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"Review On: Sustained Release Oral Drug Delivery System"

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ABSTRACT:

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered by oral conventional method in the form of tablets & capsules. Usually conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems. Sustained release drug delivery system works on many different mechanisms to control the release rate of drugs. Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches. The present article contains brief review on various formulation approaches for Sustained release drug delivery system.

Keywords: Matrix type system, oral drug delivery system, reservoir system, sustained release drug delivery system.

I. INTRODUCTION

The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and/or targeting the drug. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. Matrix system is the release system which prolongs and controls the release of the drug, which 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. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipient by matrix based formulation to desired site. It mainly by the type and proportion of polymer used in the reparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. excludes complex production procedures such as coating and pillarization during manufacturing and drug release rate from the dosage form is controlled. (1, 2)

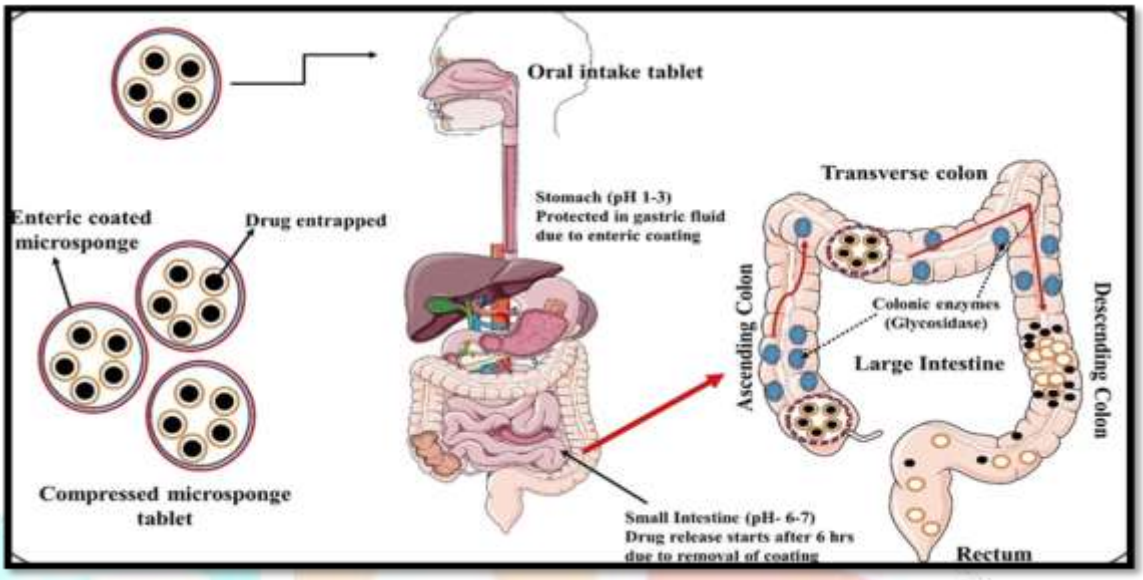

Fig No.1: Oral Drug Delivery System

Oral drug delivery method is the most widely utilized routes for administration among all alternatives that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form as term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose . In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapy.(3)

II. Rational for development of SRDDS:

1. Formulations of SRDDS minimize dosing frequency and sustained release provides availability of a drug at action site throughout the treatment to improve clinical efficiency of a drug molecule.

2. To reduce cost of treatment by reducing number of dosage requirement.

3. To minimize toxicity due to overdose which is often conventional dosage form.

4. To enhance the activity duration of a drug possessing short half-life (4)

III. ADVANTAGES:

1. Reduced side effects and toxicity

Avoids high plasma concentrations that can occur immediately after dosing with conventional formulations. Lower risk of dose-related adverse effects.

2. Enhanced therapeutic efficacy

Continuous and optimal drug exposure improves disease control. Better clinical outcomes, especially for drugs with narrow therapeutic indices.

3. Improved patient compliance

Reduced frequency of drug administration (e.g., once or twice daily instead of multiple doses). Easier for patients to follow the dosing regimen, especially for chronic conditions.

4. Consistent drug plasma levels

Maintains steady therapeutic drug concentrations over an extended period. Minimizes peaks (which can cause side effects) and troughs (which can lead to loss of efficacy) in drug levels.

5. Reduced dosing frequency.

6. Dose reduction.

7. Improved patient compliance.

8. Constant level of drug concentration in blood plasma.

9. Reduced toxicity due to overdose.

10. Reduces the fluctuation of peak valley concentration.

11. Night time dosing can be avoided (5)

IV. DISADVANTAGES

1. High Cost of Formulation:

Manufacturing sustained release systems is more complex and expensive than conventional tablets or capsules.

2. Dose Dumping Risk:

Any defect in the dosage form (e.g., coating failure) can lead to rapid release of the entire dose, potentially causing toxicity.

3. Reduced Flexibility in Dose Adjustment:

Once formulated, the dose can't be easily adjusted or divided for patients requiring individualized dosing.

4. Delayed Onset of Action:

Because the drug is released slowly, it may take longer to reach therapeutic levels, making it unsuitable for acute conditions.

5. Dependence on Gastrointestinal Transit Time:

Variability in GI motility and pH among patients can affect the release rate and absorption of the drug.

6. Not Suitable for All Drugs:

Drugs with short biological half-lives, poor absorption windows, or requiring large doses may not be suitable for sustained release formulations.

7. Difficulty in Removal After Administration:

Once administered, the drug release cannot be stopped, which can be a problem in case of adverse reactions or overdosing.

8. Development costs:

Expensive specialized equipment and inert ingredients may be required for some controlled release formulations.

9. Release rate:

The drug release rate can be altered by food and gastric transit time; as a result differences may arise in the release rate between doses.

10. Cannot crush or chew products: (6)

Controlled release products should not be crushed

V. IDEAL PROPERTIES OF SRDDS

1. It must be properly absorbed through the oral route and stable in GI fluid.

2. Medicines with short half-lives (2-4 hrs.) make excellent candidates for formulation into SR dosage forms, such as captopril and salbutamol sulphate.

3. The drug dose should not be less than 0.5 gm., and the maximum dose for SRDDS design is1.0 gm., for example, metronidazole

4. The drug's therapeutic range must be sufficiently broad in SRDDS to ensure that variations in release do not cause concentrations to rise above the minimal hazardous values.

5. Absorption throughout the GI tract- Drugs absorbed only in a specific region (narrow absorption window) may not suit SR easily.

6. High therapeutic index: Safer drugs are better suited because SR systems cannot be rapidly discontinued once ingested (7)

VI. Classification of sustained release oral drug delivery system

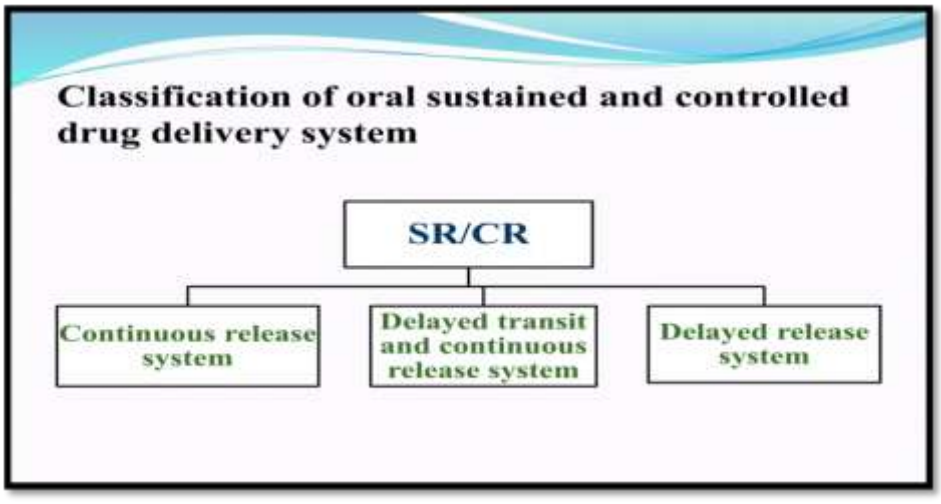

Fig No.2: Classification of Sustained Release Oral Drug Delivery System

Continuous Release System:

Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form.

1. Dissolution Controlled Release Systems:

The drug present in such system may be the one:

a. Having high aqueous solubility and dissolution rate.

b. With inherently slow dissolution rate e.g. Griseofulvin and Digoxin

c. That produces slow dissolving forms, when it comes in contact with GI fluids. Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer.

The rate of dissolution (dm/dt) can be approximated by following equation:

dm/dt = ADS/h ...(1)

Where,

A = Surface area of the dissolving particle or tablet

D = Diffusivity of the drug

S = Aqueous solubility of the drug

h = Thickness of the boundary layer

The two types of dissolution-controlled release are:

A. Matrix (or monolith) dissolution controlled systems

B. Reservoir dissolution controlled systems

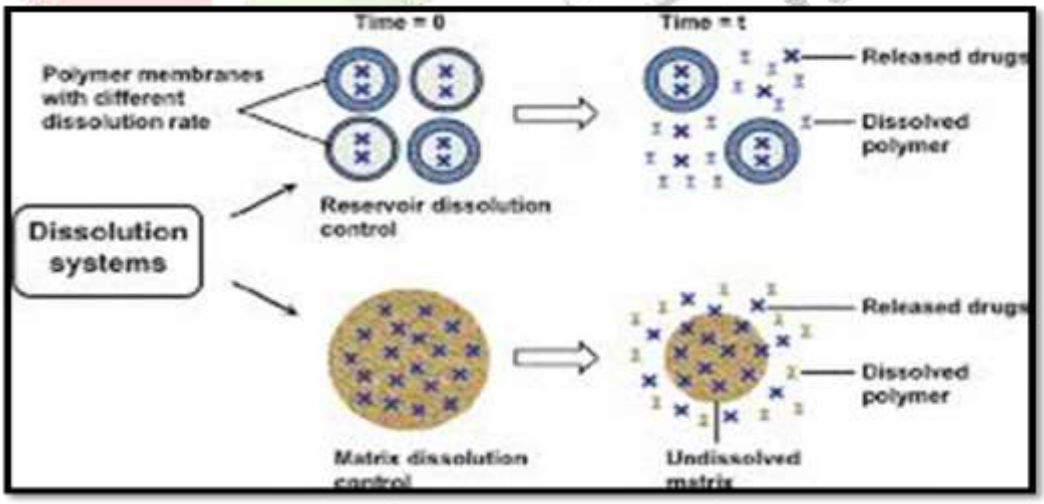

Fig No.3: Dissolution Controlled Release System

2. Diffusion Controlled Release Systems:

In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion

controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using the following equation:

dm/dt = ADK ΔC/L ...(2)

Where,

A = Area

D = Diffusion coefficient

K = Partition coefficient of the drug between the drug core and the membrane

L = Diffusion path length and

ΔC = Concentration difference across the membrane

In order to achieve a constant release rate, all of the terms on the right side of equation must be held constant. It is very common for diffusion controlled devices to exhibit a non-zero order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds. Another configuration of diffusion-controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water insoluble or a hydrophilic polymer. The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution (8, 9)

The two types of diffusion-controlled release are:

A. Matrix diffusion controlled systems

B. Reservoir devices

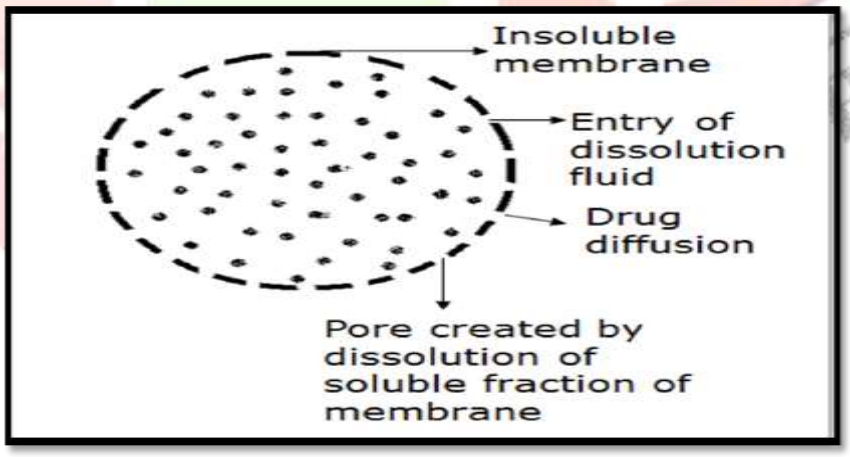

Fig No. 4: Diffusion controlled released system

3. Dissolution and Diffusion Controlled Release Systems:

In such systems, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system [10]

4. Ion Exchange Resin-Drug Complexes:

It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in gastrointestinal tract and released with excess of Na+ and Cl present in gastrointestinal tract. This system generally utilize resin compound of insoluble cross linked polymer. They contain salt forming function group in repeating position on a polymer chain (10)

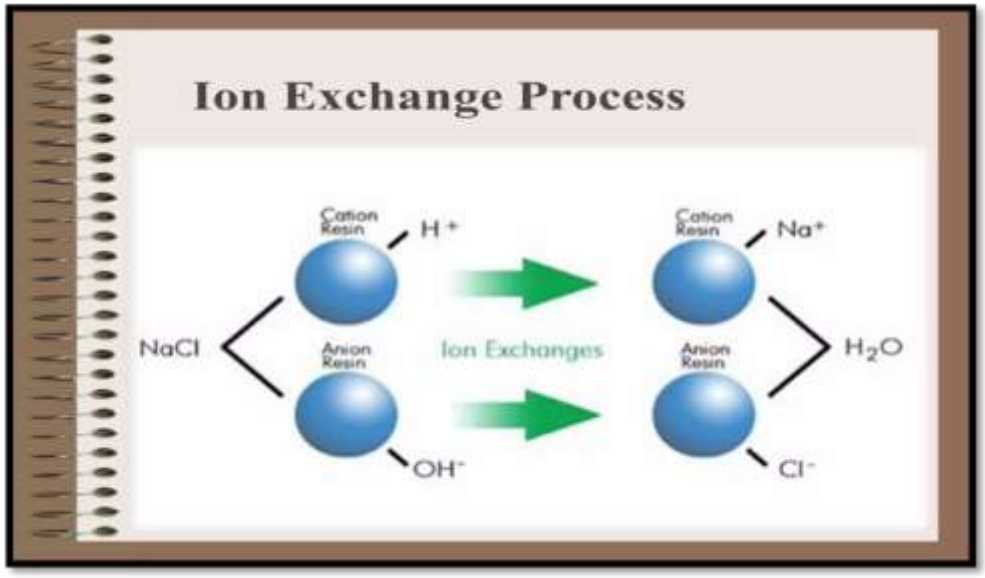

Fig No.5: Ion Exchange Resin Drug Complex

5. pH-Independent Formulation:

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However, buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation, to help to maintain to constant pH their by retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent, granulating with appropriate excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agent adjusts the fluid inside to suitable constant pH there by rendering a constant rate of drug release. (11, 12)

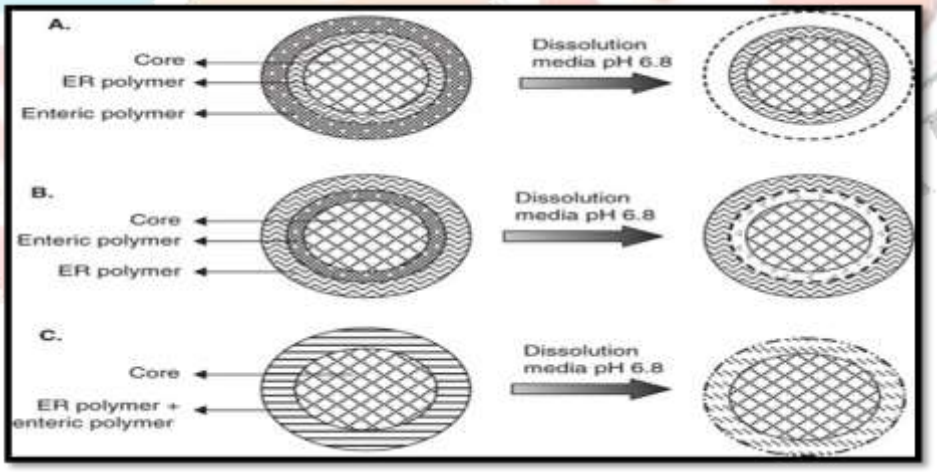

Fig No.6: pH Independent Formulation

6. Osmotic Pressure Controlled Systems:

A semi permeable membrane is placed around the tablet, particle or drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery aperture in tablet core. (13, 14)

Single chamber osmotic pump

• Elementary osmotic pump (EOP)

Multi chamber osmotic pump

• Push pull osmotic pump.

• Osmotic pump with non-expanding second chamber

Specific types

• Controlled porosity osmotic pump.

• Monolithic osmotic systems.

• Osmotic bursting osmotic pump.

• OROS – CT

• Multi particulate delayed release systems (MPDRS)

• Liquid Oral Osmotic System (L-OROS)

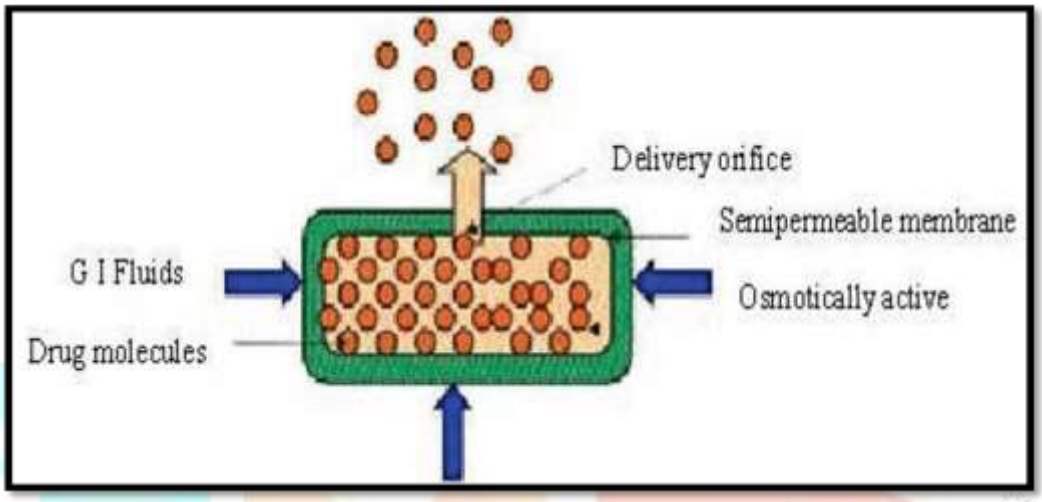

Fig No.7: Osmotic Pressure Controlled System

VII. Factors influencing oral sustained release dosage form:

Mainly two factors involved in oral sustained release dosage form design:

A. Physicochemical factor

B. Biological factor

1. Physicochemical factors:

1. Aqueous Solubility:

Most of the drugs are weak acids or weak bases Drugs with low water solubility will be difficult to incorporate into sustained release mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or gastrointestinal fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate a highly water soluble drug in the dosage form and retard the drug release especially when the dose is high. The pH dependent solubility particularly in the physiological pH range would be another problem for Sustained release formulation because of the variation in the pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral absorption. Class III (High solubility- Low permeability) & Class IV (Low solubility- Low permeability) drugs are poor candidates for Sustained release dosage form compound with solubility < 0.1 mg/ml face significant solubilisation obstacles and often compounds with solubility 10 mg/ml present difficulties to solubilisation dosing formulation. In general, highly soluble drugs are undesirable for formulation in to a Sustained release product (15, 16)

2. Partition coefficient (P (o/w)):

Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that passes though biological membrane, if partition coefficient of drug influences shows very much bioavailability because lipophilic nature of biological membrane. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have higher partition coefficient are also not suitable for oral SR drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane

3. Drug pKa and ionization at physiological PH:

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of the unionized drug. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0- 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0%

4. Drug stability:

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. If the drug in the solid state the degradation will occur in reduced rate, for the drugs that are unstable in stomach that prolong delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. This occurs due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation

a. Molecular size and diffusivity:

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion coefficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10-6-10-9 cm2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

B. Biological factor:

The absorption behavior of a drug can affect its suitability as an extended release product. The aim of formulating Sustained release product is to place a control on the delivery system. It is essential that the rate of release is much slower than the rate of absorption. If we assume the transit time of dosage forms in the absorptive areas of GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours. Otherwise the dosage form will pass out of absorptive regions before drug release is complete. Therefore, the compounds with lower absorption rate constants are poor candidates. Some possible reasons for low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis and metabolism or its site of absorption. The distribution of drugs in tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. 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. For design of sustained release products, formulation scientist must have information on disposition of the drug. **(17)** A drug which extensively metabolizes is not suitable for SR drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is poor candidate for SR delivery, as it could be difficult to maintain constant blood level. Drugs that are metabolized before absorption, either in lumen or the tissues of the intestine, can show decreased bioavailability from the Sustained releasing systems. Most intestinal walls are saturated with enzymes. As drug is released at a slow rate to these regions, lesser drug is available in the enzyme system. Hence, the systems should be devised so that the drug remains in that environment to allow more complete conversion of the drug to its metabolite.

1. Half-life:

The half-life of a drug is an index of its residence time in the body. If the drug has short half life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of 8 hours or more are sufficiently controlled in the body, when administered in conventional dosage from and Sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of 3-4 hours for formulation of drug delivery system

2. Therapeutic index:

Drugs with low therapeutic index are unsuitable for incorporation in Sustained release formulations. If the system fails in the body, dose dumping may occur, which leads to toxicity.

3. Size of dose:

If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for SRDDS. This is because the size of a unit dose Sustained release oral formulation would become too big to administer without difficulty

4. Absorption window:

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the ξ absorption window ξ. These candidates are also not suitable for SRDDS

5. Plasma concentration response relationship:

Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral SR drug delivery system

6. Concentration dependency on transfer of drug:

Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidate for oral SR delivery system. It should be of first order kinetics represents various formulation strategies for oral Sustained release drug delivery system.

VII . METHODS FOR PREPARATION:

1. Direct Compression:

Powdered materials are directly compressed without affecting their physical or chemical characteristics, such as those of a medication

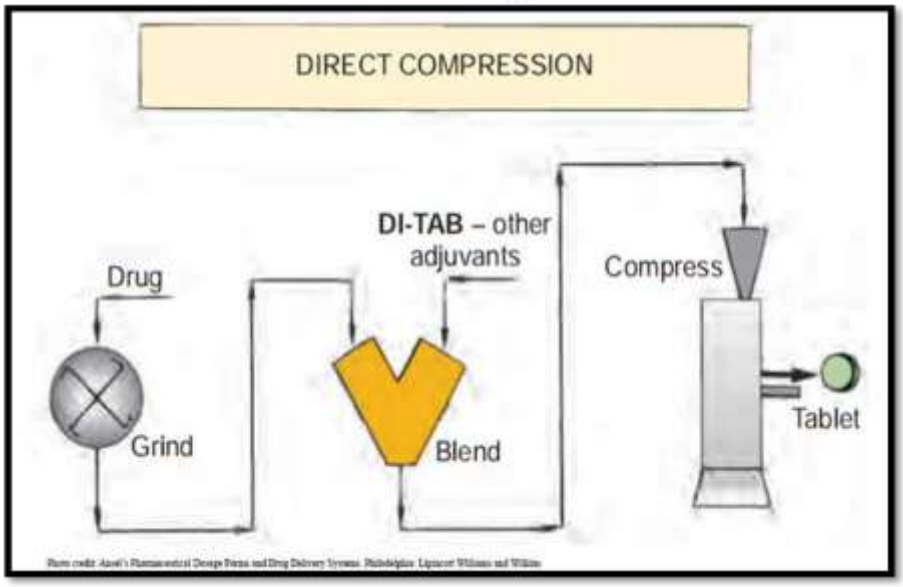

Fig No 8: Direct Compression

2. Wet Granulation:

An adequate amount of granulating agent is combined with weighed amounts of the medication and polymer in the wet granulation process. Screening of wet mass comes when sufficient cohesion has been created. After being dried and screened for dry granules, the granules are blended with lubricant. Using a single-punch tablet compression machine, the powder is compressed.

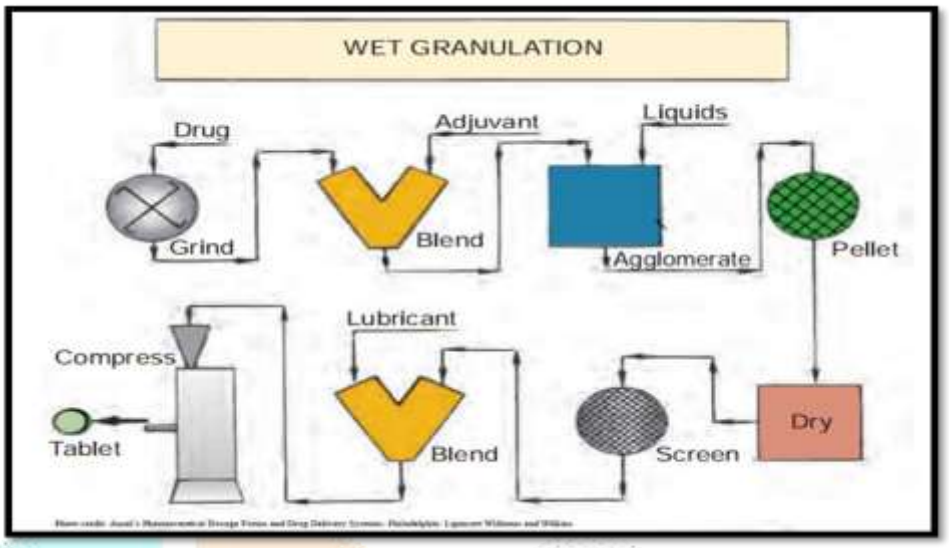

Fig No 9: Wet Granulations

3. Melt Granulation:

A substance melts during this process at a relatively low temperature. This chemical can be added to a substrate that has been heated past its melting point in molten form. Utilizing the melt granulation process, various lipophilic binders were tested.

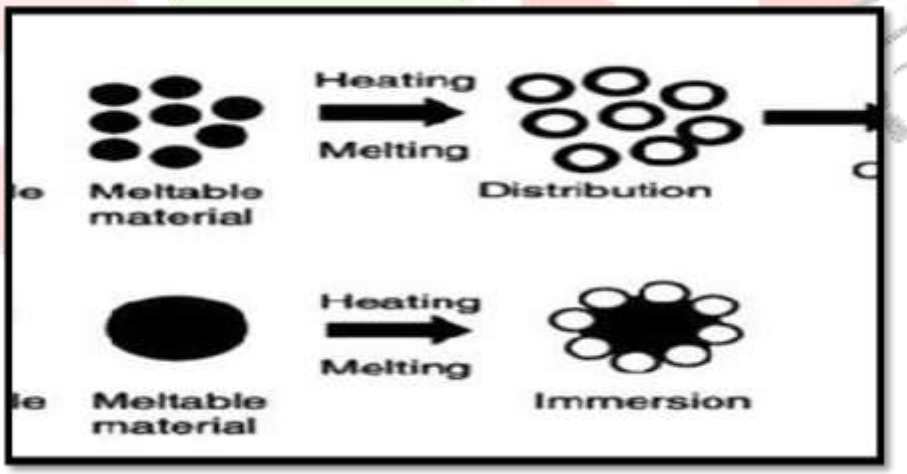

Fig No 10: Melt Granulation

4. Hot-Melt Extrusion Process:

The thermoplastic polymers are mixed with the active ingredients and fed into the barrel of the extruder through the hopper during the hot-melt extrusion process. A spinning screw moves the materials into the heated barrel. The materials melt at a high temperature, and the bulk of molten material is continually fed through the barrel's associated die.

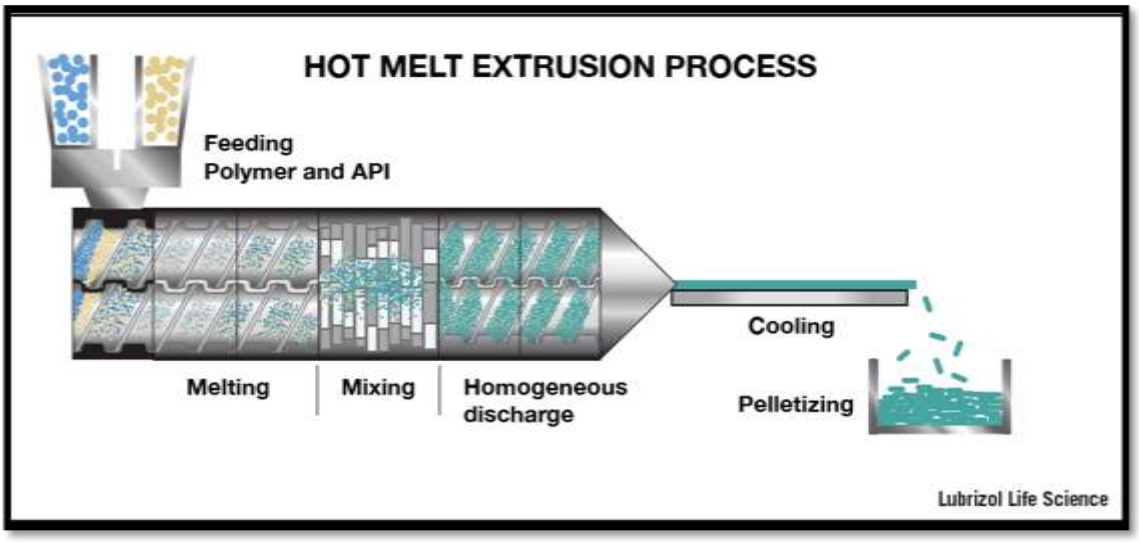

Fig No.11: Hot Melt Extrusion Process

IX . EVALUATION OF ORAL SUSTAINED RELEASE TABLETS:

1. Tablet thickness:

A micrometer screw gauge is used to measure tablet thickness. Twenty tablets are tested at random, and the average results are computed.

2. Tablet hardness:

The Monsanto hardness tester measures the tablet hardness of each batch, and average values are computed.

3. Weight uniformity:

20 tablets are chosen at random, weighed separately and collectively, and an average weight is computed.

% of weight variation= (Individual Weight- Average weight/Average Weight) × 100

4. Uniformity of content:

In order to ensure that every tablet contains the same amount of the active component with little to no fluctuation within a batch, this test is performed for uniformity of content. 30 tablets are chosen for the content uniformity test, and 10 of them are individually tested. At least nine must assay between 15% and not more than 25% of the specified potency.

5. Friability:

20 pills are weighed and put in the friability machine. The tablets are withdrawn from the chamber and weighed once more after it has been rotating for 4 minutes at a speed of 25 rpm. Weight loss is a sign of friability. When there is a weight loss of less than 0.8%, the tablets are deemed to be of high quality.

6. In vitro dissolution studies:

Studies on in vitro dissolution are performed to determine how long it takes for a specific amount of medication to dissolve in a solution under particular test circumstances. As stated in the monograph for a certain medicine or in accordance with pharmacopoeia standards, rotating paddle type and rotating basket type apparatus can be employed.

X . CONCLUSION:

The Sustained release drug delivery system is very helpful in increasing the efficiency of the dose, safety of dose as well as the patient compliance. Nowadays, the oral route of administration for Sustained release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance. The design of oral Sustained release drug delivery system depends on various factors like, physicchemical properties of drug, type of delivery system, disease being treated, patient condition, treatment

duration, presence of food, gastrointestinal motility and coadministration of other drugs. From the above discussion, we can concluded that Moreover; the reasonable cost of oral Sustained release drug delivery system has lead ease of market penetration as replacement of oral conventional drug delivery system.

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