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A DISSOLUTION METHOD FOR HARD AND SOFT GELATIN CAPSULES CONTAINING TESTOSTERONE UNDECANOATE IN OLEIC ACID

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ABSTRACT

A convenient and reproducible dissolution method for soft and hard gelatin capsules containing testosterone undecanoate in oleic acid is described. The method uses a flow-through dissolution cell and a dissolution medium the composition of which was optimized for both its capacity to dissolve the gelatin capsule wall completely and to give homogeneous filtrates of drug and oily excipient for convenient analysis of the collected fractions.

The discriminating power of the dissolution method for oily formulations of testosterone undecanoate was tested with three batches of the commercial formulation Andriol^{R}, and with two experimental formulations. The three batches of Andriol^{R}, soft gelatin capsules

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containing testosterone undecanoate in pure oleic acid, displayed biphasic dissolution patterns while dissolutions were always complete within 45 minutes. Dissolution of testosterone undecanoate from the experimental capsule formulation containing oleic acid and beeswax took about 3 hours to complete, whereas only 20% of testosterone undecanoate dissolved in the same time from the experimental capsule formulation containing a thixotropic mixture of oleic acid, beeswax and silicon dioxide.

In a study in healthy male volunteers it was found that the fast dissolving Andriol^{R} capsules gave peak plasma levels above the normal upper limit of testosterone plasma concentrations, whereas the slowly dissolving pasty hard gelatin capsules gave values within the normal range of testosterone plasma concentrations. The described dissolution method could therefore provide a promising approach to the development of new oily formulations of testosterone undecanoate with other in-vivo characteristics than those of Andriol^{R}.

INTRODUCTION

Certain lipophilic drugs show higher bioavailabilities when taken with a meal rich in fat or after co-administration with oils (1,2). This was also found with the undecanoic ester of testosterone, testosterone undecanoate, when administered in arachis oil (11). Testosterone undecanoate in arachis oil or, for better solubility, in oleic acid is effective in treatment of male hypogonadism (3). For this combination it has been demonstrated that first-pass degradation

by the enzymes of liver and gut-wall can be avoided because of gastrointestinal absorption via the lymph (4,5).

In-vitro dissolution tests of lipophilic drugs from oil-containing soft gelatin capsules have up to now been performed in the USP/NF paddle or basket apparatus or in a specially developed flow-through cell (6) or partition-permeation apparatus (7). The official methods have the serious disadvantage that the dissolution conditions for floating materials are poorly defined and sample taking is inconvenient. In a flow-through cell the site of dissolution is smaller and the flow conditions are better defined; sample taking is simple because the drug is removed from the oily excipient by continuous extraction with an aqueous perfusion medium and automatically filtered. Because of the unfavourable oil-water partition coefficient of lipophilic drugs, surface-active compounds or alcohols have been added to the aqueous dissolution media in order to avoid long dissolution times and large dissolution volumes (6,8). However, extraction of testosterone undecanoate from an oleic acid phase with any kind of perfusion medium is practically impossible; the octanol-water partition coefficients of testosterone undecanoate and oleic acid are high and differ by only one order of magnitude, logP being 8.91 and 7.55 respectively. The collected fractions from the dissolution experiment therefore always contain both testosterone undecanoate and oleic acid. One objective of this study was to find a dissolution medium in which no oil phase is formed in the collected fractions, so that homogeneous fractions can be analyzed.

Dissolution of Andriol^{R} capsules, containing testosterone undecanoate in pure oleic acid (formulation A), was studied with the in-vitro dissolution test described above. In an attempt to develop testosterone undecanoate formulations with a release different from that of Andriol^{R}, the oily content of the capsule was thickened by addition of 5% of beeswax (formulation B) or a combination of 10% of beeswax and 5% of silicon dioxide (formulation C). The in-vitro release of testosterone undecanoate from these pasty formulations might be applied for the sustained release of drugs (9). In order to see whether the developed dissolution method for testosterone undecanoate capsules would have predictive value for the in-vivo situation, a comparative study in healthy male volunteers was performed with Andriol^{R} and pasty formulation C.

MATERIALS

Andriol^{R} soft gelatin capsules (Organon International BV) contain a declared mass of 40 mg of testosterone undecanoate and about 174 mg of oleic acid (formulation A). Three batches of Andriol^{R} capsules, coded A1, A2 and A3, were investigated. These batches had been stored at room temperature (15 - 20 °C) in polyethylene bags in carton boxes for 4, 16 and 44 months, respectively. Thixotropic formulations were prepared by admixing at 60 °C 5% (w/w) of beeswax (formulation B), or by admixing 10% (w/w) of beeswax and 5% (w/w) of silicon dioxide (formulation C), to a solution of 40 mg of testosterone undecanoate in oleic acid. Formulation B was encapsulated in soft gelatin

capsules (Scherer) and formulation C was filled in hard gelatin capsules No. 2 (Elanco).

METHODS

Determination Of Testosterone Undecanoate

Testosterone undecanoate was measured spectrophotometrically after transformation to its isonicotinic acid hydrazone (10). An ethanolic solution of 500 mg of isonicotinic acid hydrazide with 0.625 ml of concentrated hydrochloric acid was prepared. Aliquots of 1.0 ml of the dissolution medium containing testosterone undecanoate were evaporated to dryness at 45 °C under a stream of nitrogen. The residues were dissolved in 4.0 ml of the isonicotinic acid hydrazide solution and shaken for one hour. Absorption of the hydrazone formed was measured at a wavelength of 380 nm with a Shimadzu UV240 spectrophotometer. The absorption of the blank solutions, containing oleic acid mixed with the isonicotinic acid hydrazide solution, was less than 1% of the absorption of the corresponding sample solutions.

Dissolution

The Langenbucher flow-through cell (Sotax, type CE-1) was provided with a nitrocellulose filter (Millipore, type AA, 0.8 µm) and thermostated at 37 +/- 0.5 °C. An HPLC pump (Knauer FR-30) was used to pump the dissolution medium, a 1:1 (v/v) mixture of isopropanol and 0.1 M hydrochloric acid, through the cell at a constant rate of 5 ml/min. Fractions of 15 ml were collected.

In-Vivo Study

This was performed as an open, randomized cross-over study in 7 healthy male volunteers. Eighty mg of

testosterone undecanoate, either as two Andriol^{R} capsules (formulation A) or as two hard gelatin capsules containing a thixotropic paste (formulation C), were administered orally. Blood samples were taken at 8.00 (time of administration), 10.00, 12.00, 14.00 and 16.00 hours. After a wash-out period of one week the experiment was repeated with the other dosage form. As testosterone undecanoate is readily hydrolyzed in blood, the plasma levels of testosterone were determined by a specific radioimmunoassay (11).

RESULTS

For the development of a practical dissolution test for gelatin capsules containing testosterone undecanoate in an oily matrix, the Langenbucher flow-through cell equipped with a pump and a fraction collector, was chosen. Various combinations of water/alcohol/surfactant mixtures and filters attached to the flow-through cell were tried. Many of these combinations gave non-reproducible results with two or three separated phases in the collected fractions. In order to avoid such inhomogeneities and to obtain accurate and reproducible results, a dissolution medium with enough dissolving power for both the gelatin capsule wall, the testosterone undecanoate and the oleic acid had to be found, together with a filter that could efficiently separate dissolved from undissolved material. In the course of the initial experiments it had been observed that the isopropanol/water ratio of the dissolution medium strongly influenced the dissolution behaviour of the Andriol^{R} capsules. In mixtures with low concentrations of isopropanol, the

gelatin shell dissolved rapidly, while the oily contents of the capsule did not dissolve or did so only extremely slowly. In media with a high concentration of isopropanol, the gelatin wall became brittle and resisted rupture for a longer time; however, once the capsule wall burst the oily contents dissolved completely, forming homogeneous solutions. Optimum perfusion conditions for Andriol^{R} capsules were given by a mixture of 0.1 M hydrochloric acid and isopropanol in a 1:1 (v/v) ratio at a speed of 5 ml/min. By using a hydrophilic nitrocellulose filter under these conditions homogeneous solutions were obtained in the collected fractions, allowing a more reliable spectrophotometric analysis of testosterone undecanoate to be made.

Dissolution profiles of three individual capsules taken from three batches of Andriol^{R} capsules which had been stored for 4, 16 and 44 months at room temperature (15 - 20 °C) are shown in Fig. 1. A large number of fractions were collected during the dissolution process, so that the discriminating power of the method was high enough to detect differences between individual capsules and between batches. The dissolution profile of Andriol^{R} appeared to be biphasic. During the first phase some leakage of the oily contents from the capsule was observed near the capsule seam. In the second phase the gelatin capsule wall fully dissolved and the remainder of the capsule content was released in a short period of time. For fresh Andriol^{R} capsules (batch A1) the first phase lasted about 15 minutes, whereas for aged capsules (batches A2 and A3) it lasted about 30 minutes. In all cases complete dissolution of testosterone undecanoate

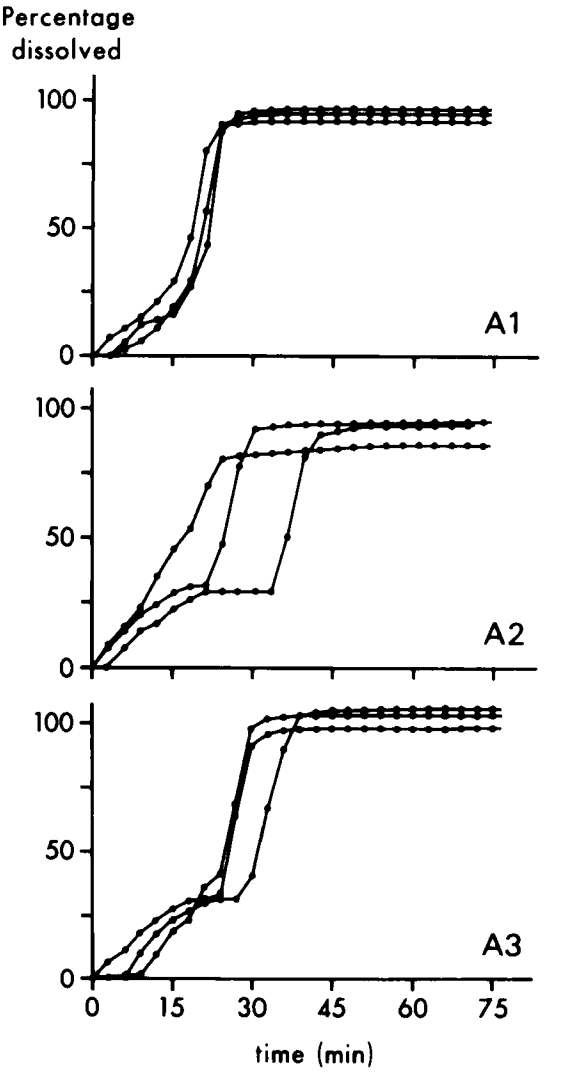

FIGURE 1
Dissolution of testosterone undecanoate from three batches of Andriol capsules: A1 after 4 months of storage, A2 after 16 months of storage and A3 after 44 months of storage. The total amount of testosterone undecanoate as percentage of the declaration is given as a function of time. The dissolution medium was a 1:1 (v/v) mixture of isopropanol and 0.1 M hydrochloric acid.

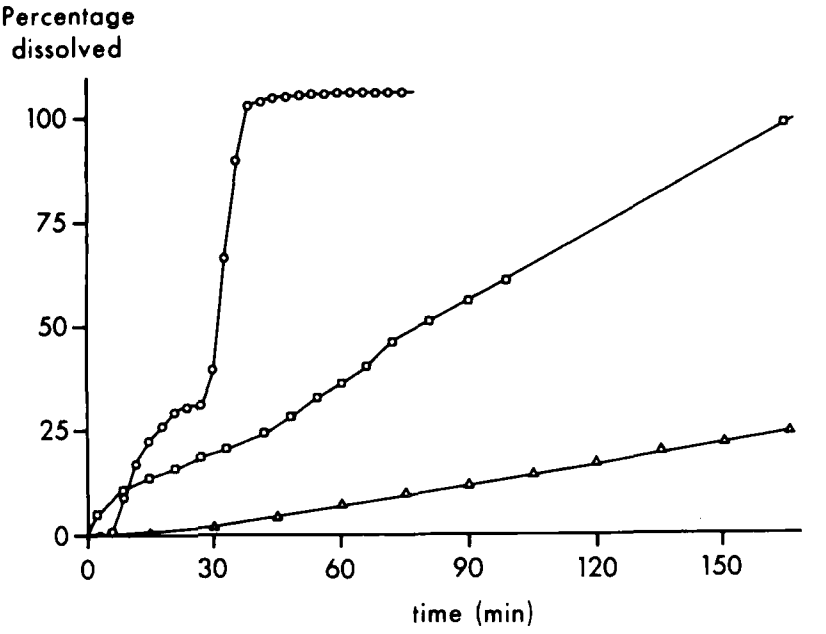

FIGURE 2
Dissolution of testosterone undecanoate from Andriol^{R} capsules (O) and thixotropic formulations B (□) and C (Δ). For details see Fig. 1.

occurred within 45 minutes. (It should be noted, however, that disintegration of Andriol^{R} capsules in water always occurs within 15 minutes.)

Both the capsule wall and the capsule contents of pasty formulation B dissolved completely within 3 hours (Fig. 2). However, the capsule wall of formulation C dissolved readily, leaving behind in the flow-through cell a pasty matrix from which after 6 hours only 30% of the testosterone undecanoate had been dissolved. In a study in healthy male volunteers the Andriol^{R} formulation was compared with the sustained release formulation C. The peak plasma testosterone levels of the volunteers receiving 80 mg of testosterone undecanoate in Andriol^{R} capsules increased to a mean

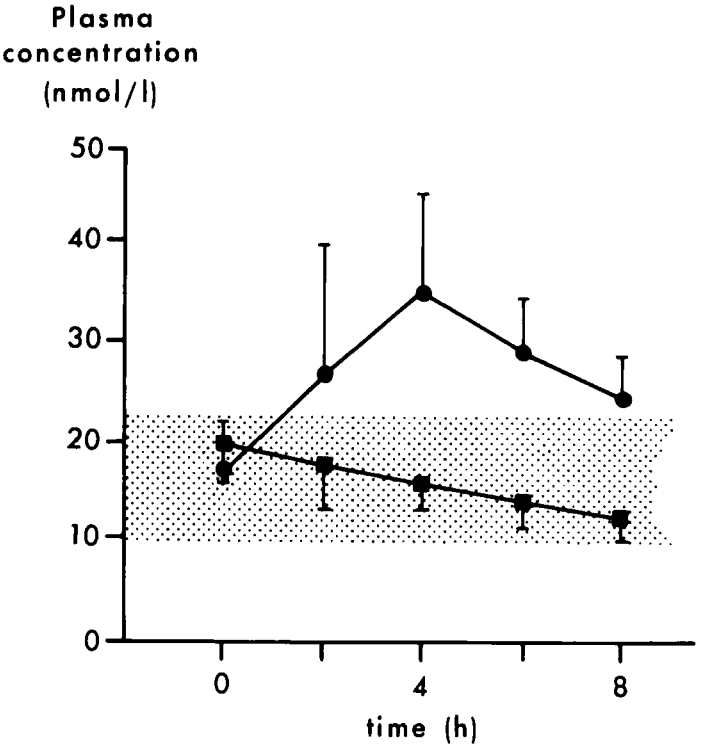

FIGURE 3
Mean plasma levels of testosterone in seven healthy male volunteers after oral administration of 80 mg of testosterone undecanoate. The shaded area represents the range of normal plasma levels of testosterone in healthy males.
Key: Andriol^{R} (●), Formulation C (■).

value of 35 nmol/l about 4 hours after dosing, which is comparable to the levels reached in the patients of a previous study (11). However, the plasma testosterone levels of the volunteers receiving 80 mg of testosterone undecanoate in the pasty formulation C remained within the range which is normal for healthy males (Fig. 3). The present study suggests a correlation between the peak plasma levels and the

in-vitro dissolution rates in the described dissolution model for oily testosterone undecanoate formulations.

DISCUSSION

A convenient and reproducible method for the dissolution of oil-containing gelatin capsules was described using a medium that dissolves both the gelatin capsule wall and its oily contents. Although the applied mixture of isopropanol and 0.1 M hydrochloric acid is non-physiological, similar dissolution media are used in two official USP XX dissolution tests, viz. those of cortisone acetate and danazol (8).

In addition to being used to control the quality of Andriol^{R} batches, the proposed dissolution method can also be used to study oil-based pasty formulations. A sustained release of the testosterone undecanoate contents was found in-vitro. A study in volunteers gave low peak plasma levels for the pasty formulation. One explanation for this finding is that only low amounts of testosterone undecanoate had been released from the dosage form, as is the case in-vitro. An alternative explanation is that the lymphatic route for testosterone undecanoate transport is shut off when the amount of free oleic acid in the intestines is too low. An indication for such a mechanism in the rat has been reported; if the concentration of fatty acids was low, impaired transport of lipophilic drugs via the chylomicrons was found (1,4).

Because a correlation with the in-vivo absorption was found, the dissolution method might be useful for the development of oily dosage forms of testosterone

undecanoate which would give peak plasma levels higher than can be reached with Andriol®. This may be achieved by looking for fast dissolving combinations of oily excipients or by applying the recently described approach of Bauer et al. (12), by making solid emulsions of testosterone undecanoate.

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