

Enhancement of Dissolution Rate of Naproxen by Lipid Based Solid Dispersions

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Abstract

Oral dosage forms have always been considered the preferred route of delivery due to their lower unit dose cost and ease of compliance. Approximately 40-70% of new chemical entities (NCE'S) display poor oral absorption characteristics, generally as a result of poor solubility, poor dissolution rate and therefore result in unsuccessful formulation of conventional oral dosage forms. There has been an increasing trend towards utilizing lipid based drug delivery system (LBDDS). In the current research work an attempt was made to improve the solubility, dissolution rate permeability of poorly water soluble drug naproxen by utilizing lipid based solid dispersions (LBSD) technology. Naproxen is a poorly water soluble drug (BCS class II). LBSD'S were prepared by using different ratios (1:1,1:3 and 1:5) of lipid based hydrophilic carrier such as gelucire 44/14 and hydrophilic inert carrier Pearlitol SD 200 by solvent evaporation technique. Phase solubility and saturation solubility studies were performed in distilled water containing increasing concentrations of these carriers showed linear increase in solubility of naproxen. *In vitro* dissolution studies revealed that dissolution rate of LBSD was higher than the pure drug and marketed formulation. *Ex vivo* studies were performed using goat intestine membrane showed permeability was increased with LBSD'S. It was found that there were no drug and excipients interactions as there was no extra peak was observed in FT-IR spectra of final formulation. Hence it can be concluded that the oral bioavailability of naproxen can be successfully improved by preparing Lipid based solid dispersions.

Key Words: lipid based solid dispersions, oral bioavailability, dissolution, naproxen, pearlitol, gelucire 44/14

INTRODUCTION:

Solubility of poorly soluble drugs is the important parameter for their oral absorption. Dissolution is the rate limiting step for such drugs in their absorption through oral route. Oral route is a major route of administration for majority of drugs. BCS class II drugs suffer less bioavailability thereby decreased therapeutic effect problems due to poor solubility and limited dissolution rate [1,2]. Solid dispersion is the mixture of a poorly soluble drug in an inert with water soluble carrier i.e the drug in hydrophobic nature and the carrier in hydrophilic nature. Solid dispersions are able to enhance the solubility and dissolution rate of poorly water soluble drugs and also improve its bioavailability². The drug in the solid dispersion may be dispersed in fine crystalline form or amorphous form in the carrier system. A combination of both, or be molecularly dispersed within the carrier excipient forming a solid solution. There are a number of proposed mechanisms of enhanced drug dissolution from solid dispersions, some of which reduction of particle size, inhibition of drug aggregation, increased drug wettability and dispersibility by the carrier [3].

A novel oral drug delivery technology which referred to as Lipid Based Solid Dispersions (LBSD) have been developed to improve oral bioavailability of poorly soluble drugs. The LBSD technology has been shown other distinct advantages compared to alternative oral formulation technologies, increasing conventional Lipid based drug delivery systems and micronized formulations [4-6]. Naproxen, (6-methyl 2-naphthyl acetic acid) non-steroidal anti-inflammatory drug, is a weak acid (pKa = 4.15) which is practically insoluble in water and the major problem associated with the formulation

and effectiveness of the naproxen is its variable oral absorption due to insufficient aqueous solubility at gastrointestinal pH, thus making dissolution the rate-determining step in the gastric absorption of naproxen [7].

The main objective of this work is to develop and evaluate lipid based solid dispersions to enhance the bioavailability of a highly permeable and a poorly soluble non steroidal anti-inflammatory drug naproxen by using various lipid based carriers.

MATERIALS:

Naproxen was obtained as a gift sample from Ranbaxy Private limited, India and Gelucire 44/14 was obtained as gift sample from Gattefosse, France.

METHODOLOGY:

Saturation Solubility Studies: Saturation solubility study of naproxen was done by adding excess amounts of drug to different solvents with increasing p^H such as 0.1 N HCL, 6.8 pH phosphate buffer, 7.4 p^H phosphate buffer and distilled water at 37 ± 0.5°C. The solutions were equilibrated under continuous agitation for 48 hr and filtered through whatman filter paper to obtain a clear solution. The samples were analyzed by UV-Spectroscopy and the concentrations in µg/ml were determined. Each sample was determined in triplicate [8].

Phase solubility study of naproxen in presence of Gelucire 44/14

Phase solubility studies were done by taking different concentrations of gelucire 44/14 (2%,4%,6%,8% and 10%) in distilled water. To each of these concentrations excess

amount of drug was added. Then these solutions were kept for shaking on shaker for 48 hours. After 48 hours samples were filtered through the whatman filter paper then the solution diluted and estimated for naproxen concentration. Three determinations were carried out for each sample to calculate the solubility of naproxen [9]

Fourier Transform Infrared Spectroscopy:

The KBr disk sample preparation technique (pressed pellet technique) was used to obtain the IR spectra of the samples on an IR spectrophotometer (SHIMADZU FTIR-8400s). The scanning range was selected between 4000 and 400 cm^{-1} . Characteristic peaks attributable to functional groups present in molecule of each drug were assigned to establish the identity [10].

Formulation of Solid Dispersions

Lipid based solid dispersions of naproxen were prepared by using hydrophilic lipid based carrier such as gelucire 44/14 in different ratios such as 1:1, 1:3 & 1:5. Pearlitol SD 200 was used as inert carrier in all the formulations. Compositions of various formulations are given in the table no. 1. LBSD of naproxen were prepared by solvent evaporation method. Naproxen 100 mg was taken and dissolved in 5 ml of methanol. To the drug required quantity of lipid based carrier and pearlitol SD 200 were added. This solution was taken in to round bottom flask, attached to the rotary flash evaporator and evaporated at 40°C, rpm was 60 for 1 hr. Solid dispersions were obtained, collected and dried in the desiccator till it was completely dried [9-11].

Table No. 1: Formulation of Lipid based Solid dispersions with Gelucire 44/14

Formulation	Drug (mg)	Gelucire 44/14 (mg)	Pearlitol SD 200 (mg)	Ratio
F1	100	100	100	1:1:1
F2	100	300	300	1:3:3
F3	100	500	500	1:5:5

EVALUATION OF LIPID BASED SOLID DISPERSIONS

Micromeritic evaluation:

Bulk density: The powder sample under test was screened through sieve no. 18 and the sample equivalent to 10 g was accurately weighed and filled in a 50 ml graduated cylinder and the powder was leveled and the unsettled volume, V_0 was noted. The bulk density was calculated in g/cm^3 by the formula [12-14].

Bulk density (ρ_0) = M/V_0 ; Where, M = mass of powder taken; V_0 = apparent unstirred volume

Tapped Density: The powder sample under test was screened through sieve no. 18 and the weight of sample equivalent to 10 g was filled in 50 ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times. Volume was considered as a tapped volume V_f . The tapped density was calculated in g/cm^3 by the formula [12-14].

Tapped density (ρ_t) = M/V_f ; Where, M = weight of sample powder taken; V_f = tapped volume

Angle of repose: When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose [12-14].

$\theta = \tan^{-1}(h/r)$; h is the height of pile, r is the radius of pile.

Carr's index: The Carr index is an indication of the compressibility of a powder [12-14].

$$C = 100 (V_B - V_T)/V_B$$

V_B is the freely settled volume of a given mass of powder; V_T is the freely settled volume of a given mass of powder

Hausner ratio: The Hausner ratio is a number that is correlated to the flowability of a powder or granular material [12-14].

$$H = \rho_T/\rho_B$$

ρ_T is the freely settled bulk density of the powder; ρ_B is the freely settled bulk density of the powder

Content Uniformity:

Solid dispersions of naproxen were taken in 50 ml of methanol in a conical flask and kept on a rotary shaker for 1 hour. After this time period, the solutions were filtered through a 0.45 μm membrane filter and diluted suitably. These samples were analyzed with UV spectroscopy. Each content determination was performed in triplicate and the average and standard deviations were calculated.

In vitro dissolution study:

Dissolution studies of pure drug and solid dispersions were performed by the U.S. Pharmacopeia (USP) XXIV type II dissolution apparatus (Electrolab, Mumbai, India) at the paddle rotation speed of 50 rpm in 900 mL of 7.4 as dissolution media at $37 \pm 0.5^\circ\text{C}$. A sample equivalent to 100 mg of the prepared solid dispersion was placed in dissolution medium. During the release studies, 5ml of sample was withdrawal at regular time intervals were 15, 30, 45, 60, 90 and 120 min using a syringe and were replaced with the same volume of buffer media for maintaining sink condition. The samples were subsequently filtered using 0.45 μm pore size membrane filters (Millipore). Then the samples were analyzed by UV Spectroscopy. Samples were performed in triplicate. The dissolution profile was examined and evaluated for amount of drug released.

Ex Vivo Permeation Studies:

Goat intestine was taken from the slaughter house. It was rinsed with Krebs-Ringer solution to remove the mucus and adhered intestinal contents. One end of the intestine segment was tied and fixed to the open tube. The pure drug, marketed drug and selected formulation equivalent to 100 mg of drug was introduced into the lumen and was tightly closed. The tissue was placed in an organ bath with continuous aeration and maintained at a temperature of 37°C. The receptor compartment consists of 50 ml of 7.4 pH Phosphate buffer. Samples were collected at regular time intervals and replaced with equal volume with 7.4 pH phosphate buffer for maintaining sink condition and the samples were filtered through 0.45 mm and quantified using UV Spectroscopy.

Ex vivo permeation Data Analysis

The cumulative amount of drug permeated during the study was determined and plotted against the time to calculate the apparent permeability (P_{app} , cm/s) using the following equation.

$$P_{app} = \frac{F}{AC_0}$$

Where F is the flux of the drug,

A is the surface area of the intestinal sac assumed to be the area of a cylinder ($2\pi rL$);

C_0 is the initial drug concentration.

RESULTS & DISCUSSION:

Saturation solubility studies of naproxen in various solvents

Solubility of pure drugs was determined in different solvents by saturation solubility method and the values obtained were given in the Table 2. From the results obtained it was observed that the drug is insoluble in distilled water and slightly soluble in other solvents.

Table No. 2 : Solubility of Naproxen in various solvents (n=3)

Solvent	Amount of Naproxen Dissolved (mg/ml) (Mean \pm SD)	Solubility
Water	0.017 \pm 0.01	Insoluble
Phosphate Buffer (pH 6.8)	5 \pm 0.08	slightly soluble
Phosphate Buffer (pH 7.4)	3 \pm 0.06	slightly soluble
0.1 N HCL	12 \pm 0.06	slightly soluble

IR Spectroscopy

The infrared spectra of pure drugs and formulations were recorded by KBr method using Shimadzu Fourier Transform Infrared Spectrophotometer. In case of formulations, drug is mixed with non volatile solvent, all carriers, coating material, and disintegrating agent and IR spectra were recorded for each solvent separately. Characteristic peaks of Naproxen were observed in pure drug IR spectra at 3000-2930 cm^{-1} (Aromatic C-H stretch, carboxylic acid O-H stretch), 1800 - 1600 cm^{-1} (C=O stretch), 1604 cm^{-1} (Aromatic C=C stretch), 1394 cm^{-1} (CH-CH₃ deformation), 1685 cm^{-1} (Carboxylic O-H out of plane deformation), 900-484 cm^{-1} (C-H out of plane deformation for substituted aromatic). From the IR spectra of formulations it was evident that pure drug in formulations undergoes no chemical reaction or interaction with any of the excipients used as there was no disappearing of any peak or no change in the position of all the peaks.

Table No. 3: Micromeritic properties of all formulations

Formulation	Bulk density* (mg/ml)	Tapped density* (mg/ml)	Carr's index* (%)	Hausner's ratio* (%)	Angle of repose* (degree)	Drug content (%)
F1	423.70 \pm 1.25	529.25 \pm 2.66	12.10	1.15	32.638 \pm 0.6	93.57 \pm 0.21
F2	397.27 \pm 2.3	617.29 \pm 2.36	12.37	1.18	33.259 \pm 0.6	98.65 \pm 0.45
F3	320.25 \pm 1.7	632.52 \pm 1.23	11.79	1.08	34.352 \pm 0.8	99.14 \pm 0.29

Overlay of IR spectra of all the formulations are given in fig.1.

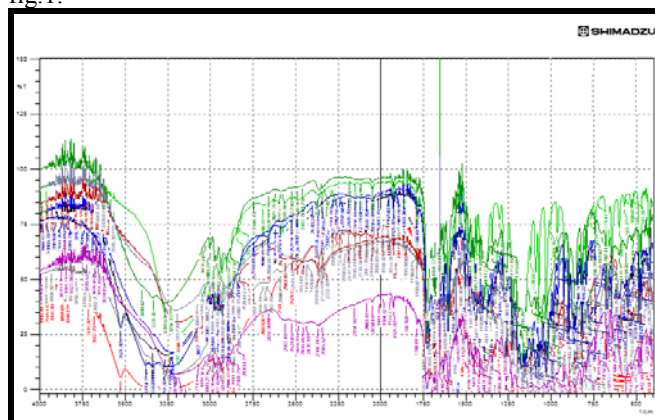


Fig.1: Overlay of IR Spectra of Naproxen formulations

Phase solubility study of naproxen in different concentrations of gelucire 44/14

The bar chart showed that the phase solubility of naproxen initially increased up to the 6 $\mu\text{g/ml}$ of gelucire 44/14 and then decreased. Based on these results the formulation ratios were prepared those were 1:1, 1:3 and 1:5 ratios.

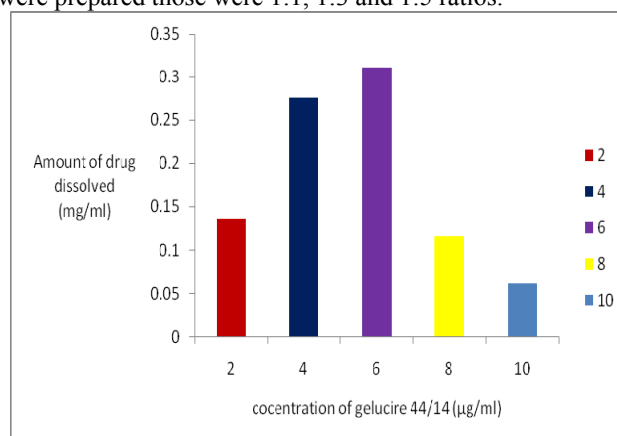


Fig. 2: Phase solubility studies (Gelucire 44/14)

Micromeritic properties of formulations

Micromeritic properties of Lipid based solid dispersions of naproxen formulations were prepared with carrier Gelucire 44/14 were listed in the table.3. Here good flow characteristics were observed with high amounts of Carrier, and low amounts of Carrier. The angle of repose and Carr's index was found to be (34.923 \pm 0.2), (13.25) which depicted good flow of the prepared LBSD's.

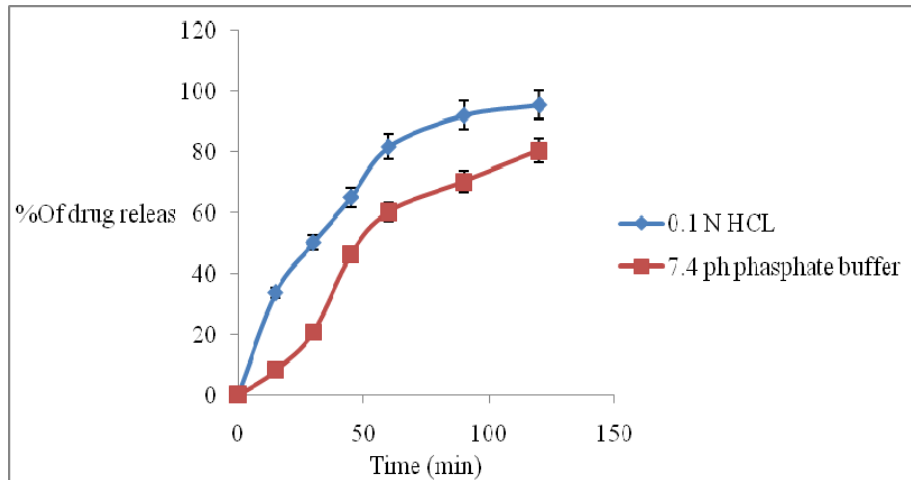


Fig.3: *In vitro* dissolution of pure drug in 0.1N HCL and 7.4 pH Phosphate buffer

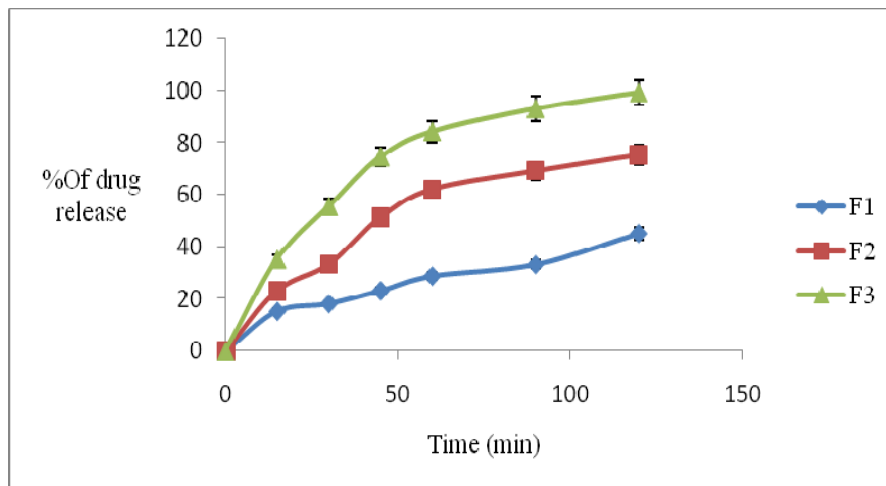


Fig.4: *In vitro* Drug release of F1, F2, F3

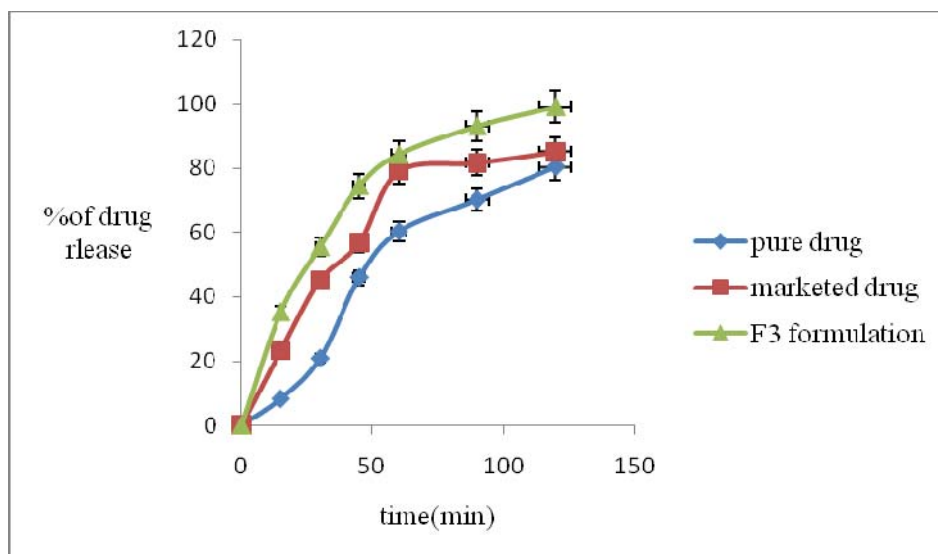


Fig.5: *In vitro* Drug release of Pure drug, F3 formulation, Marketed drug

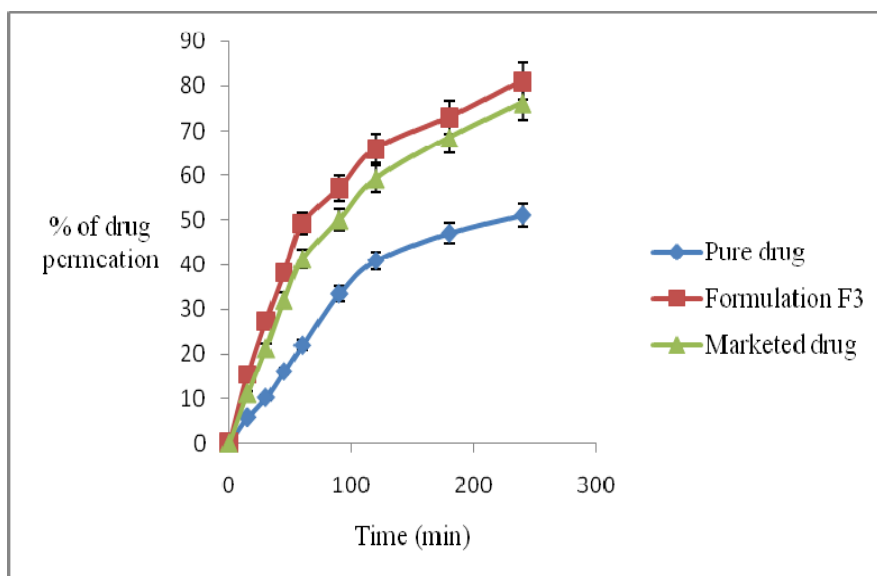


Fig. 6: *Ex vivo* Permeation studies of pure drug, formulation F3, marketed drug

***In vitro* dissolution study of pure drug**

Dissolution study of pure drug was carried out in 0.1N HCL and 7.4 P^H phosphate buffer. % drug dissolved at various time intervals and graph was plotted shown in fig.3. It was observed that the pure drug was dissolved rapidly in 0.1 N HCL than the 7.4 P^H phosphate buffer. This might be due to the basic nature of pure drug naproxen.

***In vitro* drug release**

In vitro drug release studies of all the prepared LBSD's of naproxen were carried out in 0.1 N HCL and the % of drug release was calculated at various time intervals up to 2h. Graph was plotted and showed in fig.4. It was observed from the study that the ratios of the gelucire increasing the drug dissolution rate was also increased. And it was found that formulation prepared with gelucire 50/13 have shown faster drug release than the formulations prepared with gelucire 44/14.

Comparative *in Vitro* Drug Release of Pure Drug, Marketed and Selected F3 formulation

Comparative dissolution was performed to the pure drug, marketed formulation (Inspra) and best formulation F3. The % of drug dissolved at 120 minutes was calculated. The % of drug dissolved at 2h was 80.38±1.6, 85.2±2.9, 99.05±2.19 for pure drug, marketed formulation and F3 formulation respectively. Graph is shown in fig.5. Hence it can be concluded that the dissolution rate is increased from LBSD's.

***Ex vivo* permeation studies**

Goat intestine was taken from the slaughter house. It was rinsed with Krebs-Ringer solution to remove the mucus and adhered intestinal contents. One end of the intestine segment was tied and fixed to the open tube. The pure drug, marketed drug inspra and selected formulation equivalent to 25 mg of drug was introduced into the lumen and was tightly closed.

The tissue was placed in an organ bath with continuous aeration and maintained at a temperature of 37°C. The receptor compartment consists of 50 ml of 7.4 pH Phosphate buffer. Samples were collected at regular time intervals and replaced with equal volume with 7.4 pH phosphate buffer for maintaining sink condition and the samples were filtered through 0.45 mm and quantified using uv-spectroscopy. Study was conducted for 4 hr the % of drug permeated through ileum was

Pure drug	– 51.198±1.9
Marketed product	– 76.250±0.256
F3 formulation	– 81.09±2.10

The graph was plotted time on x-axis vs % of drug permeated on y-axis. Fig.6: showed formulation F3 was better drug permeation than the pure drug and marketed product.

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