Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Issue 1, 2012

Research Article

DEVELOPMENT AND INVITRO EVALUATION OF GASTRORETENTIVE VERAPAMIL HCl FLOATING TABLETS

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Received: 30 Aug 2011, Revised and Accepted: 3 Dec 2011

ABSTRACT

The purpose of the present work is to prepare gastro retentive tablets of verapamil HCl by using different polymers like HPMC K4M, HPMC K100M and Gum Kondagogu. Sodium bicarbonate is used as gas generating agent. Initially, preformulation studies were carried out which ruled out any incompatibility between the drug and the chosen polymer(s) during stability studies in which the physical mixtures of the drug and the polymer(s) were exposed to 40°C/75% RH for three months. A suitable method could be developed for drug estimation at 278nm by UV double beam spectrophotometer. Tablets were evaluated for physical characteristics viz. Hardness, % drug release, weight variation, content uniformity, floating capacity, swelling index and the drug release profile from the tablets were studies for 24hr. The tablet exhibits controlled and prolonged drug release profile while floating over the dissolution medium. A combination of sodium bicarbonate (36mg) and citric acid (10mg) was found to achieve optimum in vitro buoyancy. The method of the manufacturing process followed was wet granulation technique for all the formulations. Formulations of F1-F4 were prepared with HPMC K4M, and F5-F8 was prepared with HPMC K100M and F9-F11 was prepared with a combination of HPMC K4M and gum kondagogu. Lactose has been added to formulations F12-F15 to find out the filler effect to the release of the drug by using the gum kondagogu as polymer. Out of the formulations F-1 to F-15, the best formulation (F9) was selected based on in vitro characterization. It was observed that the fillers had an effect as for the physicochemical characters as well as the drug release profiles. The drug release mechanism from formulation F-9 confirmed to fallowed Non-Fickian diffusion (indicates water diffusion and polymer rearrangement played an essential role in drug release).

Keywords: Gastroretentive verapamil, HCL Floating tablets.

INTRODUCTION

Not only formulating a drug for prolonged action which has absorption and solubility in the stomach, but the main assert for such drugs is to retain them in the stomach to show its action and improve the bioavailability of the drug. Several difficulties are arisen in designing a controlled release dosage form for better absorption and bioavailability. One of such difficulty is to retain the dosage form in desired area. The gastric retention dosage forms are preferred for those drugs which has absorption window in the stomach, the drugs having high solubility in the acidic environment, the drugs which cannot withstand intestinal pH and poor soluble in the intestinal pH[1]. The controlled release gastric retention dosage form can be achieved by various mechanisms such as mucoadhesive[2,3], floating[4-6], expansion[7,8], sedimentation[9,10], modified shape systems[11,12], or by the simultaneous administration of pharmacological agents[13] that delay gastric emptying. Verapamil HCl is a calcium channel blocker used in the treatment of Hypertension, Angina Pectoris, Cardiac Arrhythmias and cluster headaches[14]. When it is given orally, 90% of the drug gets absorbed through it and reaches the maximum concentration within 1-2 hrs. Verapamil HCl under goes hepatic metabolism, therefore it has very low bioavailability (10-20%) and short half-life (2.8-7.4) due to which the drug is administered in multiple doses. So to enhance the bioavailability and reduce the dosage regimen of Verapamil HCl it is best formulated as IGF tablets.

MATERIAL AND METHODS

Verapamil HCl, Hydroxy propyl methyl cellulose K4M (HPMC K4M), Hydroxyl propyl methyl cellulose K100M (HPMC K100M), and Gum kondagogu BP were gifted from Ozone International, Mumbai, India. Polyvinylpyrollidon (PVP K30), dicalcium phosphate, lactose, sodium bicarbonate, and anhydrous citric acid were procured from S.D. Fine Chemicals, Mumbai, India. All other ingredients used were of analytical grade.

Preparation of IGF Tablets

The tablets were prepared by using wet granulation method. The granules of verapamil HCl (360mg equivalent to 120mg of verapamil) were prepared by mixing HPMC K4M/ HPMC K100M/ gum kondagogue, sodium bicarbonate, citric acid and dicalcium phosphate/lactose by using PVP K30 in isopropyl alcohol as a granulating agent. The granules were dried at 60° C for 1hr or can be dried at room temperature and sieved. Finally, Talc and magnesium stearate are added to the dried granule and compressed into tablets by using single punch tablet compression machine fitted with 9.5 flat faced punch.

Characterization of floating tablets

The prepared floating tablets were evaluated for weight variation, hardness, thickness and friability. Weight variation test is done for 20 tablets, hardness by using Monsanto hardness tester, thickness for 10 tablets by using vernier caliperse, friability was determined for 20 tablets by using Roche friabilator.

Drug content uniformity

The drug content uniformity for all the formulation was determined by triturating 10 tablets and the quantity of power equivalent to single tablet was transferred into a 100ml volumetric flask. 0.1mol/L of HCl was transferred into volumetric flask (50ml) and subjected to sonication for 1hr. The solution was made up to the mark by using 0.1mol/L HCl, and suitable dilutions were prepared. The samples were observed for drug content at 278 by using UV spectrophotometer.

In Vitro buoyancy studies

In vitro buoyancy studies were done to find the buoyancy lag time and the total buoyancy time of the tablet. The test was performed by placing a tablet in 500 ml beaker containing 400 ml of 0.1N HCl, and the temperature of the medium is maintained at 37±2°C by placing the beaker in a water bath. The time between the introduction of dosage form and its buoyancy in 0.1 N HCl (lag time) the time during which the dosage form remains buoyant (total buoyancy time) were determined visually.

Swelling studies

The IGF tablets were pre weighed before undergoing swelling studies, and the pre weight tablet is denoted by W1. The test was performed by placing the tablet in a beaker containing 200ml of 0.1 N HCl. At regular time intervals (i.e. for every 1hr) up to 24hrs, the

tablet is removed from the beaker and excess surface water is distant off by using paper. The weight of swollen IGF tablet is noted down (denoted by W2).

$$SI = (W2-W1)/W1$$

In vitro dissolution studies

In vitro dissolution studies are done by using USP Type II apparatus. 900ml of 0.1N HCl is taken as dissolution medium, and the temperature of the medium is maintained at 37±0.5°C, and the paddle rotation is set at 50rpm. At regular intervals 1hr, 5 ml samples is withdrawn from the dissolution medium, and 5ml is replaced with fresh dissolution medium. The absorbance is checked at 278nm by using UV spectrophotometer.

Stability studies

Stability studies were done according to WHO guidelines between drug and formulation. The prepared IGF tablets were packed in high density polyethylene bottles and stored to 40°C/75% RH for 3 months. Tablets were analyzed for a specific time interval of 7, 15, 30, 60 and 90 days for drug content, invitro dissolution, buoyancy behaviour and other physicochemical parameters.

Table 1: Formulation Development of Verapamil HCl ER Matrix Tablets

FC	Ingrediants(mg)								
	Drug	HPMC K4M	HPMC K100M	Gum kondagogu	Sodium bicarbonate	Citric acid	PVP K30	Dicalcium phosphate	Lactose
F1	120	80			36	10	20	83	-
F2	120	100			36	10	20	63	-
F3	120	120			36	10	20	43	-
F4	120	140			36	10	20	23	-
F5	120		80		36	10	20	83	-
F6	120		100		36	10	20	63	-
F7	120		120		36	10	20	43	-
F8	120		140		36	10	20	23	-
F9	120	40		100	36	10	20	19	-
F10	120	50		80	36	10	20	32	-
F11	120	30		60	36	10	20	69	-
F12	120			80	36	10	20	19	60
F13				100	36	10	20	9	50
F14				140	36	10	20	4	15
F15				130	36	10	20	4	25

All the tablets contain 5mg Magnesium stearate, 6mg Talc. HPMC: Hydroxyl Propyl Methyl Cellulose, PVP: polyvinyl pyrrolidone

Table 2: Physicochemical Characterization of Verapamil HCl Matrix Tablets

FC	Uniformity of weight(mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (mg)	Floating lag time(s)	Total floating time (hr)	Thickness (mm)	Swelling index
F1	359.1±0.25	4.25±0.11	0.57±0.06	119.26±0.15	34.01±1.65	8.35±0.01	5.48±0.032	3.303±0.212
F2	361.5±0.20	5.00±0.77	0.54±0.09	119.61±0.35	47.52±2.40	16.40±0.06	5.46±0.046	3.312±0.312
F3	364.6±0.29	4.25±0.17	0.70±0.05	119.80±0.12	70.57±1.53	18.52±0.04	5.39±0.038	3.324±0.501
F4	360.2±0.45	5.25±0.08	0.68±0.07	119.42±0.20	42.51±1.15	23.12±0.01	5.56±0.071	3.335±0.343
F5	359.3±0.55	5.25±0.15	0.45±0.05	119.92±0.42	71.57±3.36	16.45±0.03	5.36±0.086	3.352±0.234
F6	360.5±0.48	4.20±0.20	0.63±0.05	119.34±0.25	51.05±1.15	21.30±0.01	5.40±0.036	3.412±0.341
F7	365.3±0.56	5.25±0.10	0.71±0.02	119.78±0.45	57.50±2.28	21.45±0.05	5.42±0.054	3.415±0.224
F8	364.4±0.43	4.50±0.25	0.67±0.05	119.30±0.39	62.52±1.70	22.46±0.01	5.38±0.031	3.231±0.231
F9	360.5±0.32	5.01±0.10	0.72±0.09	119.49±0.18	38.59±2.36	24.35±0.27	5.46±0.024	2.221±0.112
F10	361.2±0.29	4.05±0.15	0.61±0.08	119.35±0.27	50.61±3.07	23.50±0.26	5.52±0.038	2.115±0.231
F11	359.5±0.45	4.21±0.13	0.53±0.09	119.55±0.30	65.18±1.25	24.20±0.19	5.61±0.062	2.232±0.112
F12	363.2±0.33	5.02±0.20	0.63±0.09	119.60±0.45	49.02±2.18	23.37±0.29	5.32±0.040	3.231±0.543
F13	361.1±0.34	5.01±0.41	0.56±0.08	119.52±0.42	40.1±2.13	23.40±0.09	5.43±0.081	3.654±0.115
F14	362.3±0.5	5.02±0.23	0.63±0.09	119.61±0.31	30.5±3.11	23.35±0.15	5.49±0.016	3.534±0.123
F15	360.9±0.1	5.01±0.13	0.62±0.07	119.23±0.22	32.3±1.23	23.45±0.11	5.54±0.011	3.541±0.432

RESULTS AND DISCUSSIONS

Verapamil HCl floating tablets were prepared to retain the tablet in the stomach and show a controlled release of the drug for 24hrs, by using different polymers like HPMC K4M, HPMC K100M and gum kondagogue. Since the polymers having high gel forming capacity helps in improving buoyancy and drug releasing characteristic. Sodium bicarbonate is used as a gas generating agent and PVP K3 as a binder and disintegrating agent. Talc and magnesium stearate are used as glidant and lubricant. Lactose has been added to decrease floating lag time of the tablet. The prepared IGF tablets were tested for hardness, thickness, weight variation, friability, content uniformity, swelling index, in vitro floating lag time, in vitro buoyancy time, and in vitro dissolution studies. The composition of verapamil HCl floating tablets was given in table1.

Physicochemical charecterization of IGF tablets

The IGF tablets were tested for thickness, weight variation and hardness. The thickenss of the tablet was tested by vernier caliperse, and it was found to be between 5.32±0.040 to 5.61±0.062. The weight variation of all the formulations F-1 to F-15 was found to be between 359.1±0.25 to 364.4±0.43. The hardness was tested by using Monsanto hardness tester and hardness of the tablets was controlled between 5.25±0.10 to 4.05±0.15.

Invitro buoyancy studies

Among the several approaches for retaining the tablet in stomach, effervescent approach is used for retaining the table. The in vitro buoyancy was generated by using sodium bicarbonate and citric acid. The gas generated was trapped in the gel formed by the

hydration of the polymer and thus making the tablet density less than 1, and tablet will buoyant. It was found that, as the amount of sodium bicarbonate increases, the floating lag time decreases. Thus, sodium bicarbonate 10% was essential to achieve optimum in vitro buoyancy. Increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release. Thus, 10% sodium bicarbonate is used in all the formulations to achieve optimum in vitro buoyancy. Formulations F1-F8 was prepared by using HPMC K4M, HPMC K100M which has shorter lag time but the total buoyancy was less than 24 hr due to high solubility characteristic in gastro intestinal fluid. The formulations F9-F11 was formulated with a combination of HPMC K4M and gum kondagogu and it has short lag time and long durations of floating up to 24 hr and formulations F12-F15 was prepared by using Gum kondagogu as drug retarding agent, lactose and dicalcium phosphate as diluents. The floating lag time has been decreased due to the presence of lactose which develops pores to the tablet and looses it integrity.

Swelling studies

Swelling plays an important role in buoyancy and drug dissolution of the matrix tablets. As the concentration of polymer increases, there is an increasing uptake of water content by the polymer, which leads to the relaxation of polymer chain with volume expansion resulting in market swelling of the system. The IGF tablet comprising HPMC K4M and HPMC K100M showed higher swelling index at first 1 hr, but could not maintain its integrity up to 24hrs. The IGF tablets (F9-F11) showed a constant increase in swelling index up to 24hr. The swelling index of IGF tablet (F12-F15) was slightly high due to the presence of pore in the tablets which are created by lactose (F9-F11).

In vitro dissolution studies

In vitro dissolution studies were done by using 0.1 N HCl and the study was performed for 24 hrs and the release was calculated for 1hr interval. The in vitro drug release studies for all the formulated floating matrix tablets F-1 to F-15 were conducted for a period of 24 hrs using an Electro lab model dissolution tester USP TypeII-apparatus at 50 rpm at a temperature of 37± 0.5°C. The dissolution test was carried out in 0.1N HCl medium. The *in vitro* drug release studies revealed that formulations F1 showed a release of 99.5 in 8 h, Formulation F2 showed maximum drug release of 96.5 % in 9 h, F3 and F4 showed a release of 93.8 and 70.8 % in 10 h. The variation in drug release was due to different polymer concentrations in all the four formulations. It shows that the HPMCK4M hydrates faster and lost its physical integrity in the presence of 0.1N HCl.

Formulations F5-F8, composed of HPMC K100M, showed a release of 85.3, 75.0, 58.4 and 48.6 % in 9 h respectively. These variations in drug release were due to changes in polymer concentrations of the tablets. HPMC K100M containing IGF tablets could not maintain its matrix integrity up to 24 hrs. The percentage of drug released from formulations F9, F10, and F11 was 60.2, 72.5 and 78.2 respectively, in 10 h. This variation was considered to be due to different polymer concentrations in formulations. In Formulations, F12-F15 lactose has been added to observe the effect of lactose on release of the drug from the tablet. The addition of lactose showed a drug release of 90.6, 84.3, 74.7 and 79.4 at 10 hr respectively. This infers that lactose creates pores in the tablet so the release rate is increased and the prolonged release of drug is decreased from formulation F12-F15. Further, formulations F12, F13, F15 failed to release the drug up to 24hrs. However, formulation F-9 released the drug up to 24hrs with a floating lag time of 38.59s. Therefore, formulation F-9 was considered the best formulation among all the seven formulations of this series. The drug release profile for various formulations is shown in figure 1.

Drug release kinetics

The data obtained from in vitro dissolution studies were fitted to zero[15], First[16], Higuchi[17] and korsmeyer-peppas[18-21]. For better characterizing the drug release mechanisms from the polymeric systems, the Korsmeyer-Peppas semi-empirical model was applied.

$$Q_t/Q_\infty = k_{KP} \cdot t^n$$

Where Q_t/Q_∞ is the fraction of drug released at time t, k_{KP} a constant compromising the structural and geometric characteristics of the device, and n, the release exponent, which is indicative of the mechanism of drug release. For, the case of cylindrical geometries such as tablets, n=0.45 corresponds to a Fickian diffusion release (Case I), 0.45<n<0.89 to a non-Fickian (Anomalous) transport, n = 0.89 to a zero order (Case II) release kinetics and n>0.89 to a super Case II transport[22]. The n values are calculated from studied tablets, and the values are listed in table 3. The n values are falling between 0.4-0.8 for the fallowing tablets which indicates non-fickians mechanism was found to be predominant, which indicated that water diffusion as well as polymer rearrangement played an essential role in drug release.

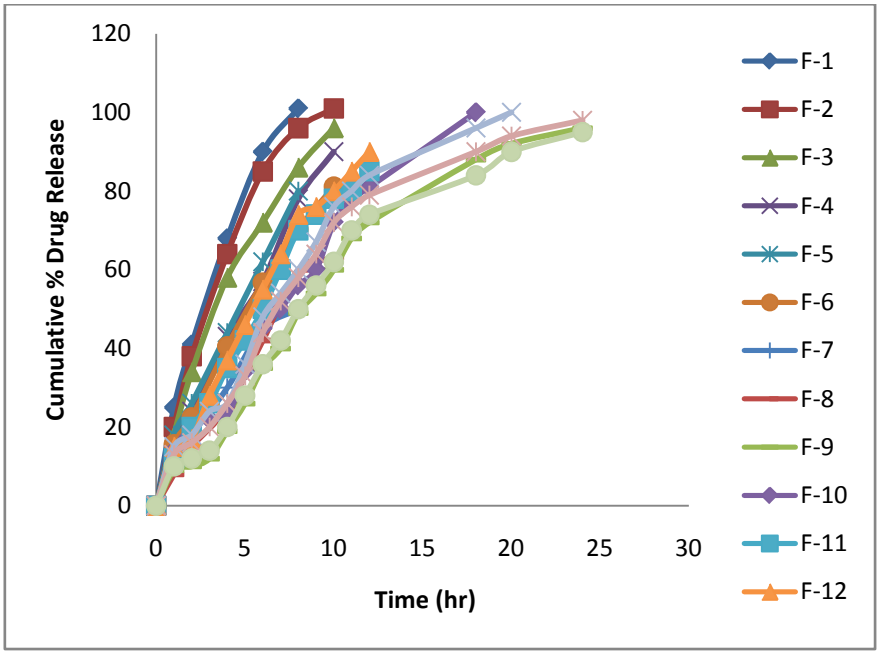

Fig. 1: *In-Vitro* dissolution profile of F1 to F15

Table 3: correlation coefficient (R^2) and release exponent (n) value for different kinetic models

Formulation	zero order	First order	Higuchi	n
F1	0.9824	0.9631	0.9853	0.6102
F2	0.9662	0.9710	0.9662	0.6321
F3	0.9535	0.9624	0.9734	0.7830
F4	0.9686	0.9878	0.9762	0.803
F5	0.9893	0.9972	0.9662	0.9412
F6	0.9660	0.9685	0.9884	0.869
F7	0.9944	0.9786	0.9946	0.7462
F8	0.9825	0.9860	0.9622	0.6312
F9	0.9848	0.9971	0.9970	0.8481
F10	0.9862	0.9643	0.9633	0.7869
F11	0.9631	0.9730	0.9814	0.8538
F12	0.9535	0.9354	0.9737	0.5843
F13	0.9713	0.9669	0.9986	0.6461
F14	0.8567	0.9888	0.9992	0.7814
F15	0.9671	0.9919	0.9841	0.8270

Stability studies

The stability studies were conducted for Formulation (F-9) containing gum kondagogue based on invitro buoyancy and invitro dissolution studies by placing the tablet in closed high density polyethylene bottles at 45°c/75% RH for 3months. The verapamil HCl does not show any substantial changes in physicochemical parameters and other tests. So the verapamil HCl tablets (F-9) are stable under the given conditions for at least 3months.

CONCLUSION

The IGF tablets of verapamil HCl were formulated by effervescent method. The IGF tablet containing gum kondagogue F-9 shown a satisfactory result with buoyancy lag time 38sec, and with total buoyancy and controlled release up to 24hrs. The tablet is stable at 45/75% for up to 3months.

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