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FORMULATION AND EVALUATION OF MONOLITHIC OSMOTIC TABLETS FOR CONTROLLED DELIVERY OF NIFEDIPINE

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ABSTRACT

An oral monolithic osmotically controlled delivery system for Nifedepine using asymmetric membrane technology was developed and evaluated. Unlike conventional osmotic systems, which require laser drilling, this system releases the drug in a controlled manner from asymmetric membrane coated core tablets. Asymmetric membrane is formed by dry process with phase inversion technology process using cellulose acetate as the coating material. Higher water influx of this membrane aids in delivery of Nifedepine, which is highly water insoluble with low osmotic pressure. The porous structure of the membrane was confirmed by scanning electron microscopy. Influence of different osmotic agents on drug release was evaluated. In vitro release studies showed that as concentration of osmotic agents was increased, the drug release was also enhanced. Drug release from the developed monolithic system was independent of external agitation and pH of dissolution media. Comparative in vitro release data was obtained using different types of coating membranes like controlled porosity membrane and dense coating membrane with mechanically drilled orifice. Osmotic pressure generated in the system was determined using freezing point osmometer. The osmotic pressure developed was found to be linearly proportional to time and concentration of osmotic agent.

INTRODUCTION: Osmotic systems for controlled drug delivery employs osmotic pressure gradient as the driving force allowing maintenance of plasma concentration within the therapeutic range. Because pharmaceutical agents can be delivered in a controlled manner over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices in past few decades. The elementary osmotic pump (EOP) was introduced by Theeuwes. The EOP is very simple to prepare and releases drug at an approximate zero-order rate.

However, the generic EOP is only suitable for the delivery of water-soluble drugs. To overcome the limitation of EOP, two-compartment, two-layer push–pull, monolithic osmotic system and sandwiched osmotic delivery system (three-layer osmotic system) were developed. All such osmotic tablet systems have a common disadvantage; a sophisticated laser- drilling technique is needed, to make the delivery orifice [1, 2]. Various attempts to increase the permeability of the coating have been reported, including addition of plasticizers in the coating, such as incorporating water-soluble additives in the coating and using multilayer composite coating.

To further increase coating permeability, an osmotic tablet was developed that consisted of a homogenous tablet core coated with an asymmetric membrane film. Herbig et al. described dip-coated tablets with an asymmetric coating solution composed of 15% cellulose acetate (CA) dissolved in acetone and either formamide or glycerol. The dip-coated tablet was air dried for 5 min and subsequently immersed in a water quench bath for 3 min. A final air-drying step was performed for at least 12 hr at ambient conditions [3].

Preparation Method for Asymmetric Membrane Coated Osmotic Tablet: The asymmetric membrane coated osmotic tablets using conventional spray-coating technique have been developed. The coating process is a dry process and the asymmetric membrane is formed by phase inversion technology controlled by evaporation of mixed solvent system. Phase inversion denotes the process of transforming a polymer in solution to a macromolecular gel. This transformation proceeds from a state in which the solvent is the continuous phase to a state where the polymer is the continuous phase. Originally, the polymer is dissolved in a solvent system that constitutes a single phase, followed by formation of two inter dispersed liquid phases. Further drying results in formation of a gel. The dry process involves use of a solvent system for both the polymer and pore former. The pore former acts as a non-solvent for polymer in this process. During membrane formation, the solvents evaporate more rapidly than pore former to create the asymmetric membrane [4].

Advantages of Asymmetric Membrane Coating Osmotic Tablet: This asymmetric membrane coating offers several significant advantages over conventional osmotic tablets. High water fluxes can be achieved using asymmetric coatings, facilitating osmotic delivery of drugs with low solubility and enabling higher release rates. The permeability of the coating to water can be adjusted by controlling the membrane structure without altering the coating material or significantly varying the coating thickness [5]. Nifedipine, a widely used antianginal and antihypertensive agent was chosen as the model drug. It is highly water- insoluble with a solubility of ≤10 µg/ml. The objective of the study was to develop once-a-day osmotically controlled asymmetric membrane coated tablets of nifedipine.[6]

MATERIALS AND METHODS: Nifedipine was obtained as a gift sample from Arch Pharmaceutical Pvt. Ltd., India. It is a yellow, crystalline powder with melting point in the range of 174–176°C. The percent purity of the drug sample was found to be 99.89 ± 0.5% on dry basis. Guar gum used as the hydrophilic swelling polymer and various osmogents like sodium chloride, potassium chloride, mannitol, spray-dried lactose, and fructose used for osmotic delivery of nifedipine were obtained from S.D. Fine Chemicals Ltd. Cellulose Acetate (Sigma Chemicals Pvt. Ltd) was used to form a semipermeable membrane. The degree of polymerization of cellulose acetate depends on the number of acetyl groups present in it. As cellulose acetate used in the study contains 39.8% acetyl content it has good tensile strength and hence forms a perfect semipermeable membrane at concentration of 2% w/v. Butanol, ethanol, glycerol (S.D. Fine Chemicals) and distilled water were employed as volatile and nonvolatile pore formers in the semipermeable membrane. Buffers of pH 1.2 (hydrochloric acid), phosphate buffer pH 6.8 (KH_2PO_4) and phosphate buffer pH 7.4 (KH_2PO_4, NaOH) were employed as dissolution media. All chemicals/reagents used were of analytical grade.

Preparation of Core Tablets: The drug, osmogents, and lubricant were weighed accurately and sieved through 85# sieve. The drug and ingredients were mixed in geometric proportion to form a uniform blend of powder ready for direct compression. The uniform blend of powder was directly compressed on a single-punch tablet machine using 10.5 mm-deep concave punches. The tablets were prepared using osmogents like sodium chloride, potassium chloride, mannitol, spray- dried lactose, and fructose in varying ratios. The tablets were evaluated for the different physicochemical parameters, viz. appearance, weight variation, thickness, hardness, friability, drug content, and in vitro release.[7]

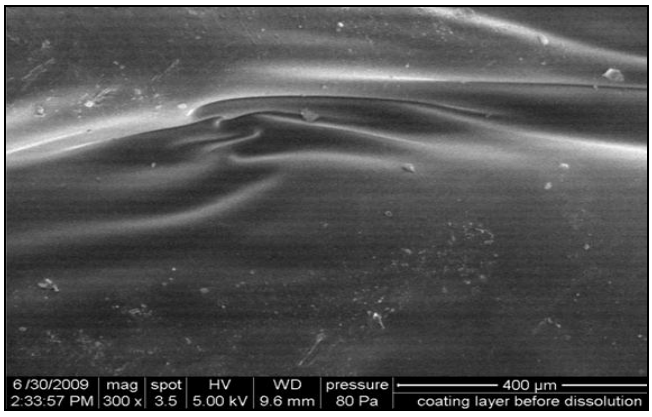
Preparation of Coating Material:

Asymmetric Membrane (AM) Coating: The coating solution used for asymmetric coating consisted of cellulose acetate dissolved in acetone containing mixture of volatile and nonvolatile pore formers. The volatile pore formers used were ethanol (2.9% w/w) and butanol (1.5% w/w). The nonvolatile pore formers used were glycerol (0.4% w/w) and water (0.5% w/w).

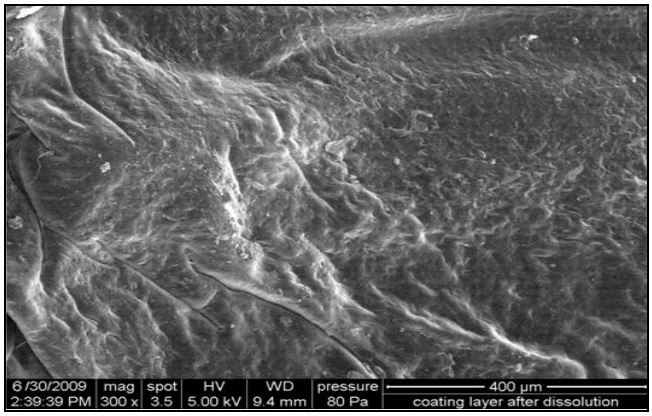
Controlled Porosity Coating: The coating solution consisted of cellulose acetate (2% w/w) with a water-soluble pore-forming agent like polyethylene Glycol 400 (PEG 400; 20% w/w) in acetone. When such system comes in contact with water, a pore-forming agent leaches out, leaving behind a micro porous structure.

Dense Coating: Cellulose acetate (2% w/w) in acetone without pore formers was used to form a dense coat. An orifice was mechanically drilled using 26-gauge needle having 0.2 mm diameter. All the coating solutions were applied to the osmotic core tablets in a conventional coating pan by a spray-coating process. The coating parameters were optimized with respect to coating pan speed (25 rpm), coating pan temperature (40–45°C), nozzle pressure (10–50 psi) and coating solution spraying rate (3–4 ml/min). After coating, the tablets were dried overnight at 60°C to remove the residual solvent. The surface morphology of the coated

tablet was studied using SEM photomicrographs [8].



A. SPM BEFORE IN VITRO DISSOLUTION



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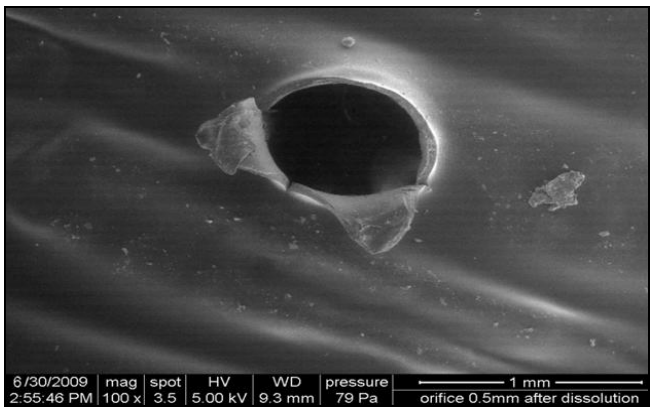

C. ORIFICE OVERVIEW AFTER IN VITRO DISSOLUTION

PHOTOMICROGRAPHS OF SURFACE MORPHOLOGY

***In- Vitro* Release Studies:** An n-octanol/phosphate buffer pH 7.4 two-phase dissolution test method using USP XXIII was employed to study the in vitro release profile. Nifedipine osmotic tablets were placed in aqueous SIF in individual dissolution vessels. The SIF saturated n-octanol was then slowly layered on the aqueous phase and stirring was begun at the specified rotation speed. During the release studies, a 5-ml sample of n-octanol phase with replacement was pipetted out and kept in vials for 1, 2, 4, 8, 12, 16, and 24 h, respectively in a dark place, following initiation of the release test. All samples were analyzed by UV Spectrophotometer (JASCO) at λmax 235 nm.[9]

Effect of Dissolution Media on the Release Profile of Nifedepine: Gastrointestinal pH differs along the tract from pH 1.2–8.0. An osmotically controlled-release system delivers its contents independent of external variables. To investigate the influence of release media on drug release, the in vitro release test was conducted in pH media 6.8, 1.2, and 7.4 respectively.

Measurement of Osmotic Pressure: Drug release from osmotic systems depends upon osmotic pressure generated within the tablet. The effect of osmotic pressure on drug release was assessed by performing in vitro release studies. Osmotic pressure generated within the tablet was determined using 3D3 Freezing point osmometer (Model 3D3 Advanced Instruments Inc). Osmometer was calibrated using standard solutions of 100 mOsm/kg and 1,500 mOsm/kg. Intact tablet was kept in a beaker containing 20 ml of dissolution medium. At intervals of 1 h each for a period of 24 h, 0.25 ml of dissolution medium was pipetted into a disposable sample cup, which was then placed into the freezing

chamber maintained at −7°C. At the start of the experiment, a probe containing a thermistor and stir wire descends into the sample. Over the next minute, the sample was super cooled below its freezing point. The stir wire then vibrates, causing rapid freezing. The equilibrium temperature (i.e., the freezing point) is measured, and a microprocessor converts the freezing point to osmolality and displays the result in mOsm/kg [10, 11].

Comparative Studies with Different Coating Membranes: The release profiles of asymmetrically coated osmotic tablets were compared with those from controlled porosity osmotic tablets and osmotic tablets with mechanically drilled orifice.

Visual Inspection of Tablets: The developed monolithic osmotic tablets were visually inspected for formation of pores. The tablet was placed in dissolution medium and photographs were taken after specified interval of time.

Statistical Analysis: Experimental results were expressed as mean ± SD values. Student's t test was performed to determine the level of significance between the monolithic tablets in which no osmotic agents were added and monolithic tablets containing various proportions of osmotic agents. Dependent variable was concentration of osmotic agent and Independent variables were pH and agitation rate. Two-way analysis of variance was used to assess the difference in release rate from the osmotic tablet with different types of osmogent. Differences were considered to be statistically significant at $p < 0.05$. The statistical data was obtained using Fast Statistics software.

RESULTS AND DISCUSSION:

Asymmetric Membrane Coating: Asymmetric membrane coatings were made via a phase inversion process. Tablets were spray coated in a conventional coating pan. The polymer solution used to form the asymmetric membrane was prepared by dissolving cellulose acetate in a mixture of at least two solvents. The solvents were chosen to have different boiling points so that the more volatile solvent is a good solvent for the polymer and a less volatile solvent is a non- solvent for the polymer. Volatile solvents used were ethanol and n-butanol as they vaporize quickly with less residual content and were of GRAS standards.

The nonvolatile pore formers used were glycerol (0.4% w/w) and water (0.5% w/w). This evaporation of the solvent mixture results in a progressive shift in composition from good- to poor solvent resulting in abrupt precipitation of the polymer, which controls the porosity of the membrane. Asymmetric membrane coatings on tablets made by phase inversion process consisted of a highly porous membrane when compared to dense coating and controlled porosity coating.

***In Vitro* Release Studies:** To demonstrate osmotic-pressure-modulated profile, Nifedepine tablets coated with an asymmetric cellulose acetate membrane were investigated. The drug release of Nifedepine formulations with different osmogents is shown. It was found that with potassium chloride as osmogent (76.2% w/w) the drug release was 50%. To increase the drug release further, a higher osmogent, i.e., sodium chloride (10.1% w/w) was used but sodium chloride alone was not able to release

the drug through the pores formed in the membrane. A combination of sodium chloride and mannitol in a ratio of 1:1.1 gave a highest release of 78.83% in n-octanol and 5% release in phosphate buffer to give a total release of 83% when compared to sodium chloride: spray-dried lactose (48%) and mannitol: fructose combination (57%). The correlation coefficient indicated linear relationship between the percent cumulative drug released and the in vitro release time and suggests that the system follows zero-order release irrespective of the proportion of the drug/osmogent (table 1).

TABLE 1: COMPARATIVE IN VITRO RELEASE KINETICS FROM MONOLITHIC OSMOTIC TABLETS

RATIO (mg)	ZERO ORDER	
	R^2	K_0 (mg h^{-1})
Nifedepine: KCl (1:6.2)	0.899	1.56
Nifedepine: NaCl (1:0.9)	0.902	1.78
Nifedepine: NaCl: mannitol (1:9.3)	0.995	2.91
Nifedepine: NaCl: spray-dried lactose (1:9.3)	0.912	1.45
Nifedepine: Mannitol: fructose (1:6.8)	0.897	1.12

R^2 correlation coefficient, K_0 zero-order rate constant

The amount of the drug released from each system depends upon the amount of osmogent as evident from the zero-order release rate constants. The correlation coefficient between the zero-order release rate constant and the amount of osmogent was found to be 0.8991 for potassium chloride, 0.9021 for sodium chloride, 0.995 for combination of sodium chloride and mannitol, 0.9121 for sodium chloride and spray-dried lactose and 0.8976 for mannitol and fructose (fig. 1). The good linear relationship in case of mannitol and sodium chloride suggests that the amount of mannitol and sodium

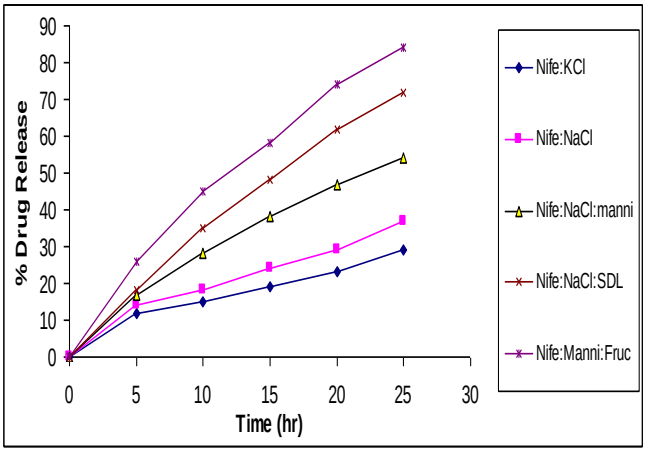

FIG. 1: DRUG RELEASE PROFILE USING DIFFERENT OSMOGENTS IN VARYING RATIO

chloride required to achieve maximum release of drug can be predicted from the regression equation obtained. Thus, AM-coated osmotic tablets showed both dissolution and diffusion controlled drug-release kinetics. The mechanism of drug release from an AM osmotic tablet consists of imbibition of water through the membrane into the tablet core, dissolution of soluble components in the core and pumping of the solution out of pores in the membrane. The imbibition of water through the membrane is driven by its thermodynamic activity gradient between the external medium, e.g., receptor solution or gastric/ intestinal fluids, and the osmotic agent(s) in the core. Dissolution of the soluble components within the core produces the activity gradient and establishes the osmotic pressure difference between the core and external environment. As water diffuses into the core, the volume of the imbibed water creates a hydrostatic pressure difference across the membrane, which forces the solution out through the pores in the coating.

Effect of Dissolution Media on the Release Profile of Nifedepine: The asymmetrically

coated osmotic tablets were evaluated for effect of different pH media on the release of the drug from the osmotic controlled-release formulations. The dissolution medium used was pH 1.2, pH 6.8, and pH 7.4. No significant change in the release rate of Nifedepine from the osmotic tablets was observed at different pH of the dissolution medium. In other words, asymmetric-coated monolithic osmotic tablets exhibited a media-independent release. Thus, it may be expected that the fluid in different parts of the gastrointestinal tract scarcely affect drug release of the asymmetric-coated monolithic osmotic system.

Effect of Agitation Rate on the Release Profile of Nifedepine: This test relates the gastrointestinal motility to the drug- release profile. The asymmetrically coated osmotic tablets were evaluated for the effect of agitation rate of dissolution medium on the release profile of Nifedepine from the pores formed in the membrane. No significant change in the release rate of Nifedepine from the osmotic tablet was observed with changes in the agitation rate. This proves that the drug release from osmotic system is not affected by GI motility.

Effect of Osmotic Pressure on the Drug Release: It was found that the osmotic pressure increased linearly with time. The plot of osmotic pressure with drug release gave a linear increase in the release rate. Thus, as the osmotic pressure increased with time the drug release was increased proportionately. Thus, rate of drug release was found to be directly proportional to the difference in osmotic pressure generated within the osmotic delivery system. The density of the coating membrane was found to increase when the concentration of cellulose acetate was increased from 2–5% w/v. As the density increases, the water ingress through the membrane decreases which results in lowering of osmotic pressure gradient inside the tablet core. Initially, chemical potential of water outside tablet is high as compared to that of inner tablet core; hence, to attain equilibrium, the water flux is from higher concentration to lower concentration through semi permeable membrane which results increase in osmotic pressure inside the tablet thus resulting in drug release. To confirm osmotic pressure as the driving force for drug release, dissolution studies were carried out using a two-phase dissolution system. Phosphate buffer 7.4 in the lower phase of the dissolution medium was replaced with phosphate buffer 7.4 containing 0.1 M NaCl as osmogent. When the dissolution medium consisted of phosphate buffer 7.4 as the aqueous phase, the drug was found to be released and when the lower phase was replaced by phosphate buffer containing osmogent, drug release was found to be retarded. Again, when the lower phase was replaced by phosphate buffer 7.4, the drug was again found to be released thereby confirming that osmotic pressure plays an important role in releasing the drug through the pores formed in the membrane.

Comparative Studies with Different Coating Membranes: It can be observed from that the tablets having asymmetric coating showed a higher release of 78.83% in n-octanol in a controlled manner when compared to osmotic formulations with mechanically drilled orifice, which gave a release of 50% in n-octanol. The drug release from controlled porosity tablets was also found to be in controlled

manner but the total amount of drug released was 62% in 24 h in n-octanol, which was lesser as compared to monolithic osmotic tablets coated with asymmetric membrane. The release rate of the drug through asymmetric membrane was found to increase due to its high permeability (fig. 2). The release rate was studied using different kinetics equations like zero-order, first-order, Higuchi and Korsmeyer equation. From the values of goodness-of-fit and correlation, it can be seen that good correlation is achieved with asymmetric membrane as compared to the other two membrane coatings (table 2).

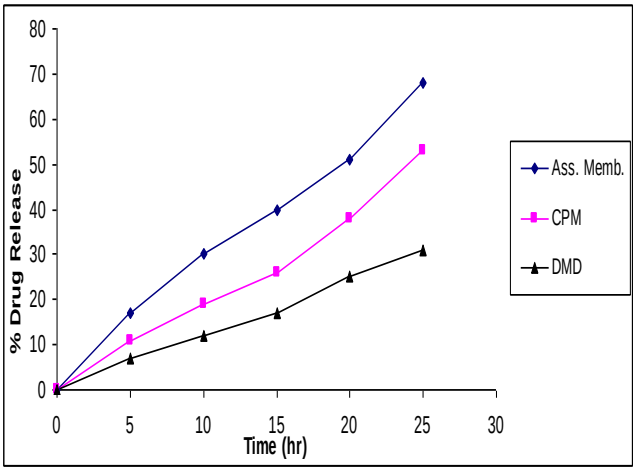

Fig. 2: DRUG RELEASE PROFILE USING DIFFERENT MEMBRANE

TABLE 2: IN VITRO RELEASE PROFILE OBTAINED USING DIFFERENT KINETICS EQUATION

BATCHES	MATHEMATICAL MODEL					
	ZERO ORDER		FIRST ORDER		HIGUCHI	
	R^2	r	R^2	r	R^2	r
Asymmetric membrane	0.9824	0.9915	0.9226	0.9625	0.8998	0.8855
Controlled porosity membrane	0.9512	0.9677	0.9234	0.9134	0.8813	0.8879
Dense coat with mechanically drilled Orifice	0.8891	0.8976	0.9345	0.9451	0.9076	0.9465

R^2: Goodness-of-fit, r correlation coefficient

Visual Inspection of Tablets: The changes in the appearance of the osmotic tablets during the dissolution process are shown. As soon as the tablet is suspended in the dissolution medium, the pores in the membrane allow the medium to enter the tablet. This starts dissolving the osmogent thus creating an osmotic pressure gradient.

Statistical Analysis: Two-way analysis of variance was carried out using concentration of osmotic agents as dependent variable and agitation rate and pH as independent variables. The effects of different concentrations of NaCl and mannitol which were used as osmogents on drug release were investigated. It was found that as the concentration of NaCl and mannitol was increased above 42% and 47%, respectively, the drug release was increased drastically. The optimum concentration for synergistic effect was between 40–45% for both the osmotic agents. Statistical data obtained from two-way analysis of variance at 5% level of significance, reveals that there is significant difference in Nifedepine release from monolithic osmotic tablet with osmotic agents and monolithic osmotic tablet without osmotic agent (between ratios F = 17.54).

TABLE 3: STATISTICAL DATA FROM TWO-WAY ANOVA ANALYSIS

FORMULATIONS	MAXIMUM NIFEDEPINE RELEASED (%)
Nifedepine: Osmogent (1:2.5)	20 ± 1.5b
Nifedepine: Osmogent (1:5)	40 ± 1.2 b
Nifedepine: Osmogent (1:10)	83 ± 1.1b
Monolithic osmotic tablet without any osmogents	11 ± 1.4b

a) Mean and standard deviation (N =6);
b) Significant difference compared to monolithic osmotic tablet without osmogents; $p < 0.05$

CONCLUSION: The results suggest that the drug delivery from asymmetric membrane is mainly controlled by the osmotic pressure generated in the tablet core. The drug release takes place via the in situ formed micro porous structure. Developed osmotically controlled oral delivery system can be used as once-a-day controlled-release formulation, thus increasing patient compliance. This system is cost effective and simple to prepare as no drilling is required and can be used for controlled delivery of water-insoluble drugs.

REFERENCE:

1. Longxiao L, and Xiangning X: Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. International Journal of Pharmaceutics 2008; 352: 225–230.
2. Thakor R, Majmudar F, Patel J, Rajput G: Osmotic Drug Delivery Systems Current Scenario: Review. Journal of pharmacy research 2010; 3(4).
3. Herbig S, Cardinal J, Korsmeyer R, and Smith K: Asymmetric-membrane tablet coatings for osmotic drug delivery. Journal of Controlled Release 1995; 35:127-136.
4. Choudhury P, Pillai M, Chauhan C, and Ranawat M: Asymmetric membrane capsule for osmotic delivery of flurbiprofen. Acta Pharm 2007; 57: 343–350.
5. Sharma S: Osmotic controlled drug delivery system Pharmainfo.net 2006; 6: 3.
6. Bhanushali R, Wakode R, Bajaj A: Monolithic osmotic tablets for controlled delivery of antihypertensive drug. Journal of Pharmaceutical Innovation 2009; 4:63–70.
7. Liu L, Khang G, Rhee JM, and Lee HB: Sandwiched osmotic tablet core for nifedipine controlled delivery. Bio-medical materials and engineering 1999; 9:297-310.
8. Liu L, Khang G, Rhee JM, and Lee HB: Preparation and Characterization of Cellulose Acetate Membrane for Monolithic osmotic tablet. Korea polymer journal 1999; 7:289-296.
9. Liu X, Chen D, and Zhang R: Evaluation of monolithic osmotic tablet system for nifedipine delivery in vitro and in vivo. Drug development and industrial pharmacy 2003; 29, 813 – 819.
10. Kanagale P, Lohray B, Misra A, Davadra P, Kini R: Formulation and Optimization of Porous Osmotic Pump–based Controlled Release System of Oxybutynin. AAPS Pharm. Sci. Tech 2007; 8: 53.
11. Sinchaipanid N, Pongwai S, Limsuwan P, Mitrevej A : Design of salbutamol eop tablets from pharmacokinetics parameters. Pharmaceutical development and technology 2003, Vol. 8, 2, 135-142.