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Review Article

Recent Patents on Modified Release Oral Dosage Forms

Atul Pund*[1,2], Atishkumar Mundada[1], Manoj Magar[2], Abhijeet Kadam[3]

[1] *SNJB's SSDJ College of Pharmacy, Neminagar, Chandwad, India*

[2] *Blue Cross Laboratories Pvt. Ltd Nasik, India*

[3] *Bombay College of Pharmacy, Santacruz East, Mumbai, India*

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*Address for Correspondence:

Mr. Atul Pund, Department of Pharmaceutics, SNJB's SSDJ College of Pharmacy, Neminagar, Chandwad, Nashik, India,

ORCID ID: https://orcid.org/0000-0002-1844-6436

Abstract

Background: Conventional oral dosage forms have limited bioavailability and frequent dosing of the drug is needed to maintain the effective therapeutic concentration in the body. This results in poor patient compliance and fluctuations in the plasma drug levels, especially in the chronic diseases and disorders.

***Objective*:** To overcome such problems and to enhance the efficiency and bioavailability of the drug, modified drug delivery systems such as extended release delivery systems (controlled release; sustained release) and delayed release delivery systems are developed which can prolong the release and hence action of the drug in the body.

***Methods*:** Through this review, we throw the light on recent patents and patent applications on modified release systems pertaining to oral dosage forms. The various free patent search databases were used to collect and analyze the information on modified release delivery systems.

***Results*:** Modified release systems such as extended release and delayed release delivery systems have been found to be of great significance due to their advantages over immediate release dosage forms. These systems are formulated using various approaches, different types of release controlling polymers such as natural, semisynthetic and synthetic polymers and found to avoid the limitations of conventional oral dosage forms.

***Conclusion*:** Modified drug release systems have potential especially, in case of the chronic diseases, mental health disorders and lifestyle diseases and disorders. These systems have unique commercial advantages which will sustain the interest of both the researchers and the pharmaceutical companies.

Keywords: Modified release systems, extended release systems, controlled release systems, sustained release systems, delayed release systems, oral dosage forms, multilayer dosage form, multilayered tablets

1. INTRODUCTION:

Drug delivery systems and their formulation technology are an essential and integral part during the delivery of drug or active agent in the right amount at the required site of action in addition to the activity of drug itself. Drug delivery systems certainly affect pharmacokinetic as well as pharmacodynamic factors along with drug properties[1,2]. Choice of drug delivery system depends upon type of drug to be delivered, its solubility and bioavailability, site of action, therapeutic index, activity etc. Hence, the selection of the drug delivery system is of utmost importance. Along with drug delivery system, route of administration also plays crucial role. The oral route is the most convenient and preferred method for administration of drugs for systemic effects. In addition, solid oral dosage forms are the most popular and convenient product forms due to their wide range of advantages [1].

Modified release dosage forms are gaining importance in addition to conventional/ immediate release dosage forms due to their distinctive benefits for drug delivery of the active agents. These are designed to regulate release of the active agent for prolonged time period depending upon requirements of the therapy. Modified release delivery systems can be further divided into two sub-categories, namely, delayed release delivery systems and extended release delivery systems (controlled release; sustained release). Delayed release dosage forms are designed to release the active agent from dosage form after certain time interval post administration. Delayed release systems are generally prepared to avoid degradation of active agent in low pH in the stomach etc., whereas, extended release dosage forms are designed to release the active agent for extended or prolonged time period at certain rate [3,4].

Extended release delivery systems provide active agent to the body for extended period of time to achieve therapeutic effect by continuously releasing active agent from a single dose. This time period is measured in hours for oral dosage forms and depends on the residence time of active agent in the gastrointestinal tract. Extended release is also termed as

prolonged release, sustained release, controlled release, slow release, depot etc.[1,4] and sometimes these terms are used interchangeably.

Advantages of Modified/Extended/Delayed release systems:[3,5]

- Reduced dosing frequency
- Improved patient compliance
- Reduction in the fluctuation in plasma drug levels
- Reduction in gastrointestinal tract irritation and related side effects
- Dose reduction
- Suitable for drugs having elimination half-life between 2 to 8 hours

Shortcomings of Modified/Extended/Delayed release systems:[3,5]

- Not cost effective
- Does not allow prompt changes in drug dosage as needed during therapy
- Less flexible dosage regimens
- Does not consider disease and patient specific drug deposition variation
- Not suitable for drugs having short biologic half life
- Not suitable for drugs which require higher doses
- Not suitable for drugs having narrow therapeutic index

Modified release drug delivery systems thus aid in achieving a therapeutically effective steady state for prolonged period of time. Hence, this review article provides an overview of recent patents pertaining to the modified release drug delivery systems with specific focus on oral dosage forms and its formulation strategies.

2. MODIFIED RELEASE DRUG DELIVERY SYSTEMS

2.1. Extended release tablets

Extended release tablets are prepared using different release controlling/retarding excipients, generally polymers ,which prolong the release of drug to the gastrointestinal tract [4]. Techniques employed for the preparation of tablets are direct compression[6-9], wet granulation[7,8], dry granulation [7], roller compaction[8] and hot melt extrusion [10].

Mohammad Amin developed disintegrating monolithic modified release tablets comprising of sustained release granules with active agent amoxicillin and potassium clavulanate. Sustained release granules were prepared by over-lubricating the drug particles which contain a core particle containing a drug; and a hydrophobic adherent layer posited over at least a portion of the core particle and hydrophobic binding layer. Over-lubricated drug particles are suspended in the hydrophobic binding material; and then a disintegrant layer deposited over the hydrophobic binding layer of the agglomerated drug particle. The tablets are prepared by over-mixing and hot melt granulation [11].

Linqiu Cao *et al.,* developed extended release excipient composition and extended release tablet formulation containing the same. Tablet formulation contains the synergistic mixture of substantially uncross-linked carboxymethyl starch, or sodium starch glycolate (SSG), and hydroxyl propyl methylcellulose and active ingredient. Mechanism for extended release using this excipient is that water or gastrointestinal fluid first hydrates the polymers at the surface of the tablet and the hydrated polymers form a viscous gelled outer layer to the tablet. This gelled outer layer consists of the polymers and all the other formulation components including the active ingredient. This outer layer serves two functions: 1. reducing the rate of water entry into the core of the tablet, and 2. controlling the diffusion rate of active ingredients out of the layer and into the surrounding liquid. Carboxymethyl starch being substantially uncross-linked was reported to be vital as the slow release properties were found to deteriorate with an increasing degree of cross-linking, since a high degree of cross-linking in the carboxymethyl starch promotes the actual fast gel dissolution instead of controlled slow release[12].

John Claude Savoir Vilboeuf *et al*., have disclosed extended release tablet effective for 24 hours, for treatment or prevention of conditions such as vomiting, esophageal gastric reflux and nausea. This tablet contains metoclopramide as active ingredient, hydrophilic and hydrophobic polymers as well as hydrophilic component which promotes water penetration within the tablet. Here, the hydrophobic polymer undergoes plastic deformation under compression and hence surrounding the drug particles. This reduced the number of pores resulting in the drug substance release[13].

Various patents on extended release tablets are summarized in the Table 1.

Table 1: Recent patents on extended release tablets

Sr. No.	Patent Number	Type of Formulation	Salient feature	Year of publication	Reference
1	US20070134315A1	Extended release pellet and tablet formulations of isovaleramide	The patent application discloses extended release formulations of isovaleramide prepared using direct compression in which a sealing coating between said inner core and said rate controlling polymer system. Rate controlling polymer system is selected from the group consisting of ammonio methacrylate copolymer, cellulose derivatives, polyvinyl acetate, and derivatives thereof. It is used to effectively treat a variety of pathological conditions such as CNS disorders.	2007	[9]

2	US7674479B2	Sustained-release bupropion hydrochloride pharmaceutical tablets	This reference discloses sustained-release tablet containing sustained release granules of bupropion hydrochloride admixed with a hydroxyalkylcellulose and an extragranular phase comprising a particulate material that provides a sustained release matrix; said particulate material is selected from the group consisting of polyvinylacetate, blends of polyvinylacetate and polyvinylpyrrolidone etc. which then is coated, with a means to provide delayed release, such as with an enteric coating composition.	2010	[14]
3	US20100278918A1	Extended release composition particularly tablet comprising nevirapine	Patent application discloses extended release tablet dosage form containing nevirapine and Hypromellose 2208 (Methocel™ K4M Premium CR) for treatment of HIV infection; wherein each tablet is compressed by a force of 10-25 kN. In-vitro dissolution profile: at least 2% w/w and no more than 30% w/w of the nevirapine is released at 2 hours; at least 20% w/w and up to 100% w/w of the nevirapine is released at 8 hours; at least 40% w/w and up to 100% w/w of the nevirapine is released at 14 hours, when dissolution is measured by the USP Paddle Method at 50 rpm at a volume of 900 mL aqueous buffer containing 6% w/w of sodium lauryl sulfate, having a pH of 6.8 at 37° C.	2010	[15]
4	US20100144800A1	An extended release tablet comprising niacin	It discloses extended release tablet containing niacin and release retarding agent selected from hydroxypropyl cellulose, polyethylene oxide or mixtures thereof. It can be prepared by wet granulation, dry granulation or direct compression process.	2010	[16]
5	US20100247646A1	An extended release tablet containing nisoldipine	This patent application discloses extended release tablets containing a core having nisoldipine, a rate-controlling hydrophilic polymer and optionally, an enteric agent. These tablets may also be coated with a release rate-controlling coating comprising of a hydrophobic polymer or enteric agent or combinations thereof, in particular ethylcellulose, and Eudragits.Tablet coating also contains a channel forming agent.	2010	[17]
6	US7776358B2	An extended release coated pharmaceutical tablet	This patent discloses extended release coated pharmaceutical tablet containing core formed of Venlafaxine besylate as active agent and lipophilic matrix material and coating over tablet core containing an ammonio methacrylate copolymer component. Dissolution profile: Time Venlafaxine 2 hours <30% 4 hours 30-55% 8 hours 55-80% 12 hours 65-90% 24 hours >80% in USP 2 apparatus using SGF, pH 1.2, medium for hours 0-2 and then SIF, pH 6.8, medium for hours 2-24.	2010	[18]
7	US7695734B2	An extended release tablet comprising pramipexole	An extended release tablet formulation prepared using direct compression comprising pramipexole in a matrix comprising at least two water swelling hydrophilic polymers wherein at least one of the at least two polymers is an anionic polymer and the other is a substantially neutral polymer. The resulting tablet formulation provids a pH-dependent release rate in the range of pH<4.5, and a pH-independent release rate in the range from pH 4.5 to 7.5, wherein the release rate in the range of pH<4.5 is higher than the release rate in the range from pH 4.5 to 7.5.	2010	[19]
8	US7863316B2	Extended release tablet of levetiracetam	This patent discloses ER tablet containing levetiracetam and water dispersible rate controlling polymer selected from HEC, HPC, sodium alginate, carbomer, sodium carboxymethyl cellulose, xanthan gum, guar gum, locust bean gum, poly vinyl acetate, polyvinyl alcohol and HPMC which is prepared by wet granulation, dry granulation or direct compression and the core is coated either in a coating pan or in a fluidized bed system. Tablet exhibiting a value of (AUCfed)/(AUCfasted) of at least 0.80 with a lower 90% confidence limit of at least 0.75. Also, the composition exhibits no food effect.	2011	[7]

9	US20110033536A1	Extended-release pharmaceutical composition of metoclopramide hydrochloride	This patent application discloses extended release composition containing hydrophilic, hydrophobic polymers as well as hydrophilic component which promote water penetration within the tablet. Tablet is administered for treatment or prevention of disorders such as vomiting, esophageal gastric reflux and nausea. Mechanism: The hydrophobic polymer shows plastic deformation properties under compression, tending to surround the drug substance particles reducing the pore quantity and dimensions in the matrix structure, delaying as a consequence the drug substance release. The hydrophilic component is part of the gel coating structure providing support.	2011	[13]
10	US8039009B2	Modified release solid oral dosage form	Patent discloses modified release solid oral dosage form for the treatment of Alzheimer's disease containing memantine and polymeric carrier substantially contributing to the modification of the release of the memantine. Polymeric carrier is a polymeric matrix is a swellable matrix and comprises hydroxypropyl methylcellulose. The dissolution rate of more than about 80% is achieved after about 12 hours and dosage form provides a Tmax of more than 10 hours.	2011	[20]
11	US20110262537A1	An extended release tablet	This patent application discloses an extended release tablet containing an inner tablet of ropinirole with one or more rate controlling polymers. The rate controlling polymers are selected from one or more of gums or its derivatives, polyuronic acid salts or its derivatives, cellulosic polymers or its derivatives, acrylic acid polymers or its derivatives and waxes. Dissolution profile: at least 5% of ropinirole is released within 1 hour; at least 10% of ropinirole is released within 2 hours; at least 35% of ropinirole is released within 6 hours; at least 50% of ropinirole is released within 12 hours.	2011	[21]
12	US20110217373A1	Extended release tablet of guanfacine	This particular patent application discloses extended release tablet containing guanfacine and one or more of pH-independent rate controlling polymer(s)	2011	[22]
13	US20110052686A1	A modified-release uncoated tablet of lamotrigine	This patent application discloses multi-layer tablet containing (a) a first portion consisting of lamotrigine in an admixture with a pH-dependent polymer such as polyacrylic and polymethacrylic acids and polyacrylate and methacrylate based polymers etc; and (b) a second portion comprising the remaining amount of lamotrigine and a pH-independent polymer such as methylcellulose, ethylcellulose, hydroxymethyl cellulose, etc. In vitro dissolution profile when measured in a USP type II apparatus, at 50 rpm, at a temperature of 37° C.±0.5° C. in 900 mL of 0.1 N HCl medium: (i) at most about 35% drug released in 2 hours; (ii) at most about 55% drug released in 4 hours; (iii) at most about 80% drug released in 8 hours; and (iv) at least about 80% drug released in 16 hours.	2011	[23]
14	US20110027361A1	An extended release tablet or capsule containing Paliperidone	This patent application discloses extended release matrix composition containing Paliperidone and matrix agent is selected from a insoluble release controlling agent such as pH dependent polymer like Eudragit® FS 30D or pH independent polymer like Eudragit® RL 100, a hydrophilic release controlling agent such as hydroxyethyl cellulose or hydroxyl propyl methyl cellulose., a fatty release controlling agent.	2011	[24]
15	US20120219625A1	An extended-release tablet comprising Clarithromycin	This patent application discloses an extended-release tablet containing Clarithromycin, a water soluble diluent and an acidic compound chosen from potassium bitartrate, sodium bitartrate and monosodium citrate; wherein the acidic compound is operable to increase a rate of dissolution of Clarithromycin. Tablet comprises a film coating surrounding the tablet. The tablet is free from polymers or contains polymer that is insufficient to function as a release controlling agent. Disclosed tablet exhibits dissolution from about 50% to about 80% at 6 hours.	2012	[25]

16	US20120201886A1	A non-osmotic coated extended release composition specifically tablet	This patent application discloses non-osmotic coated extended release composition with core containing Paliperidone with one or more pharmaceutical excipients wherein the core is coated with a release controlling composition comprising one or more hydrophobic agents and one or more hydrophilic agents. Tablet is prepared using direct compression, dry granulation, wet granulation (aqueous/non-aqueous or combination) or melt granulation.	2012	[26]
17	US20120058183A1	Tablets with modified release containing retigabine	This patent application discloses tablet containing retigabine, water-soluble excipient, and a non-water-soluble excipient wherein, use of a combination of water-soluble and non-water-soluble excipients provides modified release The tablet contains 1 to 45% by weight of the amount of active agent as an initial dose for immediate release and 55 to 99% of the amount of active agent is present as a matrix formulation for delayed release.	2012	[27]
18	US8309122B2	An analgesically effective controlled release tablet	This patent discloses controlled release tablet with a twelve hour dosing interval containing Oxymorphone wherein the controlled release delivery system comprises a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid. System further comprises a hydrophobic polymer such as alkylcellulose. Specifically, controlled release delivery system comprises a heteropolysaccharide such as xanthan gum or deacylated xanthan gum and an agent capable of cross-linking the heteropolysaccharide such as locust bean gum in presence of gastrointestinal fluid.	2012	[28]
19	US20130034604A1	An extended release monolithic tablet	This patent application discloses ER tablet containing Desvenlafaxine and release controlling agent selected from water soluble/swellable polymers such as hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, xanthan gum, karaya gum, locust bean gum, alginic acid, sodium alginate, polyvinyl alcohol, polyvinylpyrrolidone or mixtures thereof and prepared using dry/wet granulation technique.	2013	[29]
20	US8343544B2	Oral sustained-release tablet	The patent discloses oral sustained-release tablet containing 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide (KRP-197) as active agent and hydroxypropylmethylcellulose which is used for the treatment for increased urinary frequency and urinary incontinence.	2013	[30]
21	US8399016B2	Sustained-release tablet composition of pramipexole	Patent discloses sustained-release tablet used to treat Parkinson's disease or a complication associated therewith containing core comprising pramipexole dispersed in a matrix comprising (a) hydroxypropylmethylcellulose and (b) a pregelatinized starch having a tensile strength of at least about 0.15 kN cm−2 , core being substantially enclosed in a coating comprising an ethylcellulose-based hydrophobic or water-insoluble component and an HPMC-based pore-forming component. The hydrophilic polymer functions to provide extended or sustained release of the pramipexole, for example by gradual dissolution or erosion of the polymer in the gastrointestinal tract.	2013	[31]
22	US8545886B2	Extended release system in the form of a tablet or bilayer tablet	This particular patent discloses extended release system containing active substance with pH-dependent water solubility such as flibanserin, pH-dependent polymers and pH-independent polymers using process such as wet granulation, direct compression or roller compaction	2013	[8]
23	US8778417B2	Sustained-release tablet of elemene	Sustained-release tablet is obtained containing elemene as an anti-tumor active agent, more specifically mixture of β-elemene, gamma-elemene and delta-elemene, or is a β-elemene monomer and sustained-release agent is chosen from hydroxypropyl methyl cellulose, polyvinyl pyrollidone, ethylcellulose, methyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose.	2014	[32]

24	US8865778B2	A slow or extended release tablet formulation	This patent discloses extended release tablet containing synergistic mixture of substantially uncross-linked carboxymethyl starch, or sodium starch glycolate (SSG), and hydroxypropylmethylcellulose and active ingredient Mechanism: Water or gastrointestinal fluid first hydrates the polymers at the surface of the tablet and the hydrated polymers form a viscous gelled outer layer to the tablet. This layer contains not only the polymers but also all the other formulation components including the active ingredient.	2014	[12]
25	US20140335175A1	An extended release tablet formulation comprising pramipexole	It discloses an extended release tablet formulation tablets manufactured via a direct compression process comprising pramipexole in a matrix comprising one water swelling polymer. The water swelling polymer is an anionic polymer such as acrylic acid polymerisate, methacrylic acid copolymers, alginates, carrageenans, acacia, xanthan gum, chitin derivates, carmellose sodium and carmellose calcium. The resulting tablet provided a pH-independent in vitro release characteristic in the range from pH 1 to 7.5, or the resulting tablet providing a pH-dependent release characteristic with a faster release characteristic in the range of pH<4.5, and a slower and further on pH-independent release characteristic in the range from pH 4.5 to 7.5.	2014	[33]
26	US8771732B2	An oral sustained release formulation specifically tablet, powder or capsule of nalbuphine	An oral sustained release formulation as analgesic comprising nalbuphine homogeneously dispersed within a hydrophilic gel matrix wherein the hydrophilic gel matrix comprises xanthan gum, a hydrophilic cellulose ether (hydroxypropylcellulose/ hydroxypropylmethylcellulose) or both. The solid dosage form wherein 75%-100% of the nalbuphine or a pharmaceutically acceptable salt thereof is released after about 12 hours as determined using USP Apparatus III at 15 dpm in a pH 6.8 buffer at 37° C.	2014	[34]
27	US20150283084A1	Disintegrating monolithic modified release tablets containing sustained release granules	This patent application discloses modified release formulation containing sustained release granules which comprises overlubricated drug particles which contain a core particle comprising a drug; and a hydrophobic adherent layer deposited over at least a portion of the core particle and hydrophobic binding layer, wherein the one or more overlubricated drug particles are suspended in the hydrophobic binding material; and a disintegrant layer deposited over the hydrophobic binding layer of the agglomerated drug particle. Tablets are prepared by over-mixing and hot melt granulation. Active agent in the core comprises amoxicillin, potassium clavulanate.	2015	[11]
28	US9050335B1	Extended release tablet containing oxycodone and acetaminophen	Extended release pharmaceutical compositions comprising oxycodone and acetaminophen that produce a quick initial onset of analgesia, yet, maintain analgesia for about 12 hours after administration of the composition extended release component comprises extended release polymer such as polyethylene oxide.	2015	[35]
29	US9180104B2	12-hour anti-tussive modified release tablet or capsule	It discloses modified release solid oral composition containing a. solid dispersion of benzonatate and modified release pH-independent, hydrophilic or hydrophobic matrix-forming substance and b. a reverse enteric coating over the homogenous solid dispersion. Matrix-forming substance contains hydrophilic polymer such as hydroxypropyl methylcellulose and hydrophobic modified release wax or waxy substance such as glyceryl behenate. Reverse enteric coating comprises (a) a pH-dependent methyl methacrylate and diethylaminoethyl methacrylate copolymer or (b) a pH-dependent cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate.	2015	[36]

30	US9636305B2	Antiemetic extended release tablet	It discloses ondansetron tablet containing a monolithic core comprising hypromellose and ondansetron dispersed within the hypromellose, and sodium citrate anhydrous dispersed within the hypromellose. The sodium citrate anhydrous allows it to form a hardened boundary around the periphery of the hypromellose upon exposure to an aqueous medium so as to limit the rate at which the ondansetron is released from the core. This tablet yields a burst of approximately 25% ondansetron followed by a zero-order sustained release of ondansetron, and total amount of ondansetron is released over 24 hours.	2017	[37]
31	US9545399B2	An extended release racemic methylphenidate chewable tablet	The tablet contains a combination of an uncoated methylphenidate-ion exchange resin complex, a barrier coated methylphenidate-ion exchange resin complex-matrix, and an uncomplexed methylphenidate active component. Following the administration of a single dose of the prepared tablet, a therapeutically effective amount of methylphenidate is reached in less than about 20 minutes and the composition provides a twelve-hour extended release profile.	2017	[38]
32	US20180116967A1	A directly compressed extended release cyclobenzaprine tablet	This patent application discloses a directly compressed extended release cyclobenzaprine tablet using hydroxypropyl methylcellulose (HPMC) for treating a skeletal muscle disease or condition. Dissolution testing studies in which the % of cyclobenzaprine released from the tablet at 2 hours ranges from 30% to 45%, the % of cyclobenzaprine released from the tablet at 4 hours ranges from 45% to 70%, and the % of cyclobenzaprine released from the tablet at 8 hours is more than 65% in 900 mL of 0.1N HCl at 37°C. and a rotation speed of 50 rpm using USP apparatus I.	2018	[6]
33	US10172797B2	Oral, extended release abuse deterrent pill	This patent discloses an oral, extended release, abuse deterrent pill containing oxymorphone HCl and controlled release agent selected from either HPMC or combination of PVA and PVP prepared using a hot melt extrusion process. This pill exhibits less than 10% increase in the release of the oxymorphone HCl or pharmaceutically acceptable salt thereof in a simulated alcoholic gastric fluid environment	2019	[10]
34	US20200188378A1	Methylphenidate extended release chewable tablet	This particular patent application discloses extended release chewable tablet containing a sustained release methylphenidate component comprising water-insoluble, water-permeable, pH-independent barrier coated, methylphenidate-ion exchange resin complex in a polymeric matrix. Chewable tablet is capable of being divided and providing tablet portions which retain a therapeutically effective immediate release and 12 hour extended release profile.	2020	[39]
35	US10624888B2	Extended release abuse deterrent tablet or capsules	This patent discloses extended release, abuse deterrent dosage form having plurality of particles consists of a blend of polyvinyl acetate and polyvinylpyrrolidone, an optional polyethylene oxide and active agent chosen from oxycodone, oxymorphone, hydrocodone, hydromorphone, codeine, morphine preprared using hot melt extrusion process.	2020	[40]

2.2. Extended release capsules

Extended release capsules contain multi-particulate systems such as mini-tablets, beads, coated granules, tablets or caplets etc.[41–43]. Capsules provide an advantage of keeping the multi-particulate systems intact until the time of oral administration.

Singh Harinder *et al.,* have developed extended release multi-particulate composition which is filled into a capsule or a sachet and used in the treatment of angina. Multi-particulate composition is in the form of a plurality of discrete units such as pellets, granules, minitablets and beads which consists of a drug layered core containing ranolazine and an extended release coating surrounding the drug core formed of water-insoluble polymer and a pH-dependent polymer. Water-insoluble polymer is chosen from cellulose derivatives such as cellulose ethers, cellulose esters, polymethacrylic acid ester copolymers, aminoalkyl methacrylate copolymers, a copolymer of polyvinyl acetate, polyvinylpyrrolidone etc. while pH-dependent polymer is chosen from synthetic polymers such methyl acrylate acrylic acid copolymer, methyl acrylate methacrylic acid copolymer, butyl acrylate styrene acrylic acid copolymer etc. [44].

Patents on extended release capsules are summarized in the Table 2.

Table 2: Recent patents on extended release capsules

Sr. No.	Patent Number	Type of Formulation	Salient features	Year of publication	Reference
1	US7270831B2	Capsule containing sustained release beads and the immediate release beads	It discloses oral analgesic dosage form for once-a-day administration as multiparticulate systems containing (a) sustained release beads comprising sugar beads, a coating comprising morphine sulphate on the sugar beads and an overcoating comprising one or more ammonio methacrylate copolymers; and (b) immediate release beads comprising sugar beads and a coating comprising morphine sulphate on the sugar beads	2007	[41]
2	US7476403B2	The controlled release dosage form in the form of capsule filled with tablet or caplet	A controlled release dosage form containing clarithromycin, polymer having a viscosity less than 50 cps such as hydroxypropyl cellulose or hydroxypropyl methylcellulose and polymer, having a viscosity greater than 200 cps such as hydroxypropyl cellulose or hydroxypropyl methylcellulose. Dosage form provides therapeutic effect for at least 12 hours and does not exhibit an in vivo food effect.	2009	[42]
3	US20110123610A1	An extended release hard gelatin capsule with a therapeutically effective number of mini tablets	This patent application discloses an extended release hard gelatin capsule containing therapeutically effective number of mini tablets, mini tablets contains: Tolterodine incorporated in a hydrophobic matrix comprising water insoluble polymer and wax which controls release of active agent. Tablet is prepared using technique such as direct compression, dry granulation, wet granulation or melt granulation.	2011	[43]
4	US8889190B2	Extended-release topiramate capsules	This patent discloses extended-release capsule dosed once daily to patients suffering from epilepsy which contains a capsule shell comprising coated particles which contains core containing topiramate and a coating, wherein the coating contains release controlling agent(s) such as ethylcellulose, polyvinyl acetate, polyacrylate and polymethacrylate, copolymers thereof which provide extended release. Capsule shell is made up of hydroxypropyl methylcellulose	2014	[45]
5	US20170056342A1	An extended-release composition of cyclobenzaprine for oral administration in the form of a capsule containing one or more tablets	This patent application discloses an extended-release composition of cyclobenzaprine in the form of a capsule containing one or more tablets, wherein each of the tablet is a matrix-type tablet containing cyclobenzaprine. Polymer used to prepare tablet is one of water-insoluble and an enteric polymer specifically hydroxypropyl methylcellulose acetate succinate. Dissolution studies: using USP Apparatus #2, complies with the following specifications: (1) after 2 hours in 900 mL of 0.1 N HCl, at 37° C. at 50 rpm, no more than about 40% of the cyclobenzaprine is released; and (2) after 8 hours in 900 mL of 0.05 M phosphate buffer at pH 6.5, 37° C. and 75 rpm, at least about 60% of the cyclobenzaprine is released.	2017	[46]
6	US9555005B2	Extended-release topiramate capsules	This patent discloses capsule containing capsule shell comprising coated particles in which each coated particle comprises a core and a coating thereon, core contains a homogeneous mixture of topiramate and other excipients and coating contains release controlling agent(s) such as ethylcellulose, polyvinyl acetate, polyacrylate and polymethacrylate. Topiramate capsule when dosed once daily, achieves at steady-state, an AUC0-24h, Cmax, and Cmin in the subject's plasma that are within the 80% to 125% bioequivalence criteria compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.	2017	[47]

7	US20180344653A1	An extended release multiparticulate composition comprising a plurality of discrete units filled into a capsule or a sachet	This patent applicationdiscloses extended release multiparticulate composition for the treatment of angina which contains a plurality of discrete units such as pellets, granules, minitablets and beads which contains a) a drug layered core comprising ranolazineb) an extended release coating comprising a water-insoluble polymer and a pH-dependent polymer. The composition releases about 15% to about 40% of the ranolazine in an initial 2 hours in 900 ml 0.1N HCl and releases about 60% to about 90% of the ranolazine in 6 hours in 900 ml pH 6.8 phosphate buffer; when measured in United States Pharmacopoeia (USP) type II dissolution apparatus, rotating at 50 rpm at a temperature of 37° C.	2018	[44]
8	US20200054573A1	Extended release composition in the form of once-a-day capsule filled with multiparticulates	This patent application discloses extended release pharmaceutical composition of Clozapine in the form of multiparticulates such as granules, pellets, beads, spheroids in which Clozapine is first coated with a seal coat, then an acidic coat which contains osmotic agent and an extended release coat. Extended release coating is of ethyl cellulose and polyethylene glycol.	2020	[48]

2.3. Extended release multilayer dosage forms

Multilayer dosage forms are suitable for the consecutive release of two or more drugs in combination and also for sustained/extended release dosage forms wherein one layer is for loading dose such as immediate release portion and another layer is for maintenance dose i.e. sustained release portion of the same or different drug. This type of dosage form is essential for chronic conditions which require combination drug therapy and to avoid chemical incompatibility between two active agents. Multilayer dosage forms allow designing and development of different or dual release profiles in single formulation [49].

Leo B. Kriksunov *et al.,* developed tablet which contains both an immediate release region and a modified release region. The tablet is prepared from a powder blend of the active agent and a thermally sensitive material chosen from waxes, fats, fatty acid esters, polymers and phospholipids. Energy is then applied in different amounts to different regions of the tablet surface. In the regions of tablet exposed to sufficient amounts of energy, the thermally sensitive material is modified. This region forms the modified release region of the tablet. Accordingly, the region of tablet not exposed to the energy from the immediate release region of the tablet. Tablet shape is formed by compressing the powder blend in a die platen and the energy is applied to tablet shape within said die platen. Energy applied to tablet shape to modify one region is selected from conduction, convection, radio frequency, microwave, UV light, infrared, induction, laser light and ultrasonic sound. About 1 to 50 percent active agent is released in the 60 minutes and about 50 to 99 percent is released from about 60 minutes to about 24 hours after oral ingestion from the tablet prepared by the disclosed process [50].

Kyung Hun Kim *et al.,* have developed oral sustained-release triple layer tablet for once-a-day administration. The upper layer and lower layer of the tablet contain a swellable polymer. The swellable polymer is chosen from polyethylene oxide, cellulose derivatives, polyvinyl alcohol, and carbomer. The intermediate layer contains a medium transfer agent. All the three layers contain pregabalin as active agent. Medium transfer agent from intermediate layer is hydrophilic in nature which absorbs the aqueous medium such as water, gastric fluid, intestinal fluid etc. and transfers it to the upper and lower layer resulting in a further increase in their swellability. Medium transfer agent used is sugars, polyvinyl pyrrolidone, salts, organic acids, starch, microcrystalline cellulose, and low-substituted hydroxyl propyl celluloses. The tri-layer tablet formulated thus enables a drug to remain in the gastrointestinal tract for prolonged time period and thus efficient amount of drug absorption is achieved[51].

UmitCifter *et al.,* have developed a dual release tablet containing dexlansoprazole for use in the treatment of gastrointestinal disorders. Dual release tablet contains i. Dexlansoprazole in the powder form; ii. granules containing dexlansoprazole, lactose and microcrystalline cellulose; and iii. has a single enteric coating that dissolves between pH 5.5 and 6.4. Upon oral intake, the dual release of dexlansoprazole is achieved when the enteric coating of the tablet dissolves. Initially the powder form dexlansoprazole is released and a sustained release is achieved through the granular form avoiding the dumping of the complete dexlansoprazole dose[52].

Various patents on extended release through multilayer dosage form are summarized in the Table 3.

Table 3: Recent patents on extended release multi-layered dosage forms

Sr. No.	Patent Number	Type of Formulation	Salient features	Year of publication	Reference
1	US20050169991A1	A sustained release oral dosage form sometimes bi-layer tablet	This patent application discloses sustained release oral dosage form containing an effective amount of torsemide and a sustained release excipientwhich is selected from the group consisting of a gelling agent, a cellulose ether, an acrylic resin, a protein derived material, a wax, shellac, a sustained release polymer, oil, and mixtures thereof. In-vitro dissolution studies: sustained release dosage form providing dissolution rate when measured by USP 26 (2003) dissolution Apparatus type III, in pH change media with an agitation of 15 dpm in 250 ml and at 37° C. which is from 0 to about 50% torsemide released after 1 hour; from about 1 to about 60% torsemide released after 3 hours; from about 5 to about 70% torsemide released after 7 hours; from about 10 to about 95% torsemide released after 12 hours	2005	[53]
2	US7303761B2	A pharmaceutical composition specifically capsule having an extended-release first portion containing NSAIDs	It discloses a pharmaceutical composition for the treatment of inflammatory condition or disease such as osteoarthritis or rheumatoid arthritis containing a. an extended-release first portion containing therapeutically effective amounts of NSAIDs mixed with at least one retardant material for extended release delivery presenting a controlled availability of NSAIDs alongside the gastrointestinal tract and b. an immediate release second portion made of a powder a stabilized misoprostol. Both portions are encapsulated within a capsule made of hydroxyl-propyl-methyl-cellulose (HPMC) polymer. Retardant material of the first portion is selected from the group consisting of lipidic materials, acrylic and methacrylic acid polymers and copolymers, alkyl celluloses, gums, protein derived materials and a mixture thereof.	2007	[54]
3	US7682632B2	oral dosage form with controlled release opioid analgesic	This patent discloses a dosage form having particles containing (a) an opioid antagonist; (b) hydrophobic means for sequestering the opioid antagonist such as acrylic polymer. Dissolution studies: The ratio of the amount of antagonist released from the dosage form after tampering to the amount of the antagonist released from the intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37° C.	2010	[55]
4	US8231904B2	A two-layer extended release tablet for the oral administration of pralnacasan	It discloses atwo-layer extended release tablet containing rapid release layer comprising pralnacasan and croscarmellose as a disintegrant, and an extended release layer comprising pralnacasan and hydroxypropylmethylcellulose as a gel former At least 60% of the pralnacasan is released from the tablet not more than 30 minutes after administration, and at least 90% is released not more than 180 minutes after administration. It is suitable for the treatment of autoimmune diseases, type I and type II diabetes, rheumatoid arthritis, osteoarthritis or psoriasis	2012	[56]

5	US8313768B2	Tablet comprises both an immediate release region and a modified release region	This patent discloses tablet containing both an immediate release region and a modified release region, and its method of preparation is: (a) forming a tablet shape comprising a powder blend comprising active agent and a thermally-sensitive material; and (b) applying energy in different amounts to different regions of the surface of the tablet shape to form said tablet in a manner such that: (i) a first region of said tablet shape is exposed to said energy for a sufficient period of time to modify said thermally-sensitive material within said first region to form said modified release region of said tablet; and (ii) a second region of said tablet shape is not so exposed to said energy such that said second region forms said immediate release region of said tablet. Tablet releases from about 1 to 50 percent is released in the 60 minutes following oral ingestion and about 50 to 99 percent is released from about 60 minutes to about 24 hours after oral ingestion.	2012	[50]
6	US20120064159A1	Multilayer tablet having immediate release layer and extended release layer	This patent application disclosesa multilayer tablet having (a) an immediate release layer containing NSAID & acetaminophen and a substituted alkylcellulose; and (b) an extended release layer containing a NSAID and/or acetaminophen, waxand alkylcellulose or a substituted alkylcellulose In-vitro dissolution studies: the NSAID and/or acetaminophen release rate from the tablet, when measured in vitro using a USP type II dissolution apparatus (paddle) in phosphate buffer at pH 6.8 and at 75 rotations per minute, corresponds to a dissolution pattern of: a) from 20 to 70% of the total NSAID and/or acetaminophen is released after 1 hour b) not less than 50% of the total NSAID and/or acetaminophen is released after 3 hours and c) not less than 70% of the total NSAID and/or acetaminophen is released after a total of 6 hours	2012	[57]
7	US20120321713A1	Gastric retentive extended-release dosage forms	It discloses the dosage form comprising a dose of acetaminophen and a dose of an opioid, wherein the dosage form comprises an extended release matrix that imbibes fluid after administration and swells to a size sufficient to promote gastric retention of the matrix and a method for treating pain using same, Disintegration studies: within about 1 hour in an in vitro disintegration test the dosage form releases more than about 50% of the dose of acetaminophen, and wherein by about 6 hours in an in vitro disintegration test, the percent of opioid released from the dosage form is greater than the percent of acetaminophen released from the dosage form, and wherein the in vitro disintegration test is a USP type II apparatus at 37° C. in 0.1 N HCl.	2012	[58]
8	US8535715B2	A bilayer tablet having layer of metformin extended release formulation ...	This patent discloses a bilayer tablet used for the treatment of diabetes, impaired glucose tolerance, insulin resistance, hyperglycemia and hyperinsulinemia contains (1) first layer is a metformin extended release formulation comprising about metformin hydrochloride (HCl) in an sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, and other excipients (2) second layer is a sodium-dependent glucose transporter (SGLT2) inhibitor formulation having of an SGLT2 inhibitor selected from dapagliflozin, lactose anhydrous, microcrystalline cellulose, pregelatinized starch, and other excipients ; and(3) optionally a film coating that covers the first layer and the second layer	2013	[59]
9	US8563034B2	A dual release oral tablet of dexlansoprazole	This patent discloses a dual release oral tablet for use in the treatment of gastrointestinal disorders contains a) dexlansoprazole in powder form; b)dexlansoprazole in granule form, hydrophobic agents, c) a single enteric coating that dissolves at between pH 5.5 and 6.4 The hydrophobic agents are selected from hydrogenated vegetable oils, wax, wax-like substance, fats, oils, fatty acid, fatty alcohol, shellac, pullulan, agar, gellan gum, guar gum, carageenan, acacia gum, gum arabic, dextran, pectin etc. and single enteric coating that dissolves at between pH 5.5 and 6.4 comprises cellulose acetate phthalate, cellulose acetate	2013	[60]

10	US8685451B2	Multi-layered tablet for a triple combination release of active agents	This patent discloses combination release tablet having a) a drug-containing rapid release first compressed composition comprising of drug selected from the group consisting of levodopa, carbidopa, ondansetron, quetiapine and ergotamine and excipients; b) a drug-containing extended release second compressed composition comprising a release rate modifier extended release polymer, and at least one drug selected from the group consisting of levodopa, alprazolam, quetiapine, divalproex and naproxen; and c) an osmotic device comprising a drug-containing core, the core being surrounded by a membrane comprising cellulose ester and plasticizer and having a preformed passageway through it	2014	[61]
11	US8758818B2	A dual release oral tablet having a gradual release	This patent discloses a dual release oral tablet having a gradual release for use in the treatment of gastrointestinal disorders which contains a) dexlansoprazole in powder form;b) dexlansoprazole in granule form comprising the dexlansoprazole, lactose, and microcrystalline cellulose; andc) a single enteric coating that dissolves at between pH 5.5 and 6.4 Upon oral administration, the tablet achieves dual release of the dexlansoprazole in that the dexlansoprazole is released in the small intestine at pH 5.5, and then at pH 6.0 to 6.5, with prevention of dose dumping of the dexlansoprazole.	2014	[52]
12	US2020222401A1	Fixed combination of rosuvastatin and metformin solid dosage product specifically bi-layer formulation	This particular patent application discloses fixed combination of rosuvastatin and metformin solid dosage product more particularly as bi-layer tablet prepared by compressionsuch that rosuvastatin is delivered immediately to the patient and metformin is delivered in a controlled fashion over a longer course of time. For prolonged delivery of metformin, it is provided in granules comprising cellulose, a polymer, water and organically soluble cellulose (hydroxypropyl cellulose). This fixed combination tablet is used for treatment of hyperlipidemia, simultaneously with type 2 diabetes	2020	[62]
13	US10632077B2	Oral sustained-release triple layer tablet containing Pregabalin gastro-retentive sustained-release preparation	This patent discloses a multilayer tablet having an upper layer and a lower layer comprising a swellable polymer; and an intermediate layer comprising a medium transfer agent, all 3 layers contain pregabalin medium transfer agent is hydrophillic and is selected from sugars, polyvinylpyrrolidone, salts, organic acids, starch, microcrystalline cellulose, and low-substituted hydroxypropylcelluloses which absorbs the aqueous medium and transfers it to the upper layer and the lower layer.	2020	[51]

2.4. Extended release osmotic drug delivery systems

Osmotic drug delivery systems achieve extended release through osmosis. These systems follow zero order release profile [63]. Osmotic drug delivery systems are usually comprised of a core containing an active agent and an osmotic agent. The core is covered by a rate controlling semi-permeable membrane [63,64].

Juan A. Vergez *et al.,* have developed dual controlled release osmotic device which comprises of a core and a membrane surrounding the core. The core consisting of a first active agent-containing controlled release layer surrounded by a second active agent-containing controlled release layer. Membrane surrounding the core has at least one preformed passageway in communication with active agent-containing controlled release layers. From osmotic device each drug is independently released according to a timed, targeted, pseudo-first order, first order, pseudo-zero order, zero-order, and/or delayed release profile and the first and second release profiles are different[65].

More patents on extended release using osmotic drug delivery systems are summarized in the Table 4.

Table 4: Recent patents on extended release osmotic drug delivery systems

Sr. No.	Patent Number	Type of Formulation	Salient features	Year of publication	Reference
1	WO2007078895	Once daily controlled-release osmotic dosage form comprising tramadol	This patent application discloses first once daily controlled-release dosage form containing tramadol and means for controllably releasing the tramadol having at least one swellable and erodible matrix core. The means for- controllably-releasing-the-tramadol also contains at least one release-slowing coat, which contains at least one pH independent polymer, pH dependent polymer, soluble polymer, insoluble polymer or swellable polymer. Controlled-release dosage form exhibits an in- vitro release rate such that after about 2 hours from about 0 to about 22% by weight of tramadol is released, after about 4 hours from about 5 to '* about 30% by weight of tramadol is released, after about 6 hours, from about 15 to about 38% by weight of tramadol is released, and after about 8 hours	2007	[66]
2	US8329217B2	A dual controlled release osmotic device	Patent discloses a dual controlled release osmotic device containing a) a core comprising a first active agent-containing controlled release layer and a second active agent-containing controlled release layer in direct contact therewith, wherein the second active agent-containing layer surrounds the first active agent-containing layer; and the osmotic device excludes a push-layer b) a membrane surrounding the core, wherein the membrane comprises at least one preformed passageway in communication with at least one of the first and second active agent-containing controlled release layers. From osmotic device each drug is independently released according to a timed, targeted, pseudo-first order, first order, pseudo-zero order, zero-order, and/or delayed release profile and the first and second release profiles are different.	2012	[65]
3	US10172842B2	A sustained release oral osmotic tablet	Patent discloses sustained release oral osmotic tablet containing a drug compartment comprising dalfampridine, sodium chloride, HPMC; a push compartment, comprising sodium chloride, HPMC; a semipermeable membrane, coating on said tablet core and at least one passageway through said semipermeable membrane to said tablet core. It is used for treating spinal cord injury, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis or post-stroke deficiency. Fluctuation index of osmotic tablet is not more than 1.5 and exhibits the following dissolution profile when placed in a USP type II apparatus in about 500 mL of purified water at about 37° C.: between 18.95% to 29.27% of said dalfampridine is released in 4 hours; between 45.62% to 52.90% of said dalfampridine is released in 8 hours; and between 73.66% to 81.62% of said dalfampridine is released in 18 hours.	2019	[67]

2.5. Extended release matrix tablets

Matrix systems are formulated by dispersing the active agent in the suitable polymer to provide extended release of the active agent. These types of systems usually follow the linear release of the active agent [4]. For the development of matrix tablets with extended release, selection of the polymer plays crucial role [68].

Wendell G. Mendoza *et al.,* have developed an extended release matrix tablet containing potassium citrate as an active agent and matrix made up of carnauba wax. This tablet is prepared by heating the mixture of potassium citrate and carnauba wax to a temperature below the temperature at which carnauba wax liquefies [69].

The patents on extended release matrix tablets are summarized in the Table 5.

Table 5: Recent patents on extended release matrix tablets

Sr. No.	Patent Number	Type of Formulation	Salient features	Year of publication	Reference
1	US20080050429A1	Extended-release matrix formulation containing Niacin	This patent application discloses extended-release matrix tablets which are effective in reducing a serum lipid and are prepared using direct compression contains niacin, a release-retarding agent and other excipients. The release-retarding agent is selected from the group consisting of hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC or hypromellose), methylcellulose (MC), hydroxyethyl cellulose (HEC), polyvinyl pyrrolidone (PVP) and xanthan gum, etc.	2008	[70]
2	US20140302138A1	An extended release matrix tablet for once daily administration comprising Carbamazepine	This patent application discloses an extended release composition for treating epilepsy and trigeminal neuralgia containing a. a matrix core comprising Carbamazepine and b. a coating comprising at least one hydrophobic release controlling agent and at least one hydrophilic release controlling agent. Core tablets of composition can be prepared by wet granulation, dry granulation, melt granulation etc. In-vitro dissolution studies: dissolution rate when measured using the USP Type I (Basket apparatus) at 100 rpm in 1800 mL, 0.1N hydrochloric acid for first 2 hours followed by the media with pH 6.8 phosphate buffer at 37° C.±0.5° C. is configured to release: a. from about 5 to about 25% Carbamazepine after 1 hour; b. from about 10 to about 45% Carbamazepine after 4 hours; c. from about 35 to about 70% Carbamazepine after 8 hours; d. from about 55 to about 78% Carbamazepine after 12 hours; e. from about 70 to about 78% Carbamazepine after 16 hours; or f. greater than 78% Carbamazepine after 24 hours.	2014	[71]
3	US20150231267A1	Extended release potassium citrate wax-matrix tablet	This particular patent application discloses extended release matrix tablet containing potassium citrate as active agent and carnauba wax. Matrix tablet is prepared by mixing potassium citrate and carnauba wax and heating to a temperature below the temperature at which carnauba wax liquefies.	2015	[69]
4	US20190374473A1	Gastro-retentive dosage form comprising an extended release portion and an immediate release portion	This patent application discloses gastro-retentive dosage form for the treatment of myasthenia gravis which contains: an extended release portion and an immediate release portion, wherein the extended release portion contains a core comprising pyridostigmine bromide, an acid, a gas-generating agent, and a water-soluble hydrophilic polymer that swells via imbibition of gastric fluid in about 60 minutes or less to a size that prevents its passage through the pyloric sphincter; and a permeable elastic membrane surrounding the core. From the dosage form, reduced initial burst release comprises an in vitro release of between about 20% and about 35% of the pyridostigmine bromide within 2 hours of dissolution in a dissolution medium comprising 50 mM acetate buffer with 100 mMNaCl and dosage form maintains its integrity in a swollen state for a period of at least about 14 hours and capable of providing an extended plasma concentration profile for up to about 24 hours.	2019	[72]

2.6. Delayed release oral dosage forms

Delayed release dosage forms are designed to delay the release of active agent from dosage form by certain time interval after administration [3,4].

Guy Vergnault *et al.,* have developed delayed release press coated tablet using defined core geometry. Core contains active ingredient as glucocorticosteroid chosen from prednisone, prednisolone or methylprednisolone. Compression coating made up of a water insoluble or hydrophobic material is applied surrounding the core such that the coating thickness about an axis (X-Y) is thicker and less dense than the coating about an axis (A-B) which is orthogonal to the (X-Y) axis. Compression coating which surrounds the core is adequately porous about the (X-Y) plane of the tablet to allow the entry of aqueous media to the core at a rate to ensure the release of the active agent after a period of time between 2 to 6 hours. This time period is followed by the breaking of the coating along the X-Y axis.

The dissolution studies of the tablet showed that there is an average lag time of around 4 hours and at least 80% of the active ingredient is released after 4.5 hours and about 100% of the active agent is released after 5 hours[73].

Additional recent patents on delayed release oral dosage forms are summarized in the Table 6.

Table 6: Recent patents on delayed release dosage forms

Sr. No.	Patent Number	Type of Formulation	Salient features	Year of publication	Reference
1	US9884021B2	Delayed release tablet containing prednisone	This patent discloses press coated delayed release tablet with defined core containing a pharmaceutically active agent , and a compression coating around said core which is disposed within said compression coating such that the coating thickness about an axis (X-Y) is thicker and less dense than the coating about an axis (A-B) orthogonal to (X-Y), wherein said compression coating is formed of a water insoluble or poorly water soluble hydrophobic material and said coating is sufficiently porous about the (X-Y) plane of the tablet to permit the ingress of aqueous media to the core at a rate to ensure the release of the active agent after a period of time between 2 to 6 hours wherein said period of time is followed by rupture of the coating along the X-Y axis, and active agent is a glucocorticosteroid selected from prednisone, prednisolone or methylprednisolone. Dissolution studies: The tablet has an in vitro dissolution profile using USP dissolution apparatus No. 2 at a stirring rate of 100 rpm and in a dissolution medium of 500 ml of purified water such that there is a median lag time of about 4 hours and at least 80% of active is released after 4.5 hours and about 100% of the active is released after 5 hours.	2018	[73]
2	US20190125682A1	Tablets that exhibit delayed release properties	This patent application discloses tablets that exhibit delayed release properties for the treatment of a neurodegenerative disease containing (a) a core comprising the active pharmaceutical ingredient such as deferiprone and an enteric polymer which can be chosen from hydroxypropyl methylcellulose acetate succinate (HPMCAS), HPMC phthalate, polyvinyl acetate phthalate, methacrylic acid copolymers etc., and (b) an enteric coating. Pharmacokinetic parameters: single dose of the tablet provides a mean AUC∞/Cmax ratio between 3.5 hours and 6.0 hours in fasted state and/or fed state	2019	[74]
3	US20190151246A1	A delayed-release tablet/capsule	This patent application discloses a delayed-release tablet/capsule for the treatment of attention deficit hyperactivity disorder containing (a) core comprising methylphenidate and (b) release-modifying layer which comprises the combination of an enteric polymer and a hydrophobic agent.	2019	[75]
4	US10675247B2	A press coated tablet for delayed release of an active ingredient	This patent discloses a press coated tablet for delayed release of an active ingredient which contains (a) a core comprising one or more active ingredients, and; (b) an erodible delayed release barrier surrounding the core and comprising a wax and two or more grades of low-substituted hydroxypropyl cellulose (L-HPC) Drug release: The core tablet releases drug in a sustained manner over a period of 2-12 hours after initiation of drug active ingredient release.	2020	[76]
5	US20200188309A1	Delayed release tablet	It discloses a delayed release tablet containing deferiprone and enteric polymer which is chosen from hydroxypropyl methylcellulose (HPMC) acetate succinate, HPMC phthalate, polyvinyl acetate phthalate, methacrylic acid copolymers, etc. Pharmacokinetic parameter: single dose of the tablet provides a mean AUCI/Cmax ratio between 3.5 hours and 6.0 hours in fasted state and/or fed state	2020	[77]

CONCLUSION

Modified drug delivery systems such as extended release and delayed release systems through oral route have proven to be of great significance to prolong the effect of the active ingredient for sufficient time span in the body. These systems allow and regulate the drug release by designing and modifying the process of drug delivery through the choice of physicochemical properties of drug, rate controlling excipients such as different polymers and other excipients. These systems are essential, especially in the treatment of chronic diseases and conditions such as diabetes, heart diseases, gastrointestinal disorders and mental health conditions like depression, attention deficit disorder, Alzheimer's disease, Parkinson's disease as these systems overcome the limitations of frequent dosing as in case of conventional dosage forms. As these types of systems can also be formulated by using combination of approaches, they serve multiple objectives of drug delivery such as less frequent dosing, patient compliance, overcoming the incompatibility issues between the two APIs by formulating multilayer dosage forms.

4. CURRENT AND FUTURE DEVELOPMENTS

Modified drug delivery systems though oral route have numerous opportunities as they have potential to provide drug release in a modified, controlled and regulated manner. This is also highlighted from the research and development in the field and increasing number of patents on these systems. These systems are and will prove to be of great importance especially in the case of lifestyle and chronic diseases or disorders. Also, with the advancement in the novel drug delivery science, smart, targeted delivery systems could also be developed and can be applied commercially. Also, formulation of such systems have unique commercial advantages such as extension of patent portfolio, market prospects etc. therefore it will continue to attract researchers and pharmaceutical industries.

LIST OF ABBREVIATIONS

SSG: Sodium starch glycolate

HPMC: Hydroxypropyl methyl cellulose

USP: United States Pharmacopoeia

NSAID: Non-steroidal anti-inflammatory drug

HPC: Hydroxypropyl cellulose

MC: Methylcellulose

HEC: Hydroxyethyl cellulose

PVP: Polyvinyl pyrrolidone

AUC: Area under curve

HPMCAS: Hydroxypropyl methylcellulose acetate succinate

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

[1] Lachman L; Lieberman HA; Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Lea & Febiger; 1986.

[2] Chien Y. Novel drug delivery systems. Second. Taylor & Francis; 1991. https://doi.org/10.1201/b14196

[3] Gujral G; Kapoor D; Jaimini M. An updated review on modified release tablets. J Drug Deliv Ther, 2018; 8(4):5-9. https://doi.org/10.22270/jddt.v8i4.1722

[4] Perrie Y; Rades T. Pharmaceutics: drug delivery and targeting. Pharmaceutical Press; 2012.

[5] Barzeh H; Sogali BS; Shadvar S. A review on extended release matrix tablet. J Pharm Res, 2016; 15:147. https://doi.org/10.18579/jpcrkc/2016/15/4/108823

[6] Chen B-L; Huang C-W; Sun P-C. Extended release tablet of cyclobenzaprine. US2018116967A1, (2018).

[7] Jinturkar K; Kshirsagar R; Malaviya N; Rao A. Extended release formulation of levetiracetam. US7863316B2, (2011).

[8] Eisenreich W; Friedl T. Extended release tablet formulations of flibanserin and method for manufacturing the same. US8545886B2, (2013).

[9] Bhatt PP; Mcknight L; Muhuri G; Viera ML; Woldu AB. Orally administrable extended release pellet and tablet formulations of a highly water soluble compound. US2007134315A1, (2007).

[10] Kemeny SF; Myslinski NR; Thompson ER; Thompson ER. Extruded extended release abuse deterrent pill. US10172797B2, (2019).

[11] Mohammad MA. Disintegrating monolithic modified release tablets containing quadri-layer extended release granules. US2015283084A1, (2015).

[12] Cao L; Langridge JR; Van GAW. Extended release excipient and its use. US8865778B2, (2014).

[13] Costales GTDNJ; Francisco DMTDJ; Illa VM V; Savoir VJC. 24-hour sustained-release metoclopramide. US2011033536A1, (2011).

[14] Paiement N; Zerbe HG. Sustained-release bupropion and bupropion/mecamylamine tablets. US7674479B2, (2010).

[15] Cappola ML; Chen F-J; Sienkiewicz S; Snow GC. Extended release formulation of nevirapine. US2010278918A1, (2010).

[16] Arora S; Gandhi R; Issa C; Mathur RS; Raheja P. Extended release tablet formulation of niacin. US2010144800A1, (2010).

[17] Fanda AK; Prasad R; Singh RB; Verma RK; Vivek K. Extended release tablets of nisoldipine. US2010247646A1, (2010).

[18] Cucala EJ; Gallego LM; Margallo LI. Extended release venlafaxine besylate tablets. US7776358B2, (2010).

[19] Eisenreich W; Friedl T. Extended release tablet formulation containing pramipexole or a pharmaceutically acceptable salt thereof. US7695734B2, (2010).

[20] Abramowitz W; Dedhiya MG; Mahashabde S; Periclou A; Rao N; Rastogi SK. Modified release formulations of memantine oral dosage forms. US8039009B2, (2011).

[21] Nakhat P; Joshi V; Mandaogade P; Jain G kumar. Extended release dosage form of ropinirole. US20110262537A1, (2011).

[22] Vivek K; Fanda AK; Varshney S; Singh RB; Khurana L; Sreekanth N. Extended release pharmaceutical compositions of guanfacine hydrochloride. US20110217373A1, (2011).

[23] Bhavarisetti MK; Verma RK; Singh RB. Modified release lamotrigine tablets. US20110052686A1, (2011).

[24] Abraham J; Gupta V; Murugesan G; Shah B. Extended release dosage form of paliperidone. US2011027361A1, (2011).

[25] Sherman BC. Clarithromycin extended-release tablet. US2012219625A1, (2012).

[26] Kamble P; Kshirsagar R; Shinde G. Coated extended release pharmaceutical compositions containing paliperidone. US2012201886A1, (2012).

[27] Brueck S; Rimkus K. Retigabine tablets, preferably having modified release. US2012058183A1, (2012).

[28] Baichwal AR; Kao H-H; Lee D; Mccall T. Oxymorphone

controlled release formulations. US8309122B2, (2012).

[29] Achliya GS; Bora DH; Taduri VR. Extended release formulations of desvenlafaxine base. US2013034604A1, (2013).

[30] Hoshino R; Kazama K; Nakashima K. Oral sustained-release tablet, (2013).

[31] Amidon GE; Ganorkar LD; Heimlich JM; Lee EJ; Noack RM; Reo JP; et al. Sustained-release tablet composition of pramipexole. US8399016B2, (2013).

[32] Fan H; Li C; Xie T; Zeng Z; Zhan X. Anti-tumor plant-medicament sustained-release tablet of elemene. US8778417B2, (2014).

[33] Eisenreich W; Friedl T. Extended release tablet formulation containing pramipexole or a pharmaceutically acceptable salt thereof. US2014335175A1v, (2014).

[34] Baichwal AR; Carpanzano AE; Goliber P a; Sciascia T; Vogler B; Diehl ID. Sustained release formulations of nalbuphine. US8771732B2, (2014).

[35] Devarakonda K; Giuliani MJ; Gupta VK; Heasley R a; Shelby S. Pharmaceutical compositions for extended release of oxycodone and acetaminophen resulting in a quick onset and prolonged period of analgesia. US9050335B1, (2015).

[36] Chen Q-Z; Mehta H; Nelson A; Tu Y-H. Benzonatate modified release solid tablets and capsules. US9180104B2, (2015).

[37] Fathi R; Raday G. Antiemetic extended release solid dosage forms. US9636305B2, (2017).

[38] Kathala K; Perumal A; Tu Y-H. Methylphenidate extended release chewable tablet. US9545399B2, (2017).

[39] Kathala K; Perumal A; Tu Y-H. Methylphenidate extended release chewable tablet. US2020188378A1, (2020).

[40] Gaik J; Lathrop R; Nichols G; Park J; Schallom J. Extended release, abuse deterrent dosage forms. US10624888B2, (2020).

[41] Chasin M; Oshlack B. Orally administrable opioid formulations having extended duration of effect. US7270831B2, (2007).

[42] Browder M; Li B; Nangia A. Oral extended-release composition. US7476403B2, (2009).

[43] Kshirsagar R; Mundade; S; Shinde; G; Kamble; P; Sonawane; S; Mudda SM. Extended release compositions containing tolterodine and process for preparing the same. US20110123610A1, (2011).

[44] Ahmad S; Singh H; Singh RB. Extended release multiparticulates of ranolazine. US2018344653A1, (2018).

[45] Betterman SM; Patrick LM; Tantry JS. Extended-release topiramate capsules. US8889190B2, (2014).

[46] Sherman BC. Extended release dosage form comprising cyclobenzaprine hydrochloride. US2017056342A1, (2017).

[47] Betterman SM; Patrick LM; Tantry JS. Extended-release topiramate capsules. US9555005B2, (2017).

[48] Kansagra P; Patel R; Saxena M; Sehgal A; Singh B. Extended release pharmaceutical composition of clozapine. US2020054573A1, (2020).

[49] More S; Ghodekar S; Rane B; Bavaskar K; Patil M; Jain A. Multilayered tablet: a novel approach for oral drug delivery. Int J Pharm Sci Res, 2017; 9:872–82.

[50] Bunick FJ; Kriksunov LB; Luber JR; Sowden HS. Manufacture of tablet having immediate release region and sustained release region. US8313768B2, (2012).

[51] Kim KH; Lee KS; Park JS; Song WH. Pregabalin-containing, oral sustained-release triple layer tablet. US10632077B2, (2020).

[52] Cifter U; Murat UI; Oner L; Terkinli A; Turkyilmaz A. Oral tablet compositions of dexlansoprazole. US8758818B2, (2014).

[53] Jaworski TJ; Ketsela S; Sanghvi P; Sciascia T. Sustained release torsemide dosage forms. US2005169991A1, (2005).

[54] Franz M. Stabilised pharmaceutical composition comprising an extended release non-steroidal anti-inflammatory agent and an immediate release prostaglandin. US7303761B2, (2007).

[55] Oshlack B; Wright C; Haddox JD. Tamper-resistant oral opioid agonist formulations. US7682632B2, (2010).

[56] Meier H; Soennichsen C; Wesch R. Extended release formulation for pralnacasan. US8231904B2, (2012).

[57] Chauhan I; Nutalapati SRK. Multilayer oral tablets containing a non-steroidal anti-inflammatory drug and/or acetaminophen. US2012064159A1, (2012).

[58] Han C-H; Hou SYE; Reid ML. Gastric retentive extended-release dosage forms comprising combinations of a non-opioid analgesic and an opioid analgesic. US2012321713A1, (2012).

[59] Abebe A; Desai D; Martin K; Patel JM; Timmins P. Bilayer tablet formulations. US8535715B2, (2013).

[60] Cifter U; Oner L; Terkinli A; Turkyilmaz A; Murat UI. Dual release oral tablet compositions of dexlansoprazole. US8563034B2, (2013).

[61] Coppari M a; Fischbein G a; Meyer G a; Pastini AC; Ricci M a; Toneguzzo FG. Triple combination release multi-layered tablet. US8685451B2, (2014).

[62] Dias MC. Oral tablet formulation consisting of immediate release rosuvastatin and extended release metformin. US2020222401A1, (2020).

[63] Kube RS; Kadam VS; Shendarkar GR; Jadhav SB; Bharkad VB. Sustained release drug delivery system: review. Indian J Res Pharm Biotechnol, 2015; 3:246–51.

[64] Khatri N; Nikam S; Bilandi A. Oral osmotic drug delivery system: a review. Int J Pharm Sci Res, 2016; 7:2302–412.

[65] Ricci M a; Vergez JA. Dual controlled release dosage form. US8329217B2, (2012).

[66] Frisbee S; Mamajiwalla S. Modified release formulations of tramadol and uses thereof. WO2007078895A2, (2007).

[67] Chang C-W; Chang C-W; Huang S-W; Tsai Y-C; Wu J-S; Yang C-Y. Sustained release oral dosage form containing dalfampridine. US10172842B2, (2019).

[68] Tiwari SB; Rajabi-Siahboomi AR. Extended-release oral drug delivery technologies: monolithic matrix systems, 2008, p. 217–43. https://doi.org/10.1007/978-1-59745-210-6_11

[69] Dee KU; Mendoza WG; Santos RJM; Singh EC. Method for producing extended-release potassium citrate wax matrix tablet. US2015231267A1, (2015).

[70] Cefali E; Rocca JG; Zhu Y. Low flush niacin formulation. US2008050429A1, (2008).

[71] Kandikurwar A; Kshirsagar R; Shinde G. Extended release pharmaceutical compositions containing carbamazepine. US2014302138A1, (2014).

[72] Desai D; Phuapradit W; Shah NH; Shelke NB; Vaka SRK. Extended release compositions comprising pyridostigmine. US2019374473A1, (2019).

[73] Dragan C; Grenier P; Vergnault G. Delayed release tablet with defined core geometry. US9884021B2, (2018).

[74] Sherman BC; Spino M. Delayed release deferiprone tablets and methods of using the same. US2019125682A1, (2019).

[75] Fábregas VJL; Ruiz XN. Delayed-release tablets of methylphenidate. US2019151246A1, (2019).

[76] Bhardwaj V; Macdougall FJ; Mullen AB; Smith D; Stevens HNE. Press coated tablet prepared for delayed release of an active ingredient. US10675247B2, (2020).

[77] Sherman BC; Spino M. Delayed release deferiprone tablets and methods of using the same. US2020188309A1, (2020).