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A brief review on recent advances of extended release technology employed to design the oral dosage forms

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ABSTRACT:
Extended release dosage forms extend the life of a drug so that dosage regiment shifts from 3 times a day to just once or twice a day. The successful formulation of a modified release device requires a comprehensive understanding of the mechanism of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interaction. Multiparticulate dosage forms shown to be less prone to food effects than monolithic and is often the preferred formulation for extended and / or delayed release. Extended release drug formulation is conventionally produced as compressed tablets by hydrogel tablet technology. To produce these extended release tablet dosage forms, active ingredient is conventionally compounded with cellulose ethers like methylcellulose, ethyl cellulose or hydroxyl propyl methylcellulose with or without excipients and the resulting mixture is pressed into tablets. Matrix type drug delivery systems as carriers for the active ingredients are interesting and promising option in developing an oral controlled release system

Key words: Extended release dosage forms, HPMC, Edragit, hydrogel tablet, Mechanism of drug release

INTRODUCTION:

The benefits offered by modified release systems include reduced dosing frequency with improved patient compliance, better and more uniform clinical effects with lower incidence of side effects and possible enhanced bioavailability. Characteristics of a modified release system as stated by USP is "The drug release characteristics of time, course and / or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms" [1]. This includes technologies that modify the site of drug delivery. Extended release dosage forms extend the life of a drug so that dosage regiment shifts from 3 times a day dosing just once or twice a day. The successful formulation of a modified release device requires a comprehensive understanding of the mechanism of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interaction. Multiparticulate dosage forms shown to be less prone to food effects than monolithic and is often the preferred formulation for extended and / or delayed release. Extended release drug formulation is conventionally produced as compressed tablets by hydrogel tablet technology. To produce these extended release tablet dosage forms, active ingredient is conventionally compounded with cellulose ethers like methylcellulose, ethyl cellulose or hydroxyl

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propyl methylcellulose with or without excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, cellulose ethers in the tablet swell upon hydration from moisture in the digestive system, thereby limiting exposure of active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to specific organ or tissue and controlling the rate of drug delivery to the target sites. The development of the oral controlled release system has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastro intestinal tract. Matrix type drug delivery systems as carriers for the active ingredients are interesting and promising option in developing an oral controlled release system. Tablets are the preferred dosage form for many drugs and are still the most widely used formulations for both new and existing modified released products.

Approaches and technologies in the area of modified release oral drug delivery have been developed to:

i. Extend the release of drug over a number of hours, an effect accomplished either by combining the drug with release retardant materials to form a matrix core or by applying release modifying film coatings to cores containing the drugs.

ii. Delay the release of drugs for a period of time usually through the application of an applied enteric coating.

EXTENDED RELEASE TABLETS:

Drug products that provide extended or sustained drug release first appeared as a major new class of dosage forms in the late1940s and early 1950s [2].

1. Extended Release products:

Extended Release dosage forms are the ones that allow a reduction in dosing frequency to that presented by a conventional dosage form e.g. solution or an immediate release dosage form.[1,3]

2. Delayed Release products:

These are designed to release the drug from dosage form at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions as gastrointestinal pH**.**

3. Sustained release products:

These are drug delivery systems designed to provide an initial therapeutic dose that is made available upon administration, followed by gradual release of medication over an extended period of time.

4. Prolonged release products:

This term refers to preparation designed to provide a slow release of a drug at a rate, which will provide a longer duration of action in comparison to the normal single dose. Prolonged release products may show a relatively delayed onset of action due to their overall slow release rate.

5. Repeat action preparations:

These are products designed to release in initial dose immediately after administration followed by a second and /or may be a third after same period of time has elapsed.

The term-controlled release refers to drug delivery systems that provide a predictable release pattern, which is attainable by controlling the variables governing the rate of drug release from a given system. It encompasses the above-mentioned categories of extended duration as well as delayed action products, which may not necessarily provide an extended duration of action. In other words, drug products that provide a particular onset, duration, or site of action are considered controlled drug delivery systems.

Advantages of extended release dosage forms over conventional forms:

i. Reduction in drug blood level fluctuations.

ii. Reduction in dosing frequency.

iii. Improved patient convenience and compliance. With less frequency of dose administration, a patient less opts to neglect taking a dose. There is also greater patient and/or caregiver convenience with daytime and nighttime medication administration.

iv. Reduction in adverse effects, because there are fewer drug blood level peaks outside of the

drug's therapeutic range and into the toxic range, adverse effects occur less frequently.

v. Reduction in overall health care cost, although the initial cost of extended release dosage forms may be greater than that for conventional dosage forms, overall cost of treatment may be less due to enhanced therapeutic benefit, fewer side effects and reduced time required of health care personnel to dispense and administer drugs and monitor patients.

Disadvantages of Extended Release Products:

i. **Over dosage:** Being multidose preparations, there is always the possibility of sudden release of the total dose administered, which may result in some toxic manifestations or side reactions.

ii. **Loss of flexibility in dosage:** It is very difficult to adjust the dose of extended release products to a patient's response. In many cases an induction to therapy needs to be achieved by a single dosing regimen followed by careful monitoring while under a treatment with extended release preparations.

Limitations of Extended Release Tablets:

Not all drugs lend themselves to the formulation of an extended duration product. There are a number of factors to be considered in the choice of drug candidates for controlled release preparations. The most important of which are as follows:

i. Biological half-life: Drugs having exceptionally long biological half-life would tend to accumulate in body tissues. A further extension of such an accumulation may result in chronic toxic manifestations. A classical example is the group of anticoagulants, which may cause excessive bleeding from bruises with potential sudden hemorrhage [4].

ii. Therapeutic dose: Drugs that are effective only in relatively large doses simply cannot be processed into a multidose, long acting preparation due to difficulties in technical manipulation and convenience of administration. Drugs those are extremely potent such as cardiac glycosides should not be considered for a controlled release preparation due to the loss of flexibility in dosage and potential sudden release of medication [5].

iii. Blood levels and pharmacological activity: Drugs that are metabolized to pharmacologically active products are not good candidates for an extended release preparation (e.g. Alprazolam, Clonazepam). The rate of metabolism is subject to individual variations and cannot be controlled; therefore, an overall prediction of activity cannot accurately be made [6-7].

Rationale for Extended Release Dosage Forms:

i. Many drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing often is inconvenient for patient and can result in missed doses, made up doses and patient non-compliance with therapeutic regimen.

ii. Extended Release tablets and capsules are commonly taken only once or twice daily compared with counterpart conventional forms that may need to be taken three or four times daily to achieve the same therapeutic effect.

iii. Extended Release products provide an immediate release of the drug that promptly produces the desired therapeutic effect, which then is followed by the gradual and continual release of additional amount of drug to maintain this effect over a predetermined period of time.

iv. The sustained plasma drug levels provided by extended release drug products often times eliminate the need for night dosing that provides benefit not only to the patient but to the caregiver as well.

Drug Candidates for Extended Release Dosage Forms:

The drug and the therapeutic indication must be considered jointly in determining whether or not to develop an extended release dosage form. For a successful extended release product, drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time and be absorbed at a rate that will replace the amount of drug being metabolized and excreted.

The drugs best suited for incorporation into an extended release product should have the following characteristics:

i. They exhibit neither very slow nor very fast rates of absorption and excretion.

ii. Drugs with slow rates of absorption and excretion are usually inherently long acting and their preparation into extended release dosage forms isn't necessary.

iii. Drugs with very short half-lives that are less than two hours are poor candidates for extended release dosage forms because of the large quantities of the drug required for such a formulation. Similarly drugs with long biological half-lives would tend to accumulate in body tissues. A further extension of such an accumulation may result in chronic toxic manifestations [4].

iv. Drugs, which act by affecting enzyme systems, may be longer acting than indicated by their quantitative half-lives due to residual effects and recovery of the diminished biosystem [9].

v. Drugs must be uniformly absorbed from the gastrointestinal tract. Drugs absorbed poorly or at varying and unpredictable rates are not good candidates for extended release products.

vi. Drugs prepared in extended release dosage form must have good aqueous solubility and maintain adequate residence time in the gastrointestinal tract.

vii. Drugs are administered in relatively small doses. Drugs with large single doses frequently are not suitable for the preparation of extended release product because the oral dosage unit (tablet or capsule) needed to maintain a sustained therapeutic blood level of the drug would have to be too large for the patient to easily swallow.

viii. They should possess a good margin of safety. The most widely used measure of the margin of a drug's safety is its therapeutic index. The larger the therapeutic index, the safer the drug. Drugs that are administered in very small doses or possess very narrow therapeutic index are poor candidates for formulation into extended release formulation because of the technologic limitation if precise controls over release rates and the risk of dose dumping due to a product defect. Patient misuse (e.g. Chewing dosage unit) also could result in toxic drug levels.

ix. They are used in the treatment of chronic rather than acute conditions. Drugs for acute conditions require greater physician adjustment of the dosage form than that provided by extended release products.

Formulation factors influencing oral extended release dosage form design:

Because of their relative ease of production and cost compared with other methods of extended or controlled delivery, dissolution and diffusion-controlled systems have classically been of primary importance in oral delivery of medication.

Dissolution controlled systems:

A drug with a slow dissolution rate will demonstrate extended properties, since the release of drug will be limited by the rate of dissolution. This being true extended – release preparations of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier. Dissolution-controlled systems can be made to be extending in several different ways. By alternating layers of drug with rate controlling coats a pulsed delivery can be achieved. An alternative method is to administer the drug as a group of beads that have coatings of different thicknesses. Since the beads have different coating thicknesses, their release will occur in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at later times will be achieved from those with thicker coatings. This dissolution process can be considered to be diffusion-layer controlled.

Diffusion systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer [5]. In general, two types of subclasses of diffusional systems are recognized:

i. Reservoir devices; and

ii. Matrix devices.

i. *Reservoir Devices*

Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. Drug core surrounded by polymer membrane that controls release rate.

Advantages:

a. Zero order delivery is possible.

b. Release rate variable with polymer type.

Disadvantages:

a. System must be physically removed from implant sites.

b. Difficult to deliver high molecular weight compounds.

c. Generally increased cost per dosage unit.

d. Potential toxicity if system fails [10].

ii. *Matrix Devices*

A matrix device, as the name implies, consists of drug dispersed homogenously throughout a polymer matrix. Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. Obviously, for this system to be diffusion-controlled, the rate of dissolution of drug particles within the matrix must be much faster that the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions: (a) a pseudo-steady state is maintained during drug release (figure 1), (b) the diameter of the drug particles is less than the average distance of drug diffusion through the matrix, (c) the bathing solution provides sink conditions at all times, (d) the diffusion coefficient of drug in the matrix remains constant (i.e., no change in the characteristics of the polymer matrix)[11,12].

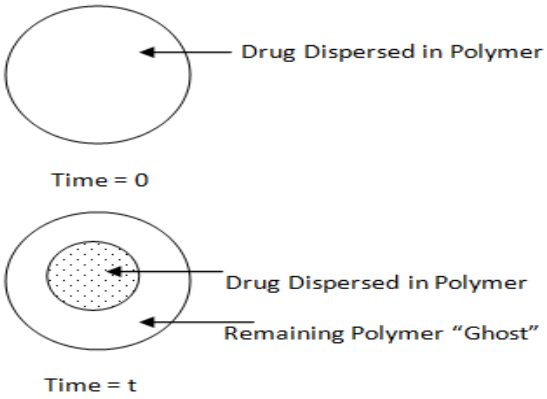

Figure 1: Matrix Diffusional System before drug release (time = 0) and after partial drug release (time = t)[5]

Higuchi has derived the rate of release of drugs dispersed in an inert matrix system [11]. The following equation can be written as

$$\frac{dM}{dh} = C_o dh - \frac{C_s}{2} \quad \ldots\ldots\ldots\ldots (1)$$

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_o = total amount of drug in a unit volume of the matrix

C_s = saturated concentration of the drug within the matrix.

From diffusion theory,

$$dM = \frac{D_m C_s}{h} dt \quad \ldots\ldots\ldots\ldots (2)$$

Where, D_m is the diffusion coefficient in the matrix. Equating Eqs. (1) and (2), integrating, and solving for h gives:

$$M = \left[C_s D_m (2C_0 - C_s)t\right]^{1/2} \quad \ldots\ldots\ldots (3)$$

When the amount of drug is in excess of saturation concentration, that is, $C_0 \gg C_s$,

$$M = (2C_s D_m C_0 t)^{1/2} \quad \ldots\ldots\ldots\ldots\ldots (4)$$

which indicates that the amount of drug released is a function of the square root of time. In a similar manner, the drug release from a porous or granular matrix can be described by

$$M = \left[D_s C_a \frac{P}{t} (2C_0 - pC_a)t \right]^{1/2} \quad \ldots\ldots\ldots (5)$$

Where, p = porosity of the matrix

t = tortuosity

C_a = solubility of the drug in the release medium

D_s = diffusion coefficient in the release medium

This 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.

For purposes of data treatment, Eq. (4) or (5) can be reduce to

$$M = kt^{1/2} \quad \ldots\ldots\ldots\ldots (6)$$

Where, k is a constant, so that a plot of amount of drug released versus the square root of time will be linear, if the release of drug from the matrix is diffusion-controlled. If this is the case, then, by the Higuchi model, one may control the release of drug from a homogeneous matrix system by varying the following parameters: (a initial concentration of drug in the matrix, (b) porosity, (c) tortuosity, (d) polymer system forming the matrix, and (e) solubility of the drug [13-17]. It is a homogeneous dispersion of solid drug in a polymer matrix.

Advantages:

a. Easier to produce than reservoir devices.

b. Can deliver high molecular weight compounds.

Disadvantages:

a. Cannot obtain zero order release.

b. Removal of remaining matrix is necessary for implanted systems.

Biodegradable and combination of diffusion and dissolution:

Bioerodible devices, however, constitute a group of systems for which mathematical descriptions of release characteristics can be quite complex. These systems can combine diffusion and dissolution of both the matrix material and the drug. The complexity of the system arises from the fact that, as the polymer dissolves the diffusion path length for the drug may change. This usually results in a moving boundary diffusion system. Zero order release can occur only if surface erosion occurs and surface area does not change with time. It is a homogeneous dispersion of drug in an erodible matrix.

Advantages:

a. All the advantages of matrix dissolution system.

b. Removal from implants sites not necessary.

Disadvantages:

a. Difficult to control kinetics owing to multiple processes of release.

b. Potential toxicity of degraded polymer must be considered.

Method for preparation of bioerodible systems is to attach the drug directly to the polymer by a chemical bond [18]. Generally, the drug is released from the polymer by hydrolysis or enzymatic reaction. This makes control of the rate of release somewhat easier.

2. Extended Release Technology for Oral Dosage Forms:

For orally administered dosage forms, extended drug action is achieved by aecting the rate at which the drug is released from the dosage form and/or by slowing the transit time of the dosage form through the gastro intestinal tract [1].

The rate of release of drug from the solid dosage forms may be modified by the technologies described below; which are based on:

a. Modifying drug dissolution by controlling access of biological fluids to the drug through the use of barrier coating.

b. Controlling drug diffusion rates from dosage forms.

c. Chemically reacting or interacting between the drug substance or its pharmaceutical barrier and site specific biological fluids.

1. Coated beads, Granules or micro spheres:

In these systems, the drug is distributed onto beads, pellets or granules /other particulate systems. Using conventional pan coating or other air suspension coating techniques, a solution of drug substance is placed onto small inert nonpareil seeds or beads made of sugar and starch or onto micro crystalline cellulose spheres. When dose of drug is large, starting granules of the material may be composed of the drug itself. Some of the granules remain uncoated to provide immediate drug release. Other granules (about two-thirds to three-fourth) receive varying coats of lipid material beeswax, carnauba wax, glyceryl monostearate, cetyl alcohol or cellulosic material like ethyl cellulose. The granules of different coating thickness are blended to achieve a mix having desired drug release characteristics.

2. Multitablet system:

Small spheroid shaped compressed minitablets 3-4mm in diameter may be prepared to have varying drug release characteristics. They then may be placed in gelatin capsule shells to provide the desired pattern of drug release [19]. Some tablets are uncoated for immediate release and others for extended drug release.

3. Embedding Drug in inert plastic matrix:

Here drug is granulated with inert plastic material like polyethylene, polyvinyl alcohol or polymethacrylate and the granulation is compressed into tablets. The drug is slowly released from inert plastic matrix by diffusion.

4. Complex formation:

Certain drug substances when commercially combined with certain other chemical agents form chemical complexes which may be only soluble in body fluids depending upon pH of environment. This slow dissolution rate provides extended release of drug**.** Salts of tannic acid, tannates prove this quality [8].

5. Ion exchange resin:

A solution of cationic drug passed through column having ion exchange resin forming a complex by replacement of hydrogen atoms. Resin-drug complex is then washed, tableted/encapsulated/suspended in an aqueous vehicle. Drug release is pH dependent and electrolyte concentration in the gastro intestinal tract. e.g. Hydrocodone polistirex suspension.

6. Osmotic pump:

Pioneer oral osmotic pump drug delivery system is oros system developed by Alza. The system composed of core tablet surrounded by semi permeable coating having 0.4mm diameter hole produced by laser beam. Core tablet has two layers, one containing and the drug layer and the other containing push layer (polymeric osmotic agent). The system operates on the principle of osmotic pressure, e.g.Glucotrol ER tablet.

7. Embedding drug in slowly eroding or hydrophilic matrix system:

In this, drug substance is combined and made into granules with an excipient material that slowly erodes into body fluids, progressively releasing drug for absorption. When these granules are mixed with granules of drug prepared without the excipient, the uncombined granules provide the immediate drug effect whereas the drug excipient granules provide extended drug action. The granule-mix may be tableted or placed into gelatin capsule shells for oral delivery.

Hydrophilic cellulose polymers are commonly used as excipient base in tableted matrix systems.

The effectiveness of these hydrophilic matrix systems is based on the successive process of:

a. Hydration of the cellulosic polymer
b. Gel formation on the polymer's surface
c. Tablet erosion
d. Subsequent and continuous release of drug

HPMC, a free flowing powder is commonly used to provide the hydrophilic matrix. Tablets are prepared by thoroughly distributing HPMC in the formulation, preparing the granules by wet granulation or by roller compaction and manufacturing the tablets by compression [20]. After ingestion, tablet is wetted by gastric fluid and polymer begins to hydrate. A gel layer forms around the surface of the tablet and an initial quantity of drug is exposed and released. As water permeates further into the tablet, the thickness of the gel layer is increased and the soluble drug diffuses through the gel layer. As the outer layer becomes fully hydrated, it erodes from the tablet core. If the drug is insoluble, it is released as such with the eroding gel layer [21]. In formulating a successful hydrophilic matrix system, the polymer selected for use must form a gelatinous layer rapidly enough to protect the inner layer rapidly enough to protect the inner tablet core from disintegrating too rapidly after ingestion. As the proportion of polymer is increased in a formulation, so is the viscosity of the gel formed with a resultant decrease in the rate of drug diffusion and drug release [21]. 20 %(in general) HPMC results in satisfactory rates of drug release for an extended release tablet formulation. However, consideration must be given to the possible effects of other formulation ingredients as fillers, tablet binders and disintegrants, E.g. of proprietary product using hydrophilic matrix base of HPMC for extended drug release is Oramorph SR tablet (Roxane) which contains morphine sulphate. Hydrophilic matrix formulations are used in the preparation of extended release capsules. When ingested, water penetrates the capsule shell, comes into the capsule fill, hydrates the outer layer of powder and forms a gelatinous plug from which drug content diffuses gradually over time as hydration continues and gelatinous plug dissolves. Solid oral dosage is overwhelmingly preferred by patients and hydrophilic matrix systems are among the most widely used means of providing controlled release in solid oral dosage forms. Hydrophilic matrix systems have been proven for over 4 decades. Matrix controlled release tablets are relatively simple systems that are more forgiving of variations in ingredients, production methods and end use conditions than coated controlled release tablets and other systems. This results in more uniform release profiles with a high resistance to drug dumping. Matrix systems are relatively easy to formulate. Tablets are manufactured with existing, conventional equipment and processing methods. This is true for almost any size tablet whether it involved direct compression dry granulation or wet granulation. Matrix systems are economical. In addition to the possibility of lower development cost and the use of conventional production

methods, the ingredients normally used are cost-effective. Hydrophilic matrix controlled release systems is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer / excipient / drug complex erodes or dissolves away [22]. Slower release rate and greater release duration correlated significantly with greater matrix swelling with negligible matrix erosion for HPMC based matrix system. It is commonly used in hydrophilic matrix drug delivery systems. It is mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxyl propyl groups. Methocel[@] hydroxyl propyl methyl cellulose as the controlled release agent in hydrophilic matrix systems offer a wide range of properties, consistently high quality and broad regulatory approval. It is a well-known excipient with an excellent safety record. HPMC polymers are very versatile release agents. They are non-ionic, so they minimize interaction problems when used in acidic, basic or other electrolytic systems. They work well with soluble and insoluble drugs and at high and low dosage levels. They are tolerant of many variables in other ingredients and production methods. HPMC polymers are produced under very controlled conditions that yield consistent properties and reproducible performance, lot to lot. They are not subjected to the range of variability sometimes encountered with polymers like guar, shellac and other botanical extracts [22-27]. When a glassy (or dry) polymer comes into contact with water or any other medium with which it is thermodynamically compatible, the solvent penetrates into the free spaces on the surface between the macromolecular chains. When enough water has entered into matrix, glass transition temperature (T_g) of the polymer drops to the level of the experimental temperature (usually 37^{o}C for release studies). Therefore, polymers with a T_g greater than 37^{o}C in their dry (glassy) state can be used to prepare swelling controlled release dosage forms [27]. Presence of solvent in the glassy polymer causes stresses, which are then accommodated by an increase in radius of gyration and end-to-end distance of polymer molecules, i.e. polymer chain gets solvated. The increase in radius of gyration of polymer molecules is seen macroscopically as swelling. The solvent molecules move into the glassy polymer matrix with a well-defined front at a particular velocity and simultaneously the thickness of swollen or rubbery region increases with time in the opposite direction. To achieve controlled release through the use of a water-soluble polymer such as HPMC, the polymer must quickly hydrate on the outer tablet skin to form a gelatinous layer. A rapid formulation of a gelatinous layer is critical to prevent wetting of the interior and disintegration of the tablet core. Once the original protective gel layer is formed, it controls the penetration of additional water into the tablet. As the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive enough to retard influx of water and control drug diffusion [28]. A fast polymer hydration and gel layer formation are particularly critical when formulating with water-soluble drugs and water-soluble excipients. Diffusion is the dominant mechanism controlling the dissolution of water-soluble drugs and the erosion of the matrix is the dominant mechanism (figure 2) controlling the release of water insoluble drugs. Generally, release of drugs will occur by a mixture of these two mechanisms. Although gel strength is controlled by polymer viscosity and concentration polymer chemistry also plays a significant role. The chemistry of HPMC encourages a strong, tight gel formulation compared to other celluloses. As a result, drug release rates have been sustained longer with HPMC than with equivalent levels of methylcellulose. Dissolution medium penetration into a swellable matrix tablet creates sharp boundaries (fronts) which separate various thermodynamic states of the polymer or various phases of the matrix. Starting from the centre of the matrix during the swelling process, following three fronts are observed.

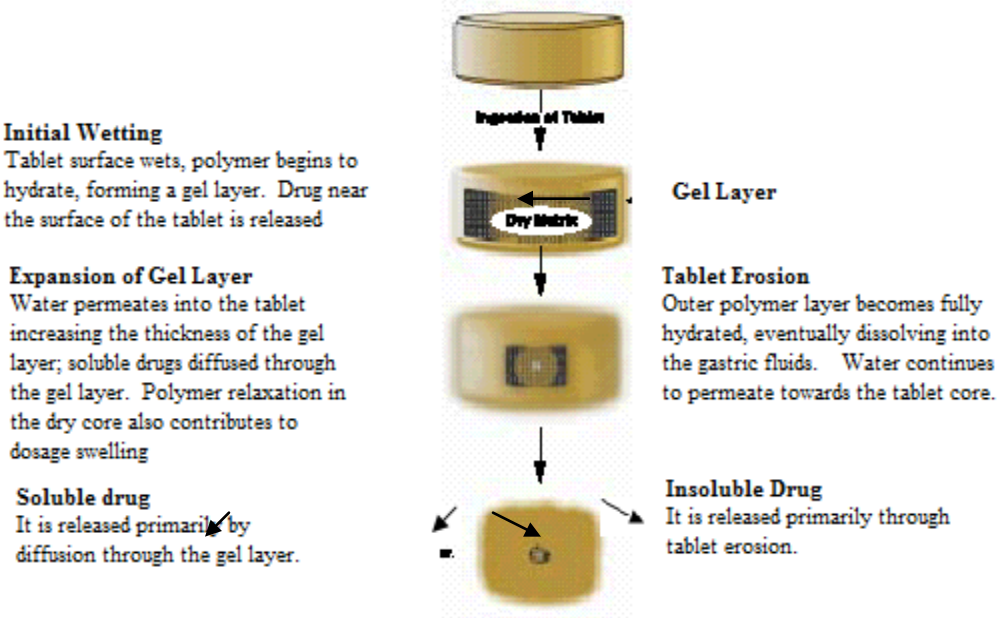

Figure 2: Mechanism of Drug Release from HPMC Matrix

Movements of three fronts are used to calculate three important parameters of the swelling/dissolution process:

a. Rate of water uptake broadly associated with position of swelling front, r_A.

b. Rate of drug dissolution depending on position of diffusion front, r_B

c. Rate of matrix erosion controlled by erosion front position, r_C.

Colombo et al., [29] have previously measured the swelling and erosion front movement concurrently with the drug release. Lee and Peppas [30] analyzed the mechanism of drug release from the matrices by photomicrography of the fronts [31, 32]. These researchers have analyzed drug delivery in terms of the behavior of the gel layer thickness and other front related parameters that may be important in this phenomenon. The importance of drug diffusion front movement in controlling the release Buflomedil pyridoxal phosphate from swellable matrix tablet was studied by Colombo et al [33]. It was concluded fro the study that diffusion front movement is the main parameter affecting the release rate, which in turn is strictly dependent on matrix prepared that is on drug solubility and type of polymer. When diffusion front moved faster due to increased solubility of the drug, release rate is higher. Therefore, dissolved drug gel layer thickness is more important in analyzing drug release from matrix tablet. It was observed that two parameters namely, diffusion front and dissolved drug gel layer thickness influence the drug release. Different grades of commercially Methocel (E, F and K) differ in the relative proportion of hydroxyl propyl methoxyl substitution. They differ in their rate of hydration with increasing amounts of hydrophilic hydroxyl propyl group leading to faster hydration in the following order: Methocel K > Methocel E > Methocel F. Effect of various polymer viscosity grades on the release of metoprolol tartrate was studied by Ranjani et al [34].For highly soluble drugs like metoprolol tartrate, a rapid rate of hydration is necessary since an inadequate polymer hydration may lead to dose dumping due to quick penetration of gastric fluids into the tablet core[35]. At two different levels (10 and 40%) on the dissolution was studied in the formulation composed of drug, lactose and selected polymers prepared by direct compression. It was observed that at a 10% level, K100LV formulation showed fastest drug release while the formulation with higher viscosity grades showed slower release rates. Similar resuslts were observed by Ford et al., for other soluble drugs such as promethazine [36]. The faster release by low viscosity grade Methocel k100LV was suggested probably due to the low polymer level that resulted in a thin film of low gel strength [37]. Changing the polymer viscosity when the polymer level was held at 40% showed

a similar but less dramatic effect of viscosity on drug release particularly at higher viscosity grade. Similar results were obtained by sung et al., for soluble drug like adinazolam mesylate [38]. Lack of difference in the drug release profiles for K15M and K100M formulation suggest the existence of a limiting HPMC viscosity, that is, drug release rate no longer decreased when viscosity was increased above 15,000cps.he higher viscosity gel layers provided a more tortuous and resistant barrier to diffusion which resulted in slower release of drug from the matrices [37].

Effect of Excipients on Drug Release from HPMC

Effect of Fillers:

Effect of fillers on drug release is dependent on drug substance, polymer level and the level of filler itself in the hydrophilic matrix tablet. The addition of soluble filler increases porosity, which results in faster diffusion and an increased rate of erosion. Ford et al., states that at low levels, solubility of filler has a small or no effect on the rate of drug release. However, differences in filler solubility can become apparent when filler levels are relatively low if dosage is relatively high and HPMC content is relatively low [39]. Addition of insoluble fillers like dibasic calcium phosphate dihydrate greater than 75% or greater of the filler fraction slows down the drug release. Increase in drug release at the 4, 6 and 12 hr time points was observed by Rekhi et al. when changing from insoluble to soluble filler. This was ascribed to a reduction in tortuosity and / or gel strength of the polymer [40]. Lapidus and Lordi showed that addition of lactose increased the release rate of chlorpheniramine more than addition of equivalent amount of calcium phosphate because lactose reduces tortuosity of diffusion pattern of the drug whereas calcium phosphate only reduces the polymer concentration [41]. Effect of HPMC/lactose ratio on adinazloam mesylate release was studied by Sung et al., [38].Tablets were prepared with different HPMC/lactose ratio (80:17, 65:32, 50:47, 35:62 and 20:77) .A greater drug release rate was observed for tablets with lower HPMC/lactose ratio. Similarly faster polymer release (HPMC) was observed for tablets with lower HPMC/lactose ratio. The study on development and evaluation of multiple unit oral sustained release dosage form for S (+) ibuprofen was done by Philip J.cox et al [42]. In this study, hydrophilic minimatrix tablets were encapsulated into hard gelatin capsules to produce multiple unit dosage forms which give uniform drug plasma levels and reproducible bioavailability .Xanthum gum, Karaya gum and HPMC were used as hydrophilic matrix to retard drug release. Initially the production of minimatrices containing drug and Xanthum gum or karaya gum in a ratio of 1:1 was attempted. Both these matrices produce serious capping problems. Therefore the excipients lactose, Encompress (Dicalcium phosphate) and Avicel (Micro crystalline cellulose PH-101) which are commonly used and have good compressibility properties were added to the formulation to improve the compression characteristics. It was observed that in the release profile of minimatrices containing xanthum gum and various excipients, drug release from Avicel is higher than Encompress and lactose respectively. The release mechanisms were anomalous (non fickian) but approached case ii transport with n values of 0.732, 0.644and 0.881 and release rates of 3.74, 3.69and 5.56%$min^{-1/2}$ for lactose, Encompress and Avicel. The minimatrices containing Avicel exhibited higher drug release than those containing Encompress. This could result from the disintegration property of Avicel. When in contact with the dissolution medium, xanthum gum absorbs water, swells and becomes a hydrated gel. At the same time, Avicel having disintegration properties promoted disintegration of minimatrices .The minimatrices were therefore easier to erode, compared with Encompress resulting in a higher release profile. In addition authors have studied to show that tablets produced with Encompress don't disintegrate readily (Rubinstein and Bodey, 1976; Koparkar et al., 1990, Fischer1992) have less tendency to erode compared with Avicel consequently showing a slower release profile [43-45]. In the release profiles of Ibuprofen minimatrices containing karaya gum and lactose, Encompress or Avicel, the rank order of release rate is Avicel > Encompress > lactose, the same that was observed with minimatrices containing xanthum gum. The contribution of polymer relaxation occurs almost exclusively throughout the entire dissolution period for all three

excipients indicating super case ii transport. The encapsulated ibuprofen minimatrices containing HPMC and lactose in a ratio of 1:1:1 showed an intermediate release profile between Ibuprofen:xanthum gum: lactose which is lower and Ibuprofen:karaya gum: lactose which is slightly higher. The release mechanism was anomalous (non fickian) transport with n value of 0.763and a release rate of 4.80%$min^{-1/2}$.

Effect of Starch 1500 (filler):

Partially pregelatinized maize starches are normally used as binder-disintegrants in immediate release tablet formulation [46]. The use of partially pregelatinized maize starches in combination with other polymers such as HPMC in extended release tablets have not been fully examined. The influence of starch 1500 on drug release from HPMC matrix was investigated by Marina and Rajabi Siahboomi [47]. It was found from the study that for both freely soluble (chlorpheniramine maleate) and slightly water soluble (theophylline) addition of 20-49.25% w/w starch 1500 resulted in a significant reduction in drug release rates. It was reported that this effect may be imparted through synergistic interaction between starch 1500 and HPMC and the filler actively forming an integral part within the gel structure. Michailova et al. characterized HPMC / partially pregelatinized starch hydrogels as filled composite systems where starch filler functions as a supporting frame while linear HPMC forms continuous disperse medium [48]. Partially pregelatinized starch hydrates to a considerably lower degree due to formulation of intramolecular hydrogen bonds in highly branched amylopectin[49].These bonds suppress polymer segments mobility and diminish degree of HPMC / partially pregelatinized starch hydrogen resulting in reduced gel layer diffusivity and decreased drug velocity from matrices with higher partially pregelatinized starch quantity [50]. 20% of HPMC and low concentration of pregelatinized starch gel structure (less than 20%) is quite porous with increased diffusion capability. With the increase in pregelatinized starch (35-49%) the swelled starch particles form strong supporting structure with comparatively strong rigidity. Therefore, use of blends of starch 1500 with other fillers (e.g. lactose) can be used for tailoring the desired release profile of HPMC matrix systems.

Effect of Binders:

Direct Compression:

The preparation of hydrophilic matrix tablets using methocel cellulose ethers is most easily accomplished by directly compressing a dry mixture of drug, HPMC and other excipients. HPMC has good compaction characteristics. However, some formulations may require a binder to increase the tablet strength. One useful excipient for direct compression is microcrystalline cellulose (MCC). It exhibits disintegrating properties at levels as low as 10%. The highest level of MCC most likely acts as a strong tablet binder to decrease the tablet porosity and thus slows the drug release. A study on diclofenac sodium controlled release from HPMC matrix showed that at low concentration MCC has no effect on drug release. In another study to test the effect of MCC on drug release, a model formulation was developed containing 5% theophylline, 30% methocel K4M and total filler level of 64.5%. The initial formulation contains dicalcium phosphate dihydrate as filler. The other formulation contains 6% and 12.9% MCC with remainder of 64.5% of filler level being dicalcium phosphate dihydrate [51]. The formulation with 12.9% MCC had the slowest release. The report therefore concludes that MCC may function in some formulation as a binder and/or disintegrant depending on the level.

Granulation:

Direct compression is not always feasible for hydrophilic matrix formulation containing methocel products. Wet and dry granulation technologies can provide better flow on tablet presses, overall improved tablet physical characteristics, uniform drug content within the dosage form and fewer industrial hygiene constraints. Wet granulation processes include low shear, high shear and fluid bed processes. One study compared the effects of low shear and high shear processes with direct compression on a controlled release matrix tablet containing HPMC and a high dose, highly water soluble drugs [52]. Drug release was not influenced by the method of tablet manufacture (wet granulation vs. direct compression) or the level of water used during wet massing of the granulation. Tablets with

good hardness and low friability values were produced using either low shear or high shear granulation techniques.

Effect of Sodium carboxy methyl cellulose:

Sodium carboxy methyl cellulose alone as the rate-controlling polymer is not practical because of accelerating release rate and poor stability, its use in conjunction with HPMC may be beneficial. With certain water-soluble drugs a blend of appropriate grades of sodium CMC and HPMC minimize the release of drug during the initial phase of the drug release profile. This tends to flatten the shape of the release profile, i.e. produce a more zero order release. [21-22]. By using a mixture of anionic Na CMC and nonionic HPMC in an optimum ratio, Baveja et al prepared nearly zero order release tablet of very soluble β-blockers, namely, propranolol HCl, Metoprolol tartrate and Alprenolol HCl [23]. These workers indicated that besides the ratio of drug to total polymer, the ratio between anionic and nonionic polymers was important to obtain zero order release till the entire drug was released from the tablet. The authors group were of the opinion that by optimizing the ratio between drug and total polymer and also the ratio between the anionic and nonionic gums, the rates of advancement of the swelling front into the glassy polymer and the attrition of the rubbery state polymer were made equal so that the diffusional path length for the drug and hence the zero order release remained nearly constant [2].

Effect of Lubricants:

These are added to reduce sticking to the punch faces and to allow easy ejection of the tablet during tablet formation. Magnesium stearate is the lubricant of choice because its plate-like crystalline structure readily deforms in a shear during the mixing and compaction process thereby coating the powder and tooling surfaces. Over lubrication could lead to coating of the hydrophobic materials on the surfaces of the tablets and thereby retard the release. This would be not only a function of lubricant but also the function of blend time with lubricant since increased mixing can lead to increased shearing of magnesium stearate particles. Shesky et al. found that magnesium stearate levels from 0.2 to 2% and blend times of 2 to 30 mins. had only a slight impact on drug release rat. Tablet ejection forces were influenced to the greatest extent by the level of lubricant in the formulation.

Use of Eudragit as a Release Retarding Polymer:

Eudragit is the trade name for copolymers derived from esters of acrylic and methacrylic acid whose properties are determined by functional groups. The individual Eudragit grades differ in their proportion of neutral alkaline or acid groups and thus in terms of physiochemical properties.

Eudragit polymers are available in a wide range of different concentration and physical forms (aqueous dispersion, organic solution, solid substances).

Pharmaceutical Properties of Eudragit

Pharmaceutical properties are determined by chemical properties of their functional groups.

Poly (meth) acrylates, soluble in digestive fluids (by salt formation)

Eudragit L, S, FS and E polymers with acidic or alkaline groups enable pH dependent release of the active ingredients.From simple taste masking via resistance solely to gastric fluid up to controlled drug release in all sections of the intestine.

Poly (meth) acrylate insoluble in digestive fluids

Eudragit RL and RS polymers with alkaline and Eudragit NE polymers with neutral groups enable controlled time release of the active by pH independent swelling.

Eudragit L30D-55: It is an aqueous dispersion of an anionic polymer of methacrylic acid and ethyl acrylate with a COOH group. The ratio of free carboxyl groups to ester groups is 1:1. It is a pH dependent polymer soluble above pH 5.5 for targeted delivery in the duodenum. It form salts with alkalis thus affording coatings, which are insoluble in gastric media but soluble in the small intestine. Enteric coating of HPMC capsules containing paracetamol was studied by Ewart T Cole et al. Two enteric polymers, Eudragit L30D-55 and Eudragit FS 30D were studied which are designed to achieve enteric properties and colonic release respectively. It was observed in the dissolution studies that capsules coated with Eudragit L30D-55 were gastro resistant for 2 hrs at pH 1.2 and capsules coated with Eudragit FS30D were resistant for a further 1 hour at pH 6.8. The product visualization technique of

gamma scintigraphy was used to establish the invivo disintegration properties of capsules coated with 8 mg cm^{-2} Eudragit L30D-55 and 6 mg cm^{-2} Eudragit FS 30D. Both capsule types were found to remain intact in the stomach which confirmed the gastro resistant properties of Eudragit L30D-55 and Eudragit FS30D polymers. Scintigraphic techniques demonstrated that for the HPMC untis coated with Eudragit L30D-55, complete disintegration occurred predominately in the small bowel in an average time of 2.4 hrs post dose and for HPMC capsules coated with Eudragit FS30D, complete disintegration occurred lower down the gastro intestinal tract towards the distal small intestine and proximal colon in an average time of 6.9 hr post dose.

3. CONCLUSIONS:

The successful formulation of a modified release device requires a comprehensive understanding of the mechanism of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interaction. Multiparticulate dosage forms shown to be less prone to food effects than monolithic and is often the preferred formulation for extended and / or delayed release. To produce these extended release tablet dosage forms, active ingredient is conventionally compounded with cellulose ethers like methylcellulose, ethyl cellulose or hydroxyl propyl methylcellulose with or without excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, cellulose ethers in the tablet swell upon hydration from moisture in the digestive system, thereby limiting exposure of active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. The development of the oral controlled release system has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastro intestinal tract. Matrix type drug delivery systems as carriers for the active ingredients are interesting and promising option in developing an oral controlled release system. Tablets are the preferred dosage form for many drugs and are still the most widely used formulations for both new and existing modified released products.

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