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Original Article

ENHANCING SOLUBILITY AND DISSOLUTION OF FENOFIBRATE BY SPRAY DRYING TECHNIQUE

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ABSTRACT

Objective: Fenofibrate, a hypolipidemic drug agent, exhibits poor water solubility and dissolution. Thus, the aim of the present study was to improve the solubility and dissolution rate of Fenofibrate by preparing microspheres by spray drying technique using Pluronic F-127.

Methods: Fenofibrate Microspheres containing different ratios of Pluronic F-127 were produced by spray drying using Chloroform as solvent to enhance solubility and dissolution rate. The prepared formulations containing different ratios of drug and Pluronic F-127were evaluated for solubility and in-vitro dissolution. The prepared formulations were characterized by DSC, FT-IR, XRD and SEM. Dissolution profile of the prepared spray dried microspheres was compared with its physical mixture and the pure sample.

Results: Spray dried microspheres exhibited decreased crystallinity. The solubility of microspheres containing Fenofibrate and Pluronic F-127(1:3w/w) exhibited three tenfold increases than the commercial Fenofibrate and dissolution of the same ratio microsphere showed 99 % release in 40 min. While same composition in physical mixture showed 37% release in 20 min.

Conclusion: Consequently, from the above result it can be concluded that spray dried microspheres of Fenofibrate is a useful technique to improve the solubility and dissolution of poor water soluble drug like Fenofibrate.

Keywords: Spray drying, Microspheres, Fenofibrate, Pluronic F-127, Solubility, Dissolution.

INTRODUCTION

Fenofibrate has been used for many years to lower cholesterol levels and its pharmacokinetics profile is well understood [1, 2]. Originally launched in 1975, it is currently on the market in more than 85 countries. The compound is practically insoluble in water and has high lipophilicity (log P = 5.24). Thus, the dissolution rate of fenofibrate is expected to limit its absorption from the gastrointestinal tract. Attempts to increase the oral bioavailability of the drug have therefore chiefly centered on particle size reduction. Increasing the rate and extent of dissolution of Fenofibrate by micronization has been shown to lead directly to an increased oral bioavailability, which in turn enables dosage reduction. Recently, ‘‘suprabioavailable’’ tablets have been developed combining the classic micronization process with a specific micro coating technology, through which micronized drug particles are coated onto hydrophilic polyvinylpyrrolidone (PVP) cores [3].

Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of very poorly soluble compounds might be improved to minimize the limitations to their oral availability. There have been numerous efforts to improve drug dissolution rates. These include (a) reducing the particle size to increase the surface area; (b) using water-soluble carriers to form inclusion complexes; (c) solubilization in surfactant systems; (d) using pro-drugs and drug derivatization; and (e) manipulation of the solid state of drug substances to improve the drug dissolution i. e. by reducing the crystallinity of drug substances through formation of solid dispersions. However, there are practical limitations to these techniques [4]. Although particle size reduction is commonly used to increase the dissolution rate, there is a practical limit to the size reduction that can be achieved by such commonly used methods as controlled crystallization and grinding. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability. Salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs which are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formation that is usually undesirable from the viewpoints of patient acceptability and marketing [5]. Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs [6, 7, 8, 9]. There are different types solid dispersion systems categorized according to the physical states of the drug and the carrier in the systems. It may be a molecular solid solution, a dispersion of amorphous or crystalline drug particles in an amorphous carrier matrix, or a combination of solution and dispersion of solids.

The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability and drug precipitation as a meta stable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture. Spray drying is one of the techniques of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size [10-13]. The large surface area of the resulting particle should result in an enhanced solubility and dissolution rate, consequently, improved bioavailability.

The aim of the present study was to improve the solubility and dissolution rate of fenofibrate by spray drying technique using different ratio of Pluronic F-127.

MATERIALS AND METHODS

Materials

All chemicals and buffers used were of analytical grade.

Methods

Preparation of microspheres

The microspheres were prepared by spray-drying technique. The spray drying was performed by Mini Spray Dryer LSD -48; (Jay Instrument & systems Pvt. Ltd. Mumbai). The different drug–

polymer ratios used for various microsphere formulations were prepared described in Table 1. The polymer solution was prepared by adding the given quantity of polymer to the Acetone as solvent. The given quantity of Fenofibrate was added to the polymer solution and the resulting mixture was spray-dried. The spray drying parameters is described in table 2.

Table 1: Spray-Dried microspheres formulation

Numbers	Formulation Code	Different ratio of polymer and drug (w/w)
Spray drying formulations		
1	SD 1	1:1
2	SD 2	1:2
3	SD 3	1:3
Physical mixture		
1	PM 1	1:1
2	PM 2	1:2
3	PM 3	1:3

Table 2: Spray-Drying Parameters

Inlet temperature (°C)	Feed pump speed %	Vacuum (mm Wc)	Aspirator level (kg/cm^2)
52	10	-70	1.5

Preparation of physical mixtures

The different drug–polymer ratios used for various physical mixtures formulations were prepared as described in Table 1 and were prepared by mixing different ratio of Fenofibrate and Pluronic F-127 in the mortar for 5 min and then sieving.

Evaluation of microspheres

Determination of percentage yield and drug content

The percentage yield of each formulation was determined according to the total recoverable final weight of microspheres and the total original weight of Fenofibrate and Pluronic F-127.

Microspheres (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, samples were measured at 250 nm. Drug content was determined from the standard plot.

Differential scanning calorimetry (DSC)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray diffraction analysis (XRD)

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV. The process parameters used were set as scan step size of 0.0170 (2θ).

Scanning electron microscopy (SEM)

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs was obtained to identify and confirm spherical nature and surface topography of the crystals.

Mechanical properties

Tensile strength of microspheres was determined by compressing 500 mg of crystals using hydraulic press at different ton/cm^2 for 1 min. The compacts were stored in desicator overnight to allow elastic recovery. The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester. The tensile strength (σ) of the Compact (ton/cm^2) was calculated using following equation.

$$\sigma = 2F/\pi Dt$$

Where, F, D and t are hardness (ton), compact diameter (cm) and thickness (cm), respectively.

Determination of solubility

Drug solubility was determined by adding excess amounts of pure Fenofibrate, their physical mixture and microspheres in distilled water at 37 ± 0.5°C, respectively. The solution formed were equilibrated under continuous agitation for 24 h and passed through a 0.8 µm membrane filter to obtain a clear solution. The absorbance of the samples was measured using UV spectrophotometer method (UV 1601 A Shimadzu, Japan) at 290 nm and the concentrations in µg/ml were determined. Each sample was determined in triplicate.

Dissolution studies of microspheres

The dissolution of pure Fenofibrate, their physical mixture and microspheres was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml of pH 7.4 phosphate buffers. The amount of dissolved drug was determined using UV spectrophotometer method (UV 1601 A Shimadzu, Japan) at 290 nm. Each sample was determined in triplicate.

Determination of the physical stability

To determine the physical stability of optimized Microspheres, a stability study of prepared Microspheres was carried out at 25°C and 60% relative humidity for 6 months according to the ICH guidelines. The spherical agglomerates were packed in high density polyethylene (HDPE) container and placed in the stability chamber. The samples were withdrawn at the interval of 0, 1, 3 and 6 months and evaluated for appearance, characterization by FT-IR and dissolution release and compared with initial results.

RESULT AND DISCUSSION

The spray dried microspheres formulations were collected and was found to be free-flowing and white in color. The percentage yield of spray dried microspheres of different ratios of drug–polymer was found to be in the range of 74-87 %. This small yield could be increased by addition of solid substance or in large scale production [14]. Drug content for the spray dried microspheres of different ratio of drug–polymer formulation was found to be in the range of 97-99 %±0.03 (Table-3).

DSC curves obtained for pure material, physical mixtures and microspheres are showed Fig. 1. In DSC curve, pure Fenofibrate had a sharp endothermic peak at 81.5°C that corresponded to the melting point of Fenofibrate. While Microspheres and physical mixture exhibit endothermic peaks at 80.12°C and 54.16°C respectively. Reduction in intensity and shifting of sharp melting peak of drug in solid dispersion indicates that the degree of crystallinity is considerably reduced and the drug is present in an amorphous form.

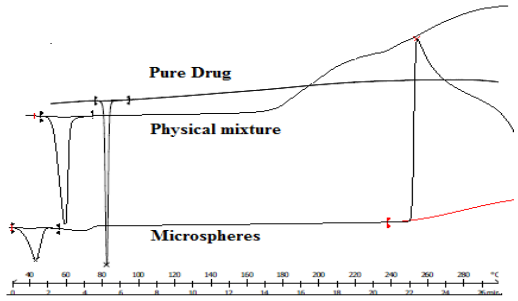

Fig. 1: DSC Spectrum of pure drug, physical mixture and microspheres

The FTIR spectra of pure Fenofibrate, Pluronic F-127, their physical mixture and microspheres are shown in fig. 2. FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements for different solid-state forms of an organic compound. Spectral variations originate due to alteration in bonds that exhibit characteristic vibration frequencies, leading to frequency shifts and splitting in absorption peaks. The FT-IR spectrum of pure drug (Fig. 2) shows characteristic peaks at 3039 cm-1 due to alkyl groups, at 3439 cm-1 due to phenol and at 1625 cm-1 due to carbonyl group. FT-IR spectra of Physical mixture and Microspheres showed broadening of the peak at 1100 cm-1 which may be due to Pluronic F-127. Hence we can say that significant interaction between drug and carrier has taken place. Also the peaks of Fenofibrate in the region of 2000 cm-1 to 400 cm-1 have disappeared in Microspheres indicating possible vander waal interaction between drug and polymer.

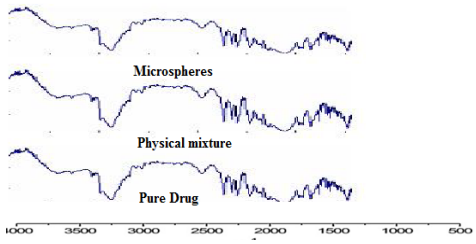

Fig. 2: FT-IR Spectrum of pure drug, physical mixture (1:3) and microspheres (1:3)

X- Ray diffraction was used to analyze potential changes in the inner structure of Fenofibrate nano crystals during the formulation of the Microspheres. The extent of such changes depends on the chemical nature and physical hardness of the active ingredient. The powder X-ray dif-fraction patterns of the pure drug, PM, and Microspheres are shown in fig. 2. The results of the DSC were further confirmed by X-ray diffraction studies (fig. 3). The characteristic peak of the Fenofibrate appeared in the 2θ range of 10–40°, The X-Ray diffraction pattern for Fenofibrate and Microspheres are presented in Fig.3 and showed marked crystallinity as evident from the sharp peaks at 2θ angles of 24.5°, 25.9° and 27.6°. The degree of crystallinity is seen to be decreased and it depends on the processing method. The XRPD of spray dried Microspheres shows further decrease in the degree of crystallinity as evident from the disappearance of the sharp peaks. The reason for this could be that spray drying is an energy intensive process where solution passes from state of relative unsaturation to supersaturation in a fraction of seconds. Further rapid evaporation of solvent from the supersaturated atomized droplets of the solution seemingly interferes with the crystal building process leading to amorphization of the drug.

The X-ray diffraction study of the drug and excipients PM showed the peak corresponding to the crystalline drug molecules present in the mixture, although their intensity was lower due to the high excipients-drug ratio employed. The diffraction pattern of the drug Microspheres showed absence, broadening and reduction of major Fenofibrate diffraction peaks, thus indicating that the Microspheres contained mostly an amorphous form (disordered state). These results could explain the observed enhancement of solubility and rapid dissolution of Fenofibrate in Microspheres.

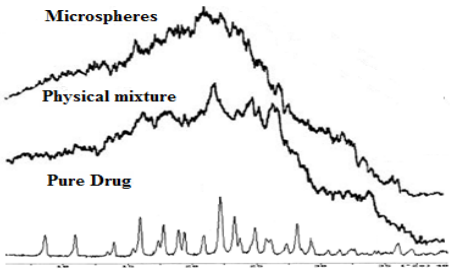

Fig. 3: X- Ray diffractogram of pure drug, physical mixture and microspheres

The SEM image of the pure drug, physical mixture and microspheres are shown in Fig. 4. The Fenofibrate particles in the physical mixture were broken into much smaller ones and irregular size (12-19 µm) and the shape of prepared microspheres are uniform and spherical in shape with small in size (4-13 µm) (Table-3).

The spherical shape of microspheres does not lead to cake formation during storage because of less point of contact thereby increasing the stability of the microsphere formulation, which is an advantage over other shapes. This could be therefore, indicate that Fenofibrate particle size has been reduced, which also accelerates solubility and dissolution.

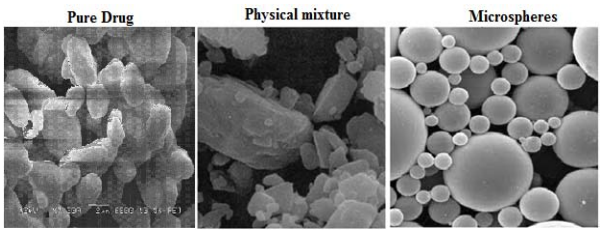

Fig. 4: SEM of pure drug, physical mixture and microspheres

Microspheres exhibited superior compressibility characteristics compared to physical mixture and pure sample of Fenofibrate drug crystals (Fig. 5). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic interparticle bonding, resulting in a lower compression force required for compressing the microspheres under plastic deformation compared to that of single crystal. Tensile strength of the same ratio of microspheres and physical mixture (1:3) showed that tensile strength of microspheres higher than physical mixture as well as the pure sample. This could be due to the increasing in the plastic interparticle bonding of microspheres [15, 16].

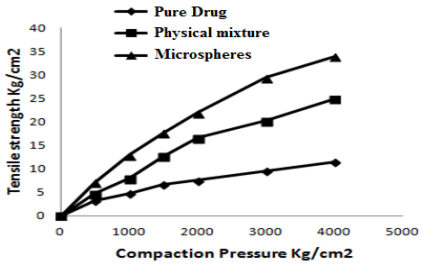

Fig. 5: Tensile strength of pure drug, physical mixture (1:3) and microspheres (1:3)

Increase in the solubility of Fenofibrate from microspheres (15.4 µg/mL) was found to be nearly three times higher than the solubility of the pure drug (5.2 µg/mL), suggesting the presence of a high amount of an amorphous form of Fenofibrate in the Microspheres, indicating super-saturation obtained from the Microspheres. Increase in the solubility of Fenofibrate from the PM (10.1 µg/mL) was nearly two times higher than pure drug. This could be due to the solubilising effect of highly water-soluble Pluronic F-127 used in the formulation. The solubility results for the different formulations are shown in table 3. The higher solubility of Fenofibrate from Microspheres may be due to the increased surface area, wettability and solubilising effect of highly water-soluble Pluronic F-127 used in the formulations.

Table 3: Solubility, Percentage yield, Drug content and Particle size microspheres

Formulations code polymer: Drug ratio(w/w)	Concentration of Fenofibrate microparticle in water (µg/ ml) SD±3	Percentage yield%	Drug content SD ±3	Particle size determination (µm) SD±3
Pure drug	5.2	--	--	--
SD 1	6.4	74.85	98.51±0.02	4-13
SD 2	11.7	79.64	98.94±0.03	7-12
SD 3	15.4	87.13	99.64±-0.01	5-13
PM 1	5.8	-	97.78±0.02	12-19
PM 2	7.5	-	97.34±0.04	15-19
PM 3	9.4	-	98.53±0.02	12-18

The dissolution of pure Fenofibrate, physical mixture and prepared microspheres in pH 7.4 phosphate buffer shown in Fig. 6, the dissolution profiles were plotted as the % release from the different microspheres, physical mixture and pure Fenofibrate versus time in minute. The rate of dissolution of pure Fenofibrate was slow compared with Fenofibrate from its physical mixtures and different microspheres formulation in 60 min.

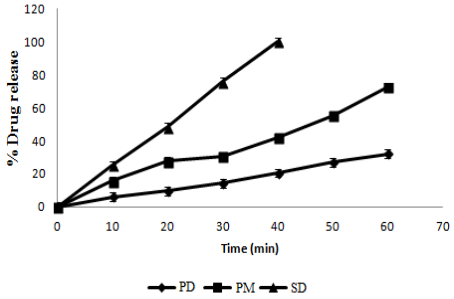

Fig. 6: Dissolution release of pure drug, physical mixture and microspheres

The % release from ratio of (1:3 w/w) drug and polymer showed more release compared to other ratios. In case of microspheres containing (1:3 w/w) showed 99% release in 40 min and at the same ratio of physical mixture showed 72% release in 60 min.

There was a significant difference in the drug release between the microspheres and physical mixture. The increase in dissolution from the microspheres and physical mixtures was probably due to the wetting and solubilizing effect of the Pluronic F-127, which could reduce the interfacial tension between the Fenofibrate and the dissolution medium, thus leading to a higher dissolution rate than pure Fenofibrate. The large surface area of the resulting microspheres should result in an enhanced dissolution rate and thereby improve the bioavailability.

The best way to guarantee stability is by maintaining their physical state and molecular structure. The results of the stability study of prepared microspheres (1:3 w/w) of Fenofibrate stored at 25 ^{0}C and 60% relative humidity for 6 month are presented in Table 4. The influence of physical stability on the prepared crystals was investigated. Prepared microspheres of Fenofibrate were stable and complied with all the properties when compared to initial results of prepared microspheres of Fenofibrate.

Table 4: Stability data of Spray dried microspheres

Testing interval	Description of Drug	FT-IR Study	XRD Study	Drug content (±SD)	Dissolution Study (±SD)
Sample name: Fenofibrate microspheres (1:3 w/w)					
Storage condition: 25^{0}C /60% RH					
Initial	White to off white	As standard	As standard	99.64±0.01	99.60±0.011
1 month	Complies	Complies	Complies	99.28±0.02	98.39±0.040
3 month	Complies	Complies	Complies	99.14±0.01	99.28±0.027
6 month	Complies	Complies	Complies	99.87±0.03	99.89±0.013

CONCLUSION

In this present study, an increased solubility and dissolution rate of Fenofibrate were achieved by preparing microspheres by spray drying technique using different ratio of Pluronic F-127. DSC, FT-IR and XRD studies showed that there is no change in the crystal structure of Fenofibrate during the spray drying process and showed that spray dried microspheres exhibited decreased crystallinity. The solubility and dissolution of the spray dried microspheres was improved significantly compared with its physical mixture and pure sample of Fenofibrate. The Fenofibrate microspheres containing 1:3 w/w (Fenofibrate: Pluronic F-127) showed highest % of drug release and solubility compare to other ratio, physical mixture and pure sample of Fenofibrate. Stability

results showed that prepared microspheres stable for 6 month as per ICH guidelines. Hence,, from the above result it can be concluded that spray dried microspheres of Fenofibrate is a useful technique to improve the solubility and dissolution of poorly water soluble drug like Fenofibrate.

CONFLICT OF INTERESTS

Declared None

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