ABSTRACT

The objective of this review is to study different novel approaches for achieving controlled release for oral administration. There is need of developing cost-effective generic products which will be comparable to the established innovator products with respect to in vivo performance. The innovator products being developed based on exhaustive research are developed utilizing novel platform technologies, have been protected with patents. These platform technologies require specialized manufacturing equipment’s and that additionally imparts overall cost to the drug product. This review also contains review on existing technologies utilized for controlling the drug release of actives and also focuses on authors work on the development of cost-effective novel approaches for developing controlled release of some selected central nervous system acting drugs viz galantamine hydrobromide (GAH) and paroxetine hydrochloride hemihydrate (PHH). The existing approved reference products of selected molecules are available on extended release multi-particulate delivery system and Geomatrix based platform technology for GAH and PHH respectively. This review also explains authors work in developing different controlled release approaches for achieving similar in vivo performance comparable to the reference product. The use of high viscosity grade of hydroxypropyl cellulose (HPC) as a release controlling matrix former has been used in order to control the release of GAH by direct compression into mini tablets offers a feasible dosage form which further can be filled into capsules. Hydroxypropylmethylcellulose (HPMC) based matrix tablets which were further coated using methacrylic acid copolymer were found to be a suitable method to formulate single layer controlled release PHH.

Keywords: Paroxetine hydrochloride hemihydrates, Galantamine hydrobromide, Aquacoat, Hydroxypropyl methylcellulose, Geomatrix technology, In vivo

INTRODUCTION

Development of pharmaceutical product formulation in a timely manner and ensuring quality is a complex process that requires a systemic, science-based approach. Information from various categories, including the property of drug substance and excipients, the interaction between material, unit operation, and equipment is gathered. Knowledge in different forms, including heuristics, decision trees, correlation, and first principle model is applied. Decisions regarding processing routes choice of excipients and equipment sizing are made based on this information and knowledge. Controlled drug delivery technology has improved over the last few decades. The controlled release system provides a constant supply of the active ingredient in vivo, usually at a zero-order rate, by constantly releasing, for a certain period of time, an amount of the drug approximately similar to the amount that is eliminated by the body. Literature review has been carried out from 1907 to till date through Chemical abstract service, Sci Finder, Google scholar, Pub Med, a library search and manual search of traditional as well as contemporary books to evaluate physicochemical, pharmaco kinetic, properties of Galantamine hydrobromide and Paroxetine hydrochloride hemihydrate, their reported formulation and pharmaco kinetic evaluation properties.

Different approaches for controlled release formulations

Conte et al. (1993) disclosed multilayer tablet systems for controlling the drug release. They disclosed novel approach as an against conventional coating approach to achieve constant drug release. The novel design where the matrix core containing active substance is restricted from contact with dissolution medium which impact in the rate of hydration & selling of polymeric matrix and the release of active is controlled in a constant manner. By increasing the extent of a barrier the active surface, systems performs the drug towards constant rate [1].

Conte et al. (1996) further studied and evaluated Geomatrix platform technology for drugs having different solubility. They studied a different type of barrier layers viz swellable and erodible. Authors studied the effect of different barrier property polymer systems with trapidil, ketoprofen and nicardipine. The study revealed that swellable polymeric barrier suits for active substances having high solubility while erodible polymeric barrier suits for sparingly soluble actives [2].

Rodriquez and Vila-Jato (1998) developed multi particulate system containing hydrophobic core which is further coated with pH dependent eudragit polymer in order to target the release of active in the colon. The system consisted of drug loaded cellulose acetate butyrate microspheres which further coated with Eudragit. The dissolution study revealed pH dependent release controlled by eudragit while the further release was controlled by cellulose acetate butyrate [3].

Khan and Jabri (1998) evaluated sustained release matrix tablets of ibuprofen using carbopol as a release controlling polymer. The formulations were prepared by direct compression method using different concentrations of carbopol. The drug release rate was found to be dependent on carbopol content in the formulation. As the content is increased the rate of release was found to be retarded. Effect of other excipients was also studied. The data revealed that formulation containing lactose shown to be slower and linear drug release than microcrystalline cellulose and starch [4].

Elenakis et al. (2000) evaluated the difference in release mechanism using carbopol and sodium alginate as release-controlling excipients. Single unit tablets and capsules and multi-unit mini tablets filled in capsules were prepared and the dissolution behavior was studied. The carbopol containing formulations were shown more swelling and less erosion as against sodium alginate [5].

Varma and Garg (2001) reported different therapeutic objectives that can met using different Geomatix technologies i) Constant or near zero order drug release ii) binary drug release for a combination of drugs from same tablet iii) positioned delivery of active at a predetermined location in the body iv) delayed release [6].
Krishniah et al. (2002) evaluated three layer matrix controlled release tablet formulation of trimetazidine dihydrochloride using guar gum. The matrix granules were prepared by wet granulation. The impact of different concentration of guar gum in active layer and support layers was studied. The formulation showed dissolution stability when studied for accelerated storage condition [7].

Tiwari et al. (2003) evaluated hydrophilic and hydrophobic matrix system for tramadol hydrochloride. Hydrophilic matrix tablets were prepared by wet granulation using HPMC while hydrophobic matrix tablets were prepared using melt granulation. Hydrophobic matrix system was found to control the release rate effectively [8].

Rao, Engh and Qui (2003) studied the effect of pH modifiers on the release rate of acidic drug divalproex sodium. Authors studied the impact of different concentration of guar gum in active layer and guar gum. The matrix granules were prepared by wet granulation using HPMC while hydrophobic matrix tablets were prepared using melt granulation. Hydrophobic matrix system was found to control the release rate effectively [9].

Royce et al. (2004) studied in vitro in vivo correlation between three different controlled release systems. The model drug was formulated in osmotic, hydrophilic matrix and reservoir technique. Although all systems showed similar dissolution profile, the in vivo outcome was different. Out of three controlled release systems, osmotic system shown good co relation of dissolution and in vivo performance [10].

Korhonen et al. (2004) studied in vivo performance of three different release rate systems in humans. The different release rate formulations of diltiazem were prepared using starch acetate. Good co relation was observed between in vitro drug release rate/extent and in vivo parameters such as Cmax and AUC. The slowest release formulation was observed to be equivalent with reference formulation [11].

Kim C (2005) studied dissolution of donut shaped three layered tablets. The matrix-based model drug core was prepared using enteric polymer HPMC acetate succinate. The top and bottom surface of core tablets were made of hydrophobic polymer ethyl cellulose. The system is reported to be useful in achieving near zero order release [12].

Jamzad and Fasahi (2006) studied in vitro drug release of glipizide by preparing two different hydrophilic matrix systems using hydroxypropyl methylcellulose and polyethylene oxide. Matrix polymer hydration, erosion were evaluated during dissolution study. The dissolution data was compared with reference product Glucotrol XL based on osmotic drug delivery. The matrix based on HPMC shown near zero order drug release when compared to reference formulation [13].

Lopes et al. (2006) studied sustained release of ibuprofen from mini tablets. The controlled release of ibuprofen was achieved by preparing mini tablets using HPMC and ethyl cellulose. The geometry of mini tablets plays an important role in drug release rate. Because of the small size of the mini tablets initial release of drug from the surface of tablets was found to be more as compared to large tablet [14].

Siepmann et al. (2008) reviewed various polymeric blends that can be used to achieve controlled release of actives. Different polymeric blends can be used for a) desired drug release b) drug release mechanism c) achieving site specific release of active in the gastrointestinal tract. However, authors reported that these polymeric blend systems are more complex and chemical as well as physical compatibility between blend components need to be checked [15].

Ishida et al. (2008) studied sustained release of pseudoephedrine hydrochloride by preparing an immediate release and sustained release mini tablets. The drug release for sustained release component was achieved by coating using a combination of hydrophilic and hydrophobic polymers [16].

Dey Majumdar and Rao (2008) reported that because of a smooth surface, uniform surface area and high strength, mini tablets provide an advantage over granules or pellets wherein less amount of release controlling polymer is required to attain sustained release of active [17].

Baloglu and Senyigit (2010) studied multi-layered matrix tablet formulations of metoprolol tartrate. Different swellable hydrophilic polymers were used in combination for controlling the drug release. The dissolution data was mapped with the target release profile determined from reported pharmacokinetic data. The three layer matrix tablet system using carrageenan as a release controlling polymer was found to have comparable drug release profile with target drug release profile [18].

Aboelwafa and Basalian (2010) studied different approaches for controlling drug release of venlafaxine hydrochloride. Hydrophilic matrix based system, wax based matrix and three-layered tablets containing hydrophobic core sandwiched between hydrophilic matrix layers. The authors optimized the formulation performance using factorial design. Further, the optimized formulation was studied for in vivo bioequivalence study using reference capsule product as a reference. The test product was shown to be bioequivalent based on AUC parameter [19].

Rao et al. (2011) studied the use of mini tablets approach for achieving sustained release of montelukast sodium. Approximately 30 % of the drug release was achieved within 1 hour by preparing immediate release minitablet portion while remaining 70% of the drug release was achieved up to 24 hours by preparing differentially coated mini tables [20].

Mamani et al. (2012) studied the effect of the different ratio of hydrophilic polymer HPMC and anhydrous dibasic calcium phosphate on theophylline release rate. Both the components in the matrix tablets have shown the impact on drug release across different pH of dissolution medium [21].

**Literature on galantamine, paroxetine and author's research contribution**

### A. Galantamine hydrobromide

Mashkovsky and Kruglikova–Ivova (1951) isolated and studied acetylcholinesterase (AChE)-inhibiting properties of galantamine [22]. Proskumina and Yakovleva (1992) reported the isolation of an alkaloid; GAH from bulbs of the caucasian snowdrops Galanthus woronowii [23]. Davis (1987) disclosed method of treating Alzheimer’s disease using parenteral administration of GAH [24]. GAH is a reversible, competitive acetylcholinesterase inhibitor used for the treatment of mild to moderate dementia of the Alzheimer’s type. The efficacy of GAH has been reported in patients with severe Alzheimer’s disease. GAH is a tertiary alkaloid, belonging to the phenanthrene chemical class [25]. GAH as per biopharmaceutical classification system would be classified as class 1 drug substance. GAH extended-release capsule dosage form has been approved by United States Food and Drug Administration (USFDA) in April 2005 and is commercially available under the trade name Razadyne ER® in the United States and available in 8 mg, 16 mg and 24 mg strengths. It is benzazepine derivative having ionization constant of 8.2. Its melting point is reported to be 246-247 °C. There are no polymorphic forms reported in the literature. [26].

The Razadyne ER® as disclosed in US Patent 7,160,559 comprises the three stage coating process to achieve the desired release profile. The product is based on reservoir controlled release multi particulate delivery system. The first stage comprises coating of GAH and water soluble film forming a polymer on inert spheres. The second stage comprises a further coating of a release rate controlling polymer membrane consisting of a combination of water soluble and water insoluble polymers. To achieve the desired release profile the third top coat is given consisting of water soluble polymer and GAH wherein the formulation is capable of releasing 20 to 40% of the total amount of GAH in 1 hour, and more than 80% of the total amount of GAH in 10 h [27]. The reference product (Razadyne ER® capsules) is based on multi particulate capsule dosage formulation. The manufacturing process involves many complicated steps and use of sophisticated equipment including fluid bed processor.

Kays et al. (2007) reported optimization of an intra-nasal GAH formulation using an in vitro tissue model, to correlate those results to in vivo bioavailability, and to compare emetic response to oral dosing. GAH permeation was enhanced without increasing...
cytotoxicity. Pharmacokinetic testing in rats confirmed the improved drug bioavailability and demonstrated an in vitro–in vivo correlation. Compared to oral dosing, intranasal GAH resulted in a dramatically lowered incidence of GI-related side effects, e.g., retching and emesis[28]. Cam et al. (2009) disclosed the tablets designed for GAH administration on the buccal mucosa, were prepared by direct compression of drug loaded eudragit® RS 100 matrices. When the tablets were coated with a lipophilic material, GAH is slowly discharged from buccal tablets, following the Higuchi kinetic [29]. Controlled delivery drug of GAH which is based on reservoir multi particulate pellet technology similar to reference formulation involving one stage coating has been reported. The researchers studied dissolution behavior of the extended release multi particulate drug delivery system by preparing pellets of GAH using extrusion/spheronization. Eudragit RS 30D & RL 30 D were used as release-retarding polymers. The test formulations were reported to follow first order release rate kinetics [30]. Sharma and Biswal (2013) are evaluated bilayer tablet approach for developing sustained release of GAH. Immediate release as a loading core and sustained release in the second layer were evaluated using HPMC as release retarding polymer. The sustained release was achieved over a period of 24 h [31]. Woo et al. (2015) evaluated transdermal patch system for delivery of GAH using carbopol polymer. The trial formulations were optimized using response surface methodology. The delivery system was reported to deliver cumulative release at 8 h [32]. Rao et al. (2015) studied different polymeric blends of GAH using konda gogu gum, sodium alginate and crosslinking agents. The sustained drug release was observed up to 12 h [33]. The authors have also developed controlled release compositions of GAH using a matrix based monolithic and reservoir based system [34, 35]. In one of the approaches based on reservoir technique, desired release profile of GAH was targeted by employing preparation of inert core mini tablets and coating of 70 % of GAH over the inert core, further controlling the release by coating composition consisting hydrophobic and hydrophilic components followed by a final coating of 30 % immediate dose of GAH. The controlled release mini tablets further filled into empty hard gelatin capsules.

The formulation G1 was manufactured by sifting lactose monohydrate and dibasic calcium phosphate dihydrate through 425 µm sieve. The sifted powder blend was then mixed for 15 min in an octagonal blender. Magnesium stearate was then sifted through 250 µm sieve and blended for 5 min in an octagonal blender. For formulation G2 the powdered blend of lactose monohydrate and dibasic calcium phosphate dihydrate was granulated by using 0.1 N hydrochloric acid in rapid mixer granulator, dried at 50 °C using the rapid dryer and sifted through 425 µm sieve. Magnesium stearate was then sifted through 250 µm sieve and blended for 5 min in an octagonal blender. Formulation G3 was manufactured by sifting mannitol and dibasic calcium phosphate dihydrate through 425 µm sieve. The sifted powder blend was then mixed for 15 min in an octagonal blender and further granulated by a solution of povidone in rapid mixer granulator, dried at 50 °C using the rapid dryer and sifted through 425 µm sieve. Magnesium stearate was then sifted through 250 µm sieve and blended for 5 min in an octagonal blender. The lubricated blends of different formulations were further used for compression into mini tablets using 10 stations single rotary compression machine. Further, these mini tablets were coated using 70 % of the dose of GAH in 10-inch gans coater.

The release controlling polymer solution of a different ratio of ethyl cellulose: hypromellose: diethyl phthalate was prepared by dissolving into ethanol [For G1–6:2:1:7, for G2 and G3:5:8:2:1:21]. Finally, the remaining 30 % of the dose of GAH was loaded by coating over controlled release reservoir mini tablets. Four mini tablets were filled in capsule shells for 8 mg strength. The round standard concave punch & die of 4.5 mm diameter was used.

The drug release profile of GAH from the mini tablets filled in capsules and the reference formulation (Razadyne ER® capsules) in pH 6.5 phosphate buffer using paddle apparatus are shown in fig. 1. The drug release showed fast dissolution during the first hour because of 30% of GAH in immediate release portion. The core mini tablets prepared using 0.1N hydrochloric acid (G2) showed pH independent dissolution as against the core mini tablets devoid of 0.1N hydrochloric acid (G1 and G3). Further, the amount of release controlling polymer required was slightly more in the case of mini tablets containing increased amount of hydrophilic component (G3 formulation containing 70% of mannitol as filler) as compared to mini tablets containing less amount of hydrophilic component (G2 formulation containing 39.6% of lactose monohydrate as filler).

The drug release of GAH from the formulations under investigations and the reference formulation was further studied in two different dissolution medias viz 0.1 N hydrochloric acid and pH 4.5 Acetate buffer in order to study the impact of pH of dissolution medium on the rate of drug release. The data is shown in fig. 2.
The formulations G1 and G2 with (46.66%, and 61% of HPC) were manufactured by sifting GAH, lactose monohydrate, HPC, and colloidal silicon dioxide through 425 µm sieve. The sifted powder blend was then mixed for 15 min in an octagonal blender. Magnesium stearate was then sifted through 250 µm sieve and mixed with previously blended drug excipient blend for 5 min in an octagonal blender. For formulations G3, G4 and G5 (with 76.49%, 78.56 % and 83.31%) additionally talc was used as a lubricant. The lubricated blends of different formulations were further used for compression into mini tablets using 8 stations single rotary compression machine. Further, these mini tablets were filled into empty hard gelatin capsule shells of size 1. One mini tablet was filled in capsule shells for 8 mg strength. The round standard concave punch and die of 5.2 mm diameter was used.

The dissolution profile of GAH from the mini tablets filled in capsules and the reference formulation (Razadyne ER® capsules) in pH 6.5 phosphate buffer using paddle I apparatus are shown in fig. 3. The release patterns of reference formulations showed fast dissolution and burst effect during the first hour. This release pattern is due to immediate release top coat on the pellets as disclosed in US Patent 7,160,559. The release of reference formulation after the first hour was further found to be slowed down due to release rate controlling polymer membrane coating of a combination of water soluble and water insoluble polymers. The similar release pattern was observed for the developed test formulation without having immediate release portion in the formulation.

Based on the two approaches for controlling the release of GAH, it was observed that mini tablets based on a hydrophilic matrix containing HPC as a release controlling polymer was easy from manufacturability perspective & also cost effective. Authors evaluated the test formulation based on hydrophilic matrix based mini tablets for in vivo bioequivalence study & concluded the bioequivalence of test formulation with reference formulation.

B. Paroxetine hydrochloride hemihydrate

PHH is a serotonin re-uptake inhibitor useful for the treatment of psychiatric problems including depression, Parkinson’s disease, anxiety disorders, obsessive-compulsive disorders, panic disorder and post-traumatic stress disorder. PHH belong to phenylpiperidine chemical class [36]. It is reported to exhibit different polymorphic forms. PHH controlled release tablet dosage form has been approved by United States Food and Drug Administration (USFDA) in Feb 1999 and is commercially available under the trade name PAXIL CR® tablets and available in 12.5 mg, 25 mg and 37.5 mg strengths. The reference product PAXIL CR® as disclosed in US Patent 4839177 and U. S. S. 5, 422, 123 is based on Geomatrix™ platform technology comprising bilayer tablet (Drug containing matrix layer & hydrophobic placebo matrix layer) further coated with enteric polymer release of PHH predominantly in the small intestine (zero order kinetics). The manufacturing process involves many complicated steps and use of sophisticated equipment including bilayer tablet compression machine.

Raghupathi et al. (2007) evaluated single layer delayed and controlled release tablets of PHH as against bilayer tablets of the reference product. The in vivo study resulted in an enhanced bioavailability of the test formulation suggesting for reducing the dose of the formulation [37].

Jin et al. (2008) studied the effects of the formulation variables-POLYOX molecular weight, the ratio of POLYOX/Aivicel PH102 and the amount of POLYOX and Aivicel PH102, hardness, HPMCP amount, eudragit L100 amount, and citric acid amount on the PHH release from POLYOX matrix tablet using the Plackett-Burman screening design. POLYOX molecular weight had significant influence on the drug release mechanism [38].

Vaidya et al. (2013) evaluated controlled release of paroxetine using high viscosity HPMC polymers and compritol ATO. The formulation with desired release profile was shown stability in dissolution for one month [39]. The authors have also studied different approaches of controlled release of PHH. In one approach the preparation of single layer controlled release containing hydrophilic matrix core was attempted wherein the release from matrix core tablets was further delayed using methacrylic acid copolymer dispersion. In this approach, 85% of the dose was included in core matrix whereas remaining 15% of the dose was included as an immediate release as an outer coating layer over delayed release coating. In another approach, hydrophobic matrix core containing methacrylic acid copolymer was prepared by wet granulation in order to delay and control the drug release. In this approach, 100% of the dose was included in the core matrix. In yet another approach the drug substance PHH was granulated with methacrylic acid copolymer dispersion and further hydrophilic matrix tablets were prepared.

The formulations P1-P8 were prepared by wet granulating 85 % of the dose with hydrophilic polymer & other excipients. The compressed matrix core tablets were further coated with an enteric polymer. The enteric coated tablets were further coated with 15 % of the dose as a top coat. The formulations P4 and P5 were further coated with ethylcellulose aqueous dispersion. The formulations P9-P12 were prepared by granulating 100 % of the dose, hydrophobic matrix components along with methacrylic acid copolymer by wet granulation and compressed into tablets. The formulations P13-P16 were prepared by using PHH granulated with 4% (P13 and P14) and 8% (P15 and P16) methacrylic acid copolymer dispersion. The granulated PHH was further used for preparing hydrophilic matrix core tablets [40].
The dissolution profile of PHH from controlled release matrix tablets and the reference formulation (PAXIL, CR® tablets) in USFDA recommended dissolution methodology (Paddle, 150 RPM): paddle apparatus at 75 RPM and basket apparatus at 100 RPM are shown in fig. 5.1, 5.2 and 5.3. The reference formulation showed no drug release in 0.1 N hydrochloric acid for 2 h in all dissolution methodologies because of the presence of methacrylic acid copolymer coating which has been reported to be solubilized at a pH of 5.5 and above.

Whereas the formulations (P1-P8) showed the release of up to 15% in 0.1 N hydrochloric acid for 2 h in all dissolution methodologies which indicated the enteric coating over 85% of the dose prevented further drug release from the core matrix. The formulation P9 prepared with granulating the hydrophilic core matrix containing methacrylic acid copolymer showed 19% drug release in 0.1 N hydrochloric acid. The release in acidic medium was controlled because of the methacrylic acid copolymer in the matrix. The formulations P10 and P12 containing varied concentrations of methacrylic acid copolymer showed slower drug release profile. It could be because of the hydrophobic effect of glyceryl behenate in the formulation. The drug release of about 6-10% was observed in acidic medium. The formulation P11 was similar to P10 with additional hydrophilic polymer added at extragranular stage significantly enhanced the drug release as compared to formulations P10 and P12. The formulation was unable to maintain the matrix integrity, and initial burst release of 66% in acidic medium was observed which further released 93% immediately in 1st hour in buffer medium.

The formulations containing methacrylic acid copolymer granulated PHH within hydrophilic matrix (P13-P16) also showed controlled drug release. The formulations containing 100 % of the dose granulated with the methacrylic acid copolymer (P13 and P16) showed slightly slower release profile as compared to the formulations P14 and P16 containing 50 % of the dose granulated with the methacrylic acid copolymer. There was no significant difference observed within P13-P16 for PHH release in acidic medium and all formulations showed PHH release of about 20-24% in acidic medium. Although there was no significant difference in the rate and extent of PHH drug release amongst the formulations P13-P16, surprisingly the formulations containing 4 % granulated PHH (P13 and P14) showed slightly slower drug release as compared to formulations containing 8% granulated PHH (P15 and P16).

The release of reference and test formulations in pH 6.8 phosphate buffers in paddle at 150 RPM was further found to be controlled due to hydration of polymer HPMC. The increase in the concentration of polymer HPMC from 8.86 % to 14.29% based on the weight of core matrix composition (P1, P6, P7 and P8) resulted in a decrease in the rate of drug release (Figure. 5). This is attributed to gel layer formation with a longer diffusion path as the content of HPMC was increased.

Based on the data from different approaches, the use of high viscosity grade of HPMC as a release controlling matrix former in order to control the release of PHH by wet granulation into single layer matrix tablet with further delayed release coat using methacrylic acid copolymer dispersion offers a feasible dosage form.

Fig. 5: Comparative PHH release profile between test formulations (P1-P9) and reference formulation (Paddle 150 RPM)

Fig. 6: Comparative PHH release profile between test formulations (P1-P4, P13 P16) and reference formulations (Basket 100 RPM)

The matrix tablets prepared by granulating with methacrylic acid copolymer also showed promising strategy and needs to be further evaluated and optimized in order to achieve comparable dissolution with reference formulation. The development approach involving granulated PHH in the hydrophilic matrix have shown to be less promising.

CONCLUSION

Reference formulation of GAH is based on the reservoir controlled release multiparticulate delivery system. Manufacturing process is reported to contain three stage coating process involves specialized equipment viz fluid bed processor. Various researchers attempted to prepare extended release formulations using Eudragit based matrix systems by preparing tablet as well as multi particulate dosage systems. Authors have studied matrix based mini tablets and reservoir based minitablets approaches and found hydrophilic matrix based minitablets approach as suitable.

Reference formulation of PHH is based on Geomatrix™ platform technology involving use bilayer compression machine. Other researcher's attempt preparing single layer delayed and controlled release systems based on hydrophilic polymers. Enhanced bioavailability was also reported for one such attempt as against the reference formulation. Authors have worked on different matrix and reservoir based systems, and HPMC-based matrix tablets which were further coated using methacrylic acid copolymer were found to be a suitable approach.

CONFLICT OF INTERESTS

The authors report no conflicts of interest. The authors are alone responsible for the content and writing of the paper.

REFERENCES


