International Journal of Current Trends in Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijctpr

Research Article **Open Access**

Formulation and Evaluation of Bilayer Floating Tablet Containing Verapamil Hydrochloride

Shivendra Pratap Singh*, Navneet Kumar Verma, Abhay Pratap Singh, Reena Singh

Department of Pharmacy, Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur, U.P. India-273209

A B S T R A C T

The objective of the present work was to develop a bilayer-floating tablet for Verapamil HCl using direct compression technology using polymers such as HPMC K100 and Carbopol 940. Sodium bicarbonate and citric acid were used as a gas generating agent. All the bi-layered floating tablet formulations were subjected to post-compression evaluation parameters such as hardness, friability, weight variation, thickness, drug content, lag time subsequently buoyancy time, and *in-vitro* dissolution studies. The assay of the formulation revealed that the drug content was within the limits. *In-vitro* floating revealed that all the formulations showed buoyancy of more than 12 hours. Dissolution tests were performed using USP dissolution apparatus at 75 rpm in pH 1.2 buffers. The tablet split in to 2 layers i.e. floating and immediate layer in the dissolution medium, which exhibited biphasic release of Verapamil HCl. The formulation F3 released 98.24% of drug at the end of 12hr. The *in-vitro* drug release data was fitted into various kinetic models and the best fit release kinetics was achieved with Peppas model.

Keywords: Verapamil hydrochloride, HPMC, Carbopol, Bilayer floating tablet

A R T I C L E I N F O

CONTENTS

Article History: Received 10 May 2016, **Accepted** 18 June 2016, **Available Online** 15 July 2016

***Corresponding Author**
Shivendra Pratap Singh
Department of Pharmacy,
Kailash Institute of Pharmacy
and Management, GIDA,
Gorakhpur, U.P. India-273209
Manuscript ID: IJCTPR3025

PAPER-QR CODE

Citation: Shivendra Pratap Singh, *et al.* Formulation and Evaluation of Bilayer Floating Tablet Containing Verapamil Hydrochloride. *Int. J. Curnt. Tren. Pharm, Res.*, 2016, 4(4): 170-175.

1. Introduction

In the present time various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension and diabetes. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over monotherapy. [1-5] From last few years; interest in developing a combination of two or more active pharmaceutical ingredients in a single dosage form has increased in pharmaceutical industry. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIS by physical separation. [6,7,8] Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. [9, 10] Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug later as second dose or in an extended release or for both immediate release. Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two layers. More layers are possible but the design becomes very special. Bi-layer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed. Verapamil is an L-type calcium channel blocker of the phenyl alkyl amine class. It has been used in the treatment of hypertension, angina pectoris, cardiac arrhythmia, and most recently, cluster headaches. It is also an effective preventive medication for migraine.

Verapamil has also been used as a vasodilator during cryopreservation of blood vessels. It is a class-IV antiarrhythmic, more effective than digoxin in controlling ventricular rate and was approved by the U.S. Food and Drug Administration (FDA) in March 1982. Verapamil is also used intra-arterially to treat cerebral vasospasm. Verapamil has been used to treat cluster headaches, but it also lists headaches as a side effect of the drug. Verapamil is used for controlling ventricular rate in supraventricular tachycardia and migraine headache prevention. Verapamil is not listed as a first line agent by the guidelines provided by JAMA in JNC-8. However, it may be used to treat hypertension if patient has co-morbid atrial fibrillation or other types of arrhythmia.[11]

2. Materials and Methods

Mesalazine (Natco Labs), Ethyl Cellulose (Signet Chemical Corporation, Mumbai, India.), Eudragit L-100, Eudragit S-100,Hydroxy Propyl Methyl Cellulose K100M, Magnesium stearate, Micro crystalline cellulose and Talc (Merck Specialities Pvt Ltd, Mumbai, India.), All other reagents used were of analytical grade.

Methodology

Drug - Excipient compatibility studies

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 [6]. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

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 [7]. 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:

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

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

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/cm3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together [7]. 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 leveled 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 [7]. The tapped

density was calculated, in gm per L, using the formula:

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 [7]. 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

Formulation development of Tablets:

Mesalazine colon targeted tablets were prepared by using compression coating technology. Initially internal core tablet containing drug and super disintegrate was formulated [7]. For the prepared core tablet compression coating is done by using various compositions of polymers. Ethyl cellulose, Polymethacrylate polymers such as Eudragit L100 and Eudragit S100 are used as polymers for compression coating. Tablets are developed in two stages.

- Preparation of core tablet containing drug and super disintegrate.
- Compression coating of prepared core tablets.

Formulation of core tablet:

The core tablets are formulated by using 250 mg of drug molecule, sodium starch glycollate as super disintegrate, Micro crystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant respectively [8]. The composition of core tablet was given in below table 1.

Table 1: Composition of core tablet

Ingredient Name	Quantity (mg)
Mesalazine	250
Sodium starch glycollate	31.25
Talc	5
Magnesium stearate	5
MCC pH102	108.75
Total weight	400

Total weight of core tablet was fixed as 400 mg. The tablets are prepared by using 9mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets:

The prepared core tablets were subjected to compression coating by using various compositions [10] of polymers such as Ethyl cellulose, Eudragit L 100 and Eudragit S 100 as coating materials. The composition of coating layer is given in below table.2. Compression coating layer was divided into two equal portions i.e., 50mg of each quantity. Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly [11]. Then the tablets are compressed by using 10mm flat surfaced punch using 8 station tablet punching machine with the hardness of 4 - 4.5 kg/cm^2.Then the prepared compression coted tablets are evaluated for various post compression parameters as per standard specifications.

Evaluation of post compression parameters for prepared Tablets: The designed formulation compression coated 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 [12]. The mean and deviation were determined. The percent deviation was calculated using the following formula.

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

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 [13].

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. Preweighed tablets were placed in the friabilator [13]. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, 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

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 Mesalazine

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 [14]. 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* drug release studies**

Drug release studies of Mesalazine core tablets:

The core tablets containing 15mg Mesalazine of were tested in (pH 6.8), for their dissolution rates [15]. Dissolution studies were performed using USP paddle type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 270 nm.

Drug release studies of Compression coated Mesalazine tablets: The release of Mesalazine from coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media [16]. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme free simulated intestinal fluid (SIF, pH 6.8) was used up to 12 hours to mimic colonic pH conditions. Drug release was measured from compression coated Mesalazine tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm and 270 nm respectively. All dissolution runs were performed for six batch. The results were given with deviation.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release [17]. 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 supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100\text{-}Qt)^{1/3} = 100^{1/3} – KHC.t$$

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 physical characteristics of BLF tablets (F1, F2, and F3) such as tablet size, hardness, friability and weight variation were determined and the results are shown in Table 03. The hardness of the formulations satisfied the acceptance criteria. The friability and weight variation was found to be within the limits specified in Pharmacopoeia. The drug content was found spectrophotometrically for all the formulations. The values are shown in Table-03. The drug content was found to be within a narrow range as specified in Pharmacopoeia (90-110%) in all formulations. Buoyancy lag time and duration of floating were determined using 100 ml beaker containing 0.1N HCl medium are shown in Table 04. The Bilayer floating formulations F1, F2 and F3 were subjected for the dissolution studies using USP dissolution apparatus II (paddle) in 900 ml of 0.1N HCl medium. Average value were obtained from the triplicate values and taken as the final value. The results are given in Figures 1. The F3 BFT was chosen as the optimized formulation because it showed maximum drug release compared to other formulation [13-16]. To analyze the Verapamil Hydrochloride release mechanism the *in vitro* release data were fitted into various release equations and kinetic models first order, zero order, Higuchi and Korsemeyer and Peppas. As indicated by the value of *R*2, the best fit model was found to be Peppas for all the formulation. The value of *n* for optimized formula F3 was 0.4083(*R*2 = 0.9958), indicating release governed by Fickian diffusion. All formulations were subjected to stability studies and results are given in Table 5 and 6. From the results it was observed that there was no significant change in physicochemical properties and release profile after the storage at for two months at three different conditions. It may be inferred that there was no degradation and change in the release system.

Table 1: Formulation of Maintenance and Loading Dose

Ingredients	Quantities in mg					
	MF1	MF2	MF3	LF1	LF2	LF3
Verapamil HCL	215	215	215	75	75	75
HPMC K100	60	60	60	--	--	--
Carbopol 940	140	120	100	--	--	--
Sodium Bicarbonate	80	80	80	--	--	--
Citric acid	50	50	50	--	--	--
Lactose	15	35	55	25	25	25

Table 2: Drug Evaluation

S.No	Parameters	Results
1	Bulk density (g/cc)	0.391
2	Tapped density (g/cc)	0.456
3	Angle of repose (ɵ)	22.63
4	Carr's index (%)	13.63

Table 3: Physical evaluation of Bilayer floating tablets of Verapamil Hydrochloride

Formulation code	Hardness (Kg/cm2)	Thickness (mm)	Friability (%)	Weight Variation	Drug Content (%)
F1	8.9	4.0	0.305	2.06	95.31
F2	8.6	4.0	0.318	1.72	97.54
F3	8.8	4.15	0.397	1.84	96.66

Table 4: Floating Properties

Formulation Batch	Lag time	Floating duration
F1	2 min, 07 sec	> 12 hrs
F2	1 min, 27 sec	> 12 hrs
F3	1min 12 seconds	> 12 hrs

Table 5: Drug Content retained for selected formulations at the end of 60 days

Stability condition	Sampling (days)	Drug Content
50C/Ambient	60	96.41%
250C/ 60 % RH	60	96.56%
400 C/ 75 % RH	60	96.21%

Table 6: *In-Vitro* drug dissolution profile of the selected formulations at the end of 60 days

Stability condition	Sampling (days)	*In-Vitro* drug dissolution profile of F3
50C/Ambient	60	95.32
250C/ 60 % RH	60	95.21
400 C/ 75 % RH	60	94.83

4. Conclusion

The present study was carried out to develop the Bi-layer floating tablet of Verapamil HCl using HPMC and carbopol. *In-vitro* dissolution studies showed % CDR increased with increase in the polymer concentration. The drug release was characterized by an initial burst of higher release followed by a slow release. Analysis of drug release mechanism showed that the drug release followed Fickian diffusion and the best fit model was found to be Peppas. Stability studies revealed that no significant change in percentage drug content and physical characters. Stability studies indicated that the selected formulation (F3) was stable. Thus, results of the current study clearly indicate, a promising potential of the Verapamil Hydrochloride floating system as an alternative to the conventional dosage form. However, further clinical studies are needed to assess the utility of this system for patients suffering from hypertension.

5. References

[1] Aggarwal Swati, Syan N, Mathur P, Bilayer Tablet Technology -Opening New Ways in Drug Delivery Systems: An Overview, International Journalof research In Pharmaceutical and Biomedical Sciences, 4 (1), 2013, 8-16.

[2] Jayprakash S, Mohamed HS, Kulathuran PK, Vignesh N, Mohamed Firthhouse PU, Boopathi M, Formulation And Evaluation of Bilayer Tablets of Metformin Hydrochloride, Asian Journal of Pharmaceutical & Health Science, 1(4), 2011, 183-188.

[3] Malathi Parnapalli, Arshad BK, Recent Approaches in Bilayered Technology: Review, International Journal of Pharmaceutical Sciences and Research, 3(12), 2012, 4681-4688.
[4] Soma C, Reddy Suryaprakash C, Tabasum SG, Varma V, An Overview on Bilayer Tablets, International Journal of Pharmacy & Technology, 4 (2), 2012, 2143-2156.
[5] Chun YW, Jonathan PK, A Comparative Study of Compaction of Binary and Bilayer Tablets, Powder Technology, Science Direct, 189,2009, 285-294.
[6] Dandare MS, Sarage RD, Bhaskara S, Bilayer Tablet: A Novel Approach For Immediate Release of Telmisartan, Hydrochlorothiazide Combination, 4(1), 2012, 3970-3983.
[7] Rajendran NN, Natarajan RR, Patel H, Formulation and Evaluation of Sustained Release Bilayer Tablets of Metformin HCl and Pioglitazone Hydrochloride, International Journal of Current Pharmaceutical Research, 3(3), 2011, 118-122.
[8] Mehul P, Sockan GN, Mani T, Challenges in the Formulation of Bilayered Tablets: A Review, International Journal of Pharma research and Development, 2(10), 2010, 30-42.
[9] Divya A, Kavitha K, Kumar MR, Dakshayani S, Jagadees Singh SD, Bilayer Tablet Technology: An Overview, Journal of Applied Pharmaceutical Science, 01 (08), 2011, 43-47.
[10] Shaikh TK, Gadhave MV, Jadhav SL, Gaikwad DD, Different Techniques of Bilayer Tablet: A Review, International Journal of Universal Pharmacy and Life Sciences, 2 (2), 2012, 450-460.
[11] Lakshmi A, Ashwini Kumar1 G, Karnaker Reddy T, Anand Kumar M. Development and invitro evaluation of gastroretentive Verapamil Hydrochloride floating tablets. *International Journal of Pharmacy and Pharmaceutical Sciences*, 4(1), 2012, 360-363.
[12] Baumgartner S, Kristel J, Vreer F, Vodopivec P, and Zorko B. *Int. J. Pharm.*, 2(5), 2001, 95
[13] ICH Harmonized Tripartite Guidelines, 2003. Stability testing of new drug substances and products. Q1A (R2).
[14] Lokendra Pal Singh, Rajesh KS, Deepak G. Umalkar, Vijay Kumar Chauhan, Viral Kumar Rana, Kamini S. Vasava. Floating Effervescent tablet: A review. *Journal of Pharmaceutical and biomedical sciences*, 5(11), 2011, 1-6.
[15] Vishnu M Patel, Bhupendra G Prajapati, Anand K Patel. Controlled Release Gastroretentive dosage form of Verapamil Hydrochloride. *International Journal of PharmTech Research*, 1(2), 2009, 215-221.