AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Design and Development of Osmotic Drug Delivery of Verapamil HCl

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ABSTRACT

The objective of this study was to develop and evaluate controlled porosity osmotic pump tablet (CPOP) system to deliver Verapamil HCl inacontrolledmannerupto24 h. The porous osmotic pump contains pore forming water soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an in situ formation of a microporous structure. Mannitol was used as an osmotic agent and cellulose acetate (CA) was used as semipermeable membrane. Polyethylene glycol 400(PEG-400) was employed as a pore forming agent as well as plasticizer for controlling membrane porosity. The influences of drug: osmogent ratio, concentration of PEG-400 and membrane thickness on the release profiles were investigated using 2^3 full factorial design and optimized batch was investigated in different environmental media and stirring rates. It was found that drug release rate increased with the amount of osmogent due to the increased water uptake, and hence increased driving force for drug release. This could be retarded by the proper concentration of channelling agent and membrane thickness in order to achieve the desired zero order release profile. This system was found to deliver Verapamil HCl at a zero order rate for24 h. The optimized formulations were subjected to stability studies as per ICH guidelines at different temperature and humidity conditions.

Keywords: verapamil hydrochloride; osmotic pump; kinetic study; 2^3 factorial designs.

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Received 4 May 2012, Accepted 15 May 2012

Please cite this article in press as: Doshi RK *et al.*, Design and Development of Osmotic Drug Delivery of Verapamil HCl. American Journal of PharmTech Research 2012.

INTRODUCTION

Conventional oral drug delivery systems supply an instantaneous release of drug, which cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility etc. Controlled release device are the most promising strategy based system over conventional drug delivery[1].

The objective of controlled drug release is to deliver a pharmacologically active agent in a predetermined, predictable, and reproducible manner. Since the formulation is metered as a portion of the entire dose at any given time and provides a reduced or once-a-day dosage regimen, controlled drug delivery offers improved patient compliance with reduced side effects. Therefore, the term controlled release includes modulated release systems as well as zero-order release systems. These systems provide actual therapeutic control despite not providing constant drug concentrations[2].

Osmotically controlled oral drug delivery systems (OCODDS) utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.(**figure**1)[3]

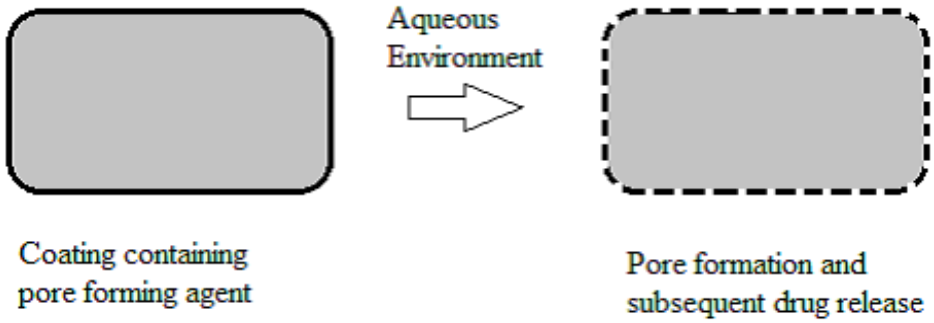


Figure 1. Mechanism of drug release by controlled porosity osmotic pump tablet

Verapamil Hydrochloride, an oral and intravenous calcium-channel blocking (CCB) agent, is useful for the treatment of angina, hypertension, and supra ventricular tachyarrhythmia[4]. It is completely absorbed from the gastrointestinal tract. Its biological half-life is 4 to 6 h with a usual dose of 40 to 120 mg three times a day. Because of the high frequency of administration and short biological half-life, the formulation of a controlled release dosage form is very useful[5].

Thus, there is a strong clinical need and market potential for a dosage form that will deliver Verapamil hydrochloride 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 extended release formulations of Verapamil hydrochloride 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 formulations evaluated after 3 months of storage at accelerated stability conditions as per ICH guidelines.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride (Astron pharmaceutical Pvt. Ltd., India) was used as the model drug. Mannitol (Maple biotech Pvt. Ltd., India) was used as an osmotic agent. Cellulose acetate (Amneal India Pvt. Ltd., India) was used as semipermeable membrane. Polyethylene glycol 400 (Finar Chemicals Pvt. Ltd., India) was employed as pore former and plasticizer for controlling membrane porosity. Microcrystalline cellulose (MCC) (Maple biotech Pvt. Ltd., India) was used as a diluent. The other chemicals used were of analytical grade and double distilled deionised water was used in all experiments.

Drug excipient interaction study

The possibility of drug excipient study was investigated by Fourier transform infrared spectroscopy (FTIR). FTIR spectra were obtained by using an FTIR spectrometer~430 (Shimadzu). The FTIR of pure drug and formulation were recorded. The drug Verapamil hydrochloride and Formulation previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:10 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders. Scans were obtained at a resolution of 4 cm^{-1}, from 2,000 to 400 cm^{-1}.[6]

Preparation of core tablet

Verapamil hydrochloride powder, Mannitol and MCC were mixed manually. These powders were then blended with magnesium stearate and talc. Resultant powder mixture was compressed into tablets on 12 mm concave punches under a pressure of 8×10^6 Pa. The weight of each tablet was determined to be within the range of 420 ± 15 mg in order to maintain the relatively constant volume and surface area. The core compositions are listed in **Table** 1.

Table 1:Core formulation of verapamil hydrochloride

Ingredients (mg/tablet)	Core code	
	A1	A2
Verapamil hydrochloride	180	180
Mannitol	90	180
MCC	140	50
Talc	5	5
Magnesium stearate	5	5

Table 2:Micro porous semipermeable membrane coating formulation

Ingredients (mg/tablet)	Coating composition	
	B1	**B2**
Cellulose acetate	3%	3%
PEG 400	10%	20%

Composition of CA was given in terms of % w/v in acetone and composition of PEG 400 was given in terms of % w/w with respect to concentration of CA.

Micro porous semipermeable membrane coating

Cellulose acetate in acetone containing different levels of pore forming agent (PEG 400) was used as coating formulation (Table 2). The weight gains of micro porous semipermeable membrane were 4% and 6%, respectively. PEG 400 also acted as hydrophilic plasticizer which enhances the physical–mechanical property of CA membrane. The coating conditions were as follows: stainless steel pan, 200 mm diameter, rotation rate of the pan- 35 rpm, nozzle diameter of spray gun- 1 mm; spray rate- 2 ml/min, spray pressure- 2 bar, drying temperature- 50°C. After coating, the tablets weredried for 12 h at 45°C to remove residual solvent.

Factorial design

In this study, 2^3 factorial design was used where three factor where evaluated each at two levels and experimental trials where performed at all 8 possible combination. The ratio of drug: osmogent, concentration of pore former and % weight gain of coating were selected as independent variable. Table 3 summarised dependent variable and independent variables on and resulted formulation were listed on Table 4.

Table 3:Experimental design: Independent and dependent variables

2^3 factorial design				
Independent variables				
Coded factor	level	X1 Drug:Osmogent ratio(Mannitol)	X2 Conc. of pore former(PEG 400)	X3 % Wt. gain
-1	Low	1:0.5	10%	4%
+1	high	1:1	20%	6%
Dependent variables				
Drug release at 2, 12, 18 h.				

Table 4:Formulation of factorial design batches.

Batch code	V1	V2	V3	V4	V5	V6	V7	V8
Ingredients(mg)	**Core tablet**							
Verapamil hydrochloride	180	180	180	180	180	180	180	180
Mannitol	90	180	90	180	90	180	90	180
MCC	140	50	140	50	140	50	140	50
Talc	5	5	5	5	5	5	5	5
Mag.stearate	5	5	5	5	5	5	5	5
Coating composition								
Cellulose acetate	3%	3%	3%	3%	3%	3%	3%	3%
PEG 400	10%	10%	20%	20%	10%	10%	20%	20%
%weight gain	4%	4%	4%	4%	6%	6%	6%	6%

In vitro drug release study

Tablets were subjected to an in vitro drug release study using the USP Type II dissolution test apparatus. Operating conditions were 37° ± 0.5° C and a paddle speed of 50 rpm with 900 ml of 0.1 N HCl (pH = 1.2) for first 2 h and then further study was conducted in 900 ml phosphate buffer (pH = 6.8) (According to IP 2010) as the medium for drug release study up to 24 h. Samples of 5 ml were withdrawn at every hour, and the same amount of liquid was replaced with fresh dissolution medium. Samples were filtered and suitably diluted, and the absorbance was measured at 278 nm in a double beam UV visible spectrophotometer (Shimadzu, Kyoto, Japan).

Release models and kinetics[7]

In order to describe the kinetics of drug release from the preparations, various mathematical equations have been proposed. The zero-order equation (Eq. 1), the first-order equation (Eq. 2), the Higuchi model (Eq. 3) and the Korsemeyer and Peppas model (Eq. 4) were used in the present study:

$m = k \times t$ ---------- eq. 1

$m = e^{a} \times e^{-bt}$ ---------- eq. 2

$m = (100 - q) \times t^{½}$ ---------- eq. 3

$Mt / M\alpha = K \times t^{n}$ ---------- eq. 4

Where, k is zero order constant, q is the Higuchi constant (% per square root of time), m is % drug released, t is the time, a is intercept, b is slope, Mt / Mα is the fraction of drug release at time t and n is diffusion exponent, if n is equal to one the release is zero-order, if n is equal to 0.5 the release is best explained by Fickian diffusion, and if $0.5 < n < 0.85$ then the release is through anomalous diffusion.

Statistical analysis

The results of ANOVA for factorial design bathes are shown in Table 5 using design expert software. To demonstrate graphically the influence of each factor on responses, the response surface plots were generated using Statistica software. The value of $P<0.05$ was considered to be significant.

Table 5.:Regression analysis values for dissolution data of formulations according to various kinetic models.

Kinetic model	Para-meter	Formulations							
		V1	V2	V3	V4	V5	V6	V7	V8
Zero order	R^2	0.998	0.997	0.996	0.998	0.999	0.999	0.996	0.998
first-order	R^2	0.893	0.907	0.920	0.931	0.884	0.888	0.896	0.912
Higuchi model	R^2	0.984	0.988	0.988	0.987	0.982	0.981	0.988	0.989
Korsemeyer	R^2	0.995	0.998	0.998	0.999	0.995	0.994	0.997	0.997
and Peppas	n	1.018	1.002	1.014	0.966	1.135	1.059	1.059	1.022

$R^2$is regression coefficient and n is diffusion exponent

Effect of pH and agitation speed

To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) and SIF (pH 6.8) for the period of 24 h. The samples (5 ml) were withdrawn at predetermined intervals and analysed after filtration through 0.45- mm nylon membrane filters.

In order to study the effect of agitation intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP-II at 50, 100 and 150 rpm. Samples were withdrawn at predetermined intervals and analysed after filtration through 0.45- mm nylon membrane filters[8].

Scanning electron microscopy (SEM)

Separated coating membranes (varying in chitosan concentration) obtained before and after the dissolution test, respectively, were examined for their porous morphology by scanning electron microscope (Institute of plasma research, Gandhinagar, India). Membranes were dried at 45° C for 12 h and stored between sheets of wax paper in a desiccators before examination. The membrane samples were sputter coated for 5–10 min with gold by using fine coat ion sputter and examined under SEM.[9]

Accelerated stability studies

Optimized formulations of Verapamil hydrochloride were packed in strips of 0.04 mm thick aluminium foil laminated with PVC. The packed formulations were stored in ICH certified

stability chambers maintained at 40° C and 75% RH for 3 months. The samples were withdrawn periodically and evaluated for drug release studies[10].

RESULT AND DISCUSSION

Drug excipient interaction study

The interaction of drug and polymer was studied by FTIR which is shown in figure 2 and it was found that there was no interaction of drug with polymer and other excipients.

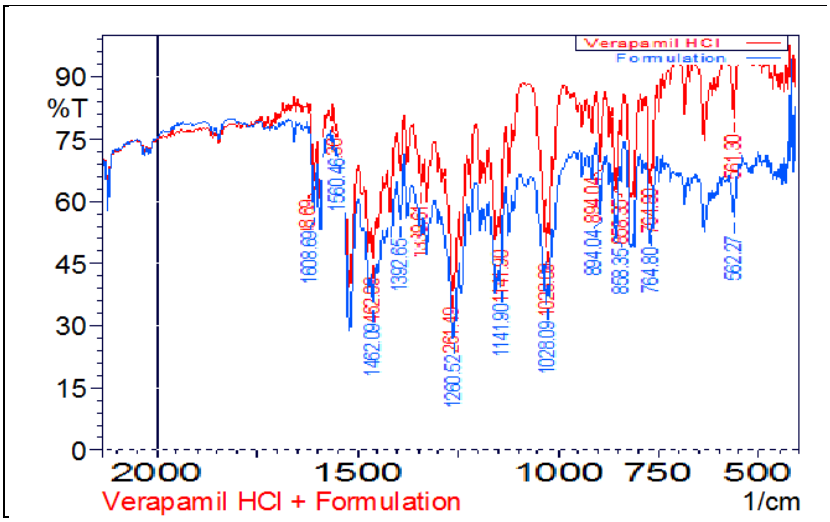


Figure 2. FTIR study of the pure drug and the drug combine with the excipient.

Influence of factors on drug release by dissolution study (figure 3)

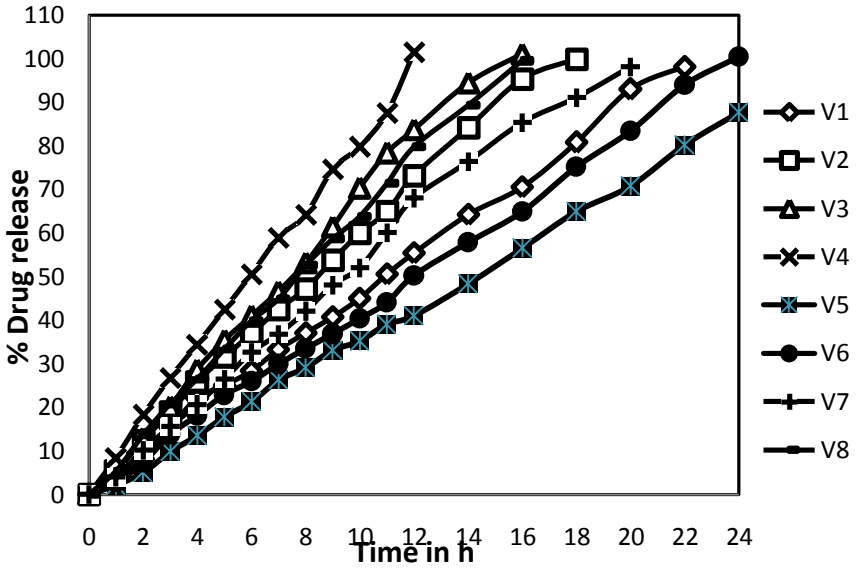


Figure 3. In vitro drug release study of factorial batches V1 to V8

Effect of concentration of osmotic agent

Different amount of osmotic agent (mannitol) was used to study drug release (drug: osmogent ratio was 1:0.5 and 1:1). Concentration of mannitol increase, water uptake inside core material is

increases as a result higher osmotic pressure creates and higher amount of drug release occur. In batch V1 drug: osmogent ratio is 1:0.5 having t90% was observed 18.2 h and in batch V2 drug: osmogent ratio is 1:1 having t90% was observed 15.7 h. As increase in concentration of osmogent, drug release also increases. So it clearly indicates that increase in concentration of osmogent, drug release also increases.

Effect of level of pore former

To study effect of the amount of pore former on drug release, cores were coated with controlling membrane containing different amount of PEG400 (10% and 20% w/w of amount of cellulose acetate). Various release patterns were obtained when different amount of PEG400 was contained in the coating membranes. When PEG400 in the membrane was used in range of 10% to 20% the membrane became too porous after coming in contact with dissolution media to control Verapamil HCl release, and a zero order release profile was observed. V1 batch contain 10% pore former, t 90% observed was 19.2 h and V3 batch contain 20% pore former, t 90% observed was 14.9 h. So it indicates that drug release increases with increases in concentration of pore former.

Effect of weight gain

To study the effect of weight gain of the coating on drug release, core tablets of Verapamil hydrochloride were coated so as to get tablets with different weight gains (4 and 6% w/w). Release profile of drug from these formulations is shown in Figure 3. V2 batch contain 4% wt. gain, t 90% observed was 15.7 h and V6 batch contain 6% wt. gain, t 90% observed was 21.8 h. It is clearly evident that drug release decreases with an increase in weight gain of the membrane.

Table 6:Multiple regression analysis for dependable variables

Batch no.	Q2	Q12	Q18	N	k
V1	8.17	55.36	80.74	1.01852*	0.044289
V2	12.41	73.16	99.95	1.002614*	0.059757
V3	13.03	83.73	101.16	1.014053*	0.06613*
V4	18.19	101.56	101.56*	0.966268*	0.089062
V5	4.95	40.98	64.90	1.135235*	0.025424
V6	7.34	50.26	75.12	1.059465*	0.03628
V7	10.15*	68.05*	91.11	1.059167*	0.046081*
V8	13.67	79.75	99.67	1.022153*	0.06214
R^2	0.99996	0.99963	0.99973	0.96511	0.99977
p	0.0117	0.0360	0.0303	0.3421	0.0285

Q2, Q12 and Q18 are the drug release at 2, 12 and18 h respectively, n is diffusion exponent and k is zero order constant.* indicate the value is insignificant at P = 0.05.

Release model and kinetic study

Zero order, Higuchi model and Korsemeyer Peppas model plots of CPOP containing hydrophilic polymers suggested linearity and endorse the opinion that the formulations may follow one of these models. The higher regression coefficient of the zero order plot seem to better fit, whereas Korsemeyer Peppas model and Higuchi models comparatively showed lesser regression coefficient values (Table 5). The n values calculated from the Korsenmayer Peppas model suggested that formulations followed n > 0.85 (Table 6). It indicates that formulations follow purely dissolution based zero order drug release.

Statistical analysis

The result of multiple regression analysis was given in table 6.

All P values of dependable variables are <0.05 except n value. n value is found to be insignificant indicate drug release was not based on diffusion, it's based on dissolution. Significant value of k indicates that drug release is zero order.

Polynomial equation for all dependable variables:

Q2 = 11.0 + 1.91 x1 + 2.77 x2 - 1.96 x3 + 0.256 x12 - 0.437 x13 + 0.110 x23 + 0.02 x123

Q12 = 34.6 + 3.78 x1 + 6.45 x2 - 4.62 x3 + 0.457 x12 - 0.754 x13 - 0.140 x23 + 0.17 x123

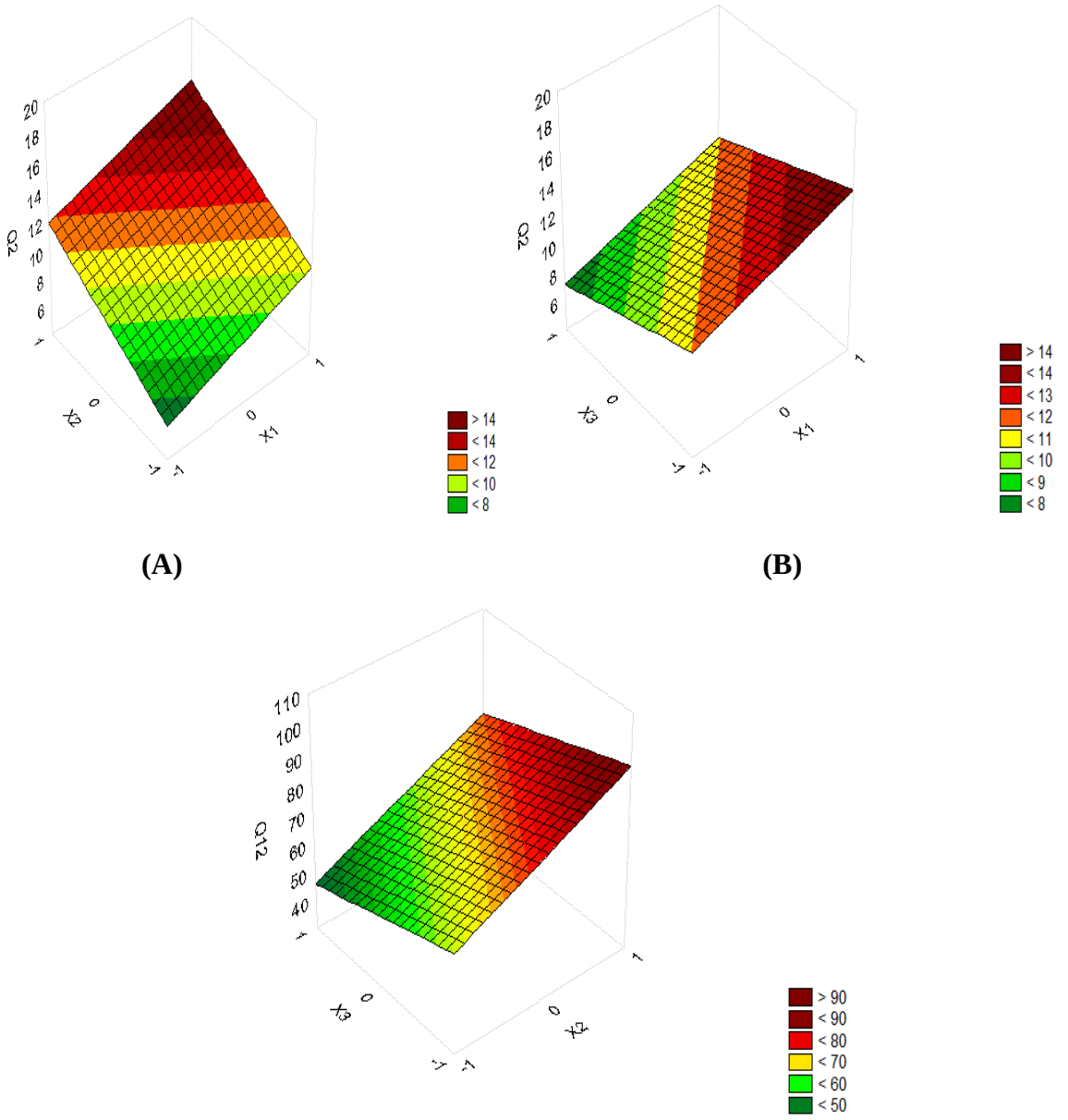
Q18 = 69.1 + 7.08 x1 + 14.2 x2 - 9.35 x3 + 0.306 x12 - 1.83 x13 - 0.026 x23 + 0.31x123

k = 0.06 + 0.01 x1 + 0.01 x2 - 0.01 x3 + 0.002 x12 - 0.002 x13 – 0.01 x23

The positive sign ofX1 and X2 indicate that as the level of X1 and X2 increases, drug release increases. The coefficient of X2 was greater than coefficient of X1 indicating that drug release effect of X2 was more compare to X1. The negative sign of X3 indicates that as X3 increases, drug release decreases. X12, X13, X23 are the interaction effect of two variables and X123 is interaction effect of three variables.

Surface Response (RSM) Plot for Q12 dependable variable

The graphical representation for effect of all factors was shown in **figure** 4 by RSM. It demonstrates that when the X1 and X2 value varied from -1 to 1, drug release increases, while X3 value varied from -1 to 1, drug release decreases. Thus the effect of X1 and X2 was decreased by increased in effect of X3 that leads to find out optimize batch that release drug for 24 h at zero order rate.



(A) **(B)**

(C)

Figure 4.Surface Response Plot for Q12 dependable variable (A) effect of X1 and X2(B)effect of X1 and X3 (C)effect of X2 and X3

Effect of pH and agitation speed

To investigate the influence of release media on drug release, in vitro release tests were conducted in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) respectively. **Figure** 5(a) shows the release profiles of the Verapamil HCl CPOP tablet in these release media. p values were both larger than 0.05 (0.590, 0.543). It indicates that there was no significant effect of media on drug release.

To study the effect of agitation rate on drug release profiles, release tests of Verapamil HCl CPOP tablet were also carried out at agitation rates of 50, 100 and 150 rpm, respectively. The profiles at various agitation rates are presented in Figure 5(b). p values were both larger than 0.05 (0.330, 0.341). It showed that a change in agitation rate did not significantly affect drug release.

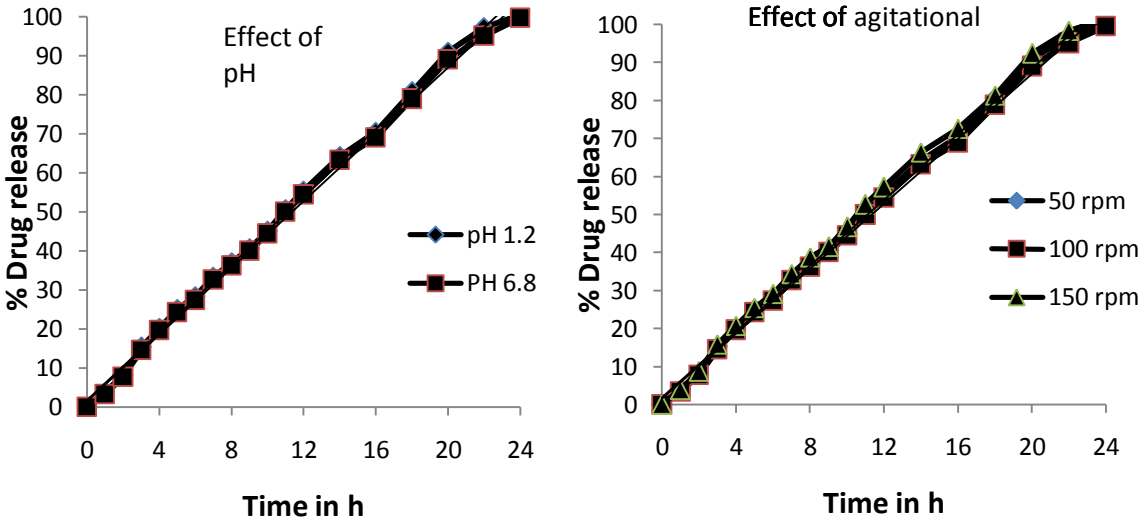
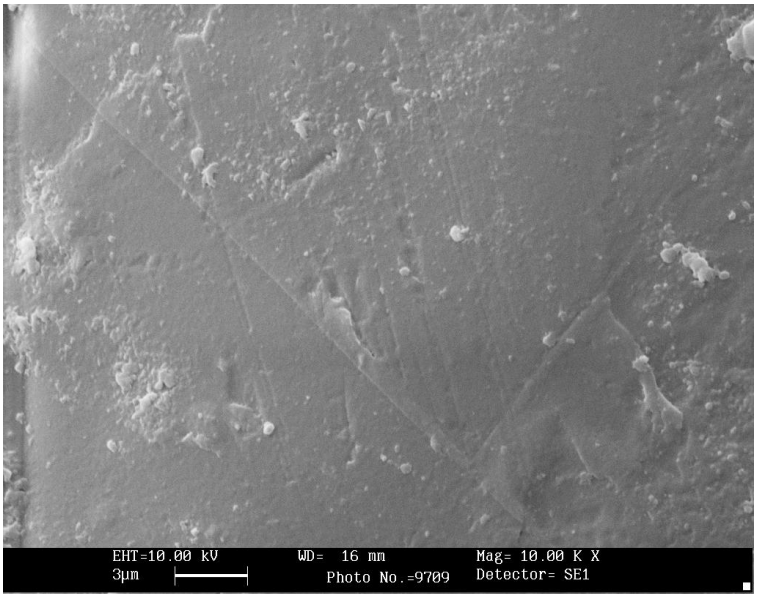


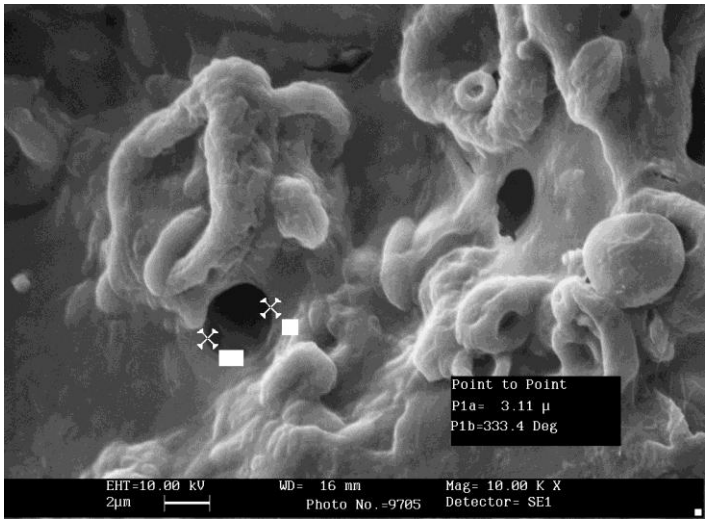
Figure 5. Effect of (a) pH on drug release (b) agitation speed on drug release of batch V1

Scanning electron microscopy

Cellulose acetate membranes obtained before and after dissolution, were studied by SEM. After the completion of dissolution, exhausted membrane contained pore former (PEG 400, 10 %) showed a micro porous region (**Figure** 6).



(a)



(b)

Figure 6. SEM of (a) before dissolution (b) after 24 h dissolution of batch V1

Stability study of optimize batch V1

It was observed that the tablet of optimized batch V1 was stable for the three months at 40° C, 75% RH as specified by the ICH guidelines (figure 7).

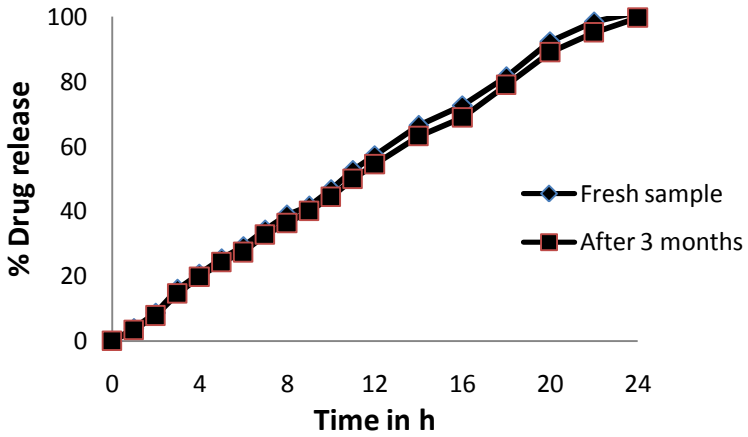


Figure 7. Stability study of optimized batch V1

CONCLUSION

The controlled porosity osmotic pump tablet of Verapamil hydrochloride had been successfully prepared. 2^3 factorial designs was adequately applied to study the effect of different formulation variables on the release profile to select optimized formulation. The optimal controlled porosity osmotic pump tablet was able to deliver Verapamil hydrochloride at the rate of approximate zero order up to 24 h, independent of release media and agitation rate. Membranes were found to develop pores after coming in contact with aqueous environment. Finally, it can be concluded that preparation of osmotic pump tablet can be simplified by coating the core tablet with a pore forming agent which is likely to be more cost effective than laser drilling.

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