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Design and Development of Controlled Porosity Osmotic tablets of Captopril

Shah Nihar¹, Kanubhai Patel²

1. Research Scholar, Shri Jagdish Prasad Jhabarmal Tibrewala University, Jhunjhunu, Rajasthan, India
2. Shri B. M Shah Pharmacy College, Modasa, Gujarat, India

ABSTRACT:

The aim of the present investigation is to design and development of controlled release formulation of Captopril based on osmotic technology to increase the resident time in order to improve the therapeutic effect of the drug by increasing its bioavailability. Captopril is antihypertensive drug, it is soluble in water; its maximum absorption is from the stomach and upper part of the intestine. So the aim to make the Oral Osmotic tablets to get maximum absorption throughout the GI Tract. A present investigation comprises a drug Captopril, Sodium Lauryl Sulphate, Tromethamine, Mannitol, Lactose, Povidone K30. The prepared tablets were subjected to post-compression parameters such as hardness, friability, weight variation, thickness, drug content, lag time subsequently buoyancy time, and *in-vitro* dissolution studies. Drug compatibility with excipients was checked by FTIR and DSC studies. The formulations F04C2 was found to be promising, which shows an *in vitro* drug release of 98.32% in 24 hrs. All the formulations exhibited diffusion dominated drug release.

Keywords: Captopril, Osmotic tablets, Controlled release

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INTRODUCTION:

Oral Controlled drug delivery is the one which delivers the drug at a predetermined rate, locally or systemically, for a specified period of time. Oral route has been the commonly adopted and most convenient route for the drug delivery. By considering the conventional dosage form of a drug and the drug profile data, such as dose, absorption rate constant, elimination rate constant, metabolic properties, drug properties and the quantity of drug needed, one can determine the desired release rate of the drug from controlled release dosage form. A variety of approaches and materials has been proposed, which could effectively be used in designing and construction of systems with potential to provide predictable, precise and reproducible pattern of controlled release or even site specific drug delivery 1.

Osmotically controlled oral drug delivery system is the one which utilizes osmotic pressure for controlled delivery of active agent. Drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract. These systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component, size of the delivery orifice, and nature of the rate-controlling membrane 2. By optimizing formulation and processing factors, it is possible to develop osmotic systems to deliver drugs of diverse nature at a pre-programmed rate.

For Correspondence:

Mr. Shah Nihar

Research Scholar,

Shri Jagdish Prasad Jhabarmal Tibrewala
University,

Jhunjhunu, Rajasthan, India

Email: nit_711@yahoo.co.in

Captopril is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II. Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyl dipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

Thus, there is a strong clinical need and market potential for a dosage form that will deliver Captopril in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance. The present study was aimed towards the development of controlled release formulations of Captopril based on osmotic technology. Different formulation variables were studied and optimized to achieve the desired release profile. The manufacturing procedure was standardized and the stability of the formulation was evaluated after 3 months of storage at accelerated stability conditions.

MATERIALS AND METHODS:

Chemicals: Captopril was obtained as a gift sample from Relis Pharmaceutica LTD, Gota, Ahmedabad. Tromethamine and Sorbitol were obtained from S.D. Fine Chemicals, Mumbai. All other ingredients were obtained from Purvi chemicals pvt limited, Ahmedabad

Compatibility Studies: Compatibility of Captopril with different excipients was tested using FT-IR Spectrophotometer 4.

Micromeritic Properties: The drug and blend of drug with excipients was evaluated for bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose 5.

Formulation of Captopril Core Tablets: The core tablets of Captopril were prepared by wet granulation technique with varying ratios of the osmogen. Drug and all the ingredients except lubricants were weighed and passed through 20 mesh screen. To the resultant powder mixture, PVP dissolved in isopropyl alcohol was added to form a coherent mass. Then the coherent mass was passed through 16 mesh screen to form granules. The wet granules were dried at 50°C for 15 minutes. The dried granules were passed through 20 mesh screen to break the lumps and to get uniform size of granules. The lubricants were passed through 40 mesh screen and mixed with the dried granules.

The lubricated granules were compressed into tablets using 8.0mm standard concave punches on a double rotary tablet machine. The composition of core tablets is listed in **Table 1**.

TABLE 1: COMPOSITION OF CORE TABLET

Ingredients	F01	F02	F03	F04
Captopril	8	8	8	8
Sodium Lauryl Sulphate	12	12	12	12
Tromethamine	25	25	25	25
Mannitol	0	50	100	150
Lactose	187	137	87	37
Povidone K30	12	12	12	12
Magnesium Stearate	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5
Aerosil	1	1	1	1
Isopropyl Alcohol	q.s	q.s	q.s	q.s
Captopril	8	8	8	8
Sodium Lauryl Sulphate	12	12	12	12

Coating of Captopril Osmotic Core Tablets: Three coating solutions of cellulose acetate in methanol and dichloromethane containing different levels of pore-forming agent i.e., sorbitol (0% w/v, 10% w/v and 20% w/v) were prepared for semi permeable membrane coating. PEG 400 acted as a hydrophilic plasticizer and was added to enhance the physical and mechanical property of cellulose acetate membrane. The coating conditions were as follows: stainless steel pan, 200mm diameter; rotation rate of the pan, 40 rpm; nozzle diameter of spray gun, 1 mm; spray rate, 3 ml/min; drying temperature, 40oC. After coating, the tablets were dried at 50oC to remove residual solvent. The coating compositions are listed in **table 2**.

TABLE 2: COMPOSITION OF COATING SOLUTION

Ingredients	C1	C2	C3
Cellulose acetate	60g	60g	60g
Sorbitol	-	6g	12g
PEG 400	6g	6g	6g
Water	58ml	58ml	58ml
Dichloromethane	870ml	870ml	870ml

Evaluation of Captopril Osmotic Tablets: The osmotic tablets of Captopril were evaluated for uniformity of weight. Thickness and diameter were measured by vernier calipers. Hardness was determined by hardness tester and friability of osmotic tablets was determined by friabilator 6.

Drug Content: Ten tablets were weighed and ground. The powder equivalent to 8mg of drug was taken, dissolved in methanol and phosphate buffer pH 6.8 in the ratio of 1:1 and suitably diluted. The absorbance of the resulting solution was measured at 376nm and the amount of Captopril was calculated 7.

Drug Content Uniformity: Ten tablets were randomly selected and tested for their drug content. Each tablet was powdered, 50 ml of methanol was added, shaken for 30 minutes and 6.8 pH phosphate buffer was added to produce 100 ml. It was then centrifuged. 10ml of the supernatant liquid was taken and diluted to 100 ml with 6.8 pH phosphate buffer. The absorbance of resulting solution was measured at the maximum at about 376 nm and the content of Captopril was calculated and compared with the label claim 8.

In-vitro release study of the Tablets: Two step-dissolution conditions were carried out in a USP Type II (paddle) dissolution apparatus to simulate the physiological conditions of GIT: 2 hours in 900 ml of simulated gastric fluid (SGF, pH 1.2) and remaining 22 hours in 900 ml of simulated intestinal fluid (SIF, pH 6.8). The stirring rate was 100 rpm and the temperature was maintained at $37\pm 0.5^\circ\text{C}$. Aliquots of dissolution medium were withdrawn at predetermined time intervals and the same volume of medium was replenished to maintain the consistent volume 9.

Effect of change in agitation speed on Drug Release: In order to study the effect of agitational intensity on the optimized formulation, release study was also performed in dissolution apparatus at various rotational speeds of 50, 100 and 150 rpm using two step-dissolution conditions (2 hours in 900 ml of SGF pH 1.2, and remaining 22 hours in 900 ml of SIF pH 6.8) in a USP Type II dissolution apparatus. The temperature was maintained at $37\pm 0.5^\circ\text{C}$. The release was studied at predetermined time intervals 10.

Effect of pH on Drug Release: In order to study the effect of pH of release medium in the drug release of optimized formulation, the *in vitro* release studies can be carried out in buffers of different pH, like pH 1.2 buffer, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer in USP type II dissolution apparatus. The temperature was maintained at $37\pm 0.5^\circ\text{C}$. The release was studied at predetermined time intervals 11.

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Effect of Osmotic Pressure: To confirm the major mechanism of drug release, release study of the optimized formulation was conducted in release media of different osmotic pressure. To increase the osmotic pressure of the release media (pre-equilibrated to $37^\circ\text{C} \pm 1^\circ\text{C}$); mannitol (Osmotically effective solute) was added to produce 1.5 atm, 3 atm and 4.5 atm respectively. The release was studied at pre determined time intervals 12.

Membrane Morphology of Porous Osmotic Tablet:

Scanning Electron Microscopy: Coating membranes of formulation obtained before and after complete dissolution of core contents were examined for their porous morphology by scanning electron microscope. Membranes were dried at 45°C for 12 hours and stored between sheets of wax paper in a desiccator until examination. The membrane was coated under an argon atmosphere with gold-palladium, and observed with a scanning electron microscope 12.

Release Kinetics of the Optimized Formulation: The *in-vitro* release data of the optimized batch was fitted to various kinetic models (Zero-order, First-order, Higuchi, Hixson - Crowell and Korsmeyer-Peppas models). The best fit was found out to describe the kinetics of drug release 12, 13.

Stability Studies: The optimized batch was subjected to the stability study at accelerated condition of $40^\circ\text{C} / 75\% \text{RH}$ for a period of 3 months. Optimized formulation was packed in blister and stored in stability chambers maintained at 40°C and 75% RH for three months. After every month tablet samples were analyzed for physical appearance, drug content and *in-vitro* release 14.

RESULTS AND DISCUSSION:

Compatibility study: From the FT-IR study the drug was found to be compatible with all the excipients.

Micromeritic Properties: The Captopril powder blends were free flowing as indicated by the values of bulk density (0.479 to 0.510 gm/ml), tapped density (0.534 to 0.585 gm/ml), compressibility index (10.29 to 12.82%) and Hausner ratio (1.11 to 1.14). Angle of repose ranged from 17.28 to 19.44. The values are given in **table 3**.

Physical Evaluation and Drug Content: The Captopril osmotic tablets were uniform in weight (0.275 to 0.278g) and the thickness (3.54 to 3.58mm) and diameter (8.912 to 8.966mm) of the tablets were uniform. The hardness of coated tablets was found to be between 5.2 and 5.8 kg/cm², while the

TABLE 3: MICROMERITIC PROPERTIES OF DRUG AND POWDER BLEND

Drug and Formulation Blends	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Compressibility Index* (%)	Hausner's Ratio	Angle of Repose
Drug	0.711±0.002	1.103±0.002	35.53±0.16	1.55±0.06	30.15±0.23
F01	0.510±0.004	0.585±0.007	12.82±0.21	1.14±0.03	19.44±0.16
F02	0.489±0.002	0.560±0.002	12.67±0.24	1.14±0.07	17.28±0.64
F03	0.479±0.003	0.534±0.006	10.29±0.28	1.11±0.05	19.43±0.17

* Mean of 3 readings

TABLE 4: PHYSICAL EVALUATION AND DRUG CONTENT

Formulation	Uniformity of weight# (g)	Diameter* (mm)	Thickness* (mm)	Hardness* (kg/cm ²)	Friability (%)	Drug content (%w/w)
F01C1	0.278±0.003	8.966±0.021	3.542±0.015	5.7±0.273	0.10±0.023	100.8±1.403
F01C2	0.277±0.004	8.952±0.031	3.538±0.029	5.7±0.447	0.16±0.021	95.61±0.894
F01C3	0.277±0.002	8.956±0.021	3.568±0.019	5.6±0.418	0.15±0.019	95.61±0.894
F02C1	0.278±0.003	8.946±0.048	3.560±0.025	5.7±0.273	0.15±0.022	100.91±0.95
F02C2	0.277±0.002	8.912±0.042	3.546±0.017	5.5±0.353	0.14±0.026	99.08±1.110
F02C3	0.277±0.003	8.950±0.010	3.574±0.009	5.6±0.418	0.13±0.021	97.29±0.998
F03C1	0.277±0.002	8.954±0.023	3.542±0.035	5.5±0.353	0.12±0.028	95.26±0.987
F03C2	0.277±0.002	8.952±0.032	3.580±0.016	5.2±0.570	0.22±0.024	99.46±1.098
F03C3	0.276±0.002	8.960±0.010	3.568±0.013	5.9±0.273	0.18±0.021	97.15±1.143
F04C1	0.275±0.002	8.934±0.040	3.566±0.005	5.3±0.447	0.62±0.022	95.98±0.987
F04C2	0.276±0.001	8.966±0.015	3.570±0.033	5.8±0.570	0.71±0.027	98.33±1.056
F04C3	0.277±0.002	8.960±0.007	3.566±0.005	5.5±0.500	0.70±0.023	99.05±1.123

* Mean of 5 readings. # Mean of 20 readings

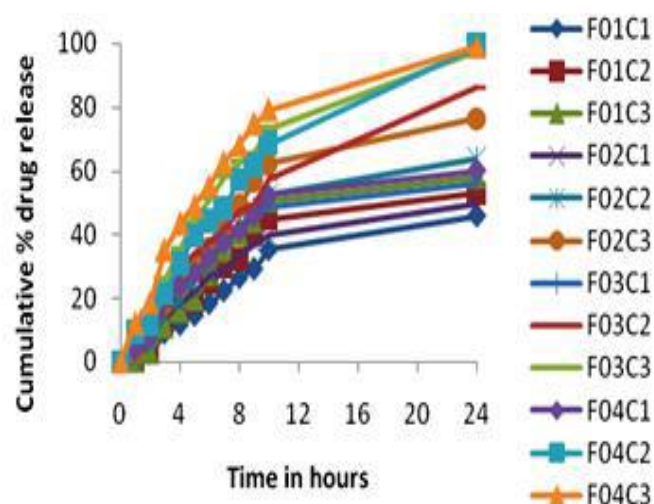
friability of osmotic tablets ranged between 0.10% and 0.71%. The tablets have enough hardness to withstand stress during transport and handling. The drug content in various formulations varied between 95.61% and 100.91% w/w (Table 4).

Uniformity of Drug content: All the formulations exhibited uniformity of drug content 8.

In-vitro release study of the Tablets: All the formulations were subjected to *in vitro* release study. The formulation F04C2 containing 60% of mannitol in core tablet and 10% of sorbitol in coating membrane has controlled release of drug for 24 hours (Figure 1).

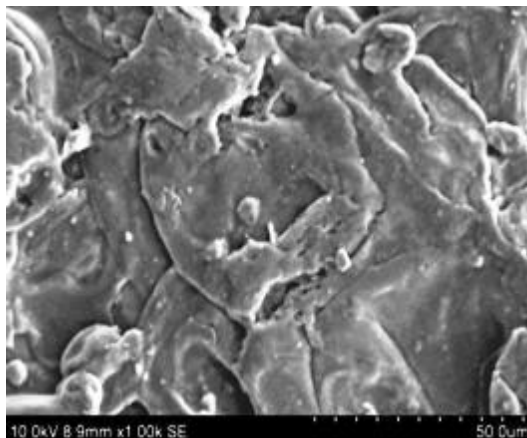
Membrane morphology of Porous Osmotic Tablets: Membranes obtained before dissolution clearly showed non porous region (Figure 7a, 8a). After 24 hours of dissolution the membrane showed pores formed owing to the dissolution of sorbitol from the membrane, (Figure 7b, 8b). The formulation with C2 coating containing 10% sorbitol produced less pores (Figure 7b) compared to formulation C3 coating containing 20% sorbitol (Figure 8b).

Release Kinetics of the Optimized Formulation: The R² values for various release models are 0.9443 for zero order, 0.8639

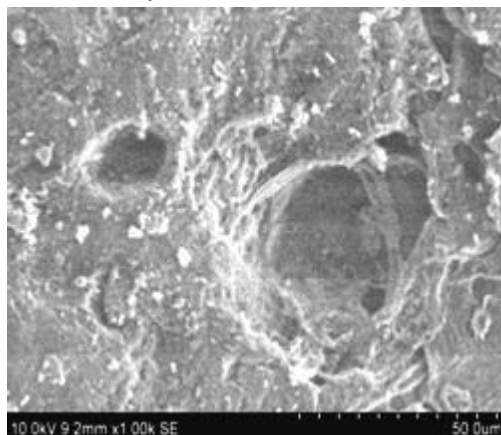
**FIGURE 1 RELEASE STUDY OF VARIOUS FORMULATIONS**

for first order, 0.9714 for Higuchi, 0.8126 for Korsmeyer Peppas and 0.9815 for Hixson Crowell kinetics. The drug release follows zero order kinetics and the mechanism followed is Hixson Crowell

Stability Studies: The osmotic tablets (F04C2) were stored at 40°C/75% RH for 3 months; there was no change either in physical appearance or in drug content. The dissolution study was conducted in the simulated physiological environment of stomach (pH 1.2), and intestine (pH 6.8), not much difference

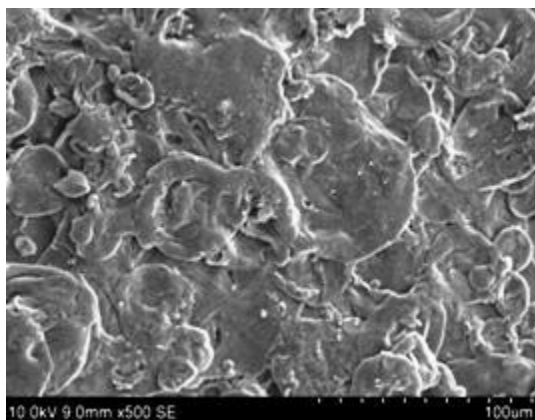


a) BEFORE DISSOLUTION

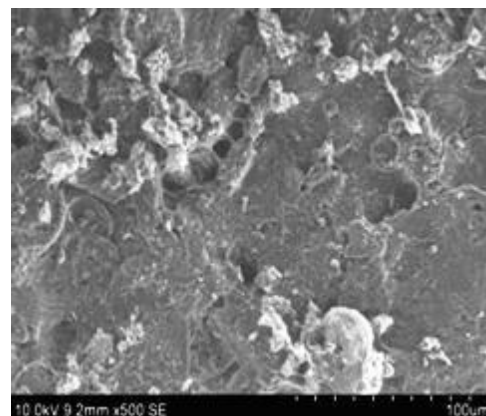


b) AFTER DISSOLUTION

FIGURE 7: MEMBRANE MORPHOLOGY OF FORMULATION F04C2 BY SCANNING ELECTRON MICROSCOPY



a) BEFORE DISSOLUTION



b) AFTER DISSOLUTION

FIGURE 8: MEMBRANE MORPHOLOGY OF FORMULATION F04C3 BY SCANNING ELECTRON MICROSCOPY

requirements for controlled release formulations. The osmotic pressure exerted by the osmogen in the core tablet and the amount of pore former in the semipermeable membrane controlled the drug release.

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was observed in the cumulative percentage release of Captopril from F04C2. Hence the formulation was found to be stable.

CONCLUSION: Captopril controlled porosity osmotic tablet was developed. Of the several formulations investigated, the formulation (F04C2) containing mannitol 60% in the core tablet and 10% of sorbitol in the semipermeable membrane as pore former has come out successfully to comply with the

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