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Simultaneous delivery of Nifedipine and Metoprolol tartarate using sandwiched osmotic pump tablet system

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ABSTRACT

The sandwiched osmotic tablet system that could deliver Nifedipine and Metoprolol tartarate simultaneously for extended period of time was developed in order to reduce the problems associated with multidrug therapy of hypertension. This system composed of a middle push layer and attached drug layers of Nifedipine and Metoprolol. The advantage of the sandwiched osmotic tablet system over the commercialized push–pull osmotic tablet system is its simplicity of preparation, as the surface identification was avoided. Polyethylene oxide 600,000 and 8,000,000 g/mole were used as thickening agent of drug layer and the expandable hydrogel of push layer, respectively. It has been observed that amount of polyethylene oxide (PEO) and KCL of the drug and push layer had profound influence on Nifedipine and Metoprolol release. Further, the release of drugs was optimized by the size of the delivery orifice, level of plasticizer and membrane thickness. The optimal osmotic pump tablet was found to deliver both drugs at a rate of approximately zero order for up to 16 h independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. The formulations were found to be stable after 3 months of accelerated stability studies. Prediction of steady-state levels showed the plasma concentrations of Nifedipine and Metoprolol to be within the desired range. Further sandwiched system had a good sustained effect in comparison with the conventional product. Hence the prototype design of the system could be applied to other combinations of drugs used for cardiovascular diseases, diabetes, etc.

1. Introduction

Oral route is one of the most extensively used routes of drug administration because of its obvious advantages of ease of administration, improved patient compliance and convenience. In immediate-release dosage forms, there is little or no control over release of drug from the dosage form, which most often results in constantly changing, unpredictable and often sub- or supra-therapeutic plasma concentration. Recently, there has been considerable interest in the development of novel drug delivery systems (NDDS) and number of products based on newer drug delivery technologies has increased significantly (Verma and Garg, 2001). Among the various NDDS available, *per oral* controlled release systems hold the major market share because of their advantages of ease of administration and better patient compliance (Speers and Bonnano, 1999).

A number of design options are available to control or modulate the drug release from a dosage form. Majority of the oral dosage forms fall in the category of matrix, reservoir or osmotic systems. Osmotic systems utilize the principles of osmotic pressure for controlled delivery of drugs (Verma et al., 2000). Drug release from these systems is independent of pH and other physiological parameters to a large extent (Theeuwes et al., 1985). The development of oral osmotic systems has a strong market potential, as evident from the marketed products and number of patents granted in the last few years (Santus and Baker, 1995).

Chronic diseases such as hypertension, diabetes, asthma etc., are treated using multidrug therapies, which are vulnerable to incidences of side-effects, poor patient compliance and slow improvement of patients. Nifedipine (NP) and Metoprolol tartarate (MP) are anti-hypertensive agents belonging to calcium channel blockers and β-blockers respectively. Generally 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

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in cardiac output and systolic BP (SBP) after acute drug administration (Dollery, 1977).

Following oral administration, peak plasma concentrations of NP were attained within 1–2 h and the elimination half life was approximately 2 h (Ramsech and Sommer, 1983) resulting in the need to administer drug every 8 h to maintain therapeutic concentrations. MP also has similar biological half life 3–4 h, necessitated repeated twice-daily administration (Kendall et al., 1980). The combination of NP with MP is more effective than individual therapy because of the synergism (Domenic, 2002). 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.

There was a report on modified push–pull osmotic system to deliver a slightly water soluble theophylline base and freely soluble salbutamol sulfate simultaneously (Prabakaran et al., 2004a). However, the modified push–pull osmotic system needed a sophisticated technique. Hence osmotically regulated asymmetric capsular system was developed to deliver slightly aqueous soluble rifampicin and freely soluble isoniazid simultaneously (Prabakaran et al., 2004b). Recently, Ouyang et al. (2005) evaluated metformin and glipizide elementary osmotic pump tablet for simultaneous delivery.

Liu et al. (2000) reported swellable core osmotic pump delivery of NP wherein middle push layer and two attached NP layers gave fairly comparable *in vitro* release features as that of commercialized push–pull osmotic tablet system. Swellable core osmotic pump technology (SCT) was developed as a drug delivery platform that can deliver drugs with moderate to poor aqueous solubility over 8–24 h period. SCT formulations consist of a core tablet that contains a drug composition and a water-swellable composition. The drug composition contains the drug, an entraining polymer (e.g., polyethylene oxide) and sugars or salts as osmotic agents. The swellable composition contains a nonionic polymer (e.g., polyethylene oxide) or an ionic polymer (e.g., croscarmellose sodium or sodium starch glycolate), which swells and expands in volume after absorption of water.

Drug release from these formulations can be controlled by the composition of the core and permeability of the membrane coating. The *in vitro* drug delivery from these formulations was extremely robust-independent of external pH and hydrodynamics, insensitive to number, position and size of the drug delivery port and relatively independent of the drug itself. Overall, the device has the characteristics that could potentially make it useful as a broadly applicable drug independent delivery system particularly suitable for poorly water soluble drugs (Thombre et al., 2004).

Based on this report, the device was prepared with slight modification, by attaching two different drug layers (NP and MP) on both sides of middle push layer. As sandwiched osmotic system can deliver drugs at controlled fashion, we made an attempt to incorporate NP and MP (which extremely differ in their solubility profile) as two separate layers to sandwich push layer. In the present study, the possibility of simultaneous controlled release of two drugs from a sandwiched osmotic system was explored.

2. Materials and methods

2.1. Materials

Nifedipine and Metoprolol were a kind gift sample from Madras Pharmaceuticals Private Limited, Chennai, India. KCL and starch was supplied from S.D. Fine chemicals, Mumbai, India. Polyethylene oxide was purchased from Sigma Aldrich, Bangalore, India. Microcrystalline cellulose, magnesium stearate and aerosil were purchased from Rolex, Mumbai, India. Cellulose acetate (CA) was obtained from Eastman Chemical Company, Kingsport, USA. All other solvents and chemicals used were of the analytical grade.

Table 1
Basic core formulation and the varying range of all chemicals.

Compact	Chemicals	Basic amount (mg)	Varying range (mg)
NP layer	Nifedipine	22	–
	PEO (MW: 6,00,000 g/mol)	60	20–60
	KCL	40	10–40
	MCC	10	10–50
	Magnesium stearate	Trace	Trace
	Starch	40	–
	Talc	10	–
	Aerosil	10	–
MP layer	Metoprolol tartarate	53	–
	PEO (MW: 6,00,000 g/mol)	60	20–60
	KCL	40	10–40
	MCC	10	10–50
	Magnesium stearate	Trace	Trace
	Starch	40	–
	Talc	10	–
	Aerosil	10	–
Push layer	Nifedipine	22	–
	PEO (MW: 80,00,000 g/mol)	60	20–60
	KCL	40	10–40
	MCC	10	10–50
	Magnesium stearate	Trace	Trace
	Starch	40	–
	Talc	10	–
	Aerosil	10	–

2.2. 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 [15]. 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° to 300 °C.

2.3. Tabletting

The basic formulation of sandwiched osmotic tablet core and the varying range of various chemicals were listed in Table 1. The loading of NP is 22 mg and MP is 53 mg. Each tablet core consists of 185 mg of NP layer, 214 mg of MP layer and 163 mg of push layer composition.

2.3.1. NP layer

NP was mixed with polyethylene oxide, KCL, microcrystalline cellulose (MCC) and starch. All the excipients were passed through sieve 120 before mixing. This mixture was moistened with 10% starch paste to proper wetness and granulated by passing through sieve 14.

2.3.2. MP layer

MP was mixed with polyethylene oxide, KCL, MCC and starch. This mixture was moistened with 8% PVP solution in isopropyl alcohol and granulated by passing through sieve 14.

2.3.3. Push layer

Polyethylene oxide was mixed with KCL, MCC and starch. This mixture was moistened with 10% starch paste and granulated by passing through sieve 14.

All these layers were dried at 40 °C for 2 h, mixture was again passed through sieve 18. Finally talc, aerosil and magnesium stearate was added to the mixture and compacted using 16/32 in. deep concave punches.

The influence of MCC was assumed to be minor; therefore, the amount of MCC was changeable to balance the weight of either push layer or drug layers to maintain the volume and surface area of either drug layer or push layer relatively constant. The sandwiched osmotic tablet core was prepared by using rotary tablet compression machine with 8 stations (Cadmac, India) fitted with 16/32 in. (12.7 mm) punches. Initially NP drug layer powder was laid into the die cavity, then the push layer powder was loaded on and compacted, after that, MP drug layer powder was added. Finally the composition was compressed.

2.4. Coating

Tablets were coated by using a pan coater and 4% (w/v) of CA in acetone containing known level of plasticizer as coating solution.

The coating conditions are outlined as follows:

Pan specification: stainless steel, spherical, 300 mm diameter.
Pan rotating rate: 18 rpm.
Spray rate: 3 ml/min.
Drying: by a heat gun.

The surface morphology of the coated tablets was smooth and uniform in appearance. After coating, the tablets were dried over night at 60 °C to remove residual solvent. Two orifices with diameter of 450 μm for drug release were drilled on both side surfaces of the coated tablet manually by a mechanical drill.

2.5. In vitro drug release

The *in vitro* release of the sandwiched osmotic pump tablet (SOPT) was carried out using 900 ml of pH 6.8 phosphate buffer as the medium in USP II dissolution apparatus at 37 °C and 50 rpm. Five-milliliter samples were taken at 0, 2, 4, 8, 12 and 24 h and filtered through 0.45 μm cellulose nitrate filter. Fresh dissolution medium (5 ml) was added after each sampling. Each study was done in triplicate and the mean values were reported.

Determination of NP: the filtrate was diluted with pH 6.8 phosphate buffer (dissolution medium) and determined at 340 nm by UV spectrophotometric method.

Determination of MP: the filtrate was determined for MP at 275 nm using UV spectrophotometric method.

2.6. Comparison of in vitro release profile

Release profiles were compared using mean dissolution time (MDT), which was calculated using following equation (Anderson et al., 1998).

$$\mathrm{MDT} = \frac{\sum_{j=1}^{n} \hat{t}_j \, \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

where j is the sample number, n the number of dissolution, $\hat{t}_j$ is the time at midpoint between t_j and $t_j - 1$ and ΔM_j the additional amount of drug dissolved between t_i and t_{i-1}. One-way analysis of variance test (ANOVA) was performed to check whether there is significant difference among the different formulations.

2.7. Effect of orifice on drug release

To study the effect of orifice on the drug release, the release of the tablets with different orifice size (250, 450, 550 and 800 μm) were investigated and compared.

2.8. Effect of coating solution on drug release

The tablet cores were prepared and coated with PEG-400 coating solution at the levels of 10, 20 and 30% of CA (w/w) and then the properties and drug release characteristics of the coated tablets were compared. Meanwhile, the tablets were prepared and coated with CA to three levels of tablet weight gain, such as 8, 12 and 16% (w/w).

2.9. Effect of pH

In order 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, pH 1.2 and SIF, pH 6.8) and pH change method (release media was simulated gastric fluid (pH 1.2) for first 2 h, followed by SIF (pH 6.8) for the remaining period). The samples (5 ml) were withdrawn at pre-determined 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.

2.10. Effect of agitational intensity

In order 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 pre-determined 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.

2.11. Osmotic pressure measurement

In order to confirm the mechanism of drug release, release studies of the optimized formulations were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride (osmotically effective solute) was added in SIF (Schultz and Kleinebudde, 1997) 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 pressure was plotted and compared.

Release profiles of optimized formulations were compared using model independent pair-wise approach, which included the calculation of 'difference factor' f_1 and 'similarity factor' f_2: the two release profiles were considered to be similar, if f_1 value was lower than 15 (between 0 and 15) and f_2 value was more than 50 (between 50 and 100). For the calculation of f_1 and f_2 values, only

one data point was taken into consideration after 85% of the drug was released (Moore and Flanner, 1996).

2.12. Accelerated stability studies

Optimized formulation from the sandwiched osmotic system was packed in strips of 0.04 mm thick aluminum foil laminated with polyvinyl chloride (PVC). The packed formulation was stored at refrigerated temperature and ICH certified stability chambers (KBF 720, Binder, Germany) maintained at 40 °C and 75% RH for 3 months. The samples were withdrawn at monthly intervals and evaluated for change in appearance, drug content, hardness, friability and release studies.

2.13. Release models and kinetics

In order 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 (Najib and Suleiman, 1985). The first order equation describes the release from systems, where release rate is concentration dependent (Desai et al., 1966). According to Higuchi model, the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion (Higuchi, 1963). Drug release data obtained was applied to different drug release models in order 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.

2.14. Prediction of in vivo performance

Known pharmacokinetic properties of drugs and various drug release parameters (R^0 and t_{Del}), which were calculated from *in vitro* release data, were used to predict blood levels of drugs (Ritschel, 1989). The predicted steady-state plasma levels of in house formulation were compared with the desired levels by calculating the percent predicted error (% PD) in C_{SSmax}, C_{SSmin} and $AUC_{0-\tau}$. Bioequivalence was anticipated (Sheskey et al., 2000) if the average % PD was less than 15% for C_{max} and $AUC_{0-\tau}$. The % PD was calculated using the following equation:

$$\%\,PD = \frac{\text{Predicted value} - \text{reference value}}{\text{reference value}} \times 100$$

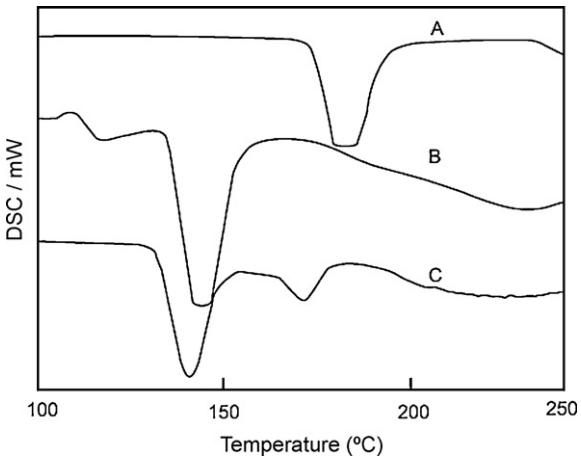

Fig. 1. DSC thermogram of (a) Nifedipine, (b) Metoprolol and (c) coated tablets of Nifedipine and Metoprolol combination SOPT.

3. Results and discussion

3.1. Drug–excipient interaction studies

Fig. 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.

3.2. Influences of tablet formulation variables on NP and MP release

Based on our preliminary study on sandwiched osmotic tablet core, two tablet formulation variables were fixed as follows:

- Polyethylene oxide molecular weight of drug layer was 600,000 g/mol.
- Whereas push layer was 8,000,000 g/mol.

To study the influence of the amount of chemicals on NP and MP release, sandwiched osmotic tablet cores with various formulations were prepared, subsequently coated with the same and drilled each side surface a circle orifice with diameter of 450 μm. The relation-

Table 2
The relationship between the cumulative released NP and MP at 24 h and core formulation variables.

Core No.	Independent variables (mg)									Dependent variable (%)	
	NP layer			MP layer			Push layer			NP	MP
	PEO	KCL	MCC	PEO	KCL	MCC	PEO	KCL	MCC		
C1	60	10	40	60	10	40	60	10	40	60.21	63.21
C2	60	20	30	60	20	30	60	20	30	66.71	71.65
C3	60	30	20	60	30	20	60	30	20	75.42	79.54
C4	60	40	10	60	40	10	60	40	10	77.62	83.32
C5	60	10	40	60	10	40	60	40	10	69.81	63.42
C6	60	20	30	60	20	30	60	40	10	72.92	73.92
C7	60	30	20	60	30	20	60	40	10	70.47	79.21
C8	60	40	10	60	40	10	60	10	40	60.42	62.35
C9	60	40	10	60	40	10	60	20	30	66.34	70.74
C10	60	40	10	60	40	10	60	30	20	72.14	77.21
C11	20	40	50	20	40	50	20	40	50	49.12	89.21
C12	30	40	40	30	40	40	30	40	40	33.24	84.45
C13	20	40	50	20	40	50	60	40	10	62.14	82.49
C14	30	40	40	30	40	40	60	40	10	70.32	79.31
C15	60	40	10	60	40	10	20	40	50	54.21	93.21
C16	60	40	10	60	40	10	30	40	40	62.35	88.43

ship between the cumulative release of NP and MP at 24 h and the core formulation variables were summarized in Table 2.

3.3. Influence of KCL amount on NP and MP release

To study the compositive influence of KCL amount on NP and MP release rate, cores were incorporated with the same amount of KCL in either drug layer or push layer. Core formulations 1, 2, 3 and 4 of Table 2 showed that percentage release and release rate of NP and MP increased significantly as there is increase of KCL amount from 10 to 40 mg.

The influence of KCL amount of drug layers and push layer were compared separately. Core formulations 4, 5, 6 and 7 revealed that KCL amount of NP layer had no significant influence on NP release and release rate since change in release observed between 10 and 40 mg was not notable. But it had profound influence on MP release and release rate.

Core formulations 8, 9, 10 and 11 revealed that KCL amount of push layer also had a significant influence on both NP and MP release pattern.

3.4. Influence of Polyethylene oxide on NP and MP release

The same amount of polyethylene oxide was incorporated in both drug layer (MW: 600,000 g/mol) and push layer (MW: 8,000,000 g/mol) to study the compositive influence of polyethylene oxide on NP and MP release rate. Polyethylene oxide used in the drug layer usually had a molecular weight from 100,000 to 600,000 g/mol whereas the polyethylene oxide used in the push layer usually had a molecule weight from 4,000,000 to 8,000,000 g/mol. Polyethylene oxide at a molecular weight of 100,000 to 600,000 g/mol acts as either drug entraining polymer for water insoluble drugs or release retardant for highly water soluble drugs (Campbell et al., 2008). Polyethylene oxide with a high molecular weight in the push layer acts as a swelling agent. It is among various hydrophilic polymers that, in presence of water, control the release of the active moiety either by swelling or by swelling/erosion by forming a hydrogel. Polyehtylene oxides have been proposed as alternatives to cellulose or other ethylene glycol derivatives in the production of controlled release drug delivery system (Jeong et al., 2002).

Core formulations 4, 13 and 14 showed that the percentage release and rate for NP was very low in case of 20 mg polyethylene oxide and it was higher in case of both 30 and 60 mg. However, MP showed higher release and rate in case of 20 mg polyethylene oxide and release rate lowered when the concentration is increased to 40 and 60 mg.

The influences of polyethylene oxide amount in drug layers and push layer were also compared separately. Core formulations 4, 15 and 16 showed that NP release and rate increased markedly as the polyethylene oxide amount of drug layer increased. It might be explained that the increase of polyethylene oxide level of NP layer increased the viscosity of drug suspension, which increased the stability, or inhibited the aggregation and precipitation of NP powder in suspension. The system functioned by a mechanism similar to that discussed by Liu et al. (2000) In brief, when the osmotic pump tablet was exposed to aqueous medium, water was influxed through the semipermeable membrane. Subsequently, KCL and polyethylene oxide were dissolved simultaneously. Then the suspension was pumped out through the orifice and a substantially constant release rate was achieved because of the osmotic pressure difference and the stable suspension.

Core formulations 4, 13 and 14 showed that MP release rate decreased, as the polyethylene oxide amount of drug layer increased. As it has a high solubility in water, the release rate would be too fast, so it is necessary to reduce the drug dissolution *in vitro*. Reports were already available for the use of polyethylene oxide as release retarding agent to deliver highly water soluble drugs Metoprolol tartarate (Pillay and Fassihi, 2000), Verapamil (Dimitrov and Lambov, 1999) and Chlorpheniramine (Zhang and McGinity, 1999a,b). The results of our present study indicated that polyethylene oxide reduced the drug release rate and the rate decreased with the increase of polyethylene oxide content. The influence of polyethylene oxide in MP layer essentially involves a mechanism, wherein the increase in the amount of polyethylene oxide control the release by producing high viscosity within the core which may restrict and delay the solvent contact with drug molecules and may increase the diffusional path length of solvent to get desired zero order release rate.

Core formulations 4, 15 and 16 showed the effect of polyethylene oxide amount of push layer on NP and MP release and its rate. Polyethylene oxide also is a swelling agent at higher molecular weight; the higher the amount of the polymer used the greater the expanding force of core tablet. Therefore, the release rate of NP and MP increased as the amount of the polymer increased from 20, 30 to 60 mg. The results showed that uniform rate of swelling of the polymer ensured that the drug is released at a relatively constant rate. The selection of a suitable concentration of polymer is crucial when designing the osmotic pump. Too much polymer will burst the osmotic device and too little concentration of polymer will produce low viscosity inside the device and thus not able to prevent precipitation of the drug powder inside the device. The visual observation of tablets at the end of the experiment showed that no crack on the surface of the tablet even with high concentration of polyethylene oxide. So, the pressure produced during swelling did not lead to rupture of the system. As the variables of both drug and push layer influenced the release pattern of drug the complexities of core formulation were analyzed by multivariable linear regression analysis (MLR).

3.5. Multivariable linear regression analysis

As core formulation variables were interlinked, changes in chemical amount to adjust NP and MP release rate resulted in the shift of MCC amount. In order to study the complexities of core formulation, all data of table were analyzed by using multivariable linear regression analysis. The regression equation for NP and MP was shown in Eqs. (1) and (2) respectively.

$$Y = -7.467 + 0.607X_1 + 0.176X_2 + 0.000X_3 + 0.384X_4 + 0.459X_5 + 0.000X_6 \quad (1)$$

$$Y = 43 - 0.051X_1 + 0.506X_2 + 0.177X_3 + 0.053X_4 + 0.411X_5 + 0.000X_6 \quad (2)$$

where X_1 to X_6 were the independent variables and Y was the dependent variable.

X_1 was amount of PEO, X_2 and X_3 were amount of KCL and MCC of drug layer respectively whereas X_4, X_5 and X_6 were amount of PEO, KCL and MCC of push layer respectively. Y was the cumulative released NP and MP at 24 h. The multiple correlation coefficient was 0.933, which proved that the regression was fine. The coefficients of X_1 to X_6 referred to the degrees of influence of relevant core formulation variables on the cumulative released NP and MP at 24 h. From the regression equation, the following conclusions could be reached: (1) A factor with a positive coefficient increased Y. (2) A factor with a large absolute value of coefficient had a profound influence on Y. In the NP layer, the absolute values of the coefficients in decreasing order were 0.607, 0.176 and 0.000, which were attributed to X_1, X_2 and X_3 respectively. In the push layer, the absolute values of coefficients in decreasing order were

Table 3
Formulation variables of sandwiched osmotic pump tablet.

Formulations	Variables		
	Orifice diameter (μm)	Amount of plasticizer (PEG-400) (%, w/w, of CA)	Coating thickness (%, w/w)
SF1	450	10	12
SF2	250	10	12
SF3	550	10	12
SF4	800	10	12
SF5	550	10	12
SF6	550	10	12
SF7	550	20	08
SF8	550	30	16

0.459, 0.384 and 0.000, which were attributed to X_5, X_4 and X_6 respectively. Therefore, PEO amount of drug layer and KCL amount of push layer have the most profound and positive influences on NP release rate. (3) The influences MCC amount of the push layer and drug layer were negligible because their coefficients (X_3 and X_6) were very small compared with other coefficients. By the way, the absolute value of coefficient of either MCC amount in the drug or push layer was minor.

In the MP layer, the absolute values of the coefficients in decreasing order were 0.506, 0.177 and −0.051, which were attributed to X_2, X_3 and X_1 respectively. In the push layer, the absolute values of coefficients in decreasing order were 0.411, 0.053 and 0.000, which were attributed to X_4, X_5 and X_6 respectively. Therefore, KCL amount of drug layer and PEO amount of push layer have the most profound and positive influences on MP release rate whereas PEO amount on drug layer has profound negative influence on MP release rate (3). The influences MCC amount of the push layer and drug layer were negligible because their coefficients (X_3 and X_6) were very small compared with other coefficients.

3.6. Delivery mechanism and optimal core formulation

The SOPT was composed of a sandwiched osmotic tablet core surrounded by CA membrane with two orifices on both side surfaces. The sandwiched tablet core of this study consisted of two outer drug layers containing NP and MP, osmotic agent KCL and thickening agent polyethylene oxide with MW of 600,000 g/mol, and a middle push layer containing osmotic agent KCL and expandable hydrogel polyethylene oxide with MW of 8,000,000 g/mol.

Based on above release rates and the statistic analysis, the release mechanism of the SOPT may be proposed as follows. In a starting-up step, water penetrated through the CA membrane and entered into the SOPT system by diffusion. Subsequently, the penetrated water dissolved KCL of the push layer and the two drug layers simultaneously. As a result, an osmotic pressure difference between the internal system and the external environment was formed. Then, the osmotic pressure differences played the role of engine to imbibe water from the environment continuously. The action of the imbibed water in the NP and MP layer was to liquefy the contents of the drug layer and produce a stable viscous suspension or solution of the drug. However, the action of the imbibed water in the push layer was quite different from that of the drug layers. The water was retained within the polyethylene oxide hydrogel structure, therefore expanding the volume of the push layer. This expansion supplied a driving force which was applied against the two outer drug layers, consequently, diminishing the volume of two drug layers. As a result, the drugs were delivered through the two opposite orifices of the SOPT. In brief, the drug release from SOPT was co-controlled by the push layer and the drug layer. The function of PEO in the NP layer was to suspend the drug stably, in case of MP to reduce release rate by acting as release retardant while the function of the push layer was to expand its volume gradually to force the drug suspension release.

It could be found that the SOPT made from the core formulation No.7 was not only able to deliver NP and MP for up to 24 h, but also at an approximately constant rate. This core formulation may be chosen as the optimal one and various formulations variables used in the study were shown in Table 3.

3.7. Influence of orifice size on NP and MP release

Aperture diameter is one of the critical parameters that greatly influences release rate, lag time and release kinetics of the osmotic drug delivery devices. Thus, the size of delivery orifice must be optimized in order to control the drug release from osmotic systems. The size of the orifice should be sufficiently large to prevent the hydrostatic pressure developed inside the device from rupturing the membrane and at the same time it should not be so large that it allows free diffusion of solute leading to loss of control over the release rate (Theeuwes, 1975). The optimal cores were coated and subsequently, drilled on each side surface with a round orifice of the same size. To determine the optimal diameter of the delivery orifice in the membranes, apertures were made in the range of 250 (SF2), 450 (SF1), 550 (SF3) and 800 μm (SF4).

Cumulative percentage and release rate profiles of NP and MP from these systems were compared (Table 4). It was found that the size of the delivery orifice significantly increases the rate of release of NP and MP. Significant difference existed in the release profiles for orifice diameters ranging from 250 to 800 μm. Mean dissolution time (MDT) at various orifice diameter of SF1, SF2, SF3 and SF4 of NP was 8.64 ± 0.407, 17.70 ± 0.679, 12.09 ± 0.198 and 13.57 ± 0.660 respectively and the F value is 153.2 and it was found to be statistically significant ($p < 0.0001$). MDT of SF1, SF2, SF3 and SF4 of MP was 12.21 ± 0.403, 6.52 ± 0.265, 10.59 ± 0.394 and 7.69 ± 0.357 respectively and the F value is 356.4 and it was found to be statistically significant ($p < 0.0001$). Orifice diameter size had profound influence on its release rate. In the following studies, an orifice diameter of 550 μm which was within the optimal range was used.

3.8. Influences of membrane variables on NP and MP release

The most straightforward method to modify the drug release profile of swellable core osmotic pump tablet is to vary the coating weight (Thombre et al., 2004). 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.

To study the influence of coating level on the release profiles of NP and MP the core formulation were coated to 8 (SF5), 12 (SF3) and 16% (SF6) weight gain up. Table 5 represents the release profiles

Table 4
Influence of orifice size on NP and MP release rate.

Time (h)	Release rate ± SEM (% h)							
	SF1 (450 μm)		SF1 (250 μm)		SF3 (550 μm)		SF4 (800 μm)	
	NP	MP	NP	MP	NP	MP	NP	MP
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	5.03 ± 0.50	4.71 ± 0.51	2.52 ± 0.37	2.93 ± 0.71	5.25 ± 0.43	5.35 ± 0.39	6.40 ± 0.41	7.15 ± 0.84
4	4.76 ± 0.38	5.03 ± 0.64	2.87 ± 0.51	3.14 ± 0.80	5.31 ± 0.40	5.57 ± 0.71	7.87 ± 0.51	7.59 ± 0.81
6	4.57 ± 1.07	5.12 ± 0.90	2.90 ± 0.52	3.20 ± 0.93	5.13 ± 0.51	5.57 ± 0.34	7.56 ± 0.59	7.72 ± 0.71
8	4.40 ± 1.14	5.15 ± 0.94	2.89 ± 0.93	3.21 ± 0.84	4.96 ± 0.60	5.56 ± 0.71	7.29 ± 0.60	7.60 ± 0.97
10	4.27 ± 1.21	5.080.70 ±	2.67 ± 0.84	3.19 ± 0.51	4.84 ± 0.28	5.56 ± 0.37	7.05 ± 0.45	7.48 ± 0.40
12	4.17 ± 1.04	4.95 ± 0.87	2.53 ± 0.81	3.14 ± 0.41	4.70 ± 0.18	5.55 ± 0.51	6.84 ± 0.87	7.35 ± 0.51
24	2.94 ± 0.83	3.30 ± 0.70	1.70 ± 1.03	2.18 ± 0.50	3.52 ± 0.30	3.80 ± 0.27	3.60 ± 0.70	4.17 ± 0.60

Table 5
Influence of membrane thickness on NP release rate.

Time (h)	NP release rate ± SEM (% h)					
	SF3		SF5		SF6	
	Mean	SEM	Mean	SEM	Mean	SEM
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	5.25 ± 0.43	5.35 ± 0.39	6.34 ± 0.47	7.57 ± 0.52	2.98 ± 0.37	3.44 ± 0.40
4	5.31 ± 0.40	5.57 ± 0.70	7.18 ± 0.52	7.82 ± 0.64	3.30 ± 0.57	3.66 ± 0.39
6	5.13 ± 0.51	5.57 ± 0.34	7.16 ± 0.54	7.82 ± 0.41	3.35 ± 0.23	3.67 ± 0.40
8	4.96 ± 0.60	5.56 ± 0.70	7.14 ± 0.45	7.79 ± 0.68	3.37 ± 0.87	3.6 ± 0.83
10	4.84 ± 0.28	5.56 ± 0.38	7.09 ± 0.97	7.76 ± 0.71	3.37 ± 0.81	3.62 ± 0.71
12	4.70 ± 0.18	5.55 ± 0.51	7.05 ± 0.77	7.74 ± 0.60	3.35 ± 0.98	3.60 ± 0.89
24	3.52 ± 0.30	3.80 ± 0.27	4.16 ± 0.52	4.17 ± 0.27	3.17 ± 0.58	3.52 ± 0.80

of osmotic devices formulated with different thickness. When the coating level went up, a gradual decrease in the percentage drug release and release rate of both NP and MP was observed. According to Liu et al. (2000) study, the increase of coating level would result in the decrease of water imbibing through the membrane; thus, both the rate of hydration of the drug layer and the expansion of the push layer were decreased, which resulted in decrease of release rate of drugs.

MDT between the different formulations SF3, SF5 and SF6 of NP at various coating thickness was 11.09 ± 0.198, 12.12 ± 0.261 and 14.52 ± 0.456 respectively, the *F* value is 10.25 and was found to be statistically significant ($p < 0.05$). MDT of SF3, SF5 and SF6 of MP was 13.71 ± 0.638, 11.48 ± 0.470 and 10.59 ± 0.394 respectively, *F* value is 29.6 and was also statistically significant ($p < 0.0001$). Formulation SF6 showed better control on release pattern of both NP and MP. So it was chosen for further optimization.

3.9. Influence of plasticizer on NP and MP release

Plasticizers are added to modify the physical properties and improve film-forming characteristics of polymers. PEG role in the membrane has been described in literature with a dual functionality of plasticizer (Zhang and McGinity, 1999a,b) and pore former (Guo, 1993). The membrane is prepared as a combination of a water insoluble polymer cellulose acetate and a water soluble component PEG. The ratio of the two components determines the water permeability. The drug release profiles showed that for the same coating weight, coatings with higher CA/PEG ratio consistent with decreasing water permeability as a function of increasing CA/PEG ratio. When the coating permeability is very high, the major resistance to water ingress may be its transport in the tablet core rather than its permeation through the coating. Thus, the CA/PEG ratio of the coating can be used as another formulation variable (along with coating thickness) to control the drug release rate. The dependence of drug release rate on the coating thickness (slower drug release with increasing coating thickness) and on the CA/PEG ratio are consistent with what is expected of osmotic delivery systems, i.e., delivery rate directly proportional to membrane permeability. To study the influence of coating level on the release profiles of NP and MP the core formulation was plasticized with 10 (SF6), 20 (SF7) and 30% (SF8) of PEG-400. Table 6 showed that increase in PEG-400 amount lead to increase in the percentage release and release rate of both NP and MP.

MDT of NP at various plasticizer level of SF6, SF7 and SF8 was 8.03 ± 0.810, 14.52 ± 0.456 and 12.27 ± 0.462 respectively and *F* value is 9.042 and statistically significant ($p < 0.001$). MDT of MP

Table 6
Influence of level of plasticizer on NP and MP release rate.

Time (h)	NP release rate ± SEM (% h)					
	SF6 (PEG 10 mg)		SF7 (PEG 20 mg)		SF8 (PEG 30 mg)	
	NP	MP	NP	MP	NP	MP
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	2.98 ± 0.3	3.44 ± 0.40	4.46 ± 0.40	5.16 ± 0.47	4.46 ± 0.47	6.30 ± 0.19
4	3.30 ± 0.57	3.66 ± 0.39	4.37 ± 0.40	5.08 ± 0.87	4.37 ± 0.09	6.16 ± 0.71
6	3.35 ± 0.23	3.67 ± 0.40	4.33 ± 0.47	5.04 ± 0.74	4.33 ± 0.50	6.11 ± 0.61
8	3.37 ± 0.87	3.64 ± 0.83	4.28 ± 0.51	5.02 ± 0.51	4.28 ± 0.64	6.07 ± 0.57
10	3.37 ± 0.81	3.62 ± 0.70	4.24 ± 0.41	5.01 ± 0.60	4.24 ± 0.62	6.03 ± 0.51
12	3.35 ± 0.98	3.60 ± 0.89	4.22 ± 0.80	4.99 ± 0.27	4.22 ± 0.68	6.00 ± 0.94
24	3.17 ± 0.58	3.52 ± 0.80	3.88 ± 0.07	4.16 ± 0.37	3.89 ± 0.57	1.17 ± 0.09

Table 7
Fitting of NP and MP release data of the optimized formulation (SF7) according to various mathematical models.

Model	Parameters used to assess the fit of model							
	R^2		Intercept		K		AIC	
	NP	MP	NP	MP	NP	MP	NP	MP
Zero order	0.9969	0.9849	0.6028	0.7371	4.17	4.91	9.83	24.13
First order	0.9154	0.6859	2.02	2.05	−0.02	−0.992	−32.42	−22.27
Higuchi	0.8140	0.8000	−3.99	−4.74	15.67	18.52	37.78	36.95

R^2, goodness of fit.
K, release rate constant for respective models (K_0 in mg/h, K_1 in h^{-1} and K_H in % $h^{1/2}$ for zero order, first order and Higuchi rate equations respectively).
AIC, Akaike information criterion.

at various plasticizer level of SF6, SF7 and SF8 was 13.71 ± 0.638, 7.28 ± 0.472 and 9.305 ± 0.340 respectively and F value is 135.3 and also statistically significant ($p < 0.0001$). Because of the hydrophilic character of PEG, it can easily leave the CA membrane and entered into the aqueous environment. As a consequence, it left behind the porous structure and thereby increased permeability of the CA membrane and the drug release rate of SOTS.

3.10. Drug release kinetics

Dissolution data of the optimized formulation was fitted to various mathematical models (zero order, first order and Higuchi) in order 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 7). 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 regression value for zero order equation indicated that the drug release from optimized formulation was independent of drug concentration.

3.11. Effect of pH

Fig. 2, showed release of NP and MP from optimized formulation of SOPT (SF7) in pH 1.2; pH change method and pH 6.8 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. The f_1 and f_2 values were found to be 3 and 77 (between pH 1.2 and pH 6.8), 4 and 72 (between pH change method and pH 6.8) for NP and 3 and 75 (between pH 1.2 and pH 6.8) and 2 and 83 (between pH change method and pH 6.8) for MP respectively. Results showed that release profile is similar in all the media, so the developed formulations show pH-independent release.

3.12. Effect of agitational intensity

The release of NP and MP from SOPT (SF7) is independent of the agitational intensity. The f_1 and f_2 values were found to be 4 and 69 for NP and 4 and 70 for MP (between 100 and 50 rpm), 6 and 65 for NP and 2 and 80 for MP (between 100 and 150 rpm) respectively. These results showed no significant difference in percentage release under different agitation rates (Fig. 3).

3.13. Effect of osmotic pressure

Optimized formulation of SOPT also showed reduced percentage release of NP and MP when osmotic pressure in the external medium was increased (Fig. 4). The results of release studies of optimized formulations in media of different osmotic pressure indicated that, the drug release is highly dependent on the osmotic pressure of the release media. NP and MP release from the formulations decreased as the osmotic pressure of the media increased. The release was inversely related to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of release from developed formulations.

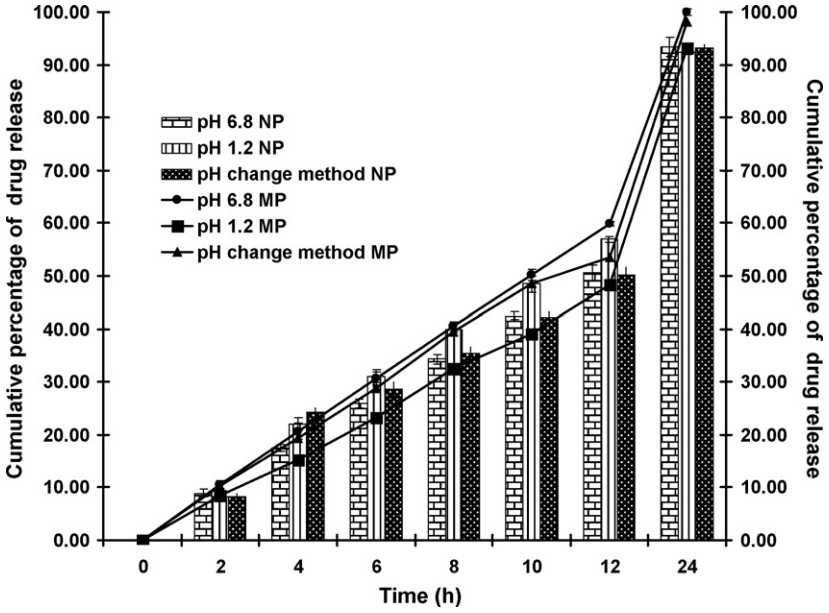

Fig. 2. Effect of pH on Nifedipine and Metoprolol release from SF7.

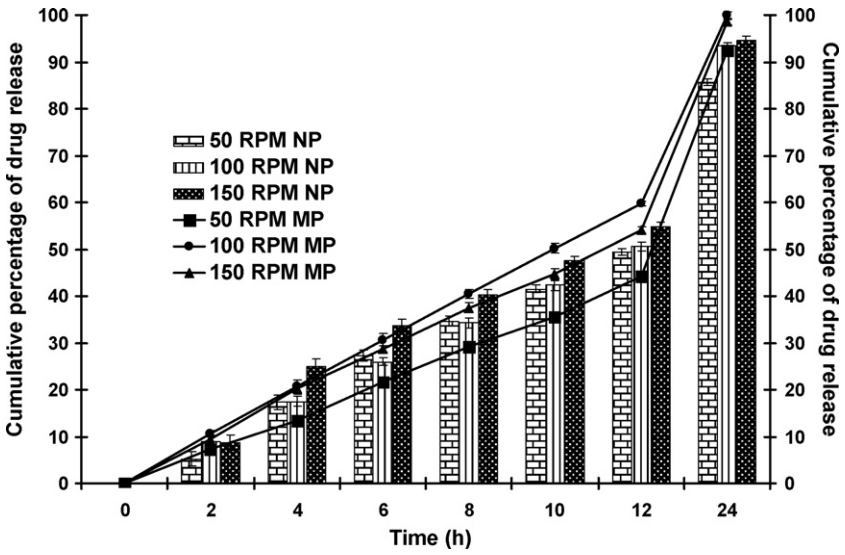

Fig. 3. Effect of agitational intensity on the release of Nifedipine and Metoprolol from SF7 formulation.

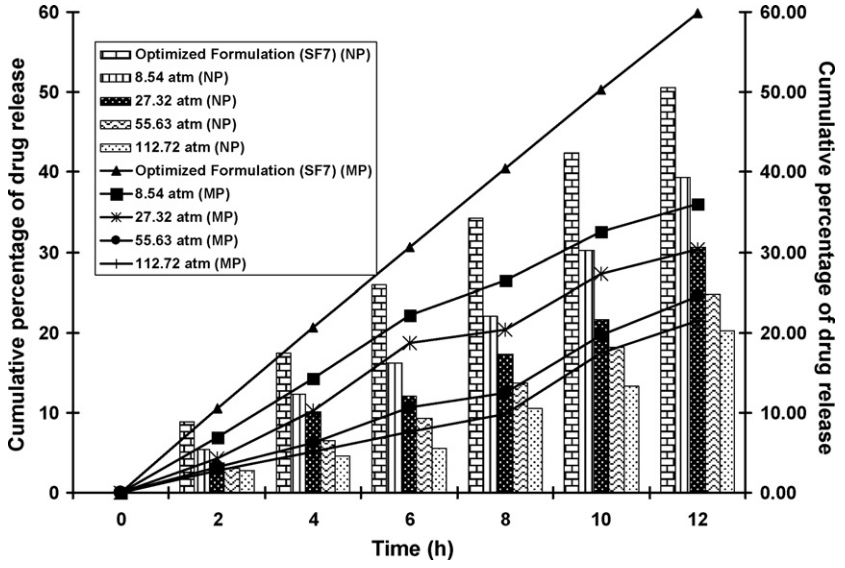

Fig. 4. Effect of osmotic pressure of the release media on Nifedipine and Metoprolol release from SF7 formulation.

3.14. Accelerated stability studies

There were no signs of any visually distinguishable changes in appearance on tablets. The formulations were found to be stable in terms of drug content, hardness, friability and release studies (Tables 8 and 9).

From the *in vitro* dissolution studies of all these systems, we could come up with the conclusion that drug release from all these systems is controlled by osmotic pressure as the major mechanism; release pattern obeyed zero order kinetics and independent of environment medium and the mobility of the gastrointestinal tract. The feasibility of extending the zero order release pattern of both the drugs were better achieved in case of developed SOPT.

3.15. Comparison of release profile of SOPT with conventional dosage form

The release rates of conventional capsules of NP, MP and SOPT system were obtained form their release profiles and are plotted it Fig. 5. It was found that in case of conventional dosage forms the

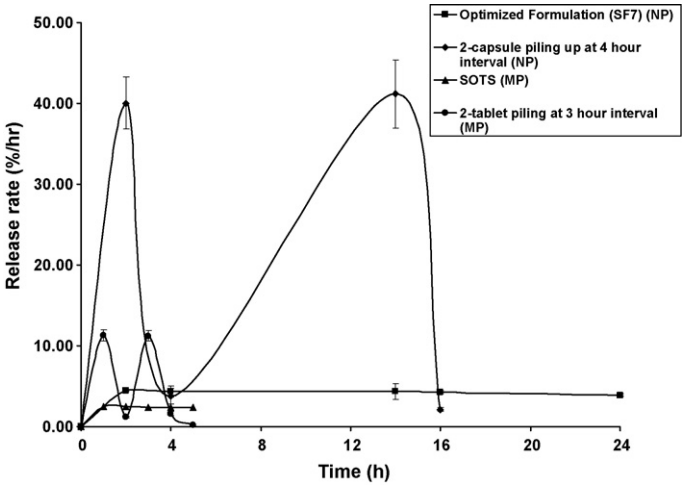

Fig. 5. Comparative release rate of Nifedipine and Metoprolol SOPT with conventional tablets.

Table 8
Evaluation of formulation of SF7 after 3 months of storage at refrigerated temperature and 40 °C.

Parameter	Initial		1 month		2 months		3 months	
	40 °C	4 °C	40 °C	4 °C	40 °C	4 °C	40 °C	4 °C
Appearance								
Hardness[c]	23.5 ± 1.89	24.6 ± 1.12	21.46 ± 3.36	23.2 ± 2.17	23.92 ± 2.62	24.8 ± 2.5	24.2 ± 2.51	24.5 ± 1.8
Friability	0.518	0.492	0.522	0.431	0.436	0.402	0.719	0.382
f_1[d]	–	–	4[a], 8[b]	1[a], 1[b]	5[a], 1[b]	4[a], 4[b]	10[a], 8[b]	2[a], 5[b]
f_2[d]	–	–	68[a], 56[b]	90[a], 87[b]	64[a] 88[b]	68[a], 69[b]	52[a] 55[b]	81[a], 65[b]
Drug content[c] (mg/tablet)	20.77 ± 0.18[a]	20.22 ± 0.27	19.72 ± 0.61[a]	20.53 ± 0.15	20.24 ± 1.07[a]	20.69 ± 0.62	19.58 ± 1.27[a]	19.71 ± 0.55
	49.27 ± 2.02[b]	51.26 ± 1.22	51.56 ± 0.52[b]	50.85 ± 1.52	50.44 ± 1.5[b]	50.47 ± 1.95	49.81 ± 1.46[b]	51.04 ± 1.39

[a] Nifedipine.
[b] Metoprolol.
[c] Values expressed as average ± S.D.
[d] Initial sample (0 months) was taken as reference to calculate f_1 and f_2 values.

Table 9
Release profile of Nifedipine from stability studies in accelerated and refrigerated temperature.

Time (h)	Temperature (40 °C)				Temperature (4 °C)			
	Initial	1 month	2 months	3 months	Initial	1 month	2 months	3 months
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	6.52	8.57	8.83	8.10	7.17	6.99	5.27	5.88
4	18.89	19.31	22.62	19.15	21.41	18.28	17.33	18.23
6	26.34	28.68	30.31	28.21	25.83	26.24	25.28	26.12
8	34.88	37.49	39.30	37.00	35.04	33.52	33.13	33.47
10	43.20	45.22	46.31	45.13	44.73	40.57	38.54	41.56
12	51.69	53.62	54.82	51.50	52.50	47.22	46.72	48.48
24	94.16	90.04	88.72	85.20	95.83	92.93	90.16	92.31

Table 10
Predicted *in vivo* performance of the developed formulation.

Release profile	Predicted C_{SSmax} (ng/ml)		% PD		Predicted C_{SSmin} (ng/ml)		% PD		$AUC_{0-\tau}$ (ng h/ml)		% PD	
	NP	MP	NP	MP	NP	MP	NP	MP	NP	MP	NP	MP
Desired[a]	91.40	49.45	–	–	4.4	2.10	–	–	4766	1935	–	–
SF7[b]	78.2	56.2	14.44	12.01	3.77	2.39	14.31	12.13	4079	2199	14.41	12

[a] Predicted from desired zero order delivery profile.
[b] Predicted from drug release studies.

release rates were very high initially and then decreased towards zero. However, in the case of SOPT, an approximately constant rate was observed up to 24 h. The total NP strength of two 10 mg conventional capsules and the total MP strength of two 25 mg conventional capsules are equal to the NP and MP strength of the individual SOPT. So two conventional capsules of NP and MP were added to a dissolution tester at a time interval of 12 h (i.e. analogous to twice-daily administration), then the simulated piling up release rates of these capsules were obtained. It was found that the conventional capsule was an immediate-release dosage form and the rate curve of two capsules of NP and MP showed sharp rate fluctuations and it looked mountain-shaped, with an initial rate of 5.11% h and valley rate of 0.55% h for NP and an initial rate of 11.31% h and valley rate of 1.21% h for MP. It was observed that SOPT system released NP at an approximately constant rate ranging from 4.46 to 4.15% h from 2 to 20 h and MP at a rate of 5.16–4.97% h from 2–16 h.

3.16. Prediction of in vivo performance

Method of superposition was used to predict steady-state plasma levels of NP and MP after administration of SF7 formulation (Ritschel, 1989). Since osmotic pumps are reported to exhibit a significant *in vitro–in vivo* correlation (McClelland et al., 1991) predicted data of steady-state plasma levels from drug release studies can be used for comparison with the desired plasma levels. Figs. 6 and 7 showed predicted steady-state plasma levels after administration of a test dose of SF7 formulation in comparison to the desired levels. Prediction of steady-state levels of NP and MP after administration of a test dose of formulation showed that peak plasma levels were 78.2 (NP) and 56.2 ng/ml (MP) but falls to 3.77 (NP) and 2.39 ng/ml (MP) before administration of the next test dose. The desired steady-state plasma levels of NP and MP were pre-

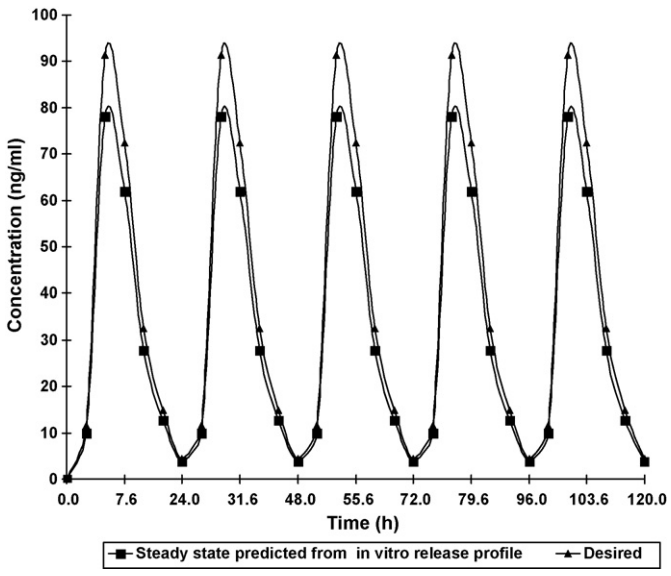

Fig. 6. Predicted steady-state plasma levels of Nifedipine after administration of SOPT formulation in comparison with the desired profile.

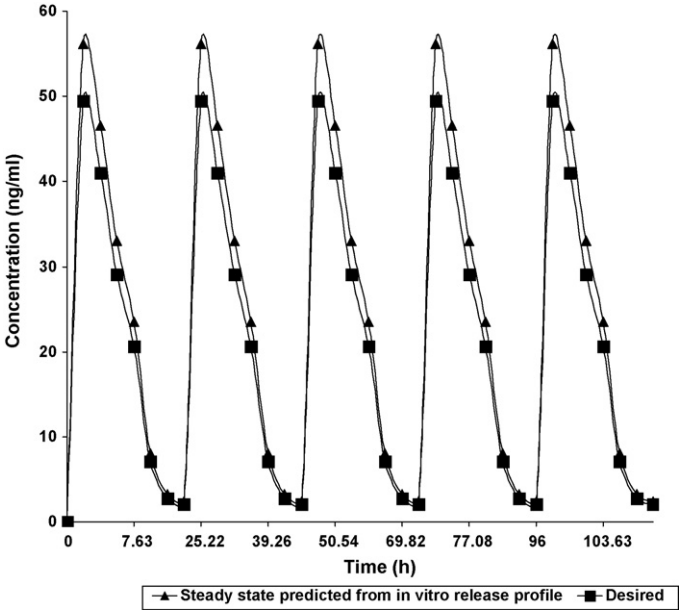

Fig. 7. Predicted steady-state plasma levels of Metoprolol after administration of SOPT formulation in comparison with the desired profile.

dicted from a theoretically designed zero order delivery system. It was clearly evident from the figures that the predicted steady-state plasma levels are very close to the desired levels. The predicted C_{SSmax}, C_{SSmin} and $AUC_{0-\tau}$ after administration of formulation of NP and MP, in comparison with the desired ones are listed in Table 10. The % PD of the steady-state parameters of SF7 formulation was calculated taking the data of desired profile as the reference. The absolute % PD was found to be less than 15%, ensuring that the formulation will produce plasma levels close to the desired ones. Thus, it can be concluded that the developed formulation (SF7) will produce plasma levels well within the therapeutic range and similar to those produced by the desired zero order delivery profile.

4. 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 order kinetics and independent of environment medium and the mobility of the gastrointestinal tract. The feasibility of extending the zero order release pattern of both the drugs were 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 insoluble drug and another freely water soluble drug) used in cardiovascular diseases, diabetes etc.

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