3. Review of Related Literature

The interest of novel drug delivery systems in the pharmaceutical arena is getting increased day-by-day since last few decades. Indeed, they become contemporary need of the present state for satisfying sophisticated therapeutic demands, which have been rationalized through impressive advancements in the medical and pharmacological areas. The target has been widely endeavoured by modified-release (MR) dosage forms which liberate the drugs in a controlled manner or at appropriate site (1, 2).

Up to the early nineties, ample of efforts were made in designing of drug delivery systems which release the active ingredients at a constant rate over an extended period of time. However, this approach, in certain cases, has exclusively neglected the principles of homeostasis which in turn deeply affects the interests and objectives of pharmaceutical scientists (3-5). The emphasis has been shifted towards improved patient compliance and concomitant reduction in dosage regimen (6).

The diurnal variations of heart rate, blood pressure, blood cell count, platelet adhesiveness, fibrinolysis, respiratory rate, airway resistance, immune system reactivity, hormone secretion, gastric pH, body temperature, urine output, tissue perfusion, mental activity and alertness, are some of the examples which depict characteristic circadian pattern (3-5, 7-9). Typically, the early morning attacks of BA, VA and RA are considered amongst the most popular 'chronopathologies' because of their evident circadian recurrence as well as high morbidity rates (3, 5, 10, 11). Also, the physiology of periodicity observed in so many body functions affects drug pharmacokinetics and pharmacodynamics as well. Hence, it is quite apparent that the time of drug administration into the body plays a vital role in determining efficacy and safety of pharmacotherapy (4, 7, 8).

These biological requirements have led to an increased interest of chronological drug delivery systems which release the drugs according to the pulsatile pattern (2, 10, 12-15). Such systems, which restrict the drug release for some specific period of time (i.e. a programmed lag time) and subsequently provide rapid and transient release of certain amount of drug molecules within a short period of time, are termed as pulsatile drug delivery systems (PDDS) (16, 17). The PDDS aims to improve therapeutic efficacy of the existing medicaments while minimizing their side effects by reducing excessive, long-lasting and unnecessary body exposure to the drug molecules. In

principle, this would apply to the treatment of several chronopathologies (18-20), a replacement therapy (21), cancer (22) and also infectious disease therapy (23).

In any domain of pharmaceutics, oral route is by far the most preferred and convenient route of administration owing to its cost-effectiveness and high patient compliance. The oral PDDS have increasingly been suggested as an appropriate means of implementing chronotherapy for circadian illnesses which have more frequent recurring during night or in the early morning hours (18, 19, 24). In such cases, if the device is purposely programmed to set off the release when symptoms are usually encountered, the bedtime intake of medication would yield pharmacological protection when the risk of disease occurrence is higher, thus sparing the patient from being awoken for drug administration or, even worse, as a consequence of its pathology. This could be highly beneficial primarily in the case of aforementioned chronological outbreaks including BA, VA and RA. Such chronomodulated drug delivery approach based on the evening dosing has proven to be suitable for reducing the incidence of early morning attacks without producing excessive side effects which may arise following bedtime administration of IR or ER formulations (2, 3, 25, 26).

The PDDS by and large can be classified into different categories like time-controlled systems, stimuli induced systems, externally regulated systems etc. (14, 16, 27-29). In later types, the release can be triggered or initiated in response to outer events such as chemical, electrical, thermal, photo, ultrasonic, magnetic or enzymatic stimulations. In contrast to such triggered PR, the former type i.e. time-controlled delivery systems possess devise inherent properties which control the onset of drug release, irrespective of external/environmental factors, and therefore became the choice of work envisaged.

Time-controlled PDDS

Time-dependent dosage forms are designed to liberate the drug load after a certain period of time so as to coincide the action of drug with the disease activity. The development of such formulations is highly desired for the treatment of chronological disorders since the peak effect of drug is specifically targeted when the disease activity is at worst. In general, Oral time-controlled PDDS can be classified into below mentioned types (2).

A. Capsule shaped systems with release controlling plugs
B. Systems with soluble or erodible coating
C. Systems with rupturable coating
D. Osmotic delivery systems
E. Systems with increasing/altered membrane permeability

A. Capsule shaped systems with release controlling plugs

Many single unit devices for PR were designed in the form of capsules, which were characterised by the presence of an additional element besides the cap and body components. Namely, all of them were provided with a release-controlling plug inserted into the body open end, which worked according to the physicochemical properties of the material it was composed of.

The Pulsincap™ was the first capsular delivery system to be proposed for time-controlled release (30, 31). It essentially consisted of a water-soluble cap and a rigid, insoluble and impermeable body, which was filled with the drug load and sealed with a hydrogel plug based on cross-linked polyethylene glycol (PEG) 8000. When it comes in contact with the aqueous liquid, the cap dissolved off rapidly and the plug began to swell as a result of water uptake, thus gradually increasing in volume until ejection from the body and consequent release of the capsule contents. The time taken for the plug removal relies upon size and position of the plug itself within the capsule body. Despite of smart design, a few concerns were raised by the apparently complicated manufacturing process and, very importantly, regarding the use of non-approved cross-linked hydrogel for the plug preparation. In this respect, several investigations were undertaken both on animals and humans to assess the safety profiles of either placebo or drug containing Pulsincap™ units (32); in particular, general tolerability related to repeated administrations of placebo Pulsincap™ was assessed on 12 subjects through a twice-daily dosing regimen extended over a 28-day period. For this study, a 190 mg hydrogel plug was employed because such a weight represented the maximum compatible with the largest capsule size envisaged for the system (size 0). The treatment was well tolerated, as no adverse reactions or side effects could be attributed to the product under examination, and was also fully complied with, as none of the enrolled volunteers exited the 28-day trial prior to completion.

The Pulsincap™ was also presented in gastro-resistant configuration, so as to exploit the time-based approach to colon delivery (33). With aim of simplifying original Pulsincap™ technology, systems based on an erodible plug instead of the hydrogel one were also proposed (34). In fact, it would have been thereby possible to overcome problems related to the use of cross-linked PEG, as well as to the need for achieving plugs with precise dimensions and highly reproducible position within the capsule body. Accordingly, ethylcellulose (EC) coated capsules containing a propranolol hydrochloride tablet on top of L-hydroxypropyl cellulose (HPC) filling were sealed by an erodible plug with varied composition and evaluated *in vitro*. L-HPC was included in the formulation because it was expected to promote the tablet expulsion after erosion of the plug owing to its marked swelling characteristics. The use of lactose and hydroxypropyl methylcellulose (HPMC) K100LV mixtures as the plug forming material demonstrated to yield the pursued PR performances. The rapid and complete liberation of drug after completion of lag time can be modulated by altering the weight (i.e. thickness and/or composition of the plug). The impact of wet granulation on the erosion behaviour and release control displayed by such plugs was explored through various experimental techniques (35). The plug prepared by wet granulation exhibited relatively longer lag time in comparison to that prepared by direct compression method. The prolongation of delay was more evident for formulations with low HPMC content (15%). Further, it was hypothesised that the reason for the less effective and more variable performances of aqueous coated capsules could reside in a less tight seal operated by the lactose and dibasic calcium phosphate-based plugs. In such systems, water influx was therefore allowed to occur through the gap between plug and inner wall of the capsule body, thus resulting in premature and erratic delivery of the contents.

Devices comprising a polypropylene impermeable capsule body, a swellable/erodible plug and effervescent excipients included in the drug formulation were proposed by Krögel and Bodmeier (36). Aiming at a Pulsincap™ like ejection mechanism of hydrated plugs, the authors first explored the outcome of swellable tablets coated with Eudragit RS100, RL100 or NE30D; however, those films underwent early rupture phenomena and, moreover, hindered the gradual plug displacement, even when lubricants were used. Hence, uncoated tableted plugs composed of various HPMC viscosity grades (HPMC E3, E5, K4M, K15M and K100M), polyvinyl alcohol

(PVA) and polyethylene oxide (PEO) (Polyox K100 and K8000), were prepared and evaluated. Alternatively, melted saturated polyglycolated glycerides (Gelucire 44/14 and 50/13) or distilled glyceryl monooleate (Myverol 18-99) were poured into the capsule opening and directly congealed in the final plug position. The release of different model drugs (chlorpheniramine maleate and ibuprofen) was delayed for time lapses which were dependent on the weight of the plug as well as the physicochemical properties and percent amount of the employed swellable polymer. Following the lag phase, a fast delivery was obtained when adding sodium bicarbonate and citric acid into the capsule body. Plug tablets formed from natural polysaccharide pectin and enzyme pectinase were also envisaged for the above-described system (37). The presence of an appropriate buffering agent (potassium dihydrogen phosphate) in the formulation allowed the pH value in the very proximity of the plug to be maintained close to the optimum 4-8 range for this enzyme activity. Besides, it prevented pectinase from being degraded via pepsin catalysis in acidic media. Analogous DIL containing capsular systems provided with high-viscosity HPMC (K4M) or guar gum swellable/erodible plugs either in tablet or powder form were proposed, in which the capsule body was rendered insoluble and impermeable through the exposure to formaldehyde vapour, which resulted in cross-linking of gelatin (38).

Recently, Ranjan *et al.* (39) have developed osmotically controlled PR capsule of montelukast sodium for the prevention of early morning attacks of asthma and allergic rhinitis. The capsule design consisted of push layer, active portion and plug positioned in bottom to top order. The system mainly comprised of sodium chloride and polyox WSR in all three layers to induce swelling dependent rupture phenomenon. The system was then coated with a semipermeable layer of cellulose acetate and drilled to plug side. The system exhibited distinct lag time according to applied coating amount followed by ER profile *in vitro* and similar results were also observed with *in vivo* pharmacokinetic study performed in rabbits.

An alternative capsular design was designed for the Programmable Oral Release Technologies (PORT™) system (40). The design comprised of a hard-gelatin capsule, covered by a semi-permeable cellulose acetate coating, an insoluble lipid plug of Gelucire 50/02, and drug-osmotic agent mixture as the inner content. Optionally, an IR dose can be housed in soluble cap portion in order to provide double-pulse delivery. The working principle of this device relied on the time-controlled expulsion of the lipid

plug following a surge in the capsule internal pressure, which, in turn, was brought about by osmotically induced water influx across the semipermeable membrane. The delay phase can be modulated by modifying coating thickness, length of the plug and/or osmotic strength of the body contents.

In view of close design and in some instances (34, 36, 38) working principle similarities with capsular devices, Egalet® technology is worth mentioning; which was proposed for both extended and PR formulations of even poorly soluble drugs (41, 42). In its 'Burst-Egalet®' configuration, such a system envisaged a cylindrical impermeable outer shell composed of cetostearyl alcohol and EC. The shell encased an inner drug core and two plugs sealing at each open side, composed of high molecular weight PEG or PEO. The release-controlling plugs and drug-containing unit were all embedded in the shell by injection-moulding. When the system comes in contact with the aqueous medium, outer plugs experienced erosion of surface. After complete erosion, the inner material was exposed to external environment and drug release was enabled. Through opportune modifications in the composition and dimensions of plug and core, the rate and time of release can be controlled.

It is to be noted that the lag time of these capsule based systems comprising release controlling plugs are considered to be highly vulnerable with respect to the variation in the plug dimensions as well as its point or depth of incorporation into the capsule. Moreover, the manufacturing process is also very complicated (34, 43-46).

B. Systems with soluble or erodible coating

There are several examples in the literature of reservoir systems provided with barrier coatings which may swell, erode and/or dissolve upon contact with aqueous fluids. In most instances, hydrophilic cellulose derivatives, such as hydroxyethyl cellulose (HEC), HPC and HPMC, are employed as the main components of the release controlling coat in view of their in principle adequate swelling behaviour, consolidated safety profile, ease of handling, availability in different grades and reasonable costs.

Many researchers focused on the use of HPMC as the release-controlling polymer; for example, various coating techniques were aimed at the application of HPMC barriers were investigated throughout the development of the Chronotopic™ systems (47-57). The Chronotopic™ technology is the marketed chronotherapeutic drug delivery system which provides the time-dependant PDDS. This device was

conceived by Gazzaniga and colleagues as a single or multiple drug units containing core, coated with hydrophilic swellable HPMC of different viscosity grade (48). The authors reported that, upon hydration, such a layer underwent increasing permeability, swelling, erosion and/or dissolution phenomena, which finally resulted in the delayed onset of a rapid release of drugs. The duration of the lag phase was dependent on the physicochemical properties of drug, amount of the applied polymer, as well as employed coating technique. By introducing appropriate design modifications, colon delivery was pursued relying on the time-based approach. For this purpose, the application of a sufficient quantity of release controlling polymer and of an outer enteric film, which might overcome the influence of highly variable gastric emptying time, was required. The possibility of attaining selective drug delivery into the colon was highlighted by Sangalli *et al.* (51, 58). The system is prepared by granulating the drug with different excipients and subsequently processed for compression to make the tablet matrix. A blend of HPMC and PEG solutions are then spray-coated above it and permitted to dry. At last, a coating of Eudragit is applied onto the outer surface of the tablet matrix. The film permits the system to remain intact until it reaches to intestine where it finally erodes and exposes the HPMC sheet to the intestinal liquid thus making the formulation to be pH-responsive (51). The achievement of the HPMC coating represented a technological challenge for the system preparation. Initially, compression coating (49) and hydro-alcoholic spray-coating of high-viscosity HPMC grades (K4M and K15M) (47-49), which were assumed to be more effective in deferring drug release but had never been used before in the role of spray-coating agents, were attempted by Gazzaniga and colleagues. Although in both cases a successful outcome was obtained in terms of physical-technological requisites and release performances, few concerns were there. Particularly, the utilization of organic solvents, which was understood to raise major ecological, safety related and eventual regulatory problems, remained a critical issue. Therefore, the feasibility of HPMC-based aqueous spray coating strategies was investigated (50, 52). As compared with higher viscosity grades, HPMC E50, in particular, was shown to afford feasible coating operations both in fluid bed and rotating pan, reasonable process time and robust formulations. An *in vivo* pharmacokinetic study with fasting volunteers pointed out the delayed appearance of the model drug antipyrine in saliva, with increase in lag time as a function of coating level (51). Also, the possibility of preparing the Chronotopic™ system employing soft- and hard-gelatin capsules was explored (53, 54). The use of such dosage forms as cores

for the device could facilitate a time-controlled release of liquid or semisolid incorporated formulations. The aqueous HPMC E50 based spray coating procedure was successfully developed and the coated capsules proved capable of, *in vitro* as well as on six fasting volunteers, programming lag times before prompt release of the model drug acetaminophen.

Either gellable or erodible HPMC barriers applied by dry coating were also exploited by Conte *et al.* (59, 60) to attain PR from tablet cores. Erodible layers, which were based on low-viscosity HPMC (E3, E5 and E50), were shown not to alter the release kinetics after the initial lag phase, whereas the rate of delivery could be controlled by swellable shells based on high viscosity HPMC (K4M and K100M).

Halsas *et al.* proposed another high viscosity HMPC (K4M) dry-coated tablet, in which the total amount of ibuprofen, chosen as the model active ingredient on account of its potential suitability for a chronotherapeutic approach to RA, was either contained in the core or partitioned between the core and coat (61). When the whole drug content was located in the inner tablet, slow release and slowly increasing drug plasma concentration preceded by a lag time were obtained *in vitro* and *in vivo*, respectively. With higher applied amount of HPMC, lag phases were prolonged and both the rate of release and bioavailability diminished. Differently, when fractions of the overall drug dose were introduced into the outer shell, a biphasic slow delivery pattern with no lag time was observed, which was reflected in double-peak plasma drug concentration profiles. The sodium alginate was also investigated as the swellable material. Its use apparently led to a faster release of the core drug fraction both *in vitro* and *in vivo*. Furthermore, the effect of blending different HPMC viscosity grades (K100 and K4M) in the coat formulation was explored (62). In particular, shorter lag time and faster release were attained when low versus high viscosity HPMC ratio was enhanced.

Further, high-viscosity HPMC was also used to coat NIF containing tablets by the dipping method (63). Delayed release curves were obtained *in vitro*, with lag time and delivery rate modulated by the coating level and adopted coating conditions. In particular, when ethanol/water ratio was raised or HPMC level reduced in the vehicle, longer lag times were observed. On the other side, rate of NIF release was diminished by extending the time during which the polymer was permitted to swell in the hydro-organic mixture prior to the dipping step. Such results were ascribed to the influence

exerted by the above-mentioned parameters on the morphology and barrier properties of the HPMC layer.

Further, exploiting the hydration properties of HPMC (K100M), Li and Zhu devised a multiparticulate system based on subunits with different delivery behaviour contained within a hard-gelatin capsule (64). Mini tablets with or without an external HPMC press-coating and HPMC mini matrices were prepared to afford immediate, prolonged and delayed-release features. Through the proper combination of diverse subunits, the authors achieved versatile NIF delivery patterns.

Another multiparticulate formulation provided with a methacrylic copolymer-based release-controlling coating was depicted by Kao *et al.* (65). The system consisted nonpareil beads loaded with DIL and externally covered by Eudragit RS layer plasticised with triethyl citrate (TEC). The PR profiles were achieved, with lag time lengthening as a function of the level of coating polymer and curing time. The delay time was credited to the time needed for complete hydration of polymer layer, thus enabling a prompt outward diffusion of drug. Hence, the authors suggested that Eudragit RS coatings might be suitable for deferring the release onset of drug molecules with high and pH-independent aqueous solubility, thereby affording selective delivery into different GI sites.

Shivakumar *et al.* built up a pH responsive multi-particulate formulation which consisted Eudragit S100 layered beads intended for chronodelivery of DIL for treatment of angina pectoris (66). The drug-containing beads were prepared by extrusion spheronization employing MCC as spheronizer and Polyvinylpyrrolidone (PVP) K30 as binder. Different coating levels of Eudragit S100 were applied to the drug-containing pellets to make the pH responsive multi-particulate formulation. *In vitro* release testing of the coated beads performed by pH changeover method demonstrated that the drug release was dependent on applied coating levels and pH of dissolution medium.

Krogel and Bodmeier developed and evaluated floating PDDS based on a reservoir design comprising of a effervescent core containing drug and a polymer coating (67). The system was fabricated using Eudragit RL polymer coating which provided a semi-permeable film with higher elongation and lower carbon dioxide permeability facilitating rapid effervescent reaction and floating process with

simultaneous restriction of drug release for a certain period of time. With the floating design, the polymeric coating didn't hinder the drug release. The polymer (HPMC or cellulose acetate) was incorporated in the core to control the drug release. Time to flotation could be modulated by the composition (filler type and concentration of effervescent) and hardness of core tablet as well as composition (polymer type and plasticizer) and thickness of outer coat. In order to achieve rapid release after the rupturing of outer coat, a quick releasing core was fabricated. The study unveiled that the duration of lag time before drug release was increased with increase in core hardness as well as level of outer coat.

Matsuo *et al.* developed and evaluated CCTs using HEC in outer coat (68). DIL, indicated in the chronotherapy of cardiovascular disease, was selected as a model drug and pulsatile delivery was attempted. The time to release onset was found to be dependent on the thickness of outer coat. The polymer particle size also played a minor role. With increase in particle size, shorter induction phases were noticed, which the authors attributed to an initially facilitated higher water uptake by powders with higher porosity.

An analogous DIL containing tablet system was proposed by Fukui and co-workers, for which, HPC was employed as the coating material (69). The system proved to delay drug delivery for a time period increasing as a function of viscosity grade as well as amount of the swellable polymer, without causing any alteration of the relevant rate.

In pursuit of time-based colon delivery, Takeuchi *et al.* prepared by spray-drying composite lactose, sodium alginate and chitosan particles, in which a sodium alginate/chitosan complex was formed (70). These powders, which showed good flowability and compaction characteristics, were applied onto acetaminophen containing tablet cores by compression coating. Release was prevented, or at least considerably slowed down, in media with pH of 1.2-5. Gelification and the erosion phenomena of the coating layer occurring in pH 6.8 fluid delayed drug delivery as a function of the amount and deacetylation degree of chitosan.

Veerareddy and Vemula developed colon targeted PR CCTs of flurbiprofen which retard the drug release in upper GI tract but gradually release in colon (71). The drug containing core tablets were produced by direct compression method and

subsequently press-coated with HPMC K4M and Eudragit S100. The optimized formulation was further examined for *in vivo* in healthy human subjects. The optimized system exhibited about 7-8 h of lag time followed by gradual release for up to 24 h both *in vivo* and *in vitro*. The X-ray imaging study in human subjects demonstrated that the tablets remained intact in upper GI tract and later on disintegrated in colon to release the drug.

Recently, the application of an Eudragit NE film containing super-disintegrant sodium starch glycolate (SSG) as a pore former, was explored in the preparation of swellable/erodible time-dependent colonic drug delivery. Tablet cores were subsequently spray-coated with a HPMC E50 followed by Eudragit NE 30D, wherein fixed quantity of SSG was available. The resulting two-layer system yielded lag phases of prolonged duration in comparison to the formulations having the HPMC layer solely. On increasing the thickness of external coat, the lag times were increased while the efficiency in deferring the drug release was decreased by enhancing the pore former amount, which in a way also lower the data variability. With enteric polymer coating, the system demonstrated gastro-resistance properties. The proposed strategy would facilitate the preparation of erodible dosage forms with reduced size, conceivably suitable as multiple-unit formulations (72).

More recently, Veluma (73) has studied the effect of double-compression coating on flurbiprofen mini-tablet cores to achieve the time-dependent PDDS. In this study, double-compression-coated tablets were prepared by first compression-coat of HPMC K100M for time-controlled release followed by pH-responsive Eudragit S100 as outer compression-coat. The optimized tablet exhibited *in vitro* lag time of about 5 h followed by ER up to 24 h with zero order release kinetics. The formulation was also evaluated for *in vivo* pharmacokinetic study using human volunteers which had demonstrated promising consistency with *in vitro* results.

Hydrophobic blends of natural waxes (carnauba and white beeswax) and surfactant (polyoxyethylene sorbitan monooleate) were employed as the release-controlling material for the Time-Clock® system (74). Such mixtures were applied by spray-coating of water dispersions kept at 75°C. When exposed to the aqueous fluids, the hydrophobic barrier was subject to a progressive redispersion, thus delaying drug release for a time period correlated with its original thickness. The pharmacokinetic

study using six volunteers demonstrated that the system exhibited reproducible lag time and, C_{max} and AUC values, relevant to the model drug salbutamol sulfate, were not significantly decreased as compared with those pertaining to a corresponding IR formulation (75, 76).

Penwest Pharmaceutical Company (Danbury, Connecticut, USA) has designed SyncroDose™ system which utilizes Penwest's TIMERx® patented matrix technology that facilitates medicaments to be liberated after a programmed lag time corresponding to circadian rhythmicity or permitting site specific drug delivery. The SyncroDose™ tablet comprises drug loaded core covered by a compression coat. The TIMERx® matrix system contains xanthan gum, locust bean gum, a semi-synthetic bacterial polysaccharide and a plant polysaccharide. These polysaccharides synergistically interact with secondary and tertiary components (77, 78). The ratio between 1:3 and 3:1 of xanthan gum to locust bean is generally preferred. The probable mechanism for the interaction between locust bean and xanthan gum includes interfacing among the helical region of xanthan gum and unsubstituted region of locust bean. The interaction leads to the formation of high strength gel analogous to the cross-linking of hydrogels. The core tablet is produced by wet granulation method and subsequently compressed. The TIMERx® matrix is fabricated by mixing the polymers and other ingredients employing wet granulation method. Dry-coating is then employed to encircle the drug-containing core (77). The SyncroDose™ technology can liberate the medicaments after a determined lag time with peak plasma levels attained around 5 h. On exposure to gastric media, the combined polysaccharide interconnect and swell to produce a tight gel with slow erodible core which releases the drug (10, 43, 79, 80). While the outer polysaccharides core might swell up, the inner core remains as such. As tablet passes through the GI tract along the pylorus and to the duodenum, the outer swellable coat experiences gradual erosion. After around 3.5 h, the erosion of coating is almost complete, revealing the drug containing core to the intestinal part where drug release is facilitated. Incorporation of the surfactants into the drug containing core presents the IR abilities. On the other hand, the core might be fabricated as controlled release matrix permitting for sustained drug release. The hydration or swelling of matrix also results in decrease in the bulk density, and thereby providing buoyancy and permitting the gelled material to float on the gastric fluids. Moreover, depend on the size of the original tablet matrix, the gelled material may swell to a extent which permits the formulation to

obstruct the pylorus opening. The physicochemical property of xanthan gum may be considered as self buffering which might be the reason why xanthan gum is robust against physiological pH variations (77). Xanthan gum also possesses mucoadhesive property allowing the formulation to be hold on in stomach facilitating the TIMERx® system to be additionally employed as a gastro-retentive drug delivery system. However, the variability of natural polymers is a concern to be considered while fabricating this system.

With respect to large scale manufacturing of CCTs, one-step dry-coated tablets (OSDRC) system has been developed (81). The technology utilizes a double structured punch (i.e. centre punch surrounded by outer punch) facilitating press-coated tablets to be fabricated in singular run. The manufacturing process contains three steps: base layer (first outer layer) compression, core tablet compression and whole tablet compression, which incorporates upper and side layer (second outer layer). Since the tablets are created in a solitary step while the punches make one rotation, there is no requirement for a different stage to convey the core tablet (81-83).

Chronotherapeutic Oral Drug Absorption System (CODAS®) manufactured by Elan Corporation (Florida, USA) is a multiparticulate formulation that compliments with circadian rhythms and provides a delayed onset of and ER delivery system (84). The technology constitutes drug containing core and a multi-layered membrane covering the core. Both the core and the multilayered membrane consisted of water insoluble and water soluble polymers. When multiparticulate come in contact with aqueous media, the water soluble coating breaks down and drug diffuses out via the available pores in the coating. The water insoluble polymers act as a obstacle and sustain the drug release (10, 85). The CODAS® technology has been employed for the chronotherapeutic formulation, Verelan® PM (verapamil HCl) which is designed for bedtime dosing and indicated for the management of early morning surge of blood pressure. After administration, this pellet filled capsule dosage form restricts the drug release for about 4-5 h followed by ER of the drug in the GI tract. The delay is obtained by the degree of non-enteric release controlling polymer coating surrounding drug containing pellets (86).

Diffucaps® manufactured by Eurand Pharmaceuticals (Pennsylvania, USA) is another multiparticulate formulation which delivers the drug as per the circadian

rhythms. The drug is coated onto a neutral core which may composed of inert particles like sugar sphere or granules. A binder like PEO, HPMC, HPC and PVP is employed to bind the drug particle to the inert core. The drug-containing core is subsequently coated with a plasticized enteric coat and later coated with a blend of enteric and water insoluble polymers. The examples of water insoluble polymers are EC, polyvinyl acetate, Eudragit RS etc. whereas the enteric polymers are cellulose acetate phthalate, HPMC phthalate, shellac etc. For separation of various layers, HPMC seal coating is generally used (87). The multiparticulates are less than 1.5 mm in diameter and by combining them with different release profile, a compound release profile can be obtained. This pH-responsive technology has been employed to fabricate InnoPran® XL, a chronopharmaceutical product of Propranolol HCl which is designed for bedtime dosing to be used for the management of early morning rise in hypertension (88). The Diffucaps® technology can also be employed for weakly basic poorly soluble drugs, by incorporating a pharmaceutically acceptable organic acid or crystallization inhibiter between second and third coating. Systems utilizing an acidic core ensure that the acidic surrounding around the drug at all times provides soluble drug in an *in vivo* microenvironment where it would otherwise remain insoluble (89, 90).

C. Systems with rupturable coating

A considerable number and variety of both single and multiple units oral PDDS are designed as a drug reservoir provided with an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomena. Such membrane undergoes partial or complete rupture within a programmable time period after the systems are presented to the aqueous fluids, hence permitting the internal core containing drug to be exposed to the dissolving medium. The film rupture accountable for drug release happens as an outcome of an increasing outward pressure, which occurs because of expansion of the inner core. This may in turn be attained by including swellable, osmotic or effervescent additives in the drug reservoir (2).

Different systems based on swellable inner core in the form of hard or soft gelatin capsule, tablet, and pellets were described, all surrounded by outer rupturable coating (91-100). In particular, spray coating of EC and methacrylic copolymer (Eudragit) films with different composition of plasticisers and pore-formers are well reported. The Eudragit afforded relatively flexible films which underwent small cracks

instead of explosive rupture upon stress application, whereas EC films completely broke up owing to their brittle characteristics.

Bussemer and colleagues proposed a PDDS based on hard gelatin capsules coated with rupturable layer (91). The drug loaded capsules were firstly coated with a swelling layer (croscarmellose sodium) and afterward with a plasticized semi-permeable polymeric coating containing water insoluble (EC) and water soluble (HPMC) polymers. An internal pressure created by the swelling layer results in the breakup of the external coat. The outcome of their study construed that the lag time increased with higher levels of outer coating layer and decreased with increasing level of the hydrophilic pore former or else by enhancing the thickness of the underlying swelling layer. The coated capsules absorbed release medium at an almost consistent rate until the swelling pressure was adequate to break the external shell. The uptake rate of medium diminished with increase in coating level whereas the extent of medium uptake was nearly same for different coating proportions. However, the authors found that the test conditions, for example surfactant incorporation in the medium or floating vs. fully immersed capsules in the medium, influenced the lag time. In a further study, soft and hard gelatine capsule formulations were compared for the release behaviour amongst which the shorter lag times were observed for coated soft gelatin capsules against analogous hard gelatin systems. This result was explained by the possibility that in hard gelatin units, which were not completely filled with powder, the swelling pressure could partly be discharged inwards. Differently, due to the complete liquid filling of soft gelatin capsules, the whole pressure developed by the expanding/swelling layer was directed onto the outer film, which was consequently subject to an earlier breakup (91, 93).

Niwa *et al.* proposed different type of EC coated gelatine capsules for the time-controlled release of medicaments in the colon (101). They investigated the effect of varying levels of EC coating on the release of drugs. Mechanically, several micropores were made at the base of EC capsules. A swellable/expandable layer comprising L-HPC was situated at base of the capsule body. Over the expandable layer, there was the drug compartment which contained a bulking agent, like starch or lactose, fluorescein and drug. The capsule was capped and sealed with concentrated EC solution. Following ingestion of such capsule, the ingress of aqueous medium was facilitated through the micropores available at the bottom of capsule body. Swelling and hydration of the inner

material increased internal osmotic pressure bringing about rupture of capsule, and thus providing burst drug release.

Jimoh *et al.* have used biodegradable capsules with a thinner layer at one end to govern the lag time of PDDS (102). Effervescent agents like sodium bicarbonate/citric acid were entrapped in poly-lactic-co-glycolic acid (PLGA) capsule. As aqueous medium entered into the capsule through the thinner side of PLGA layer, an effervescent reaction created carbon dioxide which applied the outward pressure and ultimately ruptured the capsule shell. The authors mentioned that the lag time was governed by the dimensions (membrane thickness and size) of the capsule shell and the quantity of effervescent agents.

Rupturable systems for oral PR were also designed in multiparticulate dosage forms. Ueda *et al.* developed Time-Controlled Explosion System (TES) which was fabricated using inert sucrose beads coated with overlapping layers (97). The inner layer contained the active ingredient, the intermediate layer composed of swellable L-HPC, and the external membrane was based on EC (98). The swelling dependent rupture occurred as described previously with analogous single unit systems. The authors demonstrated that the thickness of EC membrane primarily affected the lag time, irrespective of the pH values in the release environment (99). The addition of an equal amount of talc into the membrane composition shortened the lag time. TES prototypes containing a vasodilator and anti-platelet drug were evaluated *in vivo* which were found to be consistent with *in vitro* results (100). The AUC was not significantly different between fasting and fed subjects, nor between TES and IR dosage form in fasted conditions. Based on the above findings, the authors inferred a potential suitability of this TES formulation for twice daily dosing chronotherapy of ischaemic heart disease.

Hartman Kok *et al.* proposed rupturable pellets fabricated using EC plasticized with 15% w/w dibutyl sebacate (DBS) (103). The pellets contained sodium chloride as an osmotic agent, with or without a swellable polymer to enhance the core expansion. The addition of the swelling excipient was demonstrated to shorten the lag time without significant change in release rates. However, employing uniform sized subunits succeeded in achievement of fast drug delivery.

Schultz and Kleinebudde designed another rupturable multiparticulate system in the form of pellets (104). Here, the expansion process, carried out by osmotic gradient due to presence of sodium chloride in the composition of pellet, formed micrometric fissures in an outer semipermeable cellulose acetate membrane. The system exhibited the lag time proportional to the coating levels. The addition of plasticisers (TEC, or diethyl phthalate) into the composition of films led to an extended lag time and a lowered release rate owing to decrease in the relevant water permeability (105). On the other hand, the presence of talc within the membrane structure only influenced the duration of the delay phase.

Guo *et al.* developed DIC PR pellets by extrusion-spheronization (106). The drug-containing pellets were layered with a swellable inner coating followed by an aqueous EC dispersion as the outer controlled release coating employing fluidized bed coater. The lag time and drug release were modulated by the swelling material, the level of the internal swellable coating, and the external controlled coating. Further pharmacokinetic and bioavailability studies exhibited that the *in vivo* lag time was in good agreement with *in vitro* results.

Dashevsky and Mohamad developed another rupturable multi-particulate PDDS comprising of drug in core compartment; a swellable/expandable coat containing a super-disintegrant; and a water insoluble but permeable EC coat (107). The lag time was relatively shorter for theophylline layered on sugar seeds in comparison to those of pure theophylline. The lag time was modulated by the level of brittle outer coat which ruptured to provide burst drug release. The brittleness of film was enhanced with the incorporation of talc. The authors found that the penetration of aqueous medium expanded the swellable layer which resulted in the rupturing of the external film ensuing burst drug release.

Morita and colleagues have developed a single-unit pan coated device based on the swelling-induced rupture phenomenon employing an outer EC membrane (108). On account of the relevant working principle, it was named Swelling Controlled Release System (SCRS). Here, an inner tablet core containing emedastine difumarate and PVA, respectively, as the hydrophilic model drug and swellable material, was spray coated with EC and HPMC blends in different weight ratios. PVA was selected in view of its peculiar swelling behaviour, which can be modulated depending on the hydrolysis

degree. The system provided initial lag phase followed by rupturing of outer membrane providing burst release behaviour. Prior to membrane disruption, the model drug release was prevented due to the poor permeability of outer film, and typical PR profiles were achieved, wherein the delay phase was extended in duration as a function of the rupturable film thickness.

Fan and colleagues devised swelling-based rupturable system in the form of a spray coated tablet, prepared with crosspovidone as the hydrophilic swellable polymer and DIL as the model drug (109). The rupturable film was composed of EC and the gasto-resistant acrylic resin Eudragit L. The system proved to withstand the acidic pH value typical of gastric fluid and, after an additional off-release phase from the pH switch to 6.8, a rapid release of the active ingredient was observed. The lag time was primarily affected by the weight gain determined by the coating application. A key step in the overall release control was identified in the pH-dependent dissolution of the Eudragit L component, which caused pores to form within the EC membrane. The resulting penetration of water into the core brought about an increase in the swelling agent volume, until breakage of the outer insoluble film. The performances of the device were also explored *in vivo* on eight volunteers versus an IR tablet containing an equal dose of DIL. The appearance of detectable drug amounts in the plasma was clearly delayed by the delivery system in exam. No significant differences were found in the area under the curve (AUC_{0-24}) and peak plasma concentration (C_{max}) relevant to the compared formulations, thus suggesting that neither the *in vivo* rate of release nor that of absorption were altered by the device. On the other hand, lag time (t_{lag}) and t_{max} were prolonged and demonstrated to be in good agreement with *in vitro* data.

Zhang *et al.* described a single unit rupturable system in which both swelling and osmotic excipients contributed to the water uptake required for the breakup of an insoluble but permeable surrounding membrane (110). The system consisted in a tablet core containing the potent bronchodilator terbutaline sulfate, indicated in the management of asthma, and sodium chloride as an osmotic agent. HPMC E5 was used as swelling material for inner coating, whereas mixtures of Eudragit RS and RL were used to prepare the rupturable layer. The system was shown to exhibit *in vitro* pulsatile delivery performances only when both sodium chloride and HPMC were incorporated in the formulation. In particular, a prompt drug release was preceded by lag phases of increasing time as a function of level of outer coating. SEM analysis elucidated that the

drug liberation occurred through few micrometer sized gaps formed in the release controlling membrane as a result of the core expansion.

Ishino *et al.* proposed swelling dependent system which was fabricated by an outer release controlling barrier composed of co-melted PEG 6000 and hydrogenated castor oil mixtures in different ratios, which were applied onto isoniazid and calcium carboxymethylcellulose containing tablets by compression-coating technique (111). The system afforded a rapid drug release following the lag phase, which could be programmed through the opportune modification of the thickness and/or PEG 6000 content of the external coat.

Lin *et al.* have explored EC for compression-coating of DIC core tablets (112). A delayed onset and rapid liberation of drug was achieved from this system as well. The study revealed that larger EC imparted higher porosity of the coating layer and resulted in enhanced water permeability. Further, the lag time was found to be increased with increase in compression forces as well as higher level of micronized EC coating onto the drug core (113). Moreover, when embedding in the core either swellable (HPMC, SSG) or osmotic (sodium chloride) excipients, the latter proved more effective in decreasing the lag time (114). The incorporation of hydrophilic adjuvants into the outer shell formulation also shortened the onset of drug release and appeared to constitute a potentially suitable tool for the modulation of lag time (115).

Krögel and Bodmeier proposed a single unit system, which exploited a effervescent rupture inducing mechanism (67). The core tablets were prepared from citric acid/sodium bicarbonate effervescent mixture which produced CO_2 upon exposure to aqueous medium and generated outward pressure on surrounding layer required for its rupture. The outer layer was fabricated using EC plasticised with 20% w/w DBS. A rapid release of chlorpheniramine maleate was attained after distinct lag time which could be programmed by changing the hardness of core and/or the level of coating. Notably, when Eudragit RL was used in place of EC, floating dosage forms were achieved owing to higher flexibility and permeability of the membrane, which allowed water to diffuse into the inner tablet without any delay and underwent no disruption caused by subsequent gas development.

Rahemba *et al.* developed a swelling dependent rupturable system as PDDS (116). The core tablet contained salicylic acid in addition to some osmotic agents,

swellable/expandable polymers, and the surrounding osmotic covering containing a semi-permeable layer that had been scored at several locations with a razor blade. The core tablet absorbed the aqueous medium leading to its swelling, and propagated the scores of the coating along the length of the tablet. The coating ruptured completely once the scores have been fully proliferated and discharge the core material into the release media. They demonstrated that the developed system was able to produce a reproducible dissolution profile with lag time between 5 min to 2 h followed by burst drug release.

D. Osmotic delivery systems

Gastrointestinal Therapeutic Systems, more commonly referred to as osmotic pumps, were originally conceived in pursuit of zero-order release kinetics; however, the intrinsic need for an activation phase prior to the slow drug liberation was purposely relied on, in order to achieve a once-a-day Controlled-Onset Extended-Release (COER-24) formulation of verapamil hydrochloride, intended to meet chronotherapeutic requirements related to cardiovascular disease (26, 117).

The device was based on a bipartite tablet core, comprising an osmotic drug-containing compartment and a hydrophilic swellable polymer push compartment. The core was coated by a semipermeable cellulosic membrane provided with a couple of laser-drilled micropores connecting the drug with external aqueous medium. Between the core and the semipermeable film, an additional hydrophilic layer was applied, which contributed to defer the system activation. According to the OROS® Push-Pull™ working principle, water penetrated into the core across the outer coat, eventually resulting in dissolution of the active ingredient on one hand, and swelling of the hydrophilic polymer on the other. The consequent expansion of the push compartment led to a constant rate expulsion of drug solution through the laser-drilled holes. Due to the sophisticated underlying technology, verapamil hydrochloride could be released in a prolonged fashion over a period of several hours after a 4-5 h delay. This was confirmed by pharmacokinetic investigations, which pointed out a good agreement between the rate of *in vitro* release and *in vivo* results, thus suggesting that drug absorption be controlled by the osmotic system (118). Such unique delivery performances allowed higher verapamil plasma levels after evening dosing to be aligned with peak blood pressure, heart rate and myocardial oxygen demand occurring

around awakening time (119). Multi-centre clinical trials highlighted the actual benefits connected with the chronopharmacological treatment in exam, as well as the lack of adverse events differing in type or magnitude from those reported in the case of other verapamil hydrochloride formulations (119-121). Notably, Covera-HS®, a well-known antihypertensive medicinal product available on the US market, is merely based on the previously discussed COER-24 technology. Whilst the technology has been employed to certain products, it has some drawbacks. Manufacturing the system seems to be complex with the necessity of a laser-drilled hole in the semi-permeable outer coat. Moreover, blockage of the hole may restrict drug release.

E. Systems with increasing/altered membrane permeability

Few coated systems exhibits sigmoidal type of release pattern which is therapeutically advantageous for time-controlled release as well as colon targeted drug delivery. A sigmoidal release pattern is observed with Eudragit RS/RL films due to their permeability and water uptake, which is regulated by the presence of various counter ions in the dissolving medium (122).

Based on the observation that the release rate of theophylline from Eudragit RS coated pellets was significantly improved in organic acid solutions, Narisawa *et al.* developed a multiple-unit system comprising a drug (theophylline or acetaminophen)/succinic acid mixture loaded on nonpareil seeds and an outer Eudragit RS film applied by aqueous spray-coating (123, 124). Sigmoidal *in vitro* release curves were obtained for both model drugs, with lag time increasing in duration as a function of the level of applied coating. Thereafter, the device was named Sigmoidal Release System (SRS). They found that the core coated with Eudragit RS exhibited very less release rates in purified water which enhances considerably in an organic acid solution such as succinic, glutaric, acetic, citric, malic, or tartaric acid. They suggested this could a result of higher hydration of the film containing quaternary ammonium groups on interaction with the acids. The rate of drug release from the pellets coated with Eudragit NE 30D, which does not contain any quaternary ammonium groups, was not influenced by succinic acid, indicating that the quaternary ammonium groups of Eudragit RS are necessary to deliver the sigmoidal release profile.

A pharmacokinetic study carried out on three fasting beagle dogs confirmed the *in vitro* findings by providing almost superimposed lag time values. The release

behaviour of SRS containing either theophylline or propranolol hydrochloride (i.e., model drugs with markedly different water solubility) was subsequently investigated (125). For this purpose, 100 mg amounts of product lodged inside small polyester-net bags, which were proven not to alter mechanical stress nor delivery phenomena undergone by the beads in the GIT, were administered to two fasting beagle dogs at subsequent time intervals. After recovery, the beads were analyzed for residual drug content. The *in vivo* release data of propranolol hydrochloride were in good agreement with those attained *in vitro*. On the other hand, theophylline was not completely delivered from the formulation, although *in vitro* and *in vivo* lag phases were quite similar. The different *in vivo* release performances of theophylline were ascribed to the possible influence of the limited fluid volume in the distal GI tract on the dissolution process of poorly soluble drugs. The working principle of the device was also explored through various dissolution, ion exchange and glass transition temperature experiments, particularly with regard to the release-controlling mechanism operated by the Eudragit RS coat (124). It was elucidated that both the ionised and nonionised forms of organic acids were involved in enhancing the water permeability of the polymeric membrane through a corresponding improvement in the relevant hydration rate. This was accomplished by ionic interaction of the carboxylic anions with the positively charged quaternary ammonium groups and partitioning of the nonionised acid molecules into the hydrophobic segments of Eudragit RS, respectively. Moreover, following the observation that lag time was prolonged and release rate diminished by increasing the medium osmotic pressure through the addition of a nonionizable excipient (glucose), an osmotic pumping effect was also supposed to contribute to the overall SRS delivery mechanism (126). Namely, it was hypothesised that said effect could drive the liberation of drugs in a saturated solution after the critical point was reached (i.e., a time at which water influx and efflux across the polymeric membrane balanced each other).

In another similar system, theophylline and sodium acetate, acting as permeability altering salt, were coated on sugar beads followed by Eudragit RS coating. The lag time was found to be increased with increase in the level of the outer coat. Notably, the slope of the release phase was independent of the thickness of coating but was affected by the concentration of salt in the system, demonstrating that the release behaviour is reliant on the level of salt or the permeability modifier (127).

Stevens *et al.* have employed extrusion-spheronisation technology to fabricate a novel pellet system comprising DIL which was covered with a blended film coat containing EC and Eudragit RS (128). While the EC part restricted the drug release by acting as a diffusion barrier, the permeability of the Eudragit RS increased gradually. The ultimate outcome was a sigmoidal release profile.

The drug release profiles of such systems based on permeability modifications unequivocally rely on the physicochemical properties of the drug substance and its interaction with the film. Hence, with this system a PR profile might be acquired for some specific drug molecules with particular formulations but can't be generalized to all drugs (90).

Based on either single or combination of above mentioned approaches, several formulations have been patented for various types of drugs, strategies and therapeutic indications as mentioned in Table 3.1 (15).

Table 3.1 Patents involving different approaches for PR formulations (15)

Dosage form	Patent	Rationale	Ref.
Capsule	Pharmaceutical dosage form for pulsatile delivery of methylphenidate (US6555136)	Attention deficit disorder, System with multi-pulses at different time points (Combination of immediate and delayed release tablets)	(129)
Capsule	Oral pharmaceutical dosage forms for pulsatile delivery of an antiarrhythmic agent (US6500457)	Arrhythmia, system with 2-3 pulses having 8-12 h of lag time matching twice a day three times a daily dosing profile.	(130)
Capsule	Timed pulsatile drug delivery systems (US6627223)	Arrhythmia, capable of delivering therapeutic agent in position or time controlled fashion with multi-particulate-coated system	(131)
Capsule	Immediate release gastrointestinal drug delivery system (US6531152)	Diseases of alimentary tract, system able to release drug at specific locations within GI tract	(132)
Capsule	Time-controlled explosion systems and processes for preparing the same (US4871549)	Nausea, vomiting and gastric stasis, time-controlled explosion system used to reduce dose frequency and prevent undesirable side effects	(133)
Capsule	Pulsatile particles drug delivery system (US5472708)	Angina and hypertension, time-controlled system able to release drug at intestine with release controlled polymers	(134)
Capsule	Pulsatile release histamine H2 antagonist dosage form (US6663888)	Midnight GERD, system with combination of immediate and time PR beads, which release drug mimicking circadian rhythm of gastric acid secretion.	(135)
Capsule	Pulsatile drug delivery	Angina and hypertension, system	(136)

	system (US5840329)	with hydrogel as novel matrix material to control release of drug over period of time	
Capsule	Multi stage drug delivery system (US5387421)	Hypertension and congestive heart failure, predetermined PR of drug with use of osmotic system	(137)
Capsule	Process for the pulsatile delivery of diltiazem HCl and product produced thereby (US5914134)	Angina and hypertension, system able to release drug at different sites as early duodenal pulse, a medium ileal pulse and delayed colonic-specific pulse	(138)
Capsule	Multi-particulate pulsatile drug delivery system. (EP0701437)	Angina and hypertension, Osmotic multi-particulate delivery system release therapeutic agents in a sequential, pulsatile fashion	(139)
Capsule	Osmotically driven delivery device with expandable orifice for pulsatile delivery effect (US5221278)	Controlled osmotic release systems for the delivery of drugs of different class designed to release a drug through an orifice in the capsule, where the release occurring gradually as a result of inner pressure resulting from the imbibitions of fluid by the capsule from a surrounding medium.	(140)
Capsule	Osmotically driven delivery devices with pulsatile effect (US5209746)	Osmotic system which produces intermittent release of drug by virtue of capsule structure with movable partition which separates drug from osmotic agent	(141)
Tablet	Tablet for pharmaceutical use able to release active substances at successive times (US4865849)	Morning pain in rheumatic illness, system enables release of drug in successive spaced apart stages to obtain high hematic drug levels at different time intervals	(142)

Tablet	Pulsatile drug delivery system (US5229131)	Hypertension, dosage form able to release drug in controlled pulse doses responding to specific pH of GI tract. These systems has significant benefits for oral administration of first pass metabolized drugs, which demonstrate a nonlinear relationship between input rate of drug into portal system and bioavailability	(143)
Tablet	Pulsatile particles drug delivery system (US5260069)	Hypertension, unit dosage form for delivering drugs into the body in a series of sequential, pulsatile fashion. The system can be used with drugs that cannot be released by diffusion through a porous coating such as water-insoluble drugs	(144)
Tablet	Pharmaceutical compositions (US4897270)	Infection of gram-positive and gram-negative microorganisms, conventional film-coated tablets reduce the bioavailability of cefuroxime axetil and the invention overcomes this by control of the film coat rupture time and use of a tablet core, which disintegrates immediately following rupture of the film coat	(145)
Tablet	Pharmaceutical tablet suitable to deliver the active substance in subsequent and pre-determinable times (US6294200)	Gastroesophageal reflux disease, Pharmaceutical tablet dosage form, capable of delivering the active substance with three pulses to a pre-determinable release profile	(146)
Tablet	Delayed total release two pulse gastrointestinal drug	Analgesic and anti-inflammatory, a two pulse delivery device for	(147)

	delivery system (US6632451)	delivering one or more active agents at colon	
Tablet	Press coated pulsatile drug delivery system suitable for oral administration (US6372254)	Anti-inflammatory, a press-coated PDDS with an IR and an ER compartment with TPR	(148)
Tablet	Multi-unit delivery system (US5110597)	Helminth infections, system provides pulsed delivery of a single drug or different drugs or drug formulations suited to the delivery of pharmacologically. Especially suited for active peptides and protein anabolic hormones.	(149)
Tablet	Controlled release flutamide composition (US5162117)	Prostate cancer, invention provides controlled release form which is designed to provide an IR dose and a second pulsed delayed release dose	(150)
Capsule	Delivery devices with pulsatile effect (EP0627231)	Invention lies in the field of pulsatile delivery of drugs, nutrients. The pulsatile effect achieved by parameters as choice of elastic material for the band, the thickness of the band made from the elastic material, the configuration and location of the orifice, and the viscosity and surface tension of the active agent formulation	(151)

Overall it can be said that there is a wide variety research has been undertaken in the field of PDDS, however, despite of their potential therapeutic benefits, major concerns are oriented to scale up, manufacturability and reproducibility of these types of formulations. Moreover, the regulatory considerations associated with particular formulation/technology/processing also hinder the market authorization for these types of formulations; which also necessitates apt attention before initiating the developmental activities. In an attempt to ease commercial viability of the final formulation, the most conventional, popular and acceptable pharmaceutical dosage form, i.e. tablets, were opted to design and develop the envisaged PDDS. Besides, in order to satisfy contemporary regulatory demands, the whole development was improvised with QbD tools and Design of Experiment (DoE) approaches which would prospectively provide a robust formulation by indulging degree of improvement for building desired quality traits inside the product.

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