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Self-emulsifying tablets of Ibuprofen: Design, optimization and evaluation

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ABSTRACT

Self-emulsifying tablets were formulated with the objective of enhancing the bioavailability of non-steroidal anti-inflammatory drug, ibuprofen. Isotropic mixture of oil, surfactant was used to design the formulations. Goat fat and tween60 admixture was employed to formulate Self-emulsifying tablets (SETs). Different formulations were developed with varying composition of oil and surfactant by melt granulation technique and optimized. Resultant SETs were evaluated for weight variation, liquefaction time and drug content. The dissolution studies of ibuprofen from the SETs were determined in simulated gastric fluid without pepsin. Weight uniformity and absolute drug content was observed within the range in case of formulations made of admixtures of high proportion of tween60 and low content of goat fat. Liquefaction time determined was high but there was an every chance of reduction in liquefaction time due to gastric motility. Maximum drug release was shown for the formulations having high amount of tween60 and low content of goat fat. Dissolution studies revealed remarkable increase in release of the drug as compared to the standard drug. Results obtained indicated that ibuprofen could be conveniently administered in the form of SETs containing goat fat and tween60 admixtures.

Keywords: Self-emulsifying tablets, goat fat, tween-60, ibuprofen and melt granulation technique.

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INTRODUCTION

Oral route is the major route of drug delivery but 50% of drug compounds are hampered because of their high lipophilicity [1]. For these lipophilic drugs the rate determining step in absorption is the dissolution of drug which leads to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality [2,3].Thus for these types of drugs higher doses are administered than required which may have chances of leading to the toxicity problems [4]. To overcome this barrier many formulation strategies such as micronization, complexation [5] use of nanosuspension [6], cyclodextrin, micellar solubilization by surfactant, drug dispersion in carrier [7], salt formation, co-grinding [8]. However all these methods have their own limitations.

In recent years, however, much interest has been focused on lipid based formulation to tackle the formulation challenges of poorly water soluble drugs. This lipid formulation includes the incorporation of drug compound into inert lipid vehicles such as oils [9] surfactant dispersions [10,11], self-emulsifying formulations [12], emulsions [13] and liposome's [14] with particular emphasis on self emulsifying drug delivery system (SEDDS). Formulation will be of oil-in-water type of emulsion for lipophilic drug. This drug delivery system has been reported to improve *in-vivo* dissolution and therefore enhance the bioavailability of lipophilic drugs [15,16]. SEDDS or self emulsifying oil formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, alternatively one or more hydrophilic solvents and co-solvents [17]. SEDDS are usually formulated in liquid form which has some disadvantages especially in the manufacturing process, high production cost, furthermore, incompatibility problem with the capsule shell are common. The incorporation of self emulsifying mixture into solid form is desirable but challenging because self emulsifying properties are harder to achieve with solid materials. However potential advantages of solid self emulsifying dosage forms have attracted many authors [18-19]. This lipid formulation converting into tablet dosage form which is termed as liquid-solid or solid-lipid compact [20]. Formulating lipid formulation as solid dosage form by various methods like melt granulation, extrusion, wet granulation technology combines the advantages of lipid based formulations with that of solid dosage form and overcome some of short comings of liquid formulations [21]. Such formulations will form oil-in-water emulsion with gentle agitation (gastrointestinal motility) followed by dilution in aqueous media such as GI fluids [15]. Various physiological mechanisms which explain the effect of oils on absorption of lipophilic compounds includes altered gastrointestinal motility, increased bile flow and drug solubilization, increased mucosal permeability, enhanced mesenteric lymph flow, and increased lymphatic absorption [22].

Ibuprofen is a hydrophobic drug used to relief the symptoms of a wide range of illnesses such as headaches, backache, period pain, dental pain, neuralgia, rheumatic pain, muscular pain, migraine, cold and flu symptoms and arthritis.

The main objective of this study is to evaluate the suitability of goat fat as hydrophobic carrier which is having high softening point acting as lipid and tween60, a nonionic surfactant

admixture in the formulation of self emulsifying tablets(SETs) containing ibuprofen. Goat fat has been evaluated as a base for suppository formulations [23]. This will provide a cheap and readily available alternative to the costly starting materials and also reduces the processing steps than liquid emulsifying formulations.

MATERIALS AND METHODS

Ibuprofen was a generous gift from ESPI Chemicals Pvt Ltd (Hyderabad), tween 60 (polyoxyethylene sorbitan mono oleate) was provided by HYCHEM laboratories Pvt Ltd, adipose tissue of goat was obtained from our local area (from the commercial market) which was further extracted and processed in our laboratory to obtain goat fat, distilled water and other chemicals were supplied by our college were of analytical grade.

Extraction of goat fat

Goat fat was extracted from adipose tissue of "*capra hircus*" by wet rendering. Briefly, the extraneous material were manually separated from the adipose tissue and is grated and subjected to moist heat by boiling with about half its weight of water for 45 min and the molten fat was separated from aqueous phase after filtering with a muslin cloth. The extracted fat was further subjected to purification by passing it through a column of activated charcoal and bentonite (2:1) at 100^{o}C at a ratio of 10gm of fat and 1gm of column material. The fat was stored in a refrigerated until used [23].

Formulation of self-emulsifying tablets

Melt granulation technique

All the tablets were prepared to contain 200mg of ibuprofen each. Seven batches containing same amount of drug but changing the proportion of goat fat and tween60 were prepared as given in table 1. In each case appropriate quantity of goat fat and tween60 were melted in a crucible at 60^{o}c until it is homogenous. The drug 20gm was added and stirred thoroughly. The molten mass was poured into a plastic mould and allowed to set at 28^{o}c. the tablets were thereafter removed from the mould and stored in a cool place until used.

Optimization of SETs formulations

SETs were prepared with different proportions of tween60 and goat fat. By keeping drug content constant SETs were evaluated for physical characteristics such as weight uniformity, liquefaction time and absolute drug content. SETs formulations were optimized with respect to their physical properties such as weight uniformity and absolute drug content and optimized SETs were considered for further evaluation.

Evaluation of SETs

Weight uniformity

For each batch 20 tablets were randomly selected, weighed collectively and then individually. The mean ± SD values (Table 2) were calculated for all the formulations.

Liquefaction time

Liquefaction time was determined by slightly modifying the method described by Setnikar et al. From each batch one tablet was wrapped in a transparent polythene film and tied to the bulb of the thermometer by means of a thread. Now immerse the thermometer in flask containing 20ml of simulated gastric fluid (SGF) without pepsin maintained at 37±1^{o}C by means of thermo regulated heating mantle. Tablets were observed carefully and noted down the time at which tablet started melting. Average of 20 determinations was taken for each batch and values were given in table 2 [24].

Absolute drug content

From each batch 20 tablets were randomly selected, weighed and melted together and allowed to solidify with stirring. A weight equivalent to the average weight of 20 tablets was weighed and placed in 100ml of volumetric flask containing 60ml of simulated intestinal fluid (SIF) and heated up to 40^{o}C in a water bath with continuous agitation until contents were completely emulsified and made up the volume with SGF [22]. Dilutions were made and the absorbance was determined using Shimadzu UV-1800 spectrophotometer at 264nm. Same procedure was repeated three times for all the batches and the absolute drug content was calculated with reference to standard graph. The mean ± SD values were calculated for all the formulations values were given in table 2.

Dissolution studies

Dissolution profiles of SETs were determined using USP XXIV rotating basket apparatus at 37^{0}C .The rotating speed was 100rpm and the dissolution medium was 900ml of SGF. Samples (5ml) withdrawn at a fixed time intervals were filtered using whattman filter paper and were analyzed by Shimadzu UV-1800 spectrophotometer at 264nm[25]. The dissolution experiments were carried out in triplicate. The mean ± SD values were calculated for all the formulations and results were given in table 2, and represented in figure 1.

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Table 1: Optimized formulas of self-emulsifying tablets

Batch	Tween 60(gm)	Goat fat (gm)	Drug (gm)
F1	0.4	5.6	4.0
F2	1.8	4.0	4.0
F3	0.8	5.3	4.0
F4	2.0	4.0	4.0
F5	1.2	4.7	4.0
F6	1.4	4.9	4.0
F7	1.0	5.2	4.0

Table 2: Results of some evaluated physical properties of SETs

Batch	Weight uniformity$^{\infty}$ (mg)	Liquefaction time$^{\beta}$ (min)	Absolute drug content (mg)$^{\gamma}$
F1	502.4±6.18	42.44±1.59	199.8±2.38
F2	490.4±2.58	36.25±2.42	200. 2±1.92
F3	501.8±3.42	46.69±1.21	199.8±3.70
F4	500.6±1.65	37.07±1.35	200.0±2.20
F5	494.4±5.36	40.50±0.50	203.2±5.30
F6	512.0±3.80	40.00±1.07	201.0±2.50
F7	508.8±4.44	41.32±0.92	200.6±1.81

$^{\infty}$ Each value represents the mean ± S.D *n* = 20.
$^{\beta}$ Each value represents the mean ± S.D. *n* = 20.
$^{\gamma}$Each value represents the mean ± S.D. *n* =5.

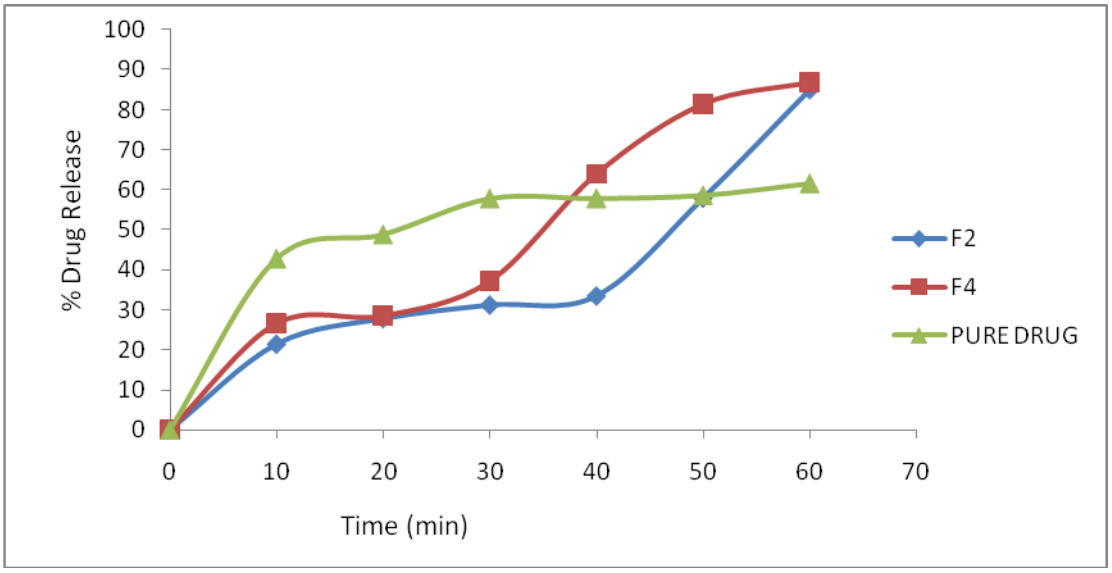

Figure 1: Drug release profile

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RESULTS AND DISCUSSION

Weight uniformity

The results of weight uniformity test were expressed as arithmetic mean of twenty tablets in each formulation. Results indicated that all the tablets had less deviation from the range passed the weight specifications.

Liquefaction time

Twenty tablets were tested for each batch and statistical results showed very low standard deviations (table2) as the liquefaction time was long at 37^{o}C and the tablet can withstand even at tropical temperatures also. If the temperature increases to more than 37^{o}C in the tropical areas, it is advised to store the tablets in conditions similar to conventional suppository formulary.

Absolute drug content

The active ingredient content was not varying widely so it showed a very low standard deviation. Because the drug was soluble in self-emulsifying base and this slight variation was may be due to weight variation or as a result of drug sedimentation during preparation.

Optimization of SETs formulations

By observing the ratios of tween60 and goat fat, increase in tween60 proportion with decrease in goat fat proportion had shown optimized results. So F2 (1.8:4.0) and F4 (2.0:4.0) were considered as best formulations as they were showing optimum results upon evaluation of their physical characteristics.

Dissolution studies

The results of drug release studies were shown in fig1, for F2 nearly 85% of the drug was released after 1 hour where as F4 shown nearly 87 % drug release. From the figure it could be seen that both formulations shown better release profile when compared to conventional dosage form.

SEDDS for lipophilic drugs were reported and showed that isotropic mixtures of oil, surfactant, solvents or co-solvents can be used for design of formulations in order to improve the oral absorption and bioavailability of highly lipophilic compounds [26,27]. The efficiency of drug incorporation into SETs is generally specific to each case depending upon the physicochemical compatibility of drug/systems [28]. The efficiency of drug delivery system can be altered either by halting charge movement through the system by direct complexation of the drug with some of the components in the mixture through its interaction with the

lyotropic liquid crystal phase [29] or by penetration into the surfactant interfacial monolayer[30-31]. The use of solid self emulsifying tablets in the delivery of diclofenac by employing goat fat and tween65 admixtures was reported [22]. In *vitro* evaluation of drug release from self micro emulsifying drug delivery system (SMEDDS) using a biodegradable homo lipid from *Capra hircus* was reported by incorporating hydrophilic and lipophilic drugs into SMEDDS. But a self emulsifying tablet of ibuprofen with admixtures of goat fat and tween60 was not yet reported. Tween60 a nonionic surfactant was chosen for this study because of its ability to form spontaneous emulsion with the homo lipid, it is considerably less toxicity compared with ionic surfactant and absence of charge which will greatly reduces its drug interaction potential [23].

In the present study the potential self emulsifying tablets were utilized for delivery of ibuprofen which has poor aqueous solubility. The SETs were formulated and evaluated for weight uniformity which showed slight deviation and it may be due to sedimentation of active drug which is insoluble in lipid and also may be due to improper filling of moulds (manual error). The time required for liquefaction of a tablet was very high but it was not a problem. The main aim of this study was to estimate the time required to melt a tablet *in vivo* under no agitation at normal body temperature. However gastrointestinal motility will lower the liquefaction time resulting in faster emulsification and penetration of aqueous fluid into tablet interior. Even this ensures the drug release even before tablet integrity fails. Absolute drug contents were showing appropriate drug content in each formulation. After optimization of all formulations F2 and F4 were chosen for dissolution studies and their drug released profiles were observed. Maximum drug release was shown for the formulation having high amount of tween60 because higher surfactant content ensures faster emulsification as tween60 is a non-ionic surfactant with no charge which reduces its drug interaction potential. High fat content reduces the rate of emulsification because of its high melting point (51^{o}C). So there was increase in drug release with increase in tween60 content and decrease in goat fat content.

CONCLUSION

The present study illustrated that poorly water soluble drugs with low and variable bioavailability can be formulated as self-emulsifying tablets (SETSs). Ibuprofen was conveniently formulated as tablets with various proportions of surfactant and fat. The batches with higher tween60: goat fat ratios gave better drug release rates. The release rate was comparable with that of conventional tablets. This method has the advantage of reliance on cheap raw materials (goat fat), fewer processing steps, require no heavy equipment. This method is suitable for lipophilic drugs to enhance the dissolution rat and absorption because of faster emulsification. Further *in vivo* evaluation of this novel dosage form is currently in progress.

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