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Research Article

FORMULATION AND EVALUATION OF OSMOTIC PUMP TABLET OF CEFADROXIL

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ABSTRACT

Objective: To developed a coated osmotic pump tablet of cefadroxil to increase its half life and to protect it from degradation in gastric fluid. Osmotic pump tablet was prepared by wet granulation technique.

Method: Here Nacl was used as osmogen and CAP as coating solution for tablet having definite orifice. The quantity of NaCl, MCC and the ratio of coating solution were optimized to obtain best release rate of the drug. Then the best Formulation was coated with single, double and triple layers with different concentration of PEG and CAP. Result: It was found that drug release rate increased with the amount of osmogen because of the increased water uptake, and hence increased driving force for drug release whereas, thickness of coating decreases the rate of release of drug.

Conclusion: Osmotic pump of cefadroxil (antibiotic) should give rapid onset of drug release as well as prolong effect. Drug release from OPT showed zero order kinetics. Osmotic pump tablet of cefadroxil showed increased half life of and protected from gastric pH.

Keywords: Cefadroxil (API), CAP (Cellulose acetate phthalate), OPT (osmotic pump tablet). PEG (polyethylene glycol).

INTRODUCTION

To increase the half life of drug as well as to protects it from degradation in gastric fluid. Many drug delivery systems have been designed by various researchers to modulate the release of drug over an extended period of time [1]. Osmotic pump tablets (OPT) or oral osmotic releasing system (OROS) are the delivery systems which is based on the osmosis for controlling the drug release. They are also known as gastro intestinal therapeutic system. It consist four main components-

- Semi-permeable membrane (SPM) that surrounds the drug core.
- Drug (API) is responsible for pharmacological activities.
- Osmogent that imbibes water and generates osmotic pressure that drives the dissolved/ dispersed drug through the delivery orifice.
- The orifice for delivery of drug. [2]

Osmogent are the agents which are used to create pressure in the osmotic system for dispensing drug. They are of inorganic or organic in nature. Types of Osmogent are:

Inorganic water-soluble Osmogent

Sodium chloride (356 atm), Potassium chloride (245 atm).

Organic polymer Osmogent

Sucrose (150 atm), Fructose (335 atm) [3]

$$\pi = n_2RT$$

In the historical development of the OPT, there were many achievements for its promotion including the Rose–Nelson pump [4] Higuchi–Leeper pump [5] Elementary osmotic pump tablet (EOPT) [6]. Osmotically controlled drug delivery system, deliver the drug in large extent and the delivery is independent to the physiological factors of gastro-intestinal tract(GIT) hence they follows zero order kinetics rate. Osmotic pressure is the colligative property, which depends on concentration of solute. Solution of different concentration is directly proportional to the osmotic pressure, hence osmosis occur till equilibrium will reach both side of SPM. An expression state osmotic coefficient:

Whereas: π = osmotic coefficient

n_2 = molar concentration of solute in the solution, R = gas constant T = absolute temperature

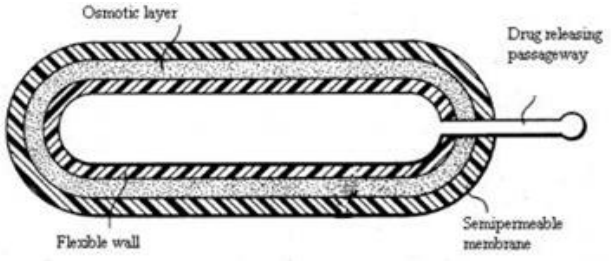

Fig. 1: Elementary osmotic pump

Elementary osmotic pump (EOP) consist single layer tablet core containing drug and an Osmogent enclosed by SPM having delivery orifice. After coming in contact with the aqueous fluids of gastro-intestinal tract, it imbibes water and forms a saturated solution of drug that is pumped through the delivery orifice at a controlled rate [7]. The EOP is release drug at an approximate zero-order rate [8]. However, it is suitable for delivery of water soluble drugs.

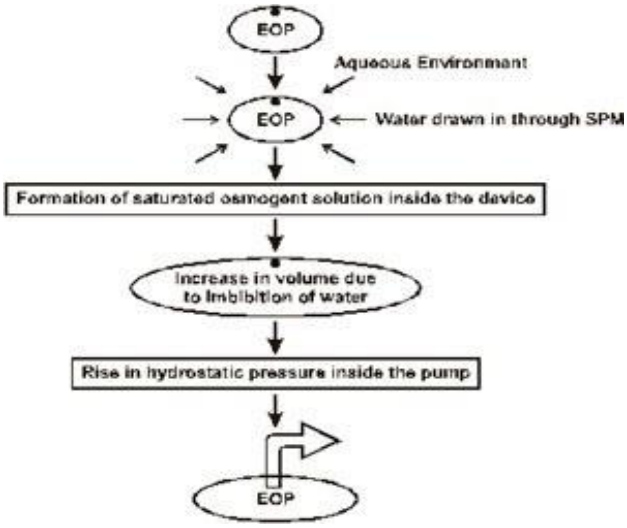

Fig. 2: Mode of action of elementary osmotic pump.

Cefadroxil was chosen as a model drug, water soluble as well most widely used as antibacterial drug. Cefadroxil is 7-[2-amino-2-(4-hydroxyphenyl) acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylicacid [9].

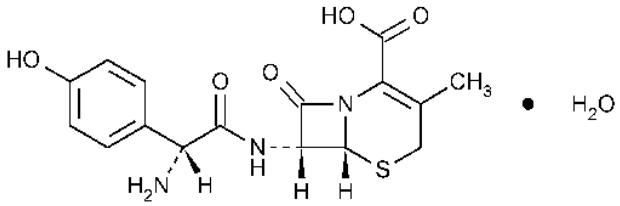

Fig. 3: Molecular structure of Cefadroxil drug

Molecular formula- $C_{16}H_{17}N_3O_5S{\cdot}H_2O$ Molecular weight- 381.40

It is used to treat urinary tract infections, skin and skin structure infections, pharyngitis, and tonsillitis. Cefadroxil is well absorbed on oral administration; food does not interfere with its absorption but binding rates of cefadroxil were 28.1% by U.F. method hence Over 90% of the drug is excreted unchanged in the urine within 24 hours. Cefadroxil have short half life of 1.5 hrs [9].

MATERIAL AND METHOD

Chemicals and Reagents

Cefadroxil (antibacterial) was a gifted sample by Solisto pharmaceutical ltd. Where Sodium NaCl, Microcrystalline cellulose (MCC), Magnesium stearate, Sodium laurate sulphate (SLS), Starch, Providone, Talc, Cellulose-acetate phthalate (CAP) Polyethylene glycol (PEG) were of analytical grade reagents.

Preparation of tablet core

The core tablet containing NaCl as osmogen prepared by wet granulation method. The sufficient amount of drug powder, sodium laurate sulphate, micro-crystalline cellulose, starch, and magnesium stearate (listed in table 1) were blended (20% solution in isopropyl alcohol) in the resulted mixture. Then formed granule by using sieves no.22, these granules were dried in hot air oven under 120° c for 15-20 min [10].

Coating of core tablet

Optimized tablet formulations were coated with single, double and triple layer of varied ratio of coating solution i.e. CAP: PEG (table 2). Each tablet was drilled, so that they have an orifice to release the drug (cefadroxil) through it.

Table 1: Optimized Formulations of tablet core.

Formulation Codes	Drug (mg)	Magnesium stearate (mg)	Talc (mg)	SLS (mg)	Starch (mg)	Providone (ml)	NaCl (mg)	MCC (mg)
F1	100	2	3	15	15	5	80	115
F2	100	2	3	15	15	5	100	95
F3	100	2	3	15	15	5	150	85

Table 2: Optimized formulations of coating solution (CAP: PEG).

Formulation code	Cellulose acetate phthalate (CAP)	Poly ethylene glycol (PEG)	
F1	3mg	3mg	
F2	3mg	3mg 1:1	1:1
F3	3mg	3mg	
F1	3mg	6mg	
F2	3mg	6mg 1:2	1:2
F3	3mg	6mg	
F1	3mg	9mg	
F2	3mg	9mg 1:3	1:3
F3	3mg	9mg	

EVALUATIONS

Preformulation studies

Preparation calibration curve

50mg of cefadroxil was dissolved in methanol and the volume was adjusted to 50ml with methanol in standard flask. Then 2ml of solution was taken out from flask in 10ml volumetric flask and volume was made up to the mark in the 10ml with methanol to given a stock solution of concentration 200µg/ml. Then made different concentrations like 1ml, 2ml, 3ml and 4ml of the from stock solution. Then each solution were transferred into series of 25ml volumetric flask added 2ml of 4N HCl solution and 2ml of 0.02N bromated-bromide solution in each flask. The contents in each flask were thoroughly mixed and allowed to stand for 5min at room temperature for complete bromination orange coloured solution formed. Then 1ml of 1% methylene blue solution was added to each flask and resulted solutions were diluted with methanol and mixed thoroughly. Then solutions were measured under U.V. spectrometer at 670nm against blank solution. A calibration curve was plotted between the absorbance values concentration of the drug. [11].

Rheological properties

Angle of repose: The angle of repose of the mixture of the drug and excipients was determined by fixed funnel method. The values were used in the following equation to get the angle of repose. Tan θ = h/r. whereas h, r and θ are the height, radius and angle of repose of the powder pile.

Bulk density: Accurately weighed 3 g of the sample was transferred to the measuring cylinder of bulk density apparatus. The apparatus was adjusted for 100 tapping and noted the final volume as tapped volume.

Tapped density (ρt) = Weight of the powder/Tapped volume of the powder

Porosity: Porosity of the powder was determined by using formula: Porosity = $[(V_b - V_p)/ V_b] \times 100$. Where V_b is the bulk volume and Vp is the true volume

Carr's index: The Carr's index of the powder was determined by using formula:

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Where, TBD is the total bulk density and LBD is the loose bulk density

Physicochemical properties of OPT

Osmotic pump tablet were studied for various physicochemical properties are as follows:

Hardness: The crushing strength of the tablets was measured using a Pfizer hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability: Ten tablets were weighed and placed in a Roche friabilator (Electro lab, India). Twenty pre-weighed tablets were rotated at 25 rpm for 4 min. The tablets were then deducted and reweighed and the percentage of weight loss was calculated. The percentage friability was measured by following formula:

Percentage friability = weight initial/(weight final- weight initial) x100

Weight variation: Randomly twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±10.5% (USPXX).

Drug content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 100 mg of cefadroxil was dissolved in 100 ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 670 nm using UV-Visible spectrophotometer (UV 1601- Shimadzu, Japan).

Disintegration time

Disintegration test (veego, India) was performed on six tablets at 37ºC in 900 ml of distilled water in accordance with USP

In-Vitro drug release

In-vitro drug release profile was evaluated by dissolution apparatus (veego, India), using 0.1N HCl.

Effect of osmogen: The optimized formulation of osmotic pump tablets were tested for the effect of osmogen on drug release. The best formulations were undergone dissolution studies in 0.1 N HCl in rotation speed of 100 rpm and 37 ± 0.5ºc using dissolution test apparatus. The amount of drug release was determined by measuring the absorbance with a U.V. spectrophotometer at 670nm.

Effect of plasticizer (PEG) on drug release profile: The optimized formulations of Osmotic pump tablets were tested for effect of plasticizer on drug release. The coated tablets were evaluated for % cumulative drug release profile under sink condition in dissolution apparatus. Effect of drug release behaviour was observed with concentration of PEG.

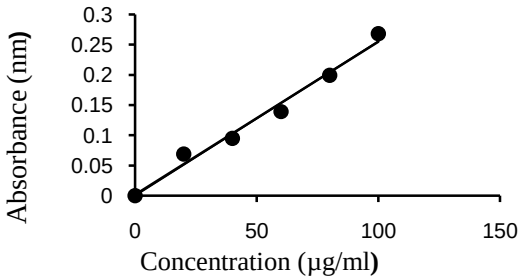

Fig. 4: Calibration curve of cefadroxil

Effect of number of layers of coating solution

The optimized tablets were coated to various numbers of layers i.e. single, double and triple layer. To study the influence of number of layers of coating on drug release profiles was evaluated by in-vitro release study.

RESULTS AND DISCUSSION

Calibration curve

A calibration curve was plotted between the absorbance values concentration of the drug (cefadroxil) by U.V spectrometer at 670nm.

Table 3: shows various parameters of calibration curve

Parameters	Values
Correlation Coefficient(R)	0.9917
T-test	15.412
p-values	2.776
Slope	388.0536
Intercept	0.1998

Table 4: Powder flow properties for formulated physical mixtures

Physical mixture of formulation	Angle of repose (º)	Bulk density (g/cm²)	Tapped density (g/cm³)	Porosity (%)	Compressibility (%)	Carr's index (%)
F1	26	0.36	0.41	13.15	13.21	12.19
F2	27	0.38	0.46	14.01	14.11	17.39
F3	27	0.28	0.36	14.47	14.54	22.22

Table 5: It shows Physicochemical parameters of prepared OPT

Formulation	Hardness (kg/cm2)	Friability (%)	Weight variation (mg)	Drug content (%)	Disintegration Time (min)
F1	8.13±1.6	0.421±1.68	300.6± 3	99.09±3.24	20
F2	8.15±0.42	0.400±1.88	202.6±2	98±2.67	18
F3	8.26±1.4	0.389±2.00	201.0± 3	99.79±3.23	10

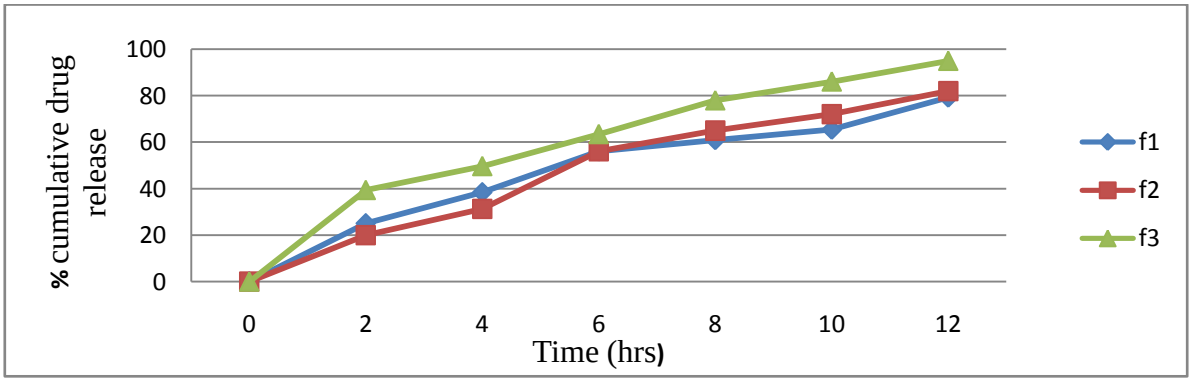

Fig. 5: In vitro release profile of cefadroxil from formulation f1, f2 and f3 containing different concentration of osmogen.

Table 6: It shows Kinetics of In-vitro drug release of osmotic pump tablet formulations.

Kinetic of formulation		F1	F2	F3
Korsmeyer peppas	R	0.991	0.987	0.991
	K_{kp}	28705.2	19561.8	45881.3
	t-test	17.10 (P)	14.16 (P)	17.02 (P)
Zero order	R	0.946	0.977	0.924
	K_0	12702.9	13143.8	15837.8
	t-test	6.534 (P)	10.44 (P)	5.404 (P)
Higuchi-Matrix	R	0.9895	0.9681	0.9973
	K_m	37759.4	38596.4	47327.5
	t-test	15.275 (P)	8.645 (P)	30.285 (P)
Hixson Crowell	R	0.4864	0.615	0.404
	K_H	-1.29	-1.30	-1.38
	t-test	1.245 (F)	1.745 (F)	0.988 (F)

Correlation coefficient (R), Korsmeyer peppas release constant (K_{kp}), Zero rate constant (K_0), Higuchi-Matrix constant, Hixson Crowell constant (K_m), passed (P), failed (F).

Effect of osmogen

The effect of osmogen on drug release profile of F1, F2 and F3 formulations are shown in Figure 5. It was observed that the release of drug was increased with increased concentration of osmogen (NaCl). This may be due to an increased in the osmotic pressure in the core tablet due to presence of different concentration of NaCl. Table 6 shows kinetics of In-vitro drug release of osmotic pump tablet formulations.

Effect of plasticizer (PEG) on release rate of drug

To study the effect of CAP and PEG (plasticizer) ratio on drug profile as 1:1, 1:2 and 1:3. It was observed that the rate of drug release increased with increased of PEG level because PEG is hydrophilic plasticizer and it could be leached easily and left porous structure, which increased membrane permeability and drug released. Figure 6 shows that increases concentration of PEG led to increases of drug release rate. Table 7 shows the student T-test of the %CDR.

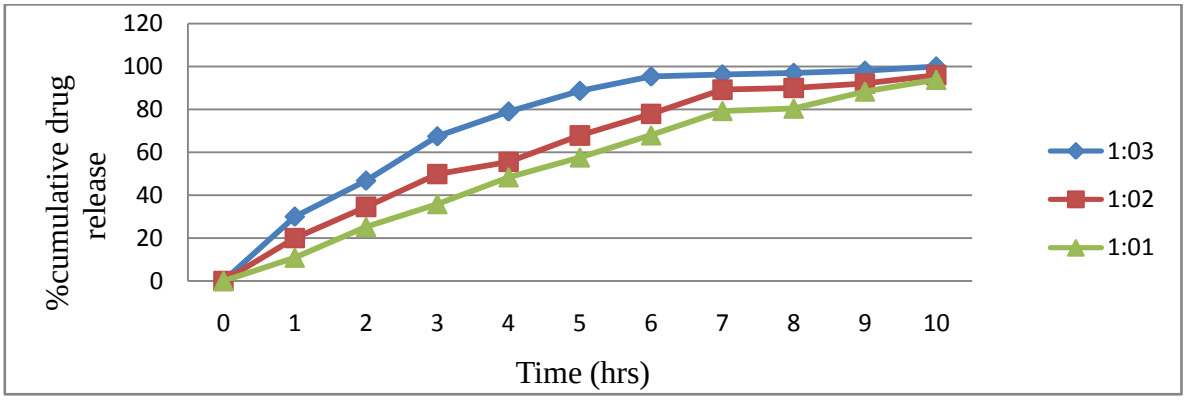

Fig. 6: Influence of plasticizer on drug release profile of f3.

Table 7: It shows student t-test for plasticizer

Parameters	1:1	1:2	1:3
T-Test	17.059	8.207	3.807
significance	Passed	Passed	passed

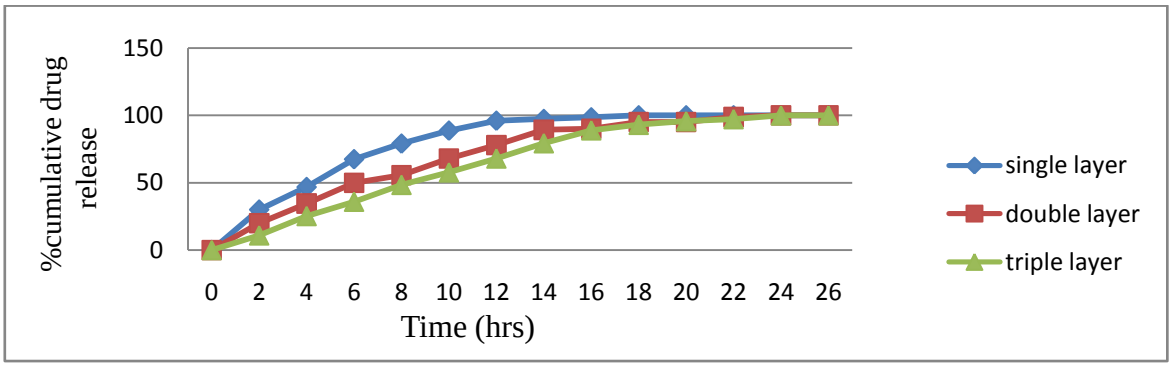

Fig. 7: It shows the effect of coating thickness on drug release rate of F3 indicates that release rate decreases with increases the thickness of coating.

Effect of number of layers of coating solution

To study the influence of number of layers of coating on drug release profiles, the optimal tablets were coated to various numbers of layers (single, double and triple layer) using coating solution with CAP: PEG (1:3) in formulation 3. Figure 7 shows that release rate decreases as the membrane thickness increases. Table 8 shows the student T-test of the %CDR.

Table 8: It shows student t-test for thickness of coating

Parameters	Single layer	Double layer	Triple layer
T-Test	2.481	6.236	10.719
significance	Passed	Passed	passed

CONCLUSION

By above experiment it has been concluded that osmotic pump of cefadroxil (antibiotic) should give rapid onset of drug release as well prolong effect. It has been observed that optimized batch the osmotic pump with better onset and prolong release rate, since the polymer used for coating and layer of coating will effect on the drug release rate and has prospect used as a controlled drug delivery system. It conclude that rate of drug release is directly proportional to concentration of osmogen (NaCl) and PEG while inversely proportional to the thickness or layers of coating.

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REFERENCES

1. Madhavi BB, Nath AR, Banji D, Ram lingam R, Madhu MN, Kumar DS: A review osmotic drug delivery system. Pharmakine 2009dec; 2:5-14.
2. Vyas S.P, Khar R.K. Controlled drug delivery, concept and advances. Vallabh prakashan, New Delhi. 200; 477-501.
3. Brahma P Gupta, Navneet thakur, Nishi P Jain, Jitendra Banweer, Surendra Jai: Osmotically Controlled Drug Delivery System with Associated Drugs. JPharm Pharmaceutics Sci 2010; 13(3) 571 - 588.
4. Rose s, Nelson J.F, Aus: J.Exp. Biol 1995; 33, 415-420.
5. Higuchi T, Leeper H. M: Improved osmotic dispenser employing magnesium sulfate and magnesium chloride. 1973; U.S Patent no. 3760804.
6. Theeuwes F. J. Pharm sci 64, 1987-1991(1975).
7. Kh.Hussan Reza, Sancheti Vikram N, Kumaravelrajan R: Formulation and Optimization of aceclofenac monolithic osmotic pump. International Journal of Pharmacy and Pharmaceutical Sciences 2011; volume 6, issue 2.
8. F. Theeuwes, T higuchi: Osmotic dispensing device for releasing beneficial agent. Us patent 1972 June; 3845770.
9. DRUG BANK. Open data Drug & Drug Target. Databases cefadroxil.
10. Chao WANG, Fei CHEN, Ji-Zhong Li, Hai Tang, Xiang Li, Ke-Shu Yan, Guan-hao YE and Wei san PAN: A Novel osmotic using core of drug –resin complexes for time controlled delivery system. The pharmaceutical society of Japan 2008; 773-782.
11. Mallapu Rani E, Hindustan Abdul Ahad, Sreenivasulu R, Mahendra Kumar P, Akula Ashwan Kumar, Siddaiah G: Spectrophotometric determination of cefadroxil in pharmaceutical dosage form by bromination method. Journal of pharmacy research 2011; 4(3), 739-740.
12. Verma R.K., Garg S. J**. Control. Release** 2002; 79, 7-27.
13. Rahul Mishra, Vijay Agarwal, Dr. U. V.S. Sara: Controlled porosity osmotic pump tablet International Standard Serial Number (ISSN): 2013; 2319-8141.
14. Hang-sheng Zheng, Dian-zhou Bi: Preparation of ondansetron HCl Osmotic pump tablets and their In-vitro drug release. Actapharmaceutica sinica 2005; volume: 40, issue: 12; 1080-1084.
15. Welling P G et al: A pharmacokinetic comparison of cephalexin and cefadroxil using HPLC assay procedures. 1985; Apr-Jun 6. (2):147-57.9.
16. Kanagale P, Lohray BB, Misra A, Davadra P, Kini R: Formulation and optimization of porous osmotic pump-based controlled release system of oxybutynin. AAPS Pharm SciTech 2007; Jul 13.8(3):E53.
17. F. Theeuwes: Oral dosage form design status and goals of oral osmotic system technology. Pharm.int 1984; 5: 293-296.
18. .Jirayu Makchit et al: Determination of Cefadroxil by Sequential Injection with Spectrophotometric Detector. Anal. Sci 2006; Vol.ume 22, 591,
19. Shailesh: Osmotic controlled drug delivery system. Pharmainfo.net 2008; May 10.
20. Sudeesh edavalath, shivanand k, kalyani prakasam, b prakash rao and goli divakar: Formulation development and optimization of controlled porosity osmotic Pump tablets of diclofenac sodium International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491 Vole 3, Issue 1, 2011
21. Brahma P Gupta, Navneet Thakur, Nishi P Jain, Jitendra Banweer, Surendra Jain: Osmotically Controlled Drug Delivery System with Associated Drugs J Pharm Pharmaceutics Sci 2010; 13(3) 571 – 588.