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Research Article

# PREFORMULATION AND EVALUATION OF FLURBIPROFEN SUSTAINED RELEASE MATRIX GRANULES USING AN ALTERNATIVE TECHNIQUE TO THE TRADITIONAL WET GRANULATION METHOD

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**ABSTRACT**

Objective: Flurbiprofen (FP) is commonly used as a non-steroidal anti-inflammatory drug. This study aims at preparation of sustained released matrix formulations of FP, in an attempt to obtain more sustained drug release rate to endow the formulator flexibility in reducing the frequency of FP dose to once daily.

Method: An alternative technique to the traditional wet granulation method was employed for developing sustained-release matrix granules of FP using Eudragit RS100 and ethyl cellulose as hydrophobic polymers. Microcrystalline cellulose (Avicel PH 101) and dibasic calcium phosphate (Emcompress) were used as water insoluble excipients. The micromeritic properties of FP and some its prepared granules were evaluated. The dissolution characteristics of FP from its prepared granules in an acidic medium of PH 1.2 and an alkaline medium of PH 7.1 were studied. The effect of the use of diethyl phthalate (DEP) as a plasticizer on the release of FP from its prepared granules was also studied. Further, the extent of the anti-inflammatory actions of some FP granules was determined and compared by that of FP intact.

Results: The results demonstrated a highly improvement in the micromeritic properties of FP prepared granules comparing by FP intact. The dissolution studies showed that FP prepared granules displayed good sustained-release patterns for their FP contents over prolonged period of time. Further, more prolonged sustained drug releases were obtained with the addition of plasticizer, DEP, to formulation process. The release kinetics showed the best fit with the two investigated diffusion models which showed the highest correlation coefficients. Finally, the anti-inflammatory study showed the superiority of FP granules in sustaining their anti-inflammatory actions for a long period of time.

Conclusion: The alternative technique reduced the labor cost of the traditional wet granulation process and improves the characteristics of granules obtained.

**Keywords**: Flurbiprofen (FP), Eudragit RS100, Ethylcellulose and Sustained-release matrix granules.

## INTRODUCTION

FP, propionic acid derivatives, used as a non-steroidal anti-inflammatory drug in the treatment of musculoskeletal and joint disorders [1]. FP half-life ranges from 2-4 h, which required repeating of daily dose to maintain the effective drug concentration [(2)]. The long oral use of FP results in some adverse effects [2]. The gastro-intestinal adverse effects, such as stomatitis, and gastrointestinal hemorrhage represented the major adverse effects [2]. Therefore, FP is a good candidate for the development of sustained-release dosage forms [1-3].

Hydrophobic polymers are widely used as matrixing agents for developing sustained-release drug formulations using wet granulation [4, 5]. These polymers provide several advantages ranging from good stability at varying pH values to well-established safe application [5]. But, two problems are found with the use of hydrophobic polymers as matrixing agents for developing sustained-release formulations through the traditional wet granulation. The first problem is that a fairly high amount of these polymers was needed to control the drug release, or multiple granulations were used to provide more sustained release which may make the process lengthy and difficulty [4]. The second problem is that many of hydrophobic polymers with high glass transition temperatures tend to be brittle and lack adhesiveness [4].

However, to overcome these problems mention above, the study used an alternative technique to the traditional wet granulation method for preparation sustained-release FP granules formulae using E-RS100 and EC, as matrix hydrophobic polymers. The alternative technique was applied through the addition of a water insoluble excipient along with a drug to facilate the wet granulation process and improves the ability of the matrix coat to retard drug release. Avicel PH101 and Emcompress were investigated as water insoluble excipients. Also, the study investigated addition of DEP, a plasticizer, along with a hydrophobic polymer to improve the latter's ability to interact with formulation excipients and thus improving retardation of drug release. The release characteristics of FP from its prepared granules were studied and analyzed according to different kinetic equations. Moreover, the extent of the anti-inflammatory actions of FP granules was determined and compared by that of FP intact.

## MATERIALS AND METHODS

### Materials

Flurbiprofen was gifted by Kahira Pharm. & Chem. Ind. Company, Cairo, Egypt. Eudragit RS100 (E-RS100), Rohm Pharm, Germany Win lab, Harborough. U. K. Ethyl cellulose (EC), Laserson and Sabetay, Paris, France. Microcrystalline cellulose (Avicel PH 101), FMC Corporation, USA. Dicalcium phosphate (Emcompress), E. Mendell Co., Inc., Carmel, New York, USA. Diethyl phathlate (DEP), Methanol, ethanol, and chemicals of dissolution media, all obtained from El-Nasr Company, Abu-Zabal, Cairo, Egypt.

### Preparation of FP granules

Different FP granules formulae were prepared and the composition of these granules formulae is listed in table (1).

The determined amounts of FP and the water insoluble excipient used were mixed in large dish using geometric dilution method, until a homogeneous mixture was obtained. The obtained mixture was kneaded with organic solution of polymers (EC or E-RS100) of concentrations; 2, 5 and 10% w/v. The wet mass obtained was sieved through sieve screen to obtain granules which were dried at 50-60 °C. The dried granules were sieved to two particle sizes (650 and 250 µm) and kept in a desiccator till used.

**Table 1: The composition of the different prepared FP granules formulae**

| F-no | FP w/w % | Avicel PH 101 w/w % | Emcompress w/w % | E-RS100 w/v % | EC w/v % | DEP w/v % |
|---|---|---|---|---|---|---|
| **F-1** | 33.5 | 64.5 | -- | 2 | -- | -- |
| **F-2** | 33.5 | 64.5 | -- | 5 | -- | -- |
| **F-3** | 33.5 | 64.5 | -- | 10 | -- | -- |
| **F-4** | 33.5 | -- | 64.5 | 2 | -- | -- |
| **F-5** | 33.5 | -- | 64.5 | 5 | -- | -- |
| **F-6** | 33.5 | -- | 64.5 | 10 | -- | -- |
| **F-7** | 33.5 | 64.5 | -- | -- | 2 | -- |
| **F-8** | 33.5 | 64.5 | -- | -- | 5 | -- |
| **F-9** | 33.5 | 64.5 | -- | -- | 10 | -- |
| **F-10** | 33.5 | -- | 64.5 | -- | 2 | -- |
| **F-11** | 33.5 | -- | 64.5 | -- | 5 | -- |
| **F-12** | 33.5 | -- | 64.5 | -- | 10 | -- |
| **F-13** | 33.5 | 64.5 | -- | 2 | -- | 5 |
| **F-14** | 33.5 | 64.5 | -- | 2 | -- | 10 |
| **F-15** | 33.5 | -- | 64.5 | -- | 2 | 5 |
| **F-16** | 33.5 | -- | 64.5 | -- | 2 | 10 |
| **F-17** | 33.5 | 64.5 | -- | 2 | -- | 5 |
| **F-18** | 33.5 | 64.5 | -- | 2 | -- | 10 |
| **F-19** | 33.5 | -- | 64.5 | -- | 2 | 5 |
| **F-20** | 33.5 | -- | 64.5 | -- | 2 | 10 |

**Evaluation of FP granules**

The prepared granules were evaluated for the following micromertic properties:

**Angle of repose**

It was measured according to the method reported by Raghuram et al. [6]. An accurately weighed of powder or granules were carefully poured through the funnel with its tip 2 cm length, to form a stable cone of powder. The funnel was maintained at fixed height in all experiments. The height (h) and diameter (d) of the formed cone were determined. The angle of repose (θ) was calculated using the following equation:

Tan (θ) = 2h/ d equation (1).

**Flow rate**

The measurement of flow rate gives a quantitative image about a material flow to predict the behavior of material during formulation process. It depends on the determination of the flow speed of a constant amount of a material through a hopper maintained at fixed height.

**Bulk density**

It was determined according to the method reported by Raghuram et al. [6], using a measuring cylinder. A suitable weight in (gm) of powder or granules was allowed to introduce into a 25-ml measuring cylinder. The volume in ($cm^3$) taken by powder or granules was determined as a volume before tapping ($V_o$). Then, the cylinder allowed to fall under its own weight onto a hard wood surface from the height of 2.5 cm at 2-s intervals. The tapping was continued until no further change in the volume was noted. The last volume in ($cm^3$) taken by powder or granules was determined as a volume after tapping ($V_f$). The bulk density was obtained by dividing the weight in (gm) volume in ($cm^3$).

**Hausner factor**

It is the ratio between bulk density before tapping ($D_0$) and that after tapping ($D_f$). It gives an idea about the flow characters of powder particles. When the ratio is lower than 1.2, the powder has a good flowability, while, the ratio more than 1.6, indicated that the flowability of the powder is bad. The ratio between 1.2 and 1.6 indicated that the powder has acceptable flowability.

**Compressibility percent**

It is a measure of the potential stability of the powder. This parameter known by Carr's index can be computed from bulk density of the powder according to the following equation [7]:

Compressibility % = $[(D_f - D_0)/ D_f] \times 100$ equation (2).

Where, $D_0$ is bulk density before tapping and $D_f$ is bulk density after tapping.

**Granules friability**

A modification of the method described by Marks and Sciarra [8] was carried out in order to assess the friability of the produced granules. Exactly, 5 gm of the dried granules of mean particle size 650 um were introduced into an Frweka tablet friabilitor. The friabilitor was left to rotate at 25 r.p.m for 4 minutes. Then, the granules were put over a preweighed 500 um sieve and were shaken for a 15 seconds. The sieve was weighted and the amount of the granules retained over, was determined. The friability of granules was calculated from the following equation:

Friability % = [(5- weight of granules retained)/5] x 100 equation (3)

**Drug content study**

A Known amount of FP prepared granules were powdered and the drug was extracted several times using 10 ml of a phosphate buffer solution (PH 7.1). The solution was filtered, suitably diluted and assayed for its FP contents spectrophotometrically at $\lambda_{Max}$ 260 nm.

**In-Vitro release study**

In-vitro release studies were carried out in U.S.P dissolution apparatus II. An amount of FP prepared granules equivalent to 100 mg of FP was placed in 500 ml dissolution medium of hydrochloric acid pH 1.2 for 2 h, then replaced with the same volume of a phosphate buffer solution pH 7.1 for 8 h. The dissolution contents were kept at 37±0.5 °C, and stirred at 50 rpm. A 5-ml sample was withdrawn and replaced with another 5-ml of a suitable fresh dissolution medium at the preselected intervals. The concentration of the drug was determined spectrophotometrically at $\lambda_{Max}$ 260 nm. Each test was performed in triplicate.

**Antiinflammatory activity study**

The anti-inflammatory activities of FP intact and some its prepared matrix granules were evaluated using trepan-blue method in adult male rats. FP granules formulae; F-3 and F-10, displayed the highest and the lowest percent release of FP at the end of dissolution studies (8 h.) were selected for this study. The method determined the effect of FP intact, granule F-3 and granule F-10, on the rate of the capillary permeability disturbance induced by intradermal injection of 0.1% of histamine solution. The rate of capillary permeability is the time taken for appearance of a blue color around the site of the intradermal injection of 0.02 ml of 0.1% of histamine phosphate

solution following an intravenous injection of 2 ml/kg of a solution of trypan-blue dye. FP intact and some its prepared matrix granules were dispersed in 2% gum acacia and given orally by lavage tube to rats weighing (200-250 g), in a dose equivalent to 50/kg of FP. The rats were divided into different groups as followed: control group was administrated an equal volume of the suspension medium, group 1 was administrated suspension of FP intact, groups 2 and 3 were administrated suspensions of FP granules formulae; F-3, and F-10, respectively. The anti-inflammatory effects were determined after dosing at time intervals; 3, 6, and 12 h. One group of rats was used for each time interval.

**Release Kinetics**

Different kinetic models including zero-order, first-order, Higuchi's equation [9] and Baker and Lonsdale [10] were applied to interpret the release rate of the drug from matrix granular systems. The best fit was found with higher correlation ($r^2$>0.98).

**RESULTS AND DISCUSSION**

**Micromeritic properties of FP granules**

The micromeritic properties of FP granules formulae; F-2, F-5, F-8 and F-11, were listed in table (2). The results demonstrated that FP intact has angle of repose of higher value, (58.7º), indicating to the poor flow property of FP intact. While, FP granules formulae; F-2, F-5, F-8 and F-11, showed more lower values of angle of repose recording 31.8 º, 33.4 º, 37.1 º and 36.7º, respectively. This indicated to the improvement of flow property of FP upon granulation process. These results confirmed by the values of flow rate recorded 0.0, 5.8, 5.7, 6.3 and 6.6 (g/sec.) for FP intact, F-2, F-5, F-8, F-11 granules, respectively.

**Table 2: The micromeritic properties of some FP granules formulae comparing by that of FP intact**

| Micromeritic property | FP intact | FF-2 | F-5 | F-8 | F-11 |
|---|---|---|---|---|---|
| **1-Angle repose (0)**[e] | 58.3º | 31.8º | 33.4º | 37.1º | 36.7º |
| **2-Flow rate (g/sec.)** | 0.0 | 5.8 | 5.7 | 6.3 | 6.6 |
| **3-Bulk density (g/cm$^2$)** | 0.25 | 0.36 | 0.36 | 0.35 | 0.35 |
| **-before tapping ($D_0$)** | 0.51 | 0.43 | 0.42 | 0.42 | 0.41 |
| **-after tapping ($D_f$)** | 2.04 | 1.19 | 1.17 | 1.2 | 1.17 |
| **4-Hausner factor** | 45.8 | 16.2 | 14.3 | 16.7 | 14.6 |
| **5-Compressibility %** | 8.9* | 3.3 | 3.5 | 3.7 | 3.8 |
| **6-Friability %** | | | | | |

*This value is related to FP control (FP+excipient granulated by ethanol only)

As shown in table (2), the value of Hausner factor of FP intact equals to 2.04, while, all the tested granules formulae recorded Hausner factor values ≤ 1.2. The values of Hausner factor obtained proved the good flow properties of all the tested granules formulae comparing by the bad flow properties of intact FP.

Compressibility percent computed from equation (2) is also related to the flowability of a free flowing material. Where, the more the material flowability, the smaller the value of its compressibility percent (< 25%). Table (2) demonstrated that the compressibility percent value of FP intact was very high (45.8%), while the compressibility percent values of the tested FP granules formulae; F-2, F-5, F-8 and F-11, were 16.2, 14.3, 16.7 and 14.6 % respectively. This means that the tested FP granules formulae have good flow properties where their compressibility percent values are less than 25%.

However, the results of the micromeritic properties investigated; Angle of repose, flow rate, Hausner factor and compressibility %, reflected the improvement of flowability of FP intact upon granulation process. Similar results were previously reported [4, 11].

Finally, with regard to the friability of granules, FP granules formulae; F-2, F-5, F-8 and F-11, recorded more lower friability % than FP intact as shown in table (2). The lower friability % of FP granules displayed the high quality characteristics of the prepared granules.

**Drug content study**

The results of drug content study showed that the drug contents were ranged between 93 and 96% (± 2.51), of their theoretical calculated drug contents for the different prepared FP granules formulae.

**In-Vitro release study**

The dissolution profiles of FP from its different prepared granules formulae (F-1 to F-12) in acidic medium of PH 1.2 are nearly similar and the differences in between are very little and difficultly to be distinguish markedly. The percent release of FP from its different prepared granules formulae (F-1 to F-12) not exceed 7.3% at the end of 2 hr., while, the percent release of FP intact reached about 28.5% at the same time period. Therefore, the displays of the dissolution profiles of FP from its different prepared granules formulae not shown.

On other side, the dissolution profiles of FP from its different prepared granules formulae (F-1 to F-12) in phosphate buffer medium of PH 7.1 are demonstrated in Figs. (1-4). The results proved that all the prepared FP granules formulae (F-1 to F-12) displayed good sustained-release patterns for their FP contents over prolonged period of time. This indicated to the good retard effects of the investigated matrixing agents, ERS-100 or EC, which may be attributed to that they are insoluble through the PH range of the digestive tract and exhibits a distinct permeability for water and soluble substance[5]. The percent release of FP from its different granules formulae (F-1 to F-12) within 30 min. ranged from 44.4 to 29.9%, while the percent release of FP intact reached 100% within the same time period. Further, the percent release of FP from its different granules formulae (F-1 to F-12) at the end of dissolution studies (8 hrs.) ranged between 70.5 and 54.6 %. This represented good results, where, the daily dose of FP could be reduced to once or twice, which improve patient compliance and highly reduced FP adverse effects specially the gastro-intestinal adverse effects.

Moreover, the dissolution results shown in Figs. (1-4) reflected that as the concentrations of ERS-100 or EC increased from 2 to 10% w/v, the percent release of FP from its different granules formulae slightly decreased. This indicated to the low effect of ERS-100 or EC concentrations on release of FP from its different granules formulae (F-1 to F-12) prepared by an alternative technique which depended on the addition of a Avicel PH 101 or Emcompress, as a water insoluble excipient, along with FP which improve the ability of the matrix agents to retard drug release without using high amounts of hydrophobic polymer or multiple granulations to provide more sustained release action.

The effect of DEP, a plasticizer, on the release of FP from its granules formulae; F-13, F-14, F-15 F-16, F-17, F-18, F-19 and F-20, was illustrated in Figs. (5-8). It is clear that a marked reduction in the release of FP from its granules prepared with 5% w/v DEP comparing by the release of FP from its granules prepared without DEP. The increase in the concentration of DEP to 10% w/v resulted in more reduction in the release of FP from its granules. This indicated to the ability of DEP to interact with hydrophobic polymer investigated, (ERS-100 or EC), improving retardation of drug release.

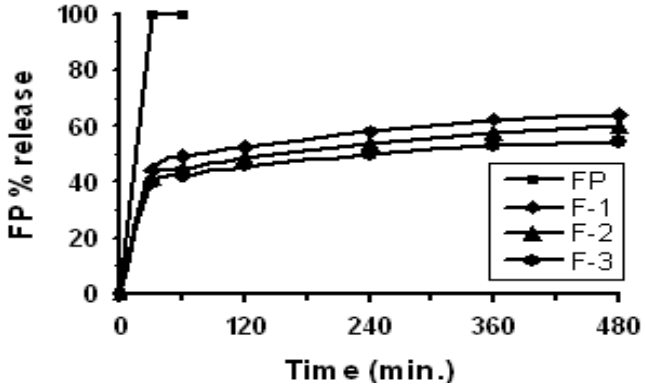


**Fig. (1): Dissolution profiles of FP from its formulae; F-1, F-2 and F-3 in phosphate buffer of PH 7.1**

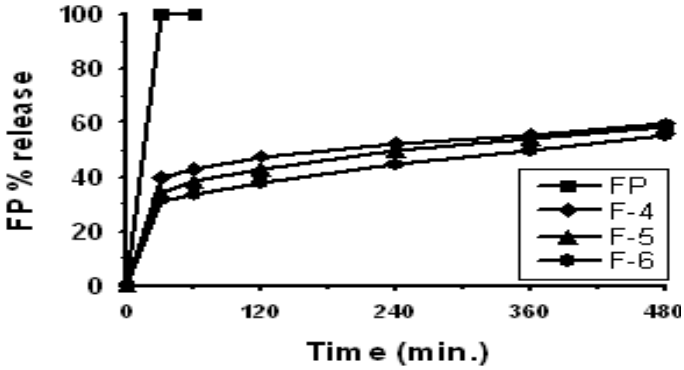


**Fig.(2): Dissolution profiles of FP from its formulae; F-4, F-5 and F-6 in phosphate buffer of PH 7.1**

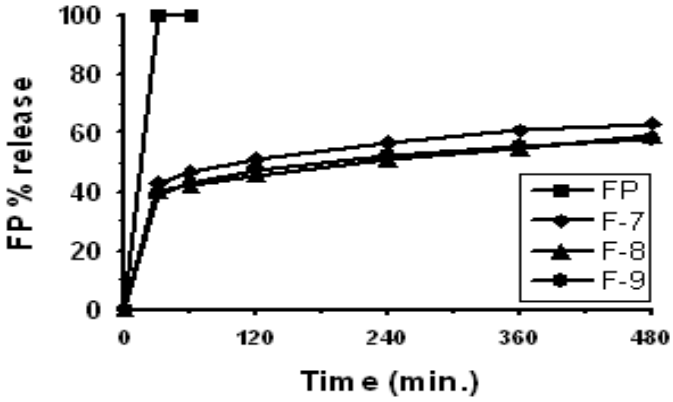


**Fig.(3): Dissolution profiles of FP from its formulae F-7, F-8 and F-9 in phosphate buffer of PH 7.1**

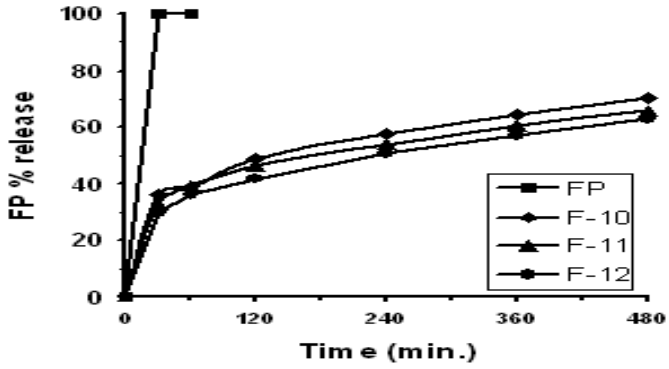


**Fig.(4): Dissolution profiles of FP from its formulae F-10, F-11 and F-12 in phosphate buffer of PH 7.1**

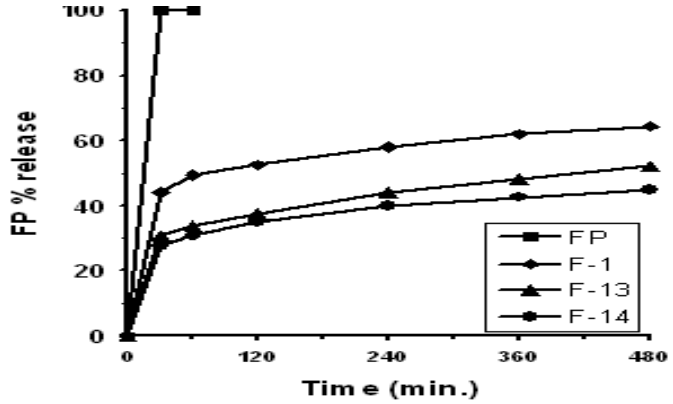


**Fig.(5): Dissolution profiles of FP from its formulae F-1, F-13 and F-14 in phosphate buffer of PH 7.1**

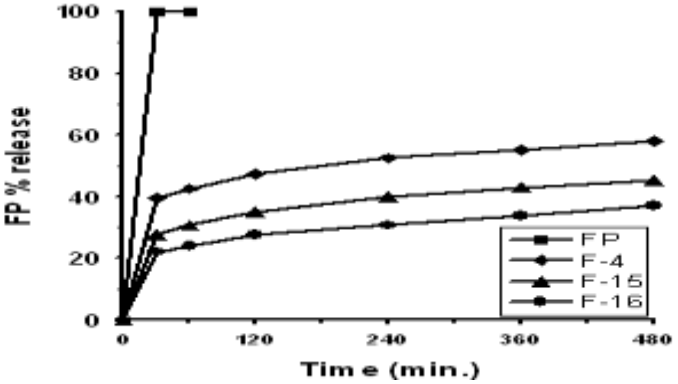


**Fig.(6): Dissolution profiles of FP from its formulae F-4, F-15 and F-16 in phosphate buffer of PH 7.1**

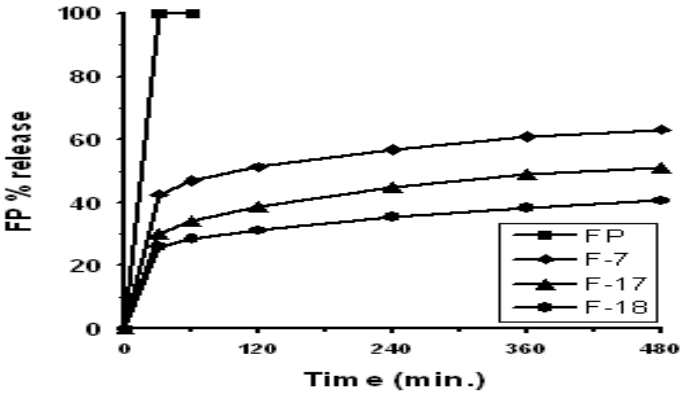


**Fig.(7): Dissolution profiles of FP from its formulae F-7, F-17 and F-18 in phosphate buffer of PH 7.1**

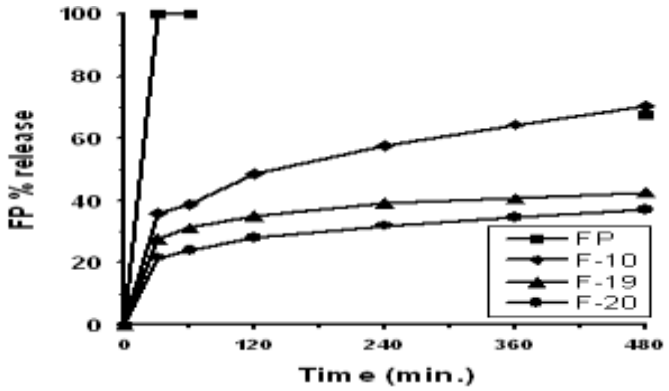


**Fig.(8): Dissolution profiles of FP from its formulae F-10, F-19 and F-20 in phosphate buffer of PH 7.1**

**Anti-inflammatory activity study**

It is worth that the anti-inflammatory activity of test systems was measured by the time taken for appearance of a blue color around the site of histamine injection. The appearance of a blue color related to the disturbance in the capillary permeability of rats following intradermal injection of histamine was taken as inflammation evidence. Thus, the more prolongation in the time of appearance of blue color, the greater anti-inflammatory activity of the test system.

The result shown in Fig. (9) demonstrated that the rats of the control group gave blue color within 2 minutes at the different time intervals. While, the rats of group 1 demonstrated a greater prolongation in the time of appearance of blue color at time interval 3 and then, the action was nearly reduced to half of its value until reach to that of control group at time intervals 6 and 12. This proved that FP intact must be administrated each 4 h. to obtain a satisfied anti-inflammatory activity along day. On other hand, the rats of groups 2 and 3 displayed a good prolongation in the time of appearance of blue color at the different time intervals; 3, 6 and 12 h. This indicated that FP granules formulae; F-3, and F-10, can be offered a good anti-inflammatory activity for longer time when taken for once or twice a day.

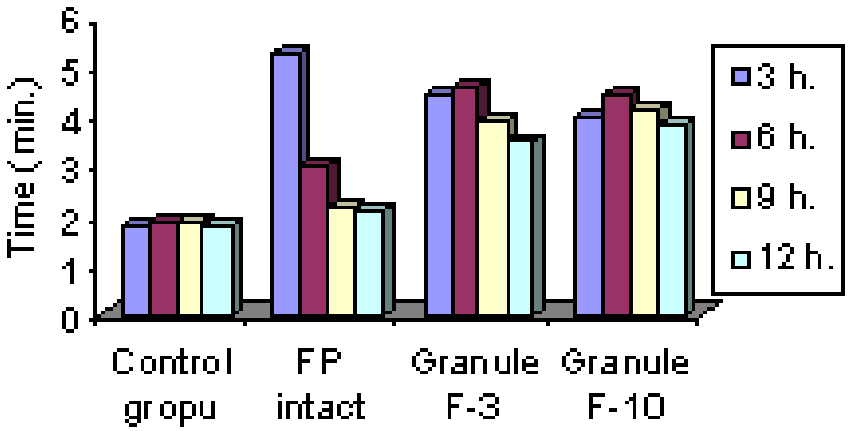


**Fig. 9: The extent of the anti-inflammatory activities of the test FP systems at different time intervals.**

**Release Kinetics**

The values of release rate constants and the corresponding correlation coefficients ($r^2$) of the applied models (zero-order, first-order, Higuchi's equation and Baker and Lonsdale) were listed in table (4). The kinetic results obtained demonstrated that the best fit was found with Baker and Lonsdale model and Higuchi's model which showed the highest correlation coefficients ($r^2$) among the other investigated models. This indicated that the release mechanism of FP from its different prepared matrix granular systems is diffusion.

**Table 3: The values of kinetic release constant (k) and correlation coefficient ($r^2$) of different kinetic models for fitting the release of FP from its granules**

| F-no | Zero-order model | | First-order model | | Higuchi diffusion model | | Baker & Lansdale model | |
|---|---|---|---|---|---|---|---|---|
| | $R^2$ | $K_0$ | $R^2$ | $K_1$ | $R^2$ | $K_H$ | $R^2$ | $K_{BL}$ |
| **F-1** | 0.9907 | 2.61 | 0.9951 | 0.059 | 0.9973 | 9.12 | 0.9963 | 0.82 |
| **F-2** | 0.9933 | 4.59 | 0.9969 | 0.083 | 0.9999 | 8.52 | 0.9984 | 0.67 |
| **F-3** | 0.9857 | 2.23 | 0.9904 | 0.043 | 0.9978 | 7.84 | 0.9930 | 0.54 |
| **F-4** | 0.9845 | 2.59 | 0.9890 | 0.051 | 0.9965 | 9.18 | 0.9917 | 0.64 |
| **F-5** | 0.9839 | 2.89 | 0.9891 | 0.056 | 0.9949 | 10.25 | 0.9921 | 0.72 |
| **F-6** | 0.9944 | 3.39 | 0.9982 | 0.058 | 0.9976 | 10.91 | 0.9998 | 0.66 |
| **F-7** | 0.9947 | 2.97 | 0.9951 | 0.069 | 0.9963 | 10.63 | 0.9966 | 0.84 |
| **F-8** | 0.9951 | 4.53 | 0.9979 | 0.085 | 0.9993 | 11.19 | 0.9993 | 1.06 |
| **F-9** | 0.9947 | 2.65 | 0.9981 | 0.052 | 0.9986 | 9.13 | 0.9992 | 0.67 |
| **F-10** | 0.9770 | 2.78 | 0.9898 | 0.064 | 0.9921 | 11.79 | 0.9938 | 0.88 |
| **F-11** | 0.9853 | 4.69 | 0.9912 | 0.089 | 0.9993 | 13.69 | 0.9994 | 1.03 |
| **F-12** | 0.9413 | 4.67 | 0.9742 | 0.082 | 0.9862 | 16.51 | 0.9923 | 1.01 |
| **F-13** | 0.9879 | 3.10 | 0.9935 | 0.052 | 0.9989 | 10.05 | 0.9976 | 0.58 |
| **F-14** | 0.9768 | 3.36 | 0.9827 | 0.051 | 0.9950 | 9.433 | 0.9951 | 0.50 |
| **F-15** | 0.9980 | 3.59 | 0.9988 | 0.055 | 0.9994 | 9.907 | 0.9997 | 0.55 |
| **F-16** | 0.9988 | 1.61 | 0.9993 | 0.023 | 0.9994 | 6.289 | 0.9998 | 0.21 |
| **F-17** | 0.9838 | 4.40 | 0.9900 | 0.075 | 0.9982 | 12.28 | 0.9949 | 0.84 |
| **F-18** | 0.9977 | 2.06 | 0.9986 | 0.036 | 0.9995 | 7.181 | 0.9996 | 0.29 |
| **F-19** | 0.9647 | 1.86 | 0.9697 | 0.029 | 0.9898 | 6.639 | 0.9760 | 0.31 |
| **F-20** | 0.9895 | 1.84 | 0.9992 | 0.026 | 0.9985 | 6.851 | 0.9957 | 0.24 |

**CONCLUSION**

Different FP granules Formulae were prepared by an alternative technique to wet granulation method using both E-RS100 and EC, as matrix hydrophobic polymers, and both Avicel PH 101 and Emcompress as water insoluble excipients. The alternative technique reduced the labor cost of wet granulation process and improves the characteristics of granules obtained. The prepared FP granules Formulae displayed good micromeritic properties and good sustained-release patterns for their FP contents over prolonged period of time. Further, more prolonged sustained drug releases were obtained with the addition of plasticizer, DEP, to formulation

process. The release kinetics showed the best fit with the two investigated diffusion models which showed the highest correlation coefficients. The anti-inflammatory study showed the superiority of FP granules in sustaining their anti-inflammatory actions for a long period of time.

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