Dissolution Behavior of Commercial Tablets Extemporaneously Converted to Capsules

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Abstract □ While conducting double-blind clinical trials, it is a common practice to convert a commercial tablet dosage form to a capsule so that it may serve as a control drug for the new drug under test. This report will show that when this was done, the *in vitro* dissolution times of drugs from the capsule dosage forms were strikingly prolonged. Various capsule adjuvants were examined, attempting to decrease dissolution times of drugs from capsules. Of the series tested, lyophilized glycine had the best positive effect in shortening the dissolution times of all drugs examined.

Keyphrases □ Dissolution behavior—commercial tablets converted to capsules □ Dissolution rates—effect of starch □ Starch—effect on dissolution

During both single- and double-blind clinical studies, a commercial tablet dosage form is frequently altered to a capsule dosage form (1). The alteration to a capsule from a tablet is usually accomplished by grinding the commercial tablet to a granular or fine powder and then adding a sufficient amount of a physiologically inert capsule adjuvant to prepare extemporaneously a capsule dosage form which is identical in appearance to the research drug.

It was of interest to study any effect on the dissolution process brought about by the conversion of commercial tablet dosage forms to extemporaneously prepared capsule dosage forms. Further, it was of interest to observe the overall effect of certain capsule adjuvants on the dissolution process with the objective of perhaps decreasing the dissolution times of drugs from a capsule formulation.

A drug's dissolution rate and *in vivo* physiological availability have been the subjects of extensive research in the pharmaceutical sciences (2–6). In a recent paper, Withey and Mainville (7) referred to various methods and apparatus for following dissolution rates. They also pointed out some important requirements for an adequate dissolution-rate test.

For this preliminary investigation, the dissolution characteristics were measured by a procedure that involved the use of a modified capsule holder designed by Paikoff and Drumm (8). For comparative purposes, T_{90} values (time required for 90% to dissolve) were obtained for three chemically different types of drugs: (*a*) acetylsalicylic acid,[1] (*b*) diphenhydramine,[2] and (*c*) meprobamate.[3]

EXPERIMENTAL

Equipment—The capsule holder-stirrer had two glass blades with a platinum wire loop attached at the bottom to hold various size capsules. The stirrer was attached to a Heller stirrer (model No. GT 21).

Procedure—A 500-ml. quantity of dissolution medium (deionized water) in an 800-ml. beaker was maintained at 37 ± 0.5° in a temperature-controlled bath. The dosage form was introduced into the medium by attaching it to the stirrer loop and then inserting the assembled unit into the beaker at a controlled height from the bottom. Constant preselected rotational speeds of 60–200 r.p.m. were used for each of the three different drugs. Aliquots for assay were withdrawn with a sampling pipet at appropriate time intervals. After each sample removal, fresh medium was added back to the dissolution test beaker to maintain a constant volume.

The methodology described was suitable for capsules and tablets of acetylsalicylic acid and for diphenhydramine, but it had to be modified for the testing of meprobamate tablets and capsules to prevent flotation of capsule fragments and larger aggregates. A stainless steel wire net (20 mesh) resting on the bottom of the dissolution test beaker was used to hold the tablets and capsules of meprobamate. The glass stirrer without the loop was used.

There was no intention of comparing the dissolution characteristics between drugs. What was examined was the dissolution characteristics of commercial tablets and those tablets after conversion to a capsule dosage form, using the equivalent methodology for both forms.

The acetylsalicylic acid samples were hydrolyzed, and the absorbance of salicylic acid was measured at 294 mμ with the Beckman DK-2A (9). Diphenhydramine was assayed by two methods, one a conductometric method in the absence of glycine and the other a spectrophotometric method using a wavelength of 277 mμ. The meprobamate was assayed according to the method of Maggiorelli (10) with a modification that included using an acetic anhydride and glacial acetic acid mixture to dissolve the evaporated residue from the chloroform–carbon tetrachloride (1:1 v/v) extract (11).

Preparation of Capsules—The capsules were prepared from uncoated commercial tablets (standard compressed tablets) by grinding the tablets to a powder (through 40 mesh) with a mortar and pestle. Sufficient amounts of various capsule adjuvants were added to the powder and mixed well, and the diluted powder was packed into an appropriately sized hard gelatin capsule (Table I).

RESULTS AND DISCUSSION

The conversion of a tablet to a capsule dosage form did bring about a marked change in the *in vitro* dissolution times of all three drugs studied (Tables II–V). Without exception, the capsule dosage form containing starch took a much longer time to release 90% of its contents than did the tablet dosage form. This phenomenon, since it was observed with three different chemical types of drugs, should be more extensively studied and the results called to the attention of designers of clinical trials because of its frequency of occurrence in blind studies. Slowing down the dissolution rate of a commercial drug used as a control in a clinical trial could severely bias the results of such trials.

The materials used as diluents to prepare the capsules (starch, urea, and various forms of glycine, Table I) had varying effects upon the dissolution times. The lyophilized form of glycine had outstandingly beneficial effects upon the dissolution times of all three chemical types of drugs (Tables II–V).

The data reported in Tables II–V are abstracted from the total experimental data developed in this study. To conserve space, data falling into sampling intervals not covered by the table have been omitted. For example, Product D, Table II, had the following experimental sampling intervals in minutes: 3, 6, 10, 12, 15, 18, and 23. Since this inclusive table has only Columns 10 and 15, the data at only these matching times are included. The minimum number of

[1] Bayer Aspirin, Glenbrook Laboratories, New York, N. Y.
[2] Dramamine, G. D. Searle & Co., Chicago, Ill.
[3] Miltown, Wallace Laboratories, Cranbury, N. J.

Table I—Formulations of Various Products

Products[a]	Weights of, g. Five Tablets	Starch Potato	Urea	Lyophilized Urea	Glycine	Lyophilized Glycine	Ball Milled Glycine	Average Weight of Mixture in Capsules, g.[b]
Diphenhydramine								
B-1	1.3494	1.0053	—	—	—	—	—	0.4735 (2)
C	1.3341	—	0.5015	—	—	—	—	0.4547 (2)
D	1.3408	—	—	1.0142	—	—	—	0.3609 (2)
B-2	1.3376	1.0000	—	—	—	—	—	0.5961 (1)
E	1.3133	—	—	—	1.0000	—	—	0.6052 (1)
F	1.3390	—	—	—	—	1.0020	—	0.5603 (1)
Acetylsalicylic acid								
B	2.0262	1.0000	—	—	—	—	—	0.6456 (0)
C	2.0202	—	1.0057	—	—	—	—	0.6717 (0)
E	2.0322	—	—	—	1.2790	—	—	0.6552 (0)
F	2.0514	—	—	—	—	1.0000	—	0.5312 (0)
Meprobamate								
B	2.3811	1.0000	—	—	—	—	—	0.6115 (0)
E	2.4034	—	—	—	1.0030	—	—	0.6201 (0)
F	2.3965	—	—	—	—	1.0047	—	0.6367 (0)
G	2.3923	—	—	—	—	—	1.0012	0.5744 (0)

[a] Product A consists of commercial tablets. [b] Number in parenthesis indicates size of capsules.

sampling intervals for any product was 4, the maximum was 13, and the average was 6 data points. The data reported are the averages of three experimental dissolution studies on each product.

After each dissolution test, orders were estimated as either an apparent first- or zero-order process after the various plots had linearized following a short, but variable, lag time. Least-squares regression lines were calculated; from the appropriate values for the equation, the T_{90} values were calculated. No special significance is claimed for any of the apparent first or zero orders reported.

Wagner (12) has suggested that apparent dissolution-rate orders are artifacts at best. This technique was used only to obtain a value to serve as a basis for the comparison of the dissolution behavior of a tablet and its extemporaneously prepared capsule.

Starch is frequently used as a disintegrating or a wet binding agent in tablet formulations. By identity test, each of the three commercial tablet formulations contained starch in varying amounts. When additional starch was added to the ground-up tablet, it did not visibly show any disintegrant or dispersing effect upon the

Table II—Comparison of Dissolution-Rate Data of Diphenhydramine

Product[a]	Percent Remaining Undissolved,[b] min. 0	5	10	15	20	30	40	50	T_{90}, min.
A	100	78.80	52.80	32.80	—[c]	—	—	—	28.40[d]
B-1	100	—	—	63.24	—	36.71	23.93	14.77	57.80[d]
C	100	—	71.20	54.11	—	23.49	—	—	40.49[d]
D	100	—	77.24	59.04	—	—	—	—	25.37[e]

[a] See Table I for formulation. [b] Each point is the average of three determinations. [c] —, no experimental value at this time. [d] Apparent first-order rate process. [e] Apparent zero-order rate process.

Table III—Comparison of Dissolution-Rate Data of Diphenhydramine with Glycine

Product[a]	Percent Remaining Undissolved,[b] min. 0	5	10	15	20	30	40	50	T_{90}, min.
A	100	79.48	—[c]	37.04	—	—	—	—	31.15[d]
B-2	100	—	—	—	60.91	48.85	38.12	28.14	91.74[d]
E	100	—	—	—	—	46.40	29.79	—	54.00[e]
F	100	—	—	—	58.73	37.00	—	—	37.68[e]

[a] See Table I for formulation. [b] Each point is the average of three determinations. [c] —, no experimental value at this time. [d] Apparent first-order rate process. [e] Apparent zero-order rate process.

Table IV—Comparison of Dissolution-Rate Data of Acetylsalicylic Acid

Product[a]	Percent Remaining Undissolved,[b] min. 0	5	10	15	20	30	40	50	T_{90},[c] min.
A	100	74.31	57.67	49.21	42.76	34.00	24.72	—	84.03
B	100	88.14	77.41	—[d]	60.57	47.85	37.27	32.27	111.11
C	100	—	58.75	33.11	—	—	—	—	39.26
E	100	—	75.83	63.88	53.22	40.28	30.42	22.43	75.64
F	100	—	67.85	46.45	28.25	—	—	—	28.22

[a] See Table I for formulation. [b] Each point is the average of three determinations. [c] Apparent first-order rate process. [d] —, no experimental value at this time.

Table V—Comparison of Dissolution-Rate Data of Meprobamate

Product[a]	Percent Remaining Undissolved,[b] min. 0	10	20	30	40	50	60	75	T_{90},[c] min.
A	100	—[d]	10.01	—	—	—	—	—	20.53
B	100	75.53	—	—	54.60	—	—	40.68	284.09
E	100	69.45	58.91	52.36	44.52	—	38.41	31.36	196.08
F	100	79.23	72.69	62.04	50.23	—	—	—	124.38
G	100	84.36	72.42	53.96	42.68	33.65	28.01	—	100.00

[a] See Table I for formulation. [b] Each point is the average of three determinations. [c] Apparent first-order rate process. [d] —, no experimental value at this time.

capsule formulation.

This observation leads one to believe that the primary granules formed from the normal disintegration of a tablet in an aqueous medium differ in some physical manner from the granules obtained by grinding up a tablet.

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Mechanism of Action of Salicylates VIII: Effect of Topical Application of Retinoic Acid on Wound-Healing Retardation Action of a Few Anti-Inflammatory Agents

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Abstract □ Oral administration of phenylbutazone, oxyphenbutazone, mefenamic acid, flufenamic acid, or indomethacin, like salicylates or corticosteroids, retards skin wound healing in rats. The healing inhibitory action of any one of these anti-inflammatory agents can be reversed by local application of retinoic acid.

Keyphrases □ Retinoic acid, topical application—inhibition of wound-healing retardation of anti-inflammatory agents □ Anti-inflammatory agents, wound-healing retardation—retinoic acid inhibition □ Salicylates, wound-healing mechanism—analogy to other anti-inflammatory agents

Recently, it has been shown that oral administration of acetylsalicylic acid, sodium salicylate, or prednisone and topical application of salicylic acid or hydrocortisone in nonionic bases (NIB) retard skin wound healing in rats (1–3). The inhibitory action of these agents is, at least, partially attributed to their anti-inflammatory action since inflammation is an essential feature in healing. Salicylates also inhibit mucopolysaccharide synthesis, which is also an essential feature in wound healing (2). Intraperitoneal injection of retinol or topical application of retinoic acid can reverse the inhibitory action of these anti-inflammatory agents (2, 3).

Phenylbutazone, oxyphenbutazone, mefenamic acid, flufenamic acid, and indomethacin are a few well-known anti-inflammatory agents. These agents, like salicylates, inhibit mucopolysaccharide synthesis (4). In the present study, it was found that all of these anti-inflammatory agents also retard wound healing, and topical application of retinoic acid can reverse the inhibitory action of these agents.