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Enhancement of solubility and dissolution rate of rifapentine by melt granulation technique

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Abstract

This work describes a melt granulation technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug, rifapentine. Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable polymers and surfactants. Granules were prepared by using polymer like different grades of polyethylene glycol and surfactant like different grades of poloxomers. The granules were characterized using powder DSC, XRD and FTIR techniques. A significant enhancement in the in vitro dissolution profiles of the melt granules was observed compared to the pure drug and drug excipient physical mixtures. DSC results indicated change in internal energy of Rifapentine with polymers and surfactant in the melted granulated. In conclusion, the results of this work suggest that melt granulation is a useful technique to enhance the solubility and dissolution rate of poorly water-soluble drugs, such as Rifapentine.

Key-Words: Rifapentine, Melt granulation, Solubilty enhancement

Introduction

Rifapentine is an antibiotic in the rifampycin family of drugs that treats pulmonary tuberculosis (TB), it is poorly soluble in water. These drugs are derived from a fungus called *Amycolatopsis mediterranei* which originated from a pine forest outside of Nice, France. The drug's brand name is Prifkin, and it is marketed by Sanofi-Aventis. It was approved by the Food and Drug Administration in June 1998. Rifapentine has a potential advantage over rifampcin because its long half-life (13 hours compared with 3 hours) could allow for less frequent dosing. A melt granulation technique is a process by which pharmaceutical powders can be efficiently agglomerated by the use of molten polymers or additives at relatively low temperature (about 600C). This process can be used for the preparation of sustained released dosage forms by using lipophilic polymers, such as glycerol monostearate, a combination of a hydrophobic material such as a starch derivative and stearic acid.

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It also can be used to prepare fast release melt granules by utilizing water-soluble polymers and surfactants, such as PEG and poloxomers. PEG has been widely used in melt granulation because of its favorable solution properties, low-melting point, rapid solidification rate, low toxicity, and low cost. In recent years, the interest in melt granulation has increased due to the advantage of this technique over traditional wet granulation, that is, elimination of water or organic solvents from the melt granulation process[1]. This negates any risk originating from residual solvents; moreover, in melt granulation the drying step is not necessary, thus the process is less consuming in terms of time and energy as compared to wet granulation . In recent years, melt granulation technique has been successfully employed to improve the solubility and dissolution rate of poorly soluble compounds and the technique has proved that melt granulation can be used to enhance the in vitro dissolution rate of ibuprofen, employing poloxamer 188 as a melting binder which is mostly used as surfactant. The objective of this work was to evaluate the feasibility of the melt granulation technique to improve the dissolution characteristics of a poorly water-soluble drug, rifapentine. In the present work, the feasibility of fast-release rate granules by melt granulation has been considered. Rifapentine was chosen as a water-insoluble model drug and PEG, poloxamer as a hydrophilic polymer and surfactant.

Polyethylene glycol (PEG) and poloxamer were employed as a melting binder, in consideration of its favourable solution properties, low melting point, rapid solidification rate, low toxicity and low cost. Along with these binders effect of lactose and crosspovidone were also studied. In-vitro release of the drug from the granules was investigated and compared to that of the pure drug and drug excipient physical mixtures. Differential scanning calorimetry and X-ray powder diffraction were utilized to investigate the crystallinity of the system.

Material and methods[3]

Materials

Rifapentine was supplied as a gift sample from Lupin Ltd, (Aurangabad, India). Poloxamer crosspovidone and Polyethylene glycol were procured from Alembic (Vadodara, India). Hydrochloric acid (HCL), lactose and were of Sun Biodiagonstics, Dehradun

Preparation of the physical mixtures

Granules were prepared in a porcelain dish. Firstly, the mixture of rifapentine and polymer (Polyethylene glycol) or poloxamer-F68 with different excipients was dry blended for 10 min .Then, this mixture was then placed in hot porcelain dish and supply the heat around 600C on temperature controlled water bath so as to melt the polymers or surfactant in which the drug was dispersed. The formed molted mass is then cooled to room temperature and at the end of the granulation process the granules were allowed to solidify at room temperature by spreading them out in thin layers on trays. Pass the melted granules through sieve no # 20 so as to form uniform granules. The cooled granules were stored in sealed bags for their evaluation. Prepared the physical mixtures of the same formulation and compared the solubility and dissolution rate with the melt granules.

Yield and Drug Content[4]

The prepared melt granules were weighed after drying, and process yield was calculated. Melted granules (300mg) were powdered, from which powder equivalent to 100 mg rifapentine was weighed and extracted using three portions of 100 ml 0.1 N HCL. Each portion was filtered through a G-4 sintered glass filter and volume was adjusted to 100 ml. After sufficient dilution with 0.1 N HCL, samples were analyzed spectrophotometrically at 480 nm. Rifapentine content was calculated by comparison with standard solution.

Saturation solubility studies

Saturation solubility studies were carried out using deionized water as a solvent. Each excessive quantity (200 mg) of Rifapentine and equivalent prepared melt granules were taken in seven screws capped test tubes with fixed volume (20 ml) of deionized water. The resultant suspension was treated at 37 0C with 100 rpm in incubator shaker. After 24 h samples were withdrawn and filtered through 0.2m filters (Millipore, Pall Life sciences, Mumbai, India). The filtrate was suitably diluted with deionized water and analyzed at 480 nm by UV visible spectrophotometer (Pharma spec 1800, Shimadzu Corporation, Kyoto, Japan).

In-Vitro Dissolution Studies

A LABINDIA Disso 2000 (Mumbai) dissolution test apparatus type I (Basket) at rotation speed of 100 rpm was used for the study. Dissolution of the drug and samples was carried out on an equivalent of 450 mg of the RIF. As per USP XXVI, 0.1 N HCL was used as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2 0C, respectively. After fixed time intervals, 5 ml of samples were withdrawn and sink condition was maintained. These samples were assayed through ultraviolet absorbance measurement at 480 nm using UV-Visible Spectrophotometer (Shimadzu UV-1800, Japan) by an analytically validated method (r2 = 0.9995). To increase the reliability of the observations, the dissolution studies were performed in triplicate.

Fourier Transforms Infrared Spectroscopy[7]

FTIR spectra of prepared formulation were recorded on Shimadzu FTIR-8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm-1 at spectral resolution of 2 cm-2 and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

Powder X-Ray Diffraction (PXRD)

Crystallinity of the drug and the samples was determined using the Philips Analytical X-RD (Model: PW 3710, Holland) with copper target. The conditions were: 40 kV voltages; 30 mA current; at room temperature. The samples were loaded on to the difffractometer and scanned over a range of 2? values form 5 to 60 0 at a scan rate of 0.02 /min.

Differential Scanning Calorimentry (DSC)

Thermal properties of the untreated drug and the samples were analyzed by DSC (TA Instruments, USA, Model: SDT 2960). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350 0C at a heating rate of 10 ^{0}C/ min, using nitrogen as blanket gas.

Stability studies

Stability studies for the samples were carried out as per ICH guidelines. The samples were kept for stability

studies at 39 ± 3 ^{0}C and 74 ± 6% RH for a period of 3 months in environmental test chamber (HMG INDIA, Mumbai). The samples were kept in glass vials sealed with rubber plugs. After 30, 60 and 90 days, the samples were taken out and analyzed for appearance, drug content and dissolution study.

Flow Properties

Flow properties of the drug and prepared melt granules were studied by determining the bulk density (s b), tap density (s t), Carr's Index and Hausner ratio. A weighed quantity of the samples was taken to determine the bulk and tap density. The properties were determined using following equations

Bulk density (s b) = Mass / Poured volume (1)

Tap density (s t) = Mass / Tapped volume (2)

Carr's Index = [(s t – s b) / s t] x 100 (3)

Hausner ratio = (s t / (s b) (4)

Wettability/ powder bed hydrophilicity study

The untreated drug, prepared melt granules were placed (1 g) on a sintered glass disk forming the bottom of glass tube on which methylene blue crystals were placed. The whole device was brought into contact with water. The time taken for the capillary rising of water to the surface so as to dissolve methylene blue crystals was noted.

Results and Discussion

XRD analysis

The physical characterization was firstly carried out by means of XRD analysis. The diffraction pattern of the prepared melt granules was compared to the RIF .The diffractograms of the granules indicated that the polymorphic form of the drug was maintained substantially unchanged after melt granulation process, and only a little reduction of the degree of crystallinity was detected in comparison with the corresponding Drug.

DSC analysis

The DSC scans of the raw RIF material and prepared melt granules. Thermal analysis completely reconfirmed the previously reported XRD findings. The thermogram of granules conducted at 10 ^{0}C/min. RIF shows a melting endotherm peak onset at 189^{0}C comparative to RIF-PEG (185 ^{0}C) and RIF-POL (174 ^{0}C). The DSC study revealed that slightly decrease in melting endotherm peak comparative to RIF.

FTIR analysis

The FTIR spectra of the prepared melt granules showed no change occur in the chemical nature and do not present great fingerprint difference comparative to RIF.

Solubility study

The solubility of prepared melt granules were significantly improved (** P<0.01) compared to RIF raw crystals and physical mixtures (PM). The melted granules prepared by incorporating of water-soluble polymers PEG and surfactant Poloxomer can improve solubility due to its hydrophilic nature and adsorbed on drug surface to improve wettability. The addition of the excipients like lactose and crosspovidone does not show significant (ns P>0.05) improvement in solubility.

In vitro dissolution of the granules[6]

The in vitro dissolution rate of all prepared granulates was increased compared to the corresponding physical mixtures and the drug alone, because of the higher hydrophilic character of the systems due to the carriers and the slight reduction of RIF crystallinity. No significant differences were attested by the analysis of variance (ns P> 0.05) between the samples with different amount of PEG, nor with the incorporation of lactose and crosspovidone into the formulation.

In conclusion, melt granulation technique has been proved to be a important process to increase the solubility, dissolution and other techniqual characteristics of RIF using PEG and Poloxomer as a melt binder, without using any solvents. Solidstate analysis indicated slightly reduction in crystallinity of the drug and no changes in its polymorphic form. The granules displayed a significant improvement in vitro drug dissolution behavior. The dissolution profiles of granules containing PEG and Poloxomer were found to be superimposable to RIF and physical mixture. However, the intragranular addition of lactose and crosspovidone were not found significant improvement in solubility and dissolution comparative to melt granules without lactose and crosspovidone.

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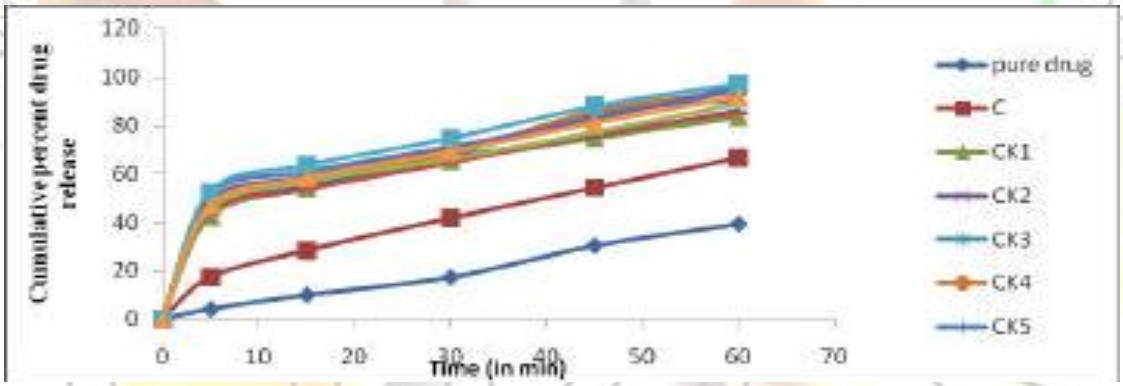

Fig. 1: Dissolution profiles of Rifapentine and mixtures of Rifapentine and PEG in 0.1N HCl at 37±0.5°C

Fig. 2: IR-Spectra of Rifapentine

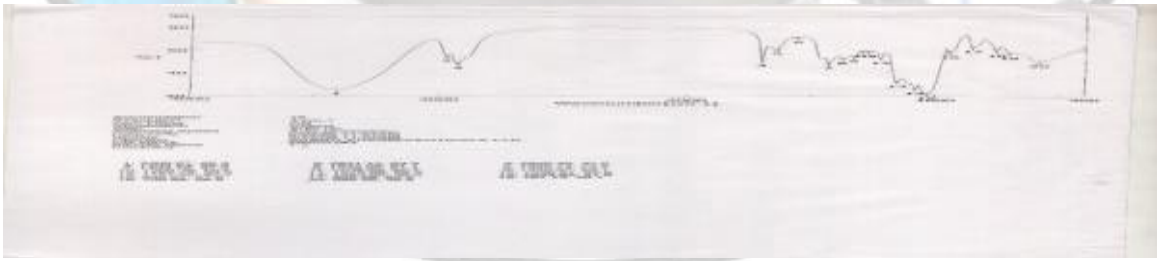

Fig 3: IR-Spectra of Formulation with PEG