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Formulation and Evaluation of Sustained Release Verapamil Hydrochloride Using Natural Polymers

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ABSTRACT:

The aim of the present study was to develop sustained release formulation of Verapamil Hydrochloride to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of HPMC polymers, Guar gum, and Xanthum gum were employed as polymers. Verapamil Hydrochloride dose was fixed as 120 mg. Total weight of the tablet was considered as 400 mg. Polymers were used in the concentration of 60, 120 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e.,96.10 % in 12 hours containing Guar gum polymer in the concentration of 180mg. It followed zero order release kinetics. For the optimized formulation alcohol effect has been studied by using various concentrations of alcohol in dissolution medium. As the concentration of alcohol increased the sustained action of polymer was decreased. Hence it was concluded that alcohol has significant effect on drug release pattern.

1. 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 (Sampath Kumar et al., 2012). 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 (Bala R et al., 2013). 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 (Irfan Bashir et al., 2013; Marwa et al., 2013). 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 has several benefits including ease of manufacture, release of 100% drug in-vivo and outstanding uniformity. The hydrophilic matrix tablets on immersion in water swiftly forms a gel layer around the tablets (Mahesh Thube et al., 2015). 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.

2. Materials and methods

Verapamil hydrochloride was obtained from Hetero labs. HPMC K100M, Guargum, Xanthan gum, PVP K30, Talc, Magnesium stearate and MCC PH 102 were obtained from sd fine chemicals Bombay, India.

2.1 Analytical method development:

2.1.1 Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl and pH 4.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

2.1.2 Preparation calibration curve:

100mg of Verapamil hydrochloride pure drug was dissolved in 100ml of 0.1 N HCl (stock solution) 10ml of solution was taken and make up to 100ml with 0.1 N HCl (100µg/ml).from this 10ml was taken and make up to 100 ml with 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 5,10,15,20,25,30,35 and 40µg/ml of Verapamil hydrochloride per ml of solution. The absorbance of the above dilutions was measured at 229 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line. Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which is determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions (Amol R. Jipkate et al., 2011).

2.2 Drug – Excipient compatibility studies

2.2.1 Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 31200 cm to 1200 cm. The resultant spectrum was compared for any spectrum changes (Mahajabeen et al., 2015).

2.3 Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing. All these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia (D. Pavani et al., 2015).

2.3.1 Angle of repose:

The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

2.3.2 Bulk density:

Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

2.3.3 Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

2.3.4 Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

2.4 Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 4.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Verapamil hydrochloride. Total weight of the tablet was considered as 400mg.

Table 1: Formulation composition for tablets

Formulation No.	Verapamil hydrochloride	HPMC K 100	Guar Gum	Xanthan gum	PVP K 30	Mag. Stearate	Talc	MCC pH 102
F1	120	60	-	-	20	4	4	QS
F2	120	120	-	-	20	4	4	QS
F3	120	180	-	-	20	4	4	QS
F4	120	-	60	-	20	4	4	QS
F5	120	-	120	-	20	4	4	QS
F4	120	-	180	-	20	4	4	QS
F7	120	-	-	60	20	4	4	QS
F8	120	-	-	120	20	4	4	QS
F9	120	-	-	180	20	4	4	QS

All the quantities were in mg

2.5 Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content (Rama Rao et al., 2016, Shanmugan et al., 2015, Bandameedi et al., 2015).

2.5.1 Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

2.5.2 Hardness:

For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

2.5.3 Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

2.5.4 Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were reweighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

2.5.5 Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of verapamil hydrochloride were accurately weighed, transferred to a 100 ml volumetric flask containing 120 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve (Ashwini Rajendra et al., 2012).

2.6 *In vitro* drug release studies

Procedure:

900ml 0f 0.1N HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered then the apparatus was operated for 2 hours and then the medium 0.1 N HCl was removed and pH 4.8 phosphate buffer was added and the process was continued for upto 12 hrs at 50 rpm. At definite time intervals 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed spectrophotometrically at 229 nm using UV-spectrophotometer.

The optimized formulation is further being subjected to dissolution by using 5%,10%,15%,20%,25%,30%,

alcohol in both the dissolution media for up to 12 hrs at 50 rpm. At definite time intervals 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed spectrophotometrically at 229 nm using UV-spectrophotometer (Wadher et al., 2011; Hareesh et al., 2015).

2.7 Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model (Suvakanta Dash et al., 2010, Higuchi et al., 1963; Korsmeyer et al., 1983).

2.7.1 Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

2.7.2 First order release rate kinetics:

The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

2.7.3 Higuchi release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$ Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

2.7.4 Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

2.7.5 Hixson-Crowell release model:

$$(100\text{-}Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

3. Results and Discussion

The present study was aimed to develop extended release tablets of Verapamil hydrochloride using various polymers. All the formulations were evaluated for physicochemical properties and in-vitro drug release studies.

3.1 Analytical Method

Graphs of Verapamil hydrochloride was taken in Simulated Gastric fluid (pH 1.2) and in pH 6.8 phosphate buffer at 298 nm and 294 nm respectively (Figure 1 and Figure 2).

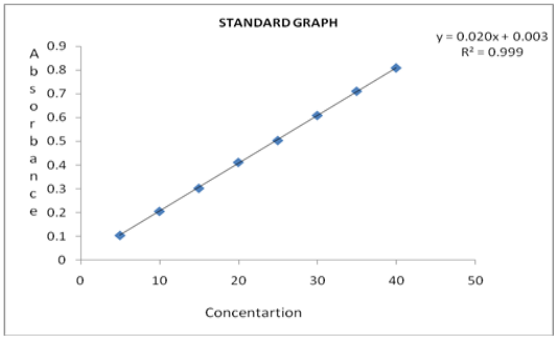

Figure 1: Standard graph of Verapamil hydrochloride in 0.1N HCl

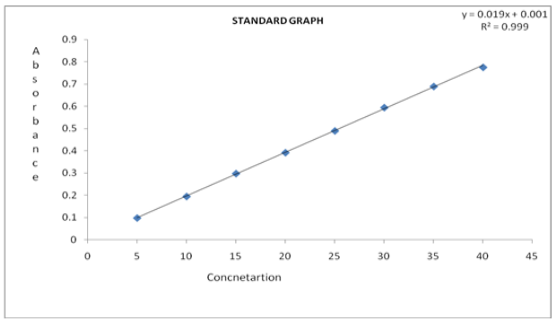

Figure 2: Standard graph of Verapamil hydrochloride pH 6.8 phosphate buffer (294nm)

3.2 Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy:

The FTIR spectra of drug, optimized formula formulation and guar gum were recorded (Figure 3, Figure 4 and Figure 5).

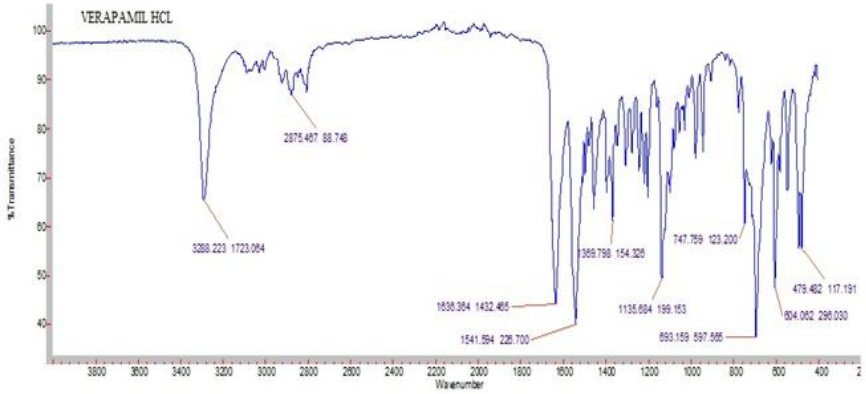

Figure 3: FT-TR Spectrum of Verapamil hydrochloride pure drug.

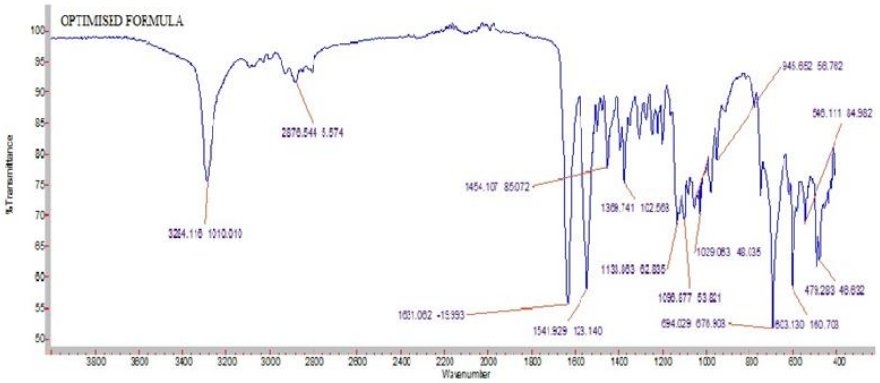

Figure 4: FT-IR Spectrum of Optimised Formulation

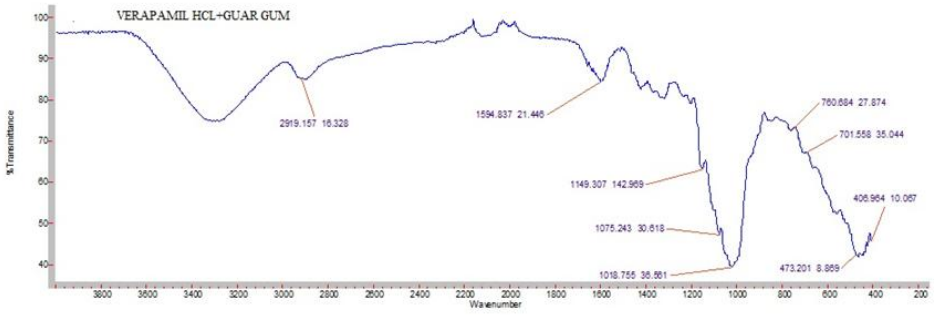

Figure 5: FTIR Spectrum guar gum

3.3 Preformulation parameters:

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18

which show that the powder has good flow properties. All the formulations has shown the hausner's ratio ranging between 0 to 1.2 indicating the powder has good flow properties (Table 2).

3.4 Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet (Table 3).

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

3.5 In-Vitro Drug Release Studies

From the dissolution data it was evident that the formulations prepared with HPMC K100M as polymer were unable to retard the drug release up to desired time period i.e., 12 hours (Table 4).

Whereas the formulations prepared with Guar gum retarded the drug release in the concentration of 180 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation (Table 5).

The formulations prepared with Xanthan gum showed more retardation even after 12 hours they were not shown total drug release (Table 6). Hence they were not considered.

The optimized formulation shown the drug release of 98.88%, 95.45%, 97.20% upto 12 hours in the 5%,10%,15% alcoholic media respectively (Table 7, Figure 6). The formulation shown 97.87% drug release in the 11th hour in the 20% alcoholic medium, in the 25% alcoholic medium 95.03% drug release in the 10th hour and in the 30% alcoholic medium the the formulation showed max drug release by the 7th hour only (Table 8, Figure 7).

3.6 Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model (Table 9, Figure 8, Figure 9, Figure 10, and Figure 11).

From the graphs it was evident that the formulation F6 was followed Zero order release kinetics.

Table 2 : Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped densit (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	24.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	25.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Table 3: In-vitro quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	412.5	4.5	0.50	6.8	99.76
F2	405.4	4.5	0.51	6.9	99.45
F3	398.6	4.4	0.51	4.9	99.34
F4	405.6	4.5	0.55	6.9	99.87
F5	403.4	4.4	0.56	6.7	99.14
F6	400.7	4.5	0.45	6.5	98.56
F7	402.3	4.1	0.51	6.4	98.42
F8	401.2	4.3	0.49	6.7	99.65
F9	398.3	4.5	0.55	6.6	99.12

Table 4: Dissolution Data of Verapamil hydrochloride Tablets Prepared With HPMC K100M In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F1	**F2**	**F3**
0.5	25.5	20.1	16.4
1	46.7	39.4	26.7
2	76.5	55.3	34.6
3	98.4	75.3	42.4
4		87.3	55.4
5		99.4	67.4
6			85.4
7			91.5
8			97.3

Table 5: Dissolution Data of Verapamil hydrochloride Tablets Prepared with Guar gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F4	**F5**	**F6**
0.5	17.25	16.42	14.62
1	38.26	25.73	19.86
2	54.16	36.63	22.35
3	72.01	45.04	31.45
4	88.26	58.25	39.80
5	97.10	65.33	45.25
6		76.41	58.24

7	84.84	66.73
8	97.80	71.34
9		75.52
10		82.17
11		87.10
12		96.10

Table 6: Dissolution Data of Verapamil hydrochloride Tablets Prepared with Xanthan gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F7	**F8**	**F9**
0.5	10.4	9.4	8.5
1	16.5	15.6	14.5
2	28.6	21.4	18.4
3	39.5	36.7	23.4
4	48.5	42.4	28.2
5	59.4	49.6	34.8
6	69.2	55.3	40.2
7	74.5	60.3	44.8
8	82.3	72.8	50.4
9	87.78	83.52	63.34
10	98.78	88.65	69.27
11		96.56	74.86
12			79.97

Table 7: Dissolution Data of Verapamil hydrochloride Optimised Formulation in the 5%, 10%, 15% alcoholic media.

Time	5%	10%	15%
0.5	7.03	8.09	3.00
1	11.77	10.05	5.01
2	17.02	15.06	9.89
3	28.89	22.05	11.08
4	39.21	29.08	15.07
5	41.21	32.07	21.98
6	52.35	40.12	32.77
7	65.07	53.04	40.02
8	78.92	60.29	48.06
9	**85.67**	71.38	53.27
10	**93.45**	80.70	68.55
11	**96.77**	**88.34**	83.01
12	**98.88**	**95.45**	97.20

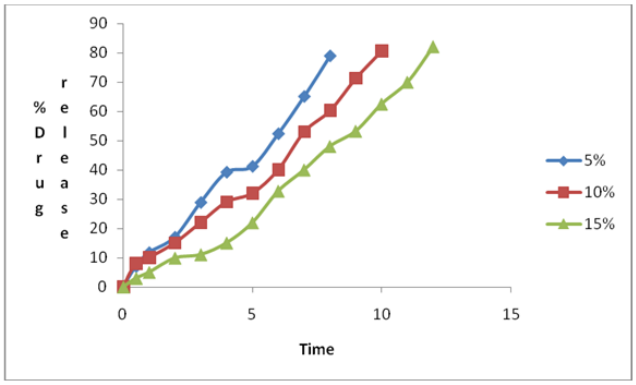

Figure 6: Dissolution profile of optimized formulation in the 5%,10%,15% alcoholic media

Table 8: Dissolution Data of Verapamil hydrochloride Optimised Formulation

Time	20%	25%	30%
0.5	5.72	3.85	4.76
1	14.23	5.10	16.78
2	26.89	8.99	28.43
3	36.78	12.30	38.12
4	49.32	18.06	44.64
5	58.12	26.83	59.76
6	72.45	33.45	69.14
7	82.44	42.16	98.65
8	90.13	75.86	
9	93.44	86.07	
10	97.77	95.03	
11	97.87		
12			

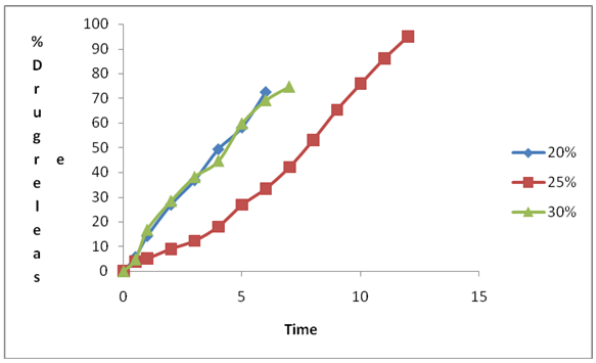

Figure 7: Dissolution profile of optimized formulation in the 20%,25%,30% alcoholic media

Table 9: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	LOG(%) RELEASE	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining
0	0		2.000				100
14.62	0.5	1.165	1.931	29.240	0.0684	-0.835	85.38
19.86	1	1.298	1.904	19.860	0.0504	-0.702	80.14
22.35	2	1.349	1.890	11.175	0.0447	-0.651	77.65
31.45	3	1.498	1.836	10.483	0.0318	-0.502	68.55
39.8	4	1.600	1.780	9.950	0.0251	-0.400	60.2
45.25	5	1.656	1.738	9.050	0.0221	-0.344	54.75
58.24	6	1.765	1.621	9.707	0.0172	-0.235	41.76
66.73	7	1.824	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	1.457	8.918	0.0140	-0.147	28.66
75.52	9	1.878	1.389	8.391	0.0132	-0.122	24.48
82.17	10	1.915	1.251	8.217	0.0122	-0.085	17.83
87.1	11	1.940	1.111	7.918	0.0115	-0.060	12.9
96.1	12	1.983	0.591	8.008	0.0104	-0.017	3.9

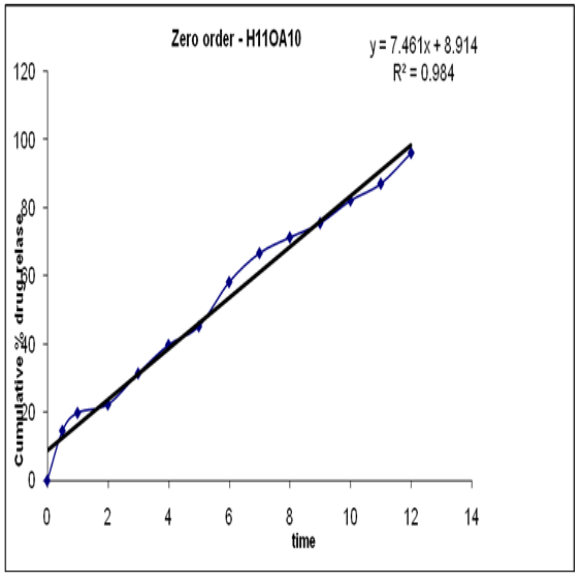

Figure 8 : Zero order release kinetics graph

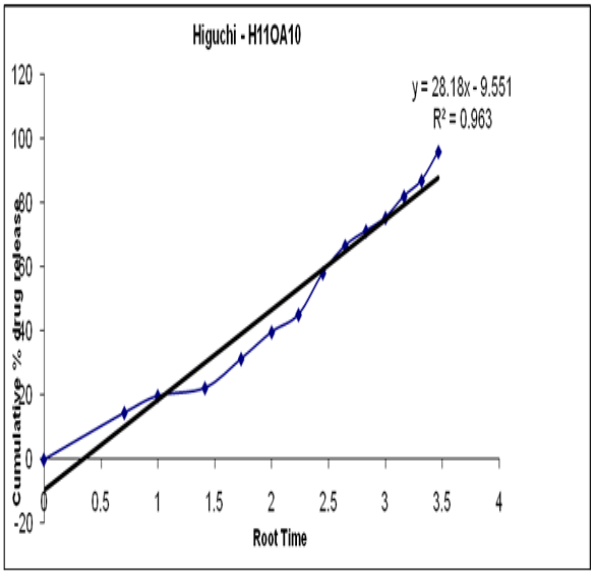

Figure 9: Higuchi release kinetics graph

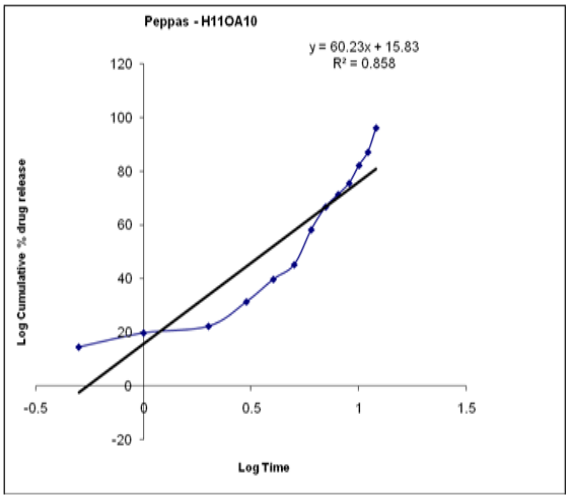

Figure 10: Kars mayer peppas graph

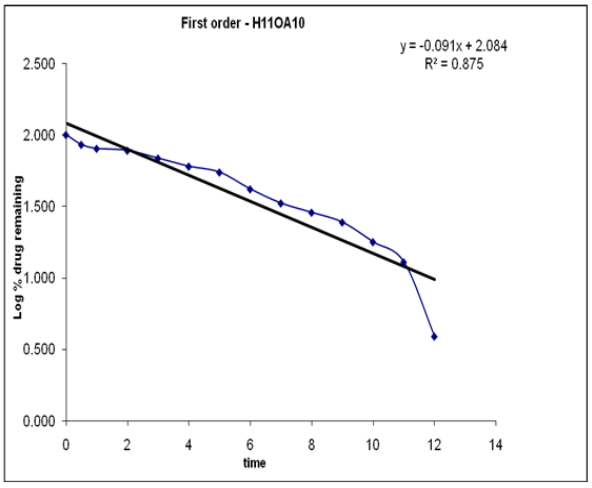

Figure 11: First order release kinetics graph

4. Conclusion

The aim of the present study was to develop sustained release formulation of Verapamil Hydrochloride to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of HPMC polymers, Guar gum and Xanthum gum were employed as polymers. Verapamil Hydrochloride dose was fixed as 120 mg. Total weight of the tablet was considered as 400 mg. Polymers were used in the concentration of 60, 120 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e., 96.10 % in 12 hours containing Guar gum polymer in the concentration of 180mg. It followed zero order release kinetics. For the optimized formulation alcohol effect has been studied by using various concentrations of alcohol in dissolution medium. As the concentration of alcohol increases the sustained action of polymer was decreased. Hence it was concluded that alcohol has significant effect on drug release pattern.

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