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Mesoporous silica based macromolecules for dissolution enhancement of Irbesartan drug using pre-adjusted pH method

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ABSTRACT

Dissolution enhancement of poorly water-soluble Irbesartan drug through formation of Irbesartan-silica based microcapsules has been investigated. The microcapsules were fully characterized using FTIR, DSC, XRD and SEM techniques. Pre-adjusted pH method has been utilized to form efficient Irbesartan–silica based microcapsules capable to enhance dissolution rate of Irbesartan drug at the challenging pH 5.5 value. The formed Irbesartan–silica based microcapsules showed large dissolution increase as Neusilin feed ratio and as pre-adjusted pH were increased. The maximum dissolution enhancement was achieved via salt formation at pre-adjusted pH 7.4 and 1:3 ratio of Irbesartan-silica based microcapsules. The successful dissolution enhancement was owed to destruction of the crystallinity of the drug accompanied with Irbesartan-silica based salt formation at elevated pH pre-adjustment leading to apparent drug dissolution.

1. Introduction

Poorly water-soluble drugs are becoming the major concern and the challenging issue for many oral drug implementations due to its direct relationship with therapeutic effectiveness and cure. Their poor solubility and hence poor bioavailability have diverted many researchers to overcome this obstacle via the enhancement of dissolution rate [1–4]. The continuous need to find new methods and technique that could enhance the poorly water-soluble drugs is in continual persistence due to unceasing emerge of new potential drugs that suffer from water solubility problems, and hence poor bioavailability in human tissues. Therefore, many techniques and methods appeared in the literature that play dominant role in the improvement of drug dissolution such as; micronization [5,6], solubilization [7], naturally occurring polysaccharides [8], salt formation [9], reduction of drug's particle size [10], micron-sized crystalline particles [11], or the solid dispersion technique [12,13].

On the other hand, stable mesoporous silica materials used in pharmaceutical formulations gains increasing attention due to its tunable porosity, high surface area, non-toxicity, and good biocompatibility, which adapt it to be used in drug delivery and/or dissolution enhancement processes [14,15]. Adsorption of drugs on silica-based materials first described in the early 1970's was re-acknowledged by the formation of synthetic grades like porous silicon dioxide (Sylysia®), polypropylene foam powder (Accurel®), porous calcium silicate (Florite®), and magnesium aluminum silicate (Neusilin®) [16–19]. Neusilin US2 have high specific surface area (~300 m^2/g), high porosity, anti-caking and flow enhancing properties. It consists of amorphous microporous magnesium aluminum silicates with an empirical formula of $Al_2O_3{\cdot}MgO{\cdot}1.7SiO_2{\cdot}xH_2O$. It has a silanol group on its surface, which makes it a potential proton donor or acceptor [20]. Meanwhile, Irbesartan drug is a strong and long effective non-peptide tetrazole derivative and an angiotensin II type 1 receptor (AT1) antagonist considered as class II drug according to biopharmaceutical classification system, and used alone or with other antihypertensive agents to treat high blood pressure [21–23]. Such potential drug suffers from poor water solubility and hence bioavailability. Therefore, in this research, mesoporous silica-based Neusilin–Irbesartan microcapsules were evaluated to enhance the dissolution of the poorly water-soluble Irbesartan drug. Different spectroscopic means was used to elucidate the guest–host microcapsules such as FTIR, DSC, XRD and SEM techniques. The formation of the microcapsules were subjected to different mixing techniques (i.e. physical mixing and solid dispersion) to enhance the dissolution at the challenging solution pH = 5.5 value. In addition, pre-adjusted pH method was also tested and verified to promptly enhance the dissolution of the poorly water-soluble Irbesartan drug.

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2. Experimental

2.1. Materials

Irbesartan drug was kindly supplied by Dar El-Dawa Pharmaceuticals, Jordan, and Neusilin US2 was also gifted by Fuji Chemical Industry Co., Japan. Mono- and di-basic phosphate buffer was used for the adjustment of different pH values. Deionized and double distillated water was used in all experiments. All other reagents were of analytical grade and used as supplied without further purification.

2.2. Spectroscopic and thermal techniques

FTIR: Shimadzu IRAffinity-1 FTIR spectrophotometer for functional groups were recorded in the range of 4000–400 cm^{-1} using KBr pellets. Differential Scanning calorimeter (DSC) model: Netzch, 204 F1 Phoenix DSC equipped with intra-cooler, Indium standard was used to calibrate the DSC temperature and enthalpy scale. The system was purged with nitrogen gas at a flow rate 70 ml/min., and heated from 30–275 °C using a heating rate of 10 °C/min. X-ray diffraction (XRD): Rigaku Goniometer Ultima IV (185 mm) X-ray powder diffractometer with cobalt radiation, at a voltage of 40 kV and a current of 20 MA. The scanning rate was 1 °/min over a diffraction angle of (2θ) and range of 3–70° with 0.02 step change. Scanning Electron Microscope (SEM): The film samples were mounted on the specimen stabs and coated with gold ion by sputtering method with (DSM 950 (ZEISS) model) (USA), Polaron (E6100) model. Micrographs were of Polaroid films.

2.3. Sample preparation and dissolution studies

For the solid dispersion samples, 150 mg of Irbesartan was put into a stoppered 100 ml round bottom flask. A small quantity of methanol just enough to solubilize Irbesartan was added, and a weighed quantity of Neusilin US2 was dispersed with shaking into drug solution. Three respective Irbesartan–Neusilin ratios was prepared as follows; 1:0.5, 1:1, and 1:3 (w/w), then methanol solvent was slowly evaporated under vacuum using a rotary evaporator (Heidolph 4000 efficient) of speed of rotation equals 40 rpm at 60 °C. Collected samples were dried at 70 °C for 72 h. The dissolution process was performed using USP XXIV type II dissolution apparatus (Dissolution tester RC-8DS). The dissolution medium used was 900 ml phosphate buffer maintained at 37 °C ± 0.5. The paddle speed was 100 rpm and 5.0 ml sample was collected periodically and replaced with equal quantity of dissolution medium. The samples were then filtered with 0.45 μm pore size membrane filter. Consequently, filtered solutions were suitably diluted and analyzed by UV spectrophotometer (Beckman DU-62 spectrophotometer) at 230 nm. Schematic representation of solid dispersion of Irbesartan and Neusilin US2 is available in Scheme 1. For the physically mixed samples three different Irbesartan–Neusilin ratios were mixed 1:0.5, 1:1 and 1:3 ratios respectively in a closed glass tube using vortex.

2.4. Microcapsules formation using pre-adjusted pH method

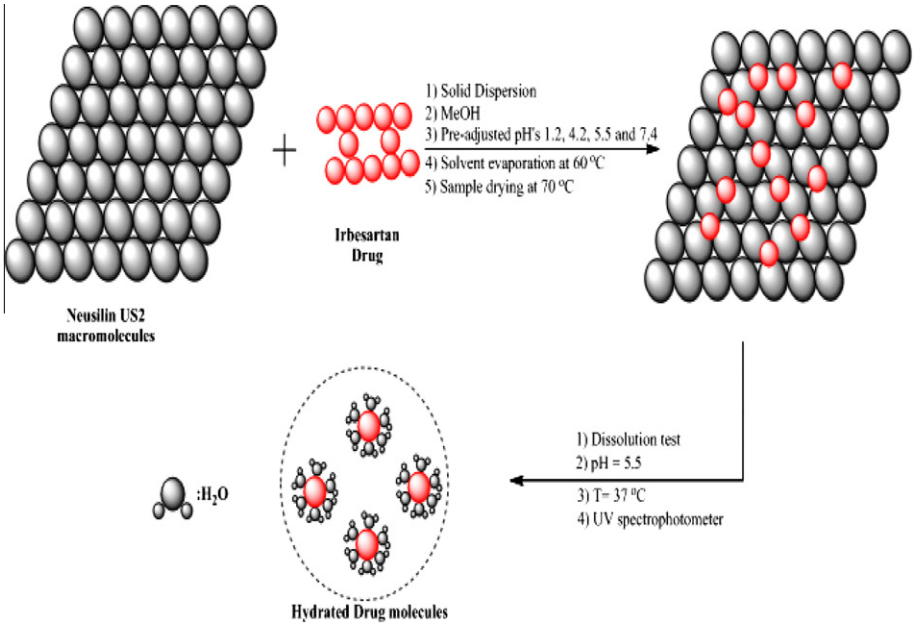
Specific amount of Irbesartan was weighed and put into a stoppered 100 ml round bottom flask. Minimum amount of methanol was added enough to solubilize Irbesartan and a weighed quantity of Neusilin US2 was dispersed in the solution. The solution was thoroughly mixed and the pH of the solid dispersion solution was adjusted to pH = 1.2. The solution was left under continuous homogenous shaking using magnetic stirrer for 30 min. After time completion, the solvent was slowly evaporated and the pre-adjusted pH 1.2 microcapsules were collected. The same procedure repeated using different pre-adjusted pH values namely 4.2, 5.5, 7.4, and different Irbesartan–Neusilin ratios. Dissolution studies using the different pre-adjusted pH microcapsules were carried out at the challenging pH 5.5 for which the drug shows the minimum drug dissolution (Section 3.2.3).

3. Results and discussion

3.1. Characterization of Irbesartan–Neusilin microcapsules

3.1.1. Fourier transform infrared (FTIR)

The FTIR spectra of Neusilin US2 and solid dispersed Irbesartan–Neusilin microspheres (1:1) illustrated in Fig. 1 and Table 1. Apparently, the OH stretching band of silanol group of Neusilin US2 in



Scheme 1. Solid dispersion and dissolution enhancement of Irbesartan and Neusilin US2.