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Enhancement of Dissolution Rate of Nimesulide by Liquisolid Compaction Technique

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Abstract: Nimesulide is a poorly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. The poor dissolution rate of water-insoluble drugs is a major problem to convert them in to a suitable dosage form which is having optimum therapeutic effects. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compacts is a promising technique towards such a novel aim. Several liquisolid tablets formulations are prepared by using PEG-400 as a non-volatile liquid vehicle, microcrystalline cellulose, Hydroxypropylmethylcellulose-E15, starch were used as carrier materials and nm-sized silica gel was used as coating materials. The empirical method as introduced by Spireas and Bolton (1999) was applied strictly to calculate the amounts of coating and carrier materials required to prepare nimesulide liquisolid tablets. Quality control tests, i.e. uniformity of tablet weight, uniformity of drug content, tablet hardness, friability test and dissolution tests were performed to evaluate each batch of prepared tablets. In vitro drug dissolution profiles of the liquisolid formulations were studied and compared with conventional formulation in simulated intestinal fluid (pH 7.4). Fourier transform infrared were used to investigate physicochemical interaction between nimesulide and the other excipients. It was found that liquisolid tablets formulated with microcrystalline cellulose produced high dissolution profile with acceptable tablet properties. The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally prepared directly compressible tablets. This was due to an increase in wetting properties and surface of drug available for dissolution.

Keywords: Liquisolid compacts, Nimesulide, Dissolution rate, Liquid load factor.

INTRODUCTION:

Liquisolid technique:

It is well known that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract .The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site, i.e. the dissolution rate is often the rate-determining step in drug absorption[1]. The poor dissolution rate of water-insoluble drugs is a major problem to convert them in to a suitable dosage form which is having optimum therapeutic effects. There are several techniques to enhance the dissolution of poorly soluble drugs including;

1)Use of water-soluble salts and polymorphic forms,
2)Reducing particle size to increase the surface area,
3)Formation of water-soluble molecular complexes,
4) Solid dispersion, co-precipitation, lyophilization, microencapsulation,
5)And the inclusion of drug solutions or liquid drugs into soft gelatin capsules

6) Solubilisation in a surfactant system
7) Manipulation of solid state of drug substance to improve drug dissolution, i.e. by decreasing crystalanity of drug substance through formation of solid solutions[2], are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs .The most common method is to increase surface area of the drug by micronisation . But, in practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tabletted.

According to spires et al., Liquisolid system refers to formulations formed by conversion of drug suspensions or solution in non-volatile solvents into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials. They are prepared by simple blending with selected powder excipients referred to as the carriers and the 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[3].

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, analgesic and antipyretic. It inhibits cyclo-oxygenase (COX-2) that may contribute to its anti-inflammatory effects. It inhibits neutrophil activation and exhibits antioxidant properties[4].

MATERIALS AND METHODS

Nimesulide was provided by Dr.Reddy's Laboratories, Hyderabad, India. Coarse granular microcrystalline cellulose, sodium starch glycolate, nm-sized amorphous silica gel, HPMC-E15, Soluble starch were gift samples from Aurabindo Pharmaceuticals Hyderabad, India. PEG400 and Propylene glycol were provided by Srichandra chemicals, Hyderabad, India. All other chemicals used were of analytical grade.

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[5]. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48h at 25°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 against blank sample (blank sample contained the same concentration of specific solvent used without drug)[6].

Application of the mathematical model for designing the liquisolid systems:

In this study, PEG 400 was used as liquid vehicle; MCC, HPMC-E15, Soluble starch were used as the carrier and nm- sized silica gel was used as coating materials. 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[7]. 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.[1,3,7,8].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,

$$R = Q / q \qquad \ldots\ldots.(1)$$

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.:

$$Lf = W / Q \qquad \ldots\ldots.(2)$$

Spireas et al.[9] 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:

$Lf = \Phi + \Phi (1/ R)$ …….(3)

So in order to calculate the required weights of the excipients used, first, from Eq. (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_o) and coating (q_o) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system, could be calculated from Eqs .(1) and (2)[10].

Preparation of liquisolid Compacts and conventional tablets:

Several nimesulide liquisolid compacts, denoted as LS-1 to LS-15 (Table 1) were prepared as follows. Nimesulide was dispersed in PEG 400 (PEG 400 was used as liquid vehicle to prepare the liquid medication)[11]. Then a binary mixture of carrier coating materials (MCC: Silica gel) was added to the obtained liquid medication under continuous mixing in a mortar. In the same way, liquisolid formulations are prepared by using HPMC-E15 and Soluble starch as carrier materials. Depending upon the type of carrier in formulation, different liquid loading factors were calculated. Then nimesulide conventional tablets were prepared by mixing the drug with MCC-Silica (with different ratios of MCC to silica), then the mixture was mixed with sodium starch glycolate (5% w/w of the formulation) for 10 min[12]. The mixture was compressed on a manual tabletting machine. This formulation was denoted as direct compression tablet (DCT).Similar DCT tablets are prepared by using HPMC-E15and Soluble starch as carrier materials[13].

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[14]. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

$Tan\ \theta = h/r$ …….(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:

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

In which, ρ_b is bulk density and ρ_{tap} is tapped density[15].

Fourier transform infrared (FT-IR) spectroscopy:

Infrared spectra of the samples (Nimesulide, MCC,HPMC ,Soluble starch,PEG400,silica gel powder, conventional and liquisolid formulations) were obtained ,using Perkin Elmer FT-IR system Spectrum BX series (Beaconsfield, Buckinghamshire,UK), in the frequency range of 4000–550 cm^{-1} at4 cm^{-1} resolution. The technique used very small amount of each sample which directly loaded into the system. Spectrum BX series software version 2.19 was used to determine peak positions[16].

Post compression studies:

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)[17]. 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 (Electrolab, Mumbai, India) for 4 min at 25 rpm[18].

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[19].

Dissolution studies:

The USP paddle method (Electrolab 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[20]. 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, 35, 40, 45, 50, 55, 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 analysed at 395 nm by UV-Visible spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulations[21].

Calculation of dissolution parameter:

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[22].

Statistical analysis:

Levene's test was applied to test the homogeneity of variances. One-way ANOVA and independent-samples T-test were applied if the variances in the groups are equal. If the variances are significantly different, Mann–Whitney test was applied. Results are quoted as statistically significant when $P < 0.05$[23].

Table 1: Formulation of Nimesulide Liquisolid Compacts:

Formulation	Liquid vehicle	Carrier (Q)	Coating material (q)
LS-1	PEG-400	MCC	Silica gel
LS-2	PEG-400	MCC	Silica gel
LS-3	PEG-400	MCC	Silica gel
LS-4	PEG-400	MCC	Silica gel
LS-5	PEG-400	MCC	Silica gel
DCT-1		**MCC**	**Silica gel**
LS-7	PEG-400	HPMC-E15	Silica gel
LS-8	PEG-400	HPMC-E15	Silica gel
LS-9	PEG-400	HPMC-E15	Silica gel
LS-10	PEG-400	HPMC-E15	Silica gel
DCT-2		**HPMC-E15**	**Silica gel**
LS-11	PEG-400	Starch	Silica gel
LS-12	PEG-400	Starch	Silica gel
LS-13	PEG-400	Starch	Silica gel
LS-14	PEG-400	Starch	Silica gel
LS-15	PEG-400	Starch	Silica gel
DCT-3		**Starch**	**Silica gel**

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

RESULTS AND DISCUSSION:

Solubility:

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 then followed by 7.4 pH phosphate buffer, Propyleneglycol, 0.1 N HCl and finally in distilled water.

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. The results of angle of repose (<40) and compressibility index (<22) indicate fair to passable flow properties of the powder mixture [9].

Post-compression Parameters:

The physical properties of nimesulide are given in Table 3 and 4. In weight variation test, the pharmacopoeial limit for the tablets of not more than 7.5% of the average weight. 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 (India Pharmacopoeia, 1996). The hardness of the tablets was found to be in the range of 3.1±0.42 to 3.6±0.52 kg/cm^2. Another measure of tablets strength is friability[10]. 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[11].

In-vitro Dissolution Study:

The cumulative mean percent of nimesulide released from liquisolid compacts containing varying amounts of carrier and coating materials (from LS-1 to LS-15) was found to vary from 15.22 ± 0.58 to 80.2 ± 0.25 in first 5 min (Figure 1,Figure 2,Figure 3). This indicates the fast release of drug is observed from above formulations. The optimized formulations LS-2 , LS-8 and LS-13 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, 23.05±0.23 and 28.28±0.24 in 5 min (Figure 1, Figure 2,Figure3). Thus the formulation LS-2 ,LS-8 and LS-13 were considered better among other formulations to produce fast release of the nimesulide .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, 23.5±0.05%, 4.7%/min, 28.2±0.08%, 5.64%/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, 2.30 for LS-2, LS-8, LS-13 respectively. The DE was found to be 84.64 for LS-2 , 58.1 for LS-8 and 72.3 for LS-13 and it is increased much, when compared with the control CT (Table 5). Overall increase in the dissolution performance of the optimized formulations described in terms of dissolution parameters (IDR, DE, RDR) compared to control DCT could be due to increased wetting properties, solubility and increased surface area of drug particles[12].

Fourier transform infrared (FT-IR) spectroscopy:

FTIR spectra of nimusulide figures revealed the presence of peaks at 3369 and 3288 cm^{-1}. The IR spectra of physical mixture matched with those of drug and sodium starch glycolate when superimposed. No specific conclusions could be drawn from the IR spectra of the liquisold. The spectra predominantly revealed many peaks of sodium starch glycolate. Other peaks showed overlapping with spectra of sodium starch glycolate. Further characterization was done using XRD and DTA to determine the interaction. XRD of liquisolid prepared by using propylene glycol and polyethylene glycol 400 revealed a reduction in peak intensity when compared with XRD of plain drug and physical mixture. The characteristic peaks identified in the drug XRD or the physical mixture was not detected. Decrease in peak intensities was probably due to dilution and may be due to some change in crystal habit or conversion to an amorphous form. No new peak was detected, hence the possibility of any conversion to polymorphic form was ruled out. Liquisolid prepared using propylene glycol as solvent showed reduced crystalline properties when compared to liquisold of polyethylene glycol 400. This could account for increased dissolution efficiency of the liquisolid prepared with polyethylene glycol 400 when compared to liquisolid prepared using propylene glycol as solvent. DSC of the pure drug showed a sharp peak at 217.28^{o}C.

Table 3: Characterization of powder mixtures:

Formulation	Angle of repose*	Bulk density	Tapped bulk density	% Carr's index
LS-1	18.12±1.6	0.292	0.357	18.2
LS-2	22.31±1.2	0.291	0.354	17.7
LS-3	28.11±1.1	0.323	0.398	18
LS-4	33.73±1.0	0.315	0.402	21
LS-5	38.56±1.6	0.315	0.402	21
LS-6	38.21±1.9	0.302	0.378	20
LS-7	37.54±1.3	0.323	0.403	19
LS-8	33.22±1.1	0.302	0.378	20
LS-9	35.34±1.2	0.315	0.402	21
LS-10	35.87±1.6	0.325	0.405	19.7
LS-11	26.37±1.0	0.323	0.398	18
LS-12	28.54±1.8	0.289	0.351	17.6
LS-13	30.12±1.1	0.302	0.378	20
LS-14	32.22±1.5	0.320	0.412	22
LS-15	36.25±1.2	0.320	0.412	22

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

Table 4: Physical properties of nimesulide liquisolid compacts:

Formulation	Weight variation* (mg)	Hardness** (Kg/cm^2)	Friability (%)	Drug content uniformity***(%)
LS-1	160.5 ± 0.15	4.0±0.25	0.15	95.8±1.74
LS-2	155.23± 1.05	3.8±0.06	0.22	97.2±0.28
LS-3	161.1 ± 1.28	3.3±0.24	0.13	98.2±0.70
LS-4	161.8 ± 0.12	3.1±0.42	0.22	96.6±0.28
LS-5	160.2 ± 0.83	3.5±0.62	0.18	98.0±0.76
LS-6	159.22 ± 1.44	3.2±0.35	0.24	95.9±0.61
LS-7	160.15 ± 1.83	3.5±0.61	0.33	99.2±1.76
LS-8	159.12 ± 1.44	3.2±0.35	0.24	95.9±0.61
LS-9	161.8 ± 1.12	3.1±0.42	0.21	96.6±0.28
LS-10	160.3 ± 0.14	3.0±0.25	0.14	95.8±1.74
LS-11	160.45 ± 0.33	3.4±0.64	0.25	99.2±0.35
LS-12	158.23± 1.15	3.5±0.86	0.32	97.2±0.28
LS-13	162.14 ± 0.74	3.6±0.52	0.26	99.9±0.70
LS-14	160.72 ± 0.283	3.5±0.62	0.18	98.0±0.76
LS-15	161.1 ± 1.28	3.3±0.28	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

Figure 1: Dissolution profile of nimesulide liquisolid compacts containing MCC as carrier:

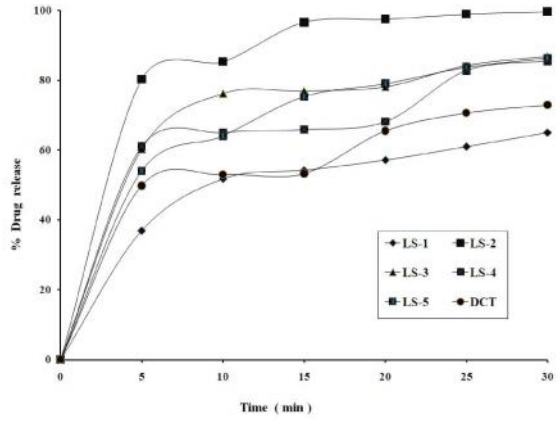


Figure 2: Dissolution profile of nimesulide liquisolid compacts containing HPMC-E15 as carrier:

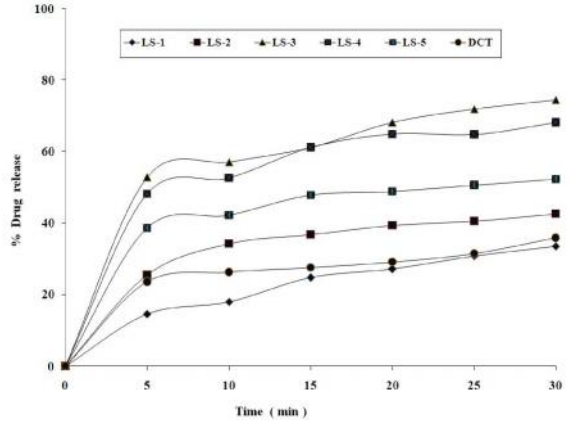


Figure 3: Dissolution profile of nimesulide liquisolid compacts containing Starch as carrier:

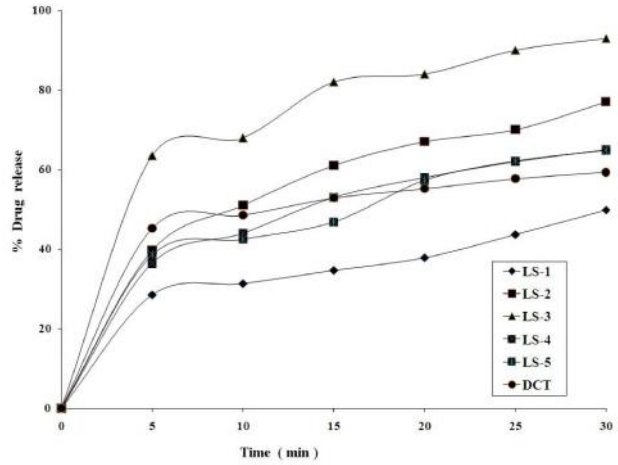


Table 5: Dissolution Parameters of optimized liquisolid compacts, conventional tablet (CT)

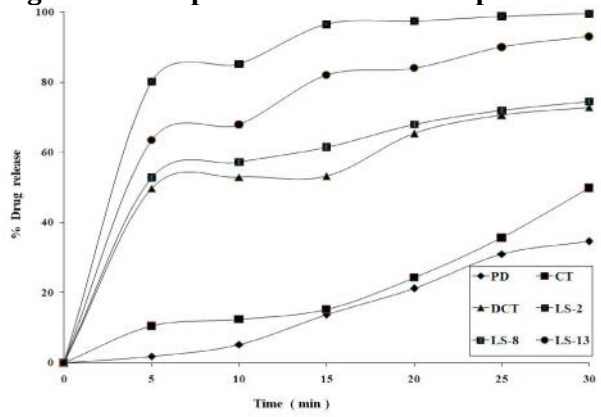
and directly compressible tablet (DCT) of nimesulide:

Formulation	(Q_5)*	IDR (%/min)	DE	RDR
Optimized (LS-2)	80.2	16.04	84.64	7.63±0.02
Optimized (LS-8)	52.8	10.56	58.1	5.02±0.04
Optimized (LS-13)	63.9	12.78	72.31	6.08±0.12
Control (CT)	10.5	2.1	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

Figure 4: Comparision of dissolution profiles of PD, CT, DCT and optimized liquisolid formulations:



PD = Plain nimesulide drug
CT = Conventional tablet
DCT= Directly compressible tablet having 5% w/w SSG.

CONCLUSION:

In conclusion, this study showed that liquisolid technique could be a promising strategy in improving dissolution of poorly water soluble drugs and formulating them in to immediate release solid dosage forms. The optimized formulations LS-2 , LS-8 and LS-13 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 DCT tablets (control) showed 35.98±0.64, 23.05±0.23 and 28.28±0.24 in 5 min (Figure 1, Figure 2,Figure3). Thus the formulation LS-2 ,LS-8 and LS-13 were considered better among other formulations to produce fast release of the nimesulide .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 (DCT) (35.6±0.34%, 7.12%/min, 23.5±0.05%, 4.7%/min, 28.2±0.08%, and 5.64%/min). The improvement in the dissolution characteristics of a Liquisolid technique changes the properties of nimesulide particles by simply dispersed the drug particles in a non volatile liquid vehicle, which in turn increase the wetting properties and surface area of drug particles, and hence improve the dissolution profiles and might be oral bioavailability of the drug.

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