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Formulation and *in-vitro* bioequivalence evaluation of verapamil hydrochloride matrix tablets with Calan R

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ABSTRACT
The purpose of the current work was to formulate Verapamil Hydrochloride (VH) sustained release matrix tablets by using natural polymers and comparison with leading national brand Calan SR of Searle Pharmaceuticals. Tragacanth and pectin were used in various concentrations. Pre compression studies *i.e.* angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner's ratio were also performed and found within the Pharmacopoeial limits. Eight formulations (F1-F8) of (VH) were prepared by direct compression method. Post compression studies i.e. Thickness, Hardness, Diameter, Friability and Dissolution studies were conducted. Different kinetic models *i.e.* zero order, first order, Highuchi model and Korsmeyer Peppas were applied to study release patterns and similarity index was calculated. Dissolution studies were carried out in phosphate buffer of pH 6.8 showed that formulations (F4 and F8) formulated with higher polymers concentration showed comparatively better drug retardation. F5 was the most comparable with the reference product. Verapamil hydrochloride released was observed non-fickian as diffusion following Higuchi model.

Key Words: Verapamil hydrochloride, Calan SR, kinetic models, matrix tablets, natural polymers.

INTRODUCTION

Dosage forms are designed to deliver optimum dose of drug to the site of action to produce desired pharmacological action and also to achieve the effective drug concentration over the preferred period of time. Oral drug delivery system is the most commonly used route of administration when compared to all other routes for various pharmaceutical products of different dosage forms. Easy administration, high patient compliance, avoiding tough sterile standards, and relatively cheap and easy formulation makes the oral dosage form as the first priority (Krishnaiah *et al.*, 2002).Verapamil Hydrochloride, a commonly used calcium channel blocker for hypertension and arrhythmias, has a biological half-life of 4 to 6 hours. It has quite good absorption profile from gastrointestinal tract; about 90% of the orally administered drug is absorbed from the gastro intestinal tract. However, it undergoes extensive first pass metabolism which results in only 20% bioavailability. Keeping in view these facts, formulating a controlled release dosage form for Verapamil Hydrochloride is gaining interest to increase the therapeutic efficacy and patient compliance (Sahoo *et al.*, 2009). Matrix tablets can be formulated by using natural polymers by direct compression of the mixture of active ingredient, retardant material and additives. The hydrophilic matrix needs water to activate the release mechanism and several benefits including ease of manufacture, release of 100% drug in-vivo and outstanding uniformity of matrix tablets. The hydrophilic matrix tablets are immersion in water swiftly forms a gel layer around the tablets (Shah *et al.*, 2012).

Aims and objectives of the present study are to formulate the sustained release matrix tablets of Verapamil Hydrochloride using natural polymers (Tragacanth and Pectin) by direct compression method. Natural polymers exhibit good drug release retarding behavior and are biocompatible & economic. Release retarding behavior of natural polymers in matrix formulations is compared to that of marketed product Calan SR taken as reference tablet.

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MATERIALS AND METHODS

Materials

Verapamil Hydrochloride used as a model drug was gifted by Searle Pakistan Ltd. Microcrystalline cellulose (diluent), aerosil (glidant), magnesium stearate (lubricant) and polymers (release retarding materials) Pectin and Tragacanth were obtained as a gift from Unexo Pharma (pvt.) Ltd. Lactose was obtained from E Merck Germany. Chemicals like hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate were obtained from Mega Pharmaceuticals (pvt.) Ltd.

Methods

Milling of all ingredients was conducted to reduce the particle size then all the ingredients were passed through sieve no. 60. Verapamil hydrochloride was mixed with different polymers (individually as well as different combination forms) one by one in different drug to polymer ratios 1:0.5, 1:1, 1:1.5 and 1:2. Eight different Verapamil Hydrochloride - polymer combinations were

Table 1: Composition of matrix tablets of Verapamil hydrochloride.

Code	Verapamil (mg)	Traga-canth (mg)	Pectin (mg)	Lactose (mg)	Mg. Stea-rate (mg)	Aerosil (mg)	PVP (mg)
F1	240	120	-	424	8	8	50
F2	240	240	-	304	8	8	50
F3	240	360	-	184	8	8	50
F4	240	480	-	64	8	8	50
F5	240	-	120	424	8	8	50
F6	240	-	240	304	8	8	50
F7	240	-	360	184	8	8	50
F8	240	-	480	64	8	8	50

made as shown in (table 1), which were then mixed with PVP, Aerosil and lactose in a poly bag and the mixture was again passed through a mesh no. 60. Magnesium Stearate was added to the blend. Twenty different blends thus obtained were weighed individually for weight-equivalent to 850 mg/ tablet and then were compressed into tablets on a single punch tablet machine.

Pre-compression studies

Angle of repose

Blend of powder was added to a funnel that was vertically placed to obtain a max height (H) cone. Radius of heap (R) was noted and (Θ) angle of repose was calculated as (Marshal, 1987).

$\Theta = \tan^{-1} (H/R)$

Bulk density

Drug and excipients mixture was sieved and then put in the graduated cylinder .The volume and weight of powder was determined (Marshal, 1987).

Bulk density= weight of powder/volume of powder

Tapped density

The tapped density was determined by tapping the cylinder having pre-weighed powder and then tapped it 100 times (Marshal, 1987).

Db = W/Vb

Db = loose bulk density, W = weight of powder, Vb = volume of powder

Carr's index

The free flowing of powder was measured by compressibility index i.e. a property with which material would flow easily (Marshal, 1987).

Carr's index (I) = (Vb-Vt) x 100 /Vb

Hausner ratio

It is indirect method for measuring ease of powder flow (Marshal, 1987).

Hausner's ratio = Dt/Db

DSC studies

The DSC analysis of pure drug, polymers and there mixture was conducted on SDT. Q600 TA USA to check any possible interactions. Drug, polymers and there combinations were triturated to make them fine in size and then heated in sealed Aluminium pan at a heating rate of 10°C/min from 0 to 210°C. The nitrogen flow was 40ml/min. Reproducibility was checked by running sample in triplicate (Ranjha *et al.*, 2010).

Table 2: Results of bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index.

Code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (°)	Hausner's ratio	Carr's index (%)
F1	0.675	0.782	24.5	1.15	16.30
F2	0.665	0.778	25.8	1.16	15.20
F3	0.65	0.750	23.6	1.15	15.78
F4	0.635	0.750	25.7	1.18	15.53
F5	0.679	0.790	24.6	1.16	16.10
F6	0.670	0.780	24.5	1.16	15.38
F7	0.655	0.772	25.6	1.17	16.35
F8	0.660	0.788	26.0	1.19	15.90

Post-compression studies

Compressed tablets were evaluated by different parameters, including appearance, thickness and diameter, weight variations, hardness, percent friability and contents uniformity (Patel *et al.*, 2012).

Dissolution studies

Dissolution studies of Verapamil Hydrochloride tablets were investigated in USP tablet dissolution test apparatus-II (Paddle apparatus) at 50 rpm. 900 ml of pH 6.8 phosphate buffer was used as a dissolution medium. An already warmed to 37±0.5°C dissolution medium was used and its temperature was maintained during the complete time of experiment. Five ml of the sample of dissolution medium was taken using syringe at specified time intervals (1 hour). The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The sample was analyzed for drug release by measuring the absorbance at 278 nm using UV-visible spectrophotometer after suitable dilutions and filtration.

Statistical analysis

Statistical analysis was done to calculate the standard deviation and mean of different parameters. Different kinetics modes were applied including;

Zero Order Kinetics ($Q_t = k_o\ t$)..... 1

First Order Kinetics ($\log Q_t = \log Q_o - k_1\ t$)..... 2

Highuchi Model ($Q_t = k_H\ t^{1/2}$)..... 3

KorsmeyerPeppas Model ($M_t / M_\infty = k_{KF} t^n$)..... 4

These models were utilized in the prediction of drug behavior and release kinetics (Sahoo *et al.*, 2009). Similarity (f2) and difference (f1) factors were also calculated by the following equations (Shah *et al.*, 2009; Gohel *et al.*, 2002).

$$f1 = \frac{\sum[R_t - T_t]}{\sum R_t} \times 100 \quad \text{..... 5}$$

$$f2 = 50.Log\left[\frac{1}{\sqrt{1+\frac{1}{n}\sum(R_t - T_t)^2}} \times 100\right] \quad \text{..... 6}$$

RESULTS

Pre-compression studies

All the results of angle of repose, bulk density, tapped density; Carr's compressibility index and Hausner's ratio were found within the limits indicating good flow properties of powder to be compressed as shown in (table 2). Differential scanning calorimetery (DSC) was performed for all the polymers and drug alone and in combination, no compatibility issue was revealed from spectra as shown in (figure 1).

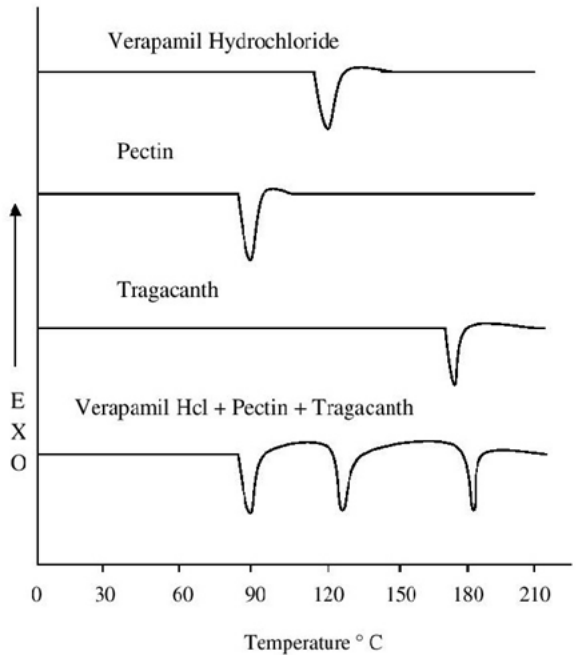

Figure 1: DSC Spectrum of drug and polymers.

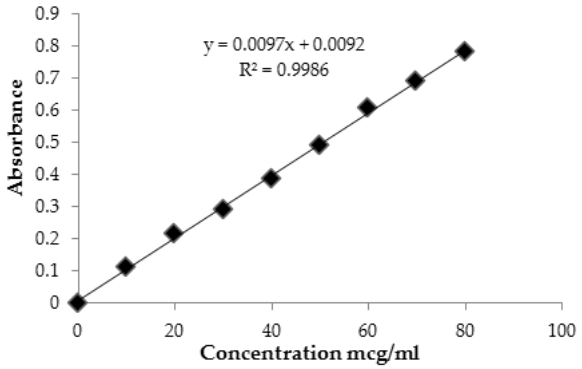

Figure 2: Calibration Curve for Verapamil hydrochloride.

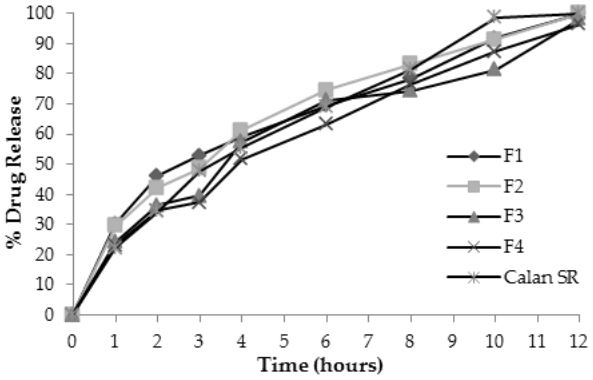

Figure 3: Drug release pattern of F1-F4 Compared to Calan SR.

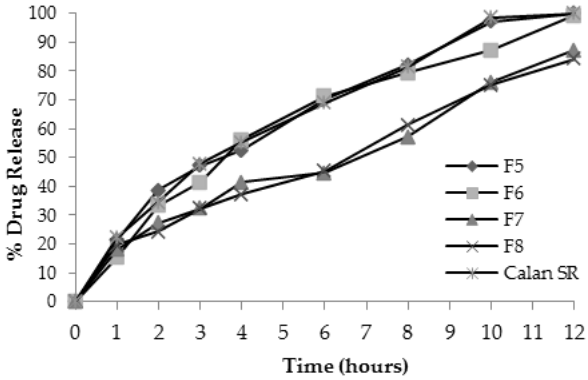

Figure 4: Drug release pattern of F5-F8 Compared to Calan SR.

Table 3: Post compression evaluation of VH matrix tablets.

Formulation	Hardness (kg/cm²)	Thickness (mm)	Drug content (%)	Friability (%)
F1	6.4 ±0.45	7.33 ±0.02	97.50±0.66	0.45 ±0.03
F2	5.8 ±0.30	7.24 ±0.04	97.75±0.24	0.33 ±0.01
F3	6.2 ±0.35	7.30 ±0.03	98.30±0.18	0.50 ±0.03
F4	6.0 ±0.40	7.35 ±0.05	97.95±0.56	0.40 ±0.02
F5	7.1 ±0.52	7.27 ±0.03	99.90±0.45	0.25 ±0.02
F6	6.6 ±0.45	7.28 ±0.02	98.60±0.35	0.52 ±0.01
F7	4.8 ±0.55	7.33 ±0.03	99.00±0.75	0.44 ±0.04
F8	7.4 ±0.44	7.29 ±0.04	98.50±0.56	0.45 ±0.02
Calan SR	7.0 ±0.56	7.26 ±0.01	99.50±0.40	0.30 ±0.03

Post compression studies

Hardness, thickness, percentage drug release and friability of all the formulations was found between 4.8-7.4 kg/cm², 7.24-7.35mm, 97.50-99.90% and 0.25-0.50% respectively, as shown in table 3.

Standard calibration curve for Verapamil hydrochloride

Standard calibration curve was plotted for Verapamil Hydrochloride was plotted by taking concentration in mcg/ml and measuring their absorbance at UV- visible Spectrophotometer. The standard calibration curve obtained was a straight line, which proved that the drug in the concentration range of 10-80 mcg/ml, obeyed the Beer's Lambert law as shown in (figure 2).

Dissolution studies

Formulations F1-F4 formulated with tragacanth showed 100, 100, 98.25 and 96.48% drug, respectively in 12 hours studies as shown in (figure 3). Formulations F5-F8 formulated with Pectin released 100, 99.37, 87.14 and 84.15% of the drug respectively in 12 hours (figure 4).

Kinetics modeling of the release data

Values of R^2 for Zero order kinetics were 0.9023 to 0.9765, for First order kinetics were 0.8215 to 0.9624, for Higuchi model 0.9613 to 0.9976 and for Peppas model these values were 0.9747 to 0.9960 while for reference tablets these values were R^2 = 0.9504 for Zero order kinetics, R^2 = 0.8907 for First order kinetics, R^2 = 0.9891 for Higuchi model and R^2 = 0.9948 for Peppas model as shown in (table 4).

Similarity index

Values of similarity factor (f_2) were found to be greater than 50 in all formulations except F7 and F8. Similarly the difference factor (f_1) ≤10 for all the formulations except F7 and F8 as shown in (table 5).

Table 4: Results of kinetic models data for F1-F8 in comparison with Calan SR.

Trial	Zero Order Kinetics	First Order Kinetics	Higuchi Equation	Peppas Model
F1	K= 7.106 R^2 = 0.9023	K= 0.3016 R^2 = 0.8634	K=28.178 R^2 = 0.9938	n = 0.4525 R^2 = 0.9916
F2	K=7.3986 R^2 = 0.9141	K= 0.3103 R^2 = 0.8943	K = 29.203 R^2 = 0.9976	n = 0.4995 R^2 = 0.996
F3	K=7.1348 R^2 = 0.9285	K= 0.2543 R^2 = 0.8276	K = 27.719 R^2 = 0.9816	n= -0.5694 R^2 = 0.9779
F4	K=7.3861 R^2 = 0.9605	K= 0.2371 R^2 = 0.9272	K= 28.281 R^2 = 0.9863	n=0.6028 R^2 = 0.9863
F5	K= 8.0585 R^2 = 0.9476	K=0.3538 R^2 = 0.9144	K=31.127 R^2 = 0.9903	n=0.6199 R^2 = 0.9907
F6	K= 8.0495 R^2 = 0.9429	K=0.3256 R^2 = 0.8215	K=31.032 R^2 = 0.9815	n=0.7215 R^2 = 0.9747
F7	K=6.5472 R^2 = 0.9722	K=0.1472 R^2 = 0.9294	K=24.6 R^2 = 0.9613	n= 0.6281 R^2 = 0.9759
F8	K=6.4654 R^2 = 0.9765	K=0.1385 R^2 = 0.9624	K=24.343 R^2 = 0.9696	n= 0.598 R^2 = 0.9747
Calan SR	K=7.9985 R^2 = 0.9504	K=0.3738 R^2 = 0.8907	K = 30.832 R^2 = 0.9891	n = -0.6245 R^2 = 0.9948

DISCUSSION

Results of the thickness test and diameters were with minimal variations found to be uniform. Weight variations for formulations comply with the official limits ± 5. Formulation F4 showed least hardness value 5.7 kg/cm^2. Hardness, % friability and drug contents of all the formulated tablets of verapamil hydrochloride complies with the official limits of 4-10 kg/cm^2,less than 1% and 95-105%respectively as per BP. Formulation trials having least polymer ratios showed least release retarding behavior, but as the ratio of polymer to drug was increased, release retarding behavior also increased significantly. F4 Formulation having drug to polymer ratio 1:2, showed satisfactory sustained release behavior comparable to that of marketed product Calan SR. Release retarding behavior of drug in F7 & F8 is much significant as compared to Calan SR but it did not comply with the official limits of USP. As the drug to polymer ratio was increased the similarity between F1 to F4 also increased but the formulation F3 showed some anomalous behavior. Although Formulation F3 is similar to marked product Calan SR, but the similarity factor value is less as compared to the formulation F1, F2 & F4. Formulation F4 was the most similar formulation to that of the reference standard. Formulation F5 showed maximum similarity with reference formulation. With the increase of polymer concentration, release retarding behavior increased. Although F6, F7, F8 were more sustained than reference formulation, but similarity factor value decreased with the increase of drug to polymer ratios. Release of the drug was observed to be influenced by the polymer concentration as, polymers concentration increased the release of the drug decreased (Patel *et al.*, 2012). Both tragacanth and pectin were the hydrophilic polymers. Initially there was greater release was observed because less hydration of the polymer but when the polymers in the tablets got hydrated release of the drug became slow gradually (Patel *et al.*, 2012; Shah *et al.*, 1998). Pectin became swell after the absorption of the aqueous media (Shah *et al.*, 2011). Slow release was observed in the formulations containing pectin because of the formation of gel layer around the tablets which can decrease the rate of erosion of the tablets

Table 5: Results of trials F1-F8 in comparison with Calan SR.

Formulation	Difference factor (f1)	Similarity factor (f2)	Difference between ref. and std. drug
F1	9.85925	58.599	Less than 10%
F2	10.236	59.5458	-do-
F3	10.4346	53.409	-do-
F4	7.18469	61.5822	-do-
F5	3.44509	79.2344	Less than 10%
F6	7.65385	60.6756	-do-
F7	24.6019	39.1549	More than 10%
F8	25.5779	38.8556	-do-

(Sriamornsak *et al.*, 2007). Higher values of Higuchi model showed that drug release pattern was according to diffusion, which was usually observed in the matrix systems formulated with the natural hydrophilic polymers. Diffusional exponent value (n) of Pappas model for formulation trials F1-F2 showed quasi Fickian type of diffusion. Drug to polymer ratio in these formulations was 1:0.5 and 1:1 respectively. Polymer used in F1 to F4 formulations was pectin in different drug to polymer ratios. The percentages of polymer in F1& F2 were 14.11% & 28.23%, respectively. Diffusional exponent value showed that at below 28% polymer concentration, pectin diffuses with a quasi-Fickian diffusion mechanism from a matrix tablet. Formulation trials F3, F4 & standard formulation Calan SR followed anomalous or non-Fickian diffusion mechanism of drug. F3 & F4 formulations were having 42% & 56% pectin polymers respectively. Diffusional exponent value (n) of Pappas model for formulation trials F5-F8 & standard formulation Calan SR showed non Fickian type of diffusion. Formulation F5 showed closed similarity with marketed product Calan SR.

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