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Research Article

A Solid Self-Emulsifying System for Dissolution Enhancement of Etoricoxib

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Abstract

Self-emulsifying drug delivery system offers a solution to improve the oral bioavailability of poorly aqueous soluble drugs. Etoricoxib, a non-steroidal anti-inflammatory drug (NSAID) is a selective cycooxygenase-2 (COX-2) inhibitor. The poor aqueous solubility of etoricoxib results variable dissolution rate, which is the major cause of poor bioavailability. In the current study, formulation of solid self-emulsifying systems for the dissolution enhancement of etoricoxib was attempted. The self-emulsifying tablet of etoricoxib containing goat fat and Tween 60 admixture was formulated by pour moulding technique using a plastic mould. The weight uniformity, drug content, liquefaction time, and in vitro dissolution in simulated gastric fluid of the formulated tablets were evaluated. There was increase in in vitro drug release with increase in Tween 60 content and decrease in goat fat content. The etoricoxib release in simulated gastric fluid followed the non-Fickian diffusion model (anomalous behaviour).

***Keywords*:** Self-emulsifying delivery, tablets, liquefaction time, goat fat, etoricoxib

Introduction

The dissolution rates of poorly aqueous soluble drugs are very important parameter for in vivo performances of their dosage forms.[1] Usually, poorly aqueous soluble drugs are characterized by a low bioavailability due to less absorption, which is a major concern of pharmaceutical industries worldwide.[2] For poorly aqueous soluble drugs, the rate-determining step in the drug absorption is the dissolution of the drugs. An improvement in drug dissolution of poorly aqueous soluble drugs results in higher plasma peaks to facilitate drug absorption and exhibit potential pharmacodynamic activity.[3-8]

Recent years lipid-based vehicles have generated a huge interest as a potential formulation approach to improve oral bioavailability of poorly aqueous soluble drugs.[9-10] Lipid-based vehicles mainly decrease the intrinsic limitations of slow and incomplete dissolution of poorly aqueous soluble drugs by facilitating the formation of solubilised phases from which absorption takes place.[11] The extent of drug absorption from lipid-based vehicles is significantly affected by the dispersability of the administered lipid carriers and drug molecules. To avoid such restrictive problems, formulation approach based on self-emulsifying systems is considered helpful.[10-12] A mixture of oil and non-ionic surfactant forms a clear and transparent isotropic solution known as self-emulsifying systems, if the mixture forms an emulsion when mixed with water.[12] Self-emulsifying drug delivery system has been reported to improve drug dissolution, and therefore improve the bioavailability of poorly aqueous soluble drugs.[10-12] Such formulations form a fine oil-in-water emulsion with gentile agitation, which may be provided by the gastrointestinal motility.

Etoricoxib, 5-chloro- 6'-methyl- 3 [4-(methyl sulfonyl) phenyl] - 2, 3' -bypyridine, is a highly selective second generation cyclooxygenage-2 (COX-2) inhibitor administered orally as an analgesic and non-steroidal anti-inflammatory drug.[2,13] Its chemical structure is shown in Fig. 1. It is used in the treatment of rheumatoid arthritis, osteoarthritis, and acute gout.[14] However, it's very low aqueous solubility and poor dissolution can cause formulation problems and limit its therapeutic application by delaying the rate of absorption and the onset of action.[15-16] In the current investigation, a solid self-emulsifying system in form of tablets was developed using a natural lipid material, goat fat and a non-ionic surfactant with a high softening point, Tween 60 for the dissolution enhancement of a poorly aqueous soluble drug, etoricoxib.

Materials and Methods

Materials

Etoricoxib was gift samples by Zydus Health Care Ltd., India. Tween 60 was purchased from Qualigen Fine Chemicals, India. Goat fat was extracted from the adipose tissue of Capra hircus through batch process in our laboratory. All other chemicals were of analytical reagent grade, and freshly prepared distilled water

was used throughout the study.

Extraction of goat fat

Goat fat was extracted from the adipose tissue of *Capra hircus*.[12] The adipose tissue was grated and subjected to moist heat by boiling with about half of its weight of water in a water bath for 60 min. The molten fat was separated from the aqueous phase after filtering with a muslin cloth. The fat was used in a refrigerator until used.

Formulation of self-emulsifying tablets

Self-emulsifying etoricoxib tablets were prepared using different proportions of goat fat and Tween 60 listed in Table 1. The appropriate amount of goat fat and Tween 60 were heated together in a crucible until complete homogeneous. Etoricoxib (6 g) was added and stirred thoroughly. The mixture was poured in a plastic tablet mould and stored in cool place until used.

Weight uniformity determination

For each batch, 20 tablets were taken and weight using a weighing balance. The results were expressed as mean values of 20 determinations. The coefficient of variation (CV) was calculated from the following equation:

$$CV\ (\%) = \text{Standard deviation} / \text{Mean} \times 100$$

Drug content determination

20 tablets for each batch were taken and placed in a 100 ml volumetric flask containing 60 ml simulated intestinal fluid, and heated to 55°C in water bath with vigorous agitation until the content emulsified completely. The volume was made up to 250 ml with simulated gastric fluid, appropriately diluted and drug content was determined using a UV-VIS spectrophotometer (Shimadzu Corporation, Japan) at 284 nm wavelength.

Liquefaction time determination

Tablets were wrapped in a transparent polythene film and tied to the bulb of a thermometer by means of a thread. The thermometer attached with a tablet was placed in a round bottom flask containing 250 ml of simulated gastric fluid without pepsin, maintained at 37±1°C by means of a thermoregulated heating mantle. The tablets were observed carefully, and melt-times of tablets were recorded.

Dissolution studies

Dissolution studies were performed in simulated gastric fluid (900 ml) maintained at 37±0.5 °C, using USP XXIII apparatus (Electrolab, India) with a paddle rotating at 50 rpm. A formulated tablet of etoricoxib was placed in the appropriate chamber containing the dissolution medium. At fixed time intervals, samples (5 ml) were withdrawn and equal amount of fresh dissolution medium was added. Withdrawn samples were filtered (Whatman filter paper No. 41) and spectrophotometrically assayed for drug content at 284nm wavelengths using a UV-VIS spectrophotometer (Shimadzu Corporation, Japan). To analyze the mechanism of drug dissolution, the *in vitro* dissolution data were fitted to various mathematical models like zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.[2-3,17] Zero-order Model: $F = K_0 t$, where F represents the fraction of drug released in time t, and K_0 is the apparent release rate constant or zero-order release constant. First-order model: $\ln (1-F) = - K_1 t$, where F represents the fraction of drug released in time t, and K_1 is the first-order release constant. Higuchi model: $F = K_H t^{1/2}$, where F represents the fraction of drug released in time t, and K_H is the Higuchi dissolution constant. Korsmeyer-Peppas model: $F = K_P t^n$, where F represents the fraction of drug released in time t, K_P is the rate constant and *n* is the release exponent, this indicates the drug release mechanism.

Again, the Korsmeyer-Peppas model has been employed in the *in vitro* drug release behavior analysis of various pharmaceutical formulations to distinguish between various release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (relaxation-controlled release).[17] When, value of *n* is ≤0.5, it is Fickian release. The *n* value between 0.5 and 1.0 is defined as non-Fickian release. When, value of *n* is ≥1.0, it is case-II transport.

Statistical analysis

All data was analyzed with simple statistics. The simple statistical analyses were conducted using MedCalc software, version 11.6.1.0.

Results and Discussion

The self-emulsifying tablet of etoricoxib containing goat fat and Tween 60 admixture was formulated by pour moulding technique using a plastic mould. The mean weight of these newly developed etoricoxib tablets were within the range, 340.82 to 366.60 mg (Table 1). Moreover, the results of weight uniformity test also showed that all tablets had low coefficients of variations (2.02 to 3.12 %). The weight variation of these tablets may be due to sedimentation of active ingredient if soluble in the base or due to non-uniformity in mould filling since it was done manually.

The etoricoxib content in self-emulsifying tablets did not vary widely (58.37 ± 0.83 to 62.25 ± 1.18 %) (Table 1). The minor variation in drug content in these tablets could be due to drug sedimentation during preparation of self-emulsifying tablets. Etoricoxib in this case was soluble in the self emulsifying base; hence the low variation in etoricoxib content might be as a result of minor weight variation.

The liquefaction time determination test was designed to estimate the time, which could take the tablets to melt *in vivo* under no

agitation at normal body temperature. However, gastrointestinal motility will likely lower the liquefaction time at gastrointestinal conditions. This could result faster emulsification and penetration of the aqueous fluid into tablet interior.[12] This might ensure faster drug release before the failing of tablet integrity. Since the liquefaction times of these tablets were long (26.12 ± 0.57 to 43.96 ± 0.93 min; Table 1) under normal body temperature, the tablets could withstand the effect of temperature increases in the tropics.

The *in vitro* dissolution of all formulated self-emulsifying tablets containing etoricoxib showed high percentages drug release in simulated gastric fluid (Fig. 2). An increased drug release was found with the increasing Tween 60 content or decreasing goat fat content in the self-emulsifying tablets. This could be due to faster emulsification by the influence of higher surfactant content. In addition, goat fat with its higher melting point (51°C) reduced the rate of emulsification when present in higher content.

The *in vitro* drug dissolution data from various self-emulsifying tablets were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi, and Korsmeyer-Peppas model. The results of the curve-fitting into these above-mentioned mathematical models are given in Table 2. When respective correlation coefficients were compared, it was found to follow the Korsmeyer-Peppas model (R^2 = 0.9901 to 0.9945) over a period of 60 min of dissolution. The values of drug release exponent (*n*) determined from *in vitro* etoricoxib release data of various self-emulsifying tablets ranged from 0.78 to 0.82 in simulated gastric fluid, which indicated anomalous (non-Fickian) diffusion.

Table 1. Composition and physical properties of self-emulsifying tablets containing etoricoxib

Batch	Composition			Physical properties		
	Goat fat (g)	Tween 60 (g)	Etoricoxib (g)	Mean weight (mg ± CV, n = 20)	Drug content (mg ± SD, n = 20)	Liquefaction time (min ± SD, n = 6)
F-1	3	27	6	340.82 ± 2.02	62.25 ± 1.18	26.12 ± 0.57
F-2	6	24	6	345.78 ± 2.84	60.18 ± 1.07	37.03 ± 0.86
F-3	9	21	6	366.60 ± 3.12	58.37 ± 0.83	43.96 ± 0.93

Table 2. Release kinetic parameters of self-emulsifying tablets containing etoricoxib

Batch	R^2				Diffusional exponent (*n*)
	Zero order	First order	Higuchi	Korsmeyer-Peppas	
F-1	0.9809	0.8756	0.7389	0.9925	0.82
F-2	0.9781	0.9119	0.7397	0.9901	0.78
F-3	0.9753	0.8484	0.8209	0.9945	0.79

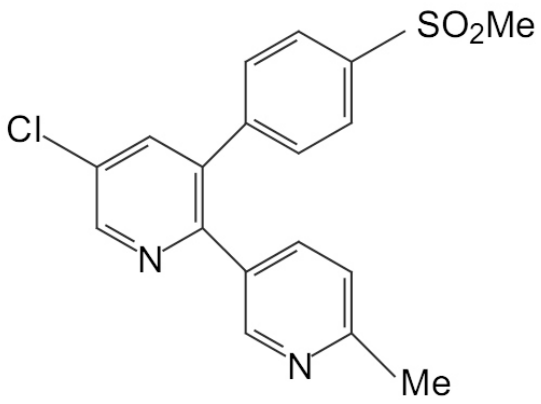

Fig. 1: Chemical structure of etoricoxib

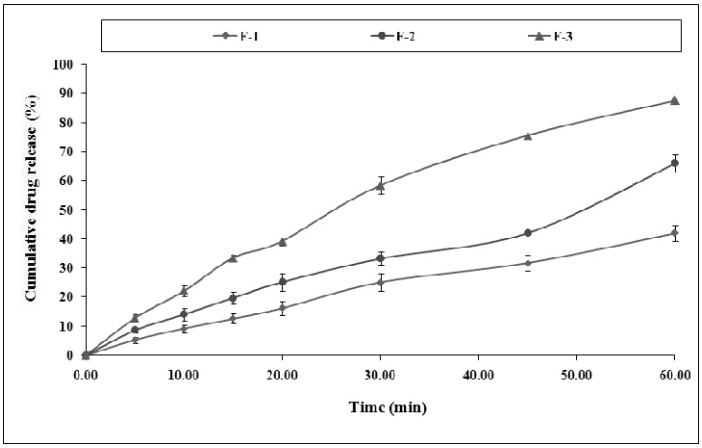

Fig. 2: Dissolution profile of etoricoxib from self-emulsifying tablets in simulated gastric fluid

Conclusion

The self-emulsifying tablets of etoricoxib showed improved drug dissolution profiles, as well as acceptable physical properties. This method has the advantages of simple processing steps and reliance on cheap raw materials such as goat fat and Tween 60. The study concludes that etoricoxib could be comfortably administered in the form of self-emulsifying tablets using goat fat and Tween 60 admixture with enhanced dissolution to improve bioavailability and effective therapy. This type of solid self-emulsifying system can be applied for other poorly aqueous soluble drugs, where the resulting emulsification promotes faster dissolution rates and absorption.

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