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Design & characterization of timolol maleate Osmotic drug delivery system

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ABSTRACT

The purpose of this study was to design and evaluate Push-Pull Osmotically Controlled Drug Delivery system of Timolol Maleate. Push pull osmotic tablets are bilayered tablets consisting of pull layer (drug layer) and push layer (polymer layer) coated with semi permeable membrane containing water leaching pore forming agents. Timolol Maleate is an oral antihypertensive agent which belongs to BCS class II drug with half life of 4 hours. Main objective to formulate this system was to achieve zero order release. The present study was also aimed to develop a system that would reduce the frequency of dosing and thus increases patient compliance. In this study an attempt was made to design formulations by using Stat-Ease design expert 9software. Opadry CA was used as film forming polymer. Sodium chloride was used as osmotic agents. This system was developed in two stages: (a) Formulation of core tablet & (b) coating of tablet core. Core tablets were evaluated for content uniformity, hardness, & weight variation while coated tablets were evaluated for film thickness and *In Vitro* release study. All the post compression and pre-compression parameters showed within limits. Selected formulation F2 having Polyox N-80 73.5% successfully retarded drug release for 24hrs and drug release follows Zero order kinetic with R^2 value of 0.987. The Korsmeyer-Peppas equation showed the R^2 value to be 0.918 and n value was 0.639 following Zero Order & Anomalous (Non-Fickian Diffusion).

Keywords: Push-Pull Osmotically Controlled Drug Delivery system, Bi-layered tablets, Stat-Ease design expert 9software, Zero order, and Korsmeyer-Peppas equation.

INTRODUCTION

The oral route for drug delivery is the most popular, desirable, and most preferred method for administrating therapeutically agents for systemic effects because it is a natural, convenient, and cost effective to manufacturing process. In these systems [2], drug dose and dosing intervals are optimized to maintain the drug concentration within the therapeutic range, thus ensuring efficacy

with minimum toxic effects. Osmotically controlled drug release formulations deliver drug due to the difference in osmotic pressure within and outside the osmotic pump [1].

The release rate from this system is not affected by gastric pH and other hydrodynamic conditions. Also, release characteristic can be easily adjusted by optimizing the release parameters [3]. To maintain the drug concentration within the therapeutically effective range, it is often necessary to take these types of dosage forms several times a day [4]. Controlled drug delivery has taken an important place in pharmaceutical development, improving the tolerability and patient compliance with prescribed dosing regimens [5]. Despite the predominant use of polymer-based systems, alternatives have been developed to decrease the influence of the various physiological factors that occur following food intake or that are dependent on patient age [6].

[7] One of the most promising technologies is the oral osmotically driven system (OODS). Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner [8]. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi-permeable membrane coat [9].

MATERIALS & METHODS

Materials

Timolol maleate (BP/USP) was the active pharmaceutical ingredient obtained as a gift sample from Ven Petro-Chem & Pharma (India) Pvt. Ltd., Mumbai [11, 10]. Polyox N80, Polyox WSR coagulant, & Opadry CA were used a excipents to design push pull osmotic tablets [12]. Microcrystalline cellulose (Avicel PH-101), Sodium Chloride, Poly Vinyl Pyrolodione (PVP K-30), Potassium dihydrogen ortho phosphate, Sodium hydroxide [13], Magnesium stearate and Talc were procured from S.D Fine chemicals (Mumbai, India). Isopropyl alcohol, Acetone and all the other chemicals used in the study were of analytical grade [14].

Method

Experimental Design

A number of preliminary experiments were conducted to determine the formulation and parameters by which the process resulted in controlled release push pull osmotic pump tablets [15]. A Response Surface Method (RSM) by using D-Optimality was used to optimize the formulations by using the Design Expert 9.0.3 version software, State Ease. The design consists of 4 factors at 2 levels.

Preparation of tablet core

The core tablets of Timolol Maleate were prepared by wet granulation. All the ingredients of tablet core except PVP K 30, talc, & magnesium stearate were passed through 80 mesh sieve, accurately weighed and thoroughly mixed.

The mixture was then granulated by using required quantity of PVP K 30 dissolved in sufficient quantity of isopropyl alcohol and the resulting wet mass was passed through 10-mesh sieve.

The granules were dried at 50^{o}C for 30 mins in hot air oven. Finally the dried granules were blended with magnesium stearate and talc for 10 mins in a polybag and were compressed into tablets having average 350mg using a single stroke tablet punching machine (Cadmach, India) fitted with a 10mm round concave punches with a pressure was 6 kg/cm^2 − 8 kg/cm^2.

Coating of tablet core

The core tablets of Timolol Maleate were coated with opadry CA in a modified automated pan coating machine (Cemach, Ahmadabad, India). The compositions of the coating solution used for coating of core tablets are given in Table No 4.5.

All the tablets were coated with varying concentrations of opadry CA in coating solution. Various components of the coating solution were added to the solvent mixture in a sequential manner. The component added first was allowed to dissolve before the next component was added. The rotating speed of the pan was kept 20rev/min.

The coating was performed using spray gun with nozzle diameter 1mm and the spray rate of 3-5 ml/min. Coating was continued until desired weight gain (10%) was obtained on the active tablets. In

all the cases, active tablets were dried at 50°C for 10 h before further evaluation.

RESULTS

Assay & Loss on Drying

The assay & Loss on Drying are done in accordance with the procedures adopted from Indian Pharmacoepia and values fall within the limit.

Table 1: Assay and LOD of Timolol Maleate

Drug	Preformulation Test		
Timolol Maleate	**Melting Point**	**Assay**	**Loss on Drying**
	202.6 **°C**	99.21±0.317	0.1004±0.0002%

Drug-Excipients compatibility study

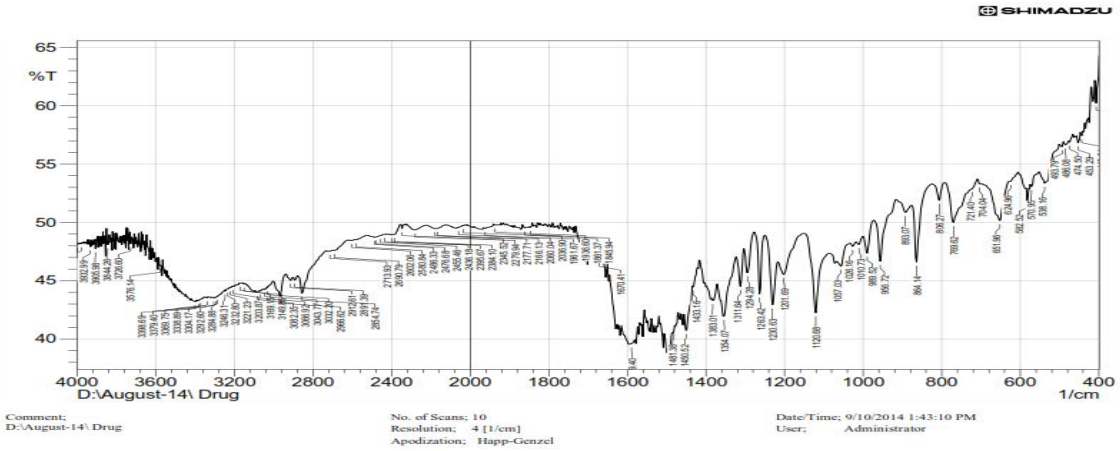


Fig.1: FTIR Spectra of Timolol Maleate Drug Sample

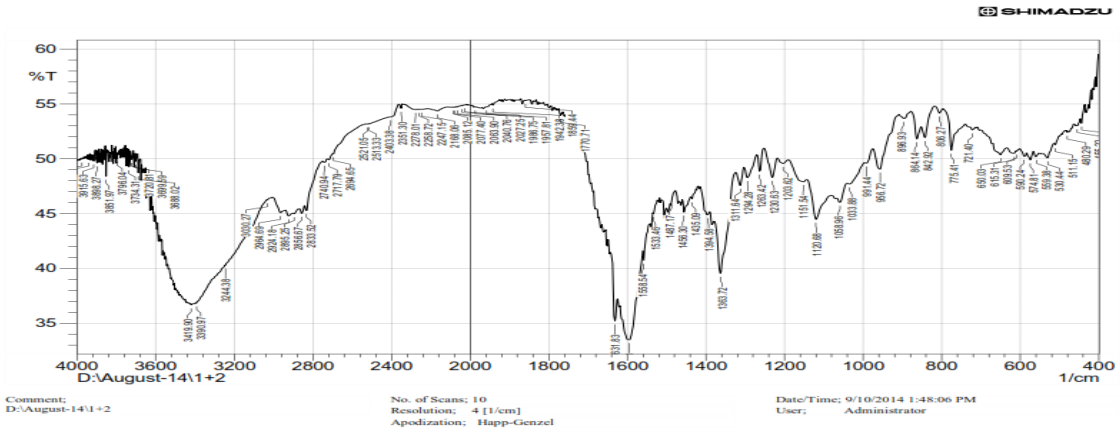


Fig.2: FTIR Spectra of Optimized Formulation (F2)

Micrometric Properties of Granules

Table 2: Micrometric Properties of Granules (Pre-compression Data)

Formulation Codes	*Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	21.21±0.03	0.44	0.52	17.18	1.22
F2	**20.28±0.06**	**0.51**	**0.58**	**13.79**	**1.16**
F3	22.65±0.05	0.54	0.61	15.12	1.19

F4	21.21±0.01	0.43	0.51	14.0	1.16
F5	22.68±0.09	0.40	0.45	11.11	1.12

Table 3: Micrometric Properties of Granules (Pre-compression Data)

Formulation Codes	*Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F6	23.62±0.07	0.43	0.52	17.03	1.08
F7	20.70±0.06	0.47	0.56	12.10	1.11
F8	21.24±0.05	0.48	0.60	18.09	1.13
F9	22.11±0.04	0.44	0.52	15.07	1.15
F10	21.09±0.02	0.42	0.51	14.05	1.17

Table 4: Micrometric Properties of Granules (Pre-compression Data)

Formulation Codes	*Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F11	22.34±0.08	0.46	0.54	12.13	1.14
F12	21.68±0.02	0.44	0.52	12.34	1.16
F13	26.43±0.006	0.475	0.566	16.07	1.19
F14	24.77±0.004	0.524	0.599	12.52	1.14
F15	26.42±0.013	0.412	0.483	14.69	1.17

Table 5: Micrometric Properties of Granules (Pre-compression Data)

Formulation Codes	*Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F16	28.19±0.006	0.488	0.537	9.12	1.10
F17	29.58±0.005	0.439	0.521	15.73	1.18
F18	28.73±0.006	0.559	0.649	13.94	1.16
F19	30.45±0.006	0.331	0.393	15.77	1.18
F20	26.43±0.013	0.362	0.428	15.42	1.18

Table 6: Micrometric Properties of Granules (Pre-compression Data)

Formulation Codes	*Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F21	19.29±0.012	0.386	0.473	18.39	1.22
F22	21.25±0.006	0.375	0.442	15.15	1.17
F23	26.27±0.005	0.434	0.497	12.67	1.14
F24	25.49±0.016	0.520	0.582	10.65	1.11
F25	27.88±0.005	0.487	0.561	13.19	1.15

*All the values represented as mean ± Standard Deviation (SD), n=3

Post-Compression Evaluation Tests

Table 7: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)	Drug Content Uniformity (%)
F1	349.8±1.48	4.12±0.052	7.50 ±0.44	0.36	98.25±1.37
F2	**350.4±0.54**	**4.16±0.074**	**7.50±0.31**	**0.39**	**100.24±1.25**
F3	348.6±0.41	4.13±0.133	5.58±0.40	0.43	99.12±2.47
F4	348.8±1.64	4.09±0.071	6.66±0.55	0.12	101.22±0.88
F5	350.6±1.14	4.14±0.084	4.25±0.57	0.54	95.28±0.80

Table 8: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate

Formulation Codes	‡ Weight Variation	* Thickness	* Hardness	Friability (%)	Drug Content Uniformity (%)

	(mg)	(mm)	(kg/cm ^{2})		
F6	3499.2±0.83	4.12±0.114	5.08±0.30	0.58	99.53±1.87
F7	350.9±0.67	4.14±0.067	5.25±0.57	0.64	93.28±1.99
F8	349.0±0.43	4.12±0.039	6.41±0.60	0.37	95.35±1.14
F9	350.5±0.80	4.98±0.88	7.00±0.44	0.77	96.34±2.18
F10	351.2±0.83	4.11±0.36	7.00±0.31	0.42	91.29±0.98

Table 9: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)	Drug Content Uniformity (%)
F11	352.1±0.93	4.06±0.46	7.50 ±0.44	0.36	98.25±1.37
F12	351.2±0.97	4.98±0.38	7.50±0.31	0.39	95.28±0.80
F13	349.2±0.83	4.25±0.37	5.08±0.37	0.48	97.35±0.43
F14	352.2±0.92	4.24±0.52	5.41±0.70	0.15	98.88±0.88
F15	352.0±1.22	4.15±0.56	4.33±0.50	0.27	94.57±1.22

Table 10: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)	Drug Content Uniformity (%)
F16	350.8±1.48	4.20±0.44	4.58±0.57	0.29	90.35±2.09
F17	348.4±1.04	4.11±0.55	4.75±0.77	0.53	99.54±2.15
F18	351.4±1.09	3.31±0.56	4.91±0.80	0.64	102.55±2.31
F19	350.7±0.65	4.95±0.75	5.08±0.86	0.71	93.78±1.56
F20	350.1±1.82	4.93±0.83	5.16±0.75	0.42	96.27±1.88

Table 11: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)	Drug Content Uniformity (%)
F21	352.3±0.84	4.33±0.59	5.25±0.67	0.66	92.55±1.56
F22	359.8±0.19	4.15±0.71	5.30±0.47	0.38	102.87±0.97
F23	349.8±0.38	4.26±0.43	5.41±0.69	0.86	100.68±1.39
F24	351.3±0.97	4.35±0.50	5.58±0.37	0.69	95.39±2.06
F25	352.9±0.90	4.31±0.44	5.66±0.65	0.37	98.90±2.31

Coating of the core tablets

Bil-ayer core tablets containing varying proportions of osmoagent and other polymers were coated with coating solution opadry CA. The tablets were coated until a desired weight gain (10%) was achieved.

The tablets were then dried at 50°C for 10 h. the tablets were then evaluated for post compression evaluation parameters. The results of which are discussed as below from Table 13- Table 17.

Table 12: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate after coating

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)
F1	379.8±1.48	5.12±0.052	7.50 ±0.44	0.36
F2	**380.4±0.54**	**5.16±0.074**	**7.50±0.31**	**0.39**
F3	378.6±0.41	6.13±0.133	5.58±0.40	0.43
F4	378.8±1.64	5.09±0.071	6.66±0.55	0.12
F5	380.6±1.14	5.14±0.084	4.25±0.57	0.54

Table 13: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate after coating

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)
F6	379.2±0.83	5.12±0.114	5.08±0.30	0.58
F7	380.9±0.67	5.14±0.067	5.25±0.57	0.64
F8	389.0±0.43	5.12±0.039	6.41±0.60	0.37
F9	380.5±0.80	5.98±0.88	7.00±0.44	0.77
F10	381.2±0.83	5.11±0.36	7.00±0.31	0.42

Table 14: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate after coating

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)
F11	382.1±0.93	6.06±0.46	7.50 ±0.44	0.36
F12	381.2±0.97	5.98±0.38	7.50±0.31	0.39
F13	389.2±0.83	6.25±0.37	5.08±0.37	0.48
F14	382.2±0.92	5.24±0.52	5.41±0.70	0.15
F15	382.0±1.22	5.15±0.56	4.33±0.50	0.27

Table 15: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate after coating

Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)
F16	380.8±1.48	6.20±0.44	4.58±0.57	0.29
F17	378.4±1.04	6.11±0.55	4.75±0.77	0.53
F18	381.4±1.09	6.31±0.56	4.91±0.80	0.64
F19	380.7±0.65	6.95±0.75	5.08±0.86	0.71
F20	380.1±1.82	6.93±0.83	5.16±0.75	0.42

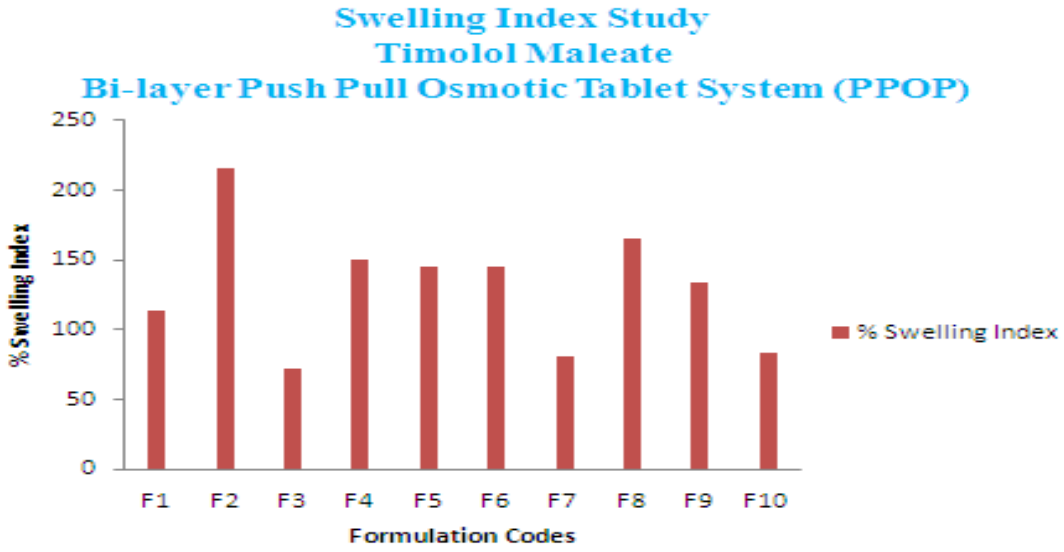
Table 16: Post compression evaluation of Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate after coating

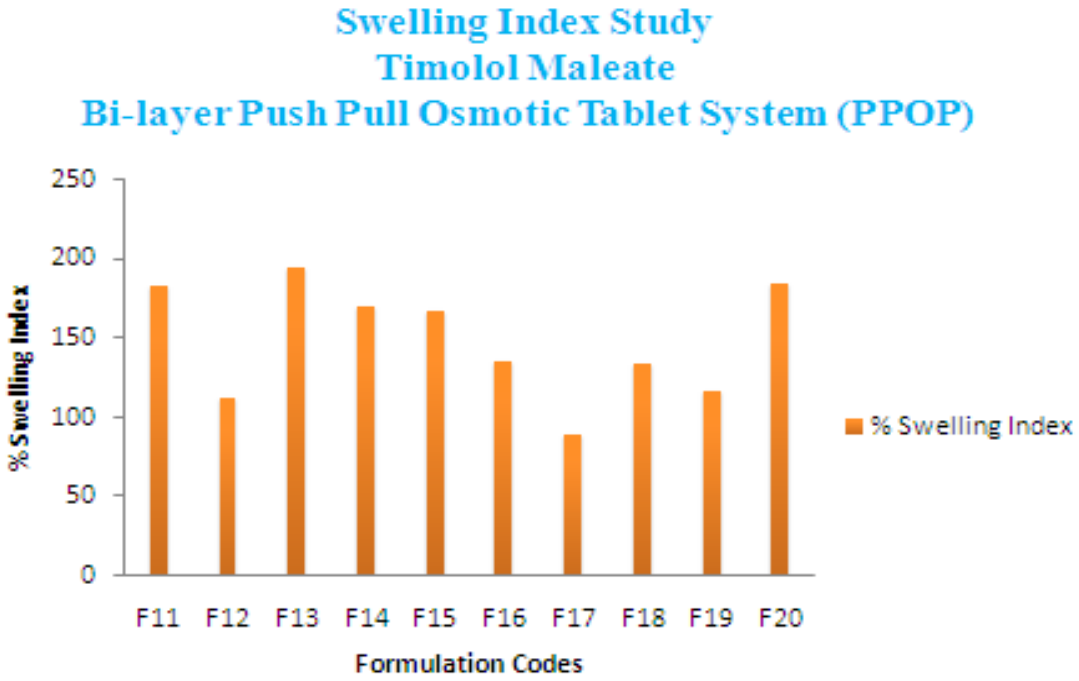
Formulation Codes	‡ Weight Variation (mg)	* Thickness (mm)	* Hardness (kg/cm ^{2})	Friability (%)
F21	382.3±0.84	5.33±0.59	5.25±0.67	0.66
F22	389.8±0.19	6.15±0.71	5.30±0.47	0.38
F23	389.8±0.38	7.26±0.43	5.41±0.69	0.86
F24	381.3±0.97	5.35±0.50	5.58±0.37	0.69
F25	372.9±0.90	5.31±0.44	5.66±0.65	0.37

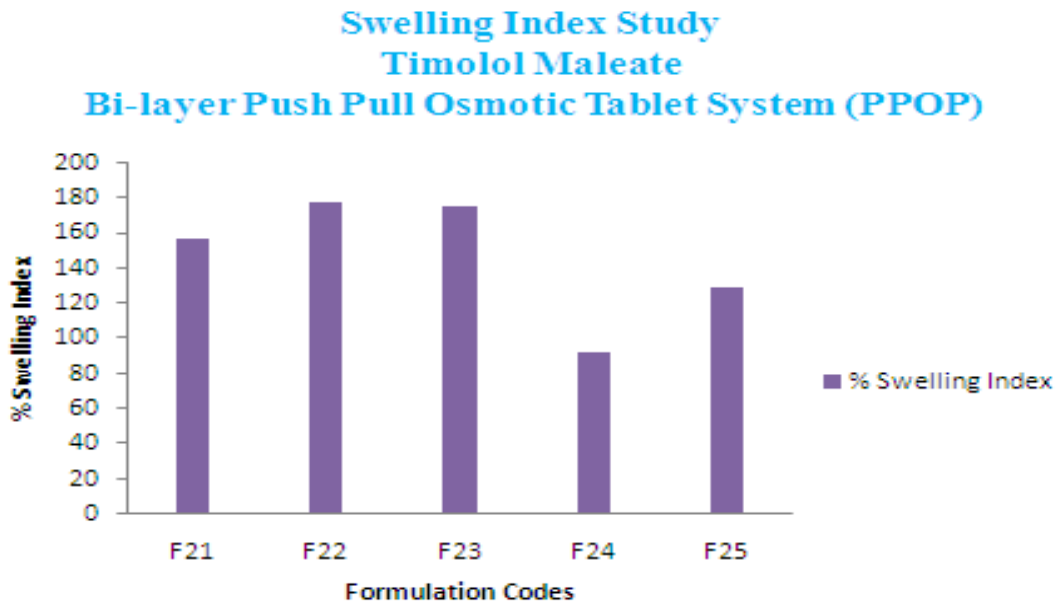
***** All the values represented as mean ± Standard Deviation (SD), n=3.

‡ All the values represented as mean ± Standard Deviation (SD), n=20.

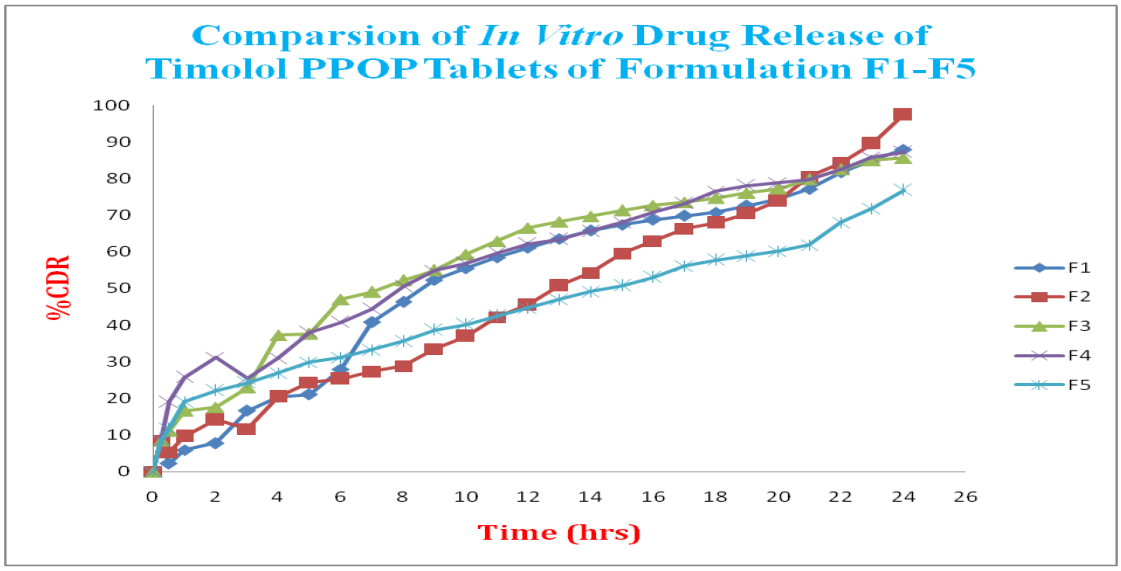
SWELLING STUDY

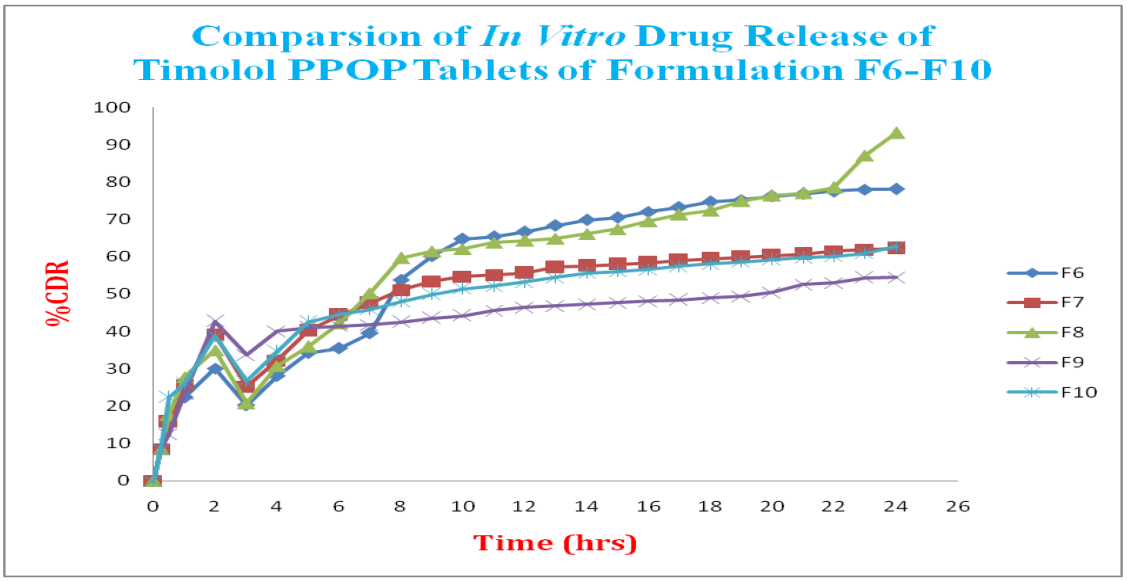






In vitro drug release studies

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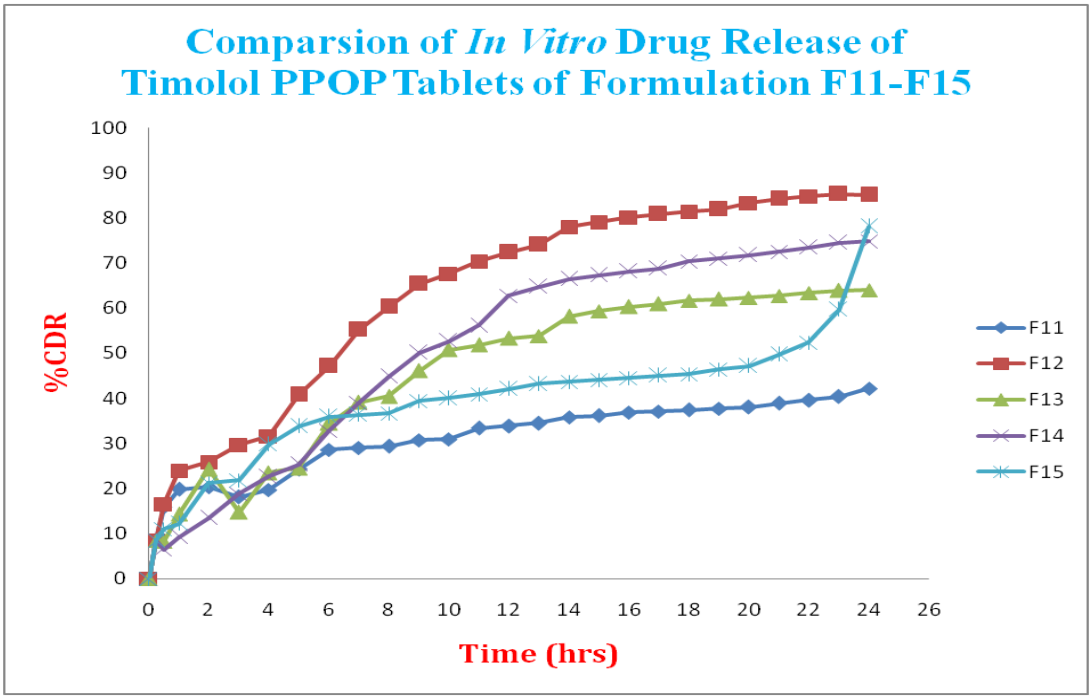
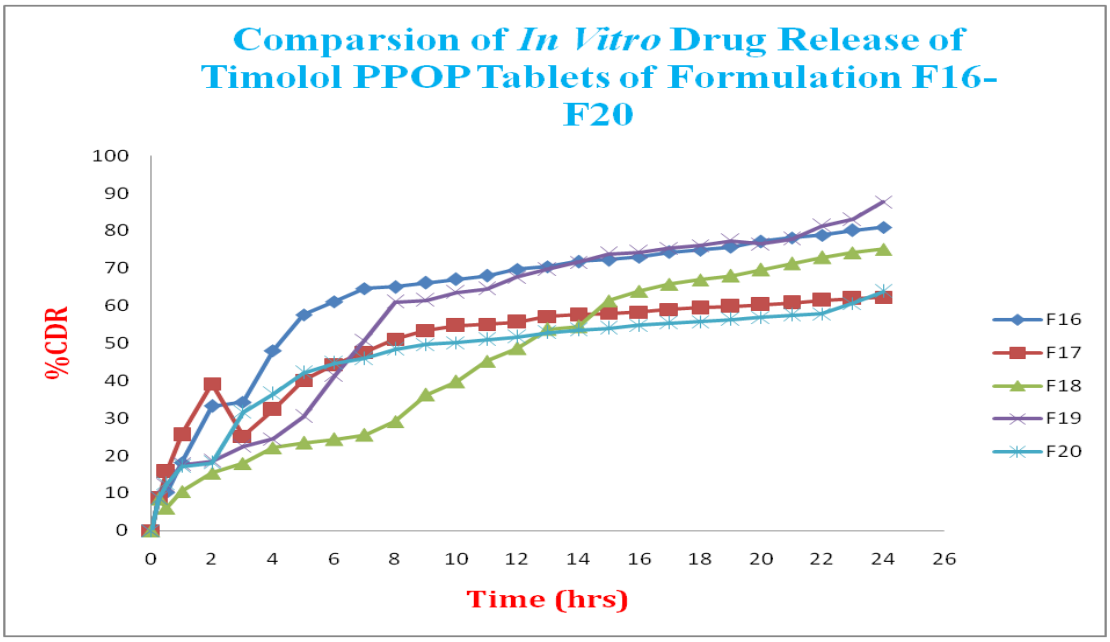
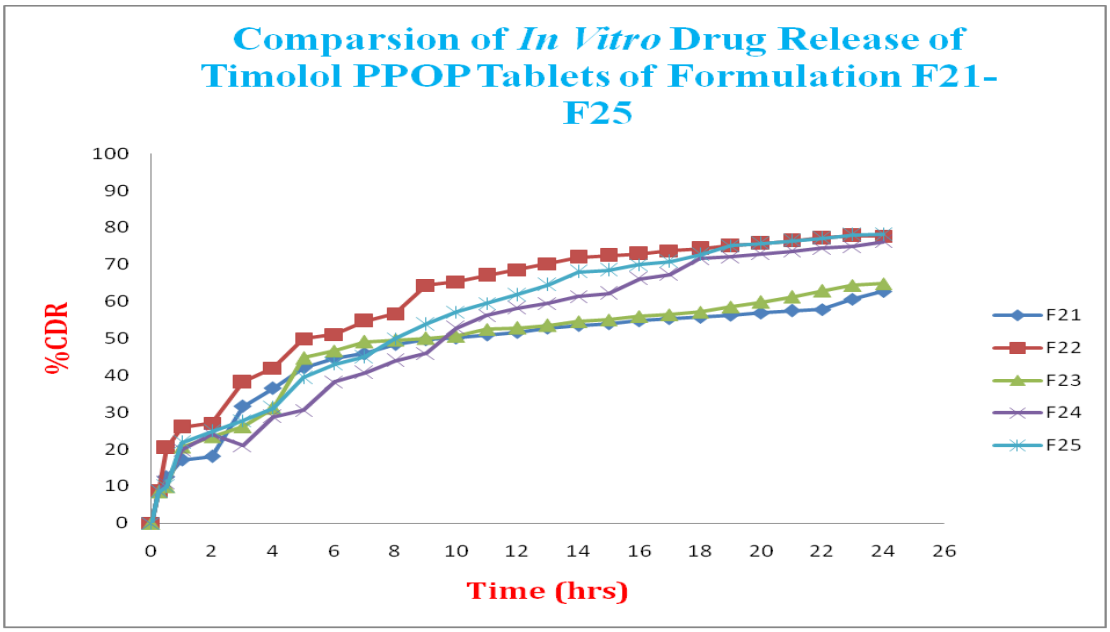
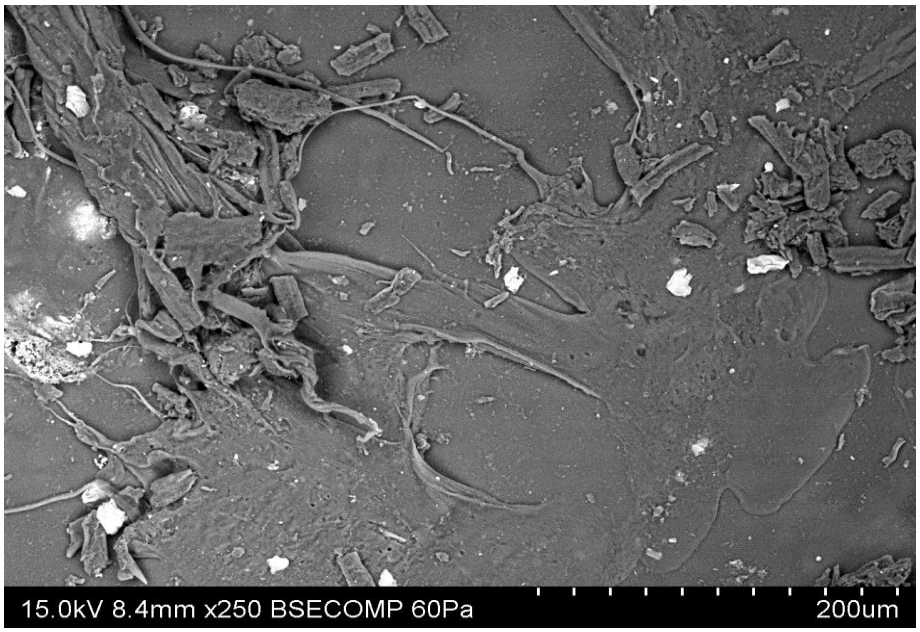
%CDR
Time (hrs)
F6
F7
F8
F9
F10


Comparsion of *In Vitro* Drug Release of Timolol PPOP Tablets of Formulation F11-F15
%CDR
Time (hrs)
F11
F12
F13
F14
F15

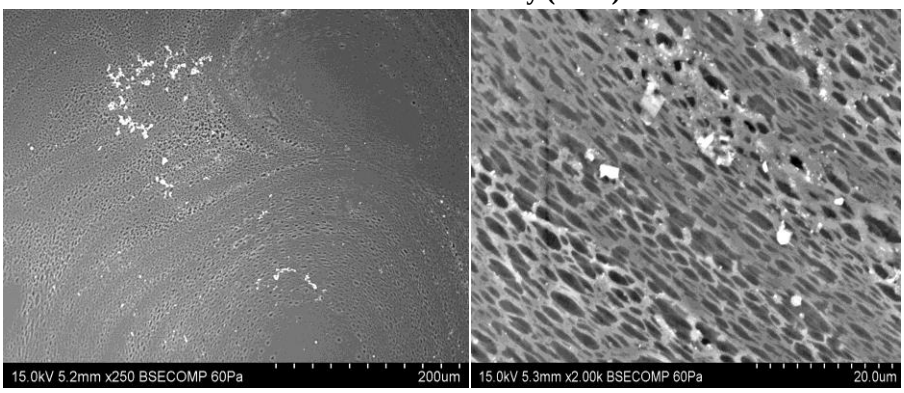

Comparsion of *In Vitro* Drug Release of Timolol PPOP Tablets of Formulation F16-F20
%CDR
Time (hrs)
F16
F17
F18
F19
F20


Comparsion of *In Vitro* Drug Release of Timolol PPOP Tablets of Formulation F21-F25
%CDR
Time (hrs)
F21
F22
F23
F24
F25

Scanning Electron Microscopy Images of Timolol Maleate Bi-layer Push Pull Osmotic Tablet System



Scanning Electron Microscopy Images of Timolol Maleate Bi-layer Push Pull Osmotic Tablet System after *In Vitro* dissolution study (Shell)



DISCUSSION

In the present work, Timlol Maleate is an Antihypertensive used in the treatment of radiating of blood vessels and glucoma, has been utilized as an active drug and it is soluble in water. An attempt has been made to timlol maleate present it in the form of osmotic tablet to provide a controlled release for prolonged period of time.

Before carrying out the formulation preformulation studies on Timolol Maleate were carried out the results of which are described as below.

PREFORMULATION STUDIES

Identification of Drug

The IR spectrum of pure drug was found to be similar to the reference standard IR spectrum of Timolol Maleate.

Table 36: IR data for estimation of Timlol Melate

S.No	Functional Group Present	Type of Vibrations	Reference Peak (cm^{-1})
1	Alcohols	**O-H Stretch**	**3200-3400**

2	Aromatic	**C-H Stretch**	**3000-3100**
3	Carboxylic Acid	**C=O Stretch**	**1630-1760**
4	Aliphatic	**C-H Stretch**	**2960-2850**
5	Aromatic	**C=C Stretch**	**1500-1600**
6	Aliphatic	**C-H Bend**	**1300-1500**
7	Alcohols	**C-O Stretch**	**1000-1200**

Melting Point

Melting point of Timolol Maleate was found to be in the range of **202.6 °C** as reported in literature, thus indicating purity of the drug sample.

Compatibility Studies

Compatibility studies of pure drug Timolol Maleate with all excipients were carried out prior to the preparation of osmotic pump tablets. I.R spectra of pure drug Timolol Maleate and combination of Timolol Maleate and excipients were obtained, which are shown in Figure No. 5.1 to 5.4. All the characteristic peaks of Timolol Maleate were present in Spectra thus indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

Calibration Graph Valsartan

The standard graph of Timolol Maleate has shown good linearity with R^2 values 0.999 and 0.999 in 0.1N Hydrochloric acid (Fig.26) and phosphate buffer pH 6.8 (Fig. 25) respectively, which suggests that it obeys the "Beer-Lambert's law" over this concentration range. The λ_{max} valsartan was found to be **294.4 nm** and **295nm** in phosphate buffer pH 6.8 and Ethanol-Water Mixture respectively.

Micrometric Properties of Granules

The Micrometric properties of granules for Bi-layer Push Pull Osmotic Tablet System (PPO) of Timolol Maleate were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio

- Angle of repose (**θ**) was found to be within 20° - 30° and Carr's index values were less than 21 for all granules of all formulations indicating good to fair flowability and compressibility.
- Hausner's ratio was found to be less than 1.25 for granules of all formulations indicating good flow properties.

Formulation development of osmotic tablet

The osmotic tablets of Timolol Maleate were prepared using wet granulation method.the osmogen layer was blended by direct compression.

Post-Compression Parameters of Matrix Tablets

The results of the weight variation, hardness, thickness, friability and drug content of the prepared matrix tablets of valsartan are given in table20.

- All the tablets of prepared formulations are compiled with the official requirements of weight variation as per I.P and U.S.P as their weights varied above 324mg i.e., ±5%.
- The hardness of the tablets ranged from 6-7 kg/cm^2 before coating and after coating and the friability values were found to be less than 0.8% indicating the prepared tablets were compact and hard thus they can withstand mechanical hazards.
- The thicknesses of the tablets were ranged from 3.31-4.95 mm.
- All the formulations satisfied the content of the drug as they contained 90-102 % of variation and good uniformity in drug content was observed.
- Thus all the physical attributes of the prepared matrix tablets were found to be practically within control.

Coating of the core tablets

Bil-ayer core tablets containing varying proportions of osmoagent and other polymers were coated with coating solution opadry CA. The tablets were coated until a desired weight gain (10%) was achieved.

The tablets were then dried at 50°C for 10 h. the tablets were then evaluated for post compression evaluation parameters. The results of which are discussed as below.

Swelling Study

The swelling studies were conducted for all formulations i.e., F1 to F25. Since, the rate of swelling is related and may affect the mechanism and kinetics of the drug release, the penetration of the dissolution medium of the matrix tablets was determined. Maximum swelling was observed in formulations F2. The swelling index of the tablets from each formulation (F1 to F25) was evaluated and the results are provided in Table 26.

In vitro drug release studies

The developed formulations of Lornoxicam were subjected to ***in vitro*** dissolution studies using USP-Type I dissolution apparatus in two media i.e. 0.1N Hydrochloric acid pH 1.2 for 2 hrs and in Phosphate buffer pH6.8 (SIF) after 2 hrs in order to simulate the conditions prevalent in the gastrointestinal tract.

All the formulations released more than 50% of drug after 24 hrs and F2 showed the highest release amongst all, hence was considered as best optimized formulation and was further evaluated for effect of various formulation variables affecting drug release from the osmotic pump tablets which are discussed as below.

Kinetic Data of *In vitro* Dissolution Data

The release rate kinetics data for the **F2** is shown in table 26 and table 27. As shown in figures 31-34, drug release was best explained by Zero-order equation, as the plots showed higher linearity ($r^2=0.987$), followed by Korsmeyer - Peppas ($r^2=0.920$) and Higuchi plot($r^2=0.918$) and first order ($r^2=0.764$). As the drug release was best fitted in the Zero order kinetics, indicating that the rate of drug release is concentration independent.

Mechanism of Drug Release

For Korsmeyer – Peppas equation indicated a good linearity ($r^2=0.920$). The diffusional exponent **"n"** was 0.639, which appears to indicating the release of drug polymer matrix formulations was found to be **Anomalous (Non-Fickian Diffusion)**.

Accelerated stability studies

The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 40^0C $\pm$ 75 % RH on optimized formulation **F2**. The formulation was found to be stable, with no change in the weight variation, thickness, and friability, hardness, drug content and *In vitro* drug release pattern. The results are tabulated in table 28.

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