Rational Development of Carbamazepine Osmotic-Controlled Release Oral Delivery System for Multiple Therapeutic Advantages

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ABSTRACT

Background: Carbamazepine is used in the management of seizures by decreasing the central nervous system disorganized electrical activity and also has analgesic properties. It exerts serious side effects in normal administration owing to the extrapyramidal effect which signifies the importance of its incorporation into the extended-release system to reduce the possible side-effects associated with the drug.

Objective: In the present study, multiple extended-release systems of Carbamazepine was formulated using various polymers. The effect of viscosity modifying polymers of different grades and its contribution to the release behaviour was examined. Different formulations were prepared and studied for their drug release potentials. Among them, selected formulations were further evaluated for dimensions of the portal.

Methodology: Trial batches were designed with osmogen and cellulose polymers along with solubility enhancer as the model drug used to have low solubility. The optimization of the formulation was done by wavering concentration of cellulose polymers and the dimensions of the release portal were determined.

Result: A new strategy for extended delivery has been accomplished by extended-release solid oral tablet formed by the combination of solubility enhancers and cellulose polymers. The arrangement of a hydrophilic polymer with a surfactant as solubility promoter and the use of cellulose polymer represents an innovative and effective approach for the delivery of poorly water-soluble. The study further can be used to deliver a cost-effective and robust system for water-insoluble drugs in a zero-order manner.

Conclusion: The rapid development of these investigational therapeutic formulations will put forward new avenues for future commercialization of drug after completion of required clinical studies.

Key Words: Carbamazepine, Osmotic, Controlled Release, Oral Delivery System, Drug release, Solubility

INTRODUCTION

The osmotic pump is an oral drug delivery system that utilizes osmotic pressure to drive drugs out.¹ Osmotic drug-delivery systems suitable for oral administrations typically consist of a compressed tablet core that is coated with a semi-permeable membrane coating.² This coating has one or more than one delivery port(s) from which a solution of the drug or suspension of the drug is completely released over the duration of time.³ The core comprises of formulation of the drug that has a water-swellable polymer and an osmotic agent.⁴ The way at which the main core absorbs aqueous content depends completely on the osmotic pressure created by the core components and the membrane coating permeability.⁵ As the core absorbs aqueous content, it swells in terms of volume, which compels the drug solution or drug suspension to come out of the tablet formulation through one or more than one delivery ports.⁶ Besides, the drug release of the osmotic system is typical zero-order.⁷

In contrast with the conventional pellets, osmotic pump tablets can maintain the stable plasma concentration and are independent of the presence or absence of food, pH of gastrointestinal.⁸ The key distinguishing feature of osmotic drug-delivery systems in comparison with other technologies used in controlled-release formulations is that they release the drug at a rate that is independent of the pH and hydrodynamics of the external dissolution medium.⁹ The
result is a formulation robust dosage form for which the in vivo rate of drug release is comparable to the in vitro rate, producing an excellent in vitro/in vivo correlation (IVIVC). An additional critical benefit of the current osmotic systems is that they are related to drugs with a large variety of aqueous solubilities. Depending on aqueous solubility, the drug is released either as a solution or as a suspension. Any drug released as a suspension must dissolve in the in vivo environment and overcome biological barriers before it becomes systemically available.

Antipsychotic drugs are proficient to diminish psychotic symptoms in an extensive assortment of circumstances, including bipolar disorder, schizophrenia, senile psychoses, psychotic depression, drug-induced psychoses, and various organic psychoses. Carbamazepine (CBZ), a dibenzazepine that acts as a sodium channel blocker, is presently used in the management of the bipolar disorder, grand mal seizures, psychomotor or focal seizures by decreasing the central nervous system disorganized electrical activity and also has analgesic properties. It is an inducer of CYP450 class of enzymes; particularly, 3A4, 1A2, 2B6, 2C9, and 2C19. CBZ exerts serious side effects in normal administration owing to the extrapyramidal effect which signifies the importance of its incorporation into the extended-release (ER) system to reduce the possible side-effects associated with the drug. The drug absorption from ER dosage forms is usually slow and erratic also at overdoses or after chronic use. Among these advantages are the ability to reduce dosing frequency and the ability to moderate a drug’s maximum (Cmax) and minimum (Cmin) blood levels, respectively which will in the due course improve the safety, toleration, and efficacy.

In the development of ER dosage form, several considerations come into play. Initially, the factors related to the manufacture and performance of the dosage form as well as the performance of the API when metered out throughout the gastrointestinal (GI) tract. The concluding factors include API solubility in diverse GI regions, the existence of intestinal metabolism and transporters (both for uptake and efflux). When an API is delivered slowly in vivo, its absorption behaviour depends on the API release rate, its transit through the GI tract and factors affecting regional API absorption. Among the oral ER dosage form options are hydrophilic matrix tablets, hydrophobic matrix tablets, ER beads, and osmotic dosage forms the selection of which option to develop depends on the desired performance characteristics of the dosage form along with its stability and manufacturability.

Not too many formulations have been reported so far. Recently, OROS formulations of oxybutynin, hydromorphone, methylphenidates, and nifedipine have shown significant results and distinct therapeutic advantages. After drawing inspiration from the above studies, in the present study, the effect of viscosity modifying polymers of different grades and its contribution to the release behaviour was examined. Different formulations were prepared and studied for their drug release potentials. Among them, selected formulations were further evaluated for dimensions of the portal.

**MATERIALS AND METHODS**

**Materials**

HPMC (K4-100) and HPMC (K15-100) were obtained as a generous gift sample from FMC International Ltd., India. Cellulose acetate was received as a gift sample from Sterochem Pvt. Ltd. All other chemicals and reagents employed in the study were of analytical grade. Double distilled water (Borosil, India) was used for the experiments.

**Preparation of Osmotic Pump Tablets**

CBZ was measured (Shimadzu AUW220D, Japan) and co-sifted through standard mesh #40 with mannitol, sodium lauryl sulfate, and dextrates. The blend was mixed with pre-meshed #40 HPMC (K4-100), HPMC (K15-100), and iron oxide yellow pre-meshed #100. The blended materials were granulated using purified water as granulating fluid (binder addition time is 20 min), dried using retsch dried (LOD 1.5- 2.5%), and sifted through mesh #30. Mill the retained granules through multi-mill fitted with 1.0 mm screen at slow speed and knife forward direction and lubricated with magnesium stearate in double cone blender at 12 rpm for 50 min duration. An appropriate amount of lubricated granules was poured into the die of the tabletting machine (tooling B Type, Cadmach CMB4D Machine), and then press it by an appropriate pressure. The targeted weight was 600 mg ± 3.0% with a hardness of 80N ± 20N. The tablet core was coated with acetone solution (95%) of Opadry cellulose acetate.

The coating solution preparation by taking 1000 ml of coating solution (acetone: water ratio of 95:5) and further dissolving Opadry cellulose in the corresponding volume of a mixture of acetone and water under continuous stirring. The coating process was continued by taking the weight of 500 g and keeping the temperature of the coating bed at 35°C ±5°C in a coating pan of a diameter of 12 inches. The process was performed at a rotating rate of 10-20 rpm, import rate of 4 g/min to 8 g/min, along with atomization speed of 1.5-2.0. The target weight gain of the coated tablet was kept between 10% w/w to 16% w/w with drilled on any one side of the tablet with appropriate depth and diameter which serves as the drug release portal. Table 1 showed the qualitative and quantitative composition of formulations.
Table 1: A prototype of formulation batches.

| Ingredients                              | CBMF1 | CBMF2 | CBMF3 | CBMF4 | CBMF5 | CBMF6 | CBMF7 |
|------------------------------------------|-------|-------|-------|-------|-------|-------|-------|
| CBM                                      | 200   | 200   | 200   | 200   | 200   | 200   | 200   |
| Hypromellose (3cps) Methocel E5 Premium LV | 36    | 36    | 36    | 12    | 24    | 30    |
| Hydroxypropyl methyl Cellulose (K4M)     | 18    | 45    | 51    | 60    | 60    | 60    | 60    |
| Hydroxypropyl methyl cellulose (K100M)   | 72    | 45    | 39    | 30    | 30    | 30    | 30    |
| Mannitol                                 | 132   | 132   | 132   | 132   | 132   | 132   | 132   |
| Dextrates hydrated                       | 129.4 | 129.4 | 129.4 | 153.4 | 141.4 | 135.4 | 135.4 |
| Ferric Oxide (Iron Oxide Sicovit Yellow) | 0.6   | 0.6   | 0.6   | 0.6   | 0.6   | 0.6   | 0.6   |
| Sodium lauryl sulfate                    | 6     | 6     | 6     | 6     | 6     | 6     | 6     |
| Magnesium stearate                       | 6     | 6     | 6     | 6     | 6     | 6     | 6     |
| Cellulose acetate                        | 84    | 84    | 84    | 84    | 84    | 84    | 84    |

Optimization of Formulation Batches

Trial batches were designed with osmogen and cellulose polymers along with solubility enhancer as the model drug used to have low solubility. Optimization of the formulation was done by wavering concentration of cellulose polymers, and dimensions of release portal. The formulation in development is intended to be extended-release and expected to follow zero-order release till 12 hrs, different cellulose polymers were used in varying amount. The model drug used belongs to BCS class II category, therefore it is necessary to improve its solubility in the media. Out of different solubility enhancers, sodium lauryl sulfate found to be effective in concentration between 0.5% w/w to 1.5% w/w. To control drug release from orifice hypromellose (3cps) Methocel E5 Premium LV, hydroxypropyl methylcellulose (K4-M), and hydroxypropyl methylcellulose (K100-M) were used. Based on the release profile of prototype formulation batches, three batches namely CBMF2, CBMF3, and CBMF7 were selected to study the effect of dimensions of release orifice on the drug release profile of the drug. Table 2 showed the qualitative and quantitative composition of release portal.

Table 2: Formulation batches based on dimensions of release portal.

| Batch No.        | Port depth (mm) | Port diameter (mm) |
|------------------|-----------------|--------------------|
| CBMF2/01         | 0.4             | 0.6                |
| CBMF3/01         | 0.4             | 0.6                |
| CBMF7/01         | 0.4             | 0.6                |
| CBMF2/02         | 0.6             | 0.8                |
| CBMF3/02         | 0.6             | 0.8                |
| CBMF7/02         | 0.6             | 0.8                |
| CBMF2/03         | 0.8             | 1.0                |
| CBMF3/03         | 0.8             | 1.0                |
| CBMF7/03         | 0.8             | 1.0                |

Dissolution study

The in vitro release of drug from the OROS formulations were studied in the simulated gastric fluid under fed-state (prepared by taking 2g NaCl, 3.2 g pepsin, 7 mL concentrated HCl in 1000 mL distilled water) in a 900 mL of dissolution medium having pH of 1.2 (Contech pH meter, USA) by using USP 33 (Type II) apparatus (Electrolab Ltd., India). The study was performed at a controlled temperature of 37±0.5°C at a rotor speed of 100 rpm. For 12 hrs duration, the experiment was conducted where after every 1 hr, 5 mL of the sample was taken out by pipette and required aliquots were prepared. The sink condition was maintained by pouring an equivalent amount of fresh dissolution medium in the apparatus. The drug was measured spectrophotometrically using a UV-Vis Spectrophotometer (Shimadzu UV-1800, Japan). The release studies from the tested formulations were performed in a triplicate manner and established after suitable calculations.

Release kinetics

The plausible mechanism(s) for the release of drugs from the fabricated OROS formulations were studied based on fit-test or goodness. The in vitro cumulative drug release data was plotted in suitable pharmacokinetic models such as zero-order (concentration-independent release), first-order (concentration-dependent release), Korsmeyer-Peppas (state of equilibrium based release), Hixson-Crowell (surface/particle dimension-dependent release), and Higuchi (square root time-dependent release).

RESULTS AND DISCUSSION

The optimized formulation revealed that to have a good osmotic system; we have to carefully select the grade and concentration
of viscosity modifying polymer, osmotic agent, drug release port diameter, and depth. Depending on its solubility in the external medium, the drug can be released as either a solution or a suspension. If the release pattern follows a suspension component, then the drug composition forms plumes at the delivery ports, which are again dispersed over time using mechanical agitation of the external medium. The plausible mechanism of drug release from the fabricated formulations (CBMF) presented mixed-type of characteristics. When the coated CBMF tablet is exposed to an aqueous medium, water diffuses through the acetate film coating because of the activity gradient of water, thereby hydrating the core. The solvation of the osmotic agents creates a constant osmotic-pressure difference between the core contents and the external environment and drug is extruded through release portal osmotic pressure generated by the osmol generating composition. Any drug released as a suspension must dissolve in the in vivo environment and overcome biological barriers before it becomes systemically available. After the drug has been delivered from the formulation, the tablet shell will remain intact.

All formulation showed at most similar release until 9 hrs, except CBMF1 and CBMF4 (Table 3). This may be due to at most concentration of hydroxypropyl methylcellulose (K4-M) and hydroxypropyl methylcellulose (K100-M). CBMF3 shows faster release than CBMF1, probably due to a decrease in HPMC K100-M; however, the extent of release is at a lower side than that of CBMF4. Factors that affect the drug release profile were the concentration of hypromellose used and the diameter and depth of release portal. According to results, the obtained ratio of HPMC K4-M and HPMC K100-M was fixed for further evaluation. In formulations CBMF5 and CBMF6, it was observed that increase in Methocel E5 Premium LV gives better drug release, in considering that, the formulation was designed CBMF7, with further increase in Methocel E5 Premium LV concentration. CBMF7 shows the intended drug release profile until 24 hrs (Figure 1).

Table 3: The dissolution profile of various fabricated CBZ formulations.

| Time (hr) | CBMF1 | CBMF2 | CBMF3 | CBMF4 | CBMF5 | CBMF6 | CBMF7 |
|----------|-------|-------|-------|-------|-------|-------|-------|
| 1        | 0     | 0     | 1±1.29| 2±2   | 0     | 14±1.77| 0     |
| 2        | 1±1.55| 5±1.37| 8±1.57| 28±1.79| 6±1.54| 16±1.82| 1±1.13|
| 3        | 8±1.84| 18±1.58| 24±1.63| 43±1.19| 12±1.66| 24±1.17| 4±1.74|
| 4        | 12±1.33| 29±1.06| 41±1.75| 66±1.24| 42±1.77| 35±1.41| 12±1.22|
| 6        | 13±1.49| 41±1.58| 56±1.88| 71±1.86| 51±1.62| 49±1.65| 29±1.35|
| 8        | 26±1.12| 56±1.11| 64±1.09| 87±1.33| 77±1.09| 66±1.47| 53±1.96|
| 10       | 33±1.76| 6±1±1.62| 70±1.74| 89±1.44| 79±1.92| 78±1.66| 81±1.17|
| 12       | 45±1.45| 66±1.83| 72±1.11| 90±1.27| 88±1.07| 84±1.05| 88±1.51|
| 24       | 53±1.68| 67±1.41| 72±1.83| 91±1.83| 92±1.13| 94±1.23| 88±1.91|

Mean ± SD; n=3

Figure 1: Dissolution profile studies of various formulation batches.
For further studies, CBMF2, CBMF3, and CBMF7 were selected to evaluate the effect of release portal on drug release (Figure 2). It has been observed that formulation CBMF7 shows drug release at a larger extent than other two irrespective of release portal diameter and depth. The same observation was noted with other formulations where a change in the depth of orifice from 0.4 mm to 0.8 mm and change in diameter from 0.6 mm to 1 mm was perceived. The range can be concluded as optimized dimensions for release portal (Table 4).

Table 4: The dissolution profile of the developed formulations based on the port dimensions.

| Time (hr) | CBMF2/01 | CBMF3/01 | CBMF7/01 | CBMF2/02 | CBMF3/02 | CBMF7/02 | CBMF2/03 | CBMF3/03 | CBMF7/03 |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| 1        | 0±1.15   | 6±1.19   | 1±1.52   | 5±1.58   | 8±1.28   | 0±1.63   | 10±1.25  | 3±1.49   | 5±1.18   |
| 2        | 15±1.44  | 22±1.74  | 3±1.96   | 17±1.92  | 26±1.23  | 5±1.66   | 19±1.39  | 25±1.72  | 5±1.18   |
| 4        | 22±1.36  | 36±1.78  | 11±1.91  | 29±1.11  | 38±1.94  | 15±1.83  | 31±1.69  | 41±1.41  | 13±1.54  |
| 6        | 39±1.71  | 56±1.84  | 26±1.55  | 40±1.57  | 54±1.37  | 28±1.95  | 41±1.21  | 59±1.56  | 31±1.51  |
| 8        | 54±1.29  | 65±1.34  | 50±1.81  | 55±1.26  | 68±1.89  | 51±1.59  | 57±1.75  | 63±1.33  | 54±1.38  |
| 10       | 61±1.22  | 69±1.65  | 82±1.76  | 62±1.97  | 69±1.48  | 85±1.92  | 62±1.86  | 72±1.12  | 87±1.57  |
| 12       | 67±1.40  | 71±1.61  | 85±1.16  | 62±1.88  | 71±1.24  | 86±1.73  | 68±1.35  | 73±1.67  | 87±1.17  |
| 24       | 67±1.13  | 72±1.87  | 86±1.68  | 64±1.99  | 72±1.53  | 87±1.31  | 69±1.79  | 73±1.27  | 89±1.43  |

Mean ± SD; n=3

Figure 2: Dissolution profile studies on the basis of port dimensions.

In overall observations, the optimized tablets showed satisfactory results with up to 80% drug release at a rate of approximately zero-order for up to 12 hr (Table 5), which indicated that the release pattern was independent of drug load (Figure 3).

Table 5: Release kinetic data from optimized formulation.

| Hour | % CR | Log % CR | SQRT - t | log Mt/Mn |
|------|------|----------|----------|-----------|
| 0    | 0    | 0        | 0        | 0         |
| 1    | 1    | 1.010    | 1.414214 | 1.079963  |
| 2    | 3    | 1.251    | 1.732051 | 0.919372  |
| 3    | 5    | 1.396    | 2        | 0.677766  |
| 4    | 13   | 1.432    | 2.236068 | 0.53378   |
| 6    | 31   | 1.393    | 2.44949  | 0.497434  |
| 8    | 54   | 1.494    | 2.645751 | 0.536956  |
| 10   | 87   | 1.601    | 2.828427 | 0.43489   |
| 12   | 87   | 1.514    | 3        | 0.328082  |
| 24   | 89   | 1.556    | 3.162278 | 0.44922   |

CONCLUSION

A new strategy for extended delivery has been accomplished by extended-release solid oral tablet formed by the combination of solubility enhancers and cellulose polymers. The arrangement of a hydrophilic polymer with a surfactant as solubility promoter and the use of cellulose polymer represents an innovative and effective approach for the delivery of poorly water-soluble. The study further can be used to deliver a cost-effective and robust system for water-insoluble drugs in a zero-order manner. The rapid development of these investigational therapeutic formulations will put forward new avenues for future commercialization of drug after completion of required clinical studies.
ACKNOWLEDGMENT

Authors have the privilege to acknowledge deep indebtedness to Dr. Bhushan Bhoyar (Research Officer, Enaltec Pharma Research Ltd.) for his immense support.

Conflict of Interest

No conflict of interest is declared regarding the publication of this manuscript.

Funding Information

No funding is associated with this work.

REFERENCES

1. Coluzzi F, Mattia C. OROS® hydromorphone in chronic pain management: when drug delivery technology matches clinical needs. Minerva Anestesiolog 2010;76(12):1072-1084.
2. Conley RG, Gupta SK, Sathyan G. Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form. Curr Med Res Opin 2006;22(10):1879-1892.
3. Bass DM, Prevo M, Waxman DS. Gastrointestinal safety of an extended-release, nondeformable, oral dosage form (OROS®). Drug Safety 2002;25(14):1021-1033.
4. Theeuwes F. Elementary osmotic pump. J Pharm Sci 1975;64(12):1987-1991.
5. Katzman MA, Sternat T. A review of OROS methylphenidate (Concerta®) in the treatment of attention-deficit/hyperactivity disorder. CNS Drugs 2014;28(11):1005-1033.
6. van Stralen JP. The clinical impact of switching attention deficit hyperactivity disorder patients from OROS®-MPH to Novo-MPH ER-C®: A paediatric practice review. Paediatr Child Health 2013;18(2):70-73.
7. Santus G, Baker RW. Osmotic drug delivery: a review of the patent literature. J Contr Rel 1995;35(1):1-21.
8. Zentner GM, Rork GS, Himmelstein KJ. The controlled porosity osmotic pump. J Contr Rel 1985;1(4):269-282.
9. Verma RK, Mishra B, Garg S. Osmotically controlled oral drug delivery. Drug Devel Industr Pharm 2000;26(7):695-708.
10. Turgeon J, Grüning R, Sathyan G, Thipphawong J, Richarz U. The pharmacokinetics of a long-acting OROS hydromorphone formulation. Exp Opin Drug Deliv 2010;7(1):137-144.
11. Ramos-Quiroga JA, Bosch R, Castells X, Valero S, Nogueira M, Gomez N, et al. Effect of switching drug formulations from immediate-release to extended-release OROS Methylphenidate. CNS Drugs 2008;22(7):603-611.
12. Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J Contr Rel 2002;79(1-3):7-27.
13. Mahapatra DK, Bharti SK. Drug Design. New Delhi, India: Tara Publications Private Limited, 2016.
14. Chhajed SS, Upasani C, Wadher SJ, Mahapatra DK. Medicinal Chemistry. Nashik: Career Publications Private Limited, 2017.
15. Mahapatra DK, Bharti SK. Handbook of Research on Medicinal Chemistry: Innovations and Methodologies. New Jersey: Apple Academic Press, 2017.
16. Mahapatra DK, Bharti SK. Medicinal Chemistry with Pharmaceutical Product Development. New Jersey: Apple Academic Press, 2019.
17. Chhajed SS, Bastikar V, Bastikar AV, Mahapatra DK. Computer Aided Drug Design. Pune: Everest Publishing House, 2019.
18. Mahapatra DK, Shivhare RS. Medicinal Chemistry-II. Nagpur: ABD Publications Private Limited, 2019.
19. Gupta S, Sathyan G. Providing constant analgesia with OROS® hydromorphone. J Pain Sympt Manag 2007;33(2):S19-S24.
20. Yilmaz S, Bilgiç A, Hergüner S. Effect of OROS methylphenidate on encopresis in children with attention-deficit/hyperactivity disorder. J Child Adol Psychopharmacol 2014;24(3):158-160.
21. McGough JJ, McBurnett K, Bukstein O, Wilens TE, Greenhill L, Lerner M, et al. Once-daily OROS® methylphenidate is safe and well tolerated in adolescents with attention-deficit/hyperactivity disorder. J Child Adol Psychopharmacol 2006;16(3):351-356.
22. Carter NJ, Keating GM. OROS® Hydromorphone Prolonged Release. CNS Drugs. 2010;24(4):337-361.
23. Olives-Morales A, Ghosh A, Aarons L, Rostami-Hodjegan A. Development of a novel simplified PBPK absorption model to explain the higher relative bioavailability of the OROS® formulation of oxbutynin. AAPS J 2016;18(6):1532-1549.
24. Butler SF, McNaughton EC, Black RA, Cassidy TA. Evaluation of the Relative Abuse of an OROS Extended-release Hydromorphone HCI Product. Clin J Pain 2018;34(7):618-628.
25. Goodman DW, Starr HL, Ma YW, Rostain AL, Ascher S, Armstrong RB. Randomized, 6-Week, Placebo-Controlled Study of Treatment for Adult Attention-Deficit/Hyperactivity Disorder: Individualized Dosing of Osmotic-Release Oral System (OROS) Methylphenidate With a Goal of Symptom Remission. J Clin Psychiatr 2017;78(1):105-114.
26. Majeed Z, Meghana MS, Sumera AP, Zafar S. Formulation and In-Vitro Evaluation of Controlled Porosity Osmotic Pump Release Tablets of Nifedipine. Int J Pharm Sci Buss Mang 2016;4(5):1-32.
27. Umareddar AA, Dangre PV, Mahapatra DK, Dhabarde DM. Fabrication of chitosan-alginate polyelectrolyte complexed hydrogel for controlled release of cilnidipine: a statistical design approach. Mater Technol 2018;27:1-1.
28. Mahajan NM, Wadhwane F, Mahapatra DK. Rational designing of sustained release matrix formulation of Ethodolac employing Hypromellose, Carbomer, Eudragit and Povidone. Int J Pharm Pharm Sci 2017;9(12):92-97.
29. Gardner-Nix J, Mercadante S. The role of OROS® hydromorphone in the management of cancer pain. Pain Pract 2010;10(1):72-77.
30. Hammenness P, Georgiopoulos A, Doyle RL, Utzinger L, Schilinger M, Martelon M, et al. An open study of adjunct OROS-methylphenidate in children who are atomoxetine partial responders: II. Tolerability and pharmacokinetics. J Child Adol Psychopharmacol 2009;19(5):493-499.
31. Stein MA, Sarampote CS, Waldman ID, Robb AS, Conlon C, Pearl PL, et al. A dose-response study of OROS methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics 2003;112(5):e404.
32. Makhija SN, Vavia PR. Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine: I. Cellulose acetate as a semipermeable membrane. J Contr Rel 2003;89(1):137-144.
33. Wilens TE, McBurnett K, Bukstein O, McGough J, Greenhill L, Lerner M, Stein MA, Conners CK, Duby J, Newcorn J, Bailey CE. A multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. Arch Pediatr Adol Med 2006;160(1):82-90.