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Formulation and Optimization of Doxofylline Controlled Porosity Osmotic Pump Tablets by Fractional Factorial Design

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Abstract

Objective: The objective of this study was formulation and optimization of doxofylline Controlled Porosity Osmotic Pump Tablets by using Fractional Factorial design with an aim to achieve zero-order release and to reduce dosage frequency. **Methods:** Doxofylline core tablets were formulated with Hydroxy Propyl Methyl Cellulose K100M, Polyvinyl Pyrrolidone K30 and Potassium chloride, sodium chloride as Osmogens. Core tablets were coated with Cellulose Acetate as Semi-permeable membrane, Sorbitol and Polyethylene Glycol 400 as pore-forming agents. Formulations were optimized by using Fractional Factorial design, with the effect of formulation variables like a different ratio's of osmogens and polymer concentration in the core tablet. Eight formulations were developed and evaluated for physicochemical Parameters and *in-vitro* drug release. **Results:** From the *in-vitro* dissolution data formulation DF1 batch was optimized showing 100.0± 0.64 % drug release in 24 hrs and exhibited zero order kinetics. The release was independent of the pH and agitational intensity. SEM studies showed the formation of pores in Semi-permeable membrane. **Conclusion:** Optimized Doxofylline Controlled Porosity Osmotic Pump Tablets were formulated, and zero order release rate was obtained. From the studies we can conclude that increase in polymer concentration drug release was decreased and with increase in concentration of osmotic agent increased drug release rate was observed which indicates the mechanism of drug release was due to osmotic pressure created by osmotic agent.

Keywords
Doxofylline, Osmotic system, semi-permeable membrane, pore-forming agent, *in-vitro* studies

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INTRODUCTION:

Oral route considered as most natural, convenient, and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process. Many Pharmaceutical products for oral delivery are immediate release type which does not control the release of drug and absorption. Oral controlled release systems provide the desired range of prolonged action with continuous release of active ingredients at pre-determined rate and time at the absorption site allowing maintenance of plasma concentration within the therapeutic range and reducing dosing frequency. Once daily controlled release preparation is often desirable with improved patient convenience [1].

Osmotic Controlled Drug Delivery systems (OCDDS) are new approach for controlled release dosage forms which utilizes osmotic pressure as a driving force for controlling delivery of drug.[2] Osmotic Pump system comprises of a tablet core includes

drug, an osmotic agent or osmogens and other exicipents with semi permeable membrane coat. Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body and agitational intensity of release media because of semi-permeable nature of the rate-controlling membrane. The drug release rate from systems dependent on osmotic pressure difference across the membrane, coating thickness, total area of coating and level of leachable agents in the coating. Controlled Porosity Osmotic Pump Tablet (CPOP) is a spray-coated tablet with a semipermeable membrane (SPM) containing leachable pore forming agents. The delivery system consists of drug core with osmogens surrounded by a semi-permeable membrane of cellulose acetate which is accomplished with channeling agents of water-soluble additives in the coating membrane release is achieved through the pores formed in the semi permeable wall in situ during the operation.

Doxofylline is an Anti-tussive and bronchodilator used in the treatment of Asthma and Chronic Obstructive Pulmonary disease. It belongs to the BCS Class III drug, oral bioavailability 63%, half-life 6-8hrs with dose 200-400 mg twice or thrice a day[3]. The present study aimed to formulate the Controlled release of 600 mg Doxofylline CPOP tablets as a once daily medication in order to reduce dosing frequency to the conventional 200 mg taken thrice daily with the goal to enhance patient compliance towards therapy. CPOP Doxofylline Tablets containing Sodium chloride, Potassium chloride as osmogens, HydroxyPropylMethylcellulose K100 M and PolyvinylPyrrolidine K 30 as other polymers, the proportion of these exicipients were as remarkable effects of an osmotic system hence chosen as formulation variables by using Fractional Factorial Design. The effect of variables was evaluated at 2 different levels, resulting in eight drug excipient combinations. Fractional Factorial Design used to examine simultaneous multiple factor determination of the effects of several factors & their interactions efficiently with fewer runs. These designs reduce the cost of experimentation.

MATERIALS AND METHODS

Materials

Doxofylline was obtained from Aurobindo Drugs Pvt. Ltd. India. Cellulose acetate was obtained from Hi-media chemicals, Potassium chloride and Sodium chloride, Hydroxy Propyl Methylcellulose K 100 M were from Fine chemicals, polyvinyl Pyrrolidone K 30 purchased from S.D Fine chemicals. Other solvents and reagents used were of Analytical grade.

METHODS

Compatibility studies

Differential Scanning Calorimetry (DSC)

The Compatibility of drug with the excipients used for the formulation development was tested using DSC. Individual samples as well physical mixture of drug and excipients were weighed about 5mg in DSC pan and crimped and scanned in the temperature range of 50°C to 300° C. Heating rate of 20° min^{-1} was used and the thermogram obtained was reviewed for evidence of any interactions with absence or change of drug peak indicates the interactions between drug & excipients. Then the Thermograms were compared with pure samples versus optimized formulation. DSC Thermograms were recorded by using PerkinElmer DSC 4000 Apparatus.

Fourier Transform infrared Spectroscopy (FTIR)

FTIR technique helps in pointing out the implications of the different functional groups of the drug and excipients by analyzing the significant changes in the shape and position of the absorbance bands. The FTIR of pure drug and formulation were recorded by KBr pellets method using Shimadzu Fourier Transform Infrared Spectrophotometer. [3&4]

FORMULATION DEVELOPMENT

Preparation of Doxofylline core tablet

Different ratio of polymers and Osmogens were chosen as formulation variables Composition in Fractional Factorial Design (2^{4-1}). Different core formulation of doxofylline were shown in Table1 and formulated by wet Granulation Technique. Accurately weighed [5] quantities of drug (doxofylline), polymer (HPMCK100M), Osmogens(Soduim chloride & Potassium Chloride) and diluent MCC were mixed in a mortar. Required quantity of binder (PVP K 30) in hydroalcholic 3% solution was added and mixed thoroughly to form a mass suitable for granulation. The dough mass was passed through sieve No.18 and dried in a hot air oven at 60°C for (15-30minutes). The dried granules were mixed with required quantities of lubricant (talc) and glidant (magnesium stearate) and were compressed to form tablets in a 16-station rotary tablet machine (Riddi, Ahmedabad, India) using 12mm concave punches. The total weight of each tablet was 960mg and containing 600mg of Doxofylline.

Coating of core tablets

The Core tablets of Doxofylline [6] were coated with semi permeable membrane (cellulose acetate) containing Sorbitol and PEG 400 as pore forming agents in an R& D coating Pan (VJ instruments, New

Delhi, India). The coating solution was prepared by taking the solvent in a glass beaker and adding the pre-weighed quantities of polymer cellulose acetate in small quantities at a time by continuous mixing and after complete solubilization of the polymer the Plasticizer and poreforming agents were added with continuous mixing. Initially pan was rotated at low speed of 6-8 rpm, inlet hot air (50^0-60^0C) when the pan gets heated, core tablet were placed in coating pan and then rotational speed of pan was adjusted to 20-30 rpm, spray rate was 1-5ml/min and the pressure of atomization was 10-15 Psi. The exhaust air temperature was 48^0C-52^0C respectively. Coated tablets were dried at 50^0C for 14hrs. The composition of Coating solution was given in Table 1.

Table 1: Formulation optimization trials of Doxofylline CPOP Tablet

Ingridents	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8
Doxofylline	600	600	600	600	600	600	600	600
HPMC K 100M	100	100	50	50	50	100	50	100
Sodium Chloride	100	100	0	100	0	0	100	0
Potassium Chloride	0	100	100	100	0	0	0	100
PVPK 30	30	50	50	30	30	50	50	50
MCC	120	0	150	70	260	200	150	120
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total Weight of core tablet (mg)	960	960	960	960	960	960	960	960
Coated Tablet (mg)								
Cellulose Acetate	35	35	35	35	35	35	35	35
Sorbitol	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
PEG 400	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Di butyl phthalate	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Acetone	300ml	300ml	300ml	300ml	300ml	300ml	300ml	300ml
Total weight of Coated Tablet (mg)	1000	1000	1000	1000	1000	1000	1000	1000
Cellulose Acetate	35	35	35	35	35	35	35	35

Effect of formulation variable on drug release (DoE Studies)

Table 2: Fractional Factorial Design (2^{4-1}):

Factor: Formulation Variables		Levels	
		-1	+1
A	HPMC K 100	50	100
B	NaCL	0	100
C	KCL	0	100
D	PVPK 30	30	50
Response			% Drug release

Evaluation of Controlled Porosity Osmotic Pump Tablet

Pre-compression Parameters of Osmotic Pump Tablets

Determination of flow property of granules

There are many formulation and process variables involved in mixing and all this can affect the characteristic of blend produced. The various characteristic properties of blend were evaluated by using Angle of repose, Bulk density, Tapped density, Carr's index, Hausner's ratio. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends.

Characterization of Controlled Porosity Pump Tablets.[7]

The prepared Doxofylline CPOP tablets were studied for their physicochemical properties like weight variation, hardness, Friabilty, thickness and drug content.

***in-vitro* drug releas studies**

The *in-vitro* drug release of Doxofylline CPOP tablets were carried out using USP Paddle-type dissolution apparatus (Electro lab, India) at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. Release studies were conducted in 0.1N HCL (pH 1.2) for the first 2 hours then, the dissolution medium was replaced with Phosphate buffer (pH 6.8). 5ml volume

Samples were withdrawn and same were replaced with fresh dissolution medium at regular intervals. Samples after filtration through membrane were analyzed with UV-Spectrophotometer at 272nm. The cumulative % drug release versus time were plotted to determine release profiles of various formulations.

Dissolution profile modeling

in-vitro drug release data were fitted to various kinetic equations. The kinetic models like zero order (% Cumulative drug release Vs time), First order (log % Cumulative drug remaining Vs time), Higuchi matrix (% Cumulative drug release Vs Square root of time)[8].

Effect of P^H on drug release from CPOP Doxofylline Tablets

Osmotically controlled release system delivers its contents independently of external environment.[9] To the study effect of P^H on drug release medium of optimized formulation, *in- vitro* drug dissolution studies were conducted in medium having different P^H of 900ml 0.1N HCL, 6.8 and 7.4 Phosphate buffer by using USP Paddle-type dissolution apparatus (Electro lab, India). Samples were withdrawn at regular intervals and analyzed by using UV-Visible Spectrophotometer (Elico, India) at 272nm. The % cumulative drug release of optimized formulation at different P^H were plotted and compared [10].

Effect of Agitational Intensity on drug release from CPOP Doxofylline Tablets

Drug release from Osmotic drug delivery system is independent of peristaltic movements of GIT which is studied by effect of agitational intensity. In this study the optimized formulation drug release profile at different agitational intensities like 50,100,150 rpm dissolution studies were performed. The % cumulative drug release of optimized formulation were plotted and compared [11].

Membrane Morphology of CPOP tablets by Scanning Electron Microscopy

To examine the changes in membrane structure of Doxofylline CPOP Tablet, surface of coated tablet SEM Analysis was conducted for the optimized formulation of Doxofylline before and after dissolution studies [12].

RESULTS AND DISCUSSION

Incompatibility studies

DSC STUDY

A DSC thermo gram of pure drug Fig (1) indicates the endothermic peak at 159.41^{0}C which corresponds to the melting point of Doxofylline. Fig (2) is the DSC Thermogram of excipients mixture. Fig (3) is the DSC thermo gram of optimized formulation showed an endothermic peak at 158.45^{0}C corresponding to drug peak and another peak at180.62^{0}C corresponds to excipients in the formulation as shown in Fig (2). As drug peak is retained in the optimized formulation this study concludes that there is no incompatibility between drug and excipients used in the formulation.

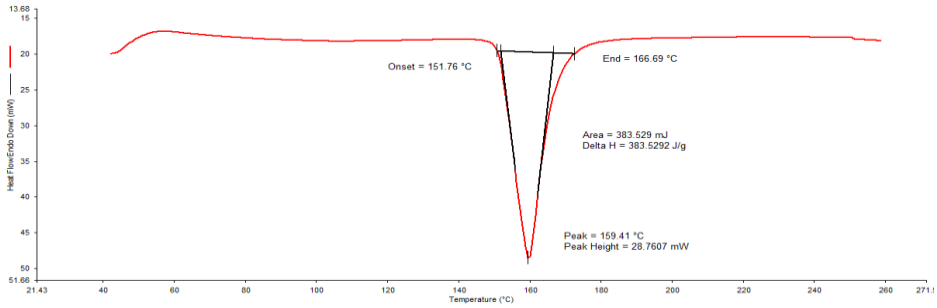


Fig. 1: DSC Thermogram of pure drug doxofylline

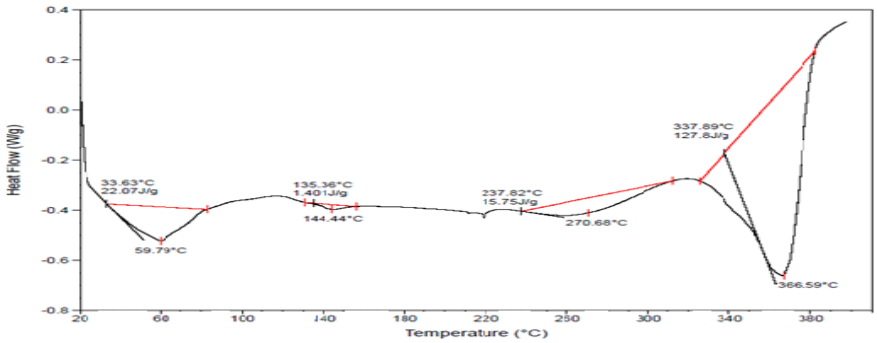


Fig. 2: DSC Thermogram of Excipients mixtures

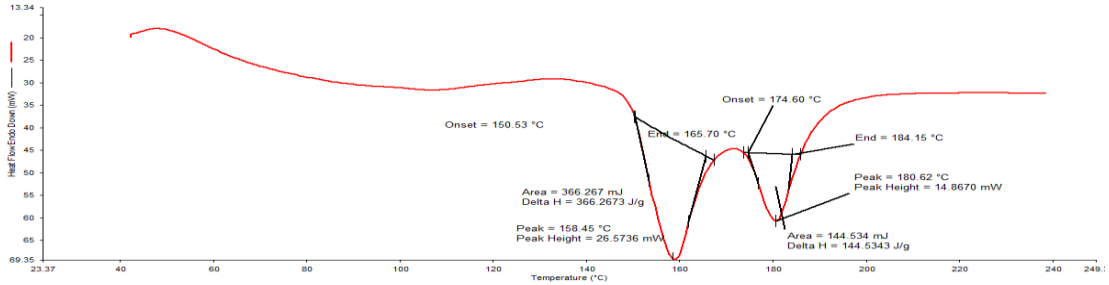


Fig 3: DSC Thermogram of Optimized formulation

Fourier Transform Infrared (FTIR) spectroscopy:
IR Spectra obtained with pure drug and optimized formulation (DF1) is shown in Fig (4& 5). Characteristic peaks of drug and excipients were obtained in optimized formulation shown in Table 3. Then the peaks of optimized formulation were compared with pure drug and excipients. As there was no interaction between the peaks of drug and excipients of optimized formulation, all characteristic drug peaks were retained in optimized formulation. This study concludes that there is no incompatibility between the pure drug and excipients used in the formulation.

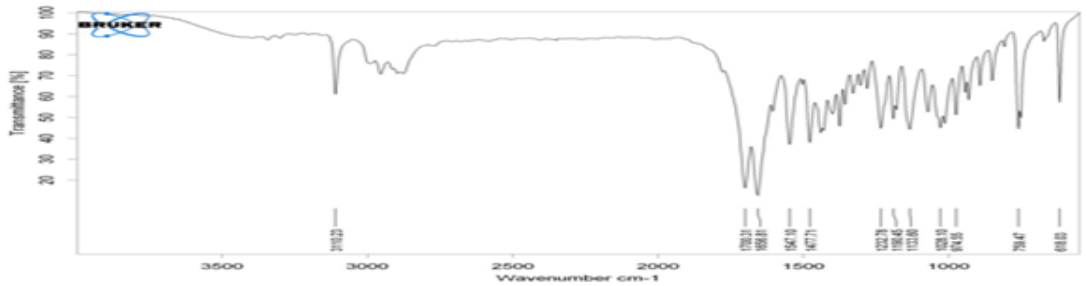


Fig. 4: FTIR graph of Pure Doxofylline

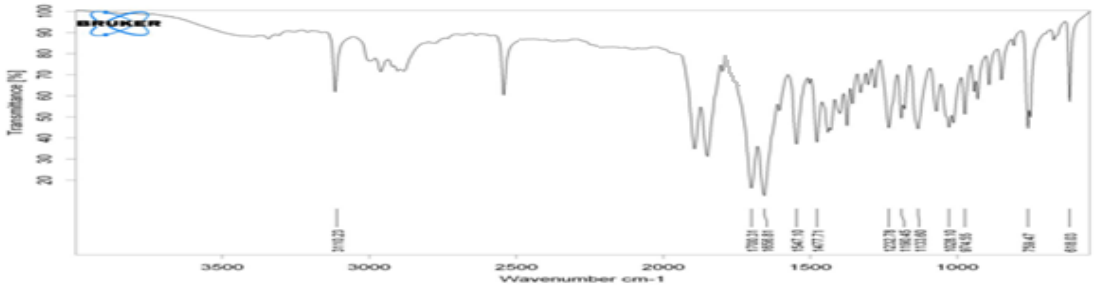


Fig. 5: FTIR graph of Optimized formulation

Table 3: Data from FTIR studies of the pure drug and Optimized formulation

Functional group	Frequencies(cm^{-1})		
	Literature value	Doxofylline Pure drug	Physical Mixture of doxofylline and HPMC K100
C=O	1750-1700	1730.38	1720.58
C-O	1200-1800	1232.75	1236.50
C=C	1650-1550	1547.33	1537.36
C=N	1600-1500	1654.83	1652.38
C-H(Ring)	3100-3000	3070.25	3074.52
C-H	2900-2800	2865.65	2863.56
C-N	1340-1250	1232.75	1222.65

Determination of flow characters of core powder blend
Various properties of granules such as Angle of repose, Bulk density, tapped density, Carr'sindex, Hausner's ratio were determined, and the results are shown in Table 4. The Angle of repose for all formulations was

found to be < 30° indicates free flowing of the material and Hausner's ratio values 0.90 indicating good flow property of granules.

Table 4: Pre-Compression Parameters of Core powder blend:

Parameters	Mean value ± S.D (n=3)
Angle of Repose	28.32± 0.12
Bulk Density	525±0.10
Tapped density	580±0.21
Carr's Index	9.48±0.13
Hausner's ratio	0.90 ± 0.09

Evaluation of Post-Compression Parameters of CPOP tablets

The Test results of Physicochemical properties of all formulations were found to be with in the Pharmacopoeia limits shown in the Table 5. The weight of tablets ranged from 961mg to 963 mg: the weight being with ±5% of average weight. Hardness of the tablets 14.5 kP and Friability was in range of 0.04-0.08% which indicates that the tablets were hard enough to retain the tumbling action of coating pan. The thickness was found to be 4.8mm. The drug content on an average was found to be 100.03%.

Table 5: Post-Compression Parameters of CPOP Tablets

Formulation	Weight Variation	Hardness (kP)	% Friability	Thickness	Assay
DF1	960±2.1	12.3-14.5	0.05	4.2-4.8	99.3
DF2	960±2.3	13.2-14.6	0.07	4.3-4.5	100.2
DF3	960±1.3	12.5-14.2	0.04	4.2-4.6	100.1
DF4	960±2.4	13.6-14.3	0.05	4.3-4.7	99.9
DF5	960±1.3	12.1-13.2	0.03	4.2-4.5	100.2
DF6	960±1.7	12.5-14.3	0.06	4.3-4.6	100.1
DF7	960±1.8	11.9-13.5	0.07	4.2-4.5	100.3
DF8	960±2.8	11.5-13.2	0.05	4.3-4.6	99.9

***in-vitro* drug release profiles of Doxofylline CPOP Tablets**

The cumulative % drug release profiles of different CPOP Doxofylline formulations were represented in Table 6 linearity of drug release were diversified remarkably by each formulation during 24 hrs. study. DF3, DF4, DF7 formulations completed the drug release with in 10hrs, DF1, DF6 and DF8 formulations could sustain the drug release up to 18hrs. More linear and sustained release were observed with DF1 and DF6 formulations.

Table 6 *in-vitro* drug release data of various Doxofylline CPOP Tablets

Time	% Drug Release							
(Hrs)	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8
0	0	0	0	0	0	0	0	0
1	4.25±1.1	14.5±1.2	10.5±1.3	12.5±1.1	8.9±1.5	5.3±1.5	10.3±2.4	5.24±2.5
2	8.35±1.5	29.2±2.3	21.5±1.4	25.7±2.2	13.8±1.6	9.6±2.5	21.2±3.5	10.28±2.6
3	12.56±2.3	44.5±3.2	31.4±2.5	36.3±2.3	23.6±3.2	15.9±1.5	31.2±4.2	16.24±3.2
4	18.25±3.2	57.8±4.2	43.7±3.6	49.8±2.5	35.8±3.4	23.6±2.3	42.6±2.5	20.25±3.4
6	26.57±4.2	70.7±4.5	63.2±3.3	72.6±2.6	46.8±3.2	31.6±3.2	62.5±2.8	30.25±4.2
8	33.54±2.2	82.1±5.6	84.5±3.5	96.7±3.2	65.4±2.5	52.4±3.6	83.4±2.9	41.26±2.5
10	43.56±1.2	90.2±3.2	100.2±4.2	100.2±3.3.	82.6±2.8	67.9±3.5	100.2±3.5	51.24±1.1
12	52.32±2.1	96.1±3.5	100.1±4.5	100.1±3.4	93.4±3.2	78.9±2.5	100.1±2.7	62.36±1.2
16	68.57±1.2	100.2±2.2	100.3±3.2	99.8±3.3	100.2±3.3	88.2±4.2	100.1±3.2	81.54±3.3
20	82.54±2.2	100.1±2.4	100.2±2.5	100.2±2.3	99.9±3.2	98.5±2.2	100.2±3.5	100.24±3.2
24	100.23±2.2	100.3±2.5	100.4±2.6	99.9±3.2	100.1±3.3	100.2±2.3	99.9±4.2	100.23±3.2

Values were expressed as mean cumulative % drug release ±S.D with n=3

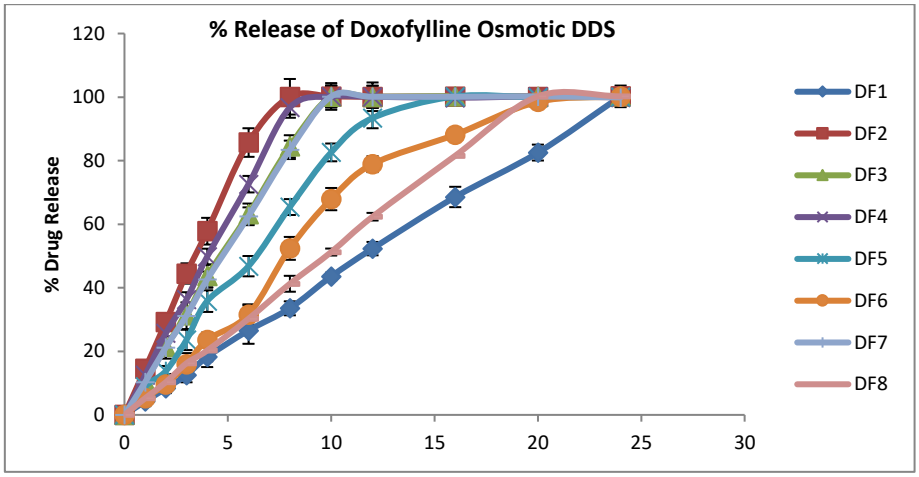


Fig. 6: *In-vitro* release Profiles of Doxofylline CPOP tablets

Dissolution Profile modeling

Dissolution data of the formulation were fit into various mathematical models (zero order, first order, to describe the kinetics of drug release. An ideal osmotic system should release the drug in zero order manner during dissolution. Goodness of fit test(R^2) was taken as a criteria for selecting the most appropriate model. DF1formulation showed zero order drug release rate with the R^2 value 0.998. Table 7 shows summary of drug release kinetics of formulations.

Table 7: Release kinetics of dissolution data

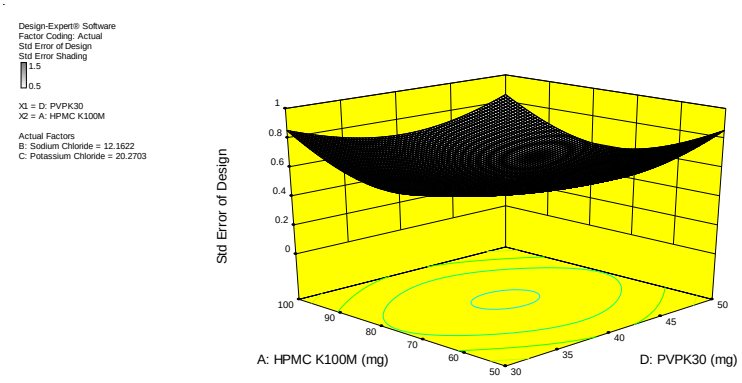
Dissolution	R^2 values							
	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8
Zero order	**0.9988**	0.2532	0.5663	0.4223	0.7801	0.9179	0.5740	0.9782
First order	0.9292	0.9440	0.9372	0.9380	0.9429	0.9343	0.9361	0.9248
Higuchi	0.9862	0.8709	0.9219	0.8961	0.9640	0.9846	0.9223	0.9888

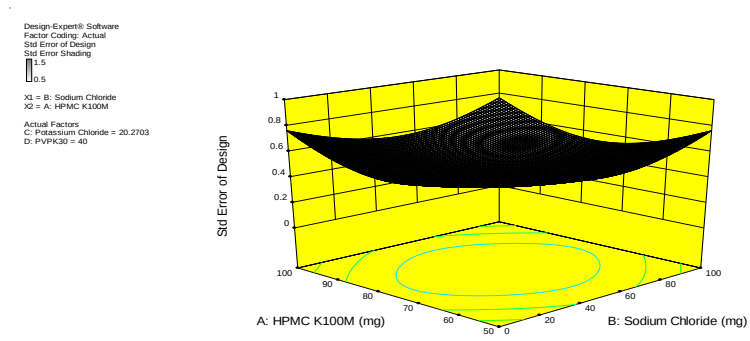
Significant Factors for Dissolution at 4hrs time point:

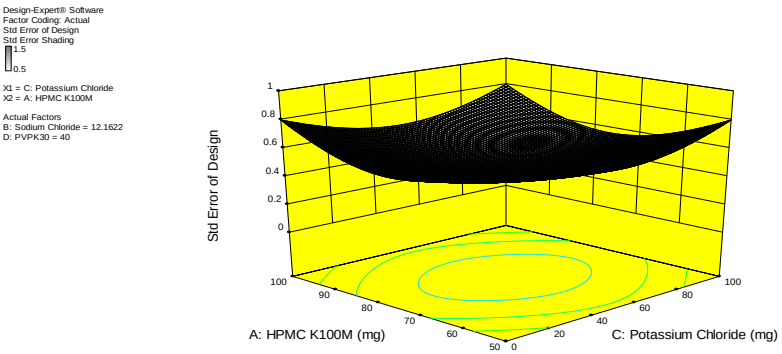
The impact of selected formulation variables on tablet dissolution at 30 min time point was evaluated and results are presented below.

Term	Stdized Effect	Sum of Squares	% Contribution
Intercept			
A-HPMC K100M	-5.85	68.45	8.52
B-Sodium Chloride	11.75	276.12	34.38
C-Potassium Chloride	12.35	305.05	37.98
D-PVPK30	3.75	28.13	3.50
AB	5.30	56.18	7.00
AC	4.80	46.08	5.74
AD	3.40	23.12	2.88
BC		Aliased	
BD		Aliased	
CD		Aliased	
ABC		Aliased	
ABD		Aliased	
ACD		Aliased	
BCD		Aliased	
ABCD		Aliased	
Lenth's ME	29.92		
Lenth's SME	71.62		

From the above table it is clear that osmotic agent's potassium chloride and sodium chloride are having significant effect on drug release then followed by HPMC K100 M and PVP K 30 respectively. Effect of each excipient and combination effect are shown pictorially below (Fig No.7,8,9).







From the surface response plot of formulation variables, images it is understood that as the amount of rate controlling polymer is increased within the tablet by keeping the concentration of remaining excipients at a constant level, it was observed that the % release is decreased and same is observed in case of PVP K 30 binder. In addition, it is also evident from the images that as the concentration of osmotic agents are increases % rate of drug release is increased, and it was very slow in their absence proving the importance of osmogenes in the formulations.

Effect of pH

The osmotically controlled release system delivers the drug contents independent of the external medium. There is no significant difference in the cumulative drug release of DF1 formulation when performed in various pH buffers. The cumulative drug release profile of DF1were plotted and shown in Fig 10. Which indicates that drug release from the system do not affect in different fluids of GIT.

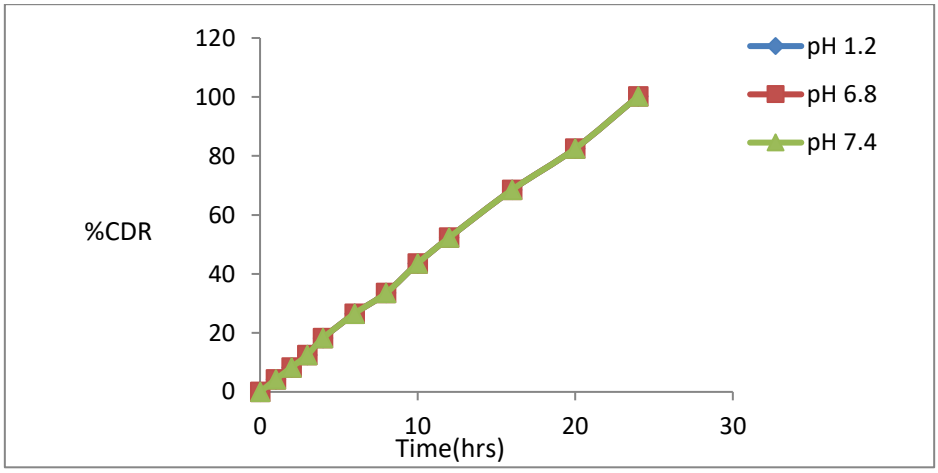


Fig.10: *in-vitro* dissolution study of DF1 in different pH Buffers (n=3)

Effect of Agitational intensity on drug release

The *in-vitro* drug release from the optimized formulation DF1 was independent of agitational intensity. The cumulative % drug release at 50, 100, 150 rpm were found be 97.02%, 98.72%, 99.02% respectively. Therefore, this study demonstrates that drug release from the formulation is independent of hydrodynamic conditions of body. The cumulative drug release profile of DF1were plotted and shown in Fig 11.

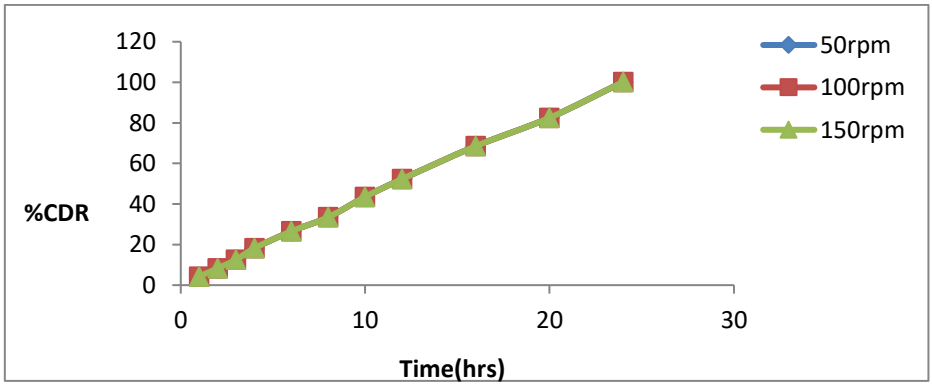
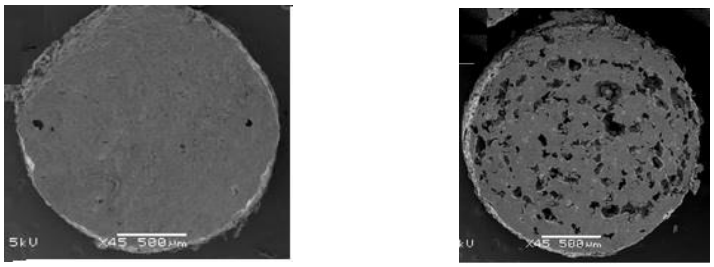


Fig.11: *in-vitro* dissolution study of DF1 at different rpm (n=3)

SEM studies of CPOP Doxofylline Tablets before and after dissolution

To examine the changes in the membrane structure, surface of coated tablets was studied using SEM. After release studies semipermeable coating was intact with formation of pores or channels, which possibly acted as exit channels for the drug. Images of tablet before dissolution were found to be non-porous. After 24hr dissolution, they revealed the pores formation in range of 1 to 50µm. The Fig 12 a & b showed SEM micrograph of membrane surface of optimized formulation DF1 having sorbitol and PEG 400 as pore forming agents.



a) Before dissolution **b) After dissolution**

Fig. 12: SEM photographs of coating membrane of DF1 before and after dissolution

CONCLUSION

Controlled porosity osmotic pump tablets of doxofylline were designed and optimized by Fractional Factorial design, where the effects of formulation variables were studied to optimize the formulation. The desired zero order release rate was obtained by optimizing amount of osomogens and polymer concentration. It is also evident from the studies that as the concentration of osmotic agents increases the % rate of drug release was increased, and it was very slow in their absence. Hence, it can be concluded that osmotic agent's ratio's play an important role during formulation of osmotic drug delivery system. From the overall results, it can be concluded that DF1 formulations have shown the Zero order release profile and desired drug release of 100% within 24 hours hence, the DF1 formulation can be considered as a once - daily tablet of Doxofylline with reduce dosing frequency.

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