ORIGINAL ARTICLE

Formulation and evaluation of verapamil hydrochloride osmotic controlled release matrix tablets

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Osmotically controlled oral drug delivery systems utilize osmotic pressure as energy source for the controlled delivery of drugs, independent of pH and hydrodynamic conditions of gastrointestinal tract (GIT). The present study was aimed to develop osmotic controlled extended release formulations of verapamil hydrochloride an angiotensin II receptor antagonist with anti-hypertensive activity. Verapamil hydrochloride matrix tablets were prepared by direct compression process using hydroxypropyl methylcellulose (HPMC) K 15M as polymeric material and mannitol as osmogen at varied concentrations. The matrix tablets were further coated with different compositions of ethylcellulose7cps and polyethylene glycol (PEG)-4000 by pan coating method. Physical parameters such as weight uniformity, drug content, hardness and friability were evaluated for uncoated tablets and were found to be within I. P limits. The coating thickness and percentage of coating applied for various tablets were also evaluated. The optimized coated tablets were further subjected to micro drilling on the upper face to get 0.5 μm orifice diameter. All the tablets were further subjected to dissolution studies by using USP apparatus II with 6.8 pH phosphate buffer as medium. These studies indicated that all the tablets were found to release the drug up to 12 hours, while coated tablets with orifice found to release the drug at zero order rate, which was in good agreement with peppas $n > 0.9$.

Key words: *Controlled release, micro drilling, osmotic pressure, verapamil hydrochloride*

INTRODUCTION

The oral route for drug delivery is the most popular, desirable and most preferred method for administrating therapeutically active agents for systemic effects, because it is a natural, convenient and cost effective to manufacturing process. Oral route is the most commonly used route for drug administration. Although different routes of administration are used for the delivery of drugs, oral route remain the preferred mode. Even for sustained release systems, the oral route of administration has been investigated the most, because of flexibility in designing dosage forms. Present controlled release drug delivery systems are for a maximum of 12 hours clinical effectiveness. Such systems are primarily used for the drugs with short elimination half life.

Osmotically controlled oral drug delivery systems (OCODDS) utilize osmotic pressure as the energy source for the controlled delivery of drugs. These systems are suitable for delivery of drugs having moderate water solubility.[1] Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT)[2] to the large extent and release characteristics can be easily adjusted by optimizing the parameters of delivery system.[3,4] Osmotic devices are most promising strategy based systems for controlled drug delivery. They are among the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems or implantable devices. Osmosis is an aristocratic bio phenomenon, which is exploited for development of delivery systems with every desirable property of an

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ideal controlled drug delivery system. Osmotic system utilizes the principles of osmotic pressure for delivery of drug.[5]

Verapamil hydrochloride is a calcium channel blocker (acts on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thus reducing heart rate and blood pressure). Approximately about 90% of verapamil is absorbed from GIT, but is subjected to very considerable first-pass metabolism in the liver and the bioavailability is only about 20%. Verapamil exhibits bi-or-tri-phasic[6] elimination kinetics and is reported to have a terminal plasma half-life of 2 to 8 hrs following a single oral dose or after intravenous administration. After repeated oral doses this increases to 4.5 to12 hrs. It acts within 5 mins of intravenous administration and in 1 to 2 hrs after an oral dose. There is considerable inter individual variation in plasma concentrations.

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 better patient compliance.

The present study was aimed towards the development of extended release formulations of verapamil hydrochloride based on osmotic technology. In this study, osmotic drug delivery systems for erapamil hydrochloride were developed. The core tablets of verapamil hydrochloride consisted of drug along with an osmotic agent and swellable polymer. The core tablets were coated with ethyl cellulose 7 cps[7,8] and PEG-4000.[9-11] After coating, orifice was drilled to obtain suitable orifice diameter for regulating the uniform release[12] of the drug.

This study was intended to evaluate the influence of formulation variables like amount of mannitol concentration, and coating solution ratios of semi-permeable membrane (SPM) on the drug release from the developed matrix tablet formulations.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride was obtained as gift sample from M/S AUROBINDO Pharma Ltd, Hyderabad. Hydroxy propyl methyl cellulose (Methocel/HPMCK_{15}M) was obtained as gift sample from M/S Colorcon Asia Pvt. Ltd, Mumbai. Microcrystalline Cellulose (Tabulose) and mannitol was obtained as gift sample from M/S Matrix Pharma Ltd, Hyderabad. Talc and magnesium stearate were obtained commercially from Loba Chemie Pvt. Ltd, Mumbai. Ethyl cellulose-7cps was obtained commercially from S. D. Fine Chem. Ltd, Mumbai. Polyethylene glycol-4000 was obtained as gift sample from Sisco Research Laboratories Pvt. Ltd, Mumbai.

PREPARATION OF OSMOTIC TABLETS

Preparation of core tablets

The osmotic core tablets of verapamil hydrochloride were prepared by direct compression process.[13,14] Verapamil hydrochloride was blended with HPMC K_{15}M in a double-cone blender for 10 min. The mixture was passed through #30 mesh sieve, and an osmotic agent (mannitol), a micro crystalline cellulose (MCC) were added in geometric dilution and blending is continued for additional 10 min. To this mixture talc and magnesium stearate which were passed through #60 mesh sieve were added and blending is continued for additional 5 min. The blend was then compressed into tablets using Clit 10 station mini press. The same procedure was employed for preparing different batches of tablets with varying mannitol concentration. To minimize processing variables all batches of tablets were compressed under identical conditions. The compressed core tablets were further evaluated for their physical parameters such as weight uniformity, friability, hardness and drug content. The composition of different tablet formulations of verapamil hydrochloride was given in Table 1.

Coating and drilling

Core tablets of verapamil hydrochloride were coated in a conventional laboratory coating pan (Scientific instrument, New Delhi, India) fitted with three baffles placed at angle of 120° having outer diameter of 10 cm. The components of coating solution were added to solvent mixture in sequential manner. The first component added was allowed to dissolve before the next component was added. Coating process was done on a batch of 100 tablets. Pan speed was maintained at 50 rpm and hot air inlet temperature was kept at 38-42°C. The manual coating procedure based on intermittent spraying and coating procedure was used with spray rate of 4-5 ml/min. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process. Coating was continued until desired coat thickness was obtained on the core tablets. In all cases coated tablets were dried at 50°C for 6 hrs before further evaluation. The composition of coating solutions used for coating of core tablets was given in Table 2. An appropriate size orifice (0.5 μm) is made on one face of all coated tablets using micro drill. (Kamlesh Engineers, Udaipur, India).

Table 1: Composition of verapamil hydrochloride optimized core tablet formulation with varying mannitol concentration

Ingredients (mg/tablet)	Formulations									
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Verapamil HCl	120	120	120	120	120	120	120	120	120	120
HPMC K_{15} M	60	60	60	60	60	60	60	60	60	60
Mannitol	30	40	50	60	70	80	90	100	110	120
MCC	137	127	117	107	97	87	77	67	57	47
Talc	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Total weight (mg)	350	350	350	350	350	350	350	350	350	350

MCC: Micro crystalline cellulose, HPMC: Hydroxypropyl methylcellulose

Evaluation of physical parameters

Before compression process, the powder blends were evaluated for flow properties such as angle of repose and Carr's index.[15] After the compression of matrix tablets they were further evaluated for physical parameters such as weight uniformity, drug content, hardness and friability.[16] The physical parameters evaluated were given in Table 3.

Drug content uniformity

Osmotic tablet of verapamil hydrochloride from a batch was taken at random and was crushed to fine powder. The powdered material was transferred into a 100 ml volumetric flask and 70 ml of 6.8 pH phosphate buffer was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100 ml by adding 6.8 pH phosphate buffer. About 10 ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using millipore filter.[16] Then the filtrate was subsequently diluted and the absorbance was measured at 278 nm. This test was repeated six times ($n = 6$) for each batch of tablets. The amounts of verapamil hydrochloride estimated from different batches were given in table 3.

In vitro dissolution studies

Dissolution studies for core formulations and coated formulations for verapamil hydrochloride controlled release osmotic tablets were performed on a calibrated 8 station (LABINDIA) dissolution apparatus equipped with paddles employing 900 ml of 0.1N 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 12 hours. The paddles were operated to rotate at 100 rpm and the temperature of the medium was maintained at 37 ± 1^0C throughout the studies. Dissolution samples were withdrawn at regular intervals up to 12 hrs and replaced with equal volume to maintain the constant volume of the dissolution medium throughout the studies. The drug content in the samples was determined by measuring the absorbance at 278 nm on ELICO double beam UV spectrophotometer after suitable dilution of the samples.[17] Necessary corrections were made for the loss of drug due to each sampling and plotted the cumulative % amount of drug released *versus* time.

The *in vitro* dissolution studies were performed 6 times for each batch of formulation as per I. P dissolution acceptance criteria, and the average of 6 values were taken for studies ($n = 6$). The dissolution profiles were depicted in Tables 4 and 5 and shown in Figures 1-4.

Characterization of osmotic tablets

Selected formulations were subjected to infrared (IR) and differential scanning calorimetry (DSC) studies to identify any possible interactions between drug and excipients. The surface characteristics of the tablets were characterized by scanning electron microscope (SEM) analysis.

Accelerated stability studies

The formulation which showed good *in vitro* performance was subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties of tablets and drug release from matrix tablets containing verapamil hydrochloride.

Table 2: Coating composition

Ingredients	Coating code				
	VP7A	VP7B	VP7C	VP7D	VP7E
Ethyl cellulose 7cps (gm)	2	1.6	1.4	1.2	1
PEG-4000 (gm)	-	0.4	0.6	0.8	1
Dichloro methane (ml)	20	20	20	20	20

PEG: Polyethylene glycol

Table 3: Evaluation of post-compressive parameters

Formulations	Weight uniformity (mg)	Hardness (Kg/cm²)	Friability (%)	Drug content (mg/tablet)
V1	347±2.0	6.1±0.3	0.15	119.2±0.3
V2	346±2.0	6.2±0.3	0.16	121.5±0.2
V3	348±4.0	6.2±0.3	0.11	120.3±0.5
V4	349±3.0	6.0±0.2	0.18	120.5±0.2
V5	346±3.0	6.0±0.2	0.12	120.4±0.1
V6	347±2.0	6.0±0.2	0.13	119.1±0.4
V7	348±2.0	6.4±0.3	0.16	120.2±0.3
V8	349±2.0	6.4±0.3	0.18	120.4±0.2
V9	348±3.0	6.4±0.3	0.14	121.5±0.3
V10	349±4.0	5.8±0.2	0.16	120.6±0.4

RESULTS AND DISCUSSION

Extended release formulation of erapamil hydrochloride osmotic tablets were developed and evaluated. Extended release osmotic tablets of verapamil hydrochloride were prepared by direct compression process. Verapamil hydrochloride osmotic tablets were prepared by using HPMC K15M as release rate retardant. All the tablets were evaluated for physical parameters such as weight uniformity, hardness, friability and drug content. Tablets were coated with coating solution containing ethyl cellulose and PEG-4000. The optimized coated tablets were further subjected to micro drilling on the upper face to get 0.5 µm orifice diameter. The composition of various tablets and coating composition were given in Tables 1 and 2. All the tablets were prepared under identical conditions to minimize the processing variables. Direct compression method was found to be suitable for drug and polymers used. The formulations were further evaluated for *in vitro* drug release. Effect of formulation variables like amount of mannitol and coating concentration was evaluated. The formulations were further subjected to characterization studies such as DSC, FTIR and SEM analysis.

Table 4: Evaluation of dissolution parameters for V1-V10 tablet formulations without pore

Formulation	Rate constant				Constant			
	Zero order		First order		Higuchi		Peppas	
	K (mg/hr)	R^2	K (hr^{-1})	R^2	K ($mg/h^{1/2}$)	R^2	*n*	R^2
V1	6.46	0.8843	0.0345	0.9917	10.39	0.9943	0.7261	0.9966
V2	6.85	0.8844	0.0471	0.9936	13.37	0.9942	0.7258	0.9966
V3	7.18	0.8889	0.0593	0.9963	15.60	0.9923	0.7020	0.9962
V4	7.36	0.8779	0.1273	0.9922	22.64	0.9945	0.5926	0.9953
V5	7.65	0.8824	0.2653	0.9411	28.07	0.9923	0.6248	0.9849
V6	7.87	0.8923	0.1557	0.9871	27.13	0.9967	0.7904	0.9997
V7	8.86	0.8939	0.2012	0.9555	28.39	0.9937	0.7604	0.9996
V8	9.15	0.8905	0.288	0.9334	30.22	0.9946	0.7535	0.9976
V9	9.37	0.8845	0.2913	0.9462	29.88	0.9972	0.7113	0.9977
V10	9.33	0.8723	0.3013	0.9534	30.72	0.9964	0.7543	0.9965

Table 5: Evaluation of dissolution parameters for coated verapamil hydrochloride tablet formulation with pore

Formulation	Rate constant				Constants			
	Zero order		First order		Higuchi's		Peppa's	
	K (mg)	R^2	K (hr^{-1})	R^2	K ($mg^{1/2}$)	R^2	*n*	R^2
VP7 C	9.558	0.9969	0.5094	0.9426	34.88	0.9883	0.9925	0.9938

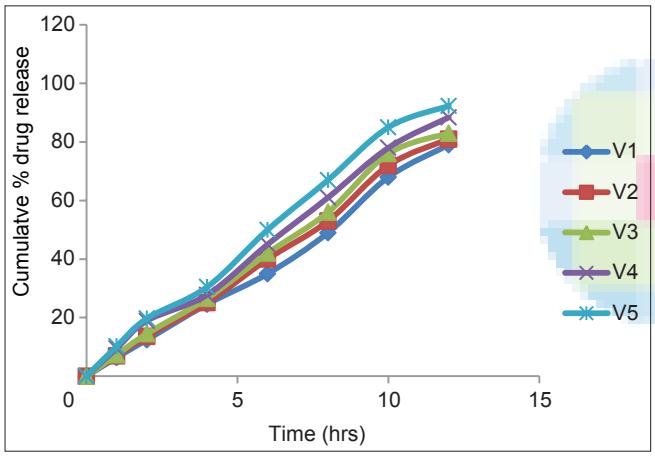

Figure 1: Dissolution profiles of V1-V5 tablet formulations

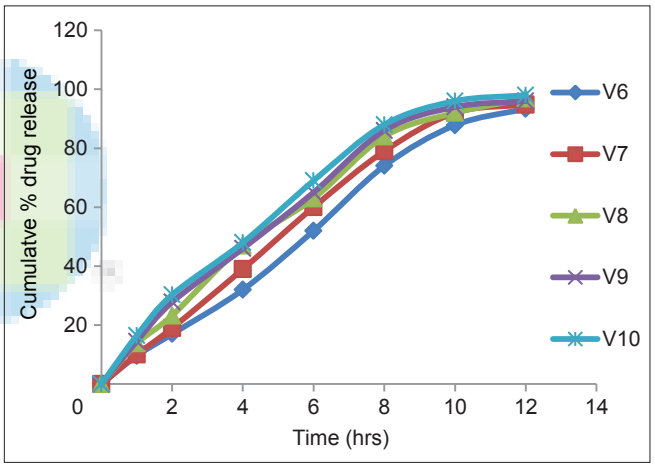

Figure 2: Dissolution profiles of VP6-VP10 tablet formulations

The flow properties such as angle of repose and Carr's index were evaluated for various powder blends and were found to exhibit good flow properties. The angle of repose values obtained for various powder blends were in the range of 20 to 30° and the Carr's index values were in the range of 12 to 16%. All the tablet formulations were found to be stable and meeting I. P specified limits for physical parameters evaluated such as weight uniformity, friability and drug content. Weight uniformity of all osmotic tablet formulations were in the range of 350 ± 5 mg. Hardness of the all osmotic tablet formulations were in the range of 5.5 to 7.0 kg/cm^2. Friability loss of all tablet formulations was found to be negligible and was in the range of 0.1-0.2%. Drug content was estimated for all osmotic tablet formulations were highly uniform with less than 1.5% variation. The physical parameters evaluated for various tablets were given in Table 3. The percentage weight gain for all the coated tablets was found to be in the range 3 ± 0.5%. The coating thickness for all the coated tablets was found to be in the range 1.32 ± 0.5 mm.

Dissolution studies for core formulations and coated formulations for verapamil hydrochloride controlled release osmotic tablets were performed on a calibrated 8 station (LABINDIA) dissolution apparatus equipped with paddles employing 900 ml of 0.1N HCl (pH = 1.2) for first 2 hours and then further study was conducted in 900 ml phosphate buffer (pH = 6.8) as the medium for drug release study was up to 12 hours. Based on the dissolution studies it was observed that tablet formulations VP1 to VP10 prepared by direct compression process were found to release the drug up to 12 hours. The drug release from the matrix tablet formulations was influenced by composition of mannitol. As the mannitol concentration was increased, the release of the drug from the matrix tablet was increased.

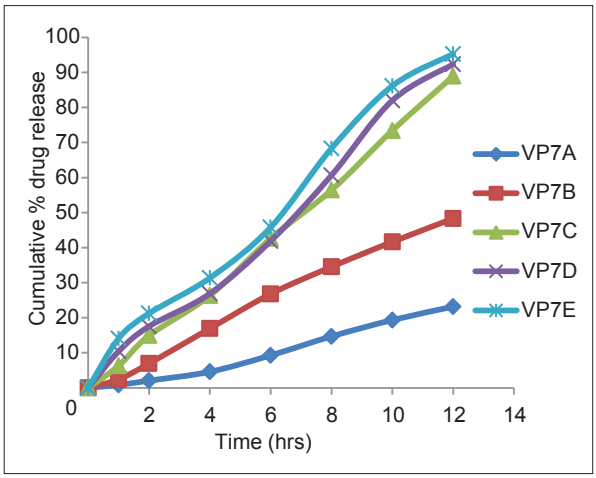

Figure 3: Dissolution profiles of verapamil coated tablet formulations

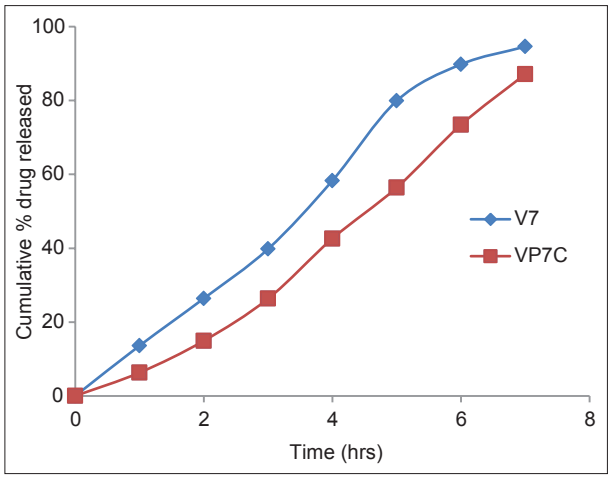

Figure 4: Dissolution profile for VP7C tablet formulation with pore FT-IR spectra

Formulation VP7 containing 25.7% of mannitol was found to be ideal concentration for extending the drug release up to 12 hours at a steady state manner. Hence, VP7 formulation was further subjected to coating with semi-permeable polymeric coat composed of various proportions of ethyl cellulose 7 cps and PEG-4000 and coating compositions were given in table 2. The coated tablets were also subjected to dissolution studies by maintaining the similar dissolution conditions for the uncoated tablets. The dissolution profiles for the formulations VP1 to VP10 were shown in the Figures 1 and 2 and the *in vitro* dissolution parameters were given in Table 5.

All the coated tablets were found to extend the drug release for more than 12 hours. The drug release from the coated tablets was influenced by composition of ethyl cellulose. As the ethyl cellulose composition is high, the formulations of VP7 A, B and C extended the drug release for more than 12 hours. Formulations VP7 D and E, the drug release was extended upto12 hours, as the composition of ethyl cellulose was decreased compared with the above formulations. As the composition of PEG- 4000 is increased in formulations VP7C, VP7D and VP7E, the channel formulation in semi-permeable membrane is gradually increased and hence the rate of drug release is increased. Among the coated formulations VP7 C having 7:3 ratio of ethyl cellulose and PEG-4000 coating composition was found to release drug at a steady state manner. Hence VP7 C was further subjected to micro drilling upon the coating surface. The micro orifice having the approximate pore size of 0.5 µm is made on the upper face of the VP7C formulation by using micro driller. Then this tablet was also subjected to *in vitro* dissolution studies. The results revealed that VP7 C formulation with micro orifice exhibited linear drug release over a period of 12 hours. Based on the dissolution data, various dissolution parameters such as zero order, first order, higuchi constant and peppas constant were evaluated for all the tablet formulations along with VP7C having micro orifice. Formulation VP7 C with micro-orifice exhibited zero order drug release profile with release rate constant value of 9.538 mg/hr and the correlation coefficient value obtained was 0.996. The release exponent (*n* value) obtained for the formulation VP7C was 0.9, which indicates that the mechanism of drug release follows zero order, which is achieved by drug diffusion from the micro orifice. The higuchi value for the formulation VP7C was linear with a R^2 value of 0.986.

The spectra of verapamil hydrochloride exhibited principle peaks at wave numbers of 2957 cm^{-1} (C-H Stretching), 2839 cm^{-1} (C-H Stretching of CH3O), 2541.49 cm^{-1} (N-H Stretching), 2236 cm^{-1} (C = N Stretching) and 1259 cm^{-1} (C-O Stretching). The spectra of optimized VP7 tablet formulation exhibited all the principle peaks present in the verapamil hydrochloride pure drug. The results revealed that there were be no major interaction between drug and excipients used in the formulation of osmotic tablets. The IR spectra of pure drug and optimized formulation were shown in Figures 5 and 6.

The DSC thermographic peaks for the pure drug verapamil hydrochloride was observer at 141.0°C, where as DSC thermographic peaks for the formulation blends were observed in the range of 140.0°C. The results revealed that there was no interaction between drug and excipients used. The DSC thermo grams of pure drug and optimized formulation were shown in Figures 7-9.

The SEM photographs for the formulations VP7 and VP7 C were taken to study the surface characteristics of the tablets. Smooth even surface was observed for the formulations VP 7 and VP7 C (with pore) before dissolution studies, where as pore enlargement and rough surface were observed in the formulation VP7 C, which may be due to the diffusion of drug through the pore. SEM photographs were shown in Figures 10-12.

Stability studies were conducted on selected formulations. Results indicated that there were no significant changes in physical parameters evaluated such as weight uniformity,

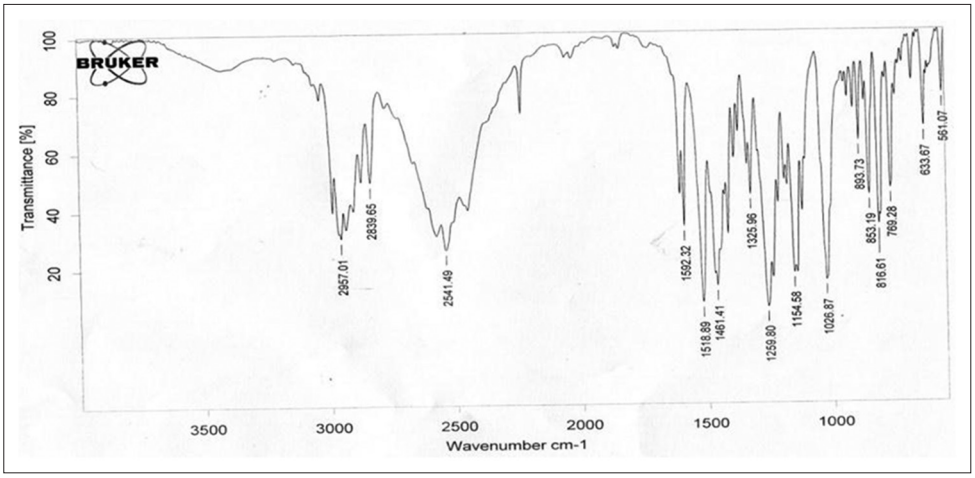

Figure 5: FT-IR spectra of verapamil hydrochloride

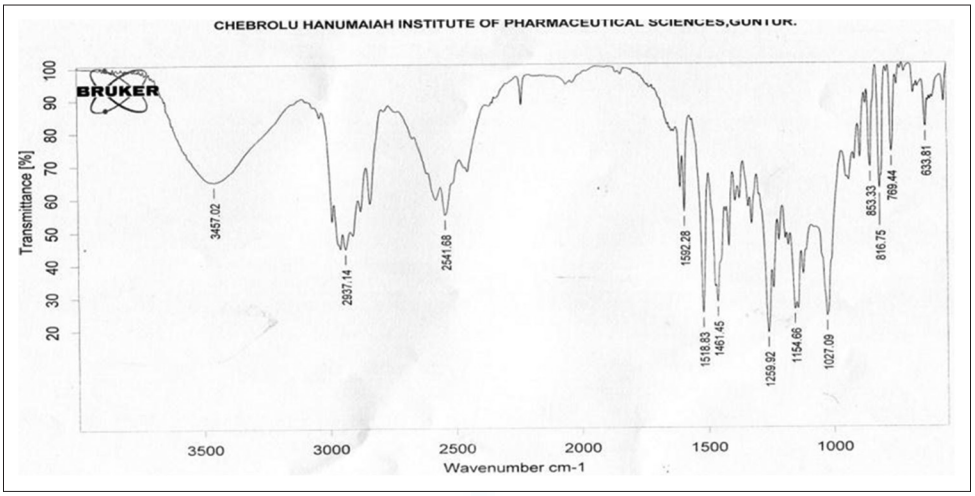

Figure 6: FT IR - spectra of verapamil hydrochloride (VP7C) formulation DSC thermo grams

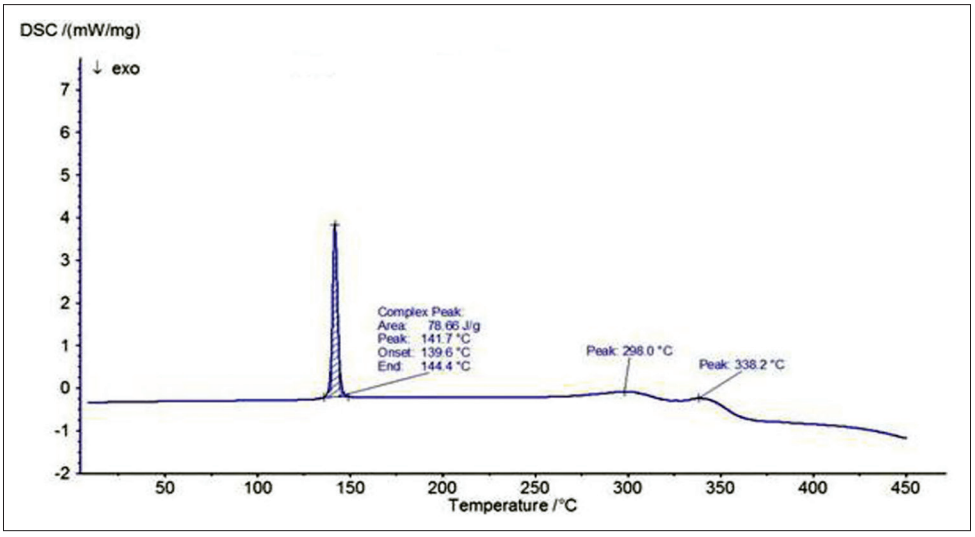

Figure 7: DSC Thermogram of verapamil hydrochloride

hardness, friability and drug content. The physical parameters evaluated for optimized formulations were given in Table 6. Drug release from the osmotic tablets after storage at different conditions remained unaltered. The drug release profiles for

Table 6: Physical parameters of optimized verapamil tablet formulation before and after storage at different conditions

Formulations	Storage condition	Weight uniformity (mg)	Hardness (Kg/cm²)	Friability (%)	Drug content (mg/tablet)
VP 7C	Before storage	348±3	5.8±0.2	0.12	120.5±0.5
	25±2⁰C, 60±5% RH	348±3	5.8±0.2	0.12	119.3±0.5
	40±2⁰C, 75±5% RH	348±3	5.8±0.2	0.13	119.2±0.5

RH: Relative Humidity

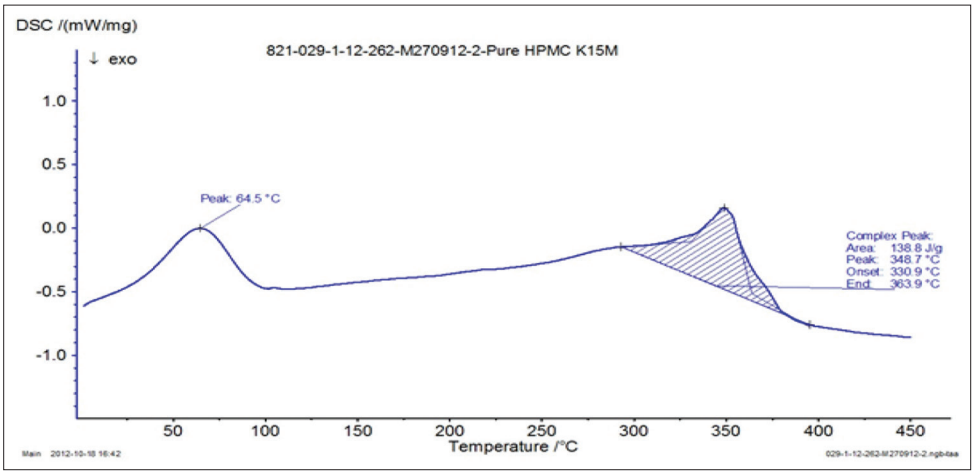

Figure 8: DSC thermogram of HPMC K15

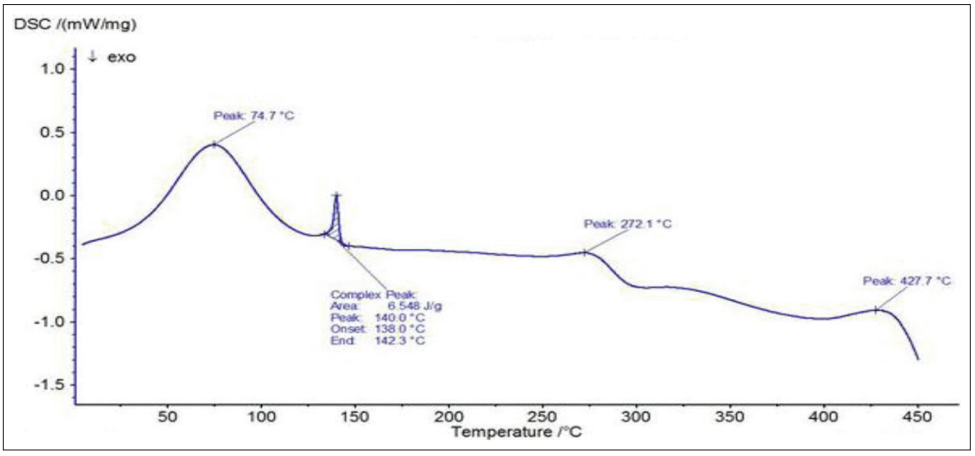

Figure 9: DSC thermogram of VP7 tablet formulation SEM analysis

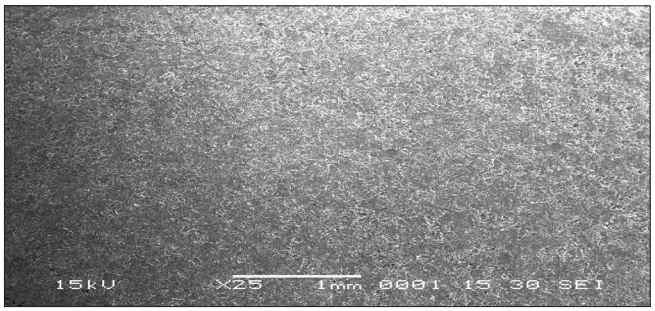

Figure 10: SEM photograph of coated VP7 C tablet formulation without pore

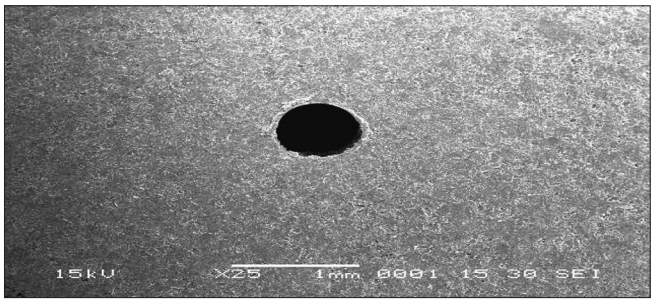

Figure 11: SEM photograph of coated VP7 C tablet formulation with pore before dissolution

the optimized formulation after storing at different storage conditions were shown in the Figure 13. Thus the selected osmotic controlled release formulations were found to be quite stable.

CONCLUSIONS

The present study has shown that it is possible to extend the release of verapamil hydrochloride by formulating

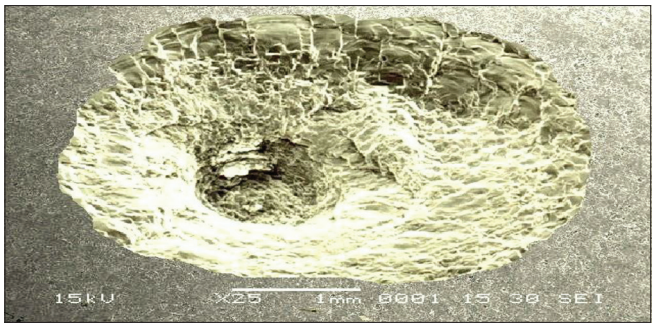

Figure 12: SEM photograph of coated VP7C tablet formulation with pore after dissolution

it as osmotic controlled release tablets employing HPMC $K_{15}M$ as polymeric material and mannitol as osmogen. The formulation with micro-orifice after coating with ethyl cellulose 7cps and PEG-4000 exhibited zero order drug release profile with constant release rate.

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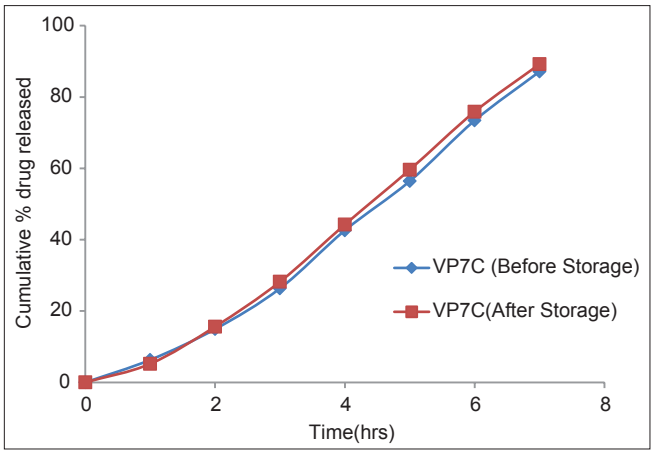

Figure 13: Dissolution profiles of optimized verapamil hydrochloride tablet formulation (VP7C) before and after storage at different conditions

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