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Thermal analysis and quantitative characterization of compatibility between diflunisal and lipid excipients as raw materials for development of solid lipid nanoparticles

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ABSTRACT

Thermal analysis and quantitative characterization were done to evaluate the compatibility between DIF and various solid lipids explored like Compritol ATO 888, cetyl palmitate; CP, stearic acid; SA, glyceryl monostearate; GMS and hydrogenated castor oil. Till date, there are no reports on evaluation of DIF-lipid excipient compatibility. The techniques employed were differential scanning calorimetry; DSC, Fourier transform infrared spectroscopy; FTIR, optical microscopy, X-ray powder diffraction; XRPD studies and isothermal stress testing studies; IST. The results of DSC studies depicted displacement of DIF melting peak in binary mixtures suggesting some interaction between them. However, during IST studies less than 2% change in drug content was observed in all stressed samples of binary mixtures. Hence, the results demonstrated that all the selected solid lipids were compatible with DIF. Further, final SLN formulation was stable for 3 months. In conclusion, DSC and IST techniques were successfully employed to evaluate the DIF-lipid excipient compatibility.

1. Introduction

Preformulation is the foremost aspect in rational development of successful pharmaceutical dosage forms. It is the investigation of all those physical and chemical properties that are considered important in development of safe, stable and efficacious dosage forms [1]. Drug excipient characterization studies are very important aspect of preformulation studies to ensure correct selection of excipients, thereby increasing the possibility of developing successful dosage forms. The potential incompatibilities can affect the efficacy and safety profile of drug product due to altered physical and chemical properties of drugs as well as excipients [2]. Incompatibility can occur between drug and excipient, excipient with another excipient, or drug with another drug in case of combination dosage forms. There are numerous approaches proposed that satisfy the drug excipient chemical compatibility test. The most versatile approach is computational, where the chemical compatibility between drug and excipient can be predicted. It involves the utilization of comprehensive database of reactive functional groups for both drugs and excipients in combination with complete knowledge of excipient and potential impurities present along with. It helps in rapid analysis without the need of bulk substance. However, computational approach cannot be used as a sole source of information to study compatibility between drug and excipients [1]. Thermal analysis based on differential scanning calorimetry (DSC) has emerged as a leading technique for evaluation of drug-excipient binary mixtures. The advantage of this technique is small sample requirement and rapid screening of incompatibilities derived from shifts in peaks or variations in corresponding enthalpies of transition [3–6]. However, the conclusions on the basis of DSC alone may often be inconclusive, the results should be confirmed with other quantitative techniques [1].

Quantitative techniques like isothermal stress testing (IST) involves storage of binary mixtures of drug and excipient at elevated temperatures with or without moisture for specified time of one month (3–4 weeks) to provide favorable microenvironment for interaction with excipients and to accelerate drug degradation. The samples were visually observed for changes in color or physical characteristics and drug content is determined quantitatively [7]. Hence, combination of both thermal (DSC) and quantitative (IST) techniques should be employed for selection of excipients.

Diflunisal (DIF) is very potent salicylic acid derivative used for treatment of pain and inflammation in osteoarthritis, rheumatoid arthritis and post-dental extraction etc [8]. Its mechanism of anti inflammatory action is through inhibition of prostaglandin synthetase [9]. DIF belongs to class II drugs with meager solubility

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and appreciable permeability as per Biopharmaceutics classification system (BCS) [10–12]. Oral administration can cause serious gastrointestinal side effects like bleeding, ulceration, cardiovascular risk etc. Severe hepatic reactions including cholestasis and/or jaundice have been reported. It is commercially available as oral formulations only. Therefore, in order to overcome the challenges associated with oral administration, our mainstream project was based on development of solid lipid nanoparticles (SLNs) as carriers for topical delivery of DIF with improved patient compliance and reduced gastrointestinal side effects. SLNs are nano-sized systems prepared from biocompatible and biodegradable lipids that are solid at room temperature. The advantages of these carriers include protection of photosensitive, moisture sensitive drugs, biocompatibility and versatility of lipids used in their preparation [13–15]. SLNs will enhance the skin penetration of DIF to produce better pharmacodynamic effect [15,16]. Moreover, DIF is highly lipophilic drug with log P of 4.44, suitable to be formulated as topical delivery system. So far, there are no reports on excipient compatibility between DIF and solid lipids used as raw material for development of SLNs.

As a part of ongoing project, the present study involved the evaluation of excipient interaction between DIF and various solid lipids, used to prepare SLNs using several analytical techniques reported in literature [7,17–19]. Briefly, the study included comparison between the Fourier transform infrared (FTIR) spectroscopy, X-ray powder diffraction (XRPD) pattern analysis, optical microscopy, DSC and IST studies of DIF-lipid excipient binary mixtures. Further, the SLN formulation was developed using one of the solid lipid and subjected to physicochemical characterization and stability studies at all the three storage conditions specified by ICH guidelines for 3 months.

2. Materials and methods

DIF was purchased from Sigma-Aldrich Corporation, Bangalore, India. Compritol ATO 888 (glyceryl behenate) was kindly supplied by Gatefosse, Germany. Glyceryl monostearate (GMS) and stearic acid (SA) were purchased from Loba Chemie Pvt. Ltd. Mumbai, India. Cetyl palmitate (CP) was procured from Merck Chemicals, Goa. Hydrogenated castor oil was kindly gifted by Jayant Agro-organics Ltd. Mumbai, India.

2.1. Preparation of DIF-excipient binary mixtures

The binary mixtures were prepared by taking equal weights of drug and excipients in 1:1 proportion (w:w) and screening them through 60-mesh sieve repetitively to obtain uniform binary mixtures. These mixtures were further used for FTIR spectroscopy, XRPD analysis, DSC analysis and optical microscopy studies. The drug and excipient in maximum expected ratios (drug: excipient; 1: 10) were taken for IST studies [19].

2.2. Optical microscopy

Optical micrographs of DIF, DIF-excipient binary mixtures were recorded using oil immersion objective at 100× magnification by optical microscope. The microscope was fitted with built-in camera (Eclipse 80*i*, Nikon Instruments Inc., Tokyo, Japan).

2.3. FTIR studies

FTIR absorption spectra were recorded using FTIR spectrometer (Perkin Elmer Co., Waltam, USA). As the samples were solid in nature, KBr discs were prepared. The samples were scanned over a range of 500–4000 cm^{-1}.

2.4. XRPD studies

The XRPD patterns of DIF were determined using X-ray diffractometer (Panalytical's X'Pert Pro, Almelo, Netherlands) with CuKα radiation, using scan range of 3–50° 2θ and scan rate 4°/min. The voltage of 40 kV and current of 60 mA was used.

2.5. DSC studies

The Differential scanning calorimeter (DSC, Q20, TA Instruments-Waters LLC, USA) was calibrated for accuracy of temperature and heat flow using the melting of pure indium (high purity grade 99.99%). Each sample (2 mg) was taken in an aluminum pan and sealed with lid. The heating was done at a rate of 10 °C min^{-1} over the temperature range of 25–250 °C. DSC curves were obtained under a nitrogen purge of 50 mL/min. The peak onset (T_{onset}), peak temperatures (T_{peak}) and enthalpy values (ΔH_f) were reported.

2.6. Isothermal stress testing (IST) studies

The DSC results were further confirmed by Isothermal stress testing (IST) studies by method previously reported by Singh and Nath with slight modification [18]. The drug and excipient blends in maximum optimal ratio were taken in 5 mL glass vials and mixed on vortex shaker for 2 min [19]. In each of the vials 10% w/w water containing 1% Tween 20 was added and drug-excipient blend was further mixed with a glass capillary (both ends of which were heat sealed). To prevent any loss of material capillary was left inside the vial. Each of the vials were sealed and stored at 50 °C in hot air oven for one month (3–4 weeks). The samples were periodically examined for change in physical appearance, color etc. The samples were quantitatively analyzed using ultra performance liquid chromatography (UPLC) analysis. Drug-excipient blends without added water and stored in refrigerator were used as controls.

For the analysis of DIF-excipient mixtures, Waters Acquity ultra performance liquid chromatography (UPLC) system equipped with autosampler and photodiode array (PDA) detector was used. The data was processed using Empower 2 software (Waters, MA, USA). The chromatographic separation was achieved using Acquity UPLC® BEH 300 C18 column, 1.7 μm. The wavelength of detection was 254 nm. The mobile phase consisted of mixture of water, methanol, acetonitrile, glacial acetic acid (55:23:20:2, v/v/v/v). The flow rate was kept at 0.5 mL/min. The injection volume employed for analysis was 0.5 μL. The stock solution of drug (1 mg/mL) was prepared in mixture of acetonitrile and water (4:1) followed by dilution with acetonitrile:water (1:1). The calibration curve was prepared from stock solution by serial dilution with acetronitrile:water (1:1) to achieve solutions containing DIF in the range 1–10 μg/mL. Aliquots of control and stressed samples were diluted with acetronitrile:water (1:1) followed by filtration through PVDF filter membrane with polypropylene housing of pore size 0.45 μm before analysis (Uniflo™ Whatman, USA). Validation of the method was performed as per ICH validation guidelines.

2.7. Formulation development and characterization

The next part of this research was to develop a successful and stable formulation using any of the above solid lipid. Out of all the explored lipids for excipient compatibilty, Compritol was selected as DIF was found to exhibit maximum solubility *i.e.*, 96.36 ± 5.57 mg/mL in this lipid. The SLNs were prepared by hot microemulsion method by a previously reported method [20]. Briefly, the lipid (Compritol) was melted 10° above its melting point. As DIF is lipophilic drug it was added to the lipid after complete melting of lipid. An aqueous phase consisting of emulsi-