ORIGINAL ARTICLE

Development and evaluation of microporous osmotic tablets of diltiazem hydrochloride

Afifa Bathool, D. V. Gowda, Mohammed S. Khan, Ayaz Ahmed, S. L. Vasudha, K. Rohitash

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, SS Nagar, Mysore, India

J. Adv. Pharm. Tech. Res.

ABSTRACT

Microporous osmotic tablet of diltiazem hydrochloride was developed for colon targeting. These prepared microporous osmotic pump tablet did not require laser drilling to deliver the drug to the specific site of action. 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 (SLS), a leachable pore-forming agent, could form *in situ* delivery pores while coming in contact with gastrointestinal medium. The effect of formulation variables was studied by changing the amounts of sodium alginate and NaCMC in the tablet core, osmogen, and that of pore-forming agent (SLS) used in the semipermeable coating. As the amount of hydrophilic polymers increased, drug release rate prolonged. It was found that drug release was increased as the concentration of osmogen and pore-former was increased. Fourier transform infrared spectroscopy and Differential scanning calorimetry results showed that there was no interaction between drug and polymers. Scanning electron microscopic 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 almost zero order up to 24 hours. The developed osmotic tablets could be effectively used for prolonged delivery of Diltiazem HCl.

Key words: Colon-specific delivery, diltiazem HCL, microporous osmotic tablet, semi permeable 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 and 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

Address for correspondence:
Mrs. Afifa Bathool,
Department of Pharmaceutics, JSS College of Pharmacy,
S S Nagara, Bannimantap, Mysore – 570 015, Karnataka, India.
E-mail: afifa18@gmail.com

Access this article online

Quick Response Code:

Website: www.japtr.org

DOI: 10.4103/2231-4040.97292

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 semipermeable 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 semipermeable membrane coat.[10,11] The oral osmotic pump tablet has several advantages such as ease to formulate, simple to operate, reduced side effects, predetermined zero order release of drug, and improved patient compliance, good *in vitro-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 (3-5 hours), high aqueous solubility with intestine as site of absorption. 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 DLZ for colon-specific delivery which could deliver the drug at constant rate for 24 hours.

MATERIALS AND METHODS

Materials

DLZ was obtained as a gift sample from Anglo French Drug Company Ltd., Bangalore. Sodium alginate and carboxymethyl cellulose sodium were purchased from Sigma-Aldrich Chemicals, Bangalore. Sodium lauryl sulfate (SLS) 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 45^{0}C for 4 hours. Dry granules were lubricated with magnesium stearate (1% w/w). The dried granules were then compressed into tablets using 8-mm flat round punches on 10-station rotary tablet machine (Rimek mini press, Mumbai). The average hardness of the compressed tablets was found to be 6.2 ± 0.50 kg/cm^2 while the average thickness was found 2.762 ± 0.298 mm. Formulation chart of prepared tablets are shown in Table 1.

Coating of the prepared tablets

Three coating solutions of cellulose acetate containing different levels of pore-forming agent SLS (15%w/v, 30%w/v, and 45%w/v) were prepared for semipermeable 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 30 rpm for 30 minutes. The coating solution was sprayed with the help of air-less spray gun (Manik Radiators Pvt. Ltd., Mumbai) at a fixed rate of 3 ml/minutes. The coated tablets were dried at 50°C for 4 hours. The average thickness and average weight gain of the tablet after semipermeable coating were found to be 2.965 ± 0.0386 mm and 6.93 ± 0.0502%, respectively. The average thickness and average weight gain of the tablet after enteric coating were found to be 3.426 ± 0.0496 mm and 14.12 ± 0.0526%, respectively.

Characterization of the tablets

Fourier transform infrared spectroscopy

FT-IR analysis was carried out for pure drug and for formulations using KBr pellet method on Fourier transform infrared spectroscopy (FTIR) spectrophotometer type Shimadzu model 8033, USA, in order to ascertain compatibility between drug and polymers used.

Differential scanning calorimetry

All dynamic differential scanning calorimetry (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 10ºC/minutes.

Scanning electron microscopy

Coated tablets with varying SLS concentration obtained before and after dissolution were examined for their surface morphology by scanning electron microscopy (SEM). The tablets were dried at 50°C for 6 hours and stored b/w sheets of wax paper in dessicator. The samples were coated with gold palladium for 120 seconds 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 hours in order to completely extract the drug. The mixture was filtered, and

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

Ingredients	F01 (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

Sodium alginate: Sodium CMC (1:1 ratio), DLZ - Diltiazem hydrochloride

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

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

SLS - Sodium lauryl sulfate

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 ± 0.5°C) in pH 1.2 hydrochloric acid buffer (900 ml) for 2 hours 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 and WHO guidelines. Optimized formulation was sealed in aluminum foil coated inside with polyethylene and kept inside stability chamber maintained at 40°C ± 2 and 75% RH ± 5 for 3 months. The samples were analyzed for drug content, *in vitro* dissolution, and 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 ± 1.17 mg to 49.16 ± 2.13 mg. All batches of prepared tablets show 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 $t_{80\%}$ values calculated from cumulative drug release *vs* 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 ($t_{80\%}$ in 15.311 hours) when compared with other formulations (F01C2, $t_{80\%}$ in 30 hours) as shown in Table 3 and 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 hours, 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 ($t_{80\%}$ in 15.311 hours) showed slower drug release when compared with F03C2 ($t_{80\%}$ in 9.846 hours) and F04C2 ($t_{80\%}$ in 7.452 hours) shown in Table 3. The formulation F01C2 showed undesirable drug release ($t_{80\%}$ in 30 hours) 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 15 hours and formulation F02C3 showed within 10 hours, while formulation F02C1 showed 76% of drug release up to 24 hours [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.

Scanning Electron Microscopy

Formulations F02C1, F02C2, and F02C3 containing varying concentrations of pore-forming agent (15%, 30%, and 45%w/w) were subjected to SEM studies before and after dissolution as shown in Figure 3. 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 studies were carried out for DLZ and formulations.

Table 3: Release kinetics, average release rate ($t_{80\%\ value}$s) for the prepared batches of microporous tablets

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Koresmeyer peppas (n)	Koresmeyer peppas (r^2)	Average release rate (%/hr)	$t_{80\%}$ (hrs)
F01C2	0.9616	0.6941	0.7991	2.361	0.8812	2.605	30
F02C2	0.9664	0.8055	0.8165	2.618	0.8345	5.225	15.311
F03C2	0.9738	0.8496	0.8232	2.391	0.8654	8.125	9.846
F04C2	0.9761	0.7768	0.8336	2.488	0.8839	10.735	7.452
F02C1	0.9720	0.8115	0.8391	2.290	0.8768	3.16	25.318
F02C3	0.9608	0.7898	0.7125	2.347	0.8453	7.74	10.335

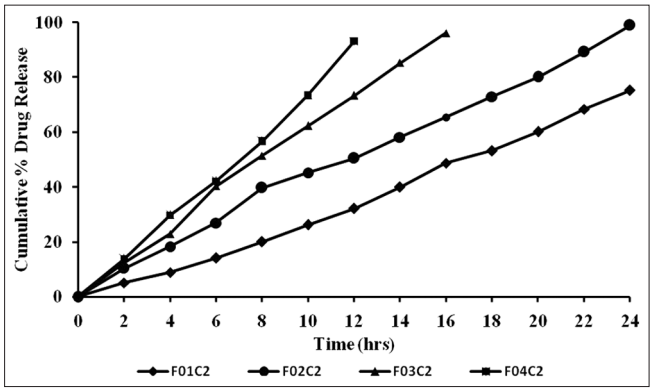

Figure 1: Effect of hydrophilic polymers on the release study of tablets

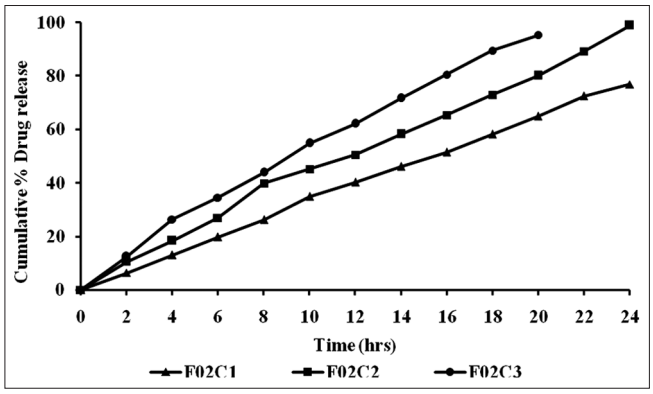

Figure 2: Effect of pore-forming agent on the release study of the optimized formulation

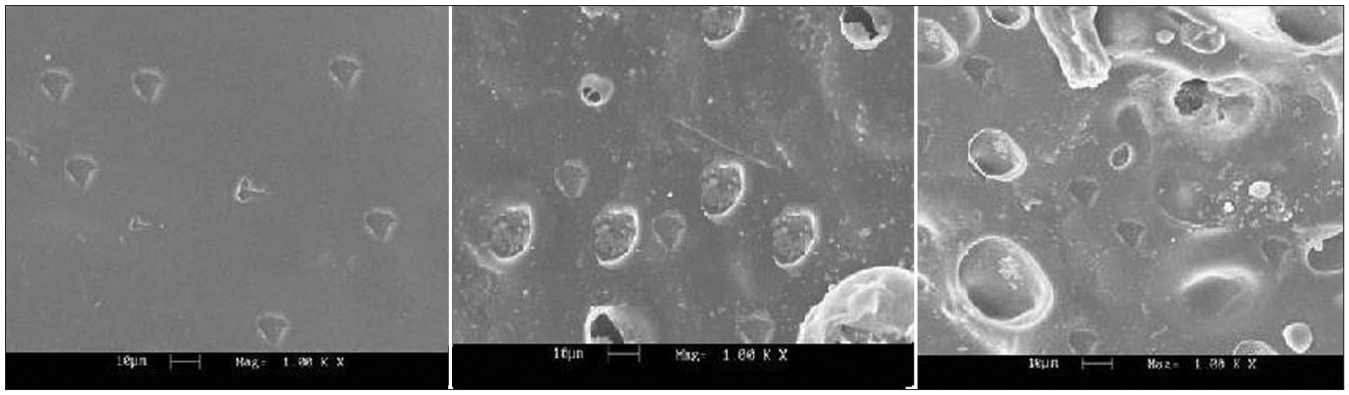

Figure 3: SEM micrographs showing the formation of pores on surface of tablets (a) 15% SLS, (b) 30% SLS, (c) 45% SLS

DSC thermogram of the DLZ and formulation F02C2 is shown in Figure 4. Pure DLZ 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.

Fourier Transform Infrared Spectroscopy

The FTIR spectra of both the pure drug and of tablet formulations showed characteristic peaks at 3433.13/cm (aliphatic C-H stretching), 2931.90/cm (O-CH3, C-H stretching), 2387.93/cm (amine HCl, N-H stretching), 1741.78/cm (acetate C = O stretch), and 773.48/cm (p-substituted aromatic C-H), thus indicating that there was no drug-polymer interaction in the formulation as shown in Figure 5.

In Vitro Drug Release Studies

Drug release of all prepared tablets was shown in Figure 1. It is clearly shown that from all batches of microporous tablets prepared, negligible drug release took place in first 2 hours 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, and F02C3 releases 12.48 + 1.35% of drug in 8 hours.

Release kinetics of the tablets prepared is shown in Table 3. The best fit model representing the mechanism of drug release from the tablets prepared was of zero order. This is further confirmed by korsmeyer-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.

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 + 0.35. The hardness was also within the limits varying between 6.4 ± 0.23 kg/cm^2. The FTIR indicated no interaction between drug, and formulation was found to be stable.

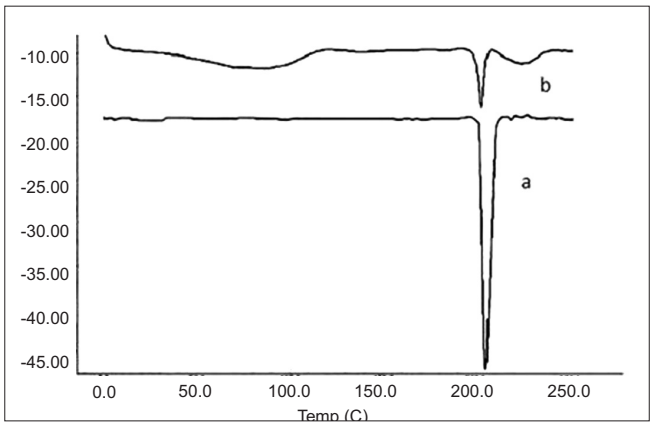

Figure 4: DSC thermograms of pure diltiazem hydrochloride and F02C2 formulation

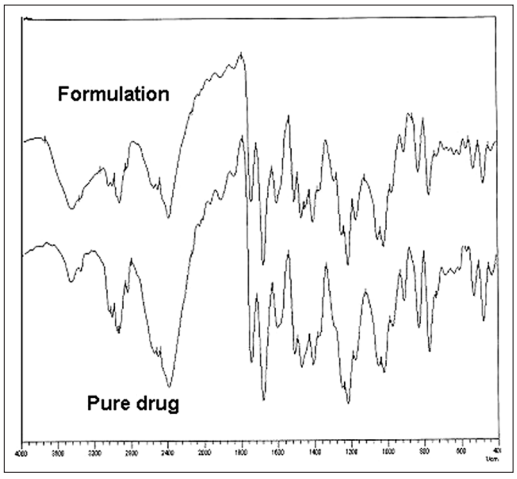

Figure 5: FTIR spectra of pure diltiazem hydrochloride and F02C2 formulation

CONCLUSION

The present study was carried out in order to develop microporous osmotic tablet of DLZ 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 *in vitro* 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 up to 24 hours.

REFERENCES

1. Khan MS, Sridhar BK, Srinatha A. Development and evaluation of pH dependent micro beads for colon targeting. Indian J Pharm Sci 2010;72:18-23.
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;9:7-13.
3. Jose S, Dhanya K, Cinu TA, Aleykutty NA. Multiparticulate system for colon targeted delivery of Ondansetron. Indian J Pharm Sci 2010;72:58-64.
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. Fomulation and *in vitro* evaluation of osmotic drug delivery system of metoprolol succinate. Int J Pharm and Pharm Sci 2010:2, 64-68.
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, Prakash Rao B, Goli D. Formulation development and optimization of controlled porosity osmotic pump tablets of diclofenac sodium. Int J Pharm and Pharm Sci 2011; 3, 80.
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;53:263-73.
9. Bindschaedler C, Gurny R, Doelker E. Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate. J Control Release 1986;4:203-12.
10. Hussan KH, Vikram SN, Kumaravelrajan R. Formulation and optimization of aceclofenac monolithic osmotic pump. Int J Pharm Sci Rev Res 2011:6:42-47.
11. Rose S, Nelson JF. A continuous long term injector. Aust J Exp Biol 1955;33:415-20.
12. Pramod K, Sanjay S, Brahmeshwar M. Development and evaluation of elementary osmotic pump of highly water soluble drug: Tramadol hydrochloride. Curr Drug Deliv 2009;6:130-9.
13. Chaffman M, Brogden RN. 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;50:32-42.

How to cite this article: Bathool A, Gowda DV, Khan MS, Ahmed A, Vasudha SL, Rohitash K. Development and evaluation of microporous osmotic tablets of diltiazem hydrochloride. J Adv Pharm Tech Res 2012;3:124-9.

Source of Support: Nil, **Conflict of Interest:** Nil.