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Review Article

Matrix Tablets: An Effective Way for Oral Controlled Release Drug Delivery

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Abstract

The purpose of this review article is to characterize all of the parameters regarding the types, polymers used, and release kinetics of matrix tablets. Matrix system was the earliest oral extended release platform for medicinal use. Matrix tablets are most commonly used methods to modulate the release profile of drugs. They are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs. Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system. This leads to the conclusion that matrix tablets seem to be most promising when developing an oral controlled release formulation.

Keywords: Controlled release; Hydrophilic matrix; Hydrophobic matrix; Matrix tablets; Polymers.
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1. Introduction

The idea behind oral controlled release technologies is that plasma levels of the drug can be optimized by controlling the delivery of the drug from the formulation into the gastrointestinal tract. Oral novel drug delivery system can be classified as *modified release*, *extended release* and delayed release. Controlled release drug delivery system is the extension of extended release type. Controlled drug release has been attempted to achieve by following classes [1, 2]:

A) Diffusion controlled system: i) reservoir type; ii) matrix type; B) Dissolution controlled system: i) reservoir type; ii) matix type; C) Ion-exchange resin-drug complexes; D) pH dependent formulations; E) Osmotic pressure controlled systems.

Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner. In a matrix system, the drug substance is homogenously mixed into

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the rate controlling material as crystalline, amorphous or in rare cases molecular dispersion [3]. These release the drug by dissolution controlled and/or diffusion controlled mechanisms [4].

2. Classification

2.1. Classification based on the characteristics of rate controlling material

2.1.1. Hydrophillic type matrix

In this system, the rate controlling materials are water soluble and/or swellable. Matrix is a well mixed composite of one or more drugs with gelling agent. Commonly available hydrophilic polymers [5] include:

• Non-ionic soluble cellulose ether, such as hydroxypropylmethylcellulose (HPMC, e.g, Methocel K100LV, K4M, K15M, K100M), hydroxypropylcellulose (Klucel GXF MXF), hydroxylethylcellulose (HEC e.g, Natrosol).

• Non-ionic homopolymers of ethylene oxide, such as poly(ethylene oxide) with a molecular weight range of 100,000 to 8000,000 (Polyox WSR N-12K).

• Water soluble natural gums of polysaccharides of natural origin, such as xanthum gum, alginate, and locust bean gum.

• Water swellable, but insoluble, high molecular weight homopolymers and copolymers of acrylic acid chemically cross-linked with polyalkenyl alcohols with varying degree of cross-linking or particle size (Carbopol 71G NF, 971P, 934P).

• Polyvinyl acetate and povidone mixture (Kollidone SR).

• Cross-linked high amylose starch.

• Ionic methacrylate copolymers (Eudragit L30D).

2.1.2. Hydrophobic type matrix

The hydrophobic matrix system was the earliest oral extended release platform for medicinal use. The concept was first introduced in 1959 e.g., Premarin tablets. In these systems the drug is mixed with an inert or hydrophobic polymer and then compressed to a tablet. Sustained release is produced due to fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles [6].

• Fatty acids, fatty acid esters, mono-, di, and triglycerides of fatty acids, fatty alcohols, waxes of natural and synthetic origins with differing melting points, as well as

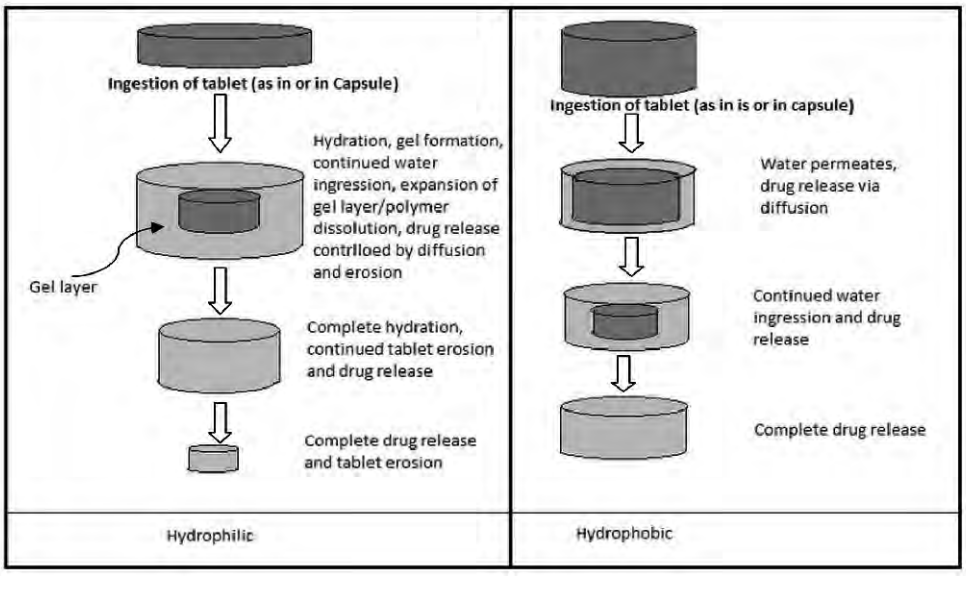

Figure 1. Hydrophilic and hydrophobic matrix system and corresponding drug release process [7].

hydrophobic polymers, are used in hydrophobic, non-swellable matrices. Examples include stearic acid, lauryl, cetyl or cetostearyl alcohol, carnauba wax, beeswax, candelilla wax, microcrystalline wax and low molecular weight polyethylene.

• Insoluble polymers include fine powders of ammoniomethacrylate copolymers (Eudragit RL100, RS 100), ethyl cellulose, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate and latex dispersions of insoluble polymers.

2.1.3. Lipid type matrix

These matrices are prepared by 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 [8].

• Carnauba wax in combination with stearyl alcohol or stearic acid has been used as retardant base for many sustained release formulation.

2.1.4. Biodegradable type matrix

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 excreted or metabolized [9].

• Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and polyanhydrides.

2.1.5. Mineral type matrix

These consist of polymers which are obtained from various species of seaweeds. Example is alginic acid which is a hydrophilic carbohydrate obtained from the species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

2.2. Classification based on porosity of matrix [10, 11]

2.2.1. Macroporous system

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 □m. This pore size is larger than diffusant molecule size.

2.2.2. Microporous system

Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50-200 Å, which is slightly larger than diffusant molecule.

2.2.3. Non-porous System

Non-porous systems have no pores and the molecules diffuses through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

3. Release kinetics

3.1. Drug release from hydrophilic matrix

Hydrophilic matrix systems are polymer-based drug delivery systems in which two competing drug release mechanism are involved [12]: Fickian diffusion release and relaxational release. The primary rate controlling materials are polymers that hydrate and swell rapidly in an aqueous medium and form a gel layer on the surface of the system. Diffusion across the gel layer is not the only drug release pathway, as erosion of the matrix following polymer relaxation also contributes to drug release [13]. Relative contribution of each component to the drug release depends on the properties of the given drug and matrix composition. Over the past three decades, various models have been explored and developed to achieve a fundamental understanding of drug release from hydrophilic matrices. Among them, a semi-empirical exponent equation that was introduced in the mid-1980s has been widely used to describe drug release from hydrophilic matrix system:

$$Q = kt^n$$

Where, 'Q' is the fraction of drug released in time 't'; 'K' is the rate constant incorporating characteristics of the macromolecular network system and the drug; and 'n' is the diffusional exponent.

It has been shown that the value of 'n' is indicative of the drug release mechanism. For n=0.5, drug release follows a Fickian diffusion mechanism. For n=1, drug release occurs by relaxational transport. For 1> n>0.5, non-Fickian diffusion behavior is observed as a result of contributions from diffusion and polymer erosion, also termed as "anomalous" release.

In order to describe relaxational transport, Peppas and Sahlin [14] derived the following equation:

$$Q= k_1t^n + k_2t^{2n}$$

Where 'k1' and 'k2' are the constant reflecting the relative contribution of Fickian and relaxational mechanisms. In the case where surface area is fixed, the value of 'n' should be equal to 0.5. Thus equation becomes:

$$Q= k_1t^{0.5} + k_2t$$

Where, the first and second terms represent drug release due to diffusion and polymer erosion, respectively. This equation was later successfully applied to describe drug release from hydrophilic matrices.

In early 1990s, additional models have been investigated to understand drug release from hydrophilic matrix. One is so called "Spaghetti" model proposed to gain insight into the complex release process from hydrophilic matrix system [15]. This model treats polymer erosion as diffusion of polymer across an unstirred 'diffusion layer' adjacent to polymer gel layer. Thus two processes contribute to drug release i.e., diffusion of drug through gel layer and diffusion of polymer across diffusion layer. In addition to the solubility of the drug molecule [16] that defines the diffusion component, polymer disentanglement concentration (Cp,dis) is used to gauge the contribution polymer diffusion/dissolution:

$$(C_{p,dis})_{eq} = 0.05\left(\frac{MW_pX_p}{96000}\right)^{0.8}$$

$$M_p \approx kt^1$$

MW_p and X_p denote the molecular weight and weight fraction of polymer in the matrix, respectively and M_p is the polymer release at time, t. C_p,dis is the intrinsic property of the polymer while $(C_{p,dis})$eq is an 'equivalent' C_p,dis of the polymer matrix. One may consider C_p,dis as equivalent solubility of the polymer, as it defines the concentration at which a polymer detaches from a pure polymer system. So the relative contribution of both mechanism can be characterized by the solubility ratio of the drug C_s to (Cp,dis)eq.

If $C_s/(C_{p,dis})_{eq} >> 1$, then $Q_t = kt^{0.5}$ (release is controlled by drug diffusion)

If $C_s/(C_{p,dis})_{eq} << 1$, then $Q_t = kt^1$ (release is controlled by polymer erosion)

3.2. Drug release from hydrophobic matrix

The hydrophobic matrix was the earliest oral extended-release platform for medicinal use. In this system, the drug is dispersed throughout a matrix. For a homogenous monolithic matrix system [17], the release behavior can be described by the Higuchi equation:

$$M_t = [DC_s(2A - C_s)t]^{1/2}$$

Where, 'M_t' is the drug released per unit area at time 't'; A is the drug loading per unit volume; 'C_s' is the drug solubility; and 'D' is the diffusion coefficient in the matrix phase.

In the case of $A>>C_s$, then equation reduces to:

$$M_t = [2DAC_st]^{1/2}$$

Thus, amount of drug released is proportional

to square root of time, A, D and Cs.

Drug release from a porous monolithic matrix system involves the simultaneous penetration of surrounding liquid, dissolution of the drug, and leaching out of the drug through interstitial channels and pores [18]. The volume and the length of the openings in the matrix must be accounted for in the diffusion equation leading to the second term of Higuchi equation:

$$M_t = \left(\varepsilon C_s \, (2A - \varepsilon C_s) \frac{D_a \, t}{\tau} \right)^{1/2}$$

'ε' and 'τ' are porosity and tortuosity of the matrix, repectively, and 'Da' is the drug diffusion coefficient in the release medium. Tortuosity is introduced to account for an increase in diffusional path length, due to branching and bending of the pores. Similarly, if A> >Cs, then equation becomes [19]:

$$M_t = \left(\frac{2 D_a A C_s \, \varepsilon \, t}{\tau} \right)^{1/2}$$

'ε' is the total porosity of the matrix after the drug has been extracted. The total porosity consists of the intrinsic porosity, 'εa', due to air or void space in the matrix before the leaching process begins, and the porosity created by extracting the drugs, 'εd', and the water soluble excipients, ε_{ex}.

$\varepsilon = \varepsilon_a + \varepsilon_d + \varepsilon_{ex} = \varepsilon_a + A/\rho + A_{ex}/\rho_{ex}$

'ρ' is the drug density, and ρex and Aex are the density and concentration of water soluble excipients.

4. Conclusion

Matrix tablets have discrete advantages which make them interesting candidate for oral controlled drug delivery system. Matrix tablets are helpful in increasing the efficiency of dose, increasing patient compliance. The problem of high cost of production, which was the disadvantage in early days, has been solved with improvement in technology. Using matrix tablet as oral controlled release formulation, many drugs, can be delivered in ways that not only improves safety and efficacy but, in some cases, permit new and more effective therapies. This review has elaborated various matrices, polymers and release mechanism from the matrix tablets.

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