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MODIFIED DISSOLUTION METHOD FOR RIFAMPIN

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It is important for any method of analysis to be acceptable that the sample is not affected during the analysis. While carrying out in-vitro dissolution assays on capsules containing rifampin, using literature methods[1,2] we obtained results which suggested that rifampin may be degrading during the procedure. Therefore, we decided to investigate this problem.

We first evaluated a dissolution procedure for rifampin capsules using 900 mL of 0.01 N HCl as the dissolution medium[1] with the USP dissolution Apparatus I at 100 rpm, 45 minutes at 37°C, recording the UV absorbance at a wavelength of 474 nm. A similar procedure provided by Merrell-Dow[2] using 0.1 N HCl as the dissolution medium and measuring the UV absorbance at 295 nm was also evaluated. These procedures are similar to the method recently proposed by the USP[3]. In both cases we found that the UV spectra (λ max 235, 255, 337 and 474 nm) obtained at different time points had different shapes and that the percent

dissolved (calculated from the absorbance at 337 nm) at 2 hours was lower than that found at 45 minutes. The wavelength λ max of 337 nm was used because it is more sensitive than 474 nm and 295 nm is a λ min.

Because of the known instability of rifamycin compounds[4] we decided to investigate these findings by high pressure liquid chromatography. A μBondapak C18 column was used with acetonitrile/0.05M potassium dihydrogen phosphate (40/60 v/v) as mobile phase at 1.5 mL/minute flow rate and with detection at a wavelength of 254 nm. Rifampin eluted at approximately 5.5 minutes. We found that rifampin decomposes 13% in 1 hour and 29% in 2 hours in 0.01 N HCl at 37°C, but only 1% and 2% in water at 37°C. In 0.1 N HCl, rifampin was found to degrade 17% in 45 minutes and 37% in 2 hours at 37°C and 6% and 12% respectively in simulated gastric fluid.

Consequently, we began a search for a dissolution medium which would not cause degradation. Unfortunately water was not suitable as the rifampin is not sufficiently soluble. Aqueous solutions of 33% isopropanol, 5% acetic acid, 0.1% Tween 80, methanol/0.1% acetic acid (40/60), isopropanol/0.1 N HCl (40/60) and polyoxyethylene lauryl ether proved to be unsuitable media as they did not achieve the required dissolution for rifampin. However, different concentrations of dilute solutions of sodium lauryl sulfate (SLS) gave acceptable dissolution parameters[5].

TABLE 1

Dissolution of Rifampin Containing Capsules in 0.4% SLS using Ultravilot and HPLC Determinations

Capsule	Wt of Rifampin powder placed in capsule	Dissolved in 45 minutes		Dissolved in 2 hours
		UV	HPLC	UV
1	302 mg	98%	99%	97%
2	328 mg	99%	98%	96%
3	352 mg	101%	100%	98%
4	303 mg	99%	99%	99%
5	327 mg	99%	98%	99%
6	352 mg	101%	99%	100%
Average	327 mg	99.5%	98.8%	98.2%
	RSD	1.2%	0.8%	1.5%

The concentration of 0.4% SLS (pH-6.8) was found to be the most appropriate without significant degradation of rifampin occurring (<2% and <4% in 45 minutes and 2 hours respectively).

Empty capsules were filled with known quantities of rifampin (equivalent to 300 mg/capsule) and their dissolution in 0.4% SLS was determined by UV and HPLC for comparison using the same standard solution for both methods. Table 1 shows the results.

Further, 9 samples of capsules containing rifampin obtained from different lots in the market were assayed by the modified method. Table 2 shows these results.

TABLE 2

Dissolution of Rifampin Containing Capsules in 0.4% SLS

% LA Dissolved (average of 6 capsules)

		15 Min		30 Min		45 Min		60 Min	
Lot	Capsule	Ave	Range	Ave	Range	Ave	Range	Ave	Range
1	150 mg	8	2-11	62	53-79	97	91-101	100	97-103
2	150 mg	7	6-13	47	24-71	87	78-90	98	97-101
3*	150 mg	5	3-15	40	23-70	77	52-96	95	83-104
4	300 mg	48	37-95	96	92-100	98	96-100	98	97-99
5	300 mg	16	10-29	89	72-103	99	91-102	99	95-103
6	300 mg	66	44-83	94	90-97	96	93-98	96	94-98
7	300 mg	28	22-38	95	92-97	99	97-101	98	95-100
8**	300 mg	29	10-51	103	95-128	105	101-128	104	100-124
9	300 mg	7	3-15	55	31-77	98	91-104	102	97-107

* Average of 24 capsules

** Average of 12 capsules

These data show that 0.4% sodium lauryl sulfate is an appropriate medium for the use in the dissolution method for rifampin. We have proposed this dissolution procedure to the USP.

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