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REVIEW ON SUSTAINED RELEASE TECHNOLOGY

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ABSTRACT

For internal route of administration, oral drug delivery remains best and the most preferred for administration for various drugs. Sustained Release is also suitable for overcome the side effect of drug and also increase therapeutic efficacy of drug. The basic concepts of sustained drug delivery system optimizes of the various parameters like biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that therapeutic efficacy is maximized, side-effects are reduced and cure of the disease is achieved easily. In pharmaceutical field, several dosage form having several advantage so that they used, in case of the Sustained release drug delivery is betterment of patient compliance, this due to reduce dose frequency, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare cost through improved therapy and shorter treatment period. The main object of this review give the complete knowledge for the sustained release dosage and its advantage, also describe the various criteria for selection of drug for the drug delivery system.

Key words: Sustained release, Drug Release, Drug Properties, Matrix Tablets

INTRODUCTION

A number of terms have been used to describe the oral dosage forms that represent modified release properties; which include delayed release, repeated action, prolonged release, sustained release, extended release and controlled release. Each drug delivery system is focused at eliminating the cyclical changes in plasma drug concentration seen after administration of conventional delivery systems. Modified release dosage forms are designed to provide quick achievement of a drug plasma level that remains constant at a value within the therapeutic range of a drug for a significant period of time or achievement of a plasma concentration of a drug that delivers at a slow rate (i.e. sustained release) that stays within the therapeutic range for a longer period of time. [(1)] Based on the assumption that a drug, which is to be incorporated into a modified release dosage form, confers upon the body characteristics of a one- compartment open model, then the basic kinetic design of such a product may be assumed to contain two portions, one that provides the initial loading dose, and one that provides the maintenance or sustained dose. To ensure that the therapeutic concentration of the drug in the body remains constant, two conditions must be fulfilled, namely 1) The zero order rate of drug release must determine the absorption rate of the drug, and 2) The rate at which the drug is released from maintenance dose (and subsequently the absorption rate) should be equal to the rate of drug elimination at the required steady-state concentration a list of important terms that describe different modified release dosage forms are defined below.[(2, 3)]

1. Modified release dosage forms

Those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic and/or convenience objectives not offered by conventional dosage forms. [(3)]

2. Controlled release

The drug is released at a constant (zero order) rate and the drug concentration obtained after administration is in variant with time. [(2, 3)]

3. Delayed release

The drug is released at a time other than immediately after administration. [5]

4. Extended release

Slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time usually between 8 and 12 hours. [6]

5. Prolonged release

The drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form. [7]

6. Repeat action

Indicates that an individual dose is released fairly soon after administration, and secondor third doses are subsequently released at intermittent intervals. [8]

7. Sustained release

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

8. Receptor targeting Sustained-release systems

Receptor targeting Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system

Table 1: Classification of sustained/controlled release systems [2, 3]

Types of System	Rate Control Mechanism
Diffusion Method Reservoir system Monolithic System	}Diffusion through membrane
Water Penetration controlled Osmotic system Swelling system	- transport of water through semi permeable membrane - water penetration into glossy polymer
Chemical controlled Monolithic system Pendant system Ion –exchange resins	-Surface erosion or bulk erosion - Hydrolysis of pendent group and diffusion from bulk polymer -Exchange of acidic or basic drugs with the ions present on resins
Regulated system Magnetic ,Ultrasound	External application of magnetic field or ultrasound to device

Advantages of sustained release dosage forms: [10]

Advantages of Sustained release dosage forms: [2, 3]

1. Decreased local and systemic side effects: - Reduced gastrointestinal irritation.
2. Better drug utilization: - Reduction in total amount of drug used. - Minimum drug accumulation on chronic dosing.
3. Improved efficiency in treatment:
4. Optimized therapy.
5. Reduction in fluctuation of drug level and hence more uniform pharmacological response.
6. Special effects e.g. sustained release aspirin provides sufficient drug so that on awakening the arthritic patient gets symptomatic relief.
7. Cure or control of condition more promptly.
8. Less reduction in drug activity with chronic use.
9. Method by which sustained release is achieved can improve the bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.

- Improved patient compliance: Less frequent dosing
- Reduced night-time dosing
- Reduced patient care time.

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

Disadvantages of sustained release dosage forms: - [2, 3]

1. It not permits prompt termination of therapy.
2. Less flexibility in dose adjustment.
3. These dosage forms are designed on the basis of average biological half life.
4. They are costly.

Biological Factors Influencing Oral Sustained-Release Dosage Form Design [2, 3]

1. Biological half-life:

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

2. Absorption :

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions.

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

Physicochemical factors influencing oral sustained-release dosage form design [2, 3]

1. Dose Size

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

2. Ionization, pKa and aqueous solubility

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

3. Partition coefficient

Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells. Meaning that the solubility of the drug may changes several orders of magnitude during its releases. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

4. Stability

Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form.

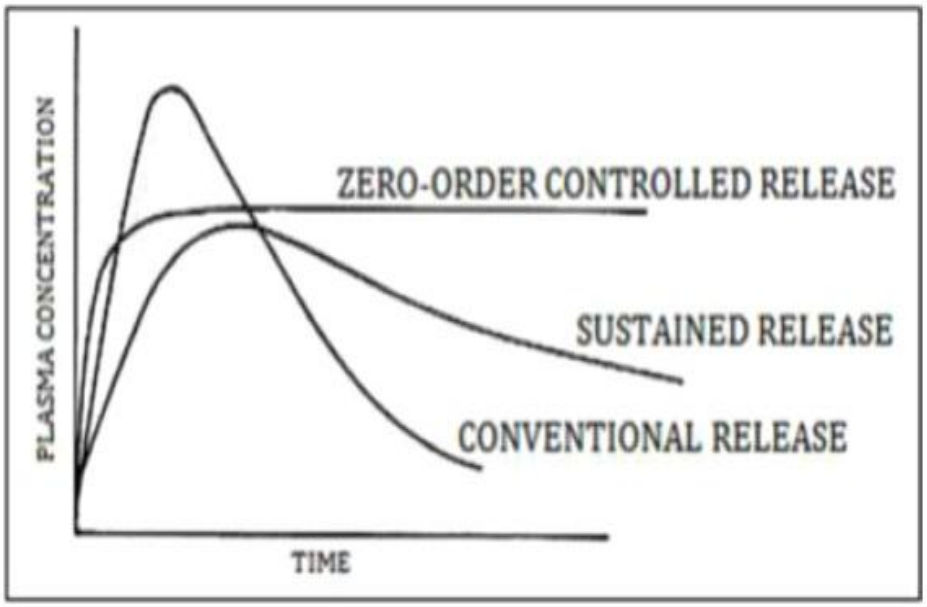
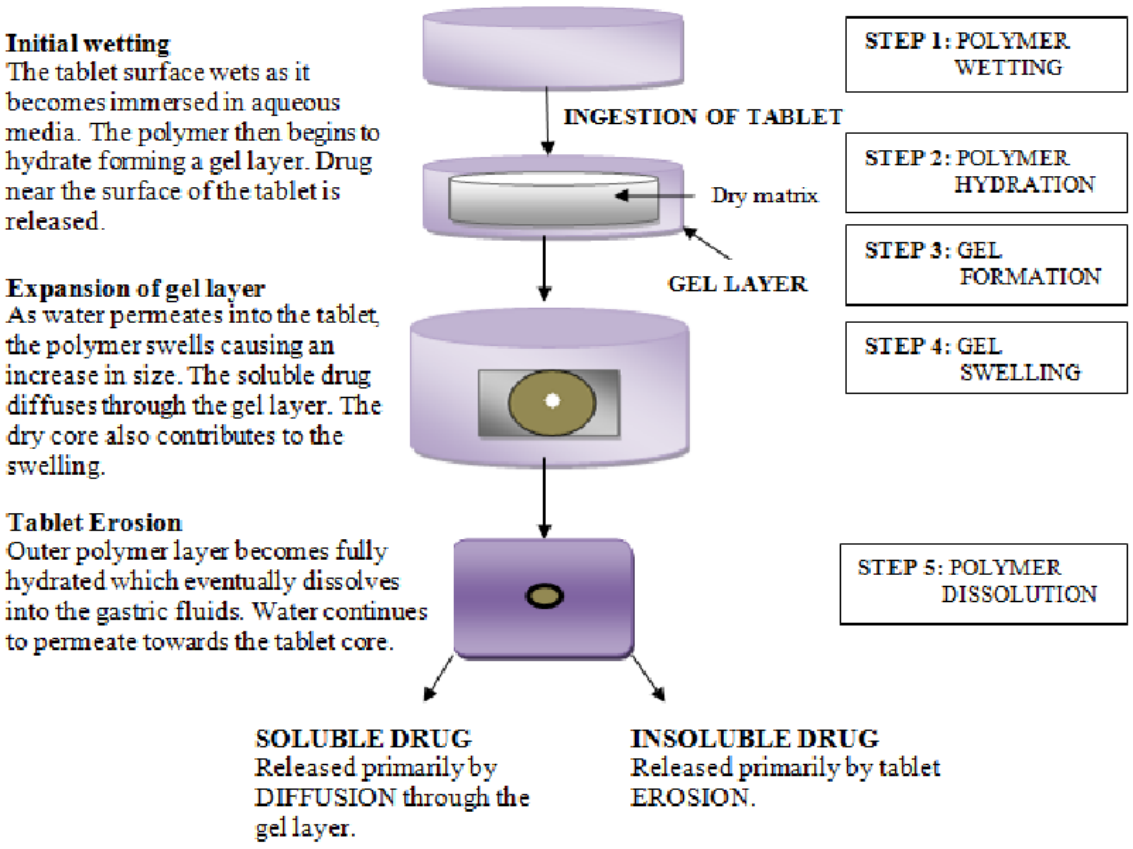


Figure 1: Plasma concentration graph [2, 3]



Drug Selection for Oral Sustained Release Drug Delivery System: [2, 3]

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I. tract, the general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient. [11]

Table 2: Parameter for Drug Selection

Content	Preferred Value
Molecular Weight/Size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to 7.8
Pk_a	Non ionized moiety > 0.1% at pH 1 to 7.8
Apparent Partition Coefficient	High
Absorption Mechanism	Diffusion
Absorbability	From all G.I. segments
Release	Should not be influenced by pH and Enzyme

Table 3: Pharmacokinetic parameter for drug selection

Parameter	Preferred Value
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	The larger Vd and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release Rate
Therapeutic concentration Cssav	The lower Cssav and smaller Vd, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Classification of SR Formulation:

The most common methods used to achieve sustained release of orally administered drugs are as follows: [12]

a. Diffusion System
i. Reservoir Device
ii. Matrix Device
b. Dissolution System
c. Osmotic System
d. Ion-exchange Resin
e. Swelling and Expansion System
f. Floating System
g. Bioadhesive or Mucoadhesive system

Matrix System: [13]

A matrix device, as the name implies, consist of drug dispersed homogeneously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster that the diffusion ate of dissolved drug leaving the matrix. (Figure 2)

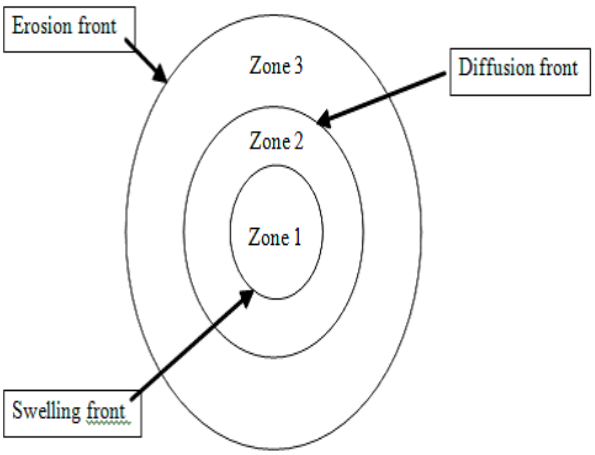


Figure 2: Matrix Tablets

- Maintains therapeutic concentrations over prolonged periods.
- Avoids the high blood concentration.
- Reduction in toxicity by slowing drug absorption.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Better drug utilization.
- Minimize drug accumulation with chronic dosing.
- Can be made to release high molecular weight

compounds.

- Increase the stability by protecting the drug from hydrolysis or other derivative changes in GIT.
- Reduction in health care cost.
- Usage of less total drug.
- Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.
- Improved patient compliance.

Disadvantages of Matrix system:

- The remaining matrix must be removed after the drug has been released.
- Greater dependence on GI residence time of dosage form.
- Increased potential for first-pass metabolism.

Types of Matrix: [15]

Hydrophobic Matrices

Hydrophilic matrix dosage forms essentially consist of a compressed blend of hydrophilic polymer and drug. According to the generally accepted mechanism, the drug release from hydrophilic matrix dosage forms starts when the tablet comes in contact with gastrointestinal fluid. The surface of the tablet hydrates to release exposed drug and at the same time form a viscous polymer mucilage or gel. This gel fills the interstices within the tablet, retarding further ingress of liquid. The concentration of polymer within the hydrated layer ranges from dilution at the outer surface to around 90% at the boundary with the drug core. Within this layer, drug in various states of dissolution (undissolved in dilute solution; in saturated solution) is distributed amongst the other ingredients of the tablets .Drug release occurs immediately from the surface (burst effect) followed by diffusion through, and / or erosion of, the hydrated layer. The relative proportions of drug released by diffusion and erosion are determined by the drug's solubility properties and by the physical and chemical nature of the hydrated polymer. This in turn is influenced by other factors, including drug characteristics, dissolution medium and other, which continue to be investigated.

Lipid matrices [16, 17]

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

Hydrophilic matrices

A matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups.

Biodegradable Matrices [2, 3, 18, 19]

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

Mineral Matrices

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali. On the Basis of Porosity of Matrix: Matrix tablets can be divided in to 3 types.

Macro porous systems

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 µm. This pore size is larger than diffusant molecule size.

Micro porous system

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50– 200 A°, which is slightly larger than diffusant molecules size.

Non-porous system

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

Drug release mechanism from tablet matrices [2, 3, 19, 20, 21, 22]

From time to time, various authors have proposed different types of drug release mechanism from matrices. It has been proposed that drug release from matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and/or the erosion of the gelatinous layer. Several kinetics models relating to the drug release from matrices are described below.

Zero-order kinetics

$W = k_1 t$

First-order kinetics

$\ln (100-W) = \ln 100 - k_2 t$

Hixon-Crowel's cube-root equation (erosion model)

$(100 - W)\ 1/3 = 1001/3 - k_3 t$

Higuchi's square root of time equation (diffusion model)

$W = k_4 t1/2$

Korsmeyer et al equation (release model)

$Q_t / Q = K\ t^n$

Where W is percent drug release at time t and k1 to k4 are release rate constants, depending on the kinetic model used. The release mechanism of a drug would depend on the dosage form selected, pH, and nature of the polymer used.

Comparison of dissolution profiles

Comparison of therapeutic performances of two medicinal products containing the same active substance is a critical means of assessing the possibility of alternative using between the innovator and any essentially similar medicinal product. The dissolution profile comparison may be carried out using model independent or model dependent method. A simple model independent approach uses a difference factor (*f1*) and a similarity factor (*f2*) to compare dissolution profiles. Matrix tablets for the last two decades have been popular in the formulation of Controlled release.

$$f1 = \frac{S_{t=1}^{n}(R_t - T_t)}{S_{t=1n} R_t} \times 100$$

$$f_2 = 50 \times \log \{[1+(1/n)\ S_{t=1}^{n}(R_t - T_t)\ 2]^{-0.5} \times 100\}$$

Where,

R_t and T_t represent the average percent dissolved at time t for reference and test, respectively, and n is the number of time points tested. Dissolution profile was considered satisfactory if *f*1 values lies below 50 (nearing zero) and *f*2 value lies more than 50 (nearing 100).The model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. Matrix tablets for the last two decades have been popular in the formulation of controlled release.

Methods of preparation [2, 3,16, 22]

Direct Compression

In this process powdered materials are compressed directly without changing the properties of the drug like physical and chemical properties.

Wet Granulation

In this method weighed quantities of drug and polymer are mixed with sufficient volume of granulating agent. After enough cohesiveness was obtained, then screening of wet mass. The granules are dried and screening of dry granules, then blending with lubricant and disintegrants to produce "running powder" tablets are compressed using a single-punch tablet compression machine.

Melt Granulation

In this process use of a substance, which is melts at relatively low temperature. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Different lipophilic binders were tried by using melt granulation technique.

DRY GRANULATION		WET GRANULATION	MOISTURE ACTIVATED DRY GRANULATION
Dispensing and Shifting		Dispensing and Shifting	Dispensing and Shifting
Dry mixing		Dry mixing	Dry mixing
Slugging	~~Slugging~~	Granulation	Granulation
Half lubrication	Lubrication	Pre-drying	~~Pre-drying~~
Compression	Compression	Shifting	~~Shifting~~
Milling		Drying	~~Drying~~
Shifting		Pre-mixing (unlubrication)	Pre-mixing (unlubrication)
Final lubrication		Lubrication	Lubrication
compression		Compression	Compression

Figure 3: Comparison between tablet granulation methods [4]

Hot-Melt Extrusion Process

In the hot-melt extrusion process, a mixture of the active ingredients, the thermoplastic polymers and other processing aids is fed into the barrel of the extruder through the hopper. The materials are transferred inside the heated barrel by a rotating screw.

The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Depending upon the dimensions of the die cylinders, films can also be produced from the extruder.

Effect of Release limiting factor on drug release [17]

i. Polymer hydration:
ii. Drug solubility
iii. Polymer diffusivity
iv. Solution solubility
v. Thickness of polymer diffusional path
vi. Thickness of hydrodynamic diffusion layer
vii. Drug loading dose
viii. Diluent's effect

Table 4: Polymers used in Matrix tablets [18, 19]

Sr no.	Types of polymers	Examples
1	Hydrogels	Polyhydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Crosslinked polyvinyl pyrrolidone (PVP)
2	Soluble polymer	Polyethylene glycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
3	Biodegradable polymers	Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters
4	Non-Biodegradable polymers	Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC)
5	Mucoadhesive Polymers	Pectin, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose
6	Natural polymers	Pectin, chitosan, guar gum

Table 5: Different drugs and polymers used in sustained- release Matrix tablets

Sr. no	Drug	Polymer
1	Ibuprofen	Cellulose acetate phthallate, Ethyl cellulose
2	Metoclopramide Hydrochloride	Hydroxy Propyl Methyl Cellulose (HPMC), Carboxymethylcellulose (CMC), Hydroxy Propyl Methyl Cellulose (HPMC), Carboxymethylcellulose (CMC),
3	Tramadol Hydrochloride	Carrageenan gum, Karaya gum, HPMC K15 .
4	Aceclofenac	Carbopol 971P, Carbopol
5	Metoprolol succinate	HPMC K100M, Xanthan gum

Evaluation of Sustained release Matrix tablets: [20, 21]

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations

Weight Variation: Twenty tablets were weighed individually and then collectively, average weight of the tablets was calculated.

Hardness: Hardness test was conducted for tablets from each batch using Monsanto hardness tester and average values were calculated.

Friability: The tablets were tested for friability testing using Roche friabilator, which revolves at 25rpm for 4min.

Thickness: The thicknesses of tablets were determined using micrometer screw gauge.

Content Uniformity: Using UV Visible spectrophotometer found the amount of the drug using the calibration curve method.

Kinetic Studies

***In Vitro* Dissolution Study:** Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 37^0C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replace. The amounts of the drug released is determined using an UV spectrophotometer a Drug dissolved at specified time period is plot as percent release versus time.

Stability Studies: Short Term Stability Study: To determine change in vitro release profile on storage, a short term stability study of the optimal batch.

***In–Vivo* Methods** once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are

- Clinical response
- Blood level data
- Urinary excretion studies
- Nutritional studies
- Toxicity studies
- Radioactive tracer techniques

Conclusion:

The main focus of this review article has been helpful for the formulation of sustained-release matrix tablets, and factor affecting the dosage form, criteria for selection of drug for sustain release delivery with advantages and disadvantages and various polymers used to design such system. Above discussion concludes that matrix tablets are helpful to increase the efficiency of dosage in eliciting desired therapeutic response related problems associated with the conventional dosage forms with overcome the patient compliance Cost effectiveness and once-daily dose are the plus points along with other benefits. More over all these comes with reasonable cost. Hence, sustained-release matrix tablets trends towards the efficacy and optimization of the dosage form design.

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