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Evaluation of an Acetic Acid Ester of Monoglyceride as a Suppository Base with Unique Properties

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ABSTRACT The objective of this investigation was to evaluate an acetic acid ester of monoglycerides made from edible, fully hydrogenated palm oil (AC-70) as a suppository base and compare it with a commercially available semisynthetic base (Suppocire AI®). Benzocaine and miconazole were used as model drugs. Suppositories were prepared by the fusion method. The drug loads in the suppositories were kept at 2% to 5% (wt/wt). In vitro release of drug from the suppositories into Sorensen's phosphate buffer (pH 7.4) was studied using a US Pharmacopeia dissolution apparatus 1 and a spectrophotometer. The melting behavior of the bases and the physical state of the drug in the suppositories were studied using a differential scanning calorimeter (DSC). Powder x-ray diffractometry was used to study any possible polymorphic changes in the AC-70 base during formulation and storage. In vitro release studies revealed that the release of benzocaine from the AC-70 suppository was substantially slower than that of the commercial AI base. At a 2.5% (wt/wt) benzocaine load, the release of drug from the AC-70 suppositories was found to be linear. This slow and linear release was attributed to the physical property of the base, which forms liquid crystalline phases in the aqueous dissolution medium. The lyotropic liquid crystalline phase has the ability to incorporate drug into its structure and can control the release kinetics of the drug from such a system. The apparent pH of the release medium (water) was decreased by 1 to 1.5 pH units when the AC-70 base was used. The DSC studies revealed that the melting range of the AC-70 base is 36°C to 38°C, which is ideal for suppository formulations. The results of these studies support the possibility of using this new base for slow-release suppository formulations. This base may be of particular interest for a drug that requires an acidic environment to maintain its activity.

KEYWORDS: Acetic acid esters; monoglycerides; suppository base; liquid crystalline phase

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INTRODUCTION

AC-70 (Danisco Culter USA Inc., New Century, KS) is a kosher-approved product commonly used in the food industry as a waxing agent, plasticizer, and coating material, as well as a base for different chewing gums. AC-70 is an acetic acid ester of monoglycerides and is derived from edible, fully hydrogenated palm oil. AC-70 currently has no use in the pharmaceutical industry; however, because of its unique composition as an acetic acid ester and its melting point of around 37°C, it may be a candidate for a suppository base with some unique properties. One of AC-70's unique characteristics is the change in the environmental pH after the dissolution of the base at body temperature. This change in pH, along with the release of acetic acid, can be potentially advantageous for a drug that requires an acidic environment for its activity. In particular, miconazole nitrate vaginal suppository in the treatment of yeast infection in postmenopausal women and 5-aminosalicylic acid suppository for the treatment of ulcerative colitis are examples where acidic environment will be beneficial for therapeutic activity. Second, monoglycerides have been reported to form lyotropic liquid phases in the presence of water [1] and have been used as sustained release drug delivery systems [2-3]. The cubic phase can be defined as a lipid bilayer that extends in 3 dimensions and is separated by water channels. This system is highly viscous and has a transparent, gel-like appearance [4]. Therefore, objectives of this investigation were to (1) evaluate the possible use of AC-70 as a suppository base and compare it with a commercially available suppository base (Suppocire AI), (2) characterize any possible polymorphic changes in AC-70 base during formulation and storage, and (3) evaluate the in vitro release characteristics of 2 model drugs (benzocaine with pKa of 2.8 and miconazole pKa 6.9 [5]) from suppositories prepared using the AC-70 and Suppocire AI (Gatteefosse Inc, Saint-Priest, France) bases.

MATERIALS AND METHODS

Materials

Benzocaine (Sigma Chemical, St Louis, MO), Grindsed ACETEM 70-00 (Danisco Cultor USA, New Century, KS), Suppocire AI, miconazole base (Professional Compounding Centers of America, Houston, TX), acetic acid, sodium hydroxide, potassium dihydrogen phosphate, disodium monohydrogen phosphate, n-octanol, and phenolphthalein (Fisher Scientific, St Louis, MO) were used as received. Commercially available miconazole suppository (Monostat-7, Walgreen, IL), was also used in 1 of the dissolution studies for comparison purposes.

Formulation of suppositories

Suppositories were prepared by the fusion method [6]. Suppository base was melted (at 40°C ± 1.0°C) in a casserole. The drug was added to the molten base with constant stirring and poured into standard (2 g) disposable molds. The suppositories were allowed to cool at an approximate rate of 1°C/min and finally were hardened at 10°C ± 2.0°C in an ice bath for 1 hour. Suppositories were stored at both room temperature (25°C) and under refrigeration.

Characterization of polymorphism and melting behavior in the formulation

Suppositories containing 5% (wt/wt) benzocaine and 2% (wt/wt) miconazole were prepared using the AC-70 base. X-ray powder diffraction and DSC studies were performed on each sample immediately after preparation, after 100 days of storage at room temperature and refrigerated temperatures. Suppository samples were exposed to CuKα radiation (45 kV × 40 mA) in a wide-angle x-ray diffractometer (Model D5005, Siemens, Madison, WI). During the x-ray diffractometric studies, the samples were top-filled into an aluminum holder because of the waxy nature of the samples. The instrument was operated in the step-scan mode in increments of 0.05°2Θ. The angular range was 5° to 40°2Θ, and counts were accumulated for 1 second at each step. The data collection program used was JADE 3.0 (Materials Data Inc, Livermore, CA). Melting characteristics of all the suppository formulations were studied using a differential scanning calometer (Model DSC-50, Shimadzu, Kyoto, Japan). Samples were heated from 30°C to 100°C at a heating rate of 10°C/min in a nonhermetically sealed aluminum pan under nitrogen purge.

Determination of pH change after dissolution of the suppository

Placebo suppositories (suppository without drug) were formulated from both Suppocire AI and AC-70 bases. Suppositories were then dispersed in either 100 mL or 200 mL of water kept at 37°C with continuous agitation from a magnetic stirrer. The pH of the medium was measured before and after complete dissolution of the suppository using an analog pH meter (Markson, Wayne, NJ) .

Determination of acetic acid content of the bases

The acetic acid content of the bases (AI and AC-70) was determined by a slightly modified US Pharmacopeia (USP) method [7]. Three grams of the base was melted in an Erlenmeyer flask at 40°C. Two drops of phenolphthalein test solution was added to the molten base and titrated against 0.2 N of NaOH solution until it became pink.

In vitro release of drugs from suppository formulations

Benzocaine suppositories

In vitro release of benzocaine from the suppositories was carried out in a USP dissolution apparatus 1 that had been slightly modified [8]. Suppositories were placed in a wire mesh basket specially designed for suppository formulations (Hansen Research Inc, Chatsworth, CA), and Sorensen's phosphate buffer (900 mL) with pH 7.4 at 37°C ± 0.5°C was used as the release medium. The conventional USP stainless steel basket was replaced with a polyurethane basket with the same external dimensions as the USP basket and 12 linear slots of 0.25 mm allowing for a porosity of 52% [9]. The buffer solution was prepared by mixing 197 mL of KH_2PO_4 solution (9.1 g/L) to 803 mL of Na_2HPO_4 solution (9.48 g/L). At predetermined intervals, 2 mL of the release medium was collected through a sample filter set (Hanson Research, Chatsworth, CA) and replaced with 2 mL of fresh buffer. The benzocaine content in the release medium was determined by a spectrophotometer at 290 nm.

Miconazole suppositories

The dissolution study of the miconazole suppositories was conducted in a similar manner as described earlier. However, because of the low solubility of miconazole in Sorensen's phosphate buffer, a biphasic dissolution medium (n-octanol and aqueous buffer system, 50% [vol/vol] of each phase) was used. At predetermined times, 2 mL of the organic phase (top layer) was collected and replaced with 2 mL of fresh n-octanol. The miconazole content in n-octanol was determined by a spectrophotometer at 270 nm.

Physical state of the drug in the formulations

The physical state of the drug in the suppository formulation was determined by DSC and powder x-ray diffractometry [10].

RESULTS AND DISCUSSION

Evaluation of the polymorphism and physical state of the drug in the suppository formulations

Polymorphism is the capability of a substance to crystallize into 2 or more different crystalline forms. Certain suppository bases have demonstrated polymorphic changes under different conditions [11,12]. Because polymorphic changes can affect the melting point of the bases, it was essential to characterize this property in this new base. The possible polymorphic changes, if any, in the AC-70 formulation were studied using both DSC and powder x-ray diffraction methods. The powder x-ray diffraction patterns of benzocaine and miconazole suppositories in AC-70 base under 2 different storage conditions are shown in Figures 1 and 2, respectively. No significant differences in the powder patterns were detected. A polymorphic change in the suppository base could result in the disappearance of some existing peaks or the appearance of some new peaks in the x-ray patterns. DSC curves of both suppositories (benzocaine and miconazole in AC-70 base) are shown in Figures 3 and 4, respectively. DSC studies revealed that the melting characteristics of the suppositories were identical under both the storage conditions. The results of both x-ray and DSC studies concluded that no polymorphic changes occurred under both these storage conditions over 100 days. DSC and x-ray diffractometry were also used to determine the physical state of the drug in the formulation. Absence of melting endotherms for both

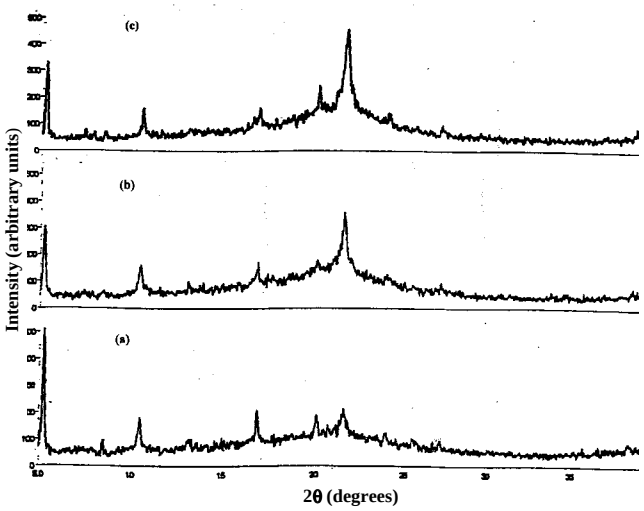

Figure 1. Powder x-ray diffraction patterns of 5% (wt/wt) benzocaine suppository in AC-70 base stored under the following controlled conditions: (a) immediately after preparation, (b) after storing it for 100 days in the refrigerator, and (c) after storing it for 100 days at room temperature.

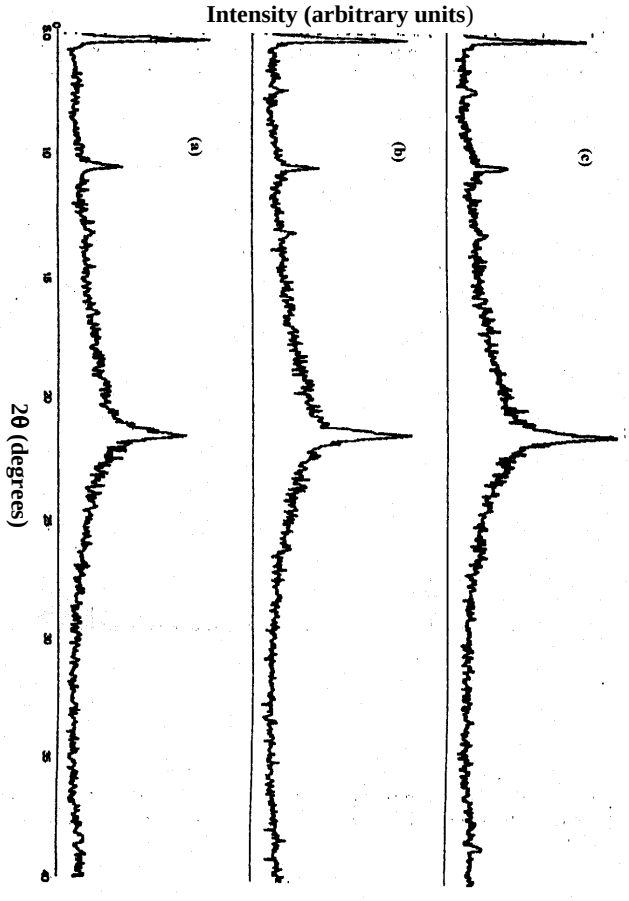

Figure 2. Powder x-ray diffraction patterns of 2% (wt/wt) miconazole suppository in AC-70 base stored under the following controlled conditions: (a) immediately after preparation, (b) after storing it for 100 days in the refrigerator, and (c) after storing it for 100 days at room temperature.

benzocaine and miconazole in the DSC thermograms of samples containing 5% (wt/wt) benzocaine and 2% (wt/wt) miconazole suppositories in AC-70 base revealed that the drug was present in a molecularly dissolved state in both formulations [10,13]. Absence of characteristic x-ray diffraction peaks for both the drugs in AC-70 suppositories containing 5% (wt/wt) benzocaine and 2% (wt/wt) miconazole further indicated that both the drugs were present in a molecularly dissolved state in the formulation.

Acetic acid content of the base and pH changes after dissolution

As discussed earlier, AC-70 is an acetic acid ester of monoglyceride prepared from edible, fully hydrogenated palm oil; therefore, exposure of this base to an aqueous environment may lead to ester hydrolysis and the eventual release of acetic acid into the release medium. Use of acetic acid in the local treatment of bacterial and fungal infections has been documented [14]. The change in the pH of the release medium (water) after complete dissolution of the suppository base was monitored for both the bases (AI and AC-70); the results are depicted in Table 1. The results of this study indicated that in the case of the AC-70 base, the pH of the medium decreased after complete dissolution of the suppository. This pH change was believed to be due to the release of acetic acid from hydrolysis of ester during the dissolution process. This pH change was also independent of the volume of the release medium used. In the case of AI suppositories, however, there was no change in the pH of the medium after dissolution. Therefore, another unique advantage of this base is that it provides an acidic environment that is beneficial for the drug's therapeutic activity. This includes miconazole vaginal suppository for postmenopausal women and 5-aminosalicylic acid suppository for the treatment of ulcerative colitis. The acetic acid content of the AC-70 was then determined using a USP method. In this study, a known amount of base was melted at 40°C and titrated against sodium hydroxide. The acetic acid content was found to be 5.3 ± 0.3 mg % (mean ± SD; n = 3). AI base did not contain any acetic acid, as expected.

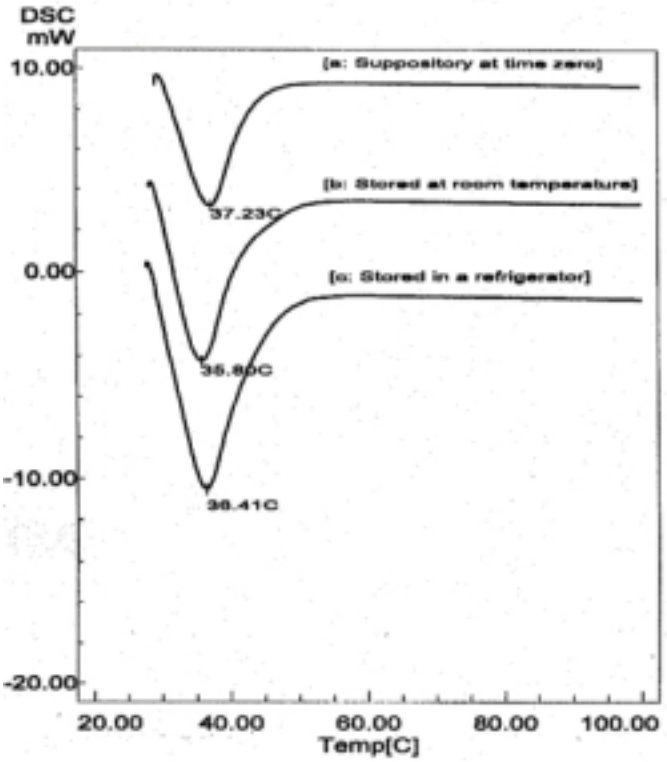

Figure 3. Differential scanning calorimetric curves of 5% (wt/wt) benzocaine suppository in AC-70 base under various storage conditions.

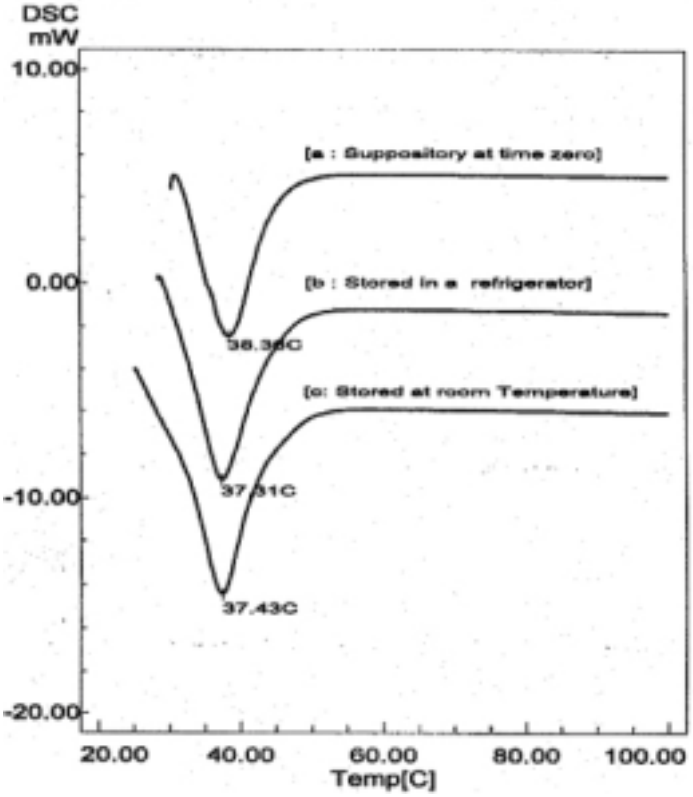

Figure 4. Differential scanning calorimetric curves of 2% (wt/wt) miconazole suppository in AC-70 base under various storage conditions

Table 1. Effect of Base Type on the pH of the Release Medium During Dissolution

Type of Base Used	Volume of the Release Medium (Water) Used (mL)	Weight of Suppository (g)*	pH of the Medium Before Dissolution*	pH of the Medium After Dissolution*
AC-70	100	1.94 ± 0.01	5.07 ± 0.15	3.73 ± 0.15
AI	100	1.94 ± 0.01	5.23 ± 0.06	5.23 ± 0.21
AC-70	200	1.96 ± 0.03	5.20 ± 0.10	3.96 ± 0.15
AI	200	1.94 ± 0.006	5.13 ± 0.06	5.17 ± 0.15

***Mean ± SD; *n* = 3.**

In vitro release of benzocaine from different suppository formulations

In vitro release of benzocaine from AI and AC-70 base suppositories containing 2 different drug loads (2.5% and 5.0% wt/wt) is shown in Figure 5. As expected, an increased drug load increased the rate and extent of benzocaine release from the suppository. The rate of release was found to be slower in the case of the AC-70 base as compared to the AI base. Interestingly, in the case of 2.5% (wt/wt) benzocaine in AC-70 suppository, an almost constant rate of release was noted. Melting of these AC-70 suppositories during dissolution produced viscous, oily droplets in the dissolution medium (formation of cubic phase), which could have served as a reservoir for this hydrophobic drug. In the case of the AI base, this droplet formation was not detected in the release medium. Monoglycerides have been shown to form cubic phases in the presence of water [1]. The nature of the cubic phases also depends on the amount of water present in the monoglyceride-water system. When the water content is 0% to 5% (wt/wt), reversed micellar phase generally forms. Lamellar phases are evident when the water content is 5% to 20% (wt/wt). The cubic phase generally forms when the water content is around 35% (wt/wt). Exposing 2 g of AC-70 base to 900 mL of aqueous dissolution medium over a prolonged period should form cubic phases in the dissolution medium. These cubic phases in turn serve as drug reservoirs and sustain the release of benzocaine in the dissolution medium. However, formation of cubic phases as a drug reservoir is not possible in the case of AI bases; therefore, this study clearly indicates that an AC-70 base can sustain the

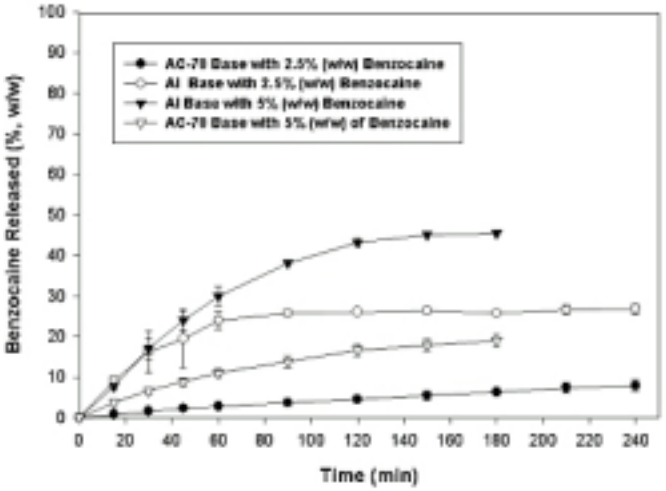

Figure 5. In vitro release of benzocaine from AI and AC-70 base suppositories containing various weight fractions of benzocaine: (closed circle) AC-70 base with 2.5% (wt/wt) benzocaine, (open circle) AI base with 2.5% (wt/wt) benzocaine, (closed triangle) AI base with 5% (wt/wt) benzocaine, and (open triangle) AC-70 base with 5% (wt/wt) benzocaine.

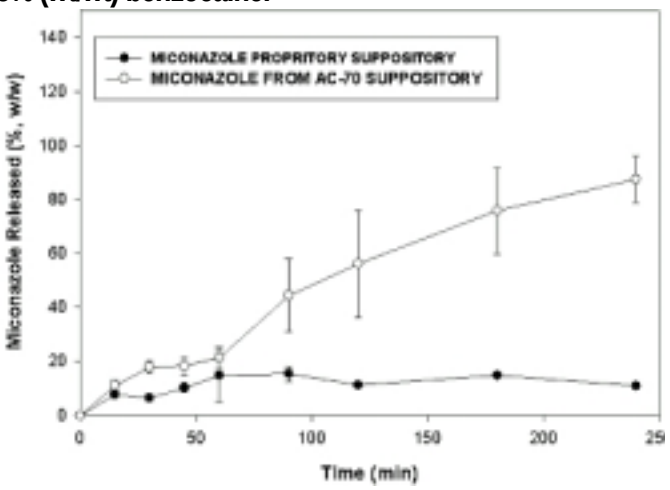

Figure 6. In vitro release of miconazole (2% wt/wt) from commercial and AC-70 suppositories.

delivery of a drug in an aqueous environment, even after the base has melted into the body fluids. In the case of the AC-70 suppository, increasing the drug load from 2.5% to 5% (wt/wt) did not result in a constant release pattern. By increasing the drug content in the cubic phase, the cubic phase can be transformed into a lamellar phase and followed by an isotropic solution phase [2]. This change in phases resulting from the presence of various weight fractions of drug in the cubic phase has been shown to affect the release kinetics of drug from such a system. This may explain the differences in the release characteristics of benzocaine from 2.5% versus 5% drug-loaded suppository formulations.

In vitro release of miconazole from different suppository formulations

The in vitro release profiles of miconazole from a commercially available formulation and AC-70 suppositories containing miconazole are shown in Figure 6. Because miconazole has a very low water solubility, 50% (vol/vol) octanol and phosphate buffer was used as the release medium. The use of this biphasic release medium was essential to overcoming the sensitivity problems encountered when analyzing the drug in the aqueous dissolution media. The release of drug to the organic phase (octanol) was monitored in this study. The release of miconazole from the commercial (AI) base was found to be significantly slower than from the AC-70 base. The commercial suppository formulation used hydrogenated vegetable oil base and polysorbate 80 as an inactive material. Furthermore, miconazole was present as a nitrate salt in this product but as a free base in the AC-70 suppositories. The solubility of miconazole nitrate in aqueous release medium is expected to be higher than that of the free base. However, the partition of this nitrate salt to the octanol phase is much lower than in the free base. Therefore, a high concentration of the free base (miconazole) in the octanol phase as compared to the miconazole salt should be expected. Because the concentration of miconazole in the octanol was used to evaluate the in vitro release characteristics of miconazole, a higher rate and extent of miconazole release from AC-70 base than from the AI base should be expected. No viscous oil droplets were observed in the aqueous phase of the dissolution medium. Constant release of miconazole was also not detected in the AC-70 suppositories containing miconazole. This can be explained by the fact that formation of cubic phases in the aqueous dissolution medium was not possible in this study because of the rapid partition of monoglycerides into the organic phase (octanol). Formation of cubic phase reservoirs containing the drug was not possible; therefore, the ability to control the release of miconazole at a constant rate was not achieved in this case.

CONCLUSION

Benzocaine release from AC-70 base containing 2.5% (wt/wt) of drug showed a constant release over at least 4 hours. This constant release was believed to be due to the formation of cubic phases that act as drug reservoirs during the dissolution of the base in the aqueous medium. AC-70 base has a potential use as a suppository base when an acidic environment is essential for better therapeutic effectiveness. AC-70 base can form liquid crystalline phase in the aqueous release medium and can thereby sustain the release of drug over a longer time as compared to a conventional suppository base.

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