A REVIEW ON SWELLABLE MATRIX TABLETS OF NSAID USING NATURAL POLYMER

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ABSTRACT

Oral drug delivery is one of the most common and convenient route for drug administration. Tablet is the most widely used oral pharmaceutical dosage form due to its ease of administration, least aseptic, and flexibility in the design of dosage form. There are various formulation strategies for sustained release tablets among which matrix tablet serves as an important tool. In simplest word, matrix is defined as a well composite of one or more drug with a gelling agent and can be formulated by either direct compression or wet granulation method. The use of different polymers in controlling the release of drugs has become the most important tool in the formulation of matrix tablets. The release of the drug through such system includes both dissolution controlled as well as diffusion controlled mechanisms. There are several advantages of matrix devices including improved patient compliance, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, and increased safety margin of a potent drug. The objective of this review focuses on oral sustained release tablets with a special emphasis on swellable matrix tablet of Non Steroidal Anti-Inflammatory Drug using natural polymer.

Keywords: Gelling Agent, Matrix tablet, Natural polymer, NSAID, Sustained release.

INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. Drug delivery system is an interface between the patient and the drug. It may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug. This distinction between the drug and the device is important, as it is the criterion for regulatory control of the delivery system by the drug or medicine control agency.

There are various anatomical routes for the administration of medical drugs into body. The selection of the route depends on the effect needed, type of the disease and type of the product. Drug will be administered either directly to the organ which suffer from disease or given systematically and targeted to the infected organ. The most common routes of drug administration include the following:

- **Oral route:** This is the oldest route which has been used for conventional and novel drug delivery. They are highly preferred because ease of administration and the highly accepted and comfortable for the patients.
- **Parenteral route:** This route means the introduction of medical therapy into the patient body through different routes other than oral route, these routes include intramuscular, intravenous, intra-arterial and subcutaneous route. This route considered as a very important role in the medical field.
- **Transdermal route:** In this route the medical treatment will apply on the body surfaces such as the skin or mucous membrane. This route of administration significantly associated with local effect rather than systemic effect. Moreover, this route will transfer the active ingredients directly to the systematic circulation without gastrointestinal and liver metabolism.
- **Inhalation route:** In this type the medical treatment will directly reach the lungs, and hence it avoids systemic effect i.e., increase the bioavailability of the drug in the system. This route is more preferable for treatment of respiratory diseases.

Traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a formulation with control release that maintain a near-constant or uniform blood level. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

Drawbacks of Conventional 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 drug concentration may lead to under medication or over medication.

- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

These drawbacks are overcome by formulating controlled release dosage form which leads to fruitful changes in medical field. Amazing feature of controlled release formulation is that they release one or more drugs continuously in predetermined pattern for a fixed period of time. More concentrated studies are paid on development of oral controlled release drug delivery systems due to flexibility in designing of dosage form. The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. These challenges can solved by control release dosage form which provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects.

Diclofenac sodium is a well-known representative of non-steroidal anti-inflammatory drugs, widely used to control pain and inflammation of rheumatic and non-rheumatic origin. The conventional tablets make the drug immediately available for absorption in upper GI tract resulting local GI toxicity varying from minor gastric discomfort to ulceration and bleeding of the mucosa. It is well documented that the GI toxicity is not only caused by the inhibition of the prostaglandin synthesis, but is probably also due to direct contact of the drug with the mucosa. In addition, due to the rapid systemic clearance of this drug, repeated daily dosing of 3 to 4 times a day is required in maintenance therapy that influences patient compliance. Sustained release formulations of diclofenac sodium are thus warranted to promote patient compliance and to reduce upper GI toxicity to some extent.

SUSTAINED RELEASE DOSAGE FORMS

Any drug or dosage form modification that prolongs the therapeutic activity of the drug is known as sustained release dosage form(SRDF).The release of the drug is retarded for a delayed and prolonged period of time in the systemic circulation. Sustained release formulation maintains a uniform blood level of drug with better patient compliance as well as increased efficacy of drug. Sustained release tablets are generally taken once or twice a day during a course of treatment whereas in dosage forms there is need to take 3-4 times dosage in a day to achieve the same conventional therapeutic action.

Sustained drug delivery systems significantly improve the therapeutic efficacy of drugs. Drug release-retarding polymers are the key performers in such systems. Sustained release delivery systems can achieve non-predictable and non-reproducible release rate, extended duration of activity for drugs with half-life 2-4hrs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance. Sustained release formulations can offer many pharmacokinetic and pharmacodynamic advantages over conventional dosage forms, including maintenance of constant therapeutic levels for a longer period of time and reduction of fluctuations in plasma drug concentrations. Sustained release formulations can reduce the risk of treatment failure due to inadequate dosing of antibiotics.

Modified release system

A) Delayed Release: These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Sustained release: These systems also provide a slow release of drug over an extended period of time and also can provide some control 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.

   1) **Controlled Release:** These systems include any drug delivery system that achieves slow release of drug over an extended period of time.
   2) **Extended Release:** Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) Site specific targeting: These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting: These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.

Rationale for developing of sustained release drug delivery systems

   - To extend the duration of action of the drug
   - To reduce the frequency of dosing
   - To minimize the fluctuations in plasma level
   - Improved drug utilization
   - Less adverse effects.

PRINCIPLE OF SRDDS

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme. The absorption pool represents a solution of the drug at the site of absorption, Kr, Ka and Ke - first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. For non-immediate release dosage forms, Kr<<<Ka that is, the release of drug from the dosage form is the rate limiting step. The drug release from the dosage form should follow zero-order kinetics, as shown by the following equation:

$Kr° = $ Rate In = Rate Out = $Ke.Cd.Vd$-------------- (1)

Where, $Kr°$ =Zero-order rate constant for drug release-amount/time

Ke = First-order rate constant for overall drug elimination-time

Cd = Desired drug level in the body – amount/volume

Vd = Volume space in which the drug is distributed in litre.

Advantages of SRDDS

- ➢ Reduced dosing frequency
- ➢ Improved patient compliance
- ➢ Reduces the fluctuation of peak-valley concentration
- ➢ Economic
- ➢ Dose reduction

Disadvantages of SRDDS

- ➢ Reduced potential for dose adjustment
- ➢ Probability of dose dumping .
- ➢ Increase potential for first-pass metabolism
- ➢ Cost of single unit higher than conventional dosage forms
- ➢ Poor *in vitro* and *in vivo* correlations.

Ideal properties of drug suitable for SRDDS

- ❖ Drug should have a shorter half-life as drugs with a longer half-life are inherently long acting drugs.
- ❖ Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur throughout the gut.
- ❖ Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- ❖ Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

Challenges for SRDDS
Dose dumping

This can greatly increase the concentration of a drug in the body and there by produce adverse effects or even drug induced toxicity. Dose dumping means the relatively large quantity of medication in a sustained release formulation is rapidly released. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index .Example:Phenobarbital.

Limited choice of selecting desired dose in the unit

In case of conventional dosage forms, the dose adjustments are much simple. Example,Tablet can be divided into two portions. In case of sustained release dosage forms, this can appear to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

Poor *in-vitro – in-vivo* correlation

In sustained release dosage form, the rate of drug release is slowly reduced to achieve drug release possibly over a large region of gastrointestinal tract. Hence the so called 'Absorption window' becomes important and gives rise to unsatisfactory drug absorption *in-vivo* despite excellent *in-vitro* release characteristics.

Patient variation

The time period required for absorption of drug released from the dosage form may vary among individuals. The co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patients.

Criteria for drug selection of SRDDS

- o Desirable half-life
- o High therapeutic index:
- o Small dose
- o Desirable absorption and solubility characteristics
- o Desirable absorption window.
- o First pass clearance.

Goals in designing SRDDS

- ➢ It would be a single dose for the duration of treatment whether it is for days or weeks, as with infection or for the life time of the patient, as in hypertension or diabetes.
- ➢ It should deliver the active entity directly to the site of action, minimizing or eliminating side effects.
- ➢ This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.

The safety margin of high potency drug can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

Drug properties influencing the design of SRDDS

The drug properties influencing the design of SRDDS are classified as:

1] Physicochemical properties of the drug

These include dose size, aqueous solubility, protein binding, molecular size, drug stability and partition coefficients.

2] Biological properties of the drug

These include absorption, distribution, metabolism, and duration of action, margin of safety, side effects of drug, disease state and circadian rhythm.

Classification of sustained release formulation

A) Diffusion sustained system:

Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount/area-time), across a membrane in the direction of decreasing concentration is given by Fick's law.

J= - D dc/dx

D = diffusion coefficient in area/ time

dc/dx = change of concentration 'c' with distance 'x'

In common form, when a water insoluble membrane surrounds a core of drug, it must diffuse through the membrane; the drug release rate dm/dt is given by,

dm/dt= ADK. C/L

Where, A = Area

K = Partition coefficient of drug between the membrane and drug core

L= Diffusion path length (that is thickness of the coat in ideal case).

C = Concentration difference across the membrane.

1) Diffusion reservoir system: In this system, a water insoluble polymeric material which covers a core of drug, will partition into the membrane and exchange with the surrounding fluid the particle or tablet. Additional drug will enter into polymer, diffuse to the periphery and exchange with the surrounding media. The drug release takes place by diffusion mechanism.

Characterization

Description*:* Drug core surrounded by polymer membrane which controls release rate.

Advantages*:* Zero order delivery is possible, release rates variable with polymer type.

Disadvantages: System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails.
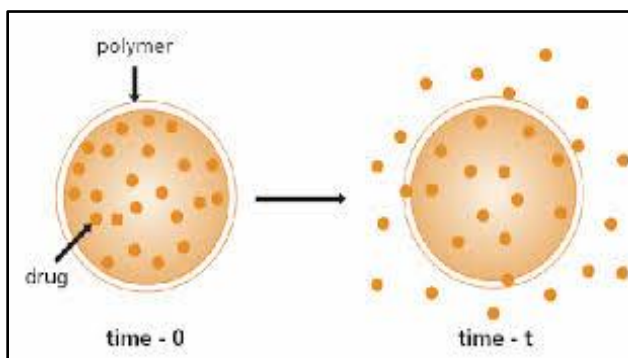

Figure 1: diffusion reservoir system

2) Diffusion matrix system: A solid drug is distributed into an insoluble matrix and the release rate of drug which generally depend on the rate of drug diffusion and the rate of solid dissolution. Higuchi has derived the appropriate equation for drug release for this system.

$$Q = D/T \ [2A–Cs] \ Cst \ ½$$

Where, Q = weight in gms of drug released per unit area of surface at time t.

D = Diffusion coefficient of drug in the release medium.

ε = porosity of the matrix.

Cs = solubility of drug in release medium.

T = Tortuosity of the matrix.

A = concentration of drug in the tablet, gm/ ml.

The release rate can be given by following equation:-

$$\text{Release rate} = AD/ \ L = [C1\text{-}C2]$$

Where, A = Area

D = Diffusion coefficient

C1 = Drug concentration in the core

C2 = Drug concentration in the surrounding medium

L = Diffusion path length

Characterization

Description: Homogenous dispersion of solid drug in a polymer mixture.

Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.
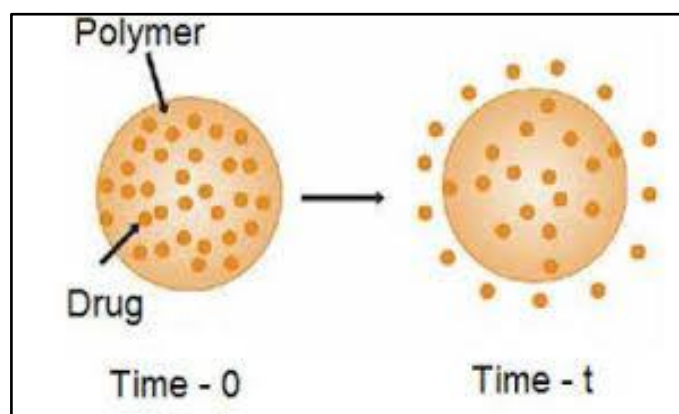

Figure 2: Diffusion matrix system

B) Dissolution sustained systems:

Drugs which have a slow dissolution rate are naturally sustained and drugs with high water solubility can be sustained by decreasing their dissolution rate through appropriate salt or derivative formation. These systems are generally employed in the manufacturing of enteric

coated dosage forms. Protection of stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the dosage form until it reaches the higher pH of the intestine.

a) Soluble reservoir system: In this system drug is coated with erodible coat, which is slowly dissolved in the contents of GI tract by alternating layers of drug with the rate controlling coats.
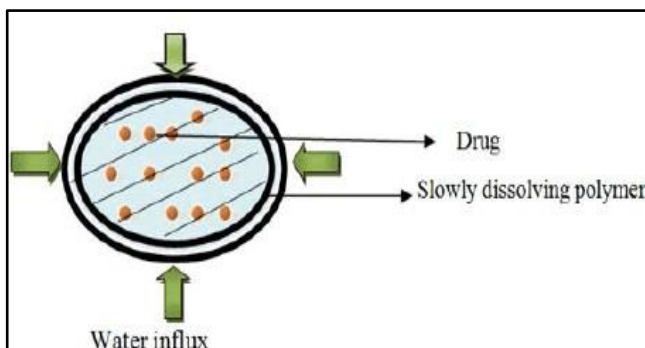

Figure 3: Soluble reservoir system

b) Soluble matrix system: It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.
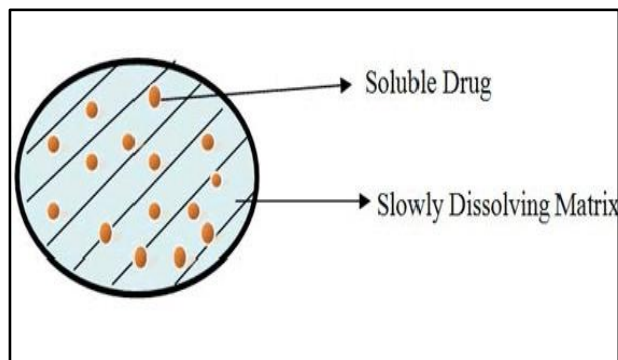

Figure 4: Soluble matrix system

C) Methods using Ion Exchange:

The use of ion exchange resin is an attractive method for sustained drug delivery as drug release characteristics largely depend only on the ionic environment of resins containing drug and is less susceptible to environmental condition like enzyme contents and pH at the absorption site. Zero order release kinetic can satisfactorily be attained using this approach. Ion exchange based delivery system represent better approach for a drug that is highly susceptible to degradation by enzymatic process. Ion exchange resin which are divided into 2 types:

       a. Cationic exchange resin
       b. Anionic exchange resin

Cationic exchange resin: Contains acidic functional group with polysteryne polymer, phenolic or carboxylic phenolic group.

Anionic exchange resin: Involves basic functional group capable of extracting anions from acidic solution. Ion exchange resins are used to sustain the effect of drug based on the concept that negatively or positively charge drug moiety combines with appropriate resin producing insoluble poly salts resonates.

Table 1: Resin type and their chemical constituent

Resin type	Chemical constituent
Strong acidic cationic exchanger	Sulfonic acid group attached to a styrene and divinyl benzene co-polymer.
Weak acidic cationic exchanger	Carboxylic acid group linked to an acrylic acid and divinyl benzene co-polymer.
Strong basic anion exchanger	Quaternary ammonium groups attached to a styrene and divinyl benzene co-polymer.
Weak basic anion exchanger	Polyalkylamine copolymer group linked to a styrene and divinyl benzene co-polymer.

D) pH– Independent formulations:

The chemical environment throughout the gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid, phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agents, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release. example. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

E) Methods using osmotic pressure:

Osmotic pressure is employed as the driving force to generate a constant release of drug. A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

Two types of osmotically sustained systems are:-

Type A contains an osmotic core with drug

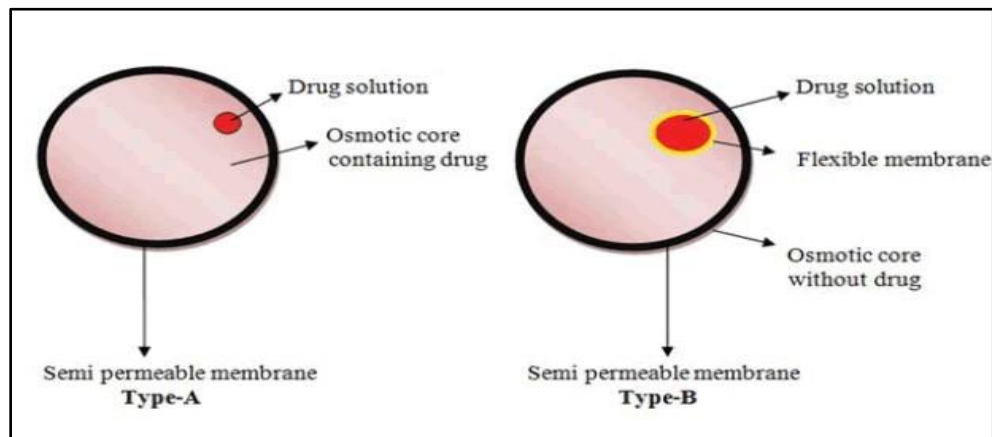Type B contains the drug in flexible bag with osmotic core surrounding.

Figure 5: Type A and B osmotically sustained system

F) Altered density formulations:

If the contents of dosage forms are not released in the GI tract then it may have a limited use. To this end, various approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

High density approach:
In this approach the density of the pellets should be more than that of normal stomach content and should therefore, be at least 1-4gm/cm^3. In preparing such formulations drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder and zinc oxide.

Low density approach:
Globular shells which have density lower than that of gastric fluid are used as carriers of drug for sustained release purpose. Polystyrol, pop rice and popcorn are used as carriers. The surface of these empty shells is undercoated with sugar or with polymeric material such as methacrylic polymer and cellulose acetate phthalate. The undercoated shell is then coated by mixture of drug with polymer such as ethyl cellulose and Hydroxy propyl cellulose. Thus the final product floats on the gastric fluid for a prolonged period, while releasing the drug slowly.

G) Swelling and expansion systems:
Conventional hydrogels swell slowly upon contact with water due to their small pore size, which usually ranges in the nanometers and low micrometer scale. However if the hydrogel has a pore size of more than 100 µm, swelling is much faster and may lead to a large increase in size. Swelling ratios of over 100 can be achieved. These swollen systems become too large to pass through the pylorus and thus may be retained in the stomach.

H) Floating systems:
If the dosage form has a lower density than the gastric fluids, it will float on a top of the stomach content, allowing for an increased time span to release the drug before the system is emptied out into small intestine. The gastric fluid has a density of approximately 1gm/cm^3. If the density of the dosage form is lower than that, it will float on the gastric fluids. These systems require the presence of sufficient fluid in the stomach and the presence of food as discussed above. Several types of low density single-unit dosage forms (tablets) and multiple-unit dosage forms (pellets)

have been developed. If a dosage form has density of larger than approximately 2.5gm/cm^3, it will sink to the bottom of the stomach and pellets may be trapped in the folds of the gastric wall.

Recent trends in sustained release drug delivery system

1) Single unit dosage form

These refer to diffusion system where the drug is uniformly distributed (dispersed / dissolved) throughout the solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a swellable or non-swellable polymer film. These systems can be classified as:

a)Monolithic system

If the release rate is controlled or sustained by incorporating hydrophilic or hydrophobic filler within the matrix then the system is called as Monolithic device where the diffusion of drug through the matrix is the rate- limiting step.

These are categorized as:

Hydrophobic/Swellable tablet

Tablet prepared by mixing the drug with hydrophobic/hydrophilic filler appear to extend the release time of the drug from the device within the GI tract after oral administration.

Floating tablet or capsule

Designing of Floating tablet or capsule is called hydro-dynamically balanced drug delivery system is based on the principle that devices with gravity lesser than that of the gastric juice of stomach retain the drug in the proximal region of the GIT.

b) Semisolid matrix system

In this system, the hydrophobic carrier occurs in an oily semisolid state where the drug is incorporated and the final mass is usually filled into gelatin capsule to prepare the dosage form.

c) Coated tablet and Similar Multilayer system

Multilayer systems are designed in such a way that the drug has to cross a barrier or membrane on its way from the device to the physiological environment. The nature and the number of barriers control the release process. In the simplest form, coated tablet comprised of a core containing the drug and a coating layer, which surrounds the core. The core is usually the drug either alone or loaded on to an inert material (hydrophilic or hydrophobic). Multilayered tablet having two or more distinct layers usually prepared by dry coating technique have also been used to formulate sustained or controlled preparations for water-soluble drugs. In this case, coating which controls the release process covers the core tablet containing the drug only partially.

d)Osmotic device

In osmotic devices, usually an osmotic agent (often with an osmotic adjuvant) is contained within a rigid compartment that is separated from the osmotic compartment by a partition. In the physiological environment the aqueous fluid penetrates across the membrane and the increased volume within the osmotic compartment pushes the drug out of the device through a delivery orifice.

2) Multiple unit dosage forms

It represents a combination of subnets of the dosage forms, the source of which may either be homogeneous or heterogeneous. It offers the advantages of releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug-excipients and drug-drug interactions are inevitable in a single unit dosage form. The various forms are as:

a) Micro granules/Spheroids.

b) Beads.

c) Pellets.

d) Microcapsules.

3) Mucoadhesive systems

It utilizes the principle of bioadhesion for optimum delivery of the drug from the device. Bioadhesion is definable as the occurrence in which one biological substance is adhered to another substance, which may either, be of biological or non-biological origin. If the substance is mucosal membrane, the phenomenon is known as mucoadhesion. Conventional controlled release dosage forms described above are restrained/localized in selected regions of gastrointestinal tract. Mucoadhesive systems are suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at target sites.

MATRIX TABLET

Matrix tablets can be defined as the oral solid dosage forms in which the drug is homogeneously dispersed or dissolved within the hydrophilic or hydrophobic polymeric matrices. The preparation of sustained release matrix tablets involves the direct compression of blend powder mixture of drug, retardant material and other additives to formulate a tablet in which the drug is dispersed in a matrix of the retardant. Alternatively, drug, retardant blend and other additives may be granulated prior to compression. These systems release the drug in a continuous manner by dissolution-controlled and diffusion-controlled mechanisms.

Advantages of matrix tablets
- Reduction in toxicity by slowing drug absorption.
- MINIMIZE THE LOCAL AND SYSTEMIC SIDE EFFECTS.
- Improvement in treatment efficacy by better drug utilization.
- Minimize drug accumulation with chronic dosing.

➢ Can be made to release high molecular weight compounds.

Disadvantages of matrix tablets

➢ The remaining matrix must be removed after the drug has been released.
➢ Greater dependence on gastro intestinal residence time of dosage form.
➢ Increased potential for first-pass metabolism.
➢ Delay in onset of drug action.
➢ Release rates are affected by food and the rate transit through the gut.

CLASSIFICATION OF MATRIX TABLETS

a) On the Basis of Retardant Material Used:
 Matrix tablets can be divided in to 5 types.
1) Hydrophobic Matrices (Plastic matrices)
 In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic 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 release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2) Lipid Matrices
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.

3) Hydrophilic Matrices
Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. In fact 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**,**

A) **Cellulose derivatives:** Methylcellulose 400 and 4000cPs, Hydroxy ethyl cellulose, HPMC 25, 100, 4000 and 15000cPs; and Sodium carboxy methyl cellulose.
B) **Non cellulose natural or semi synthetic polymers:** Agar-Agar, 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 Matrices
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.

5) 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.

b)On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Nonporous systems can be identified:

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

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

3) **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**.**

MATHEMATICAL MODELING OF DRUG RELEASE FROM MATRIX SYSTEM

Mechanism of drug transport from matrix system based on drug diffusion and polymer relaxation/ dissolution. Fick's first and second low demonstrates diffusion of the drug through the medium. There are several mathematical models proposed for drug diffusion from matrix system based on these laws.

Huguchi model.

$Ft = Q = KH \times t1/2$………… (1)

Where, Ft = the fraction of dose release at time (t).

KH = Higuchi dissolution constant.

The data obtained were plotted as cumulative percentage drug release versus square root of time. Korsmeyer-Peppas model.

$Mt / M\infty = Ktn$…………. (2)

Where, Mt / M∞ = the fraction of drug released at time t,

K = the release rate constant and

n = the release exponent.

In this model, the value of n characterizes the release mechanism of the drug as in Table .To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

Table 2. Release exponent values and related drug release mechanism.

Release exponent (n)	Mechanism of drug release
0.5	Fickian diffusion
0.5 < n < 1	Anomalous transport
1	Case-II transport

Different factors affecting rate of drug release from matrix systems

The release of drug from polymer matrix system is dependent upon the physicochemical properties of both drug and polymer as well as it is also dependent on several biological parameters.

Physicochemical factors

1. **Swelling property of polymer:** Polymer dissolution includes absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium. Therefore, study of polymer hydration/swelling process for the polymers is required.

2. **Drug solubility:** Molecular size and water solubility of the drug are determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, the release of drugs occurs by dissolution infiltration medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

3. **Solubility:** In view of *in vivo* sink condition maintained actively by hem perfusion, it is logical that all the *in vitro* drug release studies should also be conducted under perfect sink condition.

4. **Polymer diffusivity:** The diffusion of small molecules in polymer structure is energy activated process in which the diffusing molecules move to a successive series of equilibrium

position when a sufficient amount of energy of activation for diffusion E_d has been acquired by the diffusing molecules. It is dependent on length of polymer chain segment, cross linking and crystalline nature of polymers. The release of the drug may be attributed to the three factors such as polymer particle size, polymer viscosity and polymer concentration.

5. **Thickness of polymer diffusional path**: The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion: J D = D dc/dx Where, J D is flux of diffusion across a plane surface of unit area D is diffusibility of drug molecule, dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

6. **The thickness of hydrodynamic diffusion layer:** The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer δ d.

7. **Drug loading dose:** The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water-soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases. When the amount of drug present at a certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of the drug has to be considered as non-dissolved and thus not available for diffusion.

8. **Diluent's effect:** The Water soluble diluents like lactose cause marked an increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of the matrix. The reason behind this is that water-soluble filler in matrices stimulates the water penetration into inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of the drug, leads to increased drug release rate.

9. **Additives:** The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce an increase in the release rate of hydrosoluble active principles.

10. **Dose size:** For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. Compounds that require large 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 large amount of a drug with a narrow therapeutic range.

11. **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 the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Compounds with very low solubility (<0.01 mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug.

12. **Partition coefficient:** It is common to consider that the biological membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous. Sustained release drug delivery system is not required to retain in the lipophilic tissue for the longer time. In case of compounds with low partition coefficient, it is difficult for them to penetrate the membrane, resulting in poor bioavailability. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

13. **Stability:** Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. For the dosage form that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial; this is also true for systems that delay the release until the dosage form reaches the small intestine. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propantheline and probanthine are representative examples of such drug.

Biological factors

1. **Biological half-life:** Every drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove the drug from the bloodstream. Therapeutic compounds with a short half-life are generally are an excellent candidate for sustained release formulation, as this reduces dosing frequency. Normally, drugs with a half-life shorter than 2 h such as furosemide or levodopa are poor candidates for this type of preparation.

2. **Absorption:** If the transit time of any drug in the absorptive areas of the GI tract is about 8-12 h, the maximum half-life for absorption should be approximately 3-4 h; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive

site. Other attempt is to formulate low-density pellet or capsule. Another approach is that of bioadhesive materials.

3. **Metabolism:** Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from the slower-releasing dosage form.

Polymers used in the matrix

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

➢ **Hydrophilic Polymers:** Hydroxyl propyl methyl cellulose (HPMC), hydroxylpropylcellulose (HPC), hydroxylethylcellulose (HEC), Xanthangum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and co-polymers of acrylic acid.

➢ **Hydrophobic Polymers:** This usually includes waxes and water insoluble polymers in their formulation.

➢ **Waxes:** Carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene.

➢ **Insoluble polymers**: Ammoniomethacrylate co-polymers (Eudragit RL100, PO, RS100, PO), ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate.

NATURAL POLYMERS:

The use of natural gums for pharmaceutical application is attractive because they are economical, readily available, non toxic, bio compatible. Lots of natural polymers from various plant sources have been successfully used and others are being investigated as excipients in design of dosage form for effective sustained release drug delivery. Tamarind gum, okra gum, Hakea gum, Karaya gum,chia seed powder, Fenugreek mucilage are some plant sources for synthesis of polymer.The plant based polymers have been studied for their application in different pharmaceutical dosage forms like matrix controlled system, film coating agents, buccal films, microspheres, nanoparticles, viscous liquid formulations like ophthalmic solutions, suspensions, implants. These have also been utilized as viscosity enhancers, stabilizers, disintegrants, solubilizers, emulsifiers, suspending agents, gelling agents and bio adhesives, binders.

❖ **Tamarind Gum:** It is insoluble in organic solvents and dispersible in hot water to form a highly viscous gel such as a mucilaginous solution with a broad pH tolerance and adhesivity. Tamarind gum is non-newtonian and yield higher viscosities than most starches at equivalent concentrations.This have led to its application as stabilizer, thickener, gelling agent and binder in food and pharmaceutical industries. In addition to these, other important properties of tamarind seed polysaccharide (TSP) have been identified recently. They include non- carcinogenicity, mucoadhesivity, biocompatibility, high drug holding capacity and high thermal stability. This has led to its application as excipients in hydrophilic drug delivery system.

❖ **Hibiscus rosasinensis:** The plant contains cyclopropanoids, methyl sterculate, methyl-2-

hydroxysterculate, 2-hydroxysterculate malvate, and-rosasterol. Mucilage of *Hibiscus rosa-sinensis* contains L-rhamnose, D-galactose, D- galactouronic acid, and D- glucuronic acid. The leaves are used in traditional medicines as emollients , to treat burning sensations, skin disease, and constipation.

❖ **Guar gum:** Guar gum is used and investigated as a thickener in cosmetics, sauces, as an agent in ice cream that prevents ice crystals from forming and as a fat substitute that adds the "mouth feel" of fat and binder or as disintegrator in tablets. Besides being used as a matrix former for sustained release tablets guar gum has been investigated as a carrier for indomethacin for colon-specific drug delivery using *in vitro* methods.

❖ **Okra gum:** Okra gum from the pods of *Hibiscus esculentus* is one of the advantageous polysaccharides that are currently being studied in the pharmaceutical industry as a hydrophilic polymer in pharmaceutical dosage forms. Okra plant grows very fast, is grown in all soil types, and is among the most heat and drought-tolerant vegetables. It has been investigated as a binding agent for tablets and has also been shown to produce tablets with good hardness, friability, and drug release profiles. It has advantage over most commercial synthetic polymers as it is safe, chemically inert, nonirritant, biodegradable, biocompatible, and eco-friendly. Since it is widely harvested and does not require toxicology studies, it is therefore considered to be economical. Okra gum contains random coil polysaccharides consisting of galactose, rhamnose, and galacturonic acid.

❖ **Chia seed powder:**The pharmaceutical uses of chia seed powder are tablet binders,disintegrants,emulsifying and suspending agents in biphasic liquid dosage forms.Also it is used as gelling agents,stabilising agents , in transdermal and periodontal films,buccal tablets,sustaining agents in matrix tablets and coating agents in microcapsules,thickening agents,film forming for protein delivery. The health promoting benefits other than pharmaceutical uses are promoting healthy skin, reducing signs of ageing, supporting the heart and digestive system, building stronger bones and muscles.

Table 3: List of various drugs which can be formulated as a matrix tablet

DRUGS	CATEGORY	METHOD USED	POLYMER USED
Ambroxol Hydrochloride	Expectorant,Mucolytic	Direct compression	HPMC-K100M,EC, Eudragit-RS100,S100
Amlodipine	Anti-arrythmatic	Direct compression	HPMC,EC
Zidovudine	Anti-viral	Direct compression	HPMC-K4M, Carbopol-934,EC
Domperidone	Anti-emetic	Wet granulation	HPMC-K4M, Carbopol-934
Ibuprofen	Anti-inflammatory	Wet granulation	EC,CAP
Metformin Hydrochloride	Anti-diabetic	Direct compression	HPMC-K100M,EC

Phenytoin sodium	Anti-epileptic	Wet granulation	Tragacanth,Acacia, Guargum,Xanthan gum
Furosemide	Anti-diuretic	Direct compression	Guar gum, Pectin, Xanthan gum
Aspirin	Anti-inflammatory	Direct compression	EC,Eudragit-RS100, S100
Indomethacin	Anti-inflammatory	Direct compression	EC,HPMC
Ranitidine Hydrochloride	H_2 antagonist	Direct compression	Chitoson,Carbopol-934
Diltiazem	Ca^{2+}channel blocker	Direct compression	HPMC-K100M, HPMC-K4M, Sodium CMC,Karaya gum
Miconazole	Anti-fungal	Direct compression/ Wet granulation	Pectin, HPMC

CONCLUSION

The aim of this review article is the formulation of swellable matrix tablet of NSAID using natural polymer. From the discussion it can be concluded that sustained release matrix tablet are helpful in increasing the efficiency of the dose and increasing patient compliance. Hence, sustained release matrix tablet offers a vast advancement in the field of solid oral dosage forms and also these systems are especially useful in case of the patients who need a constant delivery of drug for a longer period of time.

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