Oral Dosage Form Design and Its Influence on Dissolution Rates for a Series of Drugs

FOO SONG HOM and JOHN J. MISKEL

Abstract □ The study illustrates the influence oral dosage form design has on dissolution rates for drugs from different chemical and pharmacological classes. Comparative data demonstrate that relatively insoluble drugs, when formulated in soft elastic capsules, are released faster than from commercially available tablets. Faster dissolution from soft elastic capsules is believed to be due to the more rapid dispersion of the active ingredients. Rapid dispersion of medicaments is enhanced by the use of solubilizers and/or surfactants in the formulation design. Soft elastic capsules are recommended for the formulation of low-dose medications, of relatively insoluble drugs, and of drugs where early high-blood level of the drug is indicated.

Keyphrases □ Oral dosage form design effect—dissolution rates □ Capsules, soft elastic, tablets—drug release-rate comparison □ Rotating-bottle apparatus—dissolution testing □ UV spectrophotometry—analysis

In recent years, numerous scientists have demonstrated the direct relationship between proper formulation of a dosage form and the production of a clinically effective drug product. Many correlations have been established between formulation design and therapeutic activity, reporting the interrelation of particle size, dissolution, and absorption. In a review, Nelson (1) indicated that the rate of gastrointestinal absorption of a drug is often a function of the time needed for the drug to dissolve in the fluid at the site of absorption. He pointed out that, in general, the availability for absorption decreases in the order: solution > suspension > powder-filled capsule > compressed tablet > coated tablet. However, changes in this order may occur for various reasons, but they are exceptions. Tannenbaum *et al.* (2) demonstrated that in some cases, through the use of modern pharmaceutical techniques, it is possible to produce a tablet that results in greater drug absorption than a powder-filled capsule. Wagner *et al.* (3), in their study on the effect of dosage form on serum levels of indoxole, observed that the serum level response decreases in the order: emulsion (Lipomul-Oral) ≃ soft gelatin capsule > aqueous suspension > powder-filled capsule. Aguiar *et al.* (4) studied and correlated the effects of deaggregation or dispersion, dissolution, and *in vitro* gut-permeation rates on the chloramphenicol availability from four commercial lots of capsules. Glazko *et al.* (5) observed different absorption rates from capsules containing identical amounts of chloramphenicol from different manufacturers. Similarly, Brice and Hammer (6) observed significant differences in serum antibiotic levels obtained from 16 commercially available lots of oxytetracycline capsules distributed by 13 different suppliers.

The present work is a study of the influence of soft elastic capsule and tablet dosage forms on dissolution rates for a series of chemically and pharmacologically different drugs. While it will be agreed that *in vitro* dissolution rate data do not necessarily reflect *in vivo* absorption and availability, sufficient correlation exists to justify the use of this technique to measure potential dosage form efficiency (7–12). The rotating-bottle method (13–15) is used to compare the dissolution rates of soft elastic capsules and tablets.

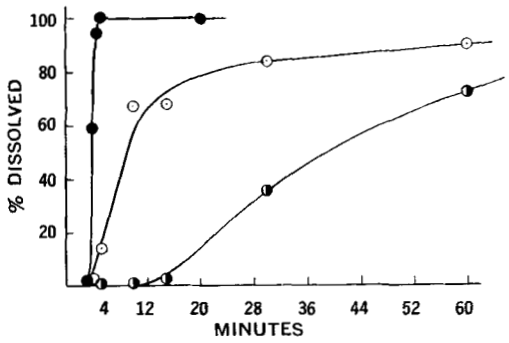

Figure 2—*Dissolution rates of ethinyl estradiol capsule and tablets in simulated gastric fluid T.S. Key: ●, soft elastic capsule; ⊙, Tablet A; and ◑, Tablet B.*

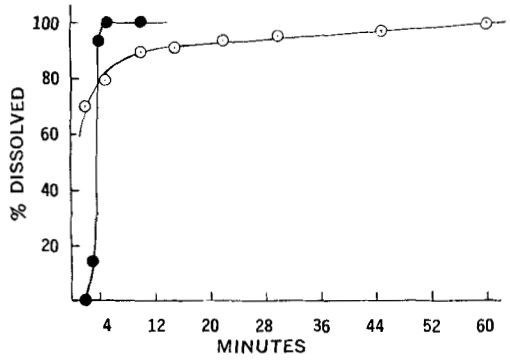

Figure 1—*Dissolution rates of hydrocortisone capsule and tablet in simulated gastric fluid T.S. Key: ●, soft elastic capsule; and ⊙, Tablet A.*

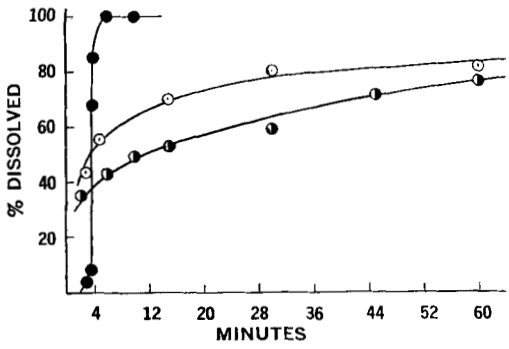

Figure 3—*Dissolution rates of diethylstilbestrol capsule and tablets in simulated gastric fluid T.S. Key: ●, soft elastic capsule; ⊙, Tablet A; and ◑, Tablet B.*

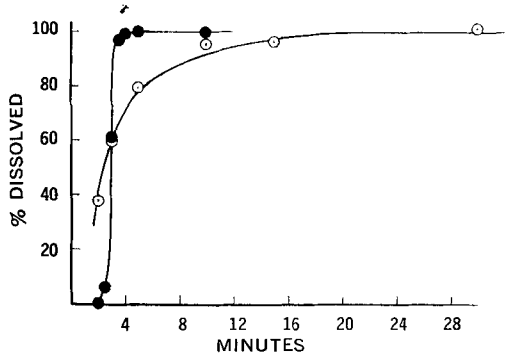

Figure 4—*Dissolution rates of phenobarbital capsule and tablet in simulated gastric fluid T.S. Key: ●, soft elastic capsule; and ⊙, Tablet A.*

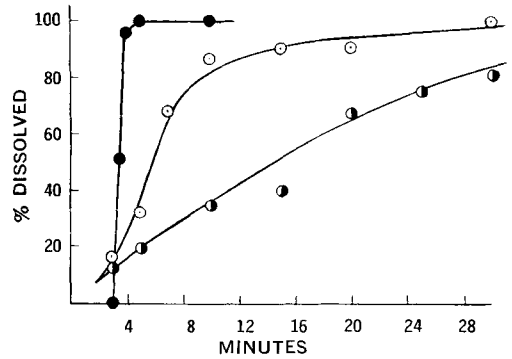

Figure 5—*Dissolution rates of reserpine capsule and tablets in simulated gastric fluid T.S. Key: ●, soft elastic capsule; ⊙, Tablet A; and ◑, Tablet B.*

EXPERIMENTAL

A drug must be formulated in one of several dosage forms, depending on its intended use. In general, a dosage form is designed for rapid and complete absorption of the drug. In some cases a dosage form may be developed for delayed action or for combined effects of quick onset and prolonged action. For rapid and complete absorption of a drug, it is best to formulate in solution. However, this is not always practical, as with very insoluble drugs. In this case the next best form is the suspension dosage form. Modern pharmaceutical technology embraces the use of surfactants and/or solubilizers to enhance the rapidity and maximum absorption of a drug. By nature, many surfactants and solubilizers are liquids at room temperature. Hence, these agents may play multifaceted roles in liquid formulations: as vehicles and interface modifiers. Formulations of a drug containing surfactants and/or solubilizers may be encapsulated conveniently in soft elastic capsules, as demonstrated in the present work which includes examples of relatively insoluble drugs.

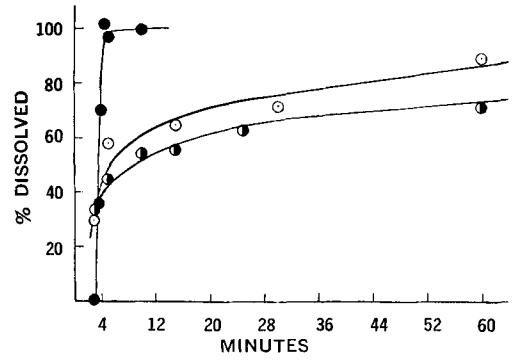

Figure 6—*Dissolution rates of digitoxin capsule and tablets in simulated gastric fluid T.S. Key: ●, soft elastic capsule; ⊙, Tablet A; and ◑, Tablet B.*

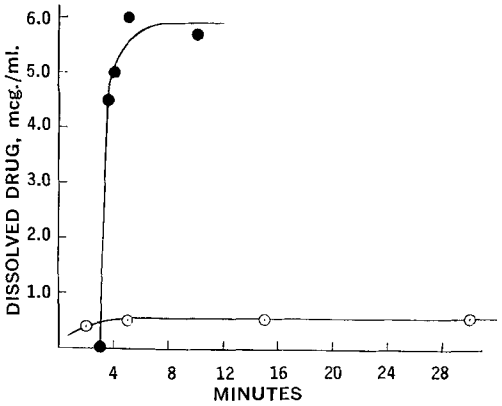

Figure 7—*Dissolution rates of bishydroxycoumarin capsule and tablet in simulated gastric fluid T.S. Key: ●, soft elastic capsule; and ⊙, Tablet A.*

Products Tested—For the purpose of this study the drugs chosen represent a number of chemical and pharmacological classes. The soft elastic capsules were manufactured using the continuous rotary die process. The drugs, where possible, were dissolved in polyethylene glycol 400 USP or suspended in various polyols with 1–3% of a nonionic surfactant. In some cases the dispersion vehicle was a nonionic surfactant or mixture of nonionic surfactants. Commercial capsules and tablets were purchased on the open market. These include "brand name" drugs and their generic counterparts.

Method—The rotating-bottle apparatus (13–15) was used for the dissolution tests in the following manner. Into each of the bottles was placed 50 ml. of simulated gastric fluid T.S. (without pepsin), and the bottles were allowed to come to temperature equilibrium in a water bath at 37.5 ± 0.1°. One tablet or capsule was added to each bottle and rotation begun at about 40 r.p.m. At suitable time intervals, a bottle was removed and the contents filtered immediately through a 0.22-μ Millipore filter in a microsyringe filter holder.[1] An aliquot of the clear filtrate was diluted and analyzed by appropriate USP (16) methods of colorimetry or spectrophotometry. Ethinyl estradiol was analyzed by a special colorimetric method (17). A technique similar to the one published by Burns *et al.* (18) was used to analyze phenylbutazone (λ = 265 mμ, 0.1 *N* NaOH). Similarly the method of UV spectrophotometry was used to analyze sulfadiazine (λ = 309 mμ, 0.1 *N* HCl) and propylthiouracil (λ = 275 mμ, H_2O).

RESULTS AND DISCUSSION

Results, where possible, were plotted as percent of the amount ultimately dissolved so as to remove differences of overages occur-

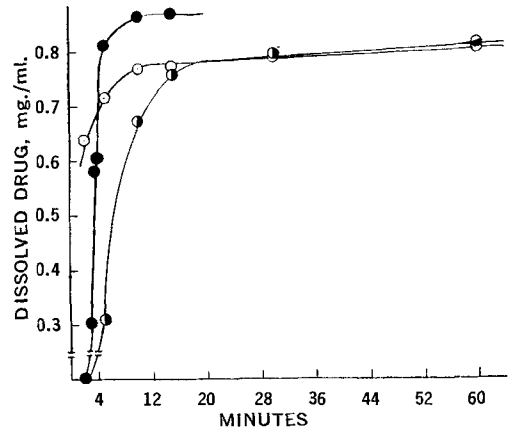

Figure 8—*Dissolution rates of sulfadiazine capsule and tablets in simulated gastric fluid T.S. Key: ●, soft elastic capsule; ⊙, Tablet A; and ◑, Tablet B.*

[1] Cat. No. XX30 025 00, Millipore Corp., Bedford, MA 01730

Table I—Dissolution Time in Minutes for 90% Drug Dissolved in Simulated Gastric Fluid at 37.5°

Drug	Dose, mg./ Capsule or Tablet	Soft Elastic Capsule,[a] min.	Tablet A, min.	Tablet B, min.
Hydrocortisone	5.0	4.0 ± 0.2	12 ± 1	
Ethinyl estradiol	0.05	4.2 ± 0.1	60 ± 2	83 ± 2
Diethylstilbestrol	0.5	4.2 ± 0.1	96 ± 8	96 ± 8
Phenobarbital	32.0	3.1 ± 0.3	9 ± 0.5	
Reserpine	0.25	3.9 ± 0.3	14 ± 2	35 ± 2
Digitoxin	0.2	4.2 ± 0.2	70 ± 8	136 ± 8

[a] Solution of drug encapsulated.

Table II—Amount in Micrograms of Drug Dissolved per Milliliter of Simulated Gastric Fluid at 37.5° after 5 Min. of Dissolution

Drug	Dose, mg./ Capsule or Tablet	Soft Elastic Capsule,[a] mcg./ml.	Tablet A, mcg./ml.	Tablet B, mcg./ml.
Bishydroxycoumarin	25.0	5.9 ± 0.3	0.6 ± 0.1	
Sulfadiazine	500.0	810 ± 5	715 ± 5	310 ± 25
Phenylbutazone	100.0	100 ± 30	1.5 ± 0.5	
Propylthiouracil	50.0	980 ± 20	380 ± 20	250 ± 20

[a] Suspension of drug encapsulated.

ring in different products. With practically insoluble drugs, where only a fraction of the dose is dissolved, the amount of drug dissolved in 1 ml. of fluid was plotted *versus* dissolution time. Completion of dissolution, the saturation point in the case of poorly soluble drugs, was taken as the time on the graph when a smooth curve through the points reached a maximum. Typical curves are shown in Figs. 1–10. Figures 1–6 are plots of percent drug dissolved *versus* time from tablets and from solutions encapsulated in soft elastic capsules. Figures 7–10 are plots of milligrams or micrograms of drug dissolved per milliliter of fluid *versus* time for commercial tablets and for suspensions encapsulated in soft elastic capsules. A cursory observation of Figs. 1–10 is sufficient to conclude that dissolution of the drug from soft elastic capsules is faster than from tablets in simulated gastric fluid T.S. (without pepsin) at 37.5°. However, a quantitative comparison may be made by observing the average time from duplicate runs for dissolution of 90% of the drug, as shown in Table I. Table II lists the average amount in micrograms from duplicate runs of relatively insoluble drugs dissolved per milliliter of fluid after 5 min. of dissolution. An examination of Table I reveals that a drug, when formulated in soft elastic capsules, will have a dissolution rate from 3 to 30 times faster than tablets. It is apparent that the increase in dissolution rate is due to the rapid dispersion of the drug when the capsule splits open. Also, the use of a proper vehicle, solubilizer, and surfactant apparently helps to enhance the dispersion of a relatively insoluble drug. Table II details the average increase, provided by the soft elastic capsule, in the apparent solubility of the drug ranging from 1.1 to 67 times that of tablets reflecting the effects of the vehicle, solubilizer, and surfactant.

The data indicate that it is possible to solubilize many low-dose, relatively insoluble drugs and to encapsulate them in soft elastic capsules of appropriate sizes. For high-dose and very insoluble drugs, it is preferable to encapsulate them as suspensions. With the applications of these two techniques in encapsulation, conceivably one can either singly or collectively use solubilizers and/or surfactants as specially designed vehicles for each drug. The soft elastic capsule is an ideal dosage form for drugs such as the oral contraceptives where submilligram unit doses are common.

An appreciation of the profound influence dosage form design has on dissolution, absorption, and efficacy (1–12) should preclude sole reliance on conventional tablet and powder-filled capsule technology in the development of "new drug" dosage forms. The costs of carrying new drug dosage forms through toxicity studies, clinical trials, and a new drug application procedure make errors in this area disastrous. Solutions and suspensions in soft elastic capsules, as well as tablets and dry-filled capsules, should be investigated in early stages of development employing *in vitro* dissolution studies. Availability as provided by the more promising dosage forms should then be appraised by *in vivo* animal studies.

CONCLUSIONS

The study illustrates the influence of oral dosage form design on dissolution rates for drugs from different chemical and pharma-

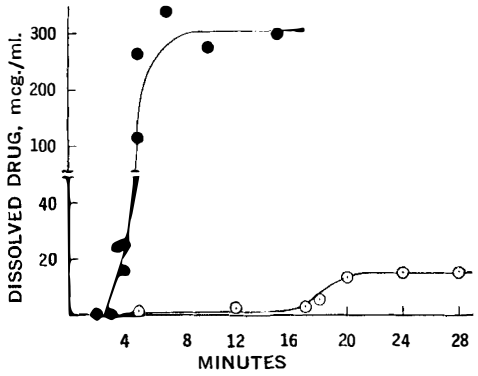

Figure 9—*Dissolution rates of phenylbutazone capsule and tablet in simulated gastric fluid T.S. Key: ●, soft elastic capsule; and ⊙, Tablet A.*

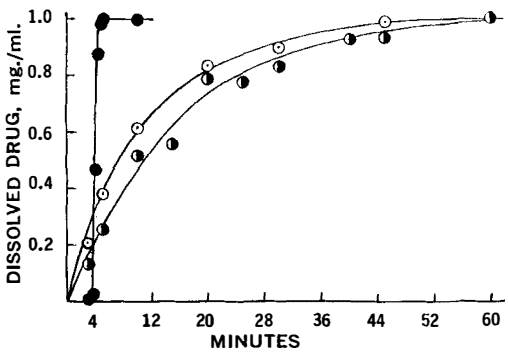

Figure 10—*Dissolution rates of propylthiouracil capsule and tablets in simulated gastric fluid T.S. Key: ●, soft elastic capsule; ⊙, Tablet A; and ◑, Tablet B.*

cological classes. It also suggests avenues that should not be overlooked when investigating new drugs or improving older medications. The results demonstrate that many relatively insoluble drugs may be readily formulated in soft elastic capsules and have faster dissolution rates than tablets in that solutions or suspensions of a drug can be readily encapsulated. Furthermore, surfactants or other compounds may be encapsulated along with the drug so as to enhance its solubility and potential absorption rate. Soft elastic capsules are recommended in the formulations of low-dose medication, of relatively insoluble drugs, and of drugs where early high-blood level of the drug is indicated.

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DRUG STANDARDS

Chemical Standardization and Quality Assurance of Whole Crude Coal Tar USP Utilizing GLC Procedures

M. GRUBER, R. KLEIN, and M. FOXX

Abstract □ A procedure has been developed which utilizes gas-liquid chromatographic (GLC) analysis for the chemical standardization of medicinal crude coal tar USP. A similar method is recommended for the determination of coal tar fractions in Liquor Carbonis Detergens (LCD) (coal tar solution USP). Data confirming that LCD and similar "extracts," "fractionates," and "synthetics" cannot be considered as generic, pharmaceutical, or medicinal equivalents of a properly standardized whole crude coal tar are presented.

Keyphrases □ Crude coal tar—analysis □ Coal tar solution—analysis □ Ethanol content, coal tar solution—determination □ GLC—analysis.

Dioscorides, a Greek physician, described nearly 2000 years ago the merits of asphaltic tar in the "Materia Medica" as a treatment for cutaneous disorders (1). The advantages of the empirical use of "tars" were subsequently emphasized by numerous investigators including Brocq (2), White (3), and Goeckerman (4, 5).

In modern times, this medication is widely prescribed for various skin diseases, such as psoriasis and eczema, which are frequently severe and occasionally disabling. In addition, this modality is routinely prescribed for seborrheic dermatitis, occupational and contact dermatitis, dermatophytosis, varicose eczema, chronic and exudative and lichenoid dermatitis, pruritis ani, and various other chronic skin disorders.

Although therapeutic response is often dramatic, the known variability of coal tar composition and consequent inconsistency of clinical results has made this medication the subject of complaint and controversy among dermatologists.

This ancient but fundamental topical drug is virtually devoid of any guardian standards of chemical composition. Consequently, almost any coal tar, regardless of its composition, may satisfy the requirements of current official compendia for crude coal tar. Practically no controls have been established to assure uniformity, potency, safety, and efficacy. It is, therefore, quite evident that the scientific development of far more definitive drug reference standards and methods of analysis for this valuable, but variable, therapeutic agent is mandatory. No proficient effort has been initiated to create an effective method to control the physical and