Development and Evaluation of Elementary Osmotic Pump for the Simultaneous Delivery of Nifedipine and Metoprolol Tartrate

Rajagopal Kumaravelrajan[1], Nallaperumal Narayanan[2], Venkatesan Suba[3]

[1]Department of Pharmaceutics, CL Baid Metha College of Pharmacy, Chennai, Tamil Nadu, India, [2]Department of Pharmaceutics, Jaya College of Paramedical Sciences, Chennai, Tamil Nadu, India, [3]Department of Pharmacology, National Institute of Siddha, Chennai, Tamil Nadu, India

Abstract

Introduction: A system that can deliver multidrugs at a controlled rate is very important to the treatment of various chronic diseases such as diabetes, asthma, and hypertension. In general, both highly and poorly water-soluble drugs are not good candidates for elementary osmotic delivery, so in the present investigation nifedipine-hydroxyproyl-β-cyclodextrin (1:1) inclusion complex was used to modulate the solubility of nifedipine (NP) within the core and metoprolol was used not only as the active ingredient but also as osmotic agent. **Materials and Methods:** NP-cyclodextrin complex was prepared by coprecipitation method. The tablets were prepared and coated with cellulose acetate phthalate-containing dibutyl phthalate as plasticizer at various concentrations. The coated tablets drilled for orifice. The orifice size, level of plasticizer, and coating thickness were used as formulation variables. Finally, the optimized formulation was studied for different pH, agitational speed, and release mechanism. The optimized formulation was also subjected to *in vivo* prediction for the desired C_{max} and C_{min} using superposition method. **Results:** Formulation variables such as orifice size, level of plasticizer, and coat thickness of semipermeable membrane were found to affect the drug release from the developed formulations. The optimal elementary osmotic pump was found to deliver both drugs at a rate of approximately zero order for up to 10 h independent of pH and agitational intensity but dependent on the osmotic pressure of the release media. **Conclusion:** Hence, the prototype design of the system could be applied to other combinations of drugs used for cardiovascular diseases, diabetes, etc.

Key words: Controlled osmotic drug delivery, elementary osmotic pump, nifedipine, metoprolol tartrate, semipermeable membrane

INTRODUCTION

Osmotic pumps are controlled drug delivery devices based on the principle of osmosis. Wide spectrums of osmotic devices are in existence, out of them osmotic pumps are unique, dynamic, and widely employed in clinical practice.[1] Osmotic pumps offer many advantages like they are easy to formulate, simple in operation, improved patient compliance with reduced dosing frequency, more consistent, and prolonged therapeutic effect is obtained with uniform blood concentration, and moreover, they are inexpensive and their industrial adaptability vis-a-vis production scale up is easy.[2] By principle, this delivery system dispenses drug continuously at a zero order rate until the concentration of the osmotically active salt in the system decreases below saturation solubility, whereupon a non-zero order release pattern results.

Chronic diseases such as hypertension, diabetes, and asthma are treated using multidrug therapies, which are vulnerable to incidences of side effects, poor patient compliance and slow

Address for correspondence:
Rajagopal Kumaravelrajan, CL Baid Metha College of Pharmacy, Thorapakkam, Chennai, Tamil Nadu, India. Phone: +91-9444650763.
E-mail: rkumaravelrajan@gmail.com

improvement of patients. Nifedipine (NP) and metoprolol (MP) tartrate are antihypertensive agents belonging to calcium channel blockers and β-blockers, respectively. In general, they are either used individually or as combination therapy to treat hypertension. NP is a vascular selective dihydropyridine calcium channel blocker which lowers arterial blood pressure by decreasing peripheral vascular resistance. MP is a cardioselective β-blocker which acts preferentially on β_1-adrenoceptors in the heart rather than β_2-adrenoceptors located in peripheral vessels and bronchi. Competitive antagonism of β_1-adrenoceptors by MP produces a negative chronotropic effect on the heart, with resulting decreases in cardiac output and systolic blood pressure (SBP) after acute drug administration.[3] Hence, the combination of NP with MP is more effective than individual therapy.[4]

Following oral administration, peak plasma concentrations of NP are attained within 1-2 h, and the elimination half-life is approximately 2 h resulting in the need to administer the drug every 8 h to maintain therapeutic concentration.[5] However, due to the rapid onset of action, short half-life, and side effect profile, a zero order dosage form with slow onset of delivery is ideal, with duration of delivery of close to 24 h. Early pharmacokinetic studies of MP have also established that it has a relatively short plasma half-life of 3-4 h and its absorption is rapid as well as consistent throughout most of the gastrointestinal tract (GIT), including the distal region.[6] As a prerequisite, a combination of both these properties makes NP and MP suitable candidates for development into a controlled release formulation.

Although controlled drug delivery systems are available separately for both drugs, a system that can deliver both drugs simultaneously at a controlled rate may ensure improved patient compliance. In addition to improved patient compliance, as a once-daily formulation, it may improve the safety profile and activity of drugs exhibiting short biological half-lives. From a technical standpoint, the controlled delivery of NP is difficult since it is practically insoluble in water and aqueous fluids due to its high crystalline nature and exhibits poor dissolution rate. The very poor aqueous solubility of NP may lead to variable dissolution rates and bioavailabilities. To overcome this problem, various types of osmotic pumps of NP-like push-pull system,[7] (Procardia XL® and Adalat®) monolithic osmotic system,[8] sandwiched osmotic tablet system,[9] asymmetric membrane osmotic pump,[10] bilayer-core osmotic pump tablet coating the indented core tablet,[11] swellable elementary osmotic pump (EOP),[12] and squeeze type osmotic tablet[13] were reported. All these systems suffer from either one or other drawbacks. Various attempts were made to improve the dissolution rate of NP, include solid dispersion in water-soluble carriers such as urea,[14] polyvinyl pyrrolidone (PVP),[15] PVP microcrystalline cellulose (PVP-MCC) and hydroxyl propyl cellulose-MCC,[16] and complexation with cyclodextrin. There was a report[17] on the feasibility of using NP-cyclodextrin complex as a core for microcapsule to obtain controlled release. Besides, there

was also a study[18] on sustained release two layered tablet formulations of NP using NP-hydroxyproyl-β-cyclodextrin (1:1) inclusion complex. So, in our present studies, we also used 1:1 NP-hydroxyproyl-β-cyclodextrin complex to improve NP dissolution rate and solubility.

Various approaches were reported to deliver water-soluble and water-insoluble drug through osmotic pump mechanism. Modified push-pull osmotic system was reported to deliver a slightly water-soluble theophylline base and freely soluble salbutamol sulfate simultaneously.[19] Similarly, osmotically regulated asymmetric capsular system was developed to deliver slightly aqueous soluble rifampicin and freely soluble isoniazid simultaneously.[20] However, both these system needed a sophisticated technique. Recently, Ouyang *et al.*,[21] evaluated EOP tablet for simultaneous delivery of metformin and glipizide which is simple in design.

In this line of research, we reported controlled porosity osmotic pump[22] and sandwich osmotic pump tablet[23] for NP and MP combination.

Based on the facts, it was decided to deliver NP β-cyclodextrin inclusion complex (NHβ-CD) complex (1:1) and MP simultaneously for an extended period *via* elementary osmotic tablets. We designed an elementary osmotic device using MP as both active ingredients and also as the osmotic agent to deliver it along with NP simultaneously for an extended period. Since MP is highly water-soluble drug, it was also decided to use hydrophilic polymers at lower concentration to reduce the release rate of it.

MATERIALS AND METHODS

Materials

NP and MP were a kind gift sample from the Madras Pharmaceuticals Private Limited, Chennai, India. KCl and starch were supplied from S.D. Fine Chemicals, Mumbai, India. MCC, magnesium stearate, and aerosil were purchased from Rolex, Mumbai, India. Cellulose acetate (CA) was obtained from Eastman Chemical Company, Kingsport, U.S.A. All other solvents and chemicals used were of the analytical grade.

Methods

Preparation of NP β-cyclodextrin inclusion complex

Solid complexes of NHβ-CD were prepared in 1:1 ratio by coprecipitation method. NP (3.23 g) was first dissolved in a small volume of acetone and then thoroughly mixed with 100 ml of ethanolic solution of carriers in a round bottom flask. The solvent was evaporated under reduced pressure at 40°C (Rotary Evaporator RE120, Buchi, Switzerland).

Drug-excipient interaction studies

Assessment of possible incompatibilities between an active pharmaceutical ingredient and different excipients forms an important part of the preformulation stage during the development of a solid dosage form. Differential scanning calorimeter (DSC) allows the fast evaluation of possible incompatibilities because it shows changes in the appearance, shift or disappearance of melting endotherms and exotherms and variations in the corresponding enthalpies of reaction.[24] The DSC thermograms of pure drug and coated tablets were recorded. The samples were separately sealed in aluminum cells and set in Perkin Elmer (Pyris 1) DSC (Waltham, MA). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50-300°C.

Preparation of core tablets

Granules were prepared by the wet granulation method. NHβ-CD, MP, starch, dicalcium phosphate, and sodium starch glycolate (SSG) were mixed well and moistened with PVP solution in isopropyl alcohol. It was granulated by passing through a 12 sieve and the granules were kept at 40°C for 1 h. After this, the granules were passed through 18 sieve and lubricated with talc, aerosil, and magnesium stearate (all 120 sieve passed). Granules were compressed by 8 station compression machine fitted with 12/32 inch deep cup punches. The core compositions are listed in Table 1.

Table 1: The basic core and coating composition of NP and MP EOP

Ingredients	Amount (mg)
NHβ-CD complex	160
Metoprolol tartrate	55
Starch	20
Dicalcium phosphate	15
PVP	15
Isopropyl alcohol	Q.S
SSG	10
Aerosil	10
Talc	10
Magnesium stearate	3

Formulation code	Coating composition amount of plasticizer (DEP) % w/w of CA	Coating thickness (%)
C1	10	8
C2	20	8
C3	30	8
CW	-	8
C4	20	12

PVP: Polyvinyl pyrrolidone, EOP: Elementary osmotic pump, SSG: Sodium starch glycolate, NP: Nifedipine, MP: Metoprolol, DEP: Diethyl phthalate

Coating and drilling

Core tablets were coated using a coating pan. CA (4% w/v) containing 20% diethyl phthalate (DEP) was used as the coating solution. The diameter of the coating pan was 300 mm; the pan-rotating rate was 22 rpm and the spray rate of the CA solution was 4 ml/min. Coated tablets were dried at 40°C for 12 h. The average weight increased after coating was 31.9 mg per tablet. The coated tablets were drilled by a mechanical drill to obtain a uniform orifice diameter of 450 μm. The composition of coating solution used is given in Table 1.

In vitro drug release

The *in vitro* release of the EOP was carried out using 900 ml of pH 6.8 phosphate buffer containing 0.5% sodium lauryl sulfate as the medium in USP dissolution apparatus II at 37°C and 100 rpm. 10 ml samples were taken at 0, 2, 4, 6, 8, 10, and 12 h and filtered through 0.45 μm filter membrane. 10 ml of fresh dissolution medium was added after each sampling. Each study was done in triplicate, and the mean values were reported. Since NP in the tablet does not induce an osmotic effect due to its property of poor water solubility, an initial lag time of 150 min was maintained to moisten of the system. The filtrate was diluted with pH 6.8 phosphate buffer (dissolution medium), and the quantity of NP and MP was determined at 340 and 275 nm using UV spectroscopic method. All experiments were carried out under strict protection from light to prevent undesirable photo-degradation of NP throughout the entire experimental procedure. The same protection was given throughout the entire process.

Formulation variables

To optimize the formulation to release the drug at a constant zero order release rate, orifice size, level of plasticizer, and coating thickness were used as formulation variables. The respective formulation code and variables were given in Table 2.

Table 2: Core formulation variables of EOP

Formulation	Variables		
	Orifice diameter (μm)	Coating composition	Coating thickness (% w/w)
EF1	450	C2	8
EF2	250	C2	8
EF3	600	C2	8
EF4	800	C2	8
EF5	800	C1	8
EF6	800	C3	8
FW	800	CW	8
EF7	800	C4	12

EOP: Elementary osmotic pump

Effect of orifice on drug release

To study the effect of orifice on the drug release, the release of the tablets with different orifice sizes (250, 450, 600, and 800 μm) were investigated and compared.

Effect of coating solution on drug release

The tablet cores were prepared and coated with DEP at the levels of 0 (FW), 10 (EF4), 20 (EF5), and 30 (EF5) % w/w of CA. Then, the drug release characteristics of the coated tablets were compared. Meanwhile, the tablets were prepared and coated with CA to two levels of tablet weight gain, such as 4 and 5% w/w.

Effect of pH

To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted in media of different pH (SGF [simulated gastric fluid], pH 1.2 and simulated intestine fluid [SIF], pH 6.8) and pH change method (release media was SGF (pH 1.2) for first 2 h, followed by SIF (pH 6.8) for the remaining period). The samples (5 ml) were withdrawn at predetermined intervals and analyzed after filtration through 0.45 μm cellulose nitrate filter. The percentage cumulative drug release of optimized formulations at various pH was plotted and compared.

Effect of agitational intensity

To study the effect of agitational intensity of the release media, release studies of the optimized formulations were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP-II at 50, 100, and 150 rpm. Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45 mm cellulose nitrate membrane filters. The percentage cumulative drug release of optimized formulations at different agitational intensity was plotted and compared.

Osmotic pressure measurement

To confirm the mechanism of drug release, release studies of the optimized formulations were conducted in media of different osmotic pressures. To increase the osmotic pressure of the release media, sodium chloride (osmotically effective solute) was added in SIF[25] and osmotic pressure was measured (Fiske Micro Osmometer, 210). The pH was adjusted to 6.8 ± 0.05. Release studies were carried out in 900 ml of media using USP II dissolution test apparatus (100 rpm). Release profiles of the optimized formulations at different osmotic pressures were plotted and compared.

Release models and kinetics

To describe the kinetics of drug release from controlled release preparations various mathematical equations have been proposed. The zero order describes the systems, where the drug release is independent of its concentration.[26] The first order equation describes the release from systems, where release rate is concentration dependent.[27] According to Higuchi model, the drug release from the insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion.[28] Drug release data obtained were applied to different drug release models to establish the drug release mechanism and kinetics. Best goodness of fit test (R^2) was taken as criteria for selecting the most appropriate model.

Scanning electron microscopy

The samples were placed on a spherical brass stub (12 mm diameter) with a double-backed adhesive tape. Small sample of the coating membrane was carefully cut from the exhausted shells (after dissolution studies) and dried at 50°C for 2 h. The mounted samples were sputter coated for 2 min with gold using fine coat ion sputter (JFC-1600, Jeol, Japan) with pressure of 8 kg Pascal and examined under scanning electron microscope (SEM) (JSM-6360, Jeol, Japan).

In vivo pharmacokinetic prediction of selected formulation

Drug release parameters (R_0 and t_{del}) obtained from *in vitro* data and the pharmacokinetic properties of drugs were used for predicting blood drug concentrations-time profiles from single dose and at steady state from multiple dosing.[29] The method of superposition was used for the steady-state concentration predictions. Values of Cssmax and Cssmin were compared with the desired values calculated from a theoretically developed controlled drug release profile.[30]

RESULTS AND DISCUSSION

Formulation development

A simple EOP system that could deliver NP and MP simultaneously for an extended period was developed to reduce the problems associated with multidrug therapy of hypertension. In general, both highly and poorly water-soluble drugs are not good candidates for elementary osmotic delivery. MP is a highly soluble drug with comparatively high dose (50 mg), whereas NP is a water-insoluble drug with a low dose (20 mg). Hence, it is a great challenge to provide satisfactory extended release of NP and MP.

In the present investigation, initially, an estimated amount of NHβ-CD was compressed without any additional substance and coated with a solution of CA in acetone (4% w/v). Since the coating material was too hard and fragile, DEP was added as a plasticizer. The coated tablets with the NHβ-CD code, which contain no orifice, were subjected to a dissolution rate test to detect whether the active material passes through the film by diffusion. Since no active material was released through the tablets during first 150 min, and that only 1.66%

of the active material was released by the end of 180 min, it was concluded that diffusion from the membrane did not influence the release of active material.

Further, the tablets were drilled with orifice diameter of 450 μm using a micro drill and subjected to the dissolution rate test. Since active material in the tablets does not induce an osmotic effect due to its property of poor solubility in water, an initial lag time of 60 min is necessary to moisten of the system, allow penetration of water into the core and for dissolving active material. Release of active material from NHβ-CD tablets with an orifice of 450 μm was observed for 3 h, and it was determined that 2.7, 5.95, and 14% was released at 60, 150, and 180 min, respectively. The onset of release of active material took place at the end of a certain time (lag-time); it apparently began after an osmotic pressure built up in the tablet. This event demonstrated that the mechanism influencing the release of active material was osmotic pressure instead of diffusion.

Earlier studies have shown that simple EOP of glipizide and metformin was developed to deliver drugs simultaneously for extended period using metformin (highly water-soluble drug) not only as an active agent but also as an osmotic agent.[20] Based on this report, we also attempted to deliver NP and MP by adding highly water-soluble MP into the NHβ-CD tablets as both active agents and also as an osmotic agent. The release of NP was enhanced owing to the osmotic effect of MP, and further, it was also delivered simultaneously. However, the *in vitro* release of MP was very fast, and 80% of the drug was released within 3 h. Hence, we have used release retardant, SSG to control the release of MP which in turn, may also cause NHβ-CD complex to be delivered in the form of suspension through orifice.

Drug-excipient interaction studies

Figure 1 depicts the DSC thermograms of NP, MP, and coated tablets. No changes in the endotherms were observed as the drug exhibited a sharp melting endotherm of NP at 185°C and MP at 146°C in the core and coated formulation. From the DSC thermograms, it was clear that no specific interaction between the drug and excipients used in the present formulation.

Influence of tablet formulation variables on drug release

To study the influence of tablet formulation variables on drug release, tablets with various variables were prepared, subsequently coated with the coating formulation C1 of thickness 8% and a circular orifice with a diameter 450 μm was drilled on one side of the surface. Based on our study, NP elementary osmotic tablet osmotic agent Kcl 40 mg was fixed as optimum osmogent. Once the tablet formulation is decided, the drug release of the system will be affected by the orifice size and membrane variables.

Influence of orifice size on NP and MP release profile

To investigate the effect of orifice size on the release of active material, orifices with diameters of 250 (EF1), 450 (EF2), 600 (EF3), and 800 μm (EF4) were formed using a micro drill and subjected to the dissolution rate test. It must be smaller than the maximum limit to minimize the contribution to the delivery rate made by diffusion through the orifice. Furthermore, it must be larger than a minimum limit, to minimize the influence of hydrostatic pressure inside the
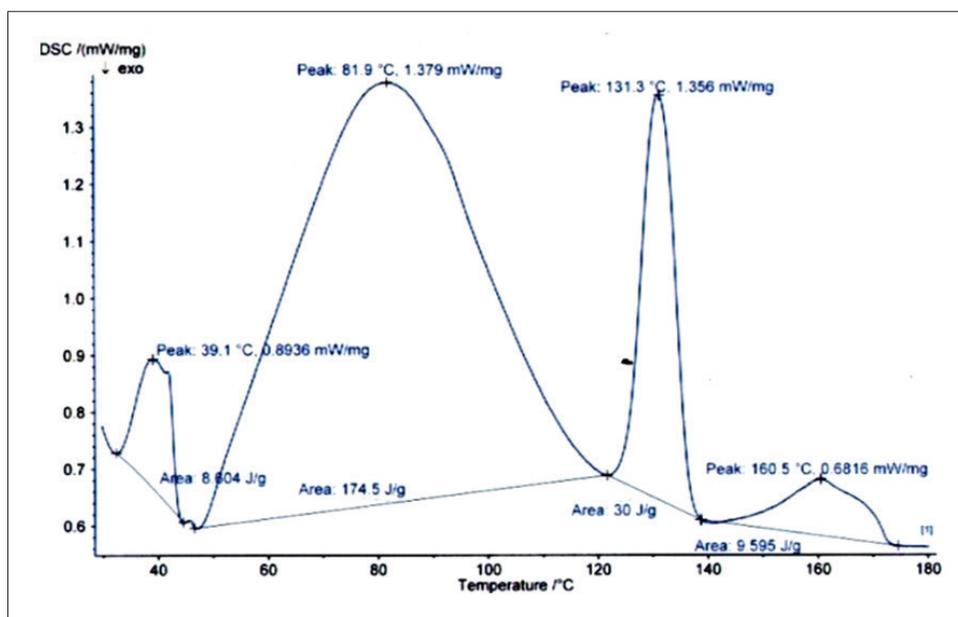

Figure 1: Differential scanning calorimeter thermogram of coated tablets of NHβ-CD complex and metoprolol combination elementary osmotic pump

system. Results showed that only 5.21% of NP and 7.93% of MP release was observed at 4th h at the orifice size of 250 μm. The agglomerated drug in suspension may occlude such a small orifice, therefore, leading to a low drug release. When it was increased from 250 to 450, 600 and 800 μm, the percentage release was increased for both NP and MP [Figure 2]. It was also evident from the results that not much difference was existed in the release profiles of NP and MP for orifice diameters ranging from 450 μm to 600 μm. The release rates were obtained and the rate deviation of EF3 and EF4 from those of the orifice with 450 μm (EF2) was analyzed by *t*-test and listed in Table 3. It showed that significant increase in release rate of NP and MP from EF2 in comparison to EF3 and EF4. The release was slow at an orifice diameter of 250 μm for both the drugs. Orifice diameter of 800 μm showed better release profile (R^2 = 0.9864 for NP and 0.9735 for MP) for NP and MP, and hence, it was optimized to study further variables.

Influence of DEP level and membrane thickness on NP and MP release

Once the core tablet formulation was decided, the membrane variables would be the key factors affecting drug release profile of the osmotic pump tablet. To study the influence of DEP level in semi-permeable membrane on drug release profile, the membrane was plasticized with various DEP levels of 0 (EFW), 10 (EF5), 20 (EF4), and 30% (EF6), and the rate deviation of EF4 and EF6 was compared with EF5 using Student's *t*-test. Figure 3 showed that increasing DEP level led to an increment in drug release. Release rates of EF4 and EF6 were significantly higher than EF5 [Table 4]. As more DEP was incorporated into the membrane, more micropores formed and higher membrane permeability obtained. Hence, EF6, which showed better control on release pattern, was adopted in the following studies.
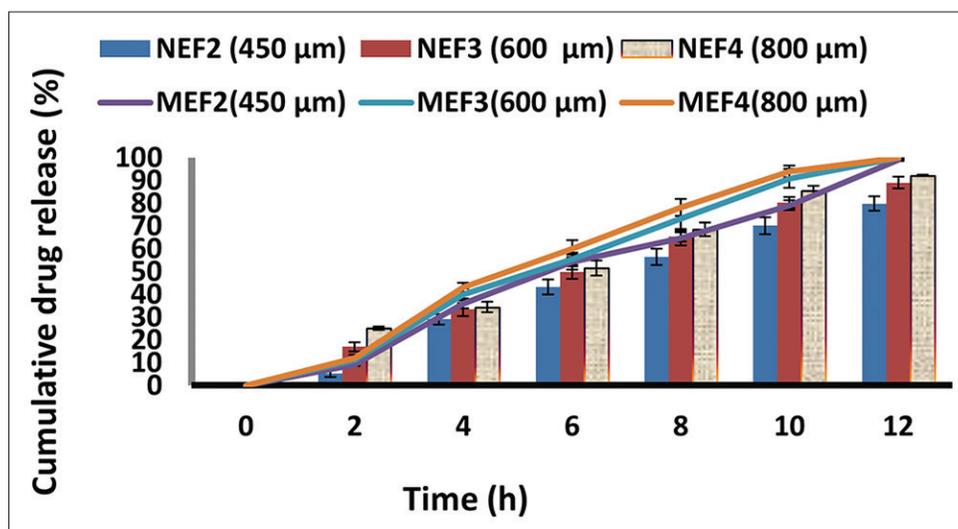

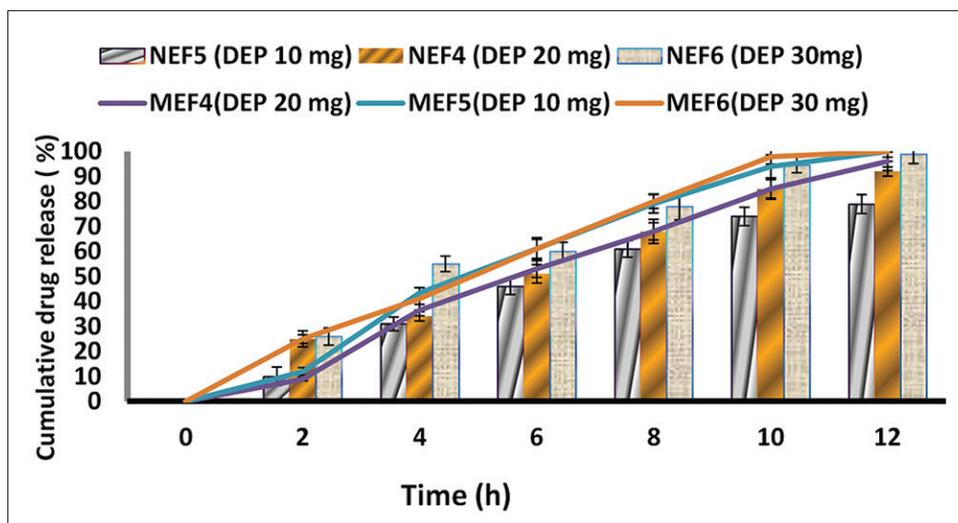**Figure 2:** Effect of orifice diameter on the release of nifedipine and metoprolol

Figure 3: Effect of level of plasticizer on the release of nifedipine and metoprolol

The most straightforward method to modify the drug release profile of osmotic pump tablet is to vary the coating weight.[31] The drug release rate was directly related to the rate that water enters the tablet core and as stated earlier, the rate of water ingress is dependent on the osmotic pressure of the core and the permeability of the coating: The thicker has lower water permeability. The drug release profiles showed that thicker coatings not only have slower release rates but also have longer lag times before the initiation of drug release.

Figure 4 showed the influence of membrane with thicknesses of 8% (EF6) and 12% (EF7) on the drug release profile. The drug release increased with the decrement in the membrane thickness because a thinner membrane increased water influx. Release rate of EF6 is significantly more than EF7 [Table 5]. It showed the release rate as a function of reciprocal of membrane weight. We found that better release profile and an approximate zero order release were obtained with membrane thickness of 12%. (EF7). So, EF7 was chosen as optimal formulation.

SEM photograph demonstrated the morphology of CA membrane which is also an important feature to the water sorption and mobility. The SEM for CA and CA containing plasticizer DEP-20 mg were shown in Figure 5a and b. As seen in this figure, CA structure seems to be more elastic and smooth and fragile with the addition of DEP as plasticizer

Effect of pH

To study the effect of pH on drug release, release studies were conducted in media of different pH. Figure 6 showed release of NP and MP from optimized formulation of EOP (EF7) in pH 1.2; pH change method and pH 6.8, respectively. The f_1 and f_2 values were found to be 4 and 70 (between SGF, pH 1.2 and pH 6.8), 4 and 72 (between pH change method and pH 6.8) for NP and 1 and 83 (between pH 1.2 and pH 6.8), 2 and 80 (between pH change method and pH 6.8) for MP, respectively. As can be seen from the figures, release profile is similar in all the media demonstrating that the developed formulations show pH-independent release.

Table 3: Influence of orifice size on NP and MP release rate (n=3)						
Time (h)	Mean±SEM					
	NP release rate±SEM (% h)			MP release rate±SEM (% h)		
	EF2 (400 µm)	EF3 (600 µm)	EF4 (800 µm)	EF2 (400 µm)	EF3 (600 µm)	EF4 (800 µm)
0	0	0	0	0	0	0
2	7.68±0.11	8.52±0.92	8.9±0.37	4.61±0.2	5.57±0.45	6.11±0.45
4	7.49±0.6	8.35±0.42	8. 61±0.38	9.21±0.76	10.01±0.91	10.85±0.53
6	7.22±0.53	8.29±0.57	8.49±0.55	9.04±0.67	9.22±0.63	10.12±0.67
8	7.05±1.61	8.16±0.41	8.45±0.54	8.08±0.70	9.16±0.72	9.84±0.47
10	7.01±0.68	8.03±0.40	8.44±0.41	8±0.78	9.09±0.73	9.43±0.44
12	6.65±0.68	7.41±0.43	7.68±0.41	8.33±0.85	8.33±0.60	8.3±0.46
P value	-	<0.003	<0.002	-	<0.01	<0.002

NP: Nifedipine, MP: Metoprolol, SEM: Standard error of mean

Table 4: Influence of level of plasticizer on NP and MP release rate						
Time (h)	Mean±SEM					
	NP release rate±SEM (%h) EF5 DEP (10 mg)	EF4 DEP (20 mg)	EF6 DEP (30 mg)	MP release rate±SEM (%h) EF5 DEP (10 mg)	EF4 DEP (20 mg)	EF6 DEP (30 mg)
0	0	0	0	0	0	0
2	5.03±0.77	8.98±0.77	10.93±0.37	4.53±0.39	6.11±0.45	12.91±0.56
4	7.80±0.59	8.61±0.59	9.78±0.38	9.12±0.72	10.85±0.53	10.36±0.86
6	7.70±0.62	8.49±0.62	9.54±0.55	8.87±0.63	10.12±0.67	10.21±0.75
8	7.62±0.52	8.45±0.52	9.26±0.54	8.51±0.72	9.84±0.47	9.93±0.85
10	7.45±0.68	8.44±0.68	9.45±0.41	8.49±0.80	9.43±0.44	9.83±0.96
12	6.58±0.32	7.68±0.32	8.33±0.41	8.07±0.76	8.33±0.46	8.33±0.85
P value	-	<0.0004	<0.0002	-	<0.0008	<0.0001

Statistical significance test was done by student's *t*-test. Release rate of EF4 and EF6 was compared with EF5. *P*<0.05 was considered to be significant. DEP: Diethyl phthalate, NP: Nifedipine, MP: Metoprolol, SEM: Standard error of mean

Effect of agitational intensity

To study the effect of agitational intensity of the release media, release studies of the optimized formulation of EOP (EF7) were carried out in USP dissolution apparatus Type II at varying rotational speeds (50, 100, and 150 rpm). It is clearly evident from Figure 7 that the release of NP and MP from EOP is independent of the agitational intensity. The f_1 and f_2 values were found to be 5 and 66 for NP and 4 and 70 for MP (between 100 and 50 rpm), 7 and 59 for NP and 3 and 68 for MP (between 100 and 150 rpm), respectively. These results showed no significant difference in percentage release under different agitation rates.

Effect of osmotic pressure

To study the effect of osmotic pressure, release studies of the optimized formulations were conducted in media of different osmotic pressures. Cumulative percentage release of NP and MP from the optimized formulation of EOP at 12 h was 90 and 99.98%. This percentage of release of NP decreased to 79.8% at 8.17 atm, 68.03% at 15.86 atm, and 59.19% at 24.48 atm. Percentage release of MP was also decreased to 90.34% at 8.17 atm, 78.5% at 15.86 atm, and 75.1% at 24.48 atm, respectively [Figure 8].

Kinetics of drug release

Dissolution data of the optimized formulation were fitted to various mathematical models (zero order, first order, and Higuchi) to describe the kinetics of drug release. Data were treated according to zero order, first order, and Higuchi using least square method of analysis [Table 6]. Best goodness of fit test (R^2) was taken as criteria for selecting the most appropriate model. When the data were plotted according to the first order and Higuchi equations, the formulations showed a comparatively poor linearity, whereas the

Table 5: Influence of membrane thickness on NP and MP release rate

Time (h)	Mean±SEM			
	NP release rate±SEM (% h) EF6 (4%)*	EF7 (5%)*	MP release rate±SEM (% h) EF6 (4%)*	EF7 (5%)*
0	0	0	0	0
2	10.93±0.39	9.02±0.60	12.91±0.56	10.08±0.75
4	9.78±0.72	8.68±0.81	10.36±0.86	9.36±0.79
6	9.54±0.63	8.55±0.82	10.21±0.75	8.69±0.54
8	9.26±0.72	8.32±0.68	9.93±0.85	8.35±0.61
10	9.45±0.80	8.23±0.74	9.83±0.96	8.35±0.70
12	8.33±0.76	7.5±0.60	8.33±0.85	8.33±0.60
P value		<0.001		<0.0006

*Percentage of cellulose acetate. Statistical significance test was done by Student's *t*-test. Release rate of EF7 was compared with EF4. *P*<0.05 was considered to be significant. NP: Nifedipine, MP: Metoprolol, SEM: Standard error of mean
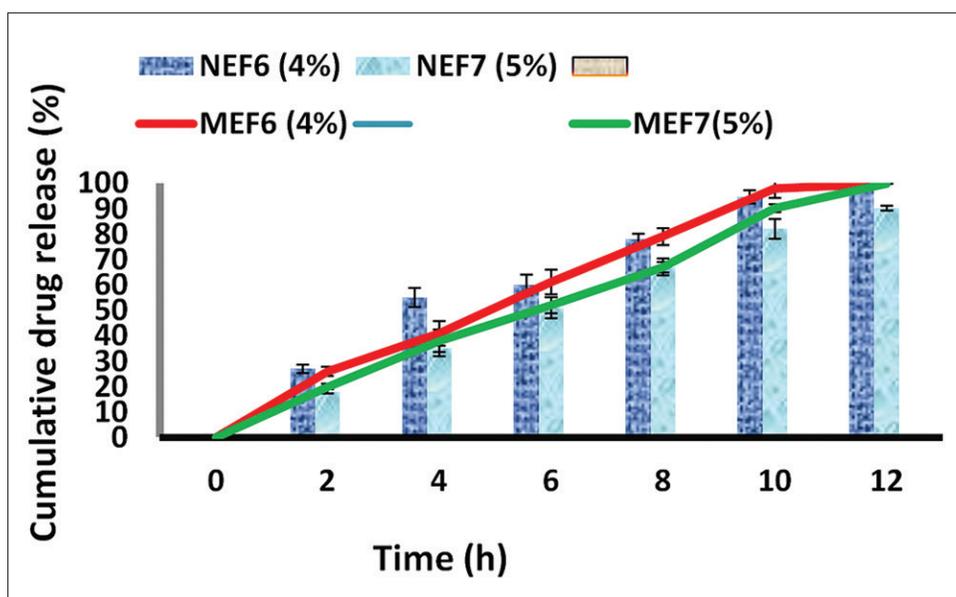

Figure 4: Effect of thickness of the membrane on the release of nifedipine and metoprolol

regression value for zero order equation indicated that the drug release from optimized formulation was independent of drug concentration.

In vivo prediction

Method of superposition was used to predict steady-state plasma levels of drugs after administration of a test dose of
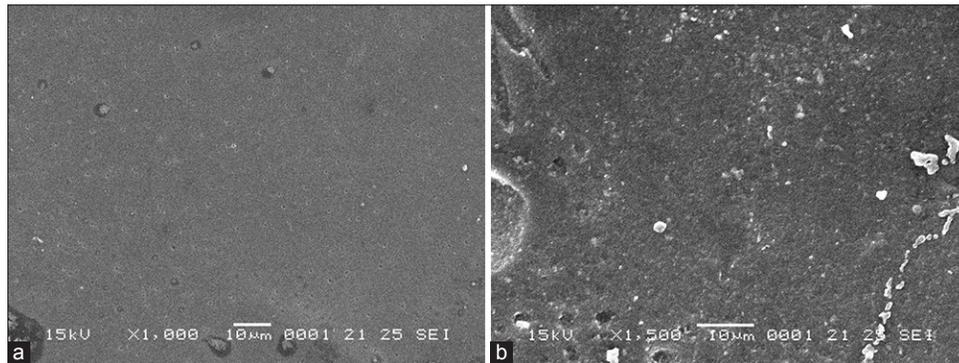

Figure 5: Scanning electron photomicrograph of surface of elementary osmotic pump tablet without (a) plasticizer with (b) plasticizer
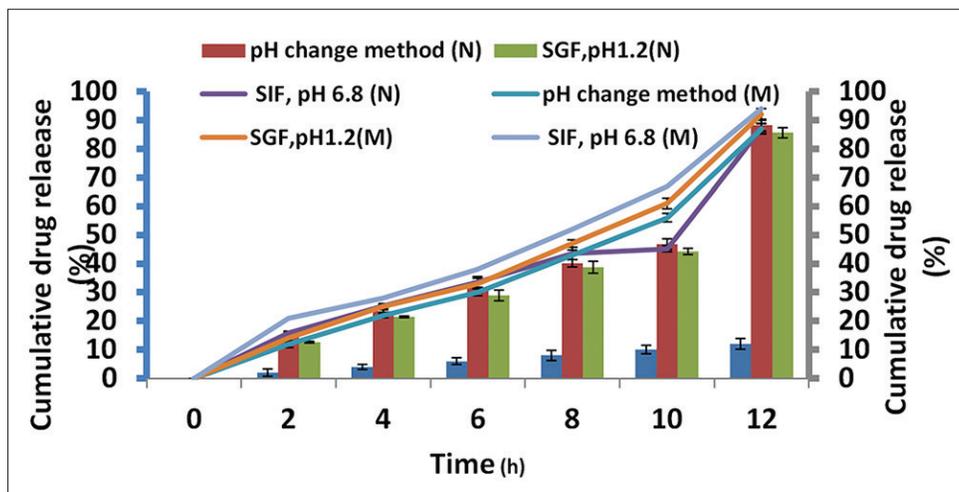

Figure 6: Effect of pH on nifedipine and metoprolol release from EF7
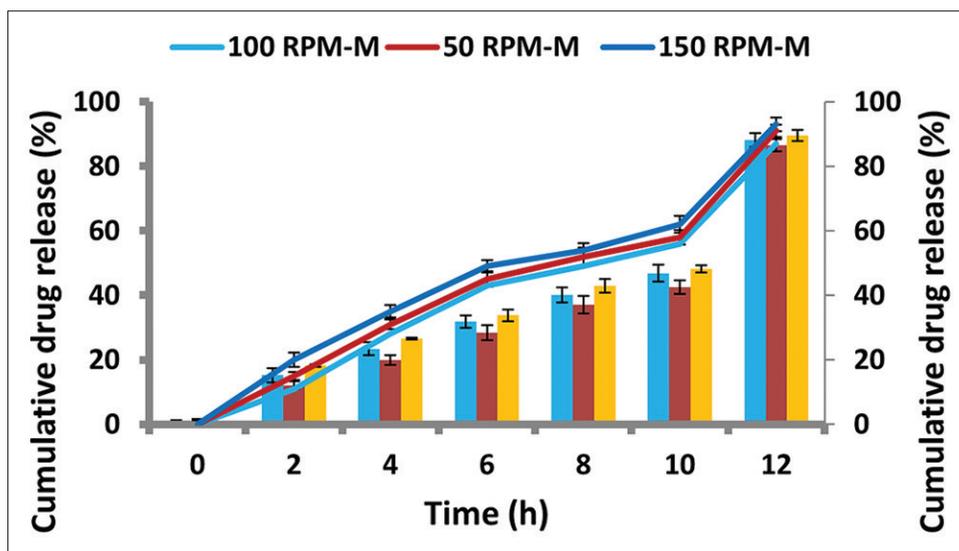

Figure 7: Effect of agitational intensity on the release of nifedipine and metoprolol from EF7 formulation

20 mg and 50 mg of NP and MP from the formulation EF7. Since osmotic pumps are reported to exhibit a significant *in vitro/in vivo* correlation predicted data of steady-state plasma levels from drug release studies can be used for comparison with the desired plasma levels.[32,33] Steady-state levels of NP and MP after administration of a test dose of formulation showed in Table 7 that peak plasma levels were 31.24 ng (NP) and 56.97 ng (MP) but falls to 16.12 ng (NP) and 28.31 ng (MP) at steady state [Figures 9 and 10]. The predicted CSS_{max} and CSS_{min} and after administration of formulation of NP and MP in comparison with the desired ones are 30.45 and 15.15 ng for NP and 51.22 and 21.82 ng for

MP. Thus, it can be concluded that the developed formulation (EF7) will produce plasma levels well within the therapeutic range and similar to those produced by the desired zero order delivery profile.

CONCLUSION

The present study developed an oral osmotic system that can deliver NP and MP simultaneously. This study suggests that drug release from these systems is controlled by osmotic pressure as the major mechanism; release pattern obeyed zero
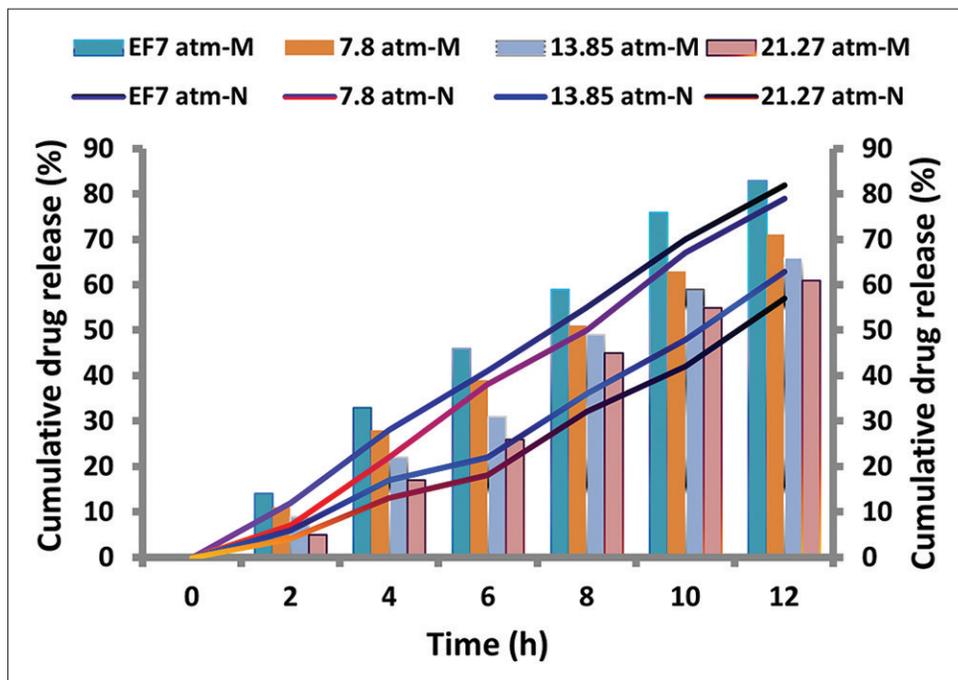

Figure 8: Effect of osmotic pressure of the release media on nifedipine and metoprolol release from EF7 formulation
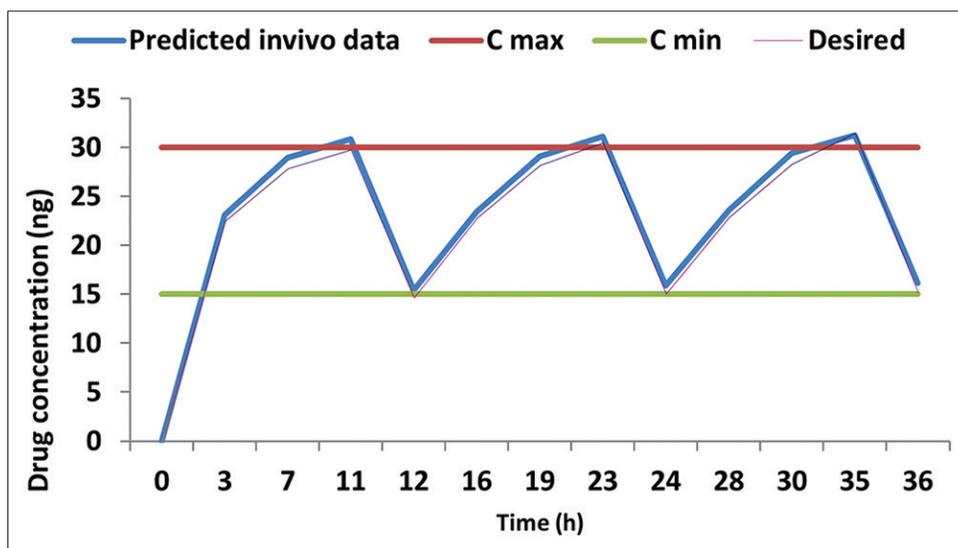

Figure 9: Predicted steady-state plasma levels of nifedipine after administration of a test dose of EF7 formulation in comparison with the desired profile

Table 6: Fitting of MP release data of the optimized formulation (EF7) according to various mathematical models

	Parameter used to assess the fit of model									
Model	R^2-M	R^2-N	r-M	r-N	Intercept-M	Intercept-N	Slope-N	Slope-M	K-N	K-M
Zero order	0.9948	0.9921	0.9974	0.996	2.09	2.84	7.688	8.38	7.69	8.38
First order	0.6059	0.9515	−0.778	−0.975	2.58	2.09	−0.082	−0.23	−0.02	−0.06
Higuch	0.9254	0.9395	0.9619	0.969	−11.91	−10.53	123.35	25.04	27.2	29.3

N: Nifedipine, M: Metoprolol, R^2: Goodness of fit, r: Correlation coefficient, K: Release rate constant for respective models (K_0 in mg/hr, K_1 in h^{-1}, and K_H in % h$^{1/2}$ for zero order, first order, and Higuchi rate equations, respectively)

Table 7: Predicted *in vivo* performance of developed formulation (EF7)

Product	Predicted Css max (ng/ml)		Predicted AUC0–τ ng hr/ml		Delivery rate R_0 (mg/h)		t_{Del} (h)	
	MP	NP	MP	NP	MP	NP	MP	NP
Desired[a]	51.35	31.5	1292.1	863.1	3.958	0.9333	8.8048	10.24
EF7[b]	56.97	31.24	1409.2	869	4.21	0.9676	8.805	10.3

[a]Predicted from desired zero order delivery profile, [b]Predicted from *in vitro* drug release studies. NP: Nifedipine, MP: Metoprolol
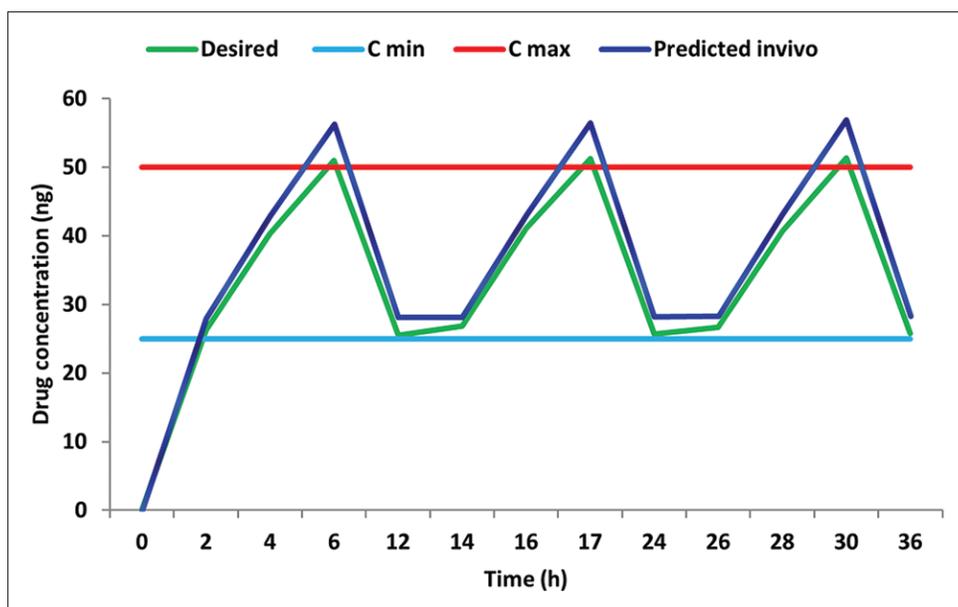
Figure 10: Predicted steady-state plasma levels of metoprolol after administration of a test dose of EF7 formulation in comparison with the desired profile

order kinetics and independent of environment medium, and the mobility of the GIT. The feasibility of extending the zero order release pattern of both the drugs was better achieved with sandwiched osmotic pump tablet system. The prototype design of the system could be applied to other combinations of drugs (one slightly water-soluble or water-insoluble drug and another freely water-soluble drug) used in cardiovascular diseases, diabetes, etc.

ACKNOWLEDGMENT

REFERENCES

1. Santus G, Baker RW. Osmotic drug delivery: A review of the patent literature. J Control Release 1995;35:1-21.
2. Theeuwes F. Elementary osmotic pump. J Pharm Sci 1975;64:1987-91.
3. Dollery CT. Pharmacological basis for combination therapy of hyper-tension. Annu Rev Pharmacol Toxicol 1977;17:311-23.
4. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: The cycle repeats. Drugs 2002;62:443-62.
5. Raemsch, KD, Sommer J. Pharmacokinetics and metabolism of nifedipine. Hypertension 1983;5:II18-24.

6. Godbillon J, Evard D, Vidon N, Duval M, Schoeller JP, Bernier JJ, *et al.* Investigation of drug absorption from the gastrointestinal tract of man. III. Metoprolol in the colon. Br J Clin Pharmacol 1985;19 Suppl 2:113S-8.

7. Theeuwes F. Oral dosage form design: Status and goals of oral osmotic systems technology. Pharm Int 1984;5:293-6.

8. Liu L, Khang G, Rhee JM, Lee HB. Preparation and characterization of cellulose acetate membrane for monolithic tablet. Korea Polym J 1999;7:289-96.

9. Liu L, Ku J, Khang G, Lee B, Rhee JM, Lee HB. Nifedipine controlled delivery by sandwiched osmotic tablet system. J Control Release 2000;68:145-56.

10. Wang CY, Ho HO, Lin LH, Lin YK, Sheu MT. Asymmetric membrane capsules for delivery of poorly water-soluble drugs by osmotic effects. Int J Pharm 2005;297:89-97.

11. Liu L, Xu X. Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. Int J Pharm 2008;352:225-30.

12. Nokhodchi A, Momin MN, Shokri J, Shahsavari M, Rashidi PA. Factors affecting the release of nifedipine from a swellable elementary osmotic pump. Drug Deliv 2008;15:43-8.

13. Park JS, Shin JH, Lee DH, Kim MS, Rhee JM, Lee HB, *et al.* A squeeze-type osmotic tablet for controlled delivery of nifedipine. J Biomater Sci Polym Ed 2008;19:31-45.

14. Sumnu M. Increasing dissolution rate and gastrointestinal absorption of nifedipine via solid dispersion. STP Pharma 1986;2:214-20.

15. Sugimoto I, Kuchiki A, Nakagawa H, Johgo K, Kondo S, Iwane I, *et al*. Dissolution and absorption of nifedipine from nifedipine-polyvinyl pyrrolidone coprecipitate. Drug Dev Indian Pharm 1980;6:137-60.

16. Chowdary KP, Ramesh KV. Improvement of dissolution rate and efficiency of nifedipine by solid dispersion in PVP-MCC and HPC-MCC. Indian J Pharm Sci 1994;56:95-9.

17. Skalko N, Brandl M, Becirevic-Lacan M, Grcic JF, Jalssenjak I. Liposomes of nifedipine and nifedipine-cyclodextrin complex: Calorimetrical and plasma stability comparison. Eur J Pharm Sci 1996;4:359-66.

18. Chowdary KP, Reddy GK. Complexes of nifedipine with beta and hydroxypropyl beta cyclodextrins in the design of nifedipine SR tablets. Indian J Pharm Sci 2002;64:142-6.

19. Prabakaran D, Singh P, Kanaujia P, Jaganathan KS, Rawat A, Vyas SP. Modified push-pull osmotic system for simultaneous delivery of theophylline and salbutamol: Development and *in vitro* characterization. Int J Pharm 2004;284:95-108.

20. Prabakaran D, Singh P, Jaganathan KS, Vyas SP. Osmotically regulated asymmetric capsular systems for simultaneous sustained delivery of anti-tubercular drugs. J Control Release 2004;95:239-48.

21. Ouyang D, Nie S, Li W, Guo H, Liu H, Pan W. Design and evaluation of compound metformin/glipizide elementary osmotic pump tablets. J Pharm Pharmacol 2005;57:817-20.

22. Kumaravelrajan R, Narayanan N, Suba V, Bhaskar K. Simultaneous delivery of nifedipine and metoprolol tartarate using sandwiched osmotic pump tablet system. Int J Pharm 2010;399:60-70.

23. Kumaravelrajan R, Narayanan N, Suba V. Development and evaluation of controlled porosity osmotic pump for nifedipine and metoprolol combination. Lipids Health Dis 2011;10:51.

24. Byrn SR, Xu W, Newman AW. Chemical reactivity in solid-state pharmaceuticals: Formulation implications. Adv Drug Deliv Rev 2001;48:115-36.

25. Schultz P, Kleinebudde C. A new multiparticulate delayed release system. Part I: Dissolution properties and release mechanism. J Control Release 1997;47:181-9.

26. Najib N, Suleiman M. The kinetics of drug release from ethyl cellulose solid dispersions. Drug Dev Ind Pharm 1985;11:2169-81.

27. Desai SJ, Singh P, Simonelli AP, Higuchi WI. Investigation of factors influencing release of solid drug dispersed in wax matrices III. Quantitative studies involving polyethylene plastic matrix. J Pharm Sci 1996;55L:1230-4.

28. Higuchi T. Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145-9.

29. Neutel JM. The use of combination drug therapy in the treatment of hypertension. Prog Cardiovasc Nurs 2002;17:81-8.

30. Ritschel WA. Biopharmaceutic and pharmacokinetic aspects in the design of controlled release peroral drug delivery systems. Drug Dev Ind Pharm 1989;15:1073-3.

31. Thombre AG, Appel LE, Chidlaw MB, Daugherity PD, Dumont F, Evans LA, *et al*. Osmotic drug delivery using swellable-core technology. J Control Release 2004;94:75-89.

32. Verma RK, Kaushal AM, Garg S. Development and evaluation of extended release formulations of isosorbide mononitrate based on osmotic technology. Int J Pharm 2003;263:9-24.

33. Verma RK, Garg S, Development and evaluation of osmotically controlled oral drug delivery system of glipizide. Eur J Pharm Biopharm 2004;57:513-25.