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Formulation and Evaluation of Gastro Retentive Tablet of Verapamil

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Abstract:

The present study to formulate and evaluate of gastro retentive floating tablets Verapamil to retard the drug release in 12hrs. The formulations were prepared by using various polymers like HPMC K15M, Xanthan gum and Ethyl cellulose floating dosage forms by direct compression method. The % drug release of Verapamil was compared with all the formulations V2 is the best with HPMC K15M was selected as optimized formulation based on drug release data and kinetic study. The order and mechanism of drug release data of V2 were identified as zero order and Higuchi mechanism whereas the drug release behavior was fitted to korsmeyer – peppas model. The floating tablets of Verapamil using HPMC K15M was successfully formulated as an approach to increase to increase gastric residence time and there by improving its bioavailability.

Keywords: Verapamil gastro retentive tablets

1. INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).[1] Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment[2] Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach[3] , low density (floating) systems that causes buoyancy in gastric fluid[4,5,6], mucoadhesive systems that causes bioadhesion to stomach mucosa[7], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach[8,9],superporous hydrogel systems[10] magnetic systems[11]etc. The current review deals with floating type gastroretentine drug delivery system.

Basic gastrointestinal tract physiology:

The stomach is divided into 3 regions anatomically: fundus, body, and antrum pylorus. The proximal part is the fundus and the body acts as a reservoir for undigested material, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states but the pattern of motility is distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is divided into following 4 phases.[12]

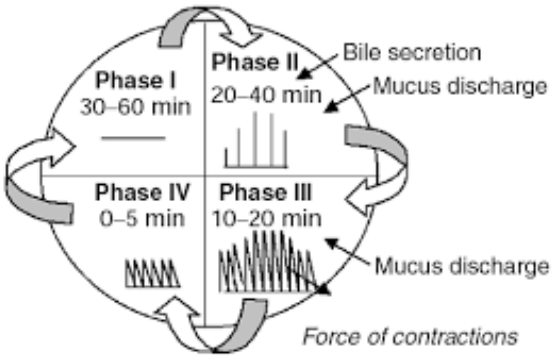

Fig 1.1: Schematic Representation of Interdigestive Motility

Phase I: This period lasts about 30 to 60 minutes with no contractions.

Phase II: This period consists of intermittent contractions that increase gradually in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III: This is a short period of intense distal and proximal gastric contractions (4-5 contractions per minute) lasting about 10 to 20 minutes these contractions, also known as "house-keeper wave," sweep gastric contents down the small Intestine.

Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase

Need For Gastroretention:

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or that degrade at the alkaline pH.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H.Pylori infections.[12]

Factors controlling gastric retention of dosage forms:

There are several factors that can affect gastric emptying of an oral dosage form which include density, size and shape of dosage form, feeding state, biological factors such as age, gender, posture, body mass index, disease state etc.

1. Effect of Dosage Form Size & Shape:

Small size tablets are emptied from the stomach during the digestive phase while large size units are expelled during the house keeping waves found that floating unit with a diameter equal or less than 7.5 mm had larger gastric residence time (GRT) compared to nonfloating units but the GRT was similar for floating and non-floating units having a large diameter of 9.9 mm. They found that GRT of nonfloating units were much more variable and highly dependent on their size which are in the order of small < medium < large

units. Moreover, in supine subjects, size influences GRT of floating and non- floating form. Tetrahedron and ring shaped devices have a better GRT as compared with other shapes.[13, 14]

2. Density:

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach [16]. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.[15]

3. Gender, Posture & Age:

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.[16]

4. Effect of Food & Specific Gravity:

To float FDDS in the stomach, the density of dosage form should be less than gastric content i.e.1.0 g/cm3. Since, the bulk density of a dosage form is not a sole measure to describe its buoyant capabilities because the magnitude of floating strength may vary as a function of time and gradually decrease after immersing dosage form into fluid as a result of development of its hydrodynamic equilibrium. Various studies have shown the intake of food as main determinant of gastric emptying rather than food. Presence of food is the most important factor effecting GRT than buoyancy. GRT is significantly increased under fed condition since onset of MMC is delayed. Studies show that GRT for both floating and non-floating single unit are shorter in fasted subjects (less than 2 hour), but significantly prolonged after meal (around 4 hour).[12]

5. Nature of Meal & Frequency of Food:

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to fed state, to increase gastric emptying rate and prolonging the drug release. Diet rich in protein and fat can increase GRT by 4-10 hours.[12]

METHODOLOGY

7.1. Analytical method development:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

10mg Verapamil pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 2, 4, 6, 8, 10µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 278nm 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 determined by least-square linear regression analysis.

7.2. 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 and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles

producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\text{Tan } \theta = h / r \quad \text{Tan } \theta = \text{Angle of repose}$$

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

Table 7.1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. 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 of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully levelled without compacting and the unsettled apparent volume, Vo, was read.

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

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

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. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle 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:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Table 7.2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

7.3. Formulation development of floating Tablets:

Procedure for direct compression method:

1. Drug and all other ingredients were individually passed through sieve no □ 60.
2. All the ingredients were mixed thoroughly by triturating up to 15 min.
3. The powder mixture was lubricated with talc.
4. The tablets were prepared by using direct compression method by using 8mm punch.

FORMULATION OF TABLETS:

Table 7.3: Formulation composition for Floating tablets

Ingredients	V1	V2	V3	V4	V5	V6	V7	V8	*V9*
Verapamil	40	40	40	40	40	40	40	40	40
HPMC K15M	20	40	60	-	-	-	-	-	-
Xanthan gum	-	-	-	20	40	60	-	-	-
Ethyl cellulose	-	-	-	-	-	-	20	40	60
$NaHCO_3$	15	15	15	15	15	15	15	15	15
PVPk30	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
MCC	105	85	65	105	85	65	105	85	65
Total Weight	200	200	200	200	200	200	200	200	200

All the quantities were in mg

7.4. Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

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 deter mining 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

Table 7.4: Pharmacopoeial specifications for tablet weight variation

Average weight of	Average weight of	Maximum percentage

tablet (mg) (I.P)	tablet (mg) (U.S.P)	difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

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

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed 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 re- weighed, and loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1-W2) / W1] \times 100$$

Where, W1 = Initial weight of tablets

W2 = Weight of the tablets after testing

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Verapamil were accurately weighed, transferred to a 100 ml volumetric flask containing 50 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.

***In vitro* Buoyancy studies:**

The *in vitro* buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In vitro* drug release studies**

Dissolution parameters:

Apparatus – USP-II, Paddle Method

Dissolution Medium – 0.1 N HCL

RPM – 50

Sampling intervals (hrs) – 0.5,1,2,3,4,5,6,7,8,10,11,12

Temperature – 37°c $\pm$ 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:

900ml 0f 0.1 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 the apparatus was operated for 12 hours and then the medium 0.1 N HCL was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 278nm using UV-spectrophotometer.

7.5: 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.

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.

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.

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.

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 I I transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

7.5. Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

8. RESULTS AND DISCUSSION

8.1. Analytical Method

a. Determination of absorption maxima

The standard curve is based on the spectrophotometer. The maximum absorption was observed at 278nm.

b. Calibration curve

Graphs of Verapamil was taken in 0.1N HCL (pH 1.2)

Table 8.1: Observations for graph of Verapamil in 0.1N HCL

Conc [µg/mL]	Abs
0	0
2	0.124
4	0.248
6	0.379
8	0.502
10	0.622

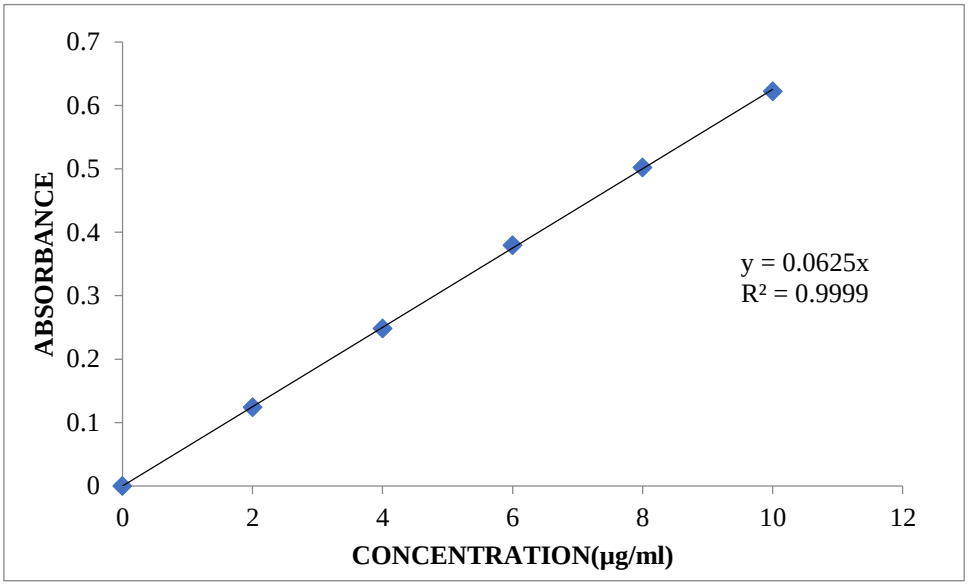

Fig 8.1: Standard graph of Verapamil in 0.1N HCL

Standard graph of Verapamil was plotted as per the procedure in experimental method and its linearity is shown in Table 8.1 and Fig 8.1. The standard graph of Verapamil showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

8.3. Pre formulation parameters of powder blend:

Table 8.2: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
V1	25.56±0.3	0.57±0.01	0.61±0.01	10.11±0.8	1.13±0.02
V2	24.67±0.3	0.53±0.01	0.68±0.03	10.23±0.5	1.12±0.03
V3	25.56±0.2	0.52±0.06	0.64±0.03	10.34±1.0	1.14±0.06
V4	23.30±0.1	0.50±0.21	0.66±0.12	10.23±0.5	1.12±0.06
V5	22.56±0.1	0.65±0.02	0.59±0.02	11.23±0.8	1.11±0.05
V6	23.89±0.2	0.50±0.04	0.68±0.04	11.34±0.6	1.14±0.03
V7	26.54±0.1	0.59±0.04	0.64±0.05	10.12±0.7	1.13±0.09
V8	23.67±0.3	0.58±0.12	0.58±0.04	10.23±1.0	1.11±0.07
V9	24.34±0.4	0.56±0.02	0.54±0.01	10.23±0.8	1.13±0.02

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 0.50±0.04 to 0.65±0.02 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54±0.01 to 0.54±0.01 showing the powder has good flow properties. The compressibility index of all the formulations

was found to be below 10.34 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.11 to 1.14 indicating the powder has good flow properties.

8.4. Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

Table 8.3*: In vitro* quality control parameters

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (sec)	Total Floating Time (Hrs)
V1		4.6	0.34	3.15	99.27	42	12
V2		4.8	0.46	3.69	98.64	36	12
V3		5.1	0.29	3.81	100.05	25	12
V4		4.0	0.62	3.79	99.82	56	12
V5		5.2	0.72	3.56	97.19	48	12
V6		4.9	0.69	3.11	98.52	40	12
V7		5.6	0.28	3.29	99.13	38	12
V8		4.5	0.47	3.50	97.68	31	12
V9		4.8	0.52	3.74	98.49	27	12

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

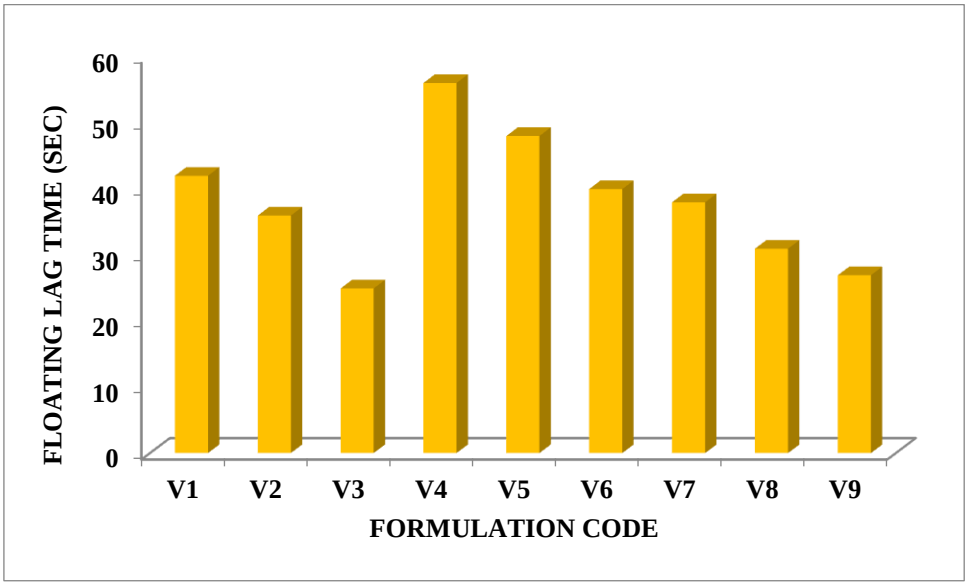

Fig 8.2: Floating lag time (sec)

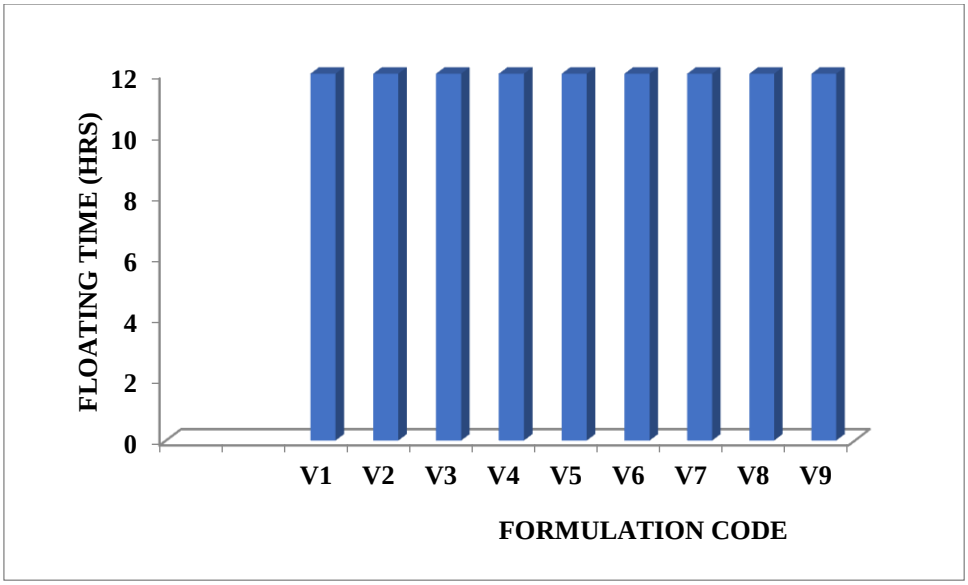

Fig 8.3: Total Floating Time (Hrs)

8.5. *In vitro* drug release studies

Table 8.4: Dissolution data of Floating tablets

Time(Hrs)	V1	V2	V3	V4	V5	V6	V7	V8	V9
0	0	0	0	0	0	0	0	0	0
0.5	13.3	19.9	21.1	7.1	8.2	11.4	12.4	10.1	7.9
1	16.9	22.1	25.3	11.5	13.9	15.9	19.8	16.6	14.0
2	25.4	31.9	30.7	17.9	18.3	22.1	26.4	22.7	19.6
3	33.2	39.0	41.5	26.8	25.3	31.6	37.1	32.2	23.4
4	39.9	48.3	49.9	33.3	31.1	34.5	42.5	38.9	26.8
5	46.1	53.6	56.8	40.1	36.6	42.8	52.2	47.6	31.5
6	53.7	61.9	64.9	48.5	45.8	51.1	61.9	53.1	37.8
7	62.8	68.1	71.8	54.7	48.4	62.8	67.7	57.3	41.4
8	71.3	76.5	78.4	58.0	54.2	69.9	74.2	62.8	46.3
9	77.9	81.7	83.1	63.4	58.4	77.3	78.9	68.9	52.1
10	82.4	89.1	91.5	78.9	62.5	79.6	88.2	75.2	57.5
11	88.1	93.5	94.2	82.4	73.1	83.0	93.4	80.6	69.2
12	94.7	99.8	98.2	93.6	83.4	96.8	98.5	87.7	75.1

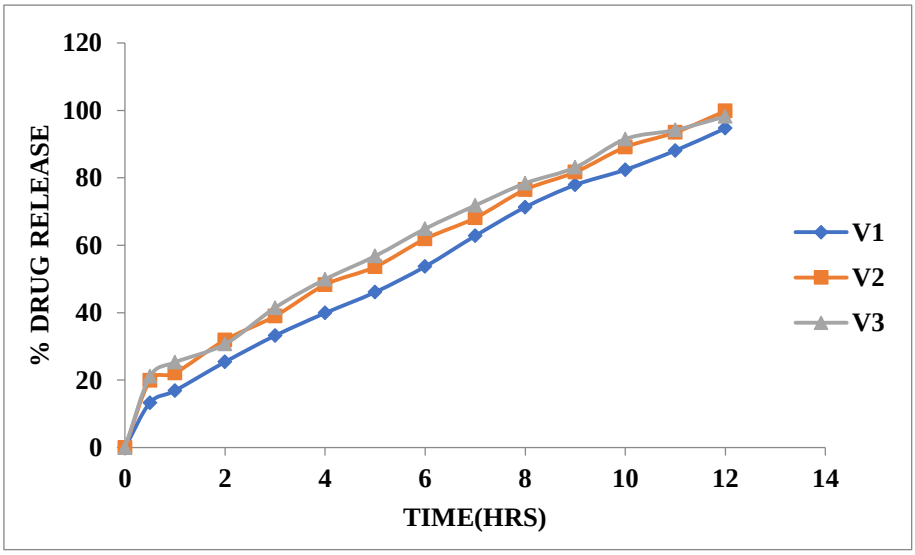

Fig 8.4: Dissolution data of Verapamil Floating tablets containing HPMC K15M

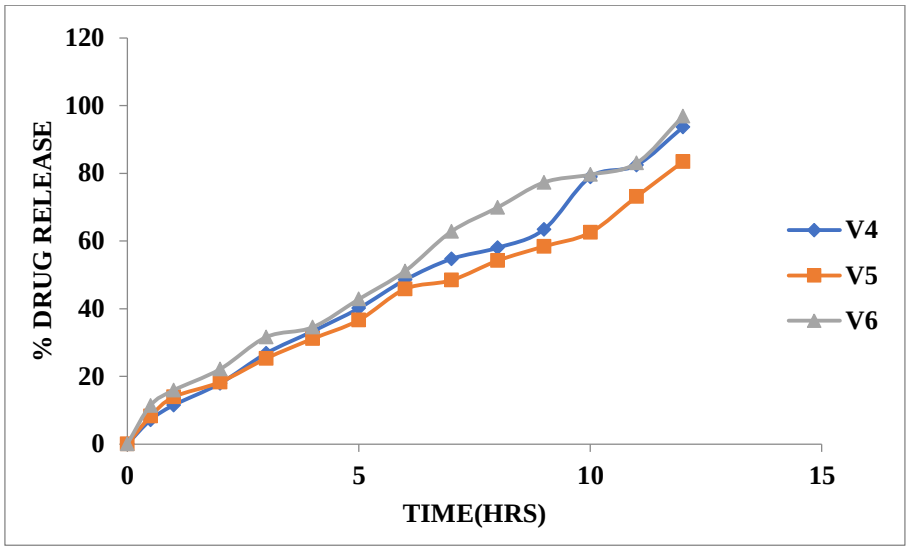

Fig 8.5: Dissolution data of Verapamil Floating tablets containing Xanthan gum

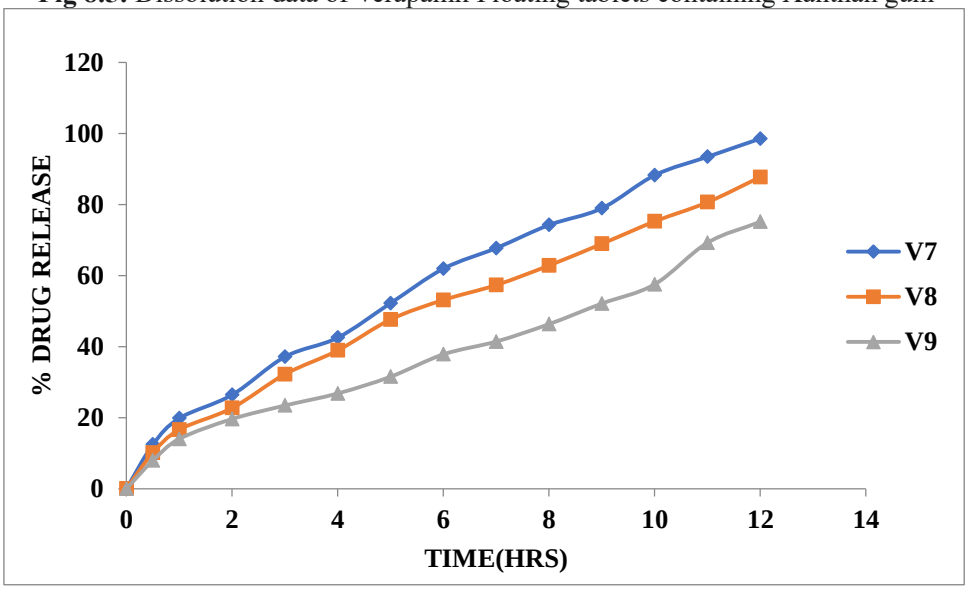

Fig 8.6: Dissolution data of Verapamil Floating tablets containing Ethyl cellulose

Whereas the formulations prepared with HPMC K15M were retarded the drug release in the concentration of 20 mg (V2 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.8% in 12 hours with good retardation.

Whereas the formulations prepared with Xanthan gum were retarded the drug release in the concentration of 60mg (V6 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.8% in 12 hours with good retardation.

Whereas the formulations prepared with Ethyl cellulose were retarded the drug release in the concentration of 20mg (V7Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.5% in 12 hours with good retardation.

Hence from the above dissolution data it was concluded that V2 formulation was considered as optimized formulation because good drug release (99.8%) in 12 hours.

Application of release rate kinetics to Dissolution data for optimised formulation:

Table 8.5: Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.9	0.5	0.707	1.299	-0.301	1.904	39.800	0.0503	-0.701	80.1	4.642	4.311	0.331
22.1	1	1.000	1.344	0.000	1.892	22.100	0.0452	-0.656	77.9	4.642	4.271	0.371
31.9	2	1.414	1.504	0.301	1.833	15.950	0.0313	-0.496	68.1	4.642	4.084	0.558
39	3	1.732	1.591	0.477	1.785	13.000	0.0256	-0.409	61	4.642	3.936	0.705
48.3	4	2.000	1.684	0.602	1.713	12.075	0.0207	-0.316	51.7	4.642	3.725	0.916
53.6	5	2.236	1.729	0.699	1.667	10.720	0.0187	-0.271	46.4	4.642	3.593	1.048
61.9	6	2.449	1.792	0.778	1.581	10.317	0.0162	-0.208	38.1	4.642	3.365	1.277
68.1	7	2.646	1.833	0.845	1.504	9.729	0.0147	-0.167	31.9	4.642	3.171	1.470
76.5	8	2.828	1.884	0.903	1.371	9.563	0.0131	-0.116	23.5	4.642	2.864	1.777
81.7	9	3.000	1.912	0.954	1.262	9.078	0.0122	-0.088	18.3	4.642	2.635	2.006
89.1	10	3.162	1.950	1.000	1.037	8.910	0.0112	-0.050	10.9	4.642	2.217	2.424
93.5	11	3.317	1.971	1.041	0.813	8.500	0.0107	-0.029	6.5	4.642	1.866	2.775
99.8	12	3.464	1.999	1.079	-0.699	8.317	0.0100	-0.001	0.2	4.642	0.585	4.057

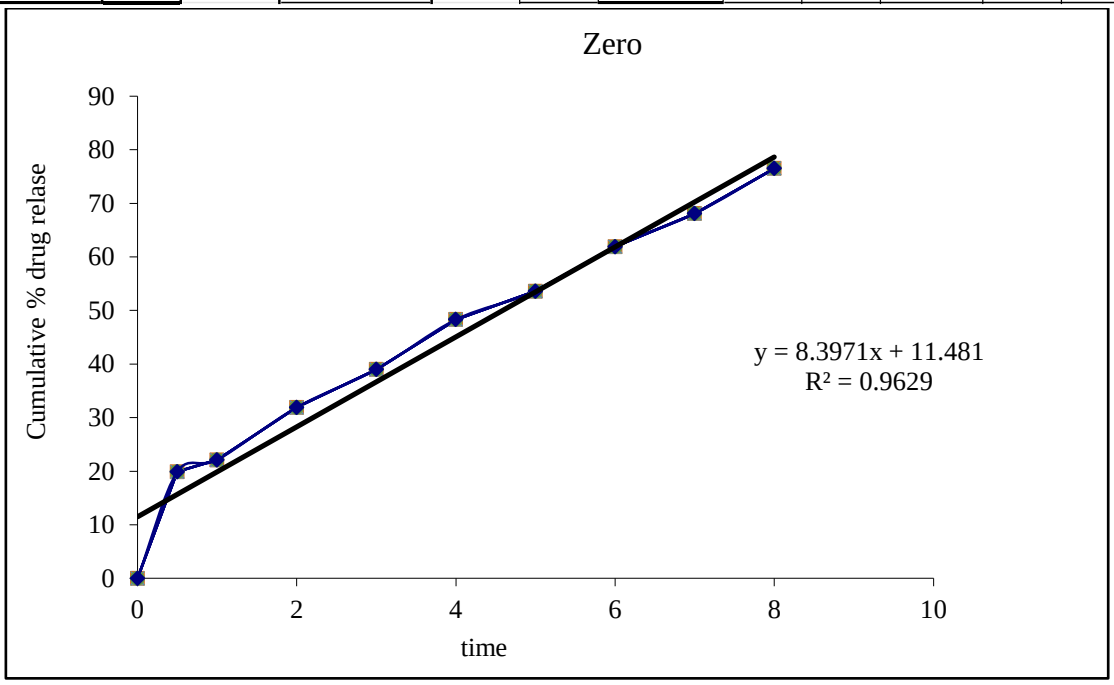

Fig 8.7: Zero order release kinetics

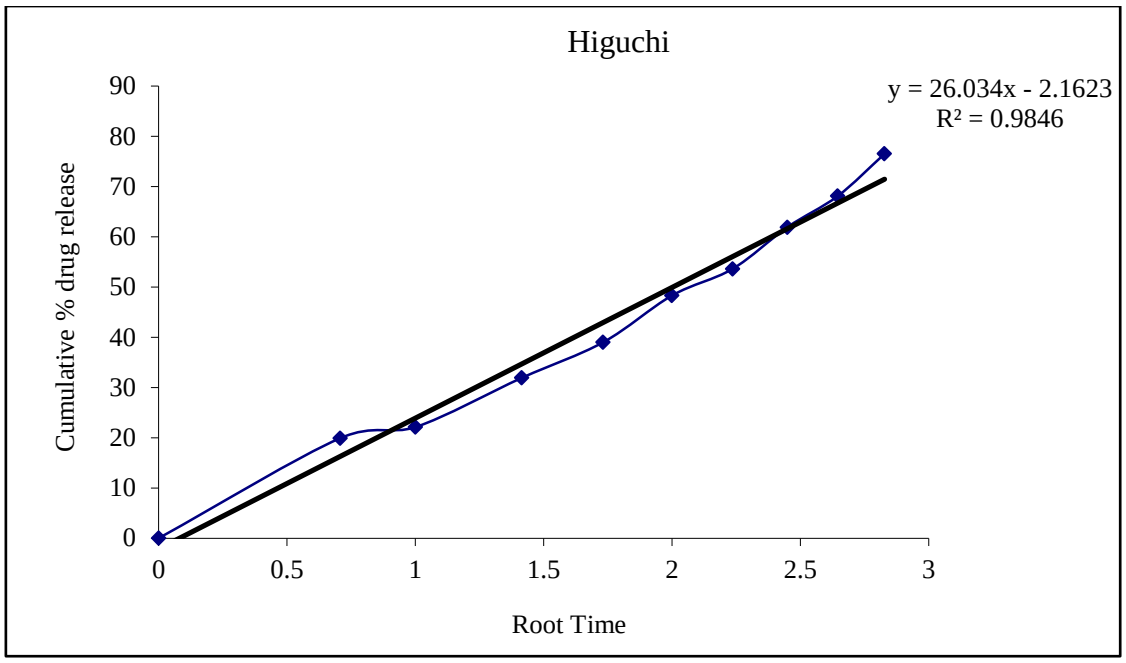

Fig 8.8: Higuchi release kinetics

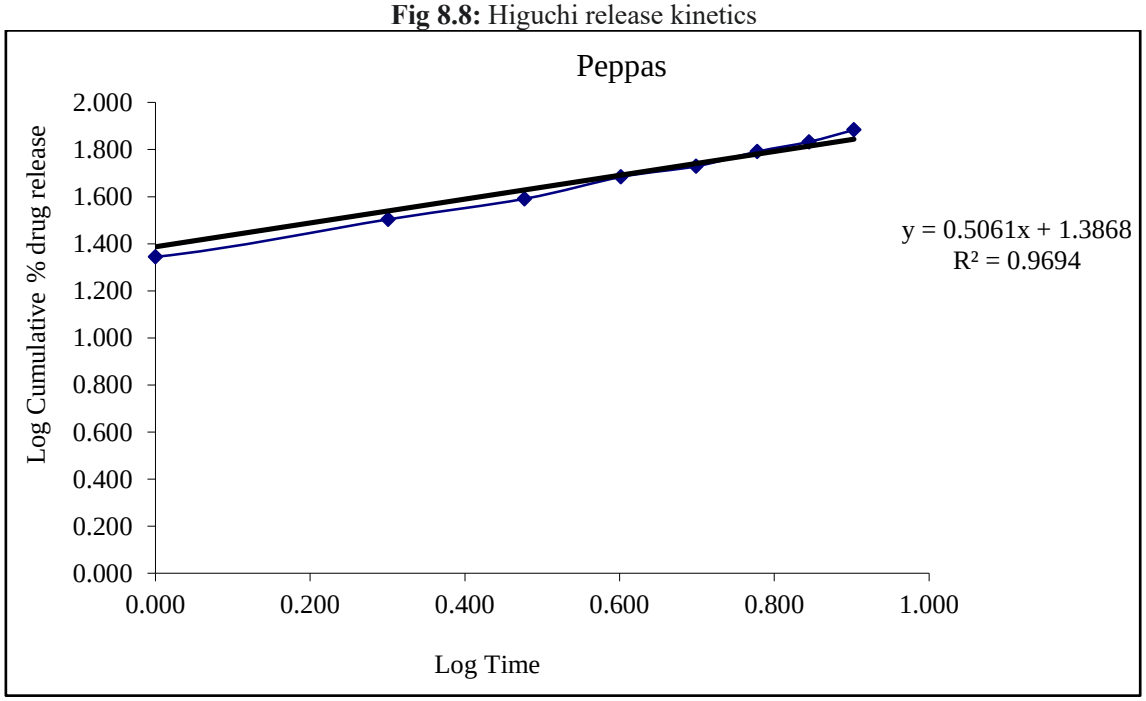

Fig 8.9: Kors mayer peppas release kinetics

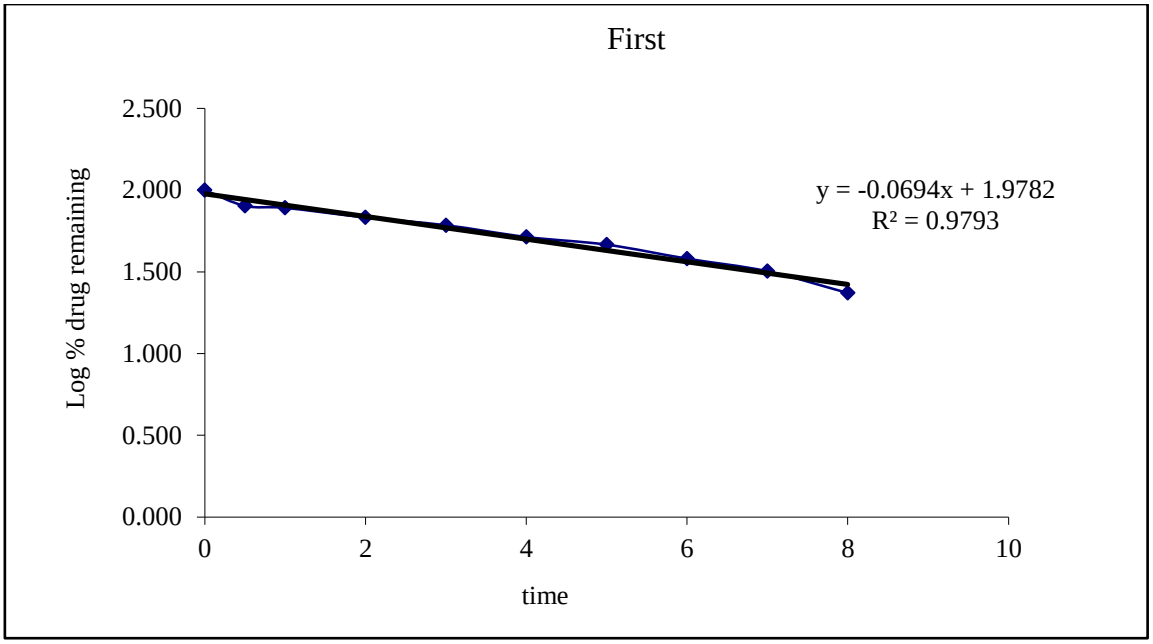

Fig 8.10: First order release kinetics

Optimised formulation V2 was kept for release kinetic studies. From the above graphs it was evident that the formulationV2 was followed **Higuchi release kinetics** mechanism.

8.6. Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy:

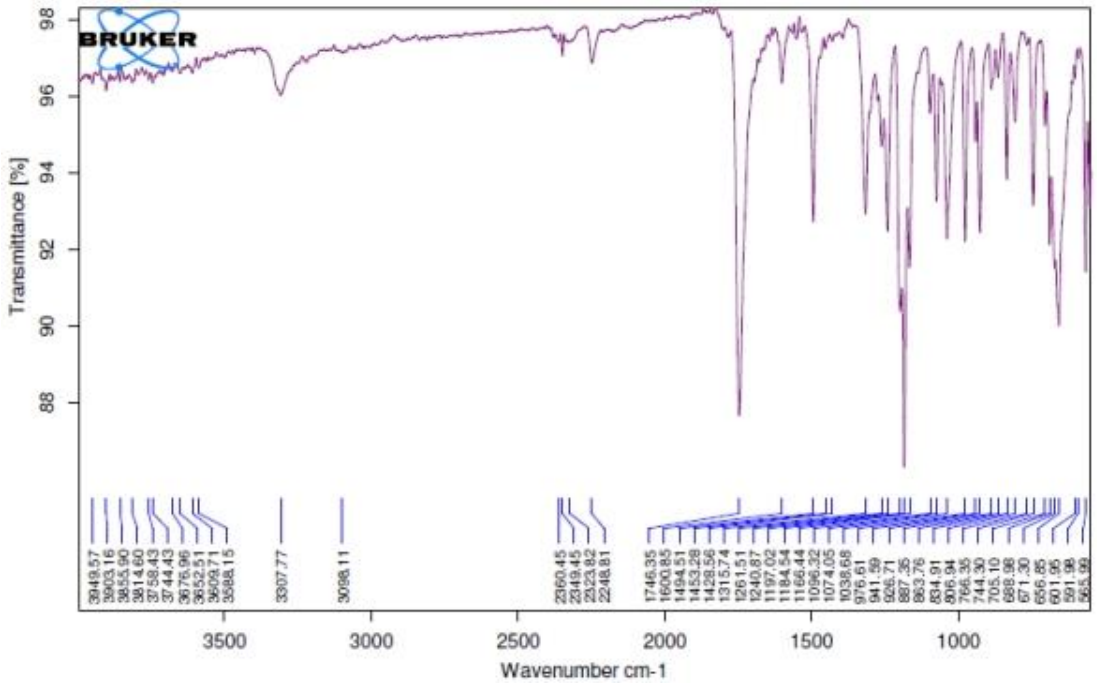

Fig 8.11: FTIR Spectrum of pure drug

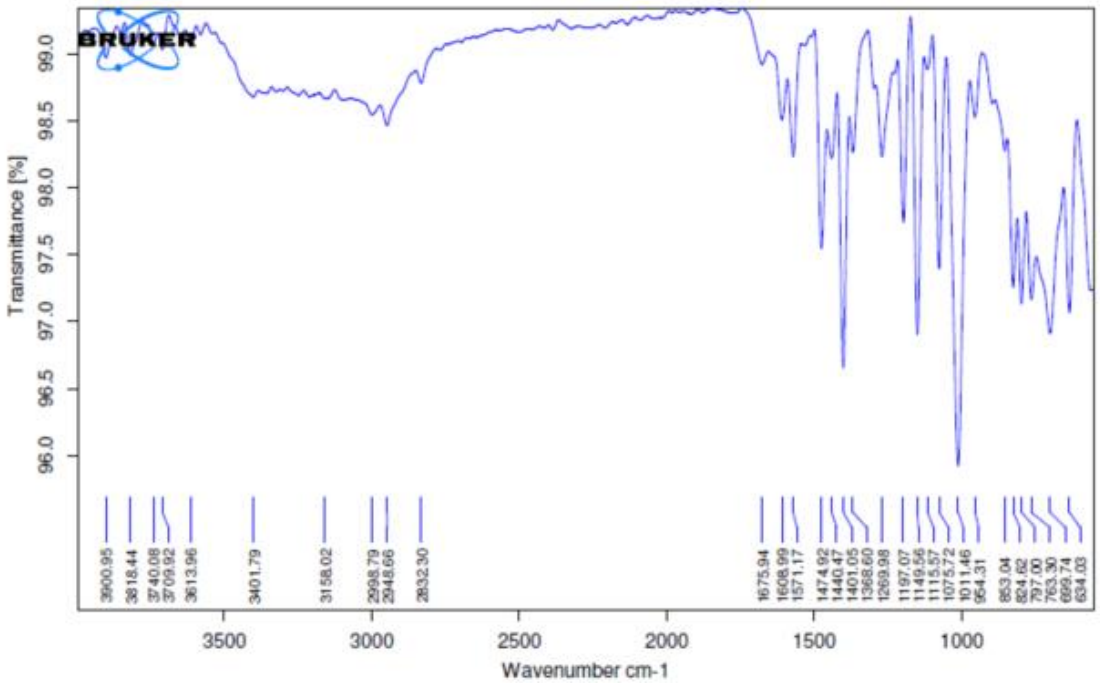

Fig 8.12: FTIR Spectrum of optimised formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Verapamil is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION

The present work described the pre-formulation and formulation development that led to the production of Verapamil Gastro retentive floating tablets by direct compression of powder blends/granules. To achieve the drug release up to 12hrs, studies have been carried out on direct compression method by using different polymers like HPMC K15M, Xanthan gum and Ethyl cellulose. The aim of the present work was completely fulfilled by the use of HPMC K15M, Xanthan gum and Ethyl cellulose as the drug release was extended up to 12hrs. Further drug release data were interpreted to determine the order, mechanism and drug release behavior from the dosage form. The results revealed that the drug release from the optimized formulation follows zero-order –kinetics and Higuchi kinetic model. The optimized formula V2 has fulfilled my objective. The drug release was found to be 99.8% in 12hrs

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