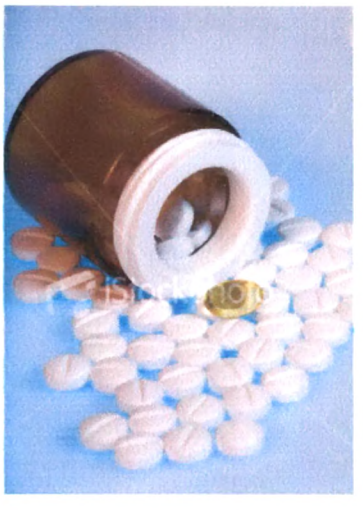
CHAPTER 3



PREPARATION AND CHARACTERIZATION

PART I

SWELLABLE POROUS OSMOTIC PUMP (SPOP)

INTRODUCTION

The SPOP controlled-release system is based on hydrophilic polymer coating. When the formulation is administered orally and reaches the stomach, gastric fluid enters inside the core through semipermeable membrane and dissolves the water soluble osmotically active agent (osmogent) and creates osmotic pressure in the core. Meanwhile, high viscosity grade swellable agent (s) present in the coating film swells and creates sponge like appearance in the membrane. The drug release occurs through the sponge like structure by osmotic mechanism. As formulation moves through the gastrointestinal tract, high viscosity grade swellable agent (s) present in the coating film swell and create more sponge like structure in the membrane and the drug release occurs through theses sponge like structure by osmotic mechanism. The formation of number of sponge like structure is irrespective of pH and time, and drug release occurs continuously by osmotic mechanism.

The mechanisms by which drug release is controlled in SPOP system are dependent on many variables. One of the principles of drug release would be osmotic pressure. However, it is obvious that the water-soluble polymer, coated throughout the tablet, hydrates on the tablet surface to form a gel layer and the drug molecules are diffused out and hence the diffusion mechanism cannot be ruled out for the present study.

It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents by changing the proportion of the semipermeable polymer, pH insensitive high viscosity grade swellable agent (s).

The SPOP comprises of the following components in the formulation(s):

A. A homogeneous core, comprising

i. A medicament, which is selected from group of water soluble, sparingly soluble or poorly soluble drugs or in combination thereof,

ii. A binder,

iii. A water-soluble osmotically active agent (osmogent).

iv. Optionally a diluent,

B. A membrane coating which covers the said core formulation, which comprises of:

i. A water insoluble and semipermeable pharmaceutically acceptable polymer,

ii. A single or a mixture of pH insensitive high viscosity grade swellable agent

iii. A single or a mixture of plasticizer.

iv. Optionally, a water slowly soluble or erodible pharmaceutically acceptable polymer.

The aim of the current study was to design a novel swellable porous osmotic pump (SPOP) based drug delivery system using various viscosity grade polymers of hydrophilic polymers, hydroxypropyl methylcellulose (HPMC) as swellable pore formers, for controlled release of, venlafaxine HCl (VH) and glipizide (GZ). The current study was also focussed on the effect of various viscosity grade pore formers, HPMC K100LV, HPMC K4M and HPMC K15M.

1. Venlafaxine HCl (VH)

VH, an antidepressant for oral administration was chosen as the model drug (Gutierrez et al., 2003 and Nemeroffa et al., 2007). VH has a solubility of 572 mg/mL in water (DeVane 1998).

2. Glipizide (GZ)

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class. It is insoluble in water and alcohol but soluble in 0.1 *N* NaOH (Verma and Garg, 2004). It is freely soluble in dimethylformamide.

Objectives of the present study were

- ✧ To design and optimize a novel swellable porous osmotic pump (SPOP) based drug delivery system using various viscosity grade polymers of hydrophilic polymers, hydroxypropyl methylcellulose (HPMC) as swellable pore formers, for controlled release of highly water soluble drug, venlafaxine HCl (VH) and water insoluble drug glipizide (GZ).
- ✧ To maintain and optimize the solubility modifying component in the core over the entire drug delivery duration, in case of glipizide SPOP
- ✧ To formulate and evaluate granules of VH and GZ.
- ✧ To formulate and evaluate core tablets of VH and GZ.
- ✧ To formulate and evaluate coated tablets of VH and GZ.

✧ The current study was also focussed on the effect of various viscosity grade pore formers, HPMC K100LV, HPMC K4M and HPMC K15M.

✧ To study the mechanism and kinetics of drug release from the optimized formulations by fitting into different dissolution models.

1. FORMULATION AND EVALUATION METHODS

– *FORMULATION OF CORE TABLETS OF VENLAFAXINE HCl*

In this osmotic system, sodium chloride was used as osmogent, lactose as diluent, povidone K-30 as binder, colloidal silicon dioxide as glidant and magnesium stearate as lubricant. Table 3.1.1 enlists the composition of core formulations prepared.

Table 3.1.1 Core formulations of Venlafaxine HCl – SPOP

Ingredient*	Batch no.				
	VA	VB	VC	VD	VE
Venlafaxine HCl	169.80	169.80	169.80	169.80	169.80
Sodium chloride	0.00	20.00	40.00	60.00	80.00
Lactose	113.70	93.70	73.70	53.70	33.70
Povidone K30	12.00	12.00	12.00	12.00	12.00
Colloidal silicon dioxide	1.50	1.50	1.50	1.50	1.50
Magnesium stearate	3.00	3.00	3.00	3.00	3.00
Total	300.00	300.00	300.00	300.00	300.00

* qty in mg / tablet

The tablets were prepared by wet granulation technique. All the raw materials were sieved through # 60 mesh. Drug (VH equivalent to 150 mg Venlafaxine) was uniformly mixed with sodium chloride and lactose in a high shear mixer granulator for 10 min. The dry blend was granulated with povidone, which was dissolved in isopropyl alcohol. The mass was dried at 50 °C and sieved through # 20 mesh and mixed with colloidal silicon dioxide. The granules were lubricated with magnesium stearate and compressed into round tablets with standard concave plain punches and dies (diameter – 9.52 mm) using 8 - station single rotary compression machine (KMP-8, Cadmach Engg, Ahmedabad, India).

– ***SCREENING OF SOLUBILITY MODIFIERS FOR GLIPIZIDE***

The excipients were chosen to span a wide range of solubility. The excipient studied were meglumine, tromethamine (TRIS), sodium bicarbonate and sodium phosphate and the saturation solubility of these excipients in water and the resulting pH of the solution were studied

Solubility measurements were carried out by adding excess amount to 100 mL water containing. Samples were stirred in a water bath (SW 23, Julabo Labortechnik, Germany) at 37 ± 0.5° C for 24 h. Samples were withdrawn and filtered through Millipore HVLP filter (0.45 μm) and the resultant pH was analysed.

– ***FORMULATION OF CORE TABLETS OF GLIPIZIDE***

In this osmotic system, meglumine was used as solubilising agent, mannitol as osmogent, povidone K-30 as binder, colloidal silicon dioxide as glidant and magnesium stearate as lubricant. Table 3.1.2 enlists the composition of core formulation prepared

Table 3.1.2 Core formulations of Glipizide – SPOP

Ingredient	Batch no.				
	GA	GB	GC	GD	GE
Glipizide	10.00	10.00	10.00	10.00	10.00
Meglumine	0.00	50.00	100.00	150.00	200.00
Mannitol	324.25	274.25	224.25	174.25	124.25
Povidone K-30	10.50	10.50	10.50	10.50	10.50
Colloidal silicon dioxide	1.75	1.75	1.75	1.75	1.75
Magnesium stearate	3.50	3.50	3.50	3.50	3.50
Total	350.00	350.00	350.00	350.00	350.00

* qty in mg / tablet

All the raw materials were sieved through # 60 mesh. Glipizide, mannitol and meglumine were mixed in a high shear mixer granulator for 10 min and granulated with PVPK-30 dissolved in isopropyl alcohol. The granules were dried, sized through a # 20 sieve and lubricated with magnesium stearate. The lubricated granules were compressed into round

tablets using 8 - station single rotary compression machine (KMP-8, Cadmach Engg, Ahmedabad, India) with standard concave plain punches and dies (diameter – 10.32 mm).

– ***EVALUATION OF VENLAFAXINE HCl AND GLIPIZIDE GRANULES***

* **Loss on drying (LOD)**

The term loss on drying is an expression of moisture content, which is calculated as follows (Eq.1),

% LOD = wt. of water in sample / total wt. of sample X 100 (1)

IR moisture balance (PM 480, Mettler Toledo, Switzerland) was used to determine LOD of the powder blend. The LOD was in the range of 1-3 % in order to maintain optimum moisture content in the granules.

* **Bulk density (BD), Tap density (TD), Compressibility index (CI) and Hausner ratio (HR)**

BD and TD refer to a measure used to describe packing of particles or granules. To determine BD and TD of the powder blend, USP method II on a tap density tester (ETD-1020, Electrolab, Mumbai, India) was used. The equation for determining BD and TD is (Eq. 2 and 3),

$$BD = \frac{W}{V_O} \quad (2)$$

$$TD = \frac{W}{V_F} \quad (3)$$

Where, W is the weight of sample and V_O and V_F are initial volume and final volume respectively (Banker and Anderson, 1987).

The CI and HR are measures of inter-particle friction and the potential powder arch or bridge strength and have been widely used to estimate the flow properties of powders. From the data obtained, CI and HR were calculated (Eq. 4 and 5),

$$CI = [(V_O - V_F) / V_O] \times 100 \quad (4)$$

$$HR = (V_O / V_F) \quad (5)$$

– ***EVALUATION OF VENLAFAXINE HCl AND GLIPIZIDE CORE TABLETS***

* **Uniformity of weight (Weight variation test)**

With a tablet designed to contain specific amount of drug, the weight of tablet is routinely measured to help ensure that the tablet contains proper amount of drug. In this test, 20 tablets were weighed individually on an electronic balance (AG-64, Mettler Toledo, Switzerland), the average weight was calculated and compared with individual weights. The percentage difference in the weight variation should be within the permissible limits (± 5%).

* **Thickness and diameter**

The thickness and diameter of the tablets were determined by using a thickness gauge (Digimatic Caliper, Mitutoyo, Japan).

* **Hardness test**

Tablets require a certain amount of strength or hardness and resistance to crushing to withstand mechanical shocks of handling in all processes. Particularly, for osmotic pumps, the hardness of the core tablets is expected to be more than 6 kg / cm^2 since they should withstand the mechanical shocks encountered during the coating process which may also influence the release rate. The hardness of core tablets were tested using a hardness tester (6-D, Dr Schleuniger Pharmatron, Manchester, NH, USA)

* **Friability test**

Friability test is performed to ensure that the tablets have sufficient strength to withstand mechanical shocks encountered during the coating process. The friability of core tablets for all the formulations were determined by friabilator (EF-2, Electrolab, Mumbai, India). The friabilator was rotated at a speed of 25 rpm for 4 minutes. Percentage friability was then calculated.

* **Drug content**

The drug content of tablet is measured to help ensure that the tablet contains specific amount of drug. Ten core tablet were selected randomly and average weight was

calculated. Analysis for Venlafaxine HCl and Glipizide was carried out as per the method mentioned in analytical methods section.

– ***COATING OF VENLAFAXINE HCl AND GLIPIZIDE TABLETS***

Tablets were spray coated by perforated pan coater (GAC – 250, Gansons Ltd., Mumbai, India), Table 3.1.3 and Table 3.1.4 summarizes the components of coating solution and the processing conditions respectively.

Table 3.1.3 The components of coating solution for SPOP tablets

Code	Ingredients*				
	Cellulose Acetate	HPMC K100LV	HPMC K4M	HPMC K15M	PEG-400
C-I	90	0	0	0	10
C-II	84	6	0	0	10
C-III	84	0	6	0	10
C-IV	84	0	0	6	10
C-V	78	12	0	0	10
C-VI	78	0	12	0	10
C-VII	83	3.5	3.5	0	10

*values given in % w/w of total solids.

The coating solutions were prepared using mixture of dichloromethane and methanol (70:30) as the coating solvent to get a 4 % total solids in coating solution. Coated tablets were dried at 50°C for 16 h and the % weight gain and thickness (Digimatic Caliper, Mitutoyo, Japan) of the coating membrane were measured

Table 3.1.4 Coating processing conditions for SPOP tablets

Processing condition	
Tablet bed size	800 gm
Inlet temperature	55 ± 2° C
Outlet temperature	42 ± 2° C
Atomizing air pressure	2.1 kp / cm^2
Peristaltic pump speed	4-5

– ***EVALUATION OF VENLAFAXINE HCl AND GLIPIZIDE COATED TABLETS***

* **Percentage weight gain**

From every batch of coating, 25 coated tablets were individually weighed and the average weight was calculated and compared with average weight of uncoated. The difference in weight was determined and the percent weight gain was calculated.

* **Coating thickness**

The thickness and diameter of the coated tablets were determined by using a thickness gauge (Digimatic Caliper, Mitutoyo, Japan).

* **Burst strength**

The burst strength of the exhausted shells after dissolution was determined to assure that the tablets would maintain their integrity in the GIT. Burst strength is the force required to break / rupture the shells. The texture analyzer (TAX T2i, Stable micro systems, U.K) with a 5 kg load cell and 25 mm aluminium cylindrical probes were utilized. Test speed of 0.8 mm/s was selected and distance moved was at 2 mm.

– ***IN VITRO DRUG RELEASE***

Table 3.1.5 summarizes the dissolution study and analytical method. In vitro drug release of the formulations were carried out using USP type I dissolution apparatus (2100C,

Distek Inc, NJ) attached with an auto-sampler (37 °C ± 0.5 °C). The drug release at different time intervals was analyzed by UV spectrophotometer (8453, Agilent Technologies, Singapore).

Table 3.1.5 *In-Vitro* Dissolution studies and analytical method

Parameters	Venlafaxine HCl	Glipizide
Dissolution media	Distilled water	Phosphate buffer, pH 6.8
USP Type	I (Basket)	I (Basket)
Volume	900 ml	500 ml
RPM	75	75
Temperature	37 °C	37 °C
Analytical method	UV spectrophotometer, 226 nm	HPLC

Release profiles were also compared using mean dissolution time or MDT, which was calculated using following equation (Eq. 6):

$$MDT = \frac{\sum_{j=1}^{n} t_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$

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

– ***STATISTICAL ANALYSIS OF DISSOLUTION DATA***

Release profiles of optimized tablets were compared by calculating two statistically derived mathematical indices, difference factor (f_1) and similarity factor (f_2) with a commercially available product, as the reference (Moore and Flanner, 1996). The difference factor (f_1) measures the percent error between two curves over all time points (Eq. 7) and the similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the test and reference products over all time points (Eq. 8)

$$f_1 = \frac{\sum_{j=1}^{n} R_j - T_j}{\sum_{j=1}^{n} R_j} \times 100 \quad (7)$$

$$f_2 = 50 \times \log\{[1 + (1/n) \sum_{j=1}^{n} (R_j - T_j)^2]^{-0.5} \times 100\} \quad (8)$$

where n is the sampling number, Rj and Tj are the percent dissolved of the reference and test products at each time point j. The percent error is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles. The pull points at 120 min intervals, beginning from the first 60 min up to one point above 85 % released were included in calculations.

– ***KINETICS OF DRUG RELEASE***

In order to understand the mechanism of drug release from the optimized system, the data were applied to various dissolution models. The zero order rate (Eq. 9) describes the system, where the drug release is independent of concentration. The first order rate (Eq. 10) describes the system, where drug release system is concentration dependent. The kinetic models also included Higuchi's (Eq. 11), where the drug release from insoluble matrix is directly proportionl to square root of time and is based on the Fickian diffusion. The Hixson-Crowell cube root law (Eq. 12), where the drug release depends on the change in surface area and diameter of the particles or tablets with time. In order to define a model, dissolution data can be further analysed by Korsmeyer-Peppas (Eq. 13), where the log of drug release is directly proportional to log time. Smallest values of sum of squared residuals (SSQ) and coorelation coefficients were taken as criteria for selecting the most appropriate model (Costa and Lobo, 2001).

$$Q_t = k_0 t \quad (9)$$

$$ln\ Q_t = ln\ Q_0 - k_1 t \quad (10)$$

$$Q_t = k_H t^{1/2} \quad (11)$$

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \quad (12)$$

$$\frac{M_t}{M_\alpha} = kt^n \quad (13)$$

where Q_0 and Q_t are the amount of drug release in time *0* and *t* respectively, k_0, k_1, k_H and k_{HC} are release rate constants for zero order, first order, Higuchi model and Hixson-Crowell rate equations, respectively. M_t is the amount of drug released at time *t* and M_α is the amount of drug released at time α, *k* is the kinetic constant and *n* is the diffusional coefficient.

- ***SCANNING ELECTRON MICROSCOPY (SEM)***

In order to elucidate the mechanism of drug release from optimized formulations based on SPOP technology, surface of coated tablets were studied using scanning electron microscope (SEM).

After dissolution studies, a small portion of sample of the coating membrane was carefully cut from the exhausted shells and dried at 50 °C for 12 h. The samples were mounted and examined for their porous morphology by Philips ESEM-TMP scanning electron microscope (SEM) (Philips, Netherlands). Samples from SPOP as detailed below were evaluated using SEM.

Coating Formulation code	**Details of coating**
C-I	Devoid of Swellable pore former
C-II	6% (w/w of CA) HPMC K100LV
C-III	6% (w/w of CA) HPMC K4M
C-IV	6% (w/w of CA) HPMC K15M
C-V	12% (w/w of CA) HPMC K100LV

C-VI	12% (w/w of CA) HPMC K4M
C-VII	3.5% (w/w of CA) each of HPMC K100LV and HPMC K4M

3 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 solubility modifier (meglumine, in case of Glipizide), osmogent, and other conventional excipients to form the core compartment. Solubility modifiers used in the core are formulated in a controlled release fashion so that the alkalinizing agents are available for longer duration with the drug and capable of modifying the microenvironmental pH of the core above the pKa of drug. The core compartment is surrounded by a membrane consisting of a semipermeable membrane-forming polymer, high viscosity grade pore forming polymers and at least one plasticizer capable of improving film-forming properties of the polymers.

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 and dissolves the drug (In case of Glipizide, the solubility modifier dissolves and elevates the microenvironmental pH of the tablet core above the pKa of the drug, thus increasing its solubility). The dissolved drug is released through the pores created after swelling of water soluble polymer(s) in the membrane.

Cellulose acetate and HPMC (HPMC K100LV, HPMC K4M and HPMC K15M) were used as water-insoluble polymer and waters-soluble polymers, respectively. PEG-400 was used as a plasticizer.

– *SCREENING OF SOLUBILITY MODIFIERS FOR GLIPIZIDE*

The excipients chosen and the saturation solubility of these excipients in water and the resulting pH of the solution is given in Table 3.1.6. It is clear from the data that in order to deliver glipizide over a useful delivery duration, such as 10–12 h, the formulations must include a suitable solubility modifier which elevates the microenvironmental pH in which glipizide has a high solubility. Among the excipients studied, meglumine and

TRIS had maximum solubility and higher pH range. However, meglumine was chosen since it provided the maximum solubility than TRIS.

Table 3.1.6 Saturation aqueous solubility of selected excipients and the resulting pH of the solution

Excipient	Excipient solubility (mg/ml)	pH of saturated solution
Meglumine	524	10.4
TRIS	418	10.3
$NaHCO_3$	56	8.1
Na_2HPO_4	45	8.9

- ***EVALUATION OF VENLAFAXINE HCl AND GLIPIZIDE GRANULES***

The values of LOD, BD, TD, CI and HR are presented in Table 3.1.7.

Table 3.1.7 Properties of the granules of developed formulations

Batch no.	Loss on drying (%)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Compressibility Index (%)	Hausner ratio
Venlafaxine HCl					
VA	1.10	0.65	0.74	12.24	1.12
VB	1.85	0.71	0.80	11.58	1.15
VC	2.11	0.66	0.76	12.55	1.18
VD	0.95	0.81	0.88	13.56	1.21
VE	1.04	0.78	0.81	11.67	1.08
Glipizide					
GA	1.08	0.72	0.81	10.79	1.19
GB	1.92	0.78	0.87	10.13	1.22
GC	1.99	0.73	0.83	11.10	1.25
GD	1.02	0.80	0.85	12.11	1.28
GE	1.11	0.85	0.88	10.22	1.15

The LOD was in the range of 0.5-3% for all the formulated batches suggesting that optimum moisture was maintained in the granules. The CI and HR were in the range of 10-13 and 1.1-1.3 suggesting good flow of granules.

– ***EVALUATION OF VENLAFAXINE HCl AND GLIPIZIDE CORE TABLETS***

The evaluation parameters along with values of the developed core formulations are presented in Table 3.1.8

Table 3.1.8 Evaluation parameters of the developed core formulations

Parameters	Weight (n=20) (mg)	Thickness (n=20) (mm)	Diameter (n=20) (mg)	Hardness (n=20) (kg/cm^2)	Friability (n=3) (%)	Drug content (n=3) (%)
Venlafaxine HCl						
VA	298.57 ± 5.2	3.81 ± 0.02	9.52 ± 0.01	6.80 ± 0.2	0.05 ± 0.01	99.75 ± 2.21
VB	301.47 ± 5.8	3.78 ± 0.03	9.51 ± 0.01	6.70 ± 0.3	0.14 ± 0.01	95.47 ± 3.47
VC	298.85 ± 6.5	3.84 ± 0.02	9.52 ± 0.09	7.10 ± 0.3	0.01 ± 0.01	101.23 ± 2.58
VD	299.47 ± 5.8	3.75 ± 0.03	9.52 ± 0.08	7.50 ± 0.4	0.24 ± 0.02	99.87 ± 3.45
VE	302.45 ± 6.1	3.84 ± 0.01	9.52 ± 0.06	7.40 ± 0.3	0.27 ± 0.02	102.82 ± 2.98
Glipizide						
GA	351.00 ± 6.2	4.11 ± 0.03	10.32 ± 0.03	6.80 ± 0.3	0.34 ± 0.01	103.39 ± 2.42
GB	352.00 ± 5.1	4.02 ± 0.04	10.33 ± 0.04	6.90 ± 0.3	0.31 ± 0.03	100.40 ± 2.87
GC	355.00 ± 4.5	4.11 ± 0.03	10.32 ± 0.04	6.50 ± 0.4	0.08 ± 0.01	101.80 ± 3.15
GD	348.00 ± 6.3	4.05 ± 0.03	10.31 ± 0.01	6.10 ± 0.3	0.21 ± 0.01	96.04 ± 3.52
GE	351.00 ± 4.2	4.08 ± 0.03	10.32 ± 0.04	6.20 ± 0.4	0.12 ± 0.01	100.32 ± 2.58

The weight variation was less than 5% for all the formulated batches suggesting uniformity of dosage form. The drug content was in the range of 95 – 105%.

– ***EVALUATION OF VENLAFAXINE HCl AND GLIPIZIDE COATED TABLETS***

The evaluation parameters along with values of the developed core formulations are presented in Table 3.1.9

Table 3.1.9 Evaluation parameters of the developed-coated formulations

Parameters	Weight (n=20) (mg)	Thickness (n=20) (mm)	Weight gain (n=20) (%)	Burst strength (n=3) (g)
Venlafaxine HCl				
VA	318.87 ± 6.3	3.93 ± 0.02	6.80 ± 0.45	300 ± 9
VB	321.67 ± 5.2	3.90 ± 0.01	6.70 ± 0.59	312 ± 8
VC	320.07 ± 6.4	3.96 ± 0.04	7.10 ± 0.25	322 ± 9
VD	321.93 ± 5.1	3.87 ± 0.04	7.50 ± 0.55	308 ± 5
VE	324.83 ± 4.8	3.96 ± 0.02	7.40 ± 0.44	374 ± 5
Glipizide				
GA	374.17 ± 5.8	4.25 ± 0.01	6.60 ± 0.58	351 ± 8
GB	372.71 ± 3.9	4.22 ± 0.01	7.10 ± 0.78	316 ± 7
GC	380.56 ± 4.5	4.28 ± 0.02	7.20 ± 0.99	325 ± 7
GD	376.29 ± 4.7	4.19 ± 0.03	6.90 ± 0.57	357 ± 5
GE	374.52 ± 5.4	4.28 ± 0.04	6.70 ± 0.78	366 ± 4

None of the developed formulations caused burst effect.

– ***IN VITRO DRUG RELEASE***

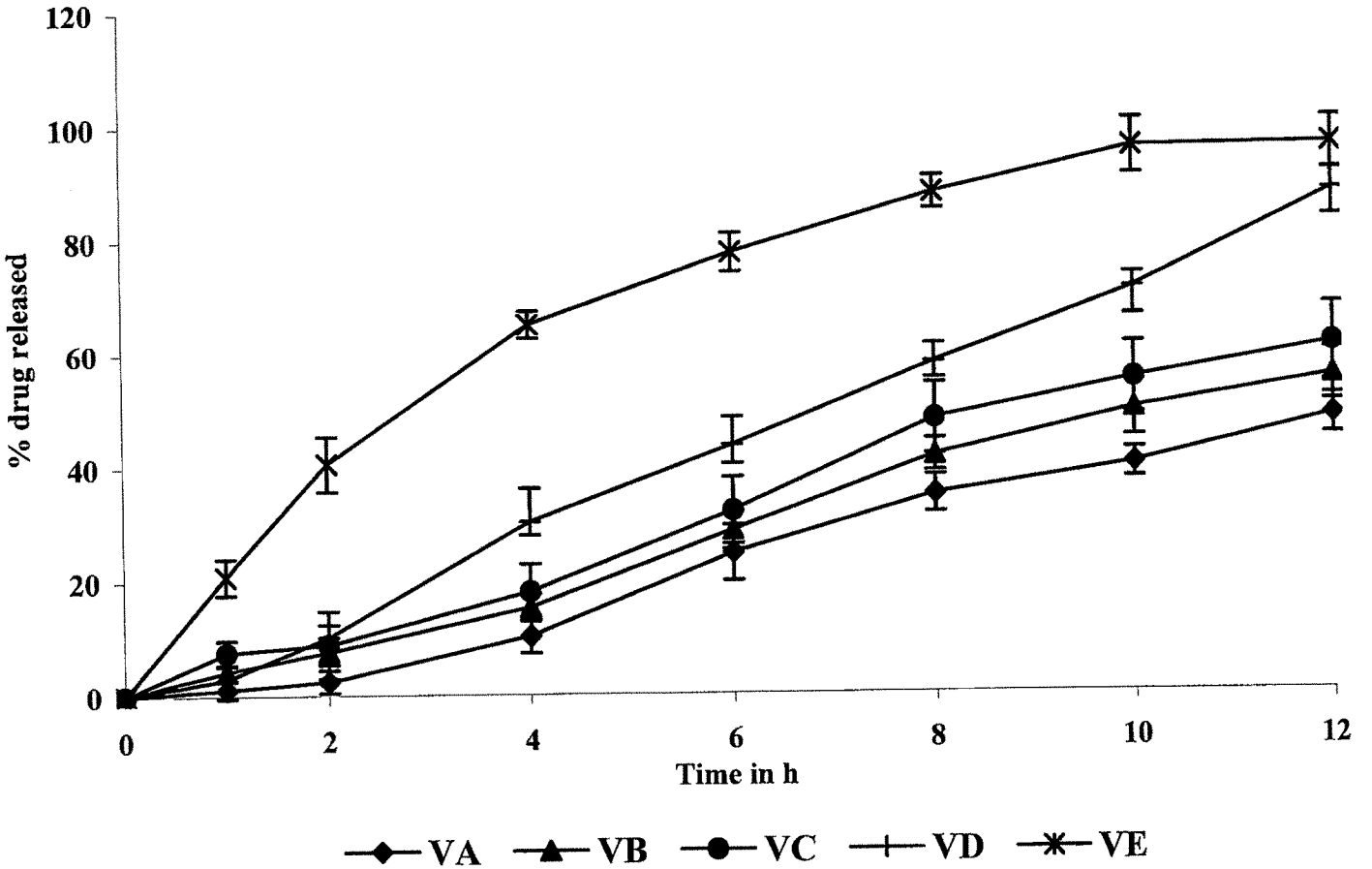
1. Venlafaxine HCl

* **Effect of osmogent amount**

To optimize the amount of osmogent to be used in the formulation and to study the effect of drug to osmogent ratio, core formulations were prepared as shown in Table 3.1.1. The amount of osmogent (sodium chloride) studied were 0, 20, 40, 60 and 80 mg per tablet. All the core formulations were coated with coating composition, C-II containing 6 % w/w (of total solids) of HPMC K100LV. Release profile from these formulations is shown in Fig. 3.1.1. It is clear from Fig. 3.1.1 that osmogent enhances the release of drug and had a direct effect on drug release. This is evidenced from formulation VA that was devoid of any osmogent in the core, showed 48.28 % drug release even after 12 h.

The use of osmogent enhanced the release beyond 50 % drug release after 12 h depending on the amount of osmogent present in the core formulation which might be

Fig. 3.1.1 In-vitro release profile of Venlafaxine HCl SPOP tablets-Effect of Osmogent



due to the increased water uptake and hence increased driving force for drug release. The drug release after 12 h for VA, VB, VC, VD and VE formulations was 48.28, 55.25, 61.24, 88.58 and 96.25 % respectively. However, the drug release after 8 h was 87.99 % in the VE formulation, which had 80 mg sodium chloride, which was very fast and hence VD formulation was chosen for further development.

2. Glipizide

* **Effect of level of solubility modifier:**

To optimize the amount of solubility modifier to be used in the formulation, core formulations were prepared as shown in Table 3.1.2. The amount of solubility modifier (meglumine studied were 0, 50, 100, 150 and 200 mg per tablet. All the core formulations were coated with coating composition, C-II containing 6 % w/w (of total solids) of HPMC K100LV. Release profile from these formulations is shown in Fig. 3.1.2. It is clear from Fig. 3.1.2 that solubility modifier enhances the release of drug and had a direct effect on drug release.

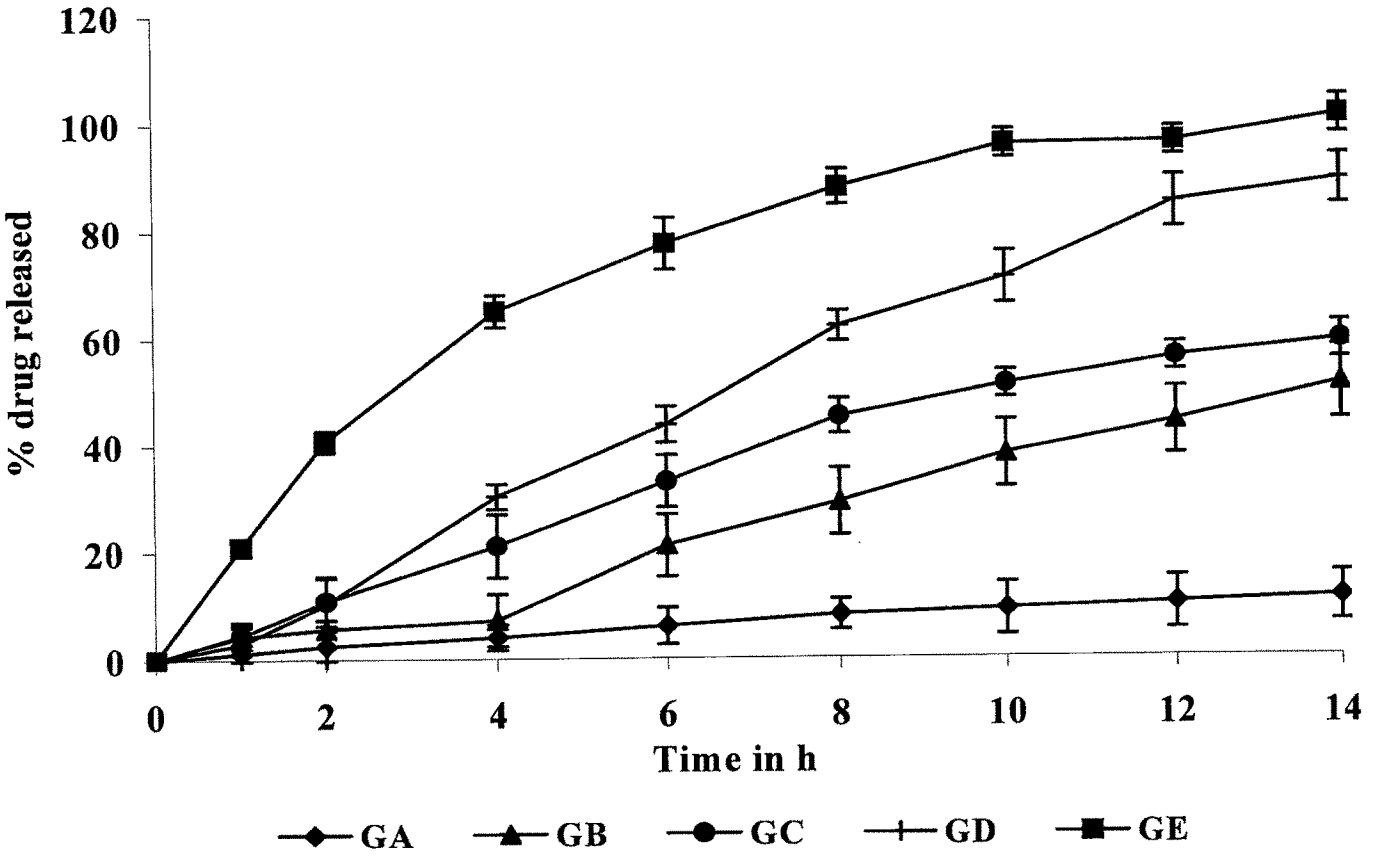
In the initial trial, core tablets of glipizide (without osmogent and solubility modifier) were coated with C-II however no drug was released till 14 h. This phenomenon could be expected either because of low osmotic pressure of the core formulation or due to poor water solubility of glipizide. To increase the osmotic pressure of core compartment, sodium chloride (osmotically active agent) was added. But this approach failed since negligible amount of drug was released even after 14 h.

Glipizide is a weakly acidic drug that is practically insoluble in water and buffer media of acidic pH 8. Meglumine was added as a solubility modifier to increase the microenvironmental pH of the core above the pKa of glipizide.

The use of solubility modifier enhanced the release depending on the amount of solubility modifier present in the core formulation. The drug release after 14 h for GA, GB, GC, GD and GE formulations was 10.18, 51.58, 59.47, 89.52 and 101.14 % respectively. However, the drug was completely released from GE formulation with 95.85 % after 8 h, which had 200 mg meglumine.

Hence core formulation of GD with 150 mg meglumine was chosen for further development.

Fig. 3.1.2 In-vitro release profile of Glipizide SPOP tablets-Effect of solubility modifier



* **Effect of viscosity grade of HPMC as pore former on drug release from VH and GZ tablets**

HPMC, which is commonly used in hydrophilic matrix drug delivery system, is mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituents (Hogan 1989). Amongst the various available commercial grades of Methocels (E, F, K), Methocel K grade which is having rapid rate of hydration was used, since an inadequate polymer hydration may lead to 'dose dumping' due to quick penetration of gastric fluids into the tablet coat. In the present study, HPMC K100LV, HPMC K4M and HPMC K15M were used as pore forming agent because they form a strong viscous gel on contact with aqueous media, which might help in controlling the delivery of highly water-soluble drugs.

Release profile from the formulation of venlafaxine (VD) and glipizide (GD) containing without HPMC coating (C-I), with HPMC K100LV (C-II), with HPMC K4M (C-III) and HPMC K15M (C-IV) coating is shown in Fig. 3.1.3 and Fig. 3.1.4 respectively.

It is clearly evident that the viscosity grade of HPMC had a direct effect on drug release and it is possible to achieve the desired release by using different types and/or combination of pore former. In case of venlafaxine, $MDT_{50\%}$ was found to be 7.12, 9.25 and 12.47 h for formulations containing HPMC K100LV (C-II), HPMC K4M (C-III) and HPMC K15M (C-IV) respectively and in case of glipizide, $MDT_{50\%}$ was found to be 6.82, 10.01 and 13.14 h for formulations containing HPMC K100LV (C-II), HPMC K4M (C-III) and HPMC K15M (C-IV) respectively.

There was statistically significant difference ($P \leq 0.05$) between the different formulations.

This might be attributed to the high viscosity nature of HPMC K15M and K4M when compared to HPMC K100LV. HPMC K15M and K4M form a stronger viscous gel on contact with aqueous media and restrict the delivery of drug. Comparative faster release of the drug from the and HPMC K100LV coating was probably due to faster dissolution of the highly water-soluble drug in the core and its diffusion out from the low viscous porous structure. In case of formulation containing without HPMC coating, only 2.65 ± 1.65 % and 10.25 ± 2.58 % drug released from venlafaxine and glipizide formulation

Fig. 3.1.3 In-vitro release profile of Venlafaxine HCl (B.No. VD) SPOP tablets- Effect viscosity grade of HPMC as pore former

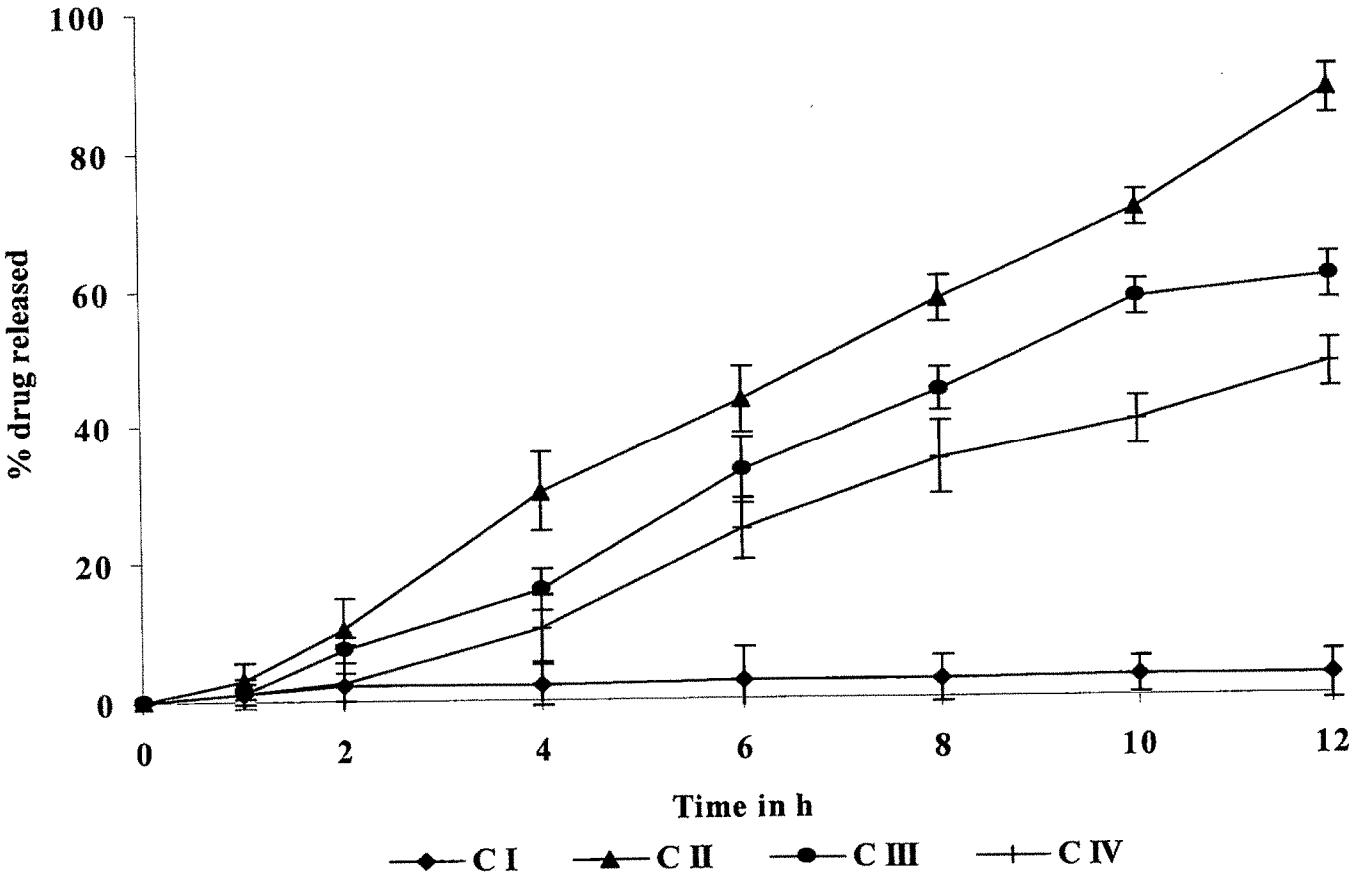
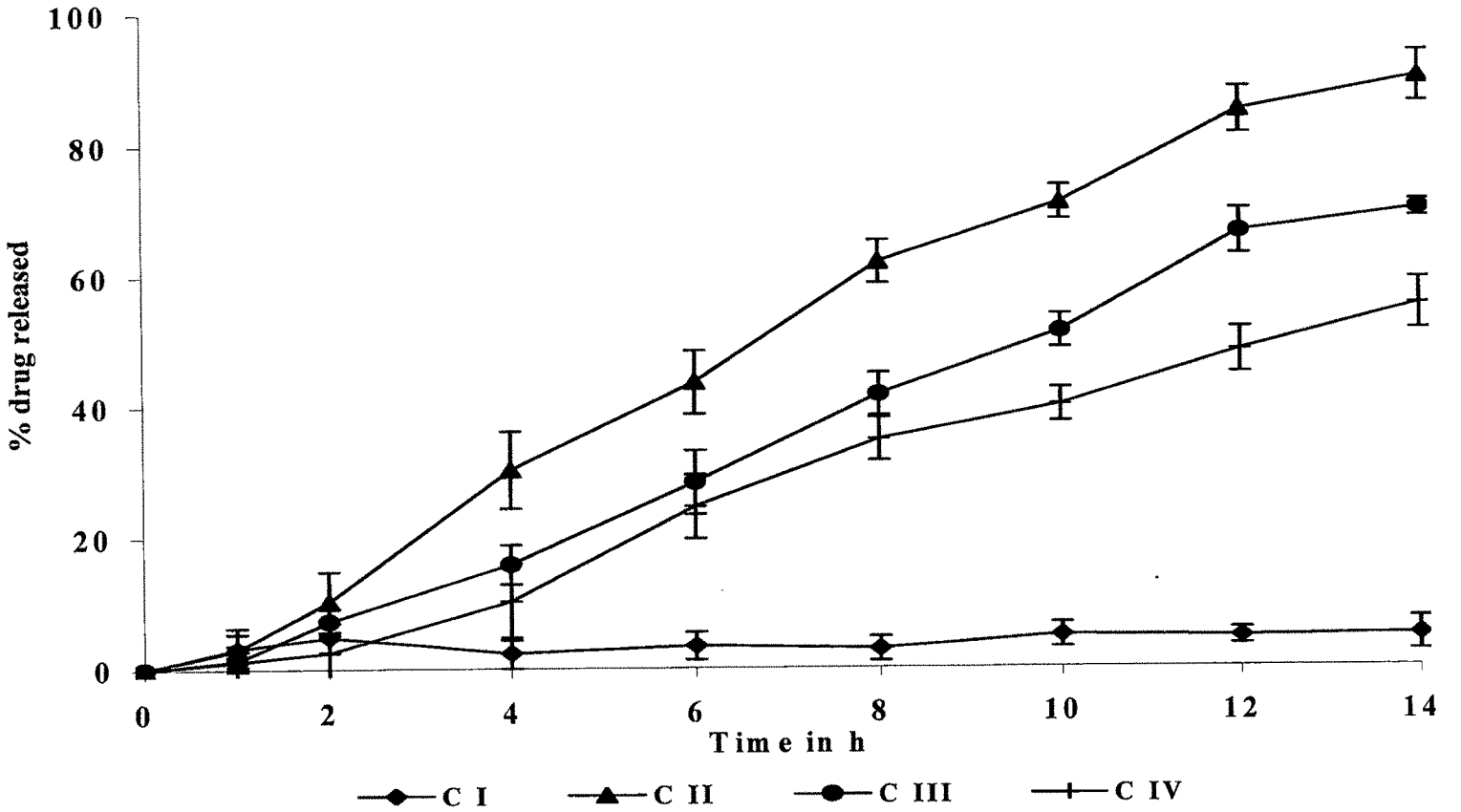


Fig. 3.1.4 In-vitro release profile of Glipizide (B.No. GD) SPOP tablets – Effect viscosity grade of HPMC as pore former



respectively. No swellable porous structures were formed which was confirmed from the SEM studies.

* **Effect of Pore Forming Level**

To study the effect of level of pore forming agent and to optimize the release profile, core formulations of VH and GZ were coated with higher level of HPMC K100LV (C-V) and HPMC K4M (C-VI) containing 12 % w/w of cellulose acetate. HPMC K15M was not studied as it was observed that the drug release was highly restricted even with lower polymer concentration level (C-IV, 6 % w/w) and difficulty in performing the coating experiment due to the high viscosity of the coating solution.

Release profile from HPMC K100LV coating (C-V) and HPMC K4M coating (C-VI) is depicted in Fig. 3.1.5 and 3.1.6.

HPMC K100LV coating

For venlafaxine, $MDT_{50\%}$ was found to be 7.12 and 3.68 h for formulations containing 6 % and 12 % HPMC K100LV respectively. And for glipizide, $MDT_{50\%}$ was found to be 6.82 and 5.12 h for formulations containing 6 % and 12 % HPMC K100LV respectively.

HPMC K4M coating

For venlafaxine, $MDT_{50\%}$ was found to be 9.25 and 7.22 h for formulations containing 6 % and 12 % HPMC K4M respectively. And for glipizide, $MDT_{50\%}$ was found to be 10.01 and 9.12 h for formulations containing 6 % and 12 % HPMC K4M respectively.

These values confirmed the effect of level of hydrophilic polymers on the release from osmotic system. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. This observation was less prominent in the case of HPMC K4M coating which could be due to more viscous pores. Increasing the level from 6 % to 12 % increases the number of swellable pores however these pores are of very high viscosity and hence the passage for the drug gets saturated.

On the other hand HPMC K100LV coating proved that the effect of level of polymer was directly proportional to the drug release. This phenomenon was observed in both the drugs.

Other workers have also obtained similar results (Zentner et al., 1985a, Okimoto et al., 1999c).

Fig. 3.1.5 In-vitro release profile of Venlafaxine HCl (B.No. VD) SPOP tablets-Effect of Pore Forming Level

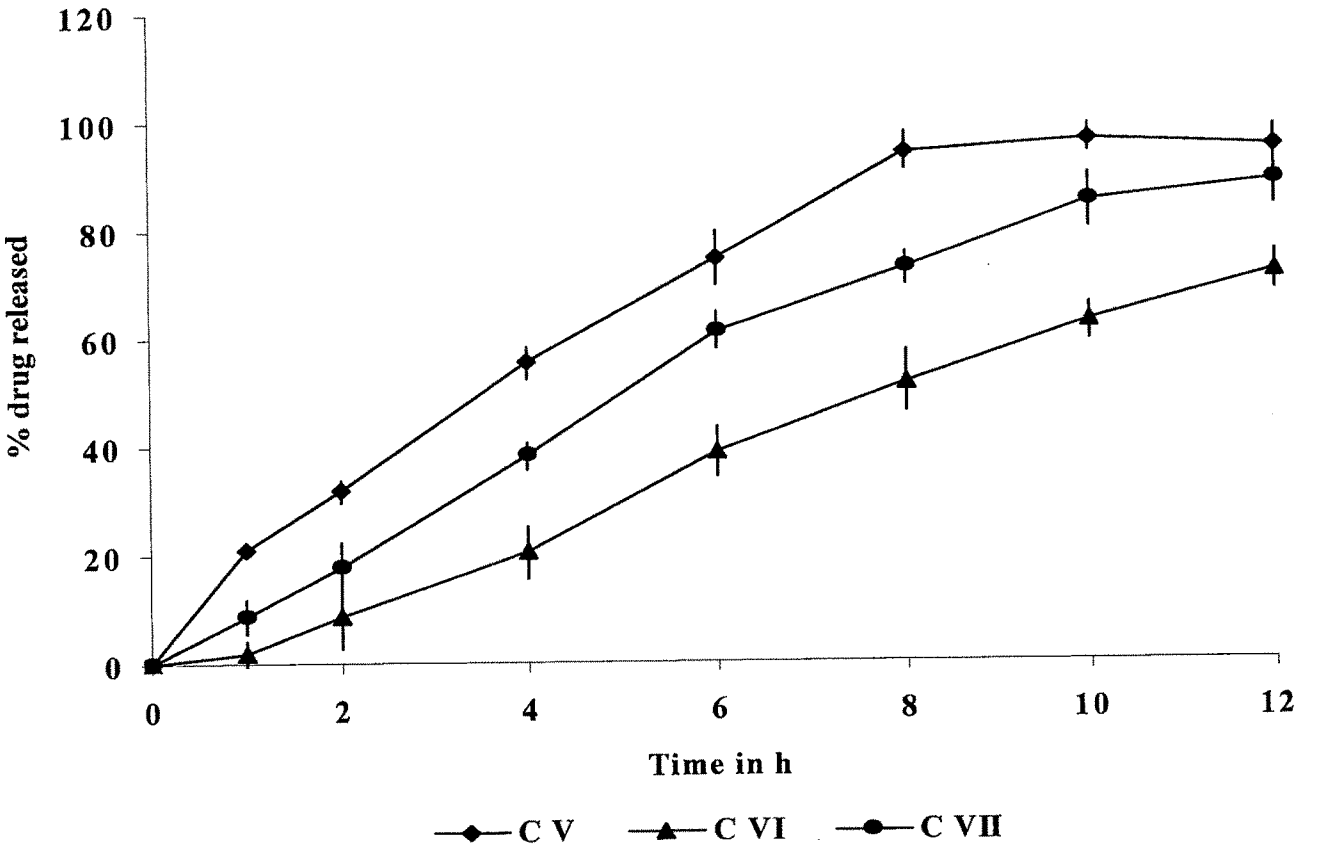
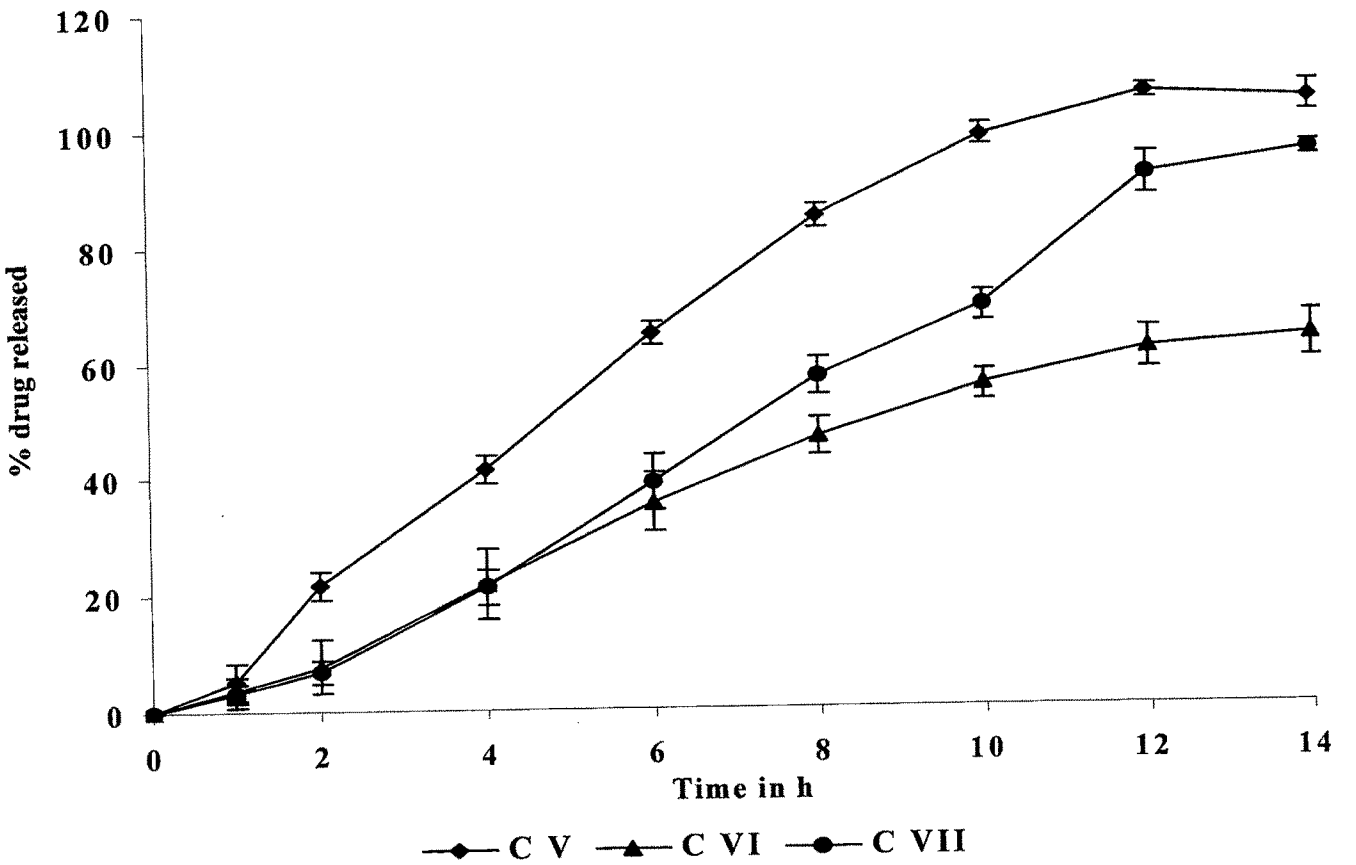


Fig. 3.1.6 In-vitro release profile of Glipizide (B.No. GD) SPOP tablets- Effect of Pore Forming Level



The level of pore former also affects the burst strength of exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in level of HPMC, the membrane became more porous after exposure to water, leading to a decrease in its strength. The results in the present study are consistent with other reports (Zentner et al., 1985a, Verma et al., 2003).

* **Combination of HPMC K100LV :HPMC K4M (1:1) coating**

The level of pore former also affected the extent of drug release. More than 95 % VH and GZ was released after 8 h and 10 h respectively, with 12 % HPMC K100LV coating (C-V) where as there was no complete release (>95%) with 6 % HPMC K100LV coating (C-II) in case of both the drugs.

Hence in order to satisfy the following points,

- ✧ release the drug completely
- ✧ control the release and get optimum drug release and
- ✧ decrease the level of pore forming polymers

a combination of coating solution with 7 % HPMC K100LV and K4M (3.5 % each of total solids) (C-VII) was prepared and coated with similar process as mentioned earlier. The drug release profile is depicted in Fig. 3.1.5 and Fig. 3.1.6 for VH and GZ respectively.

The drug release and the burst strength were satisfactory with the formulations containing a combination of HPMC K100LV and K4M as the pore former.

– ***STATISTICAL ANALYSIS OF DISSOLUTION DATA***

To evaluate the performance of the developed formulations, release profile was compared with marketed innovator products.

Effexor XR marketed by Wyeth Inc., USA is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids where as Glucotrol XL marketed by Pfizer Inc., USA is based upon push–pull osmotic pump technology. It is a bilayer tablet coated with a semipermeable membrane. Drug along with osmogents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents. The drug compartment is connected to the outside environment via a delivery orifice. After coming into contact with the aqueous environment, polymeric osmotic layer swells and

pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice.

The advantages of the in house developed system the are that it is simpler in design (single layer vs. bilayer), requires less number of manufacturing steps (no need for laser drilling), economical, and easily amenable to mass production.

Fig. 3.1.7 shows release of venlafaxine and glipizide from in-house formulations in comparison with Effexor XR and Glucotrol XL. The f_1 and f_2 values are presented in Table 3.1.10, taking the release profile of Effexor XR and Glucotrol XL as reference. These formulations were selected as the optimized formulation and used for further evaluation.

Table 3.1.10 Comparison of release profile

Product	Reference	Innovator	f_1	f_2
Venlafaxine	Effexor XR*	Wyeth Inc. USA	11.12	68.51
Glipizide	Glucotrol XL[$]	Pfizer Inc. / Alza Inc. USA	12.22	71.47

** Formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids.*
[$]Formulated as an extended-release bilayer tablet with delivery orifice for once-a-day oral administration. Drug release is controlled by osmosis

– ***KINETICS OF DRUG RELEASE***

Table 3.1.11 shows the equations used to determine the appropriate models and presents the values for all formulations. Drug release from *in house* optimised formulation fitted well into zero-order kinetics, which is confirmed by the lower sum of squared residuals (SSQ) and comparatively higher correlation co-efficient. Application of release curve to zero-order equation indicated that the drug release is independent of drug remaining in its interior. The second best model describing the release was Higuchi's followed by first-order and Hixson-Crowell.

The drug release data was further analysed for curve fitting based on Korsmeyer-Peppas model. Based on the theory that if the n value is equal to 0.5 or between 0.5 and 1.0 the release mechanism is Fick's diffusion or a non-Fickian model, respectively. The n value obtained for the optimized formulation was more than 0.5 ($n = 0.5894$, $r = 0.9864$ and $k = 2.157$) suggesting the release from this formulation follows non-Fickian diffusion.

Fig. 3.1.7 Release profile of Venlafaxine HCl (B.No. VD) and Glipizide (B.No. GD) formulation in comparison with Effexor-XR and Glucotrol XL, respectively.

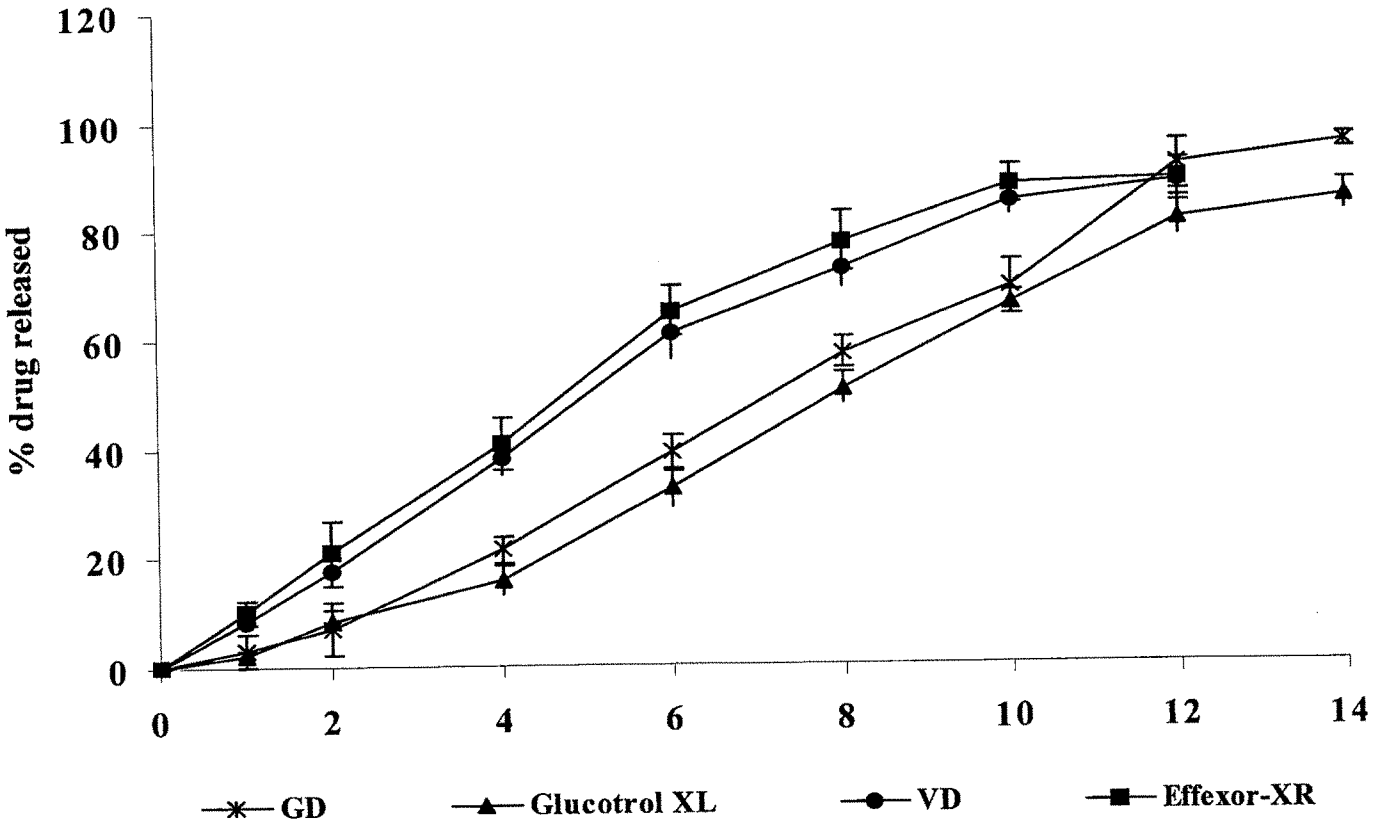


Table 3.1.11. Fitting of dissolution data of the optimized formulation to various kinetic models

Kinetic Model	Parameters					
	r		SSQ		*k*	
	VD/VIII	GD/VIII	VD/VIII	GD/VIII	VD/VIII	GD/VIII
Zero order	0.9895	0.9782	15.25	125.55	2.25	3.55
First order	0.9758	0.9664	11898.71	8004.78	-0.0108	-0.0588
Higuchi model	0.9814	0.9725	2266.31	5200.35	3.27	3.85
Hixon-Crowell model	0.9326	0.9447	17028.43	16105.25	0.1524	0.1709

r: coorelation co-efficient, SSQ: sum of squared residuals, k: release rate constant for respective models (k_0, k_1, k_H and k_{HC} for zero-order, first-order, Highuchi model and Hixon-Crowell model, respectivley

– ***SCANNING ELECTRON MICROSCOPY (SEM)***

It was expected that varying the viscosity grade and the level of swellable pore former, porosity of the membrane would vary because of swelling of pore former from the membrane. This was reflected in the release studies, wherein the release varied with varying the viscosity grade and level of swellable pore former. To further confirm this, the membrane structure of formulations of SPOP containing swellable polymers were observed after dissolution studies.

* **Effect of viscosity grade of HPMC polymer**

In case of membrane containing 0 % level of swellable pore former (C-I), there were no pores or sponge like appearance in the membrane (Fig. 3.1.8). For C-II with 6% (w/w of CA) HPMC K100LV, SEM micrograph showed formation of sponge like structure in the membrane (Fig. 3.1.9). For C-III with 6% (w/w of CA) HPMC K4M, SEM micrograph showed formation of significantly enhanced spongy structure (Fig. 3.1.10) as compared to C-II membrane. This could be due to the high viscosity nature of HPMC K4M. In case of C-IV with 6% (w/w of CA) HPMC K15M, SEM micrograph showed formation of denser sponge like appearance (Fig. 3.1.11) than C-II and C-III in the membrane. This

Fig. 3.1.8 : Scanning electron microphotograph of membrane devoid of swellable pore former (3000 X)

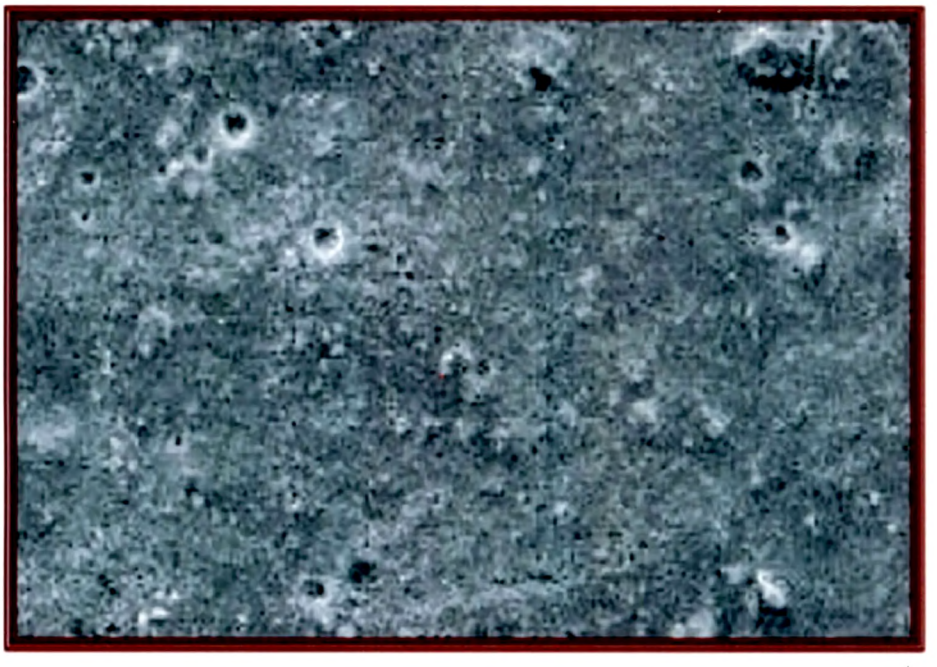


Fig. 3.1.9 : Scanning electron microphotograph of membrane containing 6% w/w of HPMC K100LV (3000 X)

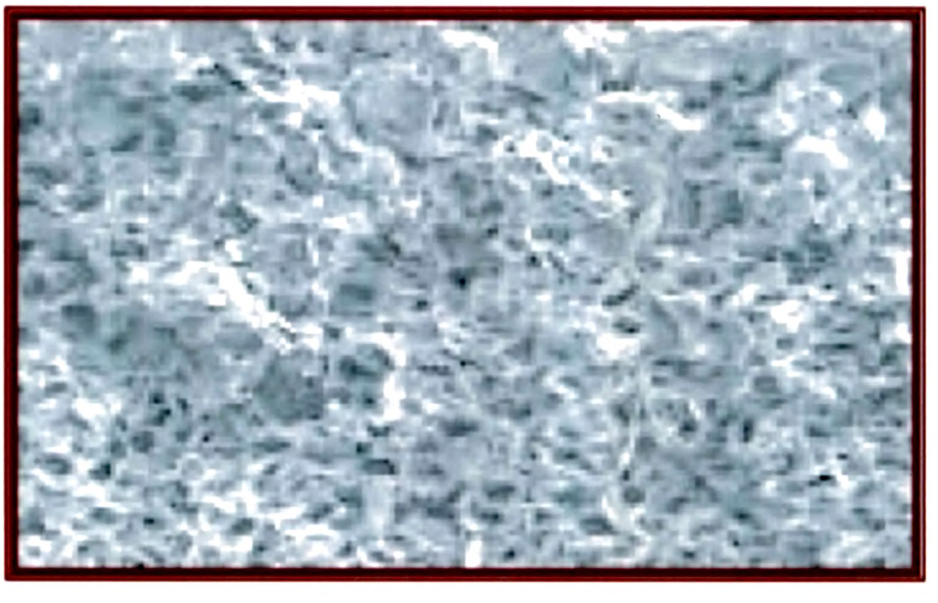


Fig. 3.1.10 : Scanning electron microphotograph of membrane containing 6% w/w of HPMC K4M (3000 X)

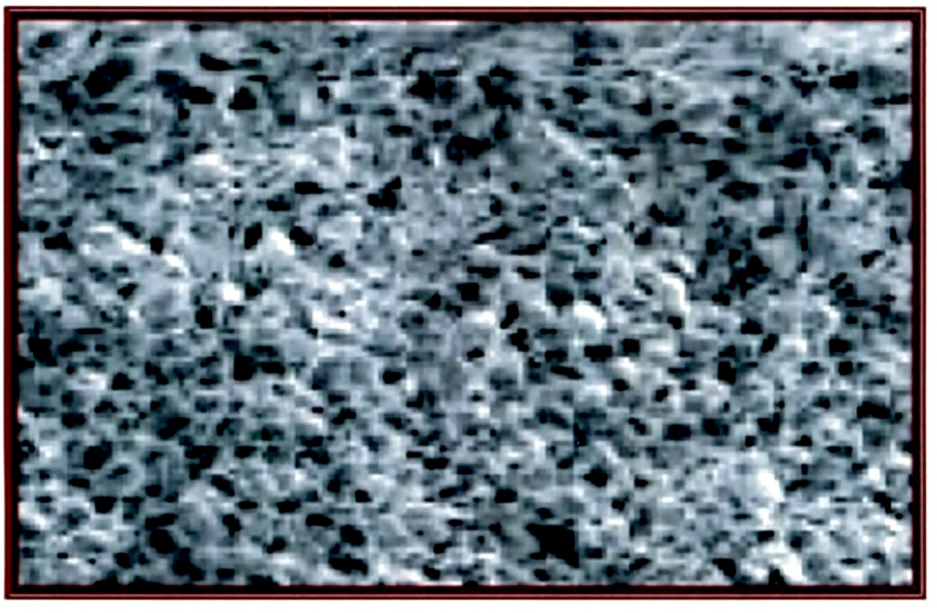
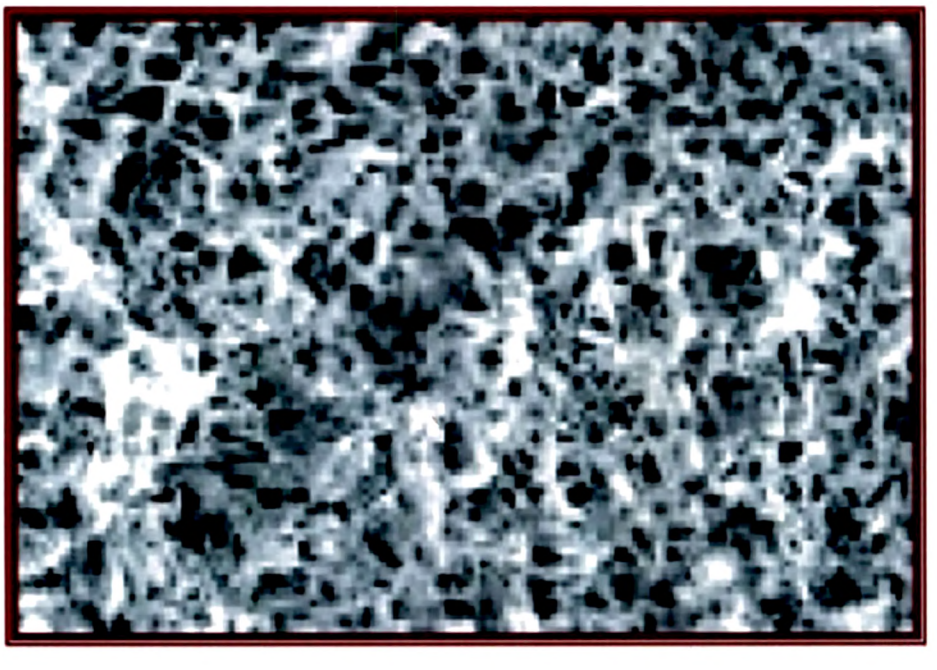


Fig. 3.1.11 : Scanning electron microphotograph of membrane containing 6% w/w of HPMC K15M (3000 X)



could be due to higher viscosity nature of HPMC K15M than HPMC K100LV and K4M. The results are consistent with the drug release studies (Fig. 3.1.3 and 3.1.4).

* **Effect of level of HPMC polymer**

In case of C-V which has 12% (w/w of CA) HPMC K100LV, SEM micrograph showed formation of thick dense skin having spongy appearance (Fig. 3.1.12) than C-II which has 6% (w/w of CA) HPMC K100LV in the membrane. This could be due to higher viscosity resulting from C-V coating membrane compared to C-II. In case of C-VI which has 12% (w/w of CA) HPMC K4M, SEM micrograph showed formation of significantly thick spongy appearance (Fig. 3.1.13) than C-III which has 6% (w/w of CA) HPMC K4M in the membrane. This could be due to higher viscosity resulting from C-VI. The results are consistent with the drug release studies (Fig. 3.1.5 and 3.1.6).

* **Combined effect of HPMC K100LV :HPMC K4M (1:1) coating**

In case of C-VII which has 3.5% (w/w of CA) each of HPMC K100LV and HPMC K4M, SEM micrograph showed formation of uniform spongy like appearance (Fig. 3.1.14) than all other coating membranes. This could be due to combined effect of higher and lower viscosity grade HPMC polymer. The results are consistent with the drug release studies (Fig. 3.1.5 and 3.1.6).

Fig. 3.1.12 : Scanning electron microphotograph of membrane containing 12% w/w of HPMC K100LV (3000 X)

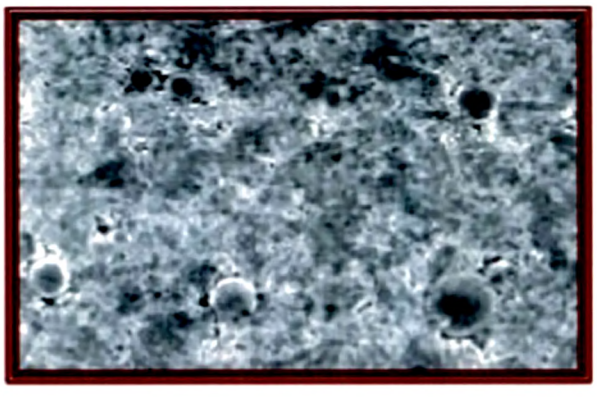


Fig. 3.1.13 : Scanning electron microphotograph of membrane containing 12% w/w of HPMC K4M (3000 X)

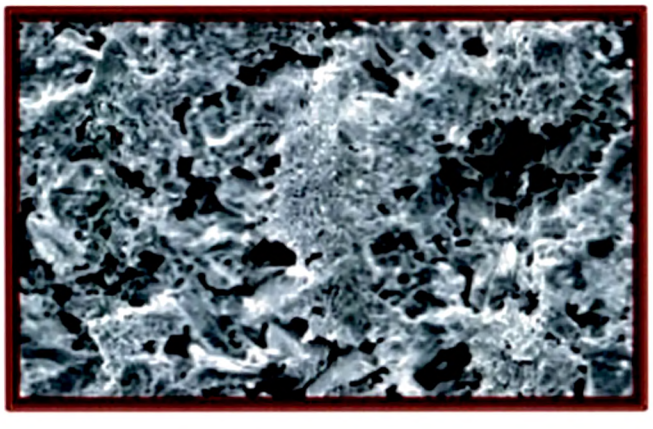
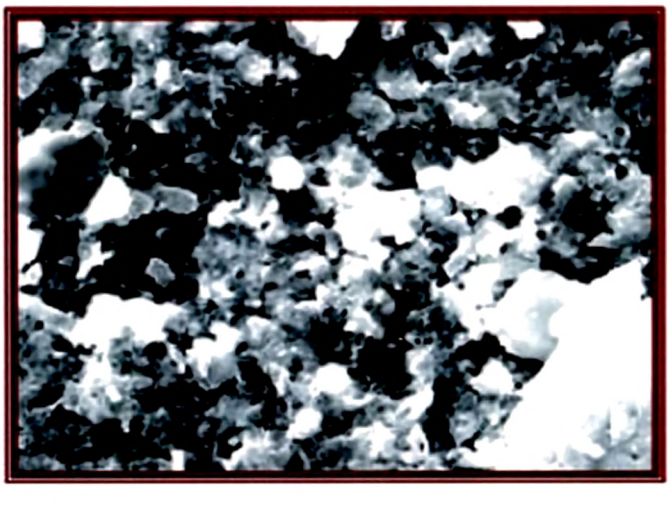


Fig. 3.1.14 : Scanning electron microphotograph of membrane containing 3.5% w/w each of HPMC K100LV and HPMC K4M (3000 X)



PART II

MONOLITHIC OSMOTIC TABLET SYSTEM (MOTS)

INTRODUCTION

Monolithic osmotic tablet systems are reported in the patent literature (Chen et al, 1998, Chen and Chou, 1998), although the information regarding the effect of tablet formulation variables, orifice size and membrane variables on drug release of this system are less well known. The MOTS controlled-release system, which is composed of a monolithic tablet coated with cellulose acetate membrane with an orifice drilled mechanically, has been described. When the formulation is administered orally and reaches the stomach, gastric fluid enters inside the core through semipermeable membrane and dissolves the water soluble osmotically active agent (osmogent) and creates osmotic pressure in the core. The drug release occurs through the orifice by osmotic mechanism. The drug release is irrespective of pH and time, and occurs continuously by osmotic mechanism.

The mechanisms by which drug release is controlled in MOTS are dependent on many variables. One of the principles of drug release would be osmotic pressure. It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents by changing the proportion of the hydrophilic polymer (s) in the core and semipermeable polymer in the coating.

The MOTS comprises of the following components in the formulation:

A. A homogeneous core, comprising

i. Medicament, which is selected from group of water soluble, sparingly soluble or poorly soluble drugs or in combination thereof,

ii. Binder (s),

iii. Swelling agent (s)

iv. Water soluble osmotically active agent (osmogent) (s)

v. Optionally diluent (s)

B. A membrane coating which covers the said core formulation, which comprises of:

i. A water insoluble and semipermeable pharmaceutically acceptable polymer,

ii. A single or a mixture of plasticizer.

iii. An orifice

The aim of the current study was to design a novel monolithic osmotic tablet system (MOTS) based drug delivery system for controlled release of metoprolol tartrate (MT) and nifedipine (NP). In case of metoprolol, various molecular weight polymers of polyethylene oxide (PEO) were used as a swelling agent and to retard the drug release. In order to enhance the solubility of nifedipine, PEG 6000, Mannitol and Poloxamer-188 were explored as solid dispersant. The current study was also focussed on the effect of various molecular weight polymers of PEO 1, 3 and 6 Lac g/mol and the effect of amount of solid dispersing agent for metoprolol and nifedipine respectively.

1. Metoprolol tartrate (MT)

MT is a selective β-1-adrenoreceptor blocking agent (Hoffman, 2001). It has a short biological half-life and the maintenance of constant plasma level of this drug is important in ensuring the desired therapeutic response and hence multiple doses are needed (Kendall et al., 1991). Frequent administration makes it a suitable candidate for controlled release dosage forms.

2. Nifedipine (NP)

NP was chosen as the model drug, a well known calcium channel blocking agent that is used to treat a variety of cardiovascular disorders, such as angina pectoris and hypertension.

Nifedipine has been shown to exist in three monotropically related modifications, modification I (m.p. 169–173 °C), which is the thermodynamically stable modification at room temperature, mod. II (m.p. 161–163 °C) and mod. III (m.p. 135 °C), which are metastable modifications (Eckert and Muller, 1977; Burger and Koller, 1996). Four different 1,4-dioxane solvates (A–D) of nifedipine have also been crystallized and are easily distinguishable using thermomicroscopy, differential scanning calorimetry (DSC) and infrared (IR) spectroscopy (Burger and Koller, 1996). Nifedipine often shows low and irregular bioavailability after oral administration (Ali, 1989).

Adalat (nifedipine tablet) is a commercialized push–pull osmotic tablet product made by Pfizer. The push pull osmotic tablet consists of two compartments, one containing drug

and the other an osmotic agent and an expandable agent. A semipermeable membrane that regulates water influx into both compartments surrounds the system. An orifice was drilled into the surface of the drug compartment to allow drug release (Theeuwes, 1984; Wong et al., 1986; Swanson et al. 1987). While the push–pull osmotic tablet succeeds in delivering water-insoluble drug, it has two disadvantages:

(1) the tablet core is prepared by compressing two kinds of compartments together, a complex technology as compared with that of monolithic tablets; and

(2) after coating, a complicated laser-drilling technology should be employed to drill the orifice next to the drug compartment (Geerke, 1997).

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. The solid dispersion of poorly water-soluble drugs in water-soluble surface-active and self-emulsifying carriers enhances drug dissolution and bioavailability (Chiou and Riegelman, 1970; Stupak and Bates, 1972; Serajuddin, 1999). An important mechanism is the reduction of the drug's particle size to the microcrystalline or molecular level for rapid dissolution and absorption. The microcrystalline state of the drug in a water-soluble carrier may be achieved by complete solubilization of the desired dose of the drug in the carrier matrix at an elevated temperature followed by crystallization of the drug, and possible crystallization of the matrix components, on cooling. Hence, the choice of a water-soluble carrier is important in the preparation of a stable solid dispersion.

The preparation and characterization of solid dispersions of nifedipine have been reported previously. The solid dispersions of nifedipine in carriers, such as polyethylene glycol (PEG) 6000 (Lin and Cham, 1996) and polyvinylpyrrolidone (Sugimoto et al., 1980), have been developed to increase drug absorption. Solid dispersions of nifedipine in PEG and phosphatidylcholine dissolve faster than the solid drug, which was attributed to the formation of lipid vesicles that entrapped a certain concentration of nifedipine (Law et al., 1992). Cogrinding of nifedipine with PEG 6000+hydroxypropyl methylcellulose also improved nifedipine dissolution (Sugimoto et al., 1998).

Kuchiki et al., (1980) attempted to develop the solid dosage forms of nifedipine which showed good absorption rate and total bioavailability. The dissolution rate of nifedipine–PVP co-precipitates exhibited rapid dissolution rate. X-ray diffraction data suggested the lack of crystallinity in the co-precipitate. The relation between the dissolution rates and average molecular weights of PVP was studied. Nifedipine in the co-precipitate was chemically stable to heat and humidity, but the dissolution rate of nifedipine from the co-precipitate stored at 21° and 75% RH markedly decreased. X-ray diffraction data revealed that it might be due to the transformation of amorphous form of nifedipine to crystalline form under higher relative humidity. Absorption of nifedipine in beagle dogs after oral administration of the co-precipitate was studied and was found to be more as compared to administration of physical mixtures.

Suzuki and Sunada (1998) worked with the objective to clarify the influence of water soluble polymers on the dissolution behavior of nifedipine from solid dispersions with combined carriers. All the solid dispersions of nifedipine were prepared by the fusion method using nicotinamide and four different water soluble polymer, HPMC, PVP, PVA and pullan. DSC & XRD reports suggested that there was conversion of crystalline nifedipine to amorphous form, which led to increased dissolution of the drug. In another study other carriers were investigated to increase the dissolution rate of nifedipine. These carriers include nicotinamide, ethylurea, polyethylene glycol 6000 and HPMC. Of these the best results were achieved with nicotinamide. Both nicotinamide and HPMC showed further improvement of dissolution.

Chutimaworapan et al., (2000) prepared solid dispersions of nifedipine with polyethylene glycols (4000 & 6000), hydroxylpropyl betacyclodextrin and poloxamer 407 in four mixing ratios were prepared by melting, solvent and kneading methods in order to improve the dissolution of nifedipine. The enhancement of the dissolution rate and the time for 80% dissolution, T80% depended on the mixing ratio and the preparation method. The highest dissolution rate and the T80% as shorter as 15 min were obtained from poloxamer 407 solid dispersions prepared by melting methods at a ratio of 1:10. The X-ray diffraction patterns of solid dispersions at higher proportion of carriers

demonstrated consistent with the results from DSC thermograms that nifedipine existed in the amorphous state.

Zajc et al., (2005) formulated solid dispersions of nifedipine with mannitol in preparations containing 10 and 50% of drug by the hot melt method. Physical properties and the dissolution behavior of binary systems as physical mixtures and solid dispersion were investigated. In all samples, the crystal structure of nifedipine was confirmed using DSC and SEM. Fourier transform infrared spectroscopy revealed there was no interaction between drug and carrier. The dissolution rate was increased.

Objectives of the present study were

- ✧ To design and optimize a novel monolithic osmotic tablet system (MOTS) based drug delivery system for controlled release of metoprolol tartrate (MT) and nifedipine (NP).
- ✧ To formulate and evaluate solid dispersions of nifedipine using hydrophilic polymers
- ✧ To formulate and evaluate granules of MT and NP
- ✧ To formulate and evaluate core tablets of MT and NP
- ✧ To formulate and evaluate coated tablets of MT and NP
- ✧ The current study was also focussed on the influence of tablet formulation variables, such as molecular weight (MW) and amount of polyethylene oxide (PEO) on release profile of MT and amount of solid dispersing agent on the release profile of NP and to propose a delivery mechanism and optimal tablet formulation for this system;
- ✧ To study the influence of orifice size and membrane variables, including the nature and amount of plasticizer as well as thickness on drug release;
- ✧ To study the mechanism and kinetics of drug release from the optimized formulations by fitting into different dissolution models.

1. FORMULATION AND EVALUATION METHODS

– *FORMULATION OF CORE TABLETS OF METOPROLOL TARTRATE*

In this osmotic system, polyethylene oxide was used as swelling polymer, sodium chloride was used as osmogent, starch as diluent, colloidal silicon dioxide as glidant and magnesium stearate as lubricant. Table 3.2.1 enlists the composition of core formulation prepared.

Table 3.2.1 Core formulations of Metoprolol – MOTS

Ingredient*	Batch no.				
	MA	MB	MC	MD	ME
Metoprolol tartrate	100.00	100.00	100.00	100.00	100.00
PEO 1 Lac g/mol	0.00	40.00	25.00	80.00	50.00
PEO 3 Lac g/mol	0.00	10.00	25.00	20.00	50.00
Sodium chloride	75.00	75.00	75.00	75.00	75.00
Starch	120.00	70.00	70.00	20.00	20.00
Colloidal silicon dioxide	2.00	2.00	2.00	2.00	2.00
Magnesium stearate	3.00	3.00	3.00	3.00	3.00
Total	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**

The tablets were prepared by wet granulation technique. All the raw materials were sieved through # 60 mesh. Drug was uniformly mixed with PEO, starch and sodium chloride in a high shear mixer granulator for 10 min. The dry blend was granulated with isopropyl alcohol. The mass was dried at 50°C and sized through # 20 mesh and mixed with colloidal silicon dioxide. The granules were lubricated with magnesium stearate and compressed into round tablets with standard concave plain punches and dies (diameter – 9.52 mm) using 8 – station single rotary compression machine (KMP-8, Cadmach Engg, Ahmedabad, India).

– ***PREPARATION OF SOLID DISPERSIONS FOR NIFEDIPINE***

Various carriers were screened at different ratios and the solid dispersions of nifedipine were prepared by melting method. The physical mixture of nifedipine and carrier was prepared manually and allowed to melt at the temperature based on the melting point of carrier (e.g. PEG 6000 : 58°C, Mannitol : 175°C, Poloxamer : 70-80°C) in a water bath (SW 23, Julabo Labortechnik, Germany). The melt was cooled at room temperature and mildly ground. The product was sieved through 0.85 mm mesh and stored under vacuum in a dessiccator to avoid moisture up take. Table 3.2.2 enlists the composition.

Table 3.2.2 Details of Solid dispersing carrier and nifedipine:carrier ratio

Sr. no.	Carrier	Nifedipine : Carrier
1.	--	1:0
2.	**PEG-6000**	1:1
3.		1:5
4.		1:10
5.	**Poloxamer-188**	1:1
6.		1:5
7.		1:10
8.	**Mannitol**	1:1
9.		1:5
10.		1:10

- ***EVALUATION OF NIFEDIPINE SOLID DISPERSION***

* ***Solubility***

Solubility measurements were carried out by adding mixtures (equivalent to 100 mg nifedipine) to 100 mL water containing 0.2% v/v of methanol (to maintain sink condition). Samples were stirred in a water bath (SW 23, Julabo Labortechnik, Germany) at 37 ± 0.5° C for 24 h. Samples were withdrawn and filtered through Millipore HVLP filter (0.45 μm) and analysed spectrophotometrically at 340 nm after suitable dilutions.

* ***Differential scanning calorimeter (DSC)***

A PerkinElmer differential scanning calorimeter (Pyris 1- DSC, Waltham, MA) was used to obtain the DSC curves of NPSD. The samples were separately sealed in aluminum cells and heated from 30 to 300 °C at a heating rate of 10 °C/min.

* ***Powder X-ray crystallography (PXRD)***

PXRD patterns were investigated on a X-ray diffractometer (Multiflex 3KW, Rigaku) with Cu/Kα as the source of radiation. For diffractometric studies, the angular range of 0-40° 2θ was scanned with a step size of 0.02° 2θ and dwell time of 0.3 seconds at each

step. The 2θ values and the intensities of the peaks were copared for both pure ingredients and NPSD.

– ***FORMULATION OF CORE TABLETS OF NIFEDIPINE***

The basic tablet formulation and the varying range of other excipients are listed in Table 3.2.3. In each formulation, the effect of starch on drug release was assumed to be negligible (Liu et al., 2000b). Thus the amount of starch was varied to maintain uniform weight of each formulation. Mannitol and potassium chloride were used as osmogents. Tablets were prepared by direct compression technique. Inclusion complex was mixed with osmogent and filler and lubricated with magnesium stearate and colloidal silicon dioxide. The lubricated blend was compressed into round tablets with concave punches (diameter – 12.70 mm) using 27 station compression machine (CMB4 D-27, Cadmach Engg, Ahmedabad, India).

Table 3.2.3 Core formulations of Nifedipine – MOTS

Ingredient*	Batch no.				
	NA	NB	NC	ND	NE
Nifedipine	30.00	30.00	30.00	30.00	30.00
Poloxamer-188	0.00	300.00	300.00	300.00	300.00
Mannitol	150.00	150.00	150.00	150.00	150.00
Potassium chloride	0.00	0.00	50.00	100.00	200.00
Starch	510.00	210.00	160.00	110.00	10.00
Colloidal silicon dioxide	3.00	3.00	3.00	3.00	3.00
Magnesium stearate	7.00	7.00	7.00	7.00	7.00
Total	**700.00**	**700.00**	**700.00**	**700.00**	**700.00**

* qty in mg / tablet

– ***EVALUATION OF MT AND NP GRANULES***

* ***Loss on drying (LOD)***

IR moisture balance (PM 480, Mettler Toledo, Switzerland) was used to determine LOD of the powder blend.

* ***Bulk density (BD), Tap density (TD), Compressibility index (CI) and Hausner ratio (HR)***

To determine BD and TD of the powder blend, USP method II on a tap density tester (ETD-1020, Electrolab, Mumbai, India) was used. From the data obtained, CI and HR were calculated.

- ***EVALUATION OF METOPROLOL TARTRATE AND NIFEDIPINE CORE TABLETS***

* ***Uniformity of weight (Weight variation test)***

In this test, 20 tablets were weighed individually on an electronic balance (AG-64, Mettler Toledo, Switzerland), the average weight was calculated and compared with individual weights. The percentage difference in the weight variation should be within the permissible limits (± 5%).

* ***Thickness and diameter***

The thickness and diameter of the tablets were determined by using a thickness gauge (Digimatic Caliper, Mitutoyo, Japan).

* ***Hardness test***

The hardness of core tablets were tested using a hardness tester (6-D, Dr Schleuniger Pharmatron, Manchester, NH, USA)

* ***Friability test***

The friabilator (EF-2, Electrolab, Mumbai, India) was rotated at a speed of 25 rpm for 4 minutes. Percentage friability was then calculated.

* ***Drug content***

Ten core tablet were selected randomly and average weight was calculated. Analysis for Venlafaxine HCl and Glipizide was carried out as per the method mentioned in analytical methods section.

- ***COATING OF METOPROLOL TARTRATE AND NIFEDIPINE CORE TABLETS***

Tablets were spray coated by perforated pan coater (GAC – 250, Gansons Ltd., Mumbai, India). Table 3.2.4 summarizes the components of coating solution and the processing conditions respectively. The coating solutions were prepared using mixture of dichloromethane and methanol (70:30) as the coating solvent to get a 4 % total solids in coating solution. Coated tablets were dried at 50°C for 16 h and the % weight gain and thickness (Digimatic Caliper, Mitutoyo, Japan) of the coating membrane were measured.

Table 3.2.4 Components of coating solution and processing conditions for MOTS tablets

Coating formulation	Amount of PEG-400 (% w/w of CA)	Processing condition	
C-I	10	Tablet bed size	800 gm
C-II	25	Inlet temperature	55 ± 2° C
C-III	40	Outlet temperature	42 ± 2° C
C-IV	25	Atomizing air pressure	2.1 kp / cm^2
C-V	25	Peristaltic pump speed	4-5

- ***EVALUATION OF METOPROLOL TARTRATE AND NIFEDIPINE COATED TABLETS***

* ***Percentage weight gain***

From every batch of coating, 25 coated tablets were individually weighed and the average weight was calculated and compared with average weight of uncoated. The difference in weight was determined and the percent weight gain was calculated.

* ***Coating thickness***

The thickness and diameter of the coated tablets were determined by using a thickness gauge (Digimatic Caliper, Mitutoyo, Japan).

* ***Burst strength***

The burst strength of the exhausted shells after dissolution was determined to assure that the tablets would maintain their integrity in the GIT. Burst strength is the force required to break / rupture the shells. The texture analyzer (TAX T2i, Stable micro systems, U.K) with a 5 kg load cell and 25 mm aluminium cylindrical probes were utilized. Test speed of 0.8 mm/s was selected and distance moved was at 2 mm.

* ***Aperture diameter***

The empty shells obtained after dissolution were used for the measurement of orifice diameter using digital microscope (Leica DMLB, Leica Microsystems GmbH, Nussloch, Germany).

– ***IN-VITRO DRUG RELEASE***

Table 3.2.5 summarizes the dissolution study and analytical method. In vitro drug release of the formulations were carried out using USP type I dissolution apparatus (2100C, Distek Inc, NJ) attached with an auto-sampler (37 °C ± 0.5 °C). The drug release at different time intervals was analyzed by UV spectrophotometer (8453, Agilent Technologies, Singapore).

Table 3.2.5 *In-Vitro* dissolution studies and analytical method

Parameters	Metoprolol tartrate	Nifedipine
Dissolution media	Distilled water	0.1N HCl, pH 1.2 , 0.5% SLS
USP Type	I (Basket)	I (Basket)
Volume	900 ml	900 ml
RPM	75	100
Temperature	37 °C	37 °C
Analytical method	UV spectrophotometer, 223 nm	UV spectrophotometer, 238 nm

Release profiles were also compared using mean dissolution time or MDT.

- ***STATISTICAL ANALYSIS OF DISSOLUTION DATA***

Release profiles of optimized tablets were compared by calculating two statistically derived mathematical indices, difference factor (f_1) and similarity factor (f_2) with a commercially available product, as the reference.

- ***KINETICS OF DRUG RELEASE***

In order to understand the mechanism of drug release from the optimized system, the data were applied to various dissolution models.

- ***SCANNING ELECTRON MICROSCOPY (SEM)***

In order to elucidate the mechanism of drug release from optimized formulations based on MOTS technology, surface of coated tablets were studied using scanning electron microscope (SEM). After dissolution studies, a small portion of sample of the coating membrane was carefully cut from the exhausted shells and dried at 50 °C for 12 h. The samples were mounted and examined for their porous morphology by Philips ESEM-TMP scanning electron microscope (SEM) (Philips, Netherlands). Samples from MOTS as detailed below were evaluated using SEM.

Coating Formulation code	**Details of coating**
C-I	10% (w/w of CA) PEG-400
C-II	25% (w/w of CA) PEG-400
C-III	40% (w/w of CA) PEG-400

3. RESULTS AND DISCUSSION

- ***FORMULATION DEVELOPMENT***

The dosage form was designed as a tablet core, coated with a rate controlling membrane. Tablet core consists of drug along with solid dispersing carrier (Poloxamer 188, in case of Nifedipine), osmogent, and other conventional excipients. Solid dispersing carrier used in the core was formulated to enhance the solubility and drug release. The core

compartment was surrounded by a membrane consisting of cellulose acetate (CA), a semipermeable membrane-forming polymer and PEG-400 as plasticizer capable of improving film-forming properties of the polymers.

CA 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 and dissolves the drug (In case of nifedipine, the solid dispersing carrier first gets dissolved and then increases the solubility of nifedipine). The dissolved drug is released through orifice.

- ***EVALUATION OF NIFEDIPINE SOLID DISPERSION***

* ***Solubility***

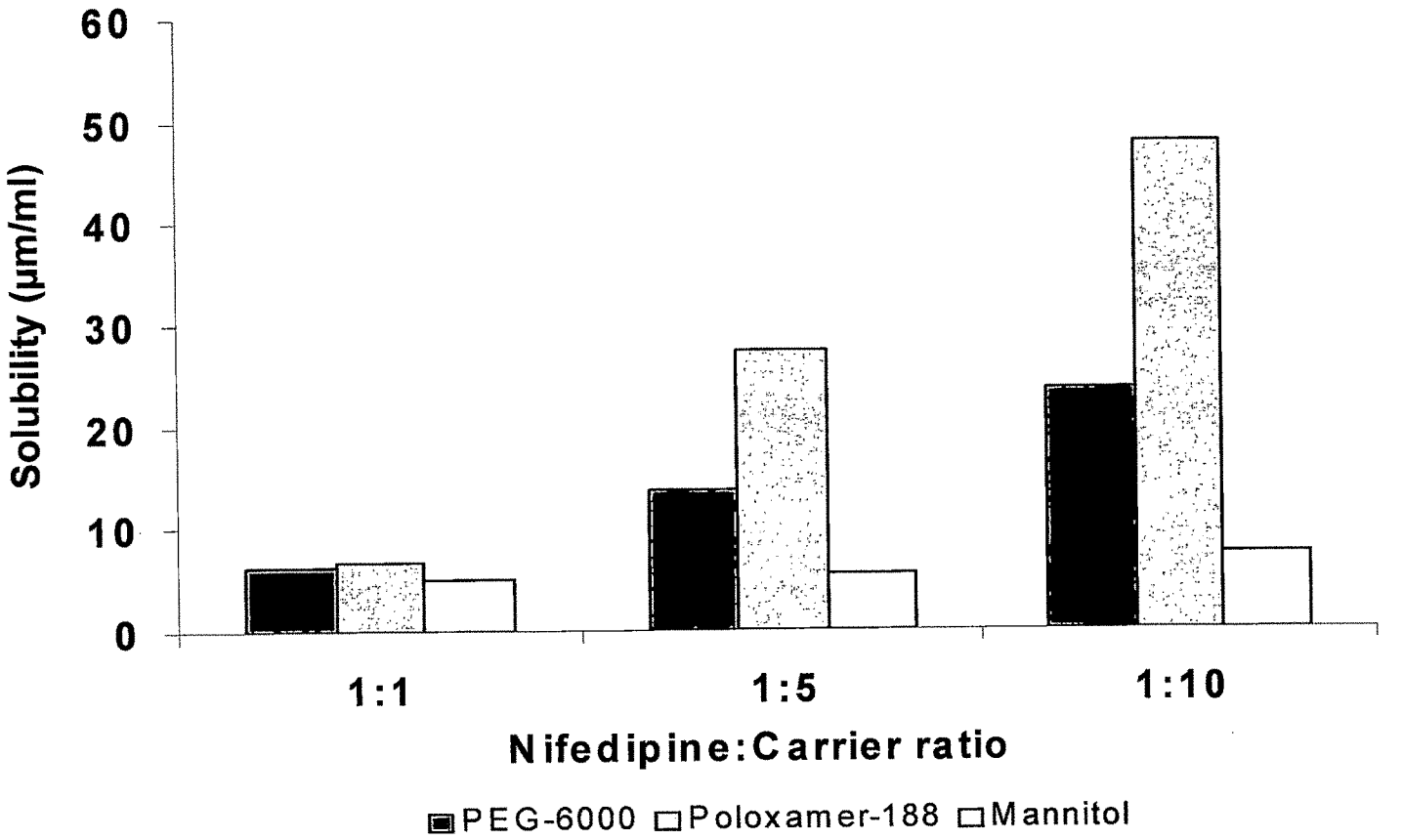
The intrinsic solubility of nifedipine, a poorly water soluble drug, is ~ 5 µg/ml at 37°C in water.

The solubility of nifedipine solid dispersions having maximum carrier (1:10) with PEG-6000, Poloxamer-188 and Mannitol as a carrier was 23.51 ± 0.17, 47.71 ± 0.52 and 7.37 ± 0.07 µg/ml respectively. The results are presented in Table 3.2.6 and Fig. 3.2.1.

Table 3.2.6 Details of Solid dispersing carrier, nifedipine:carrier ratio and solubility of solid dispersion

Sr. no.	Carrier	Nifedipine : Carrier	Nifedipine solubility (µg/ml)
1.	--	1:0	5.22 ± 0.03
2.	**PEG-6000**	1:1	6.21 ± 0.02
3.		1:5	13.67 ± 0.06
4.		1:10	23.51 ± 0.17
5.	**Poloxamer-188**	1:1	6.81 ± 0.28
6.		1:5	27.26 ± 0.37
7.		1:10	47.71 ± 0.52
8.	**Mannitol**	1:1	4.98 ± 0.07
9.		1:5	5.57 ± 0.06
10.		1:10	7.37 ± 0.07

Fig. 3.2.1 Effect of solid dispersing carrier on nifedipine solubility



There was a ~9 fold increase in the solubility of nifedipine from Nifedipine Poloxamer-188 Solid Dispersion (NPSD) from 1:10 ratio as against pure nifedipine at 37°C. This might be attributed to the surface active property of Poloxamer-188 as it is a polyoxyethylelne-polypropylene block copolymer nonionic surfactant with an HLB value of 18-23. Poloxamer-188 reduces the activity coefficient of the drug by reducing the hydrophobic interaction. The plots in Fig. 3.2.1 show the solubility diagrams of nifedipine inclusion complex. The solubility of nifedipine increased linearly with increasing concentration of Poloxamer-188 and maximum solubility obtained was with NPSD 1:10. Hence a 1:10 (drug:polymer) ratio was used for further development

* ***Differential scanning calorimeter (DSC)***

The pure nifedipine crystals gave a sharp melting endotherm at 173.89 °C (Fig. 3.2.2). Poloxamer-188 exhibited a single sharp melting endotherm at 51.29 °C. The NPSD exhibited a melting endotherm at 51.16°C and the absence of nifedipine melting peak was observed in the thermogram. These results suggest that on heating in DSC, nifedipine progressively dissolve in Poloxomer-188 and dissolves completely below the melting temperature of crystalline nifedipine. The relationship was found to be consistent with the results obtained by previous works (Vippagunta et al. 2002).

* ***Powder X-ray crystallography (PXRD)***

The powder X-ray diffractogram of pure nifedipine from 5 to 20° 2θ showed numerous distinctive peaks that indicated a high crystallinity. Poloxamer-188 also exhibited some crystallinity, as indicated by the two peaks of high intensity at 19.25° and 23.45° 2θ.

The XRD patterns of NPSD exhibited the absence of characteristic diffraction peaks of nifedipine, indicating that the crystalline characteristics of nifedipine had disappeared in these solid dispersions. Nifedipine at low concentrations may have either converted to a metastable amorphous form or may have dissolved in the matrix system to form a solid solution, or may exist in a microcrystalline form in the matrix. (Fig. 3.2.3)

Fig. 3.2.2 : DSC curves for pure nifedipine, neat Poloxamer-188 and Solid Dispersion

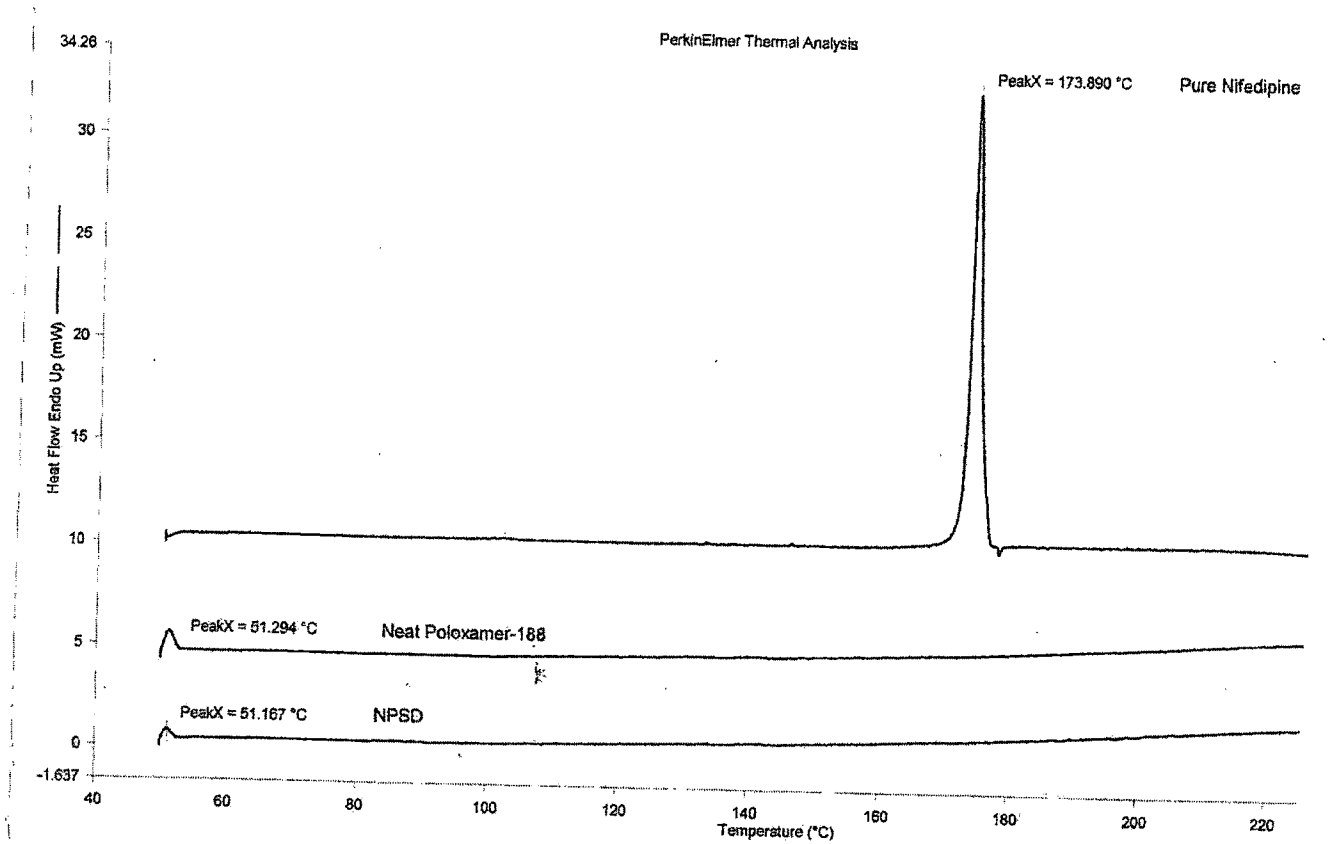
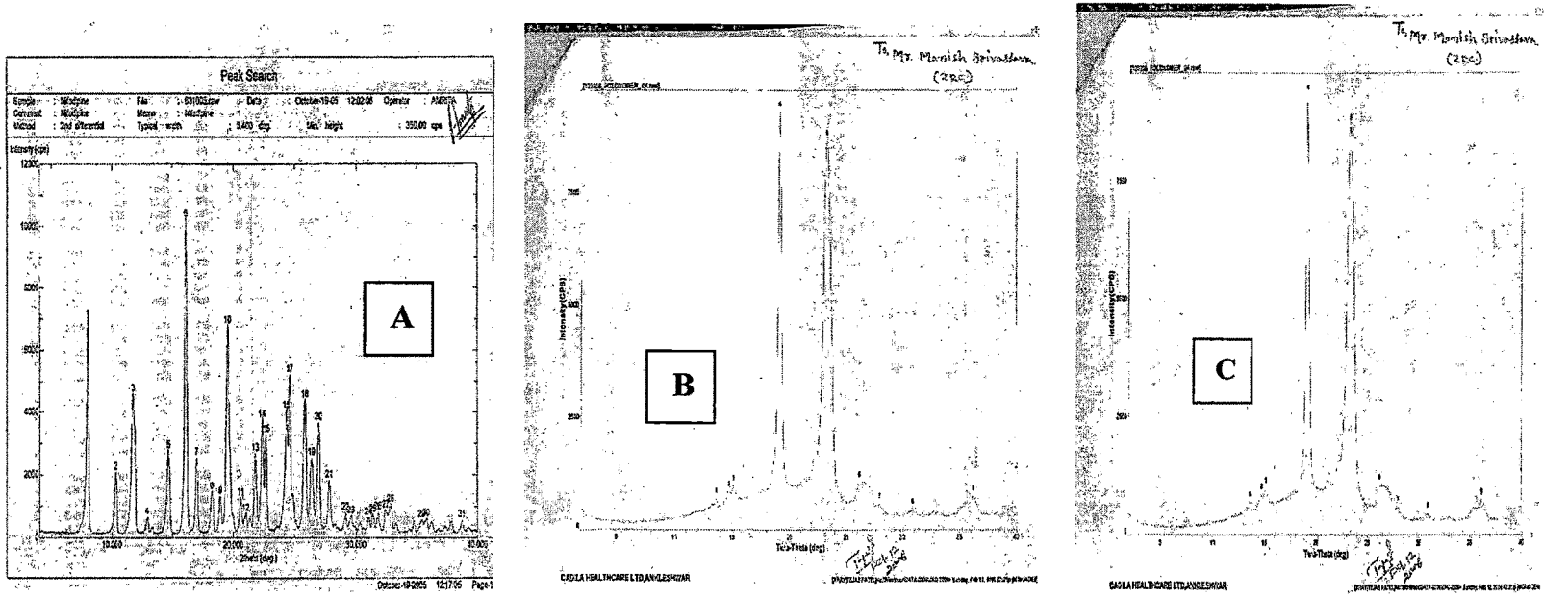


Fig. 3.2.3 : XRD diffraction patterns of

(A) pure nifedipine, (B) neat Poloxamer-188 and (C) Solid Dispersion



4.2 EVALUATION OF METOPROLOL TARTRATE AND NIFEDIPINE GRANULES

The values of LOD and BD, TD, CI and HR are presented in Table 3.2.7

Table 3.2.7 Properties of the granules of developed formulations

Batch no.	Loss on drying (%)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Compressibility Index (%)	Hausner ratio
Metoprolol tartrate					
MA	2.11	0.66	0.71	13.25	1.11
MB	1.75	0.54	0.68	12.68	1.28
MC	2.88	0.64	0.74	12.50	1.23
MD	1.66	0.57	0.68	11.57	1.26
ME	1.74	0.47	0.59	12.87	1.18
Nifedipine					
NA	1.38	0.70	0.79	11.00	1.17
NB	1.70	0.76	0.85	9.92	1.20
NC	2.29	0.71	0.81	11.21	1.23
ND	0.69	0.86	0.93	11.79	1.26
NE	0.84	0.83	0.86	9.95	1.13

The LOD was in the range of 0.5-3% for all the formulated batches suggesting that optimum moisture was maintained in the granules. The CI and HR were in the range of 9-14 and 1.1-1.3 suggesting good flow of granules.

- ***EVALUATION OF METOPROLOL TARTRATE AND NIFEDIPINE CORE TABLETS***

The evaluation parameters along with values of the developed core formulations are presented in Table 3.2.8.

Table 3.2.8 Evaluation parameters of the developed core formulations

Parameters	Weight (n=20) (mg)	Thickness (n=20) (mm)	Diameter (n=20) (mg)	Hardness (n=20) (kg/cm^2)	Friability (n=3) (%)	Drug content (n=3) (%)
Metoprolol tartrate						
MA	301.44 ± 3.2	3.88 ± 0.02	9.50 ± 0.02	4.80 ± 0.2	0.20 ± 0.01	101.28 ± 3.21
MB	297.52 ± 4.5	3.75 ± 0.02	9.50 ± 0.03	4.60 ± 0.3	0.14 ± 0.01	96.58 ± 3.99
MC	299.47 ± 3.8	3.82 ± 0.08	9.52 ± 0.01	5.20 ± 0.2	0.20 ± 0.02	99.58 ± 3.24
MD	301.57 ± 2.8	3.72 ± 0.04	9.51 ± 0.01	5.30 ± 0.1	0.15 ± 0.02	97.75 ± 2.55
ME	302.78 ± 2.7	3.86 ± 0.03	9.53 ± 0.02	5.70 ± 0.2	0.11 ± 0.01	100.57 ± 2.45
Nifedipine						
NA	702.50 ± 3.8	4.31 ± 0.03	12.70 ± 0.01	8.10 ± 0.1	0.10 ± 0.01	99.82 ± 1.88
NB	699.50 ± 5.6	4.38 ± 0.04	12.69 ± 0.01	8.00 ± 0.2	0.19 ± 0.01	95.54 ± 2.67
NC	706.50 ± 4.9	4.24 ± 0.03	12.70 ± 0.02	8.40 ± 0.1	0.06 ± 0.02	101.30 ± 2.47
ND	703.00 ± 5.2	4.45 ± 0.03	12.71 ± 0.01	8.80 ± 0.2	0.29 ± 0.02	99.94 ± 2.23
NE	702.50 ± 3.7	4.34 ± 0.05	12.70 ± 0.01	8.70 ± 0.3	0.32 ± 0.03	102.89 ± 2.48

The weight variation was less than 5% for all the formulated batches suggesting uniformity of dosage form. The drug content was in the range of 95 – 105%.

- ***EVALUATION OF METOPROLOL TARTRATE AND NIFEDIPINE COATED TABLETS***

Table 3.2.9 summarizes the evaluation parameters of the coated tablets.

Table 3.2.9 Evaluation parameters of the coated formulations

Coating formulation	Weight gain (%)		Membrane thickness (μm)		Burst strength (g)		Orifice diameter (μm)	
	MT	NP	MT	NP	MT	NP	MT	NP
C-I	6.10 ± 0.25	6.20 ± 0.45	141 ± 12	136 ± 28	341 ± 8	355 ± 6	714 ± 3	704 ± 5
C-II	6.68 ± 0.12	6.58 ± 0.32	152 ± 10	148 ± 14	348 ± 6	347 ± 8	711 ± 3	708 ± 4

C-III	6.35 ± 0.54	6.18 ± 0.57	126 ± 12	131 ± 16	342 ± 10	345 ± 9	699 ± 4	706 ± 4
C-IV	9.63 ± 0.81	9.51 ± 0.42	168 ± 16	177 ± 31	351 ± 9	354 ± 8	701 ± 4	698 ± 6
C-V	12.22 ± 0.36	12.26 ± 0.27	236 ± 42	224 ± 31	352 ± 8	341 ± 7	709 ± 4	698 ± 6

* MT : Metoprolol Tartrate, NP: Nifedipine

None of the developed formulations caused burst effect.

– ***IN VITRO DRUG RELEASE***

1. Metoprolol tartrate

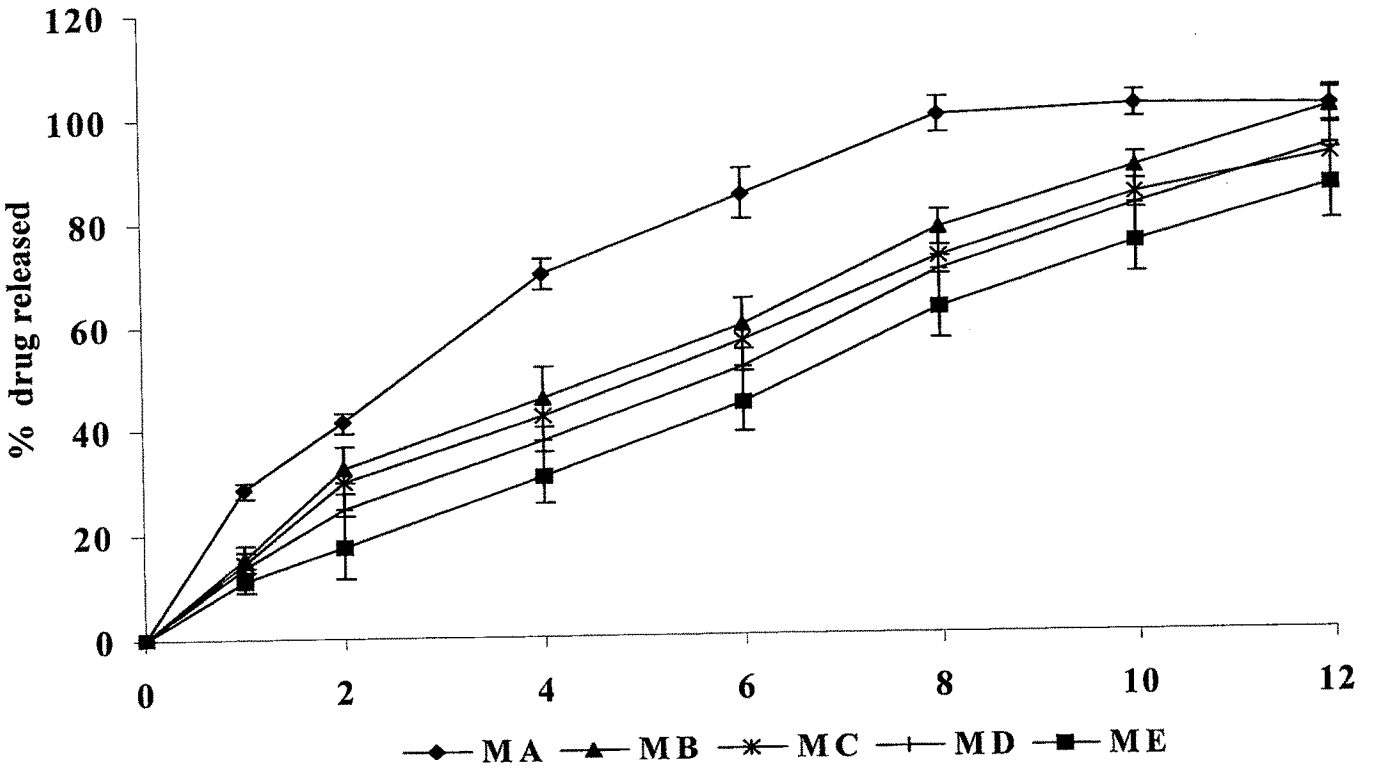
* **Influence of tablet formulation variables (amount and ratio of PEO) on drug release**

To optimize the amount of PEO to be used in the formulation and to study the effect of PEO 1 Lac g/mol and PEO 3 Lac g/mol ratio, core formulations were prepared as shown in Table 3.2.1.

All the core formulations were coated with coating composition, C-V containing 20 % w/w (of CA) PEG-400 and an orifice was drilled with 0.7 mm diameter.

Initially a batch (MA) was prepared without PEO and as expected the drug release was very quick with more than 85% released after 8h. (Fig. 3.2.4). For batch MB, the total amount of PEO was restricted to 50 mg per tablet with higher ratio of drug (2:1, Drug:PEO) and higher ratio of low mol. wt. polymer (4:1, PEO 1: PEO 3 Lac g/mol). The batch MB was prepared with 40 and 10 mg of PEO 1 and PEO 3 Lac g/mol per tablet respectively. Although the drug release in initial hours was controlled however around 80% drug got released after 8h. (Fig. 3.2.4). For batch MC, the ratio of PEO:PEO was change to 1:1, with 25 mg each of PEO 1 and PEO 3 Lac g/mol per tablet. The drug release was controlled by ~ 8% with ~72% drug release after 8h compared to the earlier batch. (Fig. 3.2.4). The batch MD, was prepared with same composition as that of MB except that the total amount of PEO was doubled to 100 mg per tablet with drug: total PEO of 1:1. The drug release was further controlled to 69.47 ± 2.33 % after 8h. (Fig. 3.2.4). In order to further control the drug release, the batch ME was prepared same as that of MD except that the PEO:PEO ratio was changed to 1:1. The initial burst release as well as the whole release profile was controlled with 11.25 ± 1.58, 62.46 ± 2.18 and 85.35 ± 2.11 % released after 1, 8 and 12 h respectively. (Fig. 3.2.4)

Fig. 3.2.4 In-vitro release profile of Metoprolol Tartrate MOTS tablets-Effect of Polyethylene oxide



* **Amount of PEO**

Fig. 3.2.4 shows the influence of amount of PEO. It is well known that, for a water-soluble polymer, higher the amount, higher is the viscosity of the polymer solution and slower dissolution rate. In the case of higher ratio of drug to total PEO (2:1, Drug:PEO), PEO swelled and dissolved quickly, but gave a solution with low viscosity, which could not hold MT suitably. As a result, the release rate was fast in formulation with higher amount of 1 Lac g/mol (MB and MC). On the other hand, in the case of equal ratio of drug to total PEO (1:1, Drug:PEO), PEO gave a solution with high viscosity, which could hold MT; however, PEO swelled and dissolved slowly (MD and ME). Therefore, the liquefaction of the tablet core and the release of MT were depressed and the release rate was slow.

* **Type of PEO**

Fig. 3.2.4 shows the influence of type of PEO. It is well known that, for a water-soluble polymer, higher the molecular weight, higher is the viscosity of the polymer solution and slower dissolution rate. Higher ratio of low mol. wt. polymer (4:1, PEO 1: PEO 3 Lac g/mol) was studied and found that PEO swelled and dissolved quickly, but gave a solution with low viscosity, which could not hold MT suitably. As a result, the release rate was fast in formulation with higher amount of 1 Lac g/mol (MB and MD). On the other hand, in the case of equal ratio of both PEO polymer (1:1) PEO gave solution with high viscosity, which could hold MT; however, PEO swelled and dissolved slowly (MC and ME). Therefore, the liquefaction of the tablet core and the release of MT were depressed and the release rate was slow.

2. Nifedipine

* **Effect of formulation variables**

To study the effect of tablet formulation variables on the drug release, core tablets with 1:10 (Drug : Poloxamer-188) ratio based formulations were prepared and coated .

* **Effect of osmogents in the core**

To study the effect of osmogent in the core formulation, core tablets were prepared with varying amounts of potassium chloride and coated with same coating formulation

(Coating Code no. C-V) and an orifice was drilled with 0.7 mm diameter. The coated formulations were studied for in-vitro dissolution studies. Fig. 3.2.5 shows that the amount of potassium chloride had a marked influence on the nifedipine release. The release rate increased as the amount of potassium chloride increased. This could be due to the following hypothesis.

The more potassium chloride was incorporated into tablet, amount of water imbibed was much higher and the more core formulation could be dissolved. As a consequence, more nifedipine was released. The percent release after 20 h with 0, 50, 100 and 200 mg potassium chloride per tablet was 42.57 ± 2.75, 66.26 ± 2.84, 86.98 ± 3.11 and 91.74 ± 4.95 respectively, suggesting that an optimum amount of osmogent is required in an osmotic system to completely release the drug.

* **Effect of weight gain (coating thickness) on the developed formulation of MT and NP**

To study the influence of membrane thickness of the coating on drug release, core tablets of ME and ND were coated so as to get tablets with different weight gains (~ 6, 9 and 12 % w/w with Coat C-II, Coat-IV and Coat-V respectively). An orifice was drilled with 0.7 mm diameter. Release profile of ME and ND from these formulations are shown in Fig. 3.13 and 3.14 respectively.

Fig. 3.2.6 and 3.2.7 shows that release rate decreased as the membrane thickness increased. This could be due to the following hypothesis.

As the thickness increased, the resistance of the membrane to water diffusion increased and the rate of imbibing water decreased and, in turn, the liquification rate of the tablet core decreased, resulting in the drug release rate decreasing. The relationship was found to be consistent with the results obtained by previous works (Verma et al. 2004). No burst effects were observed in any of the empty shells.

* **Effect of Plasticiser on the developed formulation of MT and NP**

To study the effect of plasticiser, the core tablets of ME and ND core tablets were coated by cellulose acetate containing PEG-400 of 10, 25 and 40 % w/w of cellulose acetate (See Coat C-I, Coat-II and Coat-III) with a weight gain of around 6 % and orifice of 0.7

Fig. 3.2.5 In-vitro release profile of Nifedipine MOTS tablets-Effect of osmogent

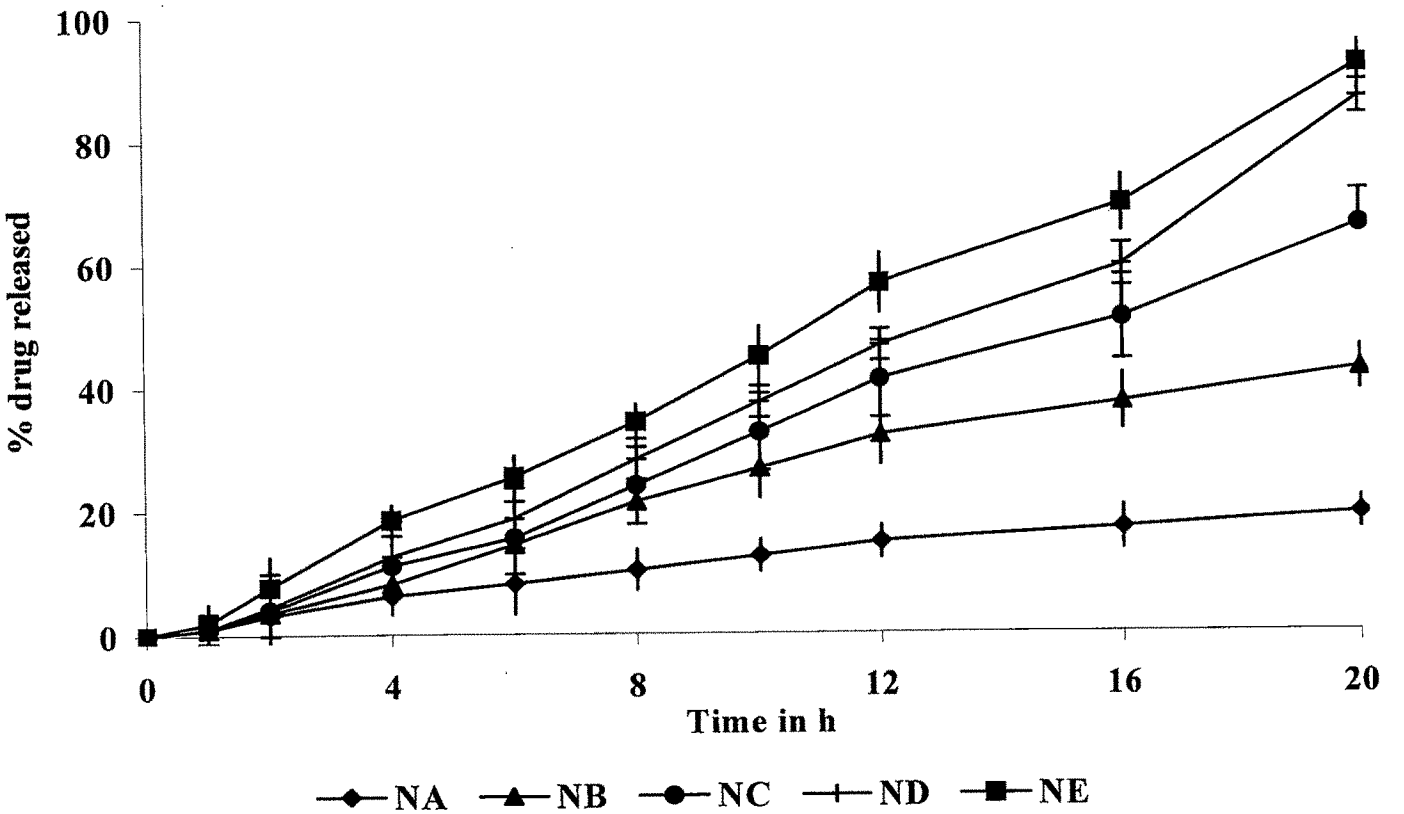


Fig. 3.2.6 In-vitro release profile of Metoprolol Tartrate MOTS tablets-Effect of weight gain

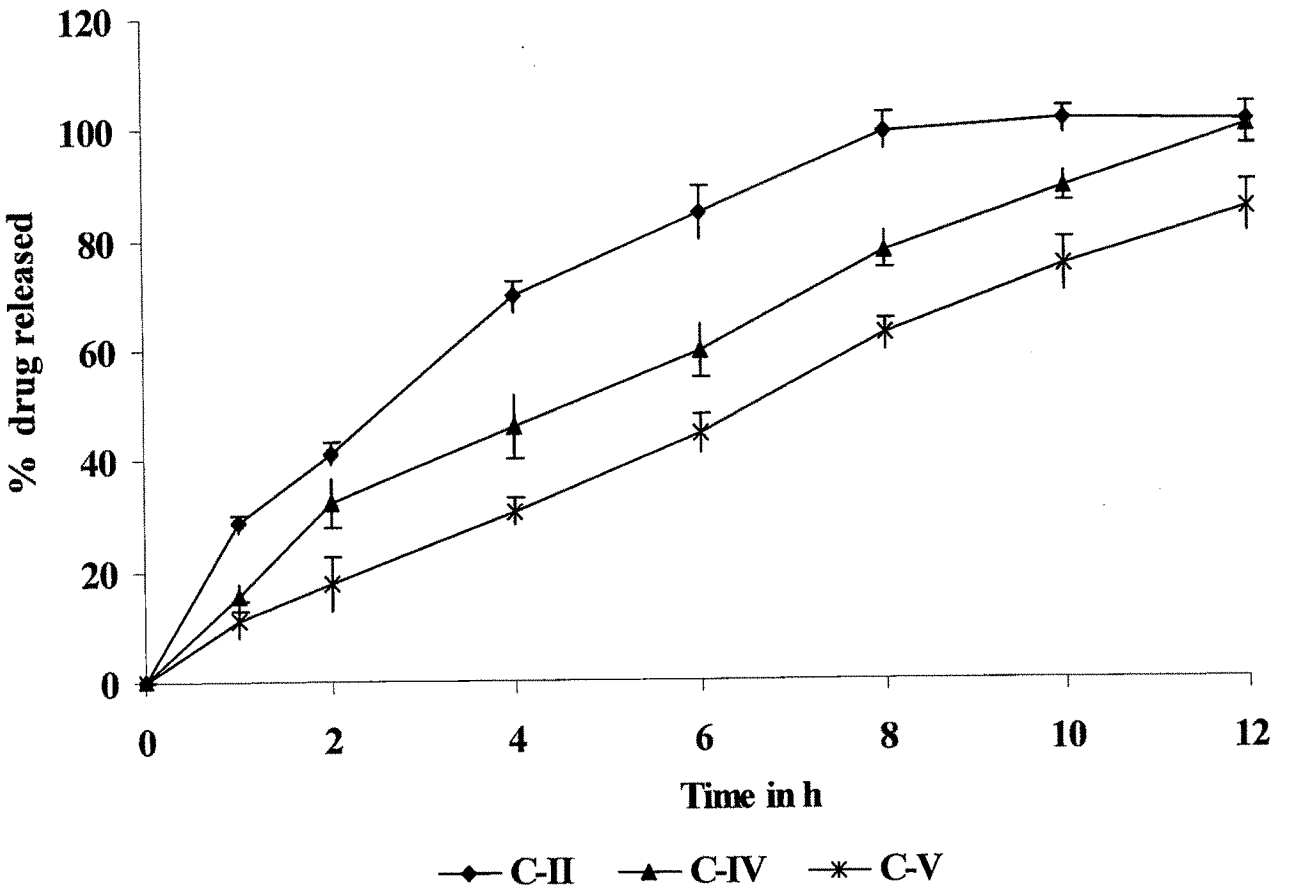
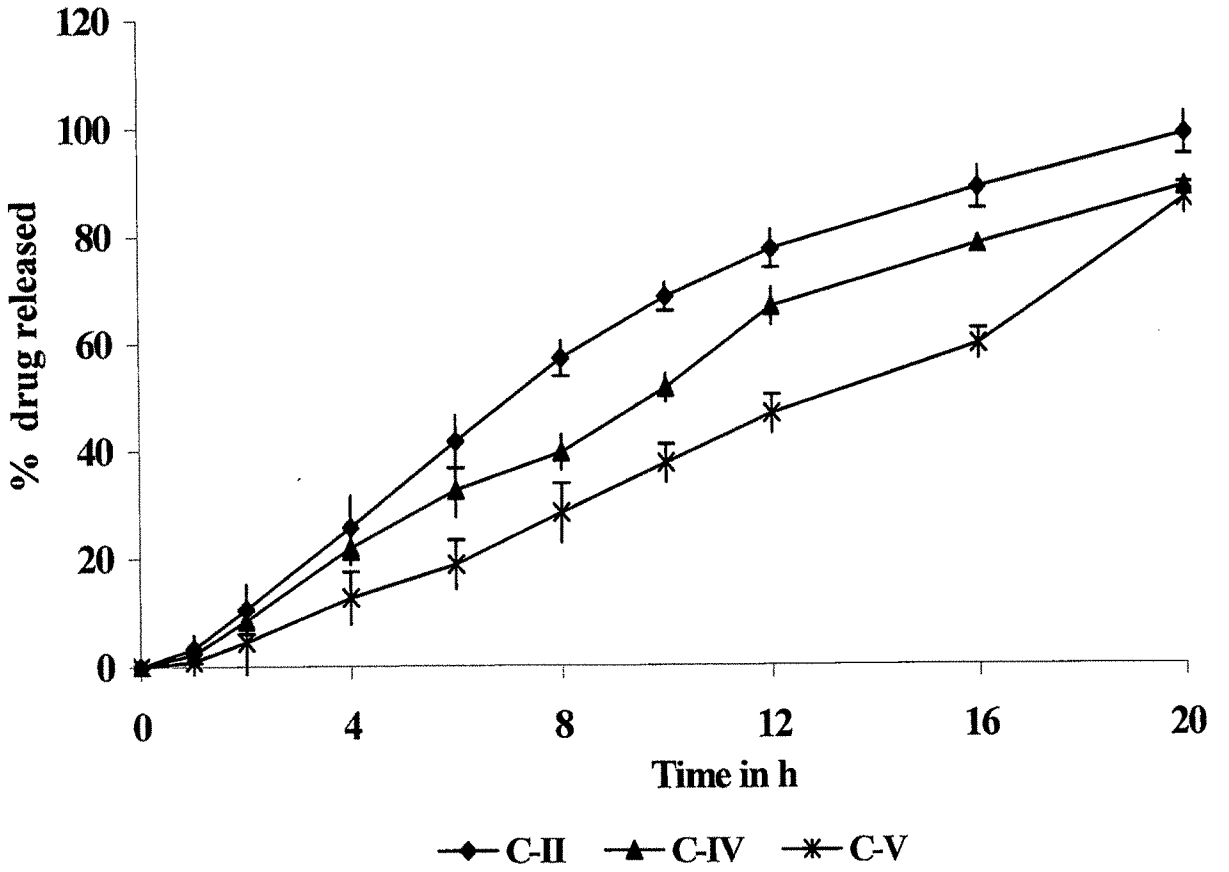


Fig. 3.2.7 In-vitro release profile of Nifedipine MOTS tablets-Effect of weight gain



mm diameter. Release profile of ME and ND from these formulations is shown in Fig. 3.2.8 and 3.2.9 respectively.

Increasing the amount of PEG in the semipermeable membrane increases void space after leaching and results in higher permeability of the membrane followed by higher drug release rate. As PEG is a hydrophilic plasticizer, it could be leached easily leaving behind the wholly porous structure, which increases membrane permeability and drug release rate.

* **Effect of orifice diameter on the developed formulation of MT and NP**

The core tablets (ME and ND) were coated with coating formulation C-IV and subsequently a circular orifice diameter was drilled on the surface coated tablets to achieve 0.41 ± 0.01 mm, 0.76 ± 0.01 mm and 1.24 ± 0.02 mm diameter.It has been reported that an appropriate range of orifice sizes are required for osmotic pumps. These must be smaller than the maximum limit to minimize the contribution to the delivery rate made by diffusion through the orifice. Also, they must be larger than a minimum limit, to minimize hydrostatic pressure inside the system (Rani et al. 2003). Fig. 3.2.10 and 3.2.11 shows the influence of orifice size on release profile. The results were in accordance with those of osmotic pumps. No significant difference existed in the release profiles for orifice diameters of 0.41 to 0.76 mm. However, the release was somewhat rapid with an orifice diameter of 1.24 mm. This may be due to the influence of diffusion from the bigger orifice. On the other hand, a longer lag time and a lower release rate were exhibited at an orifice diameter of 0 mm (i.e., without an orifice). The continuous water influx into the system without an orifice produced an increase in the volume of drug solution inside the system, therefore leading to an increase in the hydrostatic pressure inside the system. The pressure formed would cause membrane disruption and crack formation on the membrane. Subsequently, drug release was initiated via the crack. As the time of formation and the size of the crack could not be controlled or predicted, the system without an orifice was uncontrollable.

Fig. 3.2.8 In-vitro release profile of Metoprolol Tartrate MOTS tablets-Effect of plasticizer amount

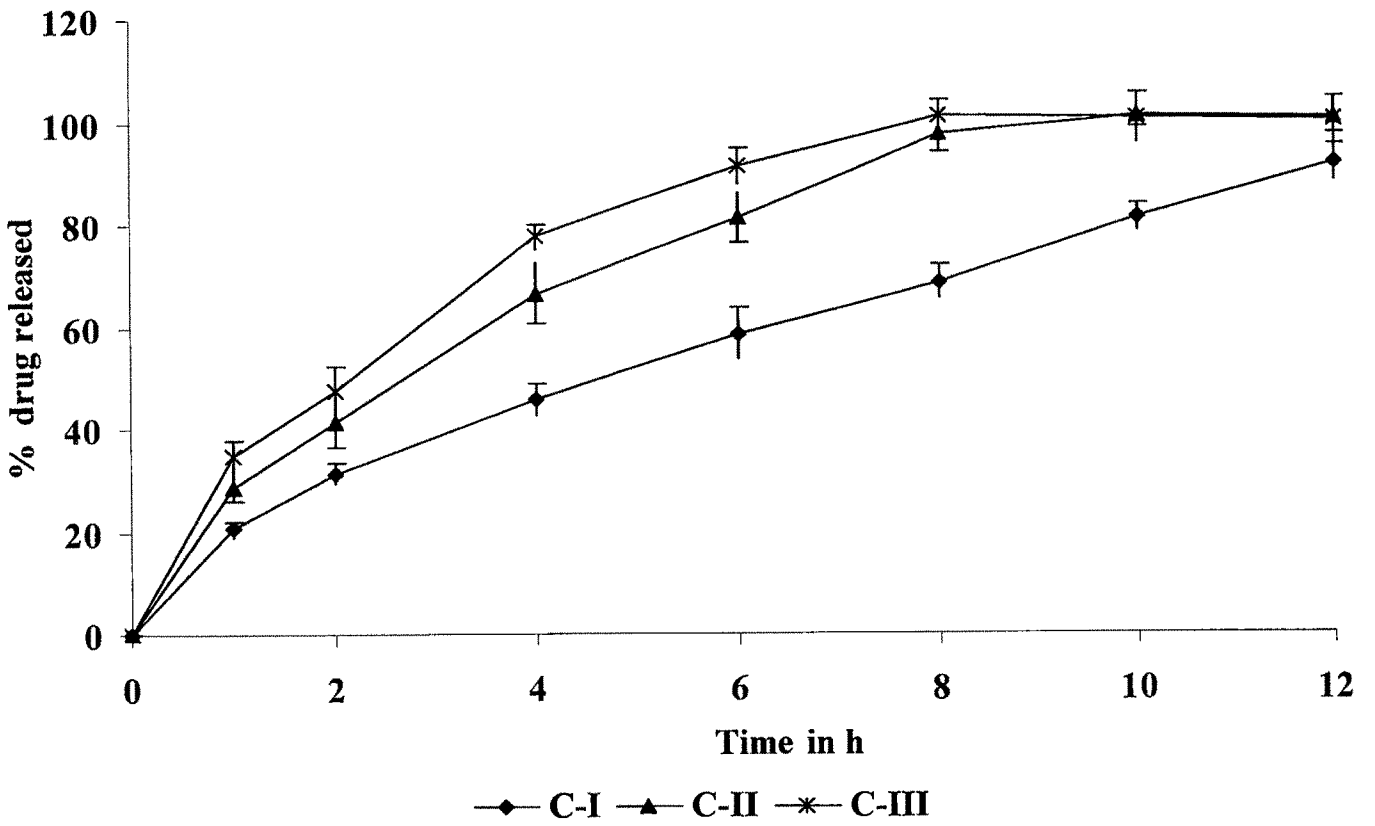


Fig. 3.2.9 In-vitro release profile of Nifedipine MOTS tablets-Effect of plasticizer amount

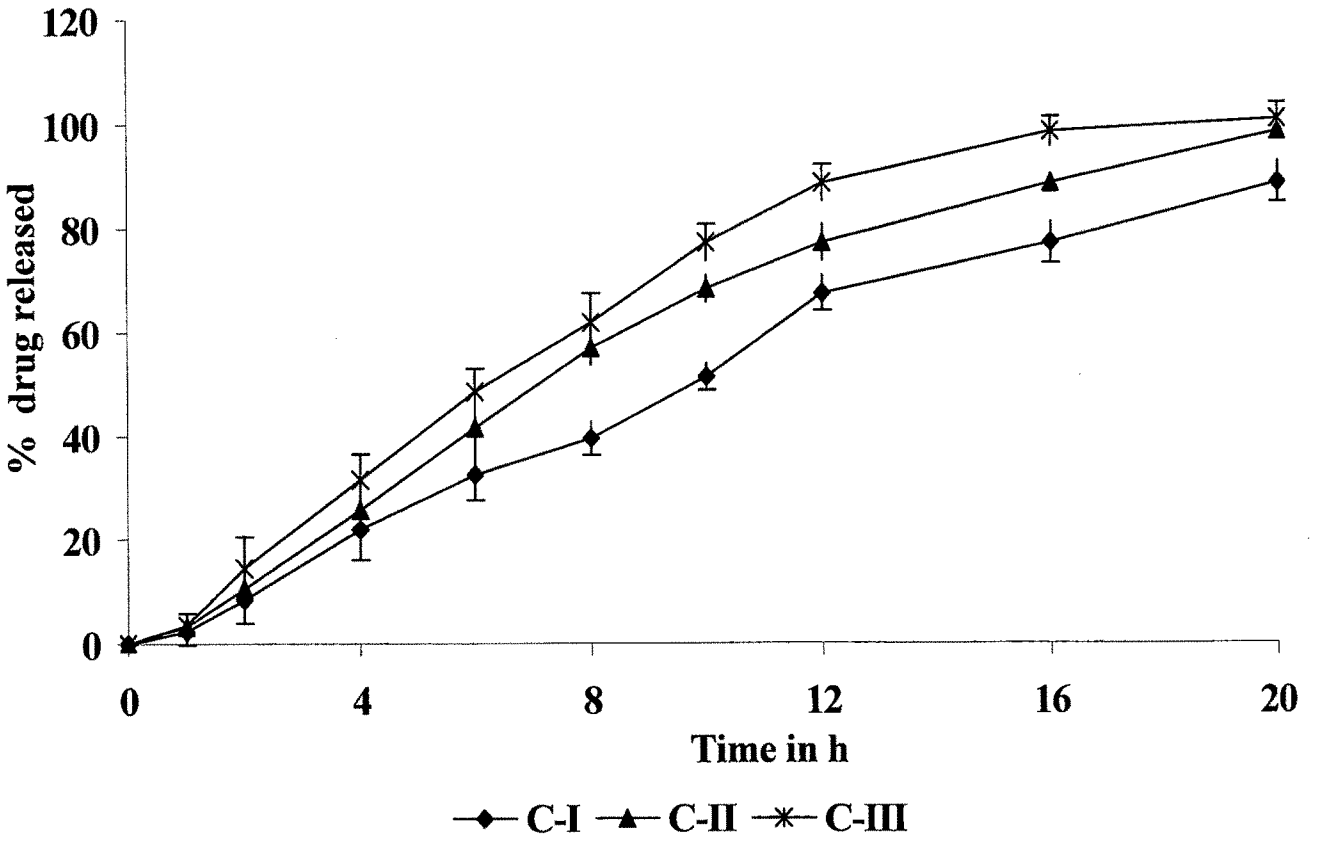


Fig. 3.2.10 In-vitro release profile of Metoprolol Tartrate MOTS tablets-Effect of orifice diameter

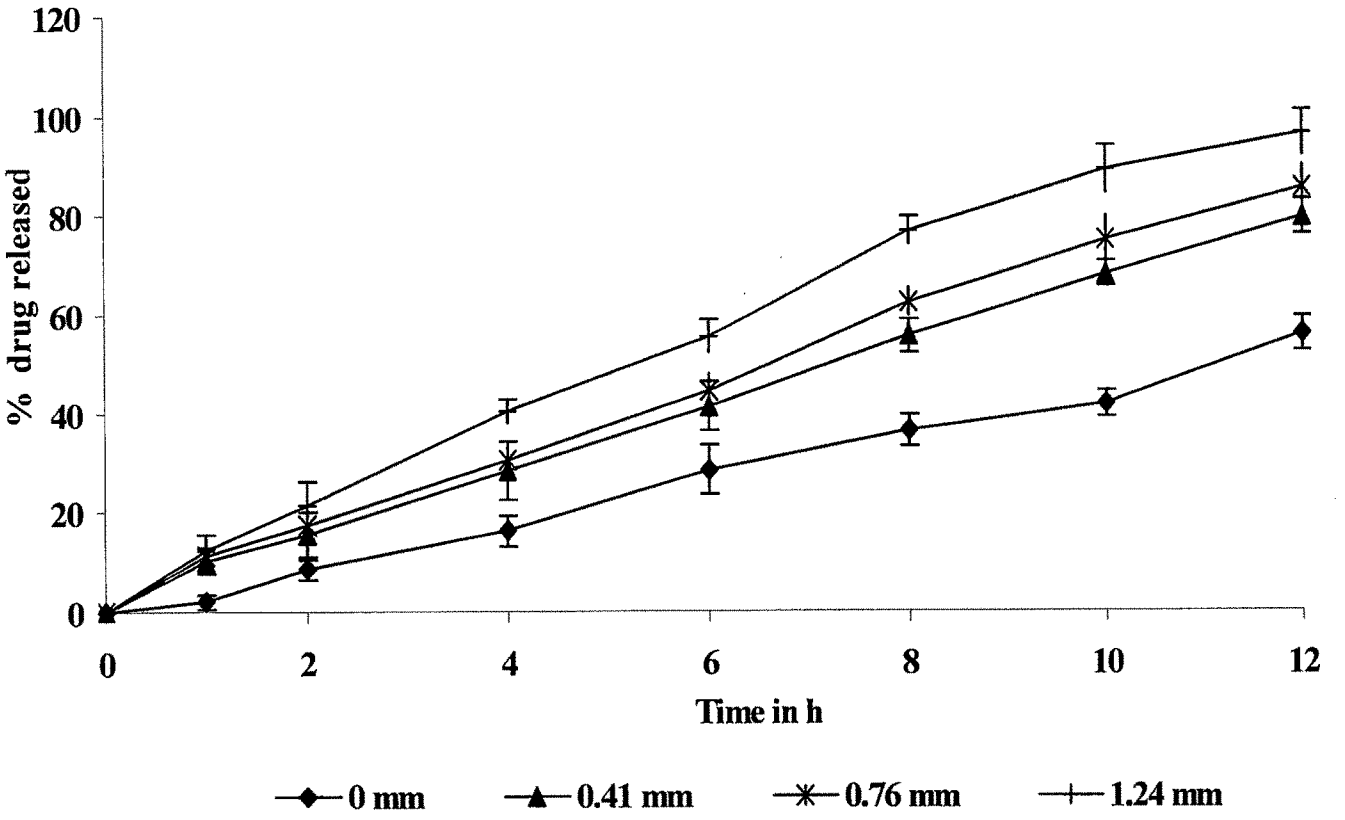
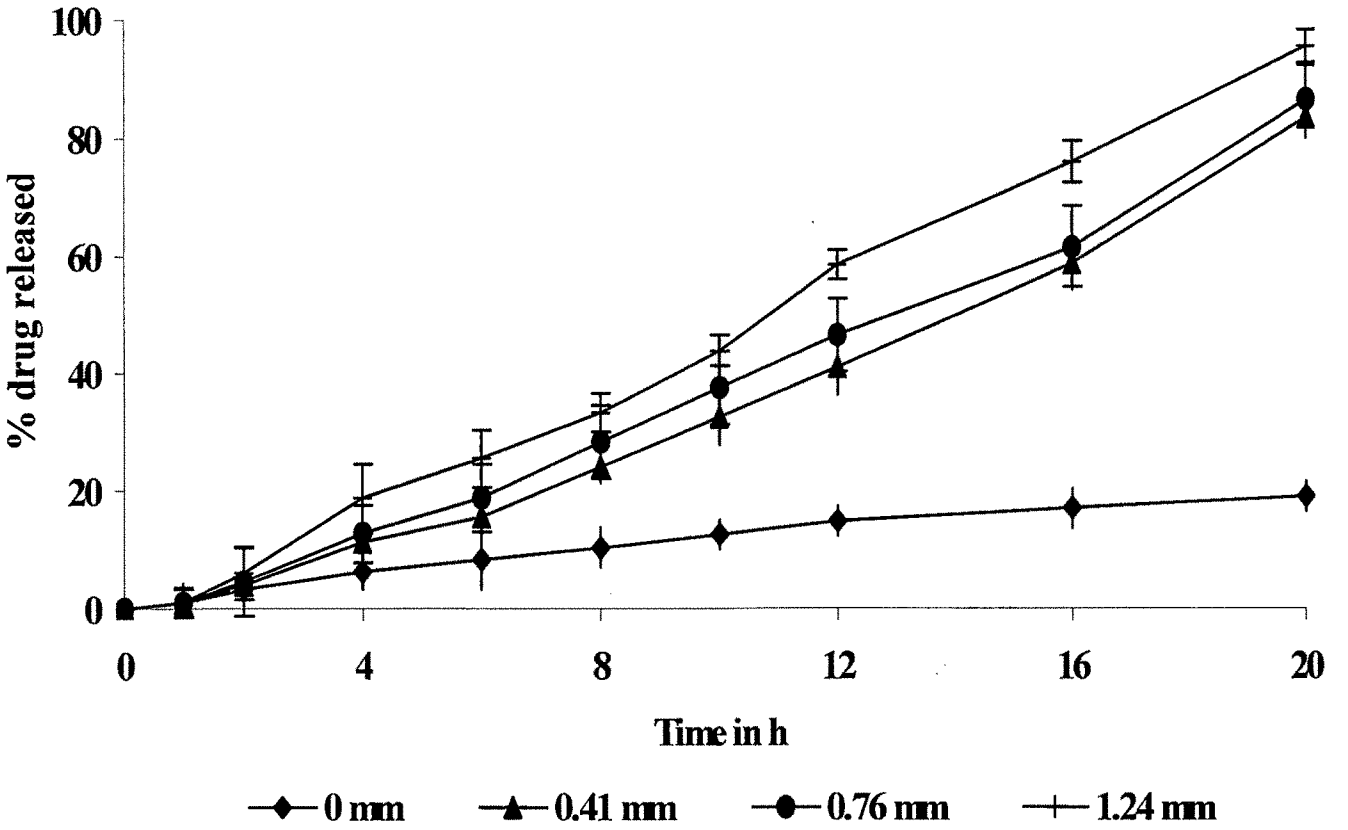


Fig. 3.2.11 In-vitro release profile of Nifedipine MOTS tablets-Effect of orifice diameter



– ***STATISTICAL ANALYSIS OF DISSOLUTION DATA***

To evaluate the performance of the developed formulations, release profile was compared with marketed innovator products.

Toprol XL marketed by AstraZeneca Inc., USA is formulated as an extended-release tablet for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids where as Procardia XL marketed by Pfizer Inc., USA is based upon push–pull osmotic pump technology. It is a bilayer tablet coated with a semipermeable membrane. Drug along with osmogents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents. The drug compartment is connected to the outside environment via a delivery orifice. After coming into contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice.

The advantages of the in house developed system the are that it is simpler in design and requires less number of manufacturing steps (single layer vs. bilayer) economical, and easily amenable to mass production.

Fig. 3.2.12 shows release of metoprolol and nifedipine from in-house formulations in comparison with Toprol XL and Procardia XL. The f_1 and f_2 values are presented in Table 3.2.10, taking the release profile of Toprol XL and Procardia XL as reference. These formulations were selected as the optimized formulation and used for further evaluation.

Table 3.2.10 Comparison of release profile

Product	Reference	Innovator	f_1	f_2
Metoprolol tartrate	Toprol XL[@]	Astra Zeneca Inc. USA	10.55	81.54
Nifedipine	Procardia XL[$]	Pfizer Inc. / Alza Inc. USA	12.54	69.29

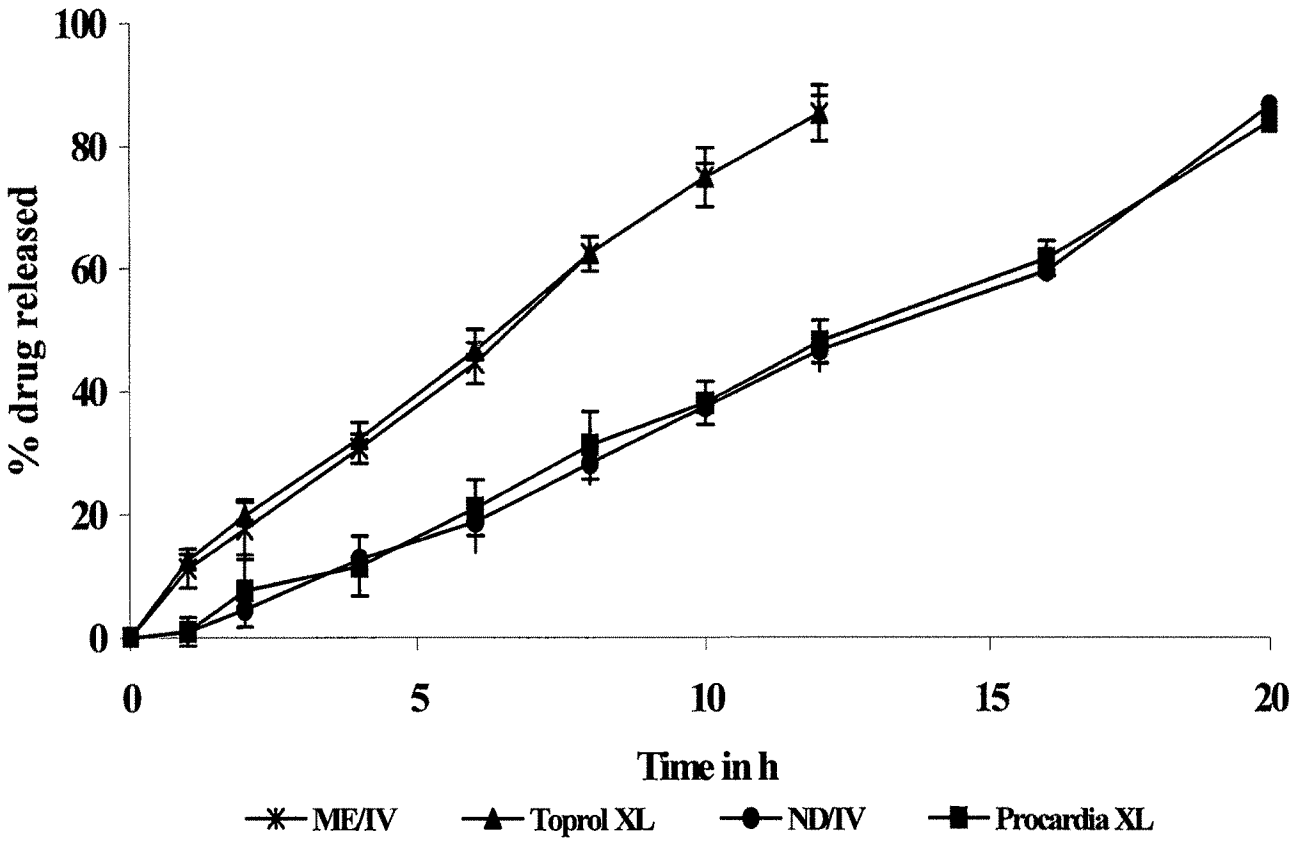
[@] *Formulated as an extended-release tablet for once-a-day oral administration. Drug release is controlled by diffusion.*

[$] *Formulated as an extended-release bilayer tablet with delivery orifice for once-a-day oral administration. Drug release is controlled by osmosis*

– ***KINETICS OF DRUG RELEASE***

Table 3.2.11 shows the equations used to determine the appropriate models and presents the values for all formulations. Drug release from *in house* optimised formulation fitted

Fig. 3.2.12 Release profile of Metoprolol Tartrate (B.No. ME) and Nifedipine (B.No. ND) formulation in comparison with Toprol-XL and Procardia XL, respectively.



well into zero-order kinetics for both the formulations (Metoprolol and Nifedipine), which is confirmed by the lower sum of squared residuals (SSQ) and comparatively higher correlation co-efficient. Application of release curve to zero-order equation indicated that the drug release is independent of drug remaining in its interior.

For metoprolol, the next best model describing the release was Hixson-Crowell, first-order and Higuchi's and for nifedipine, the next best model describing the release was first-order, Hixson-Crowell, and Higuchi's.

The drug release data was further analysed for curve fitting based on Korsmeyer-Peppas model. Based on the theory that if the *n* value is equal to 0.5 or between 0.5 and 1.0 the release mechanism is Fick's diffusion or a non-Fickian model, respectively. The *n* value obtained for the optimized formulation was more than 0.5 suggesting the release from this formulation follows non-Fickian diffusion.

Table 3.2.11 Fitting of dissolution data of the optimized formulation to various kinetic models

Kinetic Model	Parameters					
	r		SSQ		*k*	
	ME/IV	ND/IV	ME/IV	ND/IV	ME/IV	ND/IV
Zero order	0.9684	0.9866	12.21	26.58	1.01	2.83
First order	0.9275	0.9690	1357.47	1258.06	-0.0603	-0.0275
Higuchi model	0.9118	0.9421	19553.582	12596.57	2.98	3.17
Hixon-Crowell model	0.9475	0.9525	206.48	11257.76	0.1808	0.1069

r: coorelation co-efficient, SSQ: sum of squared residuals, k: release rate constant for respective models (k_0, k_1, k_H and k_{HC} for zero-order, first-order, Highuchi model and Hixon-Crowell model, respectivley

- ***SCANNING ELECTRON MICROSCOPY (SEM)***

To study the influence of amount of PEG on membrane, CA membranes were plasticised with 10, 25 and 40 % (% w/w of CA). Fig. 3.2.13, 3.2.14 and 3.2.15 shows that the increase of PEG level led to increase in formation of void space after leaching and in turn higher permeabiity of the membrane.

The results are consistent with the drug release studies (Fig. 3.2.8 and 3.2.9).

Fig. 3.2.13 : Scanning electron microphotograph of membrane containing 10% w/w PEG-400 (3000 X)

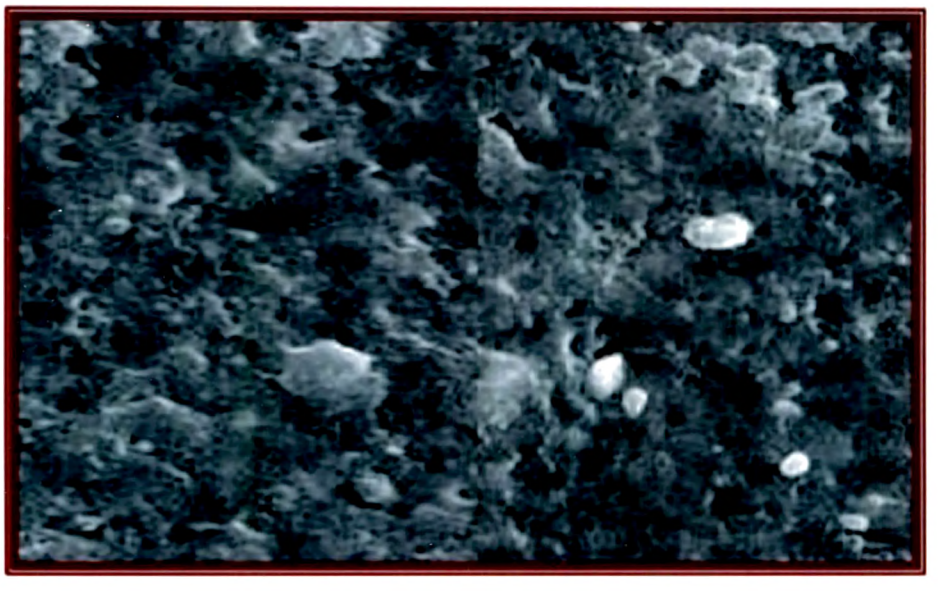


Fig. 3.2.14 : Scanning electron microphotograph of membrane containing 25% w/w PEG-400 (3000 X)

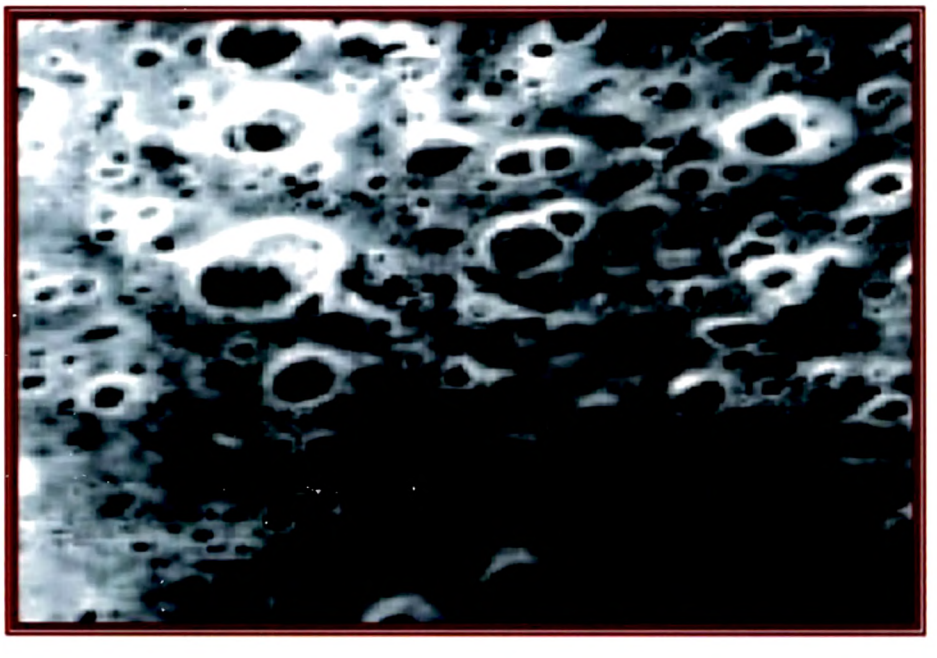
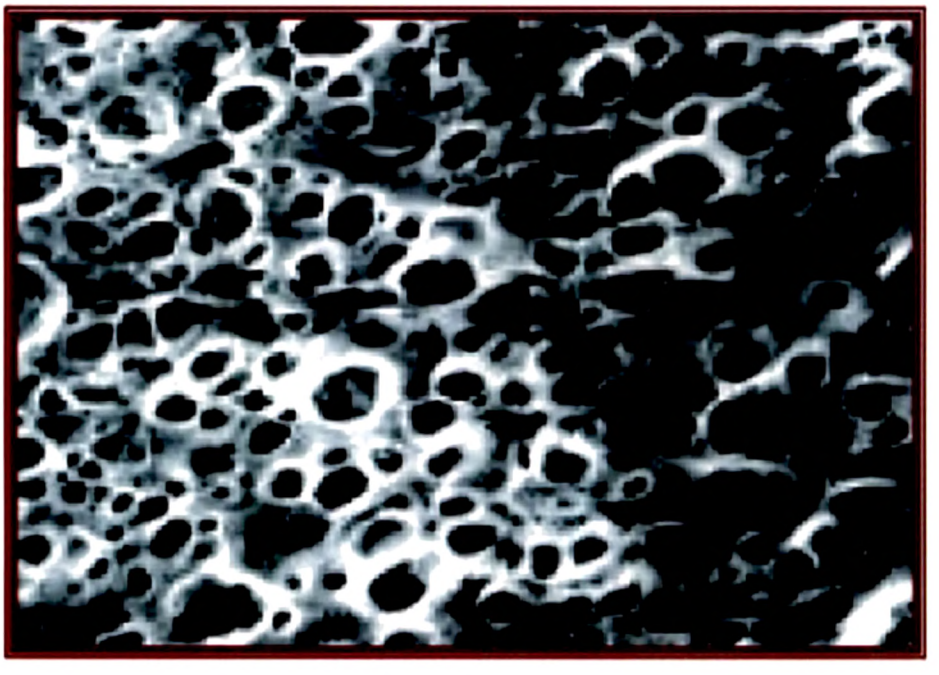


Fig. 3.2.15 : Scanning electron microphotograph of membrane containing 40% w/w PEG-400 (3000 X)



PART III

CONTROLLED POROSITY OSMOTIC SYSTEM (CPOP)

INTRODUCTION

Controlled porosity osmotic pumps (CPOP), contain water-soluble additives in the coating membrane, which dissolves after coming in contact with water, resulting in an in situ formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role (Zentner et al., 1985a).

The mechanisms by which drug release is controlled in CPOP are dependent on many variables. One of the principles of drug release would be osmotic pressure. It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents.

The CPOP comprises of the following components in the formulation (s):

A. A homogeneous core, comprising

i. A medicament, which is selected from group of water soluble, sparingly soluble or poorly soluble drugs or in combination thereof,

ii. A binder,

iii. A water soluble osmotically active agent (osmogent).

iv. Optionally a diluent,

B. A membrane coating which covers the said core formulation, which comprises of:

i. A water insoluble and semipermeable pharmaceutically acceptable polymer,

ii. A single or a mixture of pH insensitive pore forming agent,

iii. A single or a mixture of plasticizer.

iv. Optionally, a water slowly soluble or erodible pharmaceutically acceptable polymer.

The aim of the current study was to design a controlled porosity osmotic system (CPOP) based drug delivery system for controlled release of highly water soluble drug, oxybutynin chloride (OC) and sparingly water soluble drug, atenolol (AT).

The current study was also focussed on the effect of concentration of pore formers, Sorbitol, HPMC and PEG-6000. In case of OC, effects of various ratios of drug to

osmogent on the drug release were studied. In order to enhance the solubility of AT, tartaric acid was used as acidifying agent in the core formulation.

1. Oxybutynin chloride (OC)

Oxybutynin is an antispasmodic and anticholinergic agent. Oxybutynin chloride is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder.

2. Atenolol (AT)

Atenolol is a beta-adrenaceptor antagonist prescribed widely in diverse cardiovascular diseases viz. hypertension, angina pectoris, arrhythmia and myocardial infarction. The drug is also frequently indicated in the prophylactic treatment of migraine. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site. Accordingly, studies have been reported on regulation of drug release by formulating its diverse CR systems like hydrophilic matrices, osmotic pumps and transdermal drug delivery systems.

Atenolol, also known as 4-[2-hydroxy-3-[(1-methylethyl) amino]propoxy]benzeneacetamide, is a b-blocking agent, could effectively reduce systolic and diastolic blood pressures, and it is widely used alone or in combination to treat hypertension (Kamp et al. 2003). Atenolol is commercially available as conventional tablet. The tablet is usually administered two or three times a day, which would lead to large fluctuation in drug plasma concentration and side effect on human body. Controlled release systems are desirable to solve these problems. Among these, osmotic pump tablet others several advantages, such as reducing risk of adverse reactions, improving compliance of patients and exhibiting comparable in vitro/in vivo drug release.

McClelland and coworkers (1991) reported CPOP of a highly water-soluble drug, diltiazem hydrochloride (solubility more than 590 mg/ml at 37 °C). Because of very high water-solubility, the majority of the drug fraction was released predominantly at a first-

order rather than the desired zero-order rate. The solubility of diltiazem hydrochloride was reduced to 155 mg/ml by incorporation of sodium chloride (at 1 M concentration) into the core tablet formulation. The modification resulted in more than 75% of the drug to be released by zero-order kinetics over a 14–16-h period.

Controlled porosity solubility modulated osmotic pumps for delivery of drugs having low watersolubility are described in US Patents (McClelland and Zentner, 1990; Zentner and McClelland, 1991). The composition described consists of controlled release solubility modulating agents, which are either surfactants (e.g. sodium dodecyl sulfate) or complexing agents (e.g. sodium salicylate). In order to prolong the availability of these excipients within the device, they were either surrounded by a rate controlling membrane or dispersed in a matrix. In the examples, tablet cores of two different drugs, namely, simvastatin and lovastatin, along with the solubility modulating agents were prepared and coated with a microporous membrane. The release of drug from the systems was controlled for an extended period of 4–24 h. Similarly, Herbig et al. (1995) reported osmotic delivery of doxazosin, which has pH-dependent solubility. Tablet cores containing drug, along with organic acids succinic and adipic acid) to increase the solubility of doxazosin within the core, were prepared and coated with asymmetric membranes. The solubility of doxazosin was improved in the presence of organic acids and pH-independent release patterns were obtained. Use of polymer coated buffer components to modulate the drug solubility within the core is described in US patent (Ayer and Wong, 1988). Solubility of a weakly acidic drug, acetyl salicylic acid, was modified by a basic excipient, which maintains alkaline pH within the device. The drug and the solubility modifying agent (sodium acetate) were coated separately by a rate controlling film of hydroxypropyl methyl cellulose (HPMC), mixed, and compressed in the form of a tablet. The tablet cores were coated and a hole drilled in the membrane wall. Coating of sodium acetate ensures its availability within the device for prolonged period and thus solubility of the drug is controlled through out the operational life span of the device. The drug was released in predominantly zero-order fashion for the desired period of time.

Another approach of controlling drug release is by use of buffers, which react with the drug to produce a new compound having thermodynamic properties different from the

parent drug. The example of this approach have been described in US patent (Swanson and Edgren, 1982). Theophylline, along with L-tartaric acid and polyvinyl pyrrolidone (PVP), was formulated in the form of EOP. Theophylline, in presence of tartaric acid, is converted to theophylline tartarate. Theophylline free base had a solubility of 10 mg/ml and theophylline tartarate had a solubility of 220 mg/ml in water at 37 °C. Drug release from the systems was found to be constant over a period of 7 h. In another study (Verma and Mishra, 1999), solubility of a weakly acidic drug, nimesulide, was improved by using alkalinizing agents like disodium hydrogen phosphate and sodium bicarbonate. Nimesulide, along with different alkalinizing agents, was formulated in the form of EOP and release profile compared with immediate release tablets. It was found that release of nimesulide from the osmotic pumps was relatively slow and prolonged for 12 h.

Co-compression of drugs along with solubility modulating agents can also be utilized for pulsatile delivery of drugs. This was demonstrated in the case of salbutamol (Magruder et al. 1988a; Magruder et al 1988b), a highly water-soluble drug (270 mg/ml in pure water). Solubility of salbutamol was reduced by the addition of sodium chloride in the tablet core (11 mg/ml in a saturated salt solution). Salbutamol, along with sodium chloride was formulated in the form of osmotic pumps, which after coming in contact with the aqueous environment, initially imbibes water at a rate controlled by the osmotic pressure of the core formulation. Due to the presence of excess of salbutamol within the tablets, sodium chloride is depleted first from the device. This results in decrease of osmotic pressure of the solution inside the tablets and thus the rate of water flow into the tablet decreases. However, the solubility of salbutamol is increased due to a fall in sodium chloride concentration and its delivery to the body actually increases. The net result is a tablet formulation that initially delivers salbutamol at a relatively constant rate, until sodium chloride gets exhausted. After this, the remaining drug is delivered as a large pulse. Using this approach, zero-order release was achieved for about 7 h, followed by a pulsatile release of 7–9 h.

Sastry et al. (1997, 1998) reported atenolol two layer core osmotic pump tablet. While two-layer-core osmotic pump tablet could deliver water-insoluble or poorly water-soluble drugs, it had a disadvantage that a complicated side identification technology should be

employed to ensure the orifice drilled on the surface of the drug layer. Therefore, three-layer-core (Liu et al. 2000a; Stephens and Wong, 1989) osmotic pump tablet was proposed. Liu et al. (2000a) studied three layer core osmotic pump tablet with the elimination of side identification. Its core tablet consisted of a middle push layer and two attached drug layers. Two orifices were drilled on both sides of the surface after coating with avoiding side identification. However, either two-layer-core or three-layer-core osmotic pump tablet had a common disadvantage: a complicated tableting technology was needed. Therefore, some researchers made efforts to develop monolithic osmotic pump tablet (Liu et al. 2000b). This tablet could be prepared by a much easier technology.

Atenolol is a sparingly soluble drug (27 mg/ml at 37 °C). Some methods had been attempted to improve its solubility. Ficarra et al. (2000) prepared b-cyclodextrin inclusion complex. However, it was proved that atenolol solubility could not be significantly enhanced by this way. Moneghini et al. (1998) prepared atenolol solid dispersion to improve solubility. Although this method improved the solubility of atenolol somewhat, large amounts of carrier were consumed. In addition, solid dispersion had some problems, such as the difficulty of scale-up, the physical stability of dispersion, and the reproducibility of physicochemical properties, etc. (Serajuddin, 1999), which limited its commercial application.

For some alkaline drugs, it was feasible to convert them into salt by reacting with acid. Ayer et al. (1988) used citric acid, maleic acid, malic acid and succinic acid as solubility promoter to increase the solubility of haloperidol substantially.

Atenolol is an alkaline drug with imide group. Appropriate solubility of tartaric acid made it a suitable candidate for modulating solubility of alkaline drugs. Therefore, tartaric acid was used as the solubility promoter to prepare atenolol CPOP in this study. The influence of solubility promoter, pore former, osmogent and membrane thickness on drug release profile were investigated. The influences of release media and agitation rate on in vitro release profile were also evaluated.

The objective of the present study was

- ✧ To design and optimize a controlled porosity osmotic pump (CPOP) based drug delivery system for controlled release of highly water soluble drug, oxybutynin chloride (OC) and sparingly water soluble drug, atenolol (AT) using pore formers, Sorbitol and PEG-6000.
- ✧ To maintain and optimize the solubility modifying component in the core over the entire drug delivery duration, in case of atenolol CPOP
- ✧ To formulate and evaluate granules of OC and AT
- ✧ To formulate and evaluate core tablets of OC and AT
- ✧ To formulate and evaluate coated tablets OC and AT
- ✧ The current study was also focussed on the influence of tablet formulation variables, such as amount of osmogent on release profile of OC and AT and to propose a delivery mechanism and optimal tablet formulation for this system;
- ✧ To study the influence of pore former and membrane variables, including the nature and amount of plasticizer as well as thickness on drug release;
- ✧ To study the mechanism and kinetics of drug release from the optimized formulations by fitting into different dissolution models.

2. FORMULATION AND EVALUATION METHODS

– *FORMULATION OF CORE TABLETS OF OXYBUTYNIN CHLORIDE*

In this osmotic system, mannitol was used as osmogent, lactose as diluent, povidone as binder, colloidal silicon dioxide as glidant and magnesium stearate and talc as lubricant. Table 3.3.1 enlists the composition of core formulation prepared

Table 3.3.1 Composition of core oxybutynin tablets

Ingredients*	Formulation code			
	OA	**OB**	**OC**	**OD**
Oxybutynin chloride	10.00	10.00	10.00	10.00
Mannitol	0.00	50.00	100.00	200.00
Lactose	212.00	162.00	112.00	12.00
Povidone K30	12.00	12.00	12.00	12.00

Magnesium stearate	2.50	2.50	2.50	2.50
Talc	2.50	2.50	2.50	2.50
Colloidal silicon dioxide	1.00	1.00	1.00	1.00
Total	**240.00**	**240.00**	**240.00**	**240.00**
*mg / tablet				

The tablets were prepared by wet granulation technique. All the raw materials were sieved through # 60 mesh. Drug was uniformly mixed with mannitol, lactose and povidone in a high shear mixer granulator for 10 min. The dry blend was granulated with isopropyl alcohol. The mass was dried at 50 °C and sized through # 20 mesh and mixed with colloidal silicon dioxide. The granules were lubricated with magnesium stearate and talc and compressed into round tablets with standard concave plain punches and dies (diameter – 9.52 mm) using 8 – station single rotary compression machine (KMP-8, Cadmach Engg, Ahmedabad, India)..

- ***CONCENTRATION OF ATENOLOL IN TARTARIC ACID AQUEOUS SOLUTIONS***

The aim of this study was to demonstrate that the solubility modulating agents can be used to deliver a poorly water soluble drug with a pH sensitive solubility such as atenolol for extended period of time in CPOP.

FORMULATION OF CORE TABLETS OF ATENOLOL

In this osmotic system, tartaric acid was used as acidifying agent, mannitol and potassium chloride as osmogent, starch as diluent, povidone as binder, colloidal silicon dioxide as glidant and magnesium stearate as lubricant. Table 3.3.2 enlists the composition of core formulation prepared.

Table 3.3.2 Core formulations of Atenolol – CPOP

Ingredient*	**Batch no.**				
	AA	**AB**	**AC**	**AD**	**AE**
Atenolol	50.00	50.00	50.00	50.00	50.00

Tartaric acid	2.50	5.00	7.50	7.50	7.50
Mannitol	50.00	50.00	50.00	50.00	50.00
Potassium chloride	25.00	25.00	25.00	50.00	75.00
Starch	63.00	60.50	58.00	33.00	8.00
Povidone K-30	7.00	7.00	7.00	7.00	7.00
Colloidal silicon dioxide	1.00	1.00	1.00	1.00	1.00
Magnesium stearate	1.50	1.50	1.50	1.50	1.50
Total	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**
* qty in mg / tablet					

All the raw materials were sieved through # 60 mesh. Atenolol, tartaric acid, mannitol, potassium chloride, starch and povidone were mixed in a high shear mixer granulator for 10 min. The dry blend was granulated with isopropyl alcohol. The mass was dried at 50 °C and sized through # 20 mesh and mixed with colloidal silicon dioxide. The granules were lubricated with magnesium stearate and compressed into round tablets with standard concave plain punches and dies (diameter – 7.94 mm) using 8 - station single rotary compression machine (KMP-8, Cadmach Engg, Ahmedabad, India).

- ***EVALUATION OF OC AND AT GRANULES***

* ***Loss on drying (LOD)***

IR moisture balance (PM 480, Mettler Toledo, Switzerland) was used to determine LOD of the powder blend.

* ***Bulk density (BD), Tap density (TD), Compressibility index (CI) and Hausner ratio (HR)***

To determine BD and TD of the powder blend, USP method II on a tap density tester (ETD-1020, Electrolab, Mumbai, India) was used. From the data obtained, CI and HR were calculated.

- ***EVALUATION OF OC AND AT CORE TABLETS***

* ***Uniformity of weight (Weight variation test)***

In this test, 20 tablets were weighed individually on an electronic balance (AG-64, Mettler Toledo, Switzerland), the average weight was calculated and compared with individual weights. The percentage difference in the weight variation should be within the permissible limits (± 5%).

* ***Thickness and diameter***

The thickness and diameter of the tablets were determined by using a thickness gauge (Digimatic Caliper, Mitutoyo, Japan).

* ***Hardness test***

The hardness of core tablets were tested using a hardness tester (6-D, Dr Schleuniger Pharmatron, Manchester, NH, USA)

* ***Friability test***

The friabilator (EF-2, Electrolab, Mumbai, India) was rotated at a speed of 25 rpm for 4 minutes. Percentage friability was then calculated.

* ***Drug content***

Ten core tablet were selected randomly and average weight was calculated. Analysis for OC and AT was carried out as per the method mentioned in analytical methods section.

COATING OF OC AND AT CORE TABLETS

Tablets were spray coated by perforated pan coater (GAC – 250, Gansons Ltd., Mumbai, India). Table 3.3.3 and Table 3.3.4 summarizes the components of coating solution and the processing conditions respectively. The coating solutions were prepared using mixture of dichloromethane and methanol (70:30) as the coating solvent to get a 4 % total solids in coating solution. Coated tablets were dried at 50°C for 16 h and the % weight gain and thickness (Digimatic Caliper, Mitutoyo, Japan) of the coating membrane were measured.

Table 3.3.3 The components of coating solution and evaluation parameters of the coated formulations

Code	Ingredients*				
	Cellulose Acetate	**PEG-400**	**Sorbitol**	**HPMC**	**PEG-6000**
I	85.0	15.0	0.0	0.0	0.0
II	77.5	15.0	7.5	0.0	0.0
III	70.0	15.0	15.0	0.0	0.0
IV	65.0	15.0	20.0	0.0	0.0
V	70.0	15.0	0.0	15.0	0.0
VI	70.0	15.0	0.0	0.0	15.0

*values given in % w/w . 4 % total solids in coating solution.

Table 3.3.4 Processing conditions for SPOP tablets

Processing condition	
Tablet bed size	800 gm
Inlet temperature	55 ± 2° C
Outlet temperature	42 ± 2° C
Atomizing air pressure	2.1 kp / cm^2
Peristaltic pump speed	4-5

EVALUATION OF OC AND AT COATED TABLETS

* ***Percentage weight gain***

From every batch of coating, 25 coated tablets were individually weighed and the average weight was calculated and compared with average weight of uncoated. The difference in weight was determined and the percent weight gain was calculated.

* ***Coating thickness***

The thickness and diameter of the coated tablets were determined by using a thickness gauge (Digimatic Caliper, Mitutoyo, Japan).

* ***Burst strength***

The burst strength of the exhausted shells after dissolution was determined to assure that the tablets would maintain their integrity in the GIT. Burst strength is the force required to break / rupture the shells. The texture analyzer (TAX T2i, Stable micro systems, U.K) with a 5 kg load cell and 25 mm aluminium cylindrical probes were utilized. Test speed of 0.8 mm/s was selected and distance moved was at 2 mm.

– ***IN VITRO DRUG RELEASE***

Table 3.3.5 summarizes the dissolution study and analytical method. In vitro drug release of the formulations were carried out using USP type I dissolution apparatus (2100C, Distek Inc, NJ) attached with an auto-sampler (37 °C ± 0.5 °C). The drug release at different time intervals was analyzed by UV spectrophotometer (8453, Agilent Technologies, Singapore).

Table 3.3.5 *In-Vitro* Dissolution studies and analytical method

Parameters	**Oxybutynin chloride**	**Atenolol**
Dissolution media	0.1N HCl, pH 1.2	Distilled water
USP Type	I (Basket)	I (Basket)
Volume	900 ml	900 ml
RPM	75	75
Temperature	37 °C	37 °C
Analytical method	HPLC (see below)	UV spectrophotometer, 225 nm

HPLC analysis for Oxybutynin chloride

Chromatographic separation of oxybutynin was performed on a Shimadzu LC-2010C_{HT} HPLC system using YMC-Pack-CN column (4.6 mm x 250 mm x 5µm particle size).

Mobile phase used was mobile phase-A [water:methanol{800:200} + 0.2 mL triethylamine, with pH 3.5, which was adjusted by Ortho phosphoric acid] and mobile phase-B [acetonitrile] in the ratio of 70:30 at a flow rate 1.5 mL/min. Temperature of the column was maintained at 30 °C. Standard solution and dissolution samples were analysed at 203 nm using a UV detector.

Release profiles were also compared using mean dissolution time or MDT.

- ***STATISTICAL ANALYSIS OF DISSOLUTION DATA***

Release profiles of optimized tablets were compared by calculating two statistically derived mathematical indices, difference factor (f_1) and similarity factor (f_2) with a commercially available product, as the reference.

- ***KINETICS OF DRUG RELEASE***

In order to understand the mechanism of drug release from the optimized system, the data were applied to various dissolution models.

- ***SCANNING ELECTRON MICROSCOPY (SEM)***

In order to elucidate the mechanism of drug release from optimized formulations based on CPOP technology, surface of coated tablets were studied using scanning electron microscope (SEM).

After dissolution studies, a small portion of sample of the coating membrane was carefully cut from the exhausted shells and dried at 50 °C for 12 h. The samples were mounted and examined for their porous morphology by Philips ESEM-TMP scanning electron microscope (SEM) (Philips, Netherlands). Samples from CPOP as detailed below were evaluated using SEM.

Coating Formulation code	**Details of coating**
C-I	Devoid of pore former
C-II	7.5% (w/w of CA) Sorbitol
C-III	15% (w/w of CA) Sorbitol

C-IV	20% (w/w of CA) Sorbitol
C-V	15% (w/w of CA) HPMC
C-VI	15% (w/w of CA) PEG-6000

3. RESULTS AND DISCUSSION

– *FORMULATION DEVELOPMENT*

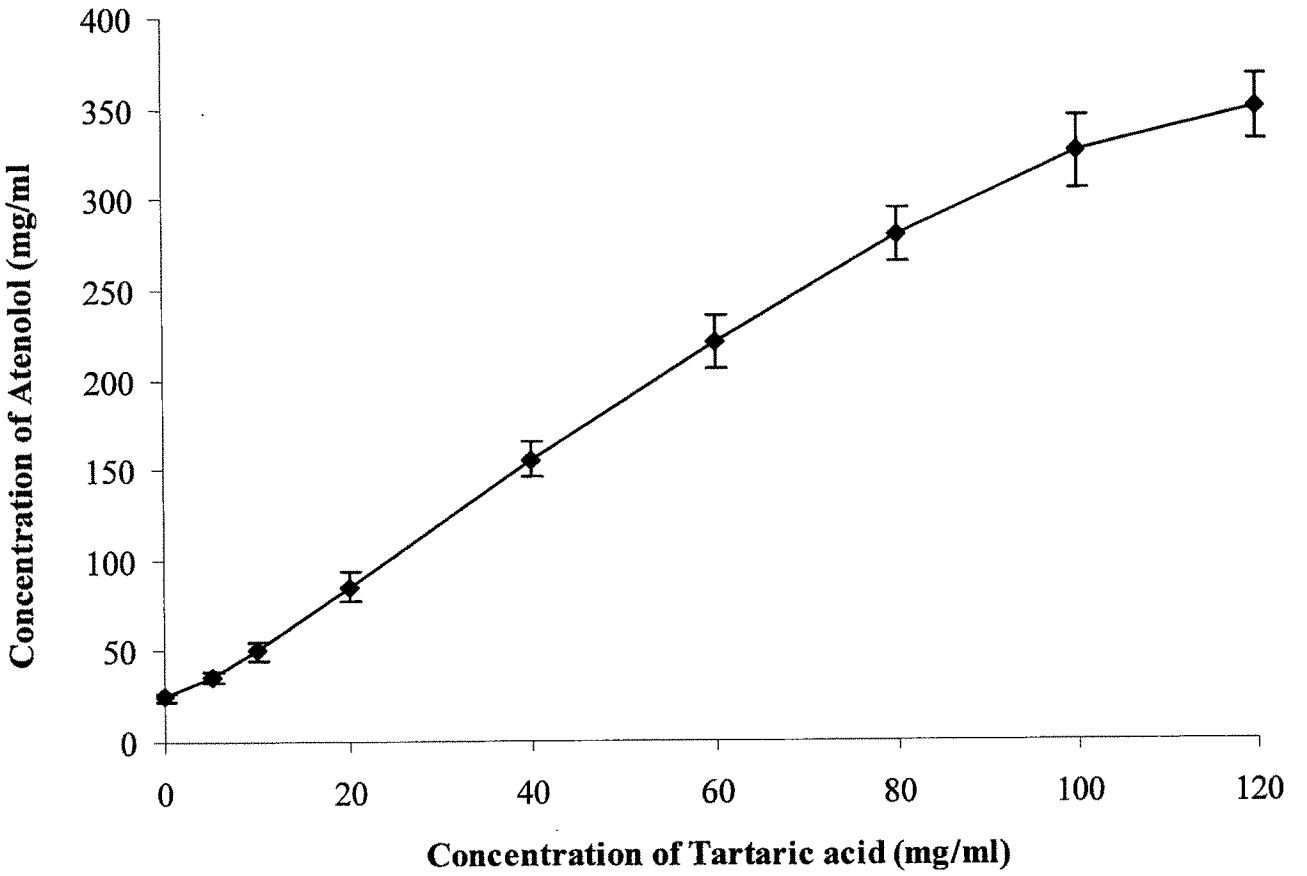
The dosage form developed was designed as a tablet core coated with a rate controlling membrane. Tablet core consists of drug along with osmogent, and other conventional excipients to form the core compartment. The core compartment is surrounded by a membrane consisting of a semipermeable membrane-forming polymer, water-soluble pore forming additives, and at least one plasticizer capable of improving film-forming properties of the polymers. 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 and dissolves the drug. The dissolved drug is released through the pores created after leaching of water-soluble additive(s) in the membrane. Cellulose acetate was used as water-insoluble polymer and sorbitol, HPMC and PEG-6000 were used as waters-soluble additive. PEG-400 was used as plasticizers.

– *CONCENTRATION OF ATENOLOL IN TARTARIC ACID AQUEOUS SOLUTIONS*

The concentration of atenolol in various concentrations of tartaric acid aqueous solution is shown in Fig. 3.3.1. The solubility of atenolol (37 °C) in deionized water was 27 mg/ml. It was clear that the concentration of atenolol in tartaric acid aqueous solution increased with the increase of original tartaric acid concentration. A more than 20-fold increase in atenolol concentration was

achieved at original tartaric acid concentration of 200 mg/ml. It could be explained by its molecular structure. Atenolol had an imide group exhibiting alkalinity. When atenolol contacted with tartaric acid aqueous solution, it reacted and changed to salt. As a consequence, atenolol became freely soluble, and the concentration was increased

Fig. 3.3.1 Concentration of Atenolol in tartaric acid aqueous solution



markedly. It could be concluded that this method should be much more suited for the solubilization of atenolol and the preparation of monolithic osmotic pump tablet compared with technologies of solid dispersion and cyclodextrin inclusion

- ***EVALUATION OF OC AND AT GRANULES***

The values are presented in Table 3.3.6.

Table 3.3.6 Properties of the granules of developed formulations

Batch no.	Loss on drying (%)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Compressibility Index (%)	Hausner ratio
Oxybutynin chloride					
OA	1.12	0.52	0.76	12.28	1.08
OB	2.48	0.57	0.81	11.95	1.35
OC	2.88	0.61	0.85	11.08	1.27
OD	1.84	0.67	0.91	10.94	1.17
Atenolol					
AA	1.96	0.48	0.72	11.79	1.28
AB	1.49	0.55	0.79	10.86	1.27
AC	3.08	0.58	0.82	11.79	1.08
AD	2.54	0.60	0.84	10.29	1.31
AE	1.46	0.64	0.88	9.91	1.28

The LOD was in the range of 0.5-3% for all the formulated batches suggesting that optimum moisture was maintained in the granules. The CI and HR were in the range of 9-13 and 1.0-1.3 suggesting good flow of granules.

- ***EVALUATION OF OC AND AT CORE TABLETS***

The values of the developed core formulations are presented in Table 3.3.7

Table 3.3.7 Evaluation parameters of the developed core formulations

Parameters	Weight (n=20) (mg)	Thickness (n=20) (mm)	Diameter (n=20) (mg)	Hardness (n=20) (kg/cm^2)	Friability (n=3) (%)	Drug content (n=3) (%)
Oxybutynin chloride						
OA	241.34 ± 1.8	3.17 ± 0.02	9.52 ± 0.01	5.30 ± 0.2	0.22 ± 0.05	99.18 ± 2.21
OB	237.14 ± 2.5	3.15 ± 0.02	9.50 ± 0.02	5.10 ± 0.3	0.16 ± 0.02	98.22 ± 2.87
OC	240.98 ± 1.6	3.12 ± 0.04	9.52 ± 0.02	5.20 ± 0.2	0.20 ± 0.01	101.28 ± 1.88
OD	241.17 ± 2.2	3.15 ± 0.03	9.51 ± 0.01	5.20 ± 0.1	0.18 ± 0.03	96.26 ± 2.85
Atenolol						
AA	202.47 ± 1.5	4.01 ± 0.01	7.95 ± 0.01	4.10 ± 0.1	0.12 ± 0.02	100.78 ± 2.87
AB	199.64 ± 2.4	4.00 ± 0.02	7.93 ± 0.02	4.20 ± 0.2	0.15 ± 0.02	99.48 ± 1.84
AC	203.87 ± 1.2	4.02 ± 0.04	7.94 ± 0.01	4.40 ± 0.1	0.12 ± 0.03	102.56 ± 3.45
AD	201.04 ± 5.6	4.05 ± 0.06	7.94 ± 0.02	4.60 ± 0.2	0.31 ± 0.04	101.76 ± 4.45
AE	201.48 ± 2.7	4.04 ± 0.04	7.94 ± 0.03	4.60 ± 0.3	0.30 ± 0.05	98.74 ± 4.79

The weight variation was less than 5% for all the formulated batches suggesting uniformity of dosage form. The drug content was in the range of 95 – 105%.

– ***EVALUATION OF OC AND AT COATED TABLETS***

Table 3.3.8 summarizes the evaluation parameters of the coated tablets

Table 3.3.8 Evaluation parameters of the coated formulations

Coating formulation	Weight gain (%)		Membrane thickness (μm)		Burst strength (g)	
	OC	AT	OC	AT	OC	AT
C-I	6.54 ± 0.68	7.06 ± 0.27	365 ± 11	392 ± 18	318 ± 8	325 ± 7
C-II	6.21 ± 0.45	6.46 ± 0.35	322 ± 18	365 ± 19	328 ± 6	331 ± 9
C-III	6.78 ± 0.35	6.45 ± 0.85	379 ± 16	368 ± 35	319 ± 10	328 ± 8
C-IV	7.15 ± 0.38	6.93 ± 0.78	398 ± 13	376 ± 34	328 ± 9	329 ± 6

C-V	6.95 ± 0.76	6.49 ± 0.74	382 ± 12	371 ± 19	318 ± 8	319 ± 5
C-VI	7.05 ± 0.33	7.12 ± 0.46	390 ± 19	398 ± 35	319 ± 9	326 ± 8

* OC : Oxybutynin chloride, AT: Atenolol

None of the developed formulations caused burst effect.

– ***IN VITRO DRUG RELEASE***

1. Oxybutynin chloride

* ***Effect of ratio of drug to osmogent***

To optimize the amount of osmogent to be used in the formulation and to study the effect of drug to osmogent ratio, core formulations were prepared as shown in Table 3.3.1. The ratio of drug to osmogent studied were 1:0, 1:5, 1:10 and 1:20. All the core formulations were coated with coating composition, C-III containing 15 % w/w (of cellulose acetate) of sorbitol. Release profile from these formulations is shown in Fig. 3.3.2. It is clear from Fig. 3.3.2 that osmogent enhances the release of drug and had a direct effect on drug release. This is evidenced from formulation OA which was devoid of any osmogent in the core, showed 61% drug release at 24h. However, the use of osmogent enhanced the release beyond 80% drug release at 24h depending on the amount of osmogent present in the core formulation which might be due to the increased water uptake and hence increased driving force for drug release.

2. Atenolol

* **Effect of level of solubility modifier**

To optimize the amount of solubility modifier to be used in the formulation, core formulations were prepared as shown in Table 3.3.2. The amount of solubility modifier, tartaric acid studied were 2.5, 5 and 7.5 mg per tablet. All the core formulations were coated with coating composition, C-III containing 15 % w/w sorbitol (of total solids). Release profile from these formulations is shown in Fig. 3.3.3. It is clear from Fig. 3.3.3 that solubility modifier enhances the release of drug and had a direct effect on drug release.

Fig. 3.3.2 In-vitro release profile of Oxybutynin CPOP tablets-Effect of Osmogent

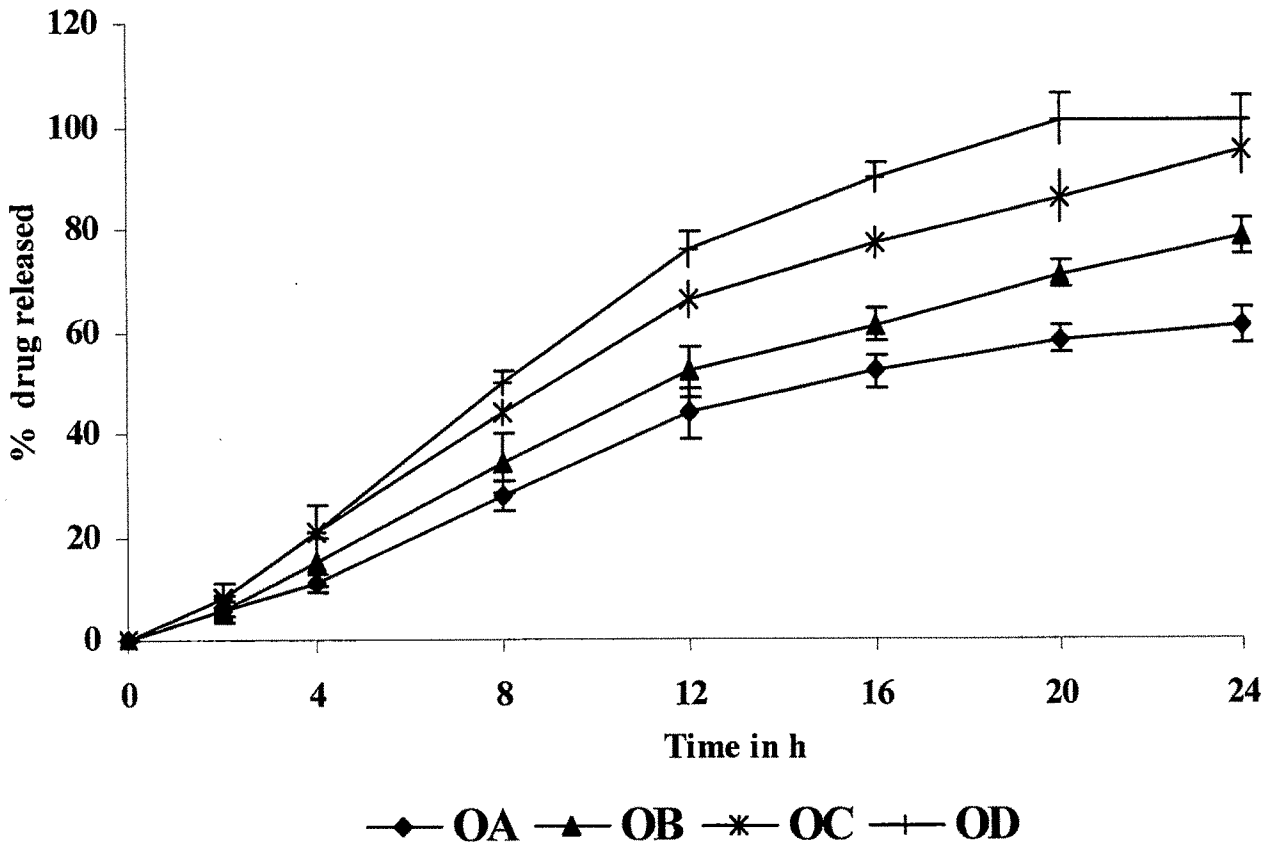
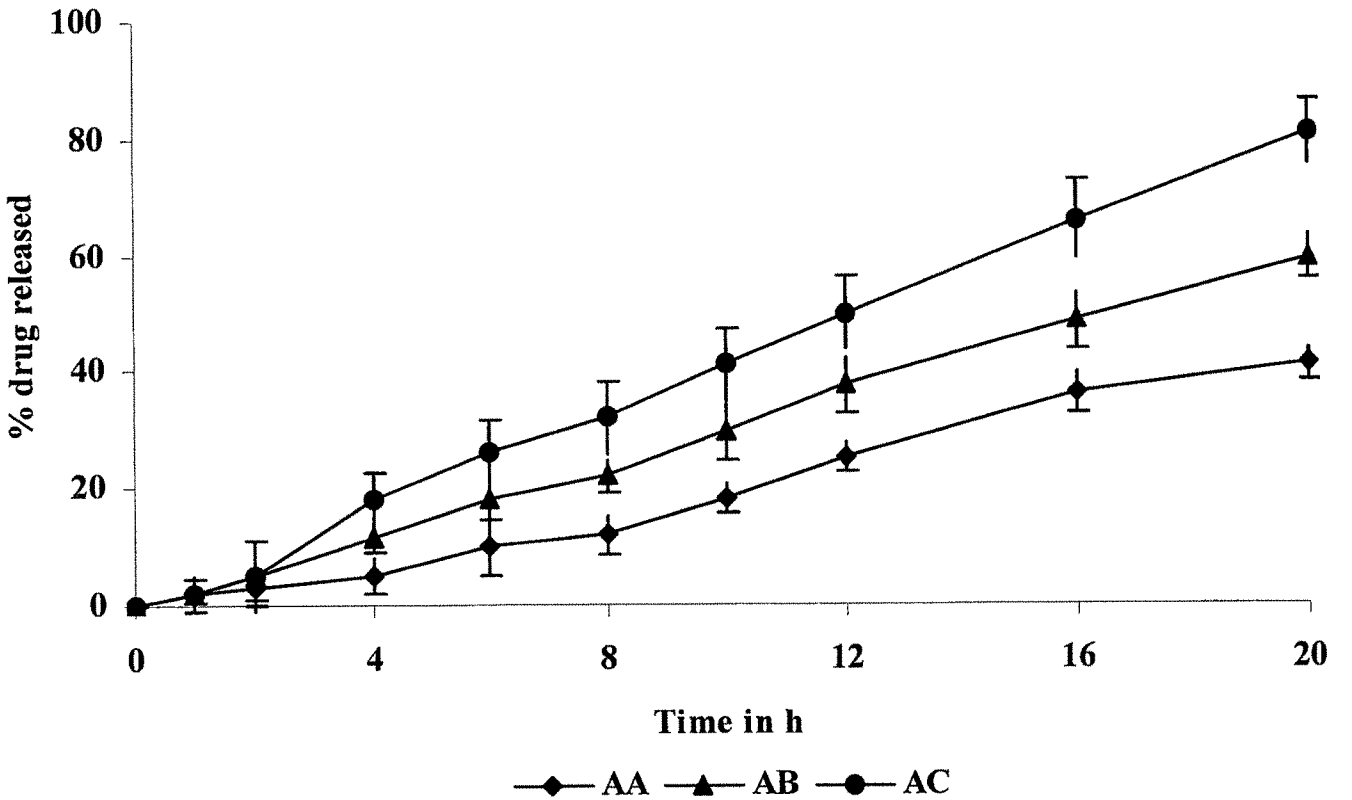


Fig. 3.3.3 In-vitro release profile of Atenolol CPOP tablets-Effect of solubility modifier



In the initial trial, core tablets of AT (without solubility modifier) were coated with C-III however around 20 % drug released even after 20 h. This phenomenon could be expected due to poor water solubility of atenolol. As reported earlier, when atenolol contacted with tartaric acid aqueous solution, it reacted and changed to salt. As a consequence, atenolol became freely soluble, and the concentration was increased markedly. Hence, the use of solubility modifier enhanced the release depending on the amount of solubility modifier present in the core formulation. The drug release after 20 h for AA, AB and AC formulations was 40.18 ± 1.88, 59.52 ± 2.81 and 81.02 ± 3.35 respectively. Hence core formulation of AC with 7.5 mg tartaric acid was chosen for further development.

* **Effect of osmogents in the core**

To study the effect of osmogent in the core formulation, core tablets were prepared with varying amounts of potassium chloride and coated with same coating formulation (C-III). The coated formulations were studied for in-vitro dissolution studies. Fig. 3.3.4 shows that the amount of potassium chloride had a marked influence on the atenolol release. The release rate increased as the amount of potassium chloride increased. The more potassium chloride incorporated into tablet, the more water was imbibed and the more core formulation could be dissolved and, as a consequence, more atenolol was released. The percent release after 20 h with 25, 50 and 75 mg potassium chloride per tablet was 81.02 ± 1.75, 89.84 ± 3.47 and 101.28 ± 5.02 respectively, suggesting that an optimum amount of osmogent is required in an osmotic system to completely release the drug.

* **Effect of level of pore former – for both OC and AT**

To study the effect of level of pore former (sorbitol), core tablets of OC and AT were coated with coating composition containing 0, 7.5, 15 and 20 % (w/w of total solid) of sorbitol (Table 2). It was found that the drug release increases with the level of sorbitol (Fig. 3.3.5 and 3.3.6). As the level of pore former increases, the membrane becomes more porous after coming in contact with the aqueous environment, resulting in faster drug release. Other workers have also obtained similar results (Zentner et al., 1985a; Okimoto et al., 1999a).

The level of pore former also affected the extent of drug release. In case of OC, maximum drug release after 24 h was 28.25, 61.58 and 91.34 % in formulations

Fig. 3.3.4 In-vitro release profile of Atenolol CPOP tablets-Effect of osmogent

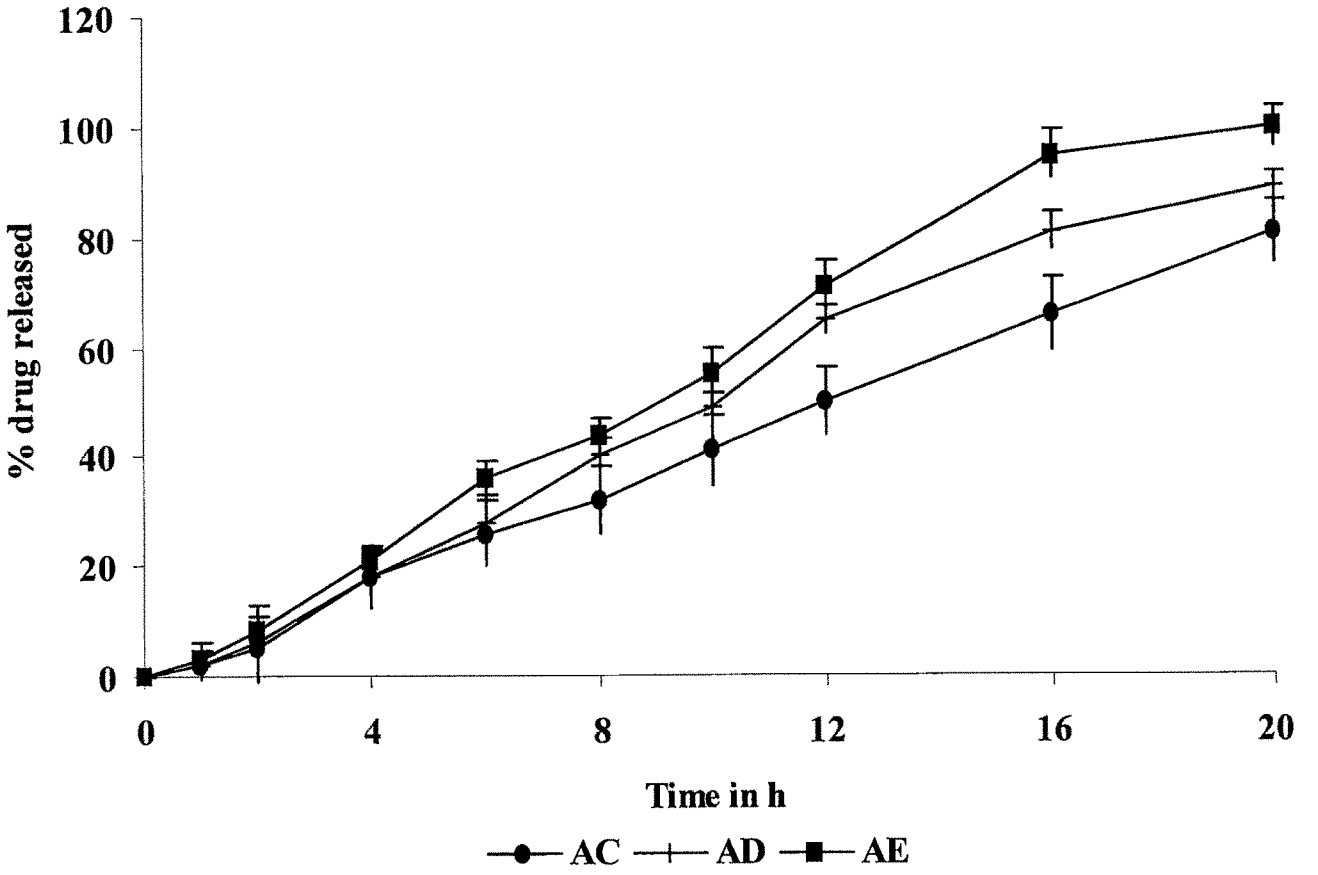


Fig. 3.3.5 In-vitro release profile of Oxybutynin CPOP tablets-Effect of level Pore former

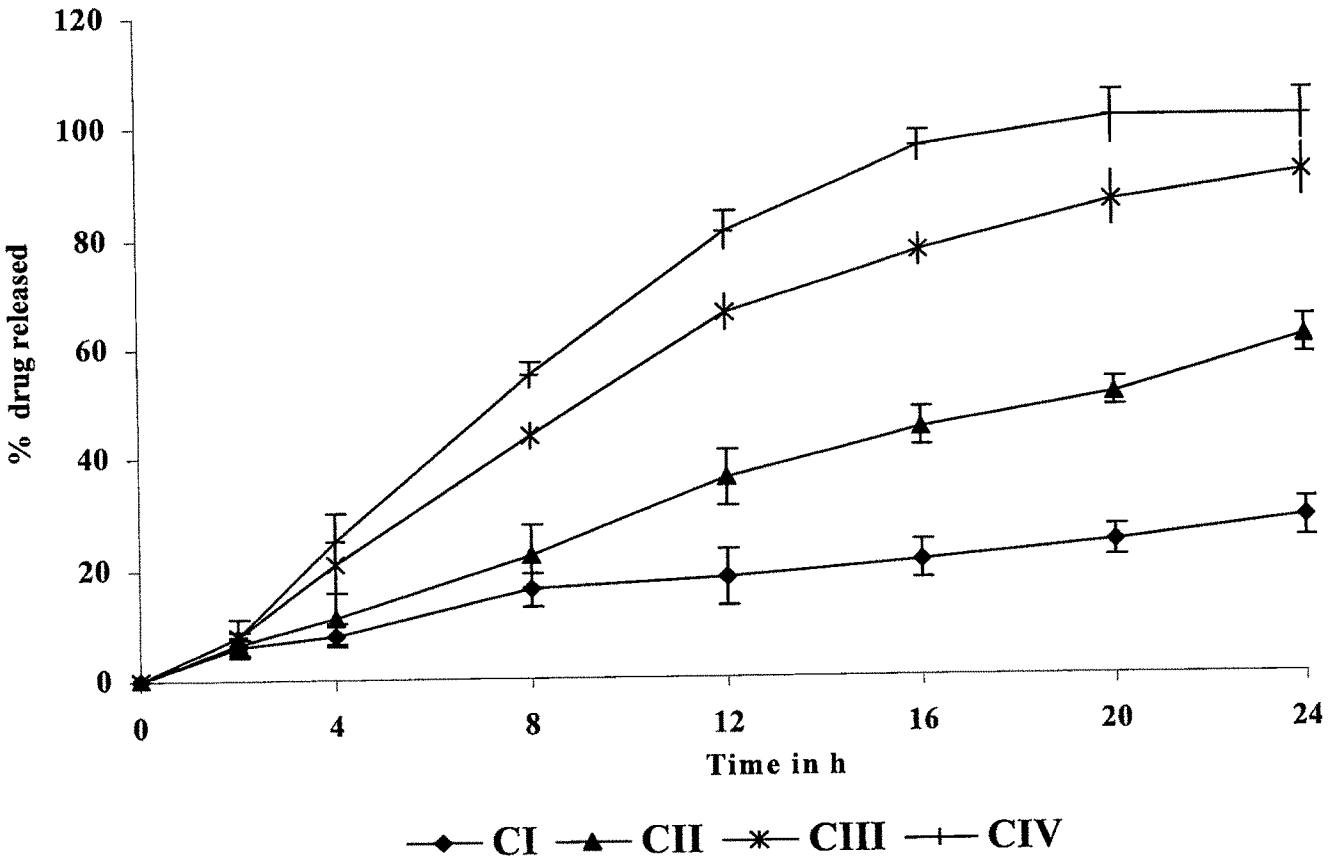
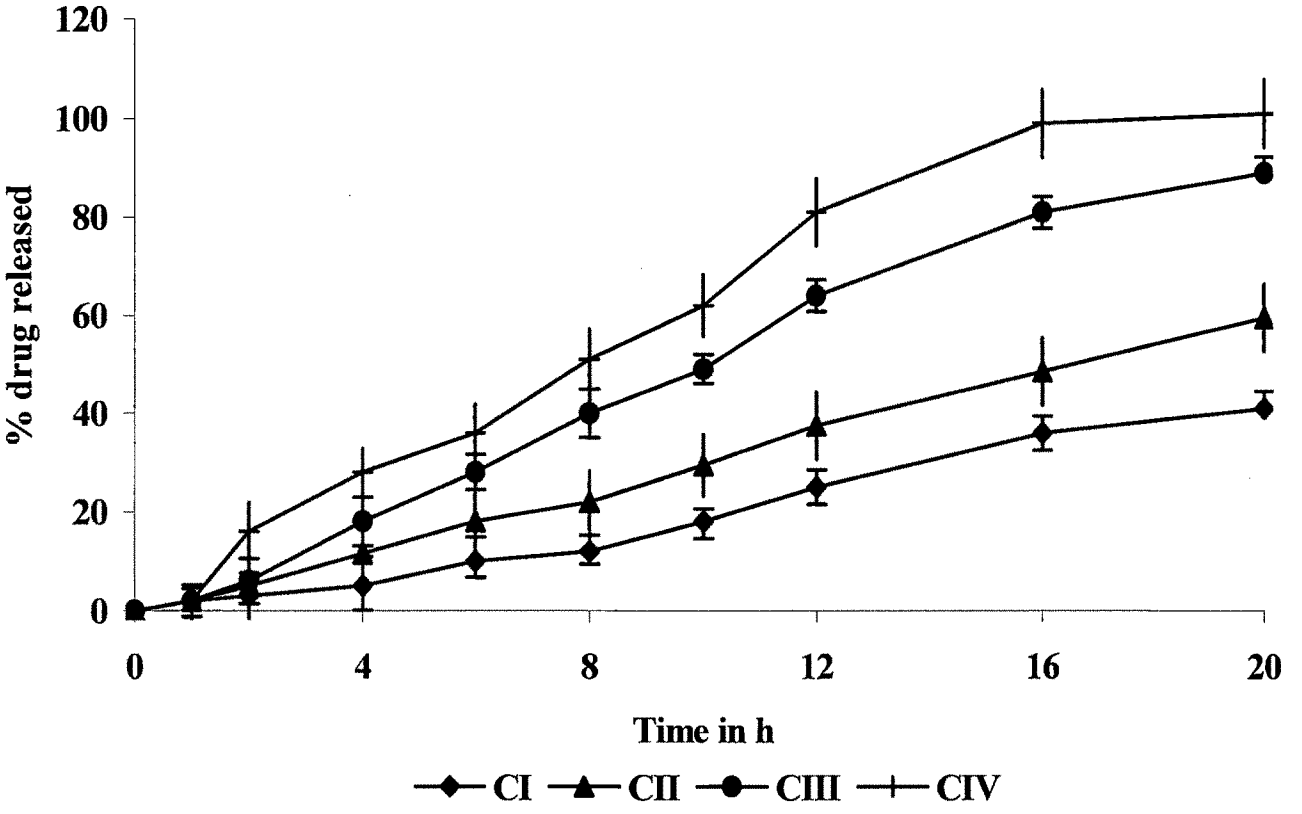


Fig. 3.3.6 In-vitro release profile of Atenolol CPOP tablets-Effect of level of pore former



containing 0, 7.5 and 15 % (w/w of total solid) of sorbitol. However with 20% of sorbitol, 101.29 % of the drug release took place in 20 h itself (Fig. 3.3.5).

Similar observation were seen with AT where maximum drug release after 20 h was 41.26, 59.96 and 89.37 % in formulations containing 0, 7.5 and 15 % (w/w of total solid) of sorbitol and with 20% of sorbitol, more than 99.16 % of the drug release took place in 16 h itself. (Fig. 3.3.6)

As the pore former level increases, the membrane becomes porous after coming in contact with the water (when the pore former leaches out of the membrane). At levels up to 10% (w/w) of pore former, numbers of pores are not sufficient to contribute to significant drug release. On the other hand, membranes that initially contained 15% (w/w) of pore former; the membrane becomes more porous after coming in contact with water. The explainable reason for the sudden change in the release profile may be that the threshold might not have reached in formulations containing 15% and less of pore former. Therefore, it can be concluded that drug release is directly proportional to the level of pore former in the membrane and this parameter can be varied to control the drug release. Another parameter affected by the level of pore former was burst strength of the exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in level of sorbitol, the membrane became more porous after exposure to water, leading to a decrease in its strength. The results in the present study are consistent with other reports (Appel and Zentner, 1991; Jensen et al., 1995). Since, satisfactory drug release and adequate burst strength were obtained in case of formulations with 15% pore former level , this concentration was selected for further studies.

* **Effect of type of pore former – for both OC and AT**

To study the effect of type of pore former, formulations were prepared by coating core tablets of OC and AT with coating compositions C-III, C-V and C-VI containing different pore formers (Sorbitol, HPMC and PEG-6000, respectively).

As evident from Fig. 3.3.7 and 3.3.8, the type of pore former affected drug release and it is possible to achieve the desired release by using different types and/or combination of pore formers. $MDT_{50\%}$ in case of OC was found to be 12.25, 10.24 and 7.46 h for formulations containing HPMC, Sorbitol and PEG-6000 respectively. Similar observation

Fig.3.3.7 In-vitro release profile of Oxybutynin CPOP tablets-Effect of Type of Pore former

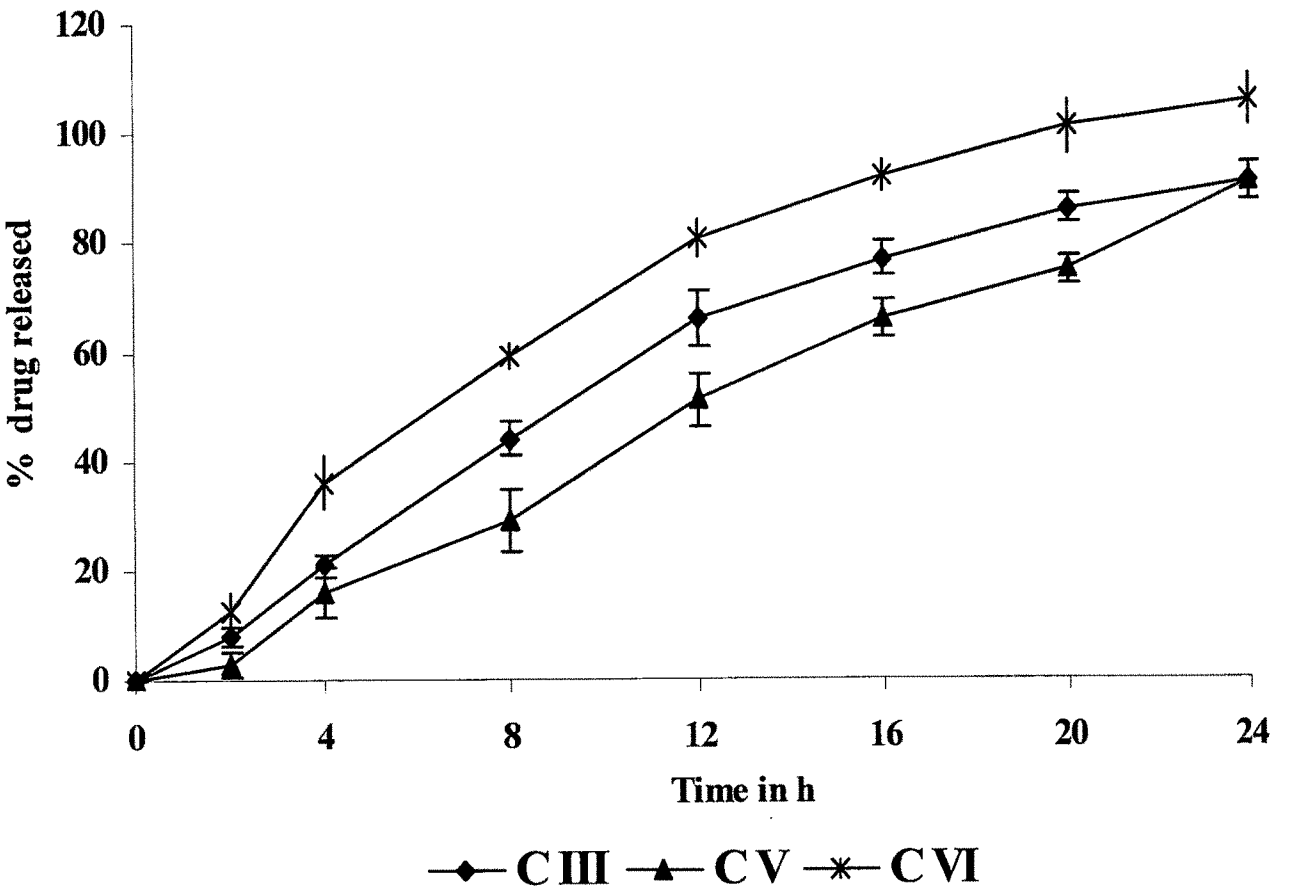
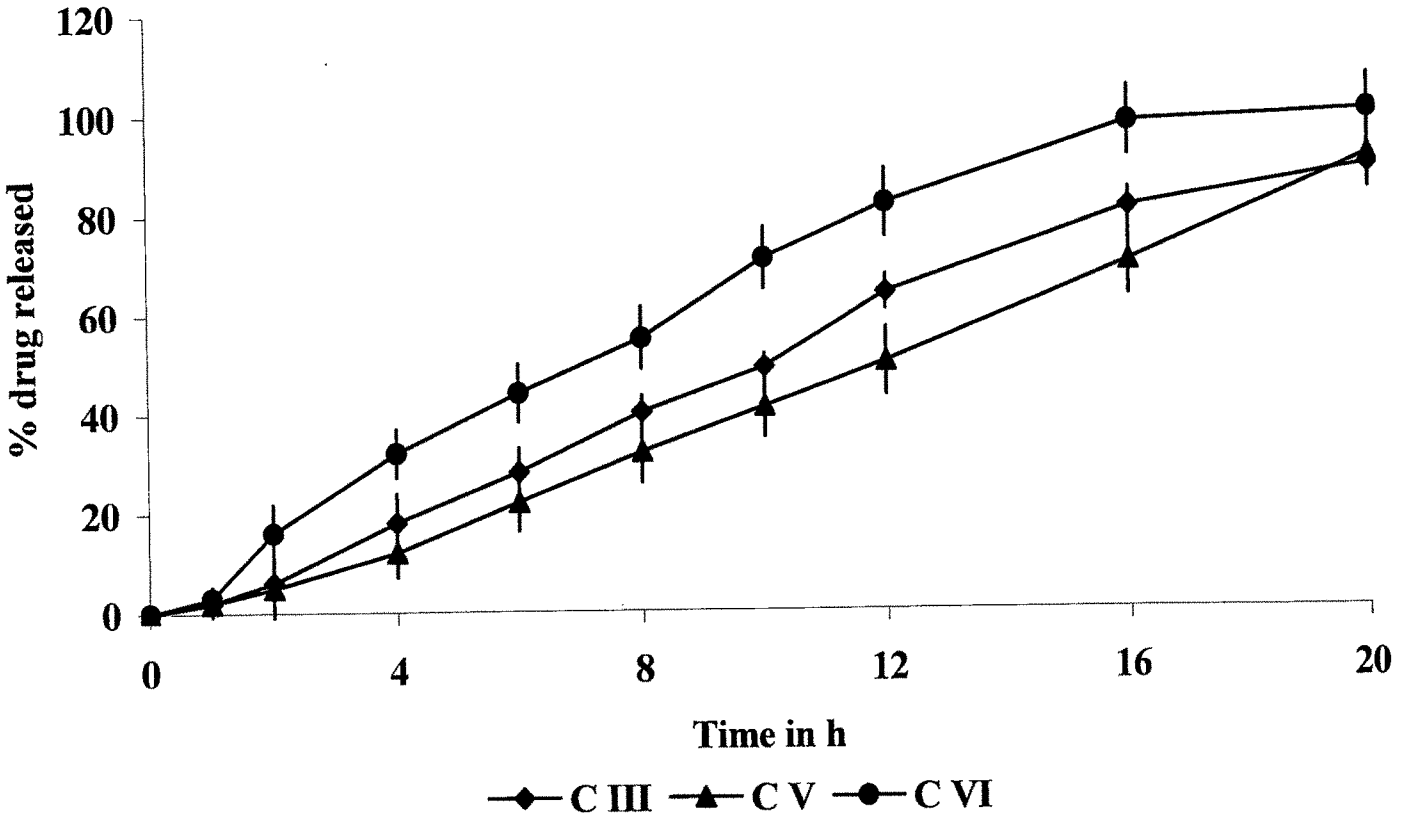


Fig. 3.3.8 In-vitro release profile of Atenolol CPOP tablets-Effect of Type of Pore former



were obtained with AT and found to be 12.01, 10.12 and 7.59 for formulations containing HPMC, Sorbitol and PEG-6000 respectively

There was statistically significant difference ($P \leq 0.05$) between the different formulations.

In addition to release, type of pore former also affected the burst strength of the exhausted shells (Fig. 3.3.9) and this parameter should also be taken into consideration while selecting the pore former. The drug release and the burst strength were satisfactory with the formulations containing sorbitol as the pore former. This formulation was selected as the "optimized" formulation and used for further evaluation

- ***STATISTICAL ANALYSIS OF DISSOLUTION DATA***

To evaluate the performance of the developed formulations, release profile was compared with marketed innovator products.

Ditropan XL marketed by Alza Inc., USA is formulated as an extended-release tablet for once-a-day oral administration. Drug release is controlled by osmotic pump technology. The drug compartment is connected to the outside environment via a delivery orifice.

The advantages of the in house developed system is that it is simpler in design and requires less number of manufacturing steps, economical, and easily amenable to mass production.

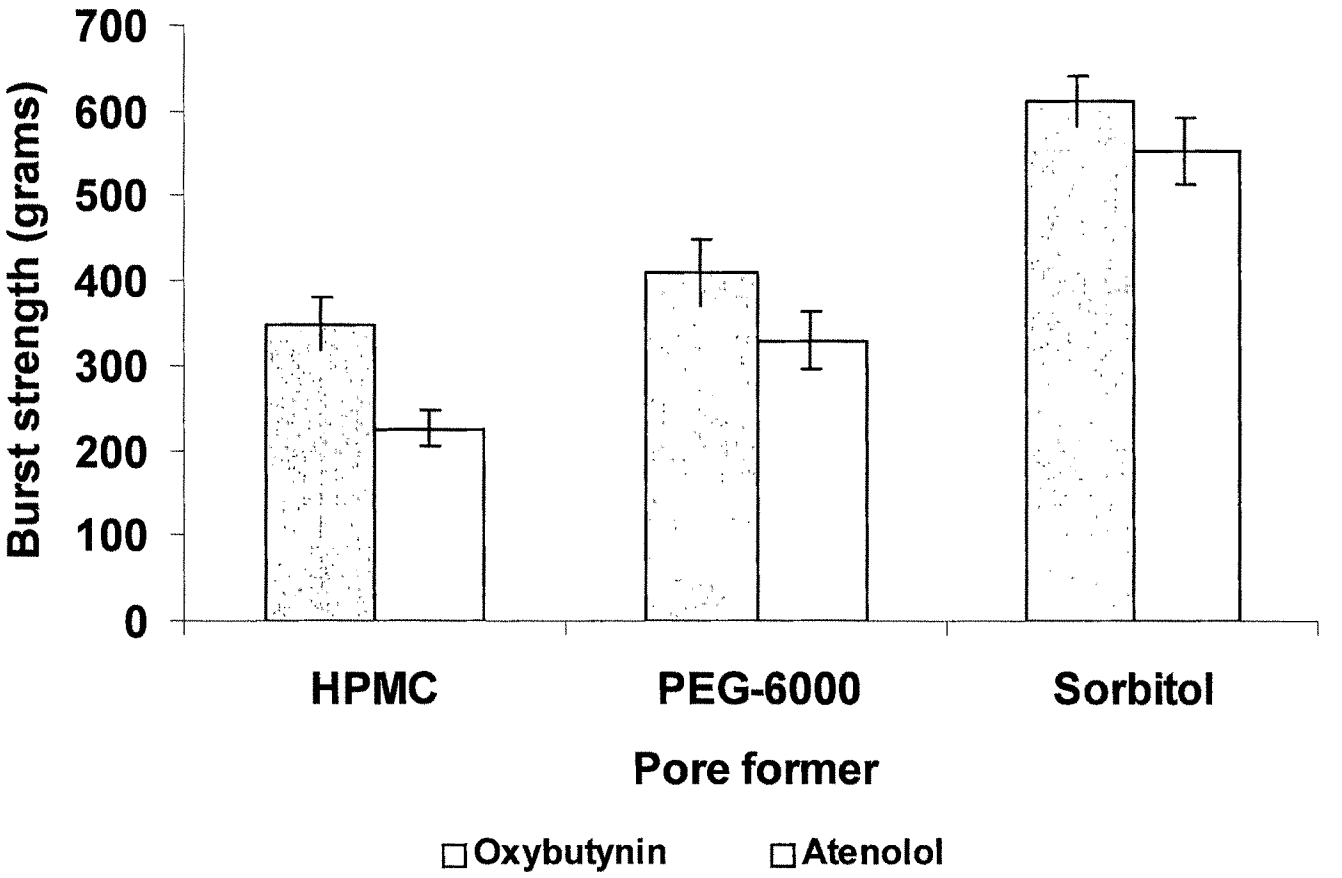
Fig. 3.3.10 shows release of OC from in-house formulations in comparison with Ditropan XL. The f1 and f2 values are presented in Table 3.3.9, taking the release profile of Ditropan XL as reference. These formulations were selected as the optimized formulation and used for further evaluation.

Table 3.3.9 Comparison of release profile

Product	Reference	Innovator	f_1	f_2
Oxybutynin chloride	Ditropan XL*	Alza Inc. USA	13.59	62.51

**Formulated as an extended-release bilayer tablet with delivery orifice for once-a-day oral administration. Drug release is controlled by osmosis*

Fig.3.3.9 Burst strength as a function of type of pore former



– ***KINETICS OF DRUG RELEASE***

Table 3.3.10 shows the equations used to determine the appropriate models and presents the values for all formulations. Drug release from *in house* optimised formulation fitted well into zero-order kinetics for both the formulations (OC and AT), which is confirmed by the lower sum of squared residuals (SSQ) and comparatively higher correlation co-efficient. Application of release curve to zero-order equation indicated that the drug release is independent of drug remaining in its interior.

For OC, the next best model describing the release was first-order, Higuchi's and Hixson-Crowell, and for AT, the next best model describing the release was first-order, Hixson-Crowell, and Higuchi's.

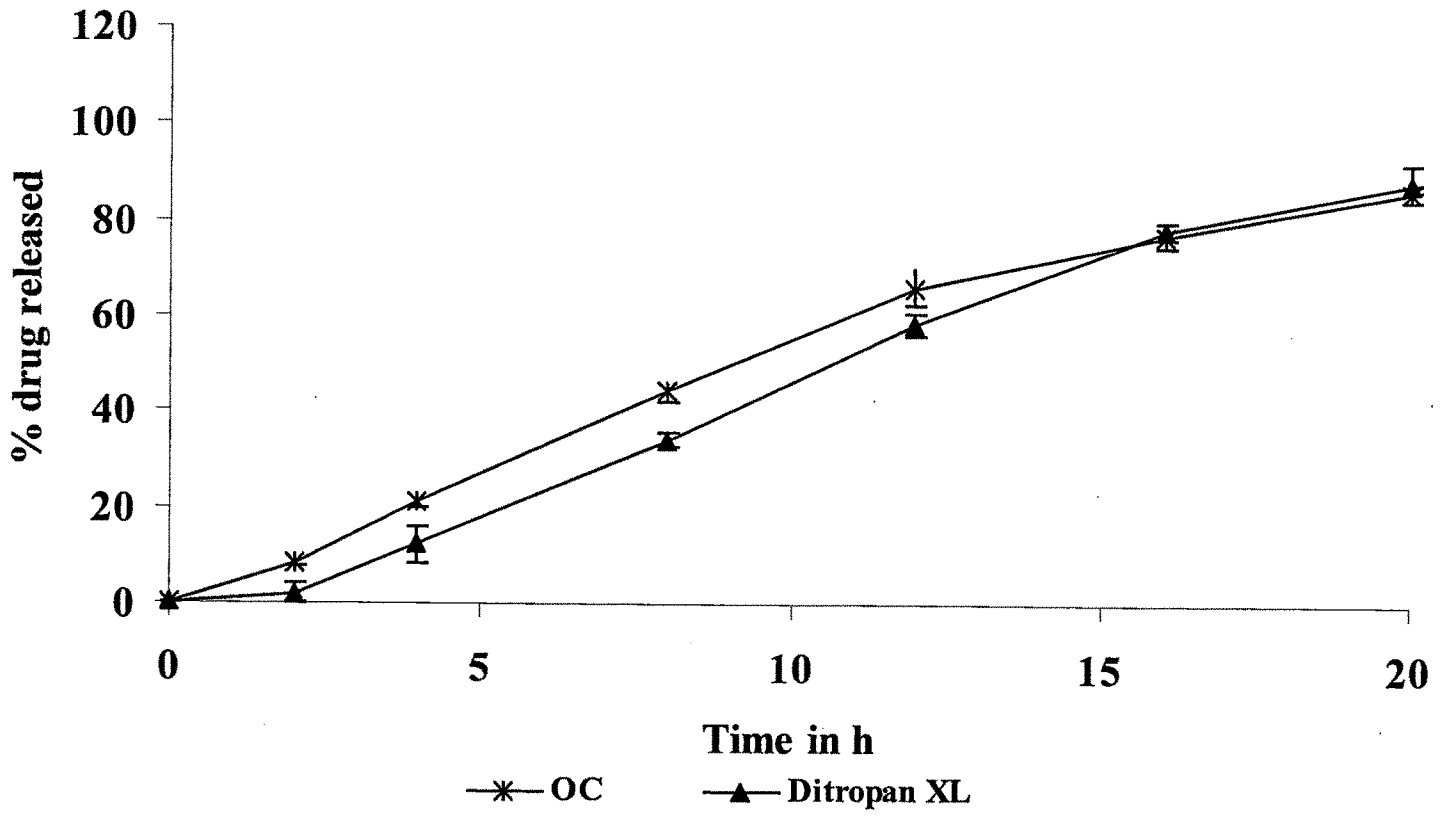
The drug release data was further analysed for curve fitting based on Korsmeyer-Peppas model. Based on the theory that if the *n* value is equal to 0.5 or between 0.5 and 1.0 the release mechanism is Fick's diffusion or a non-Fickian model, respectively. The *n* value obtained for the optimized formulation was more than 0.5 suggesting the release from this formulation follows non-Fickian diffusion.

Table 3.3.10 Fitting of dissolution data of the optimized formulation to various kinetic models

Kinetic Model	Parameters					
	r		SSQ		*k*	
	OC	AT	OC	AT	OC	AT
Zero order	0.9761	0.9882	10.09	15.62	1.64	1.79
First order	0.9358	0.9638	225.78	208.49	-0.0305	-0.0635
Higuchi model	0.9285	0.9427	1489.46	11563.52	3.79	2.75
Hixon-Crowell model	0.9118	0.9575	12438.56	2078.83	0.1726	0.1765

r: coorelation co-efficient, SSQ: sum of squared residuals, k: release rate constant for respective models (k_0, k_1, k_H and k_{HC} for zero-order, first-order, Highuchi model and Hixon-Crowell model, respectivley

Fig. 3.3.10 Comparison of In-vitro release profile of Oxybutynin with Innovator product



- ***SCANNING ELECTRON MICROSCOPY (SEM)***

It was expected that with an increase in the level of pore former, porosity of the membrane would increase because of leaching of pore former from the membrane. This was reflected in the release studies, wherein the release increased with the increase in level of pore former. To further confirm this, the membrane structure was observed after dissolution studies.

* **Effect of level of pore former**

In case of membrane containing 0 % level of sorbitol as pore former (C-I), there were no pores in the membrane (Fig. 3.3.11). It was concluded that the membrane did not develop significant porosity after coming in contact with the aqueous environment. In case of C-II, which has 7.5% (w/w of CA) of sorbitol, SEM micrograph showed formation of significantly fewer pores (Fig. 3.3.12) in the membrane. In case of C-III which has 15% (w/w of CA) of sorbitol, SEM micrograph showed formation of thin denser pores (Fig. 3.3.13) in the membrane than C-II. In case of C-IV which has 20% (w/w of CA) of sorbitol, SEM micrograph showed (Fig. 3.3.14) considerable uniform porosity after dissolution studies than C-II and C-III membrane.

The results are consistent with the drug release studies (Fig. 3.3.5 and 3.3.6).

* **Effect of type of pore former**

To study the effect of type of pore former, formulations coated with coating compositions C-III, C-V and C-VI containing different pore formers (Sorbitol, HPMC and PEG-6000, respectively) were studied.

In case of membrane containing sorbitol (C-III), formation of uniform pores was observed. (Fig. 3.3.13). For membrane containing HPMC (C-V), formation of dense pores than C-III was observed which could be due the gelling and swelling property of HPMC (Fig. 3.3.15). For membrane containing PEG-6000 (C-VI) formation of non-uniform pores were observed (Fig. 3.3.16). From these observations it can be concluded the type of pore former affects the drug release and the same has to be optimized.

The results are consistent with the drug release studies (Fig. 3.3.7 and 3.3.8).

Fig. 3.3.11 : Scanning electron microphotograph of membrane devoid of pore former (3000 X)

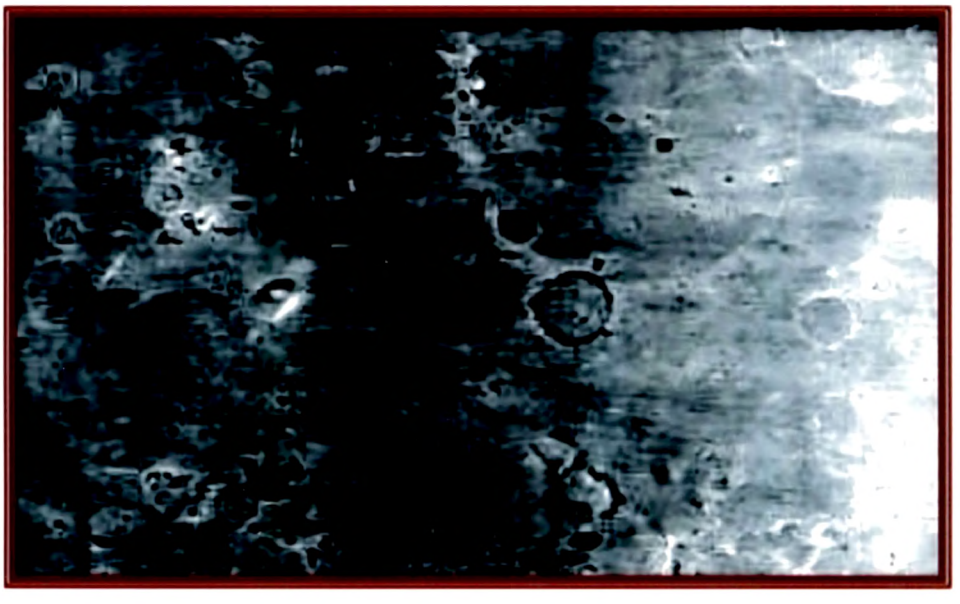


Fig. 3.3.12 : Scanning electron microphotograph of membrane containing 7.5% w/w of sorbitol (3000 X)

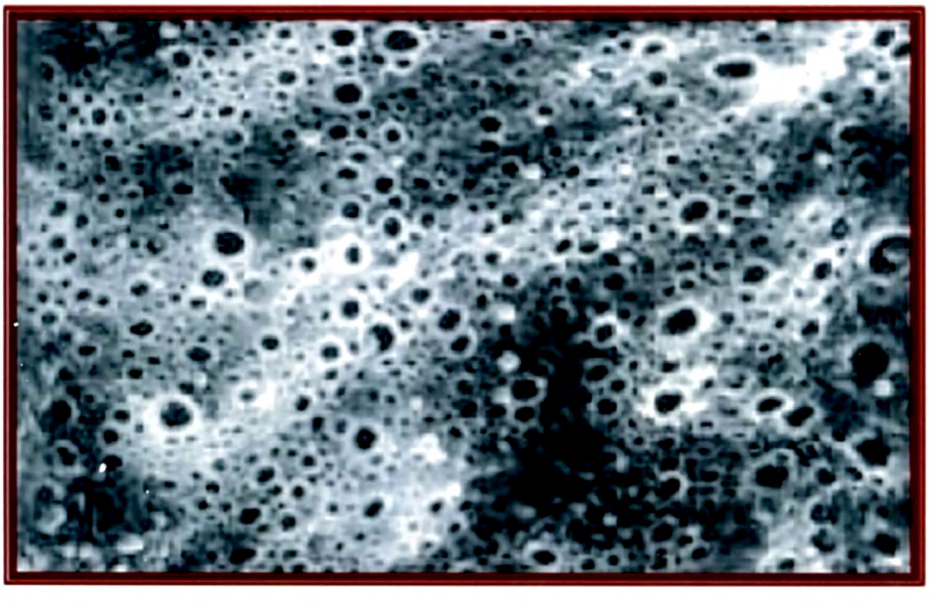


Fig. 3.3.13 : Scanning electron microphotograph of membrane containing 15% w/w of sorbitol (3000 X)

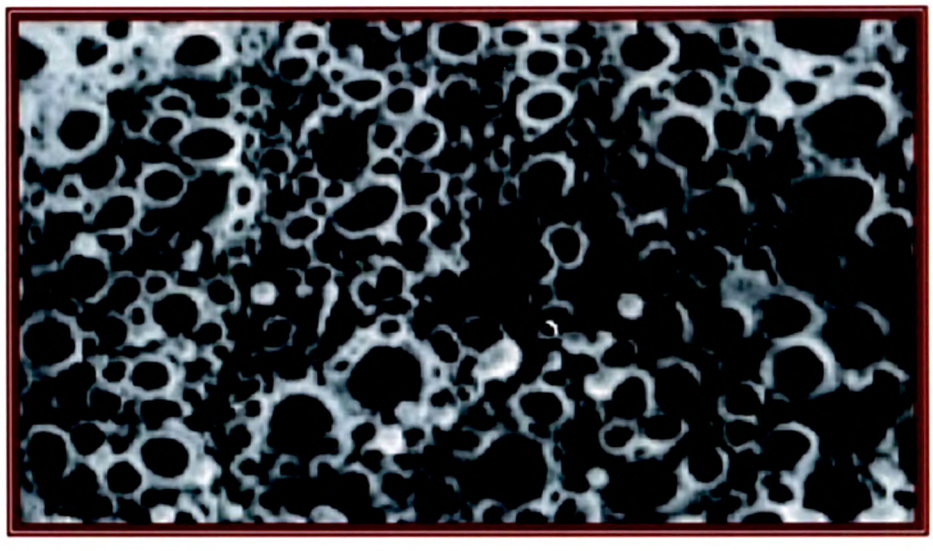


Fig. 3.3.14 : Scanning electron microphotograph of membrane containing 20% w/w of sorbitol (3000 X)

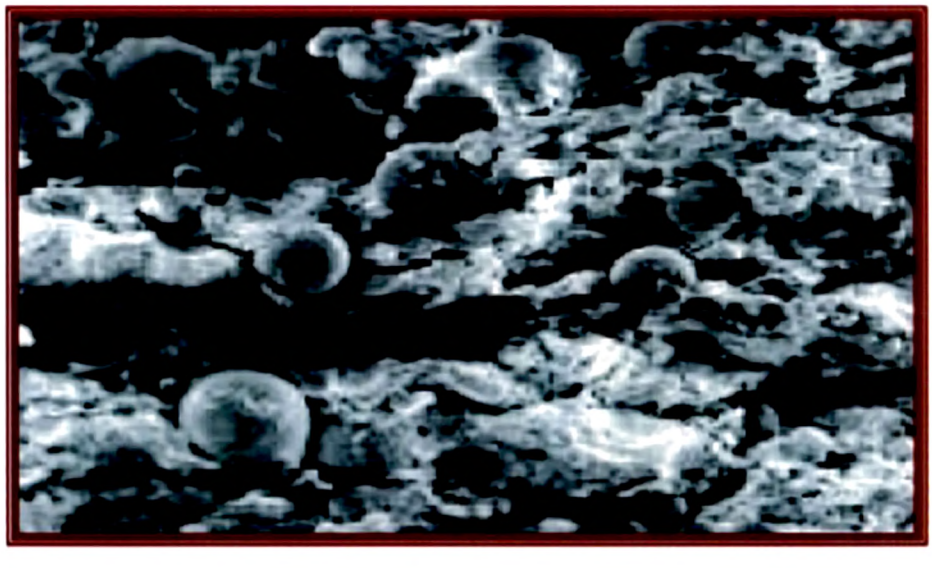


Fig. 3.3.15 : Scanning electron microphotograph of membrane containing 15% w/w of HPMC (3000 X)

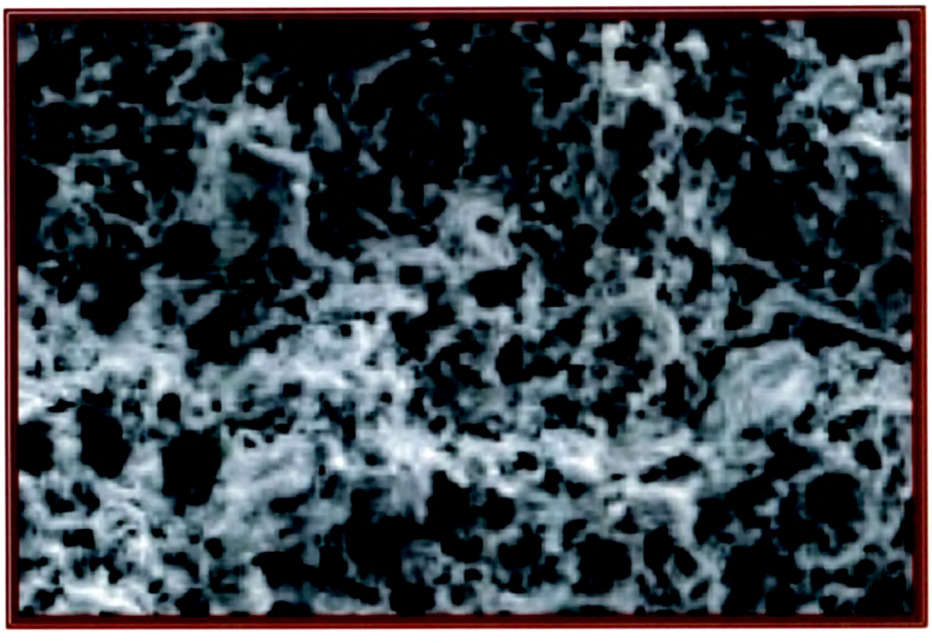
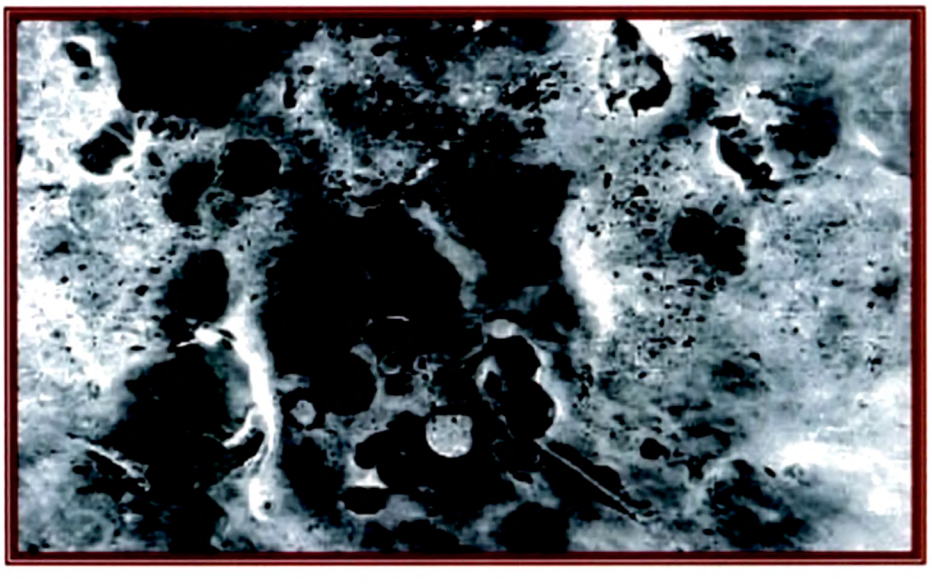


Fig. 3.3.16 : Scanning electron microphotograph of membrane containing 15% w/w of PEG-6000 (3000 X)



PART IV

PERFORMANCE EVALUATION OF OPTIMIZED FORMULATIONS

METHODS

✧ **Effect of pH**

In order to study the effect of pH and evaluate, release studies of the optimized formulations were conducted in the following physiological media of different pH,

1. Simulated gastric fluid (SGF) pH 1.2
2. Acetate buffer pH 4.5 and
3. Simulated intestinal fluid (SIF) pH 6.8

In vitro drug release of the formulations were carried out using USP type I dissolution apparatus (2100C, Distek Inc, NJ) attached with an auto-sampler (37 ± 0.5 °C). The drug release at different time intervals was analyzed by estimation of drug concentration using either UV spectrophotometer or HPLC.

In case of glipizide, nifedipine and atenolol release studies of the optimized formulations were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) for first 2 h, acetate buffer (pH 4.5) for next 2 h, followed by SIF (pH 6.8) for the remaining period. The samples were withdrawn at predetermined intervals and analyzed.

✧ **Effect of agitational intensity**

To study the effect of agitational intensity on the release, release studies of the optimised formulations were carried out using USP type I dissolution apparatus (2100C, Distek Inc, NJ) attached with an auto-sampler (37 ± 0.5 °C) at 50, 100 and 150 rpm rotational speeds. Table 3.4.1 summarizes the dissolution study. The drug release at different time intervals was analyzed by estimation of drug concentration using either UV spectrophotometer or HPLC.

Table 3.4.1 *In-Vitro* Dissolution studies

Parameters	A. SPOP		B. MOTS		C. CPOP	
	Venlafaxine HCl	**Glipizide**	**Metoprolol tartrate**	**Nifedipine**	**Oxybutynin chloride**	**Atenolol**
Dissolution media	DM water	Phosphate buffer, pH 6.8	DM water	0.1N HCl, pH 1.2 , 0.5% SLS	0.1N HCl, pH 1.2	DM water
Volume	900 ml	500 ml	900 ml	900 ml	900 ml	900 ml

✧ **Effect of osmotic pressure**

To confirm the major mechanism of drug release, release studies of the optimized formulations were carried in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride (osmotically active solute) was added in SIF and the pH was adjusted to 6.8. The osmotic pressure of the dissolution media was measured by using a vapour pressure osmometer (Wescor, USA). Before measurement, osmometer was calibrated using standards of 100, 290 and 1000 mmol/kg. Release studies were carried out in 1000 ml media using USP type I dissolution apparatus (2100C, Distek Inc, NJ) attached with an auto-sampler (37 ± 0.5 °C) at 100 rpm. To avoid any possible interference in the analysis by sodium chloride, residual drug analysis methodology was utilized for the construction of release profile.

At predetermined time points formulations were withdrawn from each vessel, cut open and the contents were dissolved in sufficient volume of SIF (pH 6.8). The drug release at different time intervals was analyzed by estimation of drug concentration using either UV spectrophotometer or HPLC.

✧ **Statistical analysis**

The release profiles obtained were compared with each other statistically to find the significant difference. Student's "t" test with Welch correction was employed for each data set by using Graphpad-Instat software (Graphpad Inc., CA, USA).

RESULTS AND DISCUSSION

✧ **Effect of pH**

In order to study the effect of pH on drug release from water soluble drugs, release studies were conducted in media of different pH. Fig. 3.4.1, 3.4.3 and 3.4.5 shows release of VH, MT and OC respectively from optimized formulation in SGF, pH 1.2; acetate buffer, pH 4.5; and SIF, pH 6.8. As can be seen from the figures, release profile is similar ($P>0.05$) in all the media demonstrating that the developed formulations show pH-independent release.

In order to study the effect of pH on drug release from low water soluble drugs, release studies of optimized formulation were conducted according to pH change method to assure a reliable in vivo performance and also to study the effect of pH on drug release. Fig. 3.4.2, 3.4.4 and 3.4.6 shows release of GZ, NP and AT respectively from optimized and it is clearly evident that the release profile is similar in both the media ($P>0.05$).

✧ **Effect of agitational intensity**

To study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in USP dissolution apparatus type I at varying rotational speed (50, 100, and 150 rpm). It is clearly evident from Fig. 3.4.7 to 3.4.12 that the release of is independent of the agitational intensity ($P>0.05$).

Based on the above results of pH and agitational intensity, it can be concluded that drug releases from optimized formulations are independent of the agitational intensity of the release media. Therefore, the formulations can be expected to show a release profile, fairly independent of the hydrodynamic conditions of the body (Verma and Garg, 2004).

✧ **Effect of osmotic pressure**

To study the effect of osmotic pressure, release studies of the optimized formulation were conducted in media of different osmotic pressure. Drug release was found to be highly dependent on the external osmotic pressure and drug release from the formulations decreased with an increase in the osmotic pressure of the release media (Fig. 3.4.13 to 3.4.18) ($P<0.05$). From these figures it was confirmed that osmotic pumping is the major mechanism of drug release from the developed formulations (Appel and Zentner, 1991; Jensen et al., 1995).

Fig. 3.4.1 In-vitro release profile of Venlafaxine (VD) SPOP tablets-Effect of pH

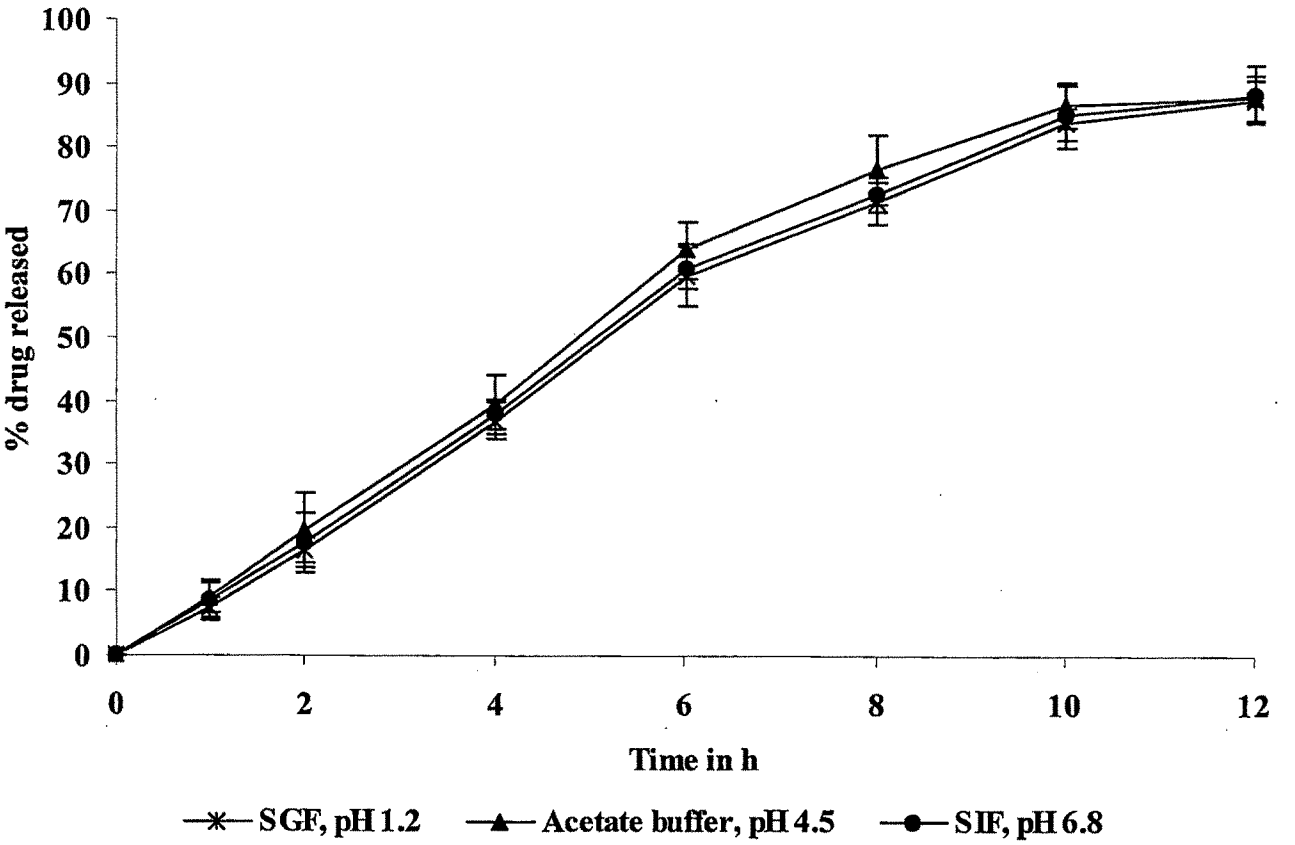


Fig. 3.4.2 In-vitro release profile of Glipizide (GZ) SPOP tablets-Effect of pH

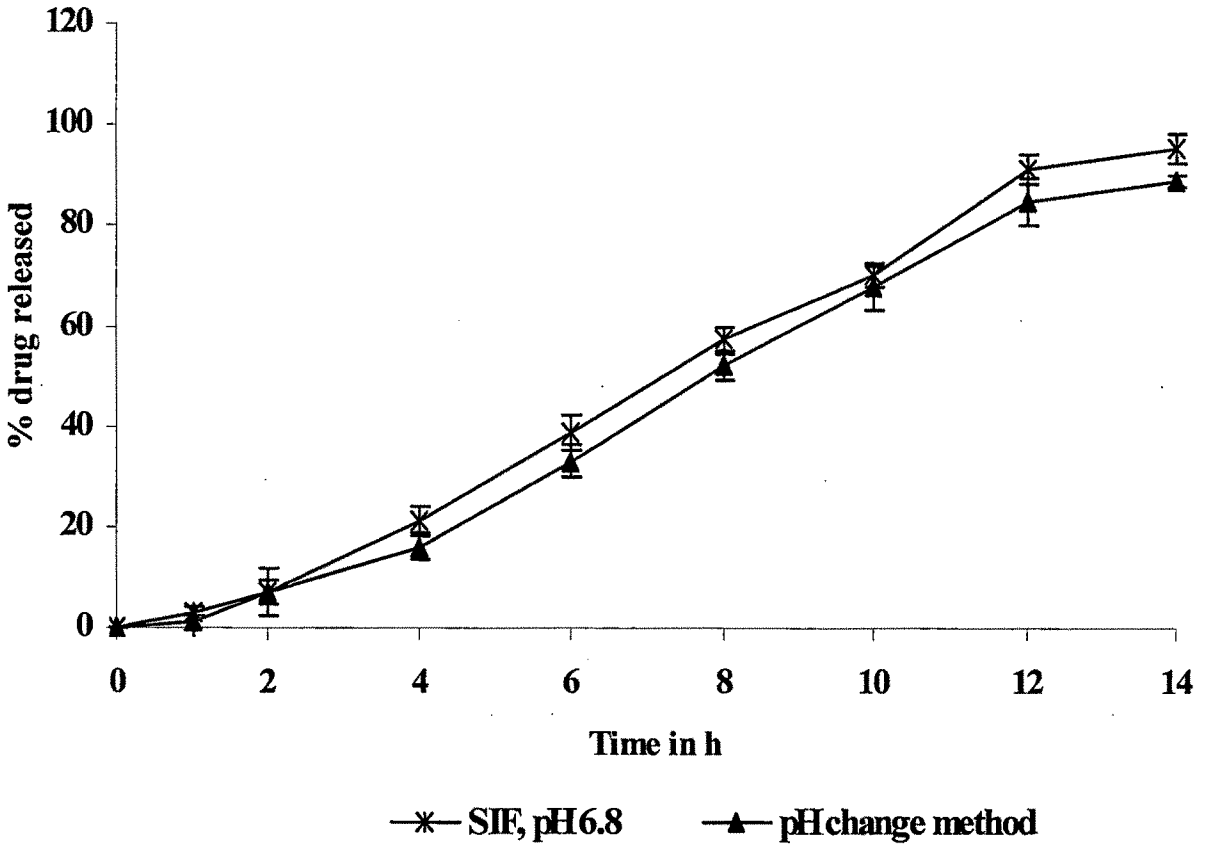


Fig. 3.4.3 In-vitro release profile of Metoprolol tartrate (MT) MOTS tablets-Effect of pH

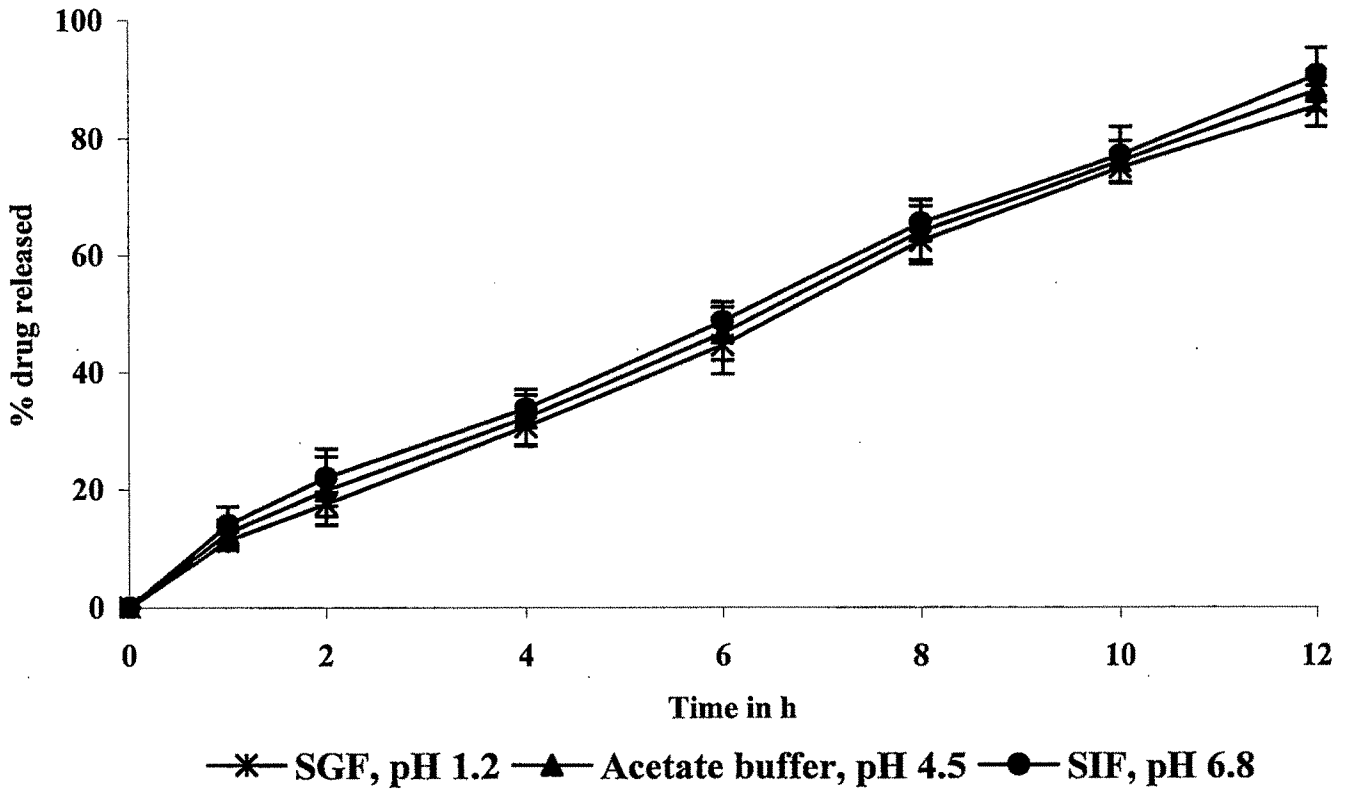


Fig. 3.4.4 In-vitro release profile of Nifedipne (NP) MOTS tablets-Effect of pH

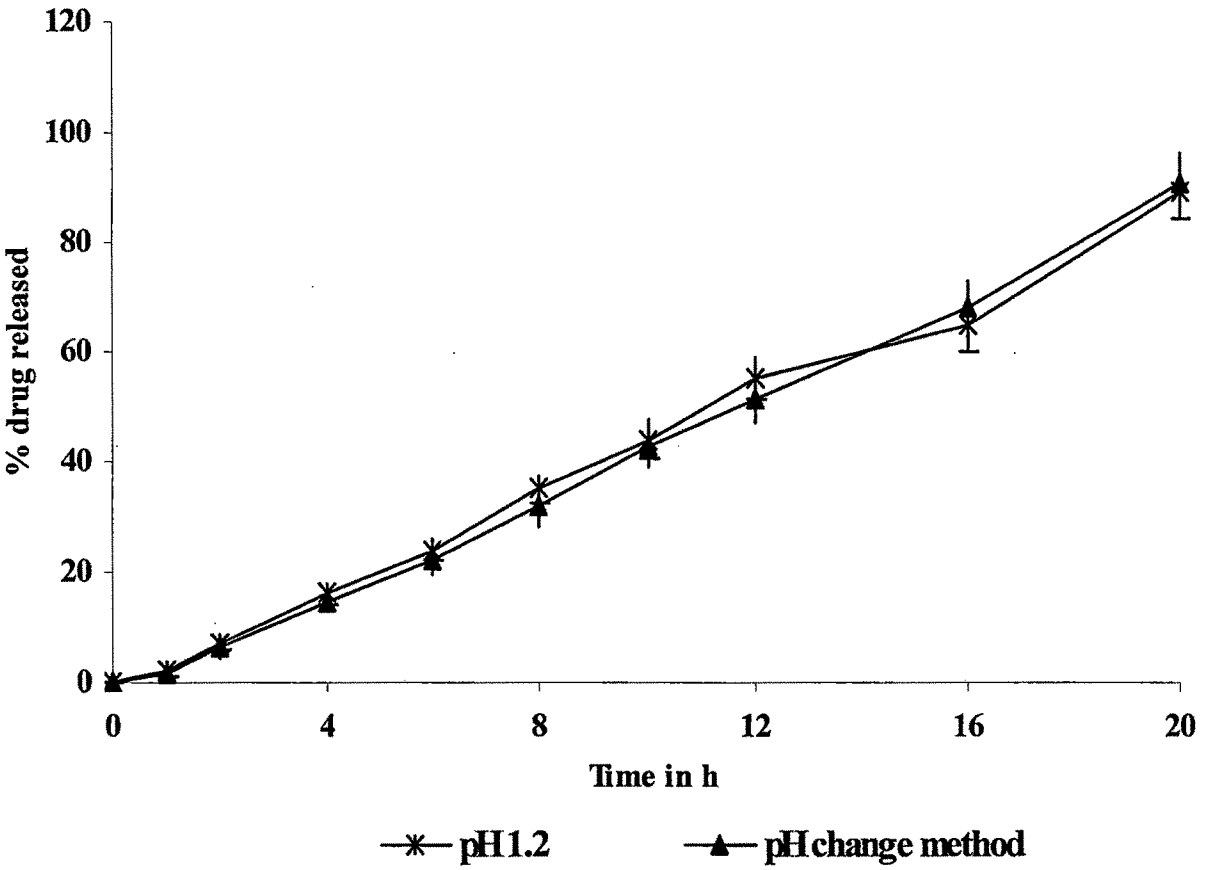


Fig. 3.4.5 In-vitro release profile of Oxybutynin chloride (OC) CPOP tablets-Effect of pH

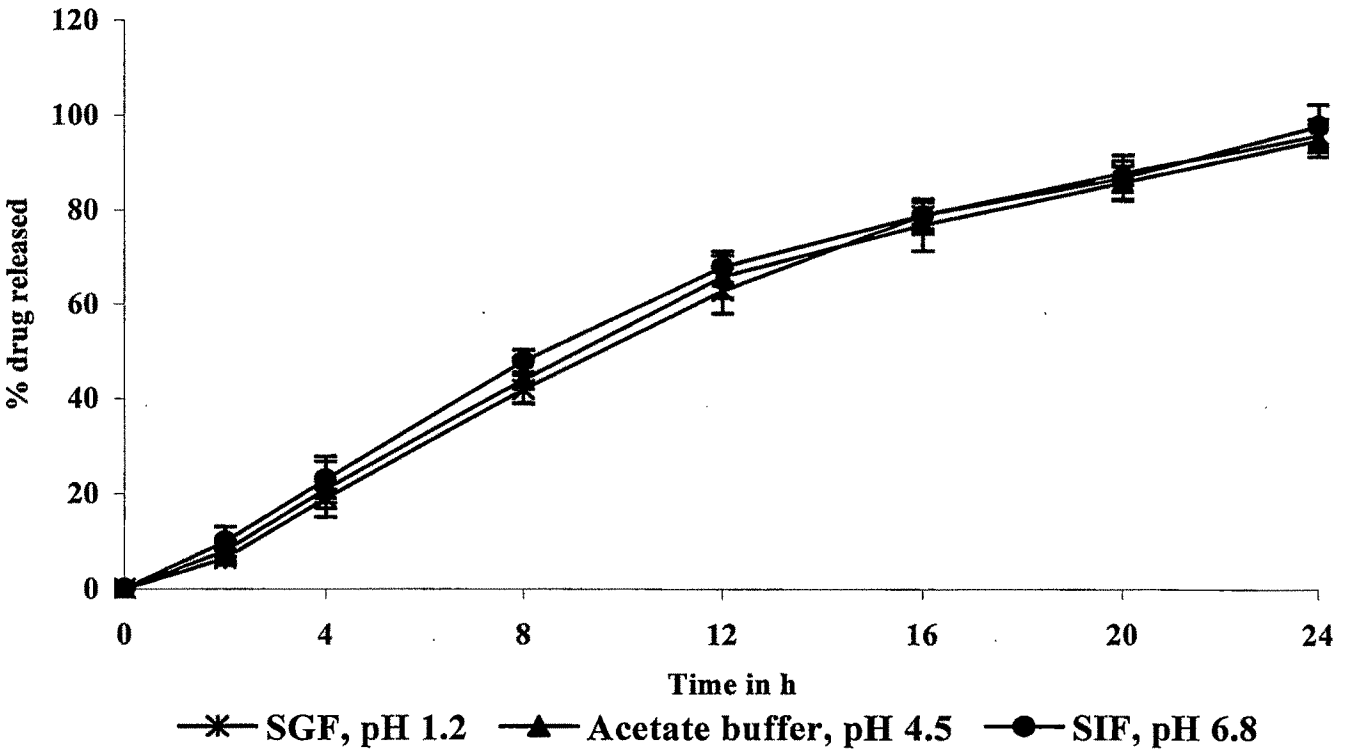


Fig. 3.4.6 In-vitro release profile of Atenolol (AT) CPOP tablets-Effect of pH

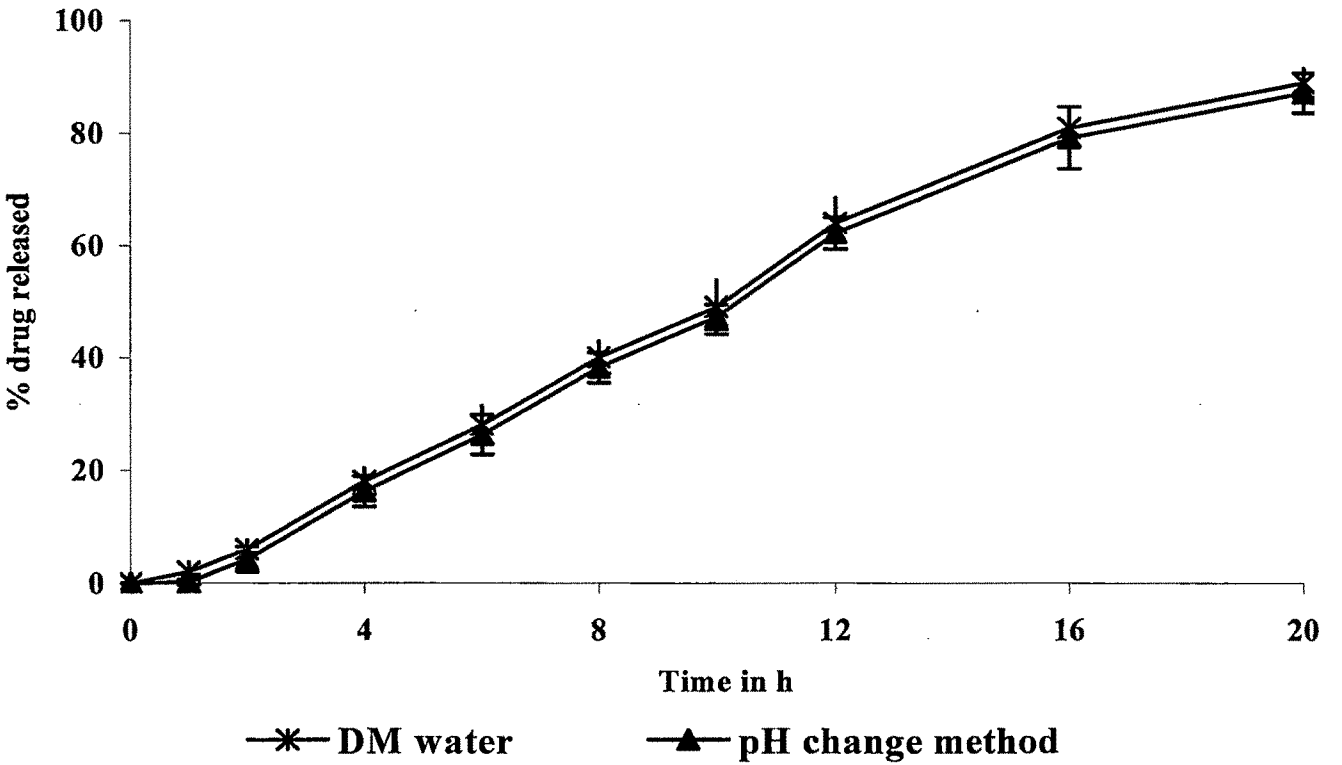


Fig. 3.4.7 In-vitro release profile of Venlafaxine (VD) SPOP tablets-Effect of agitational intensity

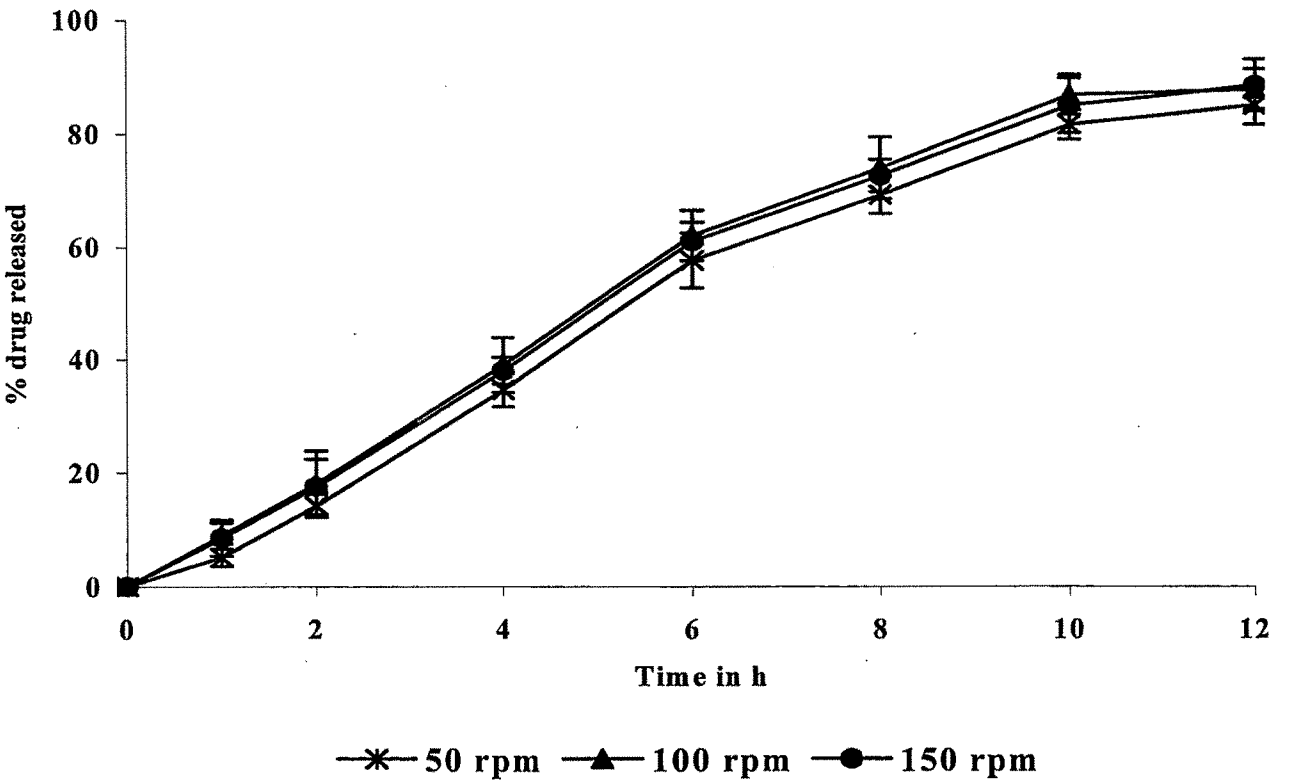


Fig. 3.4.8 In-vitro release profile of Glipizide (GZ) SPOP tablets-Effect of agitational intensity

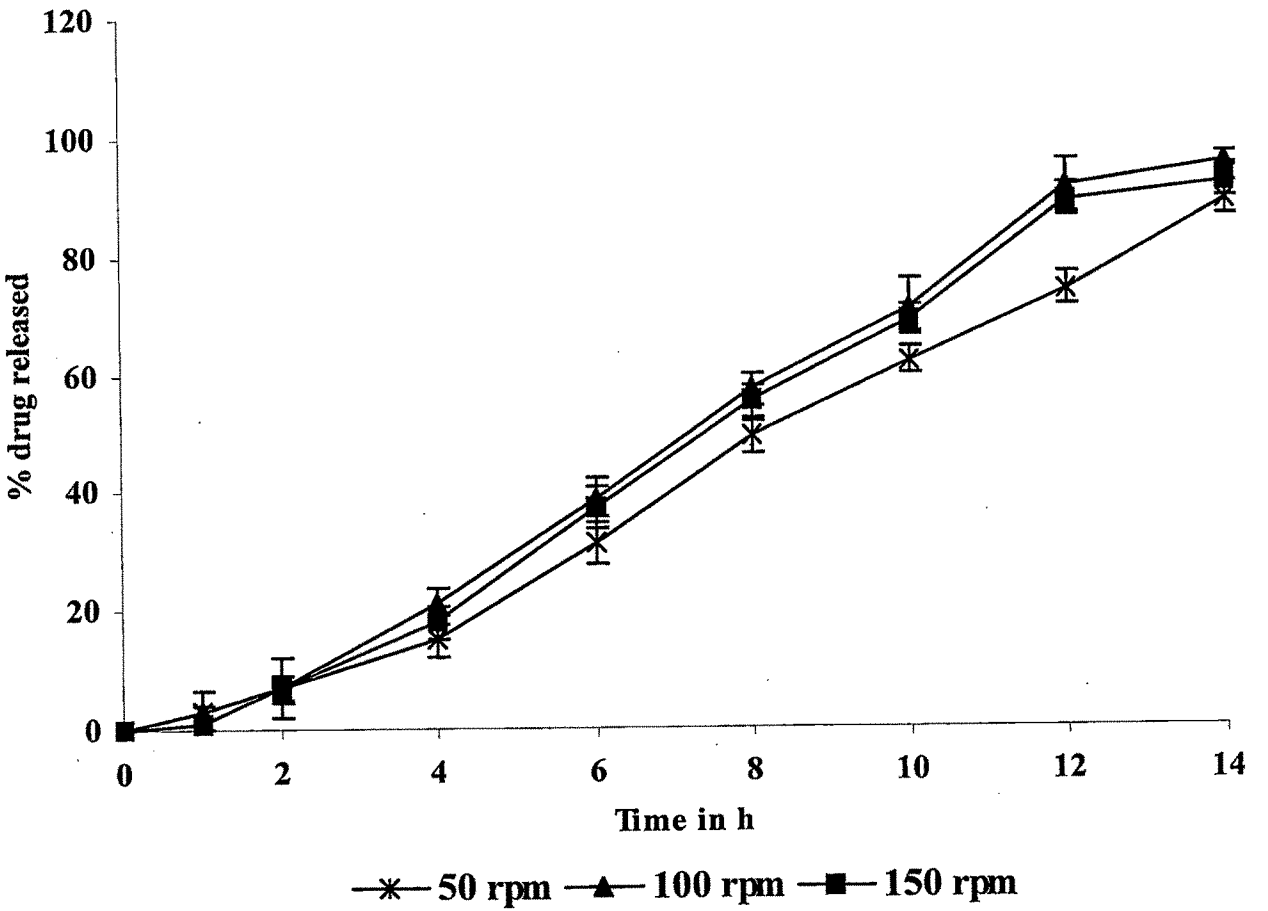


Fig. 3.4.9 In-vitro release profile of Metoprolol tartrate (MT) MOTS tablets-Effect of agitational intensity

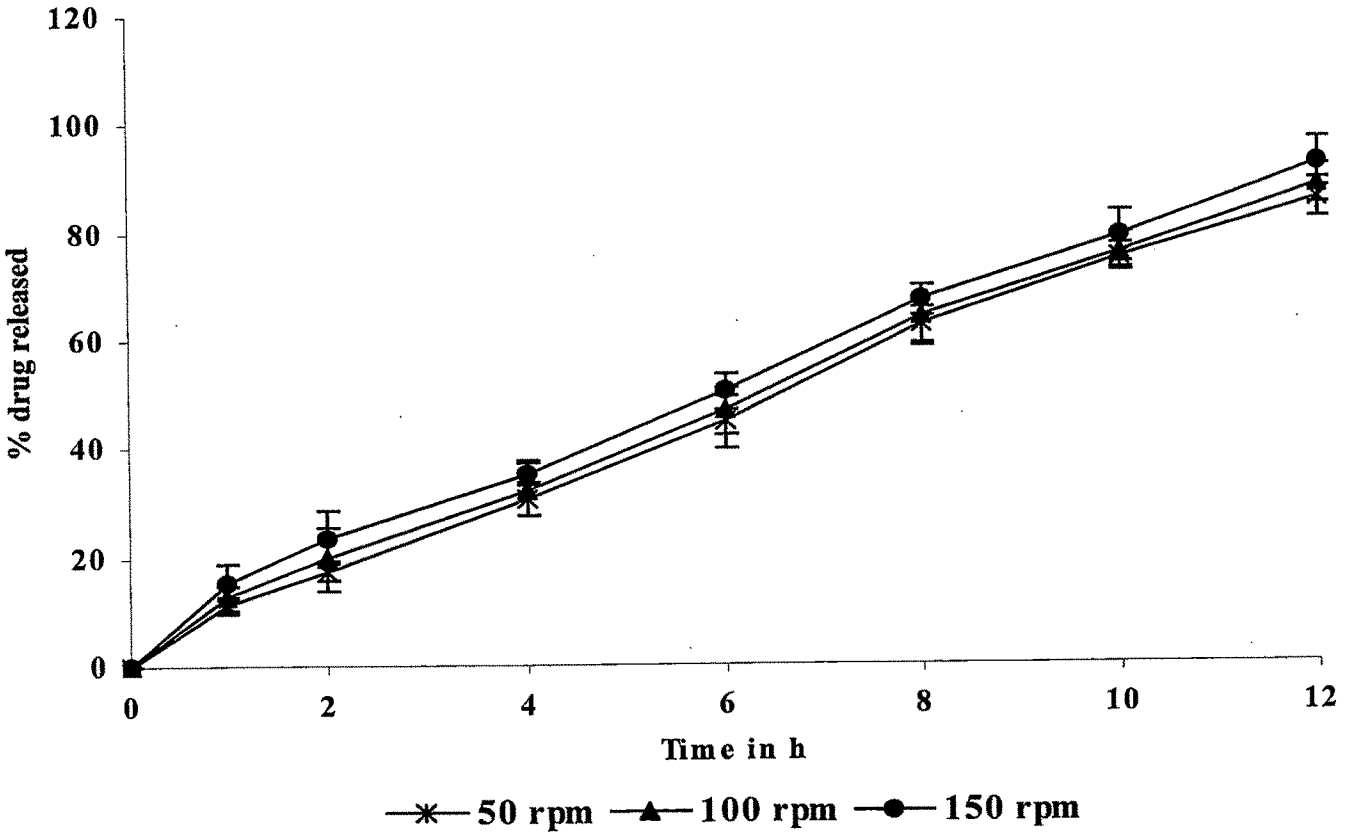


Fig. 3.4.10 In-vitro release profile of Nifedipne (NP) MOTS tablets-Effect of agitational intensity

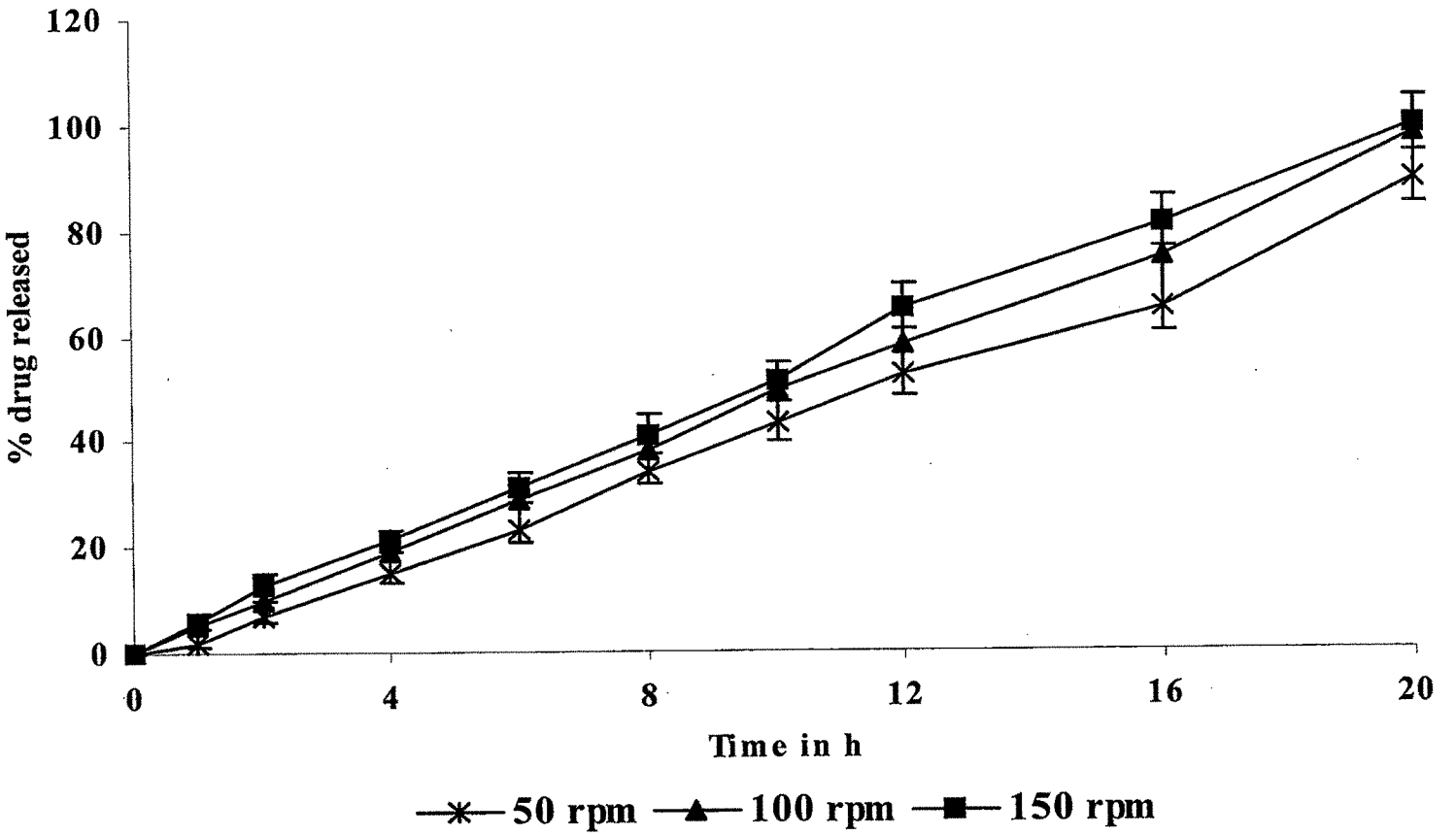


Fig. 3.4.11 In-vitro release profile of Oxybutynin chloride (OC) CPOP tablets-Effect of agitational intensity

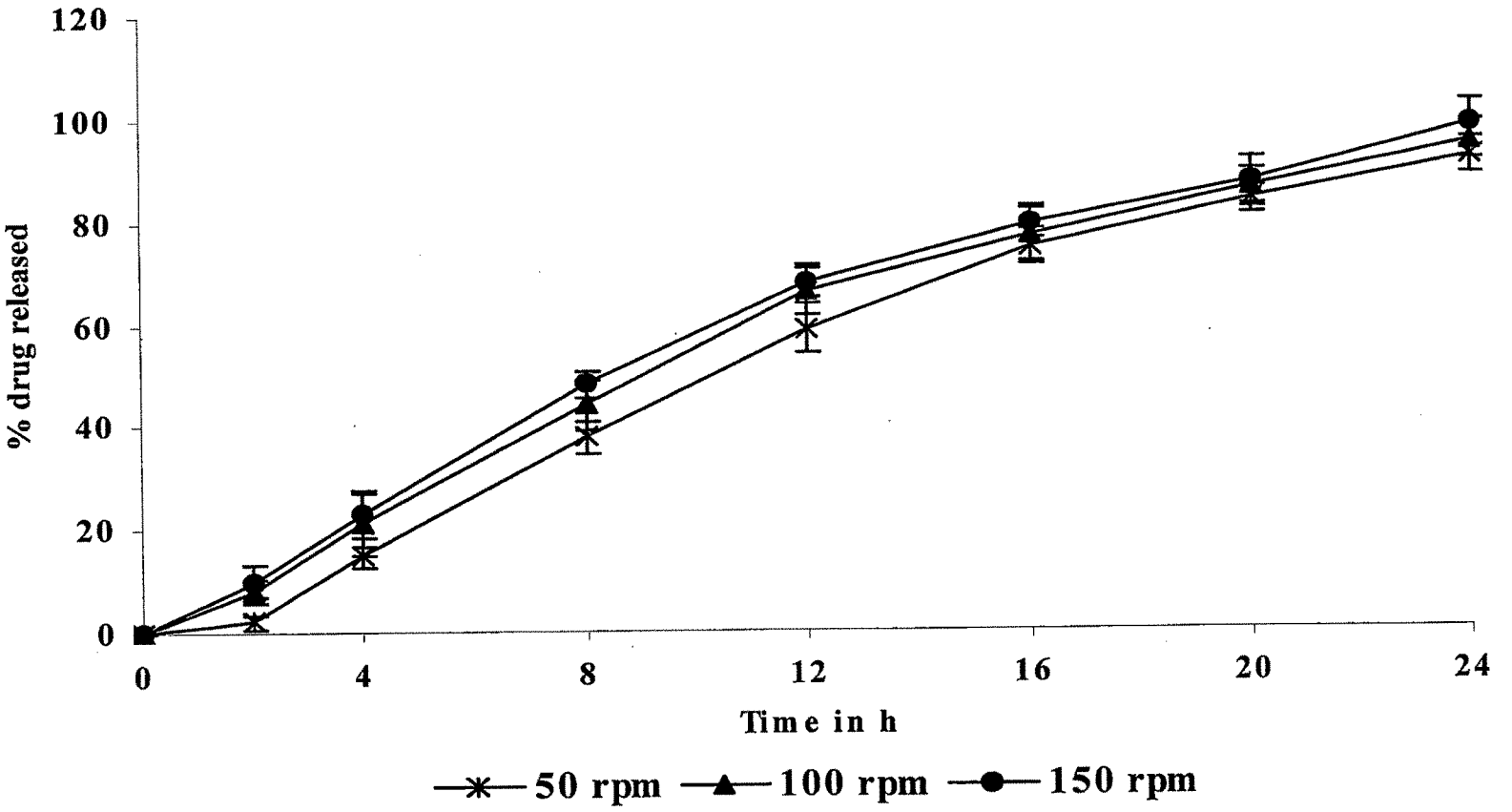


Fig. 3.4.12 In-vitro release profile of Atenolol (AT) CPOP tablets-Effect of agitational intensity

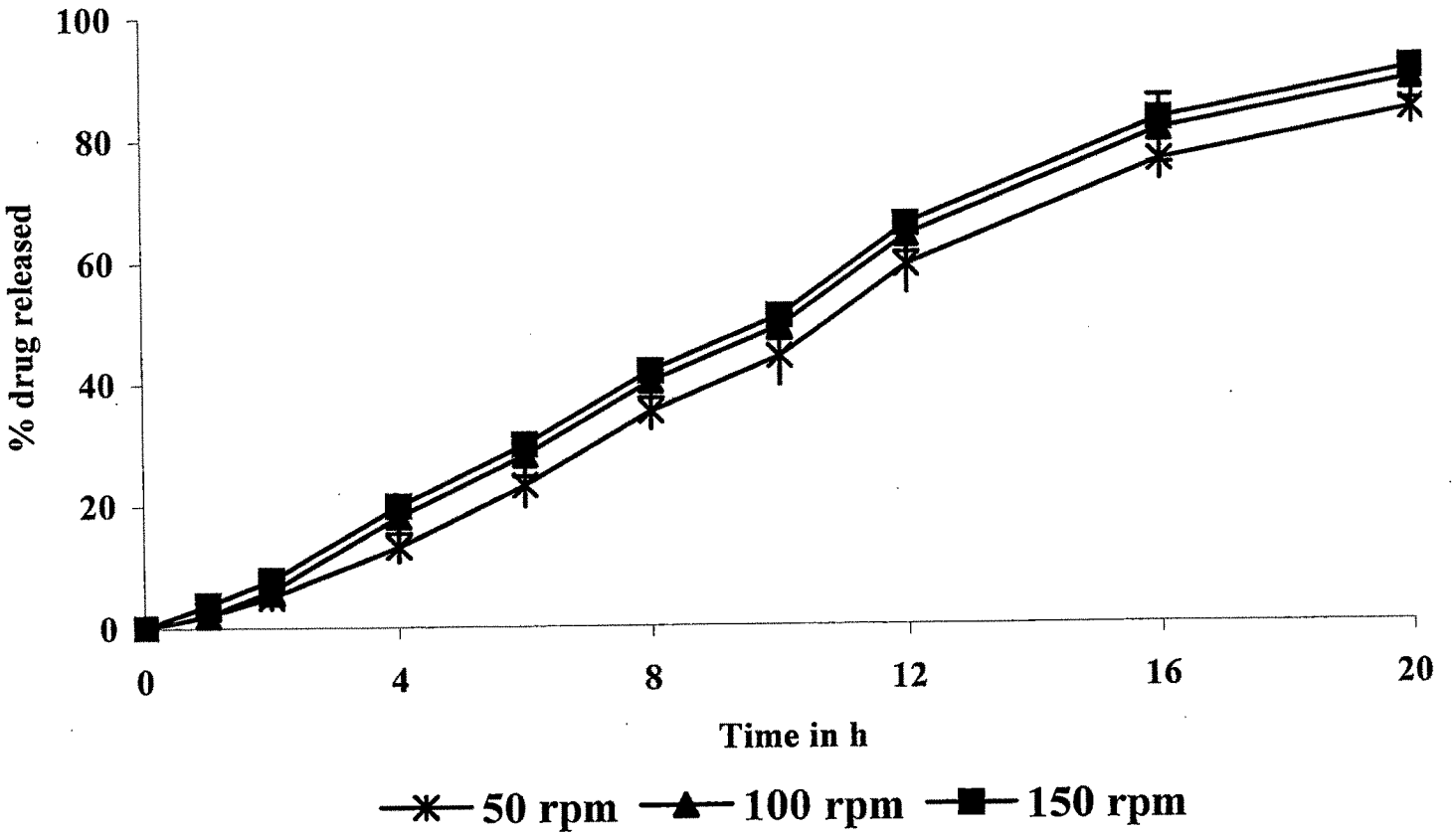


Fig. 3.4.13 In-vitro release profile of Venlafaxine HCl (VH) SPOP tablets-Effect of osmotic pressure

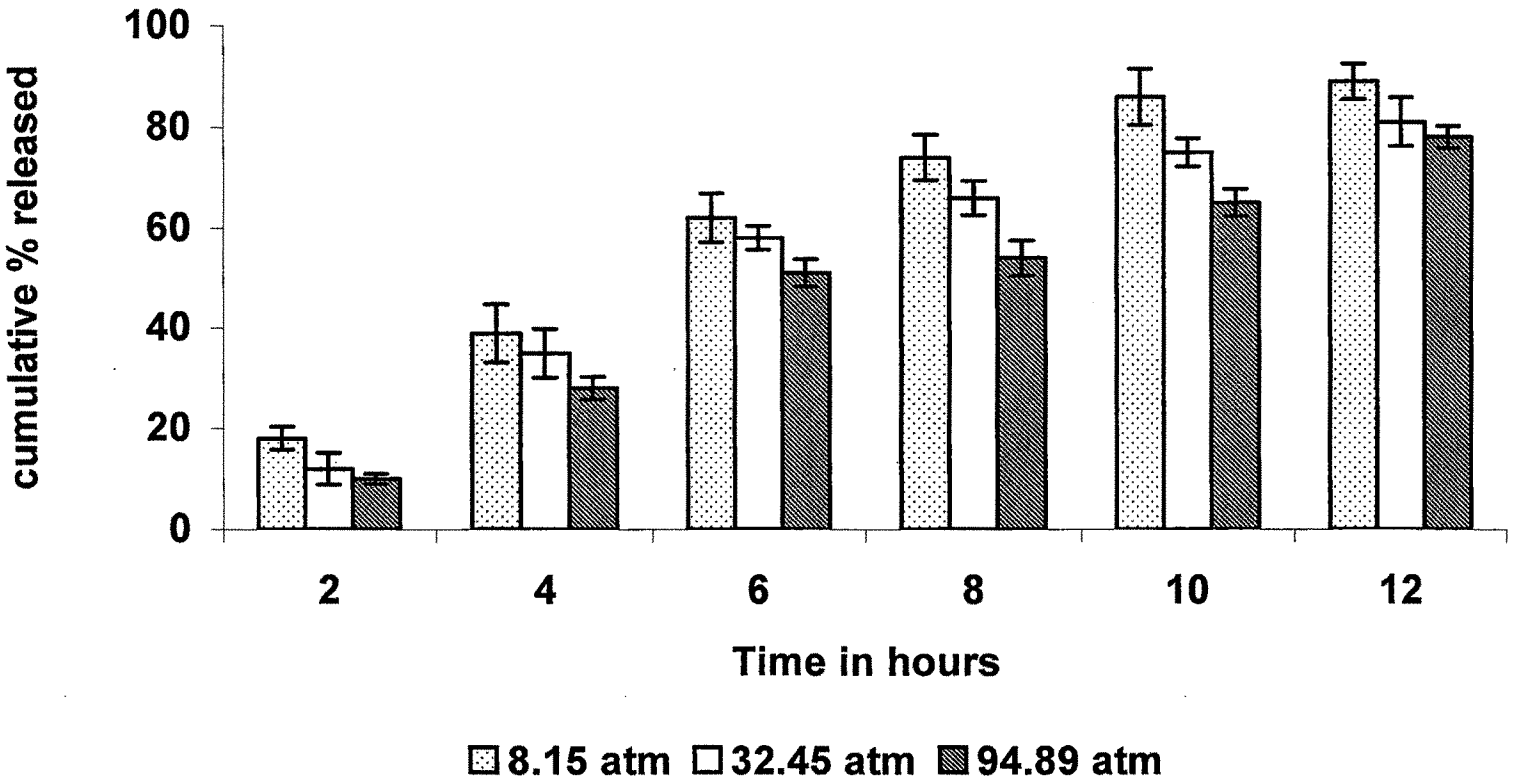


Fig. 3.4.14 In-vitro release profile of Glipizide (GZ) SPOP tablets-Effect of osmotic pressure

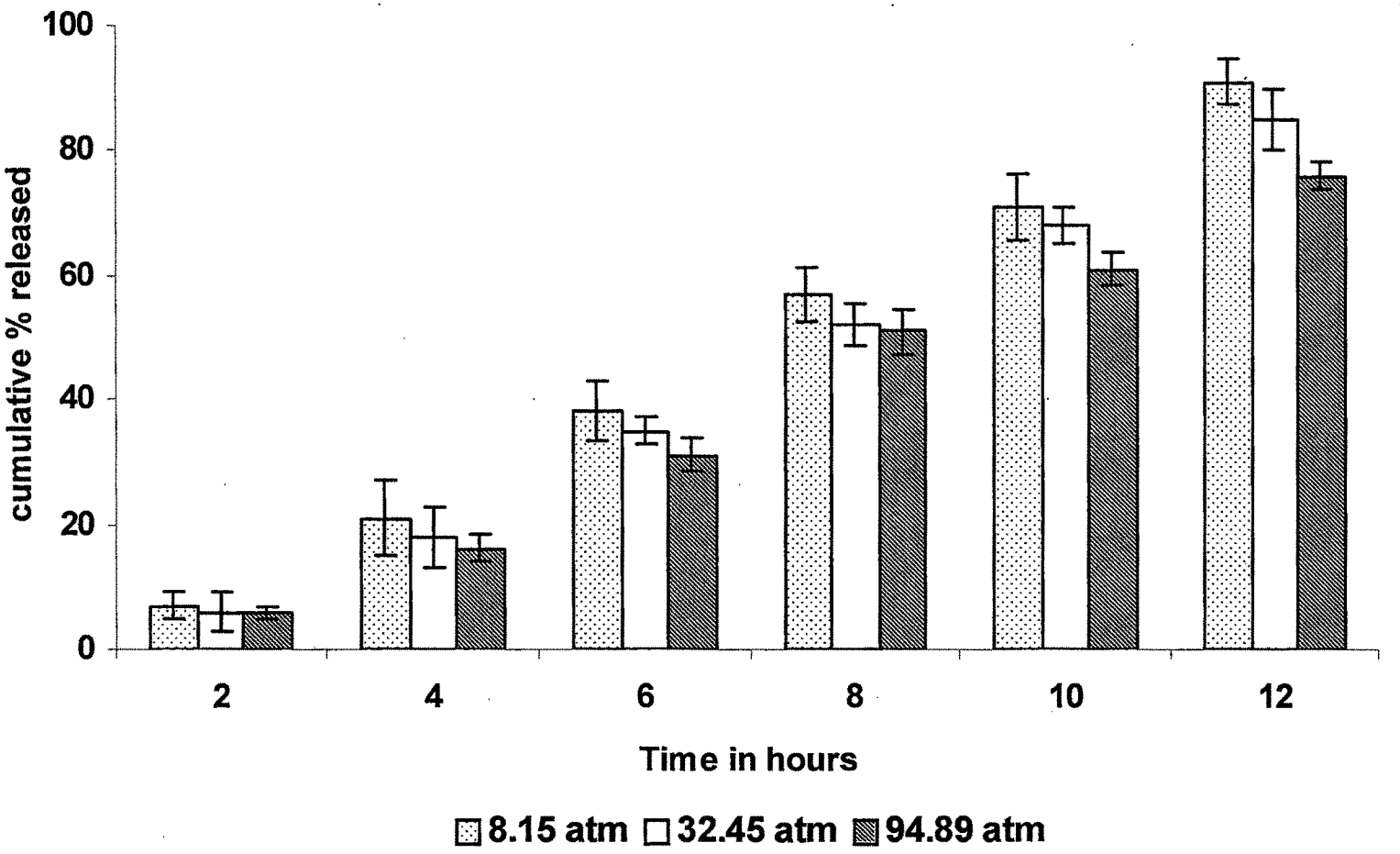


Fig. 3.4.15 In-vitro release profile of Metoprolol tartrate (MT) MOTS tablets-Effect of osmotic pressure

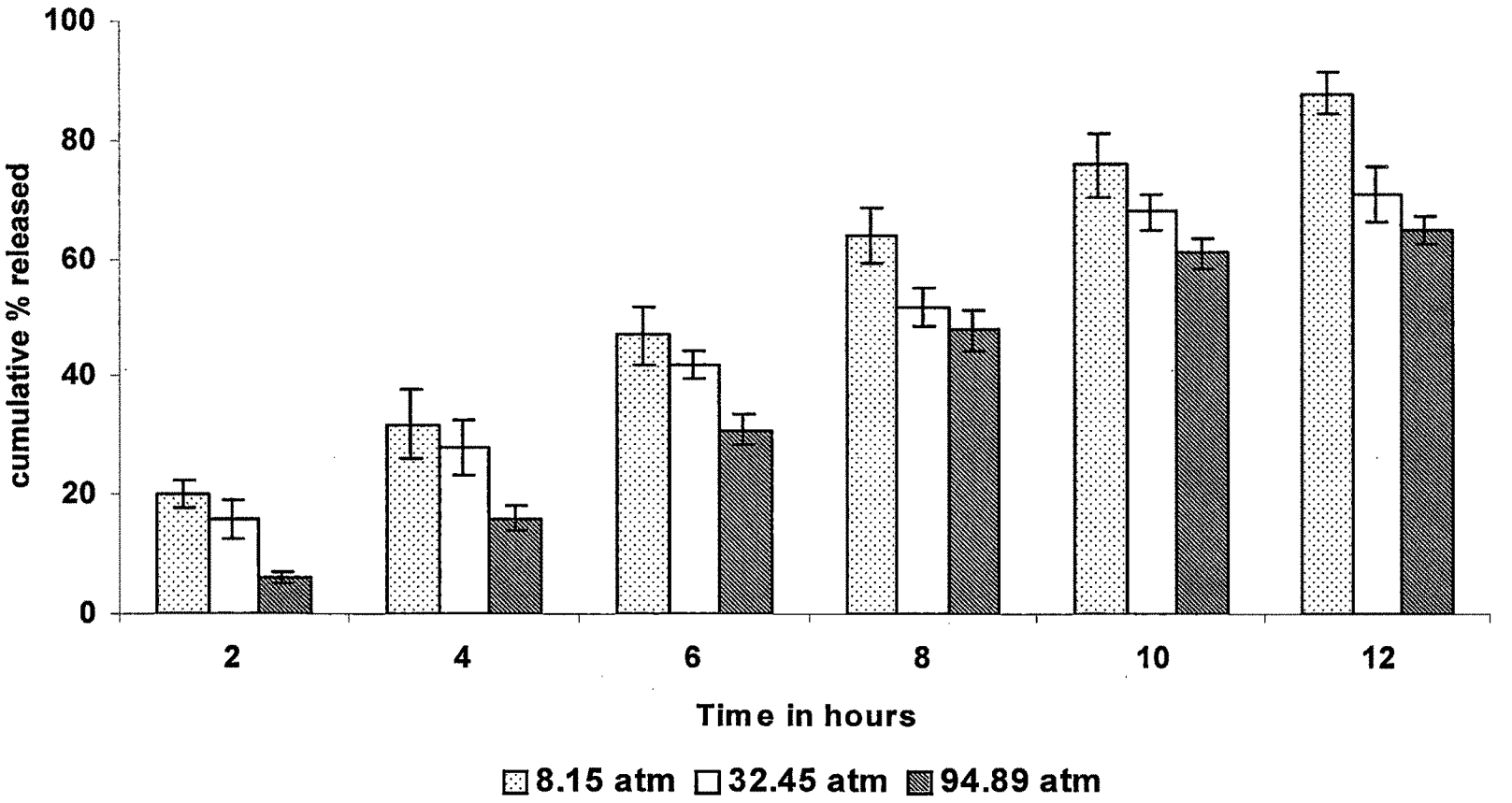


Fig. 3.4.16 In-vitro release profile of Nifedipine (NP) MOTS tablets-Effect of osmotic pressure

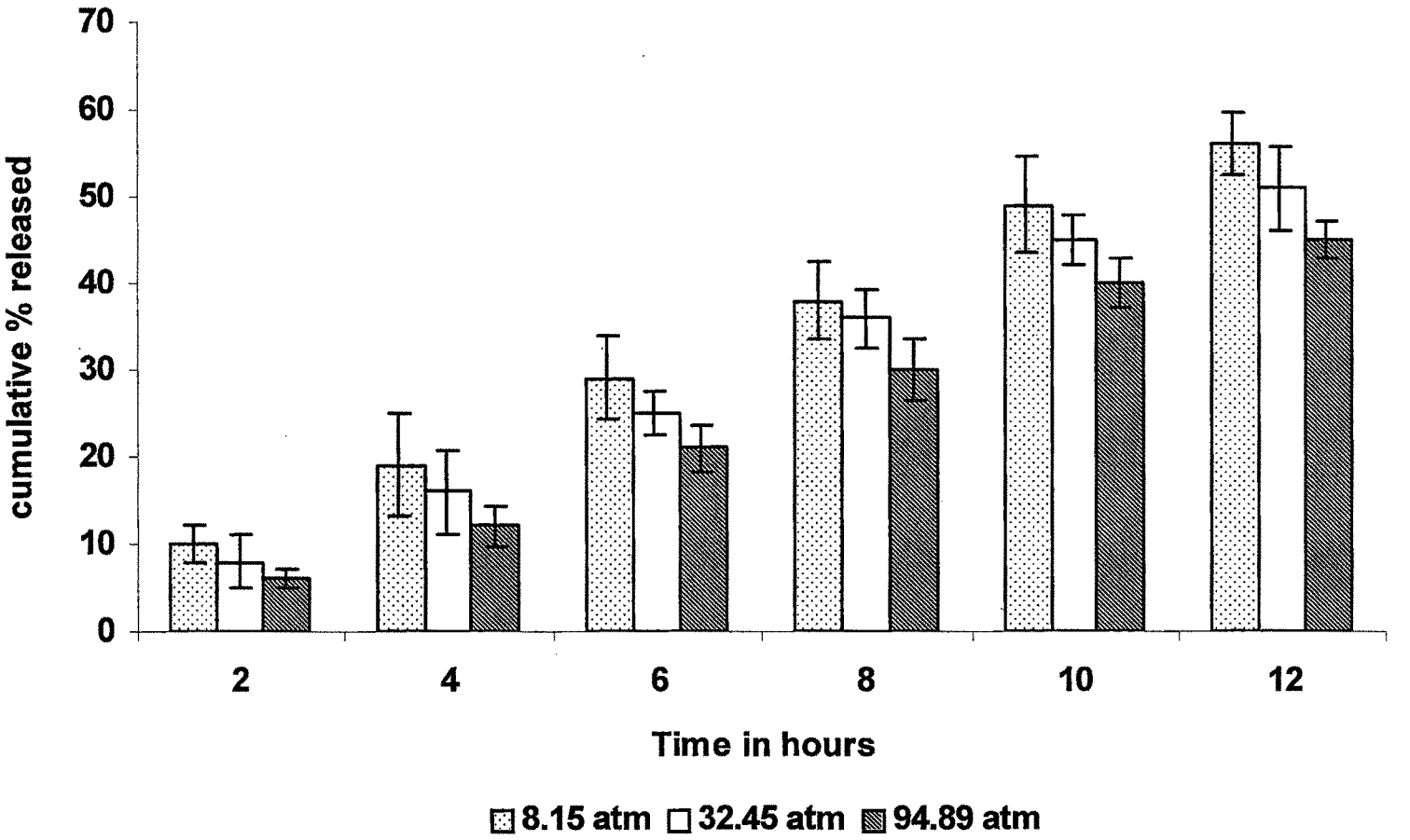


Fig 3.4.17 In-vitro release profile of Oxybutynin chloride (OC) CPOP tablets-Effect of osmotic pressure

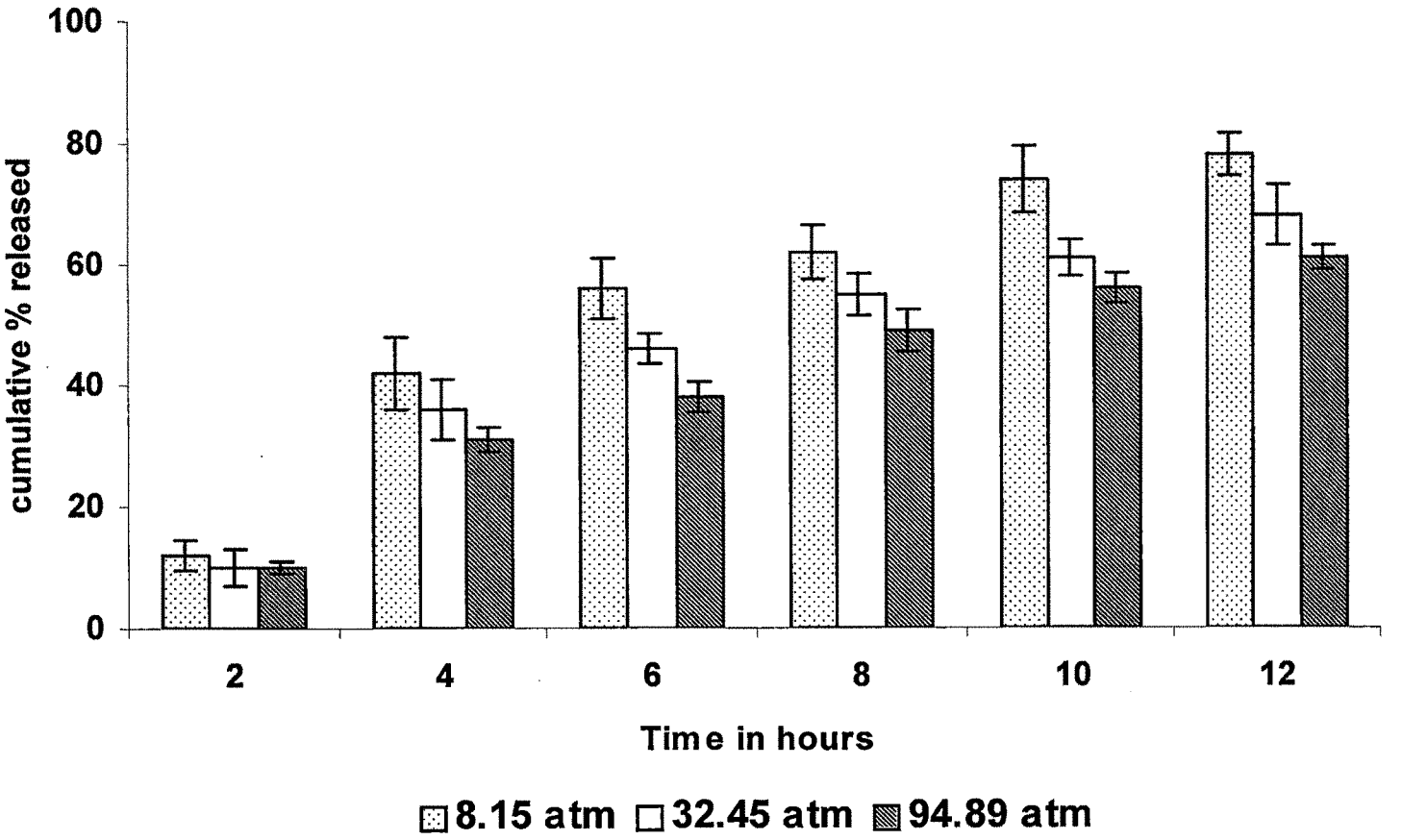


Fig. 3.4.18 In-vitro release profile of Atenolol (AT) CPOP tablets-Effect of osmotic pressure