Solid Dispersion Approach to the Formulation of Organic Liquid Drugs Using Polyethylene Glycol 6000 as a Carrier

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Abstract □ Five poorly water-soluble liquid compounds—benzonatate, clofibrate, methyl salicylate, benzyl benzoate, and *dl*-α-tocopheryl acetate—were solid dispersed in a polyethylene glycol 6000 carrier by the melting method. The solidified mass, containing up to 5 or 10% (w/w) of liquid compounds, could be pulverized, encapsulated, and tableted. In the *in vitro* dissolution studies, the active ingredients were completely dissolved in 4–14 min. The preparations were highly reproducible, and the active ingredients were shown to distribute homogeneously within the carrier matrix. This approach represents a new method in the formulation of liquid medicinal compounds. The application of the solid dispersion principle in formulating a prolonged or sustained-release dosage regimen is also discussed.

Keyphrases □ Dispersion, solid, using polyethylene glycol 6000—in formulating organic liquid drugs □ Medicinals, liquid—solid dispersed using polyethylene glycol 6000 as carrier □ Polyethylene glycol 6000—carrier for solid dispersion of benzonatate, clofibrate, methyl salicylate, benzyl benzoate, *dl*-α-tocopheryl acetate □ Sustained-release dosage—solid-dispersion technique potential

Most liquid drugs used for oral and rectal administrations are prepared in solution or emulsion forms. In certain circumstances, it may be advantageous in terms of the ease of formulating, packing, handling, and administering if one can convert the liquid dosage form into a solid dosage form of the same drug. This can be seen in drugs like vitamins A and E. This is usually accomplished by the mechanical mixing of the liquid drugs with other solid components. This conventional method of mixing, however, often may cause serious nonhomogeneity problems, especially when the concentration of the liquid ingredient is very low. Therefore, it appears worthwhile to explore an alternative method for the formulation of liquid compounds.

In the past, a number of poorly water-soluble drugs were studied (1–11) for their solid-state dispersions in physiologically inert, water-soluble carriers as a potential means to increase their dissolution and oral absorption. They, however, are limited to solid drugs at room temperature. The purpose of this preliminary investigation was to study the feasibility of such a technique for the formulation of liquid compounds or drugs by employing polyethylene glycol (PEG) 6000 as a carrier. Furthermore, the reproducibility and the homogeneity of the distribution of active drugs in the carrier were studied.

EXPERIMENTAL

Materials—The following were used: benzonatate,[1] clofibrate,[2] methyl salicylate (synthetic),[3] *dl*-α-tocopheryl acetate NF,[4] benzyl benzoate,[5] and PEG 6000.[6]

[1] Supplied by Ciba Pharmaceutical Co., Summit, N. J.
[2] Supplied by Ayerst Laboratories Inc., New York, N. Y.
[3] J. T. Baker Chemical Co., Phillipsburg, N. J.
[4] Supplied by Hoffmann-La Roche Inc., Nutley, N. J.
[5] Matheson Coleman & Bell, Norwood, Ohio.
[6] Union Carbide Corp., New York, N. Y.

Table I—Homogeneity Studies of 5% (w/w) of Benzyl Benzoate and α-Tocopheryl Acetate Dispersed in PEG 6000

Sample	Percent Recovery—Benzyl Benzoate—Lot I	Benzyl Benzoate—Lot II	α-Tocopheryl Acetate Lot I	α-Tocopheryl Acetate Lot II
1	99.6	98.1	97.6	97.0
2	100.4	98.6	97.8	98.9
3	98.6	100.7	99.3	98.2
4	98.9	100.2	98.5	97.4
Mean	99.4	99.4	98.3	98.0

Preparation of Solid Dispersions—Solid dispersion forms of the five poorly water-soluble liquid compounds in PEG 6000 were prepared by the melting method. Mixtures of various compositions of the drug and PEG 6000 (2.5, 5, and 10% w/w of drugs in the mixtures) were accurately weighed into beakers, heated directly on a hot plate with stirring until all melted, and then spread in a thin layer onto a stainless steel plate. The mixtures were cooled and solidified rapidly. The solid or semisolid masses could be removed easily from the plates and were kept in desiccators containing silica gel for 1 or 2 days for further hardening. They were then pulverized at room temperature (about 27°) in a mortar, and the 20–40 mesh particles were collected for studies reported in this communication.

Dissolution-Rate Studies—Dissolution-rate studies were conducted in 500 ml. distilled water in a water-jacketed beaker maintained at 37°. The dissolution medium was stirred by a stainless steel paddle, 5.5 × 2.7 cm., placed at the center and maintained at a rate of 100 r.p.m. by an overhead motor. About 2.5 ml. sample was taken rapidly through a washed pledget of glass wool every 2 min. for 14 min. After measurement of its absorbance by a Beckman DBG spectrophotometer, the sample was immediately poured back into the dissolution bath. The amount of the powder used for each dissolution study was equivalent to 5 mg. methyl salicylate, 5 mg. benzonatate, 2.5 mg. clofibrate, and 2.0 mg. benzyl benzoate. The wavelengths used for measuring their absorbances were 297, 310, 225, and 230 nm., respectively. They all obeyed Beer's law at the concentrations studied.

All dissolution studies were run at least in duplicate. Generally the results were quite reproducible. The recycling and flow cell system (3) was not employed in this investigation because the silicone tubing would sometimes adsorb a significant amount of drug from the solution. For example, the absorbance of 500 ml. of aqueous benzyl benzoate solution was reduced from 0.24 (4.5 mcg./ml.) to 0.18 after a few minutes of circulation.

Homogeneity Studies—Ten grams of solid dispersion forms of 5% (w/w) benzyl benzoate and α-tocopheryl acetate in PEG 6000 was prepared in duplicate. After pulverization, four samples, each containing about 0.5% of the total preparation, were taken from various parts of the container. They were dissolved in 95% alcohol and the concentrations were determined spectrophotometrically.

RESULTS AND DISCUSSION

Solid Dispersions in PEG—It was quite surprising that all the solidified masses from the drug–PEG melt mixtures containing up to 5% liquid compounds (benzonatate, clofibrate, methyl salicylate, *dl*-α-tocopheryl acetate, and benzyl benzoate) could be easily pulverized into fine particles at room temperature. This might be due to the formation of solid solutions of the drugs in the PEG 6000. Recently, Chiou and Riegelman (9) theorized that a great variety of small organic compounds with molecular weight less than 1000 could form extensive interstitial solid solutions in the high molecular weight of PEG polymers. Such contention also is

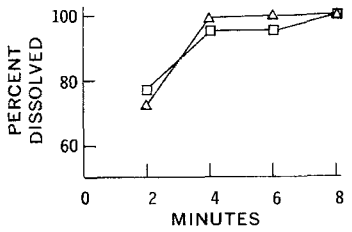

Figure 1—*Cumulative plots of dissolution from clofibrate, solid dispersed in PEG 6000. Key:* △, *2.5%; and* □, *5%.*

supported by experimental data on the indomethacin–PEG 6000 system (11) in which up to 10% of indomethacin was believed to be molecularly dispersed in the PEG 6000.

The pulverization of the 10% benzyl benzoate system also posed no difficult problem, while preparations containing 10% of other liquid compounds at the ambient temperature were not hard and brittle enough to be subdivided easily. However, they could be powdered more easily when maintained at a lower temperature such as 5°. This may be attributed to the higher viscosity of the fine liquid drops of the drugs at lower temperature when the concentrations of the drugs exceed their solubility in the carrier.

Although only PEG 6000 was tested as a carrier, it is expected that similar results can be obtained when other solid PEG polymers are used as carriers. The preparation of the solid dispersions of the five selected liquid compounds is not intended to advocate their use as dosage forms for therapeutic purpose but is rather aimed at the demonstration of such a technique for the general liquid drugs. Since only about 10% of a drug can be solid dispersed in PEG polymers, this new approach of formulation is limited to liquid drugs with low therapeutic doses, for example, below 50–100 mg. The resultant solid dispersion can be encapsulated or tableted.

One big advantage of using PEG for the solid dispersion of liquid compounds over other water-soluble polymers or inert carriers with smaller molecular weight is their low melting points (all below 67°) and their high thermal stability. Therefore, the chemical stability of the drugs generally can hardly be affected because they can be incorporated to the melt of PEG below 67°. Moreover, the preparation can be rapidly accomplished by the simple fusion process rather than by the more laborious solvent methods suggested (5, 6) for the preparation of the solid dispersions of drugs in polyvinylpyrrolidone (PVP).

Fast *versus* Slow-Release Solid Dispersion—Since the dissolution rate of a component may be affected by the second component in the multiple-component mixture (11), the selection of a water-soluble, readily dispersible carrier might lead to a formulation with fast-release characteristics, as discussed by various authors (1–10), and the selection of a poorly soluble or insoluble carrier might result in a preparation with slow, prolonged, or sustained-release property. It is then logical to assume that one could obtain desired release characteristics of a dosage form through the control of the carrier system by using different solubilities of the carrier and/or different concentrations of the carrier in the same dosage regimen. Such possibility is currently under investigation in this laboratory.

Dissolution Studies—The plots of cumulative dissolution from four poorly soluble drugs are shown in Figs. 1–4. Except for benzyl benzoate, more than 50% of the drugs dispersed in PEG 6000 dissolved in the first 2 min. and 100% in 4–8 min. However, it required 14 min. to dissolve all the solid dispersed benzyl benzoate. The dissolution rates from the pure liquid compounds were not studied because of difficulties of control of the liquid particle size and their accurate weight (less than 5 mg. used). In spite of the lack of comparison with pure compounds, the demonstrated fairly fast *in vitro* release of the compounds from dispersion systems in the moderately stirred medium indicated their high potential application for the formulation of liquid compounds. The bioavailability of such dosage forms as compared to the conventional forms, however, remains to be studied further.

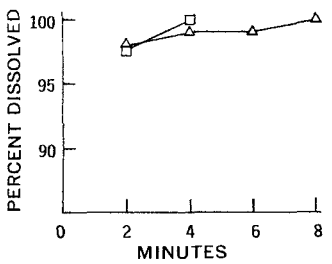

Figure 2—*Cumulative plots of dissolution from methyl salicylate, solid dispersed in PEG 6000. Key:* □, *2.5%; and* △, *5%.*

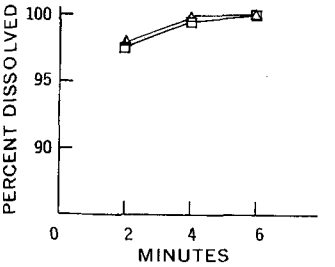

Figure 3—*Cumulative plots of dissolution from benzonatate, solid dispersed in PEG 6000. Key:* □, *2.5%; and* △, *5%.*

In these dissolution-rate studies, all the solid dispersion systems of each drug containing 2.5, 5, and 10% drug in the polymer exhibited almost the same dissolution rate within experimental error. It is not intended, however, in this preliminary report to construct a mathematical model describing quantitatively the drug-release rates from the fine powders of solid dispersion systems. Due to many similar physical properties between the PEG and the PVP polymers, it is believed that the theoretical model for the dissolution rates of high-energy PVP sulfathiazole coprecipitates from a constant-tablet surface, proposed in a recent excellent article by Simonelli *et al.* (8), may provide a possible qualitative explanation to this interesting phenomenon. If one assumes that the dissolution rate from the powder surface is rate limited by the dissolution of the controlling PEG external layer, as in the analogy to the controlling PVP layer in the high PVP weight fractions, then the dissolution rate of the drug from the same drug–PEG dispersion surface will be proportional to the drug–PEG ratio of the solid dispersion. In other words, the dissolution rate of a drug from a 5% solid dispersion will be almost twice as fast as from a 2.5% solid dispersion if their dissolution surface is the same. The total initial surface of the powders containing 5% drug will be only one-half of that containing 2.5% drug for a given amount of the active drug if they have the same particle-size distribution. If one further assumes that the dissolution rates are also proportional to the surface area of the powders under the sink condition as employed in this study, the dissolution rates of the solid dispersion powders containing 2.5, 5, and 10% drug will be expected to be all the same, as shown in Figs. 1–4. Other factors such as the possible complexation between the drug and PEG and the conversion of the molecular dispersion to particulate droplets of pure compounds may also affect their dissolution.

Homogeneity Studies—Although the solid dispersion approach has been known for almost a decade, it seems that no reproducibility and homogeneity of distribution have been quantitatively reported. It is believed that they are among the important factors to be considered. The results of the studies on benzyl benzoate and α-tocopheryl acetate are summarized in Table I. It is clear, within the experimental error, that the preparations were highly reproducible and the active ingredients were homogeneously distributed in the PEG carrier. The consistent, slightly lower recovery of α-tocopheryl acetate might be due to the lower extinction coefficient of the possible complexation with PEG, thereby resulting in lower calculated recovery values. It might also be due to the partial evap-

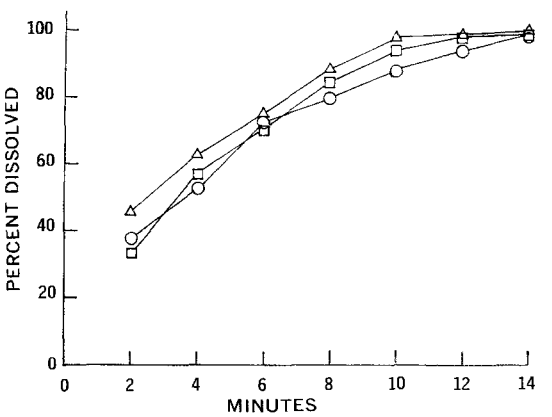

Figure 4—*Cumulative plots of dissolution from benzyl benzoate solid dispersed in PEG 6000. Key:* □, *2.5%;* △, *5%; and* ○, *10%.*

oration of the tocopheryl acetate or its adsorption to the mortar and pestle during the grinding process.

CONCLUSIONS

The solid dispersion principle was tested on five poorly soluble liquid compounds by using PEG 6000 as a carrier. They were prepared by the melting method. Below the 10% concentration, they could be pulverized, encapsulated, and tableted. The preparations were reproducible, and the active ingredients were distributed homogeneously in the solid matrix. The active ingredients were found to be released rapidly from the matrix, with complete dissolution time ranging from 4 to 14 min. This approach represents a new method for the formulation of liquid medicinal compounds, either water soluble or insoluble. It is proposed that one can formulate a prolonged or sustained-release dosage form of drugs by the careful control of the carriers.

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 28, 1969, from the *College of Pharmacy, Washington State University, Pullman, WA 99163*

Accepted for publication July 14, 1970.

Synthesis and Anticonvulsant Activity of Substituted 2-Thioquinazolin-4-ones I: Preliminary Studies

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Abstract □ A series of 2-thioquinazolin-4-ones with varying substituents on position 2, 3, or 6 was synthesized and studied for their ability to prevent maximal electroshock and chemoshock seizures in mice within the dosage range of 10–600 mg./kg. The 2-ethylthio-3-(2-phenyl)ethylquinazolin-4-one exhibited full protection against electroshock at the 100-mg./kg. level. The compound 2-carboxymethylthio-3-(2-phenyl)ethylquinazolin-4-one showed full protection against electroshock at the 600-mg./kg. level and partial activity at the 100-mg./kg. level. Other than these examples of activity, there was little significant activity in the remaining members of the series, with 2-ethylthio-3-phenylquinazolin-4-one showing only partial protection at both the 600- and 100-mg./kg. levels. With one exception within the dosage range studied, none of the compounds appeared to be active in preventing pentylenetetrazole seizures, thus indicating that the compounds possibly act in an analogous manner to diphenylhydantoin and related molecules.

Keyphrases □ 2-Thioquinazolin-4-ones, substituted—synthesis, anticonvulsant activity evaluated □ Anticonvulsants, synthesized, evaluated—substituted 2-thioquinazolin-4-ones □ Pentylenetetrazole-induced seizures—evaluation of substituted 2-thioquinazolin-4-ones anticonvulsant activity

Despite the many significant advancements that have occurred in recent years, newer, safer, and more effective CNS depressant drugs are needed for therapeutic application as anticonvulsant, sedative, or hypnotic agents. In approaching this problem, it was thought that the broad spectrum of physiological activities of the 4-quinazolones would make them good candidates for study; indeed, CNS depressant drugs have been developed from this class. The history of the development of 2-methyl-3-*o*-tolyl-4-quinazolone, methaqualone, was reviewed recently by Cain (1), and Boissier *et al.* (2) showed the *ortho*-chloro compound to be the most active from a study of the *ortho*-, *meta*-, and *para*-isomers. Hayao *et al.* (3) reported on the synthesis of a series of 3-substituted-2,4-(1*H*,3*H*)-quinazolinediones. In their examination for CNS depressant effects, one of the series was reported to approach chlorpromazine in its activity upon experimental animals (3). Burkhalter and Scarborough (4) previously reported that 2,4-(1*H*,3*H*)-quinazolinedione and the 1,3-dimethyl derivative showed protective action against electroshock and pentylenetetrazole-induced seizures in mice. Gujral *et al.* (5, 6) also noted hypnotic and anticonvulsant properties in a series of 2-alkyl-3-aryl-4-(3*H*)-quinazolones. This work was confirmed by Boissier (7). The substance 2-methyl-3-*p*-bromophenyl-4-quinazolone was reported by Bianchi and David (8) to have strong anticonvulsant properties against pentylenetetrazole-induced seizures. Gupta *et al.* (9) continued their study of substituted-4-quinazolones as CNS depressants in a report on some 2,3-disubstituted derivatives, and Chaurasia (10) reported the synthesis of potential antimalarial and ataractic thioquinazolone derivatives.

The present series of thioquinazolin-4-ones resulted from the observation of a marked decrease in coordination (11), as shown by the rota-rod test (12) and narrow strip (horizontal and inclined) test (13) when a suspension of 3-phenyl-2-thioquinazolin-4-one, which was prepared as a part of another study, was administered intraperitoneally to mice at a dosage level of 100 mg./kg. As an expansion of this observation, it was of interest to determine the effect of substituting the thio group, the aromatic ring, and altering the substituent at the 3-nitrogen to gain information as to potential anticonvulsant activity in the general structure. The results of the syntheses are summarized in Tables I and II.