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EVALUATION OF A MODIFIED PADDLE METHOD FOR DISSOLUTION TESTING

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ABSTRACT

A modification of the U.S.P. paddle method for dissolution was evaluated. A 10-mesh size circular stainless steel screen was placed at the bottom of the dissolution vessel establishing an elevated platform for the tablet. The modified method was compared with the U.S.P. paddle and basket methods utilizing three different tablet formulations of the nondisintigrating type. Two tablet formulations contained a gel forming material hydroxypropylmethylcellulose K-4000 and the third tablet formulation has tricalcium phosphate as the major filler. The active ingredients

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were either dyphylline or melperone HCl. The data were evaluated by a one-way analysis of variance combined with Ryan-Einot-Gabriel-Welsch multiple F-test for comparison between methods. The results suggest that the proposed modified paddle method for dissolution may provide the formulator with an alternative for evaluating release of drugs from solid dosage forms containing swellable gums. This method offers the advantages of continuous visual monitoring of the dosage form to ascertain its integrity and full exposure of the total surface area of the tablet without sticking to the walls of the dissolution vessel.

INTRODUCTION

The U.S.P. basket and paddle methods for dissolution testing (1) are routinely utilized by scientists to evaluate the release performance of conventional and controlled release oral dosage forms. The U.S.P. paddle method provides continuous visual monitoring of the dosage form during the dissolution process in comparison with the basket. However, nondisintigrating solid dosage forms containing high percentage of hydrophilic gums tend to stick to the wall of the dissolution vessel allowing partial exposure of the total surface area when the paddle method is used.

A modification of the paddle, which overcomes the disadvantages of both U.S.P. methods, was developed and utilized by Shenouda and Krill (2) in evaluating a controlled release solid dosage form containing a hydrophilic gum. It is the purpose of this study to compare the new modified paddle method with the

official U.S.P. methods for dissolution using gel and nongel type tablets of the nondisintigrating type.

MATERIALS AND METHODS

Three tablet formulations were utilized in this study. Hydroxypropylmethyl cellulose K-4000 (HPMC)[1] was used as a gel forming substance in two formulations: a dyphylline-HPMC matrix tablet (formulation I) and a melperone HCl-HPMC press coated tablet (formulation II). The 400 mg tablet of formulation I contained 20% HPMC and 10.0% dyphylline. Formulation II (280.0 mg/tablet) contained a total of 50.4 mg and 39.3 mg of HPMC and melperone HCl, respectively. Mannitol and zinc stearate were included in both HPMC formulations to make up the balance of the total weight of each tablet. The constituents of the third tablet (formulation III, 400.0 mg/tablet) were 10% dyphylline, 89% tricalcium phosphate, and 1% of zinc stearate.

A modified paddle method, the U.S.P. paddle and basket methods were comparatively evaluated by studying the release characteristics from the three tablet formulations. The modified paddle method utilized a 10-mesh size circular stainless steel screen approximately seven centimeters in diameter which is placed on the bottom of the dissolution vessel establishing an elevated platform for the dosage form. Water, equilibrated at 37 ± 0.5 °C, was used as the dissolution medium and all experiments were con-

[1]Dow Chemical Company, Midland, Michigan

ducted at 50 r.p.m. The release profiles of six tablets from each formulation were generated by each method. 10.0 ml aliquots were withdrawn at the appropriate time intervals for analysis which was immediately replaced by 10.0 ml of fresh solvent. At the end of each release study, the rate of stirring was increased to 200 r.p.m. for thirty minutes after which a sample was withdrawn for analysis to allow for the calculation of the active's content of each individual tablet (100%). Dyphylline and melperone HCl were spectrophotometrically analyzed at a wavelength of 273.2 nm and 247.5 nm, respectively.

RESULTS AND DISCUSSION

All release data at various sampling times are expressed as the percent of the active's content of each individual tablet. The release profiles of dyphylline from formulation I generated by the three methods are shown in Figure 1. The plot illustrates comparable release profiles for the modified paddle and the basket methods. Both methods show higher percent release than the paddle. Comparison of the percent release, obtained by the three methods, was performed using six data values at various sampling times. Using SAS statistical programs[2], a one-way analysis of variance (ANOVA) was done. Dissolution methods were then compared by the Ryan-Einot-Gabriel-Welsch (REGW) multiple F-test. All statistical analysis were made at an alpha set to 0.05. The results of statistical comparisons are listed in Table 1. The percent

[2]SAS Institute Inc., Cary, North Carolina

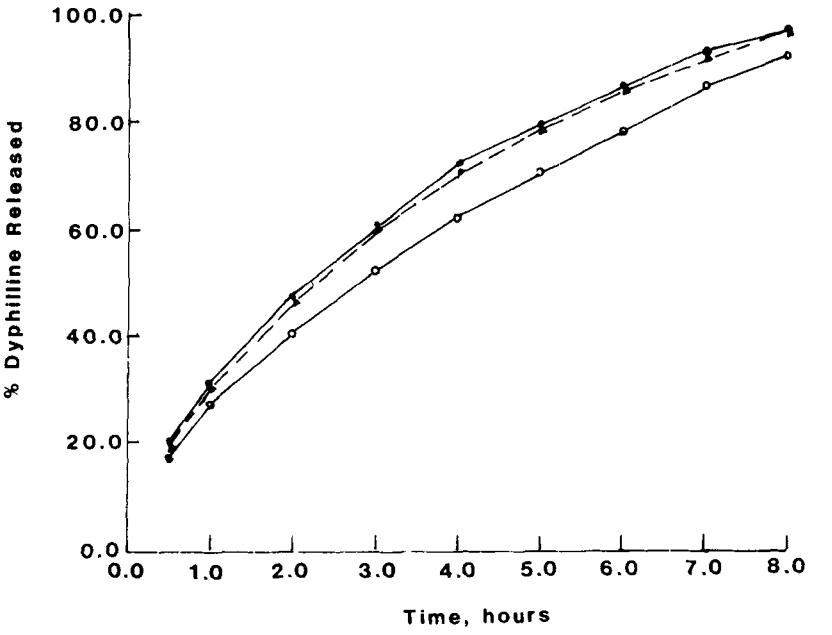

FIGURE 1

Release profiles of formulation I obtained by the three methods: ●———● modified paddle, ▲-----▲ basket, o———o paddle. Each point represents the average percent release of six tablets.

release of dyphylline from this formulation for the modified paddle and basket methods are significantly different from those obtained by the paddle. The release data obtained by the latter method are consistently smaller at all sampling times. The modified paddle shows significantly different percent release at 1.0 and 4.0 hour sampling times in comparison with the basket. This difference may be explained by a change in the geometric configuration of swollen gel and/or loss of some gel resulting from the spinning action of the basket.

TABLE 1

Results of Statistical Comparisons of Percent Release Obtained by the Three Dissolution Methods for Formulation I

Time, hrs.	Dissolution Method: Modified Paddle	Basket	Paddle
0.5	a	a	b
1.0	a	b	c
2.0	a	a	b
3.0	a	a	b
4.0	b	a	c
5.0	a	a	b
6.0	a	a	b
7.0	a	a	b
8.0	a	a	b

Results with the same letter are not significantly different. The percent release is listed in the order a > b > c.

The percent release for formulation I is linear when plotted as a function of square root of time (3) with very high correlation coefficients (r = 0.997 - 0.999) for all methods. ANOVA-REGW statistical comparison of the rates of release revealed no significant difference between the modified paddle (38.28 % $hr^{-1/2}$) and the basket (38.56 % $hr^{-1/2}$), but both rates are significantly dif-

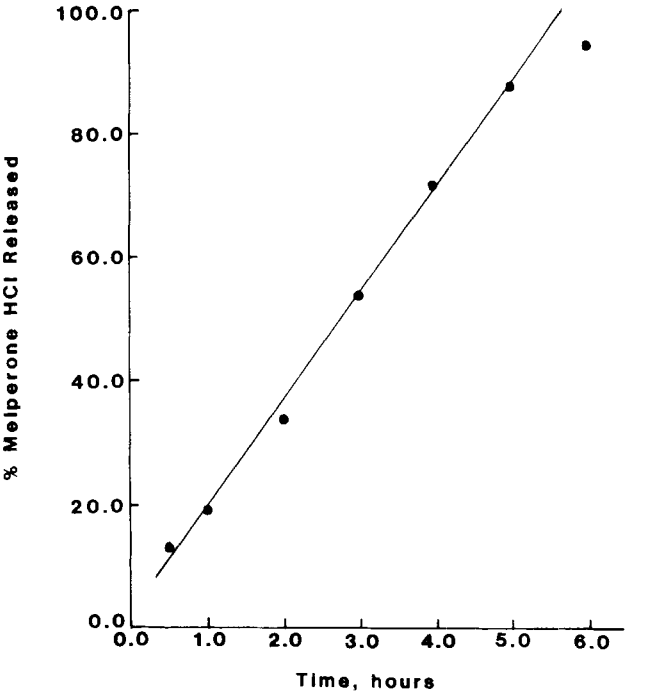

FIGURE 2

Release profile of formulation II obtained by the modified paddle method. Each point represents the average percent release of six tablets.

ferent from that of the paddle (35.65 % $hr^{-1/2}$). The lower release rate of the paddle is due to sticking of tablet to the wall of the dissolution vessel.

The zero order release profiles of Formulation II obtained by the modified paddle, basket, and paddle are illustrated in Figures 2, 3, and 4. These plots reveal that the basket release data show relatively higher variability in comparison with the other two methods. Table 2 lists the results of ANOVA-REGW statistical com-

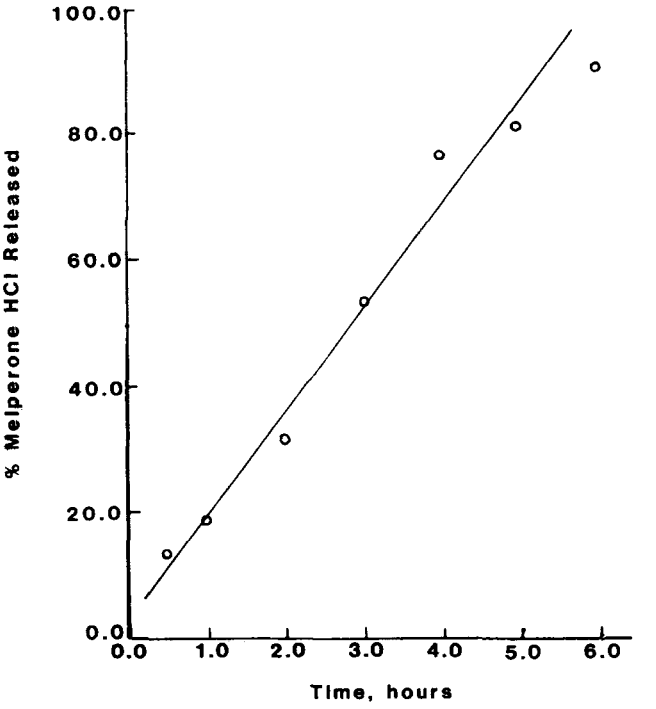

FIGURE 3

Release profile of formulation II obtained by the U.S.P. basket method. Each point represents the average percent release of six tablets.

parisons of release data generated by three methods for this formulation. The percent release for the modified paddle is significantly different from those of the paddle at all times except the 6.0 hour sampling time. In comparison with the basket method, the percent release obtained by the modified paddle is significantly different at 2.0, 4.0, 5.0 and 6.0 hour sampling times. As was observed previously with Formulation I, the percent release

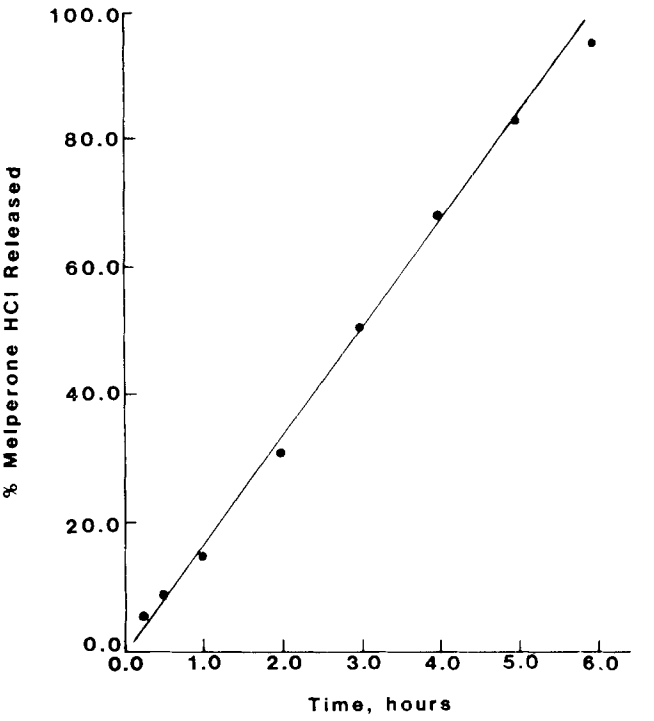

FIGURE 4

Release profile of formulation II obtained by the U.S.P. paddle method. Each point represents the average percent release of six tablets.

obtained by the basket at 4.0 hour is larger than that of the modified paddle. These statistically significant differences observed with the basket and paddle methods suggest that the U.S.P. methods may not be appropriate for studying release from gel systems.

The average zero order release rates are 17.02 ± 0.35 % hr^{-1} ($r = 0.9985$), 16.68 ± 0.40 % hr^{-1} ($r = 0.9986$), 16.55 ± 0.21 % hr^{-1} ($r = 0.9892$) for the modified paddle, the paddle, and the basket

TABLE 2

Results of Statistical Comparisons of Percent Release Obtained by the Three Methods for Formulation II

Time, hrs.	Dissolution Method		
	Modified Paddle	Basket	Paddle
0.5	a	a	b
1.0	a	a	b
2.0	a	b	b
3.0	a	a	b
4.0	b	a	c
5.0	a	b	b
6.0	a	b	a

Results with the same letter are not significantly different. The percent release is listed in the order a > b > c.

methods, respectively. Although these values show a trend of decrease in the release rates, ANOVA-REGW comparison reveal no significant differences among the rates obtained by the three methods.

The release profiles of dyphylline from Formulation III are shown in Figure 5 for the three methods. The results of ANOVA-REGW statistical comparison are listed in Table 3. In this tricalcium phosphate formulation, the release data obtained by the

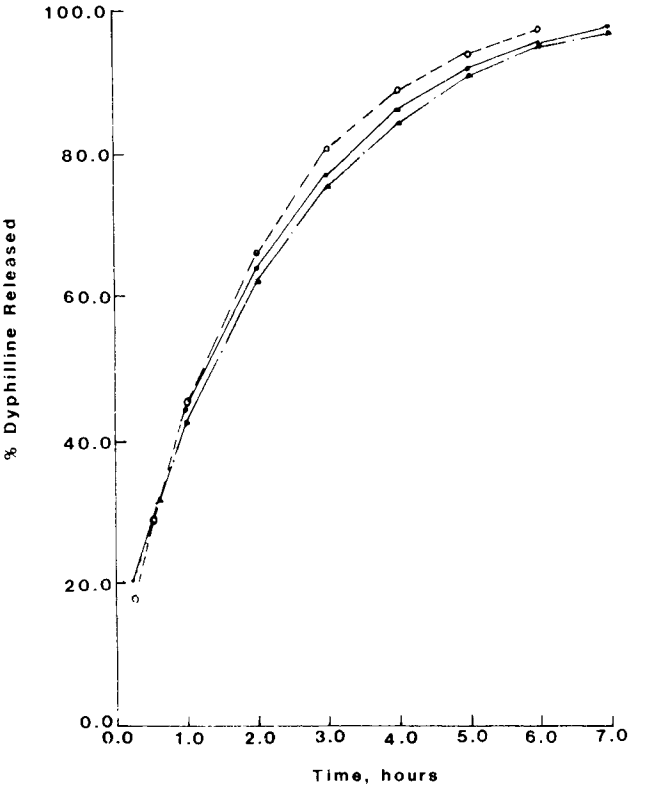

FIGURE 5

Release profiles of formulation III obtained by the three methods: o——o paddle, ●——● basket, ▲—•—▲ modified paddle. Each point represents the average percent release of six tablets.

modified paddle method are significantly lower than the paddle at all sampling times except 3.0 hour. The percent release data for the modified paddle are comparable to those obtained by the basket except at the initial sampling times.

The release from this system follows a first order. ANOVA-REGW comparison of the first order rate constants shows the release

TABLE 3

Results of Statistical Comparisons of Percent Release Obtained by the Three Methods for Dyphylline-Tricalcium Phosphate Tablets.

	Dissolution Method		
Time, hrs.	Modified Paddle	Basket	Paddle
1	b	a	a
2	c	b	a
3	a	a	a
4	b	b	a
5	b	ba	a
6	b	b	a

Results with the same letter are not significantly different. The percent release is listed in the order a > b > c.

rate for the paddle (0.565 hr^{-1}) to be significantly different from that of the basket (0.495 hr^{-1}) and the modified paddle (0.457 hr^{-1}). There is no statistically significant difference between the latter two rates. The above analysis suggest that the paddle method may be the appropriate method for this nondisintigrating nongel type formulation.

It is believed that the new modified paddle method is advantageous in studying release from gel-type dosage forms and may prove to be useful for in vitro evaluation of other types of

controlled release solid dosage forms. However, additional studies are needed to verify its universal applicability.

REFERENCES

1. The United States Pharmacopeia XXI, 1985, pp 1243-1244.
2. L.S. Shenouda and S.L. Krill, Unpublished data.
3. T. Higuchi, J. Pharm. Sci., 52: 1145 (1963).