Use of Thermoplastic Starch in Continuous Pharmaceutical Process

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Summary: Controlled release formulations of thermoplastic starch (TPS) matrix were prepared by extrusion granulation and injection molding of tablets. The compositions contained glycerol, water and on occasion urea plasticizers, glycerol-monostearate; Ca-stearate lubricants and Na-benzoate drug representing component, in addition to the starch. The lubricants and especially the urea reduce the complex viscosity of the TPS considerably facilitating the injection molding process-ability. DSC thermal analysis demonstrated, the urea is in a molecular dispersed form in the extruded granules and Raman microscopic mapping showed an under micron sized dispersion of Na-benzoate in injection molded tablets. Both the extrusion and the injection molding processing resulted retard release character of the active component.

Keywords: controlled release; drug formulation; extrusion; injection molding; Raman microscopy; thermoplastic starch

Introduction

The controlled release formulations of pharmacologically active components are increasingly used for oral administration. These formulations are mostly prepared by direct compression, wet granulation or encapsulation techniques. Melt extrusion [1] and injection-molding [2] are recently reviewed for preparation of granulates or tablets. Hydrophobic, thermoplastic polymers [3] such as synthetic cellulose derivatives, e.g. ethylcellulose, acrylic and methacrylic acid ester polymers and copolymers are proposed as matrix. Starch is not proposed for this purpose, in spite of its wide use in traditional drug formulation, because of its non-thermoplastic character. Recently injection molded starch capsules are reported as alternative to hard gelatin capsules [4]. Thermoplastic starch (TPS), plasticized by methods applied in plastic technology, can become current excipient in controlled release drug delivery [5].

This lecture demonstrates the preparation of TPS, the effect of additives, chemical modification and processing techniques on rheological, thermal characteristics and release properties. Raman microscopic chemical mapping is used as at-line method for controlling the degree of dispersion of the active ingredient in the product.

Experimental

Materials

Wheat-starch (Star), Mn: 300-1000; *Microcrystalline cellulose* (MC), Mn $\approx$ 220; *Glycerol* (Glyc); *Urea*; *Glycerol-monostearate* (GMS); *Ca-stearate* (CaSt); *Na-benzoate*; *Distilled water* (Wat).

Preparation

Granulation by extrusion, ZK 25 T twin screw laborextruder (COLLIN) with zone temperatures: 80, 100, 95 120 and 90 °C, screw speed: 10/min, contact time: 7 min; *Tableting by injection molding*, ALLROUNDER 270C type equipment (ARBURG),

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zone temperatures: 115/130/135/135/145 °C, injection pressure: 850 bar, after pressure: 500 bar, mould temperature: 15 °C, cooling time: 120 s.

Analysis

Rheology, AR2000 type complex rheometer (TA instruments Inc. USA); Thermal analysis, DSC 92 type equipment (SETARAM), 10 mg sample, with 10 °C/min heating rate, in N_2 atmosphere; *Raman-mapping*, Labram type Raman-microscope (YobinYvon), with Nd-YAG (532 nm) laser, and with parameters of 100x objective, 1000 μm hole; *Release of active component*, 1g formulation in 100 cm^3 distilled water, at room temperature, agitated with 40/min rotation, and measured the conductivity of extract.

Results and Discussion

The effect of various additives on the rheological behavior of TPS composite was investigated using compositions consisting of Str/Glyc/Wat in a weight proportion of 53/23/16. Further components, such as urea plasticizing, GMS and CaSt lubricant agent were added in a weight proportion of 8. The plasticizing was performed by compounding in twin screw extruder. The effect of additives on the complex viscosity is demonstrated in Figure 1.

The various additives influence the viscosity differently, the most intensive viscosity reducing effect can be observed with Urea. With increasing temperature a minimum of viscosity is achieved, where the lowest value and at lowest temperature is brought about by the Urea.

The degree of dispersity of Urea in compound was demonstrated by DSC tests given in Figure 2. The Urea in itself gives a sharp melting peak in the range of 140 °C. The Urea in TPS does not appear as a separate peak demonstrating, that urea is present in molecularly dispersed form.

The effect of preparation method on the release properties is demonstrated with compositions containing Str/Glyc/Wat/as TPS components, Urea/CaSt/GMS as plasticization promoting additives, Na-benzoate as model active pharmaceutical ingredient (API) and MC (the weight proportion of ingredients in sequence is 51/22/14/5/1.5/1.5/4/1). Granules were prepared by extrusion; tablets were formed by compressing of the physical mixture of the unmodified ingredients and by injection molding of the extruded granules. The release was characterized by extraction (Figure 3) and dispersion of the API in the tablets determined by Raman mapping of the surfaces (Figures 4, 5).

The conductivity of extracting medium i.e. release of API (Figure 3) from compressed tablets is very rapid. In contrast

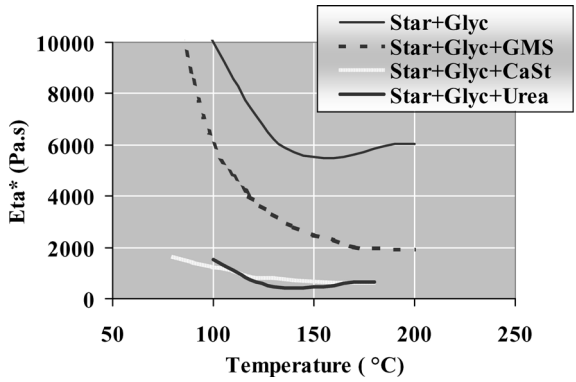

Figure 1.
Complex viscosity versus temperature of TPS composition containing different plasticizers.

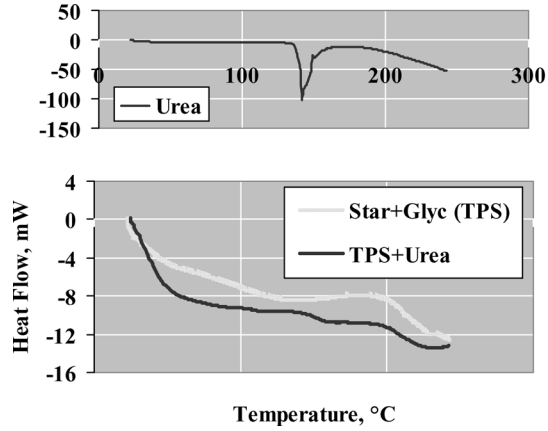

Figure 2.
DSC curves of Urea, and extruded pellets of starch-glycerol (Star + Glyc) and starch-glycerol-urea (TPS + Urea).

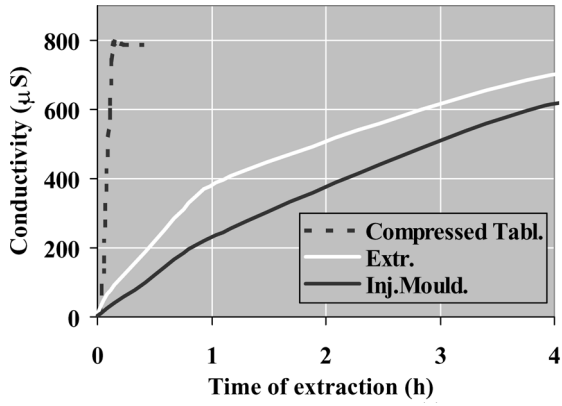

Figure 3.
Conductivity of extracting medium versus time of extraction of formulations prepared by compression, extrusion and injection molding.

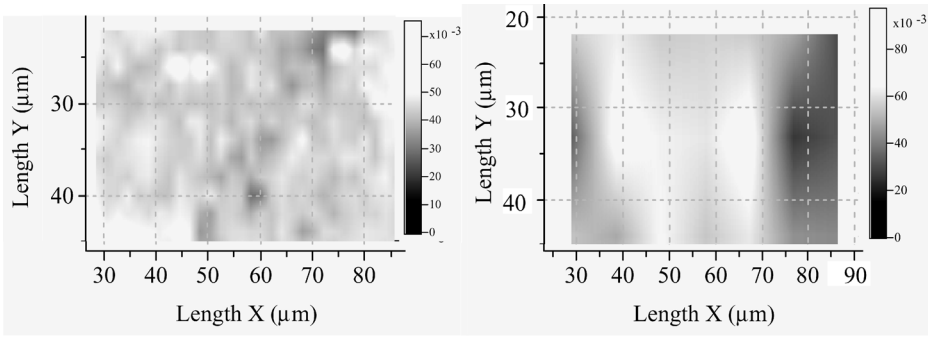

Figure 4.
Raman mapping image of the surface of compressed (a) and injection molded (b) tablets.

much less intensive leaching was detected from extruded and injection molded formulations. Injection molding produced the highest retardation effect.

The API in compressed tablet (Figure 4a) is dispersed in form of 2–4 μm particles, appearing in white spots in the picture. In injection molded formulation the API is dispersed much better, as in Figure 4b no discrete spots can be observed, but continuous white phase. The dark areas represent the MC component.

Conclusion

Thermoplastic starch can be prepared by application of additives used also in pharmaceutical formulation. Extruded granules and injection-molded tablets, prepared with thermoplastic starch matrix, have controlled release character. Extrusion and injection-molding guarantees a molecular dispersion of the active ingredient.

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