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Original Research Paper

Formulation of olanzapine nanosuspension based orally disintegrating tablets (ODT); comparative evaluation of lyophilization and electrospraying process as solidification techniques

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ABSTRACT

Olanzapine (OLAN) as an antipsychotic agent has shown its potential in effective management of psychotic disorders however its use is limited because of its poor water solubility. The aim of present work was to improve solubility of OLAN by developing a stable nanocrystal based orally disintegrating tablets (ODTs), using hyperomellose as potential stabilizer. Comparative evaluation of electrospraying and lyophilization as solidification techniques was carried out to assess its effect on solid state properties of OLAN nanocrystals before transformation to ODTs.

OLAN Nanosuspension was developed using antisolvent precipitation method and exhibited particle size, polydispersity index and zetapotential value of 223.1 ± 1.5 nm, 0.105 ± 0.4 and −17.9 ± 3.5 mV respectively. Solid powders obtained from both the solidification techniques were compared in terms of size after re-dispersion, particle morphology, surface area, pore volume and solid state of drug present. Subsequently ODTs were prepared from these powders with needful excipients and % amount dissolved was evaluated. Rate of dispersion was found to be higher for ODTs prepared using lyophilized powder (~84% in 5 min) while other characterization parameters were comparatively similar. Overall, Lyophilization resulted in powders with better bulk level properties in comparison to electrospraying process.

1. Introduction

Psychological disorders are often associated with impairment of social life, cognitive functions and daily activities of patients. Schizophrenia, doubleline personality disorders etc. are serious psychological conditions which may lead to higher suicidal mortality rates [1–3]. Various classes of compounds (typical and atypical antipsychotic agents) are available for the treatment of psychological disorders, still the condition remains worse, especially in case of geriatric patients for whom easy dose modulation and convenience of administration are of prime importance. Till date orally disintegrating tablets (ODTs) represent themselves as potential and widely acceptable candidates to tackle this problem [4,5].

Olanzapine (OLAN) as an antipsychotic agent has shown its potential in effective management of psychotic disorders and is classified as multi-acting receptor targeted antipsychotic agent. It is known to bind with numerous receptors including D2, $5HT_{1A}$, α1 and α2 with different binding affinities [6]. Despite its vast applications in psychotic disorders, OLAN suffers from the problem of poor water solubility, which leads to erratic absorption and unpredictable pharmacokinetic profiles. Researchers have reported intranasal microemulsion [7], solid dispersion [8,9], self-nanoemulsifying drug delivery systems [10], nanosuspensions [11] and many more formulation approaches to enhance solubility and improve bioavailability of drug.

Nanocrystallization has emerged as full-fledged technique to solve the problem of poor water solubility in last decade [12]. Ease of preparation and scale-up has tremendously increased the translationational potential of this technique, manifested in form of several commercially available products. Nanocrystals can be best transformed to oral products by various methods of solidification viz. lyophilization [13], spray drying [14,15], pelletization [16], electrospraying [17,18] and many more. Stability profile of nanosuspension always remains a constraint due to thermodynamically active and electrostatically charged state of nanosuspension, making them more prone to Ostwald ripening. To minimise the aggregation problem and improve the stability, nanosuspen-

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sions may be dried to form nanocrystals, which still possess the unique properties of the nanosuspensions [17]. Solidification techniques are best suited for the purpose of stabilization, as well as easy conversion of nanosuspension to solid form, without compromising the solubility advantages offered by technique.

Techniques like electrospraying and lyophilization are two such methods which can be successfully used for solidification of drug nanosuspension, despite the fact that scalability is still a big challenge with electrospraying. However compared to lyophilization, it is a single step process and can be used for both hydrophilic and hydrophobic drug materials [17].

Present study was aimed towards preparation optimization and characterization of OLAN nanocrystal based orally disintegrating tablets to counter the poor water solubility of the drug. Solidification techniques like lyophilization and electrospraying techniques were used to obtain dried nanocrystals from nanosuspension, and were compared on the basis of various physicochemical properties like size after re-dispersion, surface area, pore volume, bulk density, tapped density, angle of repose compressibility index, Hausner's ratio, and solid state of drug present. Subsequently powders obtained were converted to orally disintegrating tablets ODTs and dissolution profiles were compared by applying similarity factor.

2. Materials and methods

2.1. Materials

OLAN was received as generous gift sample from Torrent Pharmaceuticals (Ahmedabad, India). Mannitol, trehalose dihydrate, sucrose, Pluronic® F-127 and Pluronic® F-68 were obtained from Sigma-Aldrich (Germany). Polyvinylpyrrolidone K-30 (PVP K-30), polyethylene glycol 4000 (PEG 4000) and polyvinyl alcohol (PVA) (cold water soluble, average molecular weight of 160,000 and viscosity of 27–33 cP) were products of HiMedia Laboratories (Mumbai, India). Hyperomellose was obtained from colorcon. Sodium chloride, sodium hydroxide, sodium dihydrogen phosphate, dipotassium hydrogen phosphate and all other salts for buffer preparation were purchased from S D Fine Chemicals (Mumbai, India); magnesium stearate was the product of same suppliers. Talc and Pharmaburst® 500 (co-processed/mixture of excipients) were products of Luzenac Pharma (Germany) and SPI pharma respectively. All other solvents, reagents and chemicals used were of analytical grade. Water used in all the experiments was purified water from a Milli®-Q Biocel, Millipore® (USA) assembly.

2.2. Methods

2.2.1. Drug excipient compatibility studies

Compatibility of drug with excipients was evaluated using differential scanning calorimetry (DSC) [19]. All the DSC analyses were carried out using indium calibrated DSC 214 *polyma* instrument equipped with Intra-cooler (Netzsch, Germany) technology. *Proteus*® version 7.1 (Netzsch, Germany) software was used for data acquisition and analysis. Study was conducted for drug alone along with physical mixtures (1:1) of excipient with drug. Samples (1–3 mg) were accurately weighed into aluminium pans and heated under dry nitrogen (50 ml/min) in the scanning range of 20–220 °C at the rate of 10 °C/min using empty pan as reference.

2.2.2. Nanosuspension preparation

Antisolvent precipitation (bottom up method) alone and in combination with probe-sonication/high shear homogenization (HSH) (combination method) was screened for the formulation of nanosuspension. For bottom-up technique solvents were screened methanol, dichloromethane (DCM) and acetone while Milli®-Q water was used as antisolvent in all the cases. Evaluation of stabilizers was done from Pluronic® F-127, Pluronic® F-68, hyperomellose, PVP K-30 and PEG 4000. Effects of process parameters and material attributes affecting final size and polydispersity index (PDI) viz. type of stabilizer, drug to stabilizer ratio, solvent to antisolvent ratio and rotational speed for getting size and PDI in acceptable range, were also done [20].

In combination techniques, nanoprecipitation technique was either followed by probe sonication, (Ultrasonic Processor VC505, Sonics & Materials, USA) for 5 min at 25% amplitude, 2 s on and 3 s off impulse or homogenization (Polytron, USA) at 1200 rpm (rpm) for 10 min.

2.2.3. Solidification of nanosuspension

Solidification techniques with optimized parameters provide assistance of enhanced stability without compromising solubility advantage offered. At the same time solidified powder can be easily converted to solid dosage forms. Various solidification techniques frequently utilized include freeze-drying, spray drying, pelletization and electro-spraying. Two solidification techniques were evaluated for optimized batch viz. lyophilisation and electrospraying. Cryoprotectants were screened from mannitol, maltose, sorbitol, trehalose dihydrate, PVP K-30 based on freeze-thaw studies. Combination of mannitol and PVP K-30 was tried to see improvement in cryoprotectant efficiencies upon combination. Initially all the cryoprotectants were added in concentrations of 10% and then various concentrations were optimized to have permitted values of S_f/S_i ratio (where, S_f and S_i are particle size after and before freeze-thaw cycles respectively). To conduct freeze thaw studies cryoprotectants (various cryoprotectant) added nanosuspension were frozen at −80 °C for 72 h, followed by thawing at room temperature. Two such freeze-thaw cycles were performed. After thawing, particle size and PDI of the nanosuspension were determined. The cryoprotectants giving S_f/S_i ratio of 1 ± 0.3 were selected for further optimization [21]. For setting the parameters of lyophilization cycle, preliminary assessment of cryoprotectant, T_g values was done using DSC. DSC was performed in a range of −70 °C to 20 °C with a cooling and heating rate of 10 °C/min for all cryoprotectant solutions and a mixture of cryoprotectant with nanosuspension. Finally lyophilization (VirTis Genesis from SP scientific, USA) was commenced using optimized cryoprotectant in defined concentration. For lyophilization samples were frozen at −80 °C before primary and secondary drying steps. After freezing, primary drying was commenced at −40 °C with pressures of 250 mT (in between hold at −25 °C) for variable time periods. Finally secondary drying was done at temperatures of 10 °C for 500 min utilizing pressures of 210 mT.

Electro-spraying (ESPIN NANO from physics equipment company, Chennai, India) of nanosuspension was performed by adding water soluble polymer (PVA) to OLAN nanosuspension. Mannitol was further added in nanosuspension containing PVA to enhance the bulkiness and compressibility characteristics of electosprayed powder. Various processing parameters like polymer concentration, applied voltage, distance between collector and sprayer, flow rate and temperature were optimized to obtain free flowing electrosprayed powder. The conditions for electrospraying included a voltage of 25 kV, feed rate of 2 ml/h and a cabin temperature of 45 °C. A distance of 10 cm was maintained between the needle and the collector.

2.2.4. Characterization of lyophilized and electrosprayed powders

2.2.4.1. Analysis of particle size and zeta potential. Average particle size and PDI were measured by Malvern Zetasizer (Nano ZS90 series UK) working on the principle of dynamic light scattering (DLS). Zeta potential measurements were carried out using the same

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