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PREPARATION AND *IN-VITRO* EVALUATION OF FLOATING CONTROLLED POROSITY OSMOTIC PUMP TABLETS OF CAPTOPRIL

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ABSTRACT
Osmotically Controlled Drug Delivery Systems (OCDDS) are the Novel Drug Delivery Systems (NDDS) that can overcome the limitations of sustained and controlled drug delivery systems. Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Oral osmotically controlled release delivery system provide a uniform concentration of drug at the absorption site and maintains plasma concentration within therapeutic range. Osmotic pumps can be used as experimental tools to determine important pharmacokinetic parameters of new or existing drugs. At the same time, they can also be utilized to deliver drugs at a controlled and predetermined rate. The aim and objectives of Present study were to design and formulate Floating Controlled Porosity Osmotic Pump Tablets for Captopril. Optimum formulation was determined by Box-Behnken Design Expert 9.0 software and the physicochemical characteristics of formulations were found to be stable. *in-vitro* drug release studies were performed for of all formulations and delivered Captopril for a period of 12 hrs independent of pH and agitational intensity. The system FOP3 was found to be optimum. This system is simple to prepare and is cost effective, alternative to conventional osmotic delivery pump as the sophisticated laser drilling technique is not required.

KEYWORDS: Controlled porosity Osmotic pump, Captopril, Box-Behnken Design, *in-vitro* release studies.

INTRODUCTION
An ideal drug delivery system should be able to deliver an adequate amount of drug, preferably for an extended period of time, for its optimum therapeutic activity. Most of drugs having short biological half-life and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. Despite presence of varied routes of drug administration, oral route remains the preferred route of choice. This route provides maximum patient compliance, is relatively simple to formulate for the formulator and convenient for the patient to administer. Particularly oral controlled release formulation, which releases active ingredient over an extended period instead of administering a number of single doses at regular intervals, has been recognized in the pharmaceutical art. Captopril is one of the angiotensin-converting enzyme inhibitor, which is a widely used and effective drug for the clinical treatment of high blood pressure. The elimination half-life is 1.9 hours, so it is taken three times daily, and the drug's action lasts 6-8 hours. Captopril CPOP tablets, can maintain a constant therapeutic concentration and reduce the number of times the drug must be taken each day. Captopril is more stable at pH1.2 and it is unstable as pH increases i.e. above pH 4. It undergoes oxygen facilitated, first order, free radical oxidation at its thiol group to yield Captopril disulphide. Hydrolysis also occurs at the amide linkage under forcing conditions. So Floating nature is being imparted to controlled porosity osmotic pump tablets to form FCPOP to increase gastric retention and minimize degradation.

MATERIALS AND METHODS
Captopril is obtained from Yarrow Chem Products, Mumbai. HPMCK100M and HPMCK4M are obtained from Colorcon Asia Pvt. Limited. PVPK30, MCC, Dibutyl phthalate and talc are obtained from Fine-chem Limited, Mumbai, Cellulose Acetate is obtained from Sigma Aldrich.

Drug-Exicipent Interaction Studies by Differential Scanning Calorimetry (DSC)
The thermal properties of the drug and the mixture of drug and excipients are of important interest since this can help to assess the interaction among different components of the formulations. The DSC thermogram of pure Captopril showed a endothermic peak at a temperature of 106°C and DSC thermogram of Captopril + HPMC K100M + NaCl at111.3°1C. Fig 1& 2:

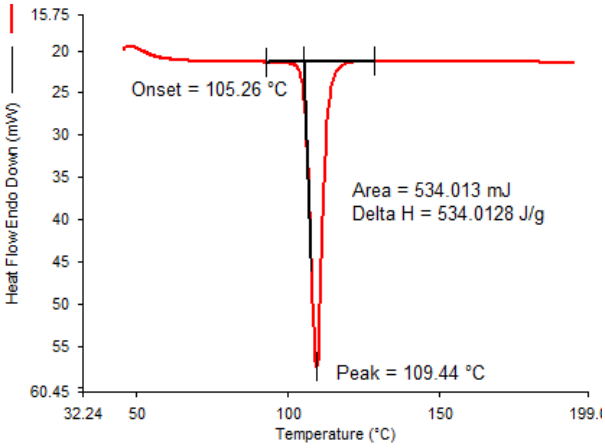


Fig. 1: The DSC thermogram of pure Captopril.

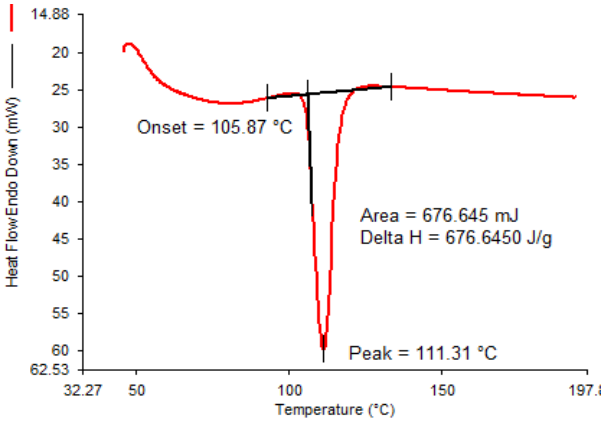
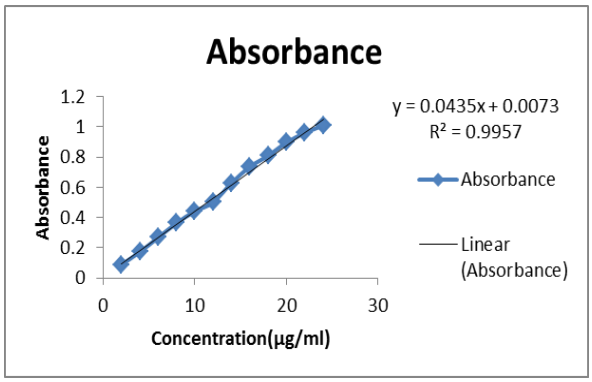


Fig. 2: The DSC thermogram of Captopril + HPMCK100M + NaCl.

Standard graph of Captopril in *1.2* pH *SGF*

Standard graph of captopril in 1.2 pH Simulated gastric fluid by making the different concentrations of 12,14,16,18,20,22,24 µg/ml of Captopril and absorbance was measured at 212 nm using a UV spectrophotometer (Elico, Ahmedabad, India).Table1, Figure 3.

Concentration	Absorbance
2	0.088
4	0.172
6	0.268
8	0.363
10	0.441
12	0.501
14	0.629
16	0.736
18	0.81
20	0.897
22	0.96
24	1.01



Experimental Design for CPOP tablets of direct compressed cores

Independent Variables	Design Level		
	Low(-1)	Middle(0)	High(+1)
Concentration of polymer (mg)	4	12	20
Concentration of Osmogen(mg)	80	140	200
Concentration of Pore former(mg)	345	690	1035

A three-factor, three levels Box-Behnken design was generated by Design-Expert 9.0 software to conduct the study. A total of 17 formulations were designed by the software with five centre points.

Ingredients	**OP1**	**OP2**	**OP3**	**OP4**	**OP5**	**OP6**	**OP7**	**OP8**	**OP9**
CAPTOPRIL(mg)	50	50	50	50	50	50	50	50	50
NaCl(mg)	140	140	200	80	200	140	140	140	140
HPMCK100(mg)	4	12	4	12	12	20	12	12	4
MCC(mg)	56	48	0	108	0	40	48	48	56
Tablet Weight(mg)	250	250	254	250	262	250	250	250	250
Coating									
Cellulose Acetate(gm)	3	3	3	3	3	3	3	3	3
Dibutylpthalate(ml)	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42
PVPK30(mg)	1035	690	690	345	1035	345	690	690	345
Solvent(ml) Acetone: Water	90:10	90:10	90:10	90:10	90:10	90:10	90:10	90:10	90:10

Preparation of Captopril core tablets (CPOP)

Core tablets of captopril were formulated using polymer HPMC K100M and NaCl as polymer and osmogen respectively by direct compression technique. Then semipermeable coating was done with different levels of pore forming agent (PVPK30). Accurately weighed quantities of (25mgcaptopril), polymer (HPMCK100M), osmogen (NaCl) and diluent MCC pH 101 were mixed

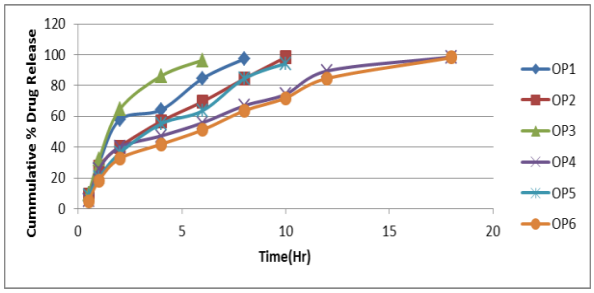
thoroughly in a motor and compressed to form tablets in a 16 station rotary tablet machine (Riddi, Ahmedabad) using 8mm round concave punches. Seventeen formulations of 100 tablets each were prepared with varying polymer and osmogen concentrations. The total weight of each tablet was 250mg and containing 25mg of Captopril.

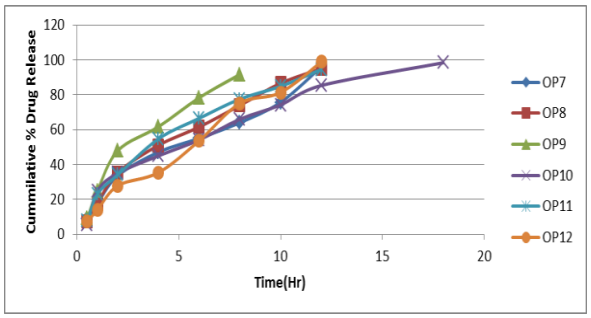
Formulae of different formulations of Captopril are shown in Table 3 and 4

Evaluation of the developed formulations: The core tablets were evaluated for Hardness, thickness, weight variation, friability and %Drug Content. Hardness of the tablet was measured by Pfizer Hardness Tester (Cadmach, Ahmedabad, India). Thickness of tablet of tablet before and after coating were measured by vernier callipers (Mitutoyo, japan).Friability was measured by Roche Friabilator. (Campbell Electronics, Mumbai).

	OP10	OP11	OP12	OP13	OP14	OP15	OP16	OP17
CAPTOPRIL(mg)	50	50	50	50	50	50	50	50
NaCl(mg)	200	140	140	80	200	80	140	80
HPMCK100(mg)	20	12	12	4	12	12	20	20
MCC(mg)	0	48	48	116	0	108	40	100
Tablet Weight(mg)	270	250	250	250	262	250	250	250
Coating								
Cellulose Acetate(gm)	3	3	3	3	3	3	3	3
Dibutylpthalate(ml)	0.42	0.42	0.42	0.42	0.42	0.42	0.42	0.42
PVPK30(mg)	690	690	690	690	345	1035	1035	690
Solvent(ml) Acetone: Water	90:10	90:10	90:10	90:10	90:10	90:10	90:10	90:10

***In vitro* evaluation was carried out by USP type II (Paddle) apparatus. The test was carried over a period of 18 hours using 1.2pH SGF. Figure 4,5,6.**





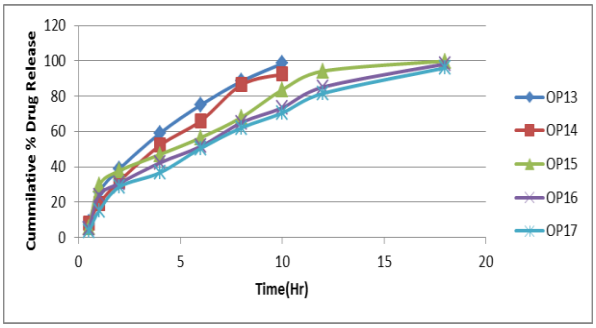
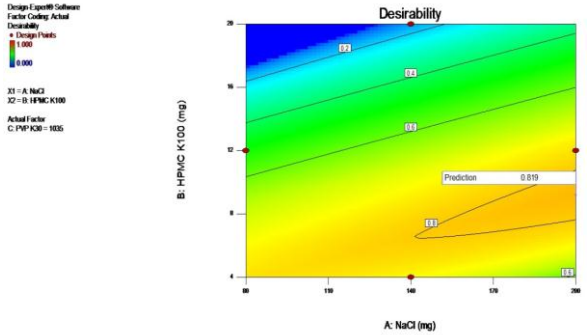


Table 5: Optimized formula given by design expert software.

Ingredients	Optimized Formula
CAPTOPRIL(mg)	50
NaCl(mg)	200
HPMCK100(mg)	9.2
Tablet Weight(mg)	259.2
Coating	
Cellulose Acetate(gm)	3
Dibutylpthalate(ml)	0.42
PVPK30(mg)	1035
Solvent(ml) Acetone: Water	90:10



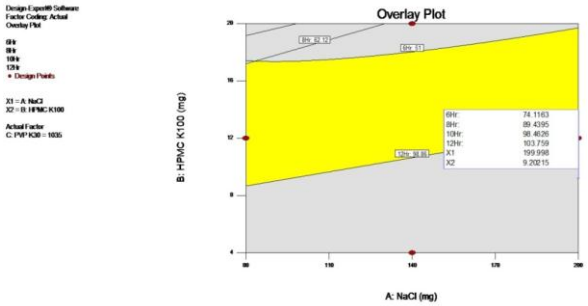


Figure 7 and 8: Desirability Plot & Overlay Plot.

Preparation of Floating Controlled Porosity OsmoticPump Tablets of Captopril

Floating CPOP were prepared by compression coating of CPOP with a gelling agent (HPMCK4M) containing gas generating agent (Sodium Bicarbonate). About one half of the coating formulation is placed in the die cavity, the CPOP is carefully positioned in the centre of the die cavity and was then filled with the remainder of the coat formulation. It was then compressed around the core tablet using 10mm round concave punches. In all the case coated tablets were dried at 50^0Cfor 10Hr before further evaluation. Table 6.

Formulation Code	HPMCK4M	SBC ($NaHCO_3$)	Talc
FOP1	156	40	4
FOP2	146	50	4
FOP3	136	60	4

Evaluation of Floating CPOP Tablets

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa et al., 1994. The tablets were placed in a 100 mL beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and to float was determined as *floating lag time*. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the *total floating time*.

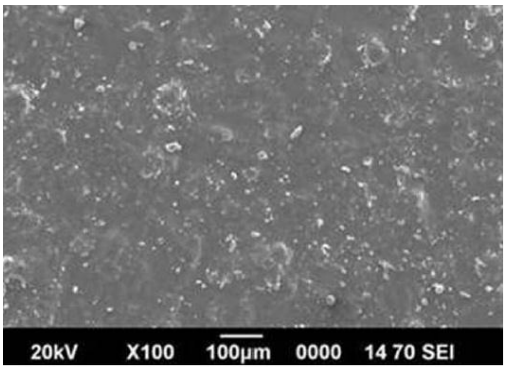
Weight variation, Thickness, Friability and Invitro release of Floating CPOP were calculated and the Optimized formulation was selected. (Table 7).

Table 8: Floating properties of Captopril FLOATING CPOP Tablets.

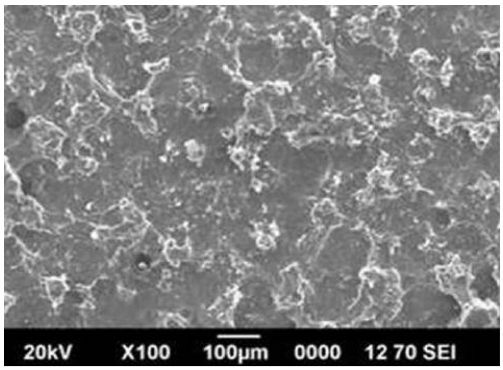
Formulation Code	Floating Lag Time(sec)	Total Floating Time(hrs)
FOP1	73	>12Hr
FOP2	52	>12Hr
FOP3	39	>12Hr

SEM studies of core tablet before and after dissolution: To investigate the changes in the membrane structure,surface of coated tablets was studied using SEM. Figure 9,10 showed SEM micrographs of membrane surface of optimized formulation containing PVPK30 as a pore former before and after dissolution studies. After dissolution studies, coating was intact without any cracks. However, there was formation of channels/pores in the membrane, which possibly acted as exit ports for the drug.(Figure 9& 10).

Formulation code	*Weight Variation*	*Thickness*	*Friability*
FOP1	451±6.24	5±0.02	0.2
FOP2	453±5	5.03±0.01	0.2
FOP3	452±4.72	5.01±0.02	0.3



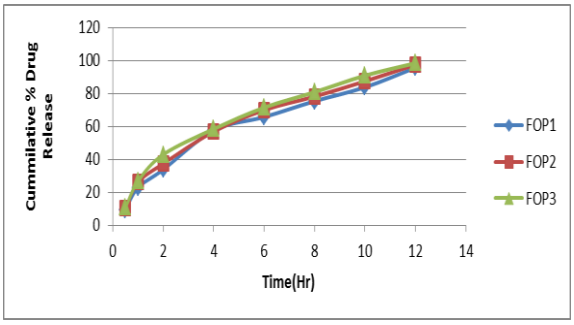
SEM of optimized tablet before dissolution.



SEM of optimized tablet after 12hr dissolution.

***In -vitro* Drug release profile of various Floating CPOP formulation (Table 9, Figure 11).**

Time(hr)	*FOP1*	*FOP2*	*FOP3*
0.5	9.49±1.01	10.43±2.08	10.93±0.7
1	22.91±1.7	26.11±2.87	26.9±1.72
2	33.83±2.15	37.43±2.77	42.98±2.3
4	57.61±1.52	56.88±1.73	58.47±1.02
6	65.7±2.68	69.9±0.66	71.43±2.19
8	75.29±2.06	78.13±1.14	80.81±1.46
10	83.75±2.71	87.39±1.95	90.83±2.21
12	95.6±1.37	97.44±1.41	98.37±0.59



Dissolution profile modeling

Dissolution data of the optimized formulations were fitted to various mathematical models (zero-order, first-order, Higuchi and Korsmeyer-Peppas) to describe the kinetics of drug release. An ideal osmotic system should

be able to release a high percentage of drug content with a constant release rate (zero order kinetics) during dissolution and the porous systems follow Higuchi model. Goodness-of-fit test (R^2) was taken as a criterion for selecting the most appropriate model.

Table 10: Regression coefficient (R^2) values of Captopril floating CPOP tablets for different kinetic models.

Formulation	% drug release	Time (hrs)	R^2 value				n value
			Zero-order	First order	Higuchi	Kores meyer- Peppas	
FOP1	95.6	12	0.9341	0.9323	***0.9897***	0.9687	0.6763
FOP2	97.44	12	0.9256	0.9629	***0.9927***	0.9620	0.6442
FOP3	98.37	12	0.9156	0.9467	***0.9912***	0.9542	0.6334

SUMMARY AND CONCLUSION

In this present study Floating Controlled Porosity Osmotic Pump Tablets of Captopril for treatment of Hypertension were prepared. Standard graphs of Captopril in 1.2pH SGF and water were prepared. DSC analysis shows that the drug Captopril is compatible with the polymer and osmogen used. There has been no drug–excipient interaction in the physical mixture as well as the final formulation as drug peak retained in DSC.

Captopril core tablets (CPOP) were formulated using polymer HPMC K100M and NaCl as polymer and osmogen respectively by direct compression technique. Then semipermeable coating was done with different levels of pore forming agent (PVPK30). Core tablets were evaluated for physicochemical parameters. The optimum formulation was determined by Box-Behnken design. Floating CPOP were prepared by compression coating of optimum CPOP with a gelling agent (HPMCK4M) containing gas generating agent (Sodium Bicarbonate). Floating lag time and Total floating time were determined. Weight variation, Thickness, Friability and *in-vitro* release of Floating CPOP were calculated and the Optimized formulation was selected.

Floating Controlled Porosity Osmotic Pump tablets of Captopril were prepared with PVPK30 as pore former. The desired release profile was obtained by optimizing concentration of osmogen, polymer and pore forming agent (PVPK30). Drug release increased with the amount of osmogen due to the increased water uptake and increased driving force for drug release. The developed formulation was found to be stable. The system delivered Captopril for a period of 12 hrs and independent of pH and agitational intensity. The system FOP3 was found to be optimum with *in-vitro* drug release 98%. This system is simple to prepare and is cost effective, alternative to conventional osmotic delivery pump as the sophisticated laser drilling technique is not required.

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