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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 8 (12): 1685-1689, 2005
ISSN 1028-8880

Application of a Few Waxy Materials on the Release of Naproxen from Polyethylene Glycol Based Suppositories

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Abstract: Applications of various percentages (0, 2, 4, 8, 12 and 16%) of Glycerol Mono Stearate (GMS), Stearic Acid (SA) and Cetyl Alcohol (CA) on the release rate of Naproxen (NP) from Polyethylene Glycol 4000 (PEG)-based suppositories were studied in order to reduce rectal mucosal damage and also to investigate their release pattern. Naproxen 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 NP and almost 65% 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. Two percent GMS containing PEG-based suppositories liberated about 69.0% of the drug within 6 h whereas maximum 45.0 and 32.0% of drug were liberated from % SA and % 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 CA>SA>GMS. Utilizing this capability of the additives, sustained release suppositories of Naproxen could be formulated.

Key words: Suppository, naproxen, dissolution, kinetics

INTRODUCTION

Controlled release technology is being actively explored in the pharmaceutical industry due to therapeutic, economic and commercial advantages[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. Naproxen is an NSAID having prominent anti-inflammatory, analgesic and antipyretic properties. It is indicated for symptomatic relief of rheumatoid arthritis and musculoskeletal disorder[7]. This drug is readily absorbed orally and reached at peak levels within 2-4 h of administration. The elimination of Naproxen from plasma is with apparent half-life of 12 to 17 h[8]. However, in acute muscuskeletal disorder and gout as well as in dysmenorrhoea the drug is taken 250 mg every 6-8 h[7].

De Muyunck and Cuvelier[9] 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.

MATERIALS AND METHODS

Materials: Naproxen (NP) (Fluka, Switzerland), Glyceryl Mono Stearate (GMS), Cetyl Alcohol (CA) and Stearic

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

Formulation No. (x 3)	NP (mg)	PEG (mg)	GMS (mg)	SA (mg)	CA(mg)
FM-1	50.0	2450	0	0	0
FM-2	50.0	2400	50	-	-
FM-3	50.0	2350	100	-	-
FM-4	50.0	2250	200	-	-
FM-5	50.0	2100	350	-	-
FM-6	50.0	2050	400	-	-
FM-7	50.0	2400	-	50	-
FM-8	50.0	2350	-	100	-
FM-9	50.0	2250	-	200	-
FM-10	50.0	2100	-	350	-
FM-11	50.0	2050	-	400	-
FM-12	50.0	2400	-	-	50
FM-13	50.0	2350	-	-	100
FM-14	50.0	2250	-	-	200
FM-15	50.0	2100	-	-	350
FM-16	50.0	2050	-	-	400

Acid (SA) (BDH, England). All the materials were used without further purification. Other chemicals were of analytical grade.

Sample preparation: Suppositories sample used for the study were prepared according to the method of Kamal *et al.*[10]. A total number of 48 formulations (18 suppositories of each weighing 2.5 g in individual formulation) of PEG-based NP suppositories were prepared by fusion method. Along with different amounts of PEG and NP, 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. The concentration of NP was kept constant at 50 mg. 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 NP powder of accurate weight for respective formulation was incorporated into the melted mass via through 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 refrigerator until use.

***In vitro* dissolution studies:** The dissolution studies of NP 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 dihydrogen 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 NP from each suppository was measured at 332 nm wavelength using Shimadzu UV-1200 Spectrophotmeter. The absorbance data were processed by a computer and consequently the percent releases of the drug at different time were obtained.

All the samples were performed triplicate and the data presented in the graphs were the mean values, where the coefficients of variation were within the limit.

RESULTS AND DISCUSSION

Kinetic studies: The results of the dissolution studies of NP 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[11]. This zero order plot showed release of NP up to 69.0% in case of suppositories containing 2% GMS (FM-2) as in Fig. 1, 45.0% in case of suppositories containing 2% SA (FM-7) as in Fig. 3 and 32.0% in case of suppositories containing 2% 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[12-14].

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 65% of the

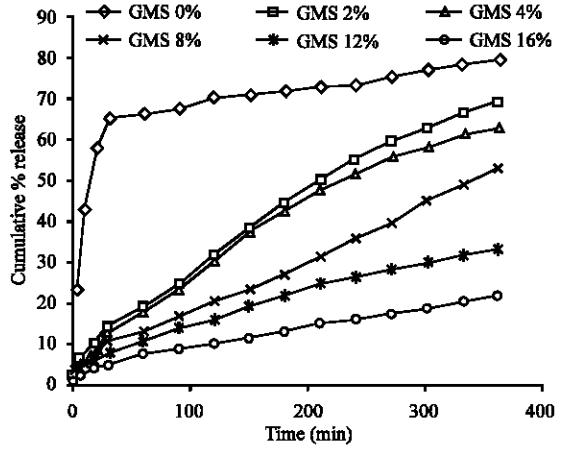

Fig. 1: Zero order plot of NP release from PEG-based suppositories containing different amounts of GMS

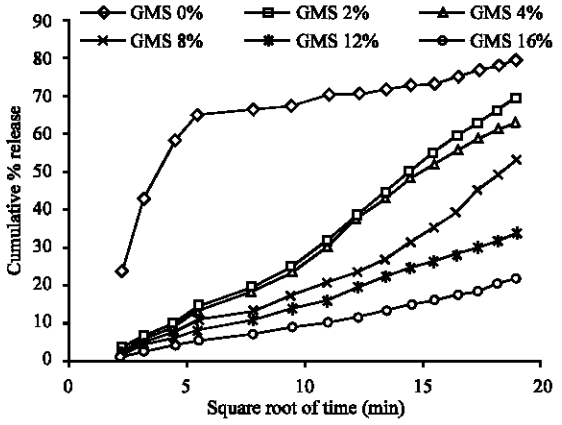

Fig. 2: Higuchi plot of NP release from PEG-based suppositories containing different amounts of GMS

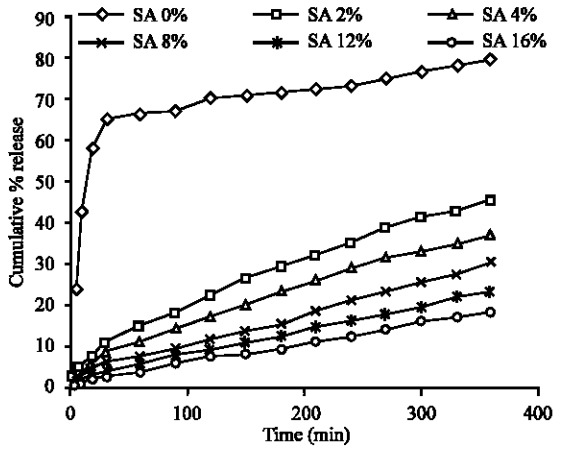

Fig. 3: Zero order plot of NP release from PEG-based suppositories containing different amounts of SA

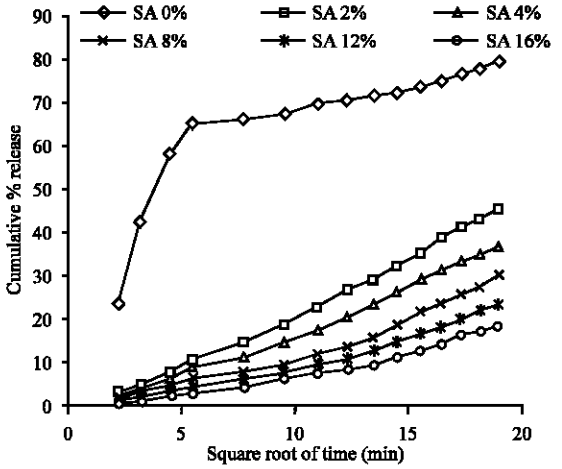

Fig. 4: Higuchi plot of NP release from PEG-based suppositories containing different amounts of SA

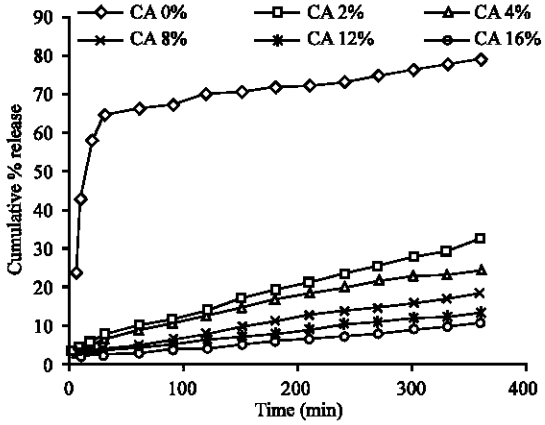

Fig. 5: Zero order plot of NP release from PEG-based suppositories containing different amounts of CA

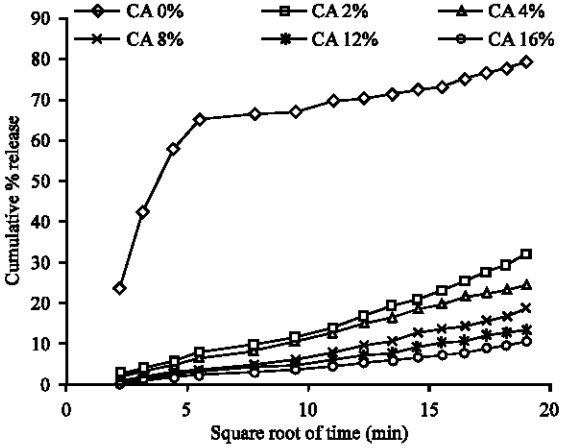

Fig. 6: Higuchi plot of NP release from PEG-based suppositories containing different amounts of CA

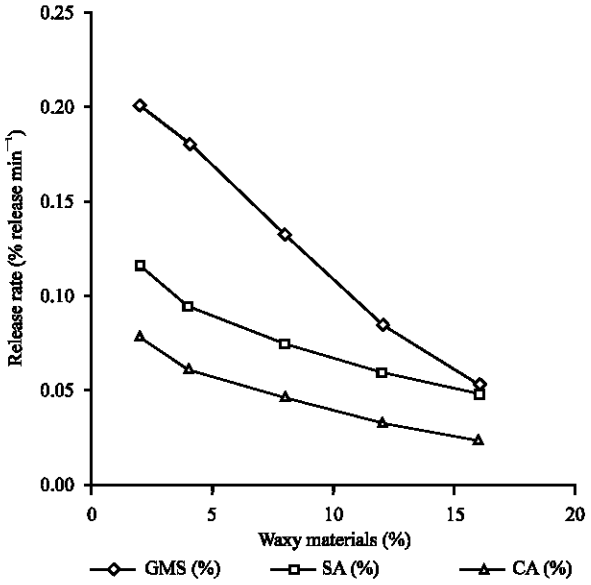

Fig. 7: Comparison of release rates of NP from PEG-based suppositories containing different amounts of GMS, SA and CA

drug was released within this period. Subsequently this 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, an NP suppository with GMS has got the highest release rate than those formulations 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 methods[15]. 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 or 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 effects of incorporated GMS, SA and CA in PEG-based suppository on the NP 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 reduced with addition of waxy materials such as GMS, SA and CA. The reduction capacity of release rates was found to be in the order CA>SA>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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