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## A novel gastro retentive controlled release drug delivery system of Verapamil Hydrochloride: Formulation and evaluation

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## ABSTRACT

*Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Verapamil HCL belongs to the class of calcium channel blockers. These medication block the movement of the calcium into the muscle cells of the coronary arteries. 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. The aim of the work is to design and evaluate verapamil HCL floating controlled release gastroretentive tablets using different hydrocolloid polymers including Carbopol, Hydroxy propyl methyl cellulose, and Xanthan gum incorporated for gel forming agent by direct compression technology. The tablets were evaluated for the physicochemical parameters such as weight variation, thickness, friability, hardness, drug content, in vitro buoyancy studies, in vitro dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. Tablet buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The in vitro dissolution studies were carried out in a USP XXII apparatus II in 0.1N HCl. All the gastroretentive tablets showed good in-vitro buoyancy. The selected tablets (F3) containing Xanthan gum released approximately 94.43% drug in 24 h in vitro dissolution study, while the buoyancy lag time was 25.8 ± 4.2 second and the tablet remained buoyancy for > 24 h. Zero order and non-Fickian release transport was confirmed as the drug release mechanism for the selected tablets (F3).*

**Keywords:** Verapamil hydrochloride, Hydroxy propyl methyl cellulose K15M, calcium channel blocker, controlled release, gastrorentative, Swelling index.

## INTRODUCTION

Under certain circumstances prolonging the gastric retention of a delivery system for achieving greater therapeutic benefit of the drug substance is desirable[1]. A controlled drug delivery

system with prolonged residence time in the stomach is of particular interest for drugs [2].The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of flotation[3], mucoadhesion[4], sedimentation[5], expansion[6], modified shape systems[7] or by the simultaneous administration of pharmacological agents that delay gastric emptying[33,34]. Verapamil HCl is a calcium channel blocker used in the treatment of several cardiovascular disorders, particularly angina pectoris supraventricular tachycardia and hypertension [9]. It is established that 90% of verapamil HCl is absorbed following its oral administration and then it reaches maximum plasma concentration within 1-2% hours. However, due to first pass effect it has low bioavailability (10-20%)[10]. It has short half-life of 4 hours, so dosing frequency is high. The physicochemical properties of verapamil HCl and its short half life make its suitable candidate for preparation of gastroretantive tablets[27,28]. Gastro retentive drug delivery systems can improve the controlled delivery of drugs that have an absorption window in the stomach by continuously releasing the drug for a prolonged period of time, thus ensuring its optimal bioavailability [8, 32]. The objective of present investigation is to prepare and evaluate gastroretentive tablets of verapamil HCl based on gel forming polymers using hydroxyl propyl methyl cellulose K15M , carbopol 940P, xanthan gum BP which will help to retain the dosage form in the stomach[26,29].

## EXPERIMENTAL SECTION

Verapamil Hcl was procured as a gift sample from (Tablets India, Chennai), polymers like Hydroxypropylmethylcellulose K15M (HPMC K15M) and Xanthan gum BP were procured as gift samples from Torrent Laboratory Ltd., Ahmedabad, India. and Carbopol 940P (CP 940P), Sodium bicarbonate, Anhydrous citric acid were procured from S.D. Fine Chemicals Ltd., Mumbai., India. And micro crystalline cellulose form (Qualigens Chemicals, Mumbai). All other chemicals and solvents used were of analytical grade.

- **Preparation of gastro retentive tablets**

The Verapamil hydrochloride (150mg) floating matrix tablets were prepared by direct compression method in three steps such as milling, mixing, and compression[30] . The drug was mixed with polymers such as carbopol 940P(F1)/ HPMC K15M(F2)/ xathan gum(F3) and other ingredients such as citric acid, sodium bicarbonate and microcrystalline cellulose in weight proportion for buoyancy of tablets[31]. The powder blend was then lubricated with magnesium stearate and talc and was compressed into tablets using suitable flat-face round tooling on a single punch tablet machine (Cadmach, Ahmedabad, India). Three formulations were prepared (F1-F3) & compression was controlled to produce a 5kg/cm2 tablet crushing strength. The tablet composition of gastoretentive tablets are shown in Table 1 [21].

- **Evaluation of granules**

The granules prepared were evaluated for the following official parameters such as bulk density, tapped density, Carr's index, Hausners ratio and angle of repose as per official procedures [22].

- **Post Compression studies**

The compressed tablets were evaluated [23] for thickness, hardness, friability, weight variation, drug content, in-vitro drug release, in-vitro buoyancy study and swelling index. The values of all the evaluation parameters are shown in (Table 2).

**Table 1: Composition of Gastroretentive tablets of verapamil HCL (F1 to F3)**

| Sr. No. | Ingredients | F1 | F2 | F3 |
|---|---|---|---|---|
| 1 | Verapamil HCL | 150 | 150 | 150 |
| 2 | Carbopol 940 P | 100 | | |
| 3 | HPMC K15M | | 100 | |
| 4 | Xanthan Gum BP | | | 100 |
| 5 | Microcrystalline Cellulose | 130 | 130 | 130 |
| 6 | Sodium bicarbonate | 60 | 60 | 60 |
| 7 | Anhydrous Citric acid (2%) | 25 | 25 | 25 |
| 8 | Magnesium stearate | 5 | 5 | 5 |
| 9 | Talc (1%) | 5 | 5 | 5 |

- **Estimation of drug content**

Weigh accurately the powder equivalent to 100mg of verapamil hydrochloride and it was shaken with 150ml of 0.1M hydrochloric acid to produce 200 ml volume. From this 10ml of the filtrate was collected and it was diluted to 100 ml with distilled water and the absorbance was measured at 278nm spectrophotometrically. Calculate the content of the verapamil hydrochloride taking 118 as the value of A (1% 1cm) at the maximum at about 278 nm. Three determinations were carried out for each batch [24].

- **In vitro buoyancy studies**

The buoyancy studies were performed by placing the tablet in a 250 ml glass beaker, containing 200 ml of0.1N HCl with tween-20 (0.02% w/v), pH 1.2, maintained at 37 ± 0.5°C in a water bath. Their physicalstate was observed for 24 h[11]. The time between introduction of the dosage form and its buoyancy on the 0.1N HCl (buoyancy 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[19].

- **Swelling study**

Gastro retentive tablet was weighed individually (W1) and placed separately in glass beaker containing 200 ml of 0.1N HCl and incubated at 37ºC ± 1ºC. At regular 1h time intervals until 24h, the tablet was removed from beaker and the excess surface liquid was removed carefully using the filter paper. The swollen tablet was then re-weighed (W2) and swelling index (SI) was calculated using the following formula [12]

$$SI = (W2 – W1)/W1 \quad \text{----------} \quad (1)$$

- **In vitro dissolution studies**

The dissolution studies were performed by using a USP XXII paddle apparatus (Disso 2000, Lab India, Mumbai, India) at a rotational speed of 50 rpm. Exactly 900 mL of 0.1N HCl was used as the dissolution medium and maintained at 37°C ± 1°C. Then, 5 mL of the dissolution medium was taken out at 30 minutes, 1 hour and thereafter every hour for 24 hours. Exactly 5 ml of fresh medium was added to the dissolution vessel after each withdrawal, to maintain a constant volume. The samples were filtered through 0.45 mm membrane filter and the concentration of drug released at different time intervals was determined by measuring the absorbance using UV-visible spectrophotometer at 278 nm against blank[25].

- **Stability studies**

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines [13]. The prepared gastroretentive tablets containing xanthan gum (F3) was selected for stability study on the basis of in vitro controlled drug release, in vitro buoyancy studies, buoyancy lag time (S), total buoyancy time (h) and their physical properties. The selected tablets of verapamil HCl (F3) packed in high density polyethylene bottle and various replicates were kept in the humidity chamber maintained at 40 °C and 75% RH for 3 months[14] (Matrix pharma, India). At the end of studies, samples were analyzed for the drug content, in vitro dissolution, floating behavior and other physicochemical parameters.

## RESULTS AND DISCUSSION

Gestroretentive tablets of verapamil-HCl were developed to increase the gastric residence 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 & cumulative drug release was calculated at every one hour time interval.The tablets were made using different gel forming polymers such as CP 940P,HPMC K15M, and Xanthan gum BP to optimize the drug content, in vitro buoyancy, swelling index and in vitro drug dissolution studies. The selection of viscosity grade of a polymer is an important consideration in the formulation of tablet Different grade of viscosity of CP 940P,HPMC K15M and Xanthan gum polymers is known to be beneficial in improving floating (buoyancy) property [11] and release characteristics. When a combination of gas entrapping as well as controlled release system is there, the use of disintegrating agent is important which does not quickly break the matrix and allows slow disintegration of the swollen matrix. Talc and magnesium stearate were employed for their glidant and lubricant property[16]. The prepared gastroretentive tablets were evaluated for thickness, weight variation, hardness, friability, drug content, swelling index, in vitro buoyancy studies and in vitro drug dissolution studies. All the studies were performed intriplicate and results are expressed as mean ± S.D. The tablets containing xathan gum (F3) showed constant drug release up to 24hrs.(94.43) as compared to tablets containing carbopol & HPMC. The data obtained from in vitro dissolution studies were fitted to zero order, first order & higuchi equation. From the in vitro buoyancy studies we observed that gel formed by hydration of polymers thus decreasing the density of tablet & tablets become buoyant.

**Table 2: Physicochemical Characterizations of Gastroretentive tablets of verapamil HCL**

| Evaluation Parameter | F1 | F2 | F3 |
|---|---|---|---|
| Thickness | 2.50 ± 0.035 | 2.40±0.045 | 2.71±0.050 |
| Average Weight (mg) | 509.1 ±0.215 | 511.4±0.145 | 514.5±0.123 |
| Weight variation (%) | 0.689±0.005 | 0.646±0.004 | 0.489±0.002 |
| Hardness(kg/cm2) | 5±0.160 | 5±0.196 | 5±0.150 |
| Friability (%) | 0.896±0.06 | 0.750±0.040 | 0.730±0.059 |
| Drug content (mg/tab.) | 151.4±0.702 | 150.9±0.363 | 148.6±0.142 |
| Buoyancy lag time(S) | 76.9±3.5 | 50.1±2.0 | 25.8±4.2 |
| Total buoyancy time (h) | >24 | 21.22±0.015 | >24 |
| Buoyancy on disturbing | Settle | float | float |

**Table 3: kinetic models for Gastroretentive tablets of verapamil HCL (F1 to F3)**

| Code | Zero order | | First order | | Higuchi | |
|---|---|---|---|---|---|---|
| | $R^2$ | Ko ($mg/h^{-1}$) | $R^2$ | K1 ($h-^{1}$) | $R^2$ | K ($mg.h^{-1/2}$) |
| F1 | 0.9869 | 2.7830 | 0.9588 | 0.0658 | 0.9843 | 16.583 |
| F2 | 0.9939 | 2.8295 | 0.9537 | 0.0725 | 0.9894 | 13.873 |
| F3 | 0.9991 | 2.7593 | 0.9699 | 0.0921 | 0.9857 | 16.102 |

**Table 4:Stability study of Gastroretentive tablets of verapamil HCL (F3)**

| **Characteristics** | **1st month** | **2nd month** | **3rd month** |
|---|---|---|---|
| Physical appearance | Off white, smooth, flat faced | Off white, smooth, flat faced | Off white, smooth, flat faced |
| Handiness (kg/cm2) | 5.4 ± 0.112 | 5.5 ± 0.225 | 5.00 ± 0.449 |
| Friability (%) | 0.838 ± 0.161 | 0.802 ± 0.260 | 0.851 ± 0.335 |
| Weight variation (%) | 0.480±0.003 | 0.500±0.003 | 0.482±0.003 |
| Swelling index (%) 12h | 2.5± 0.653 | 2.3± 0.263 | 2.4± 0.450 |
| Drug content (mg/tablet) | 115.3 ± 0.743 | 116.5 ± 0.531 | 117.7 ± 0.681 |
| Buoyancy lag time (s) | 27 ± 4.8 | 28.3 ± 4.9 | 28.1 ± 4.6 |
| Total buoyancy time (h) | 26.03 ± 0.051 | 28.81 ± 0.034 | 21.09 ± 0.066 |
| Buoyancy on disturbing | Float | Float | Float |
| In vitro release (%) 24 h. | 94.43 | 95.44 | 93.17 |

- **Physical characterization of floating tablets**

The gastroretentive verapamil HCl tablets were off-white, smooth and flat in appearnce. The results of physical characterizations are shown in Table 2.The thickness of tablets was measured by digital thickness tester (Mitutoyo, Japan) and was ranged between 2.40 ± 0.045 to 2.71 ± 0.050 mm. The weight variation for different formulations (F1 to F3) was found to be 0.489± 0.002 to 0.689±0.005 %, indicating consistency in each batch. The hardness of the tablets was measured by Monsanto tester ( Rolex Hardness Tester , Mumbai, India) and was in between 5. ±0.150 to 5 ± 0.196kg/ cm2. The friability was measured by Friabilator (Electrolab, Mumbai) and was found to be 0.730 ± 0.059 to 0.896 ± 0.06%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content was found to be 148.6 ± 0.142 to 151.4 ± 0.702mg with low standard deviation indicating batch-to-batch consistency.

- **In vitro buoyancy studies**

All the formulations were prepared by effervescent approach. Sodium bicarbonateand microcrystalline cellulose induced carbon dioxide in the presence of dissolution medium. The combination of sodium bicarbonate and anhydrous citric acid provided desired floating ability and therefore the formulation of the gastroretentive tablets so as not to compromise the matrix integrity with the possible shortest bouncy lag time and floating duration of up to 24 h. It was observed that the gas generated is trapped and protected within the gel formed by hydration of polymers, thus decreasing the density of the tablet below 1 (one) and tablet becomes buoyant[17]. The gastroretentive tablets (F2) withHPMC K15M exhibited buoyancy lag time of 50.1 ±2.0 and all floated for less duration of time (<24 h) as compared to tablets F1 and F3 which containing CP 940P,and xanthan gum respectively, with less buoyancy lag time of 46.9 ±3.5 and 25.8 ± 4.2 respectively, with total buoyancy time of more than 24 h . The formulations F1 (CP 940P) settled on disturbing during dissolution studies which might be due to their higher moisture gain which was resulted in dramatic increase in swelling of tablets which in turn,

showed decrease in floating capability upon disturbing. This showed that molecular weight distribution or viscosity of gel forming polymers influenced the in vitro buoyancy.

- **Swelling study**

Swelling is also a vital factor to ensure bouyancy and drug dissolution of the formulation. Gastroretentive tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water[20]. This gel layer governs the drug release from the formulation. The swelling index of gastroretentive tablets of F1 to F3 is shown in Fig.1. Tablets containing CP 940P (F1) showed less swelling index at the beginning but higher swelling index was observed at the end of 12 h. While HPMC K15 (F2) swelled rapidly at the beginning in 0.1 N HCl and could not remain their matrix integrity upto 12 h. Tablets containing xenthan gum (F3) showed constant increasing in swelling index upto 12 h.

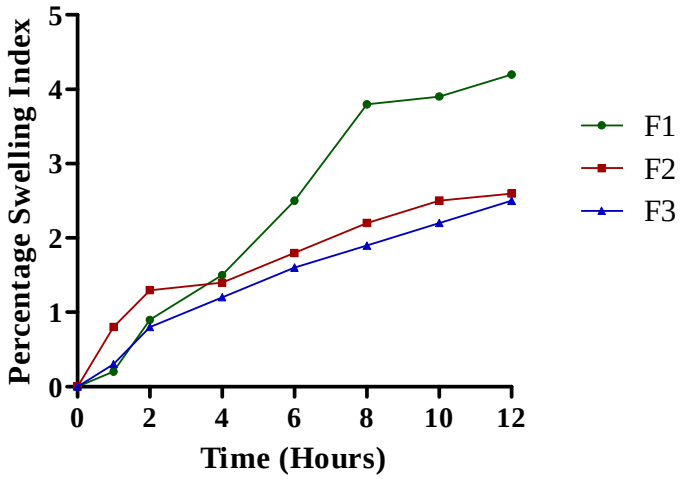



**Figure1: Swelling index of Gastroretentive tablets of verapamil HCL (F1 to F3)**

- **In vitro dissolution studies**

In vitro dissolution studies of all the formulations of gastroretentive tablets of verapamil HCl were carried out in 0.1N HCl. The study was performed for 24 h and cumulative drug release was calculated at every one hour time interval. The results are shown in Fig. 2. After 1 h the drug dissolved from gastroretentive tablets of CP940 F1 (15.67) was less than tablets containing HPMCK15 F2 (23.82). This showed that HPMC hydrated more rapidly than CP in the presence of 0.1 N HCl. But the 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 tablets F2 could not bear their matrix shape until 24 h and the released the drug before 24 h.Tablets F2 Showed release of 98.27% at the end of 22 h. Tablets containing Xenthan gum (F3) showed constant drug release up to 24 hr (94.43). This controlled release of drug from F3 could be attributed to the formation of a thick gel structure that delays drug release from the tablet matrix. The data obtained from in vitro dissolution studies were fitted to zero-order, first-order and Higuchi (Table 3). The zero-order plots were found to be fairly linear as indicated by their high regression values [18].

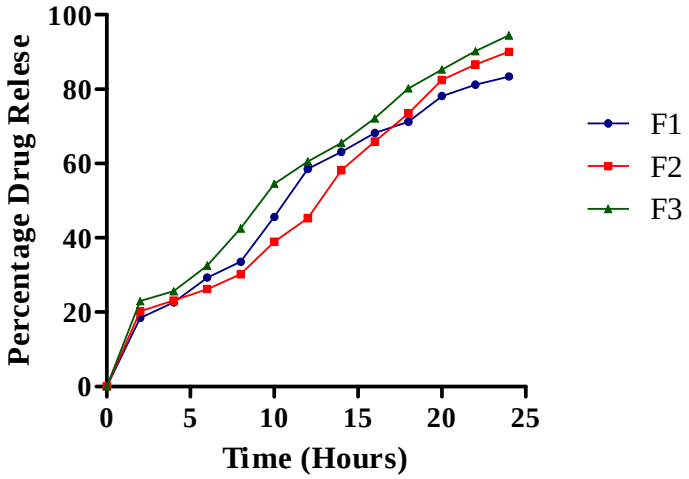
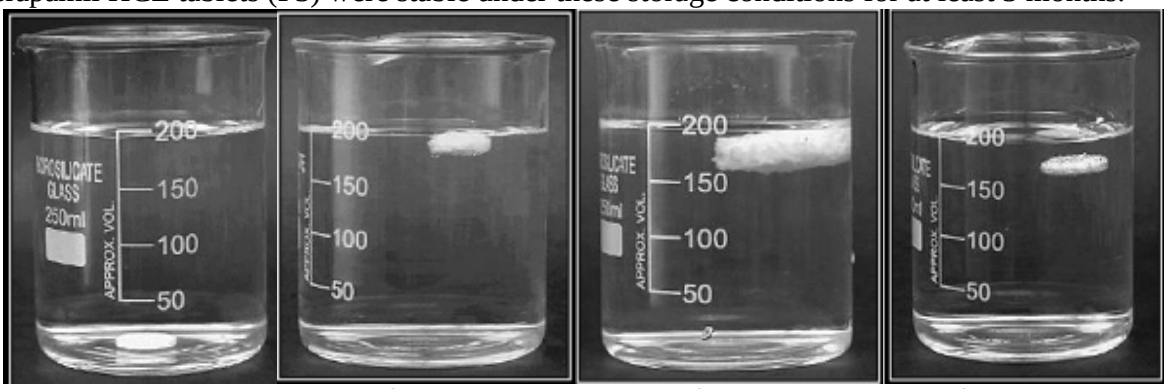



**Figure 2: Cumulative percentage drug released from gastroretentive tablets of Verapamil HCL (F1 to F3)**

- **Stability studies**

The prepared gastroretentive tablets containing Xanthan gum (F3) was selected for stability study on the basis of in vitro buoyancy and in vitro drug dissolution studies. The tablets were investigated at 40 °C/75%RH in both opened and closed high density polyethylene bottles for 3 months. The drug release rate from the gastroretentive tablets of verapamil HCL showed no significant change during storage (Table 4). Thus, it was found that the gastroretentive tablets of verapamil HCL tablets (F3) were stable under these storage conditions for at least 3 months.




**At initial time** **After 4 hrs.** **After 24 hrs.** **After 33 hrs.**

**Figure: 3 In vitro buoyancy studies (F3)**

## CONCLUSION

Controlled release gastroretentive verapamil hydrochloride tablet were successfully formulated in floating mechanism. Tablets containing xanthan gum along with gas forming agent showed short buoyancy lag time, total floating time more than 24 h. which was controlled release characteristics for 24h. as compared to tablets containing carbopol and HPMC. Good stability was observed for 3 months during stability studies.

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