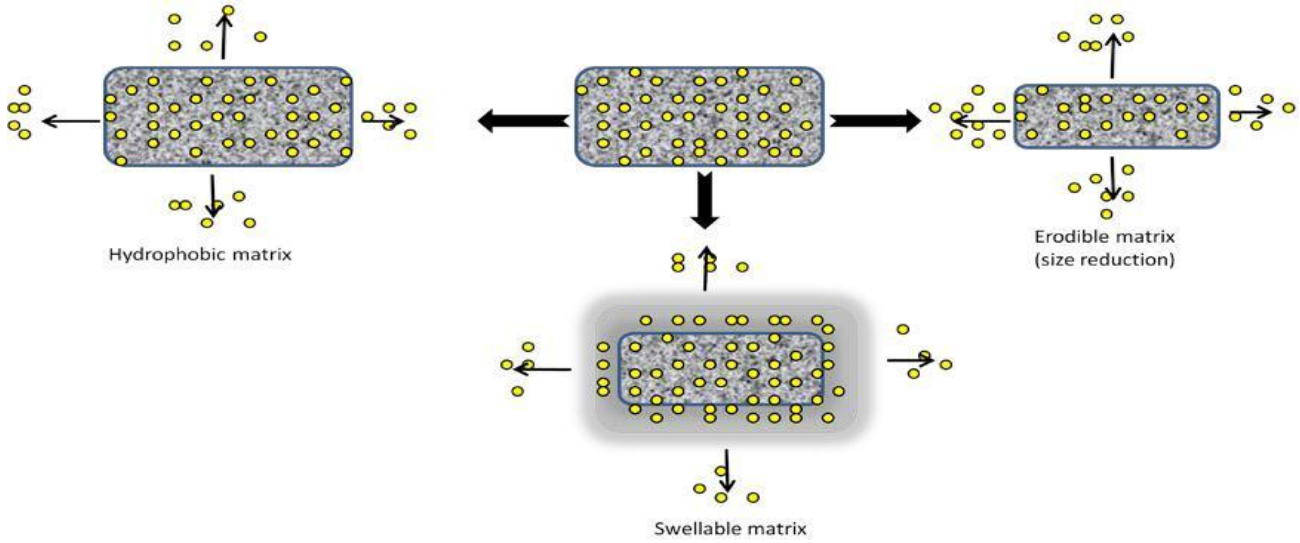

Fig. 3. Different front within a matrix tablet containing colouring agent to distinguish different swelling fronts

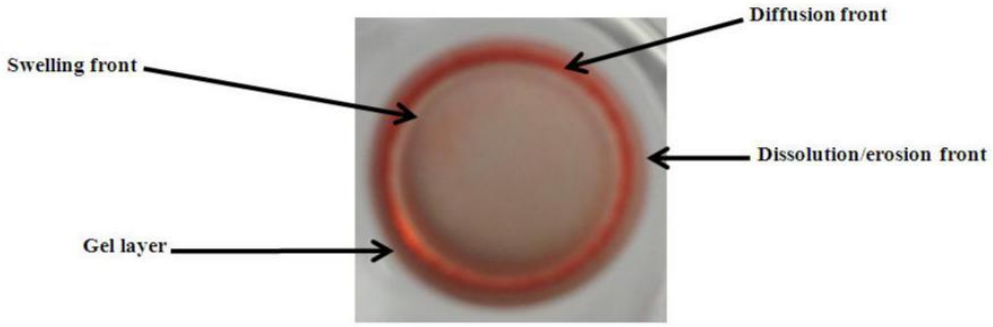

Table 1. Examples of a few polymers used in formulation of controlled release dosage forms

Hydrophilic Polymers	Methylcellulose, Hydroxy propylmethylcellulose (HPMC), Hydroxy propylcellulose (HPC),
	Hydroxyethylcellulose (HEC), Ethylhydroxyethylcellulose (E-HEC), Sodium-carboxymethylcellulose

	(Na-CMC)
Non-cellulosic	Sodium alginate, Xanthan gum, Carrageenan, Chitosan, Guar gum, Pectin, Polyethylene oxide
Hydrophobic Polymers	Ethylcellulose, Hypromellose acetate succinate, cellulose acetate, cellulose acetate propionate

CONCLUSION

Swellable matrices represent a delivery system in which various mechanisms can be adapted to the delivery programme. The choice of the hydrophilic polymer in the matrix formulation can provide an appropriate combination of swelling, dissolution or erosion mechanisms to determine *in vitro* release kinetics that are easily correlated with the *in vivo* delivery of the drug. In general, the future of swellable matrix systems is associated with the possibility of obtaining a higher specificity of oral drug release. This will depend on the availability of new functionalized biomedical polymers that can release drugs, peptides or proteins in response to external environmental conditions.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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