# In-Vitro Dissolution Enhancement of Indomethacin by Liquisolid Technique

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**ABSTRACT**

*The present research work involves the development of the liquisolid tablets containing Indomethacinas model drug using liquisolid technique. Initally, liquisolid compacts containing Indomethacin LSCB1 and LSCB2 were prepared using two concentrations 1:1 and 1:05 ratio of non-volatile liquid (Polyethyleneglycol-800) respectively and also carrier material (microcrystalline cellulose) and coating material (aerosil100) were added. Later, Indomethacin liquisolid tablet formulations IMF1, IMF3, IMF5 and formulations IMF2, IMF4, IMF6 are prepared using LSCB1 and LSCB2 liquisolid compacts and different concentration of super-disintegrant (crospovidone) are added for the tablet formulations IMF1-IMF2, IMF3-IMF4 and IMF5-IMF6 was 2%, 4% and 6% respectively. Finally, the liquisolid tablet of Indomethacin was formulated and successfully achieved the enhancement of dissolution rate of Indomethacin using liquisolid technique.*

## INTRODUCTION:

The oral route is the most preferred route of drug administration. Aqueous solubility of drugs is one of the major factors affecting desired bioavailability. The poorly water soluble drugs may have poor dissolution rate and incomplete bioavailability. The challenge for poorly water soluble drugs is the dissolution. There are different types of techniques available to increase the solubility of poorly water soluble drugs i.e., Micronization, Lyophilisation, Solid dispersions, use of complexing agents, co solvency, chemical modification, pH adjustment, solubilization by surfactants, solid solutions, inclusion of liquid drug into the soft gelatin capsules and salt formation etc.. To overcome all these types of problems the "Liquisolid Technique" was introduced. Liquisolid technology is also called as "Powder Solution Technology".1

Liquisolid compacts are acceptably free flowing and compressible powder forms of liquid medications. The liquid portion, which can be an oily liquid drug, suspension or solution of water insoluble solid drug in suitable non-volatile liquid vehicle, is incorporated into the porous carrier material. 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.2

Indomethacin was selected as a model drug for the present research work. It belongs to methylated indole derivative (2-[1- (4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetic acid) and a member of the arylalkanoic acid and is a non-steroidal anti-inflammatory drug. The plasma half-life of Indomethacin is 2.6-4.5 hours. It is potent antipyretic, analgesic, and anti-inflammatory drug. Indomethacin is nonselective COX inhibitor. It is a highly potent inhibitor of prostaglandin synthesis and suppresses neutrophil activity.

## MATERIALS AND METHODS:

Indomethacin was obatineed from gift sample from Jagsonapal Phamracaeuticals, Delhi, Aerosil was purchased from KKChempro India Pvt Ltd, Maharashtra and all other chemicals and solvents were pruchased from local market and were analytical grade.

### 1. Formulation of Indomethacin liquisolid tablets:

A mathematically calculated quantity of drug was weighed and dissolved in the appropriate amount of non-volatile liquid in a molecularly dispersed state. To obtain good flow properties trial and error methods were followed i.e., changing the carrier:coating ratioin the range from 50:1 to 5:1 as per new mathematical model expressions proposed by Liao.[6] The obtained liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed into the carrier internally and externally.

At the end, coating material was sprinkled to get dry look, adherent to the carrier material for achieving good compression properties. Liquid medication was added to carrier material which has a porous surface and closely matted fibers in its interior as cellulose. Two phenomena namely absorption and adsorption takes place, i.e., the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid onto the internal and external surface of the porous carrier particles occurs.

As per the said mathematical model, calculated quantities of Indomethacin and propylene glycol 800 was accurately weighed and mixed. This dispersed mixture was added to calculated amount of carrier and coating materials. Mixing process was followed in two steps as explained by Spireas et al.

In first stage, 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.

Followed by, in second stage, the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particles. This allows to produce final formulation of liquisolidcompacts.

The prepared liquisolid compacts were mixed with super disintegrant (crospovidone) and lubricant (magnesium stearate). The weighed amount of mixture was transferred to the die cavity and tablets were compressed using 12 mm flat punches using multi station tablet punching machine (Remik machine, Ahmedabad). Composition of formulation presented in Table No 1 and Table No 2.

**Table 1: Composition of Indomethacin liquisolid tablets**

| Ingredients (mg/ tablet) | IMF1 | IMF2 | IMF3 | IMF4 | IMF5 | IMF6 |
|---|---|---|---|---|---|---|
| Indomethacin | 25 mg | 25 mg | 25 mg | 25 mg | 25 mg | 25 mg |
| PEG 800 | 125 mg | 62.5 mg | 125 mg | 62.5 mg | 125 mg | 62.5 mg |
| Microcrystalline cellulose | 380.5 mg | 380.5 mg | 380.5mg | 380.5mg | 380.5mg | 380.5mg |
| Aerosil 100 | 76.1 mg | 76.1 mg | 76.1 mg | 76.1 mg | 76.1 mg | 76.1 mg |
| Crospovidone | 2 % | 2 % | 4 % | 4 % | 6 % | 6 % |
| Magnesium stearate | 7.2 mg | 7.2 mg | 7.2 mg | 7.2 mg | 7.2 mg | 7.2 mg |

**Table 2: Formulation of Iburofen liquisolid compacts**

| Ingredients | LSCB 1 | LSCB 2 |
|---|---|---|
| Indomethacin | 25 mg | 25 mg |
| PEG 800 | 125 mg | 62.5 mg |
| Microcrystalline cellulose | 380.5 mg | 380.5 mg |
| Aerosil 100 | 76.1 mg | 76.1 mg |

**2. Determination of solubility of Indomethacin in various solvents:**
Initally, saturated solutions were prepared by adding excess of Indomethacin to various solvents includes Propylene glycol, PEG-800, methanol, water, and phosphate buffer pH 6.8 and shaken on the automatic mechanical shaker for 48 h at 25°C under constant vibrations. These solutions were filtered, diluted and analyzed spectrophotometrically at 228 nm against suitable blank sample. Three determinations were carried out for each sample to calculate the solubility of Indomethacin.

**3. *In-vitro* disintegration test:**
The disintegration time of a tablet was determined using disintegration test apparatus (Electrolab, India). One tablet was placed in each of the 6 tubes of the basket. A disc was added to each tube and run the apparatus using phosphate buffer pH 6.8 maintained at 37±5°C as the immersion liquid. The entire assembly was raised and lowered between 30 cycles per minute in the phosphate buffer pH 6.8 maintained at 37±5°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The study was performed in triplicate and result is expressed as Mean ± SD.

**4. Drug Content Uniformity:** This test was carried out for liquisolid compacts and liquisolid tablets.
**a. Drug content of prepared liquisolid compacts:**
An accurately weighed quantity of liquisolid compacts equivalent to 25 mg of Indomethacin was taken in a 100 ml volumetric flask. The drug was then extracted by using phosphate buffer pH 6.8 by subjecting to continuous shaking on a rotary shaker for 24 h. Indomethacin in the extracted fluid was analyzed at 285 nm by using UV-visible spectrophotometer (UV-117, Shimadzu, Japan) against phosphate buffer pH 6.8 as blank. The drug content was estimated by placing experiment values in standard plot equation. The study was performed in triplicate and result is expressed as Mean ± SD.

**b. Drug content of prepared liquisolid tablets:**
The drug content was determined by crushing one tablet in glass mortar and pestle and taking the powder in 100 ml volumetric flask. The drug was then extracted by using phosphate buffer pH 6.8 for 48 h and this was filtered using Whatman filter paper and suitably diluted and finally analyzed by using UV spectrophotometer (UV-117, Shimadzu, Japan)at 228 nm against phosphate buffer pH 6.8 as blank. The drug content was estimated by placing experiment values in standard plot equation. The study was performed in triplicate and result is expressed as Mean ± SD.

**5. *In-vitro* drug dissolution studies:**
The *in-vitro* drug dissolution study was performed using eight station dissolution test apparatus (USP TDT-08L, Electrolab, India) with a paddle speed of 50 rpm. Dissolution medium consisted of 900 ml of phosphate buffer pH 6.8 maintained at 37± 0.5º C. At a predetermined time intervals, an aliquot was withdrawn and replenished with fresh medium. Amount of drug in each aliquot was assayed on a UV-Spectrophotometer (UV-117, Shimadzu, Japan) at 285 nm using phosphate buffer pH 6.8 as blank. All the trials were conducted in triplicate and result expressed as Mean ± SD.

**6. Model independent analysis:**
**a. Dissolution efficiency:** Dissolution efficiency is used to translate the profile difference into a single value. Dissolution efficiency was calculated by using following equation.

$$\boldsymbol{DE}\ \% = \frac{\int_0^t \boldsymbol{ydt}}{\boldsymbol{y_{100}}}\boldsymbol{t} \times \mathbf{100}$$

Where, y is the drug percent dissolved at time t.

**b. Mean dissolution time:** Mean dissolution time represents the mean time for drug molecules to

completely dissolve. It is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of the polymer. MDT was calculated by using the following equation.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where *'i'* is the dissolution sample number, *'n'* is the number of dissolution sample time, *'$t_{mid}$'* is the time at the midpoint between '*i'* and *'i-1'*, and *'ΔM'* is the amount of drug dissolved between *'i'* and *'i-1'*.

**7. Characterization of drug – excipients interaction:**

**FTIR study**

FTIR spectra of the optimized formulation was taken and compared with the spectrum of pure drug. The characteristic peaks of drug were obtained by scanning in the range of 4000 – 400 $cm^{-1}$ by using (FT-IR-8400, Shimadzu, Japan).

**8. Stability studies:**

The selected formulation was stored at room temperature in desiccators and at 40±2°C / 75±5 % RH for 2 months to analyze the stability of the formulations.

**RESULTS AND DISCUSSION:**

1. **Solubility Studies:** Solubility of drug in distilled water and various solvents like Methanol, Propylene glycol, Phosphate buffer pH 6.8 and Polyethylene glycol 800 were studied. It has been found that solubility results were within the apecified range.

**Table No 3: Solubility of Indomethacin using different solvents.**

| Sl. No. | Solvent / vehicle | Solubility (mg/mL) |
|---|---|---|
| 1 | Distilled Water | 0.206 ± 0.001 |
| 2 | Methanol | 14.87 ± 0.015 |
| 3 | Propylene glycol | 0.217 ± 0.002 |
| 4 | Phosphate buffer pH 6.8 | 0.026 ± 0.002 |
| 5 | Polyethylene glycol 800 | 11.53 ± 0.005 |

Values are mean±SD, n=3

2. **Drug Content:** Drug content uniformity in all formulations including liquisolid compacts was found to be in the range 88.94±2.32 to 96.41±0.80.

**Table No 4: Drug content of Indomethacin liquisolid compacts and Indomethacin liquisolid tablets.**

| Formulation | Drug content (%) |
|---|---|
| IMF1 | 88.94±2.32 |
| IMF2 | 89.25±3.31 |
| IMF3 | 96.41±0.80 |
| IMF4 | 91.24±4.00 |
| IMF5 | 92.21±2.16 |
| IMF6 | 92.24±4.18 |
| LSCB1 | 95.64±1.47 |
| LSCB2 | 92.86±0.24 |

Values are mean±SD, n=3

### 3. Characterization of Drug-Excipients interaction

#### Fourier Transform Infrared Spectroscopy (FTIR)

FT- IR spectrum of Indomethacin drug and selected formulation revealed there is no major interaction between drug and polymers used in the study.

**Table No 8: FTIR peaks at different wave numbers of Indomethacin and selected formulation.**

| Functional group | Wave number ($cm^{-1}$) | |
|---|---|---|
| | Indomethacin | Selected formulation |
| C = O stretching | 1651.12 | 1651.12 |
| C – O stretching | 1255.70 | 1255.70 |
| C – N stretching | 1159.26 | 1159.26 |
| O – H stretching of COOH (hydrogen bonded) | 3309.96 | 3313.82 |
| C – H stretching | 2860.53 | 2874.03 |
| C – H stretching of $CH_3$ | 2972.40 | 2902.96 |
| C⋯C stretching | 1575.89, 1506.46, 1444.73 | 1575.89, 1508.38, 1446.66 |
| C – H stretching (aromatic) | 3012.91 | 3072.71 |
| N – H stretching | 3427.62 | 3408.33 |

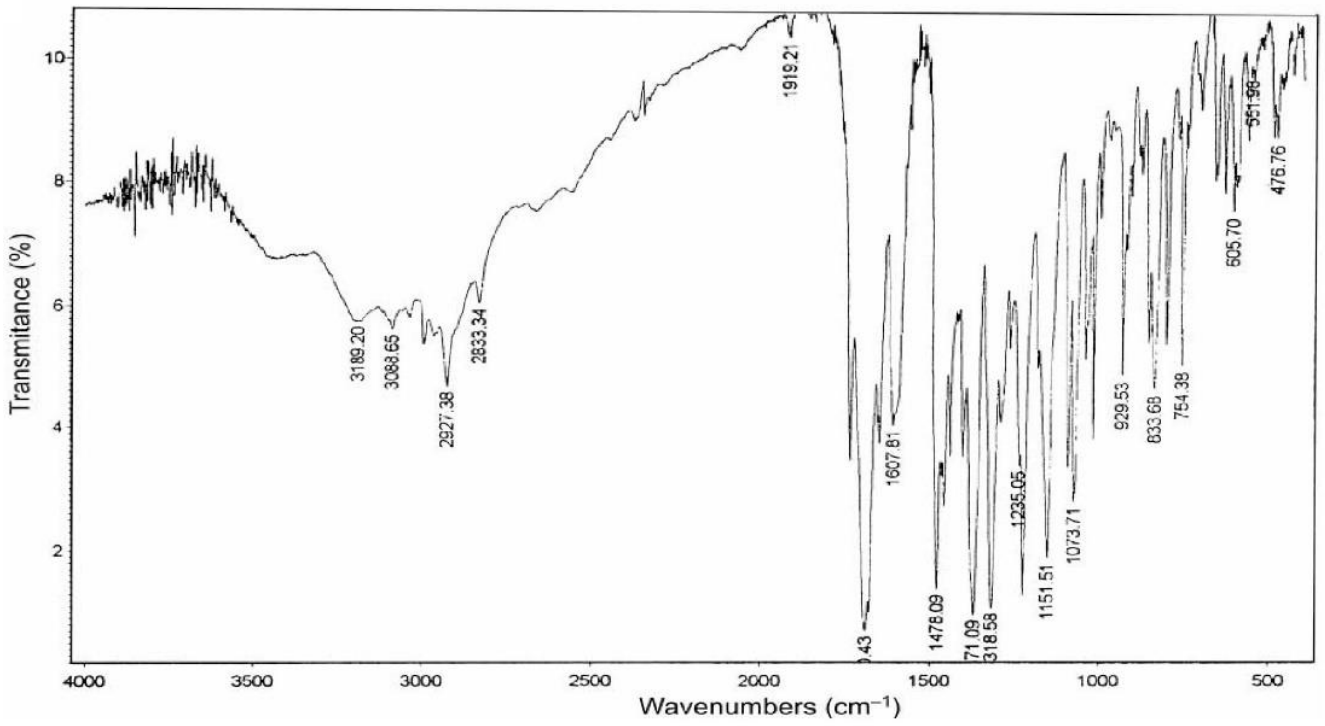


**Figure 1: FTIR Spectra of Indomethacin drug**

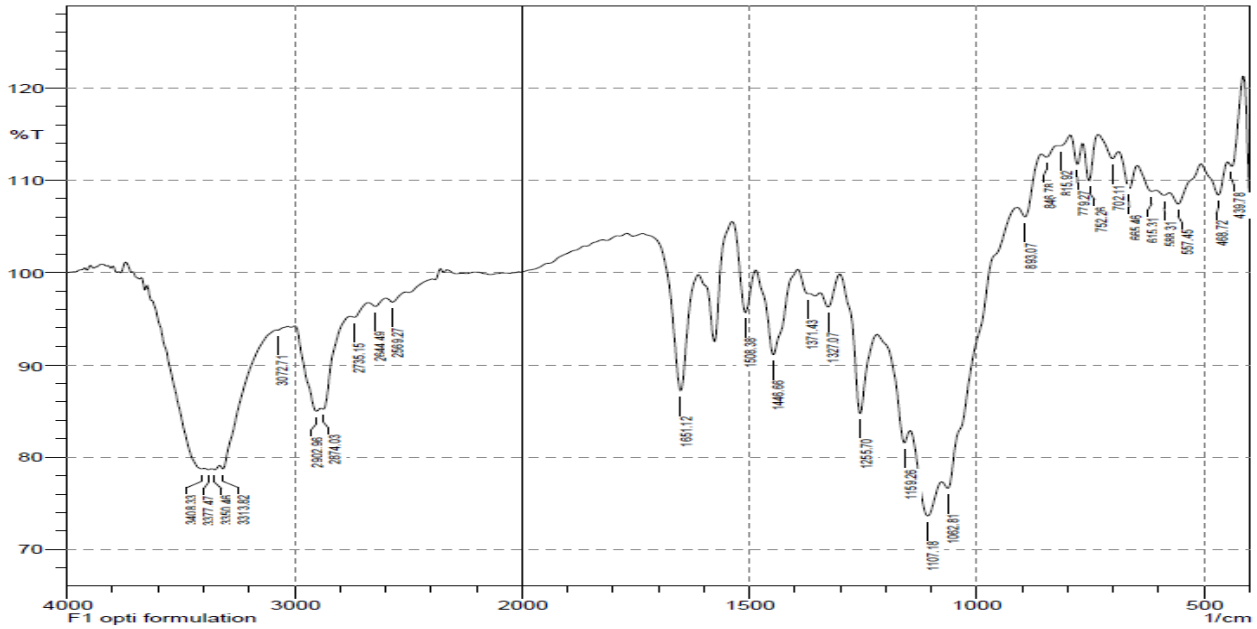


**Figure 2: FTIR spectra of selected formulation.**

## 4. *In-vitro* Dissolution Studies:

The data of i*n-vitro* Dissolution Studies from was analysed by plotting the cumulative percentage drug release vs. time (Figure 3 and 4). Initially, the *in-vitro* dissolution of Indomethacin drug was carried out and was found to be 18.77%. Later, the dissolution was carried out for all formulations including liquisolid compacts. The data for i*n-vitro* dissolution studies of liquisolid cpmpacts LSCB1 and LSCB2 and tablet formulations IMF1 to IMF6 were found 93.02±3.96 and 88.41±1.14 and 91.77±0.50, 91.28±1.77, 97.68±2.03, 89.29±1.01, 96.51±1.11 and 92.14±3.14 respectively.

**Table no 5: Comparison of *in-vitro* dissolution profile of Indomethacin, LSCB 1 and LSCB 2.**

| Time (min) | Cumulative % drug release | | |
|---|---|---|---|
| | Indomethacin | LSCB 1 | LSCB 2 |
| 0 | 0 | 0 | 0 |
| 5 | 7.69±1.59 | 68.53±4.58 | 62.64±1.12 |
| 10 | 11.84±1.87 | 75.51±7.51 | 63.49±1.12 |
| 15 | 12.66±1.75 | 83.98±1.30 | 66.23±1.23 |
| 20 | 14.40±1.07 | 86.89±0.20 | 70.84±1.90 |
| 25 | 15.97±1.22 | 89.68±2.41 | 77.09±2.28 |
| 30 | 18.77±1.26 | 93.02±3.96 | 88.41±1.14 |

Values are mean±SD, n=3

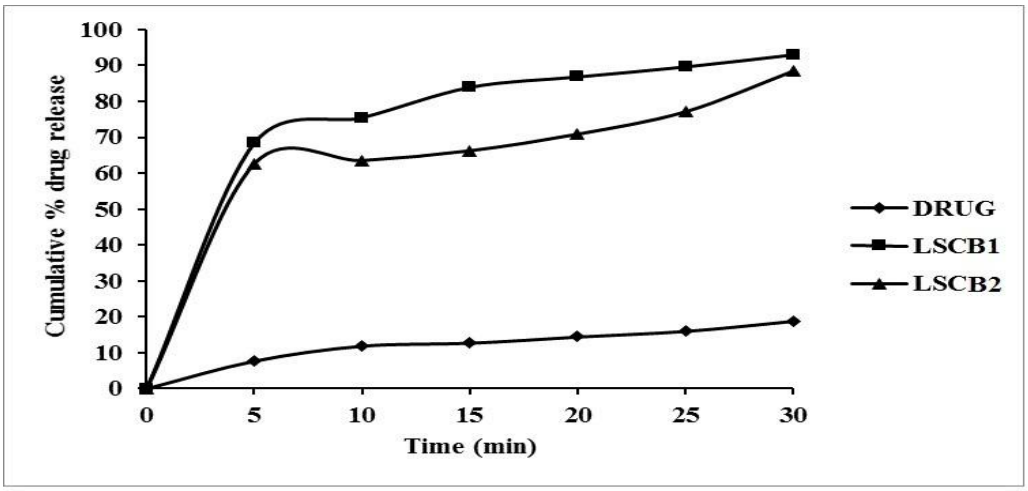


**Figure 3 : Comparison of *in-vitro* dissolution profile of Indomethacin, LSCB1 and LSCB2.**

**Table No 6: Comparison of *in-vitro* dissolution profile of IMF1, IMF2, IMF3, IMF4, IMF5 and IMF6.**

| Time (min) | Cumulative % drug release | | | | | |
|---|---|---|---|---|---|---|
| | IMF1 | IMF2 | IMF3 | IMF4 | IMF5 | IMF6 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 33.89±3.18 | 36.73±1.74 | 42.59±3.91 | 32.05±10.7 | 63.96±1.20 | 32.61±2.98 |
| 10 | 41.65±1.88 | 43.95±1.36 | 71.25±5.98 | 41.07±7.66 | 77.92±3.10 | 42.69±5.78 |
| 15 | 58.59±1.05 | 55.11±10.3 | 83.10±9.33 | 50.99±1.46 | 83.13±4.36 | 50.81±2.46 |
| 20 | 68.58±5.4 | 76.12±1.72 | 92.11±4.02 | 61.04±1.42 | 89.54±1.54 | 65.14±0.56 |
| 25 | 86.82±5.29 | 85.63±7.84 | 95.11±2.51 | 74.99±8.82 | 94.20±0.01 | 73.42±2.45 |
| 30 | 91.77±0.50 | 91.28±1.77 | 97.68±2.03 | 89.29±1.01 | 96.51±1.11 | 92.14±3.14 |

n=3 Values are mean±SD,

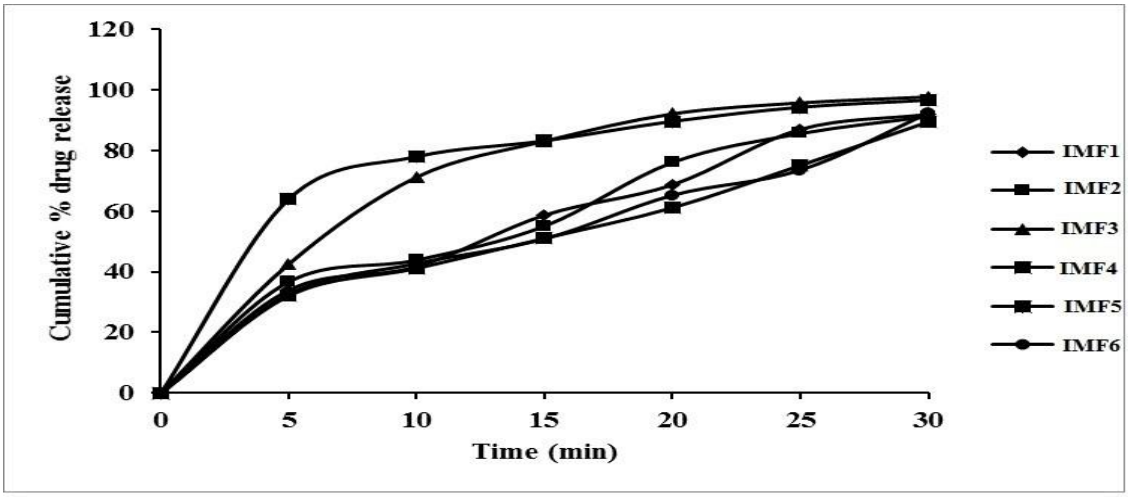


**Figure 4: Comparison of *in-vitro* dissolution profile of IMF1, IMF2, IMF3, IMF4, IMF5 and IMF6.**

**Model Independent Analysis:**

**Table No7: Model independent analysis of dissolution data**

| Formulation | MDT (min) | % $DE_{30min}$ |
|---|---|---|
| IMF1 | 11.72 | 57.32 |
| IMF2 | 11.20 | 55.86 |
| IMF3 | 7.80 | 72.65 |
| IMF4 | 12.93 | 49.67 |
| IMF5 | 6.32 | 68.11 |
| IMF6 | 13.13 | 51.36 |
| LSC 1 | 5.75 | 70.1 |
| LSC 2 | 8.25 | 62.52 |
| Pure Drug | 10.83 | 12.24 |

**Accelerated stability**

**Table No 9: Accelerated stability study of selected formulation**

| Time (min) | Cumulative% drug release | | |
|---|---|---|---|
| | 2 weeks | 4 weeks | 6 weeks |
| 0 | 0 | 0 | 0 |
| 5 | 42.59 | 42.54 | 42.49 |
| 10 | 71.25 | 70.74 | 70.34 |
| 15 | 83.10 | 82.51 | 81.91 |
| 20 | 92.11 | 91.97 | 91.17 |
| 25 | 95.71 | 95.63 | 95.58 |
| 30 | 97.68 | 96.97 | 96.17 |

**CONCLUSION:**

In the present study liquisolid compacts of Indomethacin was prepared by using PEG-800 (non-volatile liquid), microcrystalline cellulose (carrier) and aerosil (coating material). The liquisolid compacts were formulated into tablets using different concentration of super-disintegrant (crospovidone). Formulations IMF1, IMF3, IMF5 and formulations IMF2, IMF4, IMF6 were prepared by liquisolid technique with drug to liquid concentration of 1:1 and 1:0.5 respectively. Among the prepared formulations IMF3 showed release rate of about 97.68±2.03 at the end of 30 min.

MDT and % DE for formulation IMF3 was found to be 7.80 min and 72.65% respectively. The formulation IMF3 was selected as best formulation. The drug and excipients compatibility was studied using FT-IR which indicated no interaction had taken place between the drug and excipients. From the results, it can be concluded that the liquisolid tablets of Indomethacin was formulated successfully and dissolution enhancement of Indomethacin was achieved using liquisolid technique.

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