Oral Sustained Release Matrix Tablets – A Review

Shubham Udaysinh Mohite

ABSTRACT –
Matrix tablets have been the most likely forms of sustained drug release forms designated by the oral route. Matrix tablets work by maintaining a constant plasma drug concentration and sustains the drug over time and produces therapeutic action for a prolonged period. Sustained medication discharge definitions are very useful in long haul sicknesses. The polymer controls the release rate of drug. The medication discharge rate can be contemplated on lab based dissolution.

Keywords – Sustained release matrix tablet, drug selection, mechanism, drug release factors, polymers.

I.   INTRODUCTION:

Solid dosage form in which API is uniformly dispersed in hydrophilic or hydrophobic polymers which retards the release rate of drug.[1] Sustained release system give first order release kinetic study.[2] The design of sustained release matrix tablet is depend on factors such as type of delivery system, the length of therapy, the disease being treated and properties of drug, the patient.[3] Sustained release tablets are generally taken once or twice a day during a course of treatment whereas in conventional dosage form there is need to take 3 to 4 times dosage in a day to achieve the same therapeutic action. The important role behind administering a single dose of Sustained release matrix tablet is that it can be released over an extended period of time to maintain uniform concentration of drug in a blood this may lead to better patient compliance.[4] Release rate of drug is controlled by taking various batches of drug and polymer proportion and type of polymer.[5]

ADVANTAGES:
- Can be made to release high molecular weight Drugs.
- Reduce the toxicity by slowing absorption of drug.
- Effective, versatile and low cost.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Usage of total drug is less.[6]

- No see-saw fluctuations in plasma drug concentration profile.
- Temporal effects can be provided. Example. Morning effect of arthritis through bed time dosing.[7]

DISADVANTAGES:
- Achievement of zero order release is difficult.
- Possibility of dose dumping due to food, physiologic and formulation variables.
- Need of additional patient education and counseling.[5]
- High cost required for production.
- Poor in vitro-in vivo correlation.[6]

Rationale For Developing Sustained Release Matrix Tablets:
- To minimize the fluctuations in plasma level.
- Improved drug utilization.
- To decrease the frequency of dosing.
- To sustain the duration of action of the drug.
- To reduce adverse effects.[8]

Characteristics Of Drug Suitable For Sustained Release Matrix Tablet:
The ideal physicochemical and pharmacokinetic properties of medications which can be defined as Sustained Release Matrix Tablet are as per the following:
- Molecular size less than 1000 Dalton.
- Aqueous solvency have to be in excess of 0.1 mg/ml for pH 1 to pH 7.8.
- The partition coefficient have to be high.
- Elimination half-life between 2 to 8 hrs.
- Absolute bioavailability should be 75% or more.[9,10,11]
- Dose size is 0.5-1.0gm.
- Drugs should not be able to first pass metabolism.
- Drug should have wide therapeutic index. [12]

MECHANISM OF DRUG RELEASE FROM MATRIX DEVICES:
1) **Dissolution Controlled Release:**
2) **DIFFUSION CONTROLLED RELEASE:**
1) **Dissolution Controlled Release:**
Sustained release matrix tablets employing dissolution as the time limiting step are easy to

prepare. If a drug has a fast rate of dissolution it is possible to fill it into a tablet with a carrier that has a slow rate of dissolution. Dissolution process described by Noyes-Whitney equation,

$$dc/dt = KDA (Cs-C)$$

Where,
dc/dt = Dissolution rate.
KD = Dissolution rate constant.
Cs = Saturation solubility of drug.

C = The concentration of drug in solution.

Dissolution control formulations are categories as follows
- **Matrix dissolution control**
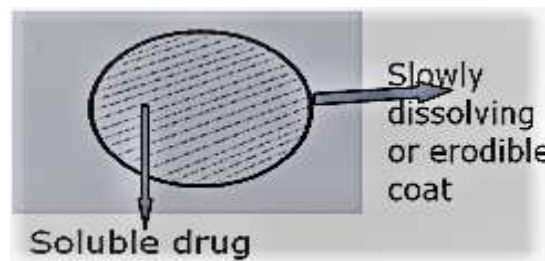- **Encapsulation dissolution control**

Matrix dissolution control
This method include compression of drug and slowly dissolving polymer.

Figure 5. Diagrammatic representation of matrix dissolution sustained system
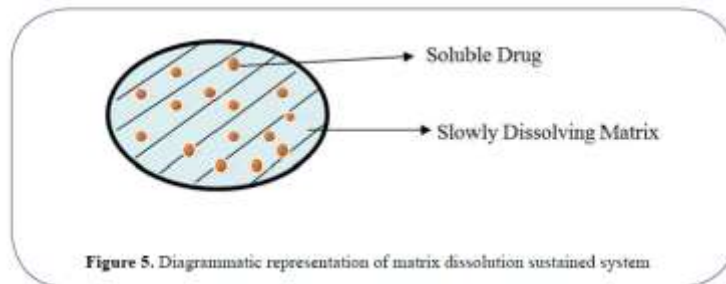
Encapsulation dissolution control
This method involves coating individual granules or particles of drug with slowly dissolving material. The coated particles can be compressed directly into tablet.
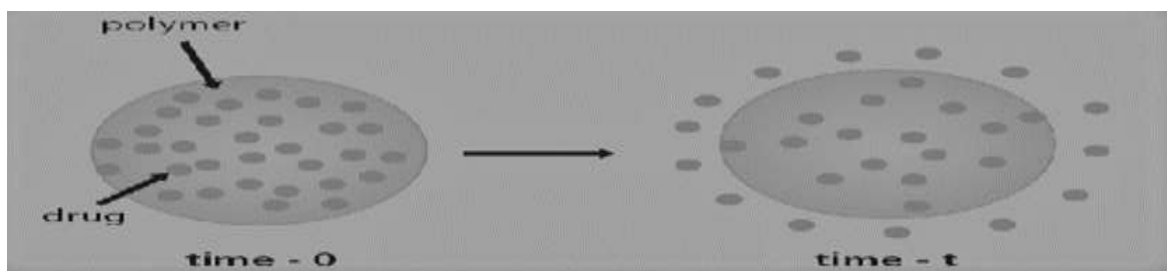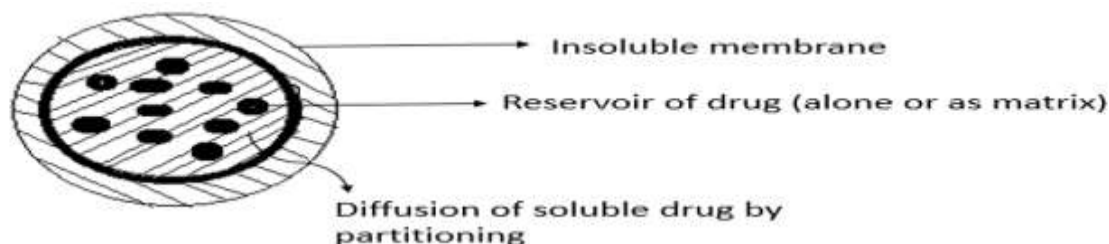

2) Diffusion controlled release:
These systems have two types which are as follows
- **Matrix diffusion control**
- **Encapsulation diffusion control**

Matrix diffusion control[13]

Encapsulation diffusion control [13]

Insoluble membrane
Reservoir of drug (alone or as matrix)
Diffusion of soluble drug by partitioning

CLASSIFICATION OF MATRIX TABLET:
1) On the basis of retardant material:
(a) Hydrophobic matrix
Water insoluble polymer.
Example – PVC, EC, MA. [13,14]

(b) Hydrophilic matrix
Water soluble polymer.
Most commercial hydrophilic matrices are obtained by compression.
Example – HPMC, HEC, HPC.[11, 13]

(c) Lipid matrix
These matrices are prepared by lipid, waxes. [13]

2) On the basis of porosity of matrix:
(a) Micro porous System
In this type of system diffusion occur through pores. For Micro-Porous system, pore size range is 50 – 200A°, which is more than diffusing molecule.
(b) Macro porous Systems
Diffusion occurs through pores of the matrix. which are of size range 0.1 to 1 µm.
Pore size is larger than diffusing molecule size.
(c) Non-Porous Systems
It does not contain pores, molecules pass in network mesh.[13]

Half life indicates residence time of drug in body.

Half life less than 2 hours	Require more quantity of drug.
Half life 8 hours or more	Drud sustained in the body.

b) Size of dose
If the dose size is large then it is not suitable for Sustained release matrix tablets, because sustained release matrix tablets of high doses create toxic reaction in body because it is stay in body for long time.

FACTORS INFLUENCING IN SUSTAINED RELEASE DRUG DELIVERY SYSTEM:
1) Physicochemical factors:
a) Partition constant (P (o/w))
In that solubility of drug is affected whether drug is water soluble or lipid soluble.
b) Drug pKa and ionization at physiological pH
Ionized drugs are not easily penetrate but nonionized drugs are easily penetrate. Nonionised drugs are 3 to 4 times more absorbed than ionised drug. The dissociation constant of acidic drug is in between 3 to 7.5 and basic drug is in between 7 to 11.
c) Aqueous Solubility
Drugs are weak acids and weak bases. BCS category I and BCS category II medication are sensible for sustained release matrix tablets. Whereas BCS III and BCS IV are poor for sustained release matrix tablets.

d) Drug stability
Drugs endure each acid/base chemical reaction and degradation by enzymes, when administered orally.

2) Biological factor:
a) Half-life

c) Absorption window
When drugs are taken orally then drugs are absorbed only in specific part of GIT.

d) Plasma concentration response relationship
Pharmacological activity is depend on the plasma drug concentration. If pharmacological activity of drug are not depend on plasma

concentration then this compounds are poor for sustained release matrix tablets.[15, 16,17,18]

Mechanism Of Drug Release From Sustained Release Matrix Tablet:
First Order Kinetics
A first order release would be predicted by the equation

$$Log\ Q_t = Log\ Q_o - K_1 t / 2.303$$

Where, Q_t = Amount of drug released,
Q_o = Initial amount of drug concentration in solution.
$K_1 t$ = First order rate constant.
It represents drug release follow first order kinetics. The constant K can be obtained multiplying slope values.

Zero Order Kinetics
Zero order release determined by -

$$Q_t - Q_0 = K_0 t$$

Where, Q_t = Amount of drug release dissolved,
Q_o = Initial amount of drug concentration in solution.
$K_0 t$ = Zero order rate constant.
This model represents an ideal release profile.

Higuchi's Model
Higuchi's Diffusion equation

$$f_t = Q = \sqrt{D\ \delta / \tau\ (2 C - \delta Cs)\ Cst}$$

Where, Q = Amount of drug released,
D = Diffusion coefficient of the drug in the matrix.
Cs = Solubility of the drug in the matrix.
δ = Porosity of matrix.
τ = Tortuosity. t = Time (h).
The equation may be simplified then equation becomes;

$$f_t = Q = K_H \times t^{1/2}$$

Where, K_H = Higuchi dissolution constant.

Peppas Korsmeyer Equation

$$A_t / A_\infty = k t^n$$

Where, k = Constant,
n = Release. t = Time.
A_∞ = Absolute cumulative amount of drug.
A_t = drug released at time t.

Hixon-Crowell Equation
Hixon-Crowell equation

$$W_0^{1/3} - W_t^{1/3} = ?t$$

Where, W_0 = Initial amount of drug.
W_t = Remaining amount of drug.
t = Time.
? = Constant (Kappa). [19, 20, 21]

METHOD OF PREPARATION OF MATRIX TABLET:
a) **Sintering Technique**
b) **Wet Granulation**
c) **Dry Granulation**
d) **Direct compression**

a) **Sintering Technique:**
For determination mechanical strength this technique is used. It involves heating of
Pre-compressed material below melting point of ingredients and then compressed.

b) **Wet Granulation:**
- Mixing of drug, polymer and diluent.
- Wet massing by addition of granulating solvent.
- Screening of wet mass.
- Drying of the wet granules.
- Screening of dry granules.
- Blending with lubricant and glidant to produce "running powder".
- Compression of granules to produce tablet.

c) **Dry Granulation:**
- Milling and mixing of drug, polymer and excipients.
- Compression into slugs or roll compaction.
- Milling and screening of slugs and compacted powder.
- Mixing with lubricant and glidant.
- Compression slugs to form tablet.[22]

d) **Direct Compression:**
- Weigh drug, polymer, and diluents and pass through sieve.
- Powder blend was prepared.
- At the time of compression lubricant and glidant are add compress the blend in tablet form.[23]

LIST OF API FORMULATED USING DIFFERENT METHOD AND POLYMER

DRUG	METHOD	POLYMERS
Ibuprofen	Wet Granulation	EC, CAP
Metformin HCL	Direct Compression	HPMC-K100M, EC
Aceclofenac	Wet Granulation	HPMC-K4M, K15M, K100M,E15,EC, Guar gum
Aspirin	Direct Compression	EC, Eudragit-RS100, S100
Diclofenac Na	Wet Granulation	Chitoson, EC, HPMCP, HPMC
Naproxen	Direct Compression / Wet Granulation	HPMC, CMC, EC, SSG
Phenytoin Na	Direct Compression	Tragacanth, Acacia, Guar gum
Ranitidine HCL	Wet Granulation	Chitoson, Carbopol-940
Propranolol HCL	Wet Granulation	Locust bean gum, HPMC
Ambroxol HCL	Direct Compression	HPMC-K100M,
Verapamil [24]	Direct Compression	HPMC-K100M, K4M, K15M[15]
Glimepiride [25]	Wet Granulation	HPMC (CPC), HPC, Ethyl Cellulose
Glipizide [26]	Direct Compression	HPMC K4M, HPMC K15M, HPMC K100M, HPMC E15 and sodium CMC
Glibenclamide [27]	Direct Compression	HPMC

Evaluation of Sustained Release Matrix Tablets:
1. Pre-compression study –
a) Angle of repose –

$$\text{Tan } \theta = h/r \text{ or}$$
$$\theta = \text{Tan}^{-1} h/r$$

Where h is height and r is radius of powder circle.

FLOW PROPERTY	ANGLE OF REPOSE
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very, very poor	More than 66

b) Bulk density and Tapped density –
Bulk density is Mass per volume.
Tapped density is tapped mass per volume.
It is expressed in gm/ml.
c) Carr`s compressibility index –

Compressibility Index	Properties
Less than 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor

32-37	Very poor
More than 38	Very, very poor [28]

d)   Hausner ratio –
Hausner ratio is tapped density upon bulk density. [29]

Less than 1.25	Good
More than 1.25	Poor

2.   Post-compression Study –
a)   Thickness of tablet –
Thickness of tablet is measured by using vernier caliper.

b)   Hardness of Tablet –
Hardness is measured by Monsanto hardness tester or Pfizer tablet tester and values are record, and mean of recorded values are taken and calculated actual hardness of tablet.

c)   Uniformity of Weight –
20 tablets are selected randomly and weighed individually. Average weight is calculated.

USP standards	Max. % difference allowed	BP/IP standards
130 mg or less	10%	84 mg or less
130mg -324 mg	7.5%	84 mg – 250 mg
More than 325 mg	5%	More than 250 mg

d)   Uniformity of content -
This test is performed for evaluating all tablets contain same amount of content or not. For this test take 30 tablets, assay of 10 tablets was carried out.

Pharmacopoeial standard	% mg
USP	Less than 25mg / 25%.
IP	Less than 10mg /10%.
BP	Less than 2mg / 2%.

e)   Friability –
        20 tablets are weighed and placed in friabilator. Before the operation all tablets are weighed individually. The chamber is rotated for 100 RPM which is covered in 4 minutes. After the operation all tablets are weighed individually. Loss in weight indicates friability.

f)   In vitro dissolution studies –
        This test is used for determine how much time required to release 100% of drug. Paddle type and basket type apparatus mostly used as mentioned in monograph of specific drug. [30]

3.   In–vivo Methods:
The in-vivo evaluation methods are:
•   Blood Level Data
•   Urinary Excretion Studies
•   Clinical Response

•   Nutritional Studies
•   Toxicity Studies
•   Radioactive Tracer Technique

4.   In-vitro Methods:
•   USP dissolution method.
•   Dialysis method
•   Beaker method
•   Rotating Bottle method
•   Rotating disc method
•   Rotating Basket method
•   Stationary Basket Method
•   Oscillating Tube method

5.   Stability Studies:
        Stability study is important for determining its shelf life. Stability changes due to conditions such as humidity and temperature. For

stability operation of a sustained release matrix tablet, tablet is stored at both low and high temperature to check formulated product is thermo stable or not and also tablet stored at high and low humidity

and check tablet is stable or not or any change occur in product .[31]

Patented Sustained Release Dosage Forms:
Report on patents of Sustained Release Matrix Tablets

- **Patel VS** has created sustained release capsule for oral administration.[32]
- **Belenduik GW et al.** formulated (CA2238930) Sustained Release pharmaceutical composition comprising a highly soluble selegiline. [33]
- **Brubaker MJ et al.** prepare (2002) sustained release delivery devices with multiple agents. [34]
- **Viscasillas S** has described (US2004) on Sustained Release devices with coated API.[35]
- **Chen J et al**. invented (CA2530113 and US20050025834) bio erodible Sustained Release Drug Delivery System. [36,37]
- **Cho SH et al**. explained (KR2005) SRDDS which sustains drug effectively in GI tract. [38]
- **Desai DS et al.** displayed (US2006) SRDDS and method**.**[39]
- **Cho SH et al**. patented (US20070275066) to SRDDS.[40]
- **Amidon GE et al**. Sustained Release composition in an orally administered tablet. [41]
- **Chen J et al**. invented (US20120016467) polymer based Sustained Release Drug Delivery System. [42]
- **Buan C et al**. generated (2012) Sustained Release formulation.[43]

II. CONCLUSION:
Sustained Release Matrix Tablets can overcome the problems of conventional oral drug delivery, improve efficacy of dosage form, improve patient compliance. As contrast with traditional medication delivery matrix supported delivery drug conveyance matrix give amazing medication discharge property. It gives therapeutic effect of drug for long duration in just a single dose.. This article may be beneficial for many researcher interested to work on the Sustained release matrix tablets.

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