The Chemist
Journal of the American Institute of Chemists

Formulation and Sustained-Release of Verapamil Hydrochloride Tablets

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Abstract: Verapamil hydrochloride effervescent tablets are the principal focus of this investigation. Material & Methods: Verapamil hydrochloride floating tablets were made using the direct compression method. HPMC-K15M, karaya gum, sodium bicarbonate, and diluents were homogenized for ten minutes before adding magnesium stearate to each tablet formulation. Each tablet had a total weight of 300 mg. HPMC was utilized in the range of 20-40 mg, and karaya gum was used in the 40-90 mg range. We used a mortar and pestle for kneading the powder combination for another 5 minutes. A Rimek rotating tablet machine was used to compress the mixture into tablet form. The formulations were tested using a variety of criteria following their production. Results & Discussion: The tablet formulation friability range was between 0.3 ± 0.0064 and 0.59 ± 0.0077%. The manufactured tablet formulation's weight fluctuation is within USP guidelines. The range of thickness was discovered to be 4.1 ± 0.48 to 4.2 ± 0.76 mm. The assay for drug content range was between 96.52 ± 0.35 and 102.13 ± 0.53%. For B1, B5, B6, B9, and B10 at 12 hours, more than 75% of the medication was released. B1 showed a maximum of 30% drug release in the first hour and a steady release for up to 12 hours. One possible explanation for B8's low drug release is the creation of a thick gel barrier on top of the tablet.

Key Words: Effervescent, Verapamil, bioequivalence, FDDS, floating tablet

1. Introduction

Floating drug delivery systems "FDDS" or hydrodynamically controlled systems are low-density systems to remain buoyant in the stomach for a long time without affecting the

rate at which the stomach empties. While floating on the gastric contents, the drug is gradually taken from the body at the desired rate. Immediately after taking the drug, the stomach's remaining systems are flushed out. A longer period of stomach retention and improved control over plasma medication concentrations are achieved as a result [1]. Additionally, a certain level of floating force (F) is needed to maintain the dose form stable on the surface of the meal so that the buoyancy retention principle can be appropriately applied. Buoyant systems can be made using granules, powders, capsules, tablets, laminated films, and hollow micro-spheres, among other things [2-15].

2. Materials & Methods

Formulation of Effervescent Floating Tablets

Verapamil hydrochloride floating tablets were made using the direct compression method. We blended HPMC-K15M, karaya gum, sodium bicarbonate, and diluents for ten minutes before adding magnesium stearate to each tablet formulation, which included the medicine. Table 1 shows the formulation chart of effervescent floating Verapamil hydrochloride tablets. Each tablet had a total weight of 300 mg. HPMC was utilized in the range of 20-40 mg, and karaya gum was used in the 40-90 mg range. A mortar and pestle were used to knead the powder combination for another 5 minutes [16,17].

Table 1. Formulation Chart of Effervescent Floating Verapamil Hydrochloride Tablets

Ingredients mg	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Verapamil Hydrochloride	120	120	120	120	120	120	120	120	120	120	120	120	120
Karaya Gum	40	40	40	40	70	70	70	70	70	90	90	90	90
HPMC K15M	20	40	30	30	20	40	20	40	30	20	40	30	30
Sodium Bicarbonate	20	20	10	30	10	10	30	30	20	20	20	10	40
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	70	50	70	50	60	40	40	20	40	30	10	30	00
Total weight	300	300	300	300	300	300	300	300	300	300	300	300	300

Technological Characteristics of Floating Tablets

Weight variation test

The average weight of 20 tablets from each formulation is calculated by weighing each tablet individually and averaging the results. The individual weights are compared with the overall average weight. The standard variation for tablets with an average weight of 350 mg is ±5% (equation 1).

$$\% \text{ deviation} = \frac{\text{Average weight of tablet} - \text{individual tablet weight}}{\text{Average weight of tablet}} * 100 \quad (1)$$

Friability

We used a Roche friabilator to grind ten pills into fine powder for four minutes at 25 rpm. They were removed, dedusted, and weighed again. The formula for calculating the percentage of friability in the tablets (equation 2) is [18]:

$$\% F = \{1-(W_t/W)\} \times 100 \quad (2)$$

where % F is percentage friability, W is the initial weight of the tablet, and W_t is the final weight of tablets after revolutions.

Hardness

The average of the three pills taken from each formulation was used in the study. As a result, the Inweka hardness tester is used to determine how hard each tablet is to the touch. It is measured in kilograms.

Thickness and diameter

Mitutoyo micrometer screw gauge is used to measure tablet thickness and diameter. Each formulation has an average of five pills taken. Millimeter (mm) is the unit of meas-urement.

Uniformity of drug content

Five pills were ground to powder at random to determine if the drug content was homogeneous. When the drug is dissolved for 5 hours with intermittent shaking, it dilutes to 100 ml of buffer and stores at room temperature. Filtration removes insol-uble residue by diluting 1 ml of the filtrate to 10 ml with buffer. We decided to measure the absorbance at its highest using a U.V. visible spectrophotometer. The trials were repeated three times for each formulation, and the mean data was recorded for each.

Drug content was calculated using the following equation (3):

$$\% \text{ Drug content} = \text{conc. } (\mu g/ml) \times \text{Dilution factor} \times 100/ 50 \quad (3)$$

Drug-excipient Compatibility Studies

Fourier transforms infrared spectroscopy (FT-IR)

Drug-excipient interaction studies were conducted to assess the drug's integrity and compatibility in the formulation. Fourier transforms infrared FT-IR spectroscopy was used to examine the pure medication and optimized formulations. FT-IR spectra of pure drug and its formulations were obtained by an "FT-IR Shimadzu 8400S" (Japan) spectrophotometer using the KBr pellet method. The samples were scanned from 400 to 4,000 cm^{-1} wave number.

Differential scanning calorimetry (DSC)

DSC was carried out on a pure sample of the medication and its powdered form. Calorimetric measurements were performed using high purity alpha-alumina discs as a reference cell. The dynamic scans were taken in a nitrogen atmosphere at the heat rate ± of 10°C min^{-1}. The energy is measured as Joules per kilocalorie [19].

In vitro floating studies [20]

Floating lag time and total floating time were used to measure *in vitro* buoyancy. A USP dissolving device was used for the test type-II (basket) using 900 ml of 0.1 N HCl buffer solutions at 100 rpm at 37 ± 0.5°C. In this experiment, the floating lag and total time are recorded as the time it took for the formulation to reach the surface of the dissolving medium and the time it took for the formulation to remain there (Figure 1).

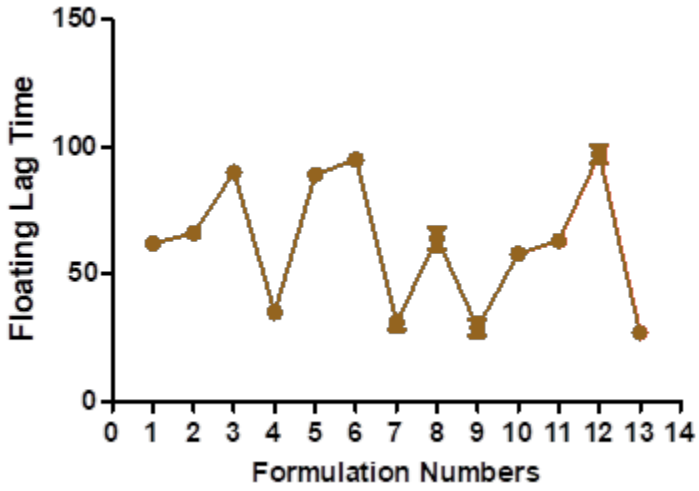

Figure 1. Effect on Floating Lag Time of Different Formulations

Water uptake studies [21]

The swelling of the polymers is based on their propensity to absorb water and expand. A USP dissolving apparatus type-II (basket) was used to dissolve the tablet in pH 1.2 hydrochloric acid buffer at 100 revolutions per minute to conduct a water absorption study (RPM). The medium was maintained at 37 ± 0.5°C throughout the study. Regularly, the tablets were taken out, weighed, and blotted to remove any extra water before being put back in. Water uptake (W.U.) (equation 4) is used to describe the swell ability of the tablets.

$$\text{W.U. (\%)} = \frac{\text{Weight of Swollen tablet - Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100 \quad (4)$$

3. Results & Discussion

Technological characteristics of floating tablets

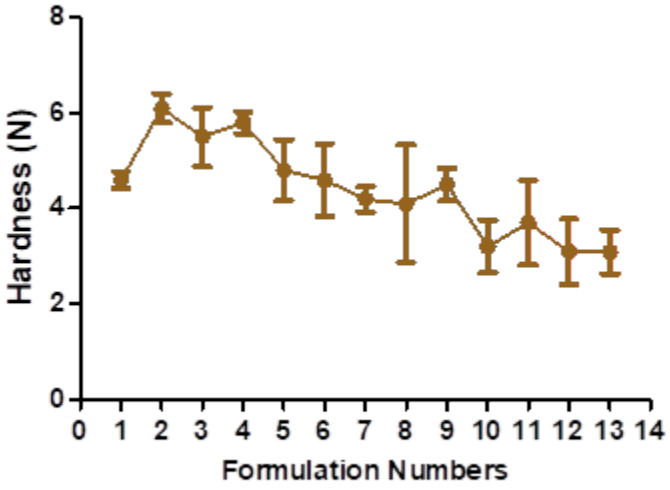

Figure 2. Effect on Hardness of Different Formulations

The hardness of floating tablets ranged from 4.1 ± 1.23 to 6.1 ± 0.306 kg (Figure 2), depending upon the mixture of the polymer used. The tablet formulation's friability ranged from 0.3 ± 0.0063 to 0.59 ± 0.0076%. The manufactured tablet formulation's weight fluctuation is within USP guidelines. The thickness is discovered to be between 4.1 ± 0.48 and 4.2 ± 0.76 mm (Figure 3). The drug content assays ranged from 96.52± 0.37 to 102.03 ± 0.53% (Figure 4).

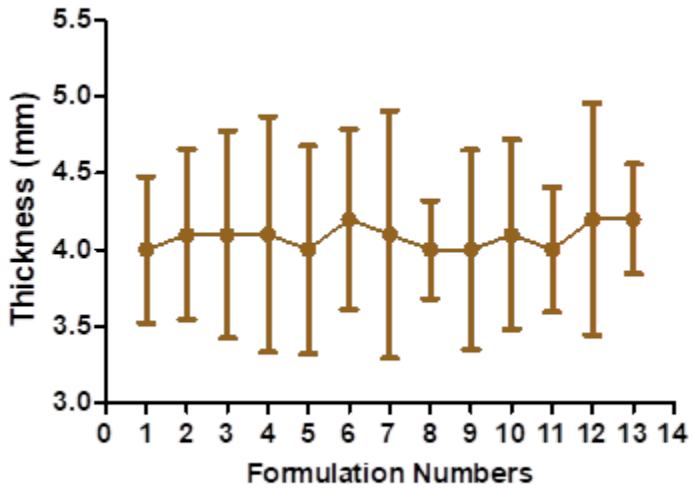

Figure 3. Effect on Thickness of Different Formulations

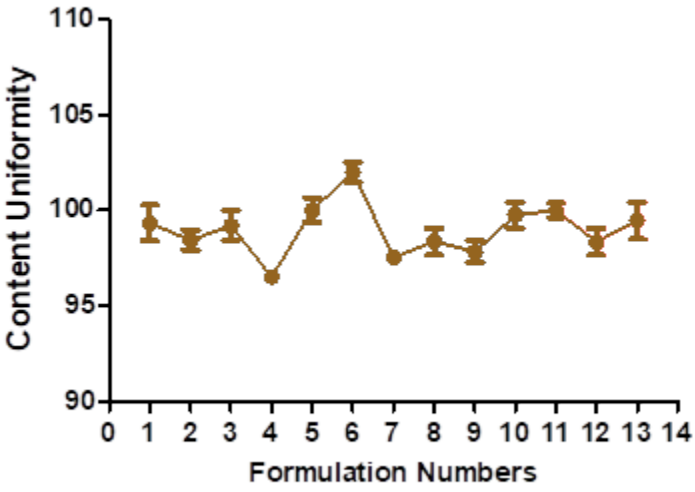

Figure 4. Effect on Content Uniformity of Different Formulations

Fourier transforms infrared spectroscopy (FT-IR)

Potassium bromide dispersion is used to measure the spectra in the solid-state. The FT-IR technology was used to capture the bands. The FT-IR spectral study found that the pure drug and the drug formulation have similar distinctive peaks with slight changes (Table 2). As a result, it was determined that the medication and polymer utilized have no chemical interaction.

Table 2. FT-IR Spectral Data of Effervescent Floating Tablet of Verapamil Hydrochloride (B1) and Verapamil Hydrochloride Pure Drug

Functional groups	Frequency of pure drug (cm^{-1})	Frequency of formulation (cm^{-1})
C-H Stretching vibrations of methyl and methylene groups	3030.5-2860	3051.49-2789.16
C-H stretching vibrations of the methoxy group	2840	2843.17
C-O stretching vibrations of the aromatic ethers	1262	1255.70
Sharp weak bond due to C=N stretching vibrations of the alkyl nitrile	2236	2235.57
Skeletal stretching vibrations of the benzene ring	1607, 1518	1599, 1518

Differential scanning calorimetry (DSC)

Screening for compatibility between drugs and excipients is made more accessible with DSC, which provides a wealth of data on potential interactions in a short period (Table 3). Verapamil hydrochloride and formulation B1 underwent a DSC study. An endothermic peak at 138.25°C, the drug's melting point, maybe seen on its therm-ogram. The melting point of the medication is found to be 139.53°C in the matrix tablet formulation B1. The medication and excipients have no interaction, according to the analysis of thermograms obtained using DSC [22,23].

Table 3. DSC Thermogram Data of Effervescent Floating Tablet of Verapamil Hydrochloride (B1) and Verapamil hydrochloride Pure Drug

Drug and formulation	T_o(°C)	T_m(°C)	T_c(°C)	Melting range(°C)
Verapamil Hydrochloride	131.21	139.54	145.74	14.10
Formulation B1	130.98	138.26	144.86	13.86

T_o - Onset of melt, T_m - Melting point, T_c - Completion of melt

***In vitro* buoyancy studies**

The tablet turns buoyant when its density drops below 1 g/ml. Tablets made with karaya gum, and HPMC has good gel strength, allowing CO_2 gas to be trapped inside and resulting in a long-lasting buoyancy. The system must float for a few minutes after contact with stomach fluid to prevent the dose form from being pushed into the small intestine with food. Experiments show that as the effervescent agent and karaya gum increases in B13, it takes longer for the system to float in the medium. The more significant concentration of effervescent agents resulted in more CO_2 being produced faster and at a higher rate. A high level of buoyancy necessitated sodium bicarbonate. In general, the gastric emptying time was 4 hours. Because Verapamil hydrochloride is absorbed mainly from the proximal section of the intestine, the longer the medicine is in the stomach, the more it is absorbed (Table 4) [24].

Table 4. Effect of Sodium Bicarbonate on Onset and Duration of Floatation of the Effervescent Floating Tablet of Verapamil Hydrochloride (B1)

Amount of sodium bicarbonate (mg)	Onset of floating (s)	Duration of floating (h)
10	92±3.88	16±0.83
20	62±2.97	21±0.38
30	32±2.52	24±0.67
40	27±0.06	18±0.78

Water uptake studies

At one hour, the B4, B6, and B7 swelled by a large percentage. At the end of 8 hours, B8 exhibited a steady increase in the proportion of swell. The use of karaya gum slows down the water intake in the first hour. During the 8 hours, the levels of B2, B3, and B5 decrease. Sodium bicarbonate concentration does not affect the swelling properties, but lactose concentration in B8 has the most significant effect ($p \geq 0.05$) (Figure 5).

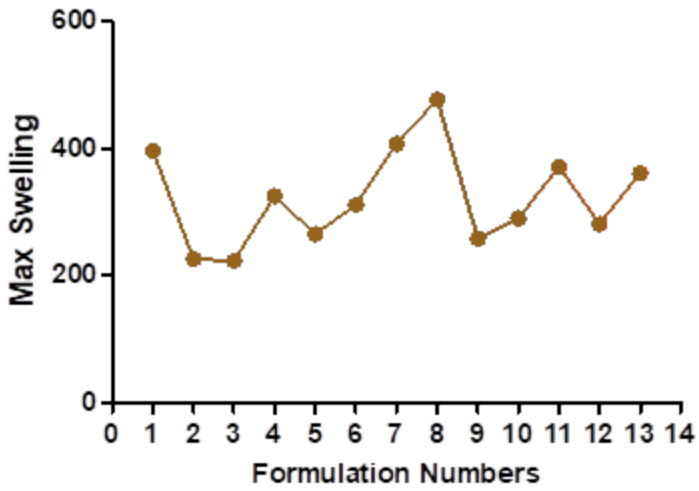

Figure 5. Effect on Max Swelling of Different Formulations

Seipmann and Peppas think that the water content of the tablet has a considerable impact on the diffusion of the medication. To understand why this can be the case, we need to understand how water affects the mobility of polymer chains. Polymer chain relaxation occurs with volume increase, resulting in a significant system swell. Higher water content can also indicate faster stomach fluid entry into the tablet, resulting in faster CO_2 gas generation and reduced floating time. As a result, the tablet swells faster and more rapidly, increasing the tablet's dimensions and decreasing diffusion rates.

***In vitro* drug release studies**

There is more than 75% drug release at 12 hours for each of the following: B1, B5, B6, B9, and B10. At a maximum of 30% in the first hour and for nearly 12 hours, the B1 maintained a steady release of the medication. B8 shows the lowest drug release of all the formulations, which may be due to the substantial gel barrier on the tablet. Other formulations with a more ex-tensive swelling index were shown to have a similar effect on drug diffusion across the gel barrier. B1 had a more excellent lactose content than any of the other samples. An infusion media dispersed into the matrix, leading to drug diffusion and controlled release from tablets (Figures 6 and 7).

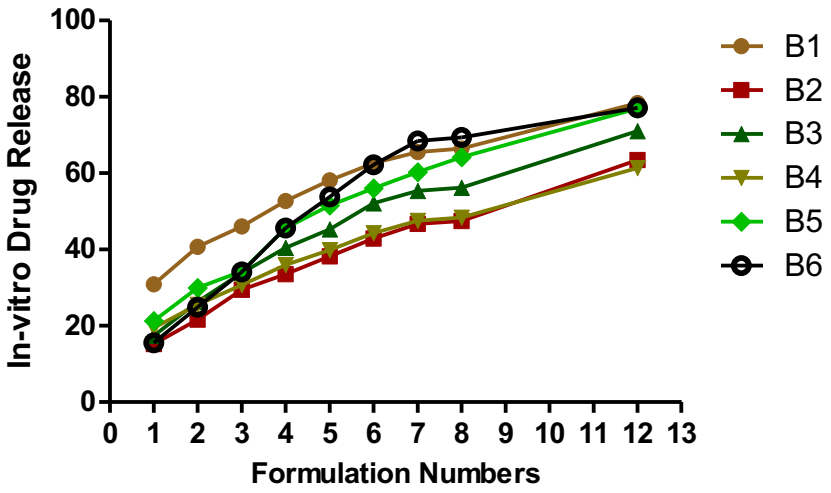

Figure 6. *In-vitro* Drug Release of Different Formulations

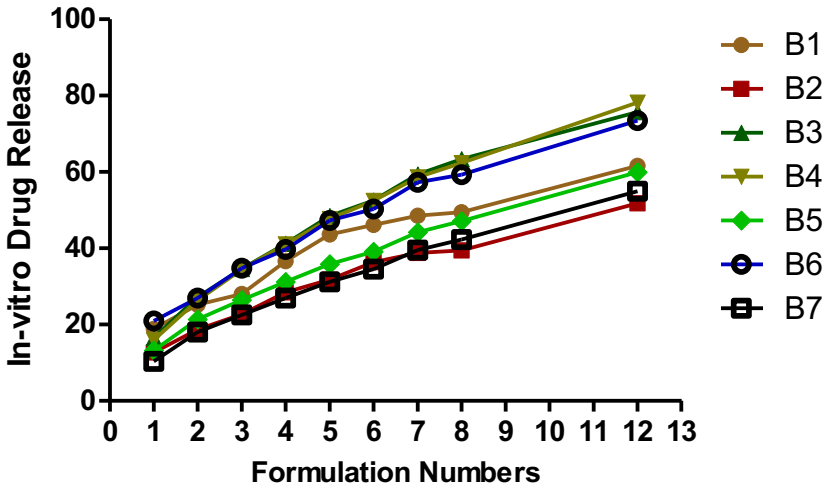

Figure 7. *In-vitro* Drug Release of Different Formulations

Mathematical model fitting of obtained drug release data

To further understand the *in vitro* drug dissolution profiles, we use various mathematical models, including the Korsmeyer-Peppas equation and Higuchi kinetics, to examine the data. The PCP disso v2.08 software was used to determine the release rates k and n for each model. In order to assess the model's accuracy, correlation coefficients (R2) were used. Table 6.08 lists the R2, k, and n values. Korsmeyer-Peppas and Matrix models were compared using R2 values; the Matrix model was found to have the best R2 values, while Korsmeyer-Peppas had the best R2 values for the other models. There is a wide range in the diffusion exponent. Fickian release was observed in B1, B4, and B7, while the non-Fickian or anomalous release was observed in other

formulations. With the Fickian release, B4 and B7 are the best-fitting matrix models; with the non-Fickian release, B5 and B12 are the best-fitting matrix models. Fickian diffusion is employed when the value of n in Korsmeyer-Peppas is 0.5 or less, whereas diffusion with n values between 0.5 and 1 is used for anomalous or non-Fickian releases. When the release mechanism is unclear or numerous types of release phenomena are possible, this model is utilized to explore the release of pharmacological polymeric dosage forms. Fick's laws are the foundation of diffusion, which describes the macroscopic transit of molecules along a concentration gradient.

Stability studies

The optimized formulation B1 was subjected to stability testing to determine the effect of formulation additions on both the chemical and biological stability of the medicine. It was tested for 12 months at 25ºC/60 percent R.H., 30ºC/65 percent R.H., and 40ºC/75 percent R.H. During the course of the study, neither the external appearance nor the pharmacological content changed appreciably. Table 5 provides the results of drug content determination during the period when the stability tests were conducted. Long-term and accelerated storage data were analyzed using Sigmaplot 12.0 software, as was the 95 percent confidence interval. According to the findings, the changes in the parameters evaluated were minor and insignificant.

Table 5. Stability Study Data of Effervescent Floating Tablet Formulation (B1) of Verapamil Hydrochloride

Stability condition	Sampling interval (months)	Physical appearance	% Drug content B1 (mean ± S.D*)
25o±2oC/60±5% RH	0	No change	99.36 ± 0.15
	3	No change	99.22 ± 0.13
	6	No change	98.44 ± 0.16
	12	No change	98.36 ± 0.17
30o±2oC/65±5% RH	0	No change	99.35 ± 0.18
	3	No change	99.14 ± 0.14
	6	No change	98.69 ± 0.18
	12	No change	98.15 ± 0.14
40º±2oC/75±5% RH	0	No change	99.36 ± 0.95
	3	No change	98.62 ± 0.78
	6	No change	96.35 ± 0.28

4. Conclusion

Direct compression was used to make the tablets. They met pharmacopeial standards for floating tablet technology. More than 8 hours later, the tablets were still floating. After 8 hours, all of the produced formulations have reached complete swelling. Therefore, the percentage of swelling was calculated at that point. More than 75% of the medication was released after 12 hours in F1, F5, F6, F9, and F10. Maximum 30 percent drug release occurred in one hour and continued for over 12 hours with F1. Formulation F1 is deemed the most optimal based on the results of the *in vitro* testing.

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