Enhancement of dissolution and bioavailability of water insoluble drug using liquisolid compact for oral application.

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Introduction

Nimesulide, a non-steroidal anti-inflammatory drug (NSAID), is administered orally or rectally twice daily for a variety of inflammation and pain states. This is a unique NSAID, not only because of its chemical structure but also because of its specific affinity to inhibit cyclooxygenase-2 (COX-2), thus exerting milder effects on the gastrointestinal mucosa

Nimesulide is superior, or at least comparable in efficacy, to other NSAIDs, but is better tolerated and has less potential for adverse reactions. Thus, selective COX-2 inhibitors should have anti-inflammatory effects devoid of side effects on the kidney and stomach.

They may also demonstrate new important therapeutic benefits as anticancer agents as well as help prevention of premature labour and even retard the progression of Alzheimer's disease

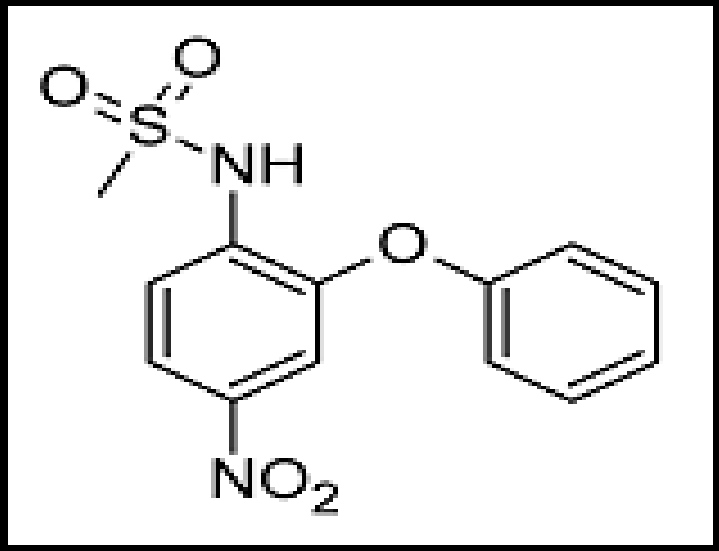

Figure 1

Nimesulide is N-(4-Nitro-2-phenoxyphenyl)methanesulfonamide

Mol. Formula: $C_{13}H_{12}N_2O_5S$; Mol. Mass: 308.31

Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water-soluble

From the historical point of view, liquisolid compacts were evolved from ‘Powdered Solutions’ which depended on preparing a true solution of the drug in a high boiling point, water-miscible solvent, which was carried out on the extensive surface of an inert carrier such as silica

Aim of Work

The aim of this study was to increase dissolution rate of nimesulide using liquisolid technique. In this study nimesulide, a poorly water-soluble, non-steroidal anti-inflammatory drug was formulated into 20 mg liquisolid tablets

Preparation of conventional tablet and liquisolid compacts

nimesulide conventional tablets were produced by mixing the drug with microcrystalline cellulose–Aerosil 200 and the additive for a period of 10 min in a cubic mixer (Erweka, TypeUG, Germany).

The mixture was mixed with Ac-Di-Sol (5%, w/w, of the formulation) for 10 min. The mixture was compressed on a 10-mm punch and die using a manual tableting machine (Riken, Japan) Several liquisolid compacts, denoted as f1 to f8 were prepared as follows.

nimesulide was dispersed in PEG 400,PG,and mixture of PEG400 or PEG and Tween 80 in a ratio 1:1.Then a binary mixture of carrier–coating materials (microcrystalline cellulose as the carrier powder and Aerosil 200 as the coating material) was added to the obtained liquid medication under continuous mixing in a mortar.

Finally, 5 %(w/w) of Ac-Di-Sol as the disintegrant, was mixed with the mixture for a period of 10 min. The final mixture was compressed using the manual tableting machine to achieve tablet hardness of 6-7kg.

Formulation characteristics of the prepared nimesulide liquisolid compacts.

Formula No	Drug %	Amount of liquid (mg)	Amount of carrier (mg) Q	Amount of coating (mg) q	Amount of disintegrant (mg)	Total weight of tablet
F1	10	200.00	1100	55.00	68.75	1443.80
F2	20	100.00	600	30.00	37.50	787.50
F3	30	66.6.00	435	21.75	27.20	669.20
F4	40	50.00	350	17.50	21.88	459.40
F5	50	40.00	300	15.00	18.75	393.80
F6	20	100.00	600	30.00	37.50	787.50
F7	20	100.00	600	30.00	37.50	787.50
F8	20	100.00	600	30.00	37.50	787.50

Evaluation of nimesulide liquisolid tablets

1. Differential Scanning Calorimetery (DSC) of the prepared liquisolid powder
2. Determination of the drug content
3. Determination of the friability, hardness, and disintegration time
4. Dissolution study
5. Determination of anti-inflammatory effect of nimesulide using liquisolid compact

RESULTS AND DISCUSSION

The very poor aqueous solubility and wettability of cox-2 inhibitors however gives rise to difficulties in the design of pharmaceutical formulations and leads to a variable oral bioavailability.

Solubility of nimesulide was determined in different solvents as propylene glycol, polyethylene glycol 400, glycerol and water. The solubility of the drug in different solvents was 63.120, 1.760, 0.218, and 0.014 mg/ml for PEG400, PG, glycerol and water respectively[15].

DSC study

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation; it is very important to establish the existence of any incompatibilities during the preformulation stage to ensure the success of the subsequent stability studies.

Figure 1 reveals the thermal behaviors of the pure components together with the thermal behavior of the final liquisolid system prepared. Nimesulide peak is clear in its DSC thermogram (Fig. 1A) demonstrating a sharp characteristic endothermic peak at 149.25°C corresponding to its melting temperature (*Tm*);

The liquisolid system thermogram in figure 2 displayed complete disappearance of characteristic peak of nimesulide a fact that agrees with the formation of drug solution in the liquisolid powdered system, i.e., the drug was molecularly dispersed within the liquisolid matrix.

Such disappearance of the drug peaks upon formulation of the liquisolid system declared that the complete suppression of all drug thermal features, undoubtedly indicates the formation of an amorphous solid solution.

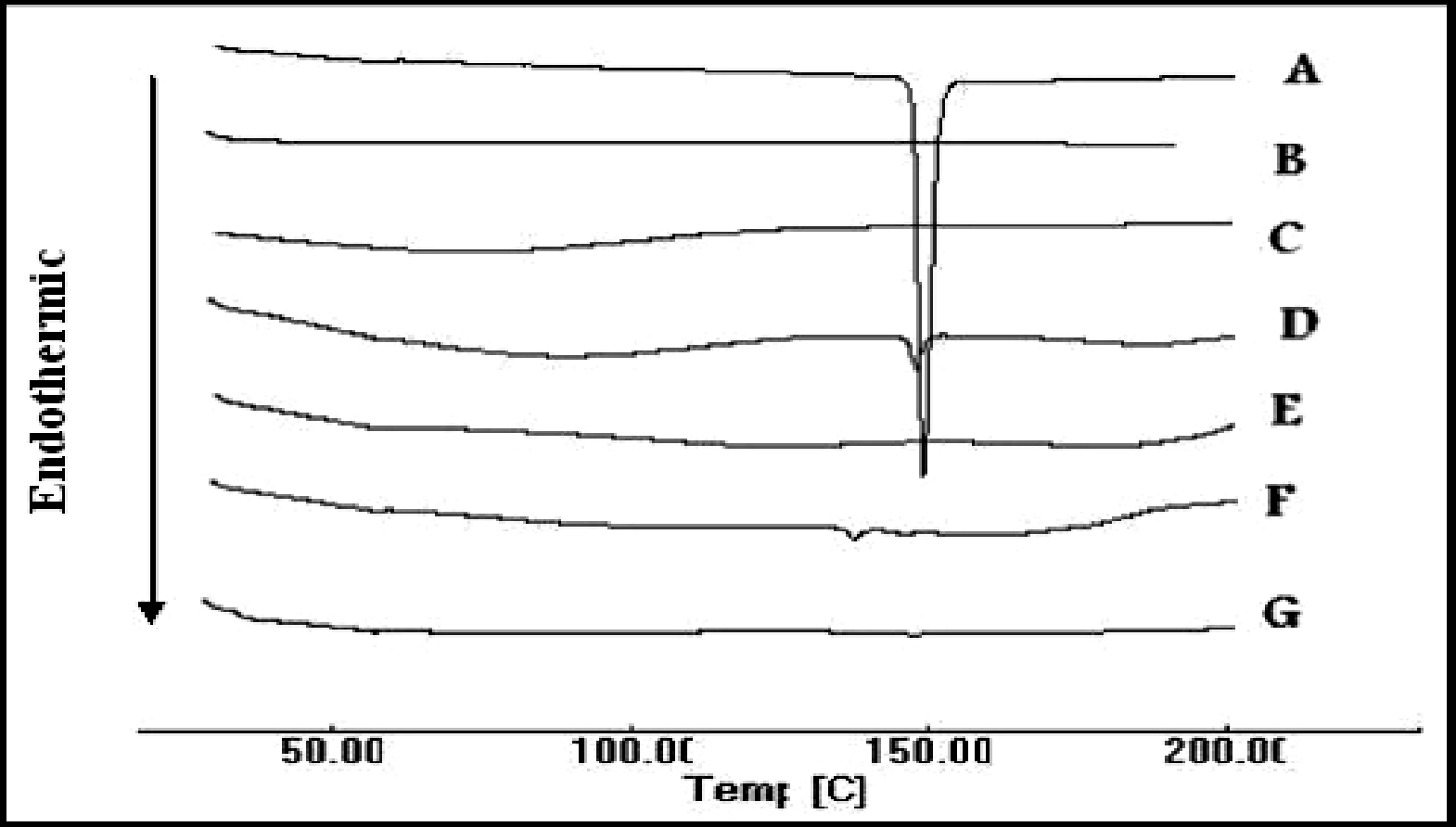

Fig1 DSC thermogram of nimesulide (A), Avicel PH102 (B), Aerosil 200 (C), physical mixture (D), liquisolid compact mixture containing PEG400 (E), liquisolid compact mixture containing PG (F), and liquisolid compact mixture containing Tween 80 (G).

Dissolution study of nimesulide liquisolid compacts

In-vitro dissolution profiles of nimesulide showed that the liquisolid compacts produced higher dissolution rates in comparison with the conventional tablet. For example, the percentages of drug released from F1, F6, F7, F8, and conventional tablets after 1 hr were 100%, 80%, 100%, 88%, and 50% at pH 1.2 respectively.

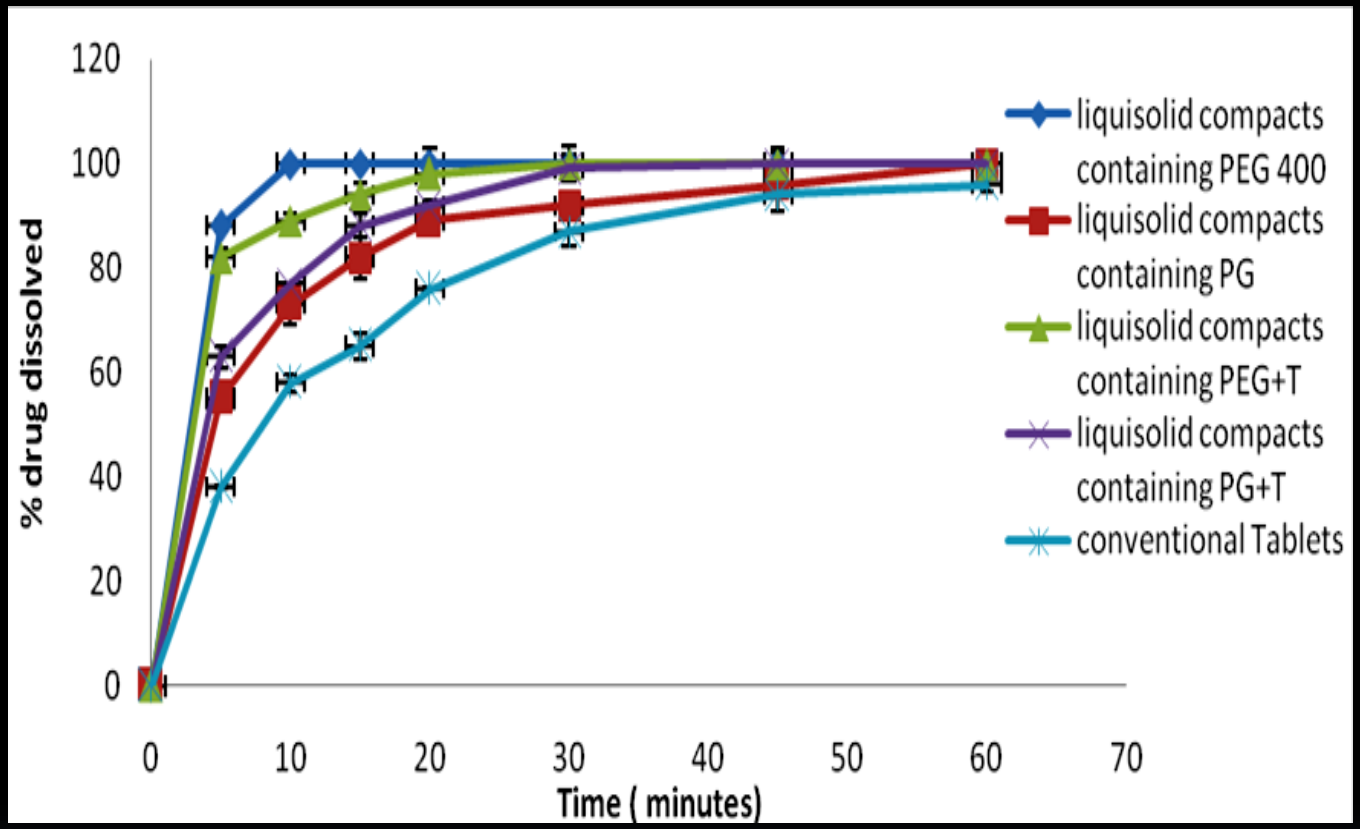

Fig.2The dissolution profile of nimesulide from different liquisolid compacts compared with conventional tablets.

Figure 3 shows the dissolution rates of different liquisolid compacts using different solvents (PEG400, PG, PEG+Tween, PG+Tween) in comparison with conventional tablets. The figure shows that dissolution rates decreased in the following order: PEG400 > PEG400+Tween > PG+Tween > PG > compressed tablets.

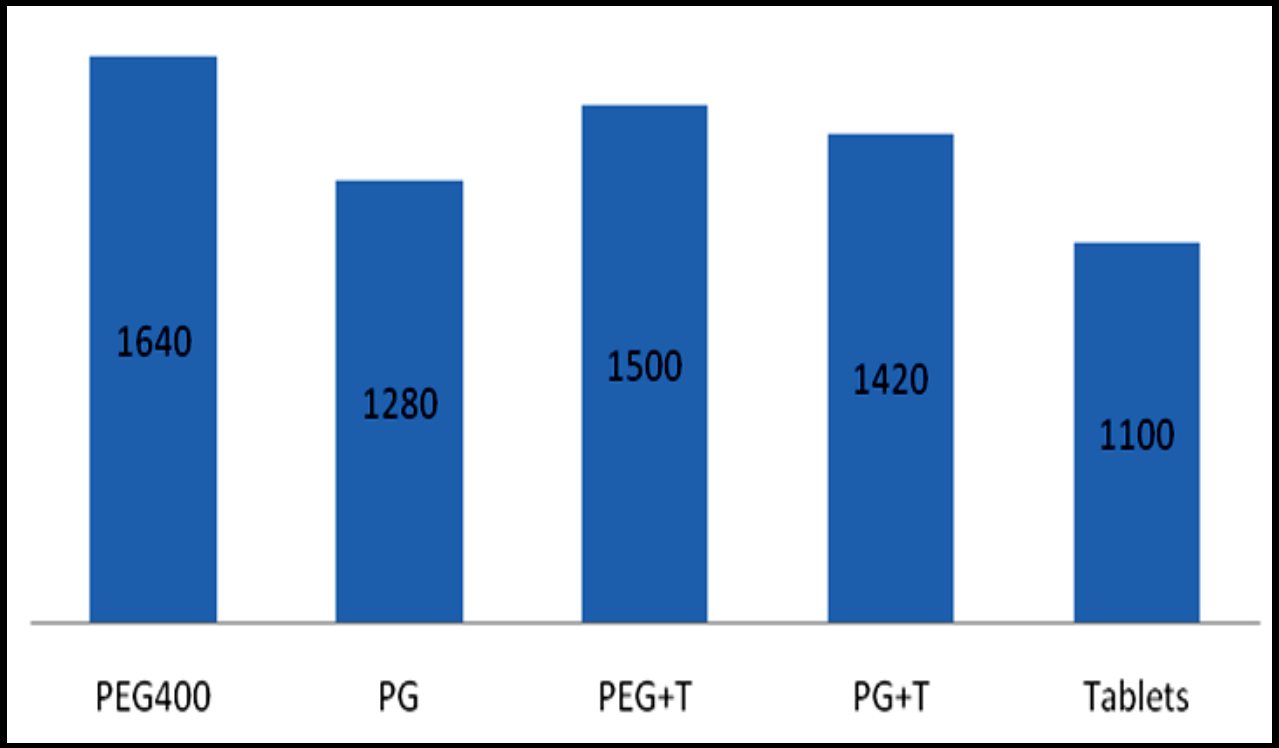

Fig. 3: The dissolution rates (*DR*) of nimesulide from different liquisolid compacts and conventional tablets.

The drug concentration in the liquid medication is one of the main factors on the performance of a liquisolid compact. The effect of drug concentration (*Cd*) in the liquid medication (PEG400) on dissolution profile of nimesulide from the liquisolid compacts in 0.1 N HCl dissolution media is shown in figure 4.

The figure shows that the increase of drug concentration from 20–50% in the liquid medication a liquisolid compact has no considerable effect on the dissolution rate. It can be seen that dissolution rate has no significant increase with an increase in the concentration of drug.

This result can be attributed to that the drug in low concentrations is in a molecular form which is more soluble than the drug in higher concentrations[3].

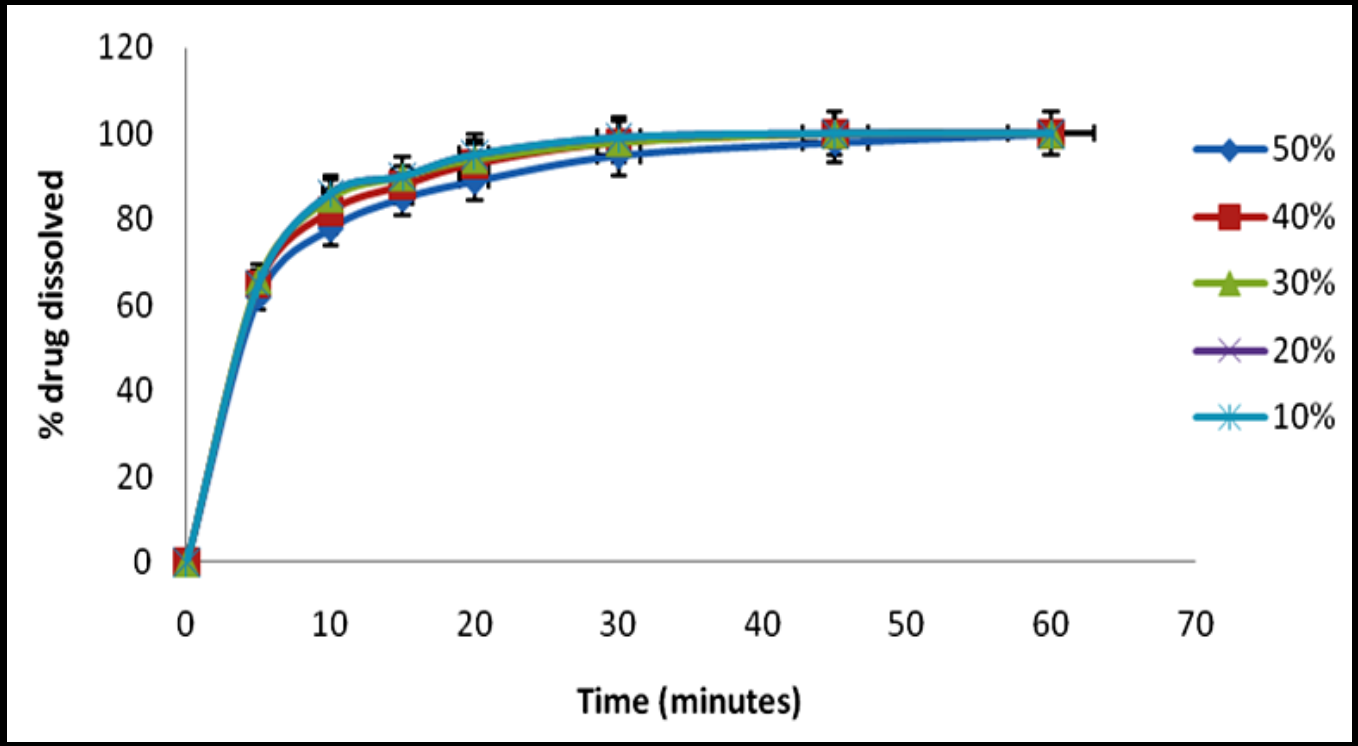

Fig. 4: Effect of different concentrations of drug on the dissolution from liquisolid compacts containing PEG.

The anti-inflammatory effect of nimesulide from liquisolid compact

The anti-inflammatory effect of nimesulide from two formulae of liquisolid compacts compared with conventional tablets. The percent inhibition observed with any formulae considered the maximum possible response for anti-inflammatory effect of nimesulide in this formula during the 4 hrs observation period.

Figure 5 showed the percent inhibition of paw edema plotted against time. From the figure it was observed that the order of suppression of swelling (percentage inhibition) was as follows: LSC (PEG) > LSC (PG) > conventional tablets.

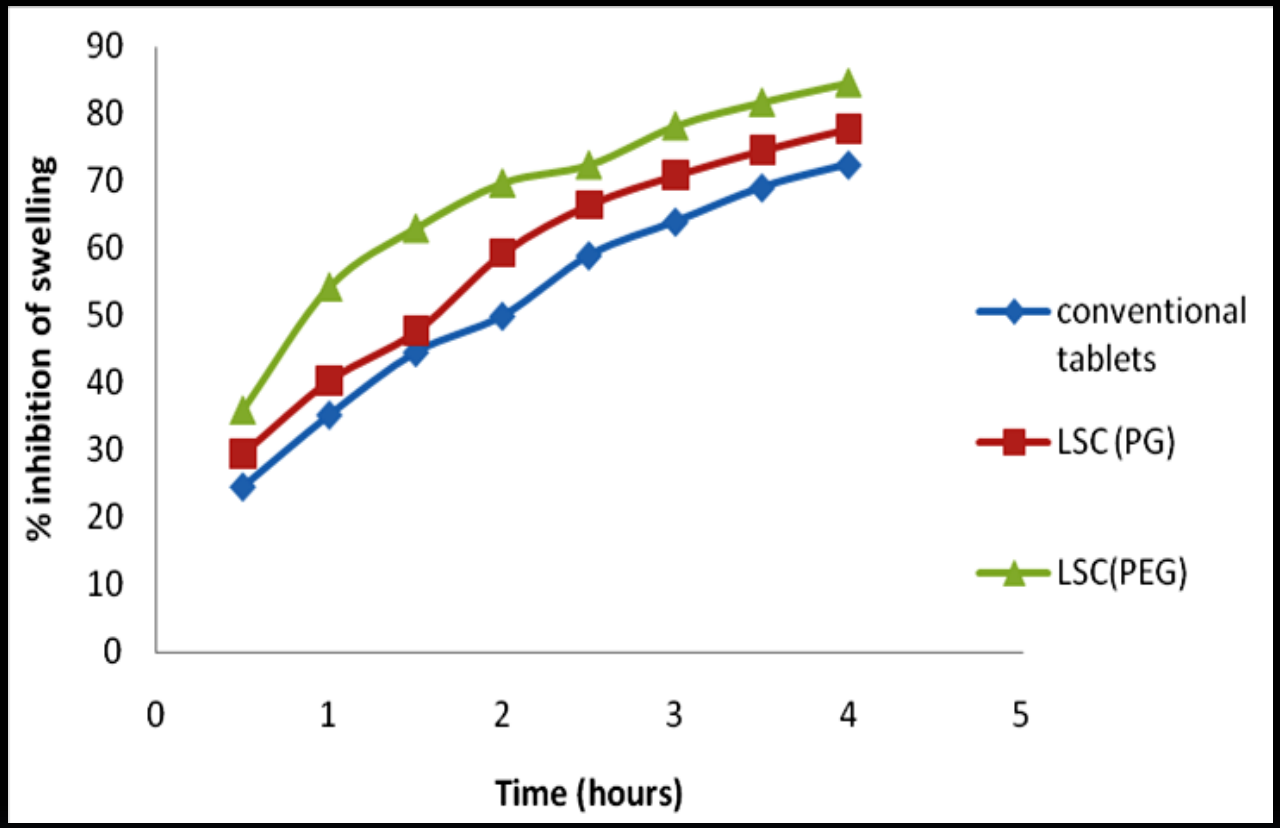

Fig. 5: The percentage inhibition of swelling from nimesulide liquisolid compacts compared with conventional tablets.

Conclusion

The liquisolid technique is the most promising method for promoting dissolution rate of poorly water-soluble drugs. The results showed that the optimum loading factor which gives good flowability and compressibility is 0.2, and the liquisolid compact containing PEG400 gives the highest dissolution rate than other formulae.

Also the results showed no increase in the amount of the drug dissolved as the concentration of the drug increases. Liquisolid compacts give a pronounced anti-inflammatory effect when compared with conventional tablets.

Acknowledgment

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- ***THANK YOU FOR YOUR ATTENTION***