INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online atwww.ijpcbs.com

Review Article

A REVIEW ON SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. This article contains the basic information regarding sustained-release formulation and also the different types of the same**.**

Keywords: Matrix system, Controlled drug delivery, Polymers.

INTRODUCTION

These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend 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 tocompression. The materials most widelyused in preparing matrix systems includeboth hydrophilic and hydrophobicpolymers. Commonly available hydrophilicpolymers includeHydroxypropylmethylcellulose (HPMC),Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Xanthan gum, Sodiumalginate, Poly (ethylene oxide) and crosslinked homopolymers and copolymers of Acrylic acid. It is usually supplied inmicronized forms because small particlesize is critical to the rapid formation ofgelatinous layer on the tablet surface. Introduction of matrix tablet as sustainedrelease (SR) has given a new break through for novel drug delivery system (NDDS) inthe field of Pharmaceutical technology. Itexcludes complex production procedures such as coating and pelletization duringmanufacturing and drug release rate fromthe dosage form is controlled mainly by thetype and proportion of polymer used in thepreparations. Hydrophilic polymer matrix iswidely used for formulating an SR dosageform.

Drawbacks Associated withConventional Dosage Forms

Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

The unavoidable fluctuations of drugconcentration may lead to undermedication or over medication.

A typical peak-valley plasmaconcentration-time profile is obtainedwhich makes attainment of steady-statecondition difficult.

The fluctuations in drug levels may leadto precipitation of adverse effectsespecially of a drug

with smallTherapeutic Index (TI) whenever overmedication occur.
Recently, several advancements in drugdelivery system have been made toovercome the drawback of conventionaldrug delivery system. These techniquesare capable of controlling the rate ofdrug delivery, sustaining the duration oftherapeutic activity or targeting thedelivery of drug to a tissue.

CLASSIFICATION OF MATRIX TABLETS

(a)On the Basis of Retardant MaterialUsed

1. Hydrophobic Matrices (Plastic matrices)

The concept of using hydrophobic or inertmaterials as matrix materials was firstintroduced in 1959. In this method ofobtaining sustained release from an oraldosage form, drug is mixed with an inert orhydrophobic polymer and then compressedin to a tablet. Sustained release is produceddue to the fact that the dissolving drug hasdiffused through a network of channels that exist between compacted polymerparticles. Examples of materials that havebeen used as inert or hydrophobic matricesinclude polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers andtheir copolymers. The rate-controlling stepin these formulations is liquid penetrationinto the matrix. The possible mechanism ofrelease of drug in such type of tablets isdiffusion. Such types of matrix tabletsbecome inert in the presence of water andgastrointestinal fluid.

2. Lipid Matrices

These matrices prepared by the lipid waxesand related materials. Drug release fromsuch matrices occurs through both porediffusion and erosion. Releasecharacteristics are therefore more sensitiveto digestive fluid composition than tototally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol orstearic acid has been utilized for retardantbase for many sustained releaseformulation.

3. Hydrophilic Matrices

Hydrophilic polymer matrix systems arewidely used in oral controlled drug deliverybecause of their flexibility to obtain adesirable drug release profile, costeffectiveness, and broad regulatory acceptance. The formulation of the drugs ingelatinous capsules or more frequently, intablets, using hydrophilic polymers withhigh gelling capacities as base excipients isof particular interest in the field ofcontrolled release. Infect a matrix is definedas well mixed composite of one or moredrugs with a gelling agent (hydrophilicpolymer). These systems are calledswellable controlled release systems. Thepolymers used in the preparation ofhydrophilic matrices are divided in to threebroad groups.

A. Cellulose derivatives

Methylcellulose400 and 4000cPs, Hydroxyethylcellulose,Hydroxypropylmethylcellulose (HPMC) 25,100, 4000 and 15000cPs; and Sodiumcarboxymethylcellulose.

B. Non cellulose natural or semi syntheticpolymers

Agar-Agar; Carob gum; Alginates; Molasses;Polysaccharides of mannose and galactose,Chitosan and Modified starches.

Polymers of acrylic acid

Carbopol-934, themost used variety.

4. Biodegradable Matrices

These consist of the polymers whichcomprised of monomers linked to oneanother through functional groups andhave unstable linkage in the backbone. Theyare biologically degraded or eroded byenzymes generated by surrounding livingcells or by nonenzymetic process in tooligomers and monomers that can bemetabolized or excreted. Examples arenatural polymers such as proteins andpolysaccharides; modified natural polymers;synthetic polymers such as aliphatic poly(esters) and poly anhydrides.

5. Mineral Matrices

These consist of polymers which areobtained from various species of seaweeds.Example is Alginic acid which is ahydrophilic carbohydrate obtained fromspecies of brown seaweeds (Phaephyceae)by the use of dilute alkali.

On the Basis of Porosity of Matrix

Matrix system can also be classifiedaccording to their porosity andconsequently, Macro porous; Micro porousand Nonporous systems can be identified:

1. Macro porous Systems

In such systems the diffusion of drug occursthrough pores of matrix, which are of sizerange 0.1 to 1 μm. This pore size is largerthan diffusant molecule size.

2. Micro porous System
Diffusion in this type of system occursessentially through pores. For micro poroussystems, pore size ranges between 50 – 200A°, which is slightly larger than diffusantmolecules size.

3. Non-porous System
Non-porous systems have no pores and themolecules diffuse through the networkmeshes. In this case, only the polymericphase exists and no pore phase is present.

EFFECT OF VARIOUS PARAMETERS ONDRUG RELEASE
Drug release kinetics may be affected bymany factors such as polymer swelling,polymer erosion, drug dissolution/diffusioncharacteristics, drug distribution inside thematrix, drug/polymer ratio and systemgeometry (cylinder, sphere).

A. Drug solubility
Water solubility of drug and molecular sizeis another important factor which isconsidered in the release of drug fromswelling and erosion controlled polymericmatrices. For drugs with reasonableaqueous solubility, release of water solubledrugs occurs by dissolution in infiltratingmedium and the release of poorly watersoluble drug are occurs by both dissolutionof drug and dissolution of drug particlesthrough erosion of the matrix tablet.

B. Polymer hydration
It is important to study polymerhydration/swelling process for themaximum number of polymers andpolymeric combinations. The moreimportant step in polymer dissolution include absorption/adsorption of water inmore accessible places, rupture of polymerpolymerlinkings with the simultaneousforming of water-polymer linkings,separation of polymeric chains, swelling andfinally dispersion of polymeric chain indissolution medium.

C. Polymer diffusivity
The diffusion of small molecules in polymerstructure is energy activated process inwhich the diffusant molecules moves to asuccessive series of equilibrium positionwhen a sufficient amount of energy ofactivation for diffusion Ed has beenacquired by the diffusant is dependent onlength of polymer chain segment, crosslinking and crystallinity of polymer. Therelease of drug may be attributed to themainly two factors-

Viscosity: Increasing themolecular weight or viscosity of the polymer in the matrix formulationincreases the gel layer viscosity and thusslows drug dissolution.

Polymer concentration: An increase inpolymer concentration causes anincrease in the viscosity of gel as well asformulation of gel layer with a longerdiffusional path. This could cause adecrease in the effective diffusioncoefficient of the drug and thereforereduction in drug release.

D. Thickness of polymer diffusional path
The controlled release of a drug from matrixtype polymeric drug delivery system isessentially governed by Fick's law ofdiffusion:

$$JD = D\, dc/dx$$

Where,JD = flux of diffusion across a plane surfaceof unit area
D = is diffusibility of drug molecule,
dc/dx = is concentration gradient of drugmolecule across a diffusion path withthickness dx.

E. Thickness of hydrodynamic diffusionlayer
The drug release profile is a function of thevariation in thickness of hydrodynamicdiffusion layer on the surface of matrix typedelivery devices. As the thickness of hydrodynamic diffusion layer increases, themagnitude of drug release value decreases.

F. Drug loading dose
The release kinetics is significantly affectedby loading dose of drug. The effect of initialdrug loading of the tablets on the resultingrelease kinetics is more complex in case of poorly water soluble drugs, with increasinginitial drug loading the relative release ratefirst decreases and then increases, whereas,absolute release rate monotonicallyincreases. In case of freely water solubledrugs, the porosity of matrix upon drugdepletion increases with increasing initialdrug loading.

G. Surface area
Both the *in vitro* and *in vivo* rate of the drugrelease, are observed to be dependentupon surface area of dosage form. Therelease of drug from small tablet is fasterthan large cylindrical tablets.

H. Effect of diluent

The effect of diluent or filler depends uponthe nature of diluent. Water solublediluents like lactose cause marked increasein drug release rate and release mechanismis also shifted towards Fickian diffusion;while insoluble diluents like dicalciumphosphate reduce the Fickian diffusion andincrease the relaxation (erosion) rate ofmatrix. The reason behind this is that watersoluble filler in matrices stimulate the waterpenetration in to inner part of matrix, dueto increase in hydrophilicity of the system,causing rapid diffusion of drug, leads toincreased drug release rate.

I. Additives

The effect of adding non-polymericexcipients to a polymeric matrix has beenclaimed to produce increase in release rateof hydrosoluble active principles. Theseincreases in release rate would be marked ifthe excipients are soluble like lactose andless important if the excipients are insolublelike tricalcium phosphate.

POLYMERS USED IN THE MATRIX

The polymers most widely used in preparingmatrix system include both hydrophilic andhydrophobic polymers.

(A) Hydrophilic Polymers

Hydroxyl propyl methyl cellulose (HPMC),hydroxyl propyl cellulose(HPC), hydroxylethyl cellulose (HEC), Xanthan gum, Sodiumalginate, poly(ethylene oxide), and crosslinked homopolymers and co-polymers ofacrylic acid.

(B) Hydrophobic Polymers

This usually includes waxes and waterinsoluble polymers in their formulation.

(C) Waxes

Carnauba wax, bees wax, candelilla wax,micro crystalline wax, ozokerite wax,paraffin waxes and low molecular weightpolyethylene.

(D) Insoluble polymers

Ammoniomethacrylateco-polymers (Eudragit RL100, PO, RS100, PO), ethylcellulose, cellulose acetate butyrate,cellulose acetate propionate and latexdispersion of meth acrylic ester copolymers.

FACTORS AFFECTING DRUG RELEASEFROM MATRIX TABLETS

1. Swelling characteristics of polymers
2. Polymer erosion
3. Drug loading
4. Drug solubility

ADVANTAGES OF MATRIX TABLETS

1. Easy to manufacture.
2. Versatile and effective
3. It has low cost.
4. Can be made to release high molecularweight compounds.
5. Suitable for both non degradable anddegradable systems.
6. No danger of dose dumping in case ofrupture.
7. Can be fabricated in a wide range of sizesand shapes.

DISADVATAGES OF MATRIX TABLETS

1. The remaining matrix must be removedafter the drug has been released.
2. The drug release rates vary with thesquare root of time.
3. Achievement of zero order release isdifficult.
4. Not all drugs can be blended with a givenpolymeric matrix.
5. Water soluble drugs have a tendency toburst from the system.
6. Poor *in vitro – in vivo* correlation.
7. Possibility of dose dumping due to food,physiologic or formulation variables.
8. Retrieval of drug is difficult in case oftoxicity, poisoning or hypersensitivityreactions.
9. Reduced potential for dosage adjustmentof drugs normally administered invarying strengths.
10. Stability problems.
11. Increased cost.
12. More rapid development of toleranceand counselling.
13. Need for additional patient educationand counselling.

CRITERIA TO BE MET BY DRUGPROPOSED TO BE FORMULATED INSUSTAINED RELEASE DOSAGEFORMS.

a) Desirable half-life.
b) High therapeutic index
c) Small dose
d) Desirable absorption and solubilitycharacteristics.

e) Desirable absorption window.
f) First past clearance.

a) Desirable half-life

The half-life of a drug is an index of itsresidence time in the body. If the drug has ashort half life (less than 2 hours), thedosage form may contain a prohibitivelylarge quantity of the drug. On the otherhand, drug with elimination half-life of eighthours or more are sufficiently sustained inthe body, when administered inconventional dosage from, and sustainedrelease drug delivery system is generallynot necessary in such cases. Ideally, thedrug should have half-life of three to fourhours.

b) High therapeutic index

Drugs with low therapeutic index areunsuitable for incorporation in sustainedrelease formulations. If the system fails inthe body, dose dumping may occur, leadingto fatalities e.g. Digitoxin.

c) Small dose

If the dose of a drug in the conventionaldosage form is high, its suitability as acandidate for sustained release is seriouslyundetermined. This is chiefly because thesize of a unit dose sustained releaseformulation would become too big, toadminister without difficulty.

d) Desirable absorption and solubilitycharacteristics

Absorption of poorly water soluble drug isoften dissolution rate limited. Incorporating such Compounds into sustained releaseformulations is therefore unrealistic andmay reduce overall Absorption efficiency.

e) Desirable absorption window

Certain drugs when administered orally areabsorbed only from a specific part ofgastrointestinal tract. This part is referredto as the 'absorption window'. Drugsexhibiting an Absorption window likefluorouracil, thiazide diuretics, if formulatedas sustained release dosage forms areunsuitable.

f) First pass clearance

As discussed earlier in disadvantages ofsustained delivery system, delivery of thedrug to the body in desired concentrationsis seriously hampered in case of drugsundergoing extensive hepatic first passmetabolism, when administered insustained release forms.

DRUG RELEASE FROM MATRIX

Drug in the outside layer exposed to thebathing solution is dissolved first and thendiffuses out of the matrix. This processcontinues with the interface between thebathing solution and the solid drug movingtoward the interior. It follows that for thissystem to be diffusion controlled, the rateof dissolution of drug particles within thematrix must be much faster than thediffusion rate of dissolved drug leaving thematrix. Derivation of the mathematicalmodel to describe this system involves thefollowing assumptions:

a. A pseudo-steady state is maintainedduring drug release;
b. The diameter of the drug particles is lessthan the average distance of drug diffusionthrough the matrix;
c. The bathing solution provides sinkconditions at all times.The release behaviour for the system can bemathematically described by the followingequation:

$$Co.\ Dh - Cs/2 \text{----- (1)}$$

Where,
DM = Change in the amount of drugreleased per unit area
Dh = Change in the thickness of the zone ofmatrix that has been depleted of drug
Co = Total amount of drug in a unit volumeof matrix
Cs = Saturated concentration of the drugwithin the matrix.
Additionally, according to diffusion theory:

$$dM = (Dm.\ Cs / h).Dt \text{----- (2)}$$

Where,
dm = Diffusion coefficient in the matrix.
h = Thickness of the drug-depleted matrix
Dt = Change in time By combining equation 1 and equation 2 and integrating:

$$M = [Cs.\ Dm.\ (2Co - Cs).\ t]^{1/2} \text{------ (3)}$$

When the amount of drug is in excess of thesaturation concentration, then:

$$M = [2Cs.\ Dm.\ Co.\ t]^{1/2} \text{----- (4)}$$

Equation 3 and equation 4 relate theamount of drug release to the square-rootof time. Therefore, if a system ispredominantly diffusion controlled, then itis expected that a plot of the drug releasevs. square root of time will result in astraight line. Drug release from a porousmonolithic matrix involves the simultaneouspenetration of surrounding liquid,dissolution of drug and leaching out of thedrug through tortuous interstitial channelsand pores. The volume and length of theopenings must be accounted for in the drugrelease from a porous or granular matrix:

$$M = [Ds.Ca.p/T.\ (2Co - p.Ca)\ t]^{1/2} \text{------ (5)}$$

Where,
p = Porosity of the matrix
t = Tortuosity
Ca = solubility of the drug in the releasemedium
Ds = Diffusion coefficient in the releasemedium.
T = Diffusion path length for pseudo steadystate, the equation can be written as:

$$M = [2D.Ca\ .Co\ (p/T)\ t]^{1/2} \text{------ (6)}$$

The total porosity of the matrix can becalculated with the following equation:

$$p = pa + Ca/\rho + Cex / \rho ex \text{------ (7)}$$

Where,
p = Porosity
ρ = Drug density
pa = Porosity due to air pockets in thematrix
ρex = Density of the water solubleexcipients
Cex = Concentration of water solubleexcipients
For the purpose of datatreatment, equation 7 can be reduced to:

$$M = k.\ t^{1/2} \text{------ (8)}$$

itof drug released versus the square root oftime will be linear, if the release of drugfrom matrix is diffusion-controlled.

A. The swelling front. With the entry ofwater into the matrix, the polymerpasses from the crystalline state to ahydrated or gelified state.
B. The erosion front or dissolution front:This separates the gelified zone fromthe matrix of the solvent.
C. Diffusion front (solid drug–drug solutionboundary): This is located between theswelling and erosion fronts and itseparates the zone of the gelified matrixcontaining the drug dissolved in themedium from the zone of the matrixcontaining the undissolved solid drug.

EVALUATION OF SUSTAINED RELEASETABLETS

Before marketing a sustained releaseproduct, it is must to assure the strength,safety, stability and reliability of a productby forming in-vitro and in vivo analysis andcorrelation between the two. Variousauthors have discussed the evaluatingparameters and procedures for sustainedrelease formulations.

1. *In-Vitro* Methods

These are:-

a. Beaker method
b. Rotating disc method
c. Rotating Bottle method
d. Rotating Basket method
e. Stationary Basket Method
f. Oscillating tube method
g. Dialysis method
h. USP dissolution method.

2. *In–Vivo* Methods

Once the satisfactory in-vitro profile isachieved, it becomes necessary to conductin-vivo evaluation and establish in-vitro invivocorrelation. The various in-vivoevaluation methods are:-

a.Clinical response
b.Blood level data

c. Urinary excretion studies
d. Nutritional studies.
e. Toxicity studies
f. Radioactive tracer techniques

3. Stability Studies

Adequate stability data of the drug and itsdosage form is essential to ensure thestrength, safety, identity, quality, purity andin-vitro in-vivo release rates that they claimto have at the time of use. A sustainedrelease product should release apredetermined amount of the drug atspecified time intervals, which should notchange on storage. Any considerabledeviation from the appropriate releasewould render the sustained release productuseless. The in-vitro and in-vivo releaserates of sustained release product may bealtered by atmospheric or acceleratedconditions such as temperature & humidity.The stability programmes of a sustainedrelease product include storage at bothnominal and accelerated conditions such astemperature & humidity to ensure that theproduct will withstand these conditions.

***In vitro- In vivo* Correlations**

The requirement of establishing good *invitro - in vivo* correlation in thedevelopment of sustained release deliverysystems is self-evident. To make ameaningful in-vitro in-vivo correlation onehas to consider not only the pharmaceuticalaspect of sustained release drug deliverysystem but also the biopharmaceutics andpharmacokinetics of the therapeutic agentin the body after its release from the drugdelivery system and also thepharmacodynamics of therapeutic agent atthe site of drug action. A simple in vitro-invitro relationship can be established byconducting in-vitro and in-vivo evaluationsof a potential drug delivery systemsimultaneously to study and compare themechanism and rate profiles of sustaineddrug release. When the in-vivo drug releasemechanism is proven to be in goodagreement with that observed in the invitrodrug release studies, then in-vitro invivocorrelation factor is derived. Forcapsule type drug delivery system the factorcan be represented as:

$$Q = \frac{(Q/t)\ \textit{In-vivo}}{(Q/t)\ \textit{In-vitro}}$$

Where,
Q/t = Rate of release

'Q' values are dependent profiles of drugdelivery systems. Upon the sites ofadministration and environmentalconditions to which the animals areexposed during treatment (study).The above relationship can be used foroptimization of sustained release Levy hasclassified *In-vivo-In-vitro* correlation in to:

A. Pharmacological correlations based onclinical observations;
B. Semi-quantitative correlations based onblood levels or urinary excretion data;
C. Quantitative correlation arising fromabsorption kinetics. While most of thepublished correlations are of semiquantitativenature, the most valuableare those based on absorption kinetics.

Bioavailability Testing

Bioavailability is generally defined as therate and extent of absorption of unchangeddrug from its site of application to thegeneral circulation. Bioavailability is definedin terms of a specific drug moiety, usuallyactive therapeutic entity, which may be theunchanged drug or as with prodrug, forinstance, a metabolite. In contrast, the term"absorption" often refers to net transportof drug related mass from its site ofapplication into the body. Hence, acompound may be completely absorbed butonly partially bioavailable as would occur,when low bioavailability is caused byincomplete absorption. Pharmaceuticaloptimization of the dosage form may bewarranted to improve absorptioncharacteristics of the drug and thereby alsoits bioavailability. Bioavailability studies areordinarily single dose comparisons of testeddrug product in normal adults in a fastingstate. A crossover design, in which allsubjects receive both, the product andreference material on different days, ispreferred. Guidelines for clinical testinghave been published for multiple dosestudies. Correlation of pharmacologicalactivity or clinical evidence of therapeuticeffectiveness with bioavailability may benecessary to validate the single significanceof sustained release claims. While singledose studies are usually sufficient toestablish the validity of sustained releasedosage form design; multiple dose studiesare required to establish optimum dosingregimen. They are also required whendifference may exist in the rate but not theextent of absorption. When there isexcessive subject-to subject variation orwhen the observed

blood levels after asingle dose are too low to be measuredaccurately. A sufficient number of dosesmust be administered to attain steady stateblood levels. According to an extensivestudy of sustained release Theophyllineproducts; for example, encapsulated formsshowed less peaking during multiple dosingand therefore better control of blood levelwithin the desired limits.

CONCLUSION

By the above discussion, it can be easilyconcluded that sustained-releaseformulation are helpful in increasing theefficiency of the dose as well as they arealso improving the patient's compatibilitymatrix forming polymers can be successfullyused to prepare Matrix tablets, releasingdrug in a controlled manner. Preparatoryprocedures easily allow adaptation ofrelease kinetics to delivery needs. Thissuitability of matrix forming polymers, tovarious drug delivery systems preparationconfirms the importance of thesespecialized excipients in pharmaceuticalapplication. They represent the choicesolution for many oral delivery problemslike fluctuating drug plasma levels, lowbioavailability, more frequent doseadministration etc. So matrix tablets canovercome the above problems ofconventional oral drug delivery.

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