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COMMUNICATION

In Vitro Release of Amoxycillin from Lipophilic Suppositories

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ABSTRACT

The in vitro release characteristics of amoxycillin from different lipophilic suppository bases were investigated using the USP rotating basket method. Suppositories containing 250 mg amoxycillin were prepared in theobroma oil and in the semi-synthetic bases Witepsol W35, Suppocire A32, Novata BD, and Novata 299. Both freshly prepared and 1-month-old suppositories were tested. Analysis of amoxycillin was performed using a validated high-performance liquid chromatographic (HPLC) technique. Release profiles differed significantly between bases, with the greatest amount of amoxycillin being released from both newly made and 1-month-old Novata BD bases (87.57 ± 8.18 and 99.66 ± 6.63%, respectively), and the lowest amount released from the newly manufactured theobroma suppositories (8.82 ± 0.75%) and the 1-month-old Suppocire A32 suppositories (7.78 ± 0.27%).

INTRODUCTION

The rectal route is a convenient means of administering drugs to patients who are unwilling or unable to swallow medication, such as unconscious patients, infants, children, and patients who are vomiting. A pediatric suppository may prove useful when children are unable to take an oral antibiotic. A good candidate for inclusion in a suppository dosage form is amoxycillin, a broad-spectrum penicillin commonly used for respiratory tract infections, otitis media, and prophylaxis prior to surgery such as tonsillectomy.

The aim of this study was to use dissolution testing as an aid in selecting a suitable suppository base for formulation with amoxycillin trihydrate. The type of suppository base used regulates the partitioning of the drug between the suppository and the rectal environment.

Pharmacopoeial specifications state as part of the definition of rectal suppositories that the suppositories should soften, melt, or dissolve at body temperature (1); however, this statement is meaningless unless a standard method of determining these qualities is given. The dissolution and release rates of drugs may influence the bioavailability of drugs from suppositories, but because

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different methods give different results, suppositories may be accepted as suitable despite inadequate melting, softening, or dissolving in the rectal environment. This suggests that quality control of suppositories by in vitro release tests is needed for the bioavailability certification. An in vitro dissolution technique should discriminate between dissolution profiles of suppositories of different composition, be reproducible, and enable in vitro–in vivo correlation in humans.

A variety of systems have been used to investigate in vitro drug release, and techniques that are in use differ mainly in the extent to which they mimic in vivo conditions (2–5). The basket, the paddle, and the flow-through techniques are the approved in vitro dissolution techniques for solid oral dosage forms in the United States Pharmacopoeia (2) and these techniques have been adapted for determination of the dissolution of drugs from rectal dosage forms (3,5–9).

MATERIALS

Rectal Dosage Systems

The bases used in this study were Novata BD (Henkel, South Africa), Novata 299 (Henkel, South Africa), Witepsol W35 (Hüls, South Africa), and Suppocire A32 (Hüls, South Africa). Theobroma oil (Elabtech, South Africa), a well-known base, was used for comparative purposes. The suppositories were produced manually on a small scale by homogenizing 250 mg amoxycillin base (290 mg of the trihydrate) (Clinimed, East London, South Africa) per suppository into the melted suppository base. The melt was poured into 1 g polished stainless steel molds, and the suppositories were left to set at room temperature. The suppositories were stored in a dark cupboard at room temperature (21°C).

METHOD

In Vitro Dissolution

The in vitro dissolution of amoxycillin from the suppositories was examined by means of the basket apparatus (Apparatus I USP XXII) (2). The conditions used were based on those specified for the dissolution of amoxycillin capsules (2). Deaerated high-performance liquid chromatography (HPLC) grade water (900 ml), at 37 ± 0.5°C, was used as the dissolution medium. The speed of rotation was 100 rpm and the mesh width of the basket was 40 mesh (10).

The dissolution tests were performed on six separate dosage units for each type of base and the analysis was carried out in triplicate. Aliquots of test solution (500 µl) were collected manually after 5, 10, 15, 30, 60, 90, 120, 180, and 240 min. One hundred microliters of each sample was mixed with 200 µl of the internal standard solution, salicylic acid 0.0015 mg/ml. The amount of dissolved amoxycillin was determined by a validated HPLC method, with UV detection at 230 nm (10).

The suppositories were tested within a week after manufacture, and again 1 month thereafter, to determine whether aging had an effect on drug release. The suppositories were stored in the dark at 21°C in a sealed container. A mass balance was performed to account for amoxycillin retained in the base after the 4 hr test period. The basket, with the remainder of the base, was warmed to approximately 40°C in 200 ml HPLC-grade water. When the base had remelted, the beaker containing the melt was sonicated either for about 10 min or until the amoxycillin had dissolved. An aliquot of this solution was then analyzed using HPLC.

HPLC Analysis

Separation was achieved on a Nova-Pak® C_{18} 60 Å 4 µm, 3.9 × 150 mm HPLC cartridge column (Waters Associates, Milford, MA). The mobile phase used consisted of methanol–phosphate buffer (pH 7, 0.05 M) (5:95). Salicylic acid (Sigma Chemical Co., Midrand, South Africa) was used as an internal standard (10).

RESULTS

In vitro dissolution profiles from the various bases are shown in Figs. 1 and 2. In the 4 hr dissolution of newly made suppositories, 87.57 ± 8.18% amoxycillin was released from the Novata BD, 85.20 ± 16.42% from the Novata 299, 44.40 ± 28.43% from the Suppocire A32, 50.40 ± 12.31% from the Witepsol W35, and 8.82 ± 0.75% from the theobroma oil (Fig. 1). When 1-month-old suppositories were tested, 99.66 ± 6.63% was released from Novata BD, 74.52 ± 3.16% from Novata 299, 7.98 ± 0.27% from Suppocire A32, 31.98 ± 2.07% from Witepsol W35, and 11.22 ± 4.04% from theobroma oil (Fig. 2).

The greatest quantity of amoxycillin released in 240 min was released from the Novata bases and the release rate for the first hour of dissolution was also highest for these bases. Both newly prepared and aged Novata bases showed a rapid release and dissolution of the drug for the first 60 min, then the drug seemed to be retained in

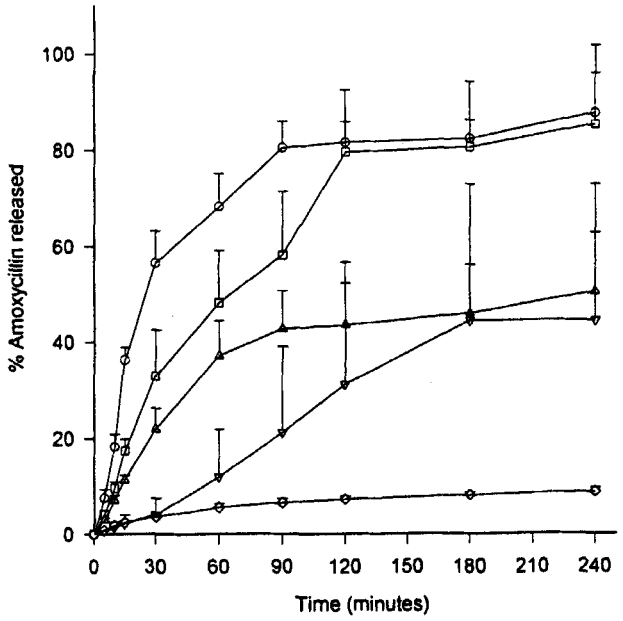

Figure 1. Amoxycillin release from suppository bases at t = 0 months, ○ Novata BD, □ Novata 299, Δ Witepsol W35, ▽ Suppocire A32, and ◇ theobroma.

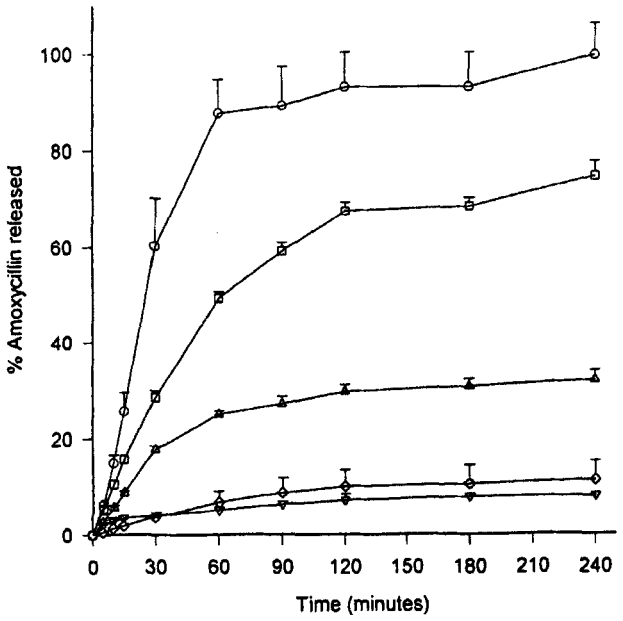

Figure 2. Amoxycillin release from suppository bases at t = 1 month, ○ Novata BD, □ Novata 299, Δ Witepsol W35, ▽ Suppocire A32, and ◇ theobroma.

the matrix and released at a slower rate between 1 and 4 hr. Within the first hour of dissolution, 68% of the drug in the fresh Novata BD suppositories had dissolved, 88% from the aged Novata BD suppositories, and almost 50% from both fresh and aged Novata 299 suppositories. No more than 40% was released from the Witepsol W35 suppositories and the fresh Suppocire suppositories, while not even 10% of the drug in the theobroma suppositories and the aged Suppocire suppositories was dissolved within the first hour of dissolution.

The amount of drug recovered when a mass balance was performed is shown in Table 1. In all cases the percentage total drug measured was approximately 100%, indicating that the amoxycillin which was not released from the suppository bases during the 240 min dissolution period was accounted for by performing the mass balance experiment.

DISCUSSION

The different brands of semisynthetic bases showed different dissolution profiles. Each brand contains a unique combination of tri-, di-, and monoglycerides which confer certain characteristics to that base. Theobroma, being primarily a mixture of fatty acid triglycerides, also showed a different dissolution profile. The nature of the base clearly has an effect on the dissolution rate and the amount of drug that is released.

It would appear that the hydroxyl value of a suppository base is of some significance to the release of the drug from a suppository. This finding is consistent with that of Othman and Muti (4). The synthetic suppository bases are mixtures of fatty acid esters with certain amounts of glycerides. The hydroxyl value of a base is determined by the presence of mono- and diglycerides and therefore represents the availability of free hydroxyl groups. The potential reactivity of a base is usually indicated by the magnitude of its hydroxyl value. A high hydroxyl value indicates that the base can adsorb water more readily and is therefore less suitable for formulations containing drugs that are easily hydrolyzed (1). Amoxycillin, which is susceptible to hydrolysis, may interact with these hydroxyl groups and degrade.

Drug release from bases with lower hydroxyl values (such as the Novata bases) was shown to be faster and more complete than from those with a higher hydroxyl value. These results could be accounted for on the basis of simple partitioning between aqueous and lipid phases (4). The partitioning of the drug when bases with

Table 1

Mass of Amoxycillin Released from Suppository Bases Within 240 min at t = *0 and* t = *1 Month*

	Mean Mass (mg) ± SD (n = 6)				
	Novata BD	Novata 299	Witepsol W35	Suppocire A32	Theobroma
t = 0 months					
240 min	218.93 ± 20.45	213.00 ± 41.10	126.30 ± 30.78	111.00 ± 71.09	22.05 ± 1.87
Mass balance	8.61 ± 6.67	48.33 ± 16.64	89.13 ± 19.65	120.83 ± 54.44	220.53 ± 21.90
% Total drug[a]	91.05 ± 6.35	104.52 ± 11.47	86.17 ± 7.95	92.73 ± 8.10	97.03 ± 8.93
t = 1 month					
240 min	248.15 ± 23.90	186.30 ± 7.91	79.95 ± 6.56	19.91 ± 0.01	29.27 ± 9.85
Mass balance	12.45 ± 14.18	60.89 ± 7.85	154.77 ± 23.58	203.28 ± 6.16	206.97 ± 20.40
% Total drug[a]	104.64 ± 2.28	98.99 ± 1.25	93.89 ± 8.32	89.29 ± 2.63	94.01 ± 4.81

[a]% Total drug = 100 (mass of drug released by 240 min + mass balance)/250.

high hydroxyl values are used, such as the Witepsol W35 and Suppocire A32, appears to favor the lipid phase.

Consideration of hydroxyl value alone could not account for these dissolution results however, since Novata BD, despite having a higher hydroxyl value than Novata 299, showed a slightly higher rate and extent of release. Examination of the solidification point showed that Novata BD has a slightly lower solidification point (30–32°C) than Novata 299 (31.5–33.3°C), which could result in a faster release of the drug (4).

On prolonged storage, semisynthetic suppository bases have been shown to be subject to hardening and lengthening of the melting time (1). The degree of hardening may be remedied by storage in a cold place, but melting characteristics, hardness, and drug release profiles begin to alter after storage for a few weeks, and the melting point may rise by 0.5°C after storage for several months (11). Storage can thus result in a marked reduction in drug release from suppositories (8). This could explain in part why after storage for a month, less amoxycillin was released when Novata 299, with a hydroxyl value of ≤5 was used, whereas the amount of amoxycillin released from Novata BD, which has a hydroxyl value of ≤15, increased.

CONCLUSIONS

The USP basket apparatus was successfully used to compare the release of amoxycillin from Novata BD, Novata 299, Witepsol W35, Suppocire A32, and theobroma suppository bases. This in vitro assessment of the suppositories enabled the identification of the base with the best release characteristics. The Novata bases, which had the lowest hydroxyl values of those bases which were compared, showed the highest rate and extent of drug release over the dissolution period and so were considered to be the most appropriate bases for the formulation of a pediatric amoxycillin suppository.

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