

Research Article

**Formulation and Evaluation of Ketoprofen by Liquisolid Compact Method**

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ABSTRACT

The main objective of present investigation was to enhance the dissolution rate of water insoluble drug ketoprofen by using liquisolid compact technique. It involves dissolving water insoluble drugs in non-volatile solvents and converting into acceptably flowing and compressible powders. Several liquisolid compact tablets were prepared by using different carrier materials such as microcrystalline cellulose, and dicalcium phosphate, and coating material such as silica gel. Propylene glycol, polyethylene glycol-400 and tween80 were used as non volatile organic liquids as vehicle. The ratio of carrier to coating material used here are 15 to 1 and 20 to 1.5 %. Sodium starch glycolate is used as disintegrant to each formulation. For obtained powder mass precompression parameters were evaluated. Then powder mass is compressed into tablets and tablets are evaluated for post compression parameters. The results showed that liquisolid compact formulation containing MCC and silica gel in 20:1 with PEG-400 as vehicle showed 99% drug release 30 minutes and it was concluded that there was no interaction between drug and excipients.

Keywords: liquisolid compact, ketoprofen, wetting, content uniformity, flow properties, hardness, friability, disintegration, dissolution

INTRODUCTION

Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists.¹ The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract. Thus, one of the major challenges in drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water.

Liquisolid technique is one of the most promising novel techniques amongst various methods to overcome dissolution problem. Liquisolid systems involves conversion of liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free-flowing, non adherent, dry looking, and readily compressible powders with the use of carrier and coating materials. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Inert, preferably water-miscible organic solvent systems with

high boiling point such as propylene glycol, liquid polyethylene glycols, and tween-80 are best suitable as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Microcrystalline cellulose and dicalcium phosphate were used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material.

Ketoprofen, 2-(3-benzoylphenyl)-propionic acid, is one of the propionic acid class of non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects.

The major problem associated with the formulation and effectiveness of the ketoprofen is its variable oral absorption due to insufficient aqueous solubility at gastrointestinal pH, thus making dissolution the rate-determining step in the gastric absorption of ketoprofen.

Therefore, ketoprofen establishes a good candidate for testing the potential of rapid-release liquisolid compacts.

MATERIALS AND METHODS**Determination of solubility**

Solubility studies of ketoprofen were carried out in water, phosphate buffer 7.4, PEG- 400, Tween 80, propylene glycol. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48 hr at 25°C under constant vibration.

After 48 hr the solution was filtered using 0.45µm micron filter paper and diluted with water and analyzed spectrophotometrically at 258 nm. The average value of three trials was taken.



Preparation of liquisolid compacts

Calculated quantities of ketoprofen and solvent were accurately weighed in a 20-mL glass beaker and then mixed well. The resulting medication was incorporated into calculated quantities of carrier and coating materials. The mixing process was carried out in three steps. In the first, the system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder.^{2,3} In the second, the liquid/powder admixture was evenly spread as a uniform layer on the surface of a mortar and left standing for approximately 5 min to allow the drug solution to be absorbed inside powder particles. In the third, the powder was scraped off the mortar surface using an aluminum spatula. Carrier: Coating material was then added to this mixture and blended in a mortar. This provided the formulation which was finally compressed into tablets using a 12mm single punch tablet compression machine after addition of 5% sodium starch glycolate as disintegrating agent.

Precompression studies

Drug content estimation

An accurately weighed amount of each preparation containing 100mg of Ketoprofen was dissolved in 100ml of methanol.⁴ The solution was passed through a vacuum filter and analyzed spectrophotometrically at 258 nm using UV-visible spectrophotometer after sufficient dilution with phosphate buffer pH of 7.4.

Flow properties

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies, otherwise, high dose variations will occur.^{5,6} In order to ensure the flow properties of the liquisolid systems that will be selected to be compressed into tablets and further evaluated for angle of repose measurements, Carr's index and Hausner's ratios.

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose (θ) was calculated using the following equation.

$$\theta = \tan^{-1} h/r$$

where h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 g of powder blend

from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = [(TBD-LBD) \times 100]/TBD$$

Hausner's ratio

Hausner's ratio was the ratio of tapped density to bulk density. It was calculated from the equation:

Hausner's ratio = Tapped density/Bulk density.

Postcompression studies

Weight variation Test

The test was performed as per USP by weighing 20 tablets individually on electric balance, calculating the average weight, and comparing the individual tablet weight to the average weight.

Friability Test

The test was performed using Roche friabilator. The device was rotated at 25 rpm for 100 revolutions. Friability was calculated by using following formula.

$$\%F = 100(W_0/W)$$

Where, W= final weight of tablets

W₀= Original weight of tablets

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined.

in vitro Drug Release Study

The dissolution study was carried out using Labindia DS 8000 dissolution apparatus. The dissolution medium was 900 ml of phosphate buffer with a pH of 7.4 kept at 37 ± 5°C. 100 mg Ketoprofen liquisolid compact tablets were kept in the baskets of dissolution apparatus rotating at 50 rpm. Samples of 5ml were withdrawn at specified time



intervals and analyzed spectrophotometrically at 258 nm using Elico Double beam SL 210 UV-visible spectrophotometer, the samples withdrawn were replaced by fresh buffer solution.^{7,8} Each preparation was tested in triplicate and the mean values were calculated as given in Table 6.

RESULTS AND DISCUSSION

Ketoprofen was selected as model drug for this study as it is class II drug which has poor solubility in water and thus ideal candidate for evaluating rapid release potential of liquisolid tablets.^{9,10} Liquisolid hypothesis states that drug candidate dissolved in liquid nonvolatile vehicle and incorporated into carrier material having porous structure and closely matted fibers in its interior, phenomenon of both adsorption and absorption occurs. This concludes that drug in the form of liquid medication is absorbed initially in the interior of particles of carrier and after saturation of this process it gets adsorbed into internal

and external surfaces of carrier. Coating materials such as silica gel which have high absorptivity and greater surface area lead the liquisolid systems desirable flow properties.

Determination of Solubility of Ketoprofen

Determination of solubility is most important aspect in formulation of liquisolid systems. It is needed ascertain formation of molecular dispersion of the drug in non-volatile solvent as shown in Table 1.

Table 1: Solubility profile of the drug Ketoprofen

S. No	Solvents	Solubility
1	Water	3.58mg/ml
2	Polyethylene glycol-400	3050 mg/ml
3	Propylene glycol	1050 mg/ml
4	Tween-80	1200 mg/ml
5	Glycerine	25 mg/ml

Table 2: Formulations containing drug, solvents, carrier, coating material and Disintegrant.

Formulations	Drug	Solvents	Carrier	Coating material	Disintegrant
F1	100 mg	PG-50mg	MCC-270 mg	aerosil-18 mg	SSG-25 mg
F2	100 mg	PG-50mg	DCP-270 mg	aerosil-18 mg	SSG-25 mg
F3	100 mg	PEG-400 - 50mg	MCC-270 mg	aerosil-18 mg	SSG-25 mg
F4	100 mg	PEG-400 - 50mg	DCP-270 mg	aerosil-18 mg	SSG-25 mg
F5	100 mg	TWEEN-80-50mg	MCC-270 mg	aerosil-18 mg	SSG-25 mg
F6	100 mg	TWEEN-80-50mg	DCP-270 mg	aerosil-18 mg	SSG-25 mg
F7	100 mg	PG-50mg	MCC-360 mg	aerosil-18 mg	SSG-25 mg
F8	100mg	PG-50mg	DCP-360 mg	aerosil-18 mg	SSG-25 mg
F9	10mg0 mg	PEG-400 - 50mg	MCC-360 mg	aerosil-18 mg	SSG-25 mg
F10	100 mg	PEG-400 - 50mg	DCP-360 mg	aerosil-18 mg	SSG-25 mg
F11	100 mg	TWEEN-80-50mg	MCC-360 mg	aerosil-18 mg	SSG-25 mg
F12	100 mg	TWEEN-80-50mg	DCP-360 mg	aerosil-18 mg	SSG-25 mg

Precompression studies

Drug content estimation

The percentage of drug uniformity was found to be between 98%-102% as shown in Table 3.

Table 3: Estimation of drug content for formulations F1-F12

Formulations	Drug Content
F1	98.7 ± 0.15
F2	98.3 ± 0.13
F3	100.1 ± 0.17
F4	99.5 ± 0.12
F5	99.2 ± 0.13
F6	98.9 ± 0.14
F7	100.7 ± 0.11
F8	100.5 ± 0.12
F9	101.6 ± 0.15
F10	101.4 ± 0.14
F11	101.0 ± 0.14
F12	100.8 ± 0.13



Flow properties

Flow properties are the important concern in the formulation and industrial production of tablet dosage form. Angle of repose is characteristic to the flow rate of powder (Table 4.)

Table 4: Precompression parameters of fomulations F1-F12

S. No	Bulk Density	Tapped Density	Angle of Repose	Carr's Index	Hausners Ratio
F1	0.71	0.85	27°2	16.47	1.19
F2	0.70	0.84	28°3	16.66	1.2
F3	0.70	0.85	27°4	17.64	1.21
F4	0.70	0.85	27°9	17.64	1.21
F5	0.71	0.86	28°5	17.44	1.21
F6	0.72	0.85	29°1	15.29	1.18
F7	0.71	0.84	28°3	15.47	1.18
F8	0.72	0.84	27°8	14.28	1.13
F9	0.74	0.83	28°6	10.84	1.12
F10	0.72	0.82	28°3	12.19	1.13
F11	0.72	0.82	27°5	12.19	1.13
F12	0.71	0.83	26°9	14.45	1.16

Post compression studies

Results of post compression were tabulated for weight variation, friability, hardness, and disintegration. The results are in acceptable limits (Table 5).

Table 5: Post compression parameters for F1 –F 12 formulations

Formulation Code	Hardness (kg/cm ²)	Weight Variation	Friability	Disintegration (min)
F1	5±0.2	523±1.2	0.135±0.024	3.5±0.2
F2	5±0.7	546±1.5	0.152±0.025	3.3±0.4
F3	5±0.7	536±1.8	0.146±0.028	3.4±0.2
F4	5±0.5	525±1.5	0.156±0.029	3.4±0.1
F5	5±0.4	530±1.7	0.148±0.034	3.2±0.3
F6	4±0.9	532±1.2	0.168±0.031	3.1±0.1
F7	4±0.8	534±1.3	0.173±0.024	2.5±0.6
F8	4±0.7	539±1.5	0.148±0.036	2.8±0.5
F9	4±0.3	538±1.3	0.134±0.021	2.6±0.2
F10	4±0.5	540±1.2	0.139±0.025	3.1±0.4
F11	4±0.3	541±1.1	0.145±0.031	2.9±0.1
F12	4±0.5	539±1.3	0.143±0.022	3.3±0.3

Table 6: *in- vitro* Drug Release Studies for formulations F1-F12.

Formulation Code	5 min	10 min	15 min	30 min	45 min	60 min
F1	15±0.3	24±0.4	32±0.6	54±0.4	85±0.1	91±0.2
F2	14±0.5	22±0.1	30±0.1	50±0.5	84±0.3	90±0.8
F3	18±0.4	28 ±0.6	39±0.7	65±0.5	85±0.1	95±0.5
F4	16±0.7	26±0.2	35±0.6	63±0.4	86±0.3	94±0.1
F5	16±0.3	24±0.4	33±0.2	59±0.2	89±0.1	93±0.3
F6	19±0.4	30±0.3	43±0.7	70±0.9	89±0.3	92±0.2
F7	20±0.3	37±0.2	48±0.5	76±0.4	95±0.4	97±0.3
F8	19±0.4	36±0.4	45±0.3	74±0.6	94±0.3	97±0.5
F9	27±0.7	47±0.6	64±0.4	86±0.8	100±0.2	--
F10	23±0.4	43±0.7	59±0.3	83±0.5	99±0.1	100±0.1
F11	24±0.2	40±0.5	54±0.7	80±0.4	98±0.3	99±0.5
F12	21±0.6	38±0.4	51±0.5	78±0.5	97±0.5	98±0.2



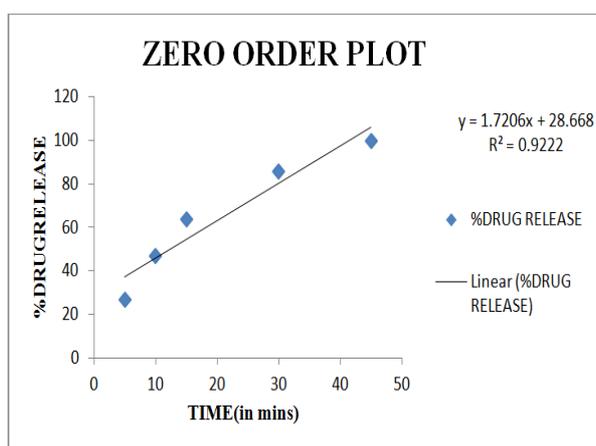


Figure 1: Zero order plot for F9 formulation

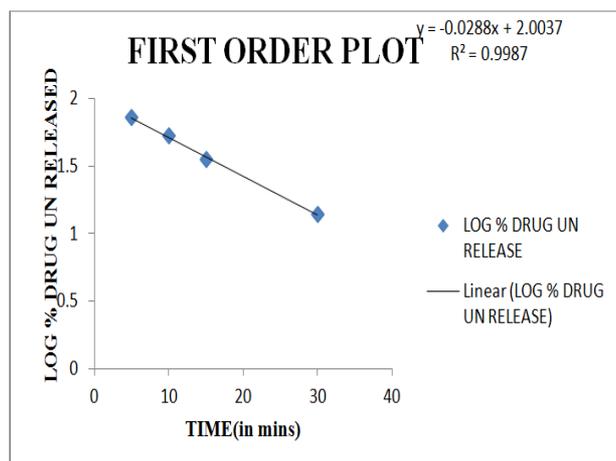


Figure 2: First order plot for F9 formulation

Phenomenon of Drug Release Kinetics

The optimized formulation F9 was subjected to graphical representation to assess the kinetics of drug release. The release of drug was observed to follow the First order release kinetics ($R^2=0.9987$). Hence the drug release was mainly found to be concentration independent as shown in Figure 1 & Figure 2.

CONCLUSION

The liquisolid compact method is a best method to enhance the dissolution rate of Ketoprofen, which is class II drug having low solubility and high permeability. Enhanced dissolution rates obtained in this study indicates that it increases oral bioavailability also. It is due to increased wetting and surface area available for dissolution. It can be concluded that formulation ,F-9 had showed better dissolution than remaining formulations. This novel approach to the formulation may be helpful to improve oral bioavailability.

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