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Studies of the dissolution characteristics of norethindrone-mestranol tablets

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Summary

Using a simple and sensitive HPLC method, dissolution studies have been performed on norethindrone-mestranol combination tablets in de-aerated water and in 30% isopropanol–water. The rate and extent of dissolution in the hydroalcoholic medium were much greater than in water. However, in a comparison of the dissolution data of products of the same dosage strengths from different manufacturers, the same rank order relationships existed for data obtained in de-aerated water and hydroalcoholic media. This would suggest that even for highly insoluble drugs an aqueous dissolution medium may be used. In these studies each component of the tablet exhibited its own dissolution rate in de-aerated water although these differences were not detected in the hydroalcoholic medium. Manufacturers should therefore exercise caution in monitoring the dissolution of only one component for quality control purposes.

Introduction

The most widely used oral contraceptives are mixtures of a synthetic estrogen and progestin. One such combination product contains mestranol and norethindrone. Unfortunately until recently, no published analytical method was available that could be used to carry out dissolution studies of these products. The lack of available analytical methods can be related to the extremely low tablet dosage strength. With the publication of a rapid method to concurrently assay norethindrone and mestranol in tablets (Sundaresan et al., 1981), a major step was taken in the search for a method that could be adapted for dissolution studies. This procedure,

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which utilized two HPLC detectors in series, was modified and shown to be applicable for carrying out dissolution studies (Goehl et al., 1982). In the present paper the dissolution characteristics of several mestranol-norethindrone tablet formulations have been studied in de-aerated water and 30% isopropanol–water.

Materials and Methods

Reagents and materials

Mestranol and norethindrone were of USP grade (U.S.P.C., Rockville, MD). Progesterone (lot 87C-0082, Sigma Chemicals, St. Louis, MO) was of reagent grade. All solvents were HPLC grade (Burdick and Jackson Laboratories, Muskegon, MI). Individual stock solutions of mestranol, norethindrone and progesterone were prepared by dissolving 10, 10 and 40 mg in 100 ml of methanol, respectively.

Equipment

A modular high-performance liquid chromatograph was used which consisted of a constant flow pump (Model M6000A, Waters Assoc., Milford, MA), an automated injector (Model WISP 710A, Waters Assoc., Milford, MA), a fixed wavelength 254 nm ultraviolet detector (Model 440, Waters Assoc., Milford, MA), a fluorescence detector set at an excitation wavelength of 230 nm and fitted with a 280 nm cut-off filter for emission (Model FS 970, Schoeffel Instruments, Westwood, NJ) and a strip chart recorder set at a speed of 0.5 cm/min (Model 9176, Varian Instruments, Palo Alto, CA). A stainless steel HPLC column (4.6 mm i.d. × 250 mm) packed with fully porous, irregularly shaped 10 μm silica to which a chemically bonded octadecyl group was attached (μ-Bondapak C-18, Waters Assoc., Milford, MA), was used. The mobile phase was a methanol–0.01 M pH 7 potassium phosphate buffer system (4 : 1). A flow rate of 1.3 ml/min was established (1500PSIG).

Dissolution procedure

Dissolution studies were performed as described previously (Goehl et al., 1981). Briefly, the U.S.P. (1980) method 2 was employed with 900 ml dissolution medium at 37°C and a paddle speed of 50 rpm. Six tablets were evaluated simultaneously using a custom-designed six-vessel dissolution apparatus meeting all the specifications of the U.S.P. (1980). The suitability of the dissolution apparatus was verified with the USP prednisone calibrator (U.S.P.C., Rockville, MD) using the paddle at 50 rpm with de-aerated water as the dissolution medium. The working standard solutions were prepared by diluting the stock solution with the appropriate dissolution medium. The dissolution media employed in the study were de-aerated water and 30% isopropanol–water. At each sampling time, 4 ml of the dissolution media were withdrawn from each vessel, filtered and all sample volumes immediately replaced. Exactly 2 ml of the filtrate was transferred to a vial and 5 μl of the internal standard solution was added and mixed. The vials were loaded into the automated injector and the device was programmed to inject a fixed volume depending on the dissolution media (50 μl for 30% isopropanol–water and 100 μl for de-aerated

water). The concentrations of the drug entities present in the dissolution media were determined from standard curves prepared by plotting peak height ratios versus the concentrations of the standard solutions.

Results and Discussion

The USP Executive Committee of Revision (Pharmacopoeial Forum, 1977) stated that the dissolution behavior of oral solid dosage forms has been shown to be a useful criterion for controlling formulation and process variables that can influence the bioavailability of the active ingredient of the dosage form'. To facilitate the development of dissolution methods new guidelines for dissolution requirements were adopted by the United States Pharmacopoeial Convention (Pharmacopoeial Forum, 1980). It was recommended that when possible, water should be used as the preferred dissolution medium. However, whatever the medium, the quantity used in the test should not be less than 3 times that required to form a saturated solution of the drug present in the dosage unit. Hydroalcoholic solutions are not recommended unless the solubility of the drug precludes the use of an aqueous medium. Therefore, solubility information of the drugs to be studied must first be examined before dissolution testing can be initiated.

Equilibrium solubilities of the two drug substances in water and 30% isopropanol–water at 37°C have been reported to be 0.58 and 140 μg/ml for mestranol and 8.8 and 680 μg/ml for norethindrone, respectively (Goehl et al., 1981). Since the highest dosage strength of mestranol in the available combination products is 100 μg, the resultant concentration after complete dissolution in 900 ml water, would be well within the suggested USP guideline of one-third of saturation when 100% of the dosage unit has been dissolved. For the norethindrone dosages of 2 mg, the resultant concentration would again be well within the suggested U.S.P. (1980) guideline limits. However, the marketed combination product containing 10 mg norethindrone should not dissolve in 900 ml of water, since the resultant concentration of 11.1 μg/ml would exceed the equilibrium solubility. Therefore, in order to accommodate the highest norethindrone dosage strength, another more favorable solvent system was desired such as a hydroalcoholic system consisting of 30% isopropanol–water. The reported equilibrium solubility of norethindrone in 30% isopropanol–water far exceeds the U.S.P. (1980) suggested solubility limit thus permitting the use of this medium for dissolution studies. By employing a solvent system in which the drugs are highly soluble, it was of interest to determine what effect, if any, the increased solubility might have on the relative dissolution of the various dosage strengths.

Dissolution profiles, in de-aerated water and 30% isopropanol–water were developed for 6 tablet formulations produced by two manufacturers (Tables 1 and 2). Only one production batch for each product was tested. The two dissolution media represent systems that meet suggested USP solubility dissolution guidelines for the drugs (except for product F) as well as a system that far exceeds the solubility guidelines. In all cases, dissolution in the hydroalcoholic medium was much faster than in de-aerated water. This was to be expected because of the lipophilicity of the

TABLE 1

PERCENT DISSOLVED ±S.D. OF LABEL CLAIM IN DE-AERATED WATER

Product (n)	Mestranol				Norethindrone			
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
A (24)	18 ± 3.8	25 ± 6.2	32 ± 9.9	38 ± 11.8	14 ± 5.3	26 ± 9.1	37 ± 14.1	43 ± 15.9
B (18)	9 ± 2.2	13 ± 2.6	17 ± 2.7	20 ± 4.0	8 ± 1.4	14 ± 2.2	17 ± 1.9	20 ± 3.0
C (18)	23 ± 3.9	36 ± 5.8	43 ± 6.9	47 ± 9.4	15 ± 2.8	25 ± 3.0	33 ± 4.3	40 ± 5.6
D (24)	21 ± 3.6	30 ± 3.9	32 ± 4.5	36 ± 6.5	30 ± 3.6	41 ± 4.9	47 ± 7.5	49 ± 8.8
E (18)	20 ± 2.6	30 ± 4.2	36 ± 4.7	41 ± 4.9	15 ± 2.4	26 ± 4.2	34 ± 5.8	41 ± 6.2
F (12)	24 ± 2.6	32 ± 3.5	37 ± 3.7	41 ± 4.9	24 ± 2.2	38 ± 2.7	45 ± 1.8	48 ± 1.9

Product code: A, Ortho-Novum 1/50-21 (1 mg norethindrone and 0.05 mg mestranol, lot 29B222); B, Ortho-Novum 1/80-21 (1 mg norethindrone and 0.08 mg mestranol, lot 29A115); C, norinyl 1 + 80 (1 mg norethindrone and 0.08 mg mestranol, lot 28368); D, Ortho-Novum 2 mg-21 (2 mg norethindrone and 0.1 mg mestranol, lot 29A026); E, norinyl 2 mg (2 mg norethindrone and 0.1 mg mestranol, lot 27964); and F, Ortho-Novum 10 mg (10 mg norethindrone and 0.06 mg mestranol, lot 18J091).

TABLE 2

PERCENT DISSOLVED ±S.D. OF LABEL CLAIM IN 30% ISOPROPANOL–WATER

Product (n)	Mestranol				Norethindrone			
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
A (18)	44 ± 9.2	70 ± 16.2	94 ± 12.2	108 ± 9.7	47 ± 13.6	71 ± 17.8	86 ± 9.5	96 ± 5.8
B (12)	33 ± 3.0	57 ± 5.1	74 ± 5.9	94 ± 8.5	30 ± 4.2	53 ± 4.2	70 ± 4.9	85 ± 6.0
C (12)	54 ± 7.6	82 ± 4.9	101 ± 4.0	106 ± 6.4	46 ± 6.9	74 ± 5.2	93 ± 3.7	100 ± 3.0
D (12)	54 ± 11.3	80 ± 15.2	97 ± 10.7	103 ± 7.2	52 ± 10.4	78 ± 12.4	91 ± 10.0	98 ± 5.9
E (12)	37 ± 5.6	62 ± 7.4	82 ± 8.2	94 ± 7.5	31 ± 5.6	57 ± 6.3	76 ± 7.6	89 ± 6.2
F (12)	34 ± 4.1	52 ± 8.8	73 ± 6.6	93 ± 7.4	33 ± 5.0	52 ± 5.7	65 ± 11.7	86 ± 6.9

Product code: see Table 1.

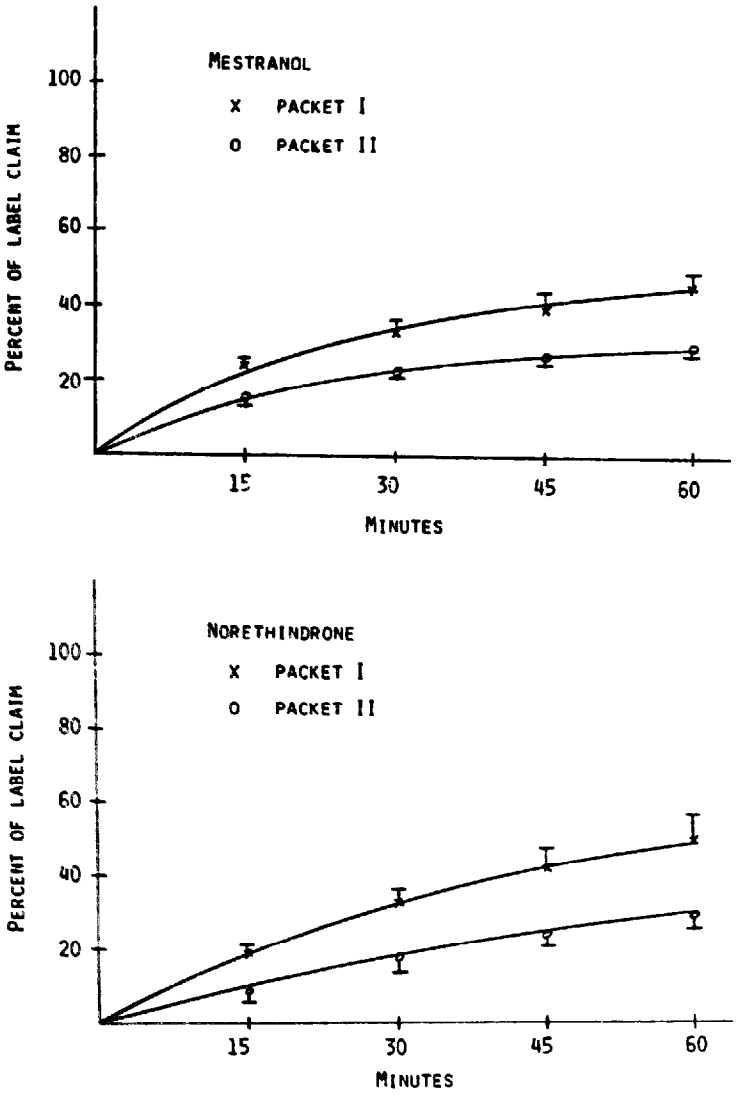

Fig. 1. Dissolution profiles for norethindrone-mestranol tablets from product A obtained from different blister packs in de-aerated water; mean ± 1 standard deviation.

drugs. However, even in de-aerated water after stirring for 4 h at 50 rpm with additional stirring for half an hour at 200 rpm, the amount dissolved was between 80 and 100% for all products.

The reproducibility of the dissolution characteristics for the 6 products was determined (Tables 1 and 2). The mean percent coefficient of variation for the dissolution of most products in both media and at all time periods was approximately 15%. A major exception was product A whose overall % C.V. varied from 21 to 38%. This variation was originally thought to be due to significant run to run reproducibility since the within-run variation was small. However, this variation was eventually traced to differences in the individual blister packs. During the dissolution survey, several different blister packs of product A were studied. All had come

from the same production batch and were stored at room temperature under the same conditions for the same period of time. The variation in the data was eventually explained by running tablets from two different blister packs in the same dissolution experiment (Fig. 1). It is postulated that perhaps the environment of the tablets prior to the packet being filled may have affected the dissolution characteristics of the product. Other possibilities include lot differences in the blister pack material or improperly sealed packets. Because of this observation, data from product A was excluded from further analysis.

In evaluating the data, all comparisons were made based on the dissolution results at 30 min. In a comparison of the results from the hydroalcoholic medium, no significant differences ($P < 0.05$) were detected in any product except for product C. In this product the percentage of mestranol was slightly higher than the percentage of norethindrone dissolved from the tablet. These same comparisons were made for all tablets in de-aerated water as the dissolution medium. Statistically significant differences ($P < 0.05$) were found in 4 of the 5 products. The observed differences in the dissolution rate for components in a combination product are not unexpected. For example, a recent publication on the dissolution of trisulfapyrimidine tablets (Wurster et al., 1981) has demonstrated that all 3 components have unique rates of dissolution. The fact that each component in the combination products exhibits its own dissolution rate indicates that the dissolution profile is related to formulation factors and is not a simple chemical solubility phenomenon. Because of the observed differences, the manufacturers initially should monitor both components for quality control purposes and exercise caution in relying upon data obtained from dissolution in a hydroalcoholic medium. Only after the manufacturer has gained sufficient experience with the product, should an attempt be made to monitor only one of the components.

Again using the 30 min dissolution values, comparisons between products having the same dosage strength but manufactured by different companies were made (Table 3). The first dosage strength studied (products B and C) contained 80 μg mestranol and 1 mg norethindrone. Product C gave much higher 30 min dissolution

TABLE 3

RANK ORDER RELATIONSHIPS OF 30 MIN MEAN DISSOLUTION VALUES IN DE-AERATED WATER (D.W.) AND HYDROALCOHOLIC (H.A.) MEDIA

Dosage (mestranol/norethindrone)	Product	Percent of label claim			
		Mestranol		Norethindrone	
		D.W.	H.A.	D.W.	H.A.
80 μg/1 mg	B	13	57	14	53
	C	36	82	25	74
100 μg/2 mg	E	30	62	26	57
	D	30	80	41	78

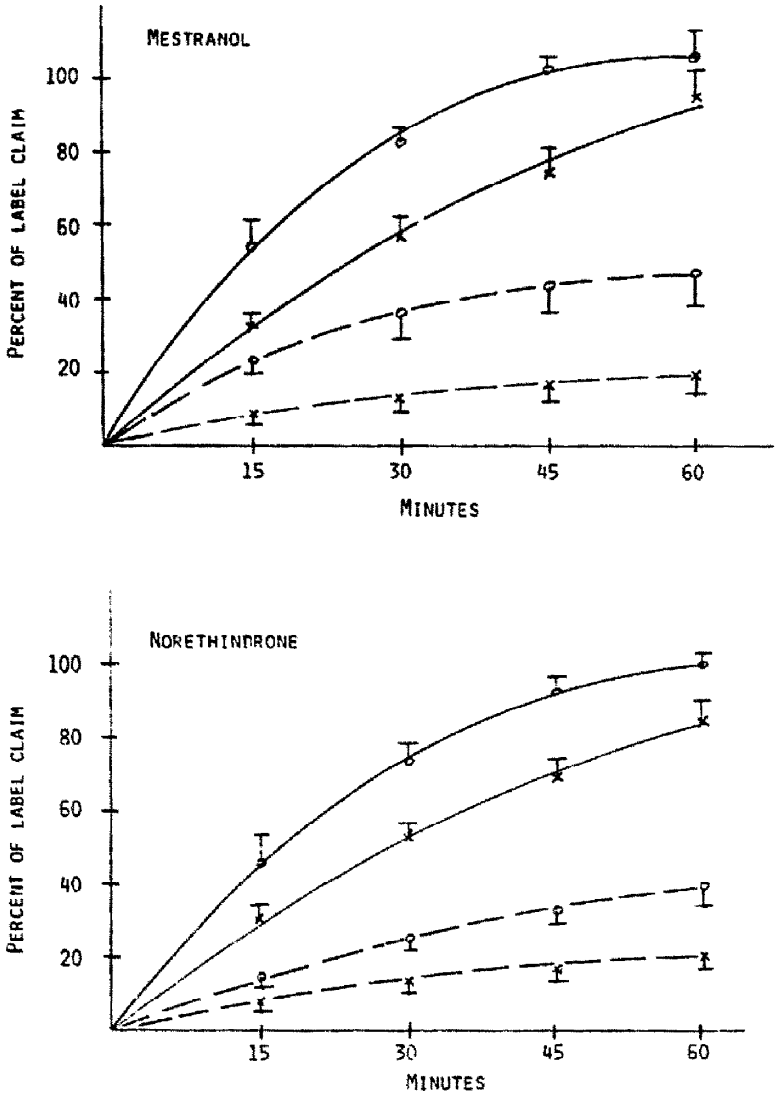

Fig. 2. Dissolution-profiles for norethindrone-mestranol tablets from products B (×) and C (○) in de-aerated water (- - - - - -) and 30% isopropanol (———); mean ± standard deviation.

values ($P < 0.05$) than product B in both media (Fig. 2). The second dosage strength studied (products D and E) contained 100 μg mestranol and 2 mg norethindrone. The performance of product D in de-aerated water and in hydroalcoholic media was better than product E ($P < 0.05$) except for the 30 min mestranol value where both D and E dissolve to the same extent (Fig. 3). Thus the same rank order relationships were established in both dissolution media. The therapeutic importance of these relationships are not known.

In summary, based on the dissolution profiles of several products that were developed in de-aerated water and 30% isopropanol–water, the following conclusions can be reached: (1) dissolution is faster in hydroalcoholic medium; (2) each

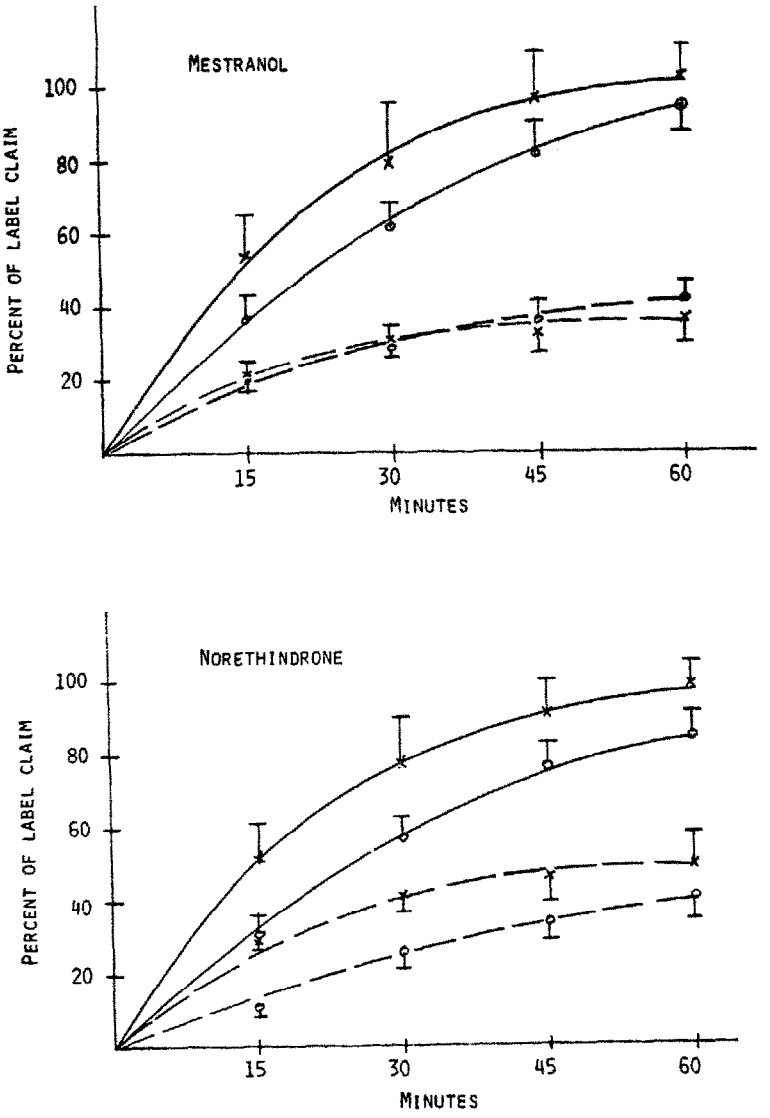

Fig. 3. Dissolution profiles for norethindrone-mestranol tablets from products D (×) and E (○) in de-aerated water (- - - - -) and 30% isopropanol (———); mean ± 1 standard deviation.

component of the norethindrone-mestranol combination tablets exhibits different dissolution rates in de-aerated water—these differences were not detected in the hydroalcoholic media; (3) a within-batch packet-to-packet difference was observed for one product; (4) the same rank order relationships exist in both aqueous and hydroalcoholic media for products of the same dosage strength produced by different manufacturers, except for the mestranol components of products D and E in de-aerated water; and (5) the data suggest that even for highly insoluble drugs, an aqueous dissolution medium may be appropriate.

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