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Original Article

CHARACTERIZATION AND INTRINSIC DISSOLUTION RATE STUDY OF MICROWAVE ASSISTED CYCLODEXTRIN INCLUSION COMPLEXES OF GEMFIBROZIL

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ABSTRACT

Objective: The aim of the present study was to carry out characterization and intrinsic dissolution rate study of microwave assisted inclusion complex of poorly water soluble, lipid lowering agent gemfibrozil [5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid] with naturally occurring β-cyclodextrins (CDs) or cycloheptaamylase.

Methods: In this work, the phase solubility study was performed to find the ratio of drug and cyclodextrin complexes. Inclusion complexes were prepared by kneading and the prepared complex was subjected to microwave drying and conventional drying techniques. The prepared complexes were evaluated by intrinsic dissolution rate studies and equilibrium solubility study. Further characterization was done by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and X-ray powder diffractometry (DSC).

Results: The phase solubility studies showed a linear A_L-type diagram indicating the formation of inclusion complexes in 1:1 molar ratio β-CD-gemfibrozil complex with maximum stability constant of 148.88 $M^{-1}$was selected for preparation of inclusion complex. The microwave dried product was identified as the inclusion complex with maximum IDR when compared to the conventional dried product.

Conclusion: This study was concluded that the microwave drying is the most suitable of the previously occurring drying techniques. Since it showed the highest solubility and IDR value.

Keywords: Gemfibrozil, Cyclodextrins, Microwave drying, Intrinsic dissolution rate

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INTRODUCTION

The bioavailability of drugs depends on the rate of dissolution in case of poorly water soluble drug where the dissolution is rate limiting step for absorption. Several methods have been used to improve the solubility of poorly soluble drugs. Solid dispersion and inclusion complexation were most widely used to enhance the solubility of poorly soluble drugs [1, 2]. The poor solubility and low dissolution rate of poorly water-soluble drugs especially those belonging to Class II of the Biopharmaceutical Classification System (BCS), can be enhanced by complexation with cyclodextrin (hydrophilic carrier) because dissolution into the gastrointestinal fluids and intestinal membrane permeation are essential steps in the absorption of orally administered drugs [3]. The solubility of the drug was found to be more with inclusion complexation method as compared to the solid dispersion technique [1]. Among the several carriers used to improve the solubility of poorly soluble drugs, cyclodextrins have been extensively studied and reported to improve solubility and dissolution [4]. Chemically they are cyclic oligosaccharides containing at least 6D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds. It has generally been assumed that the mechanism wherein, CDs exert their effects especially enhancement of solubility due to non-covalent, dynamic inclusion complexes [5].

This research work was carried out to improve the solubility of a poorly aqueous soluble drug, gemfibrozil a lipid regulating agent [6]. It can also be used to reduce the risk of coronary heart disease in people who have failed to respond to weight loss, diet, exercise and other triglyceride or cholesterol lowering drugs. The more common side effects may include abdominal pain, acute appendicitis, constipation, indigestion, nausea and vomiting [7]. Gemfibrozil is an acidic drug, pKa 4.75 [8], highly lipophilic and practically insoluble in water i.e. less than 0.1 mg/ml [9]. Complexation with a hydrophilic complexing agent namely CDs can substantially enhance the solubility, dissolution and can play a vital role in reducing the side effects. Several methods are used for the preparation of cyclodextrin inclusion complexes but kneaded complex showed higher dissolution rate than other complex [10]. Thus the dissolution rate of the drug is strongly dependent on the concentration drug: polymer ratio and the method by which is done [11]. The main objective of the present study is the complexation of gemfibrozil with β-cyclodextrin by microwave dried and conventionally dried kneading technique and to assess the complexes by intrinsic dissolution rate studies that overcome the variations related to the variable surface area of the complex.

MATERIALS AND METHODS

Materials

Gemfibrozil was obtained as a gift sample from Teva Pharmaceuticals Limited, India and β-cyclodextrin were supplied as gift sample from Albert David Pvt Ltd, Ghaziabad. All other chemicals and solvents used were of the pharmaceutical and analytical grade. Double distilled water was used throughout the study for experimental work.

Methods

Phase solubility studies

The stability constants for inclusion complex formation between gemfibrozil and β-CD was determined using the phase solubility method [12]. Phase solubility diagrams were obtained at 37±0.5 °C in double distilled water. An excess amount of gemfibrozil was added to 10 ml aqueous solutions containing increasing concentrations of the CDs (0-15 mmol).

The suspensions were shaken for 72h after which the equilibrium was reached. Then they were filtered, appropriately diluted and analyzed by UV spectrophotometer at 274 nm [13, 14]. The apparent stability constant (Ks) of the complexes were calculated from the slope of the phase solubility diagrams according to the following equation:

$$Ks = slope/So\ (1\text{-}slope) \ldots\ldots\ldots (1)$$

Where, So = Intrinsic solubility of gemfibrozil in the absence of cyclodextrins.

Preparation of inclusion complexes

Both the complexes were prepared in the 1:1 molar ratio between drug and β-cyclodextrins on the basis of the results obtained from the preliminary phase solubility studies.

Conventional dried complex

It was obtained by adding a small amount of water to β-cyclodextrins placed in a mortar and mixing to obtain a homogeneous paste. The gemfibrozil powder was then added slowly and the mixture was kneaded for 45 min. During the kneading process, few drops of water were added to maintain a suitable consistency. The resulting paste was dried on a tray dryer (conventional drier) at 45 °C for 4 h and the solid was finally ground and sifted through a 100 mesh sieve [14, 15].

Microwave dried complex

It was obtained by adding a small amount of water to β-cyclodextrins placed in a mortar and mixing to obtain a homogeneous mixture. The gemfibrozil powder was then added slowly and mixed continuously for 45 min. During the mixing process, few drops of water were added to maintain a suitable consistency. The resulting mixture was subjected to microwave drying in a microwave oven (Samsung, convection) at 900W for 2 min and grounded and shifted as above.

Evaluation of prepared inclusion complexes

Intrinsic dissolution rate studies

The intrinsic dissolution behavior was investigated according to USP apparatus I, rotating disc method for optimization of preparation method [16]. A compressed disc of material was made by slow compression of 500 mg of drug/binary mixture in a 13 mm IR disc punch and die set (HICON®, India) to compaction pressure of 600Mpa and a dwelling time of 5 min. The compressed disc was fixed to the holder of the rotating basket using a low melting point paraffin wax and successively dipped so that the top and sides are coated. The lower circular face was cleared of residual wax using a scalpel. Compressed pellets of the drug and complexes were dissolution in double distilled water (pH 6.42) that was stirred at 100 rpm and maintained at 37±0.5 °C [17]. At fixed time intervals, 5 ml aliquots were withdrawn and analyzed spectrophotometrically (Shimadzu, pharma spec 1700) at 274 nm. The dissolution was carried out in triplicate, and the IDR was determined by dividing the slope of the line by the exposed surface area.

Characterization of prepared inclusion complexes

The drug, cyclodextrin and prepared complexes were subjected to various physicochemical analysis.

Fourier transform infrared (FTIR) spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). The spectra were recorded for prepared and dried complexes. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 2000 cm^{-1}.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (Perkin Elmer DSC6) measurements were performed with 5 mg samples at a heating rate of 10 °C/min over a 50-250 °C temperature range. A nitrogen purge (20 ml/min) was maintained throughout the runs, using an empty sealed pan as a reference. Temperature and heat flow calibrations were performed using indium as a standard.

X-ray diffractometry (XRD)

Powder x-ray diffraction patterns were obtained with an x-ray diffractometer (PW3040/60 X'Pert PRO, Netherland) using Ni-filtered CuK (α) radiation (λ= 1.5405980A°) at scan step size of 0.020° under a voltage of 40kV and a current of 30mA for the generator. The investigation was performed in the 2θ range of 5-50°.

Equilibrium solubility studies

Drug solubility from conventional dried and microwave dried complexes was determined by adding an excess amount of the mixture, corresponding to the equivalent amount of drug, to 10 ml of 0.1N hydrochloric acid (pH 1.23), double distilled water (pH 6.42) and 0.2M phosphate buffer (pH 7.40). The suspensions were stirred for three days at 37 °C and filtered through 0.45 µm membrane filter, appropriately diluted and analyzed by UV spectrophotometer at 274 nm.

RESULTS AND DISCUSSION

Phase solubility studies

The phase solubility diagrams at 37 °C were obtained by plotting the equilibrium concentrations of the drug against the concentrations of β-cyclodextrin in fig. 1. It can be observed that the solubility of gemfibrozil is increased over the entire concentration range studied. Linearity was characteristic of the A_L-type system [10] and suggested that water soluble complex was formed. The slope values of 0.0610 for β-gemfibrozil complex indicated the formation of inclusion complexes in the molar ratio of 1:1. The stability constant (Ks) of the 1:1complexes for β-CD gemfibrozil complexes was calculated as 162.88 M^{-1}, reflected compatibility of the gemfibrozil and the strength of the interaction. And it was found within the limits reported to be suitable for pharmaceutical utilization [18]. The dissolution rate of the drug was strongly dependent on the relative concentration of the drug: polymer ratio. Mohanty was observed that the dispersion with 1:2 (Drug: PEG 6000) showed maximum improvement in dissolution rate of drug (seroquel) among the various solid mixtures prepared [11]

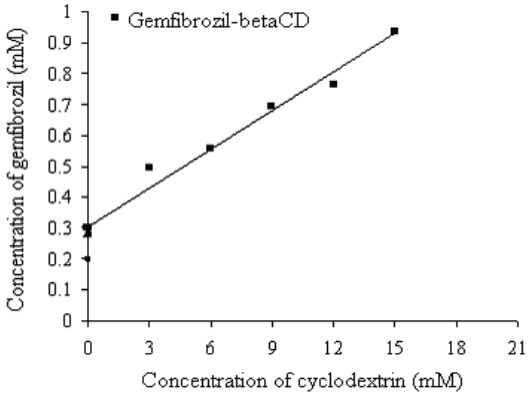

Fig. 1: Intrinsic dissolution profiles of pure gemfibrozil and β-CD complexes in double distilled water (pH 6.42)

Evaluation of prepared inclusion complexes by intrinsic dissolution rate (IDR) studies

The intrinsic dissolution rate profiles of gemfibrozil, conventionally dried complex, microwave dried complex, are represented in fig. 2. The IDR from prepared dried complexes were greater than the IDR of pure drug (0.0727 $mgcm^{-2}$ min^{-1}). When the IDR is less than 0.1 the absorption is dissolution rate limited. Thus an increasing solubility of the drug will improve dissolution and hence the absorption. Of the various methods used to enhance the solubility of BCS Class II drugs cyclodextrin complexation is an important approach. Sachan *et al.* were observed that the solubility and dissolution were found to be more in inclusion complexation than solid dispersion. [1]. The IDR of conventionally dried and microwave dried complexes were found to be 0.1380 $mgcm^{-2}$ $min^{-1}$and 0.1653 $mgcm^{-2}$ min^{-1} respectively. It results 1.89 and 2.27 folds greater than that of the pure drug, justifying the need for formation of microwave

dried inclusion complex. The higher drug release observed in the case of microwave dried product concluded that the formation of soluble inclusion complex, better wettability and reduction of particle size [19]. Hence microwave drying can be considered as a superior drying technique. Microwave heating is offering advantages of rapid drying, short processing time and energy saving process [20].

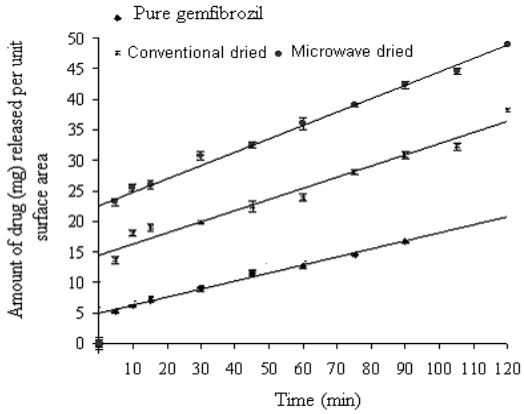

Fig. 2: Intrinsic dissolution profiles of pure gemfibrozil and β-CD complexes in double distilled water (pH 6.42), n=3±SD

Characterization of prepared inclusion complexes

Fourier transforms infrared spectroscopy

The infrared spectra of the drug, cyclodextrin, microwave dried and conventional dried complex are presented in fig. 3. Two bands of infrared spectra, at 1705.73 cm^{-1} and at 1043.30 cm^{-1}, 1127.19 cm^{-1} and 1165.76 cm^{-1} (C-O stretching) vibrations are the characteristics infrared spectra of gemfibrozil, used for analysis of the solid state interactions [21]. The spectrum of inclusion complex did not show new peaks which indicates any chemical bonds were created in the prepared complexes [22-24].

In the IR spectra of inclusion complexes, the absorption band at 1043.30 cm^{-1}, 1127.19 cm^{-1} and 1165.76 cm^{-1} disappeared and the intensity of the band at 1705.73 cm^{-1} is also significantly decreased, suggesting hydrogen bonding between gemfibrozil and β-CD in the inclusion complexes.

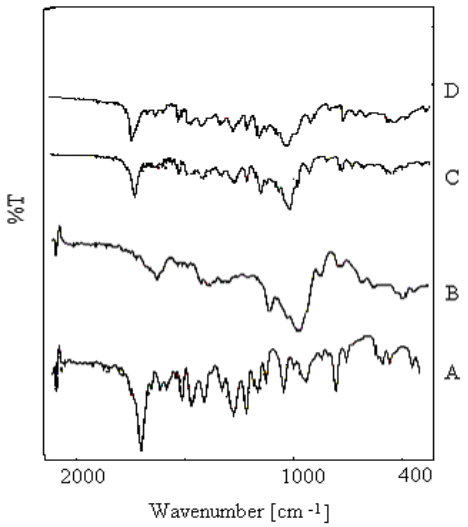

Fig. 3: Fourier transforms infrared spectra of gemfibrozil (A), β-cyclodextrin (B), conventional dried product (C) and microwave dried product (D)

Differential scanning calorimetry

The DSC thermograms revealed information on solid-state interactions between drug and cyclodextrins. The DSC thermograms of pure drug, cyclodextrin and complexed systems are shown in fig. 4. Gemfibrozil showed a typical behavior of anhydrous crystalline drug with a well-defined melting peak at 63 °C (ΔH=72.236J/g) corresponding to its melting point. But the ΔH values in conventional dried (45.256J/g) and microwave dried (38.364J/g) were slightly lower than that of pure drug and its characteristic thermal peaks at lower temperatures, strongly reduced in intensity and somewhat broadened. This indicates a partial amorphization or inclusion complexation of drug.

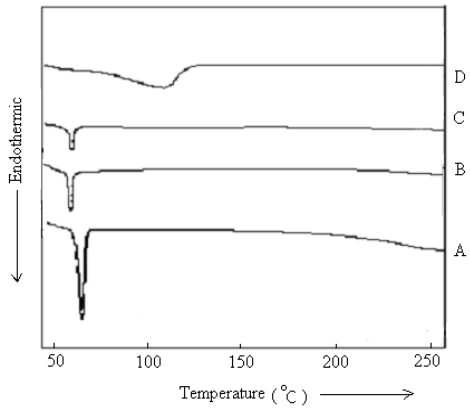

Fig. 4: DSC thermograms of gemfibrozil (A), Conventional dried product (B), Microwave-dried product (C) and β-cyclodextrin (D)

X-ray diffraction analysis (XRD)

The XRD pattern of pure drug and β-CD exhibited a crystalline diffraction pattern represented in fig. 5. Conventional dried and microwave dried product exhibited lesser and broader peaks. Microwave dried product exhibits less distinct diffraction peaks. It was suggested that a new solid phase is formed in the microwave dried product [24, 25].

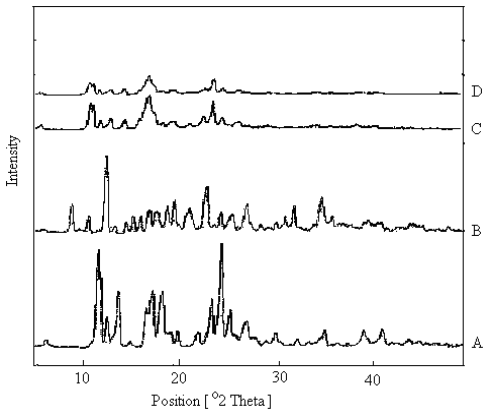

Fig. 5: X-ray diffraction patterns of gemfibrozil (A), β-cyclodextrin (B), conventional dried product (C) and microwave dried product (D)

Equilibrium solubility studies

The equilibrium solubility of drug and its inclusion complexes in acidic media (0.1N HCl, pH 1.23), double distilled water (pH 6.42) and 0.2M phosphate buffer (pH 7.40) are reported in table 1.

Gemfibrozil, the drug showed a very low solubility at pH 1.23 and increased value of solubilities was obtained for conventionally dried and microwave dried kneaded complex. It was due to the presence of hydrophilic cyclodextrin and a better wettability of the drug. Conventionally dried product showed 4.24, 5.72 and 7.98 fold and the microwave dried product showed 7.10, 10.42 and 16.83 fold solubility enhancement at pH 1.23, pH 6.42 and pH 7.40 respectively.

Table 1: Drug solubility (mg/ml) data of drug and prepared inclusion complexes

Preparations	Equilibrium solubility (mg/ml)		
	pH		
	1.23	**6.42**	**7.40**
Gemfibrozil	0.0725±0.001	0.083±0.002	1.62±0.001
Conventional dried product	0.302±0.002	0.348±0.002	11.16±0.071
Microwave dried product	0.535±0.004	0.647±0.033	16.64±0.492

Data are expressed mean±standard deviation (SD, N=3)

CONCLUSION

This study has revealed that the microwave drying is the most suitable of the previously occurring drying techniques. Since it showed the highest solubility and IDR (Intrinsic dissolution rate) value. It was concluded as microwave drying, a potential drying technique with cost and time effective. Thus future studies will be concerned with further characteristics of microwave drying.

CONFLICTS OF INTERESTS

Declared none

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