Pharmaceutical Research, Vol. 6, No. 11, 1989

Report

Design and *in Vitro* Evaluation of Dapsone-Loaded Micropellets of Ethyl Cellulose

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Received April 26, 1988; accepted April 27, 1989

A controlled-release dosage form was manufactured by dispersing ethyl cellulose sol in acetone into a medium of mineral oil. Dapsone was used as the model drug. The powdered drug was dispersed in the ethyl cellulose sol, and the formulation variables affecting the production of the discrete and spherical micropellets and their size distribution were investigated. The percentage of SPAN 80 in the formulation affected the yield and physical properties of the micropellets. The *in vitro* drug release followed first-order diffusion-controlled dissolution. More than 85% of the drug was released over 5 hr for all formulation batches, with delayed release over the drug dissolution profile.

KEY WORDS: controlled release; micropellets; ethyl cellulose; dapsone; dissolution profile.

INTRODUCTION

Dapsone (DDS) is an effective antileprotic drug. The problems of patient noncompliance (1,2) and emergence of resistant strains of *Mycobacterium leprae* (3) as a consequence of low blood levels make it necessary to develop a controlled-release formulation. Such a dosage form would also help to maintain the steady-state plasma level of dapsone and reduce the frequency of administration (4).

Among the contemporary dosage forms micropellets have shown suitable properties for drug utilization and therapeutic benefits for its prolonged drug release characteristics. The design and evaluation of gelatinised micropellets were reported earlier (5,6). The present investigation illustrates the methodology developed for the design of ethyl cellulose micropellets and their *in vitro* evaluation.

MATERIALS AND METHODS

Chemicals. Dapsone (Indian Pharmacopoeia) was received by the courtesy of Bengal Chemical and Pharmaceutical Limited, Calcutta; ethyl cellulose (BDH, England), liquid paraffin and Light liquid paraffin (SDS Fine Chemicals Ltd., Boisar), Span 80 (Fluka Chemie AG, Buchs), hexane (SDS Fine Chemicals Ltd., Boisar), acetone (E. Merck, India), potassium dihydrogen phosphate (E. Merck, India), and hydrochloric acid (E. Merck, India) were obtained commercially and used as received. All chemicals were of analytical grade. The drug was passed through a No. 100 sieve.

Preparation of the Dosage Form. Dapsone-loaded micropellets were prepared using dapsone and ethyl cellulose at weight proportions of 1:2, 1:1, and 2:1. The ranges of stirring speed were one at 400 rpm and the other at 900 rpm.

Acetone was taken in a small beaker and stirred with a magnetic stirrer. Ethyl cellulose was gradually added and the speed of the stirrer was adjusted so that there was no unwanted frothing and formation of ethyl cellulose lumps. Powdered dapsone, previously dried, was incorporated slowly into this sol while stirring continued. The resultant slurry was poured at a constant and steady stream into a 300-ml mixture of liquid paraffins medium. Seventy-five percent liquid paraffin, i.p., and 25% light liquid paraffin, i.p., were blended together to produce the medium having a desired viscosity of 87.1 cp at 30°C. Span 80 (0.1%, w/w) was added to the medium to obtain free-flowing discrete particles. Two ranges of stirring speed, 400 and 900 rpm, were used. After a few minutes, the system was cooled quickly to 10°C in ice. This condition was maintained until microdrops of ethyl cellulose formed a perfect gel. Hexane at 5°C was added dropwise to the system to promote gelation of ethyl cellulose microdrops. Stirring was continued for another 30 min.

In order to recover the rigidized pellets, the supernatant was decanted and the separated pellets were washed with chilled hexane several times until pellets were devoid of liquid paraffins. Pellets were collected and stored at room temperature (20°C) overnight and then dried in air for 18 hr.

Reproducibility of the methodology was evaluated by preparing replicate batches and determining the percentage of drug embedded. Sieve analysis of each batch was carried out to determine size distribution.

Content Uniformity. Five hundred milligrams of micropellets was weighed accurately and pulverized in a mortar and pestle. The powdered material, weighing accurately 100 mg, was transferred to an Erlenmeyer flask containing 0.1 *N* HCl as the solvent. The flask was shaken for 10 hr and diluted to 100 ml with the same solvent. An aliquot was withdrawn and suitably diluted and assayed spectrophotometrically at 290 nm (7). The reproducibility of the method-

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0724-8741/89/1100-0945$06.00/0

ology was assessed by conducting suitable recovery experiments.

In vitro *Dissolution Profile*. The *in vitro* dapsone release profile was studied using the USP XX dissolution apparatus with the rotating basket assembly. Five hundred milliliters of dissolution medium was taken at 37 ± 1°C. Accurately weighed micropellets of sieve size No. 36 were placed in the basket covered with a No. 100 mesh nylon cloth to contain the micropellets. The basket was rotated at 100 ± 5 rpm. Five milliliters of aliquots was withdrawn at 30-min intervals and replenished with the same volume of fresh medium. A 0.1 *N* hydrochloric acid solution at pH 1.2 and phosphate buffer at pH 7.2 (8) were used as the dissolution media.

RESULTS AND DISCUSSIONS

The formation of discrete and spherical micropellets of ethyl cellulose was influenced by several formulation variables. The most important variables noted were the core to coat ratio of the drug–ethyl cellulose slurry, temperature of the system during the micropellet formation, viscosity of the liquid paraffins, and technique of rigidization of the embryonic microdrops of ethyl cellulose containing dapsone. Lower viscosity of the drug–ethyl cellulose slurry produced smaller pellets and the yield was also low because of adherence of the ethyl cellulose and the drug to the wall of the vessel. The preparation and pouring of the slurry at room temperature (25–28°C) produced irregular micropellets as a result of the evaporation of significant amounts of acetone. The use of a low viscosity of the manufacturing medium led to the gradual adherence of the micropellets, resulting in the formation of an agglomerated mass. On the other hand, a high viscosity of the medium posed resistance to the micropellets to assume a spherical shape. Application of controlled heat to flash off acetone led to a sudden agglomeration of the micropellets. Optimization and proper control of these variables produced discrete and spherical micropellets at a good yield.

The results in Table I illustrate the pharmaceutical properties of the ethyl cellulose micropellets, such as the reproducibility of the content of dapsone in each of the six formulations studied. The coefficient of variation was within 5% in all cases.

As revealed from Table I and Fig. 1, the size distribution of micropellets was influenced by the drug:ethyl cellulose ratio as well as the stirring speeds. At a constant speed, the size distribution curve was observed to be shifted toward bigger micropellets as the drug:ethyl cellulose ratio was increased. Again, at higher stirring speeds, the size distribution curve moved toward the smaller micropellets. The nature of shifting of the curves in both cases was similar. A change in the solid drug content of the dispersed phase changed its viscosity and influenced the interfacial tension between the dispersed phase and the dispersion medium, with a pronounced effect on the size distribution of the micropellets. An increase in the drug:ethyl cellulose ratio increased the relative viscosity of the dispersed phase, and the subdivision of the dispersed phase into smaller ones was prevented by higher interfacial viscosity. At higher stirring speeds, the subdivision of the dispersed phase into smaller micropellets was increased. It was due to the decreased resistance of the dispersed phase toward subdivision as the stirring speed was increased.

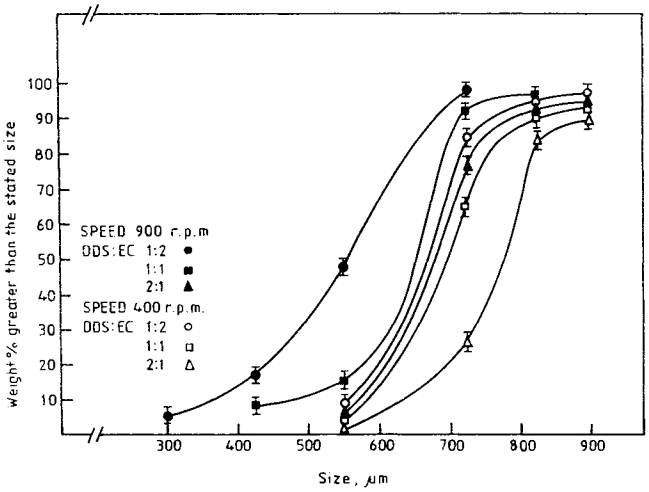

Fig. 1. Particle size distribution of ethyl cellulose micropellets.

Figure 2 represented the dissolution profile of dapsone from ethyl cellulose micropellets. Higher drug release was observed at pH 1.2 compared to the drug release at pH 7.2. At pH 1.2, 80% release occurred over 3 hr. As the gastric emptying rate is approximately 3 hr, pellets would be carried over to the intestine and dissolution would continue at intestinal pH. For any particular size range of micropellets, an increase in the drug:ethyl cellulose ratio caused faster re-

Table I. Reproducibility of the Manufacturing Process

DDS:EC ratio	Stirring speed (rpm)	Yield (%)[a]	Size range (μm)	Drug content (%)[a,b]	SD	
					Drug content	Yield
1:2	900	94.67	300–725	32.00	±0.0157	±0.832
	400	94.52	550–900	32.30	±0.0135	±0.635
1:1	900	95.88	425–825	48.20	±0.0122	±0.579
	400	95.47	550–900	48.53	±0.0169	±0.873
2:1	900	96.67	550–900	64.30	±0.0218	±0.963
	400	96.43	550–900	65.05	±0.0193	±0.927

[a] Mean results of six batches.
[b] Micropellets were of sieve size 550 μm.

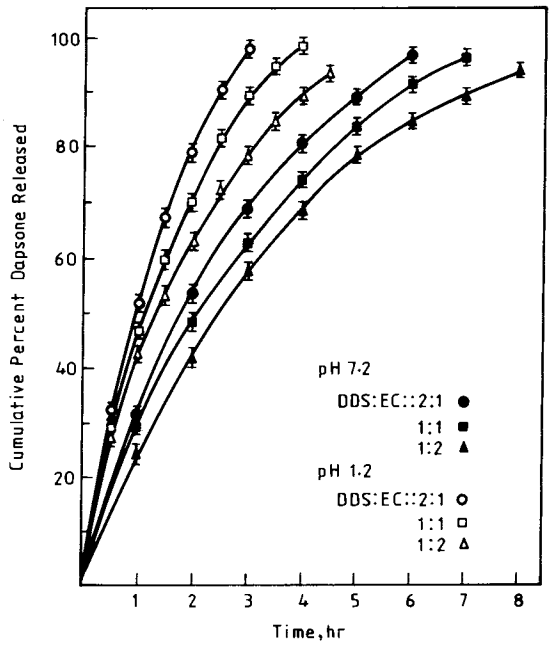

Fig. 2. Effect of core:coat ratio on the *in vitro* drug release profile at the particle size of 550 μm.

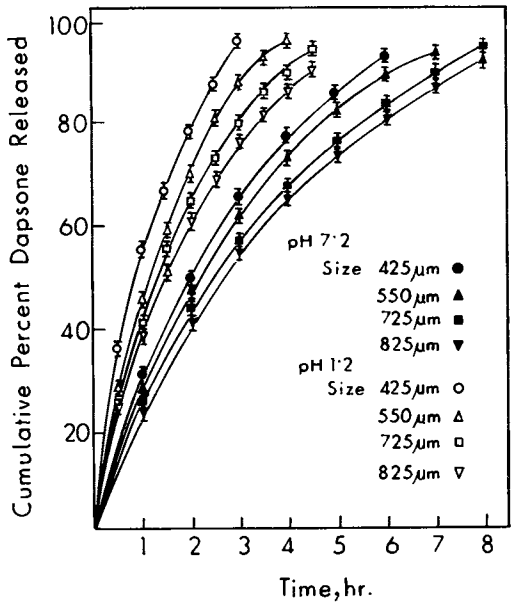

Fig. 4. *In vitro* drug release profile at different sizes of micropellets; core:coat ratio, 1:1.

lease of the dapsone. Plots of the drug content versus dissolution $t_{50\%}$ in Fig. 3 indicated that the higher the drug:ethyl cellulose ratio, for any particular size range of micropellets, the shorter was the time for 50% release of the drug. The linearity of the drug content vs time plots revealed that a uniform diffusion gradient was established and it became possible to predict the time for dissolution $t_{50\%}$ from the content of drug in a known batch of micropellets. In Fig. 3, the three particle size ranges were selected because micropellets were available from all the batches in these three particle size ranges (Fig. 1 and Table I). The results obtained with other particle sizes gave similar plots.

Figure 4 illustrated the effect of particle size on the dissolution profile of dapsone. The smaller particles released the drug rapidly. The effect might be understood in terms of a decreased diffusion path length and increased effective surface area of the micropellets. The Higuchi plot (9), shown in Fig. 5, suggests a diffusion-controlled release mechanism for the matrix system. However, the plots were nonlinear during the later phase of dissolution, indicating deviations from diffusion controlled behavior. The results obtained with other particle sizes produced similar plots.

Linearity of the plots in Fig. 3 indicated dependence of the drug release rate on dissolution $t_{50\%}$. Again, Fig. 5 illustrates that this $t_{50\%}$ dependence was maintained over the major portion of the release curve. Nonlinearity of the plots in Fig. 5 in the later phase of dissolution indicated deviation from this dependence, only when the concentration of the active agent remaining in the matrix fell below the saturation value (10). Comparison of Figs. 2, 3, and 5 thus revealed that

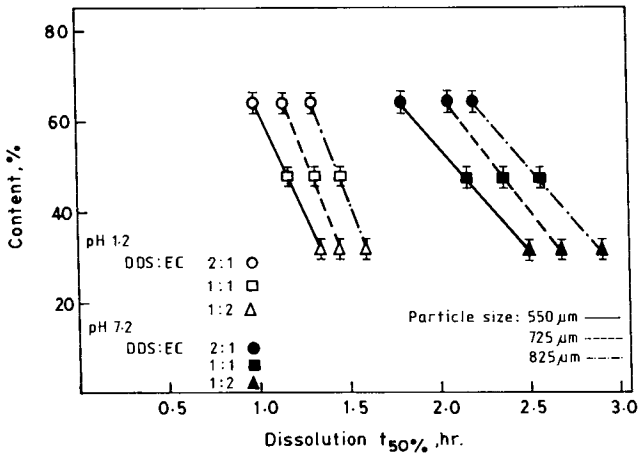

Fig. 3. Effect of the content of dapsone in micropellets on the dissolution $t_{50\%}$.

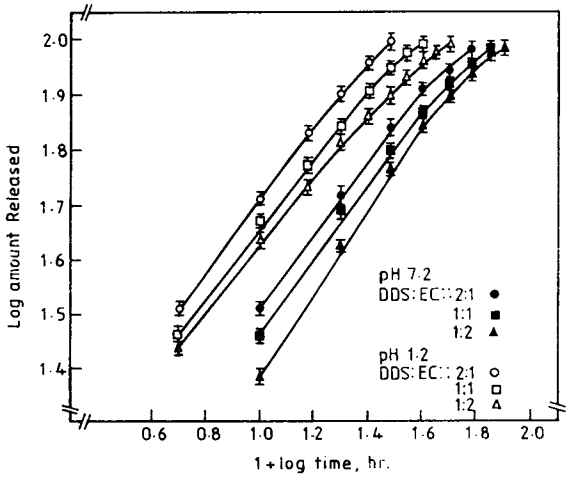

Fig. 5. Plot of log of dapsone released from micropellets against log of time; particle size, 550 μm.

the dissolution process followed first-order kinetics, whereas the initial transfer of the drug to the bulk of the dissolution fluid followed diffusional kinetics.

The production of micropellets adopting the developed technique was simple and reproducible. The drug:ethyl cellulose ratio and the size range of micropellets controlled the drug release profile of dapsone from micropellets. The dissolution $t_{50\%}$ varied linearly with the drug content in the micropellets. Therefore, suitable drug release profiles were achieved by combination of different batches of micropellets having varied drug:ethyl celluloseratio and particle size. The ethyl cellulose micropellets may prove useful for the prolonged release of dapsone and drugs in general.

ACKNOWLEDGMENTS

This work was supported by a research grant from the Council of Scientific and Industrial Research, New Delhi, India. Dapsone was generously supplied by Bengal Chemicals and Pharmaceuticals Limited, Calcutta.

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