REFERENCES

(1) L. M. Rice, C. F. Geschickter, and C. H. Grogan, *J. Med. Chem.* **6**, 388 (1963).

(2) C. H. Grogan, C. F. Geschickter, and L. M. Rice, *ibid.*, **7**, 78 (1964).

(3) R. F. Smith, D. E. Shay, and N. J. Doorenbos, *J. Bacteriol.*, **85**, 1295 (1963).

(4) R. F. Smith, D. E. Shay, and N. J. Doorenbos, *Proc. Pa. Acad. Sci.*, **36**, 113 (1962).

(5) R. F. Smith, D. E. Shay, and N. J. Doorenbos, *Appl. Microbiol.*, **11**, 542 (1963).

(6) R. F. Smith, D. E. Shay, and N. J. Doorenbos, *J. Pharm. Sci.*, **53**, 1214 (1964).

(7) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

(8) I. Guareschi, *Atti. Accad. Sci. Torino*, **36**, 443 (1900/1901).

(9) I. Vogel, *J. Chem. Soc.*, **1928**, 2010.

(10) A. Lapworth and J. A. McRae, *ibid.*, **121**, 2741 (1922).

(11) S. F. Birch, G. A. R. Kon, and W. S. G. P. Norris, *ibid.*, **123**, 1361 (1923).

(12) V. J. Harding, W. N. Haworth, and W. H. Perkin, *ibid.*, **93**, 1943 (1908).

(13) A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

(14) W. S. G. P. Norris and J. F. Thorpe, *J. Chem. Soc.*, **119**, 1199 (1921).

(15) F. Dickens, L. Horton, and J. F. Thorpe, *ibid.*, **124**, 1830 (1924).

(16) J. F. Thorpe and A. S. Wood, *ibid.*, **103**, 1586 (1913).

(17) G. A. R. Kon and J. F. Thorpe, *ibid.*, **115**, 693 (1919).

(18) K. Lundahl, J. Schut, J. L. M. A. Schlatmann, G. B. Paerels, and A. Peters, *J. Med. Chem.*, **15**, 129 (1972).

(19) R. VanHes, A. Smit, T. Kralt, and A. Peters, *ibid.*, **15**, 132 (1972).

(20) H.-L. Pan and T. L. Fletcher, *ibid.*, **10**, 957 (1967).

(21) W. Wasulko, A. C. Noble, and F. D. Popp, *ibid.*, **9**, 599 (1966).

(22) A. W. Bauer, W. M. M. Kirby, J. C. Sherris, and M. Turck, *Am. J. Clin. Pathol.*, **45**, 493 (1966).

(23) D. Perlman, K. L. Perlman, M. Bodanszky, A. Bodanszky, R. L. Foltz, and H. W. Matthews, *Bioorgan. Chem.*, **6**, 263 (1977).

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Dissolution Apparatus for Gels

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Abstract □ A modification of the USP Dissolution Apparatus 2 is presented for use in the measurement of the release of a medicinal compound from a pharmaceutical gel.

Keyphrases □ Dissolution—apparatus for gels, modification of the USP Dissolution Apparatus 2 □ Pharmaceutical gels—dissolution apparatus, modification of the USP Dissolution Apparatus 2

The *in vitro* test methods for measuring the dissolution of a medicinal compound from a tablet or a capsule are defined in the United States Pharmacopeia (USP) (1). Mathur *et al.* (2) appear to be the first to have reported *in vitro* dissolution testing of suspensions. It seems that dissolution testing of any dosage form that may restrict the delivery of molecules of the medicinal compound to the GI epithelium is advisable.

This report presents a modification of the USP Dissolution Apparatus 2, that can be used to measure dissolution profiles from pharmaceutical gels.

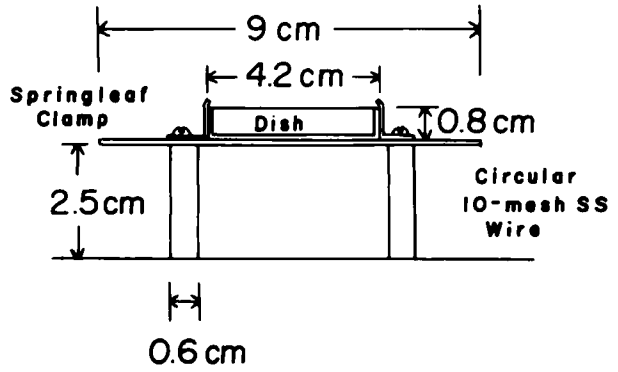

Figure 1—*Modification of the USP Dissolution Apparatus 2 for gels.*

EXPERIMENTAL

Dissolution Apparatus—A circular, 10-mesh stainless-steel cloth with a 9.0-cm diameter was fitted with four 2.5-cm plastic legs (diameter 0.6 cm) so that, as it rested on the bottom of the reaction vessel, the wire cloth was at the point of curvature of the base of the vessel. Four springleaf clamps were affixed to the upper surface of the wire cloth to hold the glass dish in the center of the platform (Fig. 1). The dish was cut from a 50-ml beaker and had 3.9-cm i.d. and an outer height of 0.8 cm.

A 5-g sample of the gel was weighed in the dish on an analytical balance, and using forceps the dish was gently lowered through the dissolution medium in the assembled apparatus and was inserted into the clamps. The time required by an experienced operator was ~30 sec. With thin gels, the level spontaneously adjusted to the horizontal plane; with very viscous gels, the surface may be leveled by use of a spatula prior to weighing. In the gels investigated, the 5-g samples completely filled the dish to the rim. If a particular gel had a high density, it would be advisable to use a greater weight, which would fill the dish. The dissolution medium was 900 ml of distilled water or 0.1 *N* HCl at 37 ± 0.5°. The paddle of the modified USP Dissolution Apparatus 2 was centrally positioned 2.5 cm above the rim of the dish. The apparatus was then started. Samples were withdrawn by a pipet through a glass filter. Ephedrine sulfate was assayed using a previously described method (3).

Dosage Forms—Tablets containing 25 mg of ephedrine sulfate was prepared by direct compression in a single-punch tablet machine. A portion of the batch was compressed to a hardness of 4 kg; the remainder was compressed to an 8-kg hardness. The formulation was:

Ephedrine sulfate[1]	25 mg
Microcrystalline cellulose[2]	190 mg
Lactose[3]	382 mg
Magnesium stearate[4]	3 mg

[1] USP.
[2] Avicel PH 101.
[3] USP, spray dried.
[4] NF.

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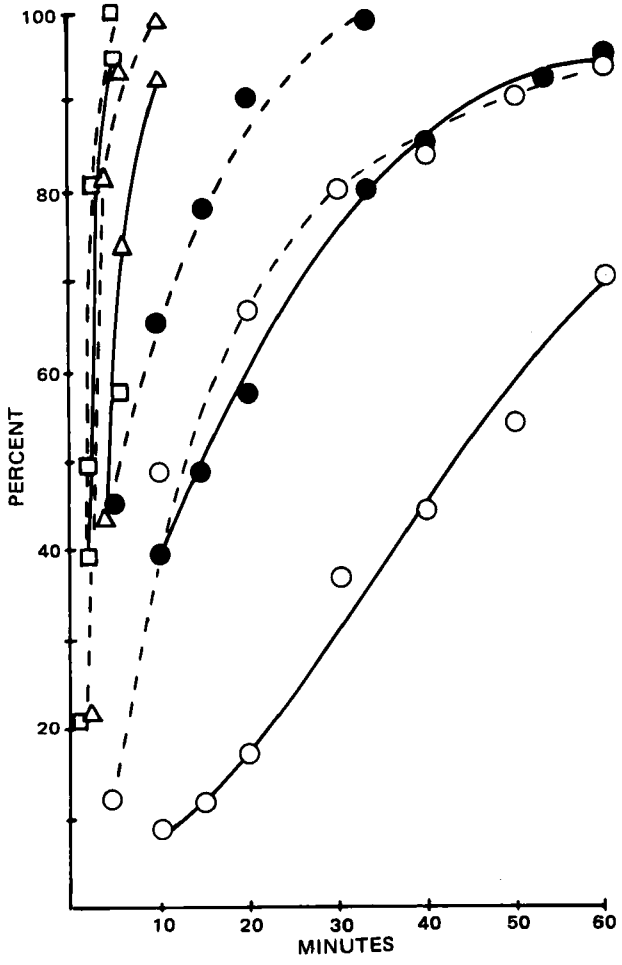

Figure 2—*Comparison of percent of ephedrine sulfate released from tablets having a hardness of 8 kg as determined by the USP Dissolution Apparatus 2 and a modification for gels at various speeds. Key: (- - -) USP; (—) modified for gel apparatus; (○) 12 rpm; (●) 30 rpm; (△) 60 rpm; (□) 100 rpm.*

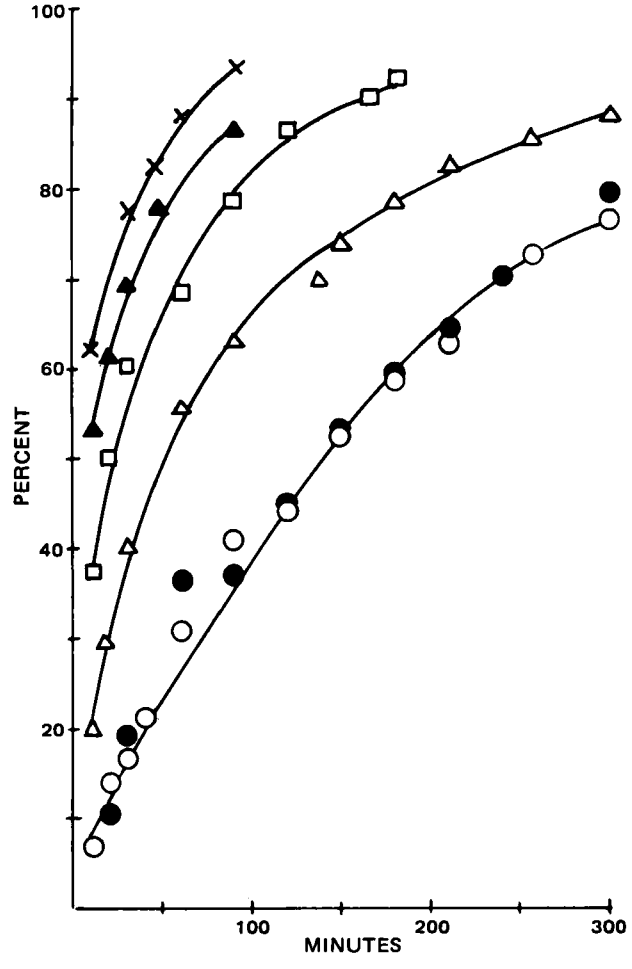

Figure 3—*Release profile of ephedrine sulfate from a methylcellulose gel at various speeds. Key: (○) 12 rpm; (●) 30 rpm; (△) 60 rpm; (□) 70 rpm; (▲) 80 rpm; (×) 90 rpm.*

The formulation of the gel used as a model was:

Ephedrine sulfate	20 mg
Methylcellulose[5]	200 mg
Distilled water	4780 mg

RESULTS AND DISCUSSION

Gels are semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid (4). Gels with wide viscosities may be used as vehicles for a dissolved or a suspended medicinal compound. The wide range of viscosities of pharmaceutical gels limits the use of the USP dissolution apparatus. For example, with USP Dissolution Apparatus 1, a gel of low viscosity may drip from the basket assembly, and a gel of high viscosity will tend to clog the wire mesh.

It is desirable to have an apparatus for all dosage forms that is not markedly different than the officially accepted dissolution apparatus. To compare the agitation and the dissolution profiles obtained by the USP Dissolution Apparatus 2 and the modification, dissolution from tablets of ephedrine sulfate was studied at 12, 30, 60, and 100 rpm in 900 ml of distilled water. The dissolution profiles are given in Fig. 2 for tablets with a hardness of 8 kg. From Fig. 2, and a similar plot for tablets with a hardness of 4 kg, the times required for 50% ($t_{1/2}$) and 66.7% ($t_{2/3}$) of the ephedrine sulfate to dissolve from the tablets were determined and are listed in Table I.

At 60 and 100 rpm (speeds frequently utilized in official tests) there is no apparent difference in the dissolution profiles as obtained by the USP Dissolution Apparatus 2 and the modification suggested for de-

[5] USP, type 400 cps.

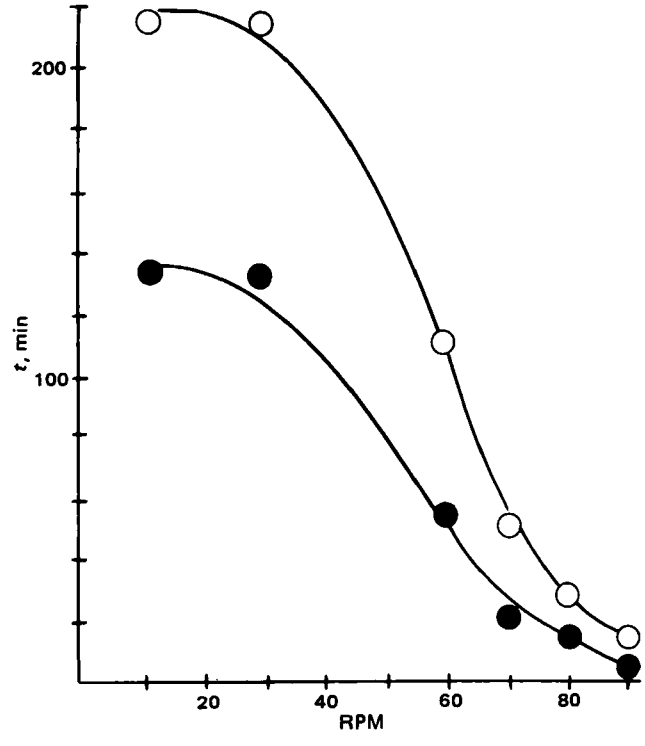

Figure 4—*Influence of speed on dissolution. Key: (○) $t_{2/3}$; (●) $t_{1/2}$.*

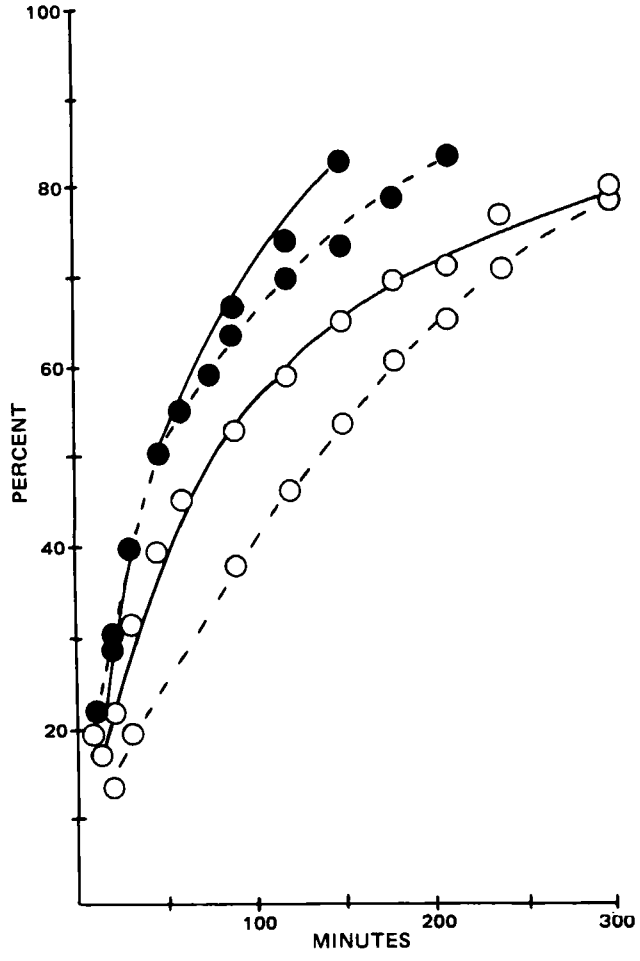

Figure 5—*Release profile of ephedrine sulfate from a methylcellulose gel in water and 0.1 N HCl. Key: (- - -) water; (—) 0.1 N HCl; (○) 30 rpm; (●) 60 rpm.*

termining the release profile from gels. Thus, at these speeds the factors contributing to dissolution are similar, and a comparison of release from a solid dosage form (tablet) and the release from a gel would be valid.

The release of ephedrine sulfate from the model gel was studied at 12, 30, 60, 70, 80, and 90 rpm as shown in Fig. 3. At the higher speeds, the agitation moves portions of the gel in a random manner so that filaments

Table I—Comparison of Dissolution as Measured by the USP Dissolution Apparatus 2 and by the Apparatus Modified for a Gel Using Compressed Tablets Containing 25 mg of Ephedrine Sulfate

Speed, rpm	$t_{1/2}$, min[a]		$t_{2/3}$, min[a]	
	USP Apparatus 2	Gel Apparatus	USP Apparatus 2	Gel Apparatus
		Hardness (4 kg)		
12	9	35	15	47
30	5	5	7	11
60	~1	2	~1	3
100	~1	1	~1	2
		Hardness (8 kg)		
12	10	43.5	19	59
30	6.5	15	11	22
60	~2	~4	~2	5
100	2	~3	~3	4

[a] Rounded to the nearest 0.5 min.

and masses of the gel may move away from the gel in the dish and at times become entwined around the shaft of the paddle. At lowest speeds, the release from the gel to the bulk of the dissolution medium is slow and requires an inconveniently long testing period (>4 hr). Intermediate speeds did not grossly disturb the gel in the dish and did not unduly prolong the release of the ephedrine sulfate; thus, 30 and 60 rpm appear to be practical speeds. The influence of speed on dissolution is shown in Fig. 4.

The release of the ephedrine sulfate from the model gel was determined in distilled water and in 0.1 *N* HCl at 30 and 60 rpm and is plotted in Fig. 5. At 30 rpm the values of $t_{1/2}$ are 135 and 80 min in water and 0.1 *N* HCl, respectively. At 60 rpm the values of $t_{1/2}$ are ~45 min in water and 0.1 *N* HCl.

REFERENCES

(1) "The United States Pharmacopeia," 20th rev., United States Pharmacopeial Convention, Rockville, Md., 1980, p. 959.

(2) L. K. Mathur, J. M. Jaffe, R. I. Poust, H. Barry, III, T. J. Goehl, V. P. Shah, and J. L. Colaizzi, *J. Pharm. Sci.*, **68**, 699 (1979).

(3) W. N. French and B. A. Reidel, *Can. J. Pharm. Sci.*, *1*, *80* (1966).

(4) "The United States Pharmacopeia," 20th rev., United States Pharmacopeial Convention, Rockville, Md., 1980, p. 1026.

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