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Development of controlled release formulation based on osmotic technology for a phenyl propanalamine hydrochloride: *in vitro*, pharmacokinetic and pharmacodynamic characterization

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Abstract

Elementary osmotic pump (EOP) for controlled release of phenyl propanolamine hydrochloride (PPA) was developed based on osmotic technology using an osmogen, sodium chloride. The formulations comprise of a core tablet coated with a semi permeable coating polymer and cellulose acetate. The coated tablets are drilled with microneedle and evaluated for physicochemical characteristics and *in vitro* release studies. The optimized formulation was evaluated for *in vivo* performance by pharmacokinetic and pharmacodynamic studies. Zero order release of PPA was achieved with increasing concentrations of osmogen. Bioavailability study in healthy volunteers reveal that the release of PPA from EOP was extended to 24 h compared to immediate release formulation which could release the drug up to 12 h and showed a statistically significant difference ($p<0.05$). The changes in blood pressure and pulse rate after administration of EOP compared to immediate release capsule are insignificant ($p>0.05$). The optimized formulation was found to be stable for 6 months. A good *in vitro-in vivo* correlation was observed and was found to be type A. The EOP containing PPA could be developed. The system can also be used for loading of other water soluble drugs.

Keywords: phenyl propanolamine, elementary osmotic pump, osmotic, extended release, bioavailability

Introduction

Phenylpropanolamine hydrochloride (PPA) belongs to the sympathomimetic amine class of drugs used in nasal decongestion associated with acute or chronic rhinitis, common cold, sinusitis, nasopharyngitis and other respiratory allergic conditions (Moffat et al. 2007). PPA is a component of many proprietary cold preparations. In larger doses, PPA is used as an appetite suppressant and is one of the most popular over-the-counter appetite suppressants in the U.S.A (Dowse et al. 1987). The effects of PPA are largely due to the result of alpha-adrenergic agonist activity resulting from both direct stimulation of adrenergic receptors and release of neuronal norephinephrine. PPA acts on α-adrenergic receptors in the mucosa of the respiratory tract producing vasoconstriction, reduction of tissue hyperemia, edema and nasal congestion, and

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increase in nasal airway patency. PPA also increases heart rate, force of contraction and cardiac output and excitability possibly by indirectly stimulating β-adrenergic receptors in the heart. PPA is readily and completely absorbed from gastrointestinal tract with mean elimination half life of 3.5 hours and has been associated with elevations in blood pressure (Brown et al. 1991, Hoffman and Lefkowitz 1996). It is available as immediate release (IR) formulation; it could result in rapid release of drug that further could cause high plasma levels of PPA. It may result in elevation of blood pressure. In IR 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. To overcome the above problems, control the release of PPA and reduce dosage frequency; a controlled release formulation would be desirable to improve patient compliance and reduce adverse reactions. In the present investigation a controlled release formulation based on osmotic technology was designed.

Oral osmotic pumps are an alternative to polymeric erodible systems (Theeuwes 1994), distinguished by their ability to release drug substances independently of the medium composition and hydrodynamics, these systems offer potential clinical benefits, such as being potentially able to mitigate the food effect (Abrahamsson et al. 1998, Wonnemann et al. 2006), increase patient compliance (Grundy and Foster 1996) and treatment tolerance (Rahima-Maoz et al. 1997). Osmotically controlled drug delivery systems are used to deliver poorly soluble drugs (Theeuwes, 1994, Thombre et al. 2004), and water soluble drugs (Theeuwes and Higuchi 1972, Theeuwes 1975, Kumar et al. 2009).

Elementary osmotic pump (EOP)s are systems for the delivery of a drug in the form of a solution that release the active material at controlled rates. These systems work with the principle of osmosis; Osmotic pressure is produced by active material in itself and/or an accompanying osmotic agent. The preparation consists of the core that contains the active material and a semi permeable membrane that coats the core, having an orifice produced by a microdrill in order to release the active material. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system (Theeuwes et al. 1985, Verma et al. 2000, Verma et al. 2002).

The aim of the present investigation is to develop a controlled release formulation for PPA based on osmotic technology using inexpensive chemicals and to characterize for *in vitro* parameters. The optimized formulation was also evaluated for *in vivo* performance based on pharmacokinetic and pharmacodynamic studies.

Materials and Methods

Phenylpropanolamine hydrochloride is a gift from Rachana Drugs Ltd, India. Sodium chloride, acetonitrile (HPLC), methanol (HPLC) and sodium heptane sulfonate were purchased form Merck, India. Cellulose acetate was purchased from Lobachemie, India. All the other materials used are of analytical grade.

Formulation of elementary osmotic pump containing PPA.

The core tablets of PPA were developed by direct compression technique and the batch size was kept as 500 tablets. PPA was mixed with sodium chloride and microcrystalline cellulose (PH102) for 15 min in a poly bag and passed through 40 #. The blend was then lubricated with magnesium stearate (sifted through

80 #) and talc (sifted through 40 #) for 5 min. The blend was subjected for flow properties like bulk and tap density, Hausner ratio and compressibility index and compressed into tablets using rotary tableting machine (Riddhi, India) using 8 mm round concave punches. The composition was shown in Table 1.

Table 1. Formulation of EOP Tablets using NaCl as osmogen

S. No.	Ingredients (mg)	Formulation codes				
		PPN-10	PPN -25	PPN-50	PPN-75	PPN-100
1	PPH	75	75	75	75	75
2	NaCl	7.5	18.75	37.5	56.25	75
3	MCC	185	166.25	147.25	128.75	110
4	Mg Stearate	1.0	1.0	1.0	1.0	1.0
5	Talc	1.5	1.5	1.5	1.5	1.5

The core tablets were coated using lab scale coating pan (VJ Instruments, India). Cellulose acetate in acetone at a concentration of (4% w/v) containing known level of plasticizer (polyethylene glycol 400, PEG 400) was used as a coating solution. The final coating solution was filtered through muslin cloth. Core tablets of PPA were placed in a stainless steel spherical pan coater along with 250 gm of placebo tablets (tablets made using 6 mm round concave punches and containing microcrystalline cellulose, starch, dibasic calcium phosphate, magnesium stearate and talc) and hot air was passed through the tablet bed for 5 min. The coating was done at a speed of 14-16 rpm, and at a spray rate 2-3 mL min^{-1}. Coating was continued until desired weight gain was obtained on the active tablets. The coated tablets were drilled with microneedle (700 mcn).

Physicochemical evaluation

Weight, thickness, hardness and friability measurement

The core and coated tablets were evaluated for weight variation using digital balance (Shimadzu, Japan). Thickness and diameter of the core and coated tablets was measured using a thickness gauge (Digimatic, Mitutoyo, Japan). Hardness and friability were measured using Pfizer hardness tester and friabilator (Roche, India), respectively.

Assay

Twenty tablets were taken and powdered; powder equivalent to one tablet was taken and was allowed to dissolve in 100 mL of distilled water by sonicating for 5 min followed by shaking for 30 min on a rotary shaker. The solution was filtered through 0.45 µ membrane filter, diluted suitably and analyzed using high performance liquid chromatography (Dowse et al. 1983)

In vitro drug release studies

The release of PPA from EOP was studied using USP dissolution apparatus I (Labindia, India). The dissolution media was 900 mL of distilled water, maintained at 37±0.5°C with a rotation speed of 100. Samples of 5 mL were collected at predetermined time intervals up to 14 h and replenished with an equivalent volume of fresh medium. The samples were filtered through a 0.45 µm membrane filter and diluted suitably with distilled water and analyzed using UV/visible spectrophotometer (Elico, India) at 276 nm. The results are expressed as mean ± S.D of six observations.

Kinetic modeling of drug release

The release kinetics was calculated using following equations 1-4, to identify the mechanism and pattern.

Zero order (Chen and Hao 1998) : $Q = k\,t$

First order (Shah et al. 1987) : $\ln Q = k\,t$

Higuchi (Higuchi 1961) : $Q = kt^{0.5}$

Korsmeyer and Peppas model (Korsmeyer et al. 1983): $Mt/M\infty = kt^{n}$

Where, Q is the amount of drug release, Mt/M∞, fraction of drug released, k is the release rate constant, t is the time and *n* is diffusion coefficient.

Stability studies

The optimized formulation (PPN100) based *in vitro* release was charged for stability according to the ICH guidelines. Sufficient number of EOPs in HDPE containers was stored in humidity chambers at 40°C/75% RH for 6 months. Samples were collected at 1, 2, 3 and 6 months and the physical appearance of the tablets and drug content in the samples was estimated.

In vivo bioavailability studies

In vivo bioavailability study was conducted in 8 healthy male volunteers (age, 24±3.5 years; body weight, 61±3.7 kg) and a randomized crossover design was employed. The ethics committee of the University College of Pharmaceutical Sciences, Kakatiya University, India, approved the study protocol. The volunteers who participated in the study were nonalcoholic and had no medication for 2 weeks prior to the study. The bioavailability of PPA (75 mg) from EOP was compared with an immediate release capsule containing 75 mg of PPA. EOP (PPN100) was administered to one group of volunteers and immediate release capsule to another group. After washout period of 15 days, immediate release capsule was administered to first group and EOP to second group of volunteers. After each treatment, blood samples of 5 mL were collected from anticubetal vein at preset intervals of 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h and were allowed to coagulate. Whole blood samples were centrifuged and serum was separated and stored at -20°C until analysis. PPA was estimated using HPLC method (Dowse et al. 1983).

Analysis of serum samples by HPLC method

Analysis of samples was performed using a Shimadzu HPLC system equipped with a LC-10AT pump, UV/Vis detector and a RP C_{18} column (Phenomenex, 250 x 4.5 mm ID, particle size 5µ) at ambient temperature. The mobile phase used was a mixture of acetonitrile and water containing 5 mM sodium heptane sulfonate at a ratio of 25:75 and at a flow rate of 1.2 mL min^{-1}. The detection was carried out at 220 nm and internal standard used was pseudoephedrine.

A calibration curve was plotted for PPA in serum in the range of 1-1000 ng mL^{-1}. A good linear relationship was observed between the concentration of PPA and the peak area with a correlation coefficient (r^2=0.999). The required studies were carried out to estimate the precision and accuracy of the HPLC method.

Sample preparation

Serum (1 mL) was taken into screw capped tubes followed by the addition of 100 µL of 1500 ng mL^{-1} solution of internal standard (pseudoephedrine). Saturated solution (200 µL) of sodium carbonate was added and mixed for 2 min. All the test tubes were extracted with 2.5 mL of chloroform then shaken for 15 min. The samples were centrifuged for 10 min at 4000 rpm. The chloroform layer was separated, to this 100 µL of 5% v/v acetic acid was added and vortexed for 3 min. Then the upper acetic acid phase (20 µL) was injected into HPLC.

Pharmacokinetic data analysis

Peak serum concentration (C_{Max}), time to reach peak serum concentration (T_{Max}) and area under serum concentration time curve (AUC) were obtained for each subject from serum concentration versus time profile using KINETICA 2000 (Version 3.0, Innaphase corporation, Philadelphia, USA). All data was statistically analyzed using Sigmastat software package (Jandel Corp., USA). Paired t-test was used for comparison of pharmacokinetic parameters. A value of $p<0.05$ was considered to be significant and results were expressed as mean ± SD.

Pharmacodynamic study

PPA is a sympathomimetic agent, is expecting to elevate the blood pressure. To find out the effect of PPA from formulations on blood pressure and pulse rate of volunteer, pharmacodynamic study was conducted. Blood pressure and pulse rate were measured at time points of 0, 0.5, 1, 1.5 and 2 h after administration.

Results and Discussion

Formulation development

The dosage form developed was designed as a tablet core coated with a rate controlling membrane. Tablet core consists of drug along with osmogen and other conventional excipients to form the core compartment. The core compartment is surrounded by a membrane consisting of a semi permeable membrane-forming polymer, water-soluble additives and defined concentration of a plasticizer capable of improving film-forming properties of the polymer. The semipermeable membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane that results in increased osmotic pressure. The osmotic pressure pushes the drug through the orifice. Cellulose acetate was used as coating polymer and PEG400 was used as plasticizer.

Physicochemical evaluation

Weight, thickness, hardness and friability measurement

The weights and thicknesses were found to be ranging from 281.7 to 284.5 mg and 5.56 to 5.81 mm respectively and were considered to be uniform as it was evidenced from relative standard deviation values, which were less than 6. The drug content was ranging from 96 to 98.8 %. The hardness was ranging from 7.4 to 7.8 kg cm^{-2}. The friability was found to be less than 1 (Table 2).

In vitro release

The results of release of PPA from EOP are shown in Fig 1. All the formulations showed lag time. Formulation PPN0 (without osmogen) showed maximum drug release among the formulations. The drug release was ranged from 78.4 to 94.4 % in formulation PPN100 to PPN0 respectively. The difference in final % of drug release was found to be statistically insignificant ($p>0.05$).

Table 2. Evaluation parameters of EOP

S.No	Code	Parameter							
		Weight (mg)	Thickness (mm)	Diameter (mm)	Friability (%)	Hardness (Kg/cm^2)	Weight gain (%)	Assay (%)	Q14 (%)
1	PPN0	284.0	5.63	8.13	0.43	7.4	4.3	97.5	94.4 ± 1.04
2	PPN25	283.2	5.58	8.24	0.56	7.6	4.2	98.8	92.1 ± 0.12
3	PPN50	284.5	5.56	8.16	0.61	7.6	4.0	96.0	84.8 ± 2.20
4	PPN75	281.7	5.81	8.21	0.54	7.8	4.3	97.2	88.0 ± 0.83
5	PPN100	284.1	5.72	8.30	0.39	7.6	4.6	98.8	78.4 ± 1.02

In first hour, there was no drug release in all the formulations indicating that the coating layer delays the release of the drug. However, the release kinetics was changed from formulation PPN0 to PPN100. Formulation PPN0 showed first order release kinetics whereas PPN100 showed zero order release kinetics as it was evidenced from correlation coefficients. As the osmogen concentration in the formulations increased, the drug release kinetics was changed from first order to zero order. This might be due to decrease in solubility of PPA in the tablet as

the osmogen concentration increases and that further decreases the release through the coating, the drug release takes places through the orifice. At low levels of osmogen the drug preferentially present in solubilized form and the release was takes place through the hydrophilic channels of the coating layer, these are expected to form around the coating layer. The incorporation of hydrophilic plasticizer, PEG400 contributes in the sorption of water from gastric fluids and imbibition of osmogen. In PPN100, the concentration of osmogen was high among the formulations, the imbibition of water results in more osmotic pressure, that further pushes the drug through the orifice and zero order release could be achieved. The release pattern was found to be non-fickian type in all the formulations as it was evidenced from release exponent ($0.94 \leq n \geq 1.07$).

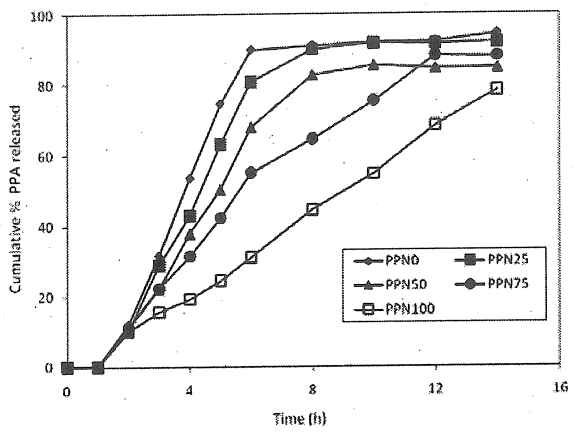

Figure 1. *In vitro* drug release profiles of EOP

In vivo bioavailability studies

The results of bioavailability study (Table 3 and Fig. 2) reveal that PPA is released from EOP and absorbed through gastro intestinal tract. The serum concentrations were observed upto 24 h after administration of EOP in contrast to IR capsule which showed the serum concentrations upto 12 h. The various pharmacokinetic parameters, C_{max}, T_{max}, $AUC_{0\text{-}t}$, AUC_{total} and MRT were compared for EOP and an immediate release capsules in all human volunteers. The C_{max} were found to be 181.2 and 325.2 ng $mL^{-1}$for EOP and capsule formulation, respectively. The pharmacokinetic parameters obtained for IR capsule are in agreement with the earlier reports (Lonner holm et al. 1984, Shargel et al. 1990, Lake et al. 1998). The mean C_{Max} value was higher for IR formulations compared to EOP and was found to be statistically significant ($P<0.05$).This may be due to rapid availability of drug to the system thereby eliciting the higher drug levels in the blood. Whereas in case of volunteers administered with EOP the values were lower, due to the slow availability of drug to the system. Since EOP functions like an extended release dosage form (controlled release) than IR capsule, there is almost two fold increase in the average C_{Max} values in IR capsule. The higher C_{Max} values for IR capsule indicate that the rate of absorption of drug is high when compared to EOP.

Table 3. Pharmacokinetic parameters of PPA in healthy human volunteers after administration of IR capsule and EOP, each containing 75 mg of PPA, values represented are mean ± SD (n=8)

Formulation	C_{Max} (ng mL^{-1})	T_{Max} (h)	AUC_{0-72} (ng h mL^{-1})	$AUC_{0-\infty}$ (ng h mL^{-1})	MRT (h)
IR Capsule	325.2 ± 48.8	1.88 ± 0.52	1444.0 ± 82.2	1575.2 ± 140.74	7.1 ± 0.8
EOP	181.2 ± 11.3	2.15 ± 0.378	1787.6 ± 61.4	2179.3 ± 193.2	12.4 ± 3.0

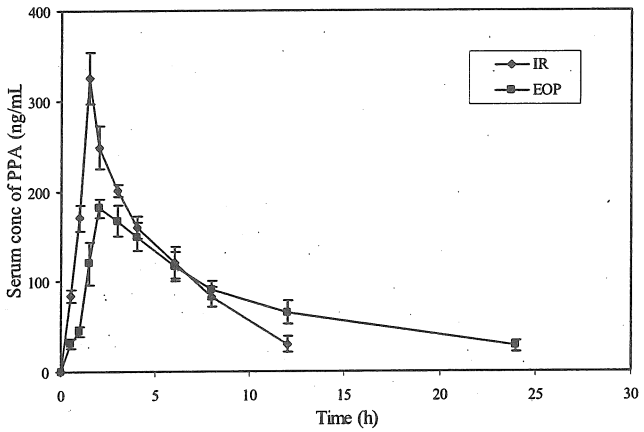

Figure 2. Serum profile of PPA after administration of IR capsule and EOP, each containing 75 mg of PPA in healthy human volunteers, values presented are mean ± SD (n=8)

The average T_{max} values were found to be 1.88 and 2.15 h, respectively, after administration of IR capsule and EOP. The T_{max} values are lower for IR capsule when compared to EOP. This may be due to the rapid dissolution followed by absorption of PPA from IR capsule than EOP. The T_{Max} value obtained for IR capsule from present study is in agreement with earlier reports (Turner et al. 2004)

The AUC_{0-t} and $AUC_{0-\infty}$ were found to be respectively, 1440 and1787.6; 1575.2 and 2179.3 ng h mL^{-1} after administration of IR capsule and EOP. The values obtained from our study are similar to the previous reports (Shargel et al. 1990). The bioavailability of PPA from EOP was showed 1.15 times more than IR capsule. The observed difference in the blood profiles for the two formulations is probably due to the different release profiles rather than the variations in their gastrointestinal transit times. The difference in values sowed statistically significant ($P<0.05$). The mean values of MRT of IR and EOP formulations were found to be 7.1 and 12.4 h, respectively, the difference was statistically significant ($p<0.05$). The MRT value for IR capsule obtained from our study is in agreement with the earlier reports (Sarveshwar Rao et al. 1999). The difference in the MRT values for EOP and IR capsule is due to the difference in the extent of absorption between the two formulations. The variation in the values may be due to the difference in the dissolution profiles.

In vitro-in vivo correlation between % drug released in vitro and AUC

PPA is a water soluble drug and it belongs to class I drug as per the Biopharmaceutics Classification System. Drugs belonging to this category are expected to show a high degree of *in*

vitro-in vivo correlation. Administration of PPA by oral route results in ready absorption from gastro intestinal tract suggests that it has good absorption throughout the GIT. In the present study, point to point correlation (type A) was observed with a correlation coefficient of 0.9685 (Fig. 3). Similar correlations were observed for other water soluble drugs by osmotic technology (Civiale et al. 1991, Turner et al. 2004).

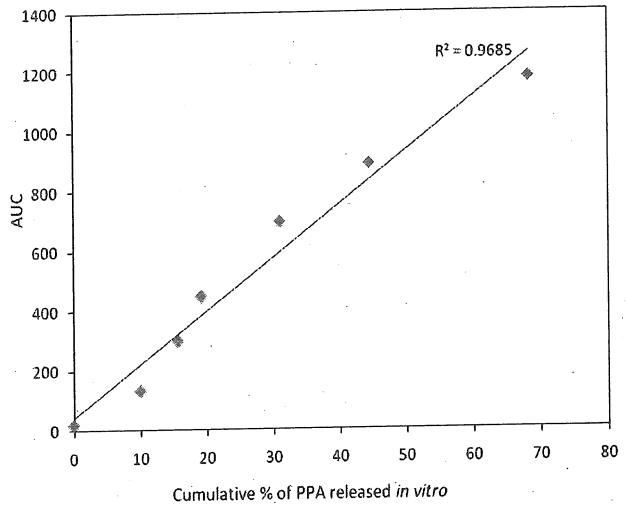

Figure 3. *In vitro-in vivo* correlation

Pharmacodynamic study

The study was undertaken to investigate the effects of PPA on pulse rate, blood pressure in normotensive human subjects following the administration of EOP and IR capsule. The results (Table 4) reveal that both pulse rate and blood pressure were found to be increased at 1.5 and 2 h after administration of IR capsule. However the enhancement rate is low after administration of EOP compared to IR formulation. The results suggesting that EOP is suitable dosage for PPA as showed an insignificant changes in pulse rate and blood pressure.

Table 4. Systolic, diastolic pressures and pulse rate in volunteers after administration of IR and EOP formulations

Time (h)	Systolic pressure (Mean ± SD)		Diastolic pressure (Mean ± SD)		Pulse rate	
	IR	EOP	IR	EOP	IR	EOP
Initial	116.3 ± 5.2	116.3 ± 5.2	80.6 ± 1.8	80.6 ± 1.7	69.3 ± 9.7	70.0 ± 11.6
0.5	116.3 ± 5.2	116.3 ± 3.8	80.6 ± 1.7	80.6 ± 1.8	69.3 ± 9.7	70.0 ± 11.6
1	118.8 ± 6.4	118.8 ± 5.6	80.6 ± 1.8	80.6 ± 1.8	70.0 ± 9.9	70.5 ± 11.2
1.5	125.0 ± 5.4	122.5 ± 7.1	85.6 ± 4.9	80.0 ± 0.0	74.0 ± 9.7	70.5 ± 11.2
2	126.3 ± 5.2	125.0 ± 4.3	85.0 ± 5.3	80.0 ± 0.0	70.5 ± 11.2	70.5 ± 11.2

Stability study

The drug content in the formulation PPN100 was found to be 96.2% after six months. The physical appearance of the tablets was white and as that of initial tablets and could not seen any visible changes on the surface. Since the decrease in drug content is less than 5 %, according to ICH guidelines two years shelf life could be assigned.

Conclusions

Elementary osmotic pump for phenyl propanolamine hydrochloride could be developed using sodium chloride as osmogen. The prepared EOP could extend the release of the drug. The developed system can also be used to control the release of other water soluble drugs. The release rate decreased with an increase in osmogen concentration. The desired release was achieved with 100% osmogen to drug. The EOP has not altered the blood pressure and pulse rate in healthy human volunteers with respect to IR capsule volunteers. There is a good *in vitro-in vivo* correlation between cumulative percent drug released from EOP and AUC values.

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References

Abrahamsson, B., Alpsten, M., Bake, B. and Jonsson, U.E. (1998). Eriksson-Lepkowska, M.; Larsson, A. Drug absorption fromnifedipine hydrophilic matrix extendedrelease (ER) tablet-comparison with an osmotic pump tablet and effect of food. *J. Control. Rel.* 52: 301–310.

Brown, N.J., Ryder, D. and Branch, R.A. (1991). Apharmacodynamic interaction between caffeine and phenylpropanolamine. *Clin. Pharmaco.l Ther.* 50: 363–371.

Chen, G.L. and Hao, W.H. (1998). In vitro performance of floating sustained release capsules of verapamil. *Drug Dev. Ind. Pharm.* 24: 1067–1072.

Civiale, C., Ritschel, W.A, Shiu, G.K, Aiache, J.M. and Beyssac, E. (1991). In vitro–in vivo correlation of salbutamol release from a controlled release osmotic pump delivery system. *Methods Exp. Clin. Pharmacol.* 13: 491-498.

Dowse, R., Ha, J.M. and Kanfer, I. (1987). Pharmacokinetics of phenyl propanolamine in humans after a single-dose study. *Int. J. Pharm.* 39: 141-148.

Dowse, R., Haigh, J.M. and Kanfer, I. (1983). Determination of phenylpropanolamine in serum and urine by high-performance liquid chromatography. *J. Pharm. Sci.* 72: 1018-1020.

Grundy, J.S. and Foster, R.T. (1996). The nifedipine gastrointestinal therapeutic system (GITS). Evaluation of pharmaceutical, pharmacokinetic and pharmacological properties. *Clin. Pharmacokinet.* 30: 28–51.

Higuchi, T. (1961). Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.* 50: 874–875.

Hoffman, B.B. and Lefkowitz, R.L. (1996). Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In *Goodman and Gilman's The Pharmcological Basis of Therapeutics*, 9th ed. McGraw-Hill, New York, pp 223.

Korsmeyer, R.W., Deolkar, G.E.P and Peppas, N.A. (1983). Mechanisms of potassium chloride from compressed, hydrophilic, polymeric matrices: effect of entrapped air. *J. Pharm. Sci.* 72: 1189–1191.

Kumar, P, Singh, S and Mishra, B. (2009). Development and evaluation of elementary osmotic pump of highly water soluble drug: tramadol hydrochloride *Curr. Drug Deliv.* 6: 130-139.

Lake, C.R., Zaloga, G., Clymer, R., Quick, R.M. and Chernow, B. (1998). A double dose of phenyl propanolamine hydrochloride, causes transient hypertension *Am. J. Med.* 8: 339-343.

Lonner holm, G., Grahnen, A. and Lindstrom, B. (1984). Steady state kinetics of sustained release phenylpropanolamine hydrochloride. *Int. J. Clin. Pharmacol. Tner. Toxicol.* 22: 39-41.

Moffat, A.C., Osselton, M.D., Widdop, B. and Watts, J. (2007). Clarke's analysis of drugs and poisons 3rd Ed. Pharma Press, USA.

Rahima-Maoz, C., Grossman, E., Nussinovitch, N., Katz, A. and Rosenthal, T. (1997). Nifedipine GITS replacing nifedipine SR: ambulatory blood pressure assessment of efficacy. *Cardiology* 88: 43–46.

Sarveshwar Rao, V.V, Rambhau, D., Ramesh Rao, B. and Sreenivas, P. (1999). Time dependent pharmacokinetic interaction between phenylpropanolamine and chlorpheniramine maleate in human subjects. *Drug. Met. Drug Inter.* 15: 259-268.

Shah, M.V, De Gennaro, M.D. and Suryakarma, H. (1987). An evaluation of albumin microcapsules prepared using a multiple emulsion technique. *J. Microencapsul.* 4: 223–238.

Shargel, L., Silvermann, H., Cohen, P., Brisson, J. and Dennis, S. (1990). Bioavailability and cardiovasucular safety of Dexatrin (PPA) from a controlled release caplet. *Biopharm. Drug Dispo.* 11: 569-583.

Theeuwes, F. (1975). Elementary osmotic pump. *J. Pharm. Sci.* 64: 1987–1991.

Theeuwes, F. (1994). Oral dosage form design—status and goals of oral osmotic systems technology. *Pharm. Int.* 5: 293–296.

Theeuwes, F. and Higuchi, T. (1972). Osmotic dispensing device for releasing beneficial agent. United States Patent 3,845,770.

Theeuwes, F., Swanson, D.R., Guittard, G., Ayer, A. and Khanna, S. (1985). Osmotic delivery systems for the b-adrenoceptor antagonists metoprolol and oxprenolol: design and evaluation of systems for once-daily administration. *Br. J. Clin. Pharmacol.* 19: 69S–76S.

Thombre, A.G., Appel, L.E., Chidlaw, M.B., Daugherity, P.D, Dumont, F., Evans, L.A.F. and Sutton, S.C. (2004). Osmotic drug delivery using swellable-core technology. *J. Control Rel.* 94: 75–89.

Turner, S., Federici, C., Hite, M. and Fassihi, R. (2004). Formulation development and human in vitro–in vivo correlation for a novel monolithic controlled release matrix system of high load and highly water soluble drug niacin. *Drug Dev. Ind. Pharm.* 30: 797-807.

Verma, R.K, Mishra, B. and Garg, S. (2000). Osmotically controlled oral drug delivery, *Drug Dev. Ind. Pharm.* 26: 695–708.

Verma, R.K., Krishna, D.M. and Garg, S. (2002). Formulation aspects in the development of osmotically controlled oral drug delivery systems. *J. Control. Re.l* 79: 7–27.

Wonnemann, M., Schug, B., Schmucker, K., Brendel, E., van Zwieten, P.A. and Blumel, H. (2006). Significant food interactions observed with a nifedipine modifiedrelease formulation marketed in the EuropeanUnion. *Int. J. Clin. Pharm. Ther.* 44: 38–48.

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