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USE OF SURFACTANT IN THE DISSOLUTION OF MEDROXYPROGESTERONE ACETATE TABLETS

Aqeel A. Fatmi*, Elizabeth A. Hickson and Gregory V. Williams, Sr.
Analytical Research and Development Department
Reid-Rowell, Inc.
901 Sawyer Road
Marietta, Ga. 30062

ABSTRACT

The use of sodium lauryl sulfate in water and 0.1N HCl as dissolution medium for medroxyprogesterone acetate tablets is investigated. The FDA's handbook of drug dissolution standards recommends the use of 0.54% sodium lauryl sulfate in water as dissolution medium for medroxyprogesterone acetate tablets to meet the recommended dissolution tolerance limits of not less than 85% in 45 minutes. This study shows that these tolerance limits can be achieved by using smaller quantities of 0.1% sodium lauryl sulfate in 0.1N HCl as dissolution medium.

INTRODUCTION

Medroxyprogesterone acetate tablets are effective in secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer (1). Medroxyprogesterone acetate is a water insoluble drug. Determination of dissolution profiles of medroxyprogesterone acetate tablets in water, gastric fluid (without enzyme) and intestinal fluid (without enzyme) failed to provide meaningful results. The use of surfactants in primary dissolution media has

*To whom correspondence is to be addressed.

been suggested to increase the dissolution rates of water insoluble drugs (2-5). The Food and Drug Administration (FDA) handbook of drug dissolution standards (6) recommends the use of 900 mL of water containing 0.54% sodium lauryl sulfate (SLS) as dissolution medium for medroxyprogesterone acetate tablets. In order to perform one dissolution test on 6 tablets, an approximate quantity of 29 g sodium lauryl sulfate will be required. The usual dose of medroxyprogesterone acetate tablets is 10 mg. Therefore, for each 10 mg tablet, the drug to surfactant ratio in 900 mL of dissolution medium is about 1:500. This high quantity of surfactant may render the medium less discriminatory and also may pose the problem of safe handling to laboratory chemists since sodium lauryl sulfate, in addition to foaming, causes irritation of eyes and skin.

This study was carried out to investigate the optimum amount of sodium lauryl sulfate required in water and 0.1N HCl dissolution media to generate satisfactory dissolution profiles of medroxyprogesterone acetate tablets.

MATERIALS AND METHODS

Materials:

Medroxyprogesterone acetate tablets, referred to as products A and B, were obtained from two different manufacturers[1]. Medroxyprogesterone acetate reference standard[2] and sodium lauryl sulfate[3] were purchased from commercial sources.

Dissolution Media:

The following dissolution media were used in the dissolution studies: water, gastric fluid without enzymes, intestinal fluid without enzyme, water with 0.54%, 0.27%, 0.135% sodium lauryl sulfate and 0.1N HCl with 0.1%, 0.05% and 0.025% sodium lauryl

sulfate. All media were freshly prepared prior to dissolution studies.

Dissolution Methodology:

The tablet dissolution profiles were determined in various media by procedure described in USP XXI using the compendial Method II (paddles) at 50 rpm agitation speed (7). Twelve tablets of each product were studied in a 12-spindle dissolution apparatus[4]. Dissolution medium (900-mL) was placed in each of 12-vessels. The temperature of the medium was maintained at 37 ± 0.5°C.

Samples were withdrawn with a glass pipet at 15, 30 and 45 minutes. (Caution: The steel cannulas should not be used to withdraw the sample, since surfactant tends to corrode the cannulas.) After the filtration with 0.8 um AA filters[5], the samples and a standard prepared in dissolution medium were assayed spectrophotometrically at 242 nm.

RESULTS AND DISCUSSION

TABLE-1 shows the results of dissolution studies conducted for medroxyprogesterone acetate tablets, 10 mg, (for products A and B) by USP Method II in water, gastric fluid (without enzyme) and intestinal fluid (without enzyme). It is clear from these results, that medroxyprogesterone acetate is not soluble in these media.

Therefore, further dissolution studies were conducted to achieve suitable dissolution profile for these tablets. In order to increase the rate of dissolution, sodium lauryl sulfate, a surfactant, was employed with primary dissolution media, water and 0.1N HCl. While these studies were in-progress in our laboratory,

TABLE-1

DISSOLUTION OF MEDROXYPROGESTERONE ACETATE IN DIFFERENT MEDIA

	% Dissolved in 45 Minutes (Mean of 6 Tablets)	
Medium	Product A	Product B
Water	14.0	0.7
Gastric Fluid	14.3	6.2
Intestinal Fluid	12.5	8.2

FDA's handbook of drug dissolution standards was published (6) which recommended the use of 0.54% sodium lauryl sulfate in water as dissolution medium. The tolerance limits require that 85% of the drug should dissolve in 45 minutes. In this study, the dissolution tests for products A and B were carried out using 0.54%, 0.27% and 0.135% sodium lauryl sulfate in water. The results are summarized in TABLE-2. These results show that both products A and B dissolute more than 85% with 0.54% sodium lauryl sulfate in water as medium. Although product A has an acceptable dissolution profile with 0.27% sodium lauryl sulfate in water as dissolution medium, product B dissolutes only 71.6%. When 0.135% sodium lauryl sulfate in water was used as dissolution medium, both products A and B failed to meet the tolerance limits criteria.

Additional dissolution studies were then conducted using 0.10%, 0.05% and 0.025% sodium lauryl sulfate in 0.1N HCl. The results are summarized in TABLE-3. These results indicate that both products A and B afford an acceptable dissolution profile with 0.1% sodium lauryl sulfate in 0.1N HCl dissolution medium. Product A also has an acceptable dissolution profile with 0.05% sodium lauryl sulfate in 0.1N HCl, whereas product B fails to meet

TABLE-2

COMPARATIVE DISSOLUTION PROFILES FOR PRODUCTS A AND B IN DISSOLUTION MEDIA CONTAINING VARYING AMOUNTS OF SODIUM LAURYL SULFATE IN WATER

		% of Medroxyprogesterone Acetate Dissolved (Mean of 12 Tablets)								
Product A	Mean:	96.5	102.2	104.4	94.6	96.3	104.7	48.0	67.0	71.8
	±SD:	3.8	3.9	3.4	9.2	3.4	3.4	4.1	8.0	8.2
	RSD:	3.6	3.7	3.4	9.7	3.5	3.2	8.6	11.9	11.4
Product B	Mean:	91.3	93.7	95.8	45.6	60.8	71.6	7.3	13.1	16.9
	±SD:	2.6	1.5	1.5	4.5	3.5	2.8	9.6	7.3	6.2
	RSD:	2.8	1.6	1.6	9.8	5.7	3.9	131.5	55.7	36.7

TABLE-3

COMPARATIVE DISSOLUTION RESULTS FOR PRODUCTS A AND B IN DISSOLUTION MEDIA CONTAINING VARYING AMOUNTS OF SODIUM LAURYL SULFATE IN 0.1N HCl

								SLS		
Product A	Mean:	79.3	87.6	95.3	76.3	84.5	88.0	45.3	34.1	48.9
	±SD:	8.0	8.4	9.4	3.4	4.5	4.0	11.1	9.1	15.5
	RSD:	10.1	9.6	9.8	4.4	5.4	4.5	24.5	26.8	31.7
Product B	Mean:	78.5	92.4	96.4	49.2	58.9	57.3	26.4	30.5	32.6
	±SD:	4.2	8.5	6.6	3.2	3.8	4.3	9.8	6.7	5.5
	RSD:	5.3	9.2	6.8	6.6	6.4	7.5	37.1	21.9	16.9

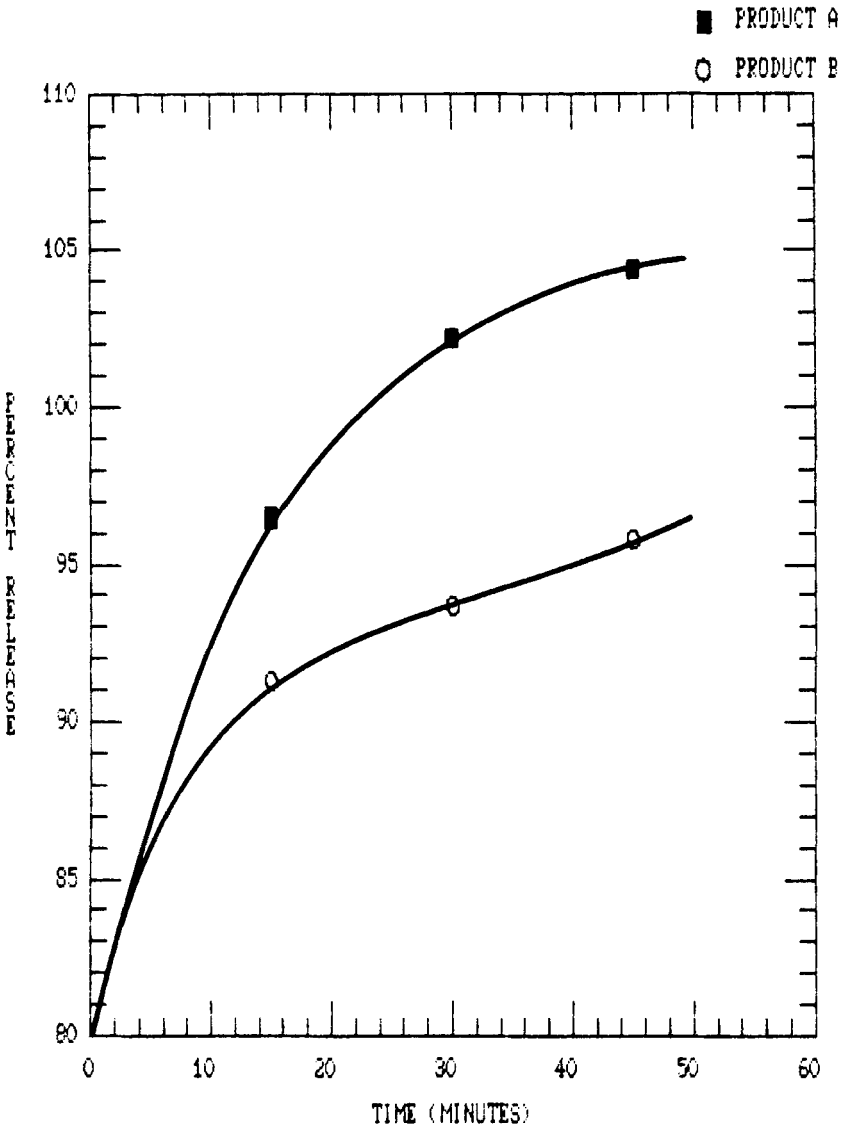

FIGURE 1: DISSOLUTION PROFILES OF PRODUCTS A AND B IN 900 mL WATER CONTAINING 0.54% SODIUM LAURYL SULFATE

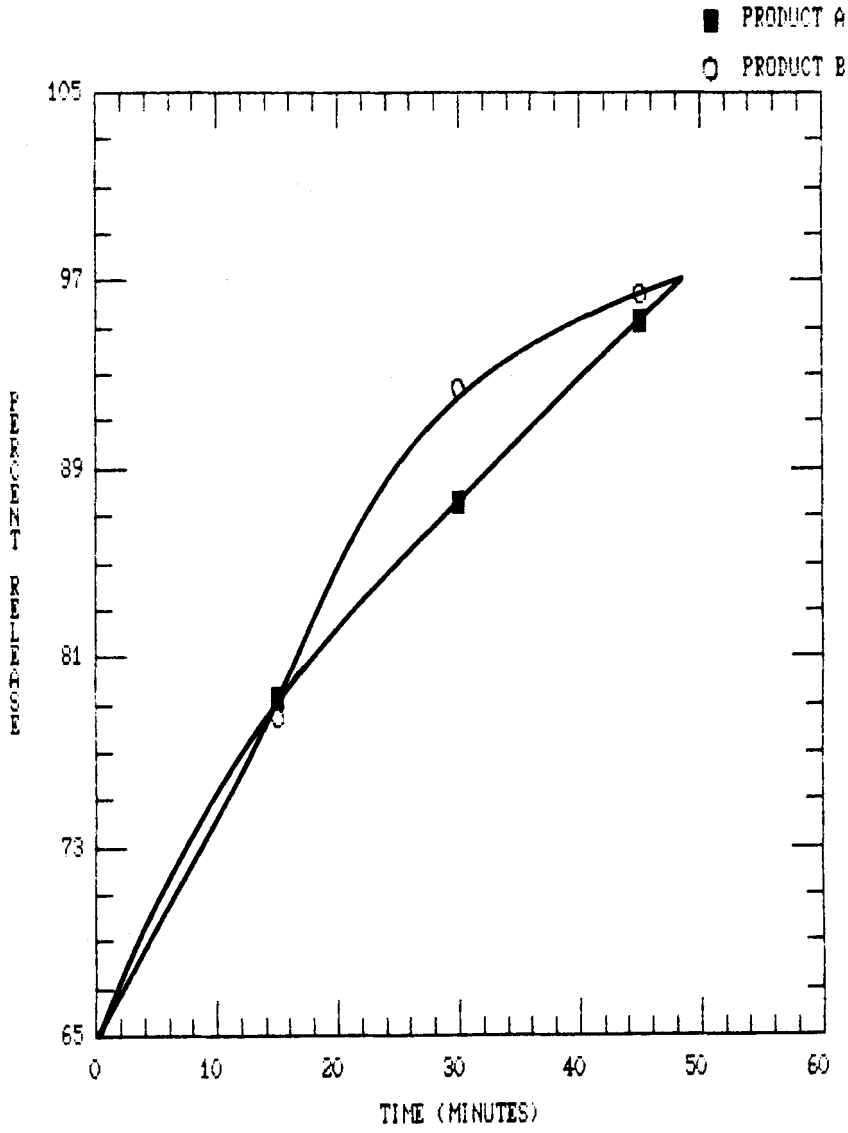

FIGURE 2: DISSOLUTION PROFILES OF PRODUCTS A AND B IN 900 mL 0.1N HCl CONTAINING 0.1% SODIUM LAURYL SULFATE

the acceptance criteria. Both products give poor dissolution results with 0.025% sodium lauryl sulfate in 0.1N HCl.

Comparative dissolution profiles for products A and B with 0.54% sodium lauryl sulfate in water are shown in Figure 1 and with 0.1% sodium lauryl sulfate in 0.1N HCl are shown in Figure 2. Since comparable and acceptable results are obtained for both product A and innovator's product B when 0.1% sodium lauryl sulfate is used in 0.1N HCl, we propose this as the medium of choice for quality control dissolution test of medroxyprogesterone acetate tablets. This will not only lower the drug to surfactant ratio (1:100) providing a more discriminatory dissolution medium, but will also help decrease the quantity of surfactant used, allowing the easier handling of the surfactant.

ACKNOWLEDGEMENT

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FOOTNOTES

1. Product A: Curretab, Lot 0-521, Reid-Rowell, Marietta, GA; Product B: Provera, Lot 363RF, The Upjohn Co., Kalamazoo, MI.
2. Sigma Chemical Company, St. Louis, MO.
3. E.I. duPont de Nemours & Co., Wilmington, DE.
4. Hanson Research Corporation, Northridge, CA.
5. Millipore Corporation, Bedford, MA.

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