

## THE PHARMA RESEARCH

E-mail: [thepharmaresearch@sudarshanonline.co.in](mailto:thepharmaresearch@sudarshanonline.co.in)  
Website: [www.thepharmaresearch.info](http://www.thepharmaresearch.info)  
E-ISSN 0975-8216 (Online)

Dr. Sayeed Ahmad  
Editor-In-Chief,  
The Pharma Research  
1455, Krishan Ganj, Pildhuwa Ghaziabad,  
U.P-245304 India

### Development and Evaluation of Microporous Osmotic tablets of Diltiazem hydrochloride

Afifa Bathool, Gowda D V, Mohammed S. Khan\*, Vikas K Gupta, Rohitash Kumar

#### Affiliation

Dept. of Pharmaceutics, JSS College of Pharmacy, JSS University, SS Nagar, Mysore-15

#### **Abstract**

Microporous osmotic tablet of diltiazem hydrochloride was developed for colon targeting. These prepared microporous osmotic pump tablet did not require laser drilling in order to deliver the drug. The tablets were prepared by wet granulation method. The prepared tablets were coated with microporous semipermeable membrane and enteric polymer using conventional pan coating process. The incorporation of sodium lauryl sulfate, a leachable pore forming agent, could form in situ delivery pores while coming in contact with gastrointestinal medium. The effect of formulation variables like amount of sodium alginate and NaCMC in the tablet core, amount of osmogen, amount of pore forming agent used in the semipermeable coating was studied. SEM studies showed the formation of pores after predetermined time of coming in contact with dissolution medium. The formation of pores was dependent on the amount of pore former used in the semipermeable membrane. *In vitro* results showed acid-resistant, timed release at an approximate zero order upto 24hrs.

**Keywords:** Microporous osmotic tablet, colon-specific delivery, diltiazem hydrochloride, semipermeable coating.

#### **Introduction:**

There has been considerable research for design of colonic drug delivery system. Colon targeting can be achieved by several ways, which include prodrugs, pH- and time-dependent systems (1). The colon is a site of interest where poorly absorbed drug molecule may have improved bioavailability (2). Colon is a reliable site for those drugs where a delay in drug absorption is required from therapeutic point of view e.g. nocturnal asthma, cardiac arrhythmias, arthritis, which are affected by circadian biorhythms(3). Colon is site of interest as it has longer retention time and appears highly responsive to agents that enhance the

absorption of poorly absorbed drugs. Colon targeting is usually advised because of various advantages such as reduced dosing frequency, chronotherapy and delivery of drug to a region that is less hostile metabolically (4).

Conventional drug delivery systems have little control over the release of drug & no control over the effective concentration at target site (5). Uncontrolled rapid release of drug cause local irritation or systemic toxicity (6). By using oral controlled drug delivery, system can provide continuous delivery of drugs at predictable and reproducible kinetics throughout the GI transit (7).

Osmotic devices are the most promising devices for the controlled drug delivery. They hold a prominent place because of their reliability and ability to deliver the contents at predetermined zero order rate for prolonged periods (8). Osmosis is the noble biophenomenon which is exploited for the delivery of drug in a controlled manner. Osmosis refers to the movement of solvent from region of lower concentration to a region of higher concentration of solute across a semi permeable membrane (9). The osmotic pump tablet is an advanced drug-delivery technique that uses osmotic pressure as driving force for delivery of drug. Osmotic Pump Tablet consists of a core including the drug and osmotic agent, other excipients and semi permeable membrane coat (10, 11). The oral osmotic pump tablet have several advantages such as ease to formulate, simple to operate, reduced side effects, predetermined zero order release of drug and improved patient compliance, good invitro-in vivo correlation (12). The rate of drug release from osmotic pump is dependent on the total solubility and the osmotic pressure of the core. Diltiazem hydrochloride (DLZ) is a calcium channel blocker, widely used for its peripheral and vasodilator properties. It is used in the management of angina pectoris, cardiac arrhythmia and hypertension. It has short half life (3-5hrs), high aqueous solubility. Hence, development of controlled release formulation is highly desirable, so as to improve therapeutic effects with reduced side effects and improved patient compliance (13, 14). The aim of the study was to design and characterize microporous osmotic tablet of diltiazem hydrochloride for colon-specific delivery which could deliver the drug at constant rate for 24hrs.

**Materials and Methods:**

**Materials:**

Diltiazem hydrochloride was obtained as a gift sample from Anglo French Drug Company Ltd., Bangalore. Sodium alginate and carboxy methyl cellulose sodium

were purchased from Sigma-Aldrich Chemicals, Bangalore. Sodium lauryl sulfate and cellulose acetate were obtained from loba chemie. Eudragit S-100 was obtained from Degussa, Mumbai. Mannitol, magnesium stearate and PVP K-30 were procured from Glenmark Pharmaceuticals Ltd., Colvale, Goa. Triethyl citrate, isopropyl alcohol and acetone were procured from Himedia laboratories Pvt. Ltd, Mumbai.

**Methods:**

**Preparation of tablets:**

The granules were prepared by wet granulation method. The dry ingredients were passed through sieve #40 and mixed. PVP K-30 (10% w/v) in isopropyl alcohol was used as a binder. The wet mass was passed through sieve #20. The resultant granules were dried at 450C for 4 hrs. Dry granules were lubricated with magnesium stearate (1% w/w). The dried granules were then compressed to obtain tablets. The average hardness of the compressed tablets was found to be  $6.2 \pm 0.50\text{kg/cm}^2$  while the average thickness was found  $2.762 \pm 0.298\text{mm}$ . Formulation chart of prepared tablets were shown in Table 1.

**Table 1: Formulation table of prepared DLZ tablets with their batch codes.**

Ingredients	FO1 (mg)	F02 (mg)	F03 (mg)	F04 (mg)
Drug	50	50	50	50
Sod alginate + NaCMC	560	400	240	120
Mannitol	200	360	520	640
Mg. stearate	24	24	24	24
Talc	16	16	16	16

**Coating of the prepared tablets:**

Three coating solutions of cellulose acetate containing different levels of pore-forming agent Sodium lauryl sulfate [SLS, (15%w/v, 30%w/v and 45%w/v)] were prepared for semi-permeable membrane coating of

the tablets. The composition of the coating solutions are given in Table 2. Triethyl citrate (2% w/w of total weight of coating materials) was added as plasticizer. The tablets were further coated with an enteric polymer Eudragit S-100. The coating was carried out by a conventional pan coater (Macro Scientific works ® New Delhi, India). The rotating speed was kept at 30rpm. The coating solution was sprayed with the help of air-less spray gun (Manik Radiators Pvt. Ltd., Mumbai) at a fixed rate of 3ml/min. the coated tablets were dried at 500C for 4hrs. The average thickness and average weight of the tablet after semipermeable coating were found to be  $2.965 \pm 0.0386$ mm and  $6.93 \pm 0.0502$ % respectively. The average thickness and average weight gain of the tablet after enteric coating were found to be  $3.426 \pm 0.0496$ mm and  $14.12 \pm 0.0526$ % respectively.

**Table 2: Composition of coating solutions with varied amount of pore forming agent.**

Ingredients	C01	C02	C03
Cellulose acetate (gms)	1.7	1.4	1.1
SLS (gms)	0.3	0.6	0.9
Triethyl citrate (ml)	2	2	2
Acetone (ml)	100	100	100

**Characterization of the tablets:**

**Fourier–Transform Infrared Spectroscopy:**

FT-IR analysis was carried out for pure drug and for formation using KBr pellet method on FTIR spectrophotometer type Shimadzu model 8033, USA in order to ascertain compatibility between drug and polymer used.

**Differential scanning calorimetry (DSC):**

All dynamic DSC studies were carried out on DuPont thermal analyzer with 2010 DSC module. The

instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10°C/min heating rate of 10°C/min.

**Scanning electron microscopic (SEM)**

Coated tablets with varying SLS concentration obtained before and after dissolution were examined for their surface morphology by SEM. The tablets were dried at 500C for 6hrs and stored b/w sheets of wax paper in dessicator. The samples were coated with gold palladium for 120s and examined under SEM. SEM photographs were taken with a scanning electron microscope Model Joel- LV-5600, USA, at the required magnification at room temperature.

**Drug Content**

In the case of drug content uniformity test, tablets were pulverized and then transferred into a 250-ml volumetric flask. The volume was adjusted with pH 7.4 phosphate buffer and kept on rotary shaker for 24 hrs in order to completely extract the drug. The mixture was filtered, and the drug was assayed spectrophotometrically at 237 nm (Shimadzu UV-1108).

**In-vitro drug release studies**

In vitro drug-release studies were performed by using a USP dissolution rate apparatus (apparatus 1, 100 rpm,  $37 \pm 0.5^\circ\text{C}$ ) in pH 1.2 hydrochloric acid buffer (900 ml) for 2 hrs as the average gastric emptying time. Then, the dissolution medium was replaced with a pH 7.4 phosphate buffer (900 ml) for rest of the dissolution studies till complete drug release was obtained. The amount of drug released from the tablets at different time intervals was determined spectrophotometrically at 237 nm (Shimadzu UV-1208). All experiments were done in triplicate.

**Stability studies**

Optimized formulation was selected to assess the stability as per ICH & WHO guidelines. Optimized

formulation was sealed in aluminum foil coated inside with polyethylene and kept inside stability chamber maintained at  $400C \pm 2$  and  $75\% RH \pm 5$  for 3 months. The samples were analyzed for drug content, in vitro dissolution, FTIR spectroscopy at the end of 3 months.

## Results and Discussion

### Drug content

The drug content of the prepared formulation was found to be in range between  $48.37 \pm 1.17$  to  $49.16 \pm 2.13$ . All batches of prepared tablets shows drug content within limits.

### Effect of sodium alginate and NaCMC

Change in the concentration of sodium alginate and NaCMC in the prepared tablets formulation leads to change in the release pattern of drug. The t80% values calculated from cumulative drug release versus time plots confirmed the effect of sodium alginate and NaCMC on the release rate of drug from the formulation. Formulation F02C2 showed slower drug release rate (t80% in 15.311hrs) when compared to other formulations (F01C2, t80% in 30 hrs) as shown in Table 3 & Figure 1. This is due to fact that, in dissolution medium, hydration of sodium alginate and NaCMC takes place leading to swelled gel like matrix which forms gel layer through which the drug diffusion takes place. These results suggest that appropriate addition of release retardants especially hydrophilic polymers (Sodium alginate + NaCMC) can control the release of highly water-soluble drug from the osmotic pumps. F03C2, F04C2 releases 80 % of the drug within 10 hrs which is not desirable for sustained drug delivery.

### Effect of osmogen

The release studies of different formulations were carried out to assess the effect of osmogen. It was noted that as the amount of osmogen (mannitol) increased, release rate also increased. The

formulation F02C2 (t80% in 15.311hrs) showed slower drug release when compared to F03C2 (t80% in 9.846hrs) and F04C2 (t80% in 7.452hrs) shown in Table 3. The formulation F01C2 showed undesirable drug release (t80% in 30hrs) as it contains less amount of osmogen, indicating the development of less osmotic pressure in tablet core.

### Effect of concentration of pore-forming agent

Formulation F02C2 showed 80% of drug release in 15hrs and formulation F02C3 showed within 10hrs, while formulation F02C1 showed 76% of drug release upto 24hrs (Table 3, Figure 2). Formulation F02C1 showed much slower drug release due to lower concentration of pore-forming agent. The results suggested that 30%w/w of pore-forming agent may be useful to affect optimum release of drug.

**Table 3: Average release rate (t80% values) for the prepared batches of microporous tablets.**

Formulation	Average release rate (%/hr)	t80% (hrs)
F01C2	2.605	30
F02C2	5.225	15.311
F03C2	8.125	9.846
F04C2	10.735	7.452
F02C1	3.16	25.318
F02C3	7.74	10.335

### Scanning electron microscopy (SEM)

Formulations F02C1, F02C2 & F02C3 containing varying concentrations of pore-forming agent (15%, 30% and 45%w/w) were subjected to SEM studies before and after dissolution. Formulations showed non-porous region before dissolution. After dissolution, formulations showed microporous region. SEM study suggested that 30 % (w/w) of SLS can be considered as an optimum concentration to obtain

maximum release rate without rupturing of the microporous membrane.

#### Differential scanning calorimetry (DSC)

DSC studies were carried out for diltiazem hydrochloride and formulations. DSC thermogram of the diltiazem hydrochloride and formulation, F02C2 is shown in **Fig 4** respectively. Pure diltiazem hydrochloride displayed sharp endothermic peak at 216°C corresponding to the melting point of the drug, and an identical peak was also observed in the tablet formulation. This result clearly indicates that the drug retains its identity in the coated formulation.

#### FT-IR spectroscopy

The FTIR spectra of both the pure drug and of tablet formulations showed characteristic peaks at 3433.13 cm<sup>-1</sup> (aliphatic C-H stretching), 2931.90 cm<sup>-1</sup> (O-CH<sub>3</sub>, C-H stretching), 2387.93 cm<sup>-1</sup> (amine HCl, N-H stretching), 1741.78 cm<sup>-1</sup> (acetate C=O stretch), 773.48 cm<sup>-1</sup> (p-substituted aromatic C-H) thus indicating that there was no drug-polymer interaction in the formulation.

#### In Vitro Drug Release Studies

Drug release of all prepared tablets was shown in

**Table 4: Release kinetics of diltiazem hydrochloride from osmotic pump tablets.**

S.No	Formulation Code	Zero Order (r2)	First Order (r2)	Higuchi (r2)	Koresmeyer Peppas (n)
1	F01C2	0.9616	0.6941	0.7991	2.361
2	F02C2	0.9664	0.8055	0.8165	2.618
3	F03C2	0.9738	0.8496	0.8232	2.391
4	F04C2	0.9761	0.7768	0.8336	2.488
5	F02C1	0.9720	0.8115	0.8391	2.290
6	F02C2	0.9786	0.8320	0.7281	2.371
7	F02C3	0.9608	0.7898	0.7125	2.347

**Figure 1.** It is clearly shown that from all batches of micro porous tablets prepared, negligible drug release took place in first 2 hrs at pH 1.2. The enteric coating hindered the drug release in stomach. This shows that enteric coating by Eudragit S100 (5% w/v) done was sufficient enough and efficiently prevents the release of drug from tablets at gastric pH 1.2. Drug release started after changing dissolution media pH to 7.4. At pH 7.4, Eudragit S100 enteric coats get dissolved as it is the characteristic of Eudragit S100 to get dissolved above pH 7. Formulation F01C2 releases 20.12±1.17%, F02C2 releases 39.78±1.32%, F03C2 releases 51.47±1.25, F04C2 releases 56.68±1.48%, F02C1 releases 6.32±1.42, F02C3 releases 12.48±1.35% of drug in 8hrs. Release kinetics of the tablets prepared is shown in **Table 4**. The best fit model representing the mechanism of drug release from the tablets prepared was of zero order. This is further confirmed by koresmeyer-Peppas model, the value of n is greater than 1 showing case II drug release or anomalous drug release indicating that two or more mechanism for the drug release are involved, that is diffusion and erosion.

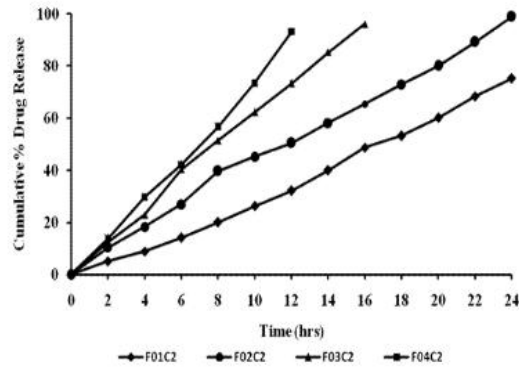


Figure 1: Effect of hydrophilic polymers on the release study of tablets.

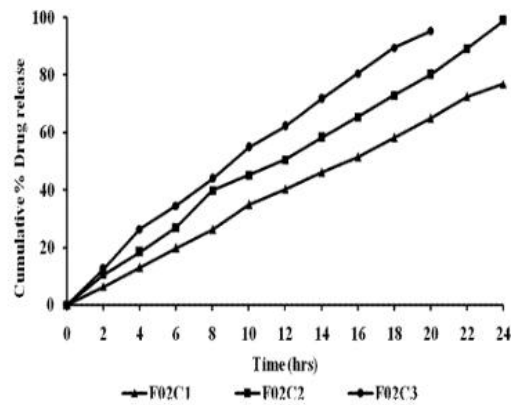


Figure 2: Effect of pore-forming agent on the release study of the optimized formulation.

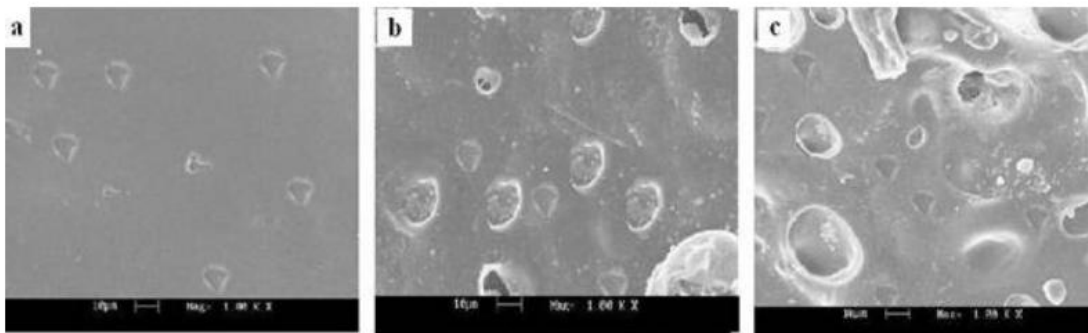


Figure 3: SEM micrographs showing the formation of pores on surface of tablets.

a)15% SLS, b) 30% SLS, c) 45% SLS.



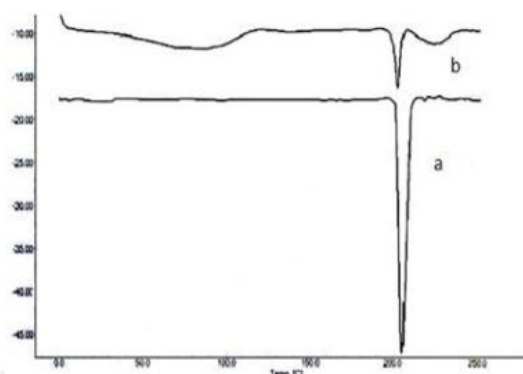


Figure 4: DSC thermograms of pure diltiazem hydrochloride and F02C2 formulation.

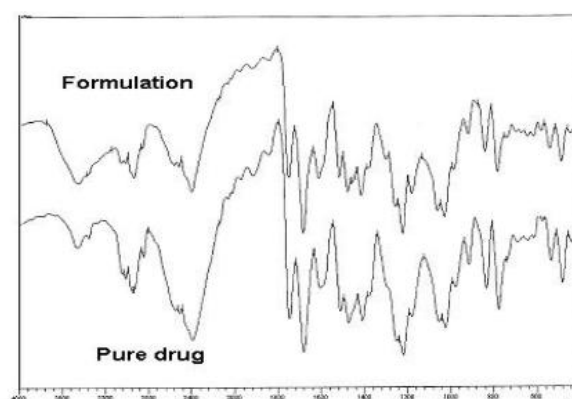


Figure 5: FTIR spectra of pure diltiazem hydrochloride and F02C2 formulation.

#### Stability studies:

During 3 months of stability studies, formulation was characterized for in vitro drug release, drug content, hardness and FTIR spectroscopy. The results indicated no significant difference in drug release. The drug content was found to be  $48.14 \pm 0.35$ . The hardness was also within the limits varying between  $6.4 \pm 0.23$  kg/cm<sup>2</sup>. The Fourier transform infrared spectroscopy (FTIR) indicated no interaction between drug, and formulation was found to be stable.

#### Conclusion:

The present study was carried out in order to develop microporous osmotic tablet of diltiazem hydrochloride for colon-specific delivery for the treatment of angina pectoris. The preparation of microporous osmotic tablet was simplified by coating the core tablet with an indentation, and the cost was reduced with the elimination of laser drilling. It may be concluded from invitro study that colon targeted coated tablets successfully maintained their integrity till the time they reach the colonic fluids. Drug release from the systems followed zero-order kinetics and proved that the system could provide required controlled release rate upto 24hrs.

#### Reference:

1. Khan MS, Sridhar BK, Srinatha A. Development and evaluation of pH dependent micro beads for colon targeting. *Ind J Pharm Sci.* Jan-Feb 2010.
2. Shahidul MI, Jakir A Chowdhury, Monira ST. Study on the Development of Diltiazem HCl Loaded Colonic Drug Delivery Systems (CDDS) Using Various Polymers and Characterization of their Release Profiles by *In Vitro* Dissolution Studies. *Dhaka Univ.J.Pharm Sci.* 2010; 9(1); 7-13.
3. Jose S, Dhanya K, Cinu TA, Aleykutty NA. Multiparticulate system for colon targeted delivery of Ondansetron. *Ind J Pharm Sci;* 2010.
4. Rathbone JM, Jonathan H. Modified release drug delivery technology. 11th ed. New York: Marcel Dekker Inc; 2002. p. 217-21.
5. Mothilal M, Damodharan N, Lakshmi KS, Sharanya VB, Srikrishna T. Formulation and in vitro evaluation of osmotic drug delivery system of metoprolol succinate. *Int J Pharm & Pharm Sci,* 2010; 2(2).
6. Eckenhoff B, Theeuwes F, Urquhart J. Osmotically activated dosage forms for rate

- controlled drug delivery. *Pharm Technol* 1981; 5: 35-44.
7. Edavalath S, Shivanand K, Kalyani P, B Prakash Rao, Goli Divakar. Formulation Development and Optimization of controlled porosity osmotic pump tablets of diclofenac sodium. *Int J Pharm & Pharm Sci.* 3(1) 2011.
  8. Meena R, Rahul S, Chelladurai S, Brahmeshwar M. Development and biopharmaceutical evaluation of osmotic pump tablets for controlled delivery of diclofenac sodium. *Acta Pharm*, 2003; 53: 263-273.
  9. Bindschaedler C, Gurny R, Doelker E. Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate. *J Cont Release.* 1986; 4: 203-212.
  10. Hussan KH, Vikram SN, Kumaravelrajan R. Formulation and optimization of aceclofenac monolithic osmotic pump. *Int J Pharm Sci Review & Research*, 2011: 6(2).
  11. Rose S, Nelson JF. A continuous long term injector, *Aust. J. Exp. Biol.* 1955; 33:415-420.
  12. Pramod K, Sanjay S, Brahmeshwar M. Development and evaluation of elementary osmotic pump of highly water soluble drug: Tramadol hydrochloride. *Current Drug Delivery*, 2009, 6, 130-139.
  13. Chaffman, M. and Brogden, R. N. Diltiazem, a review of its pharmacological properties and therapeutic efficacy. *Drugs.* 1985: 29, 387-454.
  14. Prabu SL, Shirwaikar AA, Shirwaikar A, Ravikumar G, Kumar A, Jacob A. Formulation and evaluation of oral sustained release of diltiazem hydrochloride using rosin as matrix forming material. *Ars Pharm.* 2009; 50(1): 32-42.