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LIQUISOLID COMPACT TECHNOLOGY: A NOVEL APPROACH FOR ENHANCEMENT OF DISSOLUTION AND BIOAVAILABILITY OF KETOPROFEN

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Abstract:

Liquid solid compact technology is a novel approach to enhance bioavailability of a BCS class II drug by improving its solubility and dissolution rate of the drug. Liquisols are the formulations which make the solid drug transforms into its solubilized state and further it will be converted into a free flowing powder with good flow properties that is suitable for per-oral administration.

Ketoprofen is a BCS class II drug with poor aqueous solubility and limited its bioavailability. In the present study, liquid solid technique is used to enhance the bioavailability of Ketoprofen. Liquisols of Ketoprofen were prepared using polyethylene glycol (PEG) 400 as liquid vehicle, Avicel pH 102 as carrier and Aerosil 200 as coating material. All the nine formulations were prepared using 30%, 40% and 50% concentration of drug in liquid vehicle and a Carrier: Coating ratios of 10:1, 15:1, 20:1. All the formulations were subjected for preformulation studies for drug polymer compatibility, saturation solubility studies.

The unit doses were calculated and the flow properties of the powder were estimated using Carr's index, Hausner's ratio and angle of repose. The final preparations were filled in hard gelatin capsules and subjected for dissolution studies using pH 7.4 phosphate buffer in order to find out the optimized formula. Finally, the optimized formula was compared with a marketed tablet to study the enhancement in bioavailability and the results showed a quick release of drug from Liquisols.

Keywords: *Ketoprofen, Liquisols, Mathematical model, liquid load factor, Solubility, Dissolution, Bioavailability*

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INTRODUCTION

Among the solid dosage forms tablets and capsules are the intact formulations that have good stability and able to deliver the drug into the Gastrointestinal tract. Solubility is defined as a substance that dissolves in a unit volume of a liquid substance to form a saturated solution under specified conditions of temperature and pressure. Dissolution is the rate limiting step for poorly aqueous soluble drug belonging to BCS class II particularly for oral dosage forms [1]. In order to overcome the rate limiting step, enhancement of solubility is desirable. Over the period of time several techniques like solid dispersions, molecular complexation, micronization, lyophilization, and microencapsulation have shown to enhance the solubility of the water insoluble drug [2]. Among them liquid solid compacts is one of the promising methods to enhance the drug delivery.

Liquisolid compacts (liquisols) are the solid dosage forms with acceptable flowability and compressibility nature using liquid medication (that implied oily, liquid lipophilic drug or water insoluble solid drugs dissolved in a suitable nonvolatile liquid solvent system)[3]. The liquid medication is further converted into free flowing non-adherent and readily compressible powders by absorbing them onto carrier and coating materials. Though the formulation looks solid, the drug will be in solubilized and molecularly dispersed state. Because of their intact mass flow properties may influence the drug release however; due to the wetting nature of solvent dissolution of the drug increases in aqueous medium and thereby enhances bioavailability of the drug.

Ketoprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties [4]. It belongs to biopharmaceutical classification system class II drugs characterized by low solubility and high permeability. Thus the rate limiting step for bioavailability of ketoprofen is its poor solubility in biological fluids and hence late onset of action.

In this study, Ketoprofen was selected as model drug with poor solubility characteristics. The flowability and compressibility of liquid solid compacts were estimated simultaneously using mathematical model of liquid systems which was used to calculate amounts of carrier and coating materials to be added based on new fundamental powder properties called the flowable liquid retention potential (Ø-value).

MATERIALS AND METHODS:

Materials: The following materials were used in the study: Ketoprofen (Yarrow Chem. Products, Mumbai), Avicel pH 102 (Yarrow Chem. Products, Mumbai), Aerosil 200(Otto chemi pvt.ltd. Mumbai), Poly Ethylene Glycol 400 (Yarrow Chem. Products, Mumbai) potassium dihydrogen phosphate, sodium hydroxide and magnesium stearate (Qualigens fine chemicals, Mumbai).

Determination of Ketoprofen solubility [11]

Saturated solutions of Ketoprofen in various liquid vehicles (Propylene glycol, PEG 400, Water, Tween 80) were prepared by adding excess amount of drug and mixed using mechanical shaker overnight at 37± 0.5ºC under constant vibration. The solutions were then passed through 0.45 micron filter, diluted and analyzed for drug content using UV spectrophotometer at 258nm.

Calibration Curve for Ketoprofen in pH 7.4 Phosphate buffer

Calibration of Ketoprofen was carried out in pH 7.4 phosphate buffer as per USP compendium [USP-NF 29]. 10mg of drug was accurately weighed and dissolved in 0.5 ml of methanol and make up to 100 ml using pH 7.4 phosphate buffer. The solution is further diluted 10 times using phosphate buffer to get 100µg/ml. Serial dilutions of 2,4,6,8,10 µg/ml were prepared with buffer and analyzed using UV VIS spectrophotometer at λ_{max} of 258 nm.

Preparation of Liquisolid Compacts using mathematical model

Application of mathematical model for design of liquid solid compacts

The formulations were prepared in the basis of formulation design given by Spireas et al. [5]

In this study PEG 400 is used as non-volatile solvent, avicel pH 102 and aerosol 200 were used as carrier and coating materials respectively. The drug concentrations were taken as 30%w/w, 40%w/w and 50%w/w and the carrier: coating ratio (R) was 10:1, 15:1 and 20:1.

The excipients ratio R of powder is given by

$$R=Q/q \quad \text{---- (1)}$$

Where R is the ratio of carrier (Q) and coating (q) materials present in the formulation.

Liquid loading factor (L_f) is defined as the ratio of the weight of liquid medication over the weight of the carrier powder in the liquisol system which should be a free flowing system.

$$L_f = W/Q \quad \text{----- (2)}$$

Flowable liquid retention potential (Φ value) of powder excipients was used to calculate the required ingredients amounts.

$$L_f = \Phi + Ø\,(1/R) \text{ ----- (3)}$$

Where, Φ and Ø are the Φ values of carrier and coating materials respectively. Hence, to calculate the required quantities of ingredients all the three equations were used.

Preparation of Conventional capsule of Ketoprofen

A conventional capsule of Ketoprofen was prepared using physical mixture of liquisolid system containing 25mg of drug, 200mg of AvicelpH 102, 10mg Aerosol 200, 5% Croscarmellose Sodium and 1% Magnesium Stearate. All the ingredients were mixed thoroughly and filled in a '00' size capsule.

Characterization of prepared Ketoprofen Liquisols

Drug Polymer compatibility Studies (FTIR) [10]

FTIR studies of Ketoprofen and prepared formulations were recorded for transmittance within the range of 4000 cm^{-1} to 400cm^{-1}(shimadzu, Japan FT-IR 8400 S). Samples were prepared in KBr discs (2 mg in 200mg in KBr) with a hydrostatic press at a force of 5 cm^{-2} for 5 min and the resolution was 4 cm^{-1}. Finished product samples of Ketoprofen Liquisols also were analyzed for drug compatibility studies between drug and other polymers.

Flow properties of Ketoprofen Liquisols [6]

Angle of repose (θ)

The frictional forces in a loose powder cab be measured by the angle of repose. It is indicative of flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of power and the horizontal plane.

$$\theta = \tan^{-1}(h/r) \text{ ---- (4)}$$

Where, 'h' is the height of the pile and 'r' is the radius of the pile occupied in cms. The powder mixture was allowed to flow through the funnel fixed to a stand at fixed height (h) and the angle of repose was calculated measuring the height and radius of the heap of powder.

Table 1: Standard Values for Angle of Repose 'θ'

Angle of Repose		
S.No.	**Flow Property**	**Angle of Repose(θ)**
1	Excellent	25-30
2	Good	31-35
3	Fair – aid not needed	36-40
4	Passable – may hang up	41-45
5	Poor – must agitate, vibrate	46-55
6	Very poor	56-65

Compressibility Index or Carr's Index

It is the simplest way to measure the free flow of powder. It is the ease with which a material can be induced to flow is given by the compressibility index of the granules was determined by Carr's compressibility index 'I' which is given by

$$I = \frac{Dt-Db}{Dt} X\ 100 \text{------ (5)}$$

Where, D_t is tapped density of the powder and D_b is bulk density of the powder.

Hausner's Ratio [7]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$Hausner's\ ratio = \frac{Tapped\ Density}{Bulk\ Density} \text{--------- (6)}$$

Table 2: Standard Values for Carr's index and Hausner's ratio

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
≥ 38	Extremely poor	> 1.60

Uniformity of weight

This test is performed to maintain the uniformity of weight of each capsule which should be in the prescribed range. 20 capsules of each type were weighed individually using an electronic balance, average weight was calculated and individual weight was then compared with average value to find out the deviation in weight.

***In Vitro* DisintegratingTesting [8]**

The test was carried out using 6 capsules in pH 7.4 buffer using Inco tablet disintegrating tester maintained at 37± 0.5ºC for all formulations three capsuleseach. The time in seconds required for complete disintegration of the capsule with no palable mass remaining in the bowl was measured.

***In vitro* Dissolution studies [9]**

The dissolution profile of prepared capsules was studied using USP dissolution apparatus type II (LABINDIA DS 8000, India). A volume of 900 ml pH 7.4 phosphate buffer was used as dissolution medium maintained at 37± 0.5ºC and rotating speed was set at 50rpm. 2 ml aliquots of medium was collected and the same amount was replaced using fresh medium at time intervals of 1,2,3,4,5,6,7,8,9,10 minutes. The collected samples were analyzed using UV spectrophotometer (ELICO SL-210, India). Cumulative percent drug release was calculated using an equation obtained from standard curve.

RESULTS AND DISCUSSION:

Solubility Studies of Ketoprofen in various solvents [12]

Selection of non volatile solvent is the prerequisite step for the drug as it will enhance the solubility of the drug. The solubility of Ketoprofen in PEG 400 was found to be 3450 mg/ml which is very much higher than in water, propylene glycol and Tween 80 as were represented in the table 3. Hence, PEG 400 was selected as solvent.

Table 3: Solubility of Ketoprofen in various solvents

S.NO.	SOLVENTS	SOLUBILITY
1	Water	3.56mg/ml
2	Polyethylene glycol-400	3450 mg/ml
3	Propylene glycol	1125 mg/ml
4	Tween-80	1350 mg/ml

Preparative procedure for ketoprofen LSC using mathematical design [13]

The mathematical model equation for Avicel pH 102 and Aerosil 200 in PEG 400 can be given according to the Ø and Φ values as given by spireas et al., [5] as follows:

$$L_f = 0.005 + 3.26\ (1/R) \text{ ----- (3)}$$

Based on this equation liquid loading factor was calculated followed by calculating 'W' and finally carrier and coating amounts were computed. The final unit dose was calculated including disintegrant and anti adherent.

The Liquisols of ketoprofen were prepared as represented in table no. 4.

Table 4: Composition of Ketoprofen Liquisolid formulas prepared according to mathematical model (All Liquisolid formulas contain 25 mg of Ketoprofen)

Liquid solid system	Drug conc. In liquid medication (%w/w)	Carrier: Coating ratio (R)	Liquid load factor (Lf)	Liquid vehicle (mg) PEG 400	Carrier Q (mg) Avicel pH 102	Coating (mg) Aerosil 200	Disintegrant Croscarmellose sodium (mg)	Lubricant Mag. Stearate	Unit Dose (mg)
LSC-1	30	10	0.331	58.33	176.22	17.62	14.55	2.91	291.72
LSC-2	30	15	0.222	58.33	262.74	17.51	19.08	3.91	382.66
LSC-3	30	20	0.168	58.33	347.20	17.36	23.54	4.80	472.04
LSC-4	40	10	0.331	37.5	82.32	8.23	7.57	1.5	152
LSC-5	40	15	0.222	37.5	122.74	8.18	10.75	2.15	203.6
LSC-6	40	20	0.168	37.5	162.20	8.11	11.64	2.4	225
LSC-7	50	10	0.331	25	75.52	7.55	7.05	1.4	140.12
LSC-8	50	15	0.222	25	112.61	7.5	9.01	1.8	182.11
LSC-9	50	20	0.168	25	148.8	7.44	10.93	2.18	219.35

Drug Polymer Compatibility studies: FTIR Graphs [10]

The FTIR spectrum of pure ketoprofen shows a weak peak at 2977.97-2937.79 cm^{-1} due to the presence Aromatic C-H stretch. It shows characteristic peak at 1653.79 cm^{-1} for C=O stretch of keto group and 1696.50 cm^{-1} for C=O stretch of carboxylic acid, a weak peak at 1443.31 cm^{-1} CH deformation of CH asymmetrical, 1370.55 cm for CH deformation of CH symmetrical. All these peaks of pure Ketoprofen were present in the FTIR graphs of Liquisol products indicating no interaction take place in between drug and excipients.

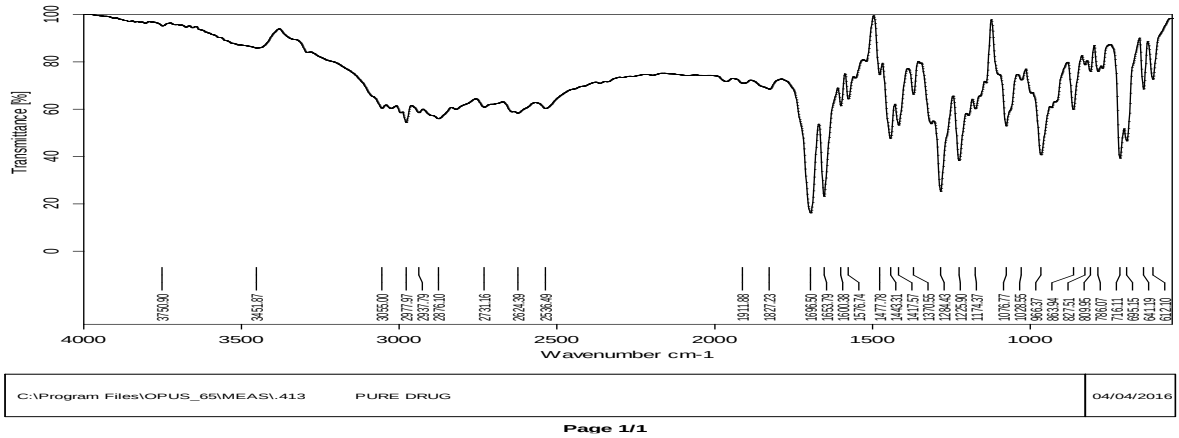

Fig1: FTIR graph for pure drug Ketoprofen

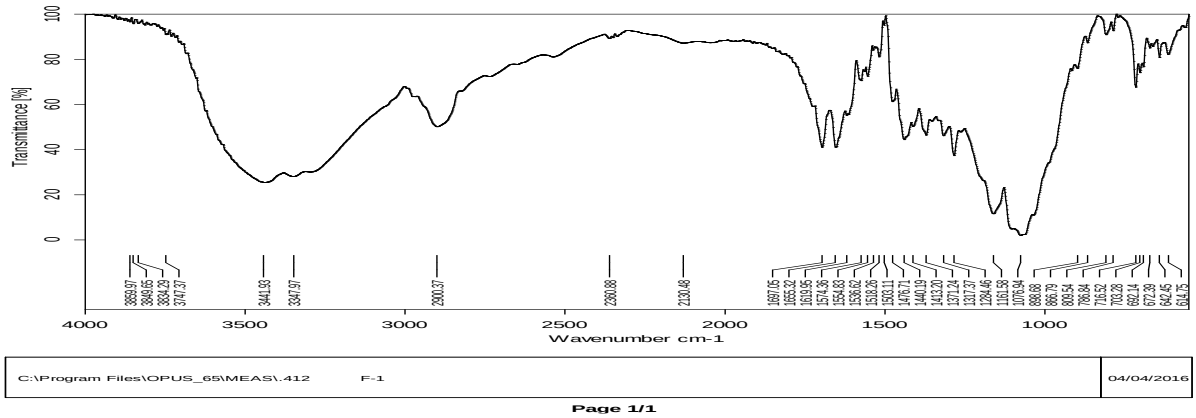

Fig 2: FTIR graph for formulation LSC 2

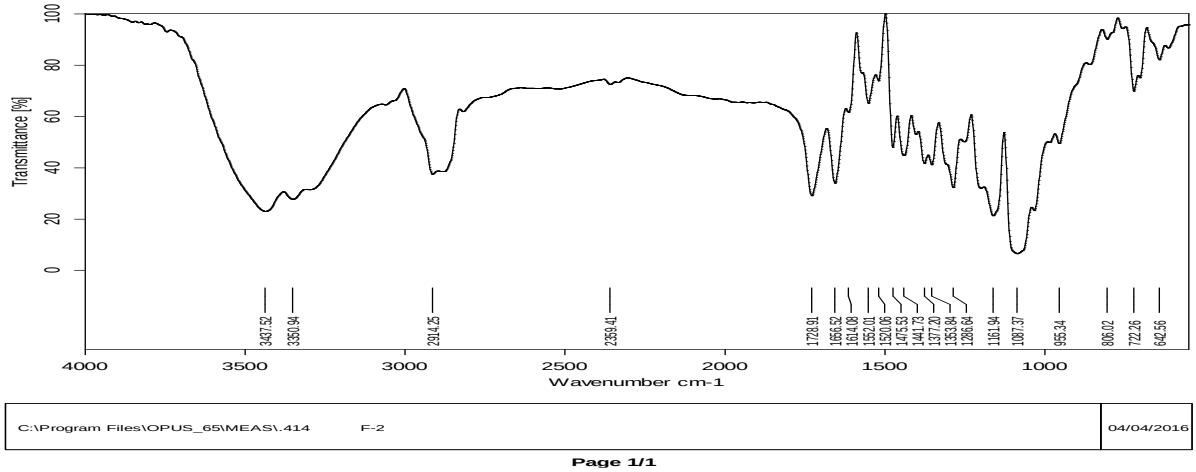

Fig 3: FTIR graph for formulation LSC 3

Calibration curve for Ketoprofen in pH 7.4 Buffer [14].

Table 5: Calibration data for Ketoprofen in pH 7.4 buffer.

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE
1	0	0
2	2	0.1045
3	4	0.236
4	6	0.3579
5	8	0.445
6	10	0.5903

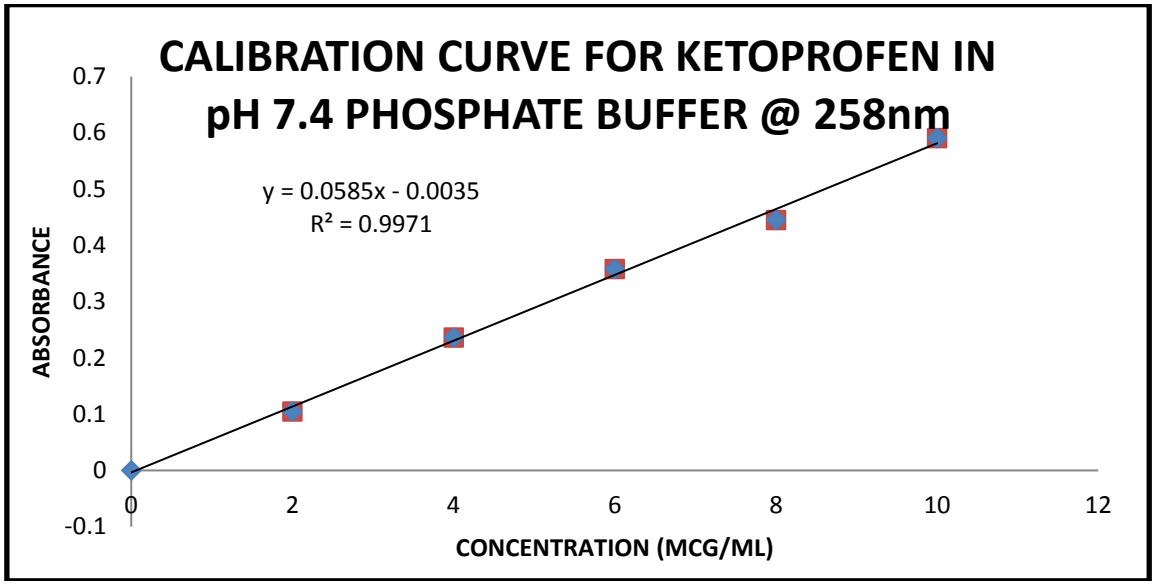

Fig 4: Calibration curve for Ketoprofen in pH 7.4 buffer at 258 nm

Evaluation studies:

Flow properties of Ketoprofen Liquisols

All the formulations were subjected to test for bulk density and tapped density, the values were used to compute Hausner's ratio and Carr's index which indicate interparticulate friction. Except LSC 5 &8 all the formulations showed good flow and LSC-5 &8 showed moderate flow. The angle of repose indicates friction and resistance between particles. The angle of repose for all the formulation blends were within the range of 27.5-31.4 indicating that all the formulations showed excellent to good flow. The moderate flow in the powder blend might be due to the wetting of non volatile liquid and hydrophilic carrier.

Table 6: Flow Properties of prepared liquisolid compacts

S.No.	Angle of Repose (Avg. of n=3)	Hausner's Ratio (Avg of n=3)	Carr's Index (Avg of n=3)
LSC-1	27.5	1.21	21.5
LSC-2	30.45	1.19	24.5
LSC-3	29.5	1.20	22.3
LSC-4	27.9	1.26	23.78
LSC-5	31.3	1.33	22.3
LSC-6	29.9	1.28	24
LSC-7	30.9	1.18	20.38
LSC-8	31.4	1.33	25
LSC-9	29.6	1.32	24.24

Evaluation of finished dosage form

Liquisols of Ketoprofen were studied for various parameters like weight variation, disintegration and drug content. The values were reported in table no. 6. The disintegration time was found between 26 – 40 sec. it was observed that there is a direct relationship between amount of carrier added and disintegration time. As the amount of carrier increase, disintegration time decreased in formulations LSC-3, LSC-6 and LSC-9. The weight variation studies were conducted for all unit doses according to Indian pharmacopoeia and all the results indicate within their limits.

The drug content for all the formulations were performed in pH 7.4 phosphate buffer and all the formulations showed an average content of 85% to 98.39% indicating that uniform mixing and homogenous distribution of drug throughout the batches.

Table 7: Evaluation studies of Ketoprofen liquisol capsules

S.No.	Formulation code	Disintegration time (sec)	Weight variation (mg)	% Drug content
1	LSC-1	35±2.5	287.5±1.18	94.45±1.77
2	LSC-2	30±2.09	378±2.64	87.40±2.55
3	LSC-3	26±3.78	470.5±1.56	90.68±2.50
4	LSC-4	37±5.85	147.3±1.33	97.24±3.08
5	LSC-5	35±1.52	200.5±1.56	92.49±1.32
6	LSC-6	29±1.52	240.16±1.91	85.27±3.0
7	LSC-7	40±2.08	138.9±1.54	98.39±1.95
8	LSC-8	39±2.08	180.31±1.15	94.13±2.25
9	LSC-9	30±2	210±2.64	91.50±2.58

Table 8: *in-vitro* studies of Ketoprofen capsules for various formulations

S.No.	Time (min)	% Drug Release								
		LSC-1	LSC-2	LSC-3	LSC-4	LSC-5	LSC-6	LSC-7	LSC-8	LSC-9
1	0	0	0	0	0	0	0	0	0	0
2	1	30.98 ±2.09	8.852 ±2.05	64.64 ±2.55	42.049 ±2.51	10.09 ±2.05	64.25 ±2.51	2.951 ±1.52	4.426 ±1.51	30.486 ±2.09
3	2	55.32 ±2.50	36.88 ±2.50	86.17 ±2.11	52.377 ±1.91	26..48 ±2.00	68.625 ±2.43	7.525 ±1.68	8.705 ±2.34	59.790 ±1.61
4	3	76.75 ±.3.1	42.78 ±2.61	93.22 ±1.51	61.967 ±2.41	55.37 ±2.55	73.25 ±1.43	10.475 ±2.51	52.52 ±1.85	70.152 ±1.23
5	4	78.125 ±1.63	45 ±2.11	93.65 ±1.41	62.705 ±1.51	61.54 ±1.63	90.46 ±1.68	14.016 ±2.55	60.93 ±1.61	85.16 ±1.51
6	5	82.25 ±2.75	48.68 ±1.52	94.07 ±2.50	64.918 ±1.61	78.50 ±1.85	91.18 ±1.31	37.033 ±1.95	80.705 ±2.43	89.46 ±1.98
7	6	83.875 ±1.91	64.91 ±2.51	98.55 ±1.09	75.246 ±2.31	79.99 ±2.31	95.48 ±1.92	52.377 ±2.11	83.501 ±2.23	96.186 ±1.68
8	7	85.5 ±2.11	75.24 ±3.00	100.21 ±1.71	80.410 ±2.55	81.59 ±1.7	99.11 ±2.11	75.984 ±2.34	85.728 ±1.54	98.670 ±2.49
9	8	90.625 ±2.03	92.21 ±1.55	-	81.885 ±2.11	86.16 ±2.11	-	83.951 ±1.52	92.803 ±1.68	99.154 ±2.55
10	9	96.375 ±2.72	95.90 ±2.51	-	85.574 ±1.96	97.06 ±2.5	-	85.279 ±1.61	95.148 ±2.21	-
11	10	99.715 ±1.68	100.39 ±1.22	-	89.262 ±1.81	-	-	90.738 ±1.25	99.12 ±1.65	-

***In vitro* dissolution study**

In vitro drug release studies were performed in phosphate buffer pH 7.4 for all the prepared formulations using USP I apparatus, rotating basket method. The values for all the formulations are reported in table no 7 and the graphs are shown in figure 5.

The release rate of the drug from all the formulations was proportional to amount of liquid loaded within the compacts i.e., the drug release is greater for 30% drug concentration than that of 40% and 50% concentrations.

It was observed that drug release was also depending on amount of carrier added. As the carrier to coat ratio increases as shown in the figures 6-8, the amount of Avicel pH 102 added increased and wetting of the compact increased and eventually drug was released quickly[15].

Based on the release rates, optimized formulation was selected as LSC 3 and the release rate was compared with conventional capsule, marketed tablet and pure drug as shown in the figure 9. It can be seen clearly that the optimized preparation LSC 3 released the drug within 8 minutes which is markedly higher than marketed tablet and conventional capsule.

Optimized Formulation	
LSC-3	
Angle of repose	29.5°
Hausner's ratio	1.17
Carr's index	20.3
Weight variation	470.5±1.56
Drug content	90.68±2.50
Disintegrating Time	26±3.78 sec
$T_{100\%}$	7 minutes

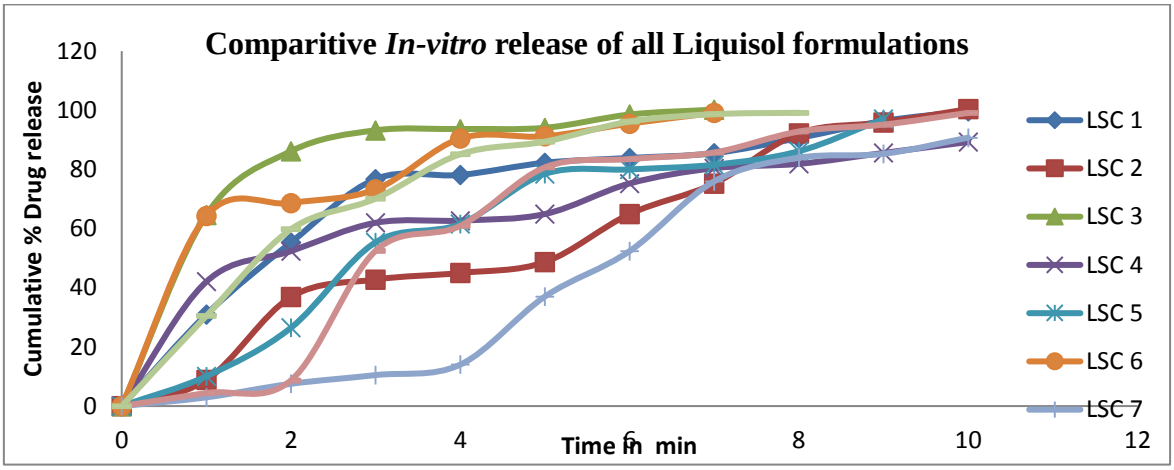

Fig 5: Comparative *In-Vitro* release of all Liquisolid formulations

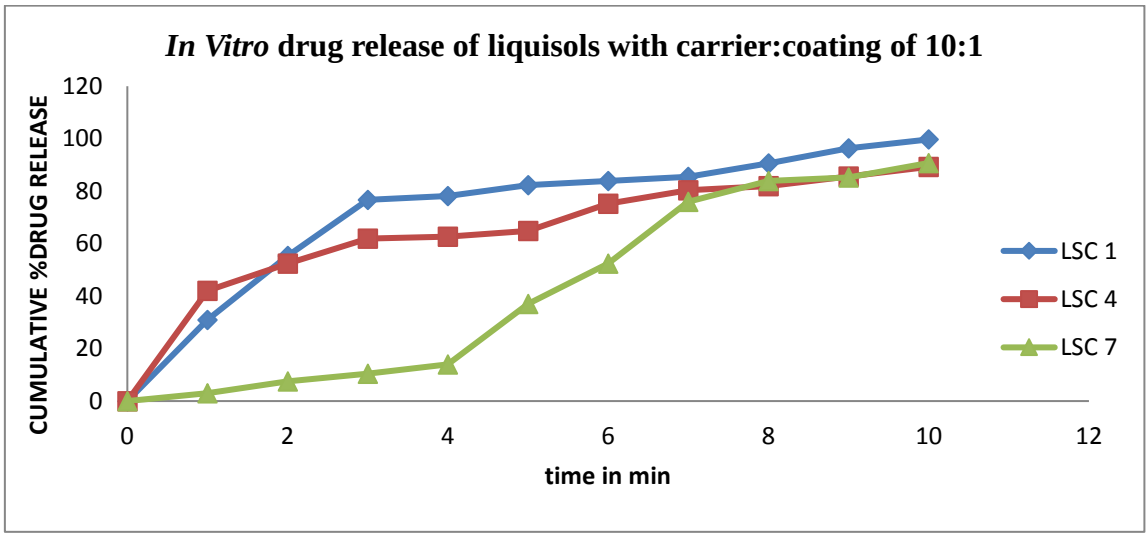

Fig 6: *In Vitro* drug release of Liquisols with carrier: coating of 10:1

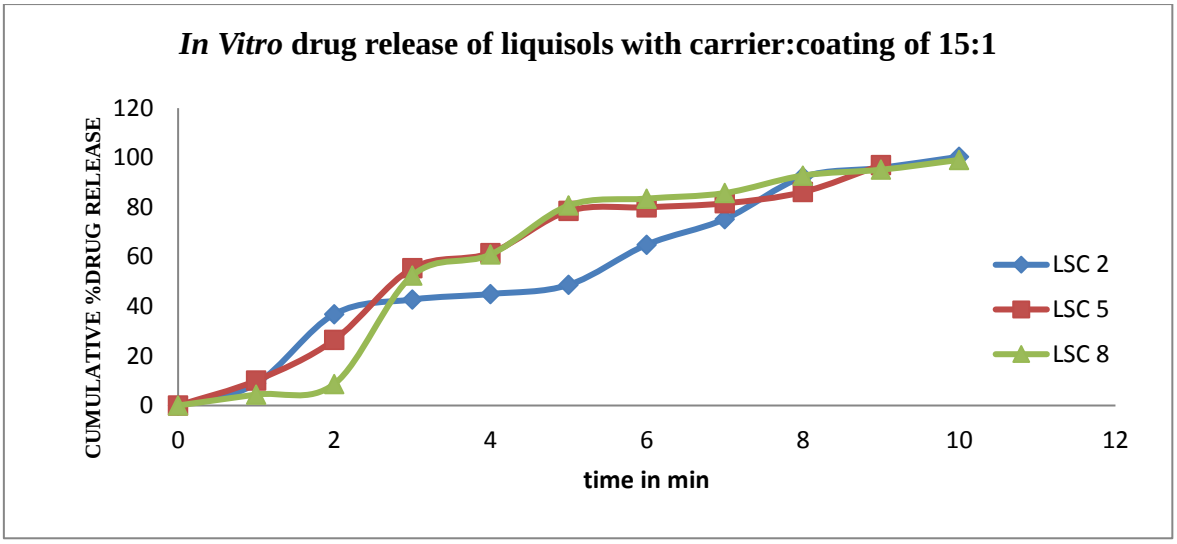

Fig 7: *In Vitro* drug release of Liquisols with carrier: coating of 15:1

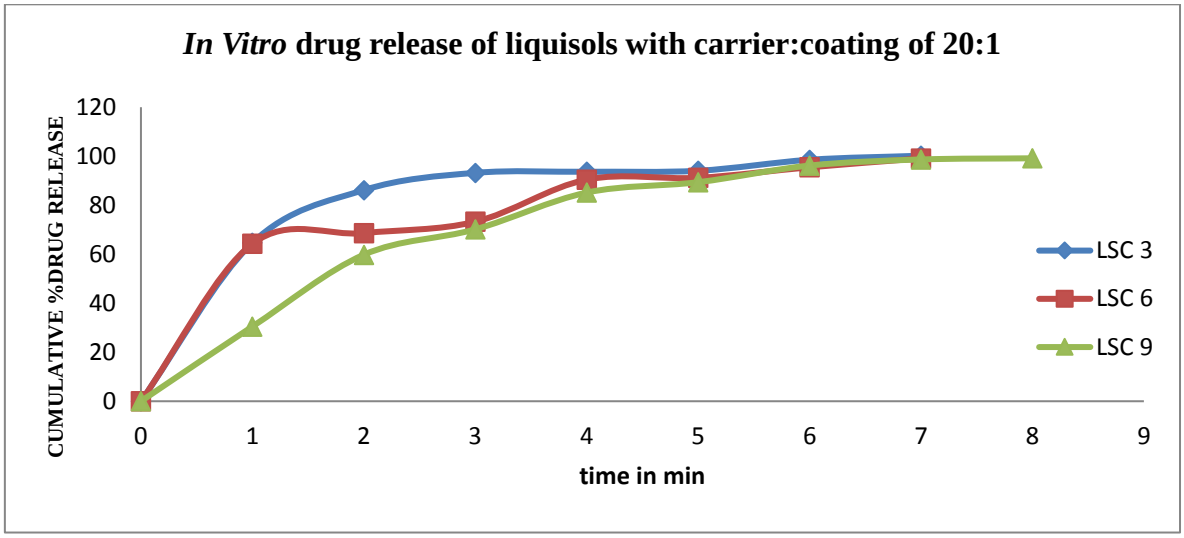

Fig 8: *In Vitro* drug release of Liquisols with carrier: coating of 20:1

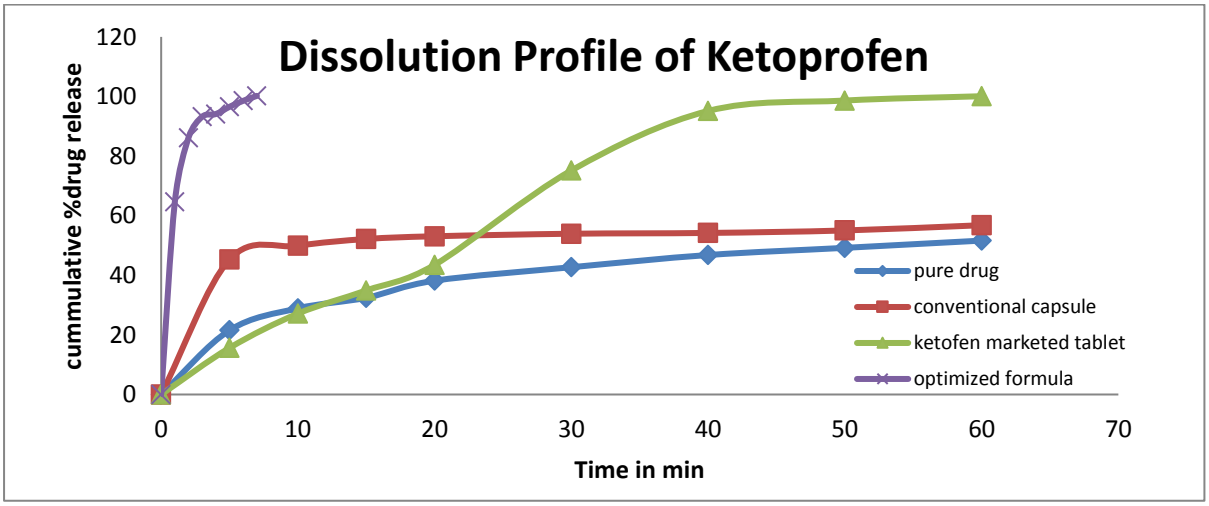

Fig 9: Comparative *In Vitro* release studies of prepared liquisol with marketed product

CONCLUSION:

Liquisolid compacts of Ketoprofen was prepared using 30%, 40% and 50% drug concentrations with carrier to coat ratios of 10:1, 15:1 and 20:1. The flow properties and the in vitro release for all the formulation studies revealed that 30% drug concentration with Excipient ratio of 20 is the best formulation, in terms of good flow and rapid release of drug from dosage form. It can also be concluded that the drug release is directly proportional to Excipient ratio and inversely proportional to drug concentration in liquid vehicle.

The increase in drug release from all the formulation is because the drug in liquid vehicle dispersed in molecular level and the surface area for dissolution is increased by addition of hydrophilic carrier. Therefore, liquid solid technique provides a promising delivery for fast release of poorly aqueous soluble drugs.

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