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Research Paper

Investigation of salt formation between memantine and pamoic acid: Its exploitation in nanocrystalline form as long acting injection

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ABSTRACT

In the present work, we prepared memantine–pamoic acid (MEM–PAM) salt by counter ion exchange in the aqueous phase to reduce the water solubility of MEM hydrochloride (native form) to make it suitable for long acting injection. The ratio of MEM to PAM in salt formation was optimized to maximize the loading efficiency and complexation efficiency. The 2:1 molar ratio of MEM to PAM salt form displayed nearly 95% complexation efficiency and 50% drug loading. The solubility was decreased by a ~1250 folds. Thermo Gravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC), and Powder X-ray Diffraction Analysis (PXRD) studies revealed the formation of new solid phase. Additionally, Nuclear Magnetic Resonance (NMR) spectroscopy confirmed the anhydrous nature of the salt form. Through Fourier transformation infrared spectroscopy (FT-IR) we identified the molecular interactions. Further, the microcrystals of the salt were transformed into nanocrystals (NCs) using high pressure homogenization. The particle size distribution and atomic force microscopy confirmed the monodispersed and spherical shape of the NCs. The *in vitro* dissolution studies were performed under sink condition in phosphate buffer saline pH 6.8. The results of MTT assay in murine fibroblast 3T3 cell line show that the NCs were less cytotoxic and more tolerable than plain MEM HCl. The *in vivo* performance of NCs administered as i.m. injection at three different doses in female Sprague–Dawley rats showed that the plasma levels lasted till the 24th day of the study. The pharmacokinetic parameters $AUC_{0-\infty}$ and C_{max} increased linearly with increasing dose. Therefore, the results suggest that injectable NCs could represent a therapeutic alternative for the treatment of AD.

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1. Introduction

Alzheimer's disease (AD), a mentally debilitating disorder, is the most common cause of dementia, which is predominant in adults above 65 years of age and is increasing hand in hand with the rise in the adult population. It manifests itself in the form of cognitive dysfunction, personality and behavioral changes, and difficulties in performing day to day activities which severely compromise the patient's quality of life and lead to increased socioeconomic burden [1].

Memantine hydrochloride (MEM HCl) is a NMDA (N-methyl-D-aspartic acid) receptor antagonist approved for the treatment of Alzheimer's disease (AD) by the US Food and Drug Administration (FDA) [2]. The formulations of MEM HCl are available in the market for daily administration in the form of tablets (immediate release), oral solution and once a daily extended release capsules [3]. However, the advantage of therapy with MEM is somewhat jeopardized by the requirement of taking this medication on a daily basis leading to patient noncompliance. Although oral administration of medication is convenient and preferred for the majority of the outpatients, it is almost impossible for an AD patient to comply with the scheduled self-medication due to cognitive and functional impairments that give way to non-compliance and subsequent treatment failure

Abbreviations: AD, Alzheimer's disease; NMDA, N-methyl-D-aspartic acid; MEM HCl, memantine hydrochloride; PAM, pamoic acid; AMA HCl, amantadine hydrochloride; HIP, hydrophobic ion pairing; NCs, nanocrystals; LC–MS/MS, liquid chromatography–tandem mass spectrometry.

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in aged patients [4]. This demands the development of a sustained release formulation, which could efficiently maintain the required therapeutic concentration for a longer period.

Physicochemical properties of an active pharmaceutical agent (API) play a vital role in product development [5]. Solubility is one such property that has a major influence on drug release characteristics, pharmacokinetics and subsequently *in vivo* efficacy. The poor solubility of APIs is a major concern in drug research. However, sometimes a different solubility profile of a drug molecule is highly desirable. Water soluble molecules, whereas being good candidates for immediate release formulations are as such, not suitable for extended release purposes. Either they have to get incorporated into a delivery system or chemically modified with a cleavable linker to form a prodrug [6].

Salt formation is a ubiquitous process in the pharmaceutical industry for modulating the physicochemical properties such as solubility, ionization, and dissolution rate of the drug molecules. In salt formation, non-covalent interactions such as electrostatic interactions, hydrogen bonding, van der Walls interactions, and π–π stacking play an impetus role [7]. The pharmaceutical salt modifications are not treated as new chemical entities and thus need not to go through a full approval process that is extensive, costly and time-consuming. Thus, it has an added advantage over chemical modification of drug substances.

The solubility of salt depends on the hydrophobicity of counter ion that is more the hydrophobicity less is the solubility. Stah et al. have presented two criteria for the hydrophobic salt formation: first is the differences in p*K*a between base and acid and secondly, the hydrophobicity of counter ion [8]. The hydrophobic salt formation is recently reported in the literature for modifying the drug release and *in vivo* performance. Schoubben et al. prepared three hydrophobic ion pairs of capreomycin with oleate, linoleate, and linolenate, and further studied them for *in vitro* efficacy against *Mycobacterium tuberculosis* [9]. Recently Cambronero-Rojas et al. reported biodegradable microparticles (MPs) of capreomycin oleate ion pair (CO) and observed that the drug release was more sustained from CO microparticles in comparison with the capreomycin sulfate microparticles [10].

Pamoic acid (Fig. 1B) is a dicarboxylic acid, which is practically insoluble in water and other common organic solvents [11]. Salt formation with pamoic acid has been widely reported for reducing the aqueous solubility of basic drugs. This US FDA approved excipient for intramuscular (i.m.) administration [12] reportedly possesses potential activity for the prevention and treatment of AD via arresting amyloidogenic process [13].

In the past recent nanocrystals (NCs) approach has been extensively used for the development of long-acting injections. They offer unique advantages over other nanocarrier systems on high drug loading [14], the inclusion of lesser excipients and industrial scalability. Baert et al. prepared NC formulation of rilpivirine (TMC278) for developing long-acting injection and showed that the nanonization of API allowed them to sustain the TMC278 levels up to 3 months after intramuscular (i.m.) or subcutaneous (s.c.) administration [15]. Further, the applicability of nanocrystals for long-acting delivery has been documented in few other studies [16,17].

Microfluidizer® technology is one of the most promising approaches that can get smaller and uniform particles without using any chlorinated and organic solvents. We recently reported the formulation development of paclitaxel (PTX) nanocrystals and moxifloxacin loaded nanoemulsions, using Microfluidizer® technology [18,19]. A combination of different processes such as turbulence shear force, impaction, cavitation forces, particle–particle attrition and particle–chamber attritions are collectively responsible for the size reduction [18]. We used D-α-Tocopherol polyethylene glycol succinate (TPGS) to prevent particle aggregation that could result from the high surface area and charge generation during high pressure homogenization [20].

Here, our focus was to prepare and study the salt form of model drug memantine with pamoic acid and further convert it to NCs for obtaining injectability and sustained release. It has been hypothesized that the interaction between a positively charged amine of memantine and the negatively charged carboxylic group of pamoic acid along with hydrophobic interactions is responsible for the salt formation.

As per our knowledge, in this study for the first time, we are reporting the development of NCs of MEM–PAM for the sustained release. The developed NCs were then characterized for size, distribution, surface morphology, cytotoxicity and *in vitro* release. Further, the *in vivo* performance of NCs was evaluated at three different dose levels.

2. Materials and methods

2.1. Materials

Memantine HCl (MEM HCl) was a kind gift from the Torrent Research Center (TRC), Gandhinagar, India. Pamoic acid (PAM) was purchased from Himedia, India. Amantadine HCl (AMA HCl), was procured from Sigma–Aldrich (MO, USA). The water used was obtained from a three stage Millipore Milli-Q plus 185 purification system (Bedford, MA, USA). All other chemicals and solvents were of analytical grade.

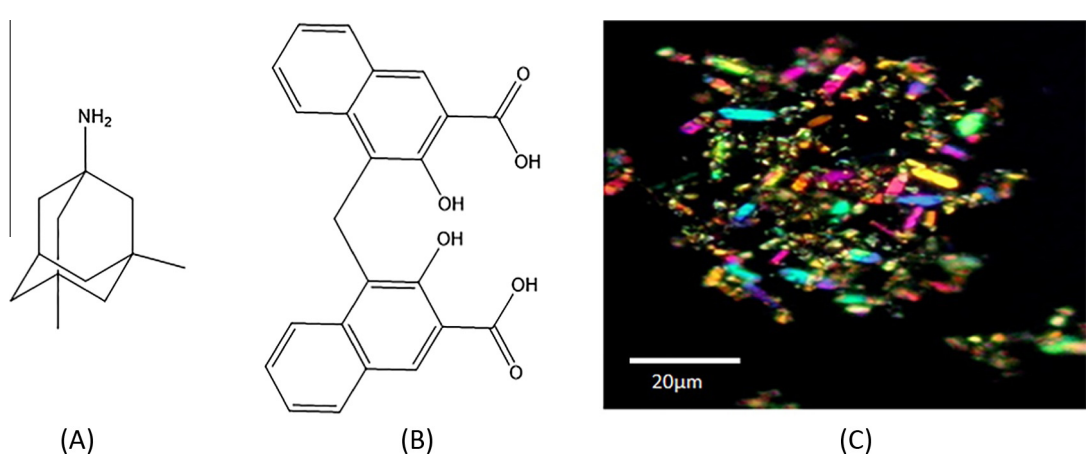

Fig. 1. (A) Chemical structure of memantine (MEM), (B) pamoic acid (PAM) and (C) microscopic image of MEM–PAM salt coarse powder under polarized light.

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