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COMMUNICATION

In Vitro Performance of Floating Sustained-Release Capsule of Verapamil

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ABSTRACT

Capsules filled with mixtures of verapamil, hydroxypropoxyl cellulose (HPC), and effervescent are proposed to provide floating sustained release over 10 hr. The effects of weight filled in the capsule, amount of HPC, and the addition of effervescent on the dissolution kinetics are studied. The conventional capsules were filled with different amounts and weights of the mixtures of verapamil, HPC, and effervescent. The release of verapamil from the capsules followed the Higuchi release model. However, when effervescent was added, a zero-order drug release was observed after the burst phase. The conventional capsule, when filled with active ingredients, polymers, and effervescent, can achieve a zero-order release system. Entrapped air was considered as a barrier to diffusion and matrix relaxation in drug release.

INTRODUCTION

When a drug is formulated with gel-forming hydrocolloids such as hydroxy-propylmethylcellulose, it swells in the gastric fluid with a bulk density of less than one. It then remains buoyant and floats in the gastric fluid, affording a prolonged gastric residence time. This floating dosage form is well known as a hydrodynamically balanced system (HBS) (1–3).

In an HBS, many methods have been reported to increase the gastric residence time. They include floating (5–8), swelling (9), adhesion (10,11), laser drill pores (12,13), and film coating. Potassium chloride has been demonstrated to exhibit a zero-order release by compressing it with hydroxypropoxyl methylcellulose (HPMC) and entrapped air to produce a tablet dosage form (14,15).

Capsule preparation could also be designed as the HBS to prolong its gastric residence time. In this report, verapamil, which was premixed with hydrophilic polymer and a low level of effervescent mixture, was used to fill a conventional hard-gelatin capsule. The kinetics of

release could be modified by adjusting the mixing ratios of polymer and effervescent mixture to achieve a zero-order manner.

MATERIALS AND METHODS

Materials

Verapamil was obtained from Recordati Incorporated of Italy. Hydroxypropoxyl cellulose of high density (HPC-H) and hydroxypropoxyl cellulose of medium density (HPC-M) were supplied by Shin-Etsu Chemical Company of Japan. The hydroxypropoxyl methylcellulose K15M (HPMC K15M) was purchased from Dow Chemicals (United States). Potassium-citrate monobase and potassium bicarbonate were supplied by Merck of Germany. Capsules were supplied by Shin-Li-Fong Company of Taiwan.

Preparation Methods for Floating Capsule

The mixture of each study formulation was manually blended homogeneously with a mortar. The well-blended powder was then manually inserted into 10 conventional capsules. The average weight of each capsule was about 200 mg. The weight of variation of each capsule was generally less than 1.0%.

Measurement of Dissolution Rate of the Capsules

From each formulation, 6 capsules were randomly sampled for the dissolution test. The dissolution studies were carried out by a USP XXIII dissolution test method II at a paddle speed of 50 rpm in water. The whole system of the dissolution test was thermally controlled at 37°C. A coil, made of stainless steel wire, was used to hold the capsule. An aliquot of 3.0 ml of the samples was withdrawn at each hour for a total of 10 hr. The samples were filtered and then analyzed at an ultraviolet (UV) wavelength of 278 nm using a spectrophotometer.

Formulation Factors that Affect the Release Kinetics

The impact of formulation variables on the release kinetics of verapamil was investigated. They were the polymer excipients, the contents of the polymer, the density of the capsules, and the presence of an effervescent. The mixture of each formulation was blended homogeneously. Different amounts of the well-blended powder, depending on the required density, were then filled into six conventional #2 capsules. The release kinetics for each formulation were then characterized.

The Content of Polymers

Preliminary study results indicated that verapamil exhibited a sustained-release behavior in the presence of HPCs. Different amounts of verapamil were mixed with different kinds of polymer (HPMC K15M, HPC-H, and HPC-M) at 1:5, 1:4, 1:3, 1:2, 1:1, 1.5:1, 2:1, and 3:1 (w/w) and were inserted into six conventional #2 capsules. Their release kinetics were studied to understand the effect of the content of polymers.

The Effect of Density of Capsule on Drug Release

Different weights (276, 242, 198, 147, and 125 mg) of the powdered mixture of verapamil and HPC-H (1:1, w/w) were inserted into six #2 conventional capsules. Their release kinetics were studied to understand the effect of the density of the capsules.

The Effect of Effervescent on Drug Release

A mixture of potassium-citrate monobase and potassium bicarbonate (1:1 w/w) was used as an effervescent to generate the gas. Verapamil at 25% (w/w) and the effervescent at 0%, 1%, 2%, 3%, 4%, 5%, and 6% (w/w) were mixed with the remaining amount of HPC-H. The 270 mg of powdered mixture was inserted into six conventional #2 capsules. The release kinetics were studied to understand the effect of effervescence in capsules.

RESULTS AND DISCUSSION

Excipients such as alginic acid, PVP K30, PEG 6000, lubric wax, and stearic acid were also studied. Within 30 min, 90% of verapamil was released. These excipients did not show the sustained-release characteristic as did HPC and HPMC. Different amounts of HPMC K15M, HPC-H, and HPC-M were mixed with verapamil; their release kinetics are shown in Fig. 1.

The formulations showed that when the ratio of polymer and verapamil as less than 1, the different sustained-release properties were revealed. However, for the formulations that had more polymer (a ratio higher than 1), the extent of sustained-release characteristics could not be differentiated.

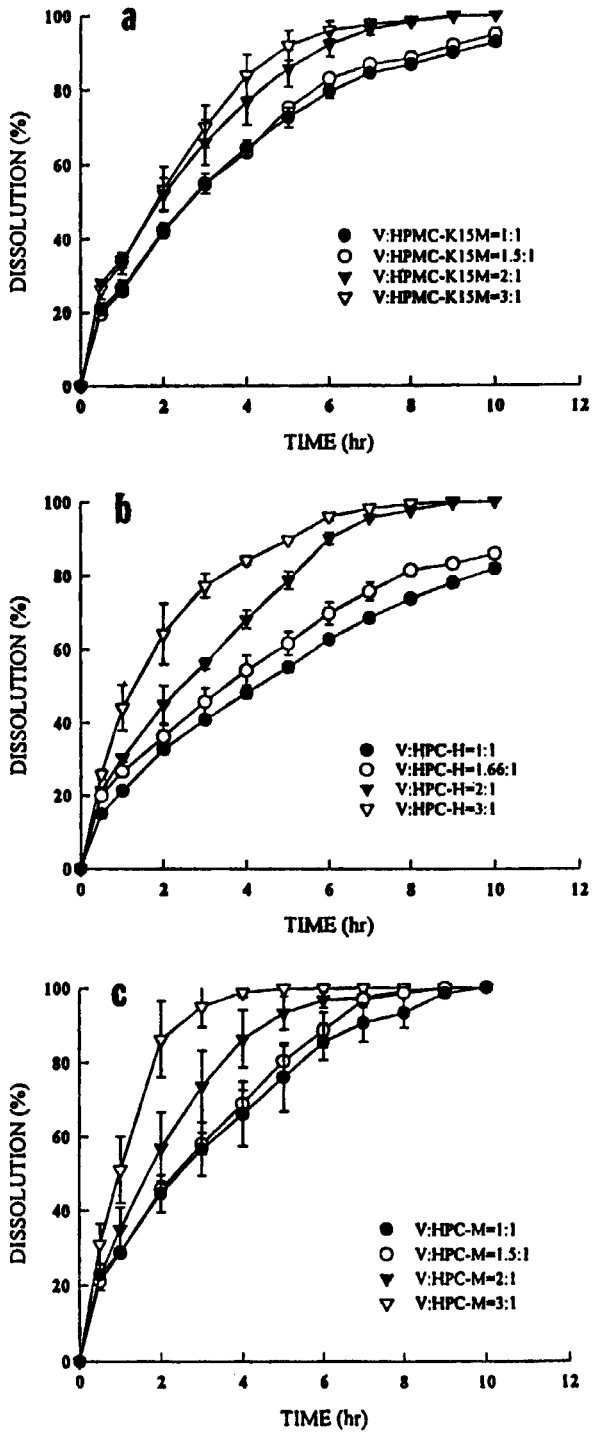

Figure 1. Release profiles for verapamil/polymer capsules for the following polymers: (a) HPMC-K15; (b) HPC-H; (c) HPC-M.

To analyze the mechanism of release of verapamil from these capsules, the data obtained were fitted to Eq. 1–5 below.

For the zero-order release kinetics (16,17),

$$F = kxt \tag{1}$$

where F is the fraction of drug release, k is the release constant, and t is the release time.

For the first-order release kinetics (18,19),

$$\ln (F) = kxt \tag{2}$$

For the Hixson and Crowell powder dissolution model (20),

$$M_t^{1/3} = M_0^{1/3} - kxt \tag{3}$$

where M_t is the amount of drug remaining after time t, and M_0 is the initial amount of drug.

For the Higuchi release model (21),

$$W_t = [D\varepsilon C_s(2W_0 - \varepsilon C_s)t]^{1/2} \tag{4}$$

where W_t is the amount of drug release after time t, D is the diffusion coefficient of drug in the matrix, W_0 is the initial drug concentration in the matrix, ε is the system porosity, and C_s is the solubility of the drug in the matrix.

For the Korsmeyer and Peppas (16) release model,

$$M_t/M_\infty = kxt^n \tag{5}$$

where M_t/M_∞ is the fractional release of drug, t is the release time, k is a kinetic constant, and n is the diffusional exponent for drug release that is dependent on the shape of the matrix dosage form (22).

In order to understand the effect of the content of polymers, mixtures of verapamil and different kinds of polymer at ratios of 1:5, 1:4, 1:3, 1:2, 1:1, 1.5:1, 2:1, and 3:1 (w/w) were inserted into six conventional #2 capsules. Their release kinetics in water were studied, and data obtained were fitted to the first-order release model, Hixson and Crowell powder dissolution model, and Higuchi release model. All the experimental data of the formulas releasing up to 80% were fit better to these three models. In most of the cases, the coefficients of determination were about 0.99. However, the higher the ratio of polymer to verapamil was, the more closely it followed the Higuchi releasing model. The slopes of release (%/hr) of different floating capsules on the Higuchi release kinetic model increase when a smaller amount of polymers was used (Fig. 2).

Peppas (23) stated that the drug-release model $M_t/M_\infty = kxt^n$, when $n = 0.5$, is a Fickian diffusion, and it is similar to the Higuchi model. An n value between 0.5 and 1.0 is defined as non-Fickian transport, and when n

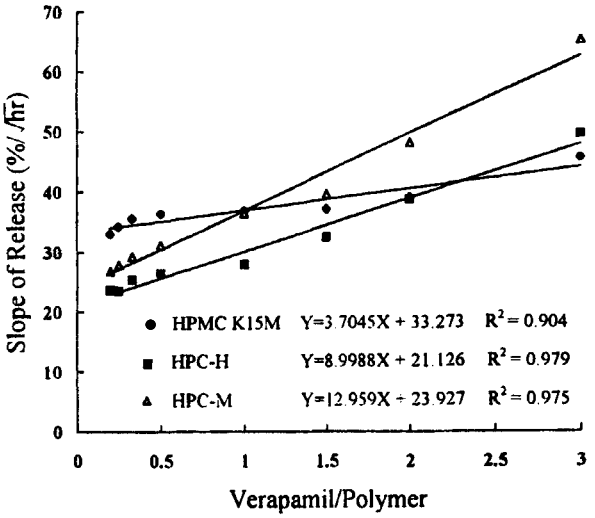

Figure 2. The slopes of Higuchi release kinetics of verapamil for various amounts of polymers used.

= 1.0, it is case II transport. Case II transport involves polymer dissolution and chain disentanglement (24). When $n > 1.0$, super case II transport is apparent. However, $n = 0.432$ and 0.85 for swellable spheres was reported for case I and case II mechanisms, respectively (22). For water-soluble drugs, the n value is about 0.7. However, for water-insoluble drugs, $n \sim 0.85$, which is near zero-order release (25).

In this study, it is interesting to observe that the release profile over 0.5 to 10 hr may be fitted to

$$M_t/M_\infty = a + kxt^n \quad (6)$$

with $R^2 > 0.98$ up to $M_t/M_\infty = 0.8$, where a is the intercept of the release. In this study, all of the different formulations of floating capsules on the Korsmeyer release kinetic model have a value in the range of $a = 1.45 \pm 0.11$ and $n = 0.50 \pm 0.07$. In most of the cases, the coefficients of determination were about 0.995. From the coefficients of determination, the Korsmeyer release kinetic model can be used to describe the release profile better than the Higuchi release kinetic model. However, the fraction of drugs released is proportional to the square root of release time in both of the release models.

In order to determine the effect of density, five different weights of verapamil:HPC-H (1:1, w/w) mixtures were inserted into conventional #2 hard capsules. The release profile shows that (Fig. 3) a less-dense floating capsule has a faster release rate. The data of drug-release fractions up to 80% were analyzed with the Higuchi release kinetic model, and they have coefficients of determination above 0.998.

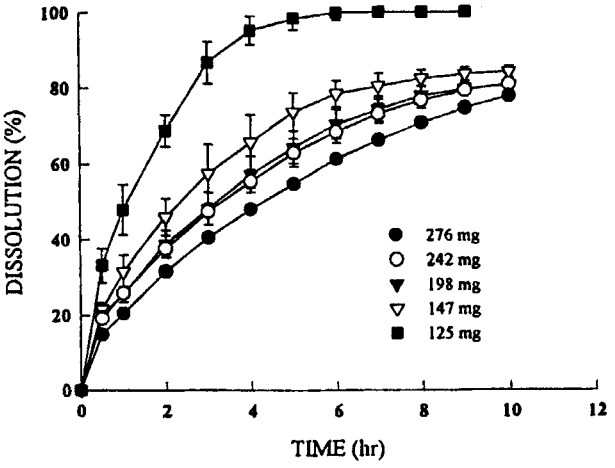

Figure 3. Release profiles for various amounts of verapamil/HPC-H filled in capsules.

The time interval for linear release in the Higuchi release kinetic model is shorter in a less-dense formula. By linear regression analysis between weight filled (147–276 mg/capsule) in the capsules and the release constant, a good linear relationship with the correlation coefficient of 0.976 was obtained. The intercept was 42.1, and the slope was 0.0575. The result indicates that the weight of the fill is a factor to be controlled.

In finding the optimal amount of effervescent reagent, 1% to 6% (w/w) was added to the formulation (verapamil: effervescent:HPC-H = $25:x:75 - x$, w/w). Each capsule was filled with 270 mg of powdered mixture. The 11-hr drug-release profiles are shown in Fig. 4 and Table 1.

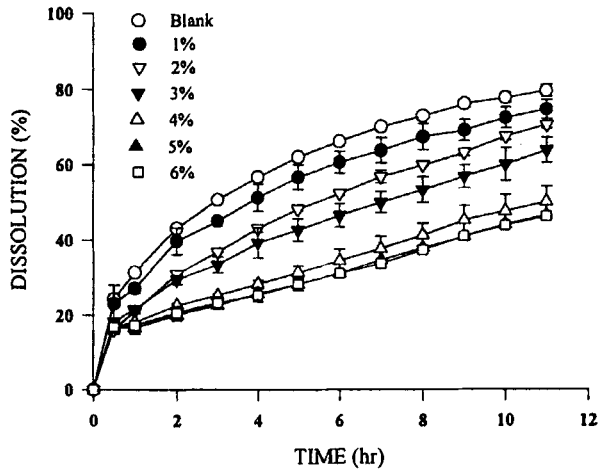

Figure 4. Release profiles for various amounts of effervescent in verapamil/HPC-H capsules.

Table 1

Dissolution Parameters of the Zero-Order Release Model and Korsmeyer Release Model for the Formulation[a] Containing Various Amounts of Effervescent

Effervescent (%)	Dissolution Interval (hr)[b]	Slope of Release (%/hr) or Diffusional Exponent (n)	Intercept of Release (%)	R^2
Zero-order release model (slope of release, %/hr)				
0	0.5–11	5.0045 ± 0.0734	31.563 ± 0.276	0.9589 ± 0.0243
1	0.5–11	4.7590 ± 0.0095	27.814 ± 2.949	0.9684 ± 0.0116
2	0.5–11	4.9955 ± 0.0315	19.465 ± 0.552	0.9847 ± 0.0054
3	0.5–11	4.1837 ± 0.2957	19.814 ± 0.968	0.9913 ± 0.0007
4	0.5–11	3.2088 ± 0.0103	15.501 ± 1.987	0.9992 ± 0.0004
5	0.5–11	2.9498 ± 0.0086	14.151 ± 0.377	0.9988 ± 0.0006
6	0.5–11	2.8658 ± 0.1685	14.565 ± 1.023	0.9983 ± 0.0012
Modified Korsmeyer model (diffusional exponent n; burst phase = 0.5 hr)				
0	0–11	0.6566 ± 0.0165	1.1204 ± 0.0869	0.9899 ± 0.0088
1	0–11	0.7888 ± 0.0043	0.9675 + 0.0021	0.9795 ± 0.0132
2	0–11	0.7640 ± 0.0033	0.9819 ± 0.0138	0.9952 ± 0.0007
3	0–11	0.8332 ± 0.0089	0.8283 ± 0.0096	0.9943 ± 0.0003
4	0–11	1.2574 ± 0.0102	0.2272 ± 0.0164	0.9910 ± 0.0008
5	0–11	1.1355 ± 0.0057	0.3244 ± 0.0043	0.9997 ± 0.0001
6	0–11	1.0606 ± 0.0080	0.4653 ± 0.0095	0.9948 ± 0.0011

[a]Each capsule was filled with 270 mg of powdered mixture (Verapamil: effervescent: HPC − H = 25:x:75 − x, w/w). A mixture of potassium-citrate monobase and potassium bicarbonate (1:1, w/w) was used as an effervescent.
[b]Time interval for linear release in Higuchi model; water was the dissolution medium; and n = 6.

From the release profiles, the burst phases were found. To fit the release data from Fig. 4, the zero-order model and the Korsmeyer model were adapted. Considering the burst effect, a modified Korsmeyer model (Eq. 7) was used.

$$\log(M_t/M_\infty - X_b) = \log k + n\log(t - t_b) \qquad (7)$$

where X_b and t_b are the fraction of release and release time at the burst phase, respectively. Using the modified Korsmeyer release model, the coefficients of determination are higher than 0.99 in most of the cases. The fitting result is shown in Table 1.

CONCLUSIONS

When polymer is mixed with verapamil and then filled into the capsule, the sustained-release effect is observed. The release constant increases when the weight of the fill decreases. In this study, an air-induced increase in the diffusional path was involved. The extent of drug release increased as the amount of air increased. A successful attempt was made to translate this observation into a zero-order drug-release system that can be easily formulated. The results presented in this study agree with the Korsmeyer drug-release model. Air entrapped inside of the capsules is considered the barrier of diffusion and matrix relaxation in the drug-release model.

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