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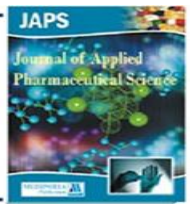

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Liquisolid Compacts: An Approach to Enhance the Dissolution Rate of Nimesulide

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ABSTRACT

The present study enlightens to enhance the dissolution rate, absorption efficiency and bioavailability of Nimesulide, a poorly soluble-highly permeable drug by preparing liquisolid compacts. Nimesulide liquisolid tablets were prepared by using polyethylene glycol-400 as a non-volatile liquid vehicle, microcrystalline cellulose, hydroxypropyl methylcellulose-E15, starch were used as carrier materials and silica gel as coating material in different ratios. They were characterized for different physical parameters to comply with pharmacopoeial limits. In vitro dissolution profiles of the liquisolid formulations were studied and compared with conventional formulation in pH 7.4 phosphate buffer and it was found that liquisolid tablets formulated with microcrystalline cellulose showed significant higher drug release rates than conventional tablets due to increase in wetting properties. DSC study showed that there is no interaction between the drug and excipients. In conclusion, development of nimesulide liquisolid tablets is a good approach to enhance the dissolution rate.

Keywords: Carrier, Dissolution rate, Liquisolid compacts, Liquid load factor, Permeable.

INTRODUCTION

Oral drug delivery is the preferred way of administration for most of the active drug molecules due to its several advantages like greater flexibility in design and high patient compliance (Kaushik *et al.*, 2004 & Hirani *et al.*, 2009). Because of greater stability, accuracy in dose, easy of production, formulation in the form of tablets is the preferred oral dosage form. But the poor dissolution rate of water insoluble drugs is the major problem for pharmaceutical formulators to prepare in the form of tablets (Seager., 1998 & Bandari *et al.*, 2008). There are several techniques to enhance the dissolution of poorly soluble drugs like use of water-soluble salts and polymorphic forms, reducing particle size to increase the surface area, formation of water-soluble molecular complexes, solid dispersion, co-precipitation, lyophilization, microencapsulation, inclusion of drug solutions or liquid drugs into soft gelatin capsules, solubilization in a surfactant system and manipulation of solid state of drug (Ohara., 2005 & Shyamala *et al.*, 2002 & Chang *et al.*, 2000 & Shaikh *et al.*, 2010 & Dobetti., 2000). From the last few years, the pharmaceutical scientists were working on development of liquisolid compacts to enhance dissolution rate of poorly soluble drugs, thereby improving efficacy of drug molecules (Yadav et al., 2009 & Spireas et al., 1999). Liquid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term “liquisolid medication” implies oily liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems.

Using this new formulation technique, a liquid medication may be converted into a dry looking, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials. Various grades of cellulose, starch, lactose, etc., may be used as the carrier, whereas very fine particle size silica powder may be used as the coating material (Javadzadeh et al., 2008; Spireas., 2002; Spireas et al., 1999).

The therapeutic effectiveness of a drug depends upon the ability of the dosage forms to deliver the medicaments to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. Some drugs having poor bioavailability are with poor aqueous solubility and or slow dissolution rate in the biological fluids. The aim of this study was to increase dissolution rate of nimesulide using liquisolid technique. In this study nimesulide, a poorly water-soluble, non-steroidal anti-inflammatory drug was formulated into liquisolid tablets consisting of similar powder excipients.

MATERIALS

Nimesulide was provided by Dr.Reddy's Laboratories, Hyderabad, India. Coarse granular microcrystalline cellulose, sodium starch glycolate, fine amorphous silica gel, HPMC-E15, soluble starch were gift samples from Aurabindo Pharmaceuticals Hyderabad, India. PEG-400 and propylene glycol were provided by Srichandra chemicals, Hyderabad, India. All other chemicals used were of analytical grade.

METHODS

Solubility Studies

To select the best non-volatile solvent for dissolving or suspending of nimesulide in liquid medication, solubility studies of nimesulide were carried out in distilled water, propylene glycol, PEG-400 and also in 0.1 N HCl and 7.4 pH Phosphate buffer solutions. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48h at 25 ^{0}C under constant vibration. After this period the solutions were filtered through a 0.45µm Millipore filter, diluted and analyzed by UV-spectrophotometer (Analytical Technologies Ltd.) at a wavelength of 395nm.

Application of the Mathematical Model for Designing the Liquisolid Systems

In this study, PEG 400 was used as liquid vehicle; MCC, HPMC-E15, soluble starches were used as the carrier and fine silica gel was used as coating material to improve the flow property due to its size, shape and also due to glidant property. To attain the flowability and compressibility of liquisolid compacts, the ''new formulation mathematical model of liquisolid systems" was employed as follows to calculate the appropriate quantities of excipients required to produce liquisolid systems of acceptable flowability and compressibility. This mathematical model was based on new fundamental powders properties (constants for each powder material with the liquid vehicle) called the flowable liquid retention potential (Φ-value) and compressible liquid retention potential (Ψ-number) of the constituent powders (carrier and coating materials) according to Spireas et al (Spireas., 2002; Spireas et al., 1999). According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used, where

$$R = Q/q \quad \ldots (1)$$

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e.

$$Lf = W/Q \quad \ldots (2)$$

Spireas et al. used the flowable liquid retention potentials (Φ -values) of powder excipients to calculate the required ingredient quantities, Hence, the powder excipients ratios R and liquid load factors Lf of the formulations are related as follows:

$$Lf = \Phi + \Phi\,(1/R) \quad \ldots (3)$$

So in order to calculate the required weights of the excipients used, first, from equation (3), Φ and Φ are constants, therefore, according to the ratio of the carrier/ coat materials (R), Lf was calculated from the linear relationship of Lf versus 1/R. next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both Lf and W, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system, could be calculated from equations .(1) and (2).

Preparation of Liquisolid Compacts and Conventional Tablet

Preparation of drug solution

For the preparation of liquisolid compacts of nimesulide, a non-volatile solvent is chosen for dissolving the drug. From the results of solubility studies and evaluation of flow properties, liquisolid powders containing PEG 400 as the liquid medicament, MCC as carrier and colloidal silica as the coating material is selected for the preparation of liquisolid compacts. Various ratios of carrier to coating materials are selected (Table 1). According to solubility of nimesulide desired quantities of drug and PEG 400 were accurately weighed in a beaker and then stirred with constantly, until a homogenous drug solution was obtained. Selected amounts (W) of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar.

Table. 1: Formulation of Nimesulide Liquisolid Compacts.

Formulation	Nimesulide concentration in PEG400	R	Lf	MCC(mg)	HPMC (mg)	Starch (mg)	Silica (mg)	Total tablet weight (mg)
F1	10%	5	0.312	400	-	-	80.0	635.0
F2	10%	10	0.312	400	-	-	40.0	592.5
F3	10%	15	0.312	400	-	-	26.5	579.0
F4	10%	20	0.312	400	-	-	20.0	572.5
F5	10%	25	0.312	400	-	-	20.0	568.2
F6	10%	5	0.312	-	400	-	80.0	635.0
F7	10%	10	0.312	-	400	-	40.0	592.5
F8	10%	15	0.312	-	400	-	26.5	579.0
F9	10%	20	0.312	-	400	-	20.0	572.5
F10	10%	25	0.312	-	400	-	20.0	568.2
F11	10%	5	0.312	-	-	400	80.0	635.0
F12	10%	10	0.312	-	-	400	40.0	592.5
F 13	10%	15	0.312	-	-	400	26.5	579.0
F14	10%	20	0.312	-	-	400	20.0	572.5
F15	10%	25	0.312	-	-	400	20.0	568.2

Mixing and Compression

The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material was added to the system and blended for 2 min. the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles. In the third stage, the powder was scraped off the mortar surfaces by means of aluminum spatula, then producing the final liquisolid formulation to be compressed. Similar formulations are prepared by using HPMC and starch as carrier materials.

Pre Compression Studies of Prepared Liquisolid Compacts

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped) and compressibility index. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

$$Tan\ \theta = h/r \qquad (4)$$

In which, θ is angle of repose, h is height of the cone and r is radius of the cone base. Angle of repose less than 30^0 shows the free flowing of the material.

The tapping method was used to determine the tapped density, bulk density and percent compressibility index. The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formulas:

$$Carr's\ Index = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100 \qquad (5)$$

In which, ρ_b is bulk density and ρ_{tap} is tapped density.

Drug-Polymer Interaction Studies

To investigate the possible physical and chemical interactions between the drug and excipients was determined by using differential scanning calorimetry. Pure nimesulide and optimized liquisolid system physical mixture was approximately 2-3 mg of samples were sealed in a 40-µl aluminum pans at a constant heating rate of 5 ^{0}C/min test were done temperature versus heat flow. Under nitrogen atmosphere the probes heating range from 5 ^{0}C to 150 ^{0}C.

Post Compression Characterization

The prepared tablets were studied for their physical properties like weight variation, hardness, friability and drug content uniformity. For estimating weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The strength of tablet is expressed by measuring hardness (Kg/cm^2) friability. The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electro lab, Mumbai, India) for 4 min at 25 rpm.

Determination of Drug Content

For estimation of drug content, ten tablets were crushed, and the aliquot of powder equivalent to 100 mg of drug was dissolved in suitable quantity of methanol/7.4pH phosphate buffer solution. Solution was filtered and diluted and drug content determined by UV-Visible spectrophotometer (Analytical Technologies, India) at 395 nm. The drug concentration was calculated from the calibration curve.

In-Vitro Dissolution Studies

The USP paddle method (Electro lab TDT-06T, USP-II) was used for all the in vitro dissolution studies. In this method, phosphate buffer having the pH of 7.4 was used as dissolution media. The rate of stirring was 100±2 rpm. The amount of nimesulide was 100 mg in all formulations. The dosage forms were placed in 900 ml of pH 7.4 phosphate buffer maintained at 37±0.1°C. At appropriate intervals (5, 10, 15, 20, 25, 30, 45 and 60 min), 5ml of the samples were taken and filtered through a 0.45 µm Millipore filter. The dissolution media was then replaced by 5ml of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were then analyzed at 395 nm by UV-Visible spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulations.

Calculation of Dissolution Parameters

Cumulative percent drug release was plotted as a function of time and percent drug release in 5 minutes (Q_5) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 5 minutes per minute. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from optimized formulation and that dissolved from the conventional formulation at 5 minutes.

RESULTS

Solubility Studies

The solubility of nimesulide in distilled water, Propylene glycol, PEG-400, 0.1 N HCl and 7.4 pH phosphate buffer is given in Table 2. The table shows that the nimesulide has highest solubility in PEG-400.

Table. 2: Solubility of Nimesulide in Various Solvents.

Liquid vehicle	Solubility (mg/ml)
Propylene glycol	2.760
Poly ethylene glycol-400	63.5
0.1 N HCl	0.621
7.4 pH buffer	13.89
Distilled water	0.014

Pre Compression Parameters

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), compressibility index and their values were shown in Table 3.The apparent bulk density and tapped bulk density values ranged from 0.291 to 0.332 and 0.354 to 0.412 respectively. The results of angle of repose and compressibility index (%) ranged from 18.22±1.12 to 38.25±1.2 and 16.092 to 22.652 respectively.

Drug-Polymer Interaction Studies

DSC studies were performed to understand the nature of the drug in the formulated tablets. DSC curves obtained for pure nimesulide and optimized formulation were shown in Figure 1. A sharp endothermic peak corresponding to the melting point of nimesulide was found at 147.4°C. An endothermic peak corresponding to the melting point of nimesulide in optimized formulation was observed at 147.4°C.

Post Compression Parameters

The physical properties of nimesulide are given in Table 4. In weight variation test, the pharmacopoeial limit for the tablets of not more than 7.5% of the average weight. The hardness of the tablets was found to be in the range of 4.0±0.25 to 6.0±0.76 kg/cm^2. Another measure of tablets strength is friability. Conventional compressed tablets that loss less than 1% of their weight are generally considered acceptable. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits. The tablets were found to contain 95.8±1.74 99.9±0.70 % of the labeled amount indicating uniformity of drug content.

In-Vitro Dissolution Study

The cumulative mean percent of nimesulide released from liquisolid compacts containing varying amounts of carrier and coating materials (from F1 to F15) was found to vary from 15.22 ± 0.58 to 80.2 ± 0.25 in first 5 min (Figure 2). This indicates the fast release of drug is observed from above formulations. The optimized formulations F2, F8 and F13 showed the 80.2 ± 0.25, 52.8 ±0.68 and 65.91 ± 0.25 drug release in the first 5 min where as the CT tablets (control) showed 35.98±0.64 in 5 min (Figure 3). The percent drug release in 5 min (Q_5) and initial dissolution rate (IDR) for optimized formulations were 80.2±0.25%, 16.04%/min 52.8±0.68,10.56%/min and 65.91±0.25%, 12.78%/min respectively. These were very much higher compared to control tablets (CT) (35.6±0.34%, 7.12%/min). The improvement in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR). The RDR was found to be 2.33, 2.38, and 2.30 for F2, F8 and F13 respectively. The DE was found to be 84.64 for F2, 58.1 for F8 and 72.3 for F13 and it is increased much, when compared with the conventional tablet (CT) (Table 5).

Table. 3: Characterization of Powder Mixtures.

Formulation	Angle of repose (^{0})*	Bulk density (g/cc)	Tapped bulk density (g/cc)	Carr's index (%)
F1	18.12±1.6	0.292	0.357	18.2
F2	22.31±1.2	0.291	0.354	17.7
F3	28.11±1.1	0.323	0.398	18
F4	33.73±1.0	0.315	0.402	21
F5	38.56±1.6	0.315	0.402	21
F6	38.21±1.9	0.302	0.378	20
F7	37.54±1.3	0.323	0.403	19
F8	33.22±1.1	0.302	0.378	20
F9	35.34±1.2	0.315	0.402	21
F10	35.87±1.6	0.325	0.405	19.7
F11	26.37±1.0	0.323	0.398	18
F12	28.54±1.8	0.289	0.351	17.6
F 13	30.12±1.1	0.302	0.378	20
F14	32.22±1.5	0.320	0.412	22
F15	36.25±1.2	0.320	0.412	22

* All values represent mean ± standard deviation, n=3

Table. 4: Physical Properties of Nimesulide Liquisolid Compacts.

Formulation	Weight variation* (mg)	Hardness**(Kg/cm^2)	Friability (%)	Drug content uniformity*** (%)
F1	160.5 ± 0.15	4.0±0.25	0.15	95.8±1.74
F2	155.23± 1.05	5.3±0.28	0.22	97.2±0.28
F3	161.1 ± 1.28	5.0±0.61	0.13	98.2±0.70
F4	161.8 ± 0.12	5.2±0.35	0.22	96.6±0.28
F5	160.2 ± 0.83	5.1±0.42	0.18	98.0±0.76
F6	159.22 ± 1.44	5.0±0.25	0.24	95.9±0.61
F7	160.15 ± 1.83	5.4±0.64	0.33	99.2±1.76
F8	159.12 ± 1.44	4.6±0.70	0.24	95.9±0.61
F9	161.8 ± 1.12	4.4±0.58	0.21	96.6±0.28
F10	160.3 ± 0.14	4.8±0.46	0.14	95.8±1.74
F11	160.45 ± 0.33	5.0±0.86	0.25	99.2±0.35
F12	158.23± 1.15	5.2±0.46	0.32	97.2±0.28
F 13	162.14 ± 0.74	6.0±0.38	0.26	99.9±0.70
F14	160.72 ± 0.283	5.6±0.52	0.18	98.0±0.76
F15	161.1 ± 1.28	6.0±0.76	0.23	98.2±0.70

* All values represent mean ± standard deviation, n=20
** All values represent mean ± standard deviation, n=6
*** All values represent mean ± standard deviation, n=3

Table. 5: Dissolution Parameters of Optimized Liquisolid Compacts and Conventional Tablets (CT) of Nimesulide.

Formulation	(Q_5)*	IDR (%/min)	DE	RDR
Optimized (F2)	80.2	16.04	84.64	7.63±0.02
Optimized (F8)	52.8	10.56	58.1	5.02±0.04
Optimized (F13)	63.9	12.78	72.31	6.08±0.12
Conventional Tablet (CT)	35.6	7.12	20.5	

Q_5-percent drug release in 5 minutes, IDR-initial dissolution rate, DE-dissolution efficiency and RDR- relative dissolution rate.
* All values represent mean ± standard deviation, n=3

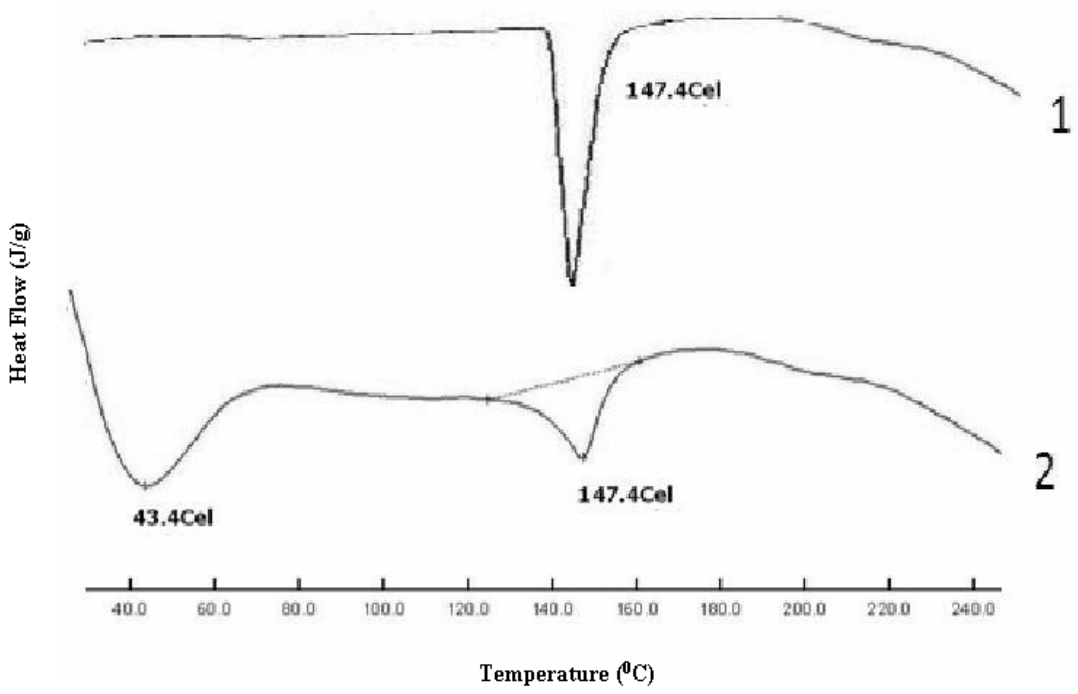

Fig. 1: DSC thermograms of 1) Nimesulide 2) Optimized formulation (F2).

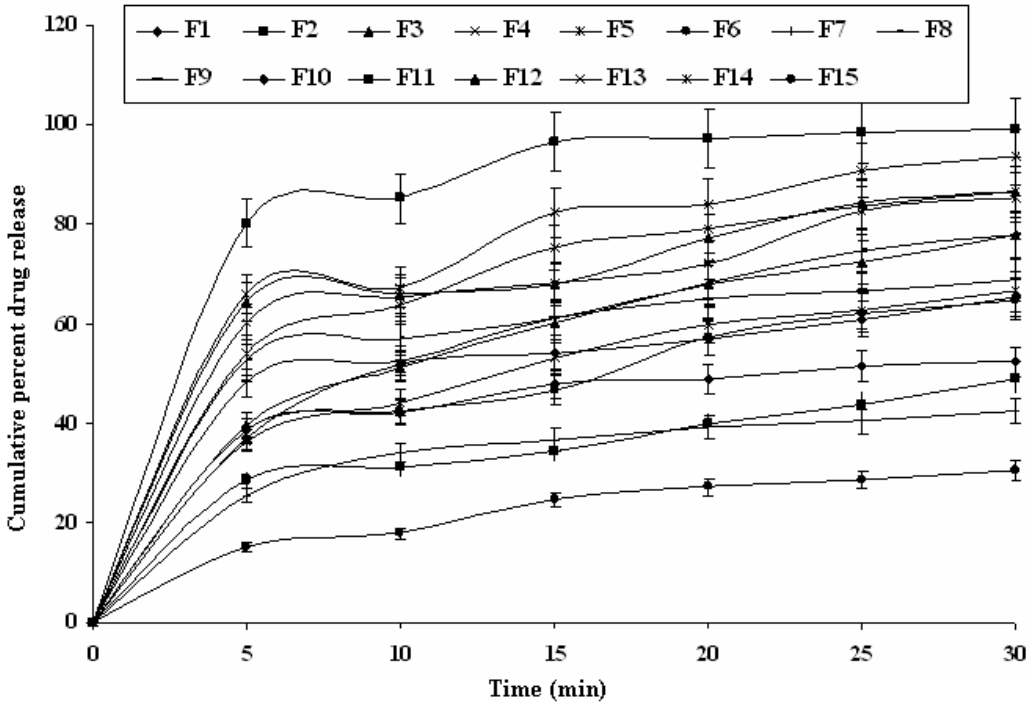

Fig. 2: Dissolution profile of nimesulide liquisolid compacts.

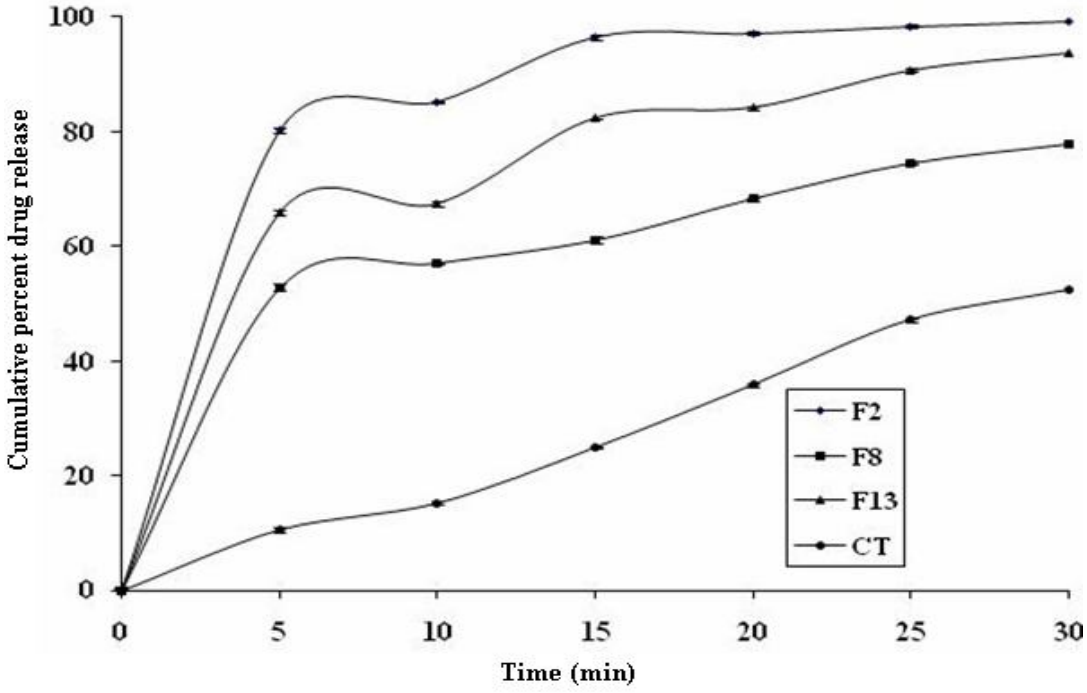

Fig. 3: Comparision of dissolution profiles of optimized liquisolid formulations and conventional nimesulide tablets (CT)

DISCUSSION

In the present study nimesulide liquisolid tablets were prepared by using polyethylene glycol-400 as a non-volatile liquid vehicle, microcrystalline cellulose, hydroxypropyl methylcellulose-E15, starch were used as carrier materials and silica gel as coating material in different ratios and they were characterized for different physical parameters and drug release studies to find the optimized formulation that shows fast dissolution rate.

From the solubility studies the results revealed that, the solubility of drug was highest in PEG-400 then followed by 7.4 pH phosphate buffer, Propylene glycol, 0.1 N HCl and poor in distilled water, which indicates the PEG-400 was better liquid vehicle. The results of angle of repose (<40) and Carr's index (<22) indicates fair to passable flow properties of the powder mixture (Staniforth et al., 2007). DSC study showed that there is no interaction between the drug and excipients. The thermograms of the optimized formulation did not show any significant shift in the endothermic peak, indicating that there was no physical change in drug in the liquisolid compacts.

The prepared tablets were studied for their physical properties like weight variation, hardness, friability and drug content uniformity they were complied with pharmacopoeial limits. The average percentage deviation of all tablet formulations was found to be within the above mentioned limit and hence all formulations passed the uniformity of weight as per official requirements (Indian Pharmacopoeia., 1996). From the physical characterization, all tablet formulations were uniform in hardness, friability and drug content uniformity. From the in vitro drug release studies, formulations F2, F8 and F13 were considered better among other formulations to produce fast release of the nimesulide when compared to other formulations. From the calculations of DE and RDR, F2 formulation showed better improvement in dissolution and it is considered as optimized formulation. Overall increase in the dissolution performance of the optimized formulation was described in terms of dissolution parameters (IDR, DE, RDR) and compared with CT (control). The improvement may be due to increased wetting properties, solubility and increased surface area of drug particles in case of liquisolid compacts. In conclusion, development of the liquisolid compacts can be a promising alternative technique for water-insoluble drugs to achieve the fast dissolution rate.

CONCLUSION

An attempt was made to develop the liquisolid compacts of nimesulide to achieve fast dissolving effect and to enhance the bioavailability. From the in-vitro drug release studies the optimized formulation F2 showed fast drug release when compared to the conventional tablet. The dissolution efficiency was found to increase by 4 times with optimized liquisolid formulations compared to conventional tablet. DSC study showed that there is no interaction between the drug and excipients. In conclusion, the liquisolid compacts technique can be a promising alternative for the formulation of water-insoluble drugs, such as nimesulide into rapid release tablets. The higher dissolution rates displayed by liquisolid compacts may also imply enhanced oral bioavailability due to the increased wetting properties and surface of drug available for dissolution.

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