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Effect of Different Waxy Materials on the Release of Ibuprofen from Polyethylene Glycol Based Suppositories

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Abstract: The effects of various percentages (0, 3, 6, 9, 12 and 15%) of Glycerol Mono Stearate (GMS), Stearic Acid (SA) and Cetyl Alcohol (CA) on the release rate of Ibuprofen (IB) from polyethylene glycol-4000 (PEG)-based suppositories were studied. Ibuprofen suppositories of PEG-4000 base were prepared using GMS, SA and CA separately in different formulations by fusion method. Dissolution studies showed a rapid release of the drug during 30-60 min from the PEG-based suppositories of IB and almost 75% of the drug was released within this period. But the incorporation of waxy additives GMS, CA and SA in the formulation reduces this rapid release rate of the drug. Three percent GMS containing PEG-based suppositories liberated about 70.0% of the drug within 6 h whereas maximum 45.0% and 51.0% of drug were liberated from 3% SA and 3% CA containing PEG-based suppositories, respectively, within the same time. The drug release reducing capabilities of the waxy additives were found to be in the following order SA>CA>GMS. Utilizing this capability of the additives, sustained release suppositories of ibuprofen could be formulated.

Key words: Suppository, Ibuprofen, dissolution, kinetics

INTRODUCTION

Sustained Release (SR) dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose[1]. So far it has been reported that many different types of controlled-release dosage forms have been developed to improve clinical efficacy of drug and patient compliance[2,3]. A number of methods and approaches have been used in their formulation and are well reviewed[4]. Products of this type have been formulated for oral, injectable and topical use, and include inserts for placement in the body cavities as well[5]. Suppositories can be formulated as one of these dosage forms. Suppository is the dosage form that is used in the rectal route. The rectal route has advantages for delivery of drugs with a narrow therapeutic index[6]. Besides SR oral dosage forms, SR rectal delivery forms are also used now-a-days for optimizing drug effects mainly in children and in elderly patients, a notion first recorded by Hippocrates. The rectal route of administration can be chosen both for local and systemic effects.

Non-steroidal Anti-inflammatory Drugs (NSAIDS) are usually good candidates for the development of controlled release preparations particularly through the rectal route to reduce or eliminate the gastrointestinal irritation. Ibuprofen is an NSAID having prominent anti-inflammatory, analgesic and antipyretic properties. De Muyunck and Cuvelier[7] reported that frequent application of PEG or pure triglycerides as suppository base induced damage resulting in ulceration and inflammation of the rectal mucosa. They further added that inclusion of monoglycerides or fatty acids in suppository base reduced rectal mucosa damage. Therefore, it is of our interest to incorporate different waxy materials as GMS, CA and SA in the PEG-based suppositories separately in different percentages in order to reduce rectal mucosa damage and to investigate their release pattern.

The purpose of this study was to prepare sustained release suppositories of IB by fusion method adding different waxy materials as GMS, CA and SA separately to the PEG-4000 base and to evaluate the influences of these excipients on the release of IB from suppositories.

MATERIALS AND METHODS

Materials: Ibuprofen (IB) (Fluka, Switzerland), Glyceryl Mono Stearate (GMS), Cetyl Alcohol (CA) and Stearic Acid (SA) (BDH, England). All the materials were used without further purification. Other chemicals were of analytical grade.

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Table 1: Formulation of PEG-based suppositories with the addition of waxy materials

Number of formulation	IB (mg)	PEG (mg)	GMS (mg)	SA (mg)	CA (mg)
FM-1	50.0	2550.0	0.0	0	0
FM-2	50.0	2473.5	76.5		
FM-3	50.0	2397.0	153.0		
FM-4	50.0	2320.5	229.5		
FM-5	50.0	2244.0	306.0		
FM-6	50.0	2167.5	382.5		
FM-7	50.0	2473.5		76.5	
FM-8	50.0	2397.0		153.0	
FM-9	50.0	2320.5		229.5	
FM-10	50.0	2244.0		306.0	
FM-11	50.0	2167.5		382.5	
FM-12	50.0	2473.5			76.5
FM-13	50.0	2397.0			153.0
FM-14	50.0	2320.5			229.5
FM-15	50.0	2244.0			306.0
FM-16	50.0	2167.5			382.5

Sample preparation: Suppositories sample used for the study were prepared according to the method of Kamal *et al.*[8]. A total of 16 formulations (6 suppositories each weighing 2.6 g in individual formulation) of PEG-based IB suppositories were prepared by fusion method. Along with different amounts of PEG and IB, these preparations contained different percentages of either GMS, SA or CA for each formulation as shown in the Table 1. It should be mentioned here that formulation 1 (FM-1) did not contain any waxy additives. IB was used as 2% of PEG-4000 in every formulation. The percentages of IB has been varied in different formulations but this will have no effect as the percent release of IB was calculated on the basis of content of IB in each formulation. The accurately weighed PEG-4000 and GMS; PEG-4000 and SA; and PEG-4000 and CA for different formulations were placed in 250 mL glass beaker separately and heated on a hot plate at 65°C just to melt the waxy ingredients. The finely divided IB powder of accurate weight for respective formulation was incorporated into the melted mass via mixing with a glass rod. The total melted mass was, with no delay, poured into the stainless steel suppository mold of three cavities each of which had about three gram capacity. The mass was left to solidify at the room temperature. The congealed torpedo-shaped suppositories were kept in a desiccator until use.

***In vitro* dissolution studies:** The dissolution studies of IB in PEG suppositories containing different amount of GMS, SA and CA in separate formulations were carried out in an Electrolab Tablet Dissolution Tester USP XXI TDT-06. The paddle rotation was set at 50 rpm and temperature was controlled at 37±2°C using 1 L dissolution medium (pH 7.2) containing 0.2 M solution of sodium hydroxide (NaOH) and potassium dihydrohen phosphate (KH_2PO_4). A ten milliliter sample was taken at regular interval which were immediately compensated for with the same amount of fresh medium previously heated to 37°C.

Analysis of drug content: The extent of release of IB from each suppository was measured at 223 nm wavelength using Shimadzu UV-1200 Spectrophotometer. The absorbance data were processed by a computer and consequently the percent releases of the drug at different time were obtained.

RESULTS AND DISCUSSION

Kinetic studies: The results of the dissolution studies of IB from the PEG-based suppositories containing various amounts of GMS, SA and CA are shown in Fig. 1-6. Figure 1, 3 and 5 show the percent release vs. time curves that are linear pattern which confirm to zero order release pattern[9]. This zero order plot showed release of IB up to 70.0% in case of suppositories containing 3% GMS (FM-2) as in Fig. 1, 45.0% in case of suppositories containing 3% SA (FM-7) as in Fig. 3 and 51.0% in case of suppositories containing 3% CA (FM-12) as in Fig. 5, within 360 min. It was revealed from these curves that the rates of release of drug were decreased when the percent of GMS, SA and CA were increased. This may be due to the increase ratio of incorporated hydrophobic materials to PEG. Hydrophobic materials retarded the wetting and penetration properties of the dissolution properties of the dissolution fluid into the suppositories.

In case of suppositories prepared with the drug and PEG (FM-1), a rapid release of the drug was observed (Fig. 1-6) during the first 30-60 min and almost 75% of the drug was released within this period. Subsequently this

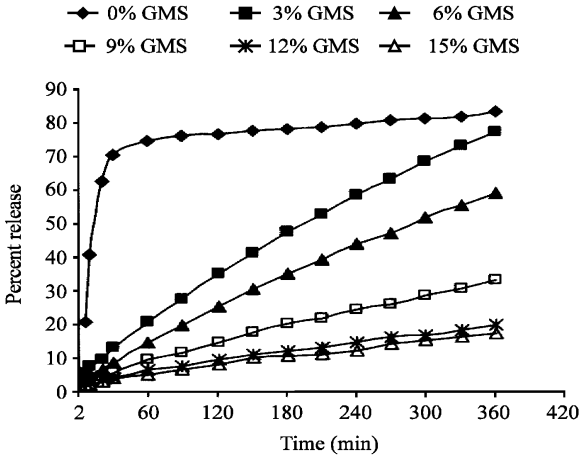

Fig. 1: Zero order plot of IB release from PEG-based suppositories containing different amounts of GMS

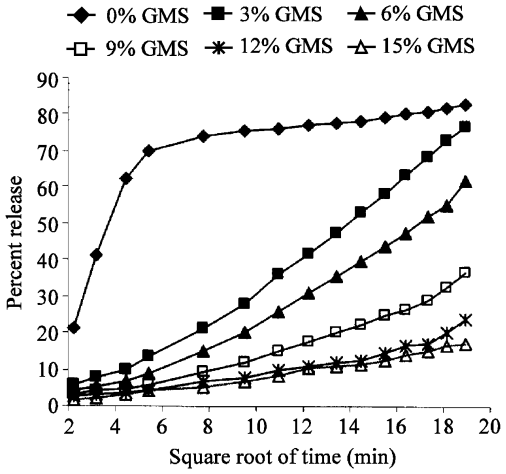

Fig. 2: "Higuchi" plot of IB release from PEG-based suppositories containing different amounts of GMS

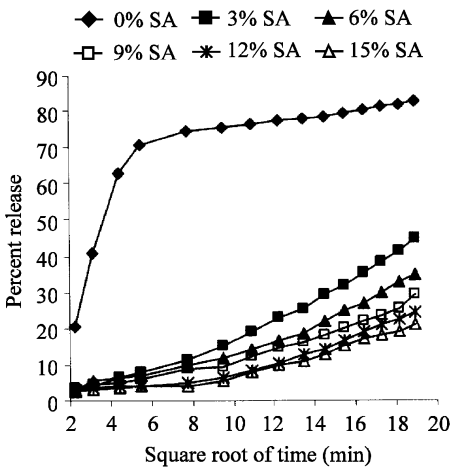

Fig. 4: "Higuchi" plot of IB release from PEG-based suppositories containing different amounts of SA

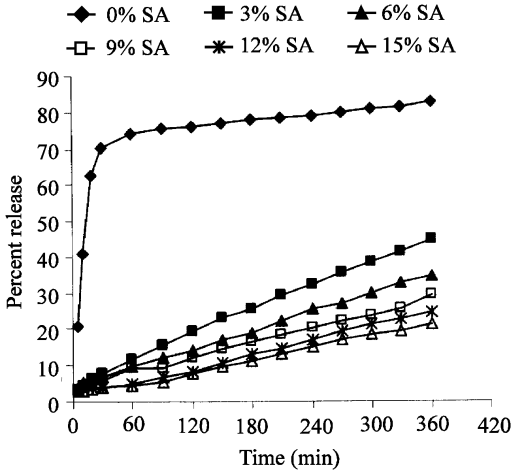

Fig. 3: Zero order plot of IB release from PEG-based suppositories containing different amounts of SA

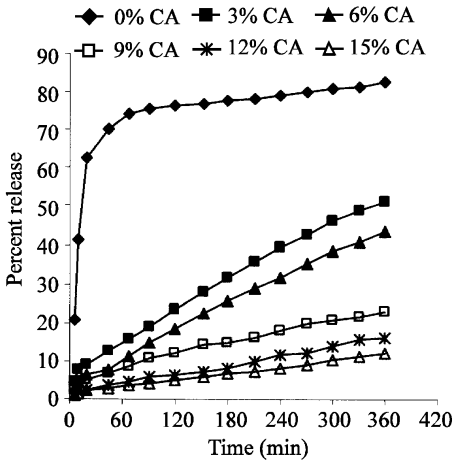

Fig. 5: Zero order plot of IB release from PEG-based suppositories containing different amounts of CA

release rate sharply decreased and within next 330 min only about 10% of the total drug was found to be released. This rapid release rate was due to the deformation and disintegration of the suppositories. It was observed that within this period (30 to 60 min) the suppositories were completely disintegrated in the dissolution media, therefore, the drug entrapped in the dosage form became free to dissolve in the dissolution media. Hence a rapid release of drug was observed and subsequently a slow release of drug was obtained. The explanation of this phenomenon may be due to the release of bound drug from disintegrated particles of PEG, which gradually dissolved in the media.

When percent release was plotted against square root of time, parabolic curves lines were obtained in each case of additives as shown in Fig. 2, 4 and 6. This suggested that drug release mechanisms did not follow Higuchi dissolution model release.

Release rates obtained from Fig. 1, 3 and 5 were plotted against percentage of GMS, SA and CA. In a comparative study, IB suppositories with GMS has got the highest release rate than those formulation with other additives (Fig. 7). Both SA and CA have got higher hardening property when included in a suppository base.

Drug usually released from suppositories in the dissolution medium by diffusion and/or erosion

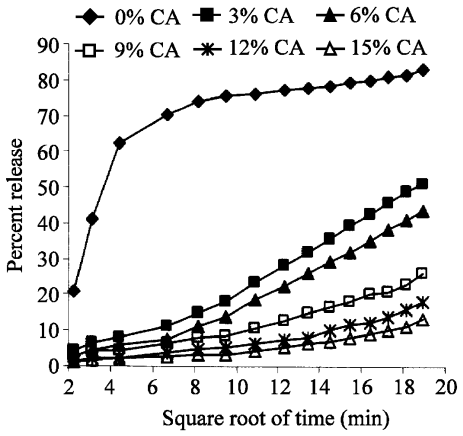

Fig. 6: "Higuchi" plot of IB release from PEG-based suppositories containing different amounts of CA

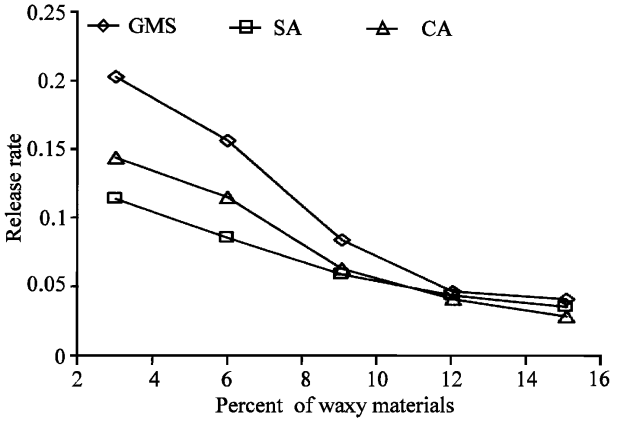

Fig. 7: Comparison of release rates of IB from PEG-based suppositories containing different amounts of GMS, SA and CA

methods[10]. In contact with medium some channels were created within the suppositories which ultimately facilitated solubilization and release of drug from the dosage form. But when the percentages of GMS, SA or CA were increased in the suppositories base, the number and size of the channels might decrease and consequently, reduction of drug release was observed.

The effect of incorporated GMS, SA and CA in PEG-based suppository on the IB release kinetics were observed. A total of 16 batches of suppositories were prepared with various amounts of GMS, SA and CA. The release rates were found reducing with addition of waxy materials such as GMS, SA and CA. The reduction capacity of release rates was found to be in the order SA>CA>GMS. Exploiting the reduction capability of the waxy additives it could be helpful to formulate a sustained release suppository with uniform and desired release rate.

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