DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(20), 2123-2133 (1992)

EVALUATION OF ENTERIC FILM PERMEABILITY: TABLET SWELLING METHOD AND CAPILLARY RISE METHOD

Robert E. O'Connor and William H. Berryman
Pharmaceutical Research and Development
Merck Frosst Centre for Therapeutic Research
Pointe Claire-Dorval, Quebec, Canada

ABSTRACT

Cellulose Acetate Phthalate, CAP, is a common enteric coating polymer and when deposited from an ammoniated aqueous system, the films appear to be water permeable. Permeability is often studied using diffusion cells; however, the characteristics of the sample test film (cast or sprayed) have always been a major concern. In this work, two novel methods, the tablet swelling method and the capillary rise method, have been developed and evaluated using two aqueous CAP systems. For the tablet swelling method, TSM, two parameters have been identified; the rate of thickness increase (RThick) and the maximum thickness (MThick). For the capillary rise method, CRM, two parameters have also been identified; the lag time (LTime) and the rate of rise (RRise) in the capillary tube. CRM can be modified to permit the calculation of water flux across the enteric film. The addition of stearyl alcohol to an aqueous ammoniated CAP system results in a reduction in RThick, MThick and RRise and an increase in LTime, which are all indicative of a reduction in film permeability.

INTRODUCTION

Enteric coating is used to protect the stomach from drugs which irritate the gastric mucosa and to protect drugs from the acidic environment in the stomach. Acid sensitive drugs, which are also degraded by water, present an additional challenge as a result of water permeation through the acid insoluble enteric film causing drug degradation. Water permeation can also affect the disintegration and dissolution behavior for enteric coated dosage forms as a result of an increase in core tablet hardness in the presence of excess moisture[1]. In addition, on-going environmental concerns and the high cost of solvent recovery have intensified the interest in the reformulation of organic solvent enteric coating systems to produce aqueous enteric coating systems. In the authors' experience, water penetration is a greater concern for enteric coated products after conversion to aqueous enteric coating formulations. Screening formulations for water permeability would provide a database for the rational selection of an appropriate aqueous film coating system.

Water permeation through an enteric film coating is governed by the laws of diffusion whether the water is in the vapor state as reported by Higuchi and Aquiar[2] or in the liquid state as described in this work. The use of diffusion cells to quantify the transport of water has been reported for both biological and synthetic membranes[2,3,4]. Permeation studies using diffusion cells require the use of a sample test film prepared by casting films on a flat surface or by removal of a film from a coated substrate. The preparation and handling of these sample test films often result in questions concerning film integrity and comparisons between sample test films and *in-situ* films. These questions are a concern in the interpretation of diffusion cell data. The objectives of this investigation were to develop methodology to evaluate *in-situ* water permeation through enteric films using actual coated tablets and to prepare a suitable test system to validate the proposed test methodology.

Stafford[5] compared the enteric properties for hydroxypropyl methyl-cellulose phthalate (HPMCP) films deposited from both organic solvent and aqueous systems. For a dosage form containing acid sensitive enzymes, Stafford described the penetration into the core tablet during acid exposure as equivalent for both organic solvent and aqueous enteric coating systems.

In a report comparing the properties of several enteric polymers in both organic solvent and aqueous coating systems, Chang[6] recommended the use of an ammoniated

aqueous solution of cellulose acetate phthalate (CAP) based on viscosity, film-forming and gastric fluid-resistance evaluations. Gastric fluid-resistance testing was evaluated by measuring the amount of theophylline released from an enteric coated pellet system in simulated gastric fluid without enzyme over a four hour time period. Drug release requires a degree of fluid penetration into the core pellets to facilitate the dissolution and diffusion of theophylline through the enteric film coating and into the test medium.

The permeability of enteric film coatings has been documented in the two preceding investigations by Stafford and Chang for two different enteric polymers. While the conversion of organic solvent formulations of both HPMCP and CAP is of current interest in our laboratory, an aqueous ammoniated cellulose acetate phthalate system has been selected as a model system to validate the test methodologies developed in our current work. Tablets coated with an aqueous ammoniated cellulose acetate phthalate system were observed to swell during the acid stage of the USP Drug Release Test for Delayed Release (Enteric-coated) Articles. This observation formed the basis for the Tablet Swelling Method. The mass transfer into the core tablet, which resulted in tablet swelling, formed the basis for the Capillary Rise Method.

MATERIALS AND METHODS

Core Tablet

The model core tablet formulation is listed in Table 1. Each core tablet contains yellow dye to facilitate observation of potential film failure in the Tablet Swelling Method and the rise of liquid in the Capillary Rise Method. A single batch of model core tablets was used for all experiments.

The core tablets were produced by a wet granulation technique using a high intensity granulator (TK Fielder, Model PMA-25). The first four components were dry mixed and granulated using purified water as the granulating solvent. The wet granulation was dried overnight at 50°C in a forced air oven (Colton, Model 1018-E), comminuted (CoMill, Model 197, 0.062" screen) and lubricated with magnesium stearate in a twin shell blender (Patterson Kelley, Laboratory Model). The core tablets were compacted on a rotary tablet press (Manesty, Model B3B) using standard concave tooling and evaluated for weight variation, hardness and friability.

The formulations for the ammoniated cellulose acetate phthalate (CAP-NH_4) coating dispersions selected for this study are listed in Table 2. For the coating dispersion

TABLE 1

Formulation for the model core tablet prepared by wet granulation

Component	Quantity per tablet (mg)
FDC Yellow No.6	1.0
Hydrous Lactose, NF	212.0
Microcrystalline Cellulose, NF	66.7
Povidone, USP	5.2
Magnesium Stearate, NF	1.4

TABLE 2

Formulations for the ammoniated cellulose acetate phthalate enteric coating dispersions plasticized with triethyl citrate with and without stearyl alcohol

Component	CAP/TEC (g)	CAP/TEC/SA (g)
Cellulose Acetate Phthalate, NF	75	75
Strong Ammonia Solution, NF *	14	14
Triethyl Citrate, NF	15	15
Stearyl Alcohol, NF	0	7.5
Purified Water, USP qs ad	800	800

* for these preliminary studies, Ammonium Hydroxide, Reagent grade was used.

with stearyl alcohol (SA), the SA was dispersed in 200 mL of purified water using a blender (Waring, Model 702CR) prior to incorporation into the CAP-NH_4 solution. Tablets were coated in a custom, 4-inch diameter, fluidized bed coating column (bottom spray) using the parameters listed in Table 3.

TABLE 3

Coating parameters used to prepare the enteric coated model tablets in a fluidized bed coating column (bottom spray)

Batch size	650 g
Column size	4" diameter (Capacity: 1 kg)
Spray rate	12 g/min
Atomization pressure	2 bar
Intake air temperature	55°C
Exhaust air temperature	41°C

Tablet Swelling Method (TSM)

Using a rotating bottle apparatus[7], individual coated tablets are placed in 50 mL of 0.1 N HCl. The bottles are rotated and maintained in a water bath at 37 °C. The thickness of the coated tablet is measured initially and with respect to time using a micrometer. From these data, two parameters are extracted; the initial slope or swelling rate (RThick) and the plateau or maximum thickness (MThick). Examples are shown in Figure 1.

Capillary Rise Method (CRM)

One face of an enteric coated tablet is drilled to a constant depth using a precision micro-drill press (Servo Products Company, Model 7100). A thin glass capillary tube is then introduced into the hole and this face of the coated tablet is covered with silicone to seal the tablet-capillary tube junction. The silicone is applied to completely cover that tablet face. After a curing time of at least 24 hours, the coated tablet-capillary tube system is placed into 0.1 N HCl maintained at 37°C. After a period of time, liquid begins to rise in the capillary tube, the height of the liquid is recorded with respect to time. From these data, two parameters are extracted; the terminal slope or rate at which the liquid rises in the capillary tube (RRise) and the x-intercept or the time it takes before the liquid begins to rise, the lag time (LTime). Examples are shown in Figure 2. A

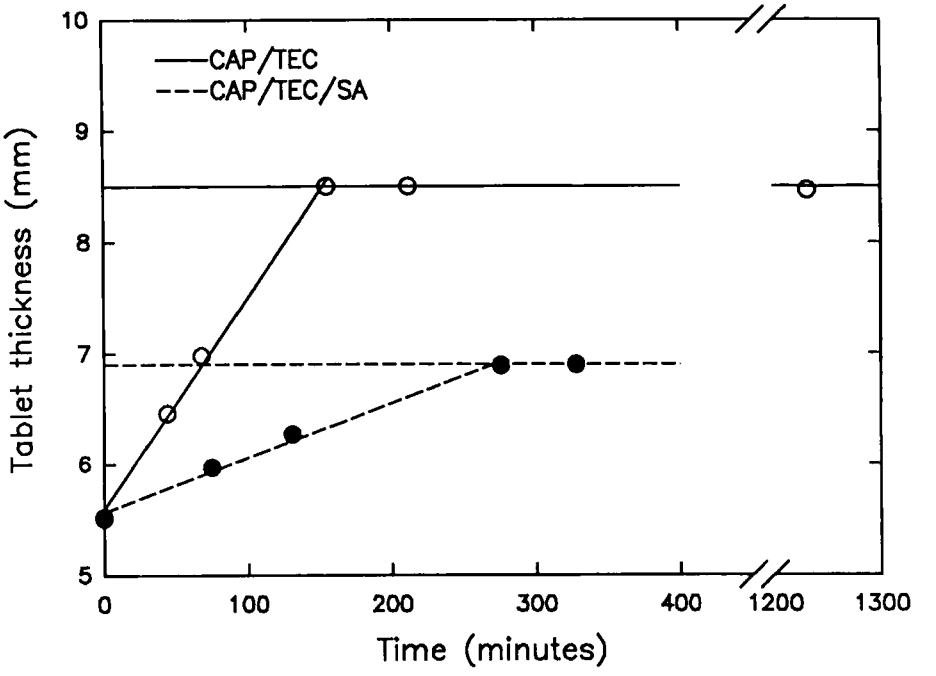

FIGURE 1

Tablet Swelling Method plots for individual enteric coated model tablets coated with cellulose acetate phthalate (CAP) plasticized with triethyl citrate (TEC) with and without stearyl alcohol (SA).

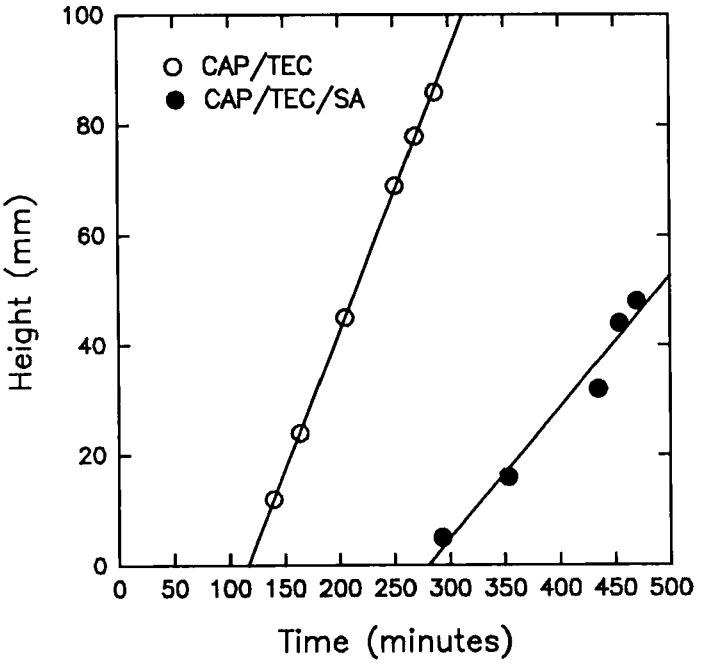

FIGURE 2

Capillary Rise Method plots for individual enteric coated model tablets coated with cellulose acetate phthalate (CAP) plasticized with triethyl citrate (TEC) with and without stearyl alcohol (SA).

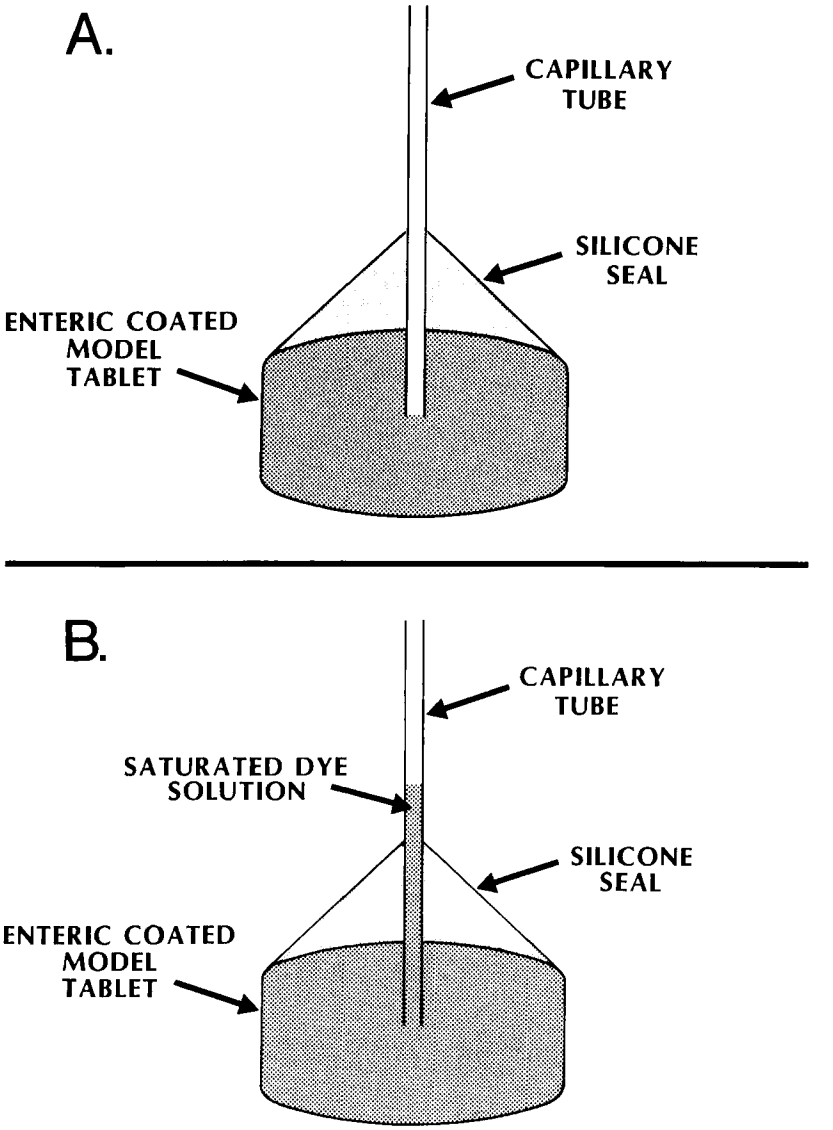

FIGURE 3
A schematic representaion of the Capillary Rise Method before (A.) and after (B.) exposure to acidic media.

TABLE 4

Physical characteristics of the model core tablets

Size	10/32 "
Weight	286.3 mg ± 0.7 (MEAN ± SD)
Hardness	11-15 kp
Friability (300 revolutions)	0.021 %

schematic representation of this experimental method is shown in Figure 3. It is interesting to note that Haslam, et al.[8], used a similar *in-situ* tablet-capillary tube system to measure the hydraulic pressure, osmotic flow properties and osmotic permeability characteristics of a controlled porosity osmotic pump coating system.

RESULTS AND DISCUSSION

The results obtained by evaluating the core tablets for weight variation, hardness and friability are listed in Table 4. These core tablets are suitable for coating purposes and should provide a uniform substrate for comparison of the selected enteric film coating formulations.

Several factors, which are independent of film composition, have been experimentally held constant in this evaluation. These include: the surface area of the film exposed to the acidic medium, the osmotic pressure and diffusion gradients, the permeability of the tablet core and the diffusional path length within the tablet. Other factors, such as, the permeability, strength and plasticity of the film, are dependent on film composition. The enteric coating has been applied to a theoretical constant weight gain and, therefore, the thickness of the film may vary slightly with the formulation.

The results obtained from the analyses of the two enteric coated model systems are summarized in Table 5. It is interesting to note that the addition of stearyl alcohol has significantly decreased the RTHick, MTHick and RRise parameters ($p<0.001$) while

TABLE 5

Results of Tablet Swelling Method and Capillary Rise Method evaluation on enteric coated model systems (MEAN ± SD)

Formulation	RThick (mm/min)	MThick (mm) *	RRise (mm/min)	LTime (min)
CAP/TEC (n=8)	0.018 ± 0.002	8.5 ± 0.2	0.47 ± 0.05	140 ± 11
CAP/TEC/SA (n=4)	0.006 ± 0.001	6.9 ± 0.1	0.21 ± 0.01	262 ± 17

* Initial thickness = 5.5 mm for both formulations.

significantly increasing the LTime parameter ($p<0.001$). In all cases, the change in the measured parameter is indicative of a reduction in film permeability, as would be expected for the addition of an hydrophobic excipient. These mean data have been calculated from a series of plots for individual enteric coated model tablets. Representative plots are shown in Figures 1 and 2 for the Tablet Swelling Method (TSM) and Capillary Rise Method (CRM), respectively. Individual plots were necessary to compensate for differences in sampling intervals during data collection.

The measured parameters, as expected, are sensitive to formulation factors. It is postulated that RThick, the swelling rate, is influenced to a greater extent by the permeability and plasticity of the film, while MThick, the maximum thickness, is largely influenced by film plasticity and film strength. It is also postulated that LTime and RRise; the lag time and rate of rise, respectively, are largely dependent on permeability. LTime may also be influenced by the initial wettability of the film surface.

The Capillary Rise Method can be modified to calculate the flux, a parameter defined by Fick's first law of diffusion[9], or the rate of water transfer across the enteric membrane per unit area during acid exposure. More specifically, the modification involves replacing the original capillary tube with a micropipet with a uniform inside diameter which permits the conversion of unit length to unit volume and, assuming a density of 1 g/mL for the saturated dye solution, unit volume to unit mass. Since no

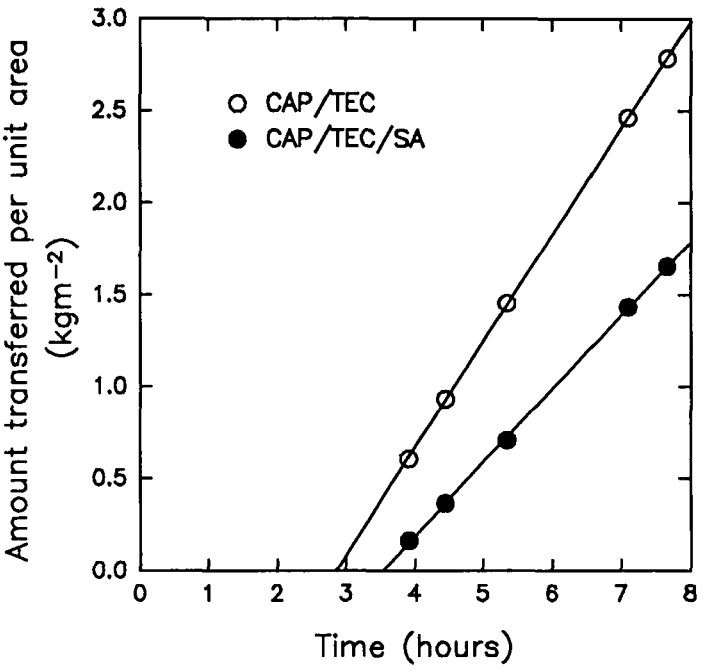

FIGURE 4

Data from the Capillary Rise Method plotted to determine flux for individual enteric coated model tablets coated with cellulose acetate phthalate (CAP) plasticized with triethyl citrate (TEC) with and without stearyl alcohol (SA).

swelling occurs with this method, an estimate of total surface area exposed to the acidic medium can be calculated using the dimensions of the tablet tooling and the tablet thickness. These calculated data for individual enteric coated model tablets can be plotted, as shown in Figure 4, to determine flux or the terminal slope. The flux values for these representative CAP/TEC and CAP/TEC/SA formulations are 0.580 $kgm^{-2}hr^{-1}$ and 0.401 $kgm^{-2}hr^{-1}$, respectively.

CONCLUSIONS

Two methods have been developed to evaluate water permeation through enteric films using actual coated tablets. These two methods are sensitive to a modification in the film coating formulation and are not restricted by the preparation and harvesting of sample test films necessary for diffusion cell testing. While the original units of measurement in the Capillary Rise Method are sufficient to rank the two model systems,

CRM can be used to calculate a first principle parameter or flux across an enteric film coating.

Stearyl alcohol was added to the ammoniated CAP formulation to increase the hydrophobicity of the enteric film and, hopefully, to reduce water permeation. Under the conditions of this study, the addition of stearyl alcohol does appear to reduce the water permeability of this enteric coated model system.

ACKNOWLEDGEMENTS

This work was presented at the AAPS Sixth Annual Meeting, Washington, DC, 1991. Mr. Berryman was a PMAC summer student during the early phase of this work. The authors' would like to thank Dr. Dale Meisner for his helpful suggestions during the preparation of this manuscript.

REFERENCES

1. G. Schepky, **Acta Pharm. Technol.**, 26, 196 (1980).
2. T. Higuchi and A. Aguiar, **J. Am. Pharm. Assoc., Sci. Ed.**, 48, 574 (1959).
3. M.Z. Biber and C.T. Rhodes, **J. Pharm. Sci.**, 65, 64 (1976).
4. A.J. Aguiar and M.A. Weiner, **J. Pharm. Sci.**, 58, 210 (1969).
5. J.W. Stafford, **Drug Dev. Ind. Pharm.**, 8, 513 (1982).
6. R.-K. Chang, **Pharm. Tech.**, 14(10), 62 (1990).
7. J.C. Souder and W.C. Ellenbogen, **Drug Stds**, 26, 77 (1958).
8. J. Haslam, A. Merfeld, J. Pipkin and G. Rork, "Measurement of Hydraulic and Osmotic Flow Properties of Controlled Porosity Osmotic Pump Tablet Coatings," AAPS 4th Annual Meeting, 1989.
9. N. Ho, Ch. 15 in "Physical Pharmacy," 3rd Edition, A. Martin, J. Swarbrick and A. Cammarata, eds.,Lea & Febiger, Philadelphia, 1983, p.399.