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REVIEW ARTICLE

Sustained Release Matrix Type Drug Delivery System: A Review

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ABSTRACT

The term "Controlled release or sustained release" is known to have existed in the medical and pharmaceutical prose for several decades. It has been constantly used to explain a pharmaceutical dosage form formulated to retard the release of therapeutic agent such that its appearance in the systemic circulation is delayed and/or protracted and its plasma profile is sustained in duration. Presently pharmaceutical industry is focusing on growth of sustained release formulations due to its intrinsic boons. 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 motivation of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetics and pharmacodynamics property of a drug in such a way that its utility is maximized, side-effects are reduced and treat of the disease is finish.

KEYWORDS

Sustained release, Polymer, Pharmacokinetics Matrix tablet

INTRODUCTION

These are the type of controlled drug distribution systems, which discharge the drug in perpetual process by together close controlled as well as spreading controlled mechanisms. To control the repeal of the drugs, which are having different solubility property the drug is out-of-the-way in bankable dihydrogen monoxide absorb substances, an unsolvable matrix of unbending non bankable dihydrogen monoxide unabsorbed resources or artificial resources.[1,2] One of the least baffled approach to the manufacture of perpetual release dosage forms involves the direct solidity of body of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively, drug and retardant blend may be granulated prior to compression. The materials most widely utilized in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylcellulose (HPC), Hydroxypropylmethylcellulose (HPMC), Hydroxyethyl -cellulose (HEC), Xanthus gum, Sodium alginate, Poly (ethylene oxide) and cross-linked homopolymers and copolymers of Acrylic acid. It is customarily supplied in micronized forms because minuscule particle size is critical to the expeditious formation of a sticky layer on the tablet surface[3,4]. Preface of matrix tablet as controlled release has given an just beginning breakthrough for novel drug distribution system (NDDS) in the ground of Pharmaceutical Technology. It omits intricate

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bearing procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer utilized in the preparations. The hydrophilic polymer matrix is widely utilized for formulating a control release dosage form. [5-7]

The major Drawbacks Associated with Conventional Dosage Forms are

- A typical peak-valley plasma concentration-time profile is obtained which makes an appropriation of the steady - state condition difficult.
- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which recurrent administration is compulsory.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- The fluctuations in drug levels may lead to precipitation of adverse effects, especially of a drug with small Therapeutic Index at any time over medication occur.
- Just, several climbing the corporate ladder in dope disjuncture course of action have been constrained to crush the complication of known abused substance bi section system. These techniques are known backwards and forwards of covering the outlay of abused substance distribution, sustaining the term of therapeutic life or targeting the distribution of drug to a tissue.[8,9]

Classification of Matrix Tablets

(A) On the Basis of Retardant Material Used

Matrix tablets can be divided into 5 types

1. ***Hydrophobic Matrices (Plastic matrices):*** In this method of obtaining sustained release from an oral dosage form, drug is commixed with an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolve drug has diffused through a network of channels that exist between compressed polymer particles. Examples of materials that have been utilized as inert or water absorb matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of capitulation of the drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of dihydrogen monoxide and gastrointestinal fluid.[10]
2. ***Lipid Matrices:*** These matrices set by the lipid waxes and generic materials. Drug release from such matrices occurs through both stoma diffusion and attrition. Dissolve character are therefore more sensitive to digestive fluid composition than to completely insoluble polymer matrix. Carnauba wax in coalescence with stearyl alcohol or stearic acid has been utilized for impulse base for many sustained release formulation.[11]
3. ***Hydrophilic Matrices:*** Water absorbs polymer matrix systems are broadly used in oral controlled drug delivery because of their elasticity to obtain a desirable drug release profile, charge efficacy and broad rigid taking. The production of the drugs in gummy capsules or more frequently, in tablets, using hydrophilic polymers with high transpire capacities as base excipients is of particular interest in the field of controlled release. Contaminate a matrix is defined as a well mixed composite of one or more drugs with a gelling agent. These systems are called salable controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups.[12]

   a) **Cellulose derivatives:** Cellulose is an organic compound with the formula $(C_6H_{10}O_5)_n$
   a polysaccharide consisting of a linear chain of several hundred to many thousands of β(1→4) linked D-

glucose units. Cellulose is mainly used to produce paperboard and paper. examples Methylcellulose 400 and 4000cPs, Hydroxy methyl cellulose, Hydroxy propyl methyl cellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxy methyl cellulose.

b) **Non cellulose natural or semi synthetic polymers:** Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches

c) **Polymers of acrylic acid:** Carbopol-934, the most used variety

4. Biodegradable Matrixes: These consist of the polymers which comprise of monomers related to one another through functional groups and have rickety link in the backbone. They are biologically corrupted or destroy by enzymes generated by nearby living cells or by a non enzymatic process in to oligomers and monomers that can be metabolized or secrete. Examples are natural polymers such as proteins and polysaccharides; adapted natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrixes: these are consisting of polymers which are obtained from various classes of seaweeds. Example is Algonac acid, which is a hydrophilic carbohydrate obtained from class of brown seaweeds (Phaephyceae) by the use of dilute alkali.

(B) On the Basis of Porosity of Matrix

Matrix system can also be classified according to their porosity and accordingly, Macro porous; Micro porous and Nonporous systems can be famous.[13]

a) Macro porous Systems: In such systems the diffusion of drug occurs through pores of matrix, which are in the size range 0.1 to 1 μm. This pore size is more cosmically continuous than diffusion molecule size.[14]

b) 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 scarcely more immensely colossal than diffusion molecule size.[15]

c) Non-porous System: Solid systems have no pores and the molecules diffuse through the method crush. In this casing, only the polymeric phase exists and no pore phase is current.[16]

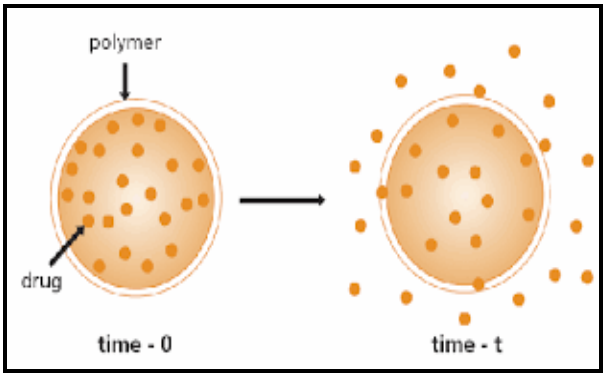

Figure 1: Schematic representation of diffusion across the Matrix[17]

Effect of Various Parameters on Drug Release[18, 19]

The mechanical analysis of controlled release of the drug reveals that partition coefficient; diffusion path thickness; diffusivity and other system parameters play various rate determining roles in the controlled release of drugs from each capsule, matrix or sandwich type drug delivery systems.

A. Drug Solubility

Water solubility of drug and molecular size is any more chief factor which is considered in the abstaining of drug from growth and erosion controlled polymeric matrices. For drugs with an acceptable aqueous solubility give up of water soluble drugs occurs by dissolution in sensitive medium and the relinquishment of poorly water soluble drug are occuring by both the dissolution of drug and dissolution of drug particles through corrosion of the matrix tablet.

B. Polymer Hydration

It is paramount to study polymer hydration/swelling process for the most number of polymers and polymeric accumulation. The more main step in polymer cease include absorption/adsorption of dehydrogenate

monoxide in more available places, break of polymer-polymer connecting' with the concurrent composing of dehydrogenate monoxide-polymer linings, disseverment of polymeric chains, swelling and lastly dispersion of polymeric chain in dissolution medium.

C. Polymer Diffusivity

The diffusion of minute molecules in polymer structure is power activated process in which the diffusion molecules circuit to a consecutive series of balance place when a sufficient amount of energy of activation for diffusion. Ed has acquired by the diffusion is needed on length of polymer chain parts, cross linking and crystalline of polymer. The abandonment of a drug may be attributed to the mainly two factors-

- **Polymer viscosity:** rising the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution.
- **Polymer concentration:** An increase in polymer attention causes an increase in the viscosity of gel as well as formulation of the gel layer with a longer diffusion path. This could cause a decrease in the effective diffusion accessory of the drug and therefore reduction in drug release.

D. Thickness of Polymer Diffusion Path

The controlled release of a drug from matrix type polymeric drug delivery system is mainly governed by Flick's law of diffusion.

$$JD = D\, dc/d \qquad \text{……..(1)}$$

Where,

JD = flux of diffusion across a plane surface of unit area

D = is the diffusibility of drug molecules, dc/dx = is a concentration grade of drug molecule across a diffusion path with width dx.

E. Thickness of Hydrodynamic Diffusion Layer

The drug release summary is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery plan. As the thickness of hydrodynamic diffusion layer increases the level of drug release value decreases.

F. Drug Loading Dose

The relinquishment kinetics is appreciably affected by load dose of drug. The effect of early drug loading of the tablets on the resulting release kinetics is more involute in case of impotently dehydrogenate monoxide soluble drugs, with elevating initial drug loading the relative release rate first decrease and then increases, whereas, absolute release rate monotonically increases. In case of liberating dehydrogenate monoxide soluble drugs, the porosity of the matrix upon drug depletion increases with addition early drug loading.

G. Surface Area and Volume

The dependence of the rate of drug release on the surface area of drug delivery device is well known experimentally and theoretically. Both the *in vitro* and *in vivo* rate of the drug release, are practical to be dependent upon surface area of dosage form. Siepman et al. found that release from small tablet is faster than large cylindrical tablets.

H. Effect of Diluents

The effect of diluents or filler depends upon the character of diluents. Water soluble diluents like lactose cause clear raise in drug release rate and relinquish mechanism is additionally move towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increment the reprieve rate of matrix. The reason behind this is that water soluble filler in matrices stimulates the water penetration into the inner part of the matrix, due to increase in hydrophilicity of the system, causing fast diffusion of drug, leads to increased drug release rate.

I. Additives

The effect of integrating non-polymeric excipients to a polymeric matrix has been charged to produce an increase in release rate of hydro soluble active values. These incrementations in release rate would be marked if the excipients are soluble like lactose

and fewer consequential if the excipients are infeasible to read like tricalcium phosphate.

Polymers Used in the Matrix

a) **Biodegradable polymers:** Polyglycolic acid, Polyanhydrides, Polyorthoesters, Polylactic acid, Polycaprolactones.

b) **Natural gums:** Karaya gum, Guar gum, Xanthus gum, Locust bean gum.

c) **Hydro gels:** Polyhydroxyethyle-methylacrylate, Cross-linked polyvinyl alcohol, Polyethylene oxide, Cross-linked polyvinyl pyrrolidone, Polyacrylamide.

d) **Non-biodegradable polymers:** Polydimethylsiloxane, Polyvinyl chloride, Ethyl cellulose, Polyethylene vinyl acetate, Polyether urethane, Cellulose acetate.

e) **Soluble polymers:** polyvinyl alcohol, Hydroxypropyl methyl cellulose, Polyvinylpyrrolidone, Polyethylene glycol.

f) **Mucoadhesive polymers:** Polyacrylic acid, Polycarbophil, Sodium carboxymethyl cellulose, Tragacanth, Pectin, Methyl cellulose.[20]

Biological Factors Influencing Release from Matrix Tablet

1. Absorption

The purport of composing a controlled release or sustained release product is to set control on the distribution system, it is essential that the rate of relinquishment is a substantial amount more gradual than the rate of absorption. If we cerebrate that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the contrivance will pass out of the potential absorptive region afore drug release is consummate. Thus correspond to a minimum evident absorption rate constant of 0.17-0.23h-1 to give 80-95% over this duration. Hence, it postulates that the absorption of the drug should occur at a rather uniform rate over the gamut of diminutive intestine. For several compounds this is erroneous. If a drug is absorbed by active convey or convey is inhibited to a categorical region of intestine, control release preparation may be deleterious to absorption. One method to provide sustaining mechanisms of distribution for compounds endeavors to maintain them within the stomach. This sanctions slow relinquishment of the drug, which then peregrinates to the absorptive site. These methods have been developed as a result of the observation that co-administration results in sustaining effect. One such effort is to formulate low density tablet. Another approach is that of bio gum materials.

2. Metabolism

Drugs those are considerably metabolized afore absorption, either in the lumen or the tissue of the intestine, can show decremented bioavailability from more gradual-ending dosage form. Hence criteria for the drug to be utilized for formulating Sustained-Release dosage form is,

1. Drug should be freely soluble in water.
2. Drug should have a larger therapeutic window.
3. Drug should have a law half-life. (<5 hrs.)
4. Drug should be absorbed throughout the GIT.
5. Even a drug that is impotently dihydrogen monoxide soluble can be formulated in control release dosage form. For identically tantamount, the solubility of the drug should be incremented by the opportune system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be barred and one should be cautious for the obviation of equipollent.

3. Distribution

Drugs with high clear volume of distribution, which control the rate of elimination of the drug, are reduced candidate for oral control release drug delivery system e.g. Chloroquine.

4. *Biological Half-life*

The customary goal of an oral control release product is to maintain therapeutic blood levels over a long period of time. To reach this, drug must enter the circulation at roughly the same rate at which it is eliminated. The elimination rate is quantifiable described by the moiety-life (t1/2). Each drug has its own quality elimination rate, which is the total of all elimination processes, counting metabolism, urinary excretion and all over processes that perpetually take out drug from the blood stream. Therapeutic compounds with short half-life are generally are first-rate candidate for control release formulation, as this can decrement dosing frequency. In general, drugs with a half-life shorter than 2 hours such as furosemide or levodopa are impecunious candidates for SR preparation. Compounds with long half-lives, more than 8 hours are additionally generally not utilized in sustaining form, since their effect is by now sustained. Examples are the Digoxin and phenytoin.

5. *Margin of Safety*

As we identify more considerably extensive the value of therapeutic index for protect is the drug. Drugs with a lesser amount of therapeutic index customarily reduced candidate for formulation of oral control release drug distribution system due to technological direct of control over release rates.[21,22]

Physicochemical Factors Influencing Release From Matrix Tablet

1. ***Partition Coefficient:*** When a drug is administered to the gastrointestinal tracts, it must traverse a variety of biological membranes to engender a therapeutic effect in an extra area of the body. It is common to consider that these membranes are lipid; consequently the partition coefficient of oil-soluble drugs becomes consequential in determining the prosperity of membrane arduousness perforation. Compounds which are lyophilic in nature having lofty partition coefficient are impotently aqueous soluble and it retain in the lyophilic tissue for the longer time. In case of compounds with minutely lowercase partition coefficient, it is very difficult for them to perforate the membrane, resulting in reduced bioavailability. Moreover, partitioning effects apply just as to the diffusion through polymer membranes. The cull of diffusion-constraining membranes must largely depend on the partitioning characteristics of the drug.
2. ***Ionization, pka and aqueous solubility:*** Permeates across lipid membranes, it is paramount to note the relationship between the pka of the compound and the absorbency environment. Theologian the drug in an unchanged form is benign for drug permeation. Regrettably, the situation is made more involutes by the fact that the drug's aqueous solubility will generally be debilitated by conversion to unchanged form. Distribution systems that are needy on diffusion or dissolution will likewise be needy on the solubility of the drug in aqueous media. Mostly drugs are impotent acids or bases. Since the unchanged form of a drug preferentially.
3. ***Dose size:*** For orally administered systems, there is an upper limit to the bulkiness size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered supreme for a conventional dosage form. This additionally holds for sustained release dosage form. Compounds that require vastly immense dosing size can sometimes be given in multiple amounts, or formulated into liquid systems. Another consideration is the margin of safety involved in the administration of a considerable amount of a drug with a narrow therapeutic range.
4. ***Stability:*** Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic deficiency. Deficiency will proceed at a frugal rate for drugs in solid state; ergo, this is the preferred composition of distribution for quandary cases. For the dosage form that are unbalanced in the stomach, systems that perpetuate distribution over entire course of transfer in the GI tract are benign; this is withal true

for systems that delay release until the dosage form reaches the minuscule intestine. Compounds that are unstable in minuscule intestine may exhibit decreased bioavailability when administered from a fortifying dosage form. This is because more drugs is distributed in the minuscule intestine and, hence, is subject to degradation. Some examples are probanthine and Propentheline.

Advantages of Matrix Tablets

1. Decrease the local and systemic side effects
2. Flexible and proficient.
3. Simple to manufacture.
4. It has low value.
5. Growth the bioavailability of some drugs.
6. Reduce the toxicity by slowing drug absorption.
7. Improvement of the ability to give special effects.
8. Increase the stability by defensive the drug from hydrolysis or other derivative changes in gastrointestinal tract.[23]

Disadvantages of Matrix Tablets

1. Increased cost.
2. High cost of preparation.
3. Success of zero order release is difficult.
4. Greater dependence on GI residence time of dosage form.
5. The remaining matrix must be abstracted after the drug has been relinquished.
6. Need for additional patient education and counseling.
7. Possibility of dose dumping due to food, physiologic or formulation variables.
8. The drug release rates vary with the square root of time.
9. Stability problems.
10. Water soluble drugs have a tendency to break open from the system.
11. More rapid development of tolerance and counseling.
12. Poor *in vitro – in vivo* connection[24]

Criteria to be met by Drug Proposed to be Formulated in Sustained Release Dosage Forms

a) Desirable half-life.

b) High therapeutic index.

c) Small dose.

d) Desirable absorption and solubility characteristics.

e) Desirable absorption window.

f) First past clearance.[25,26]

a) Desirable half-life: The moiety-life of a drug is an index of its dwelling time in the body. If the drug has a short half life (less than 2 hours), the dosage form may contain a highly astronomically immense quantity of the drug. On the other hand, a drug with an abstraction half-life of eight hours or more are amply sustained in the body, when administered in conventional dosage from, and sustained release drug division system is generally not compulsory in such cases. Preferably, the drug should have half-life of three to four hours.

b) High therapeutic index: Drugs with low therapeutic range are out of place for absorption in sustained release formulations. If the system fails in the body, dose concept may occur, leading to fatalities e.g. Digitoxin

c) Small dose: If the dose of a drug in the straight dosage form is high, its congruousness as an applicant for sustained release is solemnly undecided. This is chiefly because the size of a unit dose sustained release formulation would become too immensely colossal to administer without involution.

d) Desirable absorption and solubility characteristics: Absorption of impotently dehydrogenate monoxide soluble drug has been often dissolution rate inhibited.

Incorporate such Compounds into sustained release formulations are ergo false and may decrease overall Absorption competence.

e) **Desirable absorption window:** Certain drugs when administered orally are absorbed only from a concrete part of the gastrointestinal tract. This factor is referred to as the 'absorption window'. Drugs exhibiting an Absorption window like fluorouracil, thiazide diuretics, if formulate as sustained release dosage forms are unsuitable.

f) **First pass clearance:** As discussed precursor in disadvantage of the sustained distribution system, the distribution of the drug to the body in desired concentration is critical in an impotent position in case of drugs undergo wide excited first pass metabolism, when administered in sustained release forms' unsuitable.

Drug Release from Matrix

Drug on the outer surface uncovered to the swim solution is dissolved primary and then diffuses out of the matrix. This process is responsible for with the border between the bathing solution and the solid drug affecting toward the center. It follows that for this system to be diffusion controlled the rate of dissolution of drug particles within the matrix must be much quicker than the dispersal rate of dissolved drug exit the matrix. Derivation of the mathematical model to describe this system involves the following assumptions.

A simulated-steady state is maintained all through drug release, the diameter of the drug particles is more minutely very small amount than the average distance of drug diffusion through the matrix, the diffusion constant of drug in the matrix remains constant In a hydrophilic matrix a macromolecule there are two direct reverse mechanisms involved in the drug release. Fickian diffusion release and relaxation release. Diffusion is not the only technique by which a drug is abdicated from the matrix; the corrosion of the matrix following polymer repose contributes to the overall release. The relative contribution of all components to the total release is primarily dependent virtual on the properties of a given drug. For example, the abandonment of a carefully soluble drug from hydrophilic matrices involves the direct absorption of dihydrogen monoxide and activity of drug via a swelling-controlled diffusion mechanism. When a dehydrogen monoxide puncture into a glassy polymeric compound matrix, the polymers swell and its glass change temperature is lowered. At the constant time, the dissolved drug diffuses through this swollen tough region in the external relinquish medium. This type of diffusion and swelling does not usually follow a Fickian diffusion mechanism. The semi experiential equation to explain drug release comportment from hydrophilic matrix systems.[27]

$$Q = k\,tn \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where, Q = fraction of drug released in time t,

k = rate constant incorporating characteristics of that network system and the drug

n = the diffusion example. It has been shown that the value of n is indicative of the drug release mechanism.

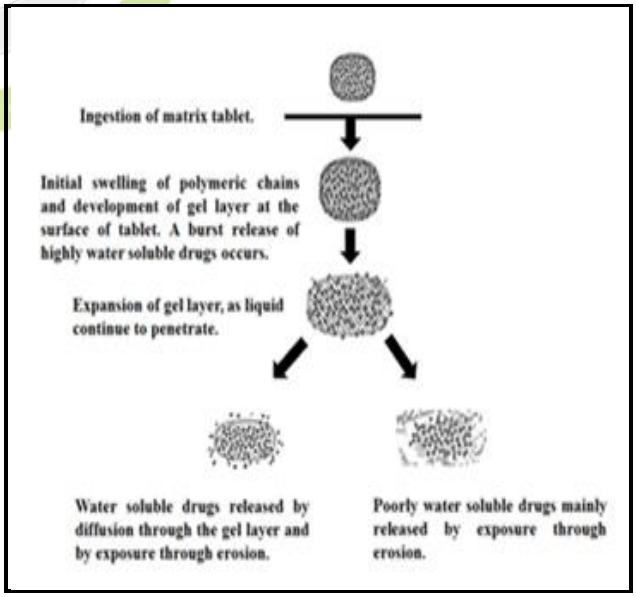

Figure 2: Drug Release from Hydrophilic Matrix Tablet Advantages[28]

With proper control of manufacturing method, reproducible release profiles are achievable.

Their predictability related to them is a little, but that characterizing coated release forms.

Their ability to include active values is large, which suits them to delivery of large doses.

The hydrophilic polymers are able to be arranged into three broad categories

(A) Non-cellulose Natural or Semi Synthetic Polymer: Non –cellulose natural are products of vegetable origin and are generally used as such; chatoyant, Agar, alginate, guar gum, modified starch are generally used polymer.

(B) Polymers of Acrylic Acid: Polymers of acrylic acid are arranged in Carbomer cluster and profitable under the name of carpool. The major disadvantage of this kind of polymer is its pH dependent gelling characteristics.

(C) Cellulose Ether: This group of semi-synthetic cellulose derivatives is that the most widely used polymers. Nonionic such as hydroxy propyl methylcellulose (HPMC) of different consistency grades are widely used group of polymers. Nonionic such as HPMC of changed viscosity grades is widely used.

Evaluation of Sustained Release Tablets

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

***1. In-Vitro* Methods**

These are:-

a) Friability Test

friability test is an antecedently weighed 10 tablets were taken in Roche friabilator and the friability was checked at 25 rpm for 4 minutes. Then the tablets were dusted and reweighed and the percentage of powder eroded during 4 minutes was recorded. The resulting tablets were weighed and the percentage loss was calculated utilizing the formula.

(Initial weight – Final weight)/Initial weight x100..... (3)

b) Hardness Test

Hardness of the tablets was tested using "Monsanto and Pfizer" hardness tester. In all the cases, means of six replicate determinations were taken.

c) Uniformity of Weight

The uniformity of weight is the average weight of the tablet was calculated by weighing 20 tablets individually and all together. The percent weight deviation of each tablet was computed as per official method.

d) Drug Content Uniformity of the Tablets

Drug content uniformity of the tablets are involved Five tablets were powdered in a mortar. From this, powder equivalent to 50 mg of the drug was taken in a 100 ml round bottom flask. It is extracted with 20 ml of 1.2 buffers for ½ hour, filtered in a volumetric flask and the filtrate was made up to the mark with 1.2 buffers. Further suitable dilutions were made and the absorbance was measured at 289 nm against the blank.

e) Weight Variation

The weight variation is twenty tablets are weighed individually and then collectively Average weight of the tablets was calculated.

f) Thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Venire Calipers. It was determined by checking ten tablets from each formulation**.**

g) Dissolution Test

The dissolution test is a drug which having a slow dissolution rate these drugs are naturally sustained and for those drugs with high water solubility, decreases their dissolution rate through appropriate salt or derivative formation. These systems are generally employed in the manufacturing of enteric coated dosage forms. Protection of the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This the inhibits release of drug from the dosage form

until it reaches the higher pH of the intestine.[29,30]

2. In–Vivo Methods

The various *in-vivo* evaluation methods are:-

a) Clinical Response

Clinical response means a response to drug intake that can be detected and appreciated by a change in signs and symptoms caused by the disease for which the drug, or whatever kind of therapy, is being taken.

b) Blood Level Data

Blood tests are sets of values used by a health specialized to interpret a set of medical test results from blood samples.

c) Urinary Excretion Studies

Compounds and their metabolites need to be abstracted from the body via excretion, customarily from side to side the kidneys (urine) or in the feces. Unless excretion is consummate, accumulation of peregrine substances can adversely affect mundane metabolism.

There are three main sites where drug excretion occurs. The kidney is the most consequential site and it is where products are excreted through urine. Biliary excretion or fecal excretion is the process that initiates in the liver and passes through to the gut until the products are determinately excreted along with waste products or feces. The last main method of excretion is through the lungs (e.g. anesthetic gases).

Excretion of drugs by the kidney involves 3 main mechanisms:

1. Glomerular filtration of unbound drug.
2. Active secretion of (free & protein-bound) drug by transporters (e.g. anions such as urate, penicillin, glucuronide, sulfate conjugates) or actions such as choline, histamine.
3. Filtrate 100-fold concentrated in tubules for a favorable concentration gradient so that it may be secreted by passive diffusion and passed out through the urine.

d) Nutritional Studies

Nutrition is the science that clarifies the interface of nutrients and other substances in food (e.g. phytonutrients, anthocyanins, tannins, etc.) in relation to maintenance, growth, reproduction, health and disease of an organism. It includes food intake, absorption, assimilation, biosynthesis, catabolism and excretion. [31]

e) Toxicity Studies

Toxicity studies are the scientific analysis of the effects of toxic chemical substances on cultured bacteria or mammalian cells. *In vitro* testing methods are employed primarily to identify potentially hazardous chemicals and/or to confirm the lack of certain toxic properties in the early stages of the development of potentially useful new substances such as therapeutic drugs, agricultural chemicals and food additives**.**

f) Radioactive Tracer Techniques

A radioactive tracer or radioactive label is a chemical compound in which one or more atoms have been superseded by a radioisotope so by virtue of its radioactive decay, it can be acclimated to discover the mechanism of chemical reactions by tracing the path that the radioisotope follows from reactants to products. Radio labeling is thus the radioactive form of isotopic labeling Radioisotopes of hydrogen, sulphur, carbon, phosphorus, and iodine have been used widely to trace the path of biochemical reactions. A radioactive tracer can withal be habituated to track the distribution of a substance within a natural system such as a cell or tissue, or as a flow tracer to track fluid flow. Radioactive tracers are additionally used to decide the location of fractures engendered by hydraulic fracturing in natural gas engenderment.[32,33]

3. Stability Studies

The stability study focuses on determining the result of aging and storage under various conditions and the effect on the release

characteristics and chemical stabilities. Stability studies were carried out to calculate the stability of F7 formulation on sustained release tablets of levofloxacin storing at 45 degrees Celsius ±2 degree Celsius after 45 days.

4. In vitro- In vivo Correlations

The compulsory of establish good *in vitr- in vivo* correlation in the magnification of sustained release distribution systems is pellucid. To compose an important in-vitro in-vivo correlation one has to consider not only the pharmaceutical aspect of sustained release drug distribution system but again the biopharmaceutics and pharmacokinetics of the therapeutic therapy in the body after its release from the drug distribution system and again the pharmacodynamics of therapeutic therapy at the site of drug action. A simple *in vitro*, *in vitro* relationship can be apperceived by conducting in-vitro and in-vivo evaluations of a possible drug distribution system at the same time to study and compare the mechanism and rate profiles of sustained drug release. When the in-vivo drug release mechanism is confirmed to be in good assertive with that observed in the in-vitro drug release studies, then in-vitro in-vivo correlation factor is derived. For capsule type drug distribution system the factor can be represented as:

(Q/t) In-vivo …….... (4)

Q= (Q/t) In-vitro…….....…… (5)

Where,

Q/t = Rate of release

'Q' values are dependent profiles of drug delivery systems. Upon the sites of administration and environmental conditions to which the animals are exposed during treatment (study).

The above relationship can be used for optimization of sustained release Levy has classified In-vivo-In-vitro correlation in to:

a) Semi-quantitative correlations based on blood levels or urinary excretion data.
b) Pharmacological correlations based on clinical observations.
c) Quantitative correlation arising from absorption kinetics.[26]

5. Bioavailability Testing

Bioavailability is defined as the rate and extent of absorption of unchanged drug from its site of application to the systemic circulation. Bioavailability is a subcategory of absorption and is the fraction of an administered dose of unchanged drug that reach the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100 percent. However, when a medication is administered via other routes (such as orally), its bioavailability generally reduce or may vary from patient to patient. Bioavailability is one of the compulsory apparatus in pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

For dietary supplements, herbs and other nutrients in which the route of administration is almost always oral, bioavailability generally designates simply the quantity or fraction of the ingested dose that is absorbed.[34]

Recent Advancements on Sustained Release Matrix Type Drug Delivery System

A fundamental type of advanced drug distribution systems is proposed: Miniaturized implants, which can be placed in minute apertures practice into the oval window. They consist of two components:

1) A cylinder, which is inserted into the aperture passing the oval window. The cylinder is partly located within the inner auditory perceiver and circumvented by perilymph. This provides direct contact to the target site, and at the same time assures implant obsession.

2) A cuboid, which is located in the middle auditory perceiver, helpful as a drug reservoir. One side of the cuboid is in direct contact with the oval window. Drug release into the cochlea occurs by diffusion through the cylindrical part of the hearing perceiver Cubes and by diffusion from the cuboid into and through the oval

window. High precision molds were acclimated to prepare two different sized Auditory perceiver Cubes by injection molding. The miniaturized implants were predicated on silicone and weighted down with different amounts of dexamethasone (10 to 30 % w/w). The systems were fully characterized afore and upon exposure to artificial perilymph at 37°C. Importantly, drug release can completely be controlled and sustained during long time periods.[35]

This study designed at employ Plackett-Burman design in screening formulation variables that affect quality of matrix-type simvastatin (SMV) transdermal film. To complete this goal, 12 formulations were prepared by casting method. The investigate variables were Eudragit RL percentage, polymer mixture percentage, plasticizer type, plasticizer percentage, enhancer type, enhancer percentage and dichloromethane fraction in the organic phase. The films were evaluated for physicochemical properties and ex vivo matrix-type simvastatin permeation. Matrix-type simvastatin initial, delayed flux, diffusivity and permeability coefficient were calculated on the deferred flux time with constraint to minimize the initial flux and approaching steady-state flux. The obtained results revealed flat films with a homogeneous distribution of matrix-type simvastatin within the films. Thickness values changed from 65 to 180 μm by changing the factors' combinations. Most of the access profiles showed sustained release feature with fast permeation phase followed by slow phase.[36]

The plan of the present work is the development and evaluation of solid lipid nanoparticles as a carrier system for topical distribution of benzocaine civilizing its local anesthesia planning to engender an expeditious acting and perdurable topical formulation. Benzocane loaded solid lipid nanoparticles were yare utilizing a full factorial design to study the control of the type of polyoxyethylene sorbitan ester surfactants as well as their concentration as autonomous variables on the particle size, entrapment efficacy and zeta potential culled as dependent variables. Design of experiment and the analysis of variance were conducted to assess the optimization of the developed formulations. The results betokened that the adipose acid chain length of tested surfactants and their concentration had a consequential effect on the studied replications.[37]

The Bi-layer tablets of tramadol hydrochloride were prepared by direct compression technique. Each tablet contains an immediate discharge layer with a sustained release layer. The immediate release layer was started to release the initial dose directly within minutes. The immediate release layer was combined with sustained release matrix made of varying quantity of Methocel K4M, Methocel K15MCR and Carbomer 974P. Bi-layer tablets were evaluated for various physical tests with weight variation, thickness and diameter, hardness and percent friability. Drug release from bi-layer tablet was studied in an acidic medium and buffer medium for two and six hours correspondingly. Sustained release of tramadol hydrochloride was observed with a controlled fashion that was characteristic to the type and extent of polymer used.[38]

Thiazolidinedione-8 (TZD-8) is an anti-quorum-sensing molecule that has the potential to prosperously obviate catheter-associated urinary tract infections, a major healthcare challenge. Sustained-release drug-distribution systems can amend drugs' therapeutic potential, by maintaining their therapeutic level and falling their side effects. Varnishes for sustained relinquishment of TZD-8 predicated on ethylcellulose or ammonio methacrylate copolymer type A were developed. The main factors affecting release rate were found to be film thickness and subsistence of a hydrophilic or swellable polymer in the matrix. The relinquishment mechanism of ethylcellulose-predicated systems matched the Higuchi model. Culled varnishes were retained on catheters for at least 8 days. Sustained-release distribution systems of TZD-8 were active against by Candida albicans biofilms. The present study demonstrates capable results a route to

developing applications for the aversion of catheter-associated infections.[39]

At present no scientific underlying principle exists for selecting a particular enabling strategy to formulate a weakly water-soluble drug, although this is critical as it will influence the *in vivo* performance of the resulting formulation. This study provides an coming into this complicated decision making process for a weakly soluble human immunodeficiency virus protease inhibitor based upon *in vivo* test results. A formulation strategy based on the molecular dispersion of this active pharmaceutical ingredient into a biphasic matrix consisting of water-insoluble poly lactic-co-glycolic acid and water-soluble polyvinylpyrrolidone was evaluated. The long-term *in vivo* performance of this strategy was compared to that of other solubility attractive approach by evaluating contact of the active pharmaceutical ingredient in male Beagle dogs. Solid dispersions, based on a PLGA/PVP matrix, were compared to solid dispersions in a pure poly lactic-co-glycolic acid matrix. Additionally, these solid dispersion strategies were compared to the strategy of particle size reduction by means of an active pharmaceutical ingredient microsuspension.[40]

The aim of this study was to contract sustained release dosage forms of acetazolamide preparing its calcium alginate chaplet and matrix tablets. Acetazolamide was incorporated into a calcium alginate chaplet using microencapsulation method. Two methods were applied to delay acetazolamide release rate. The first method is drug was incorporated into a calcium alginate chaplet either alone or with various polymers in internal phase. The second method concerned the preparation of matrix tablet from the chaplet benefiting direct compression method with or without various polymers in outside phase. The release rate of these prepared formulations and an innovator's sustained-release capsule was assessed. In-vitro dissolution studies revealed that the matrix tablets prepared by the second method containing NaCMC could sustain acetazolamide release properly and the drug released until 09 hrs.[41]

Metoclopramide is a drug which commonly used for the management of gastrointestinal disorders. It has a short biological half-life and is usually administered four times daily to maintain effective concentrations throughout the 24hrs. The aim of this study is to develop sustained-release hydrophilic matrix tablet formulations of the drug to get reproducible and unsurprising release rates, toxicity, reduction of required dose, complete duration of activity, decreased, optimized therapy, and improved patient compliance. Hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, chitosan were included in the matrix system individually or in combinations as release controlling factor by direct compression technique. Compatibility among the formulation components was assessed by Differential scanning calorimetry and Fourier transform infrared spectroscopy analysis.[42]

Productions that are able to control the release of drug have become an essential part of the pharmaceutical industry. In particular oral drug release has been the center of pharmaceutical research for many years. This type of drug delivery has been at the centre of research due to its several benefits over conservative dosage. The center of this review is on matrix tablets due to their broadly use and simplicity of the formulation. This includes the discussion of various types of matrix tablets and factors affecting the drug release from this production. The mechanism of drug release from hydroxypropyl methylcellulose matrices is also discussed.[43]

Hydrophilic matrix systems are one of the most absorbing drug distribution systems, and they are presently some of the most commonly used to control the release rate of drugs. There is an excessive amount of factors involved in drug release from hydrophilic matrix systems. The most important factors to be taken into account when developing a formulation signify on hydrophilic matrix are the percentage, solubility and drug particle size; the type of polymer, the

percentage incorporated, its degree of viscosity and the polymer particle size. Additionally consequential are the drug/polymer ratio and the amount of H_2O entering the matrix. Other factors have been shown to be involved in the relinquishment of drugs, such as the percentage and clotting of polymers and the dimensions of the matrix. The compression force is consequential among the formulation factors to the extent that it determines the amount of air attentive in the matrix. Cognizance of these factors involved in the relinquishment of the drugs is crucial for the optimal development of formulations predicated on hydrophilic systems.[44]

CONCLUSIONS

By the above discussion, it can be simply concluded that sustained-release formulation are cooperative in incrementing the efficiency of the dose as well as they are additionally ameliorating the patient's compatibility. Moreover, all these come with plausible rate. The dosage form is facile to optimize and very subsidiary in the case of the antibiotics in which irrational utilization of the same may result in conflict.

CONFLICT OF INTEREST

There is no conflict of interest.

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