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Evaluation of the surface chemistry and drug-polymer interaction of semi-crystalline micro-particles for the development of controlled release formulations

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ABSTRACT

This research work explores the surface chemistry and drug-polymer interaction in the manufactured controlled release micro-particles. Isoniazid (INH) was used as a model anti-tubercular drug while Eudragit® S100 (S100), Eudragit® L100-55 based co-processed Acryl EZE (EZE) and Ethylcellulose ECN10 (ECN10) were used as polymeric carriers. INH containing micro-particles were prepared using a mini spray dryer B-290 (Buchi, Switzerland). The drug polymer ratios were optimized at 1:1 and 1:3 to evaluate the effect of polymers on the release of the drug from the micro-particles. Solid state characterization via SEM and particle size analysis of the manufactured micro-particles showed densely aggregated spherical particles with a mean diameter <10 μm. The advanced surface analysis via EDS revealed a homogenous drug distribution on the spray dried micro-particles. The physico-chemical characterization carried out by using DSC and XRPD showed an increase in the amorphicity of the drug during the spray drying process while the chemical elemental analysis via XPS revealed a strong intermolecular interaction between the amine group of the drug and the carboxyl group of the polymers. As expected, the in vitro dissolution study showed a slow release pattern for the highly water soluble drug INH in acidic media (pH 1.2) for the first 2 h followed by a burst release upon changing the pH to 6.8. It was concluded that emerging spray drying processing can be used as a valuable tool to encapsulate drug for controlled release dosage forms by means of facilitating a possible drug/polymer interaction as outlined by novel XPS analysis.

1. Introduction

'Microencapsulation' via spray drying process is referred to a technique in which a drug in the form of a solid or liquid is encapsulated in a biocompatible and/or biodegradable polymeric matrix or pharmaceutically acceptable excipients [1]. Generally, by means of this process, the produced particles are with a diameter in the range of 1 to 1000 μm [1]. Microencapsulation technique has various pharmaceutical applications such as preparation of sustained or prolonged release medications, single layer tablet containing chemically incompatible ingredients and new formulation concepts for creams, aerosols, plasters, surgical dressings, injectable [2–5]. In the case of drugs that are poorly water soluble, microencapsulation process is carried out to achieve its increased dissolution rate with a fast onset of action [1,5]. In recent years, microencapsulation process using spray drying technique has become quite popular due to its industrial adaptability and ease of scale up process meeting the regulatory requirements [1–5].

Spray drying is, in general term, the transformation of feed (solution, suspension or emulsion) from a fluid state into a dried particulate form by means of spraying the feeding solutions into a hot drying medium (cyclone). Spray drying is a unique process whereby the final product complies with the standards concerning particle size, particle size distribution, particle shape, moisture content and bulk density in a single step operation [1,3,5,6–10]. Due to rapid solvent evaporation, spray drying is widely used in the drying of foodstuffs, pharmaceuticals, ceramics and many other substances. The most important aspect of spray drying is the automization of suspension into hot drying medium (usually air). The formation of a fine spray due to automization is the most important

Abbreviations: ANOVA, analysis of variation; BE, binding energy; DL, drug loading; DSC, differential scanning calorimetry; ECN10, ethyl cellulose N10; EDS, energy dispersive X-ray; EE, encapsulation efficiency; EZE, Eudragit L100-55 (Acryl EZE); HPLC, high performance liquid chromatography; INH, isoniazid; S100, Eudragit S100; SEM, scanning electron microscopy; SSA, specific surface area; XPS, X-ray photoelectron spectroscopy; XRPD, X-ray powder diffraction.

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Table 1
Parameters for spray drying of INH loaded microparticles with B-290, drug loading (DL) and encapsulation efficiency (EE).

	Formulations	Inlet Temp (°C)	Aspirator	Feed flow (%)	Pressure (mbar)	Yield (%)	DL[a] (%)	EE[a] (%)
F1	INH/S100 (1:1)	100	90	13	25	67	40.6	81.2
F2	INH/S100 (1:3)	100	90	13	25	64	22.8	91.2
F3	INH/EZE (1:1)	100	90	15	20	63	40.5	81.0
F4	INH/EZE (1:3)	100	90	15	20	64	23.6	94.4
F5	INH/EC10 (1:1)	100	90	13	35	72	45.1	90.2
F6	INH/EC10 (1:3)	100	90	13	35	82	22.8	91.2

[a] DL = drug loading; EE = encapsulation efficiency.

factor to gain economic production of top quality products, by maintaining optimum conditions for evaporation [1,6–12].

Controlled release drug delivery systems are aimed at achieving more predictable bioavailability of drugs and help in optimizing pharmacotherapies. As compared to conventional dosage forms, these systems provide improved efficacy, reduced side effects and avoid issue with the patient compliances [2–4]. Out of all dosage forms such as tablets or capsules, microparticles have significant advantages such as protection of drug from the gastrointestinal tract by administrating through intramuscular or subcutaneous route, ease of administration, target specific drug delivery and no need for surgery to remove empty remnants [1,2,5].

Polymers can be used for the purpose of prolonging the release and in turn bioavailability by encapsulating the active ingredient in the polymeric matrix or shell. Various polymers such as Eudragit polymers, cellulose derivatives and some natural polymers have been successfully used in the preparation of delivery systems by spray drying. The success of the process depends on a number of factors such as the type of feed, the degree of core material encapsulation and the drug/polymer ratio [13,14].

Isoniazid (INH) is a first line antitubercular drug used for the prophylaxis and therapy of tuberculosis caused by *Mycobacterium tuberculosis*. The most probable mechanism of action of isoniazid is the inhibition of synthesis of mycolic acids which is a unique component of mycobacterium cell wall [15,16]. Due to its pharmacokinetics and pharmacological properties, controlled release dosage forms of INH are prepared so that it would maximize therapeutic efficacy, reduce dosing intervals and dose related adverse effects [16]. INH is soluble in water (~14% at 25 °C, ~26% at 40 °C), with a pKa value of about 1.82 and Log P 0.64, LD_{50} 100 mg/kg (Human, oral) [16,17].

The aim of this study was to optimize and prepare INH loaded microparticles by means of spray drying techniques. For the first time, an EDS and XPS were combined to study the surface chemistry of the spray dried particles. The novelty of this reported study lies on the exploitation of novel EDS and XPS techniques to analyze the surface of the manufactured micro-particles and outline chemical interactions between the drug and polymers, respectively. Organic dispersions of either Eudragit S100 and Acryl EZE or ethyl cellulose derivatives with various drug/polymer ratios were evaluated to develop controlled release drug delivery systems of INH.

2. Materials and method

2.1. Materials

Isoniazid (INH) was purchased from Sigma Aldrich (Gillingham, UK). The polymers Ethyl Cellulose N10 (ECN10) was kindly donated by Harkeulus (Germany). Eudragit S100 (S100) and Eudragit L100-55 based co-processed polymer Acryl-EZE (EZE) was kindly provided by Evonik Industries (Germany) and Colorcon Ltd. (Dartford, UK), respectively. Absolute ethanol and other solvents for HPLC were of laboratory/pharmaceutical grade and obtained from Fisher scientific (UK).

2.2. Spray drying process

The microencapsulation process was performed in a B-290 mini spray dryer (Buchi, Basel, Switzerland). Various drug/polymer binary mixtures (1:1 and 1:3) were dissolved in ethanol (100 mL) as shown in Table 1. The processing parameters for all spray drying processes are also summarized in Table 1. Briefly, the inlet temperature was set at 100 °C while the outlet at 60 °C, the aspirator at 90% with a feed solution rate of 13–15%. The encapsulation yield was also calculated as the ratio of the mass of the microencapsulated particles obtained during the process to the mass of the initial substances added (drug and polymer).

Bulk and tap densities of the spray dried powder were also measured by taking about 1 g of sample and placing it in a 10 mL measuring cylinder. The initial reading was taken as volume. The powder in the cylinder was tapped 100 times onto a rubber mat with the help of a Tap Machine. This process was repeated 3 times. The final reading of the cylinder was then recorded and the tap density was calculated.

The entrapment efficiency and drug loading of INH in various formulations were determined according to the following procedure: approximately 20 mg of the spray dried INH loaded microparticles was weighted and dispersed into 10 mL of phosphate buffer solution (pH 7.2). The mixture was continuously stirred with magnetic stirrer for 24 h followed by a sonication at room temperature for 30 min. The solution was then centrifuged at 7000 rpm for 15 min (Sorval RC6 Plus) and the supernatant was collected via the filtration of the solutions using 45 μm pore membrane. The amount of drug encapsulated was determined by determining by HPLC as per the method described below in Section 2.9. The entrapment efficiency and the drug loading was evaluated via using the following equations (Eqs. (1) and (2)):

$$\text{Drug Loading}\,(\%) = \frac{\text{Calculated Mass of Drug}}{\text{Mass of Drug Loaded Microparticles}} \times 100 \quad (1)$$

$$\text{Encapsulation Efficiency}\,(\%) = \frac{\text{Actual Drug Loading}}{\text{Theoritical Drug Loading}} \times 100 \quad (2)$$

2.3. Particle size analysis

The particle size distributions of all spray dried powders were determined using a Mastersizer 2000 laser diffraction instrument (Malvern

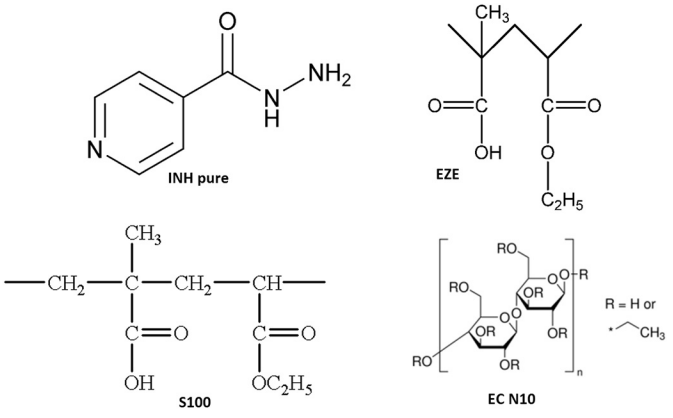

Fig. 1. Chemical structures of the drug and the polymers used.