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A Review on Modified Release Dosage form and Drug Delivery System

Mr. Pote Vishal, Mr. Sarak Akshay Mr. Nanaware Pritamsinh, Mr. Tamnar Sachin, Mr. Mogal Nitin

1.Department of Pharmaceutics, JSPM's Jayawantrao Sawant College of Pharmacy & Research, Hadapsar, Pune 411028

Abstract:

Over the past decade a great interest has been generated in replacing conventional Drug Administration by an effective delivery system release is equal to form a protected supply at a controlled speed over a long period of time. Ideally a drug to provide therapeutic action desired must quickly reach the site of action (receiver) to the optimum concentration and there for the desired time, save the others and get removed from the site, one of the most recent interesting result of pharmaceutical research is the fact that the rate of absorption of the release of the dosage form. The product so formulated is designed as a sustained action, prolonged release, prolonged action, depot, delayed action, delayed action, the products in most cases are similar in appearance.

Key words: Modified release, Sustained release, prolonged release.

Introduction:

1.1 MODIFIED RELEASE DOSAGE FORM: [1-10]

Many of the conventional medicines, such as tablets and capsules, are formulated to immediately release the active drug after administration to obtain rapid and complete systemic absorption of the drug. The modified release dosage form term is used to describe products that alter the time and speed of release of the pharmacological substance. A modified release dosage form is defined as one for which the drug - course release characteristics and / or time location are chosen to achieve therapeutic or convenience goals not offered by conventional dosage forms aside. To achieve the therapeutic effect of the preparation, it must be available for a certain minimum concentration for a fixed duration.

Conventional dosage forms give rapid release showing drug fluctuations in drug concentration in the body and require multiple doses to maintain therapeutic levels. To achieve and maintain a uniform drug concentration in the therapeutic range, modified dosage forms are developed. The goal in the design of modified-release dosage forms is to reduce the frequency of dosing or increase the effectiveness of the drug by localization at the site of action, reducing dosage or providing the required uniform drug delivery. The main goal is to achieve a stable state drug level in the blood for prolonged periods of time. The design of appropriate dosing regimens is an important element in achieving this objective. prolonged release, prolonged action, prolonged action, controlled release, prolonged action, timed release, storage and dosage forms are terms used to identify the drug delivery system.

Although these terms were used interchangeably by the manufacturer, they are designed to achieve prolonged release of the drug continuously for a long time after the administration of the therapeutic effect single dose. In

injectable dosage forms, this period can range from one day to one month. In the case of orally administered dosage forms, this period is measured in hours and is critically dependent on the time of residence of the dosage form in the gastrointestinal tract. term release has been associated with such systems by which agents can be provided automatically at predetermined rates over a long period of time. Products of this type have been formulated for injection and use topical and oral inserts for placement in body cavities. Prolonged release drug delivery system, which consists mainly of two parts: an immediate dose and a holding portion. The immediately available dose normally added directly to the supporting part of the tablet or, alternatively, is incorporated into the tablet liner with the supporting part in the tablet core is, a portion (initial charge dose) of the drug is released immediately to obtain the desired therapeutic response promptly. The residual dose of the drug (maintenance dose) is released slowly, resulting in / tissue level therapeutic drugs, which is a prolonged but not maintained constant.

Different Terminologies used in modified release:

1. Sustained release
2. Delayed release
3. Prolonged release
4. Extended release
5. Controlled release
6. Site-specific targeting and receptor targeting

Drawbacks of Conventional dosage forms:

1. Poor patient compliance, higher probability of losing the dose of a drug of short half-life for which the patient is required frequent administration.

2. Inevitable fluctuations in the concentration of drugs can lead to low drugs or medications.

3. A typical valley-peak is obtained in the plasma concentration profile that hinders the achievement of steady state.

4. Fluctuations in drug levels can lead to precipitation of negative effects especially from a drug with small therapeutic index (TI) whenever medication occurs.

Advantages of modified release formulations:

1. Improved patient compliance and comfort by reducing the frequency of administration.

2. Reduction of fluctuation of the level of steady state and therefore better control due to the constant level of drug in plasma for a long time.

3. Minimize the accumulation of drugs with chronic dosage.

4. Minimize or eliminate local and systemic side effects.

5. Maximum use of the drug to reduce the total amount of doses administered.

6. Increased safety margin of high potency drugs due to improved plasma control level of drugs.

Disadvantages of modified release formulations:

1. Administration of modified-release drugs does not allow discontinuation of therapy.

2. The doctor has less flexibility to adjust dosage regimens.

3. Possibility of dumping dose due to food, physiological variables or formulation or chewing and grinding oral formulations by the patient and, consequently, an increased risk of toxicity.

4. Poor in vitro-in vivo correlation.

5. The most expensive processes and equipment are involved in the manufacture of SRDFs.

6. Drugs absorbed at specific sites cannot be administered in the dosage form.

Modified release dosage form:

Oral dosage form

- Extended release (eg. Controlled release, sustained release, prolonged release)
- Delayed release (eg. Enteric coated)

Intramuscular Dosage Forms

- Depot injection
- Water-immiscible injections (eg. Oil)

Subcutaneous Dosage Forms

- Implants

Transdermal Delivery System

Targeted Delivery Systems

- Colon targeted

1.2 BIOPHARMACEUTICAL CLASSIFICATION SYSTEM: [11-13]

BCS is a scientific framework for classifying a pharmacological substance based on its solubility and intestinal permeability. In combination with the characteristics of dissolution in vitro of the pharmaceutical product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, which govern the rate and extent of oral absorption, the drug of the solid forms of oral-dosing of IR. The solubility rating of a drug in BCS is based on the highest dose concentration in an IR product. A drug substance is considered highly soluble when the strength is soluble in 250 ml or less of media aqueous media in the pH range of 1.0-7.5; otherwise, the substance of the drug is considered to be slightly soluble. The estimated volume of 250 ml is derived from the typical bioequivalence study protocols that prescribe the administration of a medicine to fasting human volunteers

The classification of permeability is based directly on the degree of intestinal absorption of a pharmacological substance in humans or indirectly on measurements of the transfer of mass rate through the human intestinal membrane. Animal or in vitro models capable of predicting the degree of intestinal absorption in humans may be used as alternatives, e.g. in situ rat infusion models and in vitro epithelial cell culture models. The drug is considered highly permeable when the degree of intestinal absorption is determined to be 90% or higher. Otherwise, the pharmacological substance is considered poorly permeable.

PRINCIPLE CONCEPT BEHIND BCS:

The concept behind BCS principle is that if two drugs produce the same concentration profile along the gastrointestinal tract (GI), it will result in the same plasma profile after oral administration. This concept can be summarized by applying Fick's first law in the following equation

$$J = Pw\ Cw \quad \text{..... (1)}$$

Where,

' J ' is the stream through the gut wall,

' Pw ' is the permeability of the intestinal wall to the medication, and

'Cw' is the concentration profile of in-the-wall intestinal.

In terms of bioequivalence, it is assumed that the drugs are highly permeable and highly soluble pharmaceutical products accommodated in the rapid dissolution will be bioequivalent and, if no changes are made in the formulation, the data of dissolution can be used as a substitute for pharmacokinetic data to demonstrate bioequivalence of the two pharmaceutical products. According to BCS drugs can be classified into four basic groups based on their solubility and permeability of the GIT mucosa.

DRUG CHARACTERISTICS OF VARIOUS BCS CLASSES:

Class I drugs:

Exhibiting a high number of absorption and a high number of dissolutions. Bioavailability and dissolution is very fast. Bioavailability and bioequivalence studies are unnecessary for this product. These compounds are highly suitable for the design of SR and CR formulation. Examples include Propanolol, Metoprolol, Diltiazem, Verapamil, etc.

Class II drugs:

This drug exhibited variable bioavailability and needs increased dissolution to increase bioavailability. These compounds are suitable for the design of SR and CR formulations. IVIVC is usually expected for Class II medications. Examples include Phenytoin, Danazol, Ketoconazole, mefenamic acid, nifedipine, felodipine, nicardipine, nisoldipine, etc.

Class III drugs:

The permeability is the rate-limiting step for drug absorption. These drugs exhibit a high variation in the speed and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the factors of dosage form. These drugs are problematic for controlled release development. These drugs showed low bioavailability and need improvement in permeability. Examples include Acyclovir, Alendronate, Captopril, Enalaprilat neomycin B, etc.

Class IV drugs:

These drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability, and gastric emptying form the speed limiting steps for drug absorption. These are not suitable for controlled release. Examples include Chlorthaizide, Furosemide, Tobramycin, Cefuroxime etc.

1.3 SELECTION OF DRUG CANDIDATE FOR ORAL SUSTAINED RELEASE SYSTEMS: [1,4,7,8]

The sustained release system design depends on several factors such as the route of administration, the type of administration of the system, the condition that is treated, the patient, the therapy and the properties of the drug. These are the physico-chemical and biological properties of the drug.

Physico-chemical properties: - these include

1) Aqueous solubility:

Absorption of poorly soluble drug is often limited dissolution rate. Such drugs do not increase control over its rate of dissolution and, therefore, does not seem to be a good candidate for prolonged-release systems. Drugs with good solubility in water are good candidates for oral prolonged-release formulations.

2) Partition coefficient:

Drugs that are highly soluble in lipids or very soluble in water, for example, the ends on the partition coefficient will show low flow into the tissue or rapid flow followed by tissue accumulation. Both cases are undesirable for prolonged-release formulation. Drugs with a balanced distribution coefficient are good candidates for sustained release oral formulation.

3) The stability of drug:

Like most oral prolonged-release systems are designed to release their contents over much of the length of the gastrointestinal tract. Drugs, which are unstable in the intestinal environment are difficult to formulate in prolonged-release systems.

4) Protein binding:

Extensive protein binding can be evidenced by a long Half-Life of elimination for it, and such drugs do not require sustained release dosing. However, drugs that exhibit a high degree of plasma protein binding may also bind to biopolymer in the GI tract, which may have an influence on sustained Drug Administration.

5) Molecular size and diffusivity:

Drugs in many sustained release systems should be spread through membrane or matrix velocity control, in addition to diffusion through the diverse biological membrane. The drug's ability to pass through membranes, it is called diffusivity, is a function of its molecular size (or molecular weight). A major influence on the diffusivity value, D in polymers is the molecular size of the diffusor species. The value of diffusivity is related to the size and shape of the cavities, as well as to the size and shape of diffusor species. Generally, the values of the diffusion coefficient for the intermediate molecular drugs i.e.150-400, with the flexible range of the polymer from 10-6 to 10 -9 cm2/sec, with values of the order 10-8 being the most common. For drugs with molecular weight greater than 500 it is difficult to quantify.

6) Biological half- life:

The usual objective of the sustained released product is to maintain the therapeutic blood level over a long period of time. For this purpose, the rate of drug entry into circulation should be approximately equivalent to the rate of its elimination that is quantitatively described for its Half-Life. Shorter Half-Life drugs (2-4 hours) are excellent candidates for Sustained Release Preparation as this may reduce dosing frequency.

Biological properties: These includes

1) Absorption:

To maintain a constant level of drug in the blood or tissues must be evenly released from the sustained release system and then evenly absorbed. Generally, the limiting factor in the administration of drugs of a prolonged release product is the release of the dosage form, instead of inherent absorption control. The fraction of drug absorbed by a single unsupported dose of drug may be quite low due to drug degradation, protein binding or dose-dependent absorption. Although the drug is absorbed evenly incomplete, but a sustained successful product launch can be done. Dicumarol and glycosides, gentamicin and kanamycin amino are examples, which are absorbed irregularly after oral administration, making the design of a prolonged release product more difficult. The same drugs as absorbed by specialized processes of specific sites and transport of the gastrointestinal tract are poor candidates for sustained release, for example, riboflavin.

2) Distribution: The distribution of the drug in the tissues is an important factor in the removal of the overall drug kinetics. Drugs with a high apparent volume of distribution, which in turn affects the speed of elimination of drugs are good candidates. It affects the concentration and amount of the drug in the blood or tissues.

3) Metabolism: The metabolism of a drug metabolic disorder occurs mainly in the liver. Metabolism is reflected in the constant elimination of a drug. complex metabolic patterns make the design more difficult, especially when biological activity is due to a metabolite. If the drug in chronic administration induce or inhibit enzyme synthesis, make a poor candidate for a prolonged release product due to the difficulty of maintaining uniform blood levels.

4) Duration of action:

The biological half-life and, therefore, the duration of action of a drug is influenced by its distribution, metabolism, and patterns of elimination and plays a key role in the determination of the application of the drug to the preparation as a by-product of sustained release. There is little justification for preparing a sustained-release formulation for mid-life drugs. If there are no significant differences in effectiveness when a medicine is given as a single large dose per day or in several smaller doses throughout the day, the need for a form of long-acting dosing is doubtful, for example, Phenylbutazone and phenothiazines.

5) Side effects:

Controlled release formulations may minimize the incidence of side effects by controlling the plasma concentration of the drug, e.g. controlled release levodopa has decreased the incidence of side effects and increased patient tolerance at a total higher daily dose. The Controlled Release Technique has been used more popularly to lower the incidence of gastrointestinal side effects than systemic side effects. Therefore, drugs that are likely to cause gastric irritation are best tolerated in sustained forms of release dosing, e.g. ferrous sulphate and potassium chloride.

6) Safety Margin:

The safety margin of a medicinal product is commonly indicated by its therapeutic index. A drug is considered relatively safe if its therapeutic index exceeds 10. Therapeutic index = Median toxic dose / Median effective dose.

= TD50 / ED50.

Table 1.1: Properties of drugs to be considered for modified release:

Drugs Suitable	Drugs not Suitable
Physicochemical: 1) Compounds with low molecular weight 2) Good aqueous solubility, pH independent (Penotoxyphylline) 3) With non-aqueous solubility (for Parenteral; Steroids) 4) Unionized (at least 0.1-5%) in GI tract 5) Very weak bases pKa < 5.0 (Theophylline pKa=0.7, Diazepam pKa = 3.7) sodium 6) Very weak acids pKa > 8.0 (Pentobarbital pKa =8.1) Unionized at all pH, absorb well 7) Moderately weak acids pKa 2.5-7.5 Aspirin (3.5), Ibuprofen (4.4). 8) Moderately weak bases (pKa 5.0-11.0), Codeine (8.2) Ionization depends on pH	1) Large molecular size/weight (proteins and peptides for oral) 2) Very low aqueous solubility (0.1 mg/ml) (Nifedipine, Griseofulvin) 3) Largely in ionized form in the G.I. tract 4) Strong bases (pKa > 11.0) eg: Guanethidine 5) Strong acids (pKa < 2.5) eg: Cromolyn sodium
Pharmacokinetic: 1) Short ½ (2-5 hr) Theophylline (4 hr) Sodium diclofenac (2 hr) Nifedipine (2.5 hr) Diltiazem (3.5 hr) Glipizide (3.4hr) 2) Well absorbed from all regions of GI tract	1) Drugs that exhibit Slow absorption 2) Carrier mediated transport (several vitamins) 3) Site specific absorption (Vit B12) 4) Degradation in GI tract (Nitroglycerine, Penicillin G, Erythromycin) 5) First pass hepatic metabolism (Nitroglycerin, Propranolol) 6) That induce or inhibit metabolism 7) (Rifampicin, Barbiturates, Allopurinol
Pharmacodynamic: 1) Therapeutic range of blood conc.-wide enough 2) Response α blood conc.	1) Having large dose 2) Drugs whose metabolites are also active

1.4 DESIGN OF ORAL SUSTAINED RELEASE SYSTEMS (MODIFIED RELEASE DOSAGE FORM): [1,4,6,8-10]

Most sustained release systems are solids. The following way of classification of such systems include not only the conceptual approach of design, but some elements of physiology of the GI system as well.

1. Continuous-release systems

a. Dissolution control systems

b. Diffusion control systems

c. Dissolution and diffusion control systems

d. Ion-exchange resins complexes

e. Osmotically controlled devices

f. Slow-dissolving salts or complexes

g. PH-independent formulations

2. Delayed-transit and continuous-release systems

a. Density-based systems

b. Size-based systems

c. Bio adhesive based systems

3. Delayed-release systems

a. Intestinal release systems

b. Colonic release systems

1.Continuous-release system:

a) Dissolution control systems:

Continuously release for prolonged periods can be obtained using the solution as the limiting factor of the speed of release of the drug. Some drugs dissolve slowly due to its low inherent solubility in water and acts as well as natural products of prolonged release. Cardiotonic digoxin and an antifungal drug griseofulvin are examples of slow dissolution drugs. For compounds with high aqueous solubility, it is necessary to reduce the solubility rate by some mechanism. The approach to control the rate of dissolution of such compounds based on one or both of the following techniques:

1) Stagnant – layer control
2) Encapsulation or coating, which erodes or dissolves slowly

Stagnant – layer control:

If the dissolution process is controlled by the diffusion layer, that is, the step speed limitation is the diffusion through one layer without removing the solid surface for most of the solution, one in the stagnant diffusion layer works effectively. Matrix is the most commonly used system to achieve this control solution goal. The rate of availability of the drug is controlled by the rate of penetration of the dissolving medium. Such penetration can be controlled by the porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet. A disadvantage of systems is controlled by stagnant layers that fail to give a zero-order release; that is, the release rate gradually decreases with time. This is the result of a greater diffusional distance and a decrease in the surface than solvent penetration.

Encapsulation dissolution control:

The basic approach in encapsulation is coating particles of drug with a slowly dissolving material. Coated particles can be compressed directly into tablets or inserted into gelatin capsules. Since the time required for the dissolution of the surface layer which is a function of the thickness of the layer, and its solubility in water, good control of the release rate can be achieved.

b) Diffusion control systems:

Diffusion controlled systems fall into two basic categories:

1) Reservoir devices
2) Matrix devices

Reservoir devices:

In reservoir devices, a polymer material contains water insoluble drugs. exit drugs through the system is regulated by the partition of the drug through the lining membrane. The drug penetrates the membrane and spreads to the other side, and finally enters the dissolving means. insoluble layers can be applied to a drug base by a variety of techniques. commonly used pressure painting approaches and air suspension. For smaller particles intended tablets or capsules, microencapsulation techniques are generally used. The drug coating cannot be included in the system to provide the quick dose.

Matrix devices:

The approach employs a matrix system in which the drug is compressed with a slow dissolution or insoluble polymer. The rate of drug availability is controlled by the rate of penetration of the dissolving medium through the Matrix. Since the drug is dissolved and difference, it increases the length of the diffusional path that the polymer matrix is insoluble. After creating pores, the drug will be launched shortly. Of course, the release rate is not zero-order. However, if you use a polymer that slowly dissolves Matrix where the Matrix itself is dissolved at a speed to maintain the diffusion length or not the same, it can result in almost a zero-order release. The rate of release of the drug depends on the rate of spread of the drug, but they are not of solid solution. Higuchi equation can be used to express the release speed of such a system:

$$Q = \left(\frac{DE}{T\,(2A - ECs)\,CS\,t} \right)^{\frac{1}{2}}$$

Where
Q = drug released in g per unit surface area.
D = diffusion coefficient of drug.
E = porosity of the matrix.
T = tortuosity of the matrix.
Cs = solubility of drug in release medium (g/ml)
A = concentration of drug in the tablet (g/ml)
t = time

c) Dissolution and diffusion controlled systems:

Some control systems used diffusion and dissolution in the course rate of release of the drug. The dosage form includes a drug core contained in a partially soluble membrane. When placed in the appropriate medium, the soluble portion of the membrane is dissolved away, creating pores in the remaining layer. This allows the dissolution of the drug. An example of such a coating would be a polymer coating consisting of cellulose and methylcellulose acetate. Methylcellulose is dissolved, leaving the ethyl cellulose layer intact. By varying the fraction of soluble material in a layer it is possible to easily control the surface in such a system. In addition, by incorporating more than one soluble material with different solubility rates, you can increase the release rate after a certain period of time.

d) Ion-exchange resins:

Ion exchange resins are water-insoluble crosslinked polymers containing salts that form in the position in the polymer chain. Release of the drug resin complex drug depends on the concentration and pH of the electrolyte within the gastrointestinal tract and the properties of the resin. resin-bound drug molecules are released by ion exchange with properly loaded in the GI tract as shown below,

$$Resin^{+} - Drug^{-} + X^{-} \longrightarrow Resin^{+} - X^{-} + Drug^{-}$$

$$Resin^{-} - Drug^{+} + Y^{+} \longrightarrow Resin^{-} - Y^{+} + Drug$$

Where X^{-} and Y^{+} are ions in the GI tract.

The release rate depends on the degree of crosslinking in the resin. Coating the drug resin can make a further modification of the complex release rate with hydrophobic speed limiting polymers such as cellulose waxes or ethyl alcohol [13].

e) Osmotically controlled devices:

Osmotically controlled systems use osmotic pressure as a driving force to release drugs at constant speed. It consists of a core drug surrounded by a semi-permeable membrane coating, having an orifice. The absorbed water environment passes through the membrane at a controlled speed and determines the medicinal solution output through the delivery orifice. Beats drug at a rate independent of gastrointestinal pH and mobility. The flow rate is controlled by the osmotic properties of the core and membrane area, thickness and water permeability. An elementary osmotic pump is shown in Figure 1.1.

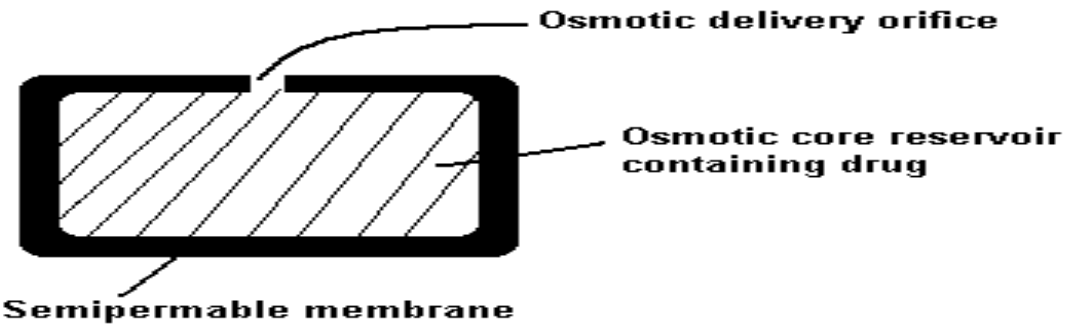

Fig. 1.1: Schematic representation of an elementary osmotic pump

f) Slow dissolving salts or complexes:

A salt or drug complex that is poorly soluble in gastrointestinal fluids can provide a prolonged release of the drug. The process of formation of the complex is usually a simple reaction acid base, as in the case of amines and tannic acid. Solutions of compounds in both suitable solvents are mixed together and the resulting complex is precipitated by the addition of another solvent or salt.

g) pH-independent formulations:

Since the pH in the GI tract varies considerably and continuously the formulation goes through it, independent of the PH formulations are particularly attractive for oral use. These formulations are prepared from an acid or base with one or more medicine buffering agents; for example, salts primary, secondary or tertiary citric acid, granular and are coated with appropriate materials. When passing the gastrointestinal fluid through the membrane, PH tamponade agents adjust to the right predetermined, constant pH at which the drug is dissolved and permeates at a constant rate regardless of the external pH.

2. Delayed-transit and continuous-release systems:

The duration of in vivo delivery from oral CR products is strongly limited due to the short time of solids and liquids GI transit. In addition, the transit time GI tends to vary greatly between and within the subject. This administration can also causes medication is variable and unpredictable. As a result, most oral dosage forms are limited to a period of 12 hours. To prolong the time of stay of delivery devices in the gastrointestinal tract, the only approach seems to delay gastric emptying; because once a dosage form empty stomach, little can be done to slow its movement through the intestine.

1) Density based systems.
2) Size based systems.
3) Bio adhesive systems.

3. Delayed-release systems:

Delayed release systems for oral controlled delivery are intended to administer the drug to a particular gastrointestinal tract, rather than continuously administer the drug after ingestion. This specific delivery site may be directed to absorption, as in the case of enteric coated tablets, or for local effects. Delivery of drugs specifically for the desired area could treat certain conditions of disease of the colon and rectum.

These systems can provide one or more of the following advantages over CR system:

1. Avoid places of possible degradation of drugs, for example, stomach acid labile drugs, stomach and fasting for labile Peptidase drugs.

2. To achieve local effects in the lower GI tract without much absorption or systemic side effects.

3. Reduce discomfort in the Upper Area

4. drug administer at a specific site absorption to achieve a high concentration in the absorbent membrane, for example, the delivery of Peyer's patches or colon bacteria.

Intestinal release:

Enteric coated tablets are examples of the approach intestinal release. This approach is often used for acid-labile drugs. In the case of aspirin, prevention of gastric irritation is objective. However, gastro-resistant formulations tend to be unpredictable in their bioavailability. Enteric coated erythromycin tablets are well known for their unpredictable and variable bioavailability.

Colonic release:

Despite a small absorption surface, the possibility of administering drugs through the mucous membrane of the colon still exists because the desired rate CR absorption formulations is generally not very high. Basically, there are two approaches to administering medicants through the colon: (1) the use of bioerodable polymers to protect the drug during passage through the upper GI tract, and the use (2) of prodrugs that are activated by bacterial degradation or metabolism.

1.5 SUSTAINED RELEASE MATRIX DRUG DELIVERY SYSTEM (MODIFIED RELEASE DOSAGE FORM):

I) Hydrophilic matrix tablet: [1,4,7,9,14-16]

The hydrophilic matrix tablet is prepared using various hydrophilic polymers such as HPMC, xanthan gum, Polyox, Carbopol etc. There are too many factors involved in hydrophilic Matrix systems of drug release. the most important factors to take when developing a formulation based on matrices, hydrophilic are the proportion, solubility, and particle size of the drug, the type of polymer, the percentage built, the viscosity and the particle size of the polymer. Also, important drug / polymer ratio and the amount of water entering the Matrix. Other factors have been shown to be involved in the administration of drugs, such as the percentage and polymer mixtures and the size of the Matrix. The compression force is important between formulation factors as it determines the amount of air trapped in the Matrix. These release systems are also called soluble bulging matrices. Generally comprising a compressed mixture of drug and hydrophilic polymer inflatable in water. They are able to swell, followed by gel formation, erosion and dissolution in aqueous media. In contact with water hydrophilic colloids components to form a hydrated matrix layer. This then controls the further diffusion of water into the Matrix. spread of the drug through the Matrix moisturized layer controls the speed of release. The outer layer was hydrated Matrix erode as it becomes more diluted; the rate of erosion depends on the nature of the colloid. The Matrix can be compressed by direct compression of the active ingredient mixture and some hydrophilic vectors or a wet granulation containing the drug and hydrophilic matrix materials. Hydrophilic Matrix requires water to activate the release

mechanism and explore numerous advantages such as ease of manufacture and excellent uniformity of Matrix tablets. Polymers used for the preparation of hydrophilic matrices are divided into three large groups as follow,

Cellulose derivatives:

Hydroxyethyl cellulose (HEC), Hydroxypropyl cellulose (HPC), Hydroxypropyl methylcellulose (HPMC), Sodium carboxymethylcellulose (NaCMC) and Methylcellulose.

Non-cellulose natural or semisynthetic polymers:

Agar-agar, Carob Gum, Xanthan gum, Guar gum, Chitosan.

Polymers of acrylic acid:

Polymers which are used in acrylic acid category are Carbopol, Eudragit.

ii) Hydrophobic matrix tablet (Wax matrix tablet): [17-22]

Compact matrix is prepared from mixtures of powder components. active compound is contained in the hydrophobic Matrix remains intact during the release of the drug. The release depends on the dissolution of the externally compact direct channeling agent, so as to form a porous matrix of tortuous capillaries. The active agent is dissolved in aqueous medium and by means of capillaries filled with water, it spreads out of the Matrix. hydrophobic Matrix systems are generally not suitable for insoluble drugs because the concentration gradient is too low to release the appropriate drug. Hydrophobic Matrix tablet is prepared using various hydrophobic polymers such as cellulose acetate, acrylaterelated polymer, polyvinyl chloride, cellulose acetate and polystyrene, etc. Wax matrices are a simple concept. They are easy to produce with standard direct compression compactor roller or hot melt granulation. The drug can be incorporated into wax, by freezing spray in the air, mixing coagulation in an aqueous medium with or without the help of surfactant techniques and spray drying. In the bulk coagulation method, the drug suspension and melted wax fat allowed to solidify and is then shredded for prolonged release of granulations. The mixture of active ingredients, waxy materials and filler can also be converted into granules by condensing the roller compactor, heating into a suitable mixture such as bed and Blender fluidized Steam or granulation with a solution of waxy material or other binder. Examples of waxy substances are Compritol Precirol, hydrogenated vegetable oil, stearic acid, beeswax, cetyl alcohol, cetostearyl alcohol, etc.

Advantages of matrix systems:

1. The carrier is generally inexpensive and generally is GRAS (Generally considered safe).

2. Can withstand high loads drugs and high molecular weight compounds.

3. Reproducible release profile. Production machines.

4. Pharmaceutical use readily available.

5. Possibility to obtain different types of release profile: zero order, first order, bimodal etc.

6. Easy to produce.

7. Since the drug is dispersed in the matrix system, accidental release of the total is less likely to occur, although sometimes rupture of the matrix material can cause unwanted release.

1.6 FACTORS AFFECTING DRUG RELEASE FROM SUSTAINED RELEASE SYSTEM: [1,3,4,9]

1. Polymer hydration:

Polymer dissolution includes water absorption / adsorption in a more accessible place, polymer-I bond breakage with water-polymer bond formation, polymer chain separation, swelling and finally polymer chain dispersion in the dissolution medium. The polymer Methocel K, due to the low content of methoxy groups, quickly moisturizes, which justifies the use in controlled-release matrices. The larger fraction HPMC hydrates faster than the smaller fraction.

2. Viscosity:

With cellulose ether, the viscosity of the polymer is used as an indication of the weight of the Matrix. By increasing the molecular weight increases the viscosity of polymers in the formulation Matrix and thus slows the dissolution of the drug.

3. Solubility of the drug:

Absorption of poorly soluble drugs is often limited speed of dissolution. Such drugs do not require any additional control over its rate of dissolution; during preformulation it is necessary to determine the solubility of the drug not only in water but also at various pH.

4. Polymer drug percentage:

The release rate increases for a smaller amount of HPMC with a poorly soluble drug. The ratio depends on the consistency of the gel is affected by the ratio of the gel.

5. Hardness and density of the tablet:

In previous studies with different compressive forces no significant difference observed in drug release patterns from tablets of different densities.

6. Effect of diluents:

Few studies, the addition of water-soluble diluents (lactose) and water-insoluble diluents (observed dibasic calcium phosphate), divergence was obtained release profile due to the difference in the solubility of the diluents and subsequent models of drug-release tablets of different density effect on the tortuosity factor. As water-soluble diluents are dissolved, it spreads out and reduces the tortuosity of the drug's spread path. But dibasic calcium phosphate is not widespread, but it is trapped inside the affected and the release of the drug from the fact that their presence necessarily reduces the concentration of gum.

1.7 MELT GRANULATION (Wax Matrix Tablet): [1,6,7,19-23]

In the granulation of the molten mass, stearic acid, hydroxypropyl methyl cellulose, wax material and hydrophobic polymers are used. PEG has been widely used in pelletizing the molten mass due to its properties such as low melting point, fast solidification speed. Melting granulation involves the removal of water or organic solvents. This reduces any residual solvents; in addition, molten granulation, the drying phase is not necessary the process takes less time and energy.

Techniques of Melt Granulation:

1. Spray Congealing:

The freezing spray melting technique is highly versatile. In addition to manufacturing multi-part dispensing system, it can be applied to process raw materials size and viscosity particulate fuse values defined for the melting sintering process. The processing of fused materials by coagulation by spraying involves spraying a hot melt wax, or fatty acid glyceride into an air chamber below the temperature point of the melt material or cryogenic melt. Spray frozen particles (10-3000 microns in diameter) are obtained by cooling. Frozen particles are strong and nonporous and there is a lack of evaporation of the solvent.

2. Tumbling Melt Granulation:

A powder mixture of fuses and non-fuses materials are fed on the seeds in a fluidized bed granulator (Fig. 1.2). Adheres the compound to the seeds with the bond forces of a spindle to form solid spherical beads. In the preparation of spherical beads, both viscosity and grain size of the hardening material should be maintained at an optimal value. high viscosity materials fuses should not be used to avoid agglomeration and seed beads producing low sphericity.

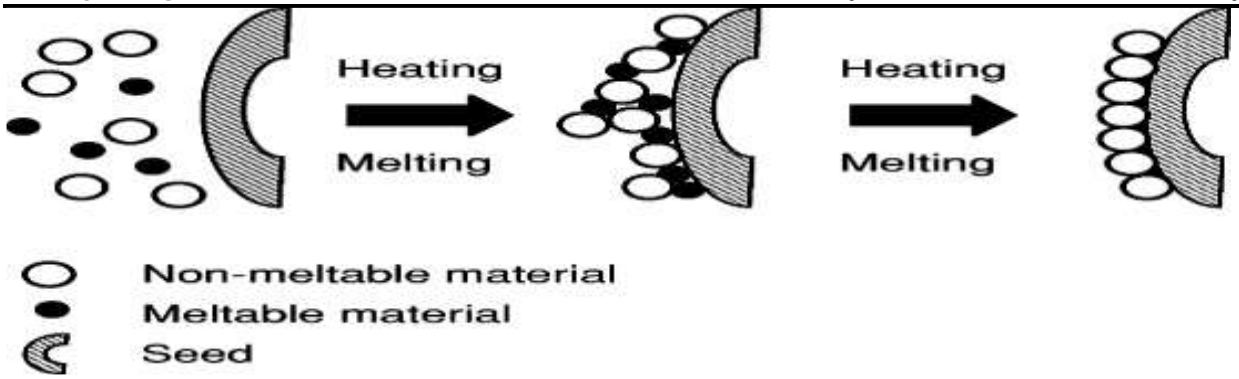

Fig. 1.2: Process of Tumbling Melt Granulation

Materials used in Wax Matrix Systems:

Wax is considered as an alternative to the design of drug-polymer sustained delivery systems because of their advantages such as low viscosity zone (thus avoiding the need of organic solvents for solubilization) absence of impurities and toxic such as catalysis and initiators monomers residues, and potential biocompatibility and biodegradability. The various meltable binders used for sustained drug delivery system are shown in the table.

Table 1.2: Hydrophobic Meltable Substances in the Melt Granulation Technique

Hydrophobic Meltable Binder	Melting Range (°C)
Beeswax	56–60
Carnauba wax	75–83
Glyceryl behenate (Compritol)	67–75
Glyceryl monostearate	47–63
Glyceryl palmitostearate (Precirol)	48–57
Glyceryl stearate	54–63
Hydrogenated castor oil	62–86
Microcrystalline wax	58–72
Paraffin wax	47–65
Stearic acid	46–69
Stearic alcohol	56–60

Melt Agglomeration:

Melt agglomeration is a process by which fine solid particles are joined in agglomerates, by stirring, kneading and stratification in the presence of a binding liquid. Dry agglomerates are obtained as the melted liquid bond is solidified by cooling. Typical examples of sintering melting processes are melting granulation and granulation of the molten mass. In a process of agglomeration melting of the hardening binder can be added as melted liquid, or as dried powder or flakes. In the latter, the binder can be heated with hot air or with a heating jacket of the melting binder point. Typically, the melting points of fused binders vary from 50 to 80 ° C.

Modes of melt agglomeration:

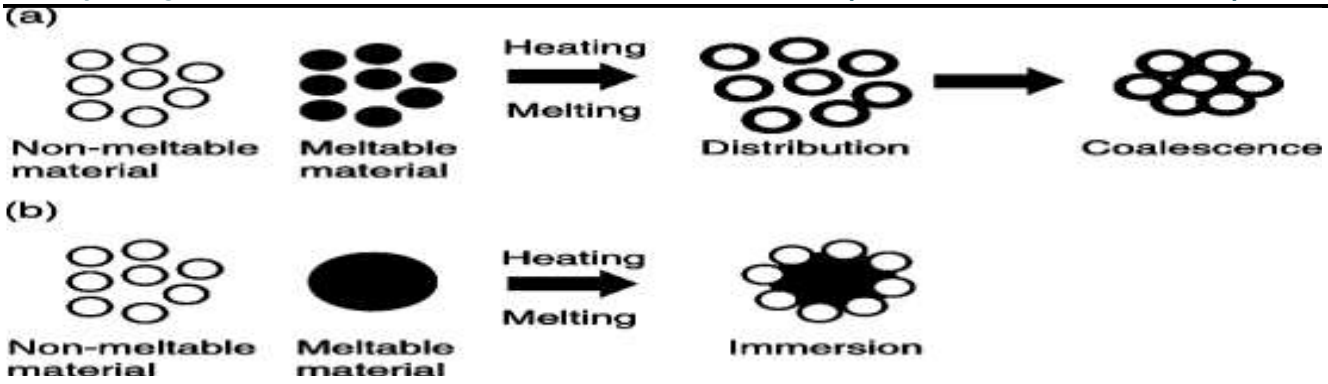

Fig 1.3: Modes of melt agglomeration: (a)Distribution and (b) Immersion

In the agglomeration mode distribution, a distribution of molten liquid bonding on the surfaces of the primary particles will occur and agglomerates are formed by coalescence between wet cores (fig.1.3). In agglomeration Immersion Mode, nuclei are formed by immersion of the primary particles on the surface of a drop of liquid in bond molten (Fig.1.3).

1.8 MULTILAYERED TABLETS: [24-26]

The tablets are research prepared for two reasons: physically or chemically incompatible ingredients separate and products repeat the action / prolonged action tablet.
1) Tablet in tablet technology
2) Layered tablets - two or three component systems (system layer and double layer coating)
Coated compression tablets: tablet inside one tablet. Tablet inlay-layer partially surrounds the core. When two or more incompatible active ingredients are administered simultaneously necessary, then better formulate tablet layers. Granules of different compressed together. Each layer is fed by a separate hopper.

Tablet in Tablet Technology: [27-29]

Compression coated tablets

This type of tablet has two parts, internal core of the active substance and the surrounding coat. The core is small and porous tablet compress prepared on a turret. For the final preparation tablets, a larger cavity is used the matrix in another turret where the first coat of material is filled in half and then the core of the tablet is transferred mechanically, again the remaining space is filled with the coat material and finally the compressive force is applied.

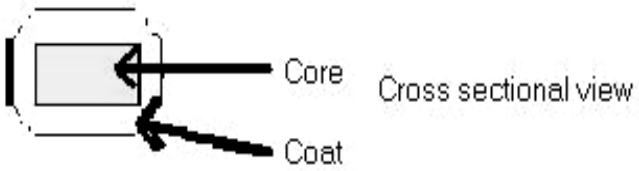

Fig.1.4: Compression Coated Tablet

Inlay tablets

In this method, only the lower part of the mold cavity is filled with coating material, and the core is placed on it. When the compression force is applied, a coating material is displaced to form the sides and compressing the entire compress. It has some advantages over compression coated tablets:
i) Requires less coating material. ii)
The core is visible, so tablets without core can be easily detected. iii)
Reduction coat a thinner tablet and, therefore, free to cover the top cover part.

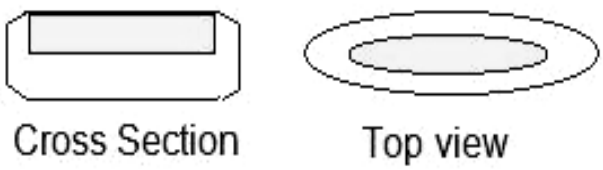

Fig. 1.5: Inlay Tablet

1.9 BILAYER TABLET TECHNOLOGY: [30-35]

Introduction:

Bi-layer tablets are new systems of Drug Administration in which the combination of two or more in a single unit is possible. They are preferred for the following reasons: 1) Co-administer two different drugs in the same dosage form. 2) To minimize physical and chemical incompatibilities. 3) RI and SR part of the drug in the same tablet, for chronic condition. Bi-layer tablets are prepared with a layer of drug for immediate release, while the second layer designed to release the drug, after either the second dose or in a prolonged release mode.

1.10 MECHANISMS OF DRUG RELEASE FROM MATRIX SYSTEMS: [34-37]

a) Diffusion- controlled systems:

Diffusion controlled release systems are divided into diffusion Matrix systems (also known as monolithic systems) and field systems. The dispensing unit can be a nearly spherical tablet or particle about 1 mm in diameter (granules). The release of the drug from a controlled release unit of diffusion in two stages: 1) The fluid surrounding the dosage form enters the release unit and dissolved drug. Thus, a concentration gradient is established between the drug inside dissolved and outside cutter. 2) The dissolved drug will spread into the pores of the release or membrane environment and then released. Thus, a dissolution phase is normally involved in the release process, but the diffusion phase is step speed control. In a matrix system, the drug is dispersed as solid particles within a porous matrix formed by a water-insoluble polymer, such as polyvinyl chloride. Initially, the particles of the drug located on the surface of the release will dissolve and quickly release the drug.

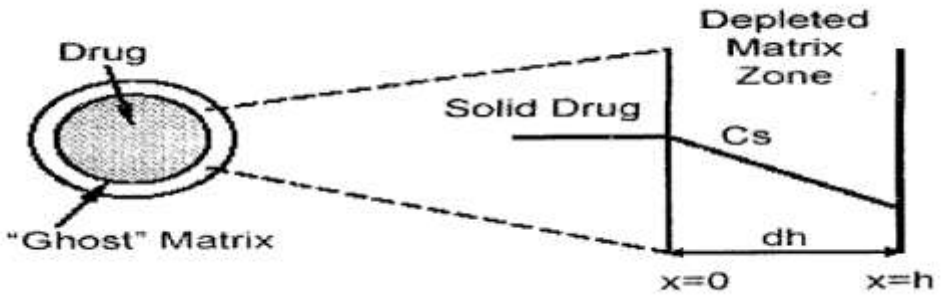

Fig. 1.7: Schematic representation of a matrix release system

If the release of drug from matrix is diffusion controlled, the amount of drug released versus the square root time will be linear.

$$M = k. t^{1/2}$$

If this is the case, one may control the release of drug from a homogeneous matrix system by varying the following parameters.

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer systems forming the matrix
- Solubility of drug

b) Dissolution Controlled systems:

A drug with slow dissolution rate demonstrated supporting properties because the drug will be limited by the dissolution rate. In principle, it seems possible to prepare prolonged-release products by decreasing the rate of dissolution of drugs that are highly soluble in water. This can be done by
1) Preparation of an appropriate salt or derivative. 2) Insertion of the drug into a tablet with a support matrix dissolution slow dissolution control (a main disadvantage is that the speed of release of the drug continuously decreases with time).

c) Erosion-Controlled Systems:

In erosion controlled extended release system the rate of erosion of the drug release is controlled by erosion of a matrix in which the drug is dispersed. Erosion in its simplest form can be described as a continuous-release matrix material (drug and carrier) from the surface of the tablet, that is, surface erosion.
A drug delivery erosion system can therefore be described in two stages:
1) The matrix material in which the drug is dissolved or dispersed, is released from the surface of the tablet.
2) The drug is subsequently exposed to gastrointestinal fluids and mixed with (if the drug is dissolved in the Matrix) or dissolved in (if the drug is suspended in the matrix) the fluid. Eroded matrix can be formed from different substances. An example is lipids or waxes, in which the drug is dispersed. Another example is polymers such as gels in contact with water (for example, hydroxyethylcellulose). The gel subsequently erodes and release the dissolved or dispersed drug into the gel. The spread of the drug in the gel can occur in parallel.

CONCLUSION:

The conventional drug delivery systems have been progressively replaced in recent years by various systems of administration of modified release drugs on the basis of high technology. A target tissue is known to be a complex process involving multiple steps in penetration and diffusion and partition. The modified drug delivery system addresses release of the initial step of this complex process, but the path to the transport of drug molecules from the delivery system to the tissue remains substantially uncontrolled. The ultimate goal is to achieve optimal treatment with maximum safety. This can be reasonably achieved by developing models is constructed from a biodegradable immunogenic backbone of the exact functional group bonded polymer. This drug-only management system is in concept phase. Its entire construction is a challenging task for the pharmaceutical and science industry.

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