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RESEARCH PAPER

Investigation of the Effect of Tablet Surface Area/Volume on Drug Release from Hydroxypropylmethylcellulose Controlled-Release Matrix Tablets

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ABSTRACT

The purpose of this study was to investigate the influence of tablet surface area/volume (SA/Vol) on drug release from controlled-release matrix tablets containing hydroxypropylmethylcellulose (HPMC). Soluble drugs (promethazine HCl, diphenhydramine HCl, and propranolol HCl) were utilized in this study to give predominantly diffusion-controlled release. Drug release from HPMC matrix tablets with similar values of SA/Vol was comparable within the same tablet shape (i.e., flat-faced round tablets) and among different shapes (i.e., oval, round concave, flat-faced beveled-edge, and flat-faced round tablets). Tablets having the same surface area but different SA/Vol values did not result in similar drug release; tablets with larger SA/Vol values had faster release profiles. Utility of SA/Vol to affect drug release was demonstrated by changing drug doses, and altering tablet shape to adjust SA/Vol. When SA/Vol was held constant, similar release profiles were obtained with f_2 metric values greater than 70. Thus, surface area/volume is one of the key variables in controlling drug release from HPMC matrix tablets. Proper use of this variable has practical application by formulators who may need to duplicate drug release profiles from tablets of different sizes and different shapes.

Key Words: *Controlled release; Hydrophilic matrix tablets; Hydroxypropylmethylcellulose; Surface area/volume ratio*

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INTRODUCTION

Hydrophilic polymers, such as hydroxypropylmethylcellulose (HPMC), are commonly used as rate-controlling polymers for controlled drug release from matrix-type dosage forms. Controlled drug release from HPMC matrix tablets may be affected by several formulation variables, such as polymer level (1–5) and molecular weight (3,4,6), drug level and solubility (3,5,7), type of excipient (5), and tablet shape and size (5,8–12). Upon exposure to aqueous media, the hydrophilic matrix swells as water diffuses into the tablet. Individual HPMC polymer particles begin to hydrate, swell, coalesce, and form a viscous phase around the exterior of the tablet. This viscous layer acts as a barrier to both the influx of water and the efflux of drug. At the HPMC matrix surface, polymer chains disentangle and further dilution of the polymer concentration in the hydrated matrix occurs.

For hydrophilic matrix tablets comprised of water-soluble, swellable polymers such as HPMC, the release kinetics are described as a coupling of drug diffusion and polymer dissolution, i.e., surface erosion. Drug release is dependent on the relative contribution of diffusion and erosion release mechanisms (8,13–15). In the case of a highly water-soluble drug, diffusional drug release may contribute significantly to overall drug release from the matrix. For relatively water-insoluble drugs and/or low viscosity grades of HPMC as rate-controlling polymer, drug release due to surface erosion may contribute significantly to overall drug release. One of the most common means of determining the dominance of diffusion is to utilize the square-root-of-time relationship established by Higuchi (16) for diffusional drug release from non-swelling, non-erodible polymeric slabs. This equation was adapted by Lapidus and Lordi (17) for swellable HPMC matrices, as shown in Eq. (1):

$$\frac{M_t}{M_0} = 2\left(\frac{\mathrm{SA}}{\mathrm{Vol}}\right)\left(\frac{D_{\mathrm{eff}}t}{\pi}\right)^{\frac{1}{2}} \tag{1}$$

where M_t is the amount of drug released at time t, M_0 is the drug dose in the original dry tablet, SA is the matrix surface area, Vol is the matrix volume, and D_{eff} is the effective drug diffusion coefficient in the matrix. To determine the applicability of the square-root-of-time relationship for analyzing release mechanisms, and therefore the diffusion release mechanism, percentage dissolved drug is plotted vs. time$^{1/2}$. For the regions that are a linear function of the square root of time, it is reasoned that diffusion dominates the overall release mechanism.

The effect of matrix geometry on drug release for controlled-release dosage forms has been reported by several researchers (11,18–21). Specifically for HPMC matrix tablets, the effect of matrix geometry on drug release has also been studied in detail (20,21). Siepmann et al. (20) developed a mathematical model for diffusional drug release from HPMC matrices. In another study, Siepmann et al. (21) examined the effect of the aspect ratio (radius/height) and the size of cylindrical matrices on drug release for diffusion-controlled systems. They stated that since small cylindrical tablets have a higher relative surface area, i.e., absolute surface area/absolute volume, the release from small tablets is faster than from large cylindrical tablets. Skoug et al. (8) also reported that two halves of a sustained release tablet had an increase in the surface area to volume ratio (SA/Vol) of about 16% relative to whole tablets. As a result, drug release from the two halves was faster than from the whole tablets. The increase in SA/Vol produced a proportionate increase in the slope of the Higuchi plots (% release vs. time$^{1/2}$).

Previous studies have examined the influence of tablet shape and size on drug release from HPMC matrix tablets; however, this research was conducted on tablets of similar tablet shape, i.e., cylindrical. The impact of varying tablet shape on the surface area to volume effect has not been addressed. Certainly the aspect ratio (radius/height) is a relevant term when comparing the relative shape of cylinders, but it is seemingly not as valuable a term as the SA/Vol may be when comparing relative drug release from tablets of varying shapes. Finally, even though the effect of SA/Vol has been discussed previously in the literature, the practical application has not yet been tested. This study examines the effect of SA/Vol on drug release from HPMC matrix tablets and applies it to a realistic situation. Occasionally, it is necessary to change the dose, size, or shape of an existing product while maintaining the same release profile. There are several ways to attempt this, but determination of the critical variable may often be a challenge. The purpose of this study was to investigate the influence of initial tablet SA/Vol on drug release from controlled-release matrix tablets containing HPMC.

MATERIALS AND METHODS

Materials

The following materials were used as received: HPMC USP Type 2208 (methoxyl content: 19–24%; hydroxypropyl content: 7–12%) with nominal viscosity of 4000 mPa sec for a 2% (w/v) aqueous solution (Methocel® K4M Premium CR, The Dow Chemical Company, Midland, MI), spray-dried lactose monohydrate (Fast-Flo® Lactose 316, Foremost Whey Products, Baraboo, WI), and dicalcium phosphate dihydrate (DI-TAB®, Rhodia, Inc., Cranbury, NJ). Magnesium stearate, NF (Mallinckrodt, St. Louis, MO) was used as a lubricant. The active ingredients used were promethazine HCl USP (Spectrum, Gardena, CA), propranolol HCl USP (Wyckoff Chemical Co., South Haven, MI), and diphenhydramine HCl USP (Wyckoff Chemical Co., South Haven, MI).

Methods

Tablet Formulations

Controlled-release formulations for the three different actives were developed. Each active was passed through a 20 mesh sieve to break agglomerates.

The promethazine HCl controlled-release formulation contained 2% w/w of promethazine HCl, 20% w/w of Methocel K4M Premium CR, 77.5% w/w of DI-TAB, and 0.5% w/w of magnesium stearate.

The two controlled-release formulations for propranolol HCl contained two levels of propranolol HCl at 10 and 20% w/w and two levels of DI-TAB at 49.5 and 39.5% w/w, respectively, and 40% w/w of Methocel K4M Premium CR and 0.5% w/w of magnesium stearate in both formulations.

The two controlled-release formulations for diphenhydramine HCl contained two levels of diphenhydramine HCl at 15 and 30% w/w and two levels of Fast-Flo 316 lactose at 44.5 and 34.5% w/w, respectively, and 40% w/w of Methocel K4M Premium CR and 0.5% w/w of magnesium stearate in both formulations.

Tablet Preparation

The formulation mixtures were compressed on a 16-station instrumented rotary tablet press (Manesty Beta press) at a speed of 100 tablets/min, with only four stations equipped. The direct compression of tablets was accomplished with the following tooling at a relatively constant compression pressure [a compression force of 17.8 kN (4000 lbf) for the 12.7 mm flat-faced round (FFR) tablet was used as the standard on which the others were based]. The tablet tooling used was as follows: 6.35, 12.7, 15.9, and 18.7 mm FFR, 10.3 mm flat-faced beveled-edge (FFBE), 12.7 mm round concave, and an oval-shaped tablet with dimensions of 6.9 mm × 12.4 mm. Tablet weights varied from 345 to 1850 mg, depending on the desired tablet SA/Vol or tablet surface area.

Tablet physical properties were conducted on 20 tablets for tablet hardness (crushing strength) and thickness. The equipment used to measure tablet hardness was a Key Model HT300 hardness tester (Key International, Englishtown, NJ). Tablet thickness was measured using an Absolute Digimatic Caliper Series No. 500 micrometer (Mitutoyo Corp., Japan).

In Vitro Dissolution Drug Release

The USP dissolution apparatus (Distek, Inc., North Brunswick, NJ) Type II (paddles) at rotation speed of 50 rpm was used for in vitro dissolution drug release testing. The dissolution medium consisted of 900 mL of deionized water at 37.0±0.5°C. Samples for the actives were automatically withdrawn, filtered in-line, and assayed on an ultraviolet (UV) spectrophotometer ($\lambda_{max} = 249$ nm for promethazine HCl; $\lambda_{max} = 289$ nm for propranolol HCl; $\lambda_{max} = 229$ nm for diphenhydramine HCl). Six tablets were studied for each formulation.

Surface Area and Volume Calculations

The tablet surface area (SA) and tablet volume (Vol) were determined for each tablet by measuring tablet band thickness. The measured tablet thickness was used in tooling-specific equations to calculate tablet surface area and volume. As an example, the following two equations, Eqs. (2) and (3), were used to calculate tablet surface area and tablet volume, respectively, for flat-faced round tablets:

$$SA = 2\pi r(r + t) \tag{2}$$

$$\frac{SA}{Vol} = \frac{2(r + t)}{rt} \tag{3}$$

where r is the radius of the 12.7 mm flat-faced round tablet and t is the band thickness (i.e., edge

thickness). It is necessary to obtain tooling-specific SA and Vol equations for each size and shape tooling used. For more complex tooling shapes, similar type equations may be provided by the manufacturers of the particular tooling.

RESULTS AND DISCUSSION

Effect of Increasing SA/Vol on Release

Matrix tablets containing HPMC with the same tablet diameter (12.7 mm FFR) and increasing tablet weight resulted in tablets with decreasing SA/Vol. Tablet dimensions for HPMC matrices with promethazine HCl are shown in Table 1. As seen in Fig. 1, the release rate of promethazine HCl increased with increasing SA/Vol values. As shown in Eq. (1), the rate of drug release is expected to be directly proportional to SA/Vol. This result is consistent with previous research performed with cylindrical tablets (20), where smaller cylindrical tablets produced faster release.

Table 1

Tablet Dimensions for 12.7 mm FFR HPMC Matrix Tablets (2% Promethazine HCl) with Increasing SA/Vol Values

Tablet Weight (mg)	Tablet Thickness (mm)	SA (mm^2)	SA/Vol (mm^2/mm^3)	Tablet Hardness (scu)
345	1.72	321.9	1.480	—[a]
675	3.32	385.8	0.917	10.2
950	4.68	440.0	0.744	15.0
1250	5.94	490.3	0.650	21.0

[a]Tablets too thin to measure accurately.

Effect of Constant Surface Area on Release

Two different sets of FFR tablets (diameters of 15.9 and 18.7 mm) of relatively constant surface area were tested to examine the effect of surface area on release. Tablet dimensions for HPMC matrices with promethazine HCl are given in Table 2. The promethazine HCl release profiles in Fig. 2 show that the surface area to volume ratio has a greater impact on release from hydrophilic matrices than the tablet surface area. Even though the surface area was held constant for these two sets of tablets, the actual order of relative release followed the order of tablet SA/Vol values.

Verifying Diffusion-Controlled Release

As discussed previously, SA/Vol was a critical variable identified in the square-root-of-time equation [Eq. (1)]. In order to utilize this parameter, diffusion-controlled release was confirmed by verifying regions of linearity for plots of percentage drug

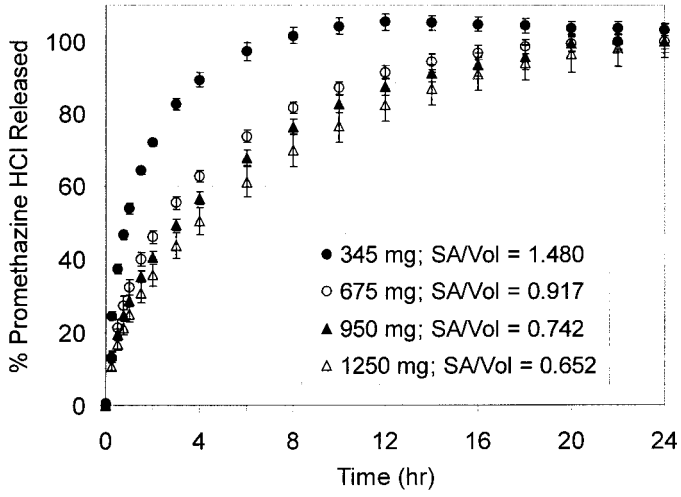

Figure 1. Percentage promethazine HCl released vs. time demonstrating the effect of increasing SA/Vol for FFR tablets, 12.7 mm diameter (mean±SD, $n = 6$).

Table 2

Tablet Dimensions for FFR HPMC Matrix Tablets (2% Promethazine HCl) with Constant Tablet Surface Area Values but Different Tablet Diameters, 15.9 and 18.7 mm

Tablet Diameter (mm)	Tablet Weight (mg)	Tablet Thickness (mm)	SA (mm^2)	SA/Vol (mm^2/mm^3)	Tablet Hardness (scu)
15.9	1850	5.74	681.9	0.601	25.1
18.7	1050	2.42	688.0	1.042	10.3

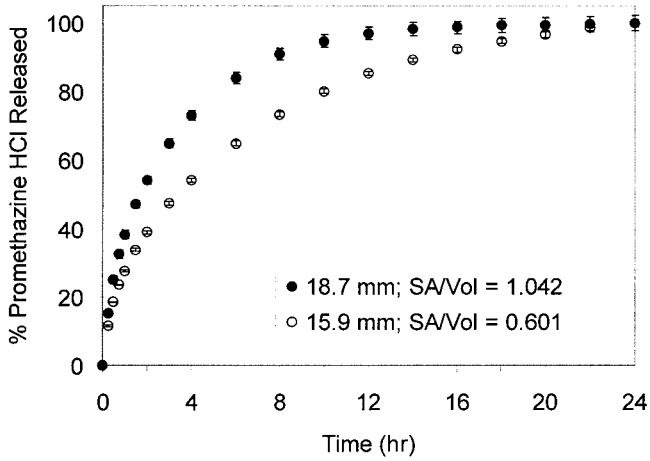

Figure 2. Percentage promethazine HCl released vs. time showing the effect of constant SA for FFR tablets with different dimensions, 15.9 and 18.7 mm diameter (mean±SD, $n = 6$).

release vs. square root of time. When a straight line exists for a period of time, it is believed that diffusion is the predominant release mechanism for that specific time interval, with the slope of the line representing the drug release rate. Since release kinetics from HPMC tablets are significantly affected by matrix swelling from polymer chain relaxation, diffusional drug release may only occur for a brief period of time in the early stages of release before significant matrix swelling.

Using the data in Figs. 1 and 2 for promethazine HCl release and calculating the slope of the linear regions for percentage drug release vs. square root of time, the relationship between drug release rate and SA/Vol is depicted in Fig. 3. This plot indicates that for a given HPMC controlled-release formulation, the relative diffusional drug release rates are directly proportional to the initial SA/Vol of matrix tablets, as predicted by Eq. (1).

Effect of Constant SA/Vol on Release

In the case of tablets having the same shape, i.e., all FFR, but increasing tablet diameter, the surface area to volume ratio was held constant by adjusting the tablet thickness through changing the tablet weight (Table 3). The release profiles vs. time for the promethazine HCl tablets are shown in Fig. 4. Drug release rates for the four groups of tablets are given in Table 4. The diffusional release rates were relatively constant for the different groups of tablets with the same SA/Vol. As a result of maintaining SA/Vol for the tablets relatively constant, the release profiles for the various tablets were very similar, and f_2 metric values were all greater than 78 (22). In addition, a constant SA/Vol for different tablet shapes (see Table 5 for tablet dimensions and geometries) resulted in similar release profiles, as shown in Fig. 5. The practical applicability of

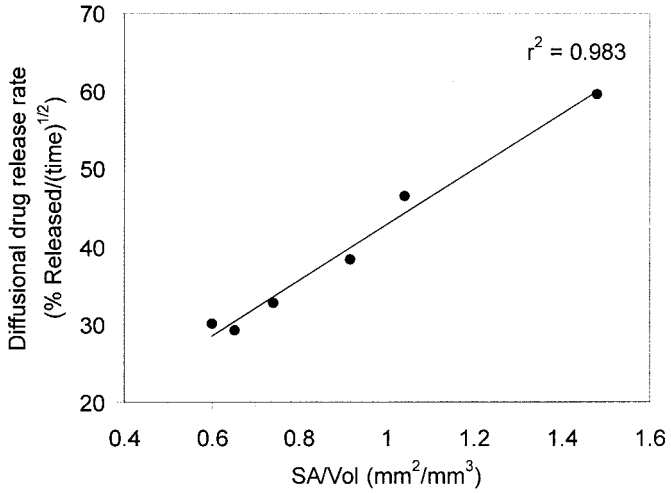

Figure 3. Diffusional drug release rate (% released/time$^{1/2}$) vs. SA/Vol (mm^2/mm^3) for promethazine HCl release from HPMC tablets.

Table 3

Tablet Dimensions for FFR HPMC Matrix Tablets (2% Promethazine HCl) with Constant SA/Vol Values but Different Tablet Diameters, 6.35, 12.7, 15.9, and 18.7 mm

Tablet Diameter (mm)	Tablet Weight (mg)	SA (mm^2)	SA/Vol (mm^2/mm^3)	Tablet Hardness (scu)	f_2 Values
6.35	345	199.1	0.924	11.5	81
12.7	675	388.5	0.906	8.4	91
15.9	950	548.7	0.905	10.1	Ref.
18.7	1245	716.3	0.904	10.6	78

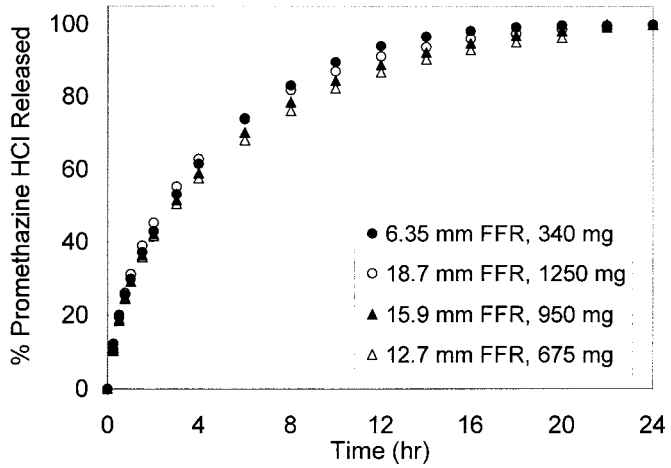

Figure 4. Percentage promethazine HCl released vs. time demonstrating the effect of constant SA/Vol for FFR tablets with different tablet diameters, 6.35, 12.7, 15.9, and 18.7 mm (error bars not shown because they are comparable in size to the symbols).

Table 4

Diffusional Drug Release Rates for Promethazine HCl from HPMC Matrix Tablets with Constant SA/Vol Values for FFR Tablets with Different Tablet Diameters

Tablet Diameter (mm)	Time Period (hr)	Diffusional Drug Release Rate (%/hr$^{0.5}$)[a]	r^2
6.35	0.08–1.5	35.5	0.998
12.7	0.08–1.0	36.5	0.999
15.9	0.08–1.5	40.0	0.999
18.7	0.08–1.5	36.5	0.999

[a]Modeling fractional release for cylindrical systems that display fickian-type diffusion is dependent on the aspect ratio of the tablet. In an earlier publication (15), drug release from tablets with an aspect ratio of 3–4 was modeled using a diffusional exponent of $n = 0.45$. Drug release was modeled using two diffusional components, $n = 0.45$ and 0.5. Both resulted in similar regions of linearity; therefore, to be consistent with the standard square-root-of-time model given in Eq. (1), $n = 0.5$ was used.

Table 5

Tablet Dimensions for Different Tablet Shapes of HPMC Matrix Tablets (2% Promethazine HCl) with Constant SA/Vol Values

Tablet Shape	Tablet Weight (mg)	SA (mm^2)	SA/Vol (mm^2/mm^3)	Tablet Hardness (scu)	f_2 Values
Oval	510	257.0	0.804	11.5	Ref.
10.3 mm FFBE	590	299.8	0.783	9.7	81
12.7 mm Round concave	730	366.2	0.776	8.8	91
12.7 mm FFR	870	424.1	0.782	10.0	77

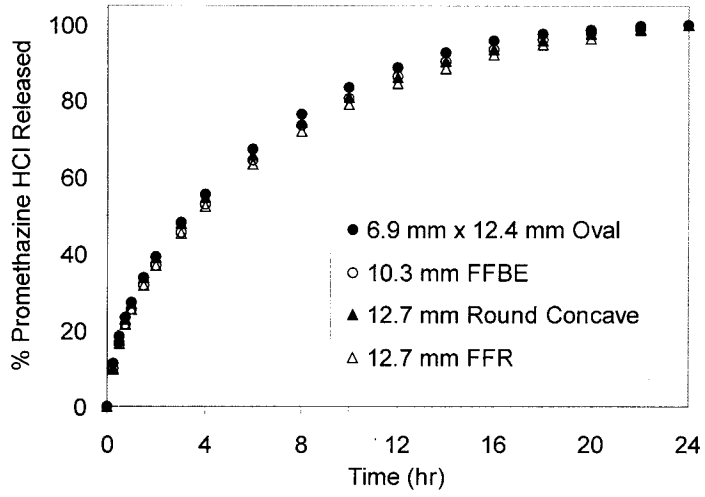

Figure 5. Percentage promethazine HCl released vs. time demonstrating the effect of constant SA/Vol for tablets with different shapes (error bars not shown because they are comparable in size to the symbols).

SA/Vol as a formulation variable is apparent, especially since the utility of this variable appears to hold for tablets of different shapes and dimensions.

Utility of SA/Vol to Affect Drug Release

The opportunity for using SA/Vol is seen in the situation of increasing the dose level for a controlled-release (CR) application and still obtaining similar drug release profiles. The two obvious ways of increasing the dose level are by either changing the formulation and increasing the drug percentage in the formulation, or increasing the tablet weight for the same formulation, thereby also increasing the total drug dose.

The following results are shown in Table 6: O-10 is an oval tablet with 10% propranolol HCl and SA/Vol value of 1.28 mm^2/mm^3; O-20 is a different formulation with 20% propranolol HCl and a similar SA/Vol value; O-10-2× is the same formulation as the control (O-10), but with double the weight and a decreased value of SA/Vol of 0.86 mm^2/mm^3. Finally, the surface area to volume ratio for formulation R-10 (12.7 mm diameter flat-faced round tablet with the same formulation as O-10) is also similar to the control. The release profiles are shown in Fig. 6. It is believed O-10-2× has the slowest release due to having the smallest SA/Vol value. The f_2 metric value for the test sample O-10-2× is less than 50 relative to O-10. All other f_2 metric values are greater than 70.

A similar exercise was performed for a controlled-release formulation for the active diphenhydramine HCl. The data for these tablets are given in Table 7 and the corresponding release profiles are depicted in Fig. 7. The diphenhydramine HCl release profiles for O-15 (control formulation), O-30 (different formulation with double the active

Table 6

Comparison of HPMC Matrix Tablets Containing 10 and 20% w/w Propranolol HCl to Study the Effect of Utilizing Constant SA/Vol Values

Sample Name	Tablet Shape (% Drug)	Tablet Weight (mg)	SA/Vol (mm^2/mm^3)	Tablet Hardness (scu)	f_2 Values
O-10	Oval (10%)	200	1.28	3.2	Ref.
O-20	Oval (20%)	200	1.20	2.8	91
O-10-2×	Oval (10%)	400	0.86	11.1	49
R-10	12.7 mm FFR (10%)	400	1.19	3.8	73

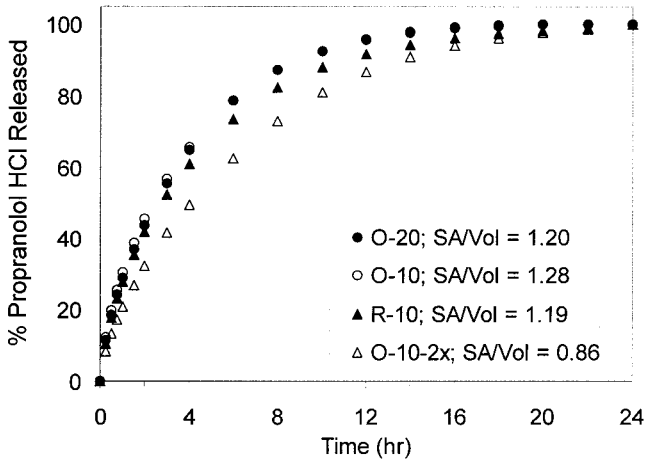

Figure 6. Percentage propranolol HCl released vs. time utilizing constant SA/Vol to duplicate controlled drug release of propranolol HCl from HPMC matrix tablets having different doses (error bars not shown because they are comparable in size to the symbols).

Table 7

Comparison of HPMC Matrix Tablets Containing 15 and 30% w/w Diphenhydramine HCl to Study the Effect of Utilizing Constant SA/Vol Values

Sample Name	Tablet Shape (% Drug)	Tablet Weight (mg)	SA/Vol (mm^2/mm^3)	Tablet Hardness (scu)	f_2 Values
O-15	Oval (10%)	200	1.13	6.3	Ref.
O-30	Oval (30%)	200	1.11	2.4	83
O-15-2×	Oval (15%)	400	0.80	15.2	49
R-15	12.7 mm FFR (15%)	400	1.07	6.3	72

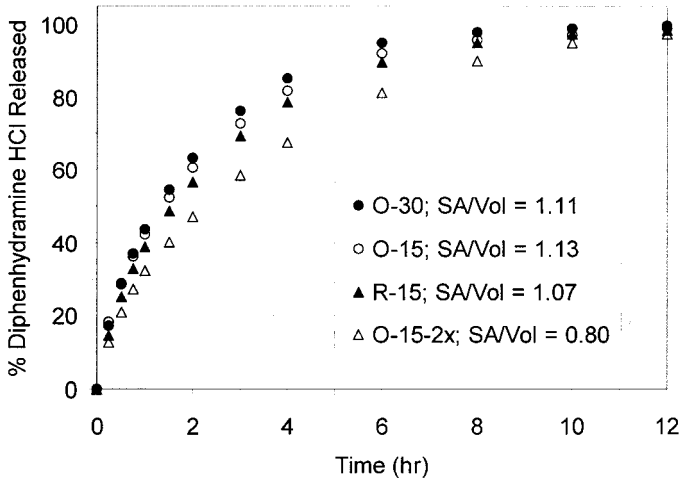

Figure 7. Percentage diphenhydramine HCl released vs. time utilizing constant SA/Vol to duplicate controlled drug release of diphenhydramine HCl from HPMC matrix tablets having different doses (error bars not shown because they are comparable in size to the symbols).

percentage), and R-15 (tablet with the same formulation as O-15 but different tablet shape and total weight) are all similar, and they have f_2 metric values greater than 70. However, O-15-2× (same formulation and tablet shape as the control sample, O-15, but with double the tablet weight) has a significantly slower release rate than O-15 (f_2 metric less than 50). Hence, SA/Vol is shown to be a variable that allows one to predictably adjust release profiles by selecting appropriate tablet shapes and dimensions that provide targeted SA/Vol values.

CONCLUSIONS

For diffusion-controlled systems, i.e., predominantly diffusional drug release, surface area/volume is a key variable in controlling drug release from HPMC matrix tablets. Surface area/volume can be utilized to duplicate drug release profiles for tablets having different sizes, shapes, and dose levels.

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