Utilization of Hydrophilic Gums for the Control of Drug Substance Release from Tablet Formulations II. Influence of Tablet Hardness and Density on Dissolution Behavior

By H. E. HUBER and G. L. CHRISTENSON

The influence of tablet hardness and density variation on *in vitro* dissolution of dye from controlled release tablets made with different types and viscosity grades of hydrophilic polymers was investigated. Tablet volumes were maintained constant and the weight varied to obtain varying degrees of hardness and density. Tablets made at varying hardness did not show markedly different release characteristics as evaluated by an *in vitro* method. Different release patterns were, however, observed with tablets prepared from different gums.

A PREVIOUS REPORT (1) from these laboratories presented data to illustrate the utilization of hydrophilic gums as a means of controlling rate of drug release from tablet formulations. It was shown that the type and concentration of gum in a formulation could markedly influence disintegration and dissolution behavior. Recently, Lapidus and Lordi (2) published the results of their related investigations on factors affecting the release of water-soluble drugs from a compressed hydrophilic matrix. Their studies were concerned with theoretical aspects of the problem and focused attention on the kinetics of drug release in the initial stages of the process and from a single face of a tablet. They were able to show that under such conditions the release pattern appeared to follow the same relationships as were proposed by Higuchi (3, 4) for solid drugs dispersed in solid matrices.

The present investigation was conducted to determine, in part, the influence of formulation and processing variables on the release rate characteristics of tablets formulated with hydrophilic gums as the delaying matrix. In this study, the relationships between tablet hardness and release rate characteristics have been investigated. It was felt that a comparison of hardness measurements would reflect, quantitatively, differences in density and porosity of tablets made at different compressional forces.

Differences in density and porosity could possibly influence the rate of tablet dissolution by, for example, affecting the initial rate of penetration of water at the tablet surface and thus the rate of formation of the gel barrier at the tablet periphery. Such considerations are of practical importance since complete uniformity of compressional force is difficult to maintain in production operations and variations of release rate as a function of processing variables must be known to maintain reasonable tablet-to-tablet uniformity with regard to release rate characteristics.

Tartrazine (FD&C Yellow No. 5) was used in this study as a tracer to evaluate release characteristics. It was chosen because of analytical considerations. The release of the dye from a tablet could be easily followed spectrophotometrically and the spectral characteristics of the dye are pH independent over the pH range investigated. In addition, the dye served to visually indicate uniformity of distribution throughout the tablet. The gums selected for this study were carboxypolymethylene (CPM), sodium carboxymethylcellulose (NaCMC), and hydroxypropyl methylcellulose (HPMC). Three different viscosity grades of the latter gum were investigated (HPMC 100 cps., 4,000 cps., and 15,000 cps.).

EXPERIMENTAL

Tablet Granulations—Five different gums were investigated, CPM, NaCMC, HPMC 100 cps., HPMC 4,000 cps., and HPMC 15,000 cps. In each formulation equal parts of lactose and gum were mixed with 0.4% micropulverized tartrazine. The mix was slugged and screened, and 2% magnesium stearate was added for lubricant.

Preparation of Tablets—Two approaches can be used to vary the hardness characteristics of tablets. A constant weight of granulation can be used and the compression pressure exerted by the machine varied through adjustment of the die fill volume. As a result, tablets of different hardness would be obtained but the tablets would also have different volumes. Alternatively, tablets with different hardness values and constant volume can be prepared by using different weights of granulation and maintaining a constant fill volume. The second approach was used, because if weight is held constant and volume varied, differences in dissolution rate could be expected as a result of differences in surface area, and therefore the data would have little value in answering the basic question regarding influence of hardness on release rate characteristics.

Granulation was weighed out on a class A prescription balance and compressed on a Stokes model F tablet machine adjusted to provide a $^3/_8$-in. flat-faced tablet 4.1 to 4.2 mm. thick and with Pfizer hardnesses of approximately 6, 10, or 15 Kg. Once the weight required to obtain a desired hardness was found, additional tablets were made and hardness checked.

Six tablets were then made by weighing out granulation and compressing it at that particular machine setting. These 6 tablets were then weighed on a Mettler balance to the nearest 0.1 mg. and their thickness measured with an Ames micrometer to the nearest 0.01 mm. Volume was calculated using $\pi r^2 h$. Apparent density was calculated from average tablet weight/volume. Three of the 6 tablets, with apparent density values on the high and low side, were used to determine an average hardness. The remaining tablets were subjected to *in vitro* dissolution.

Received April 14, 1967, from the Pharmaceutical Research and Development Department, Scientific Laboratories, The Wm. S. Merrell Co., Division of Richardson-Merrell, Inc., Cincinnati, OH 45215

Accepted for publication August 16, 1967.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

Dissolution Study—Each tablet was placed in the basket rack assembly of a USP Stoll-Gershberg apparatus, lowered into an 800-ml. beaker containing 600 ml. of simulated gastric fluid (no enzymes) maintained at 37 ± 0.5° and operated for 1 hr. At the end of 1 hr., the basket rack, with tablet, was transferred to another 800-ml. beaker containing 600 ml. of simulated intestinal fluid (no enzymes) and the operation continued. A sample of the simulated gastric fluid was filtered through Whatman No. 42 paper and its absorbance measured at 420 mμ on a Spectronic 20 colorimeter. At hourly intervals the apparatus was stopped, the volume of simulated intestinal fluid adjusted to 600 ml., operated again for a short interval to assure mixing, and a 10-ml. sample was withdrawn. After filtration and reading the absorbance, the sample was returned to the beaker. Hourly assays were made until the tablet was dissolved or 7 hr. of data were obtained. Those tablets that remained undissolved were stirred on a magnetic stirrer until dissolved and an end point assay run. Three determinations were made for each hardness value.

Percent dye released each hour was calculated on the basis of total dye released for each tablet. By treating the data in this manner, differences in tablet weight and therefore total tablet dye content were eliminated.

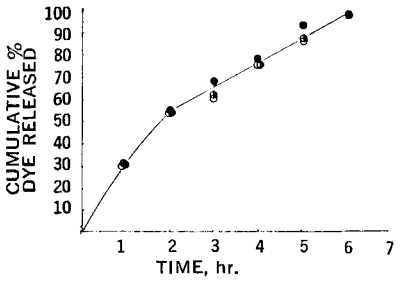

Fig. 1—Influence of tablet hardness on in vitro *dissolution of dye from CPM tablets. Key: ○, 6.1 Kg. average hardness; ◑, 12.1 Kg. average hardness; ●, 14.7 Kg. average hardness.*

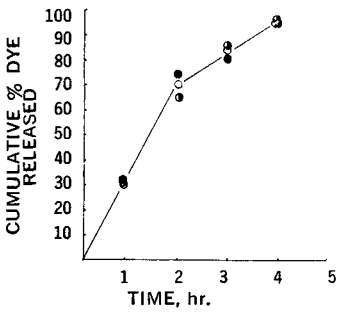

Fig. 2—Influence of tablet hardness on the in vitro *dissolution of dye from HPMC 100 cps. tablets. Key: ○, 6.3 Kg. average hardness; ◑, 8.8 Kg. average hardness; ●, 13.5 Kg. average hardness.*

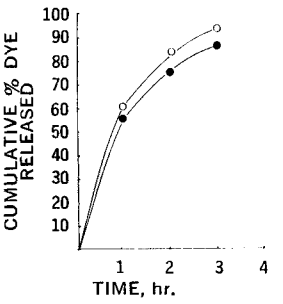

Fig. 3—Influence of tablet hardness on in vitro *dissolution of dye from NaCMC tablets. Key: ○, 5.7 Kg. average hardness; ●, 11.7 Kg. average hardness.*

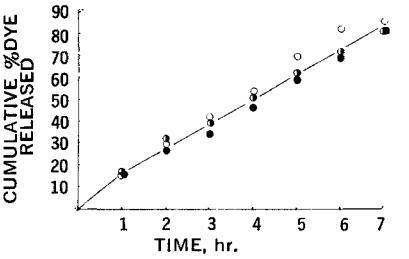

Fig. 4—Influence of tablet hardness on in vitro *dissolution of dye from HPMC 4,000 cps. tablets. Key: ○, 5.3 Kg. average hardness; ◑, 8.4 Kg. average hardness; ●, 11.8 Kg. average hardness.*

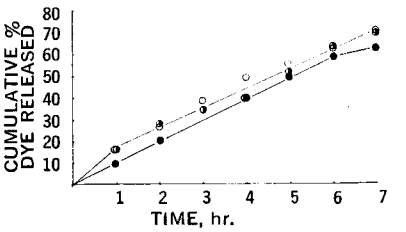

Fig. 5—Influence of tablet hardness on in vitro *dissolution of dye from HPMC 15,000 cps. tablets. Key: ○, 5.7 Kg. average hardness; ◑, 10.4 Kg. average hardness; ●, 13.7 Kg. average hardness.*

TABLE I—TABLET HARDNESS AND DENSITY

Gum	Hardness, Kg.	Apparent Density, Gm./ml.
CPM	6.1	1.03
	12.1	1.11
	14.7	1.18
HPMC, 100 cps.	6.3	1.19
	8.8	1.23
	16.6	1.30
HPMC, 4,000 cps.	5.3	1.23
	8.4	1.25
	11.8	1.29
HPMC, 15,000 cps.	5.7	1.19
	10.4	1.24
	13.7	1.28
NaCMC	5.7	1.33
	11.7	1.41

RESULTS

No significant differences in release rate of dye could be seen for tablets made with CPM, HPMC

100 cps., and HPMC 4,000 cps. at approximately 6, 10, and 15 Kg. hardness (Figs. 1, 2, and 4). Average apparent tablet densities and corresponding hardness values are shown in Table I.

HPMC 15,000 cps. and NaCMC tablets demonstrated a slightly reduced rate of dye release during the first hour of *in vitro* dissolution as a result of increased hardness and density. The rates of dye release for the remaining dissolution period remained approximately the same, regardless of tablet hardness (Figs. 3 and 5 and Table I).

DISCUSSION

The data indicate that one can expect little or no change in dissolution rate pattern as a result of alteration in tablet density and porosity for some hydrophilic gum formulations. If changes occur, they probably will appear during the initial phase of the dissolution period and the shape of the dissolution profile will not be markedly altered. Apparently, the affinity of some gums for water will overcome any deterring influence which an increased density or decreased porosity may tend to exert on the initial rate of water penetration into the tablet surface. In those cases where the gum and/or formulation exhibit a decreased affinity for water, an increase in density will deter water penetration and reduce the rate of drug substance dissolution until a gel barrier is formed. After the gel barrier is formed, the rate of drug substance release is further reduced and becomes dependent on the rate at which drug substance diffuses through the gel and the rate at which the gel barrier is mechanically removed by agitation.

SUMMARY AND CONCLUSIONS

In an investigation of *in vitro* dissolution behavior for tablets compressed to different degrees of hardness, no changes in dissolution rate pattern were observed for three formulations. In two formulations, a slightly reduced rate of dissolution was noted during the first hour; however, no marked change in the total dissolution profile was observed. Different release rate profiles were observed with tablets prepared from different gums.

REFERENCES

(1) Huber, H. E., Dale, L. B., and Christenson, G. L., *J. Pharm. Sci.*, **55**, 974(1966).
(2) Lapidus, H., and Lordi, N. G., *J. Am. Pharm. Assoc., Sci. Ed.*, **55**, 840(1960).
(3) Higuchi, T., *J. Pharm. Sci.*, **50**, 874(1961).
(4) *Ibid.*, **52**, 1145(1963).

Keyphrases

Tablet formulation dissolution
Hydrophylic resin tablet formulations
Tablet hardness
Tablet density
Simulated gastric fluid
Simulated intestinal fluid
Colorimetric analysis

Tetracyclic Phenothiazines I. Reinvestigation of the Brominations of Some Pyrido[3,2,1-*kl*]phenothiazines

By ARNOLD R. MARTIN, GERALD G. BRIGGS, and TIMOTHY J. YALE

Brominations of both 1,2-dihydro-3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (I) and its sulfoxide (VII) gave 3-hydroxypyrido[3,2,1-*kl*]phenothiazinium bromide (VI). Treatment of 3-keto-3*H*-pyrido[3,2,1-*kl*]phenothiazine (II) with bromine gave 2-bromo-3-hydroxypyrido[3,2,1-*kl*]phenothiazinium bromide (XII). Structural assignments of VI and XII have been made on the basis of their spectral properties, correcting those previously reported.

As a result of an interest in tetracyclic phenothiazine derivatives as intermediates for the synthesis of pharmacologically interesting agents, the reactions of 1,2-dihydro-3-keto-3*H*-pyrido-[3,2,1-*kl*] phenothiazine (I) and 3-keto-3*H*-pyrido-[3,2,1-*kl*]phenothiazine (II) with bromine (Scheme I) were reinvestigated. Harfenist (1) reported the bromination of I to give a "bromo derivative," which he assumed to be the bromoketone (III), on the basis of its elemental analysis. Heating of the "bromo derivative" in aqueous methanol caused its conversion to the unsaturated ketone (II). The reaction of II with bromine gave an unstable "dibromide," assumed to be the addition product (IV). Attempts to recrystallize IV reportedly gave the unsaturated bromoketone (V). The interpretation of the infrared and ultraviolet spectra of the two bromination products originally prepared by Harfenist requires reassignment of their structures.

RESULTS AND DISCUSSION

The infrared spectrum of the "bromo derivative" obtained from I lacks a carbonyl band, but shows the characteristics of an ionized amine salt, *i.e.*, a nearly continuous series of bands in the region of about 2300–2700 cm.$^{-1}$(2). The high melting point of the "bromo derivative" and its solubility behavior (it is insoluble in nonpolar solvents) further militate against the bromoketone structure III. The aromatized salt structure VI, on the other hand, is consistent with the analytical, spectral, and

Received April 14, 1967, from the College of Pharmacy, Washington Sate University, Pullman, WA 99163
Accepted for publication August 15, 1967.
Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.
This investigation was supported in part by grant MH 12425 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.