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Design and Optimization of Gastro Retentive Bilayer Foating Tablet of Verapamil HCl

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A B S T R A C T
The present study focuses on the formulation of floating tablets of Verapamil HCl to enhance its gastric residence time and therapeutic efficacy. Hydroxypropyl methylcellulose (HPMC K100M) was identified as the optimal polymer for sustaining the drug release of Verapamil HCl. An inverse relationship between drug release rate and polymer concentration was observed, attributed to increased diffusion path length with higher polymer content. The formulated tablets underwent comprehensive post-compression evaluations, demonstrating satisfactory results in tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity, and in vitro drug release. Among the formulations, F2 exhibited superior controlled drug release and floating properties. The release kinetics of the F2 formulation conformed best to the Korsmeyer-Peppas, Higuchi, and first-order models, indicating that the predominant mechanism for drug release was non-Fickian or anomalous diffusion.

Keywords: Verapamil HCl, HPMC K100M, Korsmeyer-Peppas, gastro-retentive

A R T I C L E I N F O

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C o n t e n t s

1. Introduction:

GRDDS is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption [1, 2]. As a mechanism to override this problem, erodible gastro retentive dosage forms have been developed that provide continuous controlled administration of these drugs at the absorption site [3]. In addition, these dosage forms are useful for delivering drugs incorporated into vesicles such as liposomes, nanoparticles, proteinoid microspheres and pharmacosomes etc. [4, 5]. Verapamil HCl was selected as the model drug to study the retardant efficiency of combination of polymers on the water soluble drug [6]. Verapamil HCl has short biological half-life, low pKa and good aqueous solubility that decrease with increase in pH due to which it is essential to confine its location in the upper gastro intestinal tract preferably in the stomach [7, 8]. Hence it was of prime importance to devise a floating drug delivery system that will help to minimize fluctuations in plasma drug concentration over the range of pH, help in readily absorption of the drug and also fulfill the requirements of spatial localization.

2. Methodology

Materials:

Verapamil Hydrochloride was obtained as a kind gift sample from Pharma Train Ltd. (India), HPMC K4M, Eudragit Rs 100 and Xanthum Gum was obtained from Colorcon. All other chemicals/reagents used were of

analytical grade, available commercially and used as such without further processing.

Methodology: Formulation of gastro retentive floating tablets by direct compression method processing steps involved in direct compression method: The matrix tablets were prepared by following the General Methodology as all ingredients (except magnesium stearate and talc) were weighed accurately and co sifted by passing through #40 sieve, blended in a Poly Bag for 5 min. The above blends were lubricated with # 60 Sieve passed Magnesium stearate & talc. The final blend was then compressed into tablets using 16 station tablet compression machine with an average hardness of 5.0 -6.0kg/cm2, by using 8mm to 10mm die.

Evaluation of Tablets

The formulated tablets were evaluated for the following Pre, post compression quality control studies & In vitro Buoyancy studies and dissolution studies

A) Pre Compression studies:

Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation[17].

$$\theta = \tan^{-1} (h/r)$$

Where:

θ = angle of repose

h = height in cms

r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

2. Density:

Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula[18].

Bulk density = weight of powder/ Bulk volume.

$$D_b = \frac{M}{V_0}$$

M = mass of the powder

V_0 = bulk volume of the powder.

b) Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula.

Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_f).$$

M = mass of the powder

V_f = tapped volume of the powder

3. Carr's Index:

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down[19]. The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4. Hausner's Ratio:

Hausner's Ratio is a number that is correlated to the flow ability of a powder[19].

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

B) Post compression studies:

General appearance:

The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

Average weight/Weight Variation:

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$Average\ weight = weight\ of\ 20\ tablets/20$$

$$\%\ weightvariation = \frac{Averageweight - weightofeacttablet}{Averageweight} * 100$$

Acceptance criteria for tablet weight variation (USP 29-NF 34)

Thickness: Thickness of the tablets (n=3) was determined using a Verniercalipers

Hardness test:

Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability test:

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min.

The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

$$\%\text{Friability} = [(W_1-W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test,
W_2 = weight of tablets after test

6. Assay Procedure.

Ten tablets were weighed and powdered, a quantity of powder equivalent to 100 mg of Verapamil HCl was transferred to a 100 ml volumetric flask and 10 ml methanol is added. The drug is extracted in methanol by vigorously shaking the Stoppard flask for 15 minutes. Then the volume is adjusted to the mark with 0.1N HCL and the liquid is filtered. From prepared solution take 1ml solution in 100ml volumetric flask and make up to mark with 0.1 N HCL. The Verapamil HCl content was determined by measuring the absorbance at 242 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations. Calculate the quantity in mg of Verapamil HCl in the portion taken by the formula

Assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100

7. In-vitro Buoyancy studies: The in vitro buoyancy was determined as per the method described by Rosa et al.

Floating Lag Time (FLT): A tablet was placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as the Floating Lag Time (FLT).

Total Floating Time (TFT):

A tablet was placed in a 100 ml beaker containing 0.1N HCl. The duration of time up to which the tablet constantly floats on the dissolution medium was noted as the Total Floating Time (TFT).

Matrix integrity: During the period of TFT the swelled matrix tablets were observed for integrity. For 12 hrs

8. *In vitro* Dissolution Study:

900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C\pm0.5^0C$. A tablet was placed in the vessel and was covered; the apparatus was operated up to 12 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium were analyzed spectrophotometrically at λ_{max} =279 nm using a UV-spectrophotometer (Lab India).

Table 1: Formulation of Verapamil HCl floating tablets by direct compression method

INGREDIENTS	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
VERAPAMIL HCL	80	80	80	80	80	80	80	80	80
HPMC K 100 M	20	40	60	-	-	-	-	-	-
EUDRAGIT RS 100	-	-	-	20	40	60	-	-	-
XANTHUM GUM	-	-	-	-	-	-	20	40	60
PVP K30	6	6	6	6	6	6	6	6	6
SODIUM BICARBONATE	30	30	30	30	30	30	30	30	30
MCC	80	60	40	80	60	40	80	60	40
AEROSIL	2	2	2	2	2	2	2	2	2
MG.STEARATE	2	2	2	2	2	2	2	2	2
TOTAL WEIGHT	220	220	220	220	220	220	220	220	220

Table 2: Angle of repose limits

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45

Table 3: Compressibility index limits Scale of Flow ability (USP29-NF34)

Compressibility Index (%)	**Flow Character**	**Hausner's Ratio**
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table 4: Weight variation tolerance for uncoated tablets

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

3. Results and Discussion

Table 5: Pre compression studies of Verapamil HCl Floating tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.40	0.48	16	1.2	12.73
F2	0.41	0.50	13.0	1.5	11.29
F3	0.50	0.58	13	1.16	11.58
F4	0.39	0.47	17.0	1.56	12.23
F5	0.37	0.41	9.75	1.1	12.35
F6	0.43	0.52	17.3	1.41	11.62
F7	0.44	0.50	12	1.1	9.92
F8	0.41	0.45	8.8	1.0	11.85
F9	0.39	0.48	18	1.23	11.96

The Verapamil HCl floating tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table: 5. The bulk density and the tapped density for all formulations were found to be almost similar. The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends. The angle of repose for all the formulations was found to be in the range of 9.92-12.73˚ which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Table 6: Post compression studies of Verapamil HCl floating tablets

Formulation Code	% weight variation	Thickness (mm)	% Friability	% Drug Content	Hardness (Kg/cm^2)
F1	Pass	5.06±0.11	0.142	101.3 ±1.2	5.56 ±0.057
F2	Pass	5.06±0.15	0.151	102.3 ±1.7	5.03 ±0.115
F3	Pass	5.03±0.057	0.62	100.1 ±1.2	5.01 ±0.1
F4	Pass	5.1±0.1	0.154	100.7 ±1.1	5.63 ±0.05
F5	pass	5.03±0.05	0.132	99.6±1.5	5.63 ±0.03
F6	pass	5.03±0.15	0.143	98.9 ±2.3	5.5 ±0.05
F7	pass	4.93±0.05	0.110	100.2± 1.7	5.7 ±0.1
F8	pass	5.1±0.1	0.133	100.5± 1.4	5.53 ±0.04
F9	pass	5.02±0.2	0.13	99.2±1.1	5.69 ±0.05

*Test for Friability was performed on single batch of 20 tablets

The variation in weight was within the limit. The thickness of tablets was found to be between 4.9-5.2 mm. The hardness for different formulations was found to be between 5.01 to 5.69 kg/cm^2, indicating satisfactory mechanical strength. The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content was found to be within limits 98 to 102 %.

Table 7: In vitro Buoyancy Studies of Verapamil HCl floating tablets

Formulation Code	Floating lag time(sec)n = 3	Total floating timen = 3	Matrix Integrity upto 12 hrs.n = 3
F1	20 ± 0.51	Up to 12	+
F2	40 ± 0.21	Up to 12	+
F3	80 ± 0.61	Up to 12	+
F4	20 ± 0.71	Up to 10	-
F5	30 ± 0.81	Up to 12	+
F6	35 ± 0.51	Up to 12	+
F7	24 ± 0.31	Up to 10	-
F8	20 ± 0.81	Up to 12	+
F9	36 ± 0.71	Up to 12	+

Table 8: In-vitro Dissolution results for formulation trails

Time (hrs)	% Drug released								
	F1	F2	F3	F4	F5	F6	F7	F8`	F9
0	0	**0**	0	0	0	0	0	0	0
1	35	**28**	21	48	40	47	55	45	32
2	48	**37**	38	67	57	59	68	59	43
4	61	**45**	47	86	68	71	81	70	56
6	76	**59**	56	97	88	86	98	81	68
8	88	**71**	63	100	95	98	100	91	76
10	100	**88**	78	100	100	100	100	100	85
12	100	**100**	85	100	100	100	100	100	100

Table 9: R^2 value and n result table

Formulation code	R2 value				"n" value
	Zero Order	First Order	Higuchi	Peppas	
F2	0.957	0.923	0.974	0.962	0.503

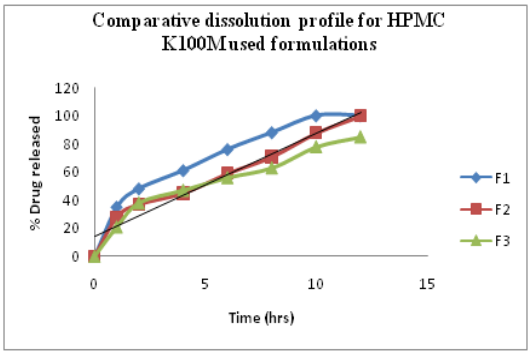

Fig.1: Comparative dissolution profile for HPMC K100M used formulations

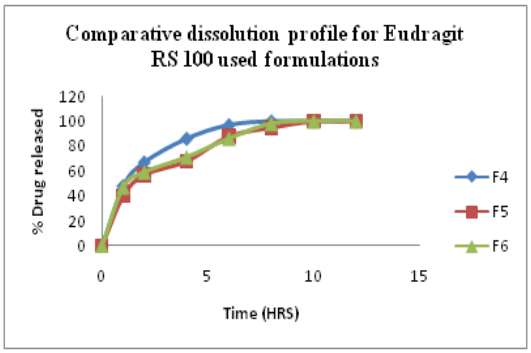

Fig.2: Comparative dissolution profile for Eudragit RS100 used formulations

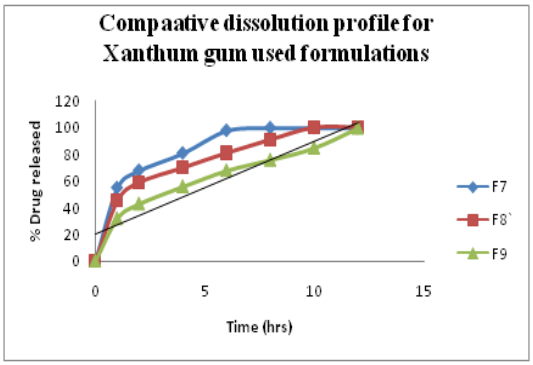

Fig.3: Comparative dissolution profile for Xanthum gum used formulations

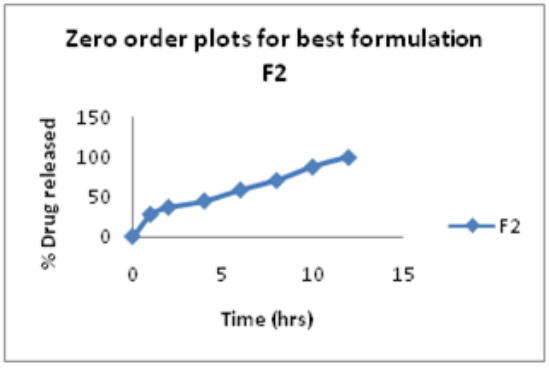

Fig.4: Zero order plot for best formulation F2

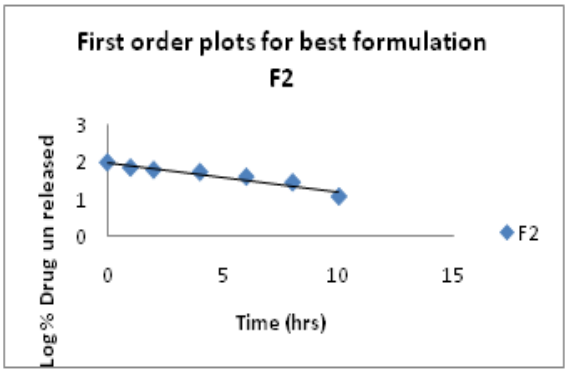

Fig. 5: First order plot for best formulation F2

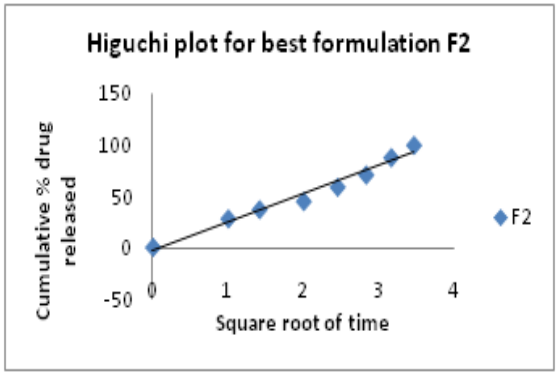

Fig.6: Higuchi plot for best formulation F2

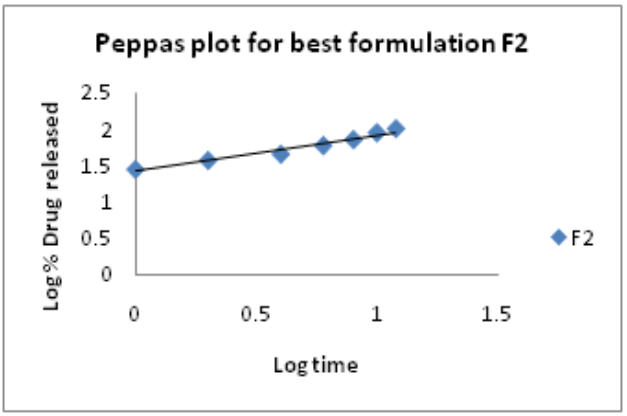

Fig.7: Korsmayerspepas plot for best formulation F2

Discussion:

Among the different control release polymers, HPMC K100M was showing highest drug release retarding capacity. F2 was showing the satisfactory results. For F2 formulation diffusion exponent n value is in between 0.45 to 0.89 so they are following non fickiananmolous diffusion model. Higuchi plots for F2 formulation are having good correlation values so the drug is releasing diffusion mechanism.

4. Conclusion

From the experimental data, it can be concluded that Floating Tablets of Verapamil HCl are formulated to increase gastric residence time and thereby improve its therapeutic efficacy. HPMC K100M was respectively showed better Sustained drug release of Verapamil HCl. When drug : polymer concentration increases the release rate decreases this is because of reason whenthe concentration of polymer increases the diffusion path length increases. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and in vitro drug release. Formulation F2 gave better-controlled drug release and floating properties in comparison to the other formulations. The release pattern of the F2 formulations was best fitted to Korsmeyer-Peppas model, Higuchi and first-order model. The most probable mechanism for the drug release pattern from the formulation was non-Fickian diffusion or anomalous diffusion.

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