Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Issue 3, 2012

Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF VERAPAMIL HYDROCHLORIDE BY MELT GRANULATION

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Received: 24 Mar 2012, Revised and Accepted: 19 May 2012

ABSRTACT

The release of Verapamil hydrochloride (VPH) from tablet made with different drug to wax ratio was investigated with a view to develop sustained-release dosage form by hot melt granulation technique. VPH shows thermal stability up to 180 °C and melts at 146 °C, followed by total degradation. Compatibility studies showed that drug is compatible with all the excipients. Hydrogenated castor oil (HCO) is a waxy material can be used in formulation of sustained release dosage form. It has also been suggested that stearic acid may be used as a sustained-release drug carrier. Because of short biological half life and repetitive administration, VPH was considered as an ideal drug for designing sustained release formulation. The effect of HCO and stearic acid (SA) was studied at different drug to wax ratios (1:1, 1:2 and 1:3 etc.). The effect of both waxes in a combined ratio (1:1:1, 1:2:1 and 1:1:2) on drug release was also studied. The results of dissolution study showed that the matrices prepared from combination of both waxes gets more retarded compare to HCO alone where as in case of SA, it was found to release the drug at faster rate. Drug release was studied by using USP type II apparatus with buffer pH 1.2 for one hour and followed by buffer pH 6.8 for seven hours. The drug release profile was compared with marketed formulation.

Keywords: Sustained release, Verapamil hydrochloride, Ethyl cellulose, Stearic acid, Hydrogenated castor oil and Melt granulation.

INTRODUCTION

It is well known about oral route of drug administration among which tablets are most popular dosage forms available in the market and most preferred by patients and physicians. In case of chronic disease condition, long term therapy will be essential. Hence conventional dosage forms are required to be administered as multiple doses which have several disadvantages. For such therapy sustain release tablets are much desirable[1]. Continuous release of active ingredients for a specific period of time in order to achieve prolonged action or drug release for prolonged period of time are the basis of sustain release dosage forms[2]. It is obvious that instead of administering numerous doses, single dose of drug that is released over an extended period of time would be more advantageous. Among various systems, matrix system is widely used for the purpose of sustained release. This system is designed in such a way that drug release from the tablet follows first order kinetics or zero order kinetics due to presence of either hydrophobic or hydrophilic polymers as an excipients to form a matrix, by which it prolongs and controls the release of drug. There by therapeutically effective drug concentration can be achieved over a prolonged period of time in the systemic circulation and improved patient compliance can be achieved[3].

Verapamil hydrochloride is a calcium channel blocker and a class IV antiarrhythmic agent used in the control of supraventricular arrhythmias and in the management of angina pectoris, hypertension and myocardial infraction. It is soluble in water, sparingly soluble in ethanol (95%), and freely soluble in chloroform. VPH has short biological half-life of 4-5 hours and hence it is necessary to administer frequently due to which VPH can be considered as a potential candidate for a design of sustained release dosage forms. Hence, sustained release tablets for VPH is formulated which in turns prolong its duration of action and reduction of usage frequency. By incorporating drug in to an insoluble carrier like ethyl cellulose (EC), PEG, eudragit RSPO drug release can be prolonged and such system can be considered as matrix system which helps in prolonging the drug release by means of diffusion[4, 5].

The USPNF 29 describes HCO as refined, bleached, hydrogenated and deodorized castor oil consisting mainly of the triglyceride of hydroxystearic acid melts at the temperature between 85 to 88 °C. It has been used in pharmaceutical formulation as a binder and controlled release matrix agent[6].

SA is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant. The USPNF 29 describes SA is derived from fats and oils which is a mixture of stearic acid and palmitic acid, the content of stearic acid is not less than 40.0 percent and sum of two is not less than 90.0 percent[6].

Melt granulation is a process in which meltable binder or mixture of binders is/are added to the mixture of drug and diluent, granulation is obtained by adding molten binder, which melts/softens at relatively low temperature, and acts as a binding liquid. Dried granules are obtained by cooling at room temperature. This method can be applicable to water sensitive material and for producing SR formulation. Waxes have been used extensively for sustaining the release of drug from matrix. Many waxes (e.g., stearic acid, mono-di and tri glycerides, glyceryl monosterate, hydrogenated castor oil, etc.) have been used[7, 8]. Since VPH has a thermal stability up to 180 °C and a melting point ranges from 144-146 °C which indicates that VPH will not be degraded during the mixing with molten wax[9].

Hence present study was aimed towards formulation and *in-vitro* evaluation of sustained release matrix tablets of VPH by melt granulation by using HCO and SA as a meltable binder.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride was obtained from Piramal Healthcare (Mumbai, India). Micro crystalline cellulose (MCC, Avicel PH 101) and Ethyl cellulose were obtained from Signet chemicals (Mumbai, India). Stearic acid was obtained from Godrej industries ltd (Mumbai, India). Hydrogenated castor oil was obtained from JRS pharma (Hyderabad, India).

Methods

Preparation of tablets

Sustained release granules were prepared using molten wax as a retarding material. For preparation of sustained release formulation hydrogenated castor oil and stearic acid were used as binders. Drug and diluent were sifted through 40 mesh sieve and dry mixed. Binder was melted on water bath (Remi, RS-24 (BL)) maintained at 75°C and dry mixture of drug-diluent was added and mixed under continuous stirring (Remi, RQ-20 Plus) to form

granules. The molten mixture was then allowed to cool and solidify at room temperature and pulverized in mortar and sieved through 20 mesh sieve. Different trials were taken at different drug: wax ratio for both waxes (1:1, 1:2, and 1:3) and also in combination of both waxes as VPH: SA: HCO (1:1:1, 1:2:1 and 1:1:2). Ethyl cellulose was passed through 60 mesh sieve and added after sifting granules and mixed well. Prior to compression magnesium stearate (60 mesh sieve) was mixed with each batch of granules for 5 min. A rotary tableting machine equipped with standard concave bevelled edge punch was used to compress tablets. The composition of various formulations of the tablets with their codes is given in Table 1.

Table 1: Composition of Verapamil hydrochloride sustained release formulations

Ingredients (mg)	Formulation								
	F1 VPH: HCO 1:1	F2 VPH: HCO 1:2	F3 VPH: HCO 1:3	F4 VPH: SA 1:1	F5 VPH: SA 1:2	F6 VPH: SA 1:3	F7 VPH:SA: HCO 1:1:1	F8 VPH:SA: HCO 1:2:1	F9 VPH:SA:HCO 1:1:2
Verapamil HCl	120	120	120	120	120	120	120	120	120
MCC PH 101	540	420	300	540	420	300	420	300	300
HCO	120	240	360	-	-	-	120	120	240
SA	-	-	-	120	240	360	120	240	120
EC	90	90	90	90	90	90	90	90	90
Aerosil	15	15	15	15	15	15	15	15	15
Mag. Stearate	15	15	15	15	15	15	15	15	15

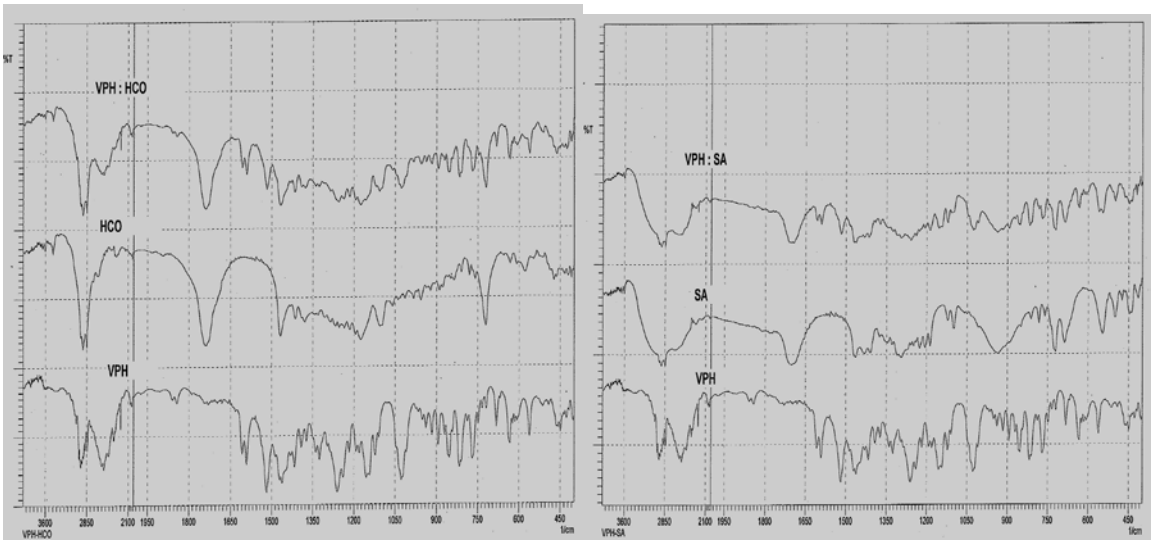

Fig. 1: IR spectra of pure drug, binders and matrices of drug and binder

Drug: wax interaction study

Pure drug, wax and prepared matrices were subjected to infrared (IR) spectroscopic study using FTIR spectrophotometer (Shimadzu-8400) by KBr (Potassium bromide) pellet technique. Each spectrum was overlayed and compared for changes in drug properties.

Evaluation of granules

Prepared granules were evaluated for various parameters such as angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index (CI) and Hausner's ratio (HR).

Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability, drug content, *in-vitro* drug release studies. Hardness of the tablets was tested using Rimek-k-DHT 100. Friability of the tablets was tested using Roche friabilator (Electrolab EF-2-USP). The thickness of the tablets was tested using vernier caliper (Mitutoyo CD-6, Japan). Weight variation test was performed according to US pharmacopoeia (USP-30) [10, 11].

***In-vitro* drug release study**

In-vitro drug release study for the prepared tablets were conducted for period of 8 hours using twelve station USP type II (Paddle) apparatus at 37°C ± 0.5°C and 50-rpm speed. The dissolution studies were carried out in 900ml media of acid buffer of pH 1.2 for one hour and in phosphate buffer of pH 6.8 for further seven hours under sink condition. At one hour and then 2, 3.5, 5 and 8 hours interval samples of 10 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. The samples withdrawn were filtered through a whatman No. 1 filter and drug content in each sample was analyzed by UV spectrophotometer (Shimadzu 1800, Japan) after suitable dilution at 278nm. The amount of drug present in each sample was calculated with the help of appropriate calibration curve and compared with reference standard. Also the *in-vitro* drug release study for marketed tablets (Calaptin SR 120 mg, Piramal Healthcare) was conducted[12].

Drug release kinetics

The data obtained from *in-vitro* drug release study was fitted to mathematical equations of different kinetics model such zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), higuchi (cumulative percentage of release versus square root of time) (Higuchi, 1963) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models (Korsmeyer et al., 1983).

The zero order rate equation (1) describes the systems where the drug release rate is independent of its concentration. The first order equation (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion equation (3). The Korsmeyer-Peppas equation (4) describes drug release as a log cumulative % drug release[13].

$$C = k_0 t \quad (1)$$

Where, K_0 is zero-order rate constant expressed as concentration/time and t is the time.

$$Log\ C = Log\ C_0 - kt / 2.303 \quad (2)$$

Where, C_o is the initial concentration of drug and K is first order constant.

$$Q = Kt^{1/2} \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$M_t / M_\infty = Kt^n \quad (4)$$

Where, M_t/M_∞ is the fraction released by the drug at time't', K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic for the drug transport mechanism.

RESULTS & DISCUSSION

Drug: wax interaction study

IR spectrums of prepared granules were compared with that of pure drug IR spectra and it was found that there is no characteristic change in the spectrum of pure drug and major peaks like C-H stretching at 2850-2810 cm^{-1} and C-H aromatic ring at 1600-1500 cm^{-1} were found to be stable even after formation of matrices of drug with HCO and SA. This indicates that the drug is compatible with the meltable binders such as HCO and SA (Fig. 1).

Evaluation of granules

Granules of proposed formulations were evaluated for angle of repose, LBD, TBD, CI and HR (Table 2). Angle of repose of the all formulations was found to be in the range of 31.32±0.43 to 34.45±0.38 indicating good flow properties. The results of LBD AND TBD for all formulations varied in the range of 0.454 gm/ml to 0.690 gm/ml and 0.460 gm/ml to 0.761 gm/ml respectively. The CI ranged from 9.13 % to 16.35 % and HR was found to be in the range of 1.12 to 1.20 indicating that all formulations showed good flow properties and compressibility[14].

Table 2: Physical properties of granules containing VPH as a SR formulation

Formulation	LBD (gm/ml)	TBD (gm/ml)	Angle of repose (Degree)	CI (%)	HR
F1	0.535	0.753	31.76±0.65	9.13	1.12
F2	0.5	0.576	31.52±0.45	13.33	1.15
F3	0.69	0.761	32.21±0.14	14.22	1.20
F4	0.672	0.46	32.09±0.18	14.24	1.19
F5	0.454	0.576	33.56±0.23	14.28	1.18
F6	0.478	0.467	34.45±0.38	14.25	1.12
F7	0.542	0.627	32.51±0.18	15.05	1.17
F8	0.576	0.681	34.25±0.36	15.38	1.18
F9	0.497	0.587	31.32±0.43	16.35	1.16

Tablet characteristics

The physical parameters such as hardness, thickness, friability and weight uniformity of all the formulated tablets were given in Table 3. Hardness of all the tablets was in the range of 8.53±0.52 kg/cm^2 to 11.53±0.15 kg/cm^2. The thickness of all the tablets was in the range of 5.35±0.18 mm to 5.39±0.04 mm. The percentage friability ranged from 0.35±0.02 % to 0.48±0.03 % i.e. less than 1%. For tablets of more then 324 mg percent deviation according to US pharmacopoeial limit is ±5% and average percent deviation of all the tablets were found within the limit hence all formulation passed the weight variation test. The drug content was found to be uniform and ranged from 96.97 % to 99.34 %.

Drug release studies

In-vitro drug release study depends on several factors such as, amount of drug, type of excipient and the manufacturing process.

Effect of wax at different drug: wax ratio on drug release

Effect of HCO on release profile of VPH (F1-F3) was studied and it was found that by using HCO alone in the ratio of 1:1 was not able to control the release from matrices and initial burst effect was observed where as in the case of 1:3 it showed that drug release was more retarded. Only ratio of VPH: HCO (1:2) showed drug release closer to marketed formulation (Fig. 2a). This was due to the hydrophobic coating of HCO on drug particle which hinder penetration of solvent molecules and hence leads to slower release of drug for a prolonged period of time. By using SA (F4-F6) its effect on drug release showed that initial burst effect has been observed and SA was not able to control the drug release (Fig. 2b). From the result it was noted that only formulation F2 containing VPH: HCO (1:2) showed drug release equivalent to marketed formulation.

Effect of combination of wax at different drug: wax ratio on drug release

The release of VPH from combination of waxes at different ratio (F7-F9) showed that drug release was very slower and it gets more retarded than that of individual waxes used (Fig. 2c). This may be due to higher lipophilicity provided by combination of both wax.

Table 3: Physical properties of sustained release VPH matrix tablets

Formulation	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	8.53±0.52	0.37±0.12	900.22±2.55	5.37±0.08	96.97
F2	9.31±0.54	0.42±0.10	897.78±3.57	5.38±0.02	97.65
F3	10.65±0.25	0.35±0.02	899.14±2.89	5.37±0.15	98.35
F4	9.95±0.38	0.45±0.23	897.36±3.28	5.39±0.04	97.48
F5	10.45±0.34	0.42±0.06	901.45±1.47	5.36±0.03	99.18
F6	11.53±0.15	0.48±0.03	898.11±2.20	5.35±0.18	98.82
F7	9.76±0.15	0.43±0.04	899.12±1.45	5.37±0.06	97.55
F8	10.02±0.34	0.38±0.11	902.24±1.76	5.38±0.13	98.16
F9	10.68±0.23	0.41±0.01	900.22±1.42	5.36±0.08	99.34

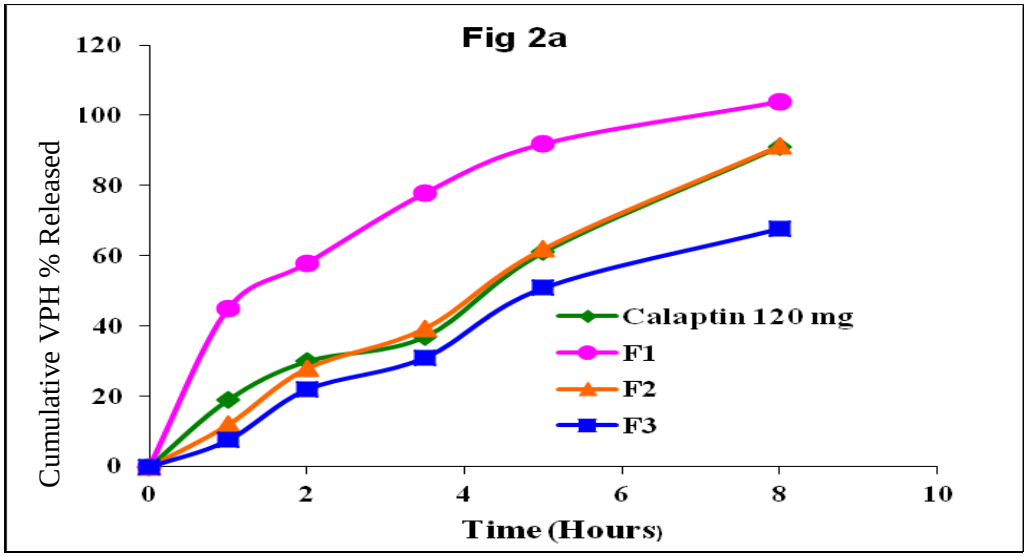

Fig. 2a: Dissolution profile of F1, F2 and F3 compared with marketed formulation

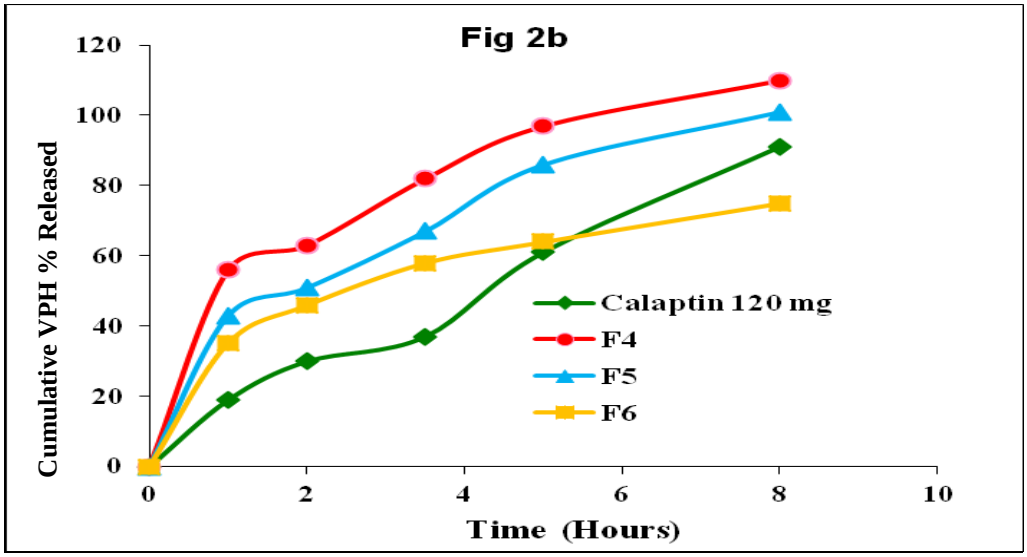

Fig. 2b: Dissolution profile of F4, F5 and F6 compared with marketed formulation

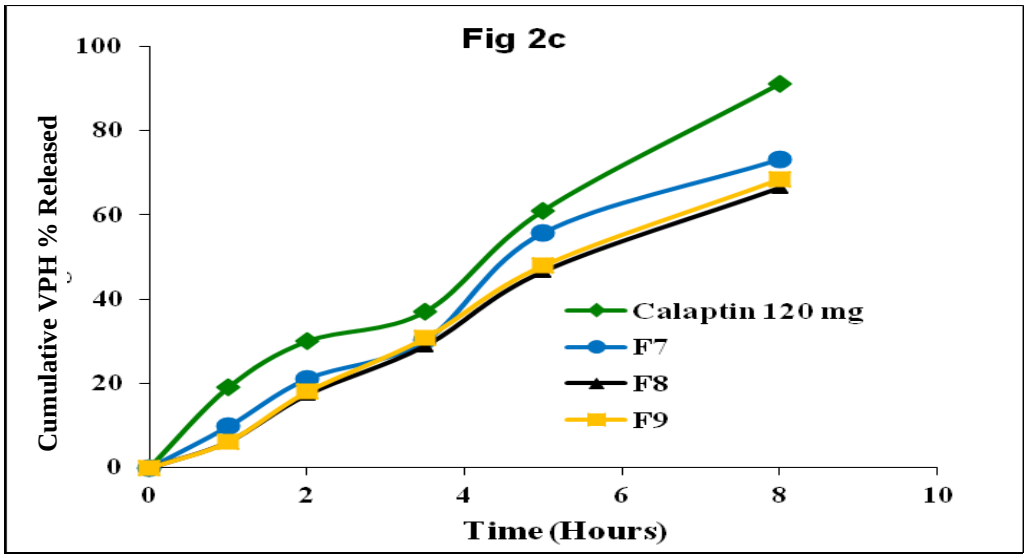

Fig. 2c: Dissolution profile of F7, F8 and F9 compared with marketed formulation

Drug release kinetics

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations. The data was analyzed by the regression coefficient method and regression coefficient value (r^2) of all batches as shown in Table 4. The drug release from F4 and F5 followed Higuchi model release kinetics. The drug release from F2, F8 and F9 followed zero order kinetic models. The drug release from F3 followed First order kinetic model. The drug release from F1, F6 and F7 followed Korsmeyer-Peppas kinetic model.

The *in-vitro* release profiles of drug from all these formulations could be best expressed by Zero-order equation as the plot showed highest linearity (r^2 = 0.9939).Four different models of drug release kinetics were plotted for optimized formulation (F2) showed in Fig. 3.

Table 4: Regression coefficient value (r^2) of different formulations

Trials	Regression coefficient value (r^2)			
	Zero order	First order	Higuchi	Korsmeyer-Peppas
F1	0.8278	0.9670	0.9812	0.9899
F2	0.9939	0.9330	0.9807	0.9893
F3	0.9805	0.9880	0.9853	0.9717
F4	0.7926	0.4840	0.9807	0.9708
F5	0.8691	0.9260	0.9818	0.9737
F6	0.7888	0.9890	0.9894	0.9964
F7	0.9779	0.9750	0.9655	0.9835
F8	0.9923	0.9920	0.9887	0.9869
F9	0.9923	0.9910	0.9922	0.9843

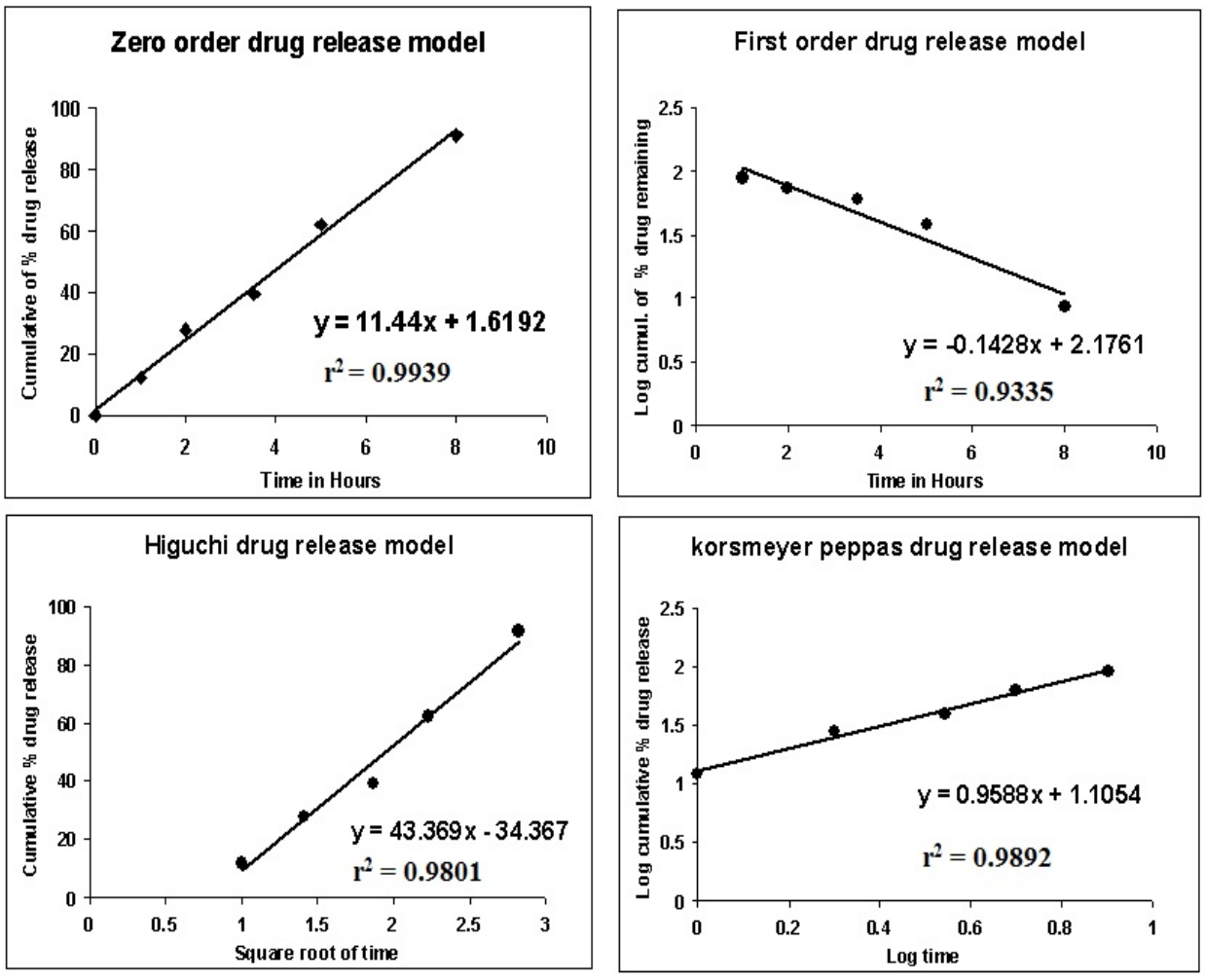

Fig. 3: Drug release kinetic models for formulation F2

CONCLUSION

The approach of the present study was to formulate and evaluate the effects of wax materials as sustained release matrix for water soluble VPH and to access the kinetics of drug release mechanism. Among all the formulations F2 containing 1:2 (VPH: HCO) showed drug release of 91.4% which is equivalent to marketed preparation and hence it is most challenging formulation among all the formulations.

Among meltable binder hydrogenated castor oil and stearic acid, hydrogenated castor oil sustain the drug release more than stearic acid. Combination of both waxes retard the drug release more than separate wax used alone. Hence the study was concluded that

hydrogenated castor oil is appropriate waxy material that can be utilized as matrix forming agent in melt granulation technique to sustain the release of water soluble drug such as VPH.

ACKNOWLEDGEMENT

The author is heartly thankful to Cadila Pharmaceuticals Limited, Ahmedabad for providing great opportunity and facilities to carry out the research work and also conveying sincere thanks to the supporting authors.

REFERENCES

1. Samal HB, Srenivas SA, Sharma H. Formulation and evaluation of sustained release zidovudine matrix tablets. Int. J. Pharm. Pharm. Sci. 2011; 3 (2): 31- 42.
2. Pahade AA, Jadhav VM, Kadam VJ. Formulation and development of a bilayer sustained released tablets of isosorbide mononitrate. Int. J. Pharma. Bio Sci. 2010; 1(4): 305-314.
3. Modi AS, Gaikvad PD, Bankar VH, Pawar SP. Sustained release drug delivery system: A Review. Int. J. Pharma. Res. Dev. 2011; 2(16): 149-160.
4. Moorthy SU, Kumawat MM, Reddy RT, Someshwar K. Formulation of sustain release solid dispersions of verapamil hydrochloride using ethyl cellulose and eudragit-RSPO. Int. J. Pharm. Pharm. Sci. 2011; 3(1): 116-122.
5. Sahoo J, Murthy PN, Biswal S, Manik. Formulation of sustained release dosage forms of verapamil hydrochloride by solid dispersion technique using eudragit RLPO or kollidon SR. AAPS Pharm. Sci. Tech. 2009; 10(1): 27-33.
6. Raymond C Rowe, Paul J Sheskey. Handbook of Pharmaceutical Excipients. 6th ed. Pharmaceutical press (RPS publishing); 2009, 128 and 697.
7. Bhagwat AD, Kawkitwar PS, Sakarkar DM. Sustained release matrices of verapamil hydrochloride using Glyceryl monosterate and stearic acid. Res. J. Pharm. Tech. 2008; 1(4): 405-409.
8. Royce A. Alternative granulation technique: Melt Granulation. Drug. Devl. Ind. Pharm. 1996; 22(9 & 10): 917-924.
9. Antonio MO, Irene MY, Lima EC, Daurte CV, Cunha AF. Thermal analysis applied to verapamil hydrochloride characterization in pharmaceutical formulations. Mol.2010; 15: 2440-2452.
10. Aulton ME. Pharmaceutics: The Science of Dosage Form Design. 2nd ed. Livingstone C. Elsevier Science Ltd. 2002; 315-20.
11. Indian Pharmacopoeia Government of India, Ministry of Health and Family Welfare. The controller of publications. New Delhi, 1996; Vol-II: 734-736.
12. The United States Pharmacopoeia United State Pharmacopeial Convention, Rockville, MD. Asian Edition 2000; 1741-1742.
13. Shoiab MH, Tazeen J, Merchant AH, Yusuf RI. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. Pak. Pharm. J. Sci. 2006; 19(2): 119-124.
14. Banker GS, Anderson NR. In: Lachman L, Lieberman HA, Kanig JL, editors, Tablets. 3rd ed. Varghese publishing house.1991, p. 297-299.