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Research Article

Development and *In Vivo* Floating Behavior of Verapamil HCl Intragastric Floating Tablets

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Abstract. A novel gastro retentive controlled release drug delivery system of verapamil HCl was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. Hydroxypropylmethylcellulose (HPMC), carbopol, and xanthan gum were incorporated for gel-forming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. *In vitro* drug release studies were performed, and drug release kinetics was evaluated using the linear regression method. The optimized intragastric floating tablet composed of 3:2 of HPMC K4M to xanthan gum exhibited 95.39% drug release in 24 h *in vitro*, while the buoyancy lag time was 36.2 s, and the intragastric floating tablet remained buoyant for >24 h. Zero-order and non-Fickian release transport was confirmed as the drug release mechanism from the optimized formulation (F7). X-ray studies showed that total buoyancy time was able to delay the gastric emptying of verapamil HCl intragastric floating tablet in mongrel dogs for more than 4 h. Optimized intragastric floating tablet showed no significant change in physical appearance, drug content, total buoyancy time, or *in vitro* dissolution pattern after storage at 40°C/75% relative humidity for 3 months.

KEY WORDS: intragastric floating tablet; sustained release; verapamil hydrochloride.

INTRODUCTION

In recent years, oral dosage forms for gastric retention have drawn more and more attention for their theoretical advantage in permitting control over the time and site of drug release. This is particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine and dissolve better in the acidic environment of the stomach (1). Oral delivery of drugs is, by far, the most preferable route of drug delivery due to the ease of administration, patient compliance, and flexibility in formulation. A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that (1) are locally active in the stomach, (2) have an absorption window in the stomach or in the upper small intestine, (3) are unstable in the intestinal or colonic environment, and (4) exhibit low solubility at high pH values (2). The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion (3), flotation (4), sedimentation (5), expansion (6,7), modified shape systems (8,9), or by the simultaneous administration of pharmacological agents (10) that delay gastric emptying.

Intragastric floating (IGF) drug delivery systems can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability (11). Verapamil HCl is a calcium channel blocker used in treatment of angina pectoris, hypertension, and supraventricular tachyarrhythmia (12). In atrial fibrillation, verapamil HCl is more effective than digoxin for controlling ventricular rate (13). It is established that 90% of verapamil HCl is absorbed following its oral administration, and then it reaches maximum plasma concentration within 1–2 h. However, due to first-pass effect, it has low bioavailability (10–20%) and short half-life (4 h) making its dosing frequency high. The physicochemical properties of verapamil HCl and its short half-life make it a suitable candidate for preparation of IGF tablet.

The objective of the present investigation is to prepare and evaluate IGF tablets of verapamil HCl, which will help to retain the dosage form in the stomach and to increase gastric residence time, resulting in prolonged drug delivery in stomach using gel-forming polymers such as hydroxypropylmethylcellulose (HPMC K4M, HPMC K15M), carbopol (CP 934P, CP 940P), xanthan gum BP. A formulation that combined excellent buoyancy and sustained release characteristics both were chosen for farther *in vivo* evaluation by X-ray study in mongrel dogs for more than 4 h.

MATERIALS AND METHODS

Verapamil HCl, hydroxypropylmethylcellulose K4M (HPMC K4M), hydroxypropylmethylcellulose K15M (HPMC K15M), and xanthan gum BP were gifts from Torrent Laboratory, Ahmedabad, India. Polyvinylpyrollidon (PVP

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K30), carbopol 934P, carbopol 940P, 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 granules of verapamil HCl (320 mg equivalent to 120 mg of verapamil HCl) were prepared by mixing required quantities of HPMC K4M/HPMC K15M/CP 934P/CP 940P/xanthan gum, sodium bicarbonate, and anhydrous citric acid by using PVP K30 in 96% *v/v* ethanol as a granulating agent (Table I). Buoyancy was achieved by addition of an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The granules were dried at 60°C for 30 min in an oven and then lubricated with magnesium stearate and purified talc. The granules were compressed into tablets using single-punch tablet compression machine (Cadmach, Ahmedabad, India), fitted with 12 mm flat-faced punches. Compression was controlled to produce a 5-kg tablet-crushing strength.

In Vitro Buoyancy Studies

The *in vitro* buoyancy was determined by buoyancy lag time per the method described by Rosa *et al*. (14). The test was performed by placing each of the tablets in a 250-mL beaker, containing 200 mL of 0.1 N HCl with Tween-20 (0.02% *w/v*), pH 1.2, maintained at 37±0.5°C in a water bath. Their physical state was observed for 24 h. The time between introduction of the dosage form and its buoyancy on the 0.1 N HCl (lag time) and the time during which the dosage form remains buoyant (total buoyancy time) were determined visually. Three replicates of each formula were performed.

Swelling Study

The IGF tablets were weighed individually (designated as W1) and placed separately in glass beaker containing 200 mL of 0.1 N HCl and incubated at 37°C±1°C. At regular 1-h time intervals until 24 h, the IGF tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen IGF tablets were then re-weighed (W2), and swelling index (SI) was calculated using the following formula (15).

$$SI = (W2 - W1)/W1 \quad (1)$$

In Vitro Dissolution Studies

The *in vitro* dissolution study was performed by using a USP XXII paddle apparatus (Disso 2000, Labindia, Mumbai, India) at a rotational speed of 50 rpm. Exactly 900 mL of 0.1 N HCl was used as the dissolution medium and was maintained at 37±1°C. Then, 5 mL of the dissolution medium was withdrawn at specified time interval until 24 h. Exact 5 mL of fresh medium was replaced to the dissolution vessel after each withdrawal to maintain a constant volume. The samples withdrawn were analyzed by using a UV spectrophotometer (Elico model, Mumbai, India) at 278 nm.

Evaluation of Gastric Retention Using X-Ray Imaging

The selected IGF tablet formula (F7) for *in vivo* investigation was reformulated with 12% BaS04 as opaqueing agent and prepared by wet granulation with 96% *v/v* ethanol followed by single-punch tablet compression machine, fitted with 9 mm flat-faced punches. The X-ray studies were carried out using three healthy male mongrel dogs having weight range of 11.22 to 12.9 kg. The permission was taken from animal ethical committee prior to experiment. In each experiment, the animals were allowed to fast overnight with free access to water, and a radiograph was made just before the administration of the IGF tablet to ensure the absence of radio-opaque material in the stomach. The formulation was administered by natural swallowing each to a group of three dogs followed by 50 mL of water. The radiographic imaging was taken from each animal in a standing position, and the distance between the source of X-rays and the animal was kept constant for all imaging, thus the observation of the IGF tablet movements could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine (Medford).

Table I. Composition of IGF Tablets of Verapamil HCl (F1 to F8)

	Formulation code							
Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Verapamil HCl	120	120	120	120	120	120	120	120
CP 934 P	100	–	–	–	–	–	–	–
CP 940 P	–	100	–	–	–	–	–	–
HPMC K4M	–	–	100	–	–	60	60	–
HPMC K15M	–	–	–	100	–	40	–	60
Xanthan gum BP	–	–	–	–	100	–	40	40
Sodium bicarbonate	50	50	50	50	50	50	50	50
Anhydrous citric acid	20	20	20	20	20	20	20	20
Talc	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5
PVP K30	20	20	20	20	20	20	20	20

Table II. Physicochemical Characterization of IGF Tablets of Verapamil HCl (F1 to F8)

Evaluation parameters	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Thickness (mm)	2.47±0.035	2.54±0.070	2.53±0.084	2.61±0.049	2.27±0.041	2.41±0.053	2.19±0.073	2.53±0.074
Weight variation (%)	0.750±0.005	0.692±0.004	0.689±0.004	0.636±0.004	0.479±0.003	0.393±0.002	0.616±0.0033	0.479±0.002
Hardness (kg/cm^2)	6.5±0.165	5.5±0.170	5.5±0.196	5.0±0.165	5.5±0.098	5.5±0.172	6.0±0.333	5.5±0.140
Drug content (mg/tablet)	121.4±0.702	118.1±0.707	119.3±0.495	120.9±0.636	119.8±0.141	118.4±0.424	120.1±0.953	119.4±0.534
Buoyancy lag time (s)	58.3±4.0	78.9±2.5	47.8±3.1	55.1±1.9	42.8±4.4	51.6±3.2	36.2±3.6	8.6±3.9
Total buoyancy time (h)	>24 h	>24 h	16.53±0.207	22.22±0.317	>24 h	>24 h	>24 h	>24 h
Swelling index (12 h)	3.264±0.105	3.579±0.094	1.990±0.086	2.201±0.079	2.301±0.064	2.615±0.092	2.250±0.083	2.739±0.096

All values are mean ± SD of three determinations

Stability Studies

To assess the drug and formulation stability, stability studies were done according to International Conference on Harmonisation and WHO guidelines (16). The IGF tablets were stored at 40°C/75% relative humidity (RH) in closed high-density polyethylene bottles for 3 months (Yorco Scientific Industries, India). Tablets were analyzed at specified time intervals for the drug content, *in vitro* dissolution, buoyancy behavior, and other physicochemical parameters.

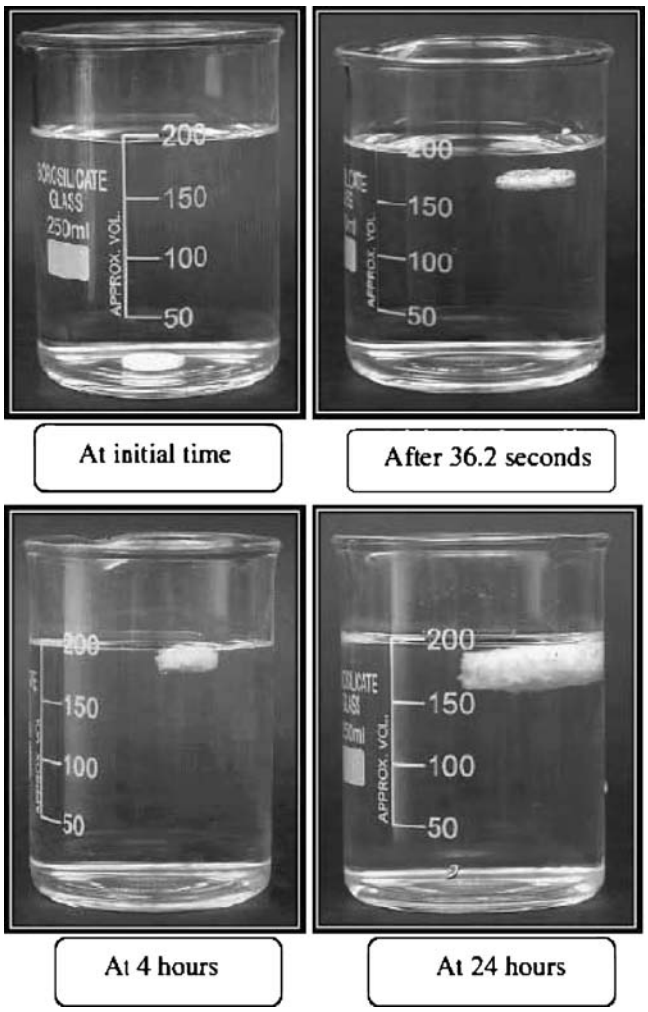

Fig. 1. *In Vitro* buoyancy studies of IGF tablet (F7)

RESULTS AND DISCUSSION

Gestroretentive tablets of verapamil HCl were developed to increase the gastric retention time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug up to 24 h. The IGF tablets were made using gel-forming polymers such as CP 934P, CP 940P, HPMC K4M, HPMC K15M, and xanthan gum BP. They are known to be beneficial in improving the buoyancy characteristics and drug release characteristics. When a combination of gas entrapping as well as controlled-release system was there, the use of disintegrating agent was important which does not quickly break the matrix and allows slow disintegration of the swollen matrix. PVP K30 in an optimized concentration (20 mg/tablet) was employed for such unique disintegrating agent (17). The talc and magnesium stearate were employed for their glidant and lubricant property (18). The composition of IGF tablets of verapamil HCl is shown in Table I. The prepared IGF tablets were evaluated for thickness, weight variation, hardness, friability, drug content, swelling index, *in vitro* buoyancy studies, *in vitro* drug dissolution studies, and *in vivo* gastric retention using X-ray imaging. All the studies were performed in triplicate, and results are expressed as mean ± SD.

Physicochemical Characterization of IGF Tablets

The IGF verapamil HCl tablets were off-white, smooth, and flat shaped in appearance. The results of physicochemical characterizations are shown in Table II. The thickness of IGF

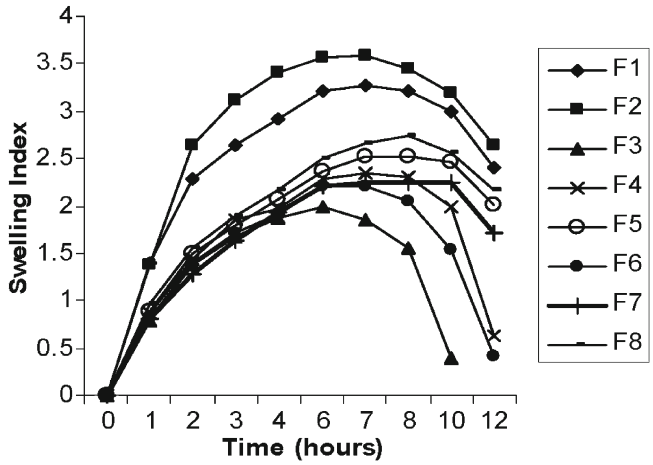

Fig. 2. Swelling index of IGF tablets of F1 to F8

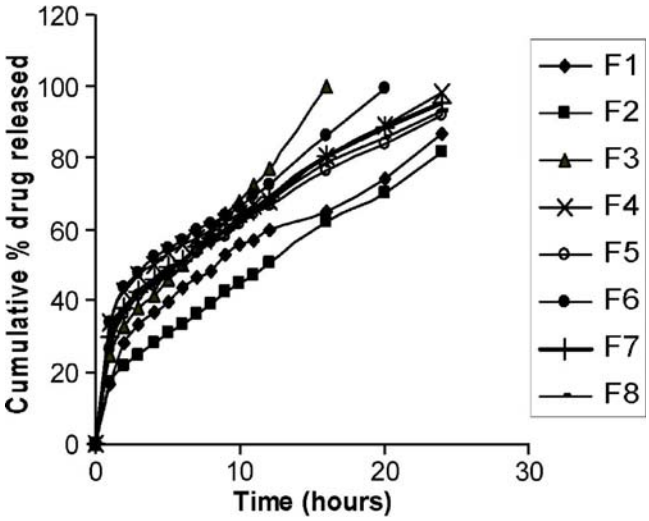

Fig. 3. *In Vitro* fissolution studies of IGF tablets of verapamil HCl (F1 to F8)

tablets was measured by digital thickness tester (Mitutoyo, Japan) and was ranged between 2.19±0.073 and 2.61±0.049 mm. The weight variation for different formulations (F1 to F8) was found to be 0.393±0.002% to 0.750±0.005%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the IGF tablets was measured by Monsanto tester (Indian Equipment Corporation Mumbai, India) and was controlled between 5.0±0.165 and 6.5±0.165 kg/cm^2.

In Vitro Buoyancy Studies

All the IGF tablet formulations were prepared by effervescent approach. The *in vitro* buoyancy of IGF tablets was induced by sodium bicarbonate and anhydrous citric cid in optimized ratio (5:2) without compromising the matrix integrity with the possible shortest bouncy lag time and buoyancy duration of up to 24 h. It was observed that the gas generated was trapped in the tablet and protected within the gel formed by hydration of polymers, thus decreasing the density of the tablet below 1, and tablet becomes buoyant (19).

The IGF tablets F1 and F2 containing CP 934P and CP 940P respectively, exhibited buoyancy lag time of 58.3±4.0 and 78.9±2.5 s, respectively, and floated till 24 h. The IGF tablets F3 and F4 contained HPMC K4M and HPMC K15M, respectively, with short buoyancy lag time of 47.8±3.1 and 55.1±1.9 s, respectively, but the total buoyancy time was less than 24 h (Table II). These might be due to rapid hydration of HPMC polymers which floated in short time as compared to IGF tablets containing CP polymers. The CP produces firm gel that entrapped the gas for longer time as compared to HPMC which has high rate of hydration and disintegrated in presence of PVP K30 (20). Same results were also observed in swelling studies where initial swelling index was observed higher in HPMC containing IGF tablets F3 and F4. The IGF tablets containing xanthan gum (F5) showed buoyancy lag time 42.8±4.4 s with total buoyancy time more than 24 h which had showed satisfactory results.

Among IGF tablets F6, F7, and F8, the IGF tablet F7 showed shortest buoyancy lag time (36.2±3.6 s) with more than 24 h total buoyancy time (Fig. 1). In dissolution studies, CP 940P containing IGF tablets F2 settled to the bottom, which might be due to their high moisture gain, which in turn showed decrease in buoyancy capability upon disturbing.

Swelling Study

Swelling is also a vital factor to ensure buoyancy and drug dissolution of the matrix tablet. The IGF tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release from the matrix tablet. Figure 2 shows the swelling index of IGF tablets of F1 to F8. The IGF tablets containing CP 934P and CP 940P (F1 and F2), respectively, showed less swelling index at the beginning but was found higher at the end of 12 h.

The IGF tablets containing HPMC K4M and HPMC K15M (F3 and F4) showed higher swelling index at the first 2 h but could not maintain their matrix integrity up to 12 h. The IGF tablets containing xanthan gum (F5) showed constant increase in swelling index up to 12 h. At the end of 12 h, IGF tablet containing HPMC K4M and xanthan gum BP (F7) was slightly less than IGF tablet containing xanthan gum BP alone (F5). But initial swelling index was observed higher in F7 than F5, which might be due to the rapid hydration of HPMC K4M.

In Vitro Dissolution Studies

In vitro dissolution studies of all the formulations of IGF tablets of verapamil HCl were carried out in 0.1 N HCl. The study was performed for 24 h, and cumulative drug release was calculated at 1-h time intervals.

Table III. Different Kinetic Models for IGF Tablets of Verapamil HCl (F1 to F8)

	Zero order		First order		Higuchi		Korsemeyer–Peppas	
Formulations code	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K (mg h$^{-1/2}$)	R^2	n
F1	0.9818	2.6573	0.9449	0.0725	0.9793	16.308	0.9866	0.5726
F2	0.9969	2.7295	0.9688	0.0585	0.9743	16.243	0.9915	0.5611
F3	0.9972	4.5870	0.8007	0.1633	0.9713	22.749	0.9959	0.6770
F4	0.9839	2.0830	0.9437	0.0725	0.9794	12.837	0.9907	0.5377
F5	0.9904	2.3586	0.8569	0.1053	0.9758	18.267	0.9934	0.5529
F6	0.9981	2.6539	0.9599	0.0912	0.9657	16.201	0.9912	0.6076
F7	0.9985	2.7681	0.9411	0.0989	0.9705	18.537	0.9915	0.6152
F8	0.9889	4.1658	0.9202	0.0529	0.9686	24.459	0.9896	0.5966

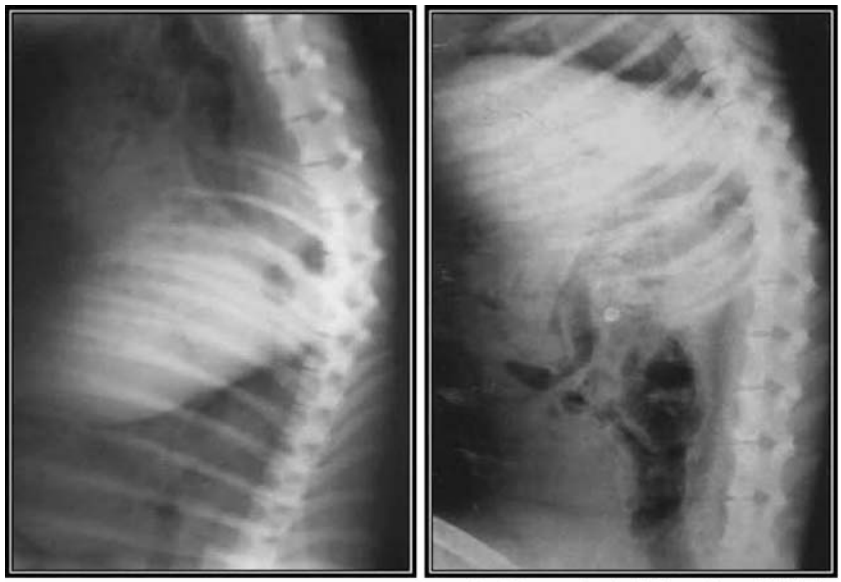

Fig. 4. Evaluation of gastric retention using X-Ray imaging

The results of *in vitro* dissolution studies are shown in Fig. 3. The higher initial drug dissolution was observed in tablets containing HPMC K4M and HPMC K15M (F3 and F4) as compared to IGF tablets containing CP 934P and CP 940P (F1 and F2).

This showed that HPMC hydrated more rapidly than CP in the presence of 0.1 N HCl. But the IGF tablets containing CP showed the drug release up to 24 h in controlled manner without changing their physical integrity in dissolution medium. Moreover, the HPMC containing IGF tablets F3 and F4 could not bear their matrix shape until 24 h and released the drug before 24 h. HPMC K4M containing IGF tablets F3 could not maintain its matrix integrity more than 16 h with release of 99.80% of drug. The IGF tablets containing HPMC K15M (F4) showed release of 98.15% at the end of 22 h; IGF tablets containing xanthan gum (F5) showed constant drug release up to 24 h (93.33%). This controlled release of drug from F5 could be attributed to the formation of a thick gel structure that delayed drug release from the IGF tablet matrix. The IGF tablets containing combination of HPMC K4M and HPMC K15M (F6) disintegrated at 19 h with drug release of 99.46%. The *in vitro* drug dissolution was slightly more rapid, by combination of xanthan gum with HPMC K4M (F7) and HPMC K15M (F8), than IGF tablets containing xanthan gum alone (F5) due to the rapid hydration of HPMC K4M.

The data obtained from *in vitro* dissolution studies were fitted to zero-order, first-order, Higuchi and Korsemeyer–Peppas equations (Table III). To confirm the exact mechanism of drug release, the data were fitted according to Korsemeyer–Peppas equation (21).

$$m_t/m_\alpha = kt^n \tag{2}$$

where m_t/m_α is fraction of drug released, k is kinetic constant, t is release time, and n is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders, and discs regardless of the release mechanism. The "n" is the slope value of log m_t/m_α *versus* log time curve. The value of "n" gives an indication of the release mechanism; when $n=1$, the release rate is independent of time (zero-order; case II transport), $n=0.5$ for Fickian diffusion, and when $0.5<n<1.0$, non-Fickian diffusion is implicated. Lastly, when $n>1.0$, super case II transport is apparent. The slope values which were less than and nearer to 1.0 suggested that the release of verapamil HCl from IGF tablets followed

Table IV. Stability Studies of Optimized IGF Tablet (F7) of Verapamil HCl

Characteristic	15 days	1 month	2 months	3 months
Physical appearance	Off white, smooth, flat faced	Off white, smooth, flat faced	Off white, smooth, flat faced	Off white, smooth, flat faced
Hardness (kg/cm^2)	5.5±0.103	5.5±0.172	5.5±0.235	5.5±0.349
Swelling index	2.261±0.085	2.254±0.108	2.253±0.092	2.241±0.101
Drug content (mg/tablet)	118.8±0.128	117.3±0.643	117.5±0.431	117.1±0.380
Buoyancy lag time (s)	34.6±3.8	36.0±4.1	37.3±4.5	35.1±4.9
Total buoyancy time (h)	26.42±0.013	25.03±0.041	28.81±0.024	20.09±0.056
In vitro drug release at 24 h	98.34±0.024	97.76±0.063	97.75±0.086	97.59±0.091

All values are mean ± SD of three determinations

non-Fickian diffusion mechanism with zero-order release kinetic.

Evaluation of Gastric Retention Using X-Ray Imaging

The prepared IGF tablets containing xanthan gum and HPMC K4M (F7) were selected for evaluation of gastric retention using X-ray imaging. Figure 4 showed the gastric retention of IGF tablet in mongrel dogs after 5 h. The *in vivo* buoyancy of IGF tablets were confirmed by X-ray imaging at 30 min regular time interval after ingestion of IGF tablet containing BaSO4. The behavior of the IGF tablet in the mongrel dog stomach was observed using a radiographic imaging technique. The IGF tablet seen in stomach of mongrel dog till 5 h (n=3) showed the confirmation of buoyancy of the IGF tablets.

Stability Studies

The prepared IGF tablets containing xanthan gum and HPMC K4M (F7) were selected for stability study on the basis of *in vitro* buoyancy and *in vitro* drug dissolution studies. The IGF tablets were stored at 40°C/75% RH in closed high-density polyethylene bottles for 3 months. The IGF tablets did not show any significant change in physicochemical parameters and other tests (Table IV). Thus, it was found that the IGF tablets of verapamil HCl tablets (F7) were stable under these storage conditions for at least 3 months.

CONCLUSION

The IGF tablets of verapamil HCl were successfully formulated by effervescent technique. The IGF tablets containing xanthan gum and HPMC K4M (F7) showed satisfactory results with short buoyancy lag time, total buoyancy time more than 24 h and controlled drug released up to 24 h. The IGF tablets were stable at 40°C/75% RH up to 3 months.

REFERENCES

1. W. Zhenping, Y. Zhanfeng, and B. Dianzhou. Design and evalvation of a two-layer floating tablet for gastric-retention using cisalpine as a model drug. *Drug Dev. Ind. Pharm*. **27** (5):469–474 (2001).
2. A. Streobel, J. Siepmann, and R. Bodmeier. Gastroretentive drug delivery systems. *Expert Opinion on Drug Delivery*. **3** (2):217–233 (2006).
3. G. Ponchel, and J. M. Irache. Specific and non-specific bioadhesive particulate system for oral delivery to the GI tract. *Adv. Drug Del. Rev*. **34**:191–219 (1998).
4. A. A. Deshpande, N. H. Shah, C. T. Rhodes, and W. Malick. Development of a novel controlled release system for gastric retention. *Pharm. Res.* **14**:815–819 (1997).
5. S. S. Davis, A. F. Stockwell, M. J. Taylor, *et al*. The effect of density on the gastric emptying of single and multiple unit dosage forms. *Pharm. Res*. **3**:208–213 (1986).
6. J. Urguhart, F. Theeuwes, inventors. Alza Corporation, assignee. Drug delivery system comprising a reservoir containing a plurality of tiny pills. US patent 4 434 153. February 28, 1994.
7. R. C. Mamajek, E. S. Moyer. Inventors. Mc Nei lab, Inc, assignee. Drug dispensing device and method. US Patent 4 207 890. June 17, 1980.
8. J. A. Fix, R. Cargill, and K. Engle. Controlled gastric emptying, III: Gastric residence time of a non disintegrating geometric shape in human volunteers. *Pharm. Res*. **10**:1087–1089 (1993).
9. F. Kedzierewicz, P. Thouvenot, J. Lemut, A. Etinine, and M. Hoffonan. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. *J. Control Release*. **58**:195–205 (1999).
10. R. Groning, and G. Heun. Dosage forms with controlled gastrointestinal passage-studies on the absorption of nitrofurantoin. *Int. J. Pharm*. **56**:111–116 (1989).
11. A. K. Bansal. Gastric-retention: a means to address regional variability in intestinal drug absorption (Drug Delivery). Pharma Techno. 1–20 (2003).
12. D. McTavish, and S. E. M. Verapamil. An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension. *Drugs*. **38**(1):19–76 (1989).
13. H. A. Klein, and E. KapIinsky. Digitalis and verapamil in atrial fibrillation and flutter. Is VP now the preferred agent? *Drugs.* **31**:185 (1986).
14. M. Rosa, H. Zia, and T. Rhodes. Dosing and testing *in vitro* of a bioadhesive and floating drug delivery system for oral application. *Int. J. Pharm*. **105**:65–70 (1994).
15. P. Dorozynski, R. Jachowicz, P. Kulinowski, S. Kwiecinski, K. Szybinski, T. Skorka, and A. Jasinski. The polymers for the preparation of hydrodynamically balanced systems - methods of evaluation. *Drug Dev. Ind. Pharm.* **30**(9):947–957 (2004).
16. B. R. Mathews. Regulatory aspects of stability testing in Europe. *Drug Dev. Ind. Pharm*. **25**:831–856 (1999).
17. N. Tomoya, K. Shin-ichi, S. Yasushi, and K. Masayuki. Preparation of floating drug delivery system by plasma technique. *Chem. Pharm. Bull*. **54**(4):514–518 (2006).
18. B.S. Dave, A. F. Amin, and M. M. Patel. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in vitro* evaluation. *AAPS PharmSciTech*. **5**(2):34 (2004).
19. F. Mamoru, A. Nicholas, and W. James. Floating hot-melt extruded tablets for gastroretentive controlled drug release system. *J. Control Release*. **115**:121–129 (2006).
20. R. Ziyaur, A. Mushir, and R. K. Khar. Design and evaluation of bilayer floating tablets of captopri. *Acta. Pharm*. **56**:49–57 (2006).
21. R. Korsmeyer, R. Gurny, and N. Peppas. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm*. **15**:25–35 (1983).