Research Article

Enhancement of Dissolution Rate of Poorly Water Soluble Diclofenac Sodium By Liquisolid Technique

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ABSTRACT

The technique of liquisolid compacts is a promising method towards enhancing the dissolution of poorly soluble drugs. In the present study, the potential of liquisolid systems to improve the dissolution properties of water-insoluble agents was investigated using diclofenac sodium as the model drug. Several formulations of liquisolid compacts having different drug concentration (40% to 60% w/w) and with varying ratios of carrier to coat (i.e., different R values, ranging from 5 to 15) were prepared. Avicel and Aerosil were used as carrier and coat material, respectively, and propylene glycol was used as a nonvolatile liquid to prepare liquid medication. The effect of added liquid on the flowability and compressibility of the final admixture was studied and the effect of drug concentration on the dissolution pattern of diclofenac sodium was investigated. Liquisolid compacts demonstrated significantly higher drug release rates than the the pure drug.

Keywords: Liquisolid compacts; Liquid medication; mathematical model; liquid load factor (LF).

INTRODUCTION

It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract[1,2]. The poor dissolution rates of water-insoluble drugs are still a substantial problem confronting the pharmaceutical industry[3,4]. 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, that is, the dissolution rate is often the rate-determining step in drug absorption[1].

Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success. The use of water-soluble salts and polymorphic forms, the formation of water-soluble molecular complexes, drug micronization, solid dispersion, co-precipitation, lyophilisation, microencapsulation, and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the major formulation tools that have been shown to enhance the dissolution characteristics of water-insoluble drugs[5]. Among them, the technique of liquisolid compacts is one of the most promising[2–4].

Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications.The term *liquid medication* implies oily, liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems termed the *liquid vehicles.* Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free-flowing, and readily compressible powder by a simple blending with selected powder excipients referred to as the *carrier* and *coating materials*[7–9]. Various grades of cellulose, starch, lactose, and so on, may be used as the carriers, whereas very fine-particle-size silica powders may be used as the coating (or covering) materials[10, 11]. In liquisolid compacts, even though the drug is in a tabletted or encapsulated dosage form, it is held in a solubilized liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution. Another advantage of liquisolid systems is that their production cost is lower than that of soft gelatin capsules because the production of liquisolid systems is similar to that of conventional tablets[7–9].

Diclofenac sodium is a non-steroidal drug having a potent anti-inflammatory, analgesic, and antipyretic effect. It is an inhibitor of prostaglandin synthetase and is also used for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, and following some surgical procedures. It has an unpleasant taste and causes gastric irritation. Diclofenac sodium is mainly

absorbed from the gastrointestinal tract[12–14]. It is sparingly soluble in water[12]. Based on the Biopharmaceutics Classification System (BCS), it can be classified as a Class II drug. Class II drugs are defined as those with high permeability but whose solubility in aqueous media is not sufficient for the whole dose to be dissolved in the gastrointestinal tract. For these substances dissolution is therefore the rate-limiting step to absorption. The choice of medium for in vitro dissolution tests is therefore expected to play a very important role in the dissolution of Class II drugs[15].

The aim of the present study was to improve the dissolution rate of diclofenac sodium using liquisolid techniques. Avicel PH102 and Aerosil 200 were employed as a carrier and coating material, respectively. Sodium starch glycolate was used as a super disintegrant. Propylene glycol (PG) was used as a liquid vehicle. The dissolution profile of liquisolid tablets was compared with that of pure drug.

Materials and Methods

Materials

The following materials were used as received: diclofenac sodium and Avicel PH 102 were obtained as gift samples from Cipla Ltd. (alkem labs, mumbai); Aerosil 200, PG, and sodium starch glycolate (SSG) were procured from Rajesh Chemicals (Mumbai, India). All other reagents and solvents used were of analytical grade.

Methods

Application of the Mathematical Model for Designing the Liquisolid Systems

In the following study several factors were varied including the ratios of drug, PG (ranging from 40% to 50% w/w), and the carrier coat ratios (i.e., different R-values, ranging from 5 to 15).

In order to address the flowability and compressibility of liquisolid compacts simultaneously, 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 (16, 17). 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) as previously discussed by Spireas *et al.* (7–9).

According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flowing and compression properties. Depending on the powder excipient ratio (R) of the powder substrate, which is the fraction of the weights of carrier (Q) and coating (q) materials present in the formulation, there is a characteristic maximum liquid load on the coating material.

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 (L_f), 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[16-18].

Hence, the powder excipients ratios R and liquid load factors L_f of the formulations are related as follows:

So, in order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ-values) of powder excipients were utilized (16, 17). In PG, the Φ value of Avicel PH 102 was found to be 0.16, while for Aerosil 200 the Φ-value used was equal to that of Cab-O-Sil M5, as they both possessed the same specific surface area and density and, according to Spireas *et al.* (17, 18), the Φ-value of a powder material is a function of its specific surface. Thus, Aerosil 200 and Cab-O-Sil M5 are expected to have similar adsorptive power (7–9), and therefore the Φ-value used for Aerosil 200 in PG was 3.31.

Using the new formulation mathematical model, the straight line equation for Avicel PH 102 and Aerosil 200 in PG will be for each R-value used, the corresponding L_f-value can be calculated. As the optimum liquid load factor L_f of a given excipients ratio is established for each formula and W is calculated according to diclofenac sodium concentration in PG, the appropriate quantities of Avicel PH 102 (Q) and Aerosil 200 (q) required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system were calculated .

Preparation of Liquisolid Compacts

The diclofenac sodium was dissolved in PG. The solution was then sonicated for 15 min, until a homogenous drug solution was obtained. Next, the calculated weights (W) of the resulting liquid medications were incorporated into the calculated quantities of the carrier material (Avicel PH 102) (Q) and

were mixed thoroughly. The resulting wet mixture was then blended with the calculated amount of the coating material (Aerosil 200) (q) using a standard mixing process to form simple admixture. Finally 5% w/w of SSG was mixed with it for 10 min. The prepared liquisolid powder systems were manually compressed into cylindrical tablets of desired weight of 50 mg strength each using a single-punch tablet machine (Cadmach, Ahemedabad, India). Round, flat-face punches and die units possessing 12-mm diameter were used. Sufficient compression load was applied in order to produce tablets with optimum hardness.

Table 1: Composition of different Diclofenac sodium liquisolid formulation prepared using PG as a liquidvehicle according to mathematical model

FORMULA	DRUG CONC. IN PG	R=Q/q	Lf=W/Q	AVICEL (Q=W/ Lf) mg	AEROSIL (q=Q/R) mg	SSG 5%Mg	UNIT DOSE WEIGHT mg
F1	40%	5	0.822	152.10	30.42	15.20	323
F2		10	0.491	254.28	25.66	21.35	427
F3		15	0.381	328.08	21.87	25.00	500
F4	50%	5	0.822	122.00	24.40	13.00	260
F5		10	0.491	203.70	20.37	17.00	341
F6		15	0.381	262.47	17.49	20.00	400
F7	60%	5	0.822	101.37	20.27	10.24	216
F8		10	0.491	169.97	16.97	13.50	284
F9		15	0.381	218.71	14.18	15.81	332

Spectrophotometeric Analysis

The spectrophotometeric analysis of diclofenac sodium was performed 0.1 N HCl at 276 nm using a UV-visible spectrophotometer (Shimadzu-1700, Kyoto, Japan). A standard curve was constructed by serially diluting an aqueous stock solution of the drug to obtain concentrations in the range of 2–20 µg/mL [21] using 0.1 N HCl the as a diluent.

Solubility Studies

Solubility studies of diclofenac sodium were carried out in five different nonvolatile solvents: PG, polyethylene glycol 400, polyethylene glycol 200, Tween 80, and glycerin. Saturated solutions were prepared by adding excess quantities of drug to the vehicles. The mixtures were sonicated for 24 h and then centrifugated. After centrifugation, filtered supernatant solutions were further diluted with methanol and analyzed spectrophotometrically at λmax of 276 nm for their drug content[22].

Preformulation Studies

Determination of angle of repose, Carr's index, and Hausner's ratio were used to characterize flow properties of the liquisolid powder systems. The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce dose variations[23,24].

Angle of Repose

Angle of repose has been used as an indirect method of quantifying powder flowability. Angle of repose for the blend of each formulation was determined by the fixed funnel method. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip at 10 cm height (H) above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of funnel. The mean diameter (2R) at the base of the powder cone was determined and, with H, the tangent of the angle of repose was given by where θ is the angle of repose.

Carr's Index

The flow properties were assessed through measuring the compressibility index.

An amount of each powder of 20 g was accurately weighed and placed in a 50-mL volumetric cylinder without compaction, and the volume occupied was measured and the initial bulk density V_o was calculated. Then the cylinder was tapped by raising it to a height of 12–14 mm and then allowing it to fall under its

own weight. This was repeated until no change in volume occurred. Then the final tapped density V_f was calculated. The Carr's index was calculated according to the equation:

IR Spectroscopy

An infrared (IR) study was carried out to check compatibility between drug and excipients. IR spectra of diclofenac sodium, Avicel, Aerosil, and final liquisolid formulation were determined by a Fourier transform infrared (FTIR) spectrophotometer using the KBr dispersion method. The baseline correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run.

Differential Scanning Calorimetry (DSC)

DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug (diclofenac sodium) and the liquisolid compacts prepared. About 5 mg of the sample were sealed in the aluminum pans and heated at the rate of 10 °C/min, covering a temperature range of 40 °C to 300 °C, under a nitrogen atmosphere with a flow rate of 100mL/min.

Evaluation of Diclofenac Sodium Liquisolid Compacts

The prepared liquisolid compacts were evaluated for the following parameters:

Friability[25]

The friability of the compacts was measured using a dual-chamber drum friability tester (Roche Friabilator, Erweka TA20, Heusenstamm, Germany) set at a rotation speed of 25 rpm. The tablet samples corresponding to 6.5 g were weighed accurately and placed in the drum. The drum was rotated for 4 min (100 rotations) and the tablets were then removed. Any loose dust from the tablets was removed and again weighed accurately and the percentage friability was calculated from the weight of the tablets before and after the test according to the equation given below.

Hardness[26]

Tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. The hardness of the liquisolid compacts prepared was evaluated using a Monsanto hardness tester (model: Mht-20).

The tablet to be tested is placed between the spindle and the anvil. The desired pressure needed to hold the tablet in position is applied by moving the screw knob in a clockwise direction. The scale is moved so that the indicator is fixed at zero. The pressure is then applied until the tablet breaks. The reading is noted, which indicates the pressure that is needed to break the tablet. The mean hardness of each formula was determined and expressed in kilograms per square centimeter (kg/cm^2).

Drug Content Uniformity[27]

The diclofenac sodium content in different liquisolid tablet formulations was determined by accurately weighing 20 tablets of each formula individually. Each tablet was then crushed and a quantity of powder equivalent to 50 mg of diclofenac sodium was dissolved in 200 mL methanol. 0.5 mL of this solution was diluted to 100 mL with methanol and measured spectrophotometrically at λmax of 276nm.

In Vitro Drug Release

The USP23 paddle apparatus 2 (Electrolab TDT-06P, Mumbai, India) was used for all the in vitro dissolution studies. Nine hundred milliliters of 0.1 N HCl was used as the dissolution media, at 50 rpm and 37 ± 0.5 °C. Appropriate aliquots were withdrawn at suitable time intervals (5, 10, 15, 20, 25, 30, 45, 60 min) and filtered through Whatman filter paper No. 41 and diluted to 10 mL with 0.1 N HCL Sink conditions were maintained throughout the study. The samples were then analyzed at λmax of 276 nm by a UV/visible spectrophotometer. The study was carried out in triplicate.

Stastical Analysis

For statistical evaluation, one-way analysis of variance (one-way ANOVA) with Tukey's multiple comparison test was used to assess the significance of the difference between dissolution rates obtained for the tested formulations and the pure drug.

Results and Discussion

Solubility Studies

The solubility of diclofenac sodium in PG, polyethylene glycol 400, polyethylene glycol 200, Tween 80, and glycerin. The table shows that diclofenac sodium has the lowest solubility in glycerin. Solubility was found to be increased when semnts such as polyethylene glycol 200 and 400 were used. The solubility of diclofenac sodium was considerably increased in the presence of PG. The solubility of the drug strongly depends on the solvent used and thus on the intermolecular forces between diclofenac sodium and the solvent

(28). Therefore, PG was selected as a nonvolatile solvent.

TABLE 2: Solubility Diclofenac sodium in various solvents

S. No.	Solvent	Solubility
1	PG	27.71±0.66 mg/ml
2	PEG 400	16.88 ±0.57 mg/ml
3	PEG 200	8.72±0.81 mg/ml
4	Tween 80	7.06±0.18 mg/ml
5	Glycerine	4.99±0.55 mg/ml

Preformulation Studies

The effect of liquid load factor (L_f), which is a ratio of the mass of liquid (PG) added to the mass of Avice 102, on lowability and compressibility of the final admixture of the powde. Increasing the L_f value in the range of 0.822 to 0.381, that is, increasing the volume of liquid vehicle, resulted in a decrease in the flowability of the final admixtures. This is evident from the increase in the angle of repose. With increase in L_f-value, the flow property was found to be reduced. It also resulted in a decrease in the compressibility of final admixture.

Flowability Parameters of Diclofenac Sodium Liquisolid Powder Systems

This is evident from the increase in the angle of repose. With increase in L_f value flow property was found to be reduced. It also resulted in a decrease in the compressibility of final admixture.

Formulae LS1 to DCT were proven to be angle of repose r passable, Carr's index is poor and Hausener's ratio is passable.

IR Interpretation

The IR spectra of pure diclofenac sodium and liquisolid compacts are shown in respectively. The IR spectra of diclofenac sodium exhibited distinctive peaks at 3390 cm^{-1} due to NH stretching of the secondary amine, 1760 cm^{-1} owing to −C = O stretching of the carboxyl ion, and at 750 cm^{-1}because of C–Cl stretching. The FTIR spectra of liquisolid compacts displayed all the characteristic peaks as that of pure diclofenac sodium, ruling out the possibility of any chemical interaction between the drug and excipients used in the formulation.

Table 3: Flowability Parameters of Diclofenac Sodium Liquisolid Powder Systems

Formulation No.	Angle of repose (θ)± SD	Carr's index ± SD	Hausner's ratio± SD
F1	39.50 ± 0.50	27.35± 0.37	1.37±0.01
F2	35.75 ±0.25	26.66± 0.50	1.36±0.01
F3	33.82 ±.0.49	26.42±0.44	1.35±0.02
F4	34.60 ±0.60	28.11±0.12	1.39±0.03
F5	31.79 ±0.61	30.07±0.52	1.43±0.01
F6	29.68 ±0.92	29.46±0.49	1.41±0.03
F7	26.57 ±1.32	22.11±0.11	1.28±0.02
F8	30.54 ±0.64	29.90±0.10	1.42±0.02
F9	36.12 ±0.80	27.79±0.10	1.38±0.01
DCT	26.57 ±1.32	16.16±0.05	1.20±0.03

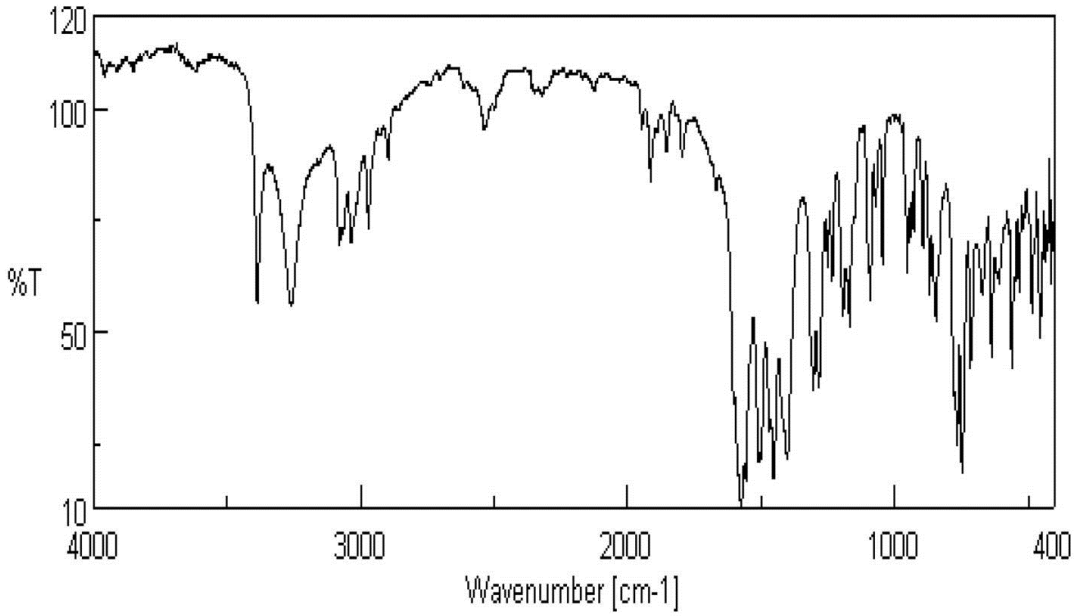

Fig. 1: Infrared spectrum of Diclofenac sodium

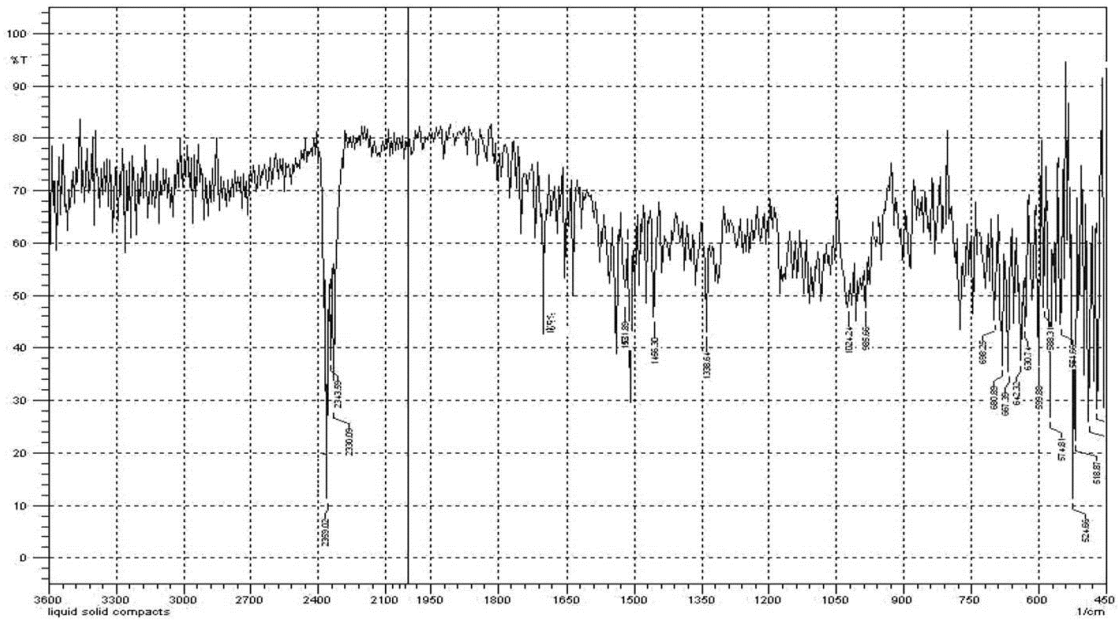

Fig. 2: IR Spectra of liquisolid compact

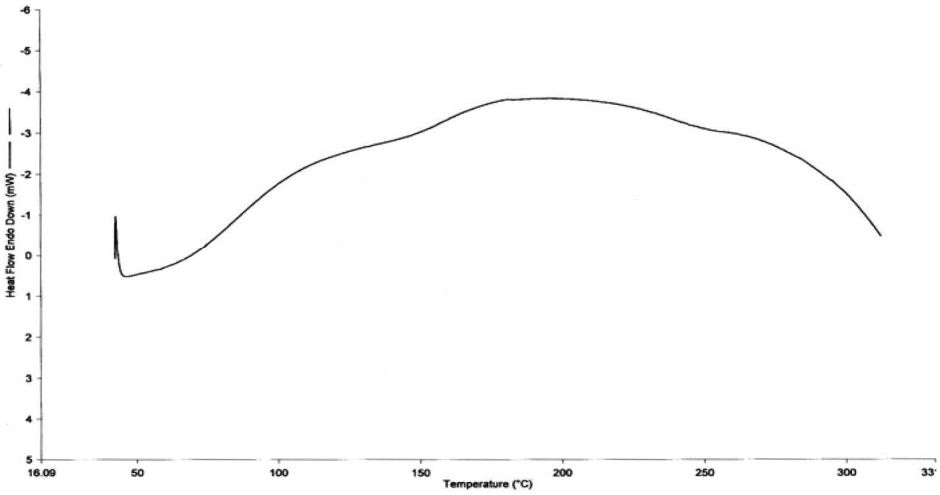

Fig. 3: DSC Thermogram of Liquisolid Compact

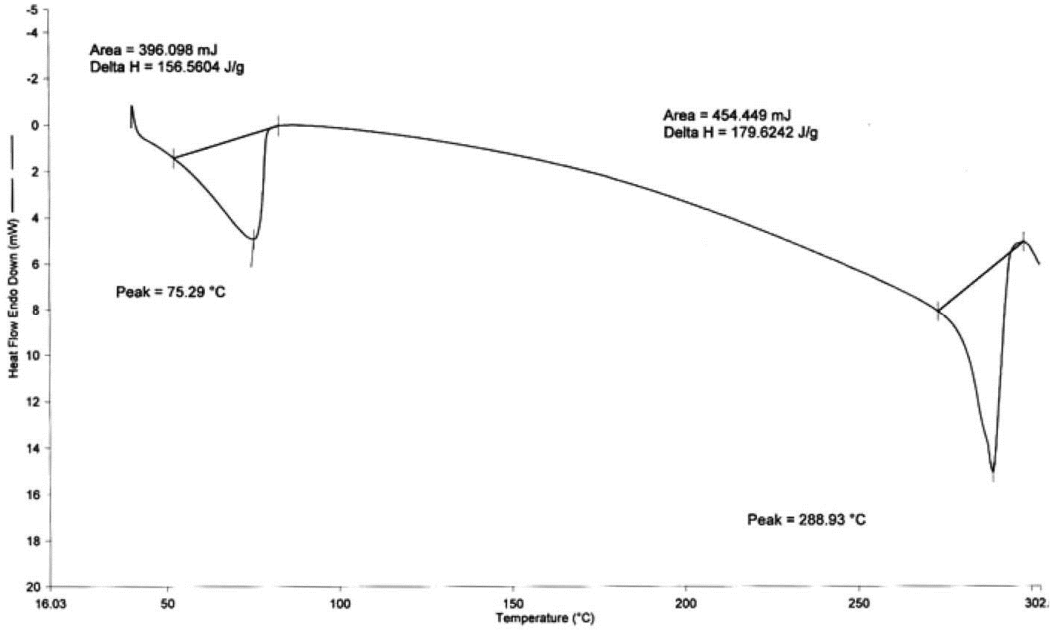

Fig. 4: DSC Thermogram of Diclofenac Sodium

Evaluation of Liquisolid Compacts

Friability

All the liquisolid compacts had acceptable friability as none of the tested formulae had a percentage loss in tablet weights that exceeded 1%. Friability below 1% is an indication of good mechanical resistance of the liquisolid compacts. This ensures that compacts could withstand to the pressure and shocks during handling, transportation, and manufacturing processes.

Hardness

Hardness was in the range of 3.0 ± 0.86kg/cm^2 to 5.0 ± 0.50 kg/cm^2. It is seen that as the amount of Avicel goes on increasing, hardness also increases. With a decrease in R-values, hardness was found to decrease. This low hardness could be attributed to the less amount of added Avicel and poor compressibility of Aerosil. Tablets with low hardness were not considered because they were not able to withstand abrasion in handling.

Drug Content Uniformity

Uniform drug content was observed for all the formulations (94.17 ±1.93 to 100.81 ± 2.29) and was within the IP specification (90–110%).

In Vitro Drug Release

All the liquisolid compacts showed higher drug release than the pure drug. The results showed that there was a significant difference ($P < 0.05$) between the release profile of the pure drug and all the liquisolid compacts. The enhanced dissolution rates of liquisolid compacts compared to pure drug may be attributed to the fact that the drug is already in solution in PG, while at the same time it is carried by the powder particles (microcrystalline cellulose and silica). Thus, its release is accelerated due to its markedly increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts[10,22]. PG facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface.

Table 4: Evaluation of Liquisolid Tablets

Formulation No.	Friability (%)	Disintegration Time (Sec)	%Drug Content
LS1	0.92±0.01	56.00±2.00	99.48±2.18
LS2	0.93±0.02	50.00±3.00	95.83±2.21
LS3	0.95±0.03	48.00±1.00	97.87±2.74
LS4	0.76±0.02	70.00±3.00	95.99±2.47
LS5	0.87±0.01	54.00±2.00	97.46±1.10
LS6	0.75±0.02	52.00±1.00	100.81±2.29
LS7	0.92±0.01	78.00±1.00	94.17±1.93
LS8	0.70±0.01	65.00±2.00	98.56±1.54
LS9	0.90±0.02	55.00±1.00	98.36±2.25
DCT	0.61±0.01	75.00±3.00	98.75±1.61
MKT	0.70±0.01	70.00±2.00	100.30±1.94

The dissolution profiles of the liquisolid tablet formulations together with the dissolution profile of pure diclofenac sodium.

A) Formulation Containing 40% Cd value

In vitro dissolution study done by paddle dissolution apparatus USP Type II, containing 0.1 N HCl as dissolution media. Cumulative percent drug release shown as below.

Table 5: **Cumulative percent Drug Release of diclofenac sodium Liquisolid Formulation containing 40%Cd**

Time (Min)	LS1	LS2	LS3	DCT
0	0	0	0	0
5	93.82±0.18	91.67±0.25	76.63±0.37	63.21±0.20
10	101.84±0.17	100.67±45	85.82±0.17	64.78±0.77

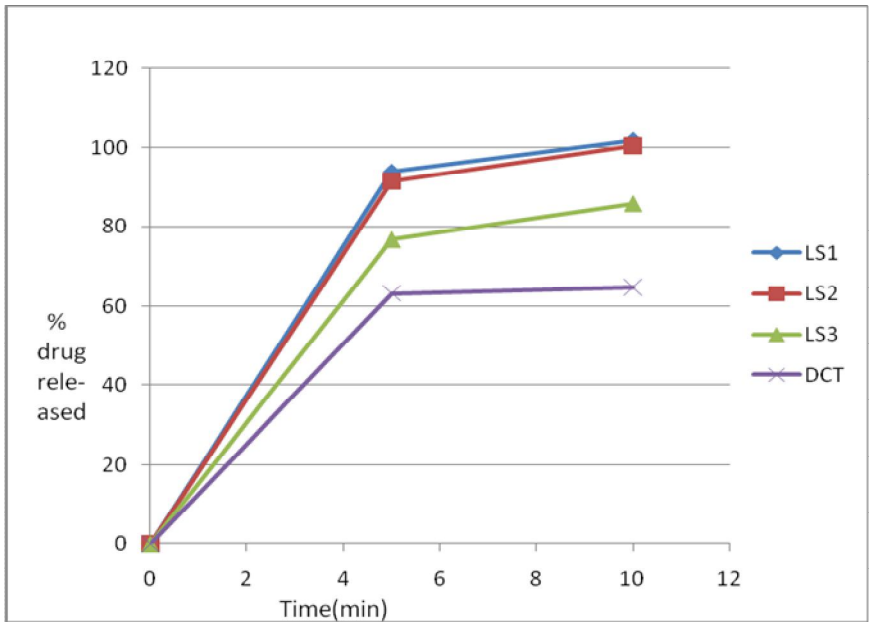

Fig. 5: Cumulative percent Drug Release of Diclofenac sodium

Liquisolid Formulation containing 40%Cd

The drug release from DCT as shown in figure was very poor. From figure, it was apparent that formulations LS1 and LS2 have the highest drug release rate. Among all the formulations, the liquisolid compact having 40% w/w drug concentration i.e(.drug:PG Ratio) exihibits greater release than liquisolid compact containing 50 % w/w drug concentration i.e. the drug: PG ratio exhibits greater release and liquisolid compact containing 60 % w/w(drug: PG ratio). From the above results it is clear that as there was increase in amount of liquid vehicle, there was increase in the dissolution rate.

B) Formulation Containing 50% Cd value

In vitro dissolution study done by paddle dissolution apparatus USP Type II containing 0.1N HCl as dissolution media. Cumulative percent drug release shown in below.

Table 6: Cumulative percent Drug Release of Diclofenac sodium Liquisolid Formulation containing 50%Cd

Time (Min)	LS4	LS5	LS6	DCT
0	0	0	0	0
5	86.30±0.70	88.56±0.50	79.85±0.42	63.21±0.20
10	93.30±0.69	100.77±0.56	87.96±0.49	64.78±0.77

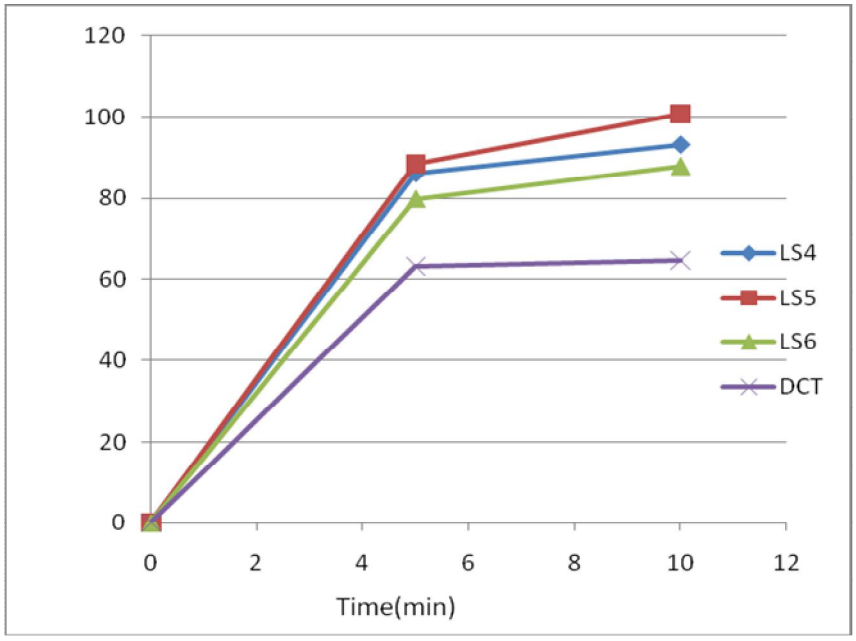

Fig. 6: Cumulative percent Drug Release of Diclofenac sodium Liquisolid Formulation containing 50%Cd

From the Cd 50% release graph it was clear that as the drug concentration decrease % drug released also decreased.

C) Formulation Containing 60% Cd value

In vitro dissolution study done by paddle dissolution apparatus USP type II, containing 0.1N HCL as dissolution media. Cumulative percent drug released shown in below.

Table 7: Cumulative Drug Release of Diclofenac sodium Liquisolid Formulation containing 60%Cd

Time (Min)	LS7	LS8	LS9	DCT
0	0	0	0	0
5	75.56±0.51	76.63±0.53	66.96±0.15	63.21±0.20
10	85.82±0.72	84.75±0.27	69.80±0.22	64.78±0.77

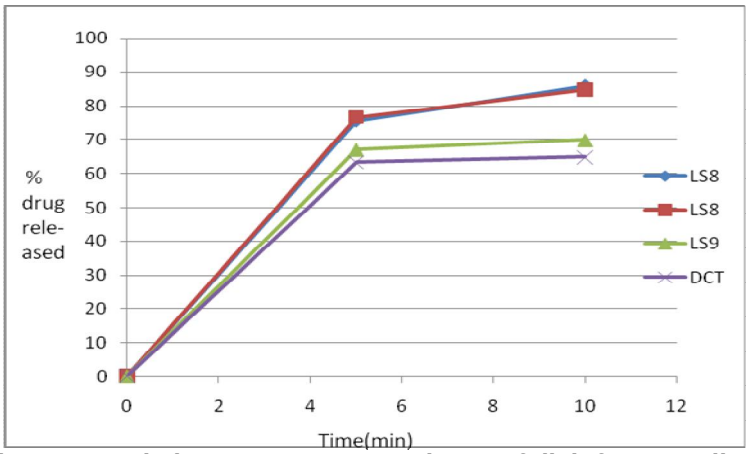

Fig. 7: Cumulative percent Drug Release of diclofenac sodium Liquisolid Formulation containing 60%Cd

Cd 60% formulation containg had lower % drug released than 40% , 50%. But it still higher than plane drug DCT, it clear that formulation show enhance dissolution rate.

CONCLUSION

The new technique of liquisolid compacts appears to be a promising alternative for the formulation of water-insoluble drugs. The higher dissolution rate displayed by liquisolid compacts is due to the increased wetting properties and surface of the drug available for dissolution. With an increase in L_f-value, flow property was found to be reduced. It also resulted in a decrease in the compressibility of the final admixture.

REFERENCES

1. Kim KH and Singh BN. Drug delivery–oral route, In: Swarbrick J, Boylen JC, Encyclopedia of pharmaceutical technology,2nd Ed, New York: Marcel Dekker Inc,2002;886-890.
2. Allen LV, Popvich NV and Ansel HC. Tablets In: Ansel's pharmaceutical dosage forms and drug delivery systems, 8 th Ed; India, B. I. publications pvt.ltd. 227-259.
3. Rudnic EM and Kottke MK. Tablet dosage forms, In: Banker GS, Rhodes CT. Modern pharmaceutics, 4th ed, New York ,Marcel Dekker Inc, 2002; 333-394.
4. Alderborn G. Tablet and compaction In: Aulton M. Pharmaceutics: The science of dosage form design, 2nd Ed, Churchill Livingstone, Longman group, Edinburgh, 2002;114-138.
5. Baboota S, Ali J and Ahuja A. Tablet, Available at http://www.pharmpedia.com/Tablet.
6. Charman SA and Charman WN. Oral modified release delivery systems, In: Rathbone MJ, Hadgraftb J, Roberts MS. Modified release drug delivery technology, New York, Marcel Dekker Inc. 2003;313-320.
7. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods, 2000;44:235-249.
8. Amidon GL, Lennernas H and Crison JR. A theoretical basis for biopharmaceutics drugs classification: the correlation of in-vitro drug product dissolution and in-vivo bioavailability. Pharm Res. 1999;12: 413-420.
9. Vikas A Saharan and Vipin Kumar. Dissolution Enhancement of Drugs. PartI:Technologies and Effect of Carriers, International Journal of Health Research, June2009;2(2):107-124.
10. Neelam Seedher and Sonu Bhatia. Solubility Enhancement of Cox-2 Inhibitors Using Various Solvent Systems AAPS PharmSciTech. 2003;4 (3)33.
11. Fahmy RH and Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablet formulation: in vitro and in vivo evaluation, Eur J Pharm Biopharm, 2008;69(3):993-1003.
12. Spiras S and Bolton SM. Liquisolid systems and methods for preparing same, United States patent 6,096,337, 2000.
13. Spiras S and Bolton SM. Liquisolid systems and methods for preparing same, United States patent 5,968,550, 1999.
14. Spiras S and Bolton SM, Liquisolid systems and methods for preparing same, United States patent 5,800,834, 1998.
15. Spireas S, Jarowski CI and Rohera BD. Powdered solution technology: principles and mechanism, Pharm. Res. 1992;9(10):1351–1358.
16. Spireas S, Sadu S and Grover R. In vitro release evaluation of hydrocortisone liquisolid tablets, J Pharm Sci, 1998;87: 867-872.
17. Spiras S, Wang T and Grover R. Effect of powder substrate on dissolution properties of methylclothiazide Liquisolid compacts. Drug Dev Ind Pharm. 1999;25:163-168.
18. Spireas S and Sadu S. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int J Pharm, 1998;166:177-188.
19. Javadzadeh Y, Navimipour B and Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water insoluble drug (carbamazepine). Int J Pharm. 2007;341:26-34.
20. Patel VP, Patel NM, Dissolution enhancement of glipizide using liquisolid tablet technology, Ind Drugs, 2008; 45(4):,P. 318-323
21. Khaled KA, Asiri YA and El-sayed YM. In vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs. Int J Pharm. 2001; 222:1-6.

22. Javadzadeh Y, Musaajrezaei and Nokhodchi A. liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. Int J Pharm. 2008;1-7.
23. Javadzadeh Y, Siahi MR and Asnaashri S. An investigation of physicochemical properties of piroxicam liquisolid compacts. Pharm Dev Tech. 2007;12:337-34.
24. Darwish AM. Dissolution enhancement of glibenclamide using liquisolid tablet technology, Acta Pharm, 2001;51:173-181.
25. Fahmy RH and Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablet formulation: in vitro and in vivo evaluation. Eur J Pharm Biopharm. 2008;69(3):993-1003
26. Vikas A Saharan and Vipin Kumar. Dissolution Enhancement of Drugs. PartI:Technologies and Effect of Carriers, International Journal of Health Research. 2009;2(2):107-124
27. Tayel SA, Soliman I and Louis D. Improvement of dissolution properties of carbamazepine through application of the liquisolid tablet technique. Eur J Pharm Biopharm. 2008;69:342-347.
28. Nokhodchi A . The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm pharmaceut Sci., 2005;8(1):8-25