Modulation of drug release by utilizing pH-independent matrix system comprising water soluble drug verapamil hydrochloride

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Abstract: The present study was undertaken to investigate the effect of hydrophilic, plastic and hydrophobic types of polymers and their content level on the release profile of drug from matrix systems. To improve therapeutic efficacy, systemic absorption and patient compliance a sustained release matrix tablets of Verapamil HCl (VHE) has been developed. VHE tablets were prepared by using various polymers like hydrophilic (HPMC K15M CR), plastic (Kollidon SR), hydrophobic (Eudragit RSPO) and combination of best two resulted polymers using direct compression. A 3^2 full factorial design was applied to study the effect of polymers on drug release. For the combination of polymers, selected factors HPMC K15 CR (X_1) and Eudragit RSPO (X_2) showed positive influence on drug release at 18 hrs and 20 hrs. The release profile of VHE formulation exhibits Higuchi model with anomalous diffusion release. Accelerated stability trials for 3 months proved reproducibility. A good correlation between the dissolution profiles and bioavailability indicated a linear relationship between *in vitro – in vivo* data. The current study attained the successful design, development and optimization of controlled release once-a-day formulation of VHE.

Keywords: Verapamil HCl; Matrix tablets; HPMC K 15M; Eudragit RSPO; optimization; *in vitro* drug release; *in vivo* evaluation.

INTRODUCTION

Conventional multiple-dosing regimens for long-acting therapies like hypertension, ischemic heart disease, bronchial asthma and rheumatoid arthritis suffers from lot of problems like elevated plasma drug levels and zigzag plasma drug concentrations leading to poor patient compliance and toxic side effects. Such problems can be rectified by controlling or sustaining the drug release. Development of controlled drug delivery system is better alternative for treatment of diseases which require multiple dose regimens. Thus in view of above, it was proposed to formulate a once a day controlled release matrix tablet formulation of Verapamil hydrochloride which would provide controlled drug level over a long duration for control of hypertension (Gallerani *et al*., 1992; Elliott, 1998).

Verapamil HCl is a calcium channel blocker used as a peripheral vasodilator. Verapamil HCl has short biological half-life of 4 hours and thus frequent administration makes it a potential candidate for the design of sustained release dosage forms. Verapamil HCl sustained release tablets prepared earlier by matrix embedded techniques using Kollidon SR or HPMC as a retardant polymers (Sahoo *et al*., 2007; Sahoo *et al.*, 2008).

Modern pharmacist well equipped with the latest and best resources will certainly not like to compromise between the acceptable and the best possible formulation, when the same can be achieved using certain methods, therefore optimization techniques have globally become a regular practice in design and development of diverse kinds of dosage forms. To simplify the process of optimization with accuracy, speed, versatility, ease of documentation, and reduction of manpower there is need of software development (Gambhire *et al.*, 2007).

The behavior of single polymer on the drug release pattern of veramapil HCl tablets were studied for the 12 hrs. The Kollidon SR gave the burst release; this is due to the high water permeability of Kollidon SR. The present work comprises design and evaluation of oral controlled release matrix tablets providing 24 hrs substantial release profile for verapamil HCl. The formulation contained a Meth-/acrylates copolymers with trimethyl-ammonio-ethylmethacrylate as a functional group copolymer (Eudragit RSPO), hydrophobic polymer along with hydroxylpropyl methylcellulose (HPMC K15 M CR) hydrophilic gelling polymer Rodriguez *et al*., 1993; Dabbagh *et al*.,1996; Makhija and Vavia 2002; Ceballos *et al*., 2007; Patra *et al*., 2007). Present study was aimed to formulate once a day formulation of Verapamil HCl and assess the influence of polymer content, polymer type and their combination on the release profile of drug from prepared matrix tablet.

MATERIALS AND METHODS

Materials

Verapamil HCl and Magnesium Stearate were received from Golden Cross Pharma (Daman, India) as a gift sample. Hydroxypropyl methylcellulose (HPMC) K15M

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CR Premium was obtained as a gift sample from Colorcon Asia Private Ltd. (Goa, India). Evonik-Degussa kindly donated the Eudragit RSPO while Kollidon SR was obtained from BASF (India). Microcrystalline cellulose was purchased from Ozone International, Mumbai, India.

Compatibility studies

The interaction between the drug and polymer was investigated by using the Fourier Transform Infrared Spectroscopy, DSC and XRD. The drug was characterized by various official test of identification.

Fourier transform infrared spectroscopy

FTIR spectra were obtained by using FTIR spectrometer affinity-1 (Shimadzu, Japan). The samples were ground and mixed thoroughly with potassium bromide. The IR spectra of drug alone and excipients alone and their combination were taken. The pellets of KBr were prepared by direct compression. Forty five scans were obtained at a resolution of $4cm^{-1}$, from 4,000 to 300 cm^{-1}.

Differential Scanning Calorimetry Study

The DSC measurements were performed on DSC-822^e (Mettler Toledo, India). The samples (equivalent to 1.675 mg of verapamil hydrochloride) were sealed in aluminum pans with inert atmosphere, by purging nitrogen at a flow (20 ml/min) with scanning rate of $10^oC\ min^{-1}$ over 25^oC to 450^oC.

X-ray Diffraction Study

To determine the XRD study was conducted for the drug - carrier interaction and crystalline nature of drug before and after formulations. For the pure drug, the polymers, and different formulations XRD patterns were obtained by using an X-ray diffractometer- AXS D8 Advance (Bruker, Japan). The XRD patterns were obtained at room temperature using Cu anode, graphite monochromatic, a voltage of 35kV, and 20 mA current. The samples were analyzed over the 2-99^o diffraction angle (2θ) range. The scanning rate was 0.5 s.

Preparation of matrix tablets

Dose of verapamil HCl sustained release matrix tablet was calculated as per Shargel *et al*., 2005. Two hundred tablets were prepared for each formulation. The amount of matrix forming polymers increases gradually for each formulation and the amount of drug and magnesium stearate were kept constant while MCC was taken in sufficient quantity to maintain a constant weight. Formulations were manufactured by blending the drug substance and the dry excipients for 10 minutes. Weighed lubricant was added and mixed for 2 minutes. Blend was directly compressed on Mastron single punch machine using the 8.00 mm round deep concave punch. The preliminary trial formulation (individual polymer) codes of the tablets are listed in table 1. For combination of polymers, formulation codes are provided in table 2. For each formulation three batches of tablets were prepared.

Table 1: Composition of Verapamil HCl tablets for individual polymers study

Formulation	Quantity per tablet (%)								
	VH_1	VH_2	VH_3	VK_1	VK_2	VK_3	VE_1	VE_2	VE_3
Verapamil HCl	19.92	19.92	19.92	19.92	19.92	19.92	19.92	19.92	19.92
HPMC K15M CR	19.92	39.84	59.76	--	--	--	--	--	--
Kollidon SR	--	--	--	19.92	39.84	59.76	--	--	--
Eudragit RSPO	--	--	--	--	--	--	19.92	39.84	59.76
Starch 1500	15.94	15.94	15.94	15.94	15.94	15.94	15.94	15.94	15.94
Magnesium Stearate	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39
MCC	43.83	23.91	3.99	43.83	23.91	3.99	43.83	23.91	3.99
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Table 2: Evaluation of different formulations of Verapamil HCl* tablets with combination of polymers

Formulation Code	Variable level in Coded form		Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Drug content (%)	Friability (%)
	Factor X_1	Factor X_2					
VHE_1	-1	-1	443 ± 0.3	2.22 ± 0.03	8.7 ± 0.3	91.35 ± 3.40	0.77
VHE_2	-1	0	456 ± 0.4	2.23 ± 0.05	8.3 ± 0.1	96.45± 2.40	0.75
VHE_3	-1	1	452 ± 0.2	2.24 ± 0.02	8.5 ± 0.4	92.12 ± 5.30	0.81
VHE_4	0	-1	456 ± 0.1	2.25 ± 0.05	8.6 ± 0.2	93.34 ± 3.10	0.76
VHE_5	0	0	450 ± 0.3	2.21 ± 0.04	8.9 ± 0.5	95.43 ± 3.40	0.82
VHE_6	0	1	444 ± 0.5	2.27 ± 0.02	8.4 ± 0.4	96.12± 5.30	0.82
VHE_7	1	-1	447 ± 0.4	2.26 ± 0.03	8.5 ± 0.1	97.11 ± 3.30	0.78
VHE_8	1	0	453 ± 0.2	2.25 ± 0.05	8.7 ± 0.4	98.24 ± 4.40	0.74
VHE_9	1	1	457 ± 0.4	2.24 ± 0.04	8.6 ± 0.2	96.31 ± 5.30	0.79

*All values are expressed as mean ± standard deviation.

All batches contained 100 mg verapamil, 11.95% Starch 1500, 2% talc, 0.39% magnesium stearate and MCC is q.s. to produce tablets of constant of 452mg ; X_1 is the amount of HPMC K15M CR; and X_2 is the is the amount of Eudragit RSPO

Development of matrix tablet formulation

The effect of variables and experimental trials were performed at nine batches by using the 3^2 factorial design. For the combination of polymer HPMC K15 CR (X_1) and Eudragit RSPO (X_2) were selected as independent variables as shown in table 3.

Table 3: Independent variables: factors and levels for full factorial design of Verpamil HCl for combination of polymers study

Factors	Levels		
	-1	0	1
X_1:amount of HPMC K15M CR (mg)	150	170	190
X_2: amount of Eudragit RSPO (mg)	60	80	100

The drug release at 18 hrs and 20 hrs were selected as dependent variables (tables 4, 5). The resulting data was fitted to OPTI- STAT, Design Expert 7.0.3 software and analyzed statically using analysis of variance (ANOVA). To study the effect of the polymer and binder on dependent variable the obtained data was fitted to 3-D response surface methodology. The composition of different combination of different polymers as per the factorial design during optimization studies are shown in tables 4 and 5.

Physical properties of tablets

The weight variation of tablets were evaluated for weight variation (n=20), hardness, friability (n=20), and drug content as per I.P 1996. Hardness of tablets was determined by Monsanto hardness tester (Campbell Electronics, Mumbai, India) and friability (n=20) test was performed using Roche friabilator (F. Hoffmann-La Roche Ltd., Basel, Switzerland). The drug content of the prepared tablets was estimated using UV spectrophotometric method. 20 tablets were taken from each batch, weighed and pulverized to a fine powder. An adequate amount of powder equivalent to 10 mg of the drug was accurately weighed, dissolved, and suitably diluted in double-distilled water and analyzed by UV spectrophotometric method at 278 nm (Shimadzu UV-1700, Japan).

Dissolution methodology

Dissolution studies were carried out by using the USP XXII type I apparatus (ElectrolabTDT-08L, Mumbai, India) at 50 rpm. The studies were performed in triplicate for 12 (individual polymer) and 24 hours (combination of polymers) in two phases (phase I: simulated gastric fluid for 2 hours, phase II: phosphate buffer of pH 6.8 for remaining hours) under sink condition. Samples were removed at the specified time intervals (1 hr), 10 ml sample was withdrawn and filtered through 0.45µ membrane and was analyzed by UV-Visible spectrophotometer at 278 nm after suitable dilutions. Drug released from dosage form at specified time was plotted as percent drug release versus time (hours).

Kinetic modeling

In this drug release study, model-dependent approach was used to compare dissolution profiles. Release data was fitted to five kinetic models; zero-order (R = k1t), first order (Log UR =k2t/2.303), Higuchi matrix (R = k3$\sqrt{t}$), Peppas–Korsmeyer (Log R = log k 4 + n log t), and Hixson–Crowell [$(UR)^{1/3}$ = k5t) equations to find the best

Table 4: Analysis of variance for 18 hr release of Verapamil HCl with HPMC K15M CR and Eudragit RSPO formulations [VHE_1-VHE_9]

Source	Sum of squares	Degree of freedom	Mean Square	F value	P value	Model Significant/ Non-significant Relative to Noise
Model	47.72	2	23.86	6.68	0.0297	Significant
X_1	36.21	1	36.21	10.14	0.0190	Significant
X_2	11.51	1	11.51	3.22	0.0479	Significant
Residual	21.42	6	3.57	-	-	-
Core total	69.14	8	-	-	-	-

Table 5: Analysis of variance for 20 hr release of Verapamil HCl formulations [VHE_1-VHE_9]

Source	Sum of squares	Degree of freedom	Mean Square	F value	P value	Model Significant/ Nonsignificant Relative to Noise
Model	57.26	2	28.63	5.82	0.0393	Significant
X_1	46.65	1	46.65	9.49	0.0217	Significant
X_2	10.61	1	10.61	2.16	0.0422	Significant
Residual	29.51	6	4.92	-	-	-
Core total	86.77	8	-	-	-	-

fit model using OPTI-STAT software. The resulting data were fitted into OPTI-STAT, Design Expert 7.0.3 software and analyzed statistically by using ANOVA (Costa and Lobo 2001; Biswal *et al*., 2008).

In vivo evaluation studies

In vivo evaluation study was carried out on healthy human volunteer, in compliance with the protocol of Institutional ethical committee (Registration No.CPBEMV-122009 under CPU, India). The bioavailability studies were carried out on the experimental formulation (VHE_9) and the commercial formulations Calaptine SR 120 mg capsules (CF). The studies were carried out in six healthy male objects with mean age of 26.33±3.01 years (range of 22 to 30 years) and mean body weight of 57.33±3.39 kg (range of 53 to 63 kg.). All the subjects were presented with full details of the investigated, both verbally and in written form, prior to providing written informed consent. Blood samples (5.0 ml) were collected between 0.0 to 48.0 hrs after administration of optimized (VHE_9) and CF. Plasma was harvested and kept at -20^{o}C till analyze by HPLC.

Stability studies

Stability trials were conducted on optimised batch (VHE_9). The tablets were stored at 40±2^{o}C and 75±5% RH as per ICH guidelines. Samples were withdrawn according to the sampling plan after every month for 3 months. Accelerated stability study batches were analyzed for physical appearance, assay and *in vitro* dissolution studies with reference to initial results of the same.

RESULTS

Fourier transform infrared spectroscopy

IR spectra of drug, drug with Eudragit and with HPMC K15M CR are shown in fig. 1. IR spectrum of Verapamil hydrochloride is characterized by the absorption of NH group at 3,467 cm−1 (Rustichelli *et ai.,* 1999) (fig. 1a). From the results, no obvious interaction between drug and both the polymers found.

X-ray diffraction study

The pure Verapamil HCl diffraction spectra shows numerous peaks at 2θ of 5.3^0, 9.0^0, 10.9^0, 17.4^0, 18.4^0, 19.2^0, 20.5^0 and 21.6^0 (fingerprint region), etc. (fig. 2d). XRD patterns of pure polymers, HPMC K15M CR, Kollidon SR, Eudragit RSPO are shown in (figs. 2a, b and c) showing characteristic peaks. Changes in peak position of Verapamil HCl were observed in tablets (figs. 2e, f, g and h). From the observation, we can conclude that there were no drug interactions in drug and polymers. The

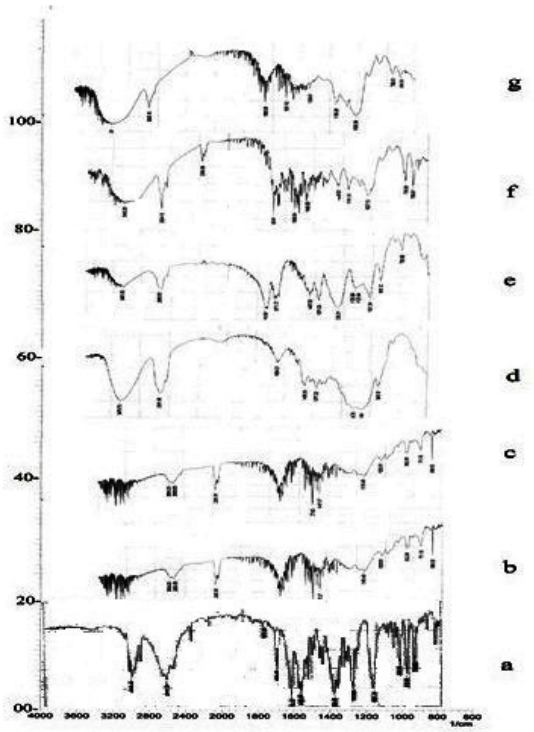

Fig. 1: FTIR spectrograms of pure Verapamil hydrochloride (a), pure Eudragit RSPO (b), Pure HPMC K15M CR (c), Pure Kollidon SR (d), pure Magnesium stearate (e) and pure Starch 1500 (f) Pure Micro-crystalline cellulose (g)

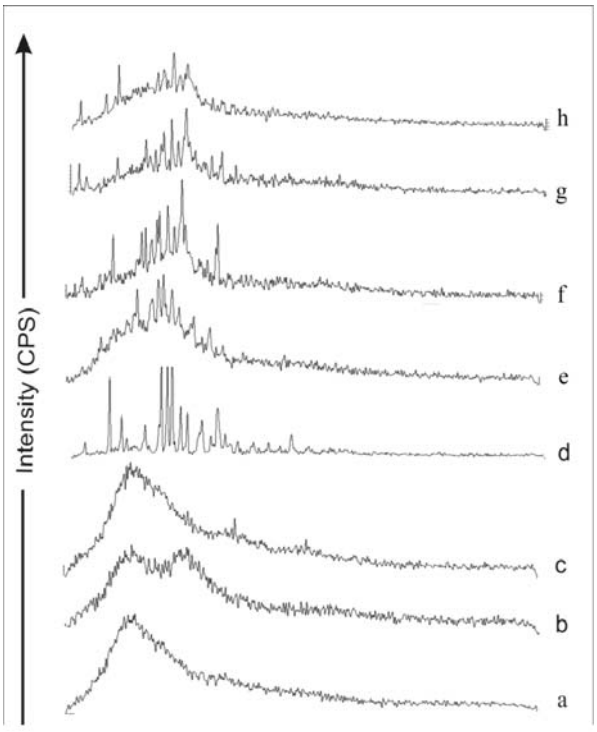

Fig. 2: X-ray diffract grams of Pure HPMC K15M CR(a), Pure Kollidon SR(b), Pure Eudragit RSPO(c), Pure Verapamil HCl (d), Verapamil HCl-HPMC K15M CR tablet (e), Verapamil HCl-Kollidon SR tablet(f), Verapamil HCl-Eudragit RSPO tablet (g), Verapamil HCl-HPMC K15M CR and Eudragit RSPO tablet (h).

reduced intensity of peaks can be attributed to presence of high amounts of polymer.

Differential scanning calorimetry

The polymer HPMC K15M CR shows broad endothermic fusion peak at 86.52°C (fig. 3a) which is due to its glass transition state. The polymer Kollidon SR shows broad endothermic fusion peak at 85.83°C (fig. 3c) whereas Eudragit RSPO shows fused melting point peak at 188.37°C (fig. 3b). The DSC curve of pure verapamil HCl exhibited a single sharp endothermic peak at 147.33°C corresponding to the melting of drug (figs. 3d). The DSC patterns of tablet formulations (VH_1, VK_3, VE_2 and VHE_9) has also shown same endothermic peak as like pure drug (figs 3e, f, g and h). These observations of DSC study indicate absence of significant interaction between drug and polymer in tablet formulations.

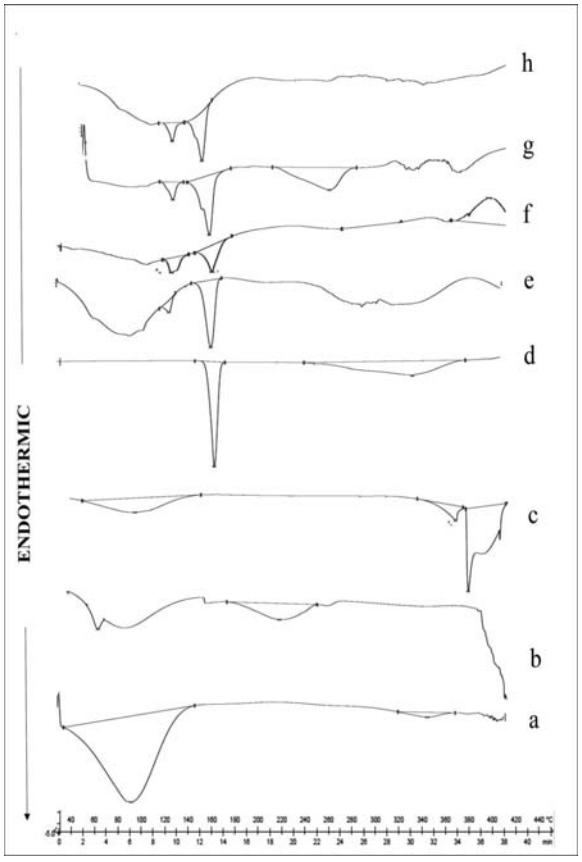

Fig. 3: DSC thermo grams of Pure HPMC K15M CR (a), Pure Eudragit RSPO (b), Pure Kollidon SR (c), Pure Verapamil HCl (d), Verapamil HCl- HPMC K15M CR tablet (e), Verapamil HCl-Eudragit RSPO tablet (f), Verapamil HCl- Kollidon SR tablet (g), Verapamil HCl - HPMC K15M CR and Eudragit RSPO tablet (h)

Polymer selection

Preliminary drug release studies were performed on nine different tablet formulations to find out the release behavior of the different polymers (individual polymer study). The selected polymers Eudragit RSPO, Kollidon SR and HPMC K15M CR Premium are hydrophobic, plastic and hydrophilic respectively. Their concentration was varied between 19.92-59.76 % w/w of the tablet (table 1). Due to high bulk density and excellent flow properties microcrystalline cellulose and starch 1500 grade were chosen for the preparation of matrix tablet by direct compression. Matrix properties of tablets were controlled by using the pH-independent release, non-ionic polymers. The tablet characteristics of preliminary trial batches are given in table 6. The dissolution data of preliminary trial nine different tablet formulations are shown in fig. 4.

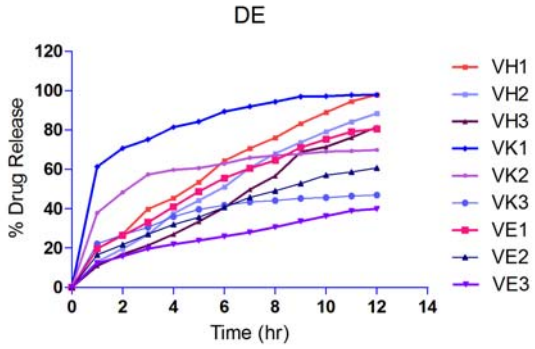

Fig. 4: Release profiles of Verapamil HCl with individual polymers.

Physical characterization of designed tablets

Prepared matrix tablets complied with all the official tests as per I.P 1996, with reference to their appearance, weight variation, thickness, hardness, friability, drug content and content uniformity for different formulations of single polymer (table 6) as well as for combination of polymers (table 2).

Factorial design

The effects of HPMC K15M CR and Eudragit RSPO on drug release from Verapamil HCl matrix tablets was studied by using a 3^2 factorial design. The 18 hr and 20 hr release for nine batches (VHE_1- VHE_9) showed a wide variation (i.e. 85.72 ± 0.92 to 95.06 ± 0.89% and 88.76±0.54 to 98.97±0.97% respectively). The drug releases profiles for combination of polymer batches are shown in fig. 5.

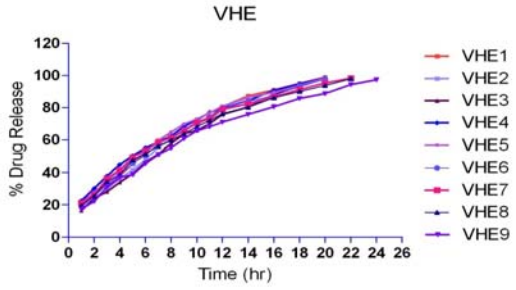

Fig. 5: Release profile of Verapamil HCl with combination of HPMC K15M CR and Eudragit RSPO as per factorial design.

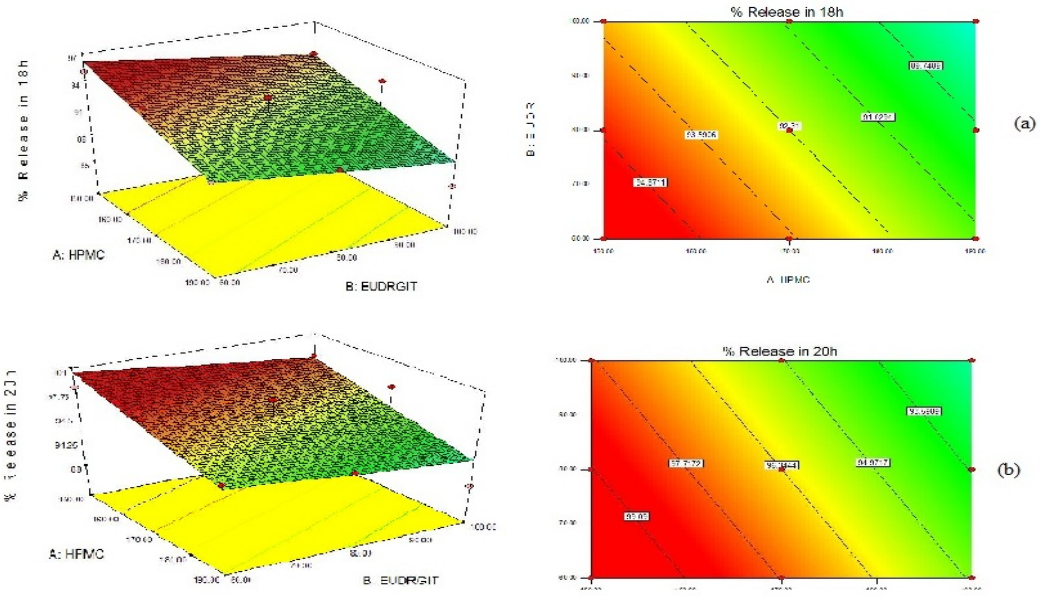

Fig. 6: Response surface and contour plots for release 18 hr of Verapamil HCl formulations [VHE_1-VHE_9] (a), Response surface and contour plots for release 20 hr of Verapamil HCl formulations [VHE_1-VHE_9] (b).

Table 4 and 5 shows ANOVA for dependent variables at 18 hr and 20 hr. The X_1 and X_2 coefficients were found to be significant at $P \leq 0.05$. Thus, VHE_9 formulation was selected as optimized formulation and selected for further studies and it gave the desired controlled release behavior for 24 hr and according to the IP requirement.

Fig. 6 (a and b) shows the plot percentage of HPMC K15M CR (X_1) and the percentage of Eudragit RSPO (X_2) versus drug release at 18 hr and 20 hr, respectively. The data confirmed that X_1 and X_2 both affect at 18th hr and 20th hr drug release.

Drug release dissolution comparative study of the verapamil HCl optimized formulation (VHE_9) and calaptine SR is show in fig. 7. CF gives the drug release for the 8 hr and as compare to the verapamil HCl (VHE_9) gives the drug release up to the 24 hr.

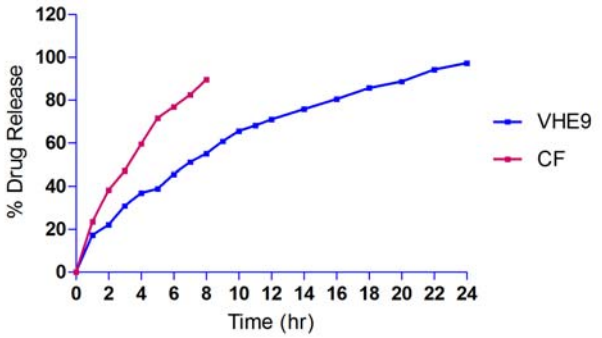

Fig. 7: Release profile of Verapamil HCl and calaptine SR (commercial formulation)

Kinetic studies and Drug release pattern

Kinetic studies and the release pattern for Verapamil matrix tablets were analyzed by various kinetic models and ranked in order of Higuchi > Korsmeyer - Peppas > Hixson-Crowell > Zero order > First-order. As shown in table 7, Higuchi model gave the highest squared correlation coefficient (0.9964) for the Verapamil HCl tablets.

***In vivo* study**

As the drug release from the VHE_9 was found to be similar to CF. The mean plasma concentration Vs time profile of VHE_9 and CF in six healthy human volunteers is presented in fig. 8. Both formulations VHE_9 and CF shows *in vivo* sustained release in a blood for a longer period of time. All other pharmacokinetics parameters are displayed in table 8.

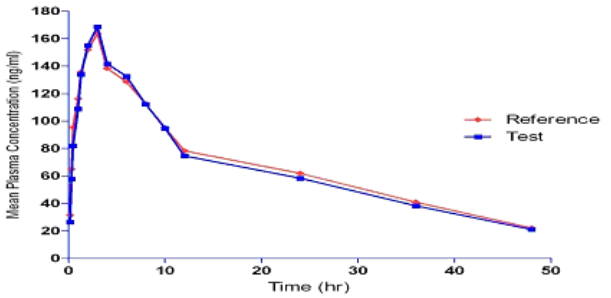

Fig. 8: Mean plasma concentration of optimized Verapamil HCl formulation

Stability study

Stability trials were conducted on three batches of 100 mg verapamil HCl tablets of formulation VHE_9. The tablets

Table 7: Diffusion kinetics and model fitting data of Verapamil HCl matrix tablets by using 3^2 factorial design for different polymers

Formulation Code	Drug Release kinetics, Correlation coefficients(r^2)					Release Exponent (n)	K $(h^1)^*$	MDT	Mechanism of Release
	Zero order	First order	Higuchi	Korsmeyer and Peppas	Hixson-Crowell				
VHE_1	0.9572	0.9702	0.9921	0.9890	0.9943	0.569	2.009	6.710	Anomalous
VHE_2	0.9554	0.9863	0.9894	0.9871	0.9952	0.601	2.005	7.043	Anomalous
VHE_3	0.9736	0.9881	0.9922	0.9924	0.9915	0.630	2.004	7.425	Anomalous
VHE_4	0.9541	0.9806	0.9976	0.9972	0.9866	0.509	1.984	6.424	Anomalous
VHE_5	0.9445	0.9914	0.9917	0.9911	0.9892	0.545	2.001	6.515	Anomalous
VHE_6	0.9533	0.9903	0.9933	0.9926	0.9903	0.572	2.000	6.790	Anomalous
VHE_7	0.9390	0.9702	0.9942	0.9923	0.9921	0.524	2.018	6.883	Anomalous
VHE_8	0.9461	0.9312	0.9951	0.9942	0.9912	0.543	2.073	7.186	Anomalous
VHE_9	0.9492	0.9390	0.9964	0.9923	0.9903	0.573	2.070	8.106	Anomalous

were stored in securitainers without a desiccant pack. The stability was monitored at 40°C/75% R. H. for up to 3 months as per ICH guidelines. A typical dissolution profiles and assay values for stability batches are provided in table 9. This developed verapamil HCl delivery system displayed excellent dissolution stability.

Table 8: Pharmacokinetic parameters of optimized Verapamil HCl formulation

Parameter	VHE_9	CF
C_{max} (ng/ml)	1123.22 ±0.371	1117.37 ±0.046
T_{max} (hr)	2.17±.0.67	2.22±0.87
AUC $(_{0-t})$ (ng/ml*hr)	19823.30±0.313	20162.93 ±0.146
AUC $(_{0-\infty})$ (ng/ml*hr)	22487.11±0.153	22872.59 ±0.184

Table 9: Three months Stability studies of Verapamil HCl for formulation VHE_9

Stability (40°C ± 2°C, 75±5% RH)	Drug Release (%)	Assay (%)
1 month	99.78±1.04	101. 92±1.74
2 months	98.32±0.98	99.56±1.54
3 months	96.27±1.24	98.64±0.97

DISCUSSION

When IR spectra of drug compared with the spectra of drug and polymers, it would appear that there was no obvious interaction between drug and the both the polymer.

The pure Verapamil HCl X-ray diffraction spectra showed that the drug was crystalline in nature. Peaks were clearly seen at the same position in the Verapamil HCl but the peak intensities were decreased to some extent. From the stated observations, we can conclude that the crystalline nature of the drug was still maintained, indicating no drug interactions in drug and polymer. The reduced intensity of peaks can be attributed to presence of high amounts of polymer.

The polymers HPMC K15M CR, Kollidon SR shows broad endothermic fusion peak whereas Eudragit RSPO shows fused melting point peak. The DSC curve of pure verapamil HCl exhibited a single sharp endothermic peak. These observations of DSC study indicate absence of significant interaction between drug and polymer in tablet formulations.

The Kollidon SR gave burst release independently of diluents microcrystalline cellulose; this is due to the high water permeability of Kollidon SR while the presence of Eudragit RSPO gave slower release profiles independently of microcrystalline cellulose presence. Drug release from HPMC matrices follows two mechanisms, drug diffusion through the swelling gel layer and release by matrix erosion of the swollen layer. Therefore, Eudragit RSPO and HPMC K15 M CR were chosen as the main matrix forming polymers for matrix tablet development to get the controlled release of drug up to 20-24 hrs.

As Increasing the concentration of either HPMC K15M CR (X_1) or Eudragit RSPO (X_2) resulted in reduction of drug release from the matrix tablets. The tablets showed good *in vitro* drug release between 20 to 24 hr for 3^2 factorial design batches. From the drug release study it can concluded that high levels of both HPMC K15M CR (X_1) and Eudragit RSPO (X_2) are suitable for the desired controlled release formulation of Verapamil HCl matrix tablets.

The drug release from prepared matrix tablets is controlled by diffusion and is independent of unreleased drug amount within the tablet. Table 7 also stated that coefficient of Higuchi order is similar to the Korsmeyer-Peppas model. The selection of adequate model was based on comparisons of the various features of each model such as higher determination coefficient, smaller standard error of model and smaller residual mean square (Oth and Moes 1989). From the above results it can be observed that water penetrated into matrix tablet by diffusion through the Eudragit RSPO. Higuchi kinetics

indicated that system majorly depends on diffusion for drug release. This may be also due to the presence of HPMC within matrix which controls the drug release through its swelling mechanism. The release exponent value of optimized formulation VHE_9 is 0.573 which indicated that system shows anomalous drug diffusion in which HPMC is a swelling dependent polymer while Eudragit is the erosion dependent polymer. From all the results it can be concluded that mixture of HPMC and Eudragit shows better control over drug release compared to alone Eudragit and HPMC.

In vivo pharmacokinetic study in healthy human volunteers' shows difference between VHE_9 with CF was significant for C_{max}, T_{max} AUC (0-t) and AUC (0-∞) and was found to be comparable indicating that the formulation exhibited comparable sustained release pattern.

In vitro percent dissolution of Verapamil HCl was compared with *in vivo* rate of absorption using the method of linear regression analysis and correlation coefficient. The study shows a good correlation between the drug dissolution and bioavailability. A high value of correlation coefficient (r^2) showed a good *in vitro-in vivo* correlation.

CONCLUSION

The Verapamil hydrochloride matrix tablet provides better control of drug release rate for the hydrophobic (Eudragit RSPO) polymer than the hydrophilic (HPMC K15M CR). The Verapamil hydrochloride matrix tablets with Kollidon SR give the burst release dissolution pattern due to its high water permeability. The Verapamil hydrochloride with HPMC K15M CR and Eudragit RSPO provides better control of drug release up to 24 hr. The *in vitro* dissolution statistical data exhibits the Higuchi kinetic model and follows the anomalous release pattern for the Verapamil hydrochloride matrix tablets (VHE_9). The *in vivo* pharmacokinetic data between the VHE_9 with CF was significant and found to be comparable indicating that the formulation exhibits comparable sustained release pattern. The study shows the good *in vitro-in vivo* correlation. The CF gives the drug release up to 8 hr as compare to verapamil HCl formulation (VHE_9) which gives the drug release up to 24 hr, conclusively the developed verapamil HCl formulation is novel and cost efficient. Conclusively, the current study attained the successful design, development and optimization of controlled release once a day formulation of verapamil HCl.

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