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Use of thermal and non thermal techniques for assessing compatibility between mirtazapine and solid lipids

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ABSTRACT

The present investigation was aimed at the evaluation of possible interactions between mirtazapine and selected solid lipids that are commonly used to develop solid lipid nanoparticles (SLNs) and nanostructured lipidic carriers (NLCs). The solids lipids explored were palmitic acid, stearic acid, glycerylmonostearate, cutina CPPH, sterotex NF, gelucire 50/13, hydrogenated castor oil and compritol 888 ATO. The techniques used were Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), Hot Stage Microscopy (HSM) and Isothermal Stress Testing (IST) studies. In some cases, the DSC results indicated the possibility of drug-solid lipid interactions which was further ruled out by performing HSM studies. Moreover, IST studies were also used to further confirm the compatibility between the drug and selected solid lipids. And the findings from these studies indicated compatibility between mirtazapine and solid lipids that can further be used to develop SLNs or NLCs.

1. Introduction

The efficacy and safety of a drug primarily depend upon its physical, chemical, biological properties and, also manufacturing processes which in turn are highly affected by the drug and excipient interactions. In order to achieve a successful dosage form, avoid wastage of costly materials, and save the time required to produce appropriate product formulation, the selection of perfect excipients is a pivotal step in the initial stages of formulation development. Moreover, thorough interpretation of the physical and chemical interactions in dosage forms is also expected under drug development that covers quality by design prototype and is encouraged by United States Food and Drug Administration and numerous regulatory bodies worldwide. Incompatibility can arise between drug-excipient, excipient-excipient and drug-drug in case of combinational dosage forms [1,2].

Various approaches satisfying the compatibility test between drug and excipient have been proposed. A Computational approach is the most flexible approach to predict the chemical compatibility between drug and excipient by employing extensive databases of reactive functional groups of drugs, excipients, and impurities. It also assists hasty analysis avoiding need of bulk substance. However, this approach alone cannot be used to study drug-excipient compatibility [3]. The thermal methods intermittently used to screen drug-excipient compatibility are Differential Scanning Calorimetry (DSC) and Hot Stage Microscopy (HSM). The advantage of DSC technique is that small amount of sample is required and rapid evaluation of incompatibilities occurred as a result of shifting in peak or variations in enthalpies of transition can be done. Although DSC is regarded as an efficient method, some researchers have reported the concomitant use of HSM in the proper identification of incompatibilities [4,5]. HSM is a visual thermal analysis technique that aids the decisive monitoring of solid state interactions such as likely dissolution of one component into another that could be mistakenly explained as incompatibility by DSC. Also, one component's degradation is not covered by another thermal event. So, the visual observation clearly differentiates between solid state interactions and incompatibilities. Like DSC, a very small amount of sample is needed for visual observation in order to perform compatibility studies [2]. But the results obtained from thermal techniques should further be confirmed by quantitative techniques such as Isothermal Stress Testing (IST).

In IST studies, a drug-excipient physical mixture is stored at elevated temperature with or without moisture for a period of 3–4 weeks. These conditions provide an environment for the accelerated degradation of the drug and possible interaction with the excipients. Then the samples are visually examined for change in color and the drug content is determined. Thus, the thermal and quantitative techniques should be employed in conjunction

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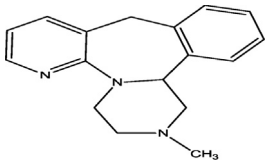
Table 1
Physicochemical properties of mirtazapine.

Properties	
Chemical structure	
Chemical name	1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c]benzazepine
Molecular formula	$C_{17}H_{19}N_3$
Molecular weight	265.35 g/mol
Melting point	114-116 °C
Solubility	Freely soluble in methanol and chloroform, insoluble in water
Log P	2.9
Dose	7.5 mg, 15 mg, 30 mg and 45 mg
Half-life	20 to 40 hours

to select appropriate excipient to achieve a successful dosage form [6].

Mirtazapine (abbreviated as 'MRT' in Tables and Figures) is an antidepressant drug used for the treatment of moderate to severe depression. It belongs to a class of noradrenergic and specific serotonin reuptake inhibitors (NaSSRIs). The physicochemical properties of mirtazapine are shown in Table 1 [7,8]. Numerous researchers reported its antipruritic effect after oral administration (7.5 mg/10 mg/15 mg once daily) mainly due to its high affinity for central and peripheral H_1 receptors, thereby inhibiting the main itch mediator i.e., histamine. It also blocks serotonin-mediated pruritus by blocking 5 HT_2 and 5 HT_3 receptors [9–13]. The antipruritic mechanism of antidepressants in managing pruritus that can occur as a result of dermatological, systemic, neurological and psychogenic disorders has been discussed recently. The topical formulations of some antidepressants have been reported in the literature for management of pruritus [14]. But, till date no topical formulation of mirtazapine has been developed and reported in the literature relating to this field. Therefore, our aim is to develop the first topical formulation of mirtazapine by incorporating in solid lipid nanoparticles (SLNs) or nanostructured lipidic carriers (NLCs) for the management of pruritus. Mirtazapine also exhibits side effects like increase in appetite, weight gain, and sedation when administered orally. So, these drug-associated side effects can be avoided; and targeted drug delivery, and patient compliance can also be achieved when the drug is delivered through the skin. Further, the lipophilic nature of mirtazapine owing to its log P value of 2.9 also supports its delivery through the skin. Also, by this time, no reports in the literature are available regarding the compatibility between mirtazapine and different solid lipids for the development of SLNs or NLCs.

The present research includes the evaluation of drug-solid lipids interaction/incompatibility using thermal techniques (DSC, HSM), Fourier-Transform Infrared (FTIR) spectroscopy, and quantitative method (IST studies) in order to develop SLNs or NLCs for management of pruritus.

2. Materials and methods

2.1. Materials

Mirtazapine (anhydrous form) was received as a generous gift sample from East West Pharma, Haridwar, Uttrakhand, India. Palmitic acid (PA), stearic acid (SA), and glyceryl monostearate (GMS) were procured from Loba Chemie Pvt. Ltd. Mumbai, India.

Table 2
Solubility of mirtazapine in different solid lipids (n = 3).

Solid lipid	Solubility (mg/mL)±S.D
Palmitic acid	111.15 ± 0.02
Stearic acid	78.76 ± 0.06
Glycerylmonostearate	93.77 ± 0.03
Cutina CPPH	121.29 ± 0.05
Sterotex NF	116.55 ± 0.02
Gelucire 50/13	32.69 ± 0.01
Hydrogenated castor oil	68.38 ± 0.01
Compritol 888 ATO	268.33 ± 0.01

Cutina CPPH (CUTINA) was purchased from Merck chemicals, Goa. Sterotex NF (STEROTEX) and Gelucire 50/13 (G50) were supplied by Abitec corporation and Gattefosse, France respectively. Hydrogenated castor oil (HCO) was received as a gift sample from Jayant Agro-organics Ltd., Mumbai, India. Compritol 888 ATO (COMP) was purchased from Gattefosse, Germany.

2.2. Solubility studies

Solubility studies of mirtazapine in different solid lipids were performed using melt solubilisation method. Mirtazapine (10 mg) was added in screw-capped culture tube, and the solid lipid was melted separately on a controlled temperature water bath. This molten lipid was then gradually added in small portions to mirtazapine with vigorous shaking using vortex shaker and again heated. The amount (mg) of molten lipid required to completely solubilise mirtazapine was visually examined [15]. From the obtained results, drug solubility in solid lipids was calculated in terms of mg/mL (Table 2).

2.3. Preparation of mirtazapine-solid lipid physical mixtures

For FTIR, DSC and HSM studies, the mirtazapine-solid lipid physical mixtures in 1:1 wt proportion ratio were prepared and screened through a 60-mesh sieve in order to obtain uniform physical mixtures. The solid lipids used are PA, SA, GMS, CUTINA, STEROTEX, G50, HCO, and COMP. For IST studies, the mirtazapine-solid lipid physical mixtures in a maximum expected ratio were prepared (i.e., 1:10) [6].

2.4. Fourier transform infrared spectroscopy studies

FTIR absorption spectra of different mirtazapine-solid lipid physical mixtures were obtained using Perkin Elmer Co., Waltam, USA spectrometer by scanning over a range of 500-4000 cm^{-1} with a resolution of 4 cm^{-1} employing KBr disc method owing to the solid nature of the samples.

2.5. Differential scanning calorimetry studies

The DSC studies of mirtazapine-solid lipid physical mixtures were performed by heating the sample at a rate of 10 °C min^{-1} starting from a temperature range of 25 °C to 250 °C using DSC, Q20, TA Instruments-Waters LLC, USA calorimeter. Each 2 mg sample was weighed and added in aluminium pan which was then sealed with the lid. DSC scans were recorded under a nitrogen purge of 50 mL/min.

2.6. Hot stage microscopy studies

HSM studies were performed using calibrated HSM Nikon Eclipse LV100 N POL (Japan) at a magnification of 50X to confirm the DSC results. A small amount of sample (i.e., mirtazapine, pure solid lipid, and mirtazapine-solid lipid physical mixture) was placed on