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# EXTENDED RELEASE ORAL DRUG DELIVERY SYSTEM

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**Abstract:** Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations. The extended release formulations may maintain therapeutic concentrations over prolonged periods. The use of extended release formulations avoids the high blood concentration. Extended release formulations have the potential to improve the patient compliance, reduce the toxicity by slowing drug absorption, Minimize drug accumulation with chronic dosing, Usage of less total drug and reduce the dose frequency, Improvement the bioavailability of some drugs. This article provides an overview of design and fabrication of extended release system and in-vitro performance of extended release formulation.

**Keywords:** Extended Release Oral Drug Delivery System, Design and Fabrication of Extended Release

## *INTRODUCTION*

**Extended release oral drug delivery system**

Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations. [1, 2, 3]

**Advantages** [2, 3]

Extended release products having many advantages.

a) The extended release formulations may maintain therapeutic concentrations over prolonged periods.

b) The use of extended release formulations avoids the high blood concentration.

c) Extended release formulations have the potential to improve the patient compliance.

d) Reduce the toxicity by slowing drug absorption.

e) Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.

f) Minimize the local and systemic side effects.

g) Improvement in treatment efficacy.

h) Minimize drug accumulation with chronic dosing.

i) Usage of less total drug.

j) Improvement the bioavailability of some drugs.

k) Improvement of the ability to provide special effects.

**Drug properties, which are suitable for, extended release formulation** [2, 3]

**a) Physiochemical Properties of the drug.**

1. Aqueous solubility: (>0.1mg/ml)
2. Partition co-efficient: (1000:1 octanol: water system)
3. Drug stability *in vivo*: (High enough, so drug remain stable during release from system)
4. Protein binding: (Drug with high protein binding will not required release modification)

5. Drug pKa & ionization at physiological pH: (pKa for acidic API= 3.0 - 7.5, pKa for Basic API = 7.0 - 11.0)
6. Mechanisms and sites of absorption: (Mechanism of absorption should not be active type and absorption window should not be narrow)
7. Molecular size and diffusivity: (Molecule size should be small (100-400 D so it can be easily diffused through polymer matrix)
8. Dose size: (<300mg)

**b) Biological Properties of Drug.**

1. Distribution: (A.P.I. with large volume of distribution is not suitable).
2. Metabolism: (A.P.I. should be metabolized with intermediate speed).
3. Half-life of drug: (2 - 8 hrs).
4. Margin of safety: (High enough so dose dumping does not cause any serious side effect).
5. Plasma concentration response relationship: (A.P.I. having linear relationship is better candidate).

**Design and fabrication of extended release system**

***Monolithic as oral extended release drug delivery system***

Monolithic ER formulations are defined as single unit formulations from which the drug release is controlled over certain period of time. According to the mechanism of drug release, monolithic extended release formulations are classified to:

**A) Diffusion controlled extended release formulations**

The release of the drug is controlled predominantly by its diffusion through a water insoluble polymeric layer. Drug dissolution also contributes to the release of the drug but to a lesser extent.

**Reservoir system[4]**

Extended release formulations where film coating constitutes the main factor in controlling drug release. The first application involved the use of pan-coating process to apply various mixtures of fats and waxes to drug-loaded pellets. Since then, a variety of coating materials and coating machines have been developed and modified.

E.g. Hardened gelatin, Methyl or ethyl cellulose, Polyhydroxymethacrylate, Methacrylate ester copolymers, Various waxes.

Ethyl cellulose and methacrylate ester copolymers are the most commonly used systems in the pharmaceutical industry.[4]

**Matrix system**[4]

Extended release formulations in which the drug is uniformly distributed through the release controlling element. Two major types of materials are used in the pharmaceutical industry to control the drug release from matrix devices; insoluble plastics and fatty compounds.

E.g.; Insoluble plastics: methylacrylatemethyl methacrylate copolymers, polyvinyl chloride, polyethylene. Fatty compounds: carnuba wax and glyceryl tristearate.[4]

**B) Dissolution controlled extended release formulations**[4]

Extended release formulations in which drug release is mainly controlled by the slow dissolution or erosion of the release-controlling element in the formulation. The system can be formulated into reservoir type by encapsulating the drug within slowly soluble polymeric membrane in the form of tablets or capsules. Another approach is to formulate the drug into a matrix system using hydrophilic swellable polymers.

E.g. Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose, Methyl cellulose, Sodium carboxymethyl cellulose.[4]

A major drawback in the dissolution-controlled system is the difficulty to maintain a constant drug release rate since the release rate changes as the size of dosage form diminishes with time.

**C) Osmotic controlled extended release formulations** [5]

They are reservoir systems into which osmotically active agents are incorporated (if the drug itself is not osmotically active) in the formulations. The dosage form is coated with a semi permeable membrane through which hole(s) are carefully drilled. Gastrointestinal fluid diffuses through the membrane and dissolves the osmotic agent(s) creating high osmotic pressure inside the reservoir. Subsequently, water convects out of the reservoir through the hole(s) under the osmotic pressure difference established carrying the drug. Drug release follows zero order kinetics independent of the pH of the gastrointestinal tract.

E.g. Semi permeable membranes: Polyvinyl alcohol, Polyurethane, Cellulose acetate, Ethyl cellulose, Polyvinyl chloride. Different types of osmotic pumps have been developed and modified to provide zero-order delivery of varieties of drugs. [5]

**D) Extended release formulation based on ion exchange resin**[6]

Ion exchange resins are water insoluble,

cross-linked polymers containing salt-forming group in repeating positions on the polymer chain. Drug is bound to the resin and its release will depend on the ionic environment including pH and electrolyte concentration of the gastrointestinal tract as well as the properties of the resin. Drug is released through an exchange process with appropriately charged molecules in the gastrointestinal tract followed by diffusion of the drug out of the resin. Most ion exchange resins used contain sulfonic groups, which can exchange cationic drugs with amine functions. [6]

***Multiparticulate as oral extended release drug delivery system***

Multiparticulate drug delivery systems can be defined as drug delivery systems in which each unit dose is comprised of many entities together shape the drug release profile. By definition, they include different size particles including granules, pellets, micro-capsules, micro-particles, nano-capsules, and nano-particles. Nonetheless, the term has been commonly used in the pharmaceutical literature to describe coated and coated pellets with size range between 0.1-1 mm. [7, 8]

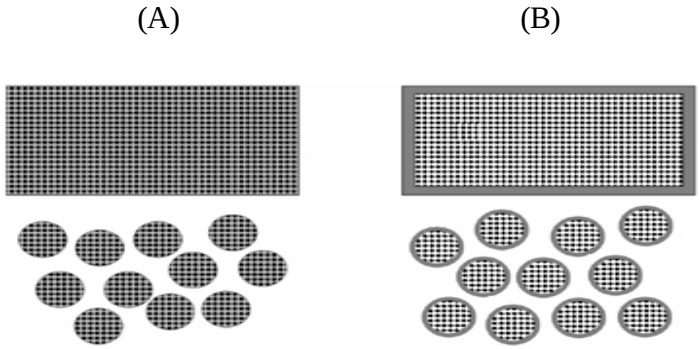


**Figure 1** Schematic presentation of: (A) matrix system and (B) reservoir system; both depicted as single and multiple unit system (size not up to scale) (Black: Drug, Gray: Release controlling polymer, white: excipients)

They have gained much attention in the last two decades, due to their flexibility during formulation development, but also due to therapeutic benefits. In fact, multiparticulates present numerous advantages over single unit dosage forms.

When taken orally, multiparticulates disperse in the gastro-intestinal tract, maximizing absorption, minimizing side effects, reduces inter and intra-patient variability and avoid the risk of local irritation.[9,10] Furthermore, the all-or-nothing effect can be circumvented and the gastric emptying time is less variable. [8, 11]

Pellets are defined as geometrical agglomerates obtained from diverse starting materials (sucrose, starch, microcrystalline cellulose, etc) and can be produced by different process conditions.[10] Pellets loaded with different drugs can be blended and formulated in a single dosage form. This allows the administration of two or more types of drugs that may or not be chemically compatible, at the same or different sites within the gastro-intestinal tract. Furthermore, pellets with different release rates from the same drug can be combined in a single unit dosage form in order to achieve the desired drug release profile.[12] Due to low surface area to volume ratio, ideal shape for film coating, good flowability, low friability, narrow particle size distribution, uniform and reproducible batches are obtained.[13, 14] Coated pellets can be compressed into tablets or filled into hard gelatin capsules as final dosage form.[8]

In order to achieve controlled drug release, pellets can be directly coated or prepared with a polymer: drug solution or dispersion (matrix/matrix coated pellets) or loaded with drug and further coated with a polymeric solution or dispersion (reservoir/reservoir coated pellets).

**A) Matrix Systems**

In matrix systems a polymer: drug solution or dispersion is granulated with excipients to form pellets or sprayed onto pellets in order to achieve controlled drug release. The drug homogeneously distributed within the polymer is dissolved, dispersed or dissolved and dispersed. These systems present several advantages as easy manufacture and low cost (1 step process), lower risk of dose dumping (if the coating accidentally ruptures) and the possibility of improvement of aqueous drug solubility. Besides, drug-polymer interactions can occur and bring benefits in terms of mechanical properties such plasticizing effect.[15,16] The main disadvantages include fast initial release[17] and incomplete release in a defined time. The latter could be avoided by coating sugar cores with different polymer: drug ratios, in which the drug was more concentrated in deeper layers of the matrix and so counteracting for the increased diffusion pathway.[18] In addition,

matrix systems were found suitable to control drug release of a highly soluble drug.[19, 20]

**Matrix solutions, matrix dispersions and drug release mechanisms**

In matrix systems, the drug and polymer are dissolved or dispersed in a common solvent and upon solvent evaporation, a solid solution (drug dissolved in the polymer) or a solid dispersion (drug dispersed in the polymer) or a combination of both is obtained. If the initial drug concentration is below drug solubility in the polymer, drug is dissolved and drug release is mainly controlled by drug diffusivity in the polymer and can be simply described by

$$\frac{Mt}{M\infty} = kt^n$$

Where Mt and M∞ are absolute cumulative amount of drug released at time t and infinity, respectively and n is the diffusional exponent which is indicative of transport mechanism.[21, 22] It is clear that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also termed as case II transport). When n = 0.5, Fickian diffusion is the rate-controlling step (case I transport). Values of n between 0.5 and 1 indicate that the contribution of both diffusion process as well as polymer relaxation control the release kinetics (non-Fickian, anomalous or first-order release). It should be noted that the two extreme values of n = 0.5 and 1 are only valid for slab geometry and n = 0.43 for a sphere. This model assumes that no significant changes occur in the matrix during drug release (constant porosity, no swelling and time independent permeability for the drug). [23]

In case of a solid dispersion, drug release rate can be approximately described by a square root of time kinetics (Higuchi, 1963).

$\frac{Mt}{A} = \sqrt{D(2Co - Cs).Cs.t}$ , for homogenous matrix

$\frac{Mt}{A} = \sqrt{D\frac{E}{T}(2Co - Cs).t}$ , for granular matrix

where Mt is the cumulative absolute amount of drug released at time t, A is the surface area of the film exposed to the release medium, D is the drug diffusivity in the polymer (homogenous matrix) and the drug diffusivity through water filled pores (granular matrix), $C_0$ represents initial drug concentration, Cs is the solubility of the drug in the carrier material for a homogenous matrix and aqueous drug solubility for a

granular matrix, E and τ represent the porosity and tortuosity, respectively. Higuchi law presents several assumptions as: 1) pseudo-steady state is maintained during release; 2) diffusion coefficient constant; 3) perfect sink conditions exist in external media; 4) drug concentration in the matrix is greater than drug solubility in the polymer and 5) no interaction between drug and polymer exist. One of the limitations of Higuchi law is the fact that linearity between amounts of drug released per unit area per square root of time is just achieved until 60% drug release. Above 60%, drug release rate declines and the linearity is lost. This is due to increased path length for drug to diffuse with time. Drug release from both solid solutions and solid dispersions are dependent on geometry of the device used.

**B) Reservoir Coated Systems**

A reservoir coated system consists of a drug layered core surrounded by a polymer. The major advantages of this system rely in the fact that very high drug loadings can be used and variable drug release profiles can be obtained, by just varying the type of polymeric membrane.

**Aqueous coating and organic coating**

Pellets can be coated with an aqueous polymeric dispersion or an organic solution in order to achieve controlled drug release. Organic coatings present many disadvantages as the dependence of viscosity on molecular weight and the concentration of polymer used. In contrast, aqueous polymer dispersions are characterized by low viscosity even at high solid contents[7], leading to a decrease in coating process time. Organic solutions present additional disadvantages like the presence of residual solvents in the coating that can create changes in film properties, environmental pollution and explosion hazards. As a result, the use of aqueous polymeric dispersions is preferred for pharmaceutical coatings. However, film formation mechanisms (aqueous versus organic) are very different [18]. With organic polymer solutions, polymer macromolecules are dissolved and this can create a high viscosity solution. During solvent evaporation, an intermediate gel-like phase is formed. After complete solvent evaporation, a polymeric film is obtained (Figure 2: A).

(A) Coating with organic solution. (B) Coating with aqueous solution.

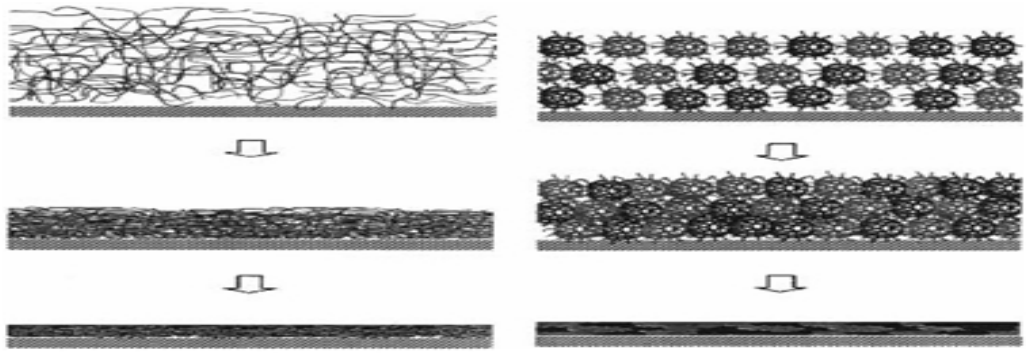

**Figure 2** Schematic presentation of (A) the film forming mechanism from organic Polymer solution (B) the film forming mechanism from aqueous polymer dispersion

In contrast, film formation from aqueous dispersions is a more complex process [18]. During drying of aqueous dispersions, polymer particles come into contact with each other in a closed packed order. The high interfacial surface tension between air and water leads to the formation of a layer of polymer spheres filled with water. The particle fusion or coalescence is then possible when the capillarity forces (air-water interfacial tension) are strong enough (Figure 2: B).[7] Usually the coating process is performed at sufficient high temperatures to guarantee softness of the discrete polymer particles. The softening is related to the glass transition temperature (Tg) of the polymer. A curing step (post coating thermal treatment) is carried out after coating process to assure complete film formation and avoid further gradual coalescence.[7] The aqueous dispersions can have additional ingredients as surfactants that act as stabilizers during the production process. Other compounds as plasticizers and anti-taking agents are used to enhance the coating process and film properties. Plasticizers are added to promote the polymer particle coalescence, softening the particles and reducing minimum film formation temperature (MFT)[7]. Film formation is related to glass transition temperature of the polymer or minimum film formation of the aqueous dispersion. The MFT is the minimum temperature above a continuous film is formed during drying under standardized conditions. Below this temperature the dry latex is opaque and powdery; however these conditions are different from drying during coating. Actually, water can decrease Tg of the some polymers (due to its plasticizing effect) and

in this case the MFT is lower than the Tg of the polymer. Tg and MFT shows a linear relationship between different polymer/plasticizer concentrations. [24]

**Drug release mechanisms**

The mechanism controlling drug release from reservoir coated pellets is often a complex process [25] and it depends on coating type and thickness[26], drug type [27] and core type [28].

One of the mechanisms is diffusion through the continuous polymer film surrounding the drug loaded core.[10] Firstly, water penetrates through the coating until reaches the pellet core. Afterwards, drug is dissolved and released. The drug is released due to the concentration gradient inside the pellet (Ci) versus outside the pellet. In the case of perfect sink conditions the amount of drug released (dM) within a certain time period (dt) can be calculated as follows (according to Fick's law of diffusion):

$$\frac{dM}{dt} = Dm.A.K.\frac{Ci}{d}$$

Dm is the apparent diffusion coefficient of the drug in the polymeric film, A the surface available for diffusion, K the partition coefficient of the drug (aqueous phase - polymeric phase), and d denotes the thickness of the film coating. [31] Unfortunately, Fick´s Law (which was only ever intended to describe diffusion in binary mixtures) cannot be extended to drug release from reservoir pellets that easily. The diffusivity for example is assumed to be constant in homogeneous, intact polymer films. However, in reality many polymers swell upon contact with medium which is known to gradually increase the diffusivity over time. In addition most polymers contain crystalline regions in which drug diffusion is negligible. Drug diffusion in the amorphous regions of polymers has been described by the so-called 'jump-and-run'-model. It was proposed that the amorphous segments in polymers contain homogeneous, semi-crystalline structures of polymer molecules which are aligned in parallel. Permeants like the diffusing drug 'run' along the tube between parallel polymer chains until reaching a 'dead-end' (a crystalline region or a point of high chain entanglement). There they are forced to 'jump' from one tube to the next, pushing and bending the polymer chains apart (Figure 4).

Drug release can occur through water filled pores (Figure 3: B, C). These pores can be due to leaching of water soluble compounds into the release medium or due to cracks formed by high hydrostatic pressure generated inside these systems upon water uptake. Drug release can be described as follows:

$$\frac{dM}{dt} = Dp.A.\frac{\varepsilon}{\tau}.\frac{Ci}{d}$$

Where Dp is the diffusion coefficient of the drug in the aqueous phase present in the channels and pores, ε the volume fraction of the pores, τ the tortuosity of the channels.[25]

Another possible mechanism controlling drug release from coated pellets is due to osmotic effects (Figure 3: D). For this mechanism to occur an osmotic active core should be surrounded by semi permeable membrane and a difference in osmotic pressure between the inner and outer side of the membrane.

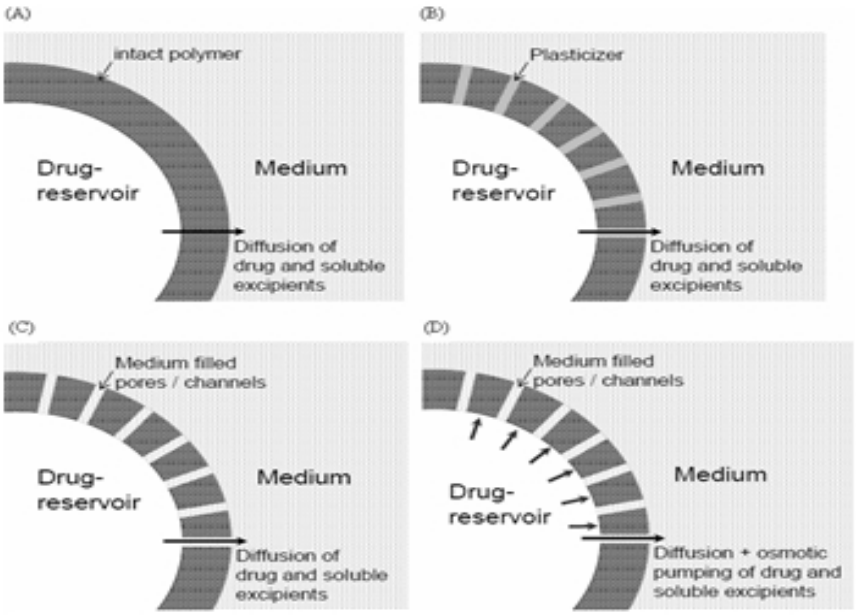


**Figure 3** Schematic presentation of typical release mechanism of coated pellets

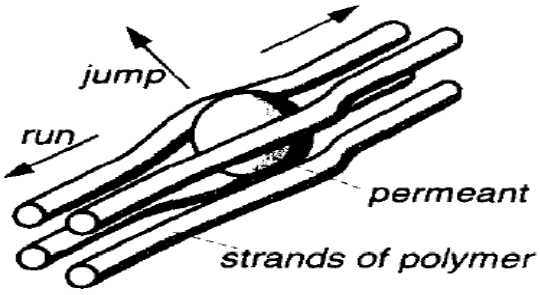


**Figure 4** The jump-and-run model of permeant diffusion through intact polymer

Osmotically driven release depends on the porosity of the polymeric membrane and the

osmotic pressure of the sugar core and the drug. Upon water uptake, drug is pushed out via pores in the coating. Drug release can be described as follows: [25]

$$\frac{dV}{dt} = \frac{A\,\theta\,\Delta\pi}{l}$$

Where dV/dt denotes the water flow, A the membrane surface area, l the membrane thickness, θ the permeability of the polymeric membrane, and Δπ the difference in osmotic pressure (neglecting the counteracting hydrostatic pressure). The overall drug release rate from coated pellets may be governed by one of the above mechanism or a combination of them.[25, 29] Parameters as core and coating swelling also contributes to the drug release rate.

The type of drug can strongly affect the resulting drug release rates. Ibuprofen diffused through the coating (due to high solubility in the polymer) while chlorpheniramine maleate diffused through micro-channels in Aquacoat coated pellets, resulting from osmotic pressure developed by the core.[30] Drug release rate can be affected by changes in surface area (during dissolution study) of the pellets.[31] The coating level also changes the mechanism of drug release. At low coating levels, drug release occurred through pores in the coating, while at high coating levels drug release rate was controlled by diffusion through the coating.[32] consequently the mechanism controlling drug release at higher coating levels was not just dependent on drug solubility but also on the polymer/dissolution medium partitioning coefficient of the drug. Drug release mechanism from ethylcellulose coatings with pore formers was investigated by several researchers. At lower pore former (HPMC) contents, drug release occurred through osmotic pumping, but above a certain value diffusion also contributed to overall drug release. Addition of small amounts of polyvinyl alcohol polyethylene glycol graft copolymer to ethylcellulose coatings was found to control drug release from coated pellets irrespective of the drug solubility and type of core formulation. The mechanism controlling drug release was shown to be diffusion through intact polymeric membranes.

The glass transition temperature of the polymer also affects the drug release mechanism. With water soluble plasticizers, the polymer was in glassy state after plasticizer migration and drug diffused through water filled pores. With water insoluble plasticizers, the polymer was in the rubbery state and a two phase release

mechanism was found. In the first phase drug was released through pores created by leaching of HPMC and in the second phase pore shrinking occurred leading to a decrease of free volume in the polymer chains. [33]

The type of coating technique (organic versus aqueous) was found to contribute to drug release mechanism in different ways. Drug release mechanism from coating with blends of a water-insoluble (ethylcellulose) and an enteric polymer (ethylcellulose: methacrylic acid ethylacrylate copolymer, Eudragit L) occurred by diffusion through the intact polymeric films and/or water-filled cracks. However, lower hydrostatic pressures were necessary to induce crack formation within aqueous coatings. Organic coatings were mechanically strong with high degree of polymer-polymer interpenetration and thus higher hydrostatic pressure was required to induce crack formation.

The polymer particle size affects the film coating structure and properties. Blends of aqueous dispersions of a water-insoluble and an enteric polymer, ethylcellulose and Hydroxypropyl methyl cellulose acetate succinate (HPMCAS) and Eudragit L were used as coating materials to control theophylline release from matrix pellets. Drug releases were similar for both types of blends in 0.1 M HCl, but significant differences were observed in phosphate buffer pH 7.4. Eudragit L particles are smaller than HPMCAS particles (nano- vs. micrometer size range) and more effectively hinder the formation of a continuous and mechanically stable ethylcellulose network.

Ethyl cellulose structures remaining upon HPMCAS leaching are mechanically stronger and drug release is controlled by diffusion through the polymeric remnants. In contrast, ethylcellulose structures remaining after enteric polymer leaching at high pH are mechanically much weaker in the case of Eudragit L. Upon exposure to phosphate buffer, water-filled cracks are formed, through which the drug rapidly diffuses out. [34]

**Curing**

After coating process and even with a product temperature 10°C-20°C above the MFT, complete film formation may not be achieved. Thus a short thermal treatment is required to complete polymer particle coalescence. At curing temperatures above the glass transition temperature, the mobility of the polymer chains increases and latex coalescence is accelerated. The curing step may be performed in an oven or in the fluidized bed coater immediately

after the coating process. Too low curing temperatures can lead to incomplete film formation, whereas too high temperatures can lead to excessive tackiness and agglomeration of the solid dosage forms. The curing step can be performed at several temperatures or different times and in the presence of controlled humidity. All these factors can potentially affect drug release rate. The slower release rates with increasing curing time were attributed to greater polymer particles coalescence.[35] In another study, the curing temperature and time were investigated. Drug release decreased with increasing temperature. At 30°C, the decrease in drug release was small and not affected by the curing time. When temperature and time of curing were increased, the resulting changes in drug release rate increased. It was suggested that at higher temperatures, more polymer molecules can overcome the energy barrier and reach a stable state, reflected by the slower release. On the contrary, at low curing temperatures, few molecules can achieve a stable state, meaning that changes in drug release are expected to occur slowly over time until the stable state is reached.[36]

Controlled humidity can be used during the curing step. The presence of humidity was more effective to complete film formation than without. Water facilitates polymer particle coalescence and it acts as plasticizer for many polymers.[37] High content of plasticizer can minimize the curing effect [38], however there is a limit of plasticizer concentration to avoid problems as stickiness during coating process or forming agglomerates of pellets during curing.

The curing effect on drug release can change depending on the type plasticizer and

coating level. For example, drug release decreased with increasing harshness (time, temperature and relative humidity) of curing conditions, when using triethyl citrate as plasticizer. In case of dibutyl sebacate and Myvacet this relationship was only seen at low coating levels.[39] the curing step can lead to drug migration through the coating, usually resulting in an increase in drug release. A seal coat was used in order to protect drug migration and stabilize drug release profiles.

**Storage stability**

Although the curing step is performed in order to complete film formation, drug release rate was reported to decrease especially under elevated humidity[40, 41]. This was mainly attributed to further gradual polymer coalescence, leading to denser films and decreased permeability for water and

drug.

Changes in drug release profiles were also observed with high glass transition temperature polymers. Faster drug release may be caused by brittle films or the formation of micro-ruptures in the film coat during storage.[36]

Thermal humidity curing was found to help to enhance coalesce of polymeric films, however presence of high levels of humidity during storage can destabilize films, originating changes in drug release rate over time. [42]

Some recent studies have shown an improvement of storage stability from aqueous polymeric systems, by adding hydrophilic polymers. Stable drug release profiles were obtained and attributed to the presence of more water trapped in these systems during film formation, facilitating particle coalescence. [43]

The degree of coalescence of latex particles at the completion of the coating process increases as the amount of plasticizer in the formulation increases, due to the plasticizer's ability to weaken polymeric intermolecular attractions. Consequently, it allows the polymer molecules to move more readily, increasing the flexibility of the polymer. While liquid plasticizers can be lost through evaporation during storage, solid-state plasticizers have the distinct advantage of remaining in the film throughout the shelf life of the dosage form.

**_In vitro_ performance of oral ER formulations**

***Dissolution testing***

Dissolution testing is an official evaluation method for solid oral dosage forms. Several Pharmacopoeial standard dissolution media and apparatuses are well documented. The method was initially developed for IR solid oral dosage form and then extended to modified release solid oral dosage forms as well as other novel/special dosage forms.[44]

The application of dissolution testing was conventionally known as a tool for ensuring batch to batch consistency. It is also an essential mean for deciding on a candidate formulation in product development. The tests should be sensitive enough to demonstrate any small variable in manufacturing of a product as well as the type and level of excipients used. Therefore, it is possible that an over-discriminatory test, although in vivo irrelevance might be suitable for these purposes. [44]

The value of dissolution test was later shifted to bioavailability prediction. Challenges in selecting the test conditions which reflect *in vivo* drug release have been of interested to many researchers.[45,46] The tests may not be Pharmacopoeial standard, they should, however, be sensitive, reliable and discriminatory with regard to the *in vivo* drug release characteristics.[44,47] The ultimate goal of the dissolution test is to predict the *in vivo* performance of products from *in vitro* test by a proper correlation, so called *in vitro/in vivo* correlation (IVIVC).[48] In certain cases, dissolution tests can be used for providing bio-waivers for lower strengths of a product once the higher strength is approved. The waivers can also be granted to some categories of post-approval changes, based on the appropriate bioavailability/bioequivalence test procedure. [49, 50]

***Bio-relevant dissolution testing***

**A) Physiological properties of the gastrointestinal tract:**

Physiological conditions vary wildly along the gastrointestinal (GI) tract. Not to mention inter subject variability, various factors within an individual, such as disease states, physical activity level, stress level and food ingestion, considerably influence the GI conditions.[51] The effects of this variability on the performance of ER systems are even more pronounced given that the dosage forms are designed to remain in the GI tract for the substantially longer period of time and transit through various conditions compared with IR systems. Inhomogeneous distribution of fluid in the small and large intestine[52] is one of many factors that potentially contribute to the variability of drug release and absorption. Physiological properties in various GI compartments with and without effect of food are presented in table 1 and table 2.

Gastric emptying time of a solid dosage form changes dramatically with the effect of co-administered food. One out of twelve capsules taken three hrs before meal and all twelve capsules taken immediately after meal remained in the stomach for at least one hrs, while in the fasted state, the majority of the capsules had left the stomach within one hrs.[52] The total time for a dosage form to empty from the stomach in the fasted state depends on the size of the dosage form, i.e. the longer time is needed for the larger, as well as the motility cycle of the stomach which is two hrs in average. The emptying for most non-disintegrating solid dosage forms with larger than one millimeter diameter occurred in the late phase II or

phase III of the cycle.[51] Co-administered food even further altered the emptying time depending on the calorie content. A delay for several hrs to empty a relatively large solid dosage form can also occur as the food will be first cleared from the stomach and return to the normal gastric motility cycle in the fasted state. The dosage form is then emptied under the phase III activity.[51] Unlike the gastric emptying, transit time in the small intestine in both fasted and fed states are not significantly different, regardless of the type of dosage forms. [51,53] The pH and osmolality of the stomach and the upper small intestine is greatly influence by co-administered food. In healthy humans, their values for the stomach increased from pH 1.7/ 140 mOsm $kg^{-1}$ up to pH 6.4/559 mOsm $kg^{-1}$ within thirty minutes postprandial and then gradually decreased to pH 2.7/217 mOsm $kg^{-1}$ after 3.5 hrs. Composition and quantity of the meal significantly affected the time require to re-establish the fasting gastric pH more than did the pH value of the meal.

**Table 1**

Physiology of the GI tract of healthy humans in fasted state

| Location | Fluid volume (ml) | Transit time Hrs. | pH | Osmolarity mOsm/kg | Buffer capacity mmol/L·ΔpH | Surface tension mN/m |
|---|---|---|---|---|---|---|
| **Stomach** | 45 | 1-2 | 1.5-1.9 | 98-100 | 7-18 | 42-46 |
| **Duodenum** | 105 | 3.6 | 6.5 | 178 | 5.6 | 32.3 |
| **Jejunum** | | | 6.8 | 271 | 2.4 | 28 |
| **Ileum** | | | 7.2 | n/a | n/a | n/a |
| **Colon** | 13 | 7-20 | 6.5 | n/a | n/a | n/a |

n/a information not available

**Table 2**

Physiology of the GI tract of healthy humans in fed state

| Location | Fluid volume (ml*) | Transit time Hrs. | pH | Osmolarity mOsm/kg | Buffer capacity mmol/L·ΔpH | Surface tension mN/m |
|---|---|---|---|---|---|---|
| **Stomach** | 800-900 | 1.4-4.0 | 3-7 | 217-559 | 14.28 | 30-31 |
| **Duodenum** | 900- | 3.8 | 5.1-5.4 | 390 | 18.30 | 28.1-28.8 |
| **Jejunum** | 1000 | | 5.2-6 | n/a | 14.6 | 27 |
| **Ileum** | | | 7.5 | n/a | n/a | n/a |
| **Colon** | n/a | n/a | 5 | n/a | n/a | n/a |

* including the volume of the meal, n/a information not available

For example, two hrs was required after a 651 mOsm/1000 kcal (pH 5.6) meal whereas only one hrs was needed for a 540 mOsm/458 kcal meal (pH 6).[54] As the average time for restoring the pH of the stomach was two to three hrs[51], dosage forms with pH-dependent controlled release, such as an enteric coated tablet, may fail to control the release when taken with or soon after meal.

Unlike the stomach and the small intestine, the movement of luminal contents in the colon did not always occur longitudinally, but also laterally in order to assist the mixing of the contents and to facilitate absorption. A food effect study with radiography revealed the remaining of some of the radio-opaque markers after 36 h at the ascending colon, whilst some of them taken only 12 hrs before the study were found at the end of the transverse colon.[51] the transit time of a dosage form was, therefore, considered as no effect of food intake.

**Effect of food on the bioavailability of drugs and dosage forms**

The presence of food within the GI tract can significantly influence the bioavailability of drugs, both by the nature of food and the drug formulations. Factors deserving critical attention for predicting bioavailability under fed conditions are;

a) An increase in solubilisation capacity by higher concentrations of bile salts and fatty acids. This factor can alter the release profiles of lipophilic drugs[55, 56] or from dosage forms that drug released is controlled by hydrophilicity[57].

b) A prolonged gastric emptying time (increased GI-residence time), thus increasing the total time available for dissolution and improve the bioavailability.[58, 59, 60] This factor, however, can also inversely affect acid labile drugs that would expose to the acidic environment of the stomach for a significantly longer period of time.

c) An elevation of the pH in the stomach altered the release pattern of pH-dependent controlling formulations as well as affected the dissolution rate of drugs with pH dependent solubility.[58]

d) Changes in the physical and biochemical barrier function of the GI tract.[61,62] The increased fluidity of the intestinal wall by lipid as well as the increased leakiness of tight junctions by high concentration of glucose can enhance the permeability of the small intestine.[61]

e) Stimulation of intestinal lymphatic transport.[62]

**Marketed products of extended release tablet**

**Table 3**

Marketed products of extended release tablet

| Brand name | Strength | Company |
|---|---|---|
| **Volix** | Voglibose 0.3 mg | Ranbaxy |
| **Seroquel XR** | Quetiapine fumarate 150 mg | Astrazeneca |
| **Ovarine – F** | Clomiphene citrate 50 mg | Matrix pharma |
| **Lostaz** | Cilostazol 50 mg | Matrix pharma |
| **Urocit – K** | Potassium citrate 1 gm | Orphan Australia |
| **Atripla** | Efavirenz 600 mg | Teva Pharm. Ltd. |

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