

## Advances in pharmaceutical development of modified-release drug formulations and products

Article (Accepted Version)

Maniruzzaman, Mohammed and Nokhodchi, Ali (2017) Advances in pharmaceutical development of modified-release drug formulations and products. *Nurse Prescribing*, 15 (5). pp. 246-252. ISSN 1479-9189

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/67442/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

### **Copyright and reuse:**

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

# Progresses in Pharmaceutical Development of Modified Release Drug Formulations and Products

Mohammed Maniruzzaman<sup>1</sup>, Ali Nokhodchi<sup>1,2</sup>

<sup>1</sup>Department of Pharmacy/Chemistry, School of Life Sciences, University of Sussex, Falmer,  
Brighton, BN1 9QJ

<sup>2</sup>Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical  
Sciences, Tabriz, Iran.

**Correspondence:** Dr M. Maniruzzaman ([M.Maniruzzaman@sussex.ac.uk](mailto:M.Maniruzzaman@sussex.ac.uk); [M.Maniruzzaman12@gmail.com](mailto:M.Maniruzzaman12@gmail.com)) and Prof. A. Nokhodchi ([A.Nokhodchi@sussex.ac.uk](mailto:A.Nokhodchi@sussex.ac.uk)),  
Department of Pharmacy/Chemistry, School of Life Sciences, University of Sussex, Falmer,  
Brighton, BN1 9QJ.

## **ABSTRACT**

The ongoing need to provide greater therapeutic efficacy and reduced side effects has accelerated the interest in modified release oral dosage forms design and development. Up to now, being developed by both formulation design strategy and manufacturing process, the modified release is one of the most common forms for oral delivery. From the need of meeting the ongoing challenges in current drug delivery, a variety of modified release platforms have been developed. This review aims to summarise recent literature with an emphasis on types of various controlled release dosage forms with reference made to the commercial excipients and polymers currently used during the formulation development.

**Keywords:** Controlled/modified release, drug delivery, delayed/sustained, modified release, APIs

Accepted

## 1. Introduction

Oral administration is one of the most common approaches with regards to drug delivery while its affectivity relies on factors including patient compliances. A reduction in patient administration frequency is one of the factors that can lead to improved compliances. The administration frequencies can be reduced if the release of the therapeutically active substances are modified/controlled in manner that it delivers the required amount of the drug for a predefined period of time. Therefore, it has been well documented that controlled release dosage forms result in much improved pharmacological activity and reduced side-effects. Controlled release dosage forms (e.g., pellets, granules) are becoming more and more important within the pharmaceutical market compared to single-unit dosage forms (e.g., tablets or capsules) (Varshosaz et al, 2012). Single unit dosage forms primarily consist of drug particles of the same release profile while multi-unit dosage forms consist of different drug particles or same drug particles but of differing release profiles with respect to onset, rate and maximum release (Verma et al, 2012; Uhumwangho and Okor, 2008). In many instances, drug substances are at their most effective when blood plasma concentrations are maintained at constant levels within a therapeutic window or when applied to the target site directly (Figure 1). This, however, is not true in all instances, as some disease states require both periods of elevated and decreased blood plasma concentrations at specific times.

## 2. Modified release dosage forms and pharmaceutical applications

Many drug candidates have been successfully formulated into controlled release systems. For example, improved bioavailability of proteins and peptides including insulin, calcitonin, vasopressin cytokine inhibitors and antibiotics has been achieved via colonic delivery by avoiding absorption within the upper part of the gastrointestinal (GI) tract and enzymatic and chemical degradation (European P, 2011; Singh, 2007). With regards to controlled drug delivery, the gastrointestinal tract is the preferred site for drug absorption for reasons such as ease of administration and therefore patient compliance and low cost. Conventional drug delivery systems are formulated to disintegrate within the stomach and absorbed in the small intestine (Hollinger and Ranade, 2004). The stomach is made up of three different regions including the fundus, body and pylorus. The fundus and body act as a reservoir while the pylorus dictates mixing and gastric emptying (Arora et al, 2005). Parameters including pH, enzymes, residence time, absorbing surface area and secretions at the site of drug release dictate drug release and absorption performance (Talukder and Fassihi, 2004).

Numerous factors associated with drug molecule properties and GI tract target environment affect the movement of drug molecules through the intestinal membrane while complete absorption is dependent on optimal permeability coefficient and solubility at the site of absorption. At the site of absorption, movement of drug molecules across the intestinal membrane can occur via trans-cellular or para-cellular pathways (Gibson, 2004). Controlled targeted delivery of peptides and proteins is achievable within the small intestine, specifically the duodenum, in addition to the delivery of antigens and allergens to M-cells within the Peyer's Patch regions (Al-Tahami and Singh, 2007). For example, gastro-retentive (or colon specific) delivery systems are only suitable for the delivery of active pharmaceutical ingredients (API's) that is not damaged within the gastric region (e.g. lesions) and that are can remain stable within a strongly acid environment such as that found in the stomach. In addition, candidate API's should not have the ability to be readily absorbed throughout the gastrointestinal tract (Talukder and Fassihi, 2004). It has been documented that both levodopa and riboflavin are delivered into controlled release gastro-retentive dosage forms due to their optimal absorption properties at the upper part of the GI tract (Hoffman et al, 2004).

In addition, controlled release of propranolol hydrochloride has been achieved for the treatment of cardiovascular disease (Eurand, 2009) in addition to a pulsed-release drug delivery system for the administration of Captopril (Wilding et al, 1991).

Diseases that can be treated with CR dosage forms have been well documented with many successful dosage form candidates in both tablet and capsular forms (Hollinger and Ranade, 2004, Colorcob 2016). For example, targeted drug delivery to the colon has been developed for the treatment of ulcerative colitis and irritable bowel syndrome (Hollinger and Ranade, 2004) while delayed release dosage forms have been successfully developed for the treatment of colorectal cancers (Colorcon, 2016).

Chronotherapy which is defined as the delivery of a drug at higher concentrations during the time of greatest need while at lower concentrations when the need is less) being another form of controlled delivery, has been successfully investigated for the treatment of diseases including asthma, hypertension, heart disease and arthritis via colonic delivery systems. Such diseases can be characterised as having periods of evening or early morning onset and so benefit from delayed release delivery systems that can yield the release of drug during the night (Al-Tahami and Singh, 2007). An example of a controlled release capsular system includes such a dosage form that has been developed for the delivery of the active ingredient methylphenidate for the treatment of attention deficit hyperactivity (ADHD) (Gothoskar et al, 2004).

The efficiency of such drug release processes is dependent on physicochemical characteristics of the drug including solubility, stability, and permeability through the GI membrane, plus physiological factors associated with GI transit time. GI motility issues can be somewhat overcome in the large intestine where conditions are well understood and predictable. Delivery to the stomach is, however, more technically challenging given increased gastric motility during digestive phases. In addition, controlled drug delivery within the colon is achievable given the drugs long residency time in conjunction with the use of absorption enhancers including micelles (Hollinger and Ranade, 2004; Van den Mooter, 2006; Verma et al, 2000). For the sake of clarity, the in vivo profiles of plasma concentration versus time for various controlled release dosage forms and conventional dosage form have been schematically shown in **Figure 2**.

### **3. Advantages and Disadvantages of Modified/Controlled Release Dosage Forms**

Oral administration of dosage forms present some issues as, in general, the time frame for absorption is dependent on the total GI residence time. In addition, certain drugs will only absorb at specific sites within the GI tract and so total residence time may not represent its time frame for absorption (Hollinger and Ranade, 2004). With regards to gastro-retentive delivery systems, many physiological factors including gastric pH and motility limit development of such systems while their performance relies on patient compliance and direction for use. For example, feeding and caloric contents of food disrupt the inter-digestive motility cycle and gastric emptying rates (Talukder and Fassihi, 2004). In general dosage forms taken before meals exit the stomach at a much faster rate than those dosage forms taken after meals. In certain circumstances where sustained drug delivery is directed at the stomach and small intestine, prolonged gastric retention can offer advantages in the form of improved bioavailability, efficacy, targeted therapy, reduction in side effects within the colon and opportunities to reduce dose size (Hoffman et al, 2004). Drug substances that suffer degradation and poor solubility within alkaline environments in addition to poorly soluble drugs within increased pH environments may be at a therapeutic advantage if formulated as a gastroretentive dosage form (Arora et al, 2005).

Modified enteric delivery systems developed for high volume formulations can result in prolonged gastric retention times, which can then release drug close to the time when the next dose is delivered, thereby resulting in potential overdose of patients (Colorcon, 2016).

Multiparticulate technology, although not exclusive to controlled release, in the form of multiple dosage forms (capsules or tablets) enables the delivery of two or more coated bead

populations allowing easy adjustment of pharmacokinetic variability and improved delivery control (Eurand, 2016). Given the nature of such formulations, populations of beads can possess differing characteristics with regards to release rates. Multiparticulate formulations for colonic delivery pose advantages over conventional single unit dosage forms, as they are less likely to be affected by food and demonstrate consistent absorption and have the ability to ensure more uniform distribution of drug to specific regions of the GI tract. However, one drawback of such an approach is that there is some uncertainty with regards to the specific location within the GI tract at which the coating may dissolve. In addition, an enteric coating may dissolve unpredictably within different patients with different disease states with regards to GI motility patterns leading to premature drug release within the small intestine. Alternatively, some enteric coating may fail to dissolve due to certain disease states leading to efficacy implications (Al-Tahami and Singh, 2007).

Advantages of time controlled explosion systems include the fact that the release rate is not dependent on solubility or dissolution rate of the drug, the release profile is independent of the dissolution medium pH value and that the drug is completely released (Singh, 2007). Several disadvantages of the push-pull systems as discussed in section five, have been documented including short delay times and slow delivery rates resulting in sub-optimal targeted delivery. As a result, many investigations into the remediation and optimisation of such a delivery system have been carried out. Recent formulation developments have therefore aimed to address both issues by improving the composition of delayed release coatings as well as rate of drug release in the colon. For example, by modifying the composition of the exterior enteric coat via incorporation of a hydrophobic compound in excess of its solubility one could prevent the influx of fluids through the coat, particularly during the transit of dosage form through the stomach (Singh, 2007). Formulations based on azo-polymers are relatively stable within the upper GI tract, however, degradation of such polymers by enterobacteria is slow. In addition, such formulations are not recommended for long-term use given their limitations with regards to toxicity (Singh, 2007).

#### **4. Types of Modified Release Dosage Forms**

Modified-release dosage forms in general, include prolonged-release, delayed-release and pulsatile release dosage forms (please see below for detailed descriptions). The generic term is often used when more specific terms such as gastro-resistant (gastric fluid resistant dosage forms intended to release active substance in the intestinal fluid through coating of embedding active substance within gastro-resistant material) or prolonged-release dosage forms (modified-

release dosage forms demonstrating slower release profile in comparison to conventional dosages forms), do not apply. The European Pharmacopoeia defines modified release dosage forms as those demonstrating rate and/or place of release that differ from that of conventional release dosage forms (Uhumwangho and Okor, 2008). A summary of some commercially available polymers used in such delivery system development is given in **Table 1**.

#### ***4.1 Delayed/Sustained Release***

Delayed or sustained release is in general term referred to a process when the release rate of a particular drug is sustained for a prolonged period of time. Delaying the release of a drug may be required to protect the stomach from an irritant drug, the drug from the stomach's gastric acid, or to deliver the drug to a specific site of the GI tract. Such release systems can yield a delay in onset of release, followed by the immediate release of a drug within the GI tract. Alternatively, such delay can be followed by an extended release of the drug within the GI tract. Delayed followed by an extended release of a drug may be beneficial for the delivery of topical medications throughout the colon. Such drug release can be achieved via coating of multiparticulates or hydrophilic matrix tablets with pH-dependent coating polymers. In addition, coating with combinations of pH-dependent coating polymers and extended release barrier membrane systems can achieve delayed release (Eurand, 2016). Sustained release systems depend on dissolution and/or diffusion in order to yield slow release of drug content. Given drug candidate information including dose, rate constants (absorption and elimination) and metabolism of a proposed sustained release system, the release rate and drug content can be assumed (Hollinger M and Ranade, 2004).

One of the main excipients used in the design of sustained release matrix tablet is hydroxylpropyl methylcellulose (HPMC or crosslinked starch). These polymers start swelling as soon as they contact water. They usually make hydrophilic gel layer around tablets which the drug release is governed by diffusion through the swollen gel layer (**Figure 3**). It has been shown that the porosity of tablet has no significant effect on the control of the release (Gao et al, 1995; Visavarungroj et al, 1990; Davis, 1985). In the case of polymers that do not make a gel layer around tablets (e.g. amylopectin) diffusion cannot be the main mechanism of the drug release and the release of drug can occur through leaching mechanism which is shown in **Figure 4**.



## **4.2 Intestinal Release**

Intestinal release dosage forms are generally designed to prevent the release of drug via a lag time, followed by rapid and complete release of the drug within the distal portion of the GI tract. Such dosage forms are appropriate for the localized treatment of disease of the colon, or delivery of a drug to an absorption site within the distal portion of the small intestine. Such systems can be achieved through a coating of multiparticulates, tablets or capsules with pH-dependent coating polymers (Colorcon, 2016).

Mucoadhesive systems extend gastric residence time and control drug delivery within the GI tract via adherence of polymers to the mucous membrane. This adherence can be controlled by factors including hydration where hydrophilic polymers become sticky and therefore retentive. Alternatively, chemical bonding including covalent, ionic or Van Der Waals forces involving the polymer of choice and the GI membrane result in retention. In addition, receptor expression of gastric cells, specific to the polymer of choice results in polymer adhesion and retention (Varum et al, 2010).

Swelling Systems can be considered as plug or floating systems. Polymers incorporated into the dosage form cause the system to swell within the GI tract. This swelling process causes a dramatic increase in dosage size leading to blockage of the pyloric sphincter or dosage floatation offering a gastro-retentive system property (Talukder and Fassihi, 2004). Floating Systems are formulated in the form of either single-unit, multiple-unit, effervescent or non-effervescent systems using gas or gel forming excipients causing them to float in or over gastric contents resulting in gastro-retention (Arora et al, 2004). Alternatively, high-Density Systems lodge themselves in the ridged internal surface of the stomach (known as the rugae) and so withstand the movements of the stomach resulting in stomach retention. Given the nature of the system with regards to an increased density, such dosage forms are retained primarily within the lower sections of the stomach (Talukder and Fassihi, 2004).

## **4.3 Enteric Release**

Enteric-coated dosage forms for delayed drug release profiles are applied for the delivery of drugs where protection from the acidic environment of the stomach is required, or there is a need to reduce irritation of the gastric lining of the stomach (Felton et al, 1993). In either case, enteric release coatings are intended to prevent the release of the drug until the dosage form has passed through the stomach (Hollinger and Ranade, 2004). After this time, rapid release of the drug in the proximal small intestine can occur. Such a release profile can be achieved through

a coating of multiparticulates or tablets with pH-dependent polymeric coating system (Colorcon, 2016).

#### **4.4 Modified Enteric Release**

Where enteric release aims to avoid the release of drug within the stomach, modified enteric release systems aim to allow for a small portion of a drug dose to be released into the stomach, with the remainder of release occurring rapidly upon passage of the dosage form into the small intestine (Marvola et al, 1999). This release system is particularly suited to drugs which demonstrate site-specific absorption in the upper portion of the GI tract, or where high dose drug delivery is required. Such a release systems can be achieved via hydrophilic pore formers in pH dependent enteric coatings.

#### **4.5 Pulsatile Release**

Pulsatile drug release is intended to deliver a burst of drug release at one or more predetermined time intervals after a predetermined lag time. The need for pulsatile release may include avoidance of drug degradation in the stomach or first pass metabolism, the ability to administer two different drugs at the same time (released at different sites in the GI tract) or for chronotherapeutic drug delivery. As an example, pulsatile release can be achieved via coating of multiparticulates with pH dependent and/or barrier membrane coating systems, followed by blending of the multiparticulates to achieve desired release profiles. In general, such time-controlled systems can be classified as either single unit (tablets and capsules) or multiple units (pellets) system (Pozzi et al, 1994).

#### **4.6 Zero Order Release**

Zero order delivery systems facilitate drug release at a rate of which is independent of time and drug concentration (e.g. commercial osmotic pump system) (Figure 5). Zero order mechanisms ensure that a steady amount of drug is released over time, minimizing peak/trough fluctuations and side effects, while ensuring that the amount of time the drug concentrations remain within the therapeutic window is optimal (Landgra et al, 2005). Osmotic tablet formulations, coated tablet matrices, and the use of polymer combinations in hydrophilic matrices are examples of possible formulation options in order to yield zero order drug release profiles (Colorcon, 2016).

## 5. Conclusions

Recent advances in drug delivery systems show a continuous improvement and development of modified release formulations and drug products for the delivery of active substances. As a result of such systems, the potential reduction in oral administrations can only lead to improvements in patient compliance. It has been demonstrated that numerous drug candidates have been successfully formulated into modified release dosage forms for the treatment of a wide range of diseases. Each of these dosage forms has both advantages and disadvantages with a number of obstacles to overcome including physiological parameters of the GI tract and chemical properties of drug candidates.

## 6. References

1. Al-Tahami K, Singh J (2007) Smart Polymer Based Delivery Systems for Peptides and Proteins. *Rec Pat Drug Deliv Form* 1: 65-71.
2. Arora S, Ali J, Ahuja A, Khar R and Baboota S (2004) Floating Drug Delivery Systems: A Review. *AAPS PharmSciTech* 6 (3): Article 47.
3. Arora S, Ali J, Ahuja A, Khar R and Baboota S (2005) Floating Drug Delivery Systems: A Review. *AAPS PharmSciTech* 6 (3): E372-E390.
4. Colorcon. Available at <http://www.colorcon.com/> [accessed on 22<sup>nd</sup> October 2016].
5. Davis SS (1985) The design and evaluation of controlled release systems for the gastrointestinal tract. *J Control Rel* 2:27–38.
6. Eurand. Available at <http://www.eurand.com/> [last accessed 30<sup>th</sup> November 2016].
7. European Pharmacopoeia, 2017. 9<sup>th</sup> Edition (9.0). Monograph 0499.
8. Felton L, Haase M, Shah N et al (1993) Physical and enteric properties of soft gelatin capsules coated with Eudragit® L30 D-55. *Int J Pharm* 113: 17-24.
9. Gao P, Nixon PR, and Skoug JW (1995) Diffusion in HPMC gels. II. Prediction of drug release rates from hydrophilic matrix extended-release dosage forms. *Pharm Res* 12, 965–971.
10. Gibson M (2004) Pharmaceutical Preformulation and Formulation - A practical guide from candidate drug selection to commercial dosage form. Interpharm/CRC.
11. Gothoskar A, Joshi A, Joshi N (2004) Pulsatile Drug Delivery Systems: A Review. *Drug Del Tech* 4:5 (<http://drug-dev.com/Main/Back-Issues/Pulsatile-Drug-Delivery-Systems-A-Review-189.aspx>)

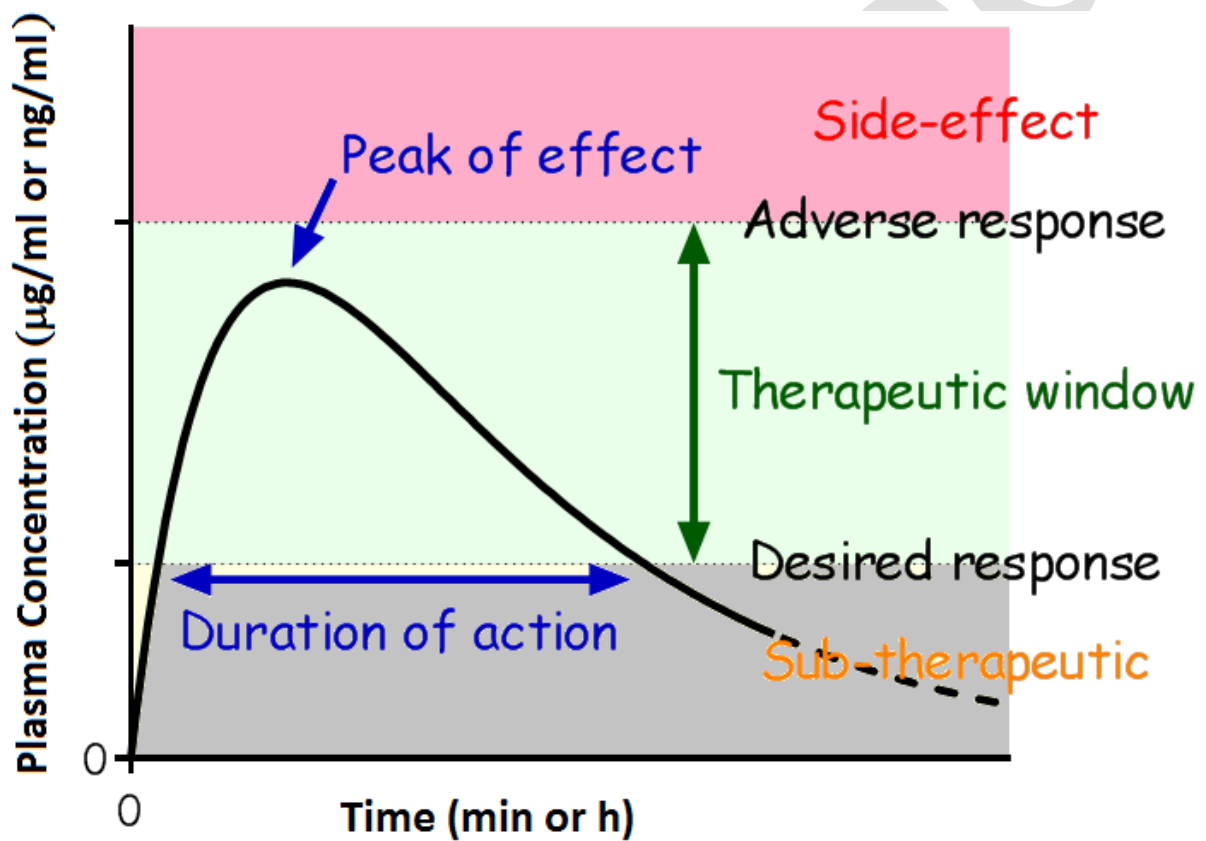
12. Hoffman A, Stepensky D, Lavy E, Eyal S et al (2004) Pharmacokinetic and Pharmacodynamic Aspects of Gastroretentive Dosage Forms. *Int J Pharm* 227: 141-153.
13. Hollinger M and Ranade V (2004) Drug Delivery Systems' (Second Edition). *CRC Press*.
14. Landgra FW, Li N and Benson J (2005) New Polymer Enables Near Zero-Order Release of Drugs. *Drug Deliv Tech* 5 (2): 48-55.
15. Marvola M, Nykanen P, Rautio S (1999) Enteric polymers as binders and coating materials in multiple-unit site specific drug delivery systems. *Eur J Pharm Sci* 7: 259-267.
16. Pozzi F, Furlani P, Gazzaniga A et al (1994) The Time Clock System: a new oral dosage form for fast and complete release of drug after a predetermined lag time. *J Con Rel* 31: 99-108.
17. Singh B (2007) Modified Release Solid Formulations for Colonic Delivery'. *Recent Patents on Drug Delivery Form* 1: 53-63.
18. Talukder R, and Fassihi R (2004) Gastroretentive Delivery Systems: A Mini Review. *Drug Dev Ind Pharm* 30 (10): 1019-1028.
19. Uhumwangho MU and Okor RS (2008) Estimation of the release profiles of multi-unit dose tablets of theophylline from the release profiles of their components. *Trop J Pharm Res* 7(2): 981-986.
20. Van den Mooter G (2006) Colon drug delivery. *Expert Opin Drug Deliv* 3(1):111-25.
21. Varshosaz J, Emami J, Tavakoli N, Minaiyan M et al (2012) Development and Evaluation of a Novel Pellet-Based Tablet System for Potential Colon Delivery of Budesonide. *J Drug Deliv* 2012: 905191.
22. Varum F, Merchant H and Basit W (2010) Oral modified formulations in motion: The relationship between gastrointestinal transit and drug absorption. *Int J Pharm* 395: 26-36.
23. Verma A, Bansal AK, Ghosh A, Pandit JK (2012) Low molecular mass chitosan as carrier for a hydrodynamically balanced system for sustained delivery of ciprofloxacin hydrochloride. *Acta Pharm* 62(2):237-50.
24. Verma R, Mishra B and Garg S (2000) Osmotically Controlled Oral Drug Delivery. *Drug Dev Ind Pharm* 26 (7): 695-708.
25. Visavarungroj N, Herman J and Remon JP (1990) Crosslinked Starch as Sustained Release Agent. *Drug Dev Ind Pharm* 16: 1091-1108.

26. Wilding I, Davis S, Bakhshae M, Stevens H et al (1991) Gastrointestinal Transit and systemic Absorption of Captopril from a Pulsed-Release Formulation. *Pharm Res* 9 (5): 654-657.

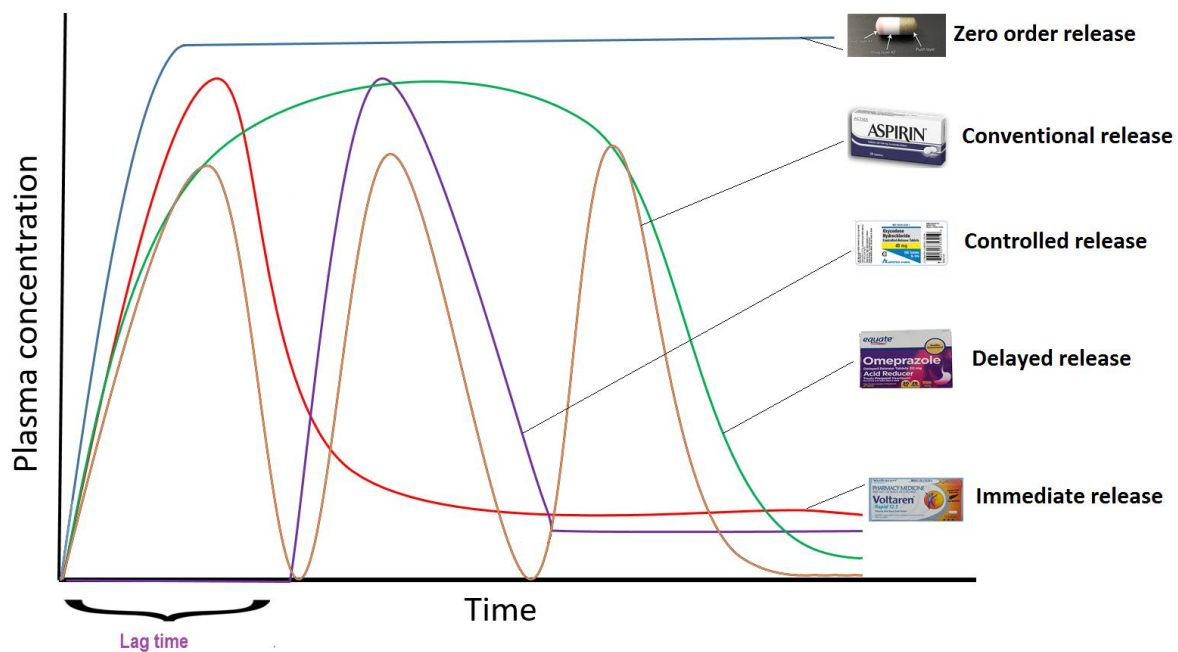
**Table 1:** Existing controlled release technologies

Name	Description	Release	Reference
SyncroDose™	A tablet core with a xanthan and locust bean gum erodible dry-coating layer. Lag time is controlled by polysaccharide ratios.	All	(Marvola et al, 1999)
Push –Pull OROS™	Multilayer tablet comprising five push-pull units for colonic release.	Colonic	(Singh, 2007)
The Pulsincap® System	Insoluble capsule body housing a drug and hydrogel plug for pulsatile release.	Pulsatile	(Gothoskar et al, 2004)
The Port® System	Gelatine capsule containing an insoluble plug, an osmotically active agent and drug coated with semipermeable membrane for pulsatile release.	Pulsatile	(Gothoskar et al, 2004)
Time Clock®	Hydrophobic surfactant coated tablet or capsule in order to rapidly release drug after a predetermined lag time for pulsatile release.	Pulsatile	(Gothoskar et al, 2004)
TARGIT® Technology	Enteric polymer, azo-polymer or fermentable sugar coated starch capsules for colonic release.	Colonic	(Singh, 2007)
COLAL™ Technology	Combinations of a mixture of amorphous amylose and ethylcellulose in addition to a water insoluble polymer for colonic release.	Colonic	(Singh, 2007)

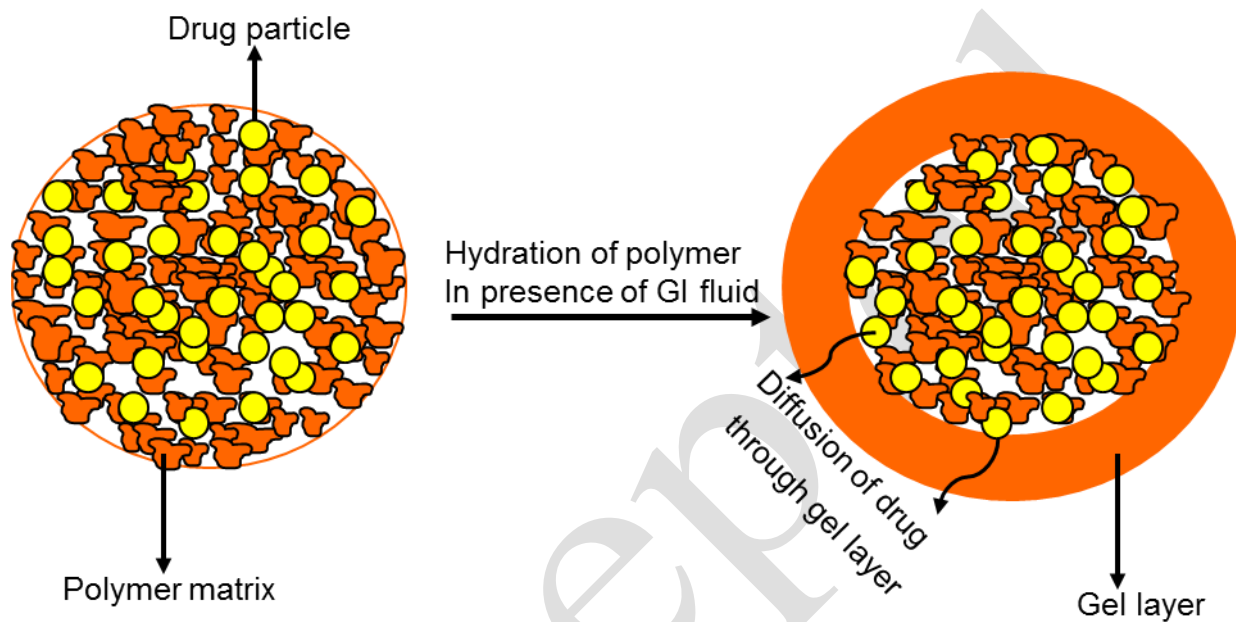
CODES™ Technology	Core tablet of drug and saccharide(s) with three coating layers for colonic release.	Colonic	(Singh, 2007)
SODAS®, IPDAS®, CODAS®, PRODAS® Technology	Elan Pharmaceuticals multiparticulate drug delivery system based on the production of controlled release beads in tablet and/or capsule form.	Controlled Delayed Sustained	(European P, 2011; Varum et al, 2010; Landgra et al, 2005)



**Figure 1:** Schematic representation of therapeutic window (plasma concentration of drug versus time after oral administration).

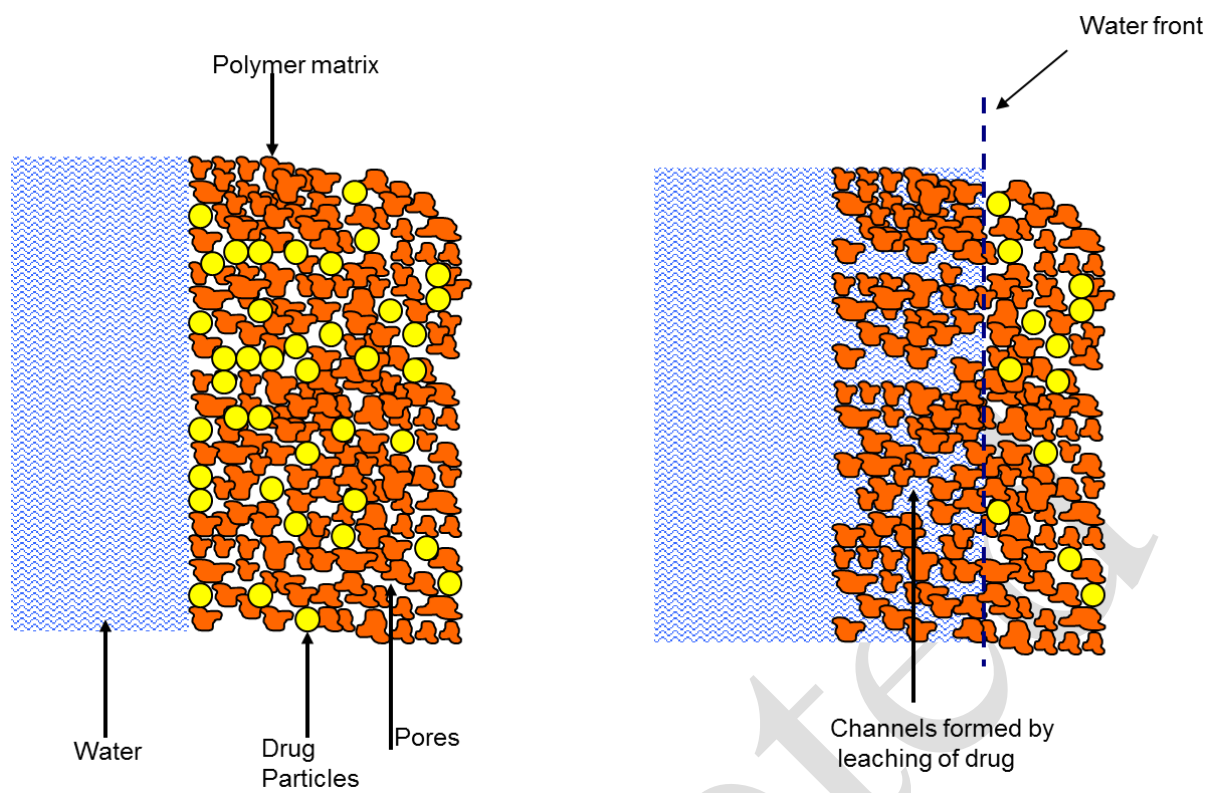


**Figure 2:** Schematic representation of drug concentration in plasma versus time for various dosage forms (various profiles obtained on the basis of various release/dissolution profiles).

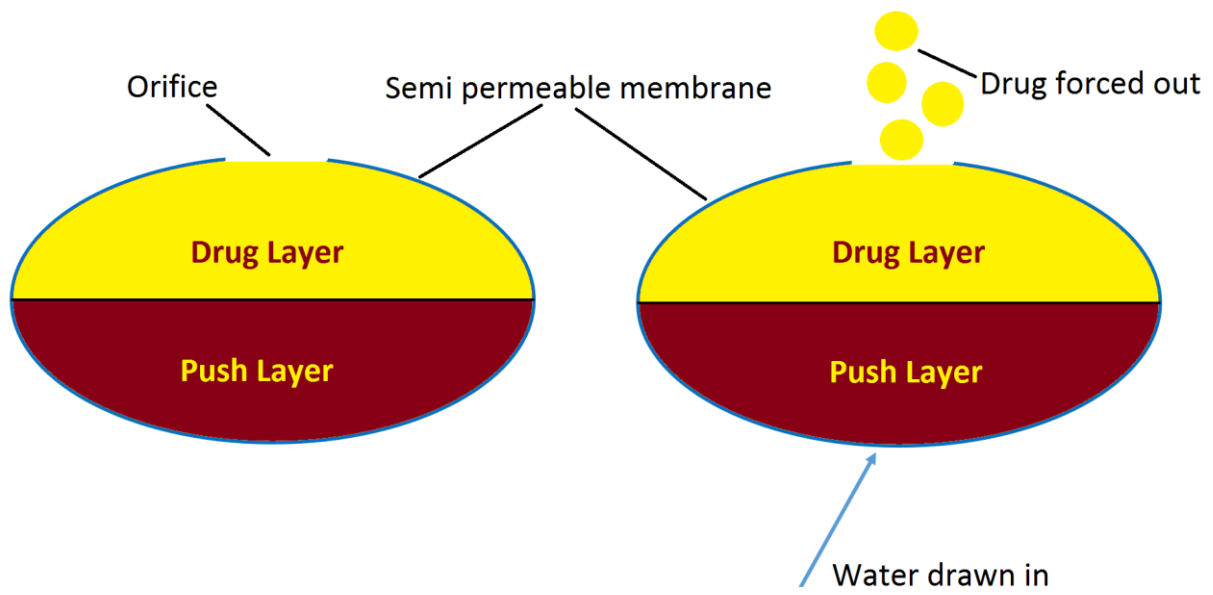


**Figure 3:** Schematic representation of drug release from HPMC tablets (yellow particles are drugs and orange particles are polymer).





**Figure 4:** Schematic representation of drug release from a leaching-based drug delivery system such as maltodextrin.



**Figure 5:** A schematic diagram of an Osmotic pump system tablet and the mechanism of drug release at Zero Order kinetics.

Accepted