Ionic Strength Dependence of Dissolution for Eudragit S-100 Coated Pellets

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INTRODUCTION

The dissolution of enteric polymers is highly dependent on pH, buffering capacity, and the hydrodynamics of the dissolution media (1-6). Ionic strength (I.S.), which is increased when buffer concentrations increase, can also influence enteric polymer dissolution. The variable in vivo disintegration times and poor in vitro-in vivo correlations observed (7-14) for enteric coated formulations can be explained by the variable nature of the above factors in intestinal media (1,15-16).

In this study, the effect of I.S. on the dissolution of Eudragit S-100 coated formulations of the hydrophobic drug, SC-41930 (Leucotriene B_4 antagonist) and a water soluble marker compound, bromocresol green (BCG) were examined in varying phosphate and sodium chloride (NaCl) concentrations.

MATERIALS AND METHODS

Materials

Sugar pellets of 16-20 mesh size were purchased from Crampton and Knowles Corp. (Mahwah, NJ). Bromocresol green, sodium salt (BCG) was purchased from Aldrich Chemical Company, Inc. (Milwaukee, WI). Polyvinyl pyrrolidone (PVP) was purchased from ISP (Wayne, NJ). Hydroxypropyl methyl cellulose (HPMC) was purchased from Dow Chemical Co. (Midland, MI). Dibutyl phthalate was purchased from Spectrum Chemical Mfg. Corp. (Gardenia, CA). Sodium taurocholate (NaTC) was purchased from Sigma Chemical Co. (St. Louis, MO.). Eudragit S-100 was purchased from Rohm Tech, Inc. (Fitchburg, MA). SC-41930 was synthesized at G.D. Searle & Co. (Skokie, IL). All reagents used were HPLC grade.

Physical Chemical Properties of SC-41930 and BCG

The aqueous solubility of SC-41930 (pK_a 4.5) at pH 3 and 7 are 0.68 and 192 μg/ml, respectively. The octanol/water distribution coefficient of SC-41930 is 1040 at 37°C and pH 7.0. The solubility of the sodium salt of BCG at pH 7.0 is greater than 10 mg/ml. The pK_a of BCG is 4.7. The octanol/aqueous distribution coefficient of BCG sodium salt is 0.48 at pH 7.0 (at room temperature).

Coating Preparations

The BCG suspension was prepared by mixing 1% BCG (w/v) and 5% PVP (w/v) in isopropyl alcohol (IPA). The enteric coating solution contained 6% Eudragit S-100 (w/w), 0.6% dibutyl phthalate (w/w), and 4% water (w/w) in IPA.

Pellet Preparation

BCG/Eudragit Pellets. 0.3 kg of 16-20 mesh sugar pellets were placed in the Wurster insert of an Aeromatic Strea-1 fluid bed granulator (Aeromatic, Inc., Towanco, NJ). The BCG suspension was added via peristaltic pump at a spray rate of 5-12 ml/min. The atomizing air pressure was 1.0 bar. The inlet air temperature was 50°C. The Eudragit S-100 solution was sprayed onto the pellets at a rate of 3-5 ml/min. Samples were taken at 250 ml intervals of solution sprayed for dissolution and particle size analysis. Agglomerates of pellets were separated from the granulations using appropriately sized sieves. The final levels of BCG and Eudragit coatings were 0.73 and 17.7—32.4% (w/w), respectively.

SC-41930/Eudragit Pellets. 0.3 kg of 16-20 mesh sugar pellets were placed in a Vector Freud CF-360 rotor granulator (Vector Corp. Marion, IA). Pellets were coated with powdered drug while being wetted with 5% HPMC in water at a rate of 25 ml/min. The rotor speed was 180-200 rpm. The air pressure was 0.7-1.2 kg/cm^2 and the inlet air temperature was 60°C. The Eudragit S-100 coating was applied within the Wurster insert of the Aeromatic fluid bed granulator as described for the BCG/Eudragit pellets. The final levels of SC-41930 and Eudragit S-100 were 14 and 11.4% respectively.

Sieve Analysis

Five gram samples of each lot of pellets produced were placed in a sonic sieve (Allen Bradley, Milwaukee, WI) for particle size analysis. The sieve sizes used ranged from 600-1700 μm (total of six sieves). The samples were pulse-sonicated for 1-2 min.

Dissolution Testing

Dissolution testing was performed using the USP paddle method in 450 or 900 ml of 0.1 N HCl, phosphate buffer (20-200 mM) or phosphate buffer (20 mM) plus 65-320 mM NaCl at pH 7.0. The buffer solutions were prepared from mono- and dibasic sodium phosphate salts. The temperature of the 6 vessel dissolution bath (Hanson Research, Northridge, CA or Vanderkamp 600, VanKel Industries, Inc., Edison, NJ) was 37°C and the paddle speed was 75 rpm. Samples of 1.5-3.0 g BCG/Eudragit S-100 pellets or 250 mg of SC-41930/Eudragit S-100 pellets were added to each vessel in triplicate. At predetermined time points, 1-3 ml samples were taken from each dissolution bath using a syringe fitted with a frit. The removed fluid was not replaced since the total amount was less than 5% of the total volume at the last

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time point. Samples were filtered through a 0.45 μ Gelman PTFE filter when the dissolution media was cloudy.

Sample Analysis

BCG Dissolution Samples. BCG dissolution samples were assayed spectrophotometrically with a Hewlett Packard 8451A Diode Array (Corvallis, OR) or Milton Roy Spectronic 1201 (Rochester, NY) spectrophotometer. Acid dissolution samples were measured at 410 nm and pH 7.0 samples were measured at 565 nm.

SC-41930 Dissolution Samples. SC-41930 dissolution samples were assayed by HPLC. A Supelco (Bellefonte, PA) Supelcosil LC-DP (diphenyl), 4.6 × 250 mm, 5 micron column was used. The UV detector was a Kratos Spectraflow model 773 (Ramsey, NJ) set at a wavelength of 230 nm. The solvent delivery system was a Waters (Milford, MA) model 590 programmable pump set at a flow rate of 1 ml/min connected to a Waters WISP model 710 B autosampler. The mobile phase consisted of 55% acetonitrile/45% triethylamine phosphate (TEAP) buffer. The TEAP buffer contained 1% triethylamine buffered to pH 2.5 with 85% phosphoric acid. The detection limit of this assay was 0.5 μg/ml of SC-41930.

Calculations

The percent of compound dissolved was calculated from the ratio of the optical density (O.D.) (for BCG) or concentration (for SC-41930, measured by HPLC) of the sample to that of the control (no Eudragit coating) corrected for the amount of Eudragit coating. In cases where the pellets completely released their drug content, the percent dissolved values were calculated using the plateau O.D. or concentration values.

RESULTS AND DISCUSSION

The particle size range of the pellets was relatively narrow. For the BCG core pellets, 93% of the total weight was collected on the 1000 μm size screen, and for the 32% Eudragit S-100 coated pellets, 78% was collected on the 1180 μm and 15.3% on the 1400 μm size screen. The SEM picture of the BCG/Eudragit S-100 (32.4%) pellets indicated a uniform, ~100 micron thick, polymer coat. In pH 7.0 and 0.1 N HCl dissolution media, BCG was released completely from the core pellets within one hour. The acid dissolution of the BCG/Eudragit S-100 (32.4%) pellets showed less than 5% BCG release by 7 h (results are not shown). In 0. 1 N HCl, the dissolution of the pellets was not affected by NaCl (165 mM) in the media. The manufacturer of Eudragit S-100 indicates that the polymer does not dissolve in a pH lower than 7.0. As expected, at pH 7.0 (20 mM phosphate) the dissolution of the BCG/Eudragit S-100 (15-32.4%) pellets showed decreasing release rates of BCG and increasing lag times with increasing amounts of Eudragit S-100 coating (see Figure 1 for the dissolution of the 32.4% Eudragit S-100 containing pellets).

In the sequential dissolution experiments in which the BCG/Eudragit S-100 (32.4%) pellets were soaked in either water or 0.1 N HCl for the first 2 h and then transferred into pH 7.0 media, the release profiles in the pH 7.0 media were

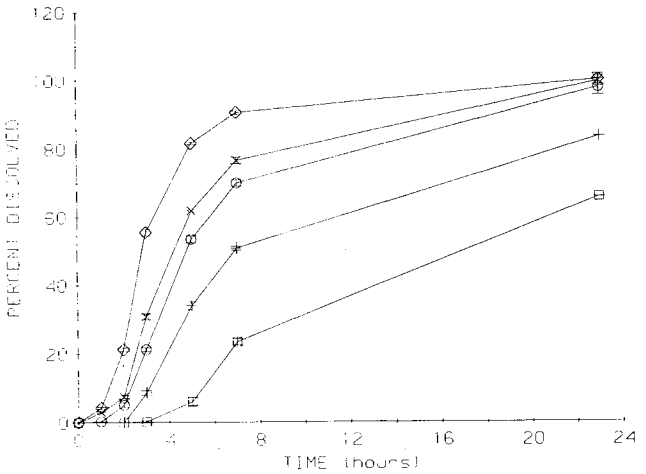

Fig. 1. The effect of phosphate concentration on the pH 7.0 dissolution of BCG/Eudragit S-100 (32.4%) pellets (1.5 g). The phosphate concentrations were 20 mM (I.S. = 0.044) (□), 50 mM (I.S. = 0.116) (+), 75 mM (I.S. = 0.179) (○), 100 mM (I.S. = 0.242) (X), and 200 mM phosphate (I.S. = 0.52) (◇) at pH 7.0. The volume of the dissolution media was 450 ml. The error bars indicate ± S.D.

superimposible to that of the dissolution curve obtained in pH 7.0 media (see the curve in Figure 1 for 20 mM phosphate media). These results illustrate that the lag time seen in the dissolution of the BCG/Eudragit S-100 (32.4%) pellets represents the time of hydration of the Eudragit S-100 coat.

The dissolution of the BCG/Eudragit S-100 (32.4%) was further studied under various concentrations of phosphate and NaCl at pH 7.0. The dramatic effects of increasing phosphate levels (20-200 mM) on the dissolution profile of the BCG pellets are shown in Figure 1. Dissolution rates were increased in the same manner when the dissolution media contained 20 mM phosphate with increasing levels of NaCl (65-320 mM) (Figure 2). The results were qualitatively similar when tris buffer was used (with and without NaCl) in the

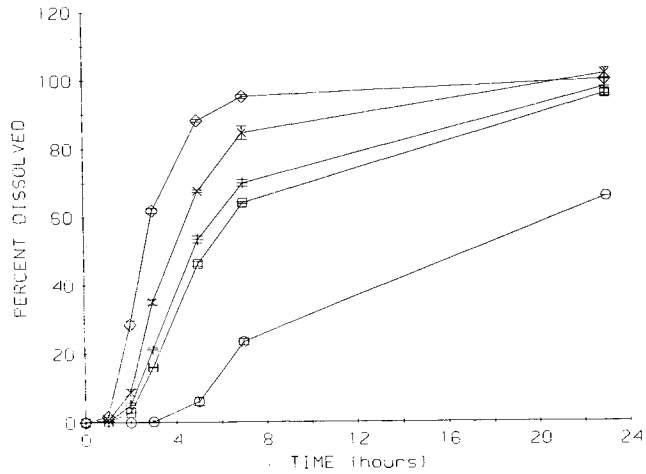

Fig. 2. The effect of NaCl concentration on the pH 7.0 dissolution of BCG/Eudragit S-100 (32.4%) pellets (1.5 g) in 20 mM phosphate media. The NaCl concentrations were 0 mM (I.S. = 0.044) (○), 65 mM (I.S. = 0.109) (□), 90 mM (I.S. = 0.134) (+), 145 mM (I.S. = 0.189) (X) and 320 mM (I.S. = 0.364) (◇). The volume of the dissolution media was 450 ml. The error bars indicate ± S.D.

dissolution media (results are not shown). The T_{50} values, representing the time for the release of 50% of the BCG content (obtained from Figures 1 and 2), are given in Figure 3 as a function of I.S. The T_{50} values appear to reach a minimum at I.S. > 0.2. At I.S. > 0.2, the Eudragit S-100 coating appeared softer during the dissolution and had extensively eroded by the end of the study. In low buffer concentration media (20 mM phosphate buffer), the thickness of the Eudragit S-100 coating on the BCG pellets did not change at the end of the 24 h dissolution period.

Similar to the BCG pellets, the release rate of SC-41930 from the Eudragit S-100 coated pellets was dramatically increased with increasing phosphate and NaCl concentration (Figure 4). The release profiles were similar when either NaCl or phosphate was used to adjust the I.S. of the media. Figures 1 and 4 indicate that the amounts of Eudragit S-100 needed to delay the dissolution of SC-41930 is significantly lower than for BCG. The lower amounts of Eudragit S-100 coating needed for SC-41930 may be a reflection of the more hydrophobic nature of this drug compared to BCG resulting in slower diffusion through the polymer coat.

The influence of buffer concentration on the release/dissolution properties of PVAP, CAP and Eudragit S and L films or coatings has been studied by several investigators (1-6). Although I.S. has been mentioned as a factor in a few studies (4,5), its role in dissolution could not be clearly distinguished from the buffering capacity effect, since, the changing I.S. in those studies was a result of the changes in buffer concentrations. Enhancement of the dissolution rates of the Eudragit S-100 coated pellet formulations at increasing I.S. could be related to changes in the pK_a of the buffer and polymer. Ionic strength can have a profound effect on the reaction rate between the polymer film and the basic buffer species (17). Further, the softening and erosion of the polymer film at I.S.> 0.2 will increase the diffusion of drug through the polymer coat. The structural effects of I.S. at pH 7.0 appears to be associated with some degree of ionization within the polymer since no such effect was seen in acid media. The softening at increasing I.S. levels can be related

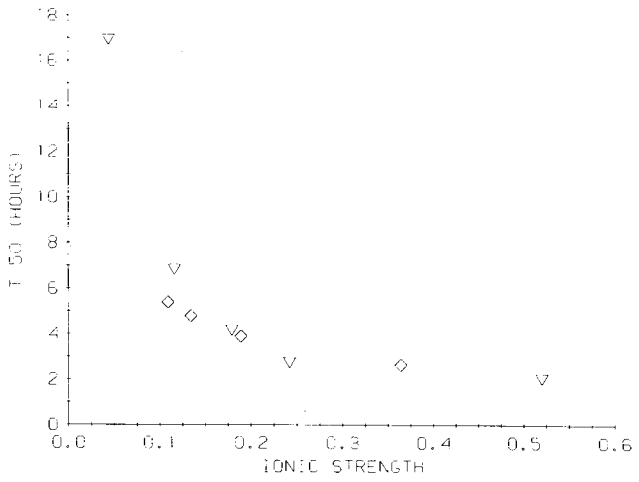

Fig. 3. The effect of I.S. on T_{50} of the formulations. The symbol (□) represents the values for phosphate buffer alone (20-100 mM) and the symbol (▽) represents the values for the 20 mM phosphate plus 65-320 mM NaCl.

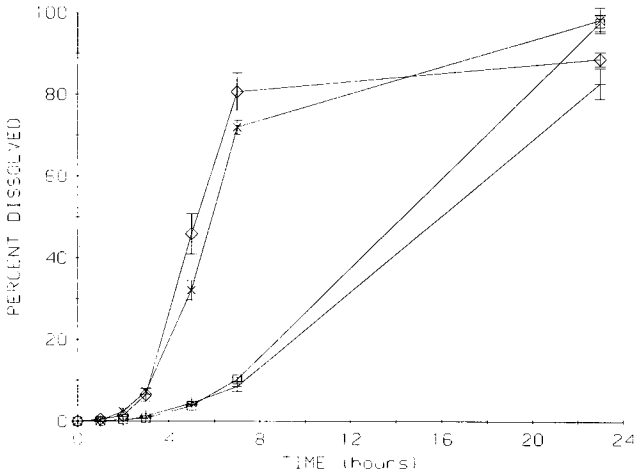

Fig. 4. The effect of phosphate and NaCl concentration on the pH 7.0 dissolution of the SC-41930 (14%)/Eudragit S-100 (11.4%) pellets (0.25 g). The symbols represent 50 mM phosphate (+) (I.S. = 0.116), 75 mM phosphate (I.S. = 0.179) (X), 20 nM phosphate plus 53 mM NaCl (I.S. = 0.097) (□), and 20 mM phosphate plus 97 mM NaCl (I.S. = 0.141) (◇). The volume of the dissolution media was 450 ml. The error bars indicate ± S.D.

to the reduction of the repulsion forces between the carboxylic ions of the repeating polymeric units (18).

The results indicate that the in vivo dissolution/release profiles of drugs from Eudragit S-100 coated pellets can be affected by the ionic composition of the intestinal fluid. Therefore, the ideal dissolution media for such formulations should mimic the I.S. value of the intestinal fluid (0.1-0.2, estimated from reference 19). In the in vivo studies, administration of enteric polymer coated formulations under fasted and fed conditions showed similar disintegration times in the intestine, after the transition times were corrected for the residence of the formulations in the stomach (13,15). These limited studies imply that the ionic composition of the intestinal fluid following the ingestion of food may be similar to that of the fasted state which would not affect the disintegration of the formulations.

In conclusion, it was found that the increases in the I.S. of the dissolution media, adjusted by either phosphate or NaCl drastically increased the dissolution rate of BCG or SC-41930 from the Eudragit S-100 coated pellets.

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REFERENCES

1. S.S. Ozturk, B.O. Palsson, B. Donohoe and J.B. Dressman. Kinetics of release from enteric-coated tablets. Pharm. Res. 5:550-565 (1988).
2. J.P. Ebel, M. Jay and R.M. Beihn. An in vitro/in vivo correlation for the disintegration and onset of drug release from enteric-coated pellets. Pharm. Res. 10:233-238 (1993).
3. J.P. Delporte. Essais de desintegration des comprimes a enrobage enterosoluble. Farmaco Ed. Prat. 30:111-139 (1975).

4. M. Hayashi, T. Nagai and H. Nogami. Factors affecting dissolution rate of cellulose acetate phthalate in aqueous solution. Chem. Pharm. Bull. (Tokyo) 18:2350-2353 (1970).
5. J. Spitael and R. Kinget. Factors affecting dissolution rate of enteric coatings. Pharm. Ind. 39:502-505 (1977).
6. J. Spitael, R. Kinget and N. Naessens. Dissolution rate of cellulose acetate phthalate and the Brönsted catalysis law. Pharm. Ind. 42:846-849 (1980).
7. M.J. Dew, R.E.J. Ryder, N. Evans and J. Rhodes. Colonic release of 5-aminosalicylic acid from a oral preparation in active ulcerative colitis. Br. J. Clin. Pharmac. 16:185-187 (1983).
8. M. Ashford, J.T. Fell, D. Attwood, H. Sharma, and P.J. Woodhead. An in vivo investigation into the suitability of the pH dependent polymers for colonic targeting. Int. J. Pharm. 95:193-199 (1993).
9. M. Ashford and J.T. Fell. Targeting drugs to the colon: delivery systems for oral administration. J. Drug Targeting 2:241-256 (1994).
10. I.R. Wilding, J.G. Hardy, R.A. Sparrow, S.S. Davis, P.B. Daly and J.R. English. In vivo evaluation of enteric-coated Naproxen tablets using gamma scintography. Pharm. Res. 9:1436-1441 (1992).
11. M. Alpsten, C. Bogentoft, G. Ekenved and L. Sölvell. Gastric emptying and absorption of acetylsalicylic acid administered as enteric-coated micro-granules. Eur. J. Clin. Pharmacol. 22:57-61 (1982).
12. J.G. Hardy, D.F. Evans, I. Zaki, A.G. Clark, H.H. Tønnesen and O.N. Gamst. Evaluation of an enteric coated Naproxen tablet using gamma scintigraphy and pH monitoring. Int. J. Pharm. 37:245-250 (1987).
13. J. Heinämäki, M. Marvola, I. Happonen and E. Westermarck. The fate of multiple-unit enteric-coated formulations in the stomach of the dog. Int. J. Pharm. 42:105-115 (1988).
14. K.K.H. Chan, P. Mojaverian, B.A. Ziehmer and V.A. John. Application of radiotelemetric technique in evaluating diclofenac sodium absorption after oral administration of various dosage forms in healthy volunteers. Pharm. Res. 7:1026-1032 (1990).
15. J.G. Hardy, J.N.C. Healey, S.W. Lee and J.R. Raynolds. Gastrointestinal transit of an enteric-coated delayed-release 5-aminosalcylic acid tablet. Aliment. Pharmacol. Therap. 1:209-216 (1987).
16. D.F. Evans, G. Pye, R. Bramley, A.G. Clark, T.J. Dyson and J.D. Hardcastle. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut 29:1035-1041 (1988).
17. J.W. Moore and R.G. Pearson. Kinetics and Mechanism, John Wiley & Sons, New York, 1981.
18. J.L. Zatz and B. Knowles. Effect of pH on monolayers of cellulose acetate phthalate. J. Pharm. Sci. 59:1750-1751 (1970).
19. In Cornelius Lentner and A. Wink. Geigy Scientific Tables, Volume 1, Ciba Geigy Limited, Basle, 1981.