THE PHARMA RESEARCH

A Journal of Pharmacy Research

Original Article

ISSN- 0975-8216

Impact- 0.529 Refer website

SUSTAINED RELEASE DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT

Among all drug delivery system, oral drug delivery is the most preferred route for administration of various drugs. Sustained release products provide advantage over conventional dosage form by optimizing biopharmaceutics, pharmacokinetics and pharmacokinetics properties of drug. Thus sustained release formulation provides important way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. Availability of wide variety of polymer and frequent dosing interval helps the scientist to develop sustained release product. These dosage forms are available in extended release, targeted release, delayed release, prolonged action dosage form. Some factors like molecular size, diffusivity, pKa-ionization constant, release rate, dose and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of sustained release formulation. These formulations are evaluated for weight variation, friability, hardness, thickness, in vitro release rate etc. The future of sustained release products is promising in some area like chrono-pharmacokinetic system, targeted drug delivery system, mucoadhesive system, particulate system that provide high promise and acceptability. This article contains various types, evaluation and factors affecting the design of sustained release formulation.

Key Words: Sustained Release System, Controlled Release System, Matrix Tablet

INTRODUCTION

Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism and excretion, eventually to becoming available for pharmacological action. Modified release dosage forms include both delayed and extended release drug products. Extended release products are formulated to make the drug available over an extended period of

time after administration. Finally this includes sustained release, prolonged release, delayed release, targeted release, and pulsatile release product *[1]*.

Sustained release formulation maintains a uniform blood level of drug with better patient compliance as well as increased efficacy of drug. Release rate from sustained release dosage form is controlled mainly by type and proportion of various natural and synthetic polymer used in the formulation. Hydrophilic polymer matrix is widely used for formulating sustained release dosage form *[2]*. There are certain considerations for the formation of sustained release formulation

- If active compound has long half life (over 6 hour) it is sustained its own.
- If the absorption of the active compound involves an active transport the development of time release product may be problematic.
- If the pharmacological activity of active compound is not related to its blood level, time releasing has on purpose.
- Finally if the active compound has short half life it would require a large amount to maintain a prolonged effective dose. In this case a broad therapeutic window is necessary to avoid toxicity *[3]*.

ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY SYSTEM *[4]*:-

1. Improved patient convenience and compliance due to less frequent drug administration.
2. Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local and systemic side effect.
3. Increased safety margin of high potency drug due to better control of plasma levels.
4. Maximum utilization of drug enabling reduction in total amount of dose administered.
5. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY SYSTEM *[4]*:-

1. Decreased systemic availability in comparison to immediate release, conventional dosage form; this may be due to incomplete release, increased first pass metabolism, increased instability, insufficient residence time for complete release site specific absorption.
2. Poor in vitro-in vivo correlation.
3. Possibility of dose dumping due to food or formulation variable or chewing of oral formulation by patient and thus, increased risk of toxicity.
4. Retrieval of drug is difficult in case of toxicity.
5. Higher cost of formulation.

6. Reduced potential for dosage adjustment of drugs normally administered in varying strength.

Different Drug delivery systems according to their mechanism of drug release:-

Modified release – Drug release only occurs some time after the administration or for a prolonged period of time or to a specific target in the body. Modified release systems can be further classified as:-

1. **EXTENDED RELEASE DOSAGE FORM *[5]*:-**

To be a successful extended release product the drug must be released from the dosage form at a predetermined rate, dissolve in git fluid, maintain git residence time. The drug having following characteristic for incorporation in to extended release product. These dosage form are further classified as

i. They show neither very slow nor very fast rate of absorption and excretion.
ii. They are uniformly absorbed from gastrointestinal tract.
iii. They are administered in small doses.
iv. They pass a good margin of safety. The most widely used measure of the margin of a drug safety in its therapeutic index that is the median toxic dose divided by median effective dose, larger the therapeutic index the safer the drug.
v. They are used in treatment of chronic rather than acute condition.

2. **TARGETED RELEASE DOSAGE FORM *[6]*:-**

The objective of targeted release dosage form is to achieve a desired pharmacological response at selected Site. This is important in cancer chemotherapy and enzyme replacement. Treatment at present drug targeting is achieved by two approaches

i. First approach involves chemical modification of parent compound to a derivative which is activated only at target site.
ii. The second approach utilize carrier such as liposome's, microsphere, Nanoparticle, cellular carrier and macromolecules to direct the drug to its Site

3. **DELAYED RELEASE DOSAGE FORM *[7]*:-**A dosage form release a discrete portion of drug at a time or times other than promptly after administration although on Portion may be released promptly after administration e.g. enteric coated dosage form

4. **PROLONGED ACTION DOSAGE FORM *[8]*:-**It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period of time.

5. **SUSTAINED RELEASE DOSAGE FORM:-**

In these dosage form drug releases at slow first order rate but not necessary at predetermined rate.

In **controlled release** dosage form drug releases at predetermined rate i.e. zero order rate.

In **sustained release** dosage form drug releases at slow first order rate but not necessary at predetermined rate.

In **conventional release** dosage form that Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug. In this system rate of drug absorption in body is not controlled by absorption process.

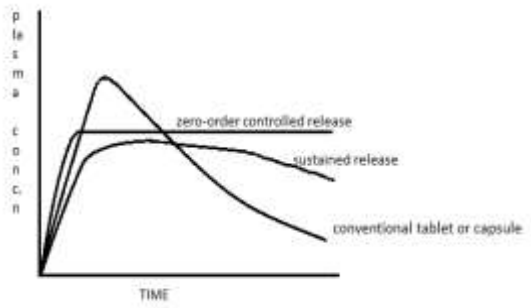


Fig 1. Plasma drug concentration Vs Time profile for conventional tablet or capsule, a sustained release formulation, and a zero-order controlled release formulation.

CLASSIFICATION OF SUSTAINED RELEASE SYSTEM *[9]*:-

Oral controlled delivery system can be classified in to the following category based on their mechanism of drug release.

1) DISSOLUTION CONTROLLED RELEASE
   i. Encapsulation dissolution control.
   ii. Matrix dissolution control.
2) DIFFUSION CONTROLLED RELEASE
   i. Reservoir devices
   ii. Matrix devices
3) ION EXCHANGE RESINS
4) OSMOTIC CONTROLLED RELEASE
5) GASTRORETENTIVE SYSTEM

1) DISSOLUTION CONTROLLED RELEASE:- Dissolution controlled release can be obtained by slowing the dissolution rate of a drug in the GIT medium, incorporating the drug in an insoluble polymer, and coating drug particle with polymeric material of varying thickness.

The rate of dissolution (dm/dt) can be shown by

Dm/dt =ADS/h

Where S is aqueous solubility of drug.

A is surface area of tablet.

D is diffusivity of drug.

H is thickness of boundary layer.

Example of drug with limited dissolution rate includes digoxin, griseofulvin, nifedipine, salicylamide.

i. Encapsulation dissolution control:-Rate of dissolution achieved by encapsulation of drug polymer matrix with relatively insoluble polymeric membrane, the coated beads can be compressed in to tablet and granules with varying thickness can be employed to achieve sustained release of drug.

Example of drug delivered in this manner is antispasmodic-sedative, combination, phenothiazine, anticholinestrase *[9]*.

ii. Matrix dissolution control:-It involves the incorporation of drug in a hydrophobic matrix.

Such as wax, polyethylene, polypropylene, ethyl cellulose or hydrophilic matrix such as Hydroxypropylcellulose, hydroxypropylmethylcellulose. The rate of drug availability is controlled by rate of penetration of dissolution fluid in to the matrix *[9]*.

2) DIFFUSION CONTROL RELEASE SYSTEM*[4]*:-It involve the diffusion of dissolved drug through polymeric barrier .the drug release rate is never zero order since the diffusional path length increases with time as the insoluble matrix gradually depleted of drug. The two type of diffusion controlled system

a. Matrix system
b. Reservoir system

a) Matrix system:-In this drug is dispersed in a matrix of rigid non swellable hydrophobic material or swellable hydrophilic material. Materials used for RIGID MATRIX are insoluble plastic such as polyvinylchloride and fatty material like stearic acid, bee wax etc. Swellable matrix:- System is popular for sustaining the release of highly water soluble drugs. The materials for such matrix are hydrophilic gum and may be of natural origin (guar gum, tragacanth). Semi synthetic (HPMC, CMC).The drug and the gum are granulated together with a solvent such as alcohol and compressed in to a tablet.

b) Reservoir system:-The systems are hollow containing an inner core of drug surrounded in a water insoluble polymer membrane. The polymer is applied by coating and microencapsulation techniques. The drug release across the membrane involve its partitioning in to membrane with release in to surrounding fluid by diffusion .the polymer commonly used in such devices are Hydroxypropylcellulose, ethyl cellulose and polyvinyl acetate.

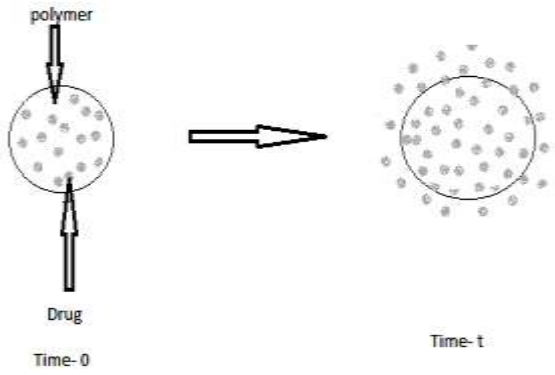


Fig 2. Representation of diffusion sustained drug release: Matrix system

3) ION EXCHANGE RESIN SYSTEM *[10]*:-Ion exchange resin complex which potentially can be prepared from both acidic and basic drugs have been more widely studied. Salts of cationic or anionic exchange resin are insoluble complexes in which drug release result from exchange of ''bound'' drug ions by ions present in GIT. Ion active

sites are distributed through the resin structure. Variable relating to the resin are degree of cross linking, which determine the permeability of the resin, its swelling potential, and the excess of the exchange sites to the drug ion. The effective Pka of the exchanging group, which determine the exchange affinity; and the resin particle size, which control accessibility to exchange ions.

The following equations represent the preparation and exchange reaction affecting drug release in vivo.

RESIN---So3Na + DRUG—HCL= NaCL + RESIN---So3.H—DRUG

RESIN---So3—DRUG—H + NaCL = DRUG-HCL + RESIN—So3Na

4) OSMOTIC CONTROLLED RELEASE SYSTEM *[11]*:-Osmotic system release a therapeutic agent at a predetermined, typically zero order, delivery rate is based on the principle of osmosis. Osmosis is the natural movement of solvent through a semi permeable membrane in to a solution of higher solute concentration to lower concentration, leading to equal concentration of solute on both sides of membrane. Osmosis system imbibes water from the body through a semi permeable membrane in to osmotic material, which swells, resulting in slow delivery of drug formulation.

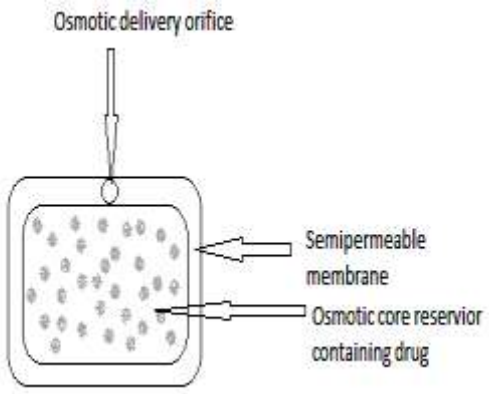
The osmotic pressure is the driving force for fluid transport through the semipermeable membrane. The greater the gradient in osmotic pressure, greater will be the rate of transport of solvent through membrane. The rate of water flow through the membrane can be written as

$$dv/dt = (A/h)\, Lp\, (\partial\Delta\pi - \Delta p)$$

dv/dt is volume flow of solvent through membrane.

A cross section area for transport, h membrane thickness, Lp hydraulic permeability of membrane, ∂ Refeclection coefficient, Δπ osmotic pressure difference across membrane, Δp is the hydrostatic pressure difference across the membrane.

Fig 3. Osmotic pump showing in the figure below:-



5) GARTRORETENTIV DRUG DELIVERY SYSTEM *[12]*:-the control Release drug delivery system possessing the ability of being retained in the Stomach are called gastro retentive drug delivery system and they

can help in optimising the oral controlled delivery of drug having absorption window by continuously releasing the drug prior to absorption window for prolonged period of time.

GASTRORETENTIVE TECHNOLOGIES ***[9]***:-A number of techniques have been used to increase the gastric residence time of dosage forms. These systems have been classified according to their basic principle of gastric retention.

1) Low density system providing sufficient buoyancy to float over the gastric content;(floating drug delivery system) FDDS can be classified in to two distinct categories

a) Non effervescent system:- It have following types.

- ❖ Colloidal gel barrier system.
- ❖ Microporous compartment system.
- ❖ Alginate beads.
- ❖ Hollow microsphere.

b) Effervescent system:-It has following types.

- ❖ Volatile liquid containing system.
- ❖ Gas generating system.

2) Mucoadhesive system.

3) Swelling system.

4) High density system.

FACTOR GOVERNING THE DESIGN OF SUSTAINED RELEASE DOSAGE FORM:-

1) MOLECULAR SIZE AND DIFFUSIVITY**:-** A drug must diffuse through a variety of biological membrane during its time course in the body. In addition to diffusion through these biological membranes, drugs in many extended release system must diffuse through a polymeric membrane or matrix *[*3*]*.

The ability of drug to diffuse in polymer, it's so called diffusivity (diffusion coefficient D) is a function of its molecular size (molecular weight). For most polymers, it is possible to release log D empirically to some function of molecular size *[*12*]*.

Log D = - SV log u + Kv = -Sm log M + km

Where v is molecular volume

M is molecular weight

Sv, Sm, Kv, Km = constant

The value of D thus is related to the size and shape of cavities as well as size and shape of drug. Generally value of the diffusion coefficient for drug of Intermediate molecular weight (i.e. 150 to 400 Da) through flexible polymer range from 10-6 to 10-9 cm2/sec. With value in the order of 10-8 being most common *[*13*]*.

The high molecular weight drugs should be expected to display very slow release kinetics in extended release device using diffusion through polymeric membrane or metrics as the releasing mechanism *[*14*]*.

2) pKa – IONISATION CONSTANT *[*15*]*:-The pKa is a measure of the strength of acid or an base. The pKa allow determining the

charge on drug molecule at any given pH. Drug molecule is active in only the undissociated state and also in unionised state. An unionised molecule crosses these lipodial membranes much more rapidly than ionised species. The amount of drug that exists in unionised form is a function of dissociation constant of a drug and Ph of fluid at absorption site. For a drug to be absorbed, it must be in unionised form at the absorption site. Drugs which exist in ionised form at absorption site are poor candidate for sustained release/controlled release dosage form.

3) RELEASE RATE AND DOSE *[16]*:- Conventional dosage form includes solution, capsule, suspension, tablet, emulsion, aerosols, ointments, these dosage form release active ingredient in to an absorption pool immediately.

   The absorption pool represents a solution of drug at the site of absorption and the Terms Kr, Ka, and Ke are the first order rate constant for drug release, absorption and overall elimination.

   For non immediate release dosage form, Kr<<<Kw that is, release of drug from Dosage form is the rate-limiting step.

   The absorptive phase becomes insignificant compared with drug release phase. Thus, the effort to develop a non immediate release delivery system must be directed to Changing the release rate by affecting the value of Kr. An example of this is antibiotic therapy, where the activity of the drug is required only during the growth phase of the Microorganism.

   The size of dosage unit becomes even more critical with highly water-soluble drugs since Even a larger amount of inactive ingredients (for example – more than 50% of the total Weight) is usually needed to provide the sustained release property, according to the Conventional SR methods *[17]*.

4) STABILITY*[18,19]*.:- One other factor for the loss of drug is through acid hydrolysis or metabolism in GIT when administered orally. It is possible to significantly improve the relative bioavailability of a drug that is unstable in GIT by placing it in a slowly controlled release form. Drugs with significant stability problems in any particular area of the G.I tract are less suitable for formulation in to controlled release system that deliver the content uniformly over the length of GIT

   Alkaline unstable drugs (in intestine and colon):- Captopril, Ranitidine.

   Acid unstable drugs (stomach):- Riboflavin, Pantaprazole, mesalazine, lansoprazole, erythromycin, rifampicin, rabeprazole, omeprazole, esomeprazole.

BIOLOGICAL FACTORS:-

1 DURATION OF ACTION *[20]*:- Duration of action is the time period for which the blood Level remains above MEC and below

MSC levels are more specifically with in therapeutic window. Drug acting for long duration are unsuitable candidate for formulation in to SR/CR forms. Receptor occupation, tissue binding, half life, metabolism, partition coefficient, irreversible binding to cells are some parameter which are responsible for long duration of action of drugs.

2 ABSORPTION WINDOW *[*22, 23*]*:- Some drugs show region specific absorption which is Related to differential drug solubility and stability in different regions of G.I.T, as a result of changes in environmental pH, degradation by enzyme, etc. These drug represent absorption window, which signifies the region of G.I tract where absorption primarily occur. Drugs released from sustained/controlled release system, after absorption window goes waste with little absorption. Hense absorption window play major role in the development of sustained/controlled release drugs

3 THERAPEUTIC INDEX *[*24*]*:- It is most widely used to measure the margin of safety of a drug.

TI =TD50 / ED50

Drugs with very small value of Therapeutic index are poor candidates for formulation in to sustained release products. A drug is consider to be safe if its T.I value is greater than 10, that is longer the value of TI, the safer the drug.

4 METABOLISM *[*25*]*:- Drugs that are significantly metabolised before absorption, either in the lumen or tissue of intestine, can show decreased bioavailability. Most intestinal

Wall enzyme system is saturable. As the drug is released at a slower rate to these regions, less total drug is presented to enzymatic process during a specific period allowing more complete conversion of a drug to its metabolite. Formulation of these enzymetically susceptible compounds as prodrug in another viable solution.

5 PROTEIN BINDING *[*21, 26*]*:- There are some drugs which having tendency to bind with Plasma protein (e.g. albumin) causes retention of drug in vascular space. The main force of attraction responsible for binding is Vander wall forces, hydrogen bonding, and electrostatic forces. In general charged compound have a greater tendency to bind a protein than uncharged compound, because of electrostatic effect

6 ABSORPTION *[*27*]*:-The rate, extent and uniformity of a drug are important factors when Considering formulation in to a controlled-release system. Since the rate limiting step in drug delivery from a

controlled release system is its release from a dosage form, rather than absorption of drug relative to its release is essential if the system is to be successful.

Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of gastrointestinal tract (absorption window) are poor candidate for sustained release *[28]*

TABLE SHOW THE DRUG TO BE FORMULATED AS MATRIX TABLET WITH POLYMER AND METHOD USED FOR ITS PREPRATION *[29-48]*:-

DRUG	POLYMER	METHOD	RESULT
1 Diltiazem hydrochloride	Rosin (natural polymer)	Direct compression	Rosin prolong the release of water soluble drug diltiazem HCL
2 Indepamide	HPMC (Methocel K 15 M CR)	Wet granulation	Release rate was decreased with increasing polymer concentration
3 Losartan potassium	HPMC (15 CPS), Ethyl cellulose, Eudragit RSPO, Eudragit RLPO	Wet granulation	Formulation having these polymer produce sustained/delayed release tablet
4 Glimepiride	Povidone, aloe barbadensis miller.	Wet granulation	These polymer use as a release retardant in preparation of sustained release matrix tablets
5 Pregabalin	Microcrystalline cellulose (MCC 101), HPMC K-100, Poly vinyl pyrolidone	Direct compression	Study show that on decreasing the proportion of HPMC K-100 and increasing the quantity of MCC 101 and PVP K 30 the drug release rate is retarded.
6 6 Zidovudine	Eudragit RS 100, Eudragit RL 100, Ethyl cellulose	Direct compression	Study show that combination of these polymers at definite proportion produces better sustained release dosage form.
7 Diclofenac	Hibiscus rosasinensis mucilage.	Wet granulation	Study show that this mucilage appears to be use as a release retardant in formulation of SR matrix tablet.
8 Aceclofenac	Guar gum, tragacanth gum, PVP K 30	Wet granulation	Combinations of these polymers provide optimum sustained release dosage form.
9 Dextromethorphan	Compritol 1888	Dry granulation	Polymer Compritol 1888 retained drug release from matrix tablet
10 Atenolol	HPMC K4M, K 100M, Guar gum, xanthan gum	Direct compression	These polymers like HPMC K4M and natural polymer was essential to achieve in vitro buoyancy. But natural polymer show better sustained release property than synthetic polymer.
11 Lornoxicam	Prosophis-Juliflora gum.	Direct compression	This gum is use as a release retardant in manufacturer of sustained release matrix tablet.
12 Metchlopramide Hydrochloride	HPMC, Carboxy methyl cellulose, sodium starch glycolate.	Direct compression/ dry granulation, Pelletiazation.	Sustained release matrix tablets of Metchlopramide HCL were prepared using different ratio of HPMC and sodium carboxy methyl cellulose.

13 Lamivudine	Tamarind kernel powder, ethyl cellulose.	Direct compression	Tamarind seed powder is used as drug release retardant in combination with ethyl cellulose.
14 Theophylline	Guar gum.	Wet granulation	With increase in polymer ratio and hardness of tablet the drug release was prolonged.
15 Furosemide	Guar gum, pectin, xanthan gum.	Direct compression	The over sustained release performance of used gum was found to be in order Guar gum > xanthan gum > pectin.
16 Ondansetron	Microcrystalline cellulose, HPMC (K 4 M, K 100 M), Pregelatinized starch.	Wet granulation	Drug release from the matrix tablet was found to be decrease with increase in drug polymer ratio.
17 Didanosine	Guar gum, xanthum gum	Wet granulation	Matrix tablets by granulation using natural polymer like xanthum gum, guar gum, was developed.
18 Salbutamol Sulphate	Ethyl cellulose, Acrylcoat S-100	Wet granulation	Drug release is retarded from formulation containing ethyl cellulose and acryl coat S-100 (2:1) ratio was selected as the optimum formulation for sustained release tablets.
19 Lornoxicam	HPMC (K4M, K 15M, K100M), Microcrystalline cellulose	Direct compression	Study show that tablet made by using HPMC can be used as SR dosage form which retard the release rate of drug.
20 Flutamide	HPMC K 4M, Sodium carboxy methyl cellulose, Xanthan gum, Guar gum, Avicel, Eudragit RSPO.	Direct compression	Formulation containing HPMC, guar gum, and Eudragit RSPO Produce a more appropriate sustained release profile than other polymer

EVALUATION OF SUSTAINED RELEASE DOSAGE FORM:-

Evaluation of these dosage form done by two ways

- Evaluation of granules
- Evaluation of tablets

Evaluation of granules involve following test:-

1. Angle of repose *[49]*:- The angle of repose was determined using the funnel method. A funnel was secured on a stand at a fixed height h) above a graph paper placed on a horizontal surface. The sample was poured until the apex of the conical pile touched the tip of funnel.

The radius of the conical pile was measured and the angle of repose calculated as follow *[50]*.

$$\theta = \mathrm{Tan}^{-1}\,(h/r)$$

2. Bulk density *[51]*: - The bulk density was calculated using equation.

$$\rho\ b = MV$$

Where ρ b = Bulk density, M = Mass of the granules in gm, V = Final untapped volume of granules in ml.

3. True density:- The true density was measured using equation.

$$\rho\ t = M/V_P$$

Where ρ *t = true density,* M =Mass of granules in gm, V_P = Final tapped volume of granules in ml.

4. Loss on drying (LOD) *[52]*:- The moisture content of the lubricated granules was analysed by using IR moisture analyzer. 5.0 gm or more quantity of granules was heated at 105^0c until the change in weight was no more observed by the instrument. The % loss in weight was recorded.

5. Compressibility index *[53]*:- This was measured for the property of a powder to be compressed; as such they are measured for relative importance of inter-particulate interactions. Compressibility index was determined by following equation.

Compressibility index = ($D_t - D_b$) × 100

Where D_t = Tapped density, D_b = Bulk density

6. Hausner ratio *[54]*:- It was calculated by following equation.

Hausner ratio = D_t / D_o

Where Dt = Tapped density, D_o = Bulk density

Evaluation of SR tablets involve following test:-

1. Weight variation *[55]*.:- To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (citizen India) and test was performed according to official method.

2. Friability *[56]*:- In this twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25rpm for 4 min. After revolution the tablet were dusted and weight.

% friability = Wo - W/ W_o × 100

Where W_o = Initial weight of twenty tablet
W = weight of 20 tablet after 100 revolution.

3. Hardness *[57]*:- Tablet hardness was measured by using Monsanto hardness tester from each batch six tablets were measured for the hardness and a average of six values was noted along with standard deviation.

4. Thickness *[58]*:- Twenty tablets from the sample were randomly taken and individual tablet thickness was measured by using digital vernier calliper. Average thickness and standard deviation values were calculated.

5 In- vitro drug release rate *[59]*:- Formulated tablet were subjected to in-vitro dissolution study using USP type I / II apparatus (paddle) at 100 rpm with temperature of water bath maintain at

37±0.5°c. Dissolution was carried in 900 ml simulated gastric fluid for 2 hrs and for further 8 hrs in simulated intestinal fluid. The release of different drugs at different time interval was measured at particular wavelength by U.V- visible spectrophotometer.

FUTURE PORSPECTIVE: - The future of sustained-release products is promising, especially in the following areas that present high promise and acceptability:

- **Particulate systems:** The microparticle and Nanoparticle approach that involves biodegradable polymers in which intact drug-loaded particles via the Peyer's patches in the small intestine could be useful for delivery of peptide drugs that cannot, in general, be given orally.

- **Chronopharmacokinetic systems:** Oral sustained drug delivery with a pulsatile release regimen could effectively deliver drugs where need exists to counter naturally occurring processes such as bacterial/parasitical growth patterns.

- **Targeted drug delivery:** Oral controlled drug delivery that targets regions in the GI tract and releases drugs only upon reaching that site could offer effective treatment for certain disease states (e.g. colon-targeted delivery of Antineoplastics in the treatment of colon cancer).

- **Mucoadhesive delivery:** This is a promising technique for buccal and sublingual drug delivery, which can offer rapid onset of action and superior bioavailability compared with simple oral delivery because it bypasses first-pass metabolism in the liver.

CONCLUSION:-

Development of sustained release oral dosage forms is important for optimal therapy regarding efficacy, safety, and patient compliance. In case of sustained release dosage forms the release of active substance, although is slower than in conventional formulation; however it is substantially affected by external environment in to which it is going to be released. From the above discussion, it can be easily concluded that sustained release formulation are helpful in increasing the efficiency of the dose as well as they also improving the patient compatibility. Some factors like absorption window, therapeutic index, pKa - ionisation constant, molecular size, tissue binding, are important in formulating effective sustained release product.

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