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The use of solid self-emulsifying systems in the delivery of diclofenac

A.A. Attama [a,*], I.T. Nzekwe [a], P.O. Nnamani [a], M.U. Adikwu [a], C.O. Onugu [b]

[a] *Department of Pharmaceutics, Drug Delivery Research Unit, University of Nigeria, Nsukka, Enugu State, Nigeria*
[b] *Mobil Oil Producing Clinic, Eket Akwa-Ibom State, Nigeria*

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Abstract

Goat fat and Tween 65 admixtures were used to formulate self-emulsifying tablets containing diclofenac. The tablets were formulated by pour moulding using a plastic mould. The tablets were evaluated using the following parameters: weight uniformity, absolute drug content, and liquefaction time. The dissolution profile of diclofenac from the self-emulsifying tablets was determined in simulated gastric fluid (SGF) without pepsin. Results obtained indicated that diclofenac could be comfortably administered in the form of self-emulsifying tablets using goat fat and Tween 65 admixtures.

Keywords: Self-emulsifying system; Tween 65; Goat fat; Diclofenac; Drug release

1. Introduction

For poorly water-soluble drugs, the rate-determining step in the absorption is the dissolution of the drug (Sekikawa et al., 1983). An improvement in the dissolution characteristics of poorly water-soluble drugs result in higher plasma peaks and in total drug absorbed. Methods like micronisation, salt formation, use of micelles, solid dispersion, cogrinding, and complexation have been used to improve the bioavailability of such drugs (York, 1988; Sugimoto et al., 1998). Formulation in the form of oil-in-water emulsion has been used for lipophilic drugs. The goat fat and Tween admixture formulation is intended to show a combination of emulsion and micelle formation.

A mixture of oil and non-ionic surfactant forms clear and transparent isotropic solution known as a self-emulsifying system (SES), if the mixture forms a microemulsion when mixed with water. This drug delivery system has been reported to improve the in vivo dissolution, and therefore enhance the bioavailability of lipophilic drugs (Shah et al., 1994; Kim and Ku, 2000). Such formulations form a fine oil-in-water emulsion with gentile agitation, which may be provided by gastrointestinal motility. A SES also improves the reproducibility of the plasma level–time profile (Armstrong and James, 1980). Various physiological mechanisms have been proposed to explain the effect of oils on the absorption of water-insoluble compounds, including altered gastrointestinal motility, increased bile flow and drug solubilisation (Muranishi et al., 1980), increased mucosal permeability (De Marco and Levine, 1969), enhanced mesenteric lymph flow (Palin et al., 1982), and increased lymphatic absorption (Armstrong et al., 1979). Drug absorption

* Corresponding author. Tel.: +234-42-770759; fax: +234-42-770644.
E-mail address: aaattama@yahoo.com (A.A. Attama).

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from aqueous solution and oil-in-water emulsion has been compared (Kakemi et al., 1972). A solid SES contains non-ionic surfactant with a high softening point, a solid fat and the included drug. Such a system may be formulated in the form of a tablet or suppository. The objective of this study was to evaluate the suitability of goat fat and Tween 65 admixtures in the formulation of self-emulsifying tablets containing diclofenac. This will provide a cheap and readily available alternative to the costly starting materials, and also cut down on processing stages. Goat fat has been evaluated as a base for suppository formulations (Attama et al., 2000).

2. Materials and methods

2.1. Materials

Diclofenac (Ciba), Tween 65 (Merck), hydrochloric acid (BDH), and sodium chloride (Fluka AG) were used as procured from their suppliers without further purification. Goat fat was obtained from a batch processed in our laboratory. Distilled water was obtained from an all-glass still. All other reagents were of analytical grade and were used as such.

2.2. Extraction of goat fat

Goat fat was extracted from the adipose tissue of *Capra hircus*. The extraneous materials were manually separated from the adipose tissue, which was then rendered by the wet process (Attama et al., 2000). The adipose tissue was grated and subjected to moist heat by boiling with about half its weight of water in a water bath for 45 min. The molten fat was separated from the aqueous phase after filtering with a muslin cloth. The fat was stored in a refrigerator until used.

2.3. Formulation of self-emulsifying tablets

All the tablets were prepared to contain 50 mg diclofenac each. Five batches of tablets containing different proportions of goat fat and Tween 65 were prepared as in Table 1. In each case, the appropriate quantities of goat fat and Tween 65 are heated together in a crucible until completely homogenous. The drug (5 g) was added and stirred thoroughly. The mix was poured into a plastic mould and allowed to set at 28 °C. The tablets were thereafter removed from the mould and stored in a cool place until used.

Table 1
Quantities of materials used for tablet formulation

Batch	Tween 65 (g)	Goat fat (g)	Diclofenac (g)
1	2	28	5
2	4	26	5
3	6	24	5
4	8	22	5
5	10	20	5

2.4. Weight uniformity

For each batch, 20 tablets were randomly selected, weighed collectively and then individually using a weighing balance (Sauter, KGD-7470, W. Germany). The result obtained was analysed statistically.

2.5. Liquefaction time

The liquefaction time was determined using a modification of the method already described (Setnikar and Fantelli, 1962). One tablet from each batch was wrapped in a transparent polythene film and tied to the bulb of a thermometer by means of a thread. The thermometer with attached tablet was placed in a round bottom flask containing 250 ml of simulated gastric fluid (SGF) without pepsin, maintained at 37 ± 1 °C by means of a thermo-regulated heating mantle. The tablet was observed carefully, and the melt time was recorded. Average of 20 determinations was taken for each batch.

2.6. Absolute drug content

Twenty tablets were weighed and melted together, and allowed to solidify with stirring. A weight equal to the average weight of the 20 tablets was weighed out and placed in a 100 ml volumetric flask containing 60 ml of SIF, and heated to 40 °C in a water bath with vigorous agitation until the content completely emulsified. The volume was made up to 100 ml with SGF, appropriately diluted and the absorbance determined in a spectrophotometer (SP6-450 UV-Vis Pye Unicam) at a predetermined wavelength of 272 nm. This was repeated five times and was done for all the

batches. The absolute drug content was calculated with reference to standard Beer's law plot for diclofenac in SGF.

2.7. Dissolution studies

The USP paddle method was adopted in this study. The dissolution medium consisted of freshly prepared SGF (300 ml) maintained at 37 ± 1 °C. A tablet was placed in the appropriate chamber of the release apparatus containing the dissolution medium, and then agitated at 100 rpm. At predetermined time intervals, 5 ml portions of the dissolution medium were withdrawn, appropriately diluted and their absorbance determined in the spectrophotometer above. The volume of dissolution medium was kept constant by replacing it with 5 ml of fresh SGF after each withdrawal. The concentrations of the samples were determined with reference to the standard Beer's plot.

3. Results and discussion

3.1. Weight uniformity

The result of weight uniformity tests (Table 2) showed that all the tablets had low coefficients of variation, and thus passed the weight specifications for compressed uncoated tablets in the compendium (Lund, 1994). Weight variation may be due to sedimentation of active ingredient if insoluble in base. In this case, however, the observed variation may be due to non-uniformity in filling the mould since it was done manually.

Table 2
Results of some evaluated physical properties of the tablets

Batch	Mean weight[a] (mg ± CV)	Liquefaction time[b] (min ± S.D.)	Drug content[c] (mg ± S.D.)
1	342.2 ± 1.5	13.1 ± 0.8	55.14 ± 1.34
2	336.4 ± 2.7	33.8 ± 0.9	56.22 ± 1.52
3	343.3 ± 2.3	42.2 ± 0.7	45.41 ± 2.17
4	367.7 ± 2.1	38.9 ± 0.7	53.51 ± 1.28
5	365.9 ± 1.5	42.9 ± 0.6	47.78 ± 2.24

[a] Each value represents the mean ± CV ($n = 20$). CV = coefficient of variation.
[b] Each value represents the mean ± S.D. ($n = 20$).
[c] Each value represents the mean ± S.D. ($n = 5$).

3.2. Absolute drug content

The active ingredient contents did not vary widely. The various batches had low standard deviations. Variation in drug content could be due to weight variation or as a result of drug sedimentation during preparation. The active ingredient in this case was soluble in the self-emulsifying base, hence the low variation in active ingredient content may be as a result of minor weight variation. The results are shown in Table 2.

3.3. Liquefaction time

The liquefaction times (Table 2) were fairly high compared to disintegration standards for compressed uncoated tablets. This may not pose any problem because agitation was not used in the test. This test was designed to estimate the time it could take the tablets to melt in vivo under no agitation at normal body temperature. At gastrointestinal conditions, however, gastrointestinal motility will likely lower the liquefaction time, resulting in faster emulsification and penetration of the aqueous fluid into tablet interior. This will ensure drug release even before tablet integrity fails. For each batch, 20 tablets were tested ($n = 20$). Statistical treatment of the liquefaction time data indicated low standard deviations (Table 2). However, the average times for the different batches were statistically significantly different ($P > 0.05$). Since the liquefaction times of the tablets were long at 37 °C, the tablets can withstand the effect of temperature increases in the tropics. However, for the tropical areas where increases up to 37 °C or greater are recorded, it is advised that the tablets should be stored in conditions similar to conventional suppository formulation.

3.4. Dissolution studies

Fig. 1 shows the dissolution profiles of the tablets at a constant agitation rate of 100 rpm. There was high percentage release in all the batches. There was increased drug release with increase in Tween 65 content or decrease in goat fat content. This is expected since higher surfactant content ensures faster emulsification. Also, goat fat with its high melting point (51 °C) reduced the rate of emulsification when present in high quantity. Formulators are, thus, provided with an array of choice with regard to the combination of Tween 65

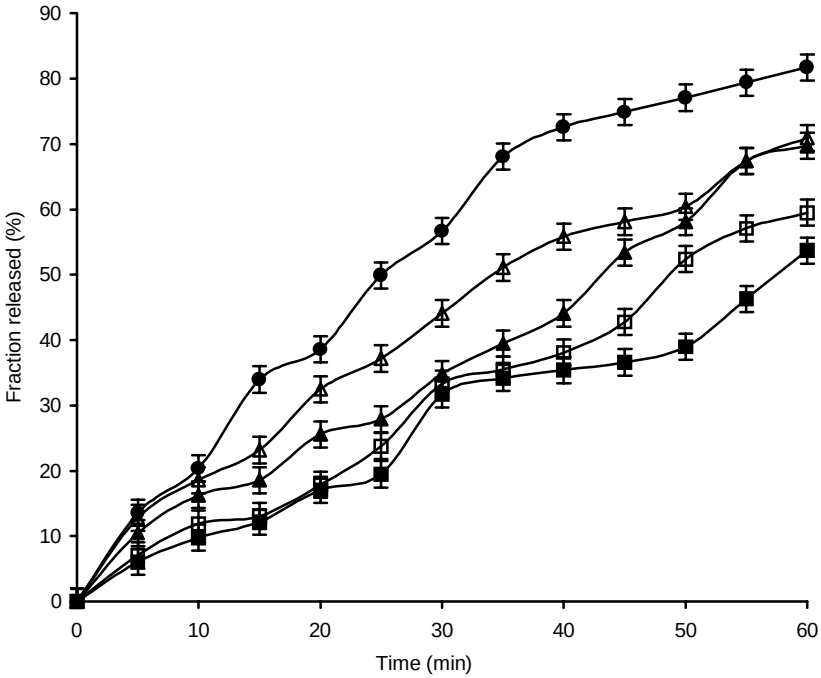

Fig. 1. Dissolution profile of diclofenac from the tablets at agitation rate of 100 rpm. ■: B1; □: B2; ▲: B3; △: B4; ●: B5.

and goat fat to be used in their formulations, taking into consideration the rate and extent of in vitro bioavailability as indicated in Fig. 1. Tween 65, a non-ionic surfactant, was chosen because absence of charge will reduce its drug interaction potential. Variability encountered with natural products is not obtainable with this fat. The goat fat used in this study was extracted using a standard procedure that has been shown to produce a reproducible product (Attama et al., 2000). The material used in this study is, therefore, a material with reproducible properties in formulation. Thus, the release studies showed low standard deviations when various batches of the fats were prepared using the stated method. There was almost 100% release in those preparations.

The release of diclofenac from the novel dosage form was further analysed using Fickian diffusion model to determine the mechanism of release of diclofenac from the tablets. To understand the release mechanism of diclofenac from the SESs, the release rate was described with the following equations:

$$\frac{M_t}{M} = kt^n \tag{1}$$

$$\log\frac{M_t}{M} = \log k + n\log t \tag{2}$$

M_t/M is the fraction of released drug at time t, k is a characteristic constant that incorporates the structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release. As the k value becomes higher, the drug is released faster. The n value of 1 corresponds to zero-order release kinetics. $0.5 < n < 1$ means a non-Fickian (anomalous) release model and $n = 0.5$ indicates Fickian diffusion (Peppas, 1985). From the plot of $\log M_t/M$ versus $\log t$ (Fig. 2), the kinetic parameters, n and k were calculated and presented in Table 3. Table 3 shows that the n values of all the batches lay between 0.5 and 1. This indicated that release of diclofenac from the self-emulsifying tablets followed the non-Fickian diffusion model (anomalous behaviour). However, values for batches 1 and 2 were approaching unity and could be said to have exhibited almost zero-order kinetics. The k values for batches 4 and 5 were higher than others indicating faster release in those batches. This is understandable since they contained higher Tween 65.

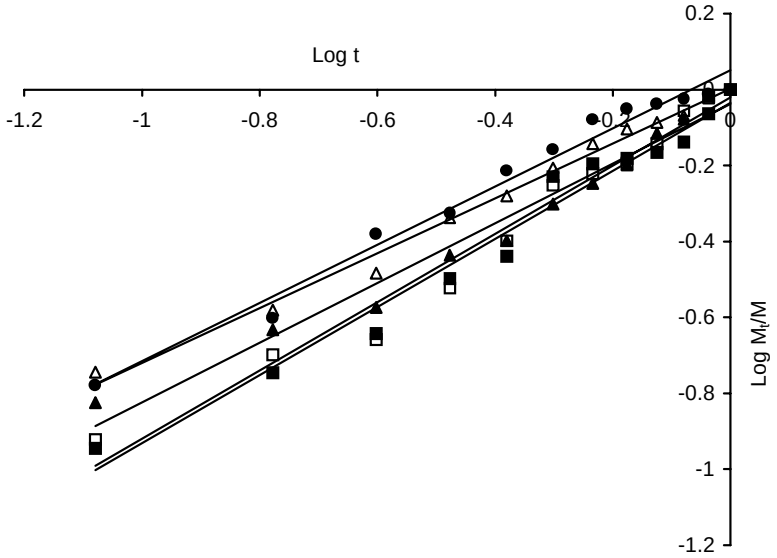

Fig. 2. Log–log plot of the amount of diclofenac released. ■: B1; □: B2; ▲: B3; △: B4; ●: B5.

Table 3
The release kinetic parameters

Batch	*n*	*k*	r^2
1	0.9028	−0.0291	0.9736
2	0.9076	−0.0144	0.9696
3	0.7919	−0.0339	0.9687
4	0.7302	0.0075	0.9896
5	0.7752	0.0564	0.9835

4. Conclusion

The tablets showed good release profiles, as well as acceptable tablet properties. The batches with higher Tween 65:goat fat content ratios gave better release rates. Under mild agitation as occurs under gastrointestinal conditions, the release rates may be comparable to those of conventional tablets. This method has the advantage of reliance on cheap raw materials such as goat fat. It also employs fewer processing steps. It is best suited for lipophilic drugs where the resulting emulsification gives faster dissolution rates and absorption. It can be used on a small scale in hospitals without need for heavy processing equipment. In vivo evaluation of this novel dosage form is currently in progress.

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