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# DISSOLUTION ENHANCEMENT OF MELOXICAM USING LIQUISOLID TECHNIQUE

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**ABSTRACT**

The limited solubility of drugs has always been a challenging task for pharmaceutical industries engaged in manufacturing and development of solid dosage forms. To overcome this problem, Liquisolid technique has gained immense popularity as a novel approach in the last decade. The present study deals with the dissolution enhancement of Meloxicam by Liquisolid Technique. An attempt has been made to formulate fast dissolving tablets of Meloxicam, a poorly water soluble drug. The dissolution rate of Meloxicam was compared with the marketed tablet. The results indicated that formulation (F11) containing microcrystalline cellulose as the carrier and aerosil as the coating material in the 20:1 ratio, displayed higher dissolution profile compared to other formulations. The prepared tablets showed good wettability, rapid disintegration, and acceptable dissolution rate compared to the marketed product. It has been observed that liquisolid technique is the most promising way for solubility and dissolution enhancement of Meloxicam. It can be concluded that liquisolid technique resulted in improved dissolution of Meloxicam.

**Keywords:** Dissolution enhancement, Liquisolid technique, Meloxicam, Poorly water-soluble drugs.

## INTRODUCTION

In the last few decades, a number of pharmaceutical researches have resulted in development of a variety of dosage forms. The ever increasing demands to meet improved quality of life have necessitated ease of medication. The oral route is the most preferred means of drug administration due to the ease, high patient compliance, and low cost of production. The most popular are tablet, capsules, suspension and various pharmaceutical solutions, thus oral route is considered as the most natural, uncomplicated, convenient and safe means of administering drugs. In spite of a variety of dosage forms, tablets are most commonly adopted dosage form[1]. In order to improve ease of drug administration, fast disintegrating tablets are widely accepted commercially[2]. Fast or rapid disintegrating tablets include fast dissolution, quick disintegration and results in fast absorption which provide rapid onset of action. Moreover, drug candidates that undergo pre-gastric absorption may show increased oral bioavailability[3]. Fast dissolving tablets provide accurate dosing, easy manufacturing and good stability[4,5]. Literature reports various methods of enhancing the dissolution characteristics of slightly water-soluble drugs[6]. These include reduction of particle size to increase surface area[7], solubilization in surfactant systems, formation of water-soluble complexes, use of pro-drug, drug derivatization and manipulation of solid state of drug substance to improve drug dissolution, i.e. by decreasing crystallinity of drug substance[8].

A number of solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances have been introduced with different degrees of success over the years[9]. The technique of "liquisolid compacts" is a new and promising addition towards achieving the same. Liquisolid systems are formulated by converting liquid lipophilic drugs or drug suspensions or solutions of water-insoluble solid drugs in suitable non-volatile solvent systems into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials. Several researchers have shown that the liquisolid technique

is the most promising method for promoting dissolution rate of poorly water-soluble drugs[10]. Literature reports application of liquisolid technique to improve the *In-Vitro* release of poorly water soluble drugs such as Aceclofenac[11], Bromhexine Hydrochloride[12], Carvedilol[13], Carbamazepine[14], Furosemide[15], Fenofibrate[16], Ibuprofen[17,18], Indomethacin[19], Ketoprofen[20], Propranolol hydrochloride[21], Lansoprazole[22], Lornoxicam[23], Tramadol hydrochloride[24].

Present study deals with the dissolution enhancement of Meloxicam using liquisolid technique. Meloxicam is widely used drug in the therapeutics for the osteoarthritis and rheumatoid arthritis treatment in adults[25].

## MATERIALS AND METHODS

The drug Meloxicam was received as a gift from Astron Research Ltd., Ahmedabad (Gujarat). All the other chemicals PEG 400, Avicel, Aerosil, Tween 80 etc., used were of analytical grade.

### *Drug-Excipient Compatibility Study*

*FTIR spectroscopy:* Fourier-transform infrared (FTIR) spectra were obtained using an FTIR spectrometer (Shimadzu 8400S, Japan). The samples (Meloxicam and excipients) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample:KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. A number of scans were obtained at a resolution of 4 $cm^{-1}$, from 4000 to 400 $cm^{-1}$. FTIR spectra of standard drug (Meloxicam) and sample drug (Meloxicam) are given in figure 1 & 2 respectively.

*Determination of Flowable Liquid Retention Potential:* Carrier (Avicel) and coating (Aerosil) material was taken from 5:1 to 50:1 ratio and drug solution in PEG 400 was added until good flow remain and liquid load factor ($L_f$) was calculated from equation:

$L_f = W/Q$

Where W = weight of liquid medication, Q = weight of carrier material

The excipients ratio R is the ratio of weight of carrier (Q) and coating (q) material of powder, given as:

$R = Q/ q$

From that different liquid load factor obtained for different carrier, coating material ratio (1/R) and graph of liquid load factor 1/R was plotted. Equation obtained was matched with following equation:

$L_f = \Phi + \theta\ (1/R)$

Where $\Phi$ and $\theta$ are the liquid retention potential of carrier and coating material respectively.

*Pre-compression Studies:* The flow properties of powders are critical for an efficient tableting operation. A good flow of powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. If a drug is identified to be "poorly flowable", at the pre-formulation stage the problem can be solved by selecting appropriate excipients. The liquisolid granules obtained were evaluated for the bulk density, tapped density, percentage compressibility or Carr's index and Hausner's ratio, which are given in table 1.

*Solubility Studies:* Solubility studies were conducted for the selection of high solubility of the pure drug form in the non volatile solvents. For the purpose, pure drug was dissolved in different non-volatile solvents. Excess amounts of pure drug were added to the non-volatile solvents, followed by saturation solution transfer to a rotatory shaker for 48 hours at $25^0$C under constant vibrations. After 48 hours, the saturated solution was filtered through a 0.45 μm filter and analyzed. Important data related to solubility are given in table 2.

*Preparation of Liquisolid Compacts:* In order to prepare liquisolid compacts, Meloxicam was dispersed in PEG 400. Then a binary mixture of carrier-coating materials (microcrystalline cellulose as the carrier powder and silica as the coating material) in the ratio of 10:1(F1 to F9), 5:1 (F10) and 20:1(F11) was added to the obtained liquid medication under continuous mixing in a mortar. Depending upon the type of carrier in formulation, different liquid loading factors ($L_f$) were employed in our liquisolid preparations. Finally, 5% (w/w) of sodium starch glycolate as a disintegrant and 1% magnesium stearate were mixed with the mixture for a period of 10 min. The final mixture was compressed using the tablet punching machine to achieve tablet hardness.

### *Formulation Studies*

*Hardness:* Hardness is the force required to break a tablet in a diametric compression test. It was measured using Monsanto tablet hardness tester.

*Friability:* Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. Pre-weighed sample of tablets was placed in the friabilator, which was then operated

for 100 revolutions. Tablets were dusted and reweighed.

*Drug Content Uniformity:* Uniformity of Meloxicam was determined by collecting a sample of 3 tablets from each batch followed by determination of drug concentration in each tablet spectrophotometrically, at 363nm. The average drug content was calculated and the percentage drug content was determined. For the purpose of study, initially nine formulations designated as F1, F2, F3, F4, F5, F6, F7, F8, and F9 were prepared using non-volatile solvent as liquid vehicle, Avicel pH 102 and Aerosil 200 were used as carrier and coating material respectively. To attain optimal Meloxicam solubility in the liquisolid formulation, concentration of the liquid vehicle was varied in different ratios i.e. drug to non-volatile vehicle ratio was varied between 1:1 and 1:9. Maximum solubility was obtained for the formulation F9 in which drug to vehicle ratio was 1:9. To determine the effect of carrier to coating ratio (R), another formulation F10 was later prepared by taking two different values of R as 5 and 20. Formulation F10 was prepared using R = 5, which resulted in a damp mass. Thus, it was not selected for further study. Formulation F11 was prepared for R = 20, which resulted in enhanced dissolution of Meloxicam. Hence, out of all formulations prepared (from F1-F11), satisfying dissolution results were obtained for formulation F11. Formulation F11 was subsequently compared with marketed formulation of the same drug.

***Dissolution Studies***

*Drug Release (In-vitro Dissolution):* The dissolution study was done in 900 ml of pH 7.4 phosphate buffer. At each sample time interval, an exact volume of the sample was withdrawn from each flask and immediately replaced with an identical volume of fresh medium to maintain a dissolution sink condition at predetermined time intervals (0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 minutes). The USP XI-II rotating paddle apparatus was used with a stirring rate of 100 rpm maintained at 37±0.5$^0$C temperature. The samples were analyzed in the spectrophotometer and the absorbance values were recorded at 363nm.

**RESULTS AND DISCUSSION**

The results obtained after conducting previously mentioned studies are discussed below:

*Infrared Spectroscopy Analysis:* For this purpose, the small amount of drug was mixed with Potassium bromide. The finely ground mixture was pressed under very high pressure (25000 psig) to form small pellet (about 1-2 mm thick) and run the pellet in IR spectroscopy. Various peaks of IR spectrum were interpreted for the presence of different groups in the structure of Meloxicam.

The peaks obtained in the spectra of each formulation correlates with the characteristic peaks (N-H, C-H, S=O, and C=O) of drug spectrum. It did not show any well-defined interaction between Meloxicam and excipients. Thus, it can be said that drug is compatible with the formulation components.

*Formulation Parameters:* For the purpose of study, initially nine formulations F1, F2, F3, F4, F5, F6, F7, F8, and F9 were prepared using non-volatile solvent as liquid vehicle, Avicel pH 102 and Aerosil 200 were used as carrier and coating material respectively. To attain optimal Meloxicam solubility in the liquisolid formulation, concentration of the liquid vehicle was varied in different ratios i.e. drug to non-volatile vehicle ratio was varied between 1:1 and 1:9. Maximum solubility was obtained for the formulation F9 in which drug to vehicle ratio was 1:9. The data obtained are given in table 3.

To determine the effect of carrier to coating ratio (R), another formulation F10 was later prepared by taking two different values of R as 5 and 20. Formulation F10 was prepared using R = 5, which resulted in a damp mass. Thus, it was not selected for further study. Formulation F11 prepared for R = 20, resulted in enhanced dissolution of Meloxicam. Hence, out of all formulations prepared (from F1-F11), satisfying dissolution results were obtained for formulation F11. Formulation F11 was subsequently compared with marketed formulation of the same drug.

*Dissolution Studies:* The USP dissolution apparatus II was used with 900 ml of pH 7.4 phosphate buffer to ensure sink conditions at 37±0.5°C; the apparatus was run at 100 rpm. Samples of the dissolution medium were withdrawn at a specified time interval and compensated by fresh dissolution medium. Samples were properly diluted and Meloxicam concentrations were analyzed spectrophotometrically at 363nm. The percentage drug released was calculated at specified time interval and plotted against time. The calculated values for percentage drug release are given in table 4. Percentage cumulative drug release was plotted against time for three formulations (F1-F3 plotted in figure 3, F4-F6 plotted in figure 4 and F7-F9 plotted in figure 5) in each graph, in order to avoid overlapping of all curves in a single graph.

Out of all the formulations from F1-F9, F9 showed highest drug release. Thus, it has been selected for further study and final formulation has been optimized using drug vehicle ratio of 1:9. The effect of carrier to coating ratio (R-value) was studied. (Space between paragraphs this and below this)

*Optimization Using R-Value:* Initially vehicle concentration was varied using R = 10. The formulation F9 was observed as best of chosen nine formulations (F1-F9). To study the effect of R on the dissolution of the formulation, optimization study was performed by changing value of R as 5 and 20. The optimized formulations thus obtained have been given in table 5. Formulation F10 with R = 5 resulted in a damp mass; therefore, further study has been done using formulation F11. Pre-compression study data and evaluation parameters for formulation are given in table 6 & 7 respectively. For the optimized formulation F11, the drug release study has been performed and the data obtained are given in table 8. These dissolution data were compared with the marketed tablet as given in table 9 and plotted in figure 6.

## CONCLUSION

From the present experimental results, it has been observed that of all the solvents screened, the best non-volatile solvent for Meloxicam is PEG 400. The investigations indicated that formulation F11 containing microcrystalline cellulose as the carrier and aerosil as the coating material in the 20:1 ratio, displayed higher dissolution profile compared to other formulations. A liquid load factor $L_f$ = 0.176, and an excipient ratio R = 20, produced a powder of optimal flow properties and readily compressible tablets without any liquid oozing out phenomenon. The prepared tablets showed good wettability, rapid disintegration, and acceptable dissolution rate compared to the marketed product. It can be said that liquisolid technique could be a promising strategy in improving dissolution of insoluble drugs and formulating immediate release solid dosage forms. It can be concluded that the liquisolid technique is an effective way of dissolution rate improvement of water insoluble drugs such as Meloxicam.

## ACKNOWLEDGEMENT

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**Table 1 – Flow properties of Meloxicam**

| Bulk Density | Tapped Density | Carr's Index | Hausner's Ratio |
|---|---|---|---|
| 1.23 gm/ml | 1.56 gm/ml | 21.1% | 1.26 |

**Table 2 - Solubility of Meloxicam in various vehicles**

| Solvent/Vehicle | Solubility (mg/ml) |
|---|---|
| Water | 0.1779 |
| Phosphate buffer solution (0.1M) pH 7.4 | 0.6790 |
| Propylene glycol | 0.3489 |
| Polyethylene glycol 400 | 7.0014 |
| Tween 80 (10%) | 0.3907 |

**Table 3 – Formulation parameters of Meloxicam liquisolid compacts**

| Formulation | Hardness ($kg/cm^2$) | Friability (%) | Weight variation (%) | Drug content uniformity (%) | Disintegration time (min) |
|---|---|---|---|---|---|
| F1 | 4.0 ± 0.5 | 0.73 ± 0.23 | 3.4 ± 0.02 | 98.6 ± 0.3 | 2.3 ± 0.02 |
| F2 | 4.1 ± 0.3 | 0.72 ± 0.32 | 2.3 ± 0.06 | 97.1 ± 0.4 | 2.2 ± 0.01 |
| F3 | 4.4 ± 0.7 | 0.59 ± 0.21 | 2.1 ± 0.09 | 97.6 ± 0.4 | 2.3 ± 0.04 |
| F4 | 4.5 ± 0.6 | 0.59 ± 0.25 | 1.8 ± 0.03 | 97.3 ± 0.3 | 2.1 ± 0.03 |
| F5 | 4.1 ± 0.2 | 0.75 ± 0.42 | 2.5 ± 0.32 | 97.8 ± 0.3 | 2.3 ± 0.04 |
| F6 | 4.1 ± 0.3 | 0.72 ± 0.44 | 2.3 ± 0.35 | 99.1 ± 0.6 | 2.4 ± 0.05 |
| F7 | 4.2 ± 0.5 | 0.56 ± 0.48 | 1.7 ± 0.28 | 99.4 ± 0.2 | 2.1 ± 0.03 |
| F8 | 4.0 ± 0.2 | 0.73 ± 0.36 | 1.1 ± 0.17 | 98.6 ± 0.4 | 2.4 ± 0.01 |
| F9 | 4.3 ± 0.7 | 0.59 ± 0.29 | 0.8 ± 0.06 | 99.2 ± 0.2 | 2.1 ± 0.02 |

**Table 4 – Percentage cumulative drug release of formulations in PBS pH 7.4**

| Time (min) | % Drug Release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| 5 | 36.2±1.3 | 39.8±1.4 | 37.2±1.9 | 40.8±2.2 | 41.3±2.6 | 42.9±2.4 | 42.3±2.2 | 44.5±2.1 | **45.3±2.1** |
| 10 | 57.4±1.2 | 59.2±2.3 | 58.4±2.1 | 60.2±2.5 | 63.6±2.1 | 65.8±2.5 | 64.6±2.4 | 67.2±2.3 | **68.3±2.1** |
| 15 | 68.9±1.4 | 71.3±2.6 | 69.9±2.3 | 72.3±2.6 | 74.8±1.5 | 76.1±1.7 | 75.8±1.5 | 78.3±1.4 | **79.3±2.5** |
| 30 | 85.1±1.4 | 85.4±1.6 | 86.1±2.5 | 86.4±2.1 | 86.5±1.3 | 88.2±1.3 | 86.9±1.4 | 89.6±1.6 | **90.6±1.6** |
| 45 | 87.8±2.3 | 88.5±1.4 | 88.8±1.2 | 89.5±1.4 | 89.8±2.3 | 90.3±1.4 | 90.8±1.7 | 91.4±1.4 | **92.4±2.5** |
| 60 | 90.3±1.3 | 90.7±1.5 | 91.3±1.2 | 91.7±1.2 | 91.4±1.5 | 91.9±2.4 | 92.1±1.1 | 92.4±2.3 | **93.5±1.5** |

**Above values are mean ± standard deviation for n = 3 (where n is number of sampling)*

**Table 5 - Optimization of formulations F10 & F11 using R-value**

| Formulation | Meloxicam (mg) | PEG 400(mg) | Avicel pH101(mg) | Aerosil (mg) | R | $L_f$ | Total weight (mg) |
|---|---|---|---|---|---|---|---|
| F10 | 15 | 135 | 247.70 | 43.54 | 5 | 0.689 | 465.91 |
| F11 | 15 | 135 | 852.27 | 42.61 | 20 | 0.176 | 1107.56 |

**Table 6 - Pre-compression studies of the optimized formulation**

| Formulation | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Carr's Index (%) | Hausner's Ratio |
|---|---|---|---|---|
| F11 | 0.541 ± 0.020 | 0.638 ± 0.011 | 15.2 ± 2.79 | 1.18 ± 0.045 |

**Table 7- Evaluation parameters of optimized formulation**

| Formulation | Weight variation | Hardness ($kg/cm^2$) | Friability (%) | Disintegration time (min) | Drug content (%) |
|---|---|---|---|---|---|
| F11 | 0.8 ± 0.13 | 5.7 ± 0.2 | 0.42 ± 0.253 | 1.5 ± 0.01 | 99.0 ± 0.5 |

**Table 8 - Percentage cumulative drug release of optimized batch F11**

| Time | % Drug release |
|---|---|
| 0 | 0 |
| 5 | 49.3 ± 2.5 |
| 10 | 70.9 ± 2.2 |
| 15 | 82.3 ± 2.8 |
| 30 | 92.6 ± 1.5 |
| 45 | 94.4 ± 2.4 |
| 60 | 95.4 ± 1.5 |

**Table 9 - Dissolution data of formulation F11 and marketed tablet**

| Time (min) | % Drug release | |
|---|---|---|
| | F11 | Marketed tablet |
| 0 | 0 | 0 |
| 5 | 49.3 ± 2.5 | 29.8 ± 0.9 |
| 10 | 70.9 ± 2.2 | 36.5 ± 1.2 |
| 15 | 82.3 ± 2.8 | 49.9 ± 2.1 |
| 30 | 92.6 ± 1.5 | 69.2 ± 1.3 |
| 45 | 94.4 ± 2.4 | 78.4 ± 1.3 |
| 60 | 95.4 ± 1.5 | 89.6 ± 1.1 |

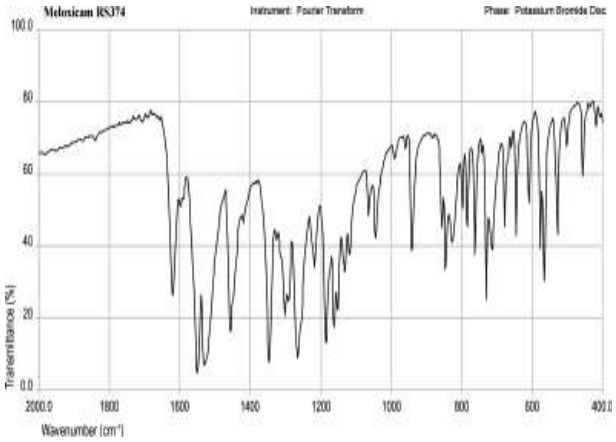


Fig. 1–FTIR spectra of standard drug (Meloxicam)

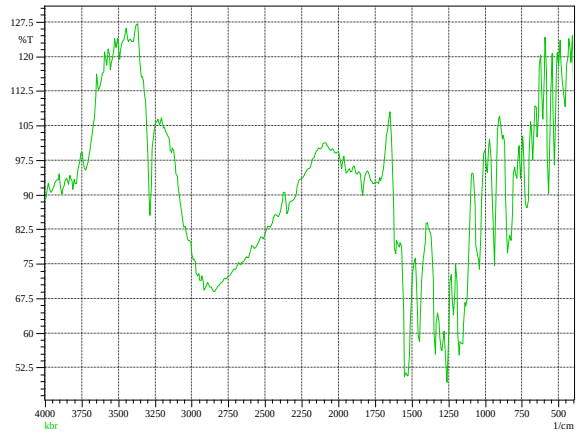


Fig. 2–FTIR spectra of sample drug (Meloxicam)

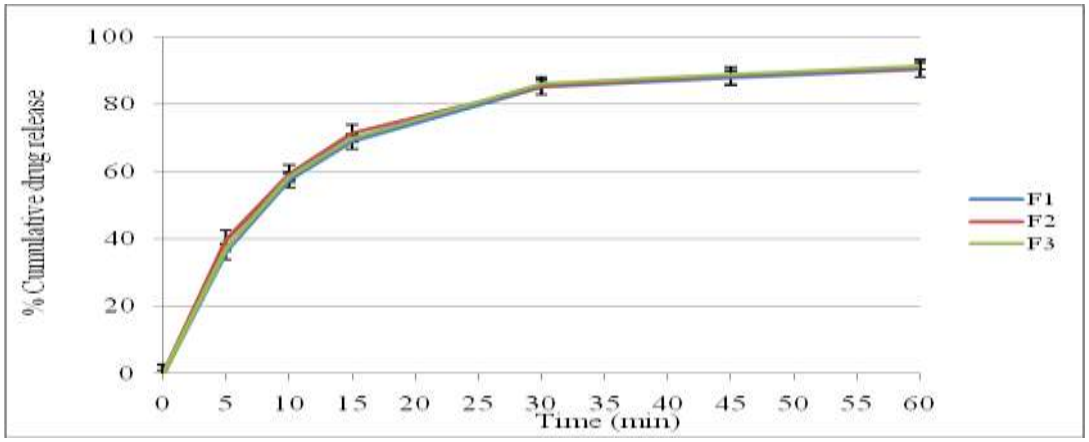


Fig. 3 – Dissolution profile of formulations F1-F3

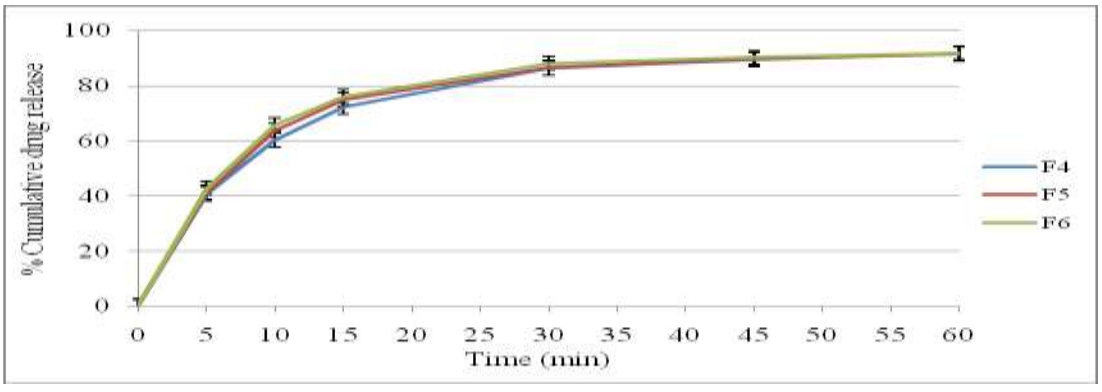


Fig. 4– Dissolution profile of formulations F4-F6

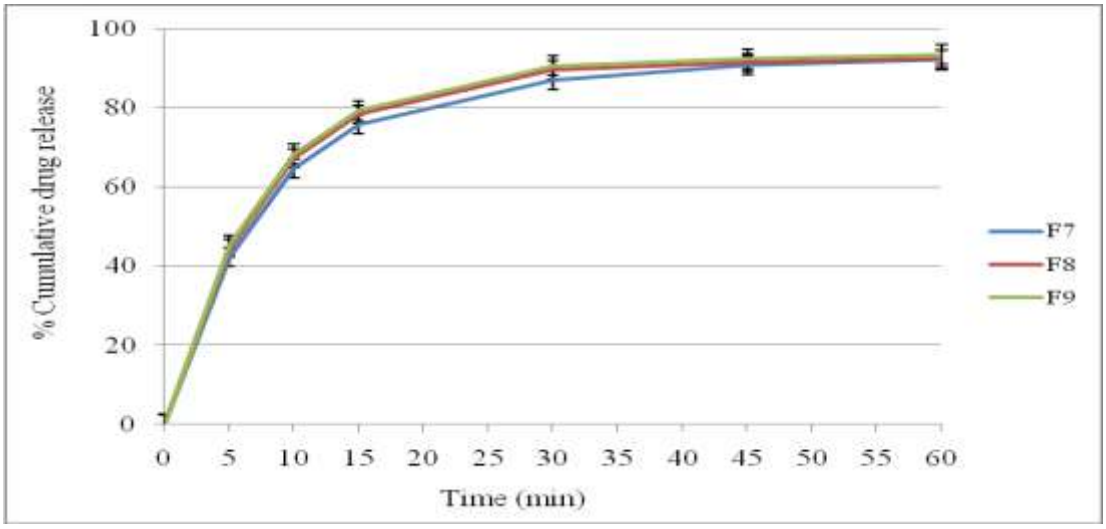


Fig. 5 – Dissolution profile of formulations F7-F9

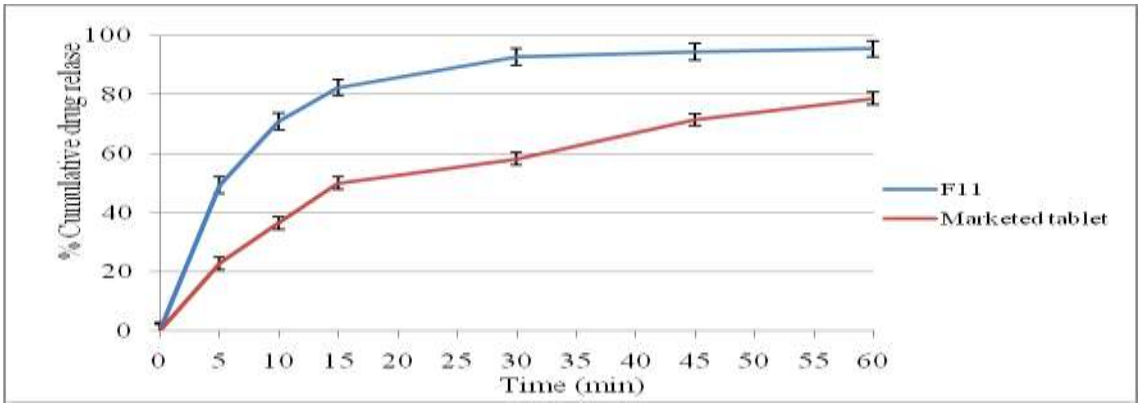


Fig. 6 – Comparison of dissolution profile of formulations F11 and marketed tablet

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