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NOVEL SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Oral sustained release product provide advantage over conventional dosage form by optimising bio pharmaceutics, pharmacokinetics and pharmacodynamic properties of drug in such a way that reduces dosing frequency to extent once a daily dose is sufficient for therapeutic management through uniform plasma concentration provide maximum utility of drug with reduction in local and systemic side effects and improving the patient compliance by preventing the fluctuation of the therapeutic concentration of the drug in the body. Developing oral sustained release matrix tablet with constant release rate has always been a challenge to the pharmaceutical technologist. Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Hydrophilic polymers have become product of choice as an important ingredient for formulating sustained release formulations. This article contains the basic information regarding sustained-release formulation and also the different types of the same.

Key Words: Sustained-release, Conventional tablet, Oral controlled release system, Matrix tablet

INTRODUCTION

The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended

use*[1]*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 pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the reparations. Hydrophilic polymer matrix is widely used for formulating a sustained release dosage form *[2, 3]* .Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems [3].Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers *[4]*. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SRoral dosage forms such as membranecontrolledsystem, matrices with water-soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water-soluble drugs *[5]*.Various drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix®technology) and osmotic pumps with laserdrilledholes (OROS® technology). These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipient*[6]*.

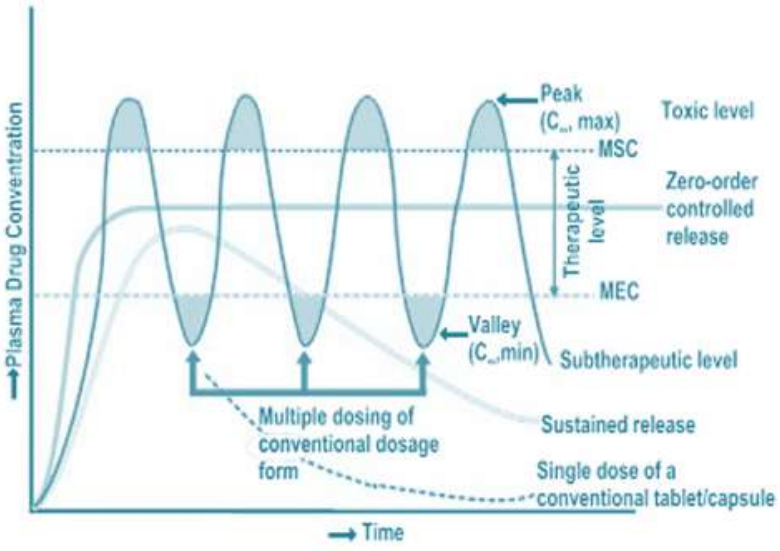

Figure1: Plasma Drug Concentration Profiles for Conventional Tablet Formulation, a Sustained Release Formulation and a Zero Order Controlled Release Formulation.

ADVANTAGES OF SUSTAINED RELEASE *[7, 8]*

1. decreased local and systemic side effects:
   - Reduced gastrointestinal irritation.
2. Better drug utilization:
   - Reduction in total amount of drug used.
   - Minimum drug accumulation on chronic dosing.
3. Improved efficiency in treatment:
   - Optimized therapy
   - More uniform blood concentration.
   - Reduction in fluctuation in drug level and hence uniform pharmacological response.
   - Special effects e.g. sustained release aspirin provides sufficient drug so that on Awakening the arthritic patient get symptomatic relief [9]
   - Cure or control of condition more promptly.
   - Less reduction in drug activity with chronic use.
   - Method the bioavailability of some drug e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.
4. Improved patient compliance:
   - Less frequent dosing.
   - Reduced night-time dosing.
   - Reduced patient care time.
5. Economy.

Although the initial unit cost of sustained release products is usually greater than that of conventional dosage form because of special nature of these products, the average cost of treatment over an extended time period may be less. Economy may also result from a decrease in nursing time and hospitalization time.

DISADVANTAGES OF SUSTAINED RELEASE *[10, 19]*

1. Usually the amount of drug in sustained release dosage form is 3-4 times and if dosage form is used improperly e.g. by chewing instead of swallowing the patient receive an overdose. Hence only such drug, which posses a substantial margin of safety can be presented in sustained release form.
2. Improper formulation may result in excessive dosage or the drug may not be complete.
3. In case of accidental failure of the product effective antidote may be difficult to employ.
4. Sustained release dosage forms are sometimes costly because of the technology involved in producing the formulation.
5. Sustained release medication should not be used with persons known to have impaired or erratic gastrointestinal absorption or kidney troubles.
6. Drugs having long biological half life are not suitable for presentation in sustained release forms e.g. Digitoxin.
7. There is little control in hands of the physician so far as dose variation is concerned.
8. It is difficult to formulate an ideal sustained release dosage form.

TYPE OF MODIFIED RELEASE DOSAGE FORMS ***[9, 11, 12]***

A number of terms and phrases have been used to describe the oral dosage forms that portray modified release properties; which include delayed release, repeated action, prolonged release, sustained release, extended release and controlled release. Each drug delivery system is aimed at eliminating the cyclical changes in plasma drug concentration seen after administration of conventional delivery systems.

Modified release dosage forms are designed to provide quick achievement of a drug plasma level that remains constant (i.e. controlled release) at a value within the therapeutic range of a drug for a significant temporal period of time or achievement of a plasma concentration of a drug that delivers at a slow rate (i.e. sustained release) that stays within the therapeutic range for a longer period of time. Based on the assumption that a drug, which is to be incorporated into a modified release dosage form, confers upon the body characteristics of a one-compartment open model, then the basic kinetic design of such a product may be assumed to contain two portions, one that provides the initial priming/loading dose, and one that provides the maintenance or sustained dose. To ensure that the therapeutic concentration of the drug in the body remains constant, two conditions must be fulfilled, namely 1) The zero order rate of drug release must determine the absorption rate of the drug, and 2) The rate at which the drug is released from the

maintenance dose (and subsequently the absorption rate) should be equal to the rate of drug elimination at the required steady-state concentration .a list of important terms that describe different modified release dosage forms are defined below.

1. Modified release dosage forms

Those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic and/or convenience objectives not offered by conventional dosage forms. *[11]*

2. Controlled release

The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is invariant with time. *[13]*

3. Delayed release

The drug is released at a time other than immediately after administration. *[14]*

4. Extended release

Slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time usually between 8 and 12 hours. *[15]*

5. Prolonged release

The drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.*[16]*

6. Repeat action

Indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.*[17]*

7. Sustained release

The drug is released slowly at a rate governed by the delivery system.

CLASSIFICATION OF SUSTAINED RELEASE DOSAGE FORMS *[18]*

There is a basic principle that governs all Sustained release dosage forms. Drug diffusion occurs from a region of high concentration to a region of low concentration. This concentration difference is the driving force for drug diffusion out of the system. The inside of the system should have lower water content initially than the surrounding medium to control the diffusion of a drug effectively. Different methods have been employed to provide sustain drug release, which include modifications to the physical and chemical properties of the drug or changes to the dosage form as indicated in Figure No. 2

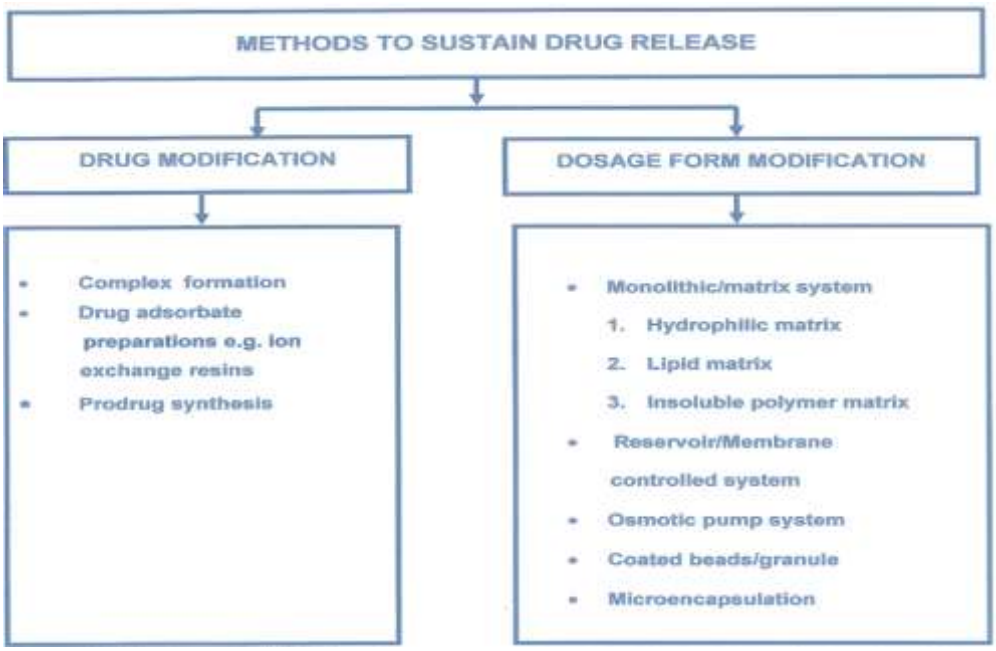

Figure No. 2: Summarized representation of the methods to Sustain drug release

DESIGN TECHNIQUES BASED ON DRUG MODIFICATION *[19]*

These methods take advantage of the changes in the physicochemical properties of drug moieties caused by complex formation, drug adsorbate preparations and prodrug synthesis. These modifications are possible only with drug moieties containing appropriate functional groups. This approach is independent of the dosage form design.

Figure No. 3 shows the mechanisms of sustained release based on drug modification. In the case of drug complexes the effective release rate of the drug is a function of two processes, including the rate of dissolution and breakdown of the complex in a solution. If the rate of dissolution is greater than the rate of dissociation, a zero-order release pattern might be achieved. In this case, the concentration of the complex is maintained at its saturation point if the solubility of the complex is sufficiently low so that excess solid complex is present during the onset of the maintenance time. If the rate of dissociation is greater than the rate of dissolution, the dissolution of the complex will be the rate-determining step.

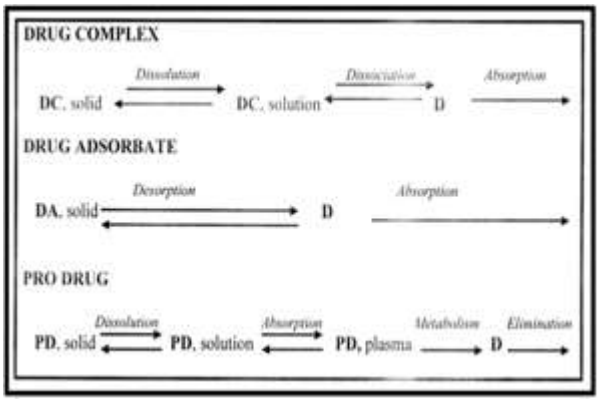

Figure No. 3: The mechanisms of sustained release based on drug modification.

Another approach for drug modification is through the formulation of a prodrug. This can be achieved through designing a bio reversible derivative (prodrug) that can afford an increased or selective

transport of the drug to the site of action (e.g., levodopa as prodrug for the central nervous system anti-Parkinsonism agent dopamine or by designing a derivative that goes everywhere in the body but undergoes bio activation only on the target.*[20]*

The solubility, specific absorption rate and elimination rate constant of an effective prodrug should be significantly lower than that of the parent drug. In drug adsorbents, drug availability is determined only by the rate of dissociation and by the access of the adsorb surface to water as well as the effective surface area of the adsorbate. [*21]*

DESIGN TECHNIQUES BASED ON DOSAGE FORM MODIFICATION *[22]*

Modified release dosage forms of this class employ either an embedded matrix or a physical barrier principle to provide slow release of the maintenance dose. The techniques used to build this matrix or barrier into the dosage form include the monolithic or matrix systems, the reservoir or membrane controlled systems, the osmotic pump systems, coated beads and microencapsulation.

A) Monolithic or matrix system *[23]*

These systems can be divided into two groups:

1) Those with drug particles dispersed in a soluble matrix, with drug becoming available as the matrix dissolves or swells and dissolves (hydrophilic colloid matrices).

2) Those with drug particles dispersed in an insoluble matrix, with drug becoming available as a solvent enters the matrix and dissolves the particles (lipid matrices and insoluble polymer matrices).

Drugs dispersed in a soluble matrix rely on slow dissolution of the matrix to provide sustained release. Excipients used to provide a soluble matrix often are those used to make soluble film coatings. Alternatively, slowly dissolving fats and waxes can be used. Synthetic polymers, such as polyorthoesters and polyanhydrides, have also been used. These polymers undergo surface erosion with little or no bulk erosion. If the matrix is presented with conventional tablet geometry, then on contact with dissolution media the surface area of the matrix decreases with time, with a concomitant decrease in drug release.

Drug particles may be incorporated into an insoluble polymer matrix. Drug release from these matrices follows penetration of fluid into the formulation, followed by dissolution of the drug particles and diffusion of the solute through fluid-filled pores. This type of delivery system would not be suitable for the release of compounds that are insoluble or those compounds that have low aqueous solubility. Excipients used in the preparation of insoluble polymers include hydrophobic polymers such as polyvinyl acetate, ethyl cellulose and some waxes. At

this point each of the three main types of monolithic/matrix systems will be discussed.

B) Lipid matrix system *[24]*

Wax matrices prepared by direct compression; hot-melt granulation or roller compression; have their active agent contained in a hydrophobic substance that remains intact during drug release. The release of the drug depends on an aqueous medium dissolving the channeling agent, which leaches out of the matrix forming capillary pores. The active ingredient then dissolves in the aqueous medium and diffuses out of the matrix, by way of the water-filled capillaries. A typical formulation consists of an active drug, a wax matrix former (hydrophobic material that are solids at room temperature and do not melt at body temperature, e.g., hydrogenated vegetable oils, cottonseed oil, soya oil, microcrystalline wax and carnauba wax), a channelling agent (soluble in the gastrointestinal tract (GIT), in water and leaches out of the formulation leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released, e.g., sodium chloride and sugars), a solubiliser and pH modifier, an anti-adherent/glidant and a lubricant.

C) Insoluble polymer matrix system *[25]*

Drugs are embedded in an inert polymer, which is not soluble in the gastrointestinal fluid. Drug release has been compared to the leaching from a 14 sponge. The release rate depends on drug molecules in aqueous solution diffusing through a network of capillaries formed between compact polymer particles. The factors influencing drug release rate from insoluble polymer matrix systems are:

- Pore structure – pore forming salts and compression force,
- Excipients – wet ability changed by the soluble and insoluble Components,
- Particle size of polymer component – influences the surface area exposed to the medium.

There are three primary mechanisms by which active agents can be released from a matrix delivery system, which involve diffusion, degradation, and swelling followed by diffusion.

Any one or all of these mechanisms may occur in a given drug release system. Diffusion occurs when a drug or other active agent/s passes through the polymer that forms the modified-release device. The diffusion can occur on a macroscopic scale as through pores in the polymer matrix or on a molecular level, by passing between polymer chains. The particle size of the insoluble matrix components influences the rate of release.

Larger Particles leading to an increase in release rate. This can be attributed to that the coarser particles producing matrix with a more open pore structure. An increase in drug loading tends to enhance the release rate, but

the relationship between the drug loading and drug release rate is not clearly defined. One possible explanation may be a decrease in the tortuosity of the matrix.

In Figure No. 4, a polymer and an active agent have been mixed to form a homogeneous system, also referred as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment.

As the release continues, its rate normally decreases with this type, since the active agent has to travel a longer distance progressively and therefore requires a longer diffusion time to release

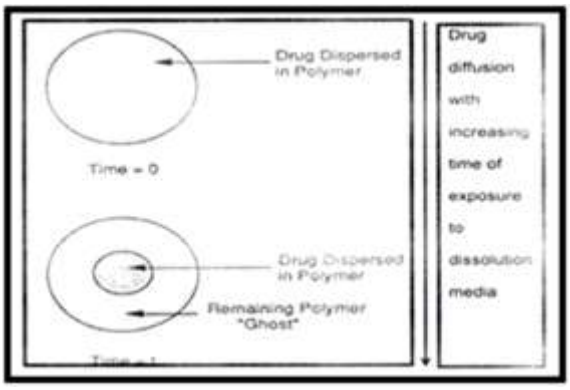

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Figure No. 4: Drug delivery from an insoluble polymer matrix diffusion system.

D) Hydrophilic colloid matrix system *[26]*

These swellable-soluble matrices are hydro gels that swell on hydration. This system is capable of swelling followed by the gel formation, erosion and dissolution in aqueous media. Their behaviour is in contrast to a true hydrogel, which swells on hydration but does not dissolve. Drug particles are dispersed in an insoluble matrix and the drug becomes available as the solvent enters the matrix and dissolves the drug particles. This is enhanced by the swelling, which is followed by the gel formation, erosion of the matrix system and the dissolution of the drug. Hydrophilic polymer matrix system comprise a mixture of the drug/s, the hydrophilic colloid, release modifiers and lubricant/glidant. Diffusion of the drug through the hydrated matrix is the rate limiting step in drug release. Two common types of hydrophilic matrix systems are the true gels which are cross-linked polymeric structures formed by chemical bonds (covalent) or physical bonds (helix formation based on hydrogen bonds or ionic interactions), for which chitosan is an excellent polymeric example, and the viscous matrices which are simple entanglements of adjacent polymer chains

E) Reservoir or membrane-controlled system *[27]*

The rate controlling part of the system is a membrane through which the drug must diffuse as shown in Figure No. 5. To allow the diffusion, the membrane has to become permeable, e.g. through hydration by water normally present in the gastrointestinal tract, or by the drug being soluble in a membrane component, such as a plasticizer. Unlike hydrophilic matrix systems, the membrane polymer does not swell on hydration to form a hydrocolloid matrix and does not erode. Two diffusion processes occur namely ‘water in’ followed by ‘drug out'. The membrane system has a polymer membrane

at the surface and the matrix system has a polymer throughout the whole system. The drug reservoir is coated with a membrane. The system is composed of the core (the drug, filler/substrate, lubricant/glidant, solubiliser), the coating (the membrane polymer, plasticizer/membrane modifier, coloring agent). Typical polymers used for the membrane are ethyl cellulose, acrylic copolymers, shellac and zein. The release-controlling polymer is film-coated onto the system. The membrane system may be formulated as a single unit system or as a multiple unit system. The single unit is essentially a tablet, which differs from conventional tablets in that its core does not disintegrate but dissolves and the formulation requires water to penetrate for the drug to dissolve so that diffusion can occur. The multiple-unit system comprises more than one discrete unit as coated spheroids (pellets, 1 mm in diameter) compressed in a tablet or filled into a hard gelatin capsule

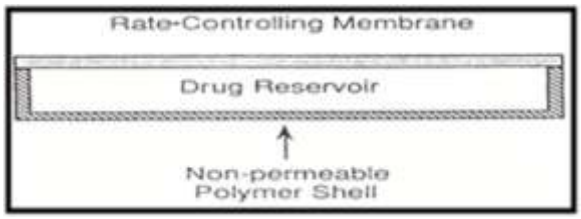

Figure No. 5: Diagrammatic representation of a slab configuration of a reservoir.

Diffusion system for the reservoir system, the drug delivery rate can remain fairly constant. In the design of a reservoir, the drug whether a solid, a dilute solution, or as a highly concentrated drug solution within a polymer matrix, is surrounded by a film or membrane of a rate-controlling material.

F) Osmotic pump *[28]*

A semi-permeable membrane surrounds a mixture of drug/s and an osmotically active constituent as in Figure No. 6. Water is taken up by osmotic action and the dissolved drug is discharged through a small orifice. The rate of drug release is controlled by the rate at which water enters through the membrane and the rate at which drug passes out of the hole/orifice and the swelling of the polymer push layer

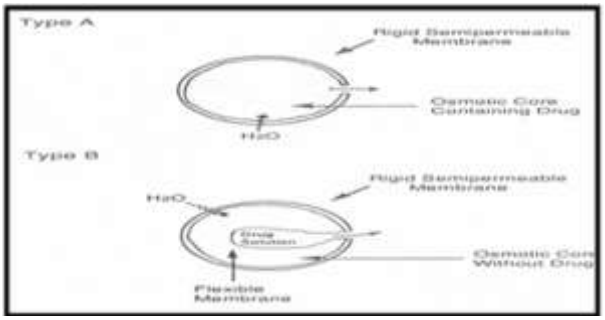

Figure No. 6: Diagrammatic representations of two types of osmotically controlled systems. Type A contains an osmotic core with drug.

Type B contains the drug in Solution in a flexible bag, with the osmotic core surrounding.

Osmotically controlled oral drug delivery system utilize osmotic pressure for controlled delivery of the active agent/s. Drug delivery from these system, to a large extent, is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs..

G) Coated beads or granules *[29]*

A solution of the drug substance in a non-aqueous solvent (e.g. alcohol) is coated onto small, inert beads or granules made of a combination of sugar and starch. When the drug dose is large, the starting granules may be composed of the drug itself. Some of the granules are left uncoated to provide immediate release of the drug. Coats of a lipid material (e.g. beeswax) or cellulose material (e.g. ethyl cellulose) are applied to the remaining granules. Some granules receive few coats, and some receive many. The various coating thicknesses produce sustained-release effect.

H) Microencapsulation *[30]*

This is a process by which solids, liquids or gases are encased in microscopic capsules. Thin coatings of a "wall" material are formed around the substance to be encapsulated.

Coacervation is the most common method of microencapsulation. This occurs when a hydrophilic substance is added to colloidal drug dispersion and causes layering and formation of microcapsules. Coacervation is carried out in three steps, under continuous agitation, namely formation of three immiscible chemical phases, deposition of the coating and rigidisation of the coating.

BIOLOGICAL FACTORS INFLUENCING ORAL SUSTAINED-RELEASE DOSAGE FORM DESIGN *[31]*

- Biological half-life:
- Absorption:
- Metabolism:
- Distribution :
- Protein binding:
- Margin of safety:

a) Biological Half Life

Therapeutic compounds with short half lives are excellent candidates for sustained release preparations, since this can reduce dosing frequency.

b) Absorption

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of drug from the dosage form. Compounds that demonstrate the absorption rate constants will properly be poor candidates for sustaining systems. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, sustained release preparation may be disadvantageous to absorptions.

c) Metabolism

Drugs that are significantly metabolized before absorption, either in lumen or tissue of intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intentional wall enzymes systems are saturable. As the drug released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite.

- Drug should have law half-life (<5 hrs.)

- Drug should be freely soluble in water.
- Drug should have larger therapeutic window
- Drug should be absorbed throughout the GIT

d) Distribution:

Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral SR drug delivery system e.g. Chloroquine

e) Protein Binding:

The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

f) Margin of safety:

As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.

PHYSIOCHEMICAL FACTORS INFLUENCING ORAL SUSTAINED-RELEASE DOSAGE FORM *[32]*

a) Dose size

In general, single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage form. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

b) Ionization, pKa and aqueous solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially penetrate across lipid membranes, it is important to note the relationship **between** the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

c) Partition coefficient

Compounds with a relatively high are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for periods, because they can localize in the lipid membranes of cells.

d) Stability

Orally administrated drugs can be subject to acid-base hydrolysis and enzymatic

degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire courses of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate bioavailability when administered from a sustaining dosage form.

MECHANISM OF DRUG RELEASE FROM MATRIX TABLET *[33, 34]*

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) A pseudo-steady state is maintained during drug release,

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.

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] 1/2 **(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] 1/2 (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 = Diffusional 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

M = k. t 1/2 (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

POLYMERS USED IN MATRIX TABLET *[35]*

a) Hydrogels

Polyhydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA).

b) Soluble polymers

Polyethylene glycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).

c) Biodegradable polymers

Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters

d) Non-biodegradable polymers

Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

e) Mucoadhesive polymers

Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin

f) Natural polymers in sustained release drug delivery

. Drug-release-retarding polymers are the key performers in such systems. Most of researchers used synthetic polymers as ethyl acrylate, methylacrylate, eudrgit for sustained and controlled drug delivery but they individually shows specific limitations such as toxicity or expensiveness of polymer. Different combinations of polymers like ethyl cellulose and hydrogenated castor oil were also tried by researchers but these combinations makes the process complicated and increase the cost of formulations. So natural polymer such as resins, polysaccharides and gums have been extensively used in the field of sustained and controlled drug delivery system because they are readily available, cost effective, eco-friendly, capable of multitude of chemical modification, potentially degradable and compatible due to natural origin. *[34]*

Table No1. Examples of natural gums used to fabricate sustained release dosage form

DRUG	NATURAL GUM	DOSAGE FORM
Terbutaline sulphate	Tamarind seed poloyose	Matrix tablet
Diltiazem hydrochloride	Rosin	Microencapsule
Diclofenac sodium	pectin	Microencapsule
Diclofenac sodium	Xanthan gum	Pellets
Propranolol hydrochloride	Xanthan gum	Matrix tablet
Diltiazem hydrochloride	Modified guar gum	Matrix tablet
Metoprolol tartrate	Xanthan/guar	Matrix tablet
Atenolol	Acrylamide-grafted-xanthan gum	Matrix tablet
Acetaminophen	High-amylose carboxymethyl starch	Matrix tablet
Chlorpheniramine Maleate	Chitosan and Xanthan gum	Hot-melt extruded Tablet
Metformin hydrochloride	Xanthan gum, chitosan	Matrix tablet
Indomethacin	Xanthan gum	Matrix tablet
Ketoprofen	Sodium alginate	Matrix tablet

CONCLUSION

By the above discussion, I have concluded that sustained-release formulations are helpful for optimal therapy regarding increasing the efficacy, safety and patient's compliance. The advantage of sustained release tablet is often being taken less frequently than instant formulation of the same drug and that they keep steadier level of the drug in blood stream. More over all these

comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance. Sustained release tablet formulated so that the active ingredient are embedded in a matrix of insoluble substances.

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