ORIGINAL ARTICLE

Design and development of controlled porosity osmotic tablet of diltiazem hydrochloride

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ABSTRACT

The present work aims towards the design and development of extended release formulation of freely water-soluble drug diltiazem hydrochloride (DLTZ) based on osmotic technology by using controlled porosity approach. DLTZ is an ideal candidate for a zero-order drug delivery system because it is freely water-soluble and has a short half-life (2-3 h). Sodium chloride (Osmogen) was added to the core tablet to alter the solubility of DLTZ in an aqueous medium. Cellulose acetate (CA) and sorbitol were used as semipermeable membrane and pore former, respectively. The effect of different formulation variables namely concentration of osmogen in the core tablet, % pore former, % weight gain, pH of the dissolution medium and agitation intensity on the *in vitro* release was studied. DLTZ release was directly proportional to % pore former and inversely proportional to % weight gain. The optimized formulation (F8) delivered DLTZ independent of pH and agitation intensity for 12 h at the upper level concentration of % pore former (25% w/w) and middle level concentration of % weight gain (6% w/w). The comparative study of elementary osmotic pump (EOP) and controlled porosity osmotic pump revealed that it superior than conventional EOP and also easier and cost effective to formulate.

Key words: Cellulose acetate, CPOP, diltiazem hydrochloride, osmogen, sorbitol

INTRODUCTION

Conventional drug delivery systems have slight control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems. An osmotic drug delivery is a very promising approach. It utilizes the principle of osmotic pressure for controlled delivery of drugs. The system is simple and easy to formulate improved patient compliance with reduced dosing frequency and prolong therapeutic effect with uniform blood concentration.[1,2]

Osmotic systems form a major segment of drug delivery products. Because of their advantages and strong market potential, it appears that the future of osmotic systems in rate-controlled oral drug delivery is promising. The osmotic systems are needed when delivery rate of zero-order, delayed or pulsed, independent of gastric pH and hydrodynamic conditions, high degree of *in vivo - in vitro* correlation (IVIVC) is required.[3,4]

Hypertension is very common, occurring in over 50% of older people, and is a major risk factor for stroke and ischemic heart disease. Angina pectoris is a type of chest discomfort caused by poor blood flow through the blood vessels (coronary vessels) of the heart muscle (myocardium). Drug treatment of hypertension and angina pectoris saves lives and prevents unnecessary morbidity. Nowadays, calcium channel blockers such as diltiazem hydrochloride (DLTZ) are widely used for the treatment of angina pectoris, arrhythmia and hypertension. However, ~ 90% of an orally administered dose of DLTZ is absorbed; only 40% of the

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oral dose reaches systemic circulation in an unchanged form. The mean absolute bioavailability of DLTZ in normal subjects ranges from 33 to 44%. The drug undergoes rapid elimination that causes a short half-life (2–3 h). Thus, frequent administration (usually three to four times a day) makes it a suitable candidate for controlled release and/or sustained release (CR/SR) preparations.[5]

DLTZ is a freely water-soluble drug belongs to Class-1 of Biopharmaceutical Classification System (BCS). Because of its very high water solubility, the majority of the drug fraction was released predominantly at a first order rate rather than the desired zero order rate. Incorporating excipients that modulate the solubility of the drug within the system could be an ideal approach to control drug release.

Controlled porosity osmotic pump (CPOP) are reliable drug delivery system and could be employed as oral drug delivery system. CPOP consists of drug and osmogen in the core and tablet is surrounded by a semipermeable membrane (SPM) containing leachable pore forming agents which in contact with aqueous environment dissolves and result in formation of micro porous membrane. The membrane after formation of pores became permeable for both water and solutes.[6-9]

Drug release from these systems is independent of pH and other physiological parameters. Zero order release characteristics could be achieved by optimizing the parameters of the delivery system.[10]

MATERIALS AND METHODS

Materials

DLTZ was obtained as a gift sample from Wockhardt Ltd, Aurangabad, India. Cellulose acetate (CA-398-10NF), Microcrystalline cellulose (MCC PH 101), Poly Vinyl Pyrrolidone (PVP K30), Signet Pharma, Mumbai, India. Sodium chloride (Loba Chemicals, Mumbai, India), Lactose (ICPA Ltd, Ankleshwar, India). All other chemicals used were of analytical grade.

Drug Analysis

DLTZ was analyzed by double-beam UV–visible spectrophotometer (Shimadzu 1700 Pharm Spec) at λ max 236.20 nm. Calibration curves were prepared in deionized water, pH 1.2, phosphate buffer 6.8 and phosphate buffer 7.4 in the concentration range of 4-20 µg/ml. No enzymes were added to pH 1.2, phosphate buffer 6.8 and phosphate buffer 7.4.[11,12]

Drug-Excipients Compatibility Study

The drug-excipients compatibility study was done by differential scanning calorimetry (DSC), using a SHIMADZU DSC-60 differential scanning calorimeter. The system was calibrated with a high purity sample of Indium. The DSC thermograms were scanned at the heating rate of 20°C/min over a temperature range of 70-300°C. Peak transitions and enthalpy of fusion were determined for the samples using TA60 integration software.

The DSC analysis shows no change in endothermic peak of DLTZ. The study indicated that there was no drug-excipient incompatibility/interaction. DSC thermograms were shown in Figure 1.

Design and Development of Controlled Porosity Osmotic Pump Tablet

The core tablets were prepared by no aqueous granulation technique by using isopropyl alcohol (IPA). The ingredients were weighed accurately and kneaded in the mortar and pestle for 15-20 min., the alcoholic solution of PVP K30 (binder) was added to produce damp mass. The mass was passed through sieve no. 22. The resultant granules were air-dried for 12 h. The dried granules were then mixed with lubricant. The core tablets were compressed at an average weight of 450 mg using 11-mm concave punches and 6-7 kg/cm^2 hardness in 12 station rotary tablet machine (Labpress, Cip Machinery Ltd.).

The core tablets were coated with coating solution of Acetone: IPA (70:30% w/w) containing cellulose acetate (4% w/w in acetone) along with pore former i.e. sorbitol (25%

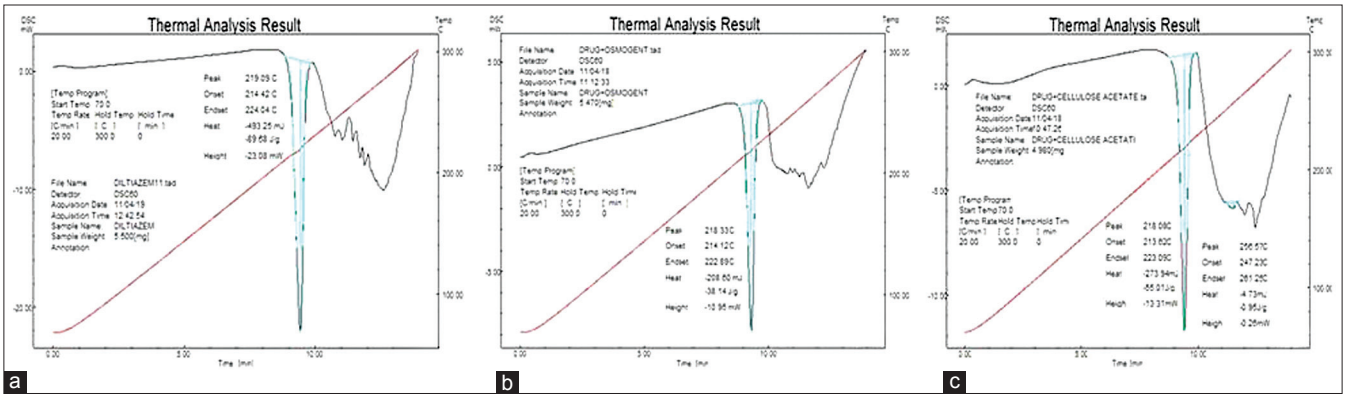

Figure 1: DSC thermograms (a) DLTZ, (b) DLTZ + Sodium chloride, (c) DLTZ + Cellulose acetate

w/w of total weight of polymer in isopropyl alcohol). The core tablets were coated using R and D pan coater (Ideal Cuers Ltd.) having 4-inch diameter pan with three baffles, pan load 15 g, pan speed 25 rpm, pump speed 1rpm, inlet temperature 45°C, air flow 1 kg/cm², spray nozzle diameter 1 mm, air gun distance from tablet bed 10 cm.

In Vitro Drug Release Study

The coated tablets were subjected to an *in vitro* drug release study as per USP Dissolution Test.1. The dissolution study was performed using the USP Apparatus 2 (Paddle) in 900 ml of deionized water for 12 h at 100 rpm and 37 ± 0.5°C. Aliquot of 5 ml were withdrawn at an interval of 1, 3, 5, 7, 9, 11 and 12 h. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper and analyzed by double-beam UV–visible spectrophotometer (Shimadzu 1700 Pharm Spec) at λ max 236.20 nm.

The Effect of Formulation Variables on Drug Release

Drug release from osmotic tablets is affected by formulation variables. The formulated tablets were evaluated to analyze the effects of variables such as the amount of osmogen in the core tablet, concentration of pore former and % weight gain by coating on drug release, pH of the dissolution medium and agitation intensity.

RESULTS AND DISCUSSION

Optimization of Sodium Chloride in Core Tablet

McClelland *et al*. suggested that incorporating sodium chloride can modulate the solubility of DLTZ within the system to control drug release.[13,14] In the present study sodium chloride was added to the core tablet to alter the solubility of DLTZ in an aqueous medium [Table 1].

During the preliminary study concentration of drug and excipients in the core tablet, % pore former (25% w/w) and % weight gain (4% w/w) was kept constant.

The results revealed that incorporating sodium chloride at a concentration of 20 mg/tablet retarded the drug release rate from 30 to 20 mg/h during a period of 6 h. No further improvement was achieved with a higher concentration of sodium chloride in the core tablet [Figure 2]. The 20 mg/tablet concentration of sodium chloride was selected as an optimized concentration of osmogen for further study.

Table 1: Optimization of sodium chloride in core tablet

Ingredients	Weight (mg)					
	D1	D2	D3	D4	D5	D6
Diltiazem hydrochloride	120	120	120	120	120	120
Sodium chloride	5	10	15	20	25	30
PVP K30	30	30	30	30	30	30
Lactose	30	30	30	30	30	30
MCC	240	240	240	240	240	240
Magnesium stearate	5	5	5	5	5	5
Talc	2	2	2	2	2	2
Total weight	432	437	442	447	452	457

Evaluation of Consistency of Coat

To study the consistency of coat, formulations were formulated using sodium chloride (30 mg) as an osmogen (excess of osmogen to burst the external coat). The tablet comprised DLTZ (120 mg), sodium chloride (30 mg), PVP K30 (30 mg), lactose (30 mg), MCC (243 mg), magnesium stearate (5 mg) and talc (2 mg). The tablets were then coated with a coating composition (25% w/w pore former), which was constant for the formulations to get a weight gain of 1, 2, 3, 4, 5, 6, 7, and 8% w/w. The results revealed that as the % weight gain increased, the consistency of coat increased but the drug release decreased [Table 2].

Effect of Various Concentrations of Pore Former and % Weight Gain on Drug Release

In order to study the effect of various concentration of pore former and % weight gain on *in vitro* drug release, the tablets were coated as per factorial design formulations [Table 3].

The results revealed that the increase in the concentration of pore former the drug release increased, but again reduced

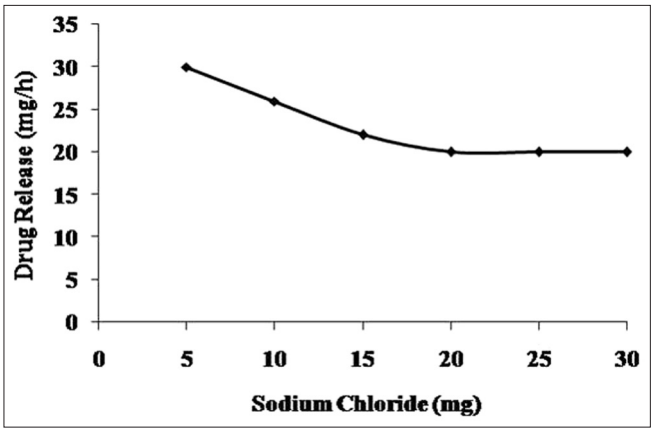

Figure 2: Effect of sodium chloride on drug release

Table 2: Evaluation of consistency of coat

Formulation code	% Weight gain	% release	Coat consistency
D1	1	105.19	+
D2	2	98.09	+
D3	3	85.65	+
D4	4	69.06	++
D5	5	65.91	++
D6	6	60.30	+++
D7	7	51.38	+++
D8	8	38.94	+++

+: Burst, ++: Swell, +++: No change

the drug release after an increase in the external coat thickness i.e. % weight gain [Figures 3 and 4]. Pore former (sorbitol) produces a significant effect on release profile. A decrease in pore former concentration, system fails to release 100% drug. The dissolution profiles of all formulations F1-F8 revealed that formulation F8 meets USP Dissolution Test 1 acceptance criteria.

Table 3: Formulation of factorial design formulations

Ingredients (mg)	Formulations								
Core tablet	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
DLTZ	120	120	120	120	120	120	120	120	120
Sodium chloride	20	20	20	20	20	20	20	20	20
PVP K30	30	30	30	30	30	30	30	30	30
Lactose	30	30	30	30	30	30	30	30	30
MCC	243	243	243	243	243	243	243	243	243
Mg. stearate	5	5	5	5	5	5	5	5	5
Talc	2	2	2	2	2	2	2	2	2
Total weight	450	450	450	450	450	450	450	450	450
Coating									
X_1 [% Sorbitol (w/w)]	15	15	15	20	20	20	25	25	25
X_2 [% Weight gain (w/w)]	4	6	8	4	6	8	4	6	8

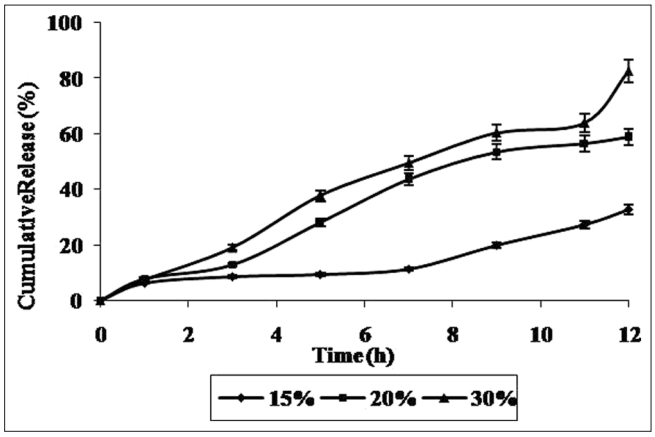

Figure 3: Effect of various concentrations of pore former on drug release

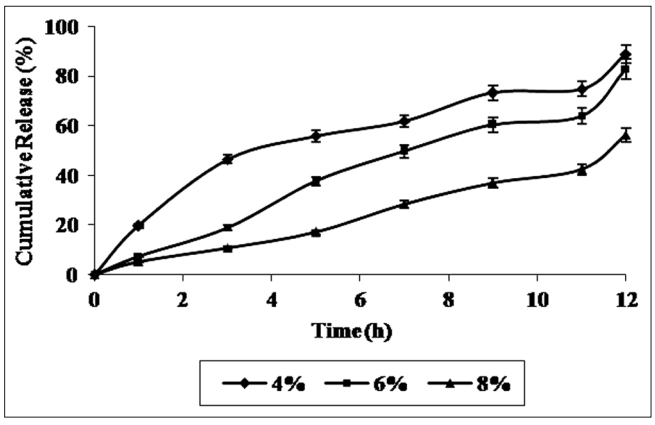

Figure 4: Effect of %weight gain on drug release

Analysis of Data by Design Expert Software

The 3^2 factorial design was selected to study the effect of independent variables % pore former (X_1) and % weight gain (X_2) on dependent variables Q_3, Q_9 and Q_{12}. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses [Eq.1]

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2 \quad [1]$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i(b_1, b_2, b_{12}, b_{11} and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1, X_2, X_{12}, X_{11}, and X_{22}), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The Q_3, Q_9 and Q_{12} for the nine formulations of design showed a wide variation. The responses of the formulations prepared by 3^2 factorial designs were observed. The responses clearly indicate that the Q_3, Q_9 and Q_{12} values are strongly dependent on the selected independent variables. The fitted regression equations relating the responses Q_3, Q_9 and Q_{12} are shown in the following equations, respectively [Eqs. 2-7].

Final Equations in Terms of Coded Factors:

$$Q_3 = 11.91 + 5.7415\ X_1 - 4.1554\ X_2 - 4.5812\ X_1X_2 + 2.2438\ X_1^2 + 0.2912\ X_2^2 \quad [2]$$

Final equations in Terms of Actual Factors:

$$Q_3 = 11.91 + 5.7415*\text{Pore Former} - 4.1554*\text{Weight Gain} - 4.5812*\text{Pore Former}*\text{Weight Gain} + 2.2438*\text{Pore Former}^2 + 0.2912*\text{Weight Gain}^2 \quad [3]$$

(r^2=0.9598)

Final Equations in Terms of Coded Factors:

$$Q_9 = 46.31 + 17.3936\ X_1 - 16.9835\ X_2 - 3.4985\ X_1X_2 - 2.6627\ X_1^2 - 6.4698\ X_2^2 \quad [4]$$

Final equations in Terms of Actual Factors:

$$Q_9 = 46.31+17.3936*\text{Pore Former}-16.9835*\text{Weight Gain} - 3.4985*\text{Pore Former}*\text{Weight Gain} - 2.6627*\text{Pore Former}^2 - 6.4698*\text{Weight Gain}^2 \quad [5]$$

(r^2=0.9478)

Final Equations in Terms of Coded Factors:

$Q_{12} = 53.44 + 22.5435\ X_1 - 19.0482\ X_2 + 0.2078\ X_1X_2 + 6.8697\ X_1^2 - 10.429\ X_2^2$ [6]

Final equations in Terms of Actual Factors:

Q_{12} = 53.44+22.5435*Pore Former–19.0482*Weight Gain + 0.2078*Pore Former*Weight Gain + 6.8697*Pore Former^2 – 10.429*Weight Gain^2 [7]

(r^2=0.9711)

The regression coefficient values are the estimates of the model fitting. The r^2 was high indicating the adequate fitting of the quadratic model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e., positive or negative.

The first variable X_1 (% Pore Former) showed positive coefficient in case of responses Q_3, Q_9 and Q_{12} i.e., increase in % pore former result in increased total release after 12 h. The second variable X_2 (% Weight Gain) showed negative coefficient for responses Q_3, Q_9 and Q_{12} i.e., increase in % weight gain result in decreased total release after 12 h.

ANOVA study

Evaluation and interpretation of research findings are important and the p-value serves a valuable purpose in these findings. The coefficients of X_1 and X_2 were found to be significant at $P < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. Overall both the variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 7.1.4 software.

Response surface plot

The response surface plots were generated using Design Expert 7.1.4 software, Figure 5 to observe the effect of independent variables on the response studied such as Q_3, Q_9 and Q_{12}, respectively. The response surface plots reveal that various combinations of independent variables X_1 and X_2 may satisfy any specific requirement (i.e. maximum drug release upto 12 h) while taking into consideration of various factors involved in dosage form.

Grid analysis

The grid analysis was performed for selection of the optimized level for Q_3, Q_9 and Q_{12}. The best results for Q_3, Q_9 and Q_{12} was obtained at the upper level concentration of % pore former (25% w/w) and middle level concentration of % weight gain (6% w/w) which revealed the release profile (Q_3, Q_9 and Q_{12}) as per the USP Test 1 acceptance criteria. The formulation F8 was selected as optimized formulation.

Effect of pH on drug release

To study the effect of pH, optimized formulation (F8) was subjected to dissolution studies separately in pH 1.2, Phosphate buffer 6.8 and Phosphate buffer 7.4 for 9 h. The system was independent of the pH since there was no difference in the drug release. This was an important performance test because, if the semipermeable membrane was truly selective, diffusion of ions into the osmotic pump would be negligible which should affect the release profiles. In other words, the osmotic tablets exhibited media independent release. Thus, the fluid in different parts of GI tract will scarcely affect drug release from the osmotic system.

Effect of agitation intensity on drug release

To study the effect of agitation intensity, optimized formulation (F8) was subjected to dissolution in deionized water at 50, 75 and 100 rpm. There was no significant difference in the release profile of the system with change in agitation intensity. Thus the optimized formulation (F8) delivered DLTZ independent of hydrodynamic conditions.

Surface morphology study

To evaluate the surface morphology of the coating membrane, surfaces of the optimized formulation (F8) were examined using scanning electron microscopy (SEM) both before and after dissolution (XL30 ESEM TMP+EDAX, Philips) [Figure 6]. Membranes were dried at 45°C for

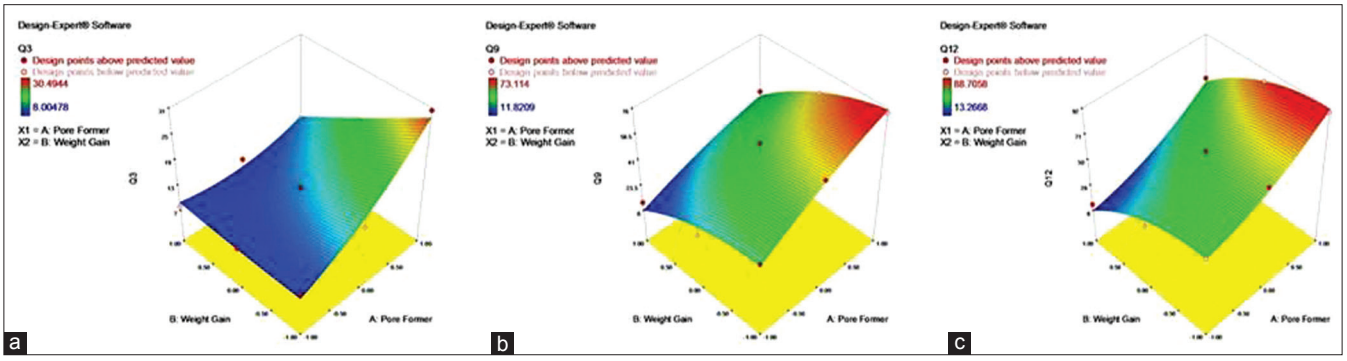

Figure 5: Response surface plots (a) Q3, (b) Q9, (c) Q12

12 hours and stored between sheets of wax paper in a dessicator until examination.

Figure 6 [a] shows membrane structure before dissolution, initially the surface of coated tablets was smooth before coming into contact with aqueous environment and coats appeared to be free of pores. A microporous structure of the membrane after dissolution was observed from Figure 6 [b], which shows SEM of membrane after dissolution. This significant porosity has resulted due to leaching of water-soluble additive i.e., sorbitol during dissolution through which drug release takes place.

Stability study

The optimized formulation (F8) was packed in aluminium foil and subjected to stability studies as per ICH guidelines, 40°C ± 2°C/75% RH ± 5% RH (Thermolab).[15] Samples were withdrawn at time intervals of 1, 2 and 3 month. The samples were evaluated for appearance; assay and *in vitro* release profile [Table 4].

The results revealed no significant change in the parameters. Therefore, the formulation F8 is considered to be stable.

Comparative study of CPOP and EOP

The formulation for EOP comprised of DLTZ (120 mg), sodium chloride (20 mg), PVP K30 (30 mg), lactose (30 mg), MCC (243 mg), magnesium stearate (5 mg) and Talc (2 mg) and coated with 6% weight gain (optimized level of factorial formulation was considered) without pore former (sorbitol). The new formulated tablets were drilled with mechanical drill. Orifice size 0.5 mm, 0.8 mm and 1 mm were selected [Table 5]. The orifice size was observed by optical microscopy (Olympus CX31) for coated tablets [Figure 7]. The dissolution profile of EOP system was compared with optimized formulation F8.

From the dissolution profile of EOP system it was found that formulation F10 having orifice size 0.5 mm delivered drug upto 8 h and formulation F11 (0.8 mm orifice size) for 6 h. Formulation F12 with orifice size 1 mm released 100% drug within 4 h. The study revealed that CPOP is superior to conventional EOP, because optimized formulation F8 delivered DLTZ for 12 h and also easier and cost effective to formulate [Figure 8].

CONCLUSIONS

The release of highly water soluble DLTZ is modulated through incorporation of optimized concentration of sodium chloride into the core tablet. A 3^2 factorial design was performed, and the desired release of DLTZ from the CPOP was achieved through careful monitoring of the selected formulation variables. The variables % pore former (sorbitol) and % weight gain (cellulose

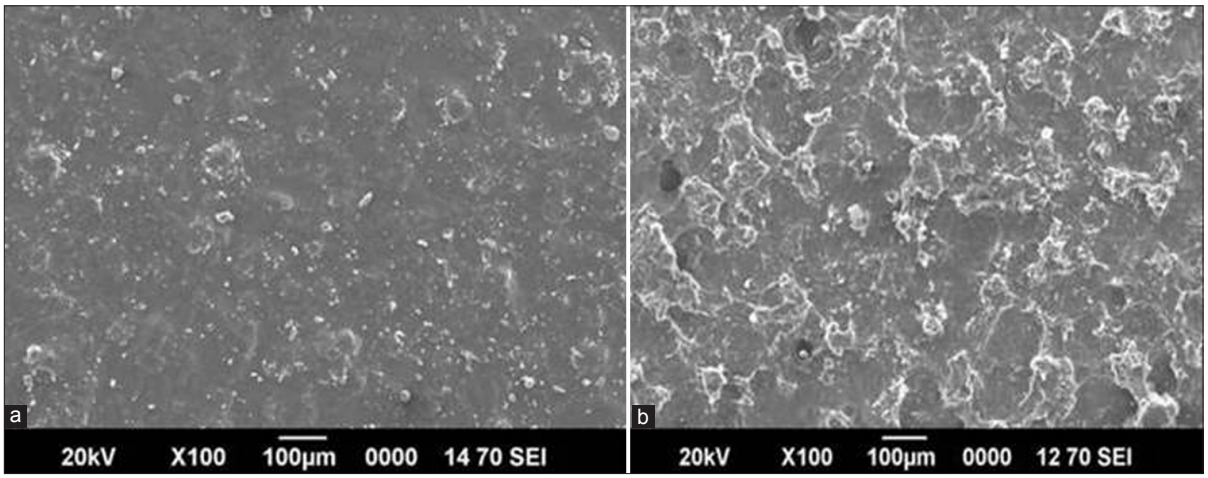

Figure 6: SEM microphotographs of DLTZ CPOP tablet at 100x (a) before dissolution, (b) after dissolution

Table 4: Stability study

Tests	Limits	Initial	1 month	2 months	3 months
Appearance	No change	No change	No change	No change	No change
Assay	Diltiazem hydrochloride USP (NLT 90% to NMT 110% of labeled amount of Diltiazem hydrochloride)	101.60	101.52	101.44	100.40
Cumulative release (%)	3 h = 10 to 25	18.94	18.80	18.65	18.47
	9 h = 45 to 85	60.29	60.10	59.95	59.73
	12 h = NLT 70	82.65	82.61	82.45	82.21

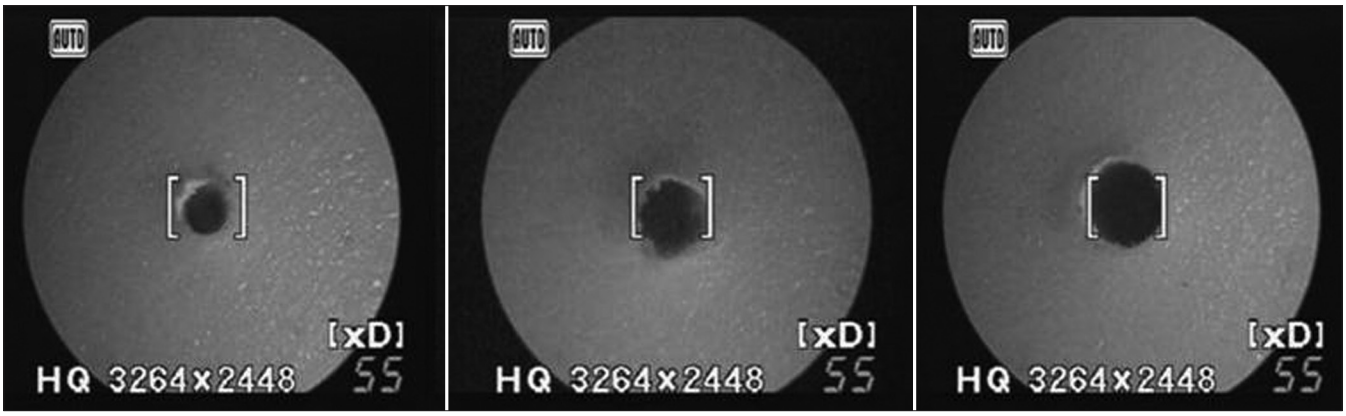

Figure 7: Optical microscopy of EOP (F10, F11, F12)

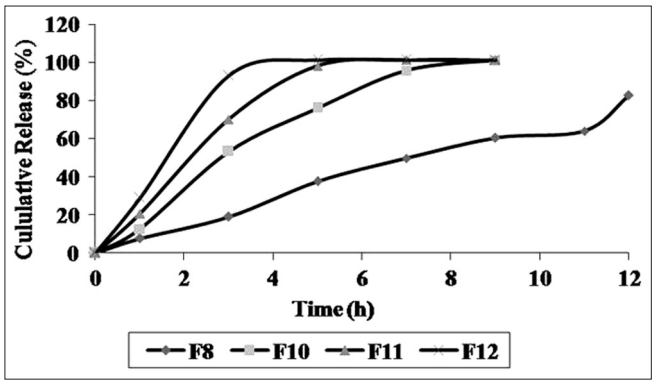

Figure 8: Dissolution profile of CPOP and EOP tablets (F8 and F10-F12)

Table 5: Orifice size of EOP tablets

Formulation code	Orifice size (mm)
F10	0.5
F11	0.8
F12	1

EOP- Elementary osmotic pump

acetate coat weight) evaluated in the study exhibited significant effect on the responses Q_3, Q_9 and Q_{12} of the formulations. It is evident that increase in concentration of pore former the drug release from the system was found to be increased, but again reduced the drug release after an increase in the external coat thickness i.e., % weight gain. The grid analysis was performed for the selection of optimized level for release profile (Q_3, Q_9 and Q_{12}) revealed F8 as the optimized formulation. The best results for Q_3, Q_9 and Q_{12} was obtained at the upper level concentration of % pore former (25% w/w) and middle level concentration of % weight gain (6% w/w) which revealed the release profile (Q_3, Q_9 and Q_{12}) as per the USP Test.1 acceptance criteria. The optimized formulation (F8) delivered DLTZ independent of pH and agitation intensity and was found to be stable. The comparative study of EOP and CPOP revealed that EOP failed to deliver DLTZ for long period (NMT 8 h), but CPOP delivered DLTZ for 12 h. Thus, CPOP is superior to conventional EOP and also easier and cost effective to formulate. Finally, it is concluded that release of DLTZ is significantly controlled from the controlled porosity osmotic delivery system and thus it is a promising approach for the treatment of angina pectoris and in the management of hypertension.

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