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COMMUNICATION

Factors Affecting Zero-Order Release Kinetics of Porous Gelatin Capsules

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ABSTRACT

Porous gelatin capsules were prepared by entrapping gas bubbles or by drilling in the capsule wall with syringe needles. After hardening by formaldehyde, the capsules were supposed to provide a floating sustained release over 10 hr. Different pore sizes, pore numbers, pore orientational symmetry on the capsule wall, the amount of the effervescent material added to prepare the capsule, the exposure time to formaldehyde, and excipient selected were studied to evaluate their influences on the dissolution kinetics. The gelatin capsules were prepared by adding various amounts of effervescent material or by drilling in the capsule wall with a syringe and then hardening by formaldehyde. Verapamil was used as the model drug and starch or lactose was the only excipient. Verapamil and excipient were mixed and used to fill the prepared capsule. The release of verapamil from the capsules follows the zero-order drug release and was observed after the burst phase. The porous capsule, when filled with the mixture of active ingredients and excipient, can achieve a zero-order release system.

INTRODUCTION

The conventional hard-gelatin capsule exhibits a crosslinking reaction of the gelatin molecule when exposed to formaldehyde vapors, resulting in an indisintegratable capsule. The relevance of using porous capsules or drilling pores on capsules is increasingly gaining prominence in recent years. The use of a carbon dioxide laser to drill the exit pores in an osmotic pump (1) and capsule (2) has been reported. Drilling the crosslinked gelatin capsule with a different number of pores or different a pore area to design a controlled-release dosage form is also achievable.

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In this study, gas bubbles were entrapped in the wall of capsules to prepare the porous capsule, or different sizes of syringe needles were used to drill pores on capsules in order to obtain zero-order release kinetics. The dissolution profiles of these capsules with different (*a*) pore sizes, (*b*) pore numbers, (*c*) pore orientational symmetry, and (*d*) amounts of the effervescent materials were studied using verapamil as the model drug.

MATERIALS AND METHODS

Materials

Verapamil was purchased from Recordati (Milan, Italy). Acetonitrile, methanol, ammonium acetate, triethylamine, acetic acid, potassium citrate mono-base, and potassium bicarbonate were obtained from Merck (Darmstadt, Germany). Gelatin 250 B was supplied by Toshoku America Co. (NY)

Preparation Method of Porous Capsule

Two types of capsules were used in this study. Type A capsule was prepared by entrapping CO_2 gas in the capsule wall to make the pores. This was executed by dissolving gelatin in water at 80–85°C and adding a 0.55–2.17% effervescent material, a mixture of potassium citrate mono-base and potassium bicarbonate (1:1, w/w), at 60°C. The solution was cooled to 55°C, and the mold pin (coated with sunflower oil) was dipped into the gelatin solution and then reverted. After 20 min, a bladder was used to cut off the extra gel, and then the solution was allowed to stand for 5 hr at ambient temperature before the mold was removed. Three batches of type A capsule were produced in order to determine the consistency of the quality of the capsules. The commercial #2 hard gelatin capsules were used in type B capsule. Pores of the capsule were drilled with syringe needles. The outside diameters of syringes were 0.634, 0.9, 1.02, and 1.63 mm. Needles were heated on a Bunsen burner first and then the pores were immediately drilled. The pores' orientations on capsules were drilled into symmetric and asymmetric positions.

Preparation of Gastrointestinal (GI)-Tract-Resistant Capsules

The capsules of type A and B, after preparation, were exposed to formaldehyde vapors for 2–8 hr and then stored in a 50°C oven for 30 min in order to remove the formaldehyde. The effects of exposure time to formaldehyde on type A capsules were studied. The content of formaldehyde in the wall of type A capsule was determined with a derivatized HPLC method by reacting the formaldehyde with phenelzine. The whole capsule was covered in 2 ml of 0.005 M phenelzine in methanol, left to stand for 3 hr, and then injected into a C18 column. To study the effect of pH of the dissolution medium, water and 0.1 N HCl were used and the tests were carried out according to USP XXIII dissolution test method II at a paddle speed of 50 rpm.

Formulation of the Controlled-Release Capsules

Lactose or starch was used as a diluent which was then mixed with verapamil in a proportion of 4:1. An amount of 177 ± 3 mg of the mixtures was inserted into the type B porous capsules. However, for type A porous capsules, 177 ± 3 mg of the mixture of verapamil and starch were used in a ratio of 1:1.

The Residual Effect of Formaldehyde on Verapamil

Each of three type B capsules, unexposed and exposed to formaldehyde, were used as the control and test group, respectively. They were filled with 177 ± 3 mg of the mixture of verapamil:starch (1:4). The test group, after exposure to formaldehyde for 8 hr and standing for more than 7 days, were analyzed with HPLC. The peak areas of verapamil in the control and test capsules were analyzed with Student's *t*-test.

HPLC Conditions

An LC-6A HPLC apparatus (Shimadzu, Tokyo, Japan) equipped with a loop (volume 20 μl), a Nuclosil 5 μm C-18 (4.6 × 300 mm) column, and an SPD-6AV UV spectrometric detector was used. For formaldehyde determination, a solution of 50% (v/v) methanol in water was used as the mobile phase. The operating conditions were flow rate 1.0 ml/min, UV detection at 238 nm, and an attenuation of 0.02 aufs. A C-18 column using acetonitrile:triethylamine 7.3 mM pH 3.5 (40:60, v/v) as mobile phase could be employed in the measurement of verapamil. The operating conditions were, flow rate 1.0 ml/min, UV detection at 278 nm, and an attenuation of 0.02 aufs.

Measurement of Capsule Dissolution Rate

The porous capsules of verapamil with different numbers of pores (o.d. 0.9 mm), pore symmetry in position, and different pore sizes (0.634, 0.9, 1.02, and 1.63

mm) were used to measure the dissolution profile. The dissolution studies were carried out according to the USP XXIII dissolution test method II at a paddle speed of 50 rpm in water 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 sample was withdrawn at each hour for 10 hr. The samples were filtered and then analyzed at 278 nm using a spectrophotometer and the drug dissolution profiles were subsequently plotted.

RESULTS AND DISCUSSION

In this study, pores in the wall of type B capsules were drilled using various sizes of syringe needles (Fig. 1), then filled with a mixture of 1:4 (w/w) verapamil and lactose or starch.

The formulation, with starch as diluent, filled in the four-pore (0.9 mm) type B capsules, showed a zero-order release profile as shown in Fig. 2. The formulation with starch as diluent shows a faster dissolution profile because of higher solubility of lactose in water (>20% w/w).

The microscopic observation of the inside of the capsule wall after dissolution test revealed that in the pores of the capsules, clusters of starch granules were found. This may be because the solubility of starch in water is less than 0.1% (w/w) and the starch granule (2–32 μm) may swell and block the pores in the capsules (3). The release model may therefore become a membrane-controlled mechanism causing a zero-order release. In the later studies, corn starch was used as the diluent. The densities of the capsule dosage forms were between 0.762 and 0.789 mg/ml. They had a lower density than gastric fluids and buoyed on stomach contents as floating dosage forms.

To analyze the release mechanism of verapamil from these capsules, the data obtained were fitted into the equation of Korsmeyer (4,5):

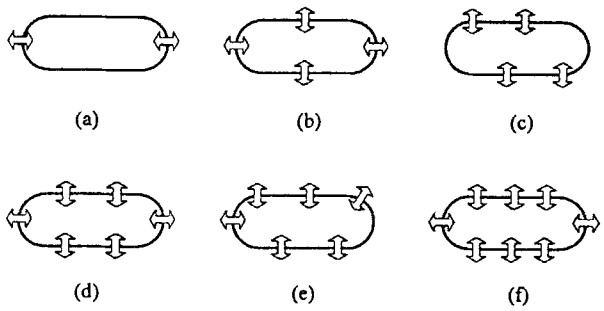

Figure 1. Different number of pores and symmetry in drilled type B capsule (c, e, asymmetric pores).

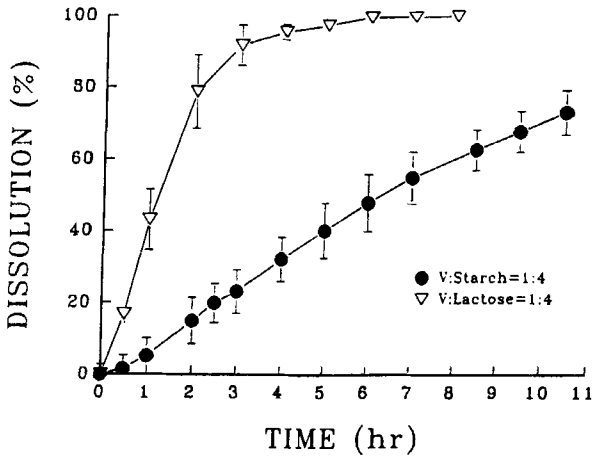

Figure 2. Release of verapamil in diluents lactose or starch as a function of time from type B capsules in which 4 pores (0.9 mm) were drilled symmetrically (water as dissolution medium, $n = 6$).

$$M_t/M_\infty = k \times t^n \quad (1)$$

where M_t/M_∞ is the fractional release of drug, t is the release time, k is the release constant, and n is the diffusional exponent for drug release. It is dependent on the shape of the matrix dosage form. According to Ritger (6), $n = 0.5$ for a Fickian diffusion, $0.5 < n > 1.0$ for non-Fickian transport, and $n = 1.0$ for case II transport. When $n > 1.0$, super case II transport is apparent. Case II transport involves polymer dissolution and chain disentanglement (7).

In this study, it is interesting to note that the release profile between 0.5 and 10 hr can be fitted into

$$M_t/M_\infty = a + k \times t^n \quad (2)$$

with $R^2 > 0.98$ up to $M_t/M_\infty = 0.8$, where a is the intercept of the release.

To harden type A capsules, they were exposed to formaldehyde vapors for 2,4, and 7 hr. The content of formaldehyde in each capsule was determined with HPLC and was less than 1.0 μg. This was also less than a case reported (8) for a formaldehyde-allergic woman after Hepatitis B vaccine injection that contained 20 μg of formaldehyde. The 10-hr drug release data shown in Table 1 reveal that a 2-hr exposure to formaldehyde could cause a >90% drug release. The exposure time to formaldehyde for capsule hardening was therefore set at 2 hr in these studies.

To find the optimal amount of effervescent material to add to gelatin, 0.55, 1.01, and 2.17% (w/w) of an equal amount of mixture of potassium citrate mono-base

Table 1

The Effects of Dissolution Medium and Exposure Time of Capsule to Formaldehyde on Dissolution

Exposure Time (hr)	Dissolution Time (hr)	Slope of Release (%/hr)	Intercept of Release	R^2	Release Exponent, n
Water as dissolution medium					
2	0.5–7	10.6	0.898	0.992	0.982
4	0.5–10	6.91	-5.88	0.992	0.934
7	0.5–10	2.64	-1.19	0.970	1.01
0.1 N HCl solution as dissolution medium					
2	0.5–7	13.1	1.63	0.994	0.984
4	0.5–10	8.41	-7.04	0.970	1.02

and potassium bicarbonate were used. A 10-hr drug release profile in Fig. 3 shows that 2.17% of effervescent material added has the potential to release verapamil to >90% in 12 hr. In this study, 2.17% of effervescent material was used.

The effects of pH of dissolution medium on water and 0.1 N HCl are shown in Table 1. Verapamil, a weak base, showed a higher dissolution rate in the acidic medium.

Three batches of type A capsule were produced according to the method mentioned above, in order to examine the quality consistency of the capsules. The verapamil release profiles of these three batches in water are shown in Fig. 4. The release kinetics shows similar release behavior within three batches.

The HPLC analytical method has been validated as a stability-indicating method (9). The control and test capsules of type B which contained verapamil were dissolved in 200 ml of water. The mean concentration of three verapamil capsules in the control and test were 0.178 (CV = 2.07%) and 0.175 (CV = 1.13%) mg/ml, respectively. They showed no significant difference in verapamil concentration by t-test ($\alpha = 0.05$). The residues of formaldehyde in the capsules did not affect the concentration of verapamil.

When 2–8 pores (o.d. 0.9 mm) were symmetrically drilled in the wall of a type B capsule, the dissolution profiles shown in Table 2 with n values in the range of 0.814–1.27 represent approximately a zero-order release kinetics. The higher the number of pores, the higher the kinetic constant and the intercept. Intercept represents a burst effect of these capsules.

The higher the number of pores in the capsule walls, the lower the n value, and diffusion-controlled kinetics

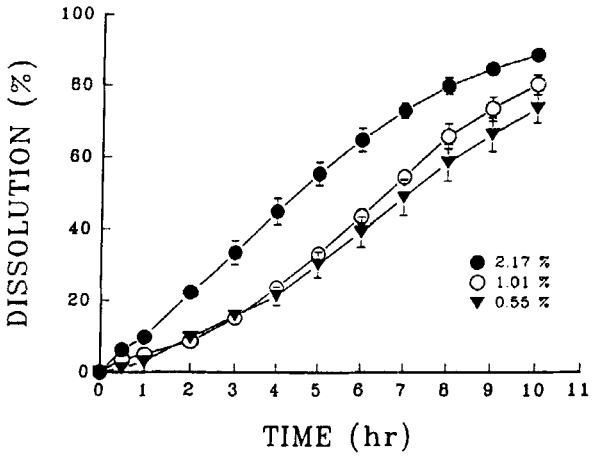

Figure 3. Release of verapamil in starch as a function of time from type A capsules with the addition of different amounts of effervescent material and exposure to formaldehyde for 2 hr (water as dissolution medium, $n = 6$).

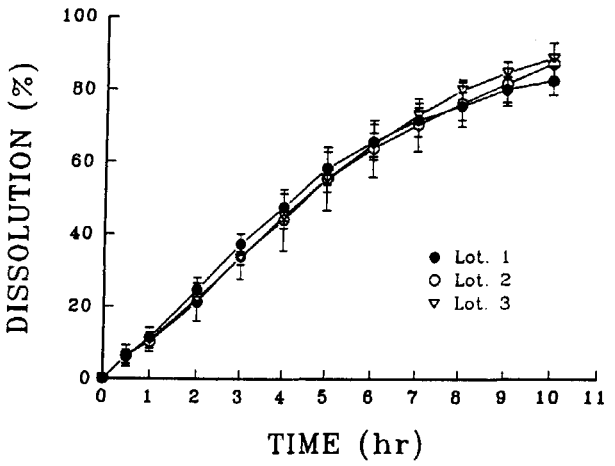

Figure 4. Release of verapamil in starch as a function of time from type A capsules of different lots (water as dissolution medium, $n = 6$).

Table 2

The Effect of Pores in Type B Capsule Walls on Dissolution

No. of Pores[a]	Area (mm^2)	Dissolution Time (hr)	Slope of Release (%/hr)	Intercept of Release	R^2	Release Exponent, n
2	1.27	0.5–10	6.05	-3.82	0.999	1.27
4	2.54	0.5–10	7.30	0.365	0.988	1.16
6	3.82	0.5–10	8.41	2.67	0.989	0.980
8	5.09	0.5–7	11.4	7.99	0.982	0.977
4[b]	2.54	0.5–10	7.23	3.15	0.984	1.04
6[b]	3.82	0.5–10	7.59	5.36	0.990	0.814

[a]Pore size, 0.9 mm.
[b]Asymmetric pores.

became important in these cases. However, it was found that symmetry of pores was not a factor affecting drug release (Table 2).

When capsules were drilled with different pore sizes (0.634, 0.900, 1.02, and 1.63 mm), the release data in Fig. 5 show that the bigger the pore size, the higher the released fraction. The pore sizes larger than 0.9 mm show n values significantly greater than 1 and a Fickian diffusion is characterized in this situation.

The logarithm of drug release constant (k) from Table 2 had higher relations with area of pores (Fig. 6). They were found from the mathematics model as

$$\log k = 0.7013 + 0.06757X \quad (3)$$

where the k is release constant and X is the total area (in square millimeters) of pores and could describe the release profile with a correlation coefficient of 0.9948.

The release behaviors of this study were evaluated by the Korsmeyer exponential release equation. The drug release from both types A and B porous capsules, with a range of M_t/M_∞ = 0.02–0.8, were found to be generally linear. After a lag time of about 0.5 hr, the drug release shifted toward a constant release rate which was probably because of the change in the relative importance of the matrix relaxation and drug diffusion rates (10). Carbon dioxide entrapping inside of the capsule wall is considered to be a diffusional barrier. The porous and crosslinked capsules, when filled with a simple formulation such as a drug mixed with starch, may exhibit a zero-order release.

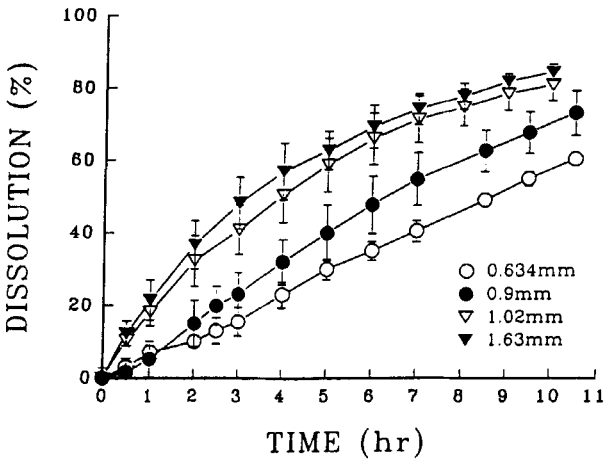

Figure 5. Release of verapamil in starch as a function of time from type B capsules which were drilled with various diameters of four symmetrical pores and exposed to formaldehyde for 2 hr (water as dissolution medium, n = 6).

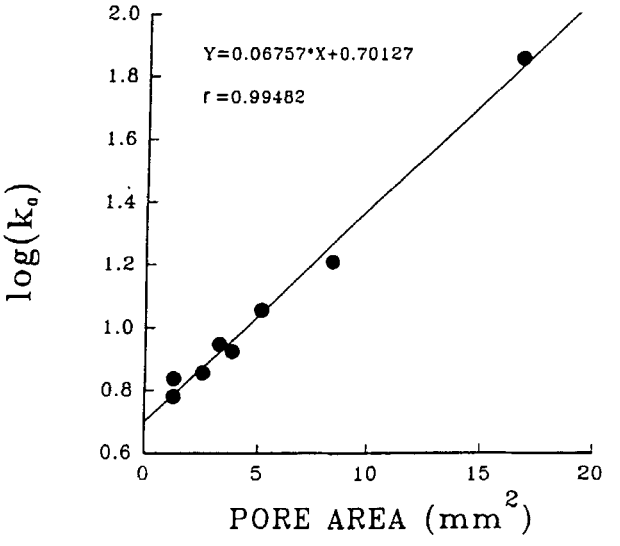

Figure 6. Fitting of release behavior for release slopes of verapamil from type B capsules to the total area of pores.

CONCLUSIONS

Several factors may have been responsible for the sustained release of verapamil from porous and crosslinked gelatin capsules. The starch in the formulation which precipitates on pores of the capsule wall may cause the system to work as a membrane. A zero-order release was hence observed. The total area of the pores on the capsule, the time of exposure to formaldehyde, and the amount of effervescent materials that were added in preparing the capsules are the other factors.

A zero-order drug release system was achieved by simply inserting the mixture of drug and starch into the porous and crosslinked capsules, which can easily be manufactured.

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