



## A Matrix-Based Advancement in Controlled Release Drug Delivery System

Rachna Dhankhar<sup>1</sup> and Asha<sup>2\*</sup>

<sup>1</sup>Department of Chemistry, Maharshi Dayanand University, Rohtak, Haryana-124001

<sup>2</sup>Department of Basic and Applied Sciences, Bhagat Phool Singh Mahila Vishwavidyalaya, Khanpur Kalan, Sonapat, Haryana-131305

\*Email: [arana5752@gmail.com](mailto:arana5752@gmail.com)

### ABSTRACT

Owing to severe side effects of low and high drug doses, controlled drug release concept gained ample scientific attention in past decades. Consequently, numerous attempts have been made to develop state of the art drug delivery system in recent times. Among several approaches, targeted drug delivery protocols have been emerged as the most promising solution as it involve sustainable release of drugs over a desirable period, minimum side effects, optimum bioactivity etc. Chiefly, in targeted delivery, the drug will be active only on a particular target area in the body (for e.g., in cancerous cells in the body to treat the cancer). Further, the researchers are working on such formulations that the release will be sustained and released over a period in desirable/required amounts. In the present review, the deep insights of controlled release drug delivery systems are highlighted along with detailed overview of recent advancements and future prospects in this field.

**Keywords:** drug delivery, targeted delivery, matrix method, controlled release drug.

DOI Number: 10.14704/nq.2022.20.6.NQ22451

NeuroQuantology 2022; 20(6):4598-4609

4598

### Introduction

Drug delivery can be defined as the formulations, approaches, techniques, and systems to transport a pharmaceutical product/compound (drug) into the body in the amounts needed by the body to get the desired healing/therapeutic effect safely from the drug. Drug delivery technologies may modify drug release profile, or it changes the absorption and the distribution pattern or changes in the manner that the drug gets eliminated from the body. These improvements will help to improve the efficiency of the drug and its safety (Ekenseair *et al.*, 2012).

From the past many years, most of the industries of pharmaceutical only developed medicine which were either taken orally (in form of tablets and syrups) or injected (Verma *et al.*, 2001). This is because the synthesis of new drug for more effect on a particular target is very time consuming and money consuming. Now a days while developing new drug, most of the pharmaceutical industries are working on its mode of delivery inside the body to the target. Because most of the drug we are

using these days, its rate of action and selectivity reduced by taking it as simple tablets due to biological activity of the bodies. While developing new drug for a disease, if we deliver optimum amount of drug on a particular target with without loss of drug, its activity increases, and drug become more effective. So, these types of modifications improve the selectivity as well as reactivity of that drug to the target. So, controlled release of drug delivery system has substantially transformed the approach of development of drug delivery. We can achieve following benefits with controlled release drug delivery system:

- improvement of therapeutic index of drug
- can predict the rate of drug delivery to the body which can help to predict the amount of drug required
- enhance the activity as well as selectivity
- lesser side effect
- no need of frequent drug dosing
- optimized therapy (Park, 1997)

So, to get these benefits, the design of drug delivery should be modified, which in turn depends on several factors as mentioned below:



- Physical properties: state of aggregation, melting point, solubility of drug, size etc.
- Chemical properties: functional group and substituent present in drug molecule, stereochemistry of drug
- Route of administration inside the body
- Nature of system we use (delivery vehicle) and drug release pathway
- Active action for targeting
- Pharmacokinetics and pharmacodynamics

The technology of drug delivery could bring commercial as well as therapeutic importance to all the health protection goods. Most of the pharmaceutical companies apply the strategy of low drug dose with high potential of work (Park, 2000). So, most of the companies work on development of drug delivery systems and they got excellent return on their investments on new drug system. The development of safe and effective drug dosage forms and drug delivery systems requires a need of understanding of physiochemical principles that allow drug to be formulated into pharmaceutical dosage form (Breimer, 1999). When we develop advanced controlled release drug delivery system, following factor comes into the mind

1. Chemical structure and size of drug that are delivering to target cell
2. Physiochemical properties of that drug and Pharmacokinetics at whole body
3. Appropriate drug vehicle (macromolecule carrier)
4. Permeability of system for release of drug etc. (Patrick, 2001)

### Routes of administrations

Drug can deliver inside the body via many ways which are classified on the basis of their route of administration. Here we are explaining mainly five drug delivery routes for drug delivering:

**1. Oral.** This is widely used and on the most expedient method for delivery of drug. The drug is swallowed in the mouth which is then absorbed in the gastrointestinal track (Patel *et al.* 2011). It is a very stable type of drug delivery and can be modified with different methods and materials (Kretlow *et al.* 2007).

**2. Pulmonary.** A wide variety of drug is delivered by this method in which drug is taken through mouth to lungs in form of powder with specific device via inhalation (Patrick, 2001). Lungs provide striking atmosphere for the bio molecules like nucleic acids, proteins etc. due to the small metabolic activity that allow systemic delivery devoid in liver passage. It is extensively used for the treatment of chronic obstructive pulmonary disease (Arunachalam, 2010), cystic Fibrosis (Shah *et al.*, 2012), and asthma (Jaspart *et al.*, 2007). It gives rapid and limited action of drugs (Schleh *et al.*, 2011). This system depends upon several factors which are listed below:

- a) Particle properties (size, density, hygroscopic constant, shape, and charge) of drug
- b) Flow rate of drug (Islam and Cleary, 2012)
- c) Properties of respiratory tract (Daniher and Zhu, 2008)

But it is not a convenient method because it is not very easy to take. Also owing to the rapid elimination of drugs from the lungs or due to the metabolism of drug, the activity period is short lived (Shaik, 2012).

**3. Transdermal.** Transdermal drug delivery system is also recognized as drug loaded patches dosage which is applied on skin of the patients to give them therapeutic effect. This method is most useful method of delivery of lipophilic drug in human system (Iordanskiia, 2000). The adhesive of the transdermal drug delivery system is significant for the quality of the product, efficacy, and the safety. So, therapeutic effect also depends on adhesive used in TDDS (Transdermal drug delivery system). Poor adhesive may result in improper dosing of drug to the patient (Aqi and Ali, 2002). So, this is also a very important field of research. So many matrix-based formulation have been developed for several drugs (Wokovich *et al.*, 2006).

**4. Injection.** In this method, a drug is infused, by putting the drug in the form of fluid into the body. A syringe is used for the purpose which contains a hollow needle and is used to pierce through the skin upto a



requisite depth so that the drug can be forced into the body (Ekenseair *et al.*, 2012). The injection method follows a route to administer the drug which is different from the digestive tract (Verma *et al.*, 2001). Injection method is used when the drugs are not apt for the oral delivery. The injection method has its advantages such as it supplies only the proper amount of drug to patient which is required and has a speedy and efficient therapeutic effect (Park, 1997). But this method has its disadvantages also. It causes pain, instant drug release, fear of the needle in patients, risk of infections at the site of piercing and dependency on specialists or nurses for delivery of the drug (Breimer, 1999).

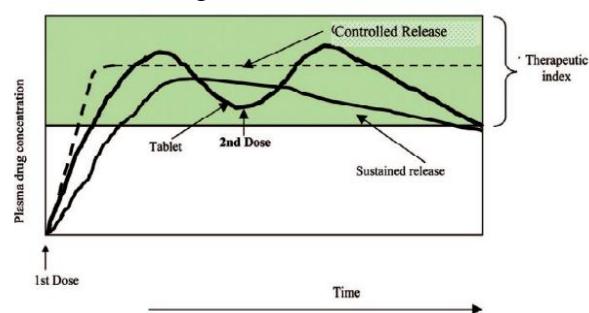
There are two different strategies being adopted to solve these problems. One approach focuses on improving the current technology of injection. The other focus on development of the other methods for delivery.

**5. Implantable.** Implantation based drug delivery system has the advantage of maintenance of a steady release of drug at the specific site of action. Therefore, this method is safe, and it can be relied upon more. This method can be classified into three different systems: implantable pump systems, the implants which can be biodegradable or non-biodegradable and the most recent implants. Here drug release depends on diffusion of drug through polymer, non-biodegradable polymers used to prepare dosage forms, dissolution of drug and usage of biodegradable polymers (Ekenseair *et al.*, 2012).

### Mechanism for drug delivery

There are various factors which determine the speed at which the drug is absorbed in the body. It depends upon the methods and the routes by which the drug is administered. Further, it depends on the properties of the drug itself like drug solubility, molecular size, charge etc. Also, it depends upon other factors like the site at which the drug is administered, pH, enzymatic presence in the body, area of the surface, active transport mechanisms etc. The profile followed by the drug levels inside the blood is shown in the

figure 1. The level of the drug in the blood increases firstly after the drug has been administered and thereafter decreases with time. The cycle repeats itself after the next dose is administered. The level of the drug in the blood should remain in a specific range. The maximum limit of the drug in the blood is limited by toxicity, as beyond a certain limit, it becomes toxic. The minimum limit of the drug in the blood is the level below which a drug remains ineffective. For long term administration of the drug, the level of the drug in the blood should remain in between the maximum and minimum level as illustrated in Figure 1.



**Figure 1.** Profiles of Concentration for the drug delivered by sustained release device, tablet or controlled release device

Among the many ways for drug delivery, oral administration has been prevailing because it has been the most suitable mode for drug delivery and the foremost choice for choosing the delivery course. There have been several limitations for orally drug delivery as posed by the human physiology as a very few drugs are stable in the route. Considerable amount of hefty molecular drugs, for instance proteins, could not be absorbed unbroken from Gastrointestinal (GI) tract because they are degraded. Moreover, somewhat short GI transportation time (roughly several hours) restricts the drug delivery to 12 hours or so, except the drugs that are very well absorbed in the large intestine. For developing little molecular drugs based upon the protein drugs, a limitation of oral drug delivery has a major influence (Ekenseair *et al.*, 2012). However, we are having several methods of drug delivery, still we are focusing on development of oral drug delivery system. Matrix based drug delivery system has been

one of the powerful modifications in oral drug delivery system.

### Drug release from matrix-based oral controlled drug delivery system

Amongst the orally controlled drug delivery technologies matrix technology has time and again proven the best because of its high intensity reproducibility, minimalism, easiness in manufacture process, easiness in upgrade as well as process confirmation and durability of raw material. Within the region of matrix formulation, technological development has made the controlled-release product augmentation smoother than earlier. Also, it has enhanced on the practicability for delivering a large array of drugs by means of various biopharmaceutical plus physicochemical property (Varma *et al.* 2004).

Among a variety of strategies that has been taken into account for manipulating the geometry tablet, formulation characteristic along with the polymer variables has been extensively used so as to achieve the proper discharge for drug.

In order to illustrate the mass transport procedure, which is engaged in the matrix-based drug release, many simple empirical plus multifaceted mechanistic theories, which considers the dispersion, dissolution and inflammation simultaneously, has been developed. The selection of an apt model for the drug release should be done very carefully and it will provide an insight to the fundamental mass transport method. Moreover, it is also helpful in the prediction of the consequence of device design consideration on resultant drug-release rate. For the improvement of the formulation development process and for the minimization of the number of trials in the final optimization, there should be a fundamental knowledge of release kinetics as well as the mechanisms of drug release from matrix system (Varma *et al.* 2004).

#### Advantages of Matrix tablets

1. Easy to manufacture, less expenditure, less consumption, resourceful and valuable.
2. Compounds with high molecular weights could be made to release.

3. To evade high concentration of blood, prolong release formulation has been used.

4. Therapeutic concentrations can be maintained for prolonged time by the sustain release formulations.

5. Reduction of toxicity by dawdling the absorption of drug.

6. Minimization of all the local as well as systemic aftereffect.

7. Efficiency in the treatment has also been improved.

8. Increment in the stability via protection of the drug by hydrolysis and any another derivative formation within the gastrointestinal tract.

9. Minimization of the drug build up by means of persistent dosage.

10. Whole drug less consumption.

11. Bioavailability of a few drugs also gets improved (Shahrukh *et al.* 2019)

#### Disadvantages of matrix tablets

1. The residual matrix has to be removed.

2. Many aspects namely, food plus the rate of transition throughout gut have an effect on the drug release rate.

3. The release rate of the drug changes with square root of the time (t). With the increment in diffusional resistance and decrement in the productive area by diffusion front the release rate decreases regularly (Shahrukh *et al.* 2019)

#### Classification of matrix tablets

**1. Based on Retardant Material Used.** Classification can be done in five types which are as follows:

**1.1. Hydrophobic Matrix (Plastic matrices).** This notion of the use of the hydrophobic materials like matrix materials had been established in 1959. It consists of mixing of drug with the hydrophobic polymer which is then compressed to a tablet. Due to the diffusion of the drug, all the way through the group of channels which are present in between the compacted polymer, sustained drug release has been produced. Polyethylene, ethyl cellulose, PVC and acrylate polymers are being used as hydrophobic matrix (Shahrukh *et al.*, 2019)

**1.2. Lipid Matrices.** They are synthesized from the lipid waxes. These matrices release



the drug via erosion and pore diffusion. The wax i.e the Carnauba wax when combined with stearic acid is being employed for the retardant base in a large variety of formulation for sustained release (Deepika *et al.*, 2018).

**1.3. Hydrophilic Matrices.** Owing to the flexible behaviour for obtaining a requisite profile for drug release, wide regulatory acceptance, and low cost, these matrices are being extensively used. Drugs formulation in gelatinous capsules or in the tablets consist of hydrophilic polymers which are having high gelling ability.

The polymers utilised in the synthesis of above-mentioned matrices have been classified into three categories:

- Cellulose derivatives: Sodium carboxymethylcellulose, Methylcellulose 400 & Hydroxypropyl methylcellulose 25, 100, 4000 and 15000cPs; Hydroxyethyl cellulose.
- Natural/semi synthetic polymers (non cellulose): Polysaccharides of mannose and galactose, Carob gum, Agar-Agar, Chitosan, Alginates, Molasses, Modified starches (Patel *et al.*, 2011)
- Acrylic acid Polymers: Carbopol-934, the widest variety (Varma *et al.* 2004).

**1.4. Biodegradable Matrices.** In this type of matrix, there are polymers which consist of the monomers bonded to each other via the functional groups and unstable linkage is present in the backbone. Biological degradation of these matrices is done by the surrounding living cells or through enzymatic processes and they degrade into oligomers along with monomers which can then be excreted. Natural polymers viz. polysaccharides and proteins, man-made polymers like aliphatic poly anhydrides along with some customized natural polymers are examples of this matrix (Bisht *et al.*, 2016).

**1.5. Mineral Matrices.** Mineral matrices consist of the polymers which come from the different seaweed species. Alginic acid (hydrophilic carbohydrate) which is obtained by brown seaweeds (Phaeophyceae) is an example of mineral matrix (Bisht *et al.*, 2016).

**2. On the basis of Matrix Porosity.** According to the porosity Matrix system has been classified as:

**2.1. Macro porous Systems.** In the macro porous system, the drug diffusion happens by means of pores of the matrix whose size lies in the scale of 0.1 -1  $\mu\text{m}$  which is greater than the size of diffusant molecule.

**2.2. Micro-porous System.** Here the drug diffusion takes place via pores only whose size lies in the range 50-200  $\text{\AA}$  (somewhat bigger than size of diffusant molecule)

**2.3. Non-porous System.** In this system, diffusion takes place via network meshes. No pores are present here, only polymeric phase is there.

### Polymers used in matrix tablet

**1. Hydrogels.** Polyhydroxyethyl methacrylate, cross-linked polyvinyl pyrrolidone, crosslinked polyvinyl alcohol, Polyacrylamide, Polyethylene oxide.

**2. Soluble polymer.** Polyethylene glycol, Polyvinyl pyrrolidone, polyvinyl alcohol.

**3. Biodegradable polymer.** Polylactic acid, Polycaprolactone, Polyglycolic acid, Polyorthoester, polyanhydrides.

**4. Non-biodegradable polymer.** Polyethylene vinyl acetate, Polyether urethane, Polydimethylsiloxane, ethyl cellulose, cellulose acetate, Polyvinyl chloride.

**5. Mucoadhesive-polymers.** Sodium carboxymethyl cellulose, tragacanth, Polyacrylic acid, polycarboxiphil, Methyl cellulose, pectin.

**6. Natural gums.** Guar gum, Locust bean gum, xanthan gum, karaya gum (Deepika *et al.*, 2018).

### Mechanism of drug release from matrix tablet

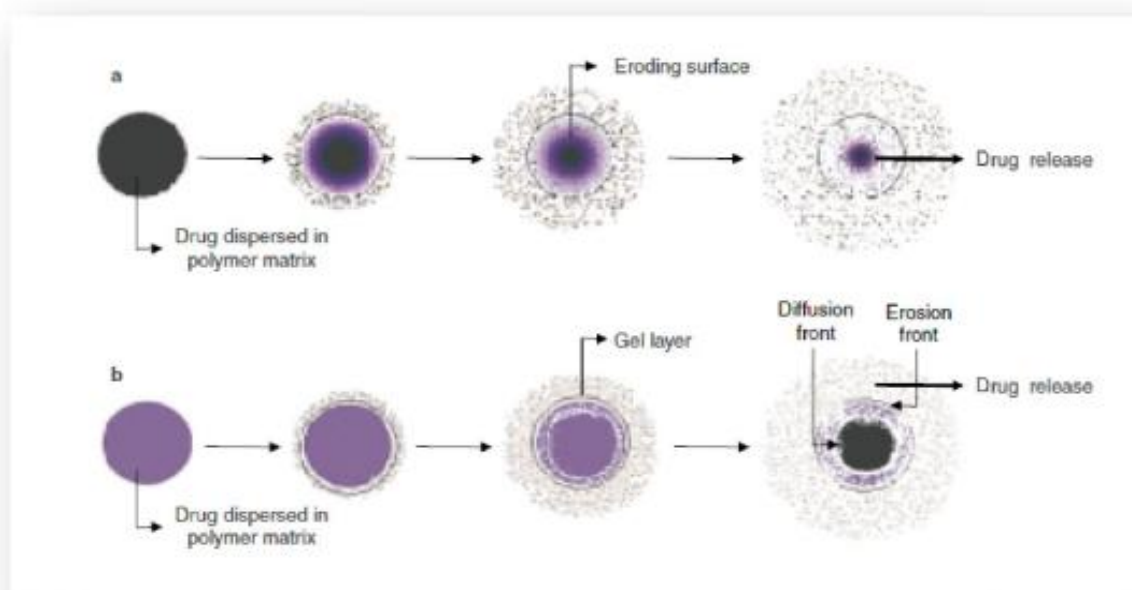
Hydrophilic matrices consume the water on surface, subjecting to the aqueous fluid and then the hydration of the polymer starts thereby forming a gel layer. A gel dispersion barricade along with the surface erosion controls the drug release. Then, there may occur an initial rupture of the soluble drug caused by surface leakage. After that there occurs an impulsive change from



glassy to rubbery state when the matrixes consisting of the glassy polymer approach the aqueous medium. Then the initially unperturbed state of the individual polymer chain soaks up water thereby escalating its end-to-end distance plus the radius of gyration into a novel state which is solvated result from the reduction of the transition temperature of polymer. The polymer transition temperature depends on the thermodynamic interactions along with the temperature of the polymer-water system and is governed by distinctive concentration of

the swelling agent. Then there is an increase in the volume of the matrix caused by swelling and there observed a sharp dissimilarity among glassy and rubbery regions. The repeatability of drug release could be increased on the molecular basis by activating the convective drug transport (Varma *et al.* 2004).

As the time goes by, water permeates deep in the core, thereby escalating the width of the gel layer. Alongside the outer layers gets completely hydrated and begin solubilising or wearing away.



**Figure 2:** Diagrammatic representation for release of drugs in the drug delivery system in which there is a matrix dispersion-controlled release, and the drug is uniformly distributed in (i) a hydrophilic along with swellable polymer and (ii) erodible polymer matrix

The rate of drug release starts reducing when water arrive at the core of the system and the drug concentration becomes lower than the solubility value (Varma *et al.* 2004).

If the matrix system is inert then the eluting medium disperse or wear away the polymer out of the surface-forming porous network inside the middle portion. Drugs which are soluble permeates via this aqueous filled permeable system. And if the drug is poorly soluble which is dispersed in the inert polymer system, then it is released majorly via erosion. In figure 2 there is a schematic demonstration of mechanism for the release of drugs.

The drug release in case of erodible matrices is caused by the erosion of the polymer from the matrix's surface whereas in case of hydrophilic matrices, the release of drug is caused by gel layer's formation and dynamics of the gel layer with respect to time. The gel layer will keep on becoming thicker and correspondingly the rate of drug release will decrease. But the hydration will increase the dissolution rate of the drug.

Thus, the factors which play greater role in the release of the drug are mainly two: Firstly, the rate at which the aqueous medium penetrate in the matrix after which a relaxation process will occur and secondly, the speed at which the matrix erodes. Thus,

in consequence of these two concurrently happening processes, two fronts will emerge:

One front will be of swelling and the other front will emerge due to the erosion. The separation between these two fronts which is termed as thickness of the diffusion layer will be determined by the speeds on which these two fronts occur with respect to each other. Thus, the polymer, if gel at a slower rate, solvent will go deeper in the glassy matrix and therefore, will dissolve the drug. Thus, the thickness of the layer of the gel is crucial in drug release. Also, the stability of the thickness of the layer of the gel will play similar crucial role. However, the thickness along with the arrangement of the layer of gel will depend upon time also and will keep on changing with time (Varma *et al.* 2004).

The thickness of the gel layer variation time will be constituting 03 stages:

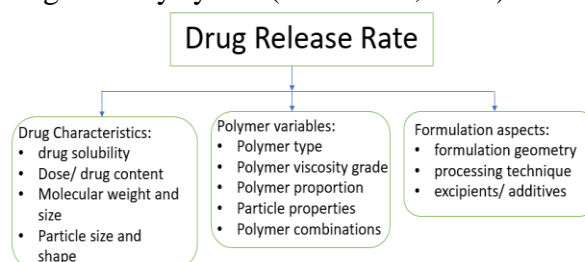
- Firstly, the swelling of the polymer will increase initially
- Thereafter, the width of gel layer would be constant.
- In third stage, there will be a decrease in the thickness of the gel due to reduction of glassy core itself.

In the case of hydrophilic polymer, the gel's growth is dependent upon the pace of the swelling of the penetration front and the rate of erosion of exterior surface of the gel. But generally, erosion of the gel is slower than the swelling as polymer concentration plays an important role. Polymer concentration will go upto a threshold value which is also called as the polymer disentanglement concentration, can be defined as the value of the concentration of the polymer in a state of hydration and further, there will be no interaction of polymer-polymer. If the penetration of water is more than the polymer disentanglement, then the layer of the gel will keep on growing. However, if the penetration of water is less than the polymer disentanglement, there will be a very little or no effect on the thickness of the gel layer.

In recent times, various methodology is being employed to effectively observe the phenomenon of swelling of the matrix tablets, in determination of the gel layer thickness and movements of the front. One such technique is optical imaging. Other complex techniques are nuclear magnetic resonance, cryogenic scanning electron microscopy, confocal laser scanning microscopy and technique like pulsed- field gradient spin-echo NMR. By using these techniques, the layer of thickness of the gel is measured which in turn depends upon the swelling and the erosion fronts. Using imaging analysis, the diffusion front is located which lies between the swelling and the erosion fronts. The diffusion front depends upon the solubility of the drug and its loading. The front condition will in turn determine the rate of drug release and this drug release rate necessarily equivalent to the speed of bringing the drug to the diffusion front.

### Effect of release limiting factor on drug release

By doing the analysis of controlled release of drugs by studying the mechanism it has been found that the diffusivity, thickness of the diffusional path and the partition coefficient and various other system factors play a vital role in the rate determination of the controlled drug release from whichever capsules or sandwich types or matrices-based drug delivery system (Patel *et al.*, 2011).



**Figure 3.** Variables influencing the kinetics plus mechanism of release of drug from matrix tablets

**1.Polymer hydration.** For getting the maximum polymers and its combinations, it is very significant to study the polymer



hydration. For the most part the essential stage in the dissolution of polymers comprises of the absorption/adsorption of water in nearby place, the shattering of the polymer-polymer connectivity along with the instantaneous formation of the water-polymer connectivity, polymeric chain division, inflammation and then diffusion of the polymeric chain (Reddy *et al.*, 2017).

**2. Drug solubility.** The molecular size of drug plus its aqueous solubility plays a vital role in the determination factor for the release of drug from the swelling polymeric matrix. Drugs with reasonable solubility in water gets released by the dissolution in the infiltrating medium whereas the drugs having poor aqueous solubility gets released through dissolution as well as dissolution of drug units by means of matrix tablet erosion (Reddy *et al.*, 2017).

**3. Solution solubility.** Taking into consideration the in vivo (biological) sink situation, which is being maintained energetically through hem perfusion, it's reasonable to conduct the entire in vitro study of drug release in ideal sink condition. This helps in achieving a superior correlation and simulation between the profile of in vitro release of drug as well as in vivo drug administration.

**4. Polymer diffusivity.** Division of small molecules of the polymer composition, is energetically activated procedure that includes the movement of the diffusant molecules into a consecutive sequence of equilibrium position. In equilibrium position the diffusion activation energy depends on the cross linkages, polymer crystallinity and polymer chain length (Reddy *et al.*, 2017). Drug release might be accredited to the following three aspects:

**4.1. Particle size of polymer.** It has been stated by Malamataris that greater the hydroxypropyl methyl cellulose content lower will be the effect of particle size on the rate of drug release of propranolol hydrochloride and vice versa.

**4.2. Polymer viscosity.** For the cellulose ether polymers, matrix weight is indication of viscosity. More the molecular weight more will be the viscosity of gel layer which in turn increases the resistance of the gel to erosion plus dilution, thereby controlling the dissolution of drug.

**4.3. Polymer concentration.** Polymer concentration is directly proportional to the gel viscosity and inversely proportional to the drug effective diffusion coefficient. Increase in the concentration of polymer causes a reduction in release of drugs. Polymer concentration also changes the mechanism of release of drugs (Sung and Kim, 2020).

**5. Width of the hydrodynamic diffusion layer.** Profile of drug release is a function of the thickness of hydrodynamic diffusion layer. An increase in the thickness decreases the value of drug release.

**6. Loading dose of drug.** The drug loading dose affects the solubility of the drug and kinetics of release of drugs. The relative release rates of feebly water-soluble drugs first reduce and then increase with the increasing dose of drug loading. On the other hand, the porosity of matrices of water-soluble drugs increases with the increase in drug loading dose and that leads to an increase in the absolute rate of drug transfer. If the quantity of drug (in feebly water-soluble drugs) present in the matrix surpasses the quantity of soluble drug, then the surplus drug not offered for diffusion as the excess drug has been considered undissolved (Sung and Kim, 2020).

**7. Surface area and volume.** It has been observed theoretically as well as experimentally that drug release in vivo plus in vitro rate is dependent on the surface area of the dosage form.

**8. Additives.** Addition of non-polymeric filler to the polymer matrix increases the rate of release of hydro soluble active principles. The increment is significant if the filler is soluble viz. Lactose. Furthermore, it becomes



less significant if the filler is insoluble viz. tricalcium phosphate

### Biological Factors Influencing Release from Matrix Tablet

**1. Biological half-life.** The general goal of an orally given product is that it is able to maintain therapeutic blood levels for the required time period. Every drug is having its individual half-life which is essentially the addition of every procedure which eliminates the drug from the blood stream such as metabolism, excretion through urine etc. The compounds having shorter half-life are good for use 'as drug as it reduces the repetition of the doses (Fenton *et al.*, 2018). However, the compounds with half-life less than two hours are also not suitable as it will require a very high frequency and repetitive dose to be administered. e.g., furosemide or levodopa. Also, the compounds having half-life more than eight hours are also not suitable as they remain for longer time and their effects are already sustained. e.g., Digoxin and phenytoin (Adepu and Ramkrishna, 2021).

**2. Absorption.** The formation of sustained release is done to have a command over the drug delivery method. So, it becomes essential that the speed of drug release will be at a lesser pace than absorption rate. Suppose the time of transition for most of the drugs inside the penetration region of Gastrointestinal tract is 8 to 12 hours, then the maximum absorption half-life would be approximately 3-4 hours, or before the completion of drug release the device would flake out from the probable regions of absorption. Consequently, it is believed that drug absorption should take place at a moderately consistent rate throughout the small intestine. But this is not true always for all the compounds. Sustained release synthesis might be detrimental to absorption. If the drug has been absorbed through some active transport or the transport has been restricted to a particular section of the intestine. So, one of the methods for preparing the sustaining delivery mechanism

aims to maintain them inside the stomach only resulting in the slow drug release which is then moved to the absorption site. Formulation of low-density capsule and preparation of bioadhesive materials results from the outcome of the observation that the sustaining effect results from co-administration.

**3. Metabolism.** There can be a reduction in the bioavailability of time-consuming drug releasing dosage form of the drugs which are metabolized prior to absorption either in the intestine tissue or lumen. Therefore, the criterion for a drug to be employed for developing the sustained-release dosage form is as follows:

- Low half time of the drug (<5 hrs)
- Good solubility of the drug in water
- The therapeutic window of the drug should be large.
- Absorption of the drug throughout the gastrointestinal tract.

For devising a feebly water-soluble drug in sustained release dosage form, firstly the drug's solubility has to be increased by an appropriate system and then the formulation is done (Fenton *et al.*, 2018). During this process the crystallization of the drug must be avoided, and care should be taken for its prevention (Adepu and Ramkrishna, 2021).

**4. Distribution.** All the drugs that are having high perceptible volume allocation, that affects the elimination rate of the drug, are not usually employed for oral sustainable release (SR) drug delivery system viz. Chloroquine (Adepu and Ramkrishna, 2021).

**5. Protein Binding.** Generally, all the drugs bound somewhat with tissue proteins or plasma. The Pharmaceutical response of the drug is dependent on the unrestrained drug concentration instead of the total concentration (Fenton *et al.*, 2018). The binding of proteins with drugs has a considerable part in the curative effect nevertheless of the dosage kind. Greater binding to plasma leads to an increment in the biological half-life, hence SR drug



delivery system not needed for such drugs (Adepu and Ramkrishna, 2021).

**6. Margin of safety.** It is known that safer drugs are the one with higher therapeutic index value. Drugs having lower therapeutic index are generally not used for articulation of oral sustainable release drug delivery system because of the technological control limitation above drug release rates (Adepu and Ramkrishna, 2021).

### Physicochemical Factors Influencing Release from Matrix Tablet

**1. Size of the dose.** For those drugs which are given orally, there will always be upper margin for the size of the dose which could be delivered. The maximum size of the drug which can be administered orally ranges between 0.5-1.0 g. Thus, the drugs which are required to be given in more amount, it necessitates that either it is given in multiple amounts, or it may be administered by converting it into liquid form. The other concern is safety's margin while giving a large amount of drug and that too with a low therapeutic range (Mondal, 2018).

**2. Solubility in the aqueous medium, its ionization and pka.** Almost every drug is either a weak base or a weak acid. As the unperturbed drug form preferably passes through the lipid membranes, it becomes vital for knowing the relation among the compound's pka & its surroundings in which it is going to be absorbed. The drug in its unvaried form is good for the penetration of the drug. But the situation becomes complex if the drug is converted to unchanged form. In this situation, drug's solubility decreases in aqueous media. Generally, the delivery system depends upon the dissolution or diffusion on its solubility in aqueous mediums. The form of the dose must be effective in body as the pH in the different parts of the body is different. For e.g.; the stomach is acidic while the small intestine is neutral. Thus, the compounds which are very less soluble (less than 0.01mg/ml) are going to be sustained and their dissolution will

limit the release of the drug. Thus, the lesser soluble compounds will not be desirable as the diffusion of the drug will be low (Patel *et al.* 2011).

**3. Partition Coefficient.** In the GI tract, when a drug is given, it has to cross different biological membranes so that it can generate a curative effect in the desired body area. Generally, these biological membranes are lipids. Thus, the partition coefficient plays a vital role in deciding the effectiveness of penetration of barriers of membrane of oil-soluble drugs. It has been found that the lipophilic compounds that are having a high partition coefficient value are not much soluble in aqueous medium and they remain in the lipophilic tissue for a much larger duration. Conversely, the compounds that are having a low partition coefficient can hardly penetrate the membrane which results in their lesser bioavailability (Varma *et al.* 2004).

**4. Stability of the drug.** Generally, drugs which are given orally gets hydrolyse by acids and bases and degrades by enzymes. This breakdown does occur at a lesser rate for solid state drug. Therefore, solid form is one of the most ideal compositions for delivery of drug in difficult cases. The forms of the doses that delays release over the whole route of transition in the Gastrointestinal tract are considered better. Similarly, it is better for the systems that discharge the drug late until the dose form arrives at the small intestine. The compounds which are not stable in stomach shows increased bioavailability as maximum drugs are being delivered in the small intestine. Conversely, the compounds which are not stable in small intestine shows decreased bioavailability and consequently are subject to breakdown e.g. propanthine and propantheline (Mondal, 2018).

### Conclusions

Release of drug using matrix-based drug delivery systems is dependent upon the physical as well as the chemical properties of



the drug being administered. Also, it depends upon the type of the matrix polymer, its geometry and on its constituents/composition. Various theories in the field suggest that a greater control on the release of the drug is possible by managing the mechanistic principles of the polymer and its formulation variables while designing the device. There are different mathematical models available which illustrates the mechanism of the release of the drug and its contribution in the kinetics of the drug release. Thus, using these mathematical models in the developmental stage the formulation can help in better optimisation in the least number of trials for formulation.

However, there are some limitations also of matrix-based delivery systems. One such limitation is its being time-dependent and the rate of release goes down with the increment of time. Generally, the path-length of the diffusion is determined by the process of diffusion and erosion. The path length of diffusion of the drug changes the process of release of the drug to a mechanism which is handled by the erosion, dissolution and relaxation of the polymeric matrix rather than the process controlled by diffusion. Thus, the want for zero-order release can be achieved by managing the process of the release of the drug by utilising the erosion/relaxation-based method instead of diffusion controlled based release of the drug. Therefore, further studies in the kinetics of the release of the drug and its correlation to the dynamic behaviour of the process of the release of the drug can help in managing the variables which can provide for good formulation optimisation.

## References

- Adepu S and Ramkrishna S. Controlled Drug Delivery Systems: Current Status and Future Directions. *Molecules* 2021; 26(19): 5905.
- Aqil M and Ali A. Monolithic Matrix Type Transdermal Drug Delivery Systems of Pinacidil Monohydrate: In Vitro Characterisation. *European Journal of Pharmaceutics and Biopharmaceutics* 2002; 54: 161–164
- Arunachalam A, Transdermal Drug Delivery System- A Review, *Current Pharma Research* 2010; 1(1): 70-81.
- Kumar, S. (2022). A quest for sustainium (sustainability Premium): review of sustainable bonds. *Academy of Accounting and Financial Studies Journal*, Vol. 26, no.2, pp. 1-18
- Allugunti V.R (2022). A machine learning model for skin disease classification using convolution neural network. *International Journal of Computing, Programming and Database Management* 3(1), 141-147
- Bisht T, Rishiwer P and Kumar P. Review on Matrix Tablet. *Indo Global journal of Pharmaceutical Research* 2016; 6(1): 38- 42.
- Breimer DD, Future Changes for Drug Delivery. *Journal of Controlled Release* 1999; 62: 3–6.
- Daniher DI and Zhu J. Dry Powder Platform for Pulmonary Drug Delivery. *Particuology* 2008; 6: 225–238
- Deepika B, Sameen S, Nazneen N, Madhavi A, Rajul KN, Rao KNV and Dutt KR. Matrix Drug Delivery System: A review. *European Journal of Pharmaceutical and Medical Research* 2018; 5(1): 150-154
- Ekenseair AK, Boere KW, Tzouanas SN, Vo TN, Kasper FK and Mikos AG. Synthesis and Characterization of Thermally and Chemically Gelling Injectable Hydrogels for Tissue Engineering, *Biomacromolecules* 2012; 13: 1908–1915.
- Fenton OS, Olafson KN, Pillai PS, Mitchell MJ and Langer R. Advances in Biomaterials for Drug Delivery. *Advanced Materials* 2018; 30: 1705328.
- Iordanskiia A.L, Feldsteinb MM, Markina VS, Hadgraftc J and Platea NA. Modeling of the Drug Delivery from a Hydrophilic Transdermal Therapeutic System Across Polymer Membrane. *European Journal of Pharmaceutics and Biopharmaceutics* 2000; 49: 287-293.
- Islam N and Cleary MJ. Developing an Efficient and Reliable Dry Powder Inhaler for Pulmonary Drug Delivery—A Review for Multidisciplinary Researchers. *Medical Engineering & Physics* 2012; 34(4): 409–427.
- Jaspart S, Bertholet P, Piel G, Dogne JM, Delattre L and Evrard B. Solid Lipid Microparticles as a Sustained Release System for Pulmonary Drug Delivery. *European*



- Journal of Pharmaceutics and Biopharmaceutics 2007; 65: 47-56.
- Kretlow JD, Klouda L and Mikos AG. Injectable Matrices and Scaffolds for Drug Delivery in Tissue Engineering. *Advance Drug Delivery Reviews* 2007; 57: 263–273.
- Mondal N. The Role of Matrix Tablet in Drug Delivery System. *International Journal of Applied Pharmaceutics* 2018; 10(1): 1-6.
- Park K. *Controlled Drug Delivery: Challenges and Strategies*. American Chemical Society: Washington DC, 1997.
- Park K and Marshy R. *Controlled Drug Delivery: Designing Technologies for the Future*. ACS Symposium Series 752, American Chemical Society: Washington DC 2000.
- Patel H, Panchal DR, Patel U, Brahmbhatt T and Suthar M. A Review on Matrix Tablets. *Journal of Pharmaceutical Science and Bioscientific Research* 2011; 1(3): 143-151.
- Patrick GL, *Introduction of Medicinal Chemistry* 2001, 251-253.
- Reddy AM, Karthikeyan R, Vejandla RS, Divya G and Babu PS. Controlled Release Matrix Drug Delivery System – A Review. *International Journal of Allied Medical Sciences and Clinical Research* 2017; 5(2).
- Sagogiorgas CT, Krebs J, Pukelsheim M, Beck G and Luecke T. *European Journal of Pharmaceutics and Biopharmaceutics* 2010; 76: 75–82.
- Schleh C, Rutishauser BR and Kreyling WG. *European Journal of Pharmaceutics and Biopharmaceutics* 2011; 77: 350–354.
- Shah ND, Shah VV and Chivate ND. Pulmonary Drug Delivery- A Promising Approach. *Journal of Applied Pharmaceutical Science* 2012; 02(06): 33-37.
- Shahrukh M, Ahmed AY, Abbas J, Khan R, Rumana U and Patel A. A Review on Matrix Drug Delivery System. *World Journal of Advance Health Care Research* 2019; 3(4): 133-143
- Shaik MR, Korsapati M and Panati D. Polymers in Controlled Drug Delivery Systems. *International Journal of Pharma Sciences* 2012; 2(4): 112-116
- Sung YK and Kim SW. Recent Advances in Polymeric Drug Delivery Systems. *Biomaterials Research* 2020; 24(12): 1-12.
- Varma MVS, Kaushal AM, Garg A and Garg S. Factors Affecting Mechanism and Kinetics of Drug Release from Matrix-Based Oral Controlled Drug Delivery Systems. *American Journal of Drug Delivery* 2004; 2(1): 43-57
- Verma RK and Garg S. Current Status of Drug Delivery Technology and Future Directions. *International Journal of Pharmaceutical Technology* 2001; 25(2): 1-14.
- Wokovich AM, Prodduturi S, Doub WH, Hussaain AS and Buhse LF. Transdermal Drug Delivery System (TDDS) Adhesion as a Critical Safety, Efficacy and Quality Attribute. *European Journal of Pharmaceutics and Biopharmaceutics* 2006; 64: 1-8
- Yadav RP, Sheeba FR, Sharma M, Bhargav A, Kumar Y and Patel AK. The Role of Matrix Tablet in Oral Drug Delivery System. *Asian Journal of Pharamceutical Research and Development* 2021; 9(2): 80-86

