Dissolution Modulating Mechanism of Flurbiprofen Solid Dispersions: Characterization, Physical Stability and in vivo Performance: Formulation Considerations and optimization study

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ABSTRACT

Present work studied interaction between Surelease, Urea, and Eudragit RL100 (RL) polymers with nonsteroidal anti-inflammatory drug FLP. Solid dispersions at different weight ratios were prepared by fusion (Method A) and coevaporation (Method B). Characterization of solid dispersions (SDs) included elemental analysis, Fourier transform (FTIR), Differential scanning calorimetry (DSC), Powder X-ray diffractionmetry (XRD), Scanning electron microscopy (SEM) as well as wettability study, angle of repose, aqueous solubility determination, in vitro and in vivo drug release. FTIR studies showed the stability of FLP. DSC and XRD studies confirmed the amorphous state of FLP in its SDs. SEM showed the formation of effective SDs of FLP with polymers. Pre-formulation studies showed increased hydrophilicity but a non-significant increase in lipophilicity of the SDs. IDR value is only 0.03a0.001 mg/cm2min. whereas wettability of solid dispersions was found to be controlled. Angle of repose shows good flowability characteristics. The dissolution rate of FLPSDs prepared by method A was significantly greater than that from method B. Method A with urea and RL provides slower and more gradual increase in dissolution rate than those of FLP when polymer ratios were increased. TF20 possess longer duration of action compared to FLP.

Key words: Flurbiprofen, Surelease, Urea, Solid dispersion, in vitro study, in vivo study.

INTRODUCTION

The concept of solid dispersions dates back to 1961 when Sekiguchi & Obi found that the administration of a fused mixture of the poorly water-soluble drug sulphathiazole and the water soluble carrier urea produced an enhanced absorption of the drug in rabbits. Subsequently, hundreds of papers have been published detailing the physico-chemical properties, phase equilibrium and pharmacological activity of solid dispersion-based drug-carrier systems. However, only few drug products based on solid dispersions have reached the market, mainly because of physico-chemical instability and scale-up problems.\(^4\) Solid dispersions are generally prepared by either a solvent method, whereby the drug and carrier are dissolved in a mutual solvent followed by solvent removal, or by a melting method, whereby drug-carrier mixtures are prepared by co-melting/cooling.\(^3\) The disadvantage of the solvent method is the use of organic solvents with issues of toxicity, safety hazards and solvent residuals and also the possible precipitation of the drug into various polymeric forms, which have different solubilities and bioavailabilities. Therefore, melting is often the method of choice for the preparation of solid dispersions despite the potential problem of heat-induced degradation of drugs and carriers.\(^4\)

Eudragit RL100 (RL) is copolymer of acrylic and methacrylic acid esters that contain a low level of quaternary ammonium groups. Eudragit acrylic resins exhibit a broad spectrum of physicochemical properties and are used in a variety of pharmaceutical applications, such as film coating of oral formulations and preparation of controlled-release drug systems (eg, micro- and nano particulate systems). In developing new drug delivery systems, many studies have been carried out to investigate the influence of Eudragit acrylic resins on the release of drugs from matrices. The nature of drug and polymers, and their reciprocal interactions, significantly influence the drug release pattern. In particular, the incorporation and release of non-steroidal anti-inflammatory drugs (NSAIDs) from polymers was shown to be strongly dependent on the acidic nature of the drug, which allows chemical interactions, physical interactions, or both to occur (zwitterionic adducts, ion pairs, ion-exchange resin behavior) with the ammonium group on the RL backbone. Surelease, an aqueous polymeric dispersion of ethyl cellulose, is a latex coating system of fully plasticized ethylcellulose dispersion with 25% (w/w) solids content. It contains dibutyl sebacate and oleic acid as plasticizers, and fumed silica as an anti-adherent in vehicle of ammoniated water. Several papers have reported on the use of aqueous polymeric dispersions in the formulations of controlled drug delivery systems and various factors and variables which affect the rate and/or kinetics of drug release from such systems.

Flurbiprofen (FLP) is practically insoluble in water, freely soluble in alcohol and in methylene chloride. It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and migraine. It is given in usual doses of 150 to 200 mg daily by mouth in divided doses. To reduce the frequency of administration and to improve patient compliance, an extended release formulation of FLP is desirable.

In this study, the solid dispersion technique was applied to extend the dissolution and improve oral bioavailability of FLP using different carriers. The feasibility assessment of this approach, the physical characteristics, in vitro dissolution, and in vivo bioavailability of the solid dispersion are presented in this report.

Experimental

Materials

FLP was supplied by Sun Pharma, Mumbai, India. Eudragit RLPO (RLPO) was gifted by Rohm Pharma, Germany. Urea was obtained from Showa Chemicals Inc., (Japan). Surelease was generously gifted by Colorcon, Germany. Lactose, Talc and Magnesium Stearate was purchased from Merck India Limited, Mumbai. Other chemicals were of analytical grade. Double distilled water was used throughout the studies.

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Drug – Excipient Compatibility Screening
For this study, Urea, surelease and Eudragit RL100 were selected as excipients. FLP and selected excipients were taken in ratio similar to that to be taken in formulation. Water was added in a quantity of 0.45 % w/v as a worst case. The mixtures prepared were placed in vials, sealed and stored in an oven at a temperature of 50°C ± 1°C for two weeks. At the end of two weeks the mixtures were observed for their physical state and analyzed by TLC.5

Intrinsic Dissolution Studies (IDR)
500 mg of drug was compressed in a 13 mm IR disc punch and die, set for 5 minutes at 500 MPa compaction pressure. Punch set was re lubricated by 5%w/v stearic acid in chloroform. Fixed the disc on holder of basket of dissolution apparatus by using low melting paraffin wax. Cleared off the wax from lower face of the disk with the help of blade. Dissolution was carried out at 100 rpm in 1 ltr distilled water. Maintained the temperature at 37°C. Samples have been taken at various time intervals.6

Preparation of FLP Solid Dispersions
Physical mixing
Physical mixtures of FLP with polymers were prepared by mixing the required amount of FLP and polymers in a glass mortar for 5 min. The prepared mixture was then passed through sieve no. 100 and stored in desiccators until further use. Placebo solid dispersion was prepared by the same method.7,8

Fusion Method
Solid dispersions containing 1:1, 1:2 and 1:5 ratios as well as a solid dispersion of FLP with combination of Urea and surelease were prepared by the solvent evaporation - fusion technique (Method A). An ethanol solution of FLP in a round bottomed flask was warmed in a water bath (75°C) until a clear solution was obtained. The required amount of polymer was then added, and the mixture was warmed for 30 seconds in the water bath and vigorously mixed. The flask containing the drug-polymer-solution was then attached to a rotary evaporator (Model R114, Buchi, Switzerland). Ethanol was removed under vacuum at 75°C. After 15 min, the hot-water bath was replaced with an ice-water bath to cool the mixture. After another 15 min, the ice-water bath was removed but the vacuum was maintained for 6 h. The resulting white solid was removed from the round bottomed flask, transferred to a crystallization dish, and placed in a vacuum oven at room temperature for 10 h to remove any residual ethanol. The dispersions were then ground with a mortar and pestle and sifted (Dispersion A).7,8

Coprecipitation Method
FLP and polymers were dissolved in dichloromethane (50 ml) and transferred to diethyl ether (100 ml) at 0°C while being gently stirred. The precipitates obtained were filtered using Whatman no. 1 filter paper (Whatman International Ltd., England) and dried in vacuum desiccator. The dried samples were milled and sifted to get coprecipitates (Dispersion B) (Method B).7,8

Determination of Drug Content
10 mg of each solid dispersion were accurately weighed and dissolved in 10 ml of volumetric flask with pH 7.4, filtered and 1 ml of sample was diluted with double distilled water up to 10 ml and assayed spectrophotometrically for FLP at 247 nm using calibration curve based on standard solutions in double distilled water. Results are expressed both as the drug content (mg incorporated drug) and percent incorporation (actual amount of drug in solid dispersions Vs initially added amount).

The studies were conducted in triplicate.

Determination of Partition Coefficient
Partition coefficient was determined according to Hansch method between 10 ml n-octanol and 10 ml buffer of varying pH (1.2, 6.8 and 7.4). Buffers and n-octanol were added to the separating funnel. Both phases were saturated for 60 minutes with intermittent shaking. Weighed amount of amorphous FLP and FLP solid dispersions (FLPSDs) were added to different separating funnels and again shaken for 30 min. to achieve drug distribution in both phases. The separating funnel was allowed to stand for 5 min. Both aqueous and organic layers were separated. Organic layer suitably diluted and analyzed by UV spectrophotometer for FLPSDs. Aqueous layer was separated, suitably diluted with phosphate buffer pH 7.4 and analyzed by UV spectrophotometer for FLP.

Aqueous Solubility Determination
The solubility of FLPSDs was determined. Briefly, excess amounts of the solutes were added in HCl buffer pH 1.2, phosphate buffer pH 6.8 and 7.4 and equilibrating them at 25°C on water bath shaker. After 72 hours the samples were withdrawn, filtered, diluted and analyzed by UV spectrophotometer at 247 nm.

Wettability Studies
Pure drug, weighing 1 g was placed in sintered glass funnel of 27 mm internal diameter. Bridge was formed at the neck of the funnel with the help of cotton plug. The funnel was held in upright position in a beaker filled with water such that the water level in the beaker just touched the cotton plug. Methylene blue powder was layered over the surface of pure drug in the funnel. The time required to raise the water through the drug till wetting of methylene blue powder occurred was recorded. The procedure was followed for all the SDs.11

Angle of Repose
To get an idea about flowability properties of the solid dispersions, angle of repose for all the solid dispersions was determined. If the angle exceeds 50°, the material will not flow satisfactorily, whereas materials having values near the minimum flow easily and well. The rougher and more irregular the surface of the particles, the higher is the angle of repose. The angle of repose was measured by passing FLPSDs through a sintered glass funnel of internal diameter 27 mm on the horizontal surface. The height (h) of the heap formed was measured with a cathetometer, and the radius (r) of the cone base was also determined. The angle of repose (Θ) was calculated from Θ = tan⁻¹(h/r).11

Humidity Studies
Samples of FLP, F12 and F20 were placed in plastic trays, weighed and kept in glass humidity chambers. Aqueous solution of 100mL volume containing a specific concentration of sodium hydroxide was placed at the bottom of each humidity chambers to obtain the desired relative humidity conditions. The samples were exposed to relative humidity conditions of 40%, 70% and 100% for 7 days. The humidity chambers were sealed using petroleum jelly and Parafilm™ to prevent moisture entry or escape. After seven days the samples were removed and analyzed to determine any possible effects of water sorption.13

FTIR Spectroscopy
IR spectra of pure drug and of F1 to F18 were obtained with a FTIR spectrophotometer, Shimadzu 8201 PC, using KBr disks (about 10 mg sample for 100 mg drug KBr). The scanning range used was 4000 to 400 cm⁻¹ at a scan period of 1 minute.
**Differential Scanning Calorimetry**

Thermal analysis was performed on the drug, F1 to F18 using a PERKIN – ELMER DSC-7. Samples (10-15 mg) were weighed and sealed into 40 μl aluminium pans. DSC runs were conducted over a temperature range of 20°C to 140°C at a rate of 10°C / minute in nitrogen atmosphere.

**X-RAY Powder Diffraactometry**

Diffraction patterns of F1 to F18 were recorded with a PW 3040/60 X' Pert PRO, Netherland. A voltage of 40 kV and a current of 30 mA for the generator were used, with Cu as the tube anode material. The solids were exposed to Cu-K radiation (α1=1.54060 Å and α2=1.54439 Å, with a α1/α2 ratio of 0.5), over a range of 20 angles from 10°C to 30°C, at an angular speed of 1° (20) per minute.

**Scanning Electron Microscopy**

Morphology of solid dispersion particles was characterized by scanning electron microscopy using LEO 435 VP, UK. Solid dispersions were fixed on supports with carbon glue and coated with gold using gold sputter model in a high vacuum evaporator. Samples were then observed with scanning electron microscopy.

**Preparation of Solid Dispersion Tablets**

Pure FLP, F12 and F20 containing 75 mg each of FLP were mixed with lactose (56.8% w/w), tcalc (2% w/w) and magnesium stearate (1% w/w) compressed in 7 mm dies at a pressure of 1370 lbs using tablet punching machine. All ingredients were triturated in a mortar for 15 min. The mixture was then compressed with an IR press (1.3-cm punch, pressure: 2-3 ton).

**In vitro Dissolution Study**

The dissolution studies were performed using United States Pharmacopeia NF 27 type II dissolution test apparatus. FLPSDs equivalent to 300 mg drug were placed in 750 mL of 0.1 M HCl (pH 1.2) and stirred at 50 rpm and 37°C for 2 hours. Exactly 250 mL of a 0.2 M trisodium phosphate solution was then added to achieve a pH 6.8 value. 2 mL samples were taken at selected time intervals and analyzed spectrophotometrically at 247 nm. Analysis of data revealed that aqueous solubility of FLP and FLPSDs is almost uniform in all solid dispersion systems and was in good agreement with theoretical drug content.

**Bioavailability Studies**

Bioavailability studies were carried out under Institutional Animal Ethical Committee Approval No. (IAEC/PSIT/1273/ac/09). Six male albino rabbits, average weight 2.75 kg (range 2.5-3 kg) were used. The animals were kept on standard diet during testing periods. Investigated TFLP, TF20 were given orally in the fasting state at a dose level of 100mg/kg body weight, in such a way that each rabbit received a dose of each preparation at weekly intervals. Blood sample (2 ml each) were collected from the ear vein into heparinized tubes at 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hr after administration and immediately centrifuged at 2500 rpm for 10 min; plasma obtained was kept at -20°C until determination. The drug content in plasma was determined.

**RESULTS AND DISCUSSION**

**Drug - Carrier Compatibility Screening**

At the end of two weeks the mixtures were observed for their physical state. The result showed that incompatibility was observed when 0.45% moisture was added in the mixture and in absence of moisture the physical mixtures were compatible with each other. Any interaction with drug and carrier was ruled out with the help of TLC studies. In TLC the comparable Rf values of chromatogram and the absence of additional spots indicates that there is no interaction between drug and various carriers.

**Determination of Drug Content**

Table 1 and Table 2 summarizes the theoretical and actual drug content of prepared solid dispersions. Estimation of drug content in different samples revealed 93.62-100% of expected values. The drug content was uniform in all solid dispersion systems and was in good agreement with theoretical drug content.

**Partition Coefficient and Aqueous Solubility Study**

Results revealed that log P value of drug and solid dispersion decreases with increase in pH, this may be due to increased solubility of drug candidates at higher pH so more distribution of drug in aqueous phase (Figure 1). The enhancement of log P values for SD compared to FLP may be due to non ionic nature of the SD moiety as compared to the ionic nature of FLP. Thus F12 should improve drug delivery of FLP. Saturated solubility of FLP and F1 to F18 in different pH after 48 h was shows in Figure 2. Results revealed that aqueous solubility of FLP and FLPSDs increases with increasing pH. This phenomenon may be explained by an increase in the ionization of the compounds with an increase in pH and subsequent higher aqueous solubility. Solubility of FLP increased substantially through the pH range, the reason for this is that the parent drug is having carboxylic group experiencing a higher degree of ionization with increased pH. Increased solubility of FLPSDs in comparison to FLP may be due to increased polarity.

**Wettability and Angle of Repose**

Time required for rising water through capillary action to wet the methylene blue powder was found to be in the range of 3 to 5 minutes for all the solid dispersions, which was significantly less when compared with 15 minutes for pure drug. For all the SDs, angle of repose was deter-
mined. It was found to be in the range of 29°C to 35°C. This illustrates the free flowability of SDs and their ability to be used for formulation into solid dosage forms.

Moisture Content Determination
FLP was hardly hygroscopic, whereas F20 adsorbed 2% (w/w) moisture when equilibrated at 75% RH. Because the hygroscopicity was reversible and no crystallization was observed by XRD, the solid dispersion proved physically stable under the moisture conditions.

Solid Dispersion Properties
FT-IR spectra of FLP and FLPSDs (Figure 3) showed characteristic broad peak of FLP in the range of 2500 to 3500 cm\(^{-1}\) due to hydrogen bonding. The characteristic peaks of FLP at 1698 cm\(^{-1}\) and 2920 cm\(^{-1}\) were due to carbonyl and hydroxyl stretching, respectively. These bands were still visible in F1 to F6 suggesting that there was no interaction between FLP/Polymers in F1 to F6 (physical mixtures), while it totally disappeared in corresponding F7 to F18 resulting in a broad band as well as altered stretching and bending vibrations. This result suggested the possibility of intermolecular hydrogen bonding between FLP and polymers in co-evaporates and coprecipitates. These interactions were made while the molecules were in solution that is when the distances between the molecules were so small that association between the functional groups is possible. There was no interaction between the drug and polymers. The DSC scans for the F6, F12 and FLP were examined, and found that the sharp melting point of pure FLP appeared at 114°C whereas no such peak was observed in solid dispersion prepared with Surelease (Figure 4), suggesting that FLP was molecularly dispersed and in an amorphous form. The dispersion of FLP in F7 to F18 matrix at 1:1, 1:2 and 1:5 weight ratios resulted in complete suppression of drug fusion peak suggesting possible solid solution of drug in polymer. The X-ray powder diffraction patterns of SDs along with those of drug and polymer are shown in Figure 5. Significant reduction in the peak intensities was observed in the XRD patterns of F12 indicate reduced crystallinity of drug. While F6 shows the presence of FLP peaks in the physical mixture. Crystallinity of drug in solid dispersions is always less than that observed in corresponding physical mixtures. Scanning electron micrographs of FLP, F6 and F12 are shown in Figure 6. FLP appears as irregular shaped crystals and the presence of urea results a smooth parallelogram shape. The solid dispersion and physical mixture formulations were characterized by relative

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<th>Table 1: Properties of Flpsds (F1-F10)</th>
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<th>Table 2: Properties of Flpsds (F11-F20)</th>
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bulky particles. The surface of SDs was similar to that of pure polymers, indicating that FLP was adsorbed and homogeneously dispersed into polymers at the molecular level. On the other hand, in case of the physical mixture, the adherence of FLP particles on the surface of polymers due to physical mixing can be clearly observed.

**Dissolution Studies of Solid Dispersions**

The dissolution of plain drug in basic medium was completed only within 3 hrs. As aspected since FLP is an acidic drug, the amount of dissolved drug in intestinal fluid was greater than that observed in gastric fluid. The SDs displayed better dissolution properties with respect to FLP alone. The improvement of FLP dissolution characteristics upon polymeric dispersion was more evident to simulated intestinal fluid, which is in accordance with higher stability constants for dispersions between drug and polymers in alkaline media. Figure 7 depicts the release profiles of FLP from SDs with different levels of SSC and RL 100 in pH 1.2 and pH 7.4 dissolution media. It can be seen that F12 demonstrated more prolonged release profiles than F18 and other SDs. It was observed that increasing the amount of SSC level resulted in a reduction in FLP release rate and a linearization of drug release curves. RL coevaporates usually displayed higher dissolution rates than its CPs. Because RL100 is freely permeable, increasing drug to polymer ratio (1: 1 to 1: 5) dramatically slowed the release time and amount of dissolved drugs. The presence of polymer SSC also reduces the invasive initial drug dissolution observed immediately after pH change for pure drug powders. Moreover, the drug release in dissolution medium of pH 1.2 was considerably lower than that of pH 7.4 especially at lower SSC levels. Also the release rates in case of SDs having lower SSC levels were highly dependent as compared to the release rates from SDs containing higher SSC levels. This might be due to the reason that at lower SSC levels void spaces around FLP could be higher than that higher SSC levels. It is known that drug release rate is dependent on the equilibrium solubility of the drug, which in turn is dependent upon the pH of its solution. FLP being acidic in nature has greater solubility in alkaline medium than that of acidic ones, therefore the pH dependent release profiles, at lower SSC levels, followed the trend observed for the solubility of FLP. The data suggest that drug release from SSC dispersions occurs via water filled pores. At higher SSC levels the differences between the release rates in different media were narrowed. The effect of differences in water solubility on release rate is compensated by the different amount of non-ionized moiety present at that pH, thereby narrowing the differences in release rates. Because of poor aqueous solubility and wettability of FLP, we employed the highly water soluble urea as immediate release compound, in the expectation of an enhanced initial release rate of FLP. Thus in the next step, an optimization of the release profile of FLP was attempted by the combination of urea and surelease in different molar ratios F19 and F20. The effect of the varying molar ratios on the release behavior of the formulations (F19, F20) in simulated gastric and intestinal pH was shown in figure 7. The release patterns from the different formulations reflected that of each component i.e., FLP corresponding to the fast releasing fraction was rapidly released and then residual amount of drug was gradually released from the slow-releasing fraction, according to zero-order kinetics. Indeed, the drug release occurred in two stages: faster release in the initial stage (upto 1 hr) and slower release in second stage. Compared to FLP alone, the drug release rate from F19, F20 was significantly suppressed, a result of the retarding effect of the hydrophobic complex in the mixture. It was evident from these results that the FLP release rate could be critically modified by changing the mixing ratio of hydrophilic and hydrophobic polymer ratio. From inspection of the dissolution profiles, among F19, F20 seemed to be suitable for our purpose with regard to the release pattern and release time. This formulation provided a sufficiently slow release of the drug for a longer period of time following an initial rapid dissolution (about 40% drug release at stomach pH).

**Dissolution Studies of Solid Dispersion Tablets in Simulated Gastroenteric Environment**

FLP was used as model drug because of its short half life, good solubility in ethanol and poor solubility in water. By combining two polymers well tailored dissolution profiles could be obtained. The total drug released in 12 h is 95% for TF19 and 98% for TF20. The dissolution a profile of active compounds from tablets obtained from pure drug powders or Urea and SSC coevaporates is plotted in Figure 8. The pure drugs displayed a similar behavior, typical of acidic molecules, with only a little amount of drugs dissolved in the external medium during the first 2 hours at pH 1.2. After the pH change to 7.4, the curves showed an almost instantaneous and complete dissolution of the drugs. The kinetic analysis of the dissolution curves of FLP-Urea and –RL100 systems, gave a better fit for the Fickian and dissolutive equations, whereas the first-order and cube-root of time (Hixson-Crowell) analysis fitted more poorly with the experimental data. Thus, the various interactions occurring between drugs and polymers led to a complex mechanism of drug release, in which both the drug solubility in the external medium and its diffusion capacity within the polymer network played an important role.

**Stability Studies**

The in vitro release from tablets stored at room temperature- 60% RH, 40°C-60% RH and 40°C-81% RH for twelve weeks did not show any significant difference, indicating that neither the temperature nor the humidity had a profound effect on in vitro release rate (Table 3). It is thus possible to scientifically formulate controlled release FLP tablets by using this drug in combined polymeric dispersions.

**Table 3: Stability Studies of Selected Solid Dispersion Tablet (TF20)**

<table>
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<tr>
<th>No of Weeks</th>
<th>Hardness (kg/cm²)</th>
<th>Visual Appearance</th>
<th>% of FLP Released</th>
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<td><strong>Room Temperature-60% Relative Humidity</strong></td>
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<td>98.99%</td>
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<tr>
<td>12</td>
<td>6.25</td>
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<td>99.34%</td>
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<tr>
<td><strong>40°C-60% Relative humidity</strong></td>
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<tr>
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<td><strong>40°C-81% Relative humidity</strong></td>
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Figure 1: Partition coefficient study of FLP and its polymeric dispersions in 0.1 N HCl (pH 1.2), pH 6.8 and phosphate buffer (pH 7.4).

Figure 2: Aqueous solubility study of FLP and its polymeric dispersions in 0.1 N HCl (pH 1.2), pH 6.8 and phosphate buffer (pH 7.4).

Figure 3: FTIR spectroscopy of FLP, F6, F12, F18.

Figure 4: DSC run of FLP, F6 and F12.

Figure 5: XRD spectra of FLP, F6 and F12.

Figure 6: Scanning Electron Micrograph of FLP, F6 and F12.
Bioavailability Studies

The graphical illustration of mean values of FLP level in plasma after administration of a single oral dose of the investigated co evaporate tablet (TF20) as a function of time (Figure 9) reveals a distinct difference between the biological performance of the co evaporate tablet and the tablet of pure drug (TFLP). This is evident by comparing values of the peak plasma level following administration of TF20, with that following administration of TFLP; the former value is less than 54 µg/ml, while the latter exceeds 65 µg/ml. FLP level in plasma was found to follow first-order kinetics. The co evaporate tablet shows slowest rates of absorption and elimination as well as greatest half-life time value and area under plasma-level time curve. In conclusion, FLP can be formulated in form of a co evaporate tablet with combined polymers to prepare extended release form of the drug. This form, in addition to possessing longer duration of action compared to the drug of relatively short half-life time, would also minimize the side effects of the drug in virtue of its lower peak plasma level.

CONCLUSION

SDs displayed better dissolution properties with respect to FLP alone. FLP release from F19 and F20 showed that fast releasing fraction was rapidly released and then residual amount of drug was gradually released from slow releasing fraction according to zero order kinetics. This study showed that it is feasible to control FLP release from SDs by controlling the complex formation between urea and surelease. Drug leakage can be then modulated on the basis of specific therapeutic needs (ie, a rapid or extended drug release).
ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

None

ABBREVIATIONS USED

FLP: Flurbiprofen
F1: Physical Mixtures of Drug: Eudragit RL100 (1:1); F2: Physical Mixtures of Drug: Eudragit RL100 (1:2); F3: Physical Mixtures of Drug: Surelease (1:1); F4: Physical Mixtures of Drug: Eudragit RL100 (1:2); F5: Physical Mixtures of Drug: Surelease (1:5); F6: Coprecipitates of Drug: Eudragit RL100 (1:5); F7: Coprecipitates of Drug: Eudragit RL100 (1:1); F8: Coprecipitates of Drug: Eudragit RL100 (1:2); F9: Coprecipitates of Drug: Eudragit RL100 (1:1); F10: Coprecipitates of Drug: Surelease (1:2); F11: Coprecipitates of Drug: Surelease (1:2); F12: Coprecipitates of Drug: Surelease (1:5); F13: Coprecipitates of Drug: Eudragit RL100 (1:5); F14: Coprecipitates of Drug: Surelease (1:1); F15: Coprecipitates of Drug: Eudragit RL100 (1:2); F16: Coprecipitates of Drug: Surelease (1:1); F17: Coprecipitates of Drug: Surelease (1:2); F18: Coprecipitates of Drug: Surelease (1:5); F19: Coprecipitates of Drug: Eudragit RL100 (1:5); F20: Coprecipitates of Drug: Urea + Surelease (1:0.5 + 0.5); TF20: Tablet of TF20; PM: Physical mixture; CE: Coevaporates of Drug: Surelease (1:5); F18: Coprecipitates of Drug: Surelease (1:5); F19: Coprecipitates of Drug: Eudragit RL100 (1:5); F20: Coprecipitates of Drug: Urea + Surelease (1:0.5 + 1.5); TF20: Tablet of TF20; PM: Physical mixture; CE: Coevaporations; CP: Coprecipitate; BSS: Between Sum Square; CSS: Column Sum Square; ESS: Error Sum Square; f1: Difference factor; f2: Similarity factor.

REFERENCES


PICTORIAL ABSTRACT

- Poorly water soluble Flurbiprofen
- Table of contents
- Sustained release Flurbiprofen solid dispersion
- Solid dispersion dissolution rate
- In vivo study

Pictorial Abstract
Flurbiprofen (FLP) is practically insoluble in water, freely soluble in alcohol and in methylene chloride. It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and migraine.

It is given in usual doses of 150 to 200 mg daily by mouth in divided doses. To reduce the frequency of administration and to improve patient compliance, an extended release formulation of FLP is desirable. In this study, the solid dispersion technique was applied to extend the dissolution and improve oral bioavailability of FLP using different carriers.

The feasibility assessment of this approach, the physical characteristics, in vitro dissolution, and in vivo bioavailability of the solid dispersion are presented in this report.

Pre-formulation studies showed increased hydrophilicity but a non-significant increase in lipophilicity of the SDs. Wettability of solid dispersions was found to be controlled and angle of repose showed good flowability. Consequently, it was determined that the solid dispersion technique (Method A) with urea and Eudragit RL provides a promising way to increase the dissolution rate which appeared slower and more gradual than those of the pure drug, when polymer ratios were increased.

Tablet of optimized ratio of solid dispersion (TF20) possess longer duration of action compared to pure drug of relatively short half-life.