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Formulation and Evaluation of Flurbiprofen Solid Dispersion

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ABSTRACT

Flurbiprofen has poor water solubility since it was considered as Class II in Biopharmaceutical Classification System (Low water solubility and high permeability). Solid dispersion is able to improve solubility of poor water soluble medications. Therefore, Flurbiprofen is drug candidate for this formulation. Nine formulations of drug with two different polymers, Poloxamer and Polyvinylpyrrolidone (PVP), were prepared and evaluated for production yield, entrapment efficiency and dissolution studies. The results demonstrated that formulations (F6 and F7) with poloxamer were significantly enhanced Flurbiprofen release.

1. INTRODUCTION

Poor aqueous solubility of hydrophobic drugs is one of the major difficulties encountered in pharmaceutical preparations. Their solubility is a rate limiting step for absorption, achieving desired concentration of drug in systemic circulation and optimum bioavailability to get desired pharmacological response. There are many strategies for improving drug solubility including chemical and physical modifications of drug and other methods such as crystal engineering, particle size reduction, salt formation, complexation, addition of solvent or surface-active agents, solid dispersion and so forth. Selection of solubility enhancing method depends on site of absorption, drug property, and required dosage form characteristics [1, 2].

Solid dispersion is one of the solid dosage forms that consist of two main components including hydrophobic drug and hydrophilic matrix. The matrix can be either amorphous or crystalline. Solid dispersion can be prepared by dispersion of one or more active pharmaceutical ingredient (API) in an inert matrix at solid state that prepared by the solvent, melting, and melting solvent method. The hydrophobic drug can be dispersed in crystalline particles or in amorphous particles (clusters). There are many types of solid dispersion involving solid eutectic mixture, solid solution, glass solution and suspension and amorphous precipitations in crystalline carrier. Rapid dissolution rates of the drug which result in a reduction in pre-systemic and an increase in the rate and extent of the drug absorption, both can lead to the need for lower doses of the drug. However, instability is the major difficulty related to the formulation which represented by changing in crystallinity leading to a decrease in dissolution rate of aging. Temperature and moisture have a deteriorating effect on solid dispersions than on physical mixtures. [1, 3, 4, 5, 6, 7, 8]

Solid dispersion has numerous advantages. Firstly, it reduces the particle size increasing the surface wettability and dissolution rate which leads to enhance solubility and then bioavailability. Secondly, it has been demonstrated that solid dispersion particles have high degree of porosity accelerating drug release profile. [9]

Flurbiprofen is non-steroidal anti-inflammatory drugs (NSAIDs) which belongs to the phenyl alkanoic acid derivative family. It is primarily used orally for arthritis or dental pain and as a pre-operative anti-miotic (in an ophthalmic solution). Additionally, it is used topically prior to ocular surgery in order to reduce or prevent intraoperative miosis. Flurbiprofen belongs to Class II of the Biopharmaceutical Classification System (BCS) which has low solubility and high permeability. Therefore, it is a good model drug for solid dispersion formulation (10).

The chemical structure of Flurbiprofen is shown in Figure 1. This study explains the effect of solid dispersion formulation on the Flurbiprofen solubility.

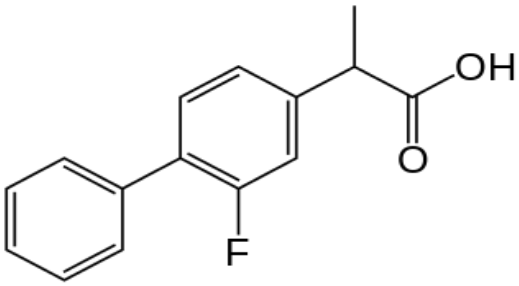

Figure 1: Structure of Flurbiprofen

2. MATERIALS AND METHODS

2.1. Materials

Flurbiprofen was purchased from Hetero drugs limited, India, Polyvinylpyrrolidone (PVP) from Sigma Chemical Co. (Aldrich), USA, Poloxamer from Himedia, India, Sodium hydroxide and Potassium di-hydrogen orthophosphate from Merck, Germany, Hydrochloric acid and Dichloromethane from Riedel-De-Haen AG seelze, Germany and Methanol from BDH , England. All other chemicals used were of analytical grade.

2.2. Method

2.2.1. Characterization of Flurbiprofen

2.2.1.1. Determination of Flurbiprofen melting point.

The melting point of Flurbiprofen powder was measured according to USP using capillary tube method. The tube was dipped in the drug powder closed from one end and placed inside the melting point apparatus, the temperature was increased gradually. The temperature at which the powder converted to liquid was recorded as the melting point. [(11)] (All the measurements were carried out in triplicate and results presented as mean ± standard deviation)

2.2.1.2. Determination of Flurbiprofen λmax

Flurbiprofen solution of 12 µg/ml in methanol was prepared. This solution was scanned by UV-visible spectrophotometer from 200-400 nm and the λmax of the drug was determined.

2.2.1.3. Calibration curve of Flurbiprofen

Calibration curve of Flurbiprofen was made in 0.1N HCl and Phosphate buffer of pH 6.8 by preparing a serial of dilutions of Flurbiprofen with different concentrations (1, 2, 4, 8, 10, 15, 20 µg/ml) from stock solution containing 40mg/100ml Flurbiprofen. The absorbance was then measured at the λmax of the drug. The measured absorbance was plotted against the respective concentrations.

2.2.1.4. Solubility study

Determination of solubility is an important factor in the formulation of poorly soluble drugs. Saturated solutions of drug were prepared by adding excess amount of Flurbiprofen in distilled water shaking by the shaker water bath for 48h at 25°C under constant vibrations. The solutions were filtered through a 0.45 µm filter, diluted and analyzed by UV spectrophotometer. [12]

2.2.2. Preparation of Flurbiprofen solid dispersion formulations

The Flurbiprofen formulas were prepared by solvent evaporation method. The drug and different polymers in different ratios, as explained in Table 1, were dissolved in 20 ml dichloromethane, poured in petri dish and placed in oven at 40°C overnight to ensure complete evaporation of the solvent. The solid dispersion collected and stored for further investigations.

Table 1: The composition of Flurbiprofen solid dispersion formulas.

Formula code	Flurbiprofen (mg)	PVP (mg)	Poloxamer (mg)
F1	100	100	-
F2	100	200	-
F3	100	400	-
F4	100	50	-
F5	100	25	-
F6	100	-	25
F7	100	-	50
F8	100	-	100
F9	100	-	200
F10	100	-	400

2.2.3. Evaluation of Flurbiprofen solid dispersion formulations

2.2.3.1. Determination of Production Yield

The production yield of all of the solid dispersion was determined by calculating the initial weight of the solid raw materials and the final weight of the obtained solid dispersion then calculated according to the equation below:

$$\text{Production yield} = \frac{\text{Practical weight}}{\text{Theoretical weight (polymer + drug)}} \times 100$$

2.2.3.2. Entrapment efficiency of Flurbiprofen solid dispersion

The Flurbiprofen content in the solid dispersion was determined spectrophotometrically. A sample of Flurbiprofen equivalent to 10 mg was dissolved in 10 ml of methanol. The solution was diluted suitably with Phosphate Buffer (pH 6.8) and spectrophotometric absorbance was measured. The drug content was calculated from the calibration curve and expressed as percent entrapment efficiency as explained in the equation below. [13]

$$\text{Entrapment efficiency} = \frac{\text{Actual weight of Flurbiprofen}}{\text{Theoretical weight of Flurbiprofen}} \times 100$$

2.2.3.3. Dissolution study of the formulas

Dissolution studies were performed for the pure Flurbiprofen and the prepared drug solid dispersion by using USP apparatus Type II. The dissolution was carried out using phosphate buffer (pH 6.8) to simulate intestinal fluid. The stirring rate was 75 rpm. An equivalent of 40 mg of pure Flurbiprofen and Flurbiprofen solid dispersion were placed in 900 ml dissolution medium and maintained at 37±3 °C. At appropriate time intervals (5, 10, 15, 20, 30, 45 and 60 min), 5 ml samples were taken and filtered through a 0.45 μm filter paper. The dissolution medium was replaced with 5 ml of fresh dissolution fluid to maintain sink condition. The collected samples were analyzed using UV spectroscopy. [14]

2.2.3.4. Fourier Transform Infrared (FTIR) Spectroscopy of Flurbiprofen

FTIR spectra of pure Flurbiprofen, PVP, Poloxamer and the drug with its solid dispersion were obtained by a Perkin-Elmer Fourier transform infrared spectrophotometer using KBr pellets were prepared by gently mixing the sample with KBr (1:100). The scanning range used was 2000 to 400 cm^{-1}. The pure drug was taken and the physical mix with each polymer on formula of Flurbiprofen solid dispersion (F6).

3. RESULT AND DISCUSSION

3.1. Characterization of Flurbiprofen

3.1.1. Determination of Flurbiprofen melting point

The measured melting point of Flurbiprofen was found to be 113°C. This result was confirmed by number of references. Additionally, it reflects the purity of the drug powder used in the study. [15]

3.1.2. Determination λmax of Flurbiprofen

The scanned solution contains 10 µg/ml of Flurbiprofen in methanol by UV spectrophotometer at 200-400 nm gave maximum peak with λmax at 247nm as shown in the spectrum in Figure 2. This result is in agreement with the reported one (16).

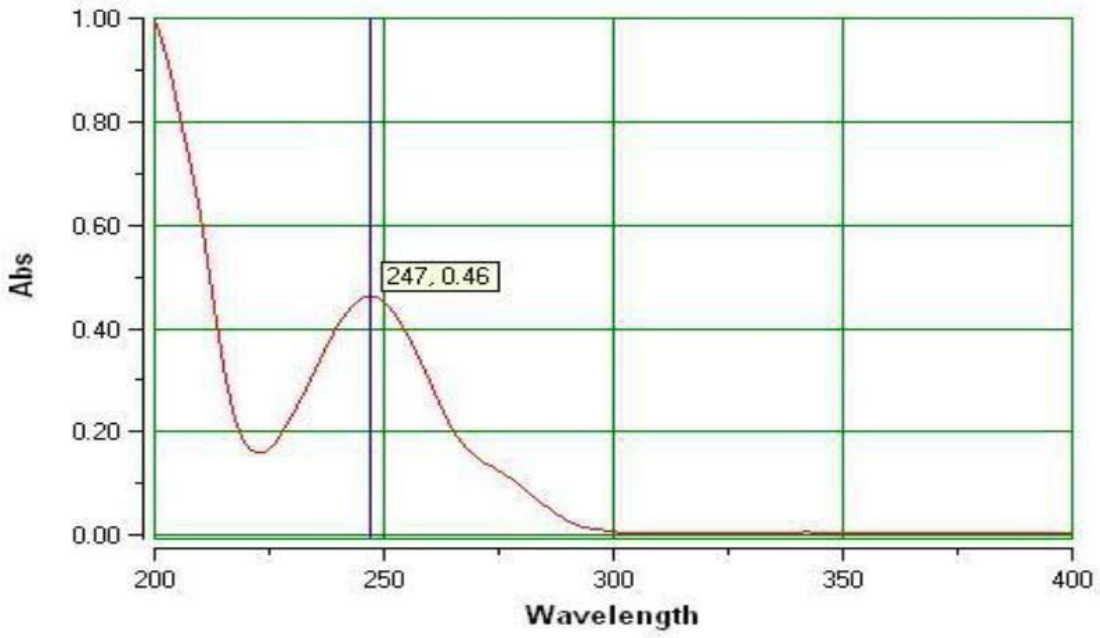

Figure 2: The spectrophotometer spectrum shown the λ max of the Flurbiprofen.

3.1.3. Calibration curve of Flurbiprofen

The calibration curves of the drug in phosphate buffer and HCl are shown in Figure 3 and 4, respectively. A straight line was obtained by plotting the absorbance versus concentration. This indicates that calibration curve obeys Beer's law within the range of concentrations used.

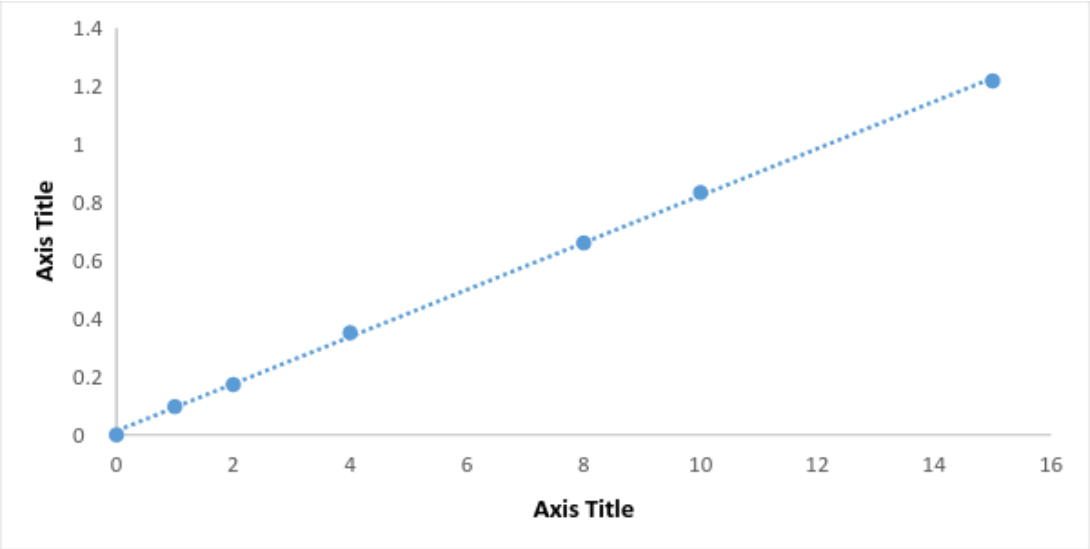

Figure 3: The calibration Curve of Flurbiprofen in phosphate buffer.

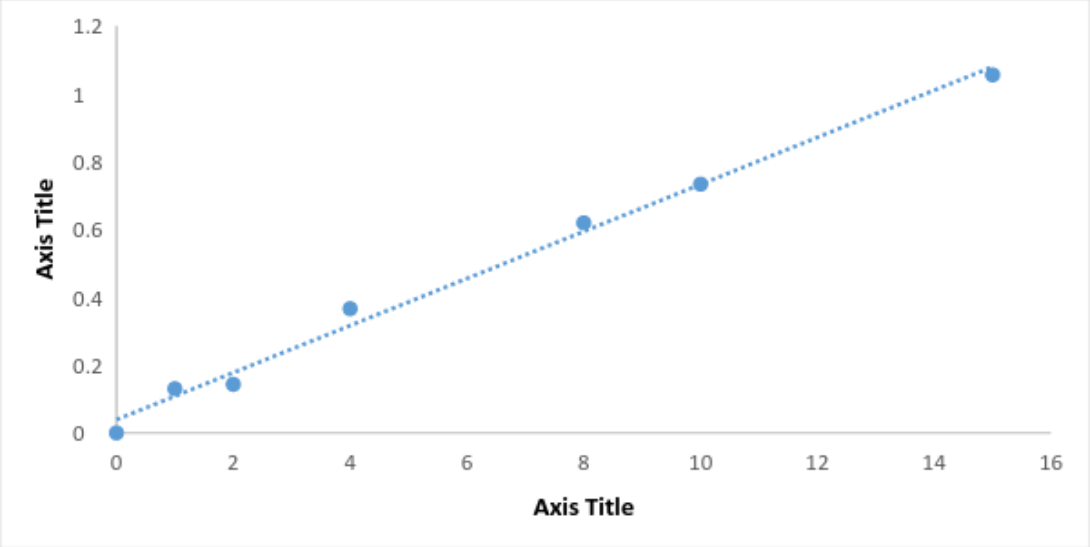

Figure 4: Calibration curve of Flurbiprofen in HCl.

3.1.4. Solubility study

Saturation solubility was performed to get the maximum amount of drug dissolved in the media. This study helped to decide the type and volume of media to be used. It was useful

especially for drugs with poor solubility. Furthermore, by this study, the maximum strength of drug that can be released from a formulation, will be known. Saturated solutions were prepared by adding excess of both Flurbiprofen solid dispersion and pure Flurbiprofen in three different media which were distilled water, 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) shaking by the shaker water bath for 48h at 25°C. Solutions were filtered through a 0.45 µm filter to remove any insoluble particles that is negatively affecting the results.

The results of saturation solubility study were shown in Table 2. The results revealed that the pure Flurbiprofen has poor water solubility. This fact is expected since Flurbiprofen is a BCS Class II drug. Similarly, the solid dispersion was expected to increase the solubility of the drug in all media because it is molecularly dispersed within the formulation structure that contains voids and channels which greatly increase the drug surface area exposed to the dissolving media.[2, 17]

The low solubility enhancement in 0.1N HCl (pH 1.2) was attributed to maximum solubility of the pure drug in this media. However, the solubility enhancement is low in Phosphate buffer (pH 6.8) because the drug is insoluble at this pH since it shows low solubility in the pH range of 3-9 (pH dependent solubility). Flurbiprofen solid dispersion has shown maximum solubility enhancement in water which could be due to the neutral amphoteric nature of water.[18]

Table 2: Solubility of Flurbiprofen solid dispersion in water

Formula	Solubility (µg/ml)
Pure drug	5.04
F1	2.81
F2	2.72
F3	3.56
F4	2.65
F5	2.50
F6	9.80
F7	11.68
F8	3.88
F9	3.50

3.2. Entrapment Efficiency

The entrapment efficiency is an important measurement for microparticulate systems. It gives a clear idea about the encapsulation power and the production and scale-up capabilities of that particular technique. Some of the microparticulate techniques, such as liposomes, suffer from low entrapment efficiency whereas others, like solid dispersion method, have good or even excellent entrapment efficiency.

Entrapment efficiency was obtained to determine exactly how much Flurbiprofen was entrapped in the formulation which in turn is necessary to calculate the equivalent weight of Flurbiprofen solid dispersion to that of the marketed product.[19] The Flurbiprofen solid dispersion formulas gave acceptable entrapment efficiency with average of 86%, as illustrated in Table 3.

Table 3: The percentage yield and entrapment efficiency of Flurbiprofen solid dispersion formulas

Formula	% Yield	Entrapment efficiency (%)
F1	65%	90%
F2	60%	111%
F3	74%	60%
F4	32%	79%
F5	47%	96%
F6	85%	88%
F7	84%	89%
F8	60%	67%
F9	80%	98%

3.3. Fourier Transform Infrared (FTIR) Spectroscopy of Flurbiprofen:

The FTIR spectra, as shown in Figure 5, demonstrated no significant difference between the solid dispersion formulations and pure Flurbiprofen characteristic peaks, therefore; there may be no interaction between the drug and polymers. The spectra showed characteristic broad peaks of the drug at 1698 and 2920 cm−1 were because of carbonyl and hydroxyl stretching, respectively. However, FTIR spectra of Flurbiprofen and solid dispersion of the drug showed

characteristic broad peak of Flurbiprofen in the range 3400 to 1700 cm−1 because of hydrogen bonding.[20, 21, 22]

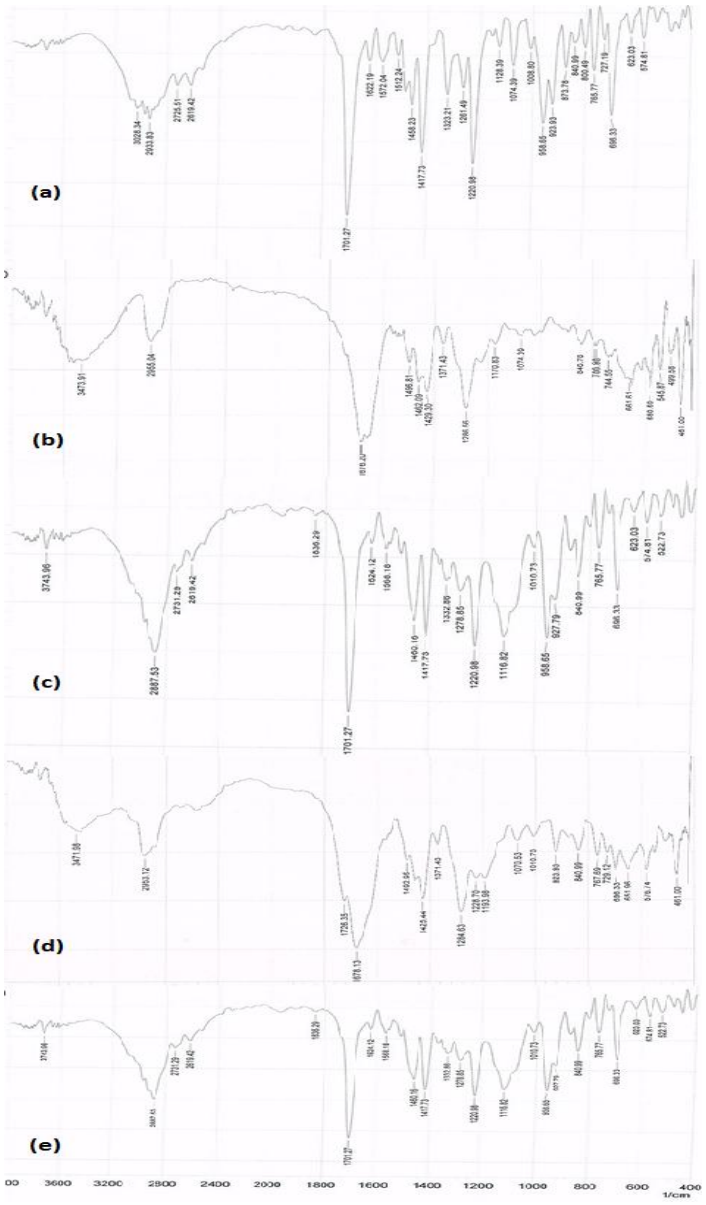

Figure 5: FTIR spectra of Flurbiprofen, the polymers and the formulations, as (a) represent pure drug, (b) PVP, (c) poloxamer, (d) Flurbiprofen and PVP, and (e) Flurbiprofen and poloxamer

3.4. Modified *In-vitro* Dissolution Studies of Flurbiprofen

The modified dissolution study demonstrated that the release profile of Flurbiprofen was significantly improved as solid dispersion than that of marketed product, as illustrated in Figure 6, 7 and 8. F6 and F7 had significantly higher drug release than the conventional dosage form. This could reflect positively on the onset of drug action. Therefore, it could

clinically expect that the effect will be faster from the solid dispersion than other usual formulas as its dissolution, and hence absorption since the solid dispersion polymer matrix made a network which improves the drug solubility. The release profile of Flurbiprofen was better in phosphate buffer. It can be expected that this fact does not affect on Flurbiprofen solid dispersion clinical performance since it was dissolved previously in stomach and becomes ready for the absorption process and bypass the dissolution step which is the rate limiting step for BCS Class II drugs like Flurbiprofen solid dispersion.[23]

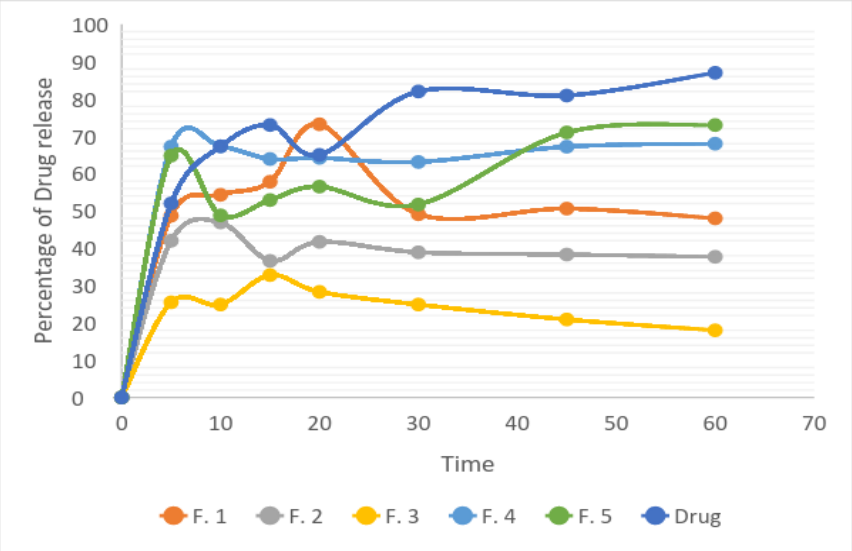

Figure 6: Percent of Flurbiprofen release in dissolution study from formulations using PVP as main polymer, as drug represent Flurbiprofen conventional formulation

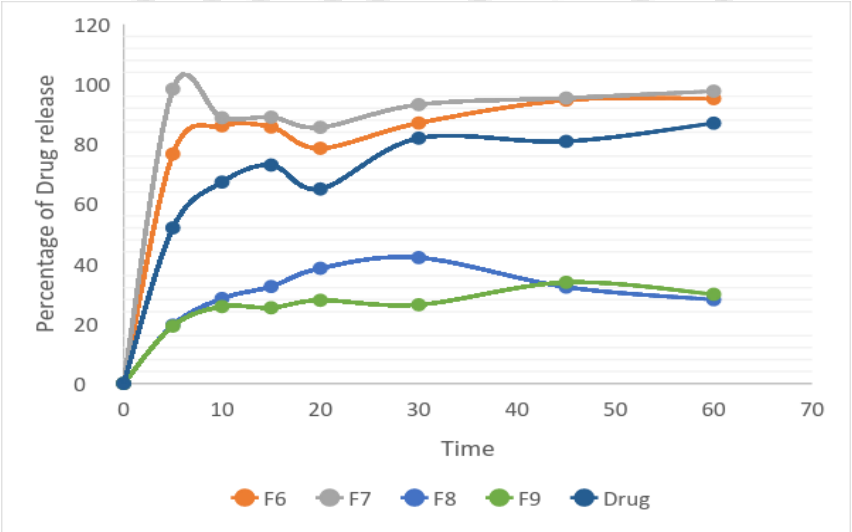

Figure 7: Percent of Flurbiprofen release in dissolution study from formulations using poloxamer as main polymer, as drug represent Flurbiprofen conventional formulation

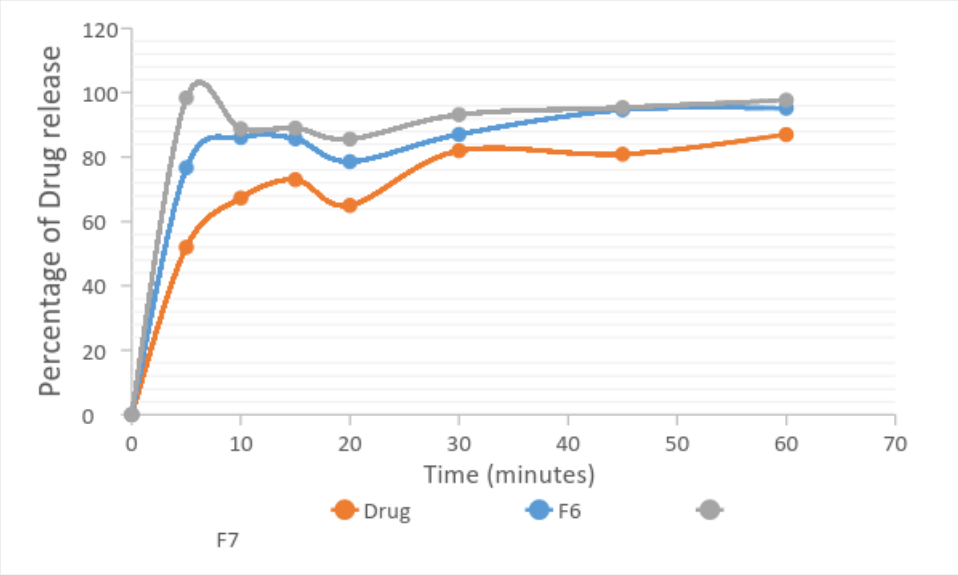

Figure 8: Percent of Flurbiprofen release in dissolution study from the best formulations (F6 and F7), as drug represent Flurbiprofen conventional formulation.

CONCLUSION

Solubility of Flurbiprofen was significantly improved when formulated as solid dispersion since it is molecularly dispersed within the formulation structure that contains voids and channels which greatly increase the drug surface area exposed to the dissolving media. Formulations containing poloxamer (F6 and F7) significantly enhance the drug solubility. This could reflect positively on the onset of drug action and bioavailability.

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