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Effect of Natural and Synthetic Polymers on Drug Release in the Formulation Extended Release Tablets of Isoniazid

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ABSTRACT:

The oral route is the most frequently used route for the administration of drugs. Many of the pharmaceutical dosage form are formulated as sustained release dosage form to retard the release of a therapeutic agent such that its appearance in the systemic circulation is prolonged and its plasma profile is sustained in duration. Matrix tablets serves as an important tool for oral extended- release dosage forms. Hence, problems like patient compliance, drug targeting, local side effects, frequent administration and fluctuations in blood concentration levels. Oral extended release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency.

Extended-release drug-delivery system reduces the dosing frequency of certain drugs by releasing the drug slowly over an extended period of time Matrix tablets may be formulated by wet granulation or direct compression methods by dispersing solid particles within a porous matrix formed of hydrophilic and hydrophobic polymers. The use of different classes of polymers in controlling the release of drugs has become the most important aspect in the formulation of matrix tablets. The drug release in matrix drug delivery systems by both dissolution-controlled as well as diffusion controlled mechanisms. KEYWORDS: Direct compression, extended-release, hydrophilic and hydrophobic polymers, matrix tablets, wet granulation.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. [1] The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[2]

Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as the “oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants”. These systems release drug in continuous manner by dissolution controlled and diffusion-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes.

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However at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. Two different release mechanisms are operative, either of which is zero-order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient's blood level's in a narrow range, above the minimum effective level and below toxic level. This type of sustained-release tablet has clearly shown the potential of the tablet as a reliable sustained release dosage form with good release profile precision.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pillarization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression.

Advantage of Matrix Tablet

1. Easy to manufacture.
2. Versatile, effective and low cost.
3. Can be made to release high molecular weight compounds.
4. The sustained release formulations may maintain therapeutic concentrations over prolonged periods. 5. The use of sustain release formulations avoids the high blood concentration.
6. Sustain release formulations have the potential to improve the patient compliance.
7. Reduce the toxicity by slowing drug absorption.
8. Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
9. Minimize the local and systemic side effects.
10. Improvement in treatment efficacy.
11. Minimize drug accumulation with chronic dosing.
12. Usage of less total drug.
13. Improvement the bioavailability of some drugs.
14. Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.

Disadvantages of Matrix Tablet

1. The remaining matrix must be removed after the drug has been released.
2. Greater dependence on GI residence time of dosage form.
3. Increased potential for first-pass metabolism.
4. Delay in onset of drug action.
5. Release rates are affected by food and the rate transit through the gut.
6. Release rate continuously diminishes due to increased diffusional resistance and decrease in effective area at the diffusion front.

1. Hydrophobic Matrices (Plastic matrices)

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion.

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Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups:

A. Cellulose derivatives: Methyl cellulose 400 and 4000 cPs, Hydroxyethylcellulose, Hydroxypropylmethyl cellulose (HPMC) 25, 100, 4000 and 15000cPs, and sodium carboxymethylcellulose.

B. Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

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

4. Biodegradable Matrices

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and polyanhydrides.

5. Mineral Matrices

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

TERMINOLOGY:

Modified release delivery systems may be divided conveniently in to four categories.

A) Delayed release
B) Sustained release
- ✓ Controlled release
- ✓ Extended release

C) Site specific targeting
D) Receptor targeting

A) Delayed Release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Sustained release:

During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities,

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expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

1. Controlled Release:

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

2. Extended Release:

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) 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.

D) 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 within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

DESIGN AND FORMULATION OF ORAL SUATAINED RELEASE DRUG DELIVERY SYSTEM:

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion. Sustained (zero-order) drug release has been attempted to be achieved with various classes of sustained drug delivery system:

A) Diffusion sustained system.
   i) Reservoir type.
   ii) Matrix type
B) Dissolution sustained system.
   i) Reservoir type.
   ii) Matrix type
C) Methods using Ion-exchange.
D) Methods using osmotic pressure.
E) pH independent formulations.
F) Altered density formulations.

DIFFUSION SUSTAINED SYSTEM:

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by Fick's law.

J= - D dc/dx.

D = diffusion coefficient in area/ time
dc/dx = change of concentration 'c' with distance 'x'
In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane.
The drug release rate dm/ dt is given by

dm/ dt= ADKΔ C/L

Where;
A = Area.

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K = Partition coefficient of drug between the membrane and drug core.
L= Diffusion path length (i.e. thickness of coat).
Δc= Concentration difference across the membrane.

i) Reservoir Type:

In the system, a water insoluble polymeric material encases a core of drug (Figure 4.). Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

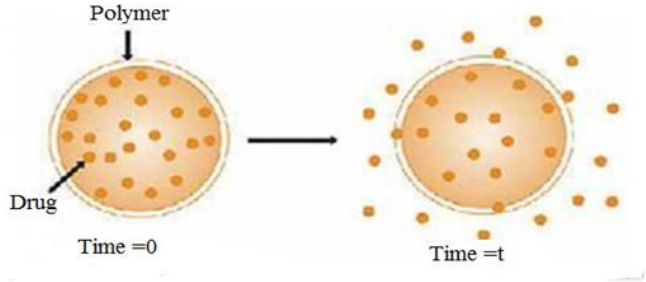

Figure 3: Schematic representation of diffusion sustained drug release: reservoir system

CHARACTERIZATION:

Description: Drug core surrounded by polymer membrane which controls release rate.

Advantages: Zero order delivery is possible, release rates variable with polymer type.

Disadvantages: System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails

ii) Matrix Type:

A solid drug is dispersed in an insoluble matrix (Figure 5.) and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. Higuchi has derived the appropriate equation for drug release for this system:

$Q = D\varepsilon / T [2A - \varepsilon Cs] Cst^{1/2}$

Where;
Q = Weight in gms of drug released per unit area of surface at time t.
D = Diffusion coefficient of drug in the release medium.
ε = Porosity of the matrix.
Cs = Solubility of drug in release medium.
T= Tortuosity of the matrix.
A = Concentration of drug in the tablet, as gm/ ml.

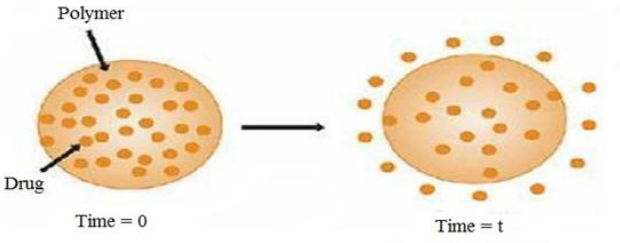

Figure 4: Schematic representation of diffusion sustained drug release: matrix system

CHARACTERIZATION:

Description: Homogenous dispersion of solid drug in a polymer mixture.

Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system. A third possible diffusional mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat.

The release rate can be given by following equation.

Release rate = AD / L = [C1- C2]

Where;
A = Area.
D = Diffusion coefficient.
C1 = Drug concentration in the core.
C2 = Drug concentration in the surrounding medium.
L = Diffusional path length.

Thus diffusion sustained products are based on two approaches the first approach entails placement of the drug in an insoluble matrix of some sort.

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The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid.

DISSOLUTION SUSTAINED SYSTEMS:

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

i) Reservoir Type:

Drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract. By alternating layers of drug with the rate controlling coats as shown in figure, a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. Although this is not a true sustained release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness. This is shown in figure. Since the beads have different coating thickness, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

ii) Matrix Type:

The more common type of dissolution sustained dosage form (as shown in figure 4). It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion

Two types of dissolution sustained pulsed delivery systems

- ✓ Single bead type device with alternating drug and rate-controlling layer.
- ✓ Beads containing drug with differing thickness of dissolving coats.

Amongst sustained release formulations, hydrophilic matrix technology is the most widely used drug delivery system due to following advantages

- ✓ Provide desired release profiles for a wide therapeutic drug category, dose and solubility.
- ✓ Simple and cost effective manufacturing using existing tableting unit operation equipment
- ✓ Robust formulation.
- ✓ Broad regulatory and patient acceptance.
- ✓ Ease of drug release modulation through level and choice of polymeric systems and function coatings.

Methods Using Ion Exchange:

It is based on the formation of drug resin complex formed when anionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastro intestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract.

Anion Exchangers: Resin+ - Drug- + Cl- goes to Resin+- Cl-+ Drug-

Cation Exchangers: Resin-- Drug+ + Na+ goes to Resin- - Na+ + Drug+

These systems generally utilize resin compounds of water insoluble cross linked polymer.

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They contain salt forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is sustained by the area of diffusion, diffusional path length and rigidity of therein which is function of the amount of cross linking agent used to prepare resins. The release rate can be further sustained by coating the drug resin complex by microencapsulation process.

Methods Using Osmotic Pressure:

A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

Two types of osmotically sustained systems are

- ✓ Type A contains an osmotic core with drug.
- ✓ Type B contains the drug in flexible bag with osmotic core surrounding.

pH– Independent Formulations:

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

Altered Density Formulations:

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

High Density Approach:

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm3.

Low Density Approach:

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose.

POLYMERS USED IN THE MATRIX[22]:

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

A) Hydrophilic Polymers:

Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homo polymers and co-polymers of acrylic acid.

B) Hydrophobic Polymers:

This usually includes waxes and water insoluble polymers in their formulation Waxes: carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene. Insoluble polymers: Ammoniomethacrylate co-polymers (Eudragit RL100, PO, RS100, PO), ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate and latex dispersion of meth acrylic ester copolymers.

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DRUG RELEASE FROM MATRIX[23,24]:

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. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

- ❖ A pseudo-steady state is maintained during drug release;
- ❖ The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;
- ❖ The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

DM/Dh = Co. Dh - Cs/2 (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

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix. Additionally, according to diffusion theory:

DM = (Dm. Cs / h).Dt (2)

Where:

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

Dt = Change in time

By combining equation 1 and equation 2 and integrating:

M = [Cs. Dm. (2Co−Cs). t] ½ (3)

When the amount of drug is in excess of the saturation concentration, then:

M = [2Cs. Dm. Co. t] ½ (4)

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

M = [Ds.Ca.p/T. (2Co – p.Ca) t] ½ (5)

Where:

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusion path length

For pseudo steady state, the equation can be written as:

M = [2D.Ca .Co (p/T) t] ½ (6)

The total porosity of the matrix can be calculated with the following equation:

p = pa + Ca/ ρ + Cex/ ρex (7)

Where: p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

Cex = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

M = k. t ½ (8)

Where k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- ✓ Initial concentration of drug in the matrix
- ✓ Porosity
- ✓ Tortuosity
- ✓ Polymer system forming the matrix
- ✓ Solubility of the drug.

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COMPONENTS OF MATRIX TABLETS[22,23]:

These include:

- ✓ Active drug
- ✓ Release controlling agent(s): matrix formers
- ✓ Matrix Modifiers, such as channelling agents and wicking agents
- ✓ Solubilizers and pH modifiers
- ✓ Lubricants and flow aid
- ✓ Supplementary coatings to extend lag time further reduce drug release etc.
- ✓ Density modifiers (if required)

A) Matrix formers:

Hydrophobic materials that are solid at room temperature and do not melt at body temperature are used as matrix formers. These include hydrogenated vegetable oils, cotton seed oil, soya oil, microcrystalline wax and carnauba wax. In general such waxes form 20- 40% of the formulation.

B) Channelling agents:

These are chosen to be soluble in gastrointestinal tract and to leach from the formulation, so leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released. The drug itself can be a channelling agent but a water soluble pharmaceutical acceptable solid material is more likely to be used. Typical examples include sodium chloride, sugars and polyols. This choice will depend on the drug and desired released characteristics. These agents can be 20-30% of the formulation.

C) Solubilizers and pH modifiers:

It is often necessary to enhance the dissolution of drug. This may be achieved by the inclusion of solubilising agents such as PEGs, polyols and surfactants. If the drug is ionisable then the inclusion of buffers or counter ions may be appropriate. On occasions the dissolution enhancer may also be the channelling agent.

D) Anti-adherent or glident:

Heat is generated during compaction of the matrix can cause melting of the wax matrix forming compounds and sticking to the punches. Something is needed to cope with the sticking; suitable anti adherents include talc and colloidal silicon dioxide. These materials also can act as glidants and improve the flow of formulations on the tablet machine. The typical amounts used will depend on the anti adherent used, for example 0.5-1% for colloidal silicon dioxide and 4-6% for talc. Magnesium stearate, if added, can also act as an anti-adherent.

1.8. BASIC PRINCIPLE OF DRUG RELEASE[22]:

In solution, drug diffusion will occur from a region of high concentration to the region of low concentration. This concentration gradient is the driving force for the drug diffusion, out of a system. Water diffuses into the system in analogous manner. There is an abundance of water in the surrounding medium and system should allow water penetration. The inside of the system has low water content initially than the surrounding medium.

1.9. EFFECT OF RELEASE LIMITING FACTOR ON DRUG RELEASE[13, 16]:

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

A) Polymer hydration:

It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

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B) Drug solubility:

Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C) Solution solubility:

In view of in vivo (biological) sink condition maintained actively by hem perfusion, it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D) Polymer diffusivity:

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion Ed has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallanity of polymer.

The release of drug may be attributed to the three factors viz,

i. Polymer particle size

ii. Polymer viscosity

iii. Polymer concentration.

i. Polymer particle size:

Malamataris stated that when the content of hydroxyl propyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low.

He also justified these results by considering that in certain areas of matrix containing low levels of hydroxyl propyl methylcellulose led to the burst release.

ii. Polymer viscosity:

With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

ii. Polymer concentration:

An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

E) Thickness of polymer diffusional path:

The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

JD = D dc/dx

Where,

JD is flux of diffusion across a plane surface of unit area

D is diffusibility of drug molecule; dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

F) Thickness of hydrodynamic diffusion layer:

It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer δd.

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G) Drug loading dose:

The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

H) Surface area and volume:

The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the in vitro and in vivo rate of the drug release, are observed to be dependent upon surface area of dosage form. Siepman et al. found that release from small tablet is faster than large cylindrical tablets.

I) Diluent's effect:

The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J) Additives:

The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

List of various drugs which can be formulated as a matrix tablet with polymer and method used or its preparation are shown in table.

Drugs	Category	Method used	Polymer used
Ambroxol HCl	Secretolytic agent	Direct compression	Methocel K15MCR, PVP K30[34]
Diclofenac Sodium	Anti-inflammatry	Wet granulation	Pectin, Guar gum[35]
Metformin hydrochloride	Antidiabetic	Direct compression	Chitosan, Ethyl cellulose HPMC, Xanthan gum[36]
Cefpodoxime	Antibiotic	Direct compression	HPMC (K4M), HPMC (K100M) and Xanthan gum[37]
Lamivudine	Antiviral	Direct compression	HPMC (Methocel K15M CR) Avicel 102[38]
Terbutaline sulphate	Bronchodilator	Wet granulation	HPMC K200M, Ethyl cellulose[39]
Indomethacin	Anti-inflammatory	Wet Granulation	Hibiscusrosa-sinensis, Microcrystalline cellulose, Magnesium stearate[40]
Nateglinide	Antidiabetic	Wet Granulation	Xanthan gum, Guar gum[41]
Zidovudine	Anti viral	Wet granulation	HPMC, Xanthan gum, ethyl cellulose[42]
Furosemide	Antidiuretic	Direct Compression	Guar gum, Xanthum gum, Pectin[43]
Theophylline	Respiratory depressant	Wet Granulation	HPMC 15 CPS, HPMCP, Eudragit L 100, Eudragit RLPO, Polyvinyl acetate, Alginic acid[44]
Venlafaxine Hydrochloride	Anti-depressant	Wet Granulation	Eudragit RLPO and RSPO, Lactose[45]

CONCLUSION

The focus of this review article has been on the formulation of sustained-release matrix tablets, advantages and disadvantages and various polymers used to design such system. By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility matrix forming polymers can be successfully used to prepare Matrix tablets, releasing drug in a controlled manner. This suitability of matrix forming polymers, to various drug delivery systems preparation confirms the importance of these specialized excipients in pharmaceutical application. They represent the choice solution for many oral delivery problems like fluctuating drug plasma levels, low bioavailability, more frequent dose administration etc. So matrix tablets can overcome the above problems of conventional oral drug delivery.

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