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Preparation and Stability Study of Diclofenac Sodium Suppositories

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Abstract: The investigation was carried out by the addition of variable percentages (0, 2, 4, 8 and 12%) of either Aluminum Stearate (AS) or Dioctyl Sodium Sulphosuccinate (DOSS) in Glycerol Monostearate (GMS)-based suppositories of Diclofenac Sodium (DS). DS suppositories of GMS base were prepared using AS and DOSS separately in different formulations by pour moulding method. Dissolution studies were carried out in USP Dissolution Tester using phosphate buffer (pH 7.4) as the dissolution medium maintaining the temperature at $37 \pm 2^\circ\text{C}$. The effects of AS and DOSS were evaluated on the release rate of DS from the GMS-based suppositories. The hydrophobic nature of GMS retarded the drug release markedly, while the inclusion of increasing percentage of AS and DOSS in GMS-based suppositories enhanced the release rate of DS to a considerable extent. Throughout the investigation, the release patterns in both cases were found to be square root of time dependent; indicating diffusion type of drug release. Formulation of DS suppositories with 12% DOSS gave sustained drug release profile. The stability studies of the DS suppositories containing 12% as well as DOSS have proved these formulations to be stable dosage forms.

Key words: Suppository, Diclofenac sodium, sustained release, dissolution, stability study

Introduction

During recent years, there has been an upsurge of research into providing sustained release (SR) formulations. It is being actively explored in the pharmaceutical industry due to therapeutic, economic and commercial advantages (De Haan and Lerk, 1984). SR dosage forms are designed to achieve, a prolonged therapeutic action by continuously releasing medication over an extended period of time after administration of a single dose. SR dosage forms can be designed in many ways. Suppositories may be formulated as one of these dosage forms. In the 1930s, several unwanted side effects and disadvantages inherent to oral therapy focused attention, principally in Europe, on the rectal route for administering drugs (Coben and Lieberman, 1986). The rectal route has advantages for delivery of drugs with a narrow therapeutic index (Taylor and Simpkins, 1981). DS is a drug of narrow therapeutic index and suitable for inclusion in suppositories. Suppositories of Diclofenac Sodium (Volteran[®]) are widely used for clinical purposes. Since the disappearance of Diclofenac after administration of Volteran[®] is somewhat rapid (Riess *et al.*, 1978), patients with rheumatoid arthritis sometimes do not sleep well due to the short-term action of Volteran[®]. Therefore a long-acting suppository of Diclofenac sodium with sustained plasma concentration would be helpful to the therapeutics of patients. Another important purpose of preparing DS in suppository dosage form was to overcome the problem of rapid transient high plasma Diclofenac concentration. Glycerol Monostearate is such a waxy material which was used as an excellent suppository base (Ferdous *et al.*, 1993). It retarded the release of DS from the suppositories markedly and therefore some other ingredients were added to increase the release rate (Ahmed, 1995). Hence the effects of waxy materials such as AS and DOSS were studied on the release of DS from GMS-based suppositories. The stability studies of these products were also studied.

Materials and Methods

Diclofenac sodium was supplied as courtesy by Ciba-Geigy (Basle, Switzerland), glycerol monostearate, aluminum stearate and dioctyl sodium sulphosuccinate were obtained from BDH Chemicals Ltd. (Poole, England). All the materials were used

without further purification. Other chemicals and solvents were of analytical grade.

Sample preparation: A total of 9 formulations (six suppositories each weighing 1 gm in individual formulation) of GMS-based DS suppositories were prepared by pour moulding (Coben and Lieberman, 1986). Along with different amounts of GMS and DS, these preparations contain different percentages of either AS or DOSS for each formulation as shown in Table 1 and 2 separately. It should be mentioned here that formulation 1 (FM-1) did not contain any additive. DS was used as 10% of GMS in every formulation. The accurately weighed GMS and AS or GMS and DOSS for different formulations were placed in 250 ml glass beaker and heated on hot plate at 65°C just to melt. The finely divided DS powder of accurate weight for respective formulation was incorporated into the melted mass with proper mixing. The melted mass was then immediately poured into the stainless steel suppository mould. The mass was left to solidify at the room temperature. The congealed torpedo-shaped suppositories were kept in desiccator until use.

In vitro dissolution studies: The dissolution studies of DS in GMS-based suppositories containing different amounts of AS and DOSS in respective formulations were carried out in Electrolab Tablet Dissolution Tester USP. The paddle rotation was set at 50 rpm and the temperature was controlled at $37 \pm 2^\circ\text{C}$ using 1 litre dissolution medium of pH 7.4 as chamber volume containing potassium dihydrogen phosphate, KH_2PO_4 (0.17%) ; sodium hydroxide, NaOH (0.0391%r and water. A five milliliter sample was taken at regular interval of 20 minutes during first hour and thereafter, every 30 minutes up to 180 minutes (as the paddle method had been adopted) which were immediately compensated with the same amount of fresh medium previously heated to 37°C .

Analysis of drug content: Drug content of the sample solution, i.e., the quantity of DS release was spectrophotometrically determined by measuring absorbance of the withdrawn samples at 280nm on a Pye-Unicam SP8-400 spectrophotometer, the reference being the buffer solution. The absorbance data were put to a computer software

Table 1: Percentage (%) and quantity (Qnt.) of GMS, AS and DS for the preparation of six suppositories each weighing 1 gm

Formulation (FM)	GMS		AS		DS	
	%	Qnt. (gm)	%	Qnt. (gm)	%	Qnt. (gm)
Fm - 1	91	5.46	0	0	9	0.54
FM - 2	89.1	5.346	2	0.12	8.9	0.534
FM - 3	87.3	5.238	4	0.24	8.7	0.522
FM - 4	83.6	5.016	8	0.48	8.4	0.504
FM - 5	80.0	4.80	12	0.72	8.0	0.480

Table 2: Percentage (%) and quantity (Qnt.) of GMS, DOSS and DS for the preparation of six suppositories each weighing 1 gm

Formulation (FM)	GMS		DOSS		DS	
	%	Qnt.(gm)	%	Qnt. (gm)	%	Qnt. (gm)
FM - 1	91	5.46	0	0	9	0.54
FM - 6	89.1	5.346	2	0.12	8.9	0.534
FM - 7	87.3	5.238	4	0.24	8.7	0.522
FM -8	83.8	5.016	8	0.48	8.4	0.504
FM - 9	80.0	4.80	12	0.72	8.0	0.480

program and consequently the percent releases of the drug were obtained.

Stability Studies: Stability tests were performed for the Diclofenac sodium in suppositories containing only 12% AS and 12% DOSS. Suppositories were kept in a desiccator where the relative humidity (RH) was maintained at 76% using saturated NaCl solution for a period of four months. The samples were withdrawn after one month intervals and the drug was extracted with methanol. In order to ascertain the stability of compounds present in the methanol extract, ascending one dimensional TLC technique was adopted. In this method the sample drug in methanolic solution was spotted on a silica coated TLC plate against the standard drug solution in methanol and was allowed to run with a mobile phase which was a mixture of toluene/formic acid/n-hexane (10:1.5:1). After development of the chromatogram, the plate was taken out of the tank, dried, observed under UV light and sprayed with a mixture of chromate/sulphuric acid reagent which was prepared by dissolving 0.5 gm of potassium dichromate in 80 ml of water and slowly adding 20 ml of concentrated sulfuric acid, then degradation products of DS as secondary spots were checked. The physical appearance of the suppositories were also checked up for four months.

Results and Discussion

Kinetics studies: The results of the dissolution test of DS from the GMS suppositories containing various amounts of AS and DOSS were shown in Fig.1-4. Figure 1 and 3 show that the percent release vs. time curves are parabolic which indicate that drug release from suppositories did not follow the zero order mechanism (Higuchi, 1963). This phenomenon could be attributed to the hydrophobicity of GMS. So it did not dissolve in the dissolution medium and the drug release was markedly hindered. The parabolic curves also predict that they might confirm the square root of time dependent release fashion curve. In Fig. 2 and 4 almost straight lines were obtained which indicated a square root of time dependent release i.e. release pattern was diffusion controlled (Higuchi, 1963). It was found in Fig. 1 and 3 that about 40% of DS was released from GMS-based suppositories containing 12% AS (FM-5). 90% from the suppositories containing 12% DOSS (FM-9) and only 22% from GMS-based suppositories

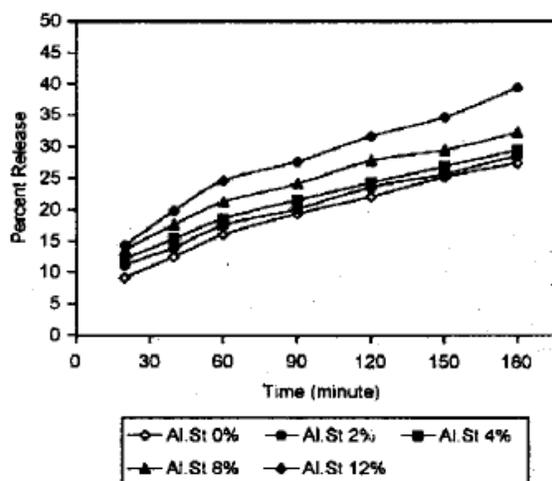


Fig. 1: Release of DS from GMS-based SR suppositories containing different amounts of AS

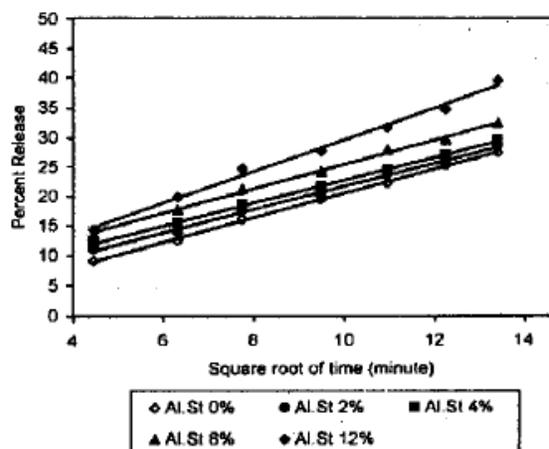


Fig. 2: Square root of time dependent release of DS from GMS-based SR suppositories containing different amounts of AS

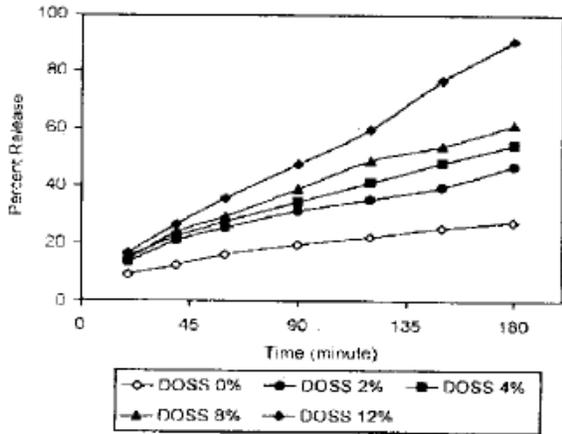


Fig. 3: Release of DS from GMS-based SR suppositories containing different amounts of DOSS

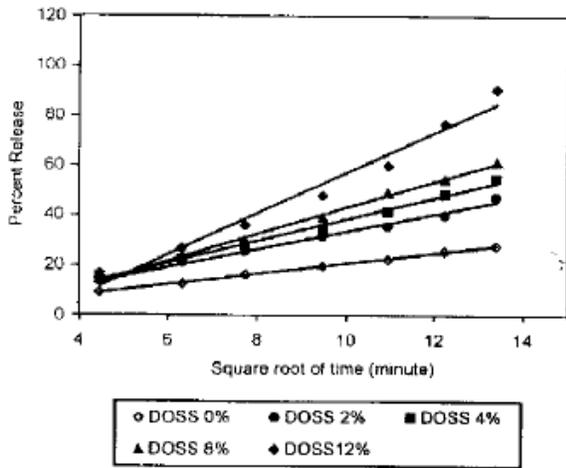


Fig. 4: Square root of time dependent release of DS from GMS-based SR suppositories containing different amounts of DOSS

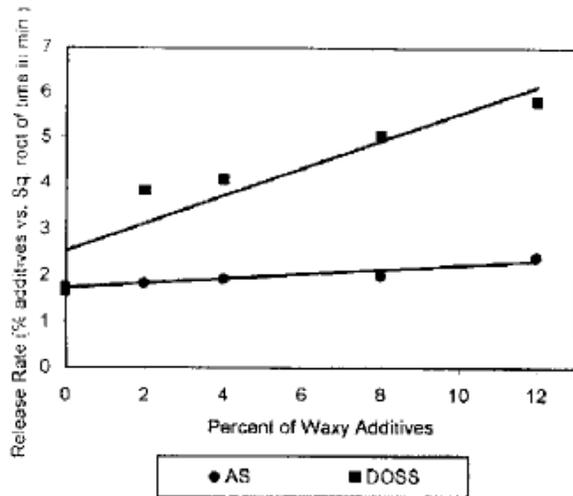


Fig. 5: Comparison of release rate of DS from GMS-based SR suppositories containing different amounts of AS or DOSS respectively

containing no additives (FM-1) in 3 hours. So, AS and DOSS enhanced the release of DS from GMS-based suppositories. AS which is hydrophobic waxy material caused only a small increase of release rate of DS. The slight increase in percent release with increasing AS percentage might be due to the decreasing GMS concentration in the unit sample keeping total weight constant and probably because AS is a little bit less hydrophobic. It ensues that DOSS possessed greater release enhancing capability than that of AS. It might be due to its surface action. It disrupts hydrophobic interaction of water at nonpolar solute-water interface and thereby increases drug dissolution (Fiese and Hagen, 1990).

Release rates were obtained from Fig. 2 and Fig. 4 and plotted against percentages of AS and DOSS, respectively in Fig. 5. It shows that release rate was increased linearly with increasing percentage of AS or DOSS. DOSS proved to be more efficient than AS in enhancing the release of DS from the suppositories.

Stability studies: In UV light and chromate/sulfuric acid spray detection, the R_f value for the spots of the sample solution complied with that of the standard Diclofenac solution. So, DS was detected and no other secondary spot was seen which proved the absence of any degradation product of DS in the suppositories. Physical appearance of the suppositories was also checked for four months but no appreciable change was noticed. So it was assumed that these waxy materials (GMS, AS and DOSS) are completely compatible excipients in the preparation of DS suppositories.

Conclusion

A total of 9 batches of suppositories were prepared with various percentages of AS and DOSS with GMS and DS. The effects of AS and DOSS on the DS release from GMS-based suppository was observed. About 90% DS was released from FM-9 in 1 litre of dissolution fluid in 3 hours. So it is expected that the release will be minimized when given in the rectum where only 3-5 ml of rectal fluid exists. Therefore 12% DOSS (FM-9) could give DS suppositories a reasonable sustained release profile.

Stability test of suppositories containing only 12% of additives (FM-5 and FM-9) was also performed at normal storage conditions for 4 months. Least DS release rate was shown by suppositories containing only GMS. Incorporation of AS and DOSS enhanced the release pattern of DS. DOSS had a more profound effect on release rate of DS than that of AS. No noticeable physical nor chemical changes of the preparations were observed during four months high relative humidity stability study.

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