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Potato Starch in Pharmaceutical Technology – A Review

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ABSTRACT

Unmodified/native potato starch (*Amylum solani*) is a white, odourless and inert multifunctional excipient which is widely used not only in conventional pharmaceutical operations, such as tableting, capsule filling or granulation, but also in novel formulation technologies as a filler (diluent), binder or disintegrant. In order to improve processability or extend the range of potato starch application, different types of modification have been introduced. The present review describes the functional properties of potato starch which promote its utilization in pharmaceutical technology, provides an overview of practised starch modifications and summarizes the uses and applications of native potato starch and its modifications in drug formulation.

Keywords: copolymers, drug formulation, excipient, microspheres, starch derivatives, tablet

CONTENTS

UNMODIFIED/NATIVE POTATO STARCH

Key properties

Various starches possess an official status in several Pharmacopoeias (e.g. Ph Eur, USPNF, BP, DAB, PFX, JP and Ph Hg). Due to their special characteristics, only a few starches, and especially potato starch, are frequently used as pharmaceutical excipients (**Table 1**). Like starches in general, potato starch is a naturally-occurring biopolymer in which glucose is polymerized into amylose and amylopectin, forming a densely-packed, semicrystalline, B-type structure. Starch granules are built up from alternating amorphous and crystalline lamellae, in which amylose and amylopectin are embedded (Jenkins *et al.* 1995; Buléon *et al.* 1998). Besides the two main polymers, starches also contain small quantities of minor components, such as proteins and lipids.

Potato starch (*Amylum solani*) is a fine white powder, which is an odourless, tasteless, non-toxic and non-irritant substance (Swarbrick *et al.* 2002). The Ph Eur describes exact tests of identity and purity. Furthermore, official standards are specified for pH (between 5.0 and 8.0), iron content (not more than 10 ppm), total protein content (not more than 0.1%), quantity of sulphur dioxide (not more than 50 ppm), loss on drying (not more than 20%) and sulphate ash (not more than 0.6%). The critical point of potato starch application for pharmaceutical aims is linked to its carbohydrate nature. As pure carbohydrates, starches tend to suffer microbial contamination. Potato starch is not allowed to contain more than 10^3 bacteria and more than 10^2 fungi per gram.

Dry, unheated, powdered starch is stable, if protected from high humidity. Starches in general are compatible with the majority of active pharmaceutical ingredients. Only a few incompatibilities are known, e.g. starches are not applicable as fillers in the presence of strongly acidic compounds, since they partially hydrolyse on drying.

Starch granules are insoluble in alcohol, most solvents and cold water. However, when heated in excess water, starch granules swell, and the partially-ordered structures are disrupted at the gelatinization temperature, resulting in an increase in viscosity (Biliaderis *et al.* 1980; Waigh *et al.* 1999; Szepes *et al.* 2007a). The swelling characteristics are closely related to the amylose content of starches (Miles *et al.* 1985). The amylose content and consequently the gelatinization temperature of potato starch have been suggested

Table 1 Sources and characteristics of various starches (Ph Eur)

Type of starch	Extracted from	Particle shape	Particle size (μm)
Corn (maize)	seed	round or polygonal	5-25
Potato	root	egg-shaped	15-100
Rice	seed	polygonal	3-8
Wheat	seed	round or elliptical	2-10 or 20-35

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Invited Review

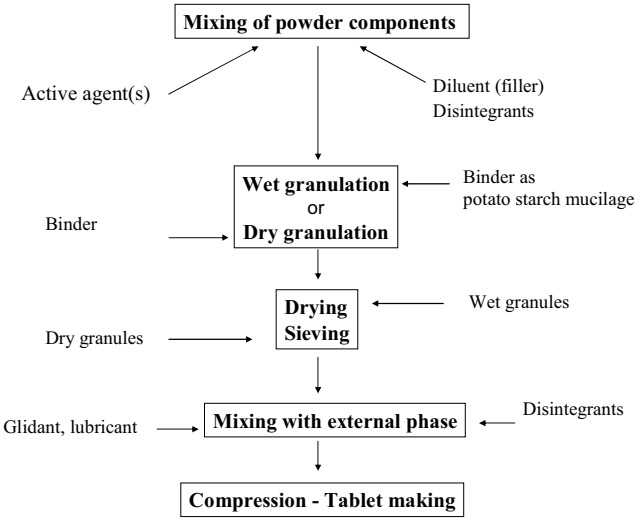

Fig. 1 Application of potato starch in the tablet manufacturing process by wet and dry granulation.

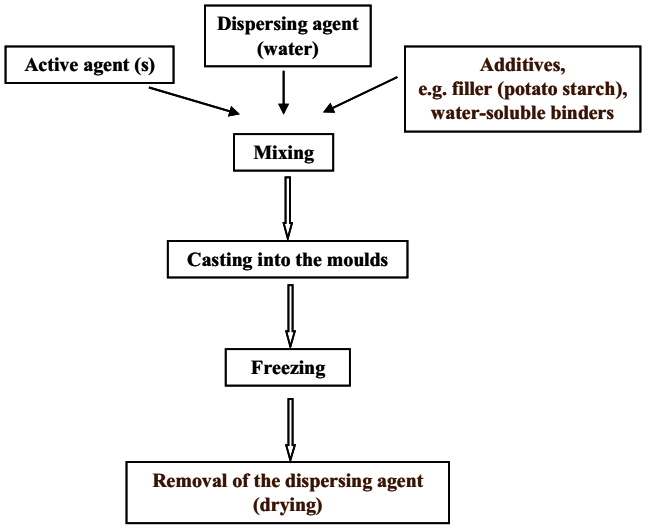

Fig. 2 Schematic diagram of the freeze-casting process.

to vary with the environmental conditions during the growth of the potato tubers (Cotrell *et al.* 1995).

Potato starch is regarded as a multifunctional pharmaceutical auxiliary. It is utilized as a filler/diluent and disintegrating agent in solid dosage forms. It additionally, finds application in the form of starch paste (mucilage) as a binder in solid dosage formulation via the wet-granulation process (**Fig. 1**). Hence, it is clear that the amylose-amylopectin ratio, crystallinity and gelatinization properties of potato starch are key characteristics which strongly influence the compaction behaviour (plastic-elastic deformation), swelling properties and other formulation properties of potato starch. These pharmaceutical features have an essential impact on the final product properties, such as tablet strength, disintegration and drug dissolution (Swarbrick *et al.* 2002; Rowe *et al.* 2003; Talja *et al.* 2008).

A flow diagram of the tablet-making process with wet and dry granulations demonstrates the importance of potato starch in the preparation of solid dosage forms (**Fig. 1**). The first stage is a powder-mixing process. In this step, the potato starch may act as a filler, a disintegrating agent or both. The process of granulation (second stage) may be essentially one of size enlargement, and it serves several purposes in the tablet-manufacturing process (better flow property, compressibility, bioavailability, etc.). The powder mixture is wetted by granulation liquids (e.g. potato starch mucilage) and dried by different heating methods. If the active agent is unstable in the presence of liquids, the dry granulation process is used with potato starch (in solid form), for instance, as binder. When the drying process (wet granulation) and the compaction of the powder mixture (dry granulation) are complete, several important excipients (*e.g.* potato starch as intragranular disintegrant) are added to the formulation. After mixing, it can be pressed by tablet machine into tablets. The effects of potato starch on the properties of solid dosage forms are discussed by additional parts.

Uses and applications of native potato starch in drug formulation

Potato starch is frequently used as a ***filler*** (diluent) in standardized triturates of colorants (pigments) or potent drugs to facilitate subsequent mixing or blending processes in manufacturing operations. Potato starch is also suitable for the volume adjustment of the fill matrix in dry-filled capsules (York 1980).

Besides its utilization in traditional pharmaceutical processes, *e.g.* tableting, capsule filling, or powder preparation for oral or topical use (e.g. dusting powder), potato starch can also be applied in novel pharmaceutical operations such as the freeze-casting process.

Freeze-casting is a complex shape-forming technique, which has been utilized for the preparation of soft tablets. The soft tablet is a highly porous solid dosage form which is manufactured without compression by tableting equipment and exhibits special product properties, e.g. rapid drug dissolution. The first step of the freeze-casting process is the preparation of an aqueous suspension containing the active pharmaceutical ingredient and other water-dispersible or water-soluble excipients (**Fig. 2**). When the aqueous suspension is moulded into a form-giving tool and undergoes freezing, the volume expansion related to ice formation results in the 'cold compression' of the suspended solid particles. After evaporation of the ice crystals, a porous solid body can be obtained (Walther *et al.* 2005). The open pores are the negative image of the former ice crystals (**Fig. 3A**). However, high porosity is always related to poor mechanical properties. Adequate mechanical strength is achieved by using water-soluble binding agents (citric acid and saccharose), which stabilize the matrix via recrystallization during drying (**Fig. 3B**).

Potato starch is an ideal filler in the freeze-casting process (Szepes *et al.* 2007b, 2007c). Aqueous suspensions of theophylline and potato starch exhibit sufficient flowability and can be poured into the moulding form without difficulty, the sedimentation of the suspended particles being prevented during the freezing process (Szepes *et al.* 2007b). As illustrated in **Fig. 4**, the suspensions can be characterized by thixotropic flow. The primary advantage of thixotropic behaviour is that it confers pourability under shear stress and viscosity when the shear stress is removed at rest.

Direct compression is possible for only a limited number of pharmaceuticals. To optimize the flowability and compressibility of the ingredients, solid substances are often tabletted after a granulation process (**Fig. 1**). Potato starch can be used as a solid dry ***binder*** (dry granulation or roller compaction) and as a component of the granulation fluid (wet granulation). The freshly prepared starch mucilage utilized as a granulation fluid usually contains 5-25% (w/w) of the polymer (Swarbrick *et al.* 2002). During the wet granulation process, the starch mucilage covers the particles and forms a macromolecular film on the particle surface upon drying. The solid bridges generated between the particles during solvent evaporation ensure the adequate mechanical properties of the granules.

The major disadvantageous powder characteristics which limit the application of starches in dry granulation and direct compression are their poor flowability, high lubricant sensitivity and elastic deformation during compression (Bolhuis *et al.* 2006). Elastic compaction behaviour is

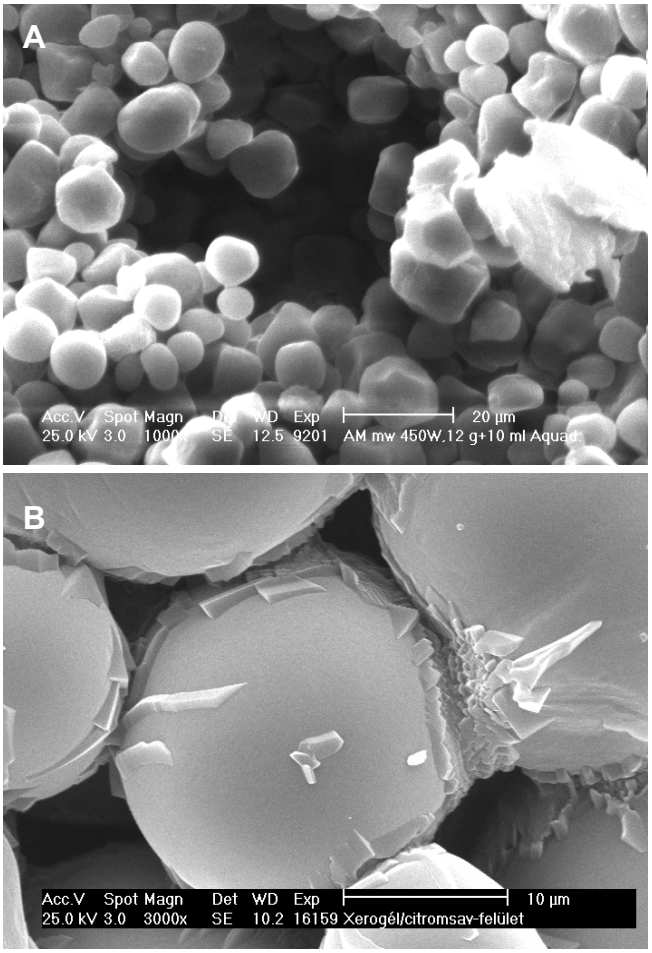

Fig. 3 SEM pictures of potato starch matrices prepared by the freeze-casting technique. Figure reprinted from **Szepes A, Ulrich J, Farkas Zs, Kovács J, Szabó-Révész P** (2007b) Freeze-casting technique in the development of solid drug delivery systems. *Chemical Engineering and Processing* **46**, 230-238, ©2006, with kind permission of Elsevier B.V.

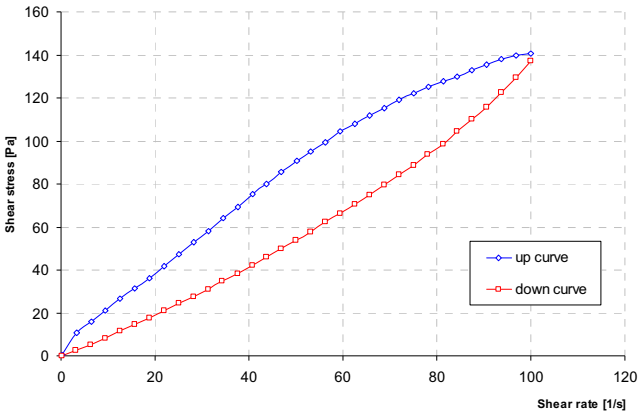

Fig. 4 Flow curve of an aqueous suspension containing potato starch and theophylline. Figure reprinted from **Szepes A, Ulrich J, Farkas Zs, Kovács J, Szabó-Révész P** (2007b) Freeze-casting technique in the development of solid drug delivery systems. *Chemical Engineering and Processing* **46**, 230-238, ©2006, with kind permission of Elsevier B.V.

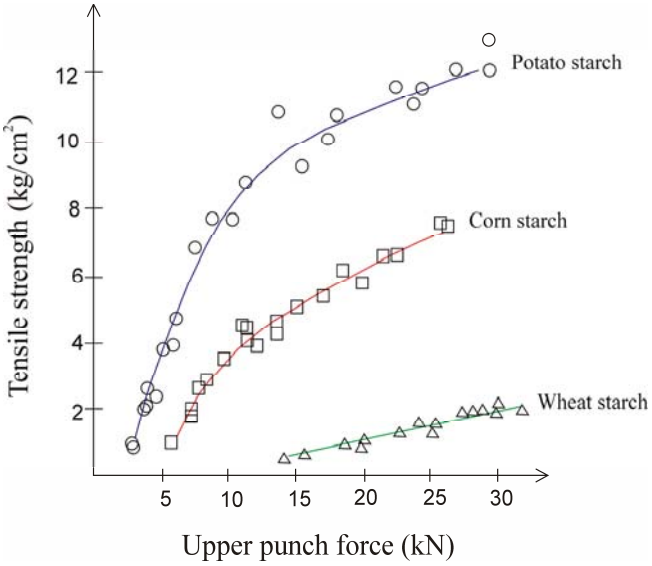

Fig. 5 Influence of compaction force on tensile strength (hardness) of different starches. Figure reprinted from **Rowe RC, Sheskey PJ, Weller PJ** (2003) *Handbook of Pharmaceutical Excipients* (4th Edn), pp 603-608, ©2003, with kind permission of Pharmaceutical Press and American Pharmaceutical Association.

known to exert a negative influence on the mechanical properties of the compacts. Comparison of the tensile strengths of wheat, corn and potato starches reveals that native potato starch exhibits the best compactibility. Accordingly, the use of potato starch as binder is preferred in the dry granulation process (**Fig. 5**).

Disintegrants are added to solid formulations to ensure that, on contact with a liquid, the tablet breaks up into small fragments, which promotes rapid disintegration and drug dissolution. Ideally, tablets should disintegrate into individual drug particles in order to obtain the largest possible effective surface area during dissolution.

The most common disintegrant is potato starch, which is applied in a concentration of 3-15% (w/w) in traditional tablet formulations (Ingram *et al.* 1966; Patel *et al.* 1966; Lowenthal 1973; Rudnic *et al.* 1982). As mentioned above, starch particles swell on contact with water and the swelling mechanism subsequently disrupts the tablet structure (List *et al.* 1979; Caramella *et al.* 1984; Hódi *et al.* 1992). However, starch particles have also been suggested to facilitate disintegration by particle-particle repulsion.

The swelling force plays an essential role in the mechanism of disintegration of tablet formulations produced by using high pressures. Several authors have reported a close correlation between the compression force and the swelling force of starches. The higher the compression force during tableting, the higher the swelling force of the starch particles during disintegration.

Low compression pressures (5 kN) lead to insufficient particle deformation and a loose tablet texture, while high pressures (e.g. 25 kN) result in more compact tablet structures with highly deformed potato starch particles (Szabó-Révész *et al.* 1986) (**Fig. 6**).

The pressure has a considerable influence on the tablet hardness and the swelling force, and consequently, on the time of tablet disintegration. **Table 2** includes the above-mentioned parameters of tablets produced via direct compression (without granulation) by an eccentric tablet ma-

Table 2 Physical parameters of tablets containing potato starch and microcrystalline cellulose (from Szabó-Révész *et al.* 1986).

Pressure (kN)	Hardness (N)	Disintegration time (s)	Swelling force (bar)
5	33	19	1.381
15	116	21	1.690
25	147	26	2.167

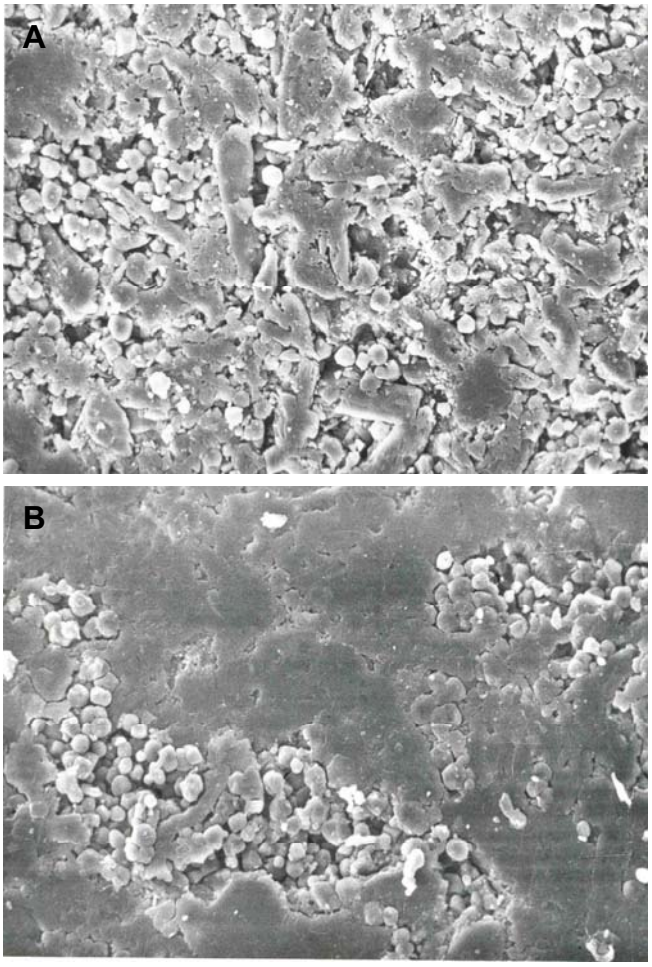

Fig. 6 SEM pictures of tablet surface containing potato starch and microcrystalline cellulose. Pressure: 5 kN (A); 25 kN (B). Figure printed from **Szabó-Révész P, Pető K, Pintye-Hódi K** (1986) Untersuchung der Verwandbarkeit von mikrokristallinen Cellulosen bei der Herstellung von Phenobarbital-Tabletten. *Pharmazeutische Industrie* **48**, 289-291, ©1986, with kind permission of Editio Cantor, Verlag für Medizin and Naturwissenschaften GmbH, Aulendorf.

chine at different pressures. Higher pressure (25 kN) and consequently higher swelling force (2.167 bar) result in faster dissolution, which can be explained in terms of the higher efficiency of the disintegration process (particle by particle).

MODIFIED POTATO STARCH

Practised modifications of potato starch for pharmaceutical aims

As summarized above, potato starch possesses several physico-chemical properties which promote its utilization with the aim of drug formulation. However, its unfavourable characteristics, such as its poor flowability and elastic compaction behaviour, must be optimized. Furthermore, with regard to the current requirements of drug formulation and development, polymer characteristics often have to be modified or improved to ensure special product performance and functionality (Andreev 2004; Jobling 2004).

The practised starch modification procedures which result in valuable excipients for drug formulation are summarized in **Table 3**.

The techniques for the ***physical modification*** of starch include mechanical, thermal and thermomechanical processing of the polymer. It should be noted that isostatic ultrahigh pressure (IUHP) and microwave irradiation are currently of no practical importance in starch processing. These physical treatments are regarded as non-conventional

Table 3 Practised modifications of potato starch for pharmaceutical aims

Physical modification
Mechanical
Thermal
Thermomechanical
Chemical modification
Derivatization/Substituted starch
Monostarch substituation
Polymer grafting/graft copolymers
Cross-linking
Depolymerization
Enzymatic modification
Enzyme-catalysed hydrolysis
Enzyme-catalysed cyclization

methods of starch modification and have not provided commercially available excipients so far (Tomasik *et al.* 1995). The research focusing on their pharmaceutical application is currently at a laboratory scale. The results, however, are very promising.

Ultrahigh pressure treatment is a preservation technique frequently used in the food industry, since it offers a gentle alternative for the sterilization and pasteurization of heat-sensitive substances (Hendrickx *et al.* 2003). Biopolymers, such as starches and proteins, display changes in their native structure under high hydrostatic pressure, analogous to the changes occurring at high temperatures (Knorr *et al.* 2006). A number of papers are available in the literature which describe the differences induced in the gelatinization mechanism of starches by heat and pressurization (Hibi *et al.* 1993; Stute *et al.* 1996; Katopo *et al.* 2002; Blaszczak *et al.* 2005). This topic is therefore not discussed in detail here.

Since *microwave irradiation* enables rapid and uniform heating (volumetric heating), microwave technology has received considerable attention in the pharmaceutical industry. There are a wide variety of applications of microwaves in this field, such as microwave-assisted drug synthesis, microwave-vacuum drying of heat-sensitive substances in the wet granulation process, the sterilization of injections and infusions, or the enhancement of the dissolution rate of poorly water-soluble drugs from microwave-prepared solid dispersions (Joshi *et al.* 1989; Sintzel *et al.* 1998; Genta *et al.* 2002; McMinn *et al.* 2005; Kelen *et al.* 2006; Papadimitriou *et al.* 2008). As starch is one of the most commonly used excipients in drug formulation, and the critical properties of both raw and in-process materials must be controlled during the manufacturing process to ensure the final product qualities, studies focusing on the effects of microwave irradiation on the structure and physico-chemical properties of starches are of essential practical importance.

Pregelatinized starches are prepared by heating an aqueous slurry of the polymer, followed by a thermal dehydration process via drum drying, extrusion or a controlled pregelatinization spray-drying technique (Herman *et al.* 1989a, 1989b). Mechanical stress coupled with heat transfer (thermomechanical processing) leads to irreversible, partial or complete damage to the polymer structure and generates a cold-water-swelling and partly water-soluble starch modification (Andreev 2004).

During the production of *thermoplastic starch*, the polymer is heated in the presence of water in injection-moulding machines or extruders (Stepto 2006). As a consequence, the polymer/water mixture is subjected to both thermal (heat) and mechanical energy (shear), which results in the formation of a homogeneous melt.

Potato starch undergoes many ***chemical reactions*** characteristic of alcohols, which can be explained by the presence of numerous hydroxy groups in the structure. The D-glucopyranosyl units of potato starch can be modified, e.g. by esterification, etherification or hydrolysis (BeMiller 1997). The chemically modified products include starch derivatives and the modifications obtained by debranching of

the polymer structure. Starch derivatives can be prepared by esterification of the glucopyranosyl rings with different chemical agents (monostarch substitution) or by coupling starch with synthetic polymers (polymer grafting). A frequently used starch modification strategy is controlled degradation, during which depolymerization of the starch macromolecule occurs. The debranching reactions are based on the fact that the glycosidic links in starch molecules are vulnerable to acids, oxidizing agents and amylases.

Enzymatic modification means hydrolysis or cyclization catalysed by different enzymes, which results in the formation of dextrins.

Uses and applications of potato starch modifications in pharmaceutical technology and drug formulation

The possible application of **IUHP** has been investigated with the aim of drug formulation (Szepes *et al.* 2008). Aqueous suspensions of potato and maize starches containing theophylline as a model drug have been processed by IUHP and the mechanism of drug dissolution from the pressurized samples has been investigated, with an aqueous theophylline suspension as reference (**Fig. 7**).

The hydrogels exhibit different dissolution profiles, which can be attributed to the different pressure sensitivities of the polymers, depending on their botanical origin. The drug dissolution from the hydrogel containing potato starch as a gel-forming polymer can be characterized by the Hixson-Crowel kinetic model, which refers to vertical drug release from the matrix. The mechanism of theophylline release from the maize starch gel obtained by IUHP processing is mainly governed by Fickian diffusion, although the relaxation of the pressurized polymer chains plays an increasing role during the dissolution process.

Microwave irradiation does not result in significant changes in the particle morphology and particle size distribution of potato starch (Szepes *et al.* 2005). The micromorphological parameters, such as the specific surface area, mesopore volume and pore diameter, are not changed significantly after microwave treatment. Volumetric heating results in reversible moisture loss from the polymer (Szepes *et al.* 2007d). During storage (25 ± 2°C, 50 ± 5% RH for 6 months), potato starch readsorbs 50% of its initial moisture content by the third day of storage, with a moisture uptake rate of 10-11 mg/g/day, depending on the conditions of microwave treatment. The water-retention capacity and swelling power of potato starch are increased irreversibly, and its swelling capacity is increased reversibly by dielectric heating. The changes in swelling characteristics are in accordance with the results of the X-ray studies, which reveal that volumetric heating degrades the crystallinity of the polymer (**Fig. 8**). Microwave irradiation reduces the surface free energy and the polarity of tablets containing potato starch and microcrystalline cellulose. The tensile strengths of the compacts are decreased, while their wetting properties are enhanced by the physical processing of potato starch.

From investigations relating to IUHP and microwave irradiation, it can be concluded that starches of different botanical origins (e.g. potato and maize starches) exhibit different susceptibilities against physical treatments, which permits the utilization of these methods as selective means of starch modification.

Conventional ***pregelatinized starches*** (e.g. Paselli WA4®: pregelatinized potato starch) deform plastically and find utilization as direct compaction excipients in tablet formulations (Te Wierik *et al.* 1997a, 1997b). They form a soft gel layer on contact with the dissolution medium, which acts as a barrier for drug diffusion, resulting in a non-linear drug release profile. In order to achieve controlled drug release, a new generation of pregelatinized starches, the Preflo® starches, were prepared via gelatinization followed by precipitation (retrogradation) (Sanghvi *et al.* 1993). The Preflo modified potato starches (P-250, PI-10 and PJ-20)

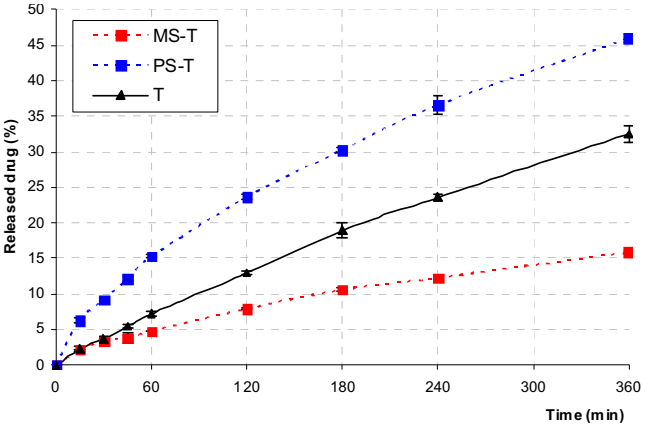

Fig. 7 Profile of theophylline dissolution from starch hydrogels prepared via isostatic ultrahigh pressure. MS = maize starch; PS = potato starch; T = theophylline. Figure printed from **Szepes A, Makai Zs, Blümer C, Mäder K, Kása Jr. P, Szabó-Révész P** (2008) Characterization and drug delivery behaviour of starch-based hydrogels prepared via isostatic ultrahigh pressure. *Carbohydrate Polymers* **72**, 571-578, ©2007, with kind permission of Elsevier Ltd.

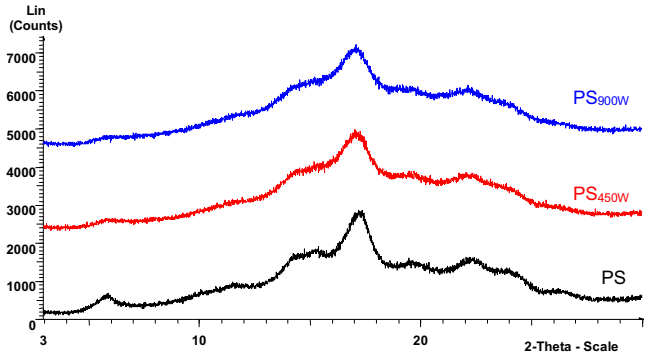

Fig. 8 X-ray curves of potato starch (PS) subjected to microwave irradiation (at 450 W, at 900 W). Figure printed from **Szepes A, Mohnicke M, Szabó-Révész P** (2007d) Water sorption behavior and swelling characteristics of starches subjected to dielectric heating. *Pharmaceutical Development and Technology* **12**, 555-561, ©2007, with kind permission of Informa Healthcare USA, Inc.

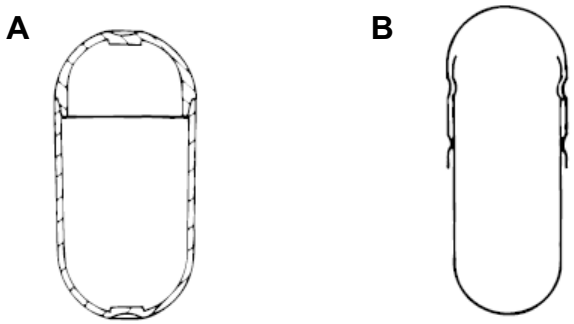

Fig. 9 Injection-moulded starch capsule (A) and conventional dip-moulded hard gelatine capsule (B). Figure printed from **Stepto RFT** (1997) Thermoplastic starch and drug delivery capsules. *Polymer International* **43**, 155-158, ©2000-2008, with kind permission of John Wiley and Sons, Ltd.

demonstrate good flowability and undergo plastic deformation during tableting. Dissolution studies reveal that Preflo starches are good candidates as hydrophilic matrix-forming agents for oral drug delivery.

The ***thermoplastic processing*** of natural hydrophilic polymers in the presence of water is widely used to obtain polymer materials utilized in many industrial applications. The first commercial thermoplastic starch polymer was the drug-delivery capsule Capill® (**Fig. 9**). The injection-moulded liquid-filled Capill® capsules are a possible alternative

for hard gelatine capsules because of their reduced susceptibility to changes under storage conditions. Further advantages of thermoplastic starch capsules are the smaller closure area and the suitability for enteric coating (Burns *et al.* 1996; Stepto 1997).

Cross-linking of the polymer chains leads to network formation via intermolecular bridges between the molecules. The cross-links reinforce hydrogen bonds to hold the granules together, which initiates considerable changes in the gelatinization properties and leads to retarded swelling properties (Bharadwaj *et al.* 2000). Contramid® is a free-flowing, highly compressible powder in the dry state, which is obtained by cross-linking of high amylose starch (Rahmouni *et al.* 2001, 2002). On contact with water, Contramid® forms a surface membrane that is able to control the drug release from orally administered solid dosage forms, such as tablets. This excipient has been applied for the once-daily formulation of tramadol, due to its high drug-loading capacity and ability to maximize therapeutic efficacy and minimize side-effects (Kardu *et al.* 2007).

The preparation and application of biodegradable microspheres have been widely investigated recently with the aim of increasing the systemic absorption of drugs with short biological half-lives and pronounced instability. In general, ***degradable starch microspheres*** are produced by cross-linking hydrolysed potato starch with epichlorhydrin via the emulsion polymerization process. However, the cross-linking reaction is very time-consuming, and special efforts have therefore been made to shorten the reaction time by using other cross-linking agents, such as formaldehyde (Selek *et al.* 2007). Hydrolysed potato starch exhibits several desirable characteristics, such as the ability to entrap a wide range of drug molecules, which promotes its application in the preparation of degradable starch microspheres. The utilization of starch in dosage forms intended for pulmonary drug delivery has the great advantage that the polymer can be degraded by α-amylase, which is also present in the broncho-alveolar fluid. In addition, starches do not stimulate an albumin-like antigen response *in vivo*. These microspheres have been reported to be capable of parenteral and nasal administration (Illum *et al.* 2001; Mao *et al.* 2004). Furthermore, starch microspheres have been introduced as drug carriers for the chemoembolization of tumours, in combination with the simultaneous local delivery of chemotherapeutic agents (e.g. Spherex®) (Liu *et al.* 2006; Morise *et al*. 2006).

Poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) are widely used polymer components of biodegradable microspheres for sustained-release protein delivery. These are usually prepared by dispersing an aqueous protein solution in an organic polymer solution to create a water-in-oil emulsion and then extracting/evaporating the solvent (Woo *et al.* 2001; Jiang *et al.* 2003). Two major shortcomings of these drug-delivery systems are that the manufacturing process can have a disadvantageous influence on the protein stability, and solvent evaporation can lead to the burst release of the active agent during drug dissolution. In order to overcome these problems, ***composite microspheres*** are prepared by using hydroxyethyl and acryloyl-hydroxyethyl starch. The therapeutic protein is incorporated into starch hydrogel microparticles by a swelling technique and, in a following step, the microparticles are encapsulated in a poly(D,L-lactide-co-glycolide) matrix by using the solvent extraction/evaporation method.

Substitution of starch with alkylating agents provides modifications with increased swelling properties. Hetastarch® is ***ethoxylated amylopectin*** derived from potato starch, which is a complex mixture of derivatized amylopectin molecules with various molecular sizes (Hulse *et al.* 1983). Hetastarch is applied as a diluent and binder in solid dosage forms and as a plasma volume expander for parenteral administration (Hespan® - injection, Hextend® - infusion).

Carboxymethylated starches are obtained by treating native starch with acetic acid in an alkaline medium. It is to be noted that the commercially available products are carboxymethylated and cross-linked potato starches characterized by a high water-absorption capacity and rapid swelling (Young *et al.* 2005, 2007). The capability of water absorption and subsequent swelling make them excellent disintegrants in tablet formulations prepared either by wet granulation or by direct compression (Guyot-Herman *et al.* 1983). A well-known member of this group is ***sodium starch glycolate*** (Explotab®, Primojel®, Vivastar®), which has been described as a superdisintegrant typically used in tablet formulations and for enhancement of the dissolution rate in solid dispersions (Chowdary *et al.* 2000). Although this potato starch modification exhibits poor compactibility and a highly hygroscopic nature, these unfavourable properties do not significantly affect the final product quality, since superdisintegrants are usually added to formulations in small quantities (1-5% (w/w)).

Starch acetates have been reported as multifunctional direct compaction excipients, since they exhibit good flow properties and plastic deformation during the tableting process (Korhonen *et al.* 2000). They form mechanically strong tablets with various disintegration times, depending on the substitution degree of the polymer. Starch acetates are traditionally prepared via the chemical reaction of barley starch with acetic acid or acetic anhydride in aqueous solution (Bolhuis *et al.* 2006). However, potato starch acetate has been investigated as a novel film-forming polymer (Tarvainen *et al.* 2002, 2003; Tuovinen *et al.* 2003). Compared to ethylcellulose coatings used as reference, potato starch acetate films display better mechanical properties and lower water vapour and drug permeabilities.

Starch phosphates are obtained by heating dry mixtures of different types of starch and ortho-, pyro- or tripolyphosphoric acid salts (Swarbrick *et al.* 2002). *Monostarch phosphates* exhibit good gel- and film-forming properties. *Starch phosphate diesters* contain ester bridges between two or more starch chains. Due to the cross-links, these starch derivatives can be characterized by retarded swelling and resistance to heat, agitation and low pH. The modified physical properties of distarch phosphates promote their application in antiseptic powders, because they do not swell during steam sterilization (Andreev 2004).

Octenyl succinate-modified starches are permitted food additives in the USA and Europe (Kuentz *et al.* 2006). The substitution of hydrophilic starch moieties by lipophilic *n*-octenylsuccinic acid groups results in a starch modification with increased hydrophobicity.

These modified starches are prepared by coupling a hydrophilic polysaccharide chain with hydrophobic groups, and can therefore be regarded as amphiphilic derivatives with surface-active properties. In contrast with traditional surfactants, which are able to disrupt the membrane structure and exhibit cytotoxicity, hydrophobically modified starches demonstrate good *in vivo* tolerability (Baydoun *et al.* 2004). A further advantage of these derivatives is that they are tasteless, while most oral surfactants have a bitter taste. Since the majority of new chemical entities synthetized by modern drug discovery exhibit poor wetting properties and the lack of water solubility, amphiphilic starches provide a new alternative with which to overcome formulation problems concerning wetting, solubilization and bioavailability enhancement. HiCap® 100 and Capsul® HS are commercially available octenyl succinate-modified waxy maize starches. The physical characterization of such modified potato starch has also been reported. However, this potato starch derivative does not possess adequate rheological properties and is likely to find only limited application in drug formulation (Bao *et al.* 2003).

Cationic starches are starch derivatives of great commercial value that are used in the paper industry as wet-end additives. They are tertiary or quaternary aminoalkyl ethers manufactured by the reaction of a basic starch slurry with a tertiary or quaternary amine containing a halogenated alkyl group (Swarbrick *et al.* 2002). As compared to native starch, these starch modifications are characterized by lower gela-

tinization temperatures and improved swelling properties. Vermeire *et al*. (1999) examined the emulsifying properties of different cationic potato, maize and waxy maize starches, assuming that positively charged emulsions exhibit prolonged residence in the skin or the cornea, thereby enhancing lipophilic drug biodisposition. Emulsions prepared from cationic starches with a high degree of substitution have furnished promising results concerning stability and droplet size distribution.

Starch sulphates are widely utilized in the sizing of paper and textiles and as food additives. The chemical modification of starch by using sulphating agents results in derivatives that gelatinize at lower temperatures than those for native starches, and possessing a high water-retention capacity (Cui *et al.* 2007). Besides the modified physical properties, sulphated oligo- and polysaccharides have gained much attention recently due to their biological effects, such as their anti-viral and anti-HIV activities. Sulphation is carried out by using strongly hydrolytic sulphating agents (sulphuric acid, sulphamic acid, sulphur trioxide, *etc*.), which can lead to extended degradation of the polymer chains. Furthermore, the organic solvents used as reaction medium are environmentally hazardous. Cui *et al.* described a new sulphation route for potato starch in aqueous medium in order to avoid the drawbacks of the traditional reaction.

Spraying acid on dry starch granules and parallel heating results in random hydrolysis of the polymer chains to short fragments called ***dextrins***. These acid-etched modifications, obtained via partial hydrolysis, are soluble in cold water and possess a good gel-forming ability (Manelius *et al.* 2005). Polysaccharide gels prepared by using hydrolysed starch are characterized by reduced viscosity, enhanced transparency and high stability on storage (Belyaev 2000).

When starch granules are dispersed in an aqueous solution of an acid (HCl or H_2SO_4) and the suspension is heated up to a temperature close to gelatinization onset, more extensive hydrolysis occurs, resulting in ***maltodextrins***. Maltodextrins can also be obtained via enzymatic hydrolysis catalysed by microbial α-amylase (e.g. Paselli SA2®: enzymatically hydrolysed potato starch). Both amylose and amylopectin undergo hydrolytic cleavage of the α-(1→4)-glucose bonds and form water-soluble oligosaccharides. Maltodextrins have been reported to behave plastically during the tableting process and to form strong tablets. These characteristics promote their application as direct compaction excipients in tablet formulations. However, it must be noted that these starch derivatives exhibit high lubricant sensitivity. Potato maltodextrins have been found to be suitable matrix-forming agents for the preparation of freeze-dried tablets and matrix mini-tablets manufactured via melt granulation followed by compression (Corveleyn *et al.* 1998; de Brabander *et al.* 2000). The oligosaccharides have been successfully applied as amorphous cryoprotectants and binders in lyophilized dry emulsion tablets, enhancing the delivery of poorly water-soluble drugs, while sustained drug release is observed for matrix mini-tablets based on a combination of microcrystalline wax and potato maltodextrin. The coprocessing of active pharmaceutical ingredients with maltodextrin solutions via spray-drying has improved the physical properties of the active compound, such as powder flowability and compressibility. Co-spray-dried powders have been selected for formulation optimization in direct compression (Gonissen *et al.* 2008).

Amylodextrin is a linear starch polymer which is prepared from potato starch by enzymatic hydrolysis followed by precipitation, filtration and dehydration. From the aspect of drug formulation, the key characteristic of this polymer is that amylodextrin does not swell in water (Steendam *et al.* 2001). As a consequence, the mechanism of drug release from dosage forms containing amylodextrin is not controlled by a swelling boundary gel-layer; instead, the drug dissolution is based on a leaching mechanism. The dissolution medium penetrates the matrix through the pores and dissolves the dispersed drug particles. Due to the porous and tortuous network formed by the cavities left after dissolution of the drug particles, the profile of drug release from leaching-type devices can be characterized by the Higuchi square root time model.

Cyclodextrins are crystalline, water-soluble, cyclic oligosaccharides that can be obtained via the enzymatic cyclization of starch by cyclodextrin-glycosyltransferase. The toroidal structure of cyclodextrins is built up from six (α), seven (β), or eight (γ) glucopyranose units containing a hydrophobic central cavity and a hydrophilic outer surface. This structure allows the molecular encapsulation of hydrophobic hostmolecules in the central cavity, while the hydrophilic surface characteristics result in improved wettability and water-solubility (Sourbaji *et al.* 2000; Taneri *et al.* 2002; Challa *et al.* 2005).

Packaging on a molecular level is a widely used formulation strategy for the bioavailability enhancement of poorly water-soluble drugs (Aigner *et al.* 1996; Amin Kreaz *et al.* 1999). Furthermore, the formation of inclusion complexes can contribute to improvements in physical and chemical stability (protection against evaporation, oxidation, heat, light, *etc*.) and in odour and taste masking. Via complexation with cyclodextrins, liquids can be transformed into a crystalline form suitable for tabletting, or incompatible compounds can be mixed and used together. β-Cyclodextrins are applied as binders in tablets, while highly-swelling cyclodextrin polymers are effective tablet disintegrants.

The possible application of starch as a ***polymeric carrier for drug immobilization*** has been reported (Jantas *et al.* 2007). Starch-salicylic acid adducts were synthetized via the covalent coupling of the bioactive compound to the reactive hydroxy groups of starch. A gradual release of the bioactive agent was achieved via hydrolytic or enzymatic cleavage of the covalent bonds.

Graft copolymerization has become a popular method in natural polymer processing in order to eliminate or diminish unfavourable characteristics and improve processability (Bravo-Osuna *et al.* 2005). Starch-acrylic acid graft copolymers have been synthetized to enhance the bioadhesion capacity of native maize, rice and potato starches via ^{60}Co irradiation. The grafted polymers have been successfully utilized as bioadhesive drug carriers for systemic delivery in tablet formulations developed for the buccal application of testosterone and theophylline (Ameye *et al.* 2002; Geresh *et al.* 2004).

A ***new generation of graft copolymers*** contain semi-synthetic starch derivatives**,** such as hydroxypropyl (Perfectamyl®) and carboxymethyl derivatives (Quicksolan®) of potato starch, and synthetic polymers (methyl methacrylate and hydroxypropyl methacrylate) (Bravo-Osuna *et al.* 2005). These grafted copolymers, produced by the Ce(IV) redox initiation method, have been introduced as direct compaction excipients for oral controlled-release matrixes (Goni *et al.* 2002). Substitution with an acrylic component modifies the particle characteristics of native starch, such as particle size and morphology, micromeritics, flow properties and compressibility, and decreases the hygroscopicity.

CONCLUDING REMARKS

Potato starch is a renewable and biodegradable resource which can be modified in order to obtain products with specific properties. The tremendous diversity of potato starch modifications and their functional properties have extended the range of starch application considerably in recent decades. Besides the traditional auxiliary materials, potato starch derivatives and copolymers are finding increasing utilization in drug formulation and pharmaceutical product design. The literature reveals that extensive research activity is continuing in this field. Novel studies are focusing on starch application for specific formulations such as degradable microspheres, once-daily preparations, pulmonary and trans-nasal mucoadhesive dosage forms and colon drug delivery systems. Promising results have been reported on the biological (*e.g*. anti-viral) activity of chemically modified starches, and further progress is expected in the field of

controlled drug delivery, achieved by coupling starch polymers with bioactive compounds.

REFERENCES

Aigner Z, Dombi G, Kata M (1996) Increasing solubility characteristics of D-norgestrel with cyclodextrins. *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **25**, 145-148

Ameye D, Voorspoels J, Foreman P, Tsai J, Richardson P, Geresh S, Remon JP (2002) *Ex vivo* bioadhesion and *in vivo* testosterone bioavailability study of different bioadhesive formulations based on starch-g-poly(acrylic acid) copolymers and starch/poly(acrylic acid) mixtures. *Journal of Controlled Release* **79**, 173-182

Amin Kreaz RM, Abu-Eida EY, Erős I, Kata M (1999) Freeze-dried complexes of furosemide with β-cyclodextrin derivatives. *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **34**, 39-48

Andreev PV (2004) Using modified starch in Russian pharmaceutical industry. *Pharmaceutical Chemistry Journal* **38**, 447-450

Bao J, Xing J, Phillips DL, Corke H (2003) Physical properties of octenyl succinic anhydride modified rice, wheat and potato starches. *Journal of Agricultural and Food Chemistry* **51**, 2283-2287

Baydoun L, Furrer P, Gurny R, Müller-Goymann CC (2004) New surface-active polymers for ophthalmic formulations: evaluation of ocular tolerance. *European Journal of Pharmaceutics and Biopharmaceutics* **58**, 169-175

Belyaev EY (2000) New medical materials based on modified polysaccharides. *Pharmaceutical Chemistry Journal* **34**, 607-612

BeMiller JN (1997) Starch modification: Challenges and prospects. *Starch/Stärke* **49**, 127-131

Bharadwaj TR, Kanwar M, Lal R, Gupta A (2000) Natural gums and modified natural gums as sustained-release carriers. *Pharmaceutical Development and Industrial Pharmacy* **26**, 1025-1038

Biliaderis CG, Maurice TJ, Vose JR (1980) Starch gelatinization phenomena studied by differential scanning calorimetry. *Journal of Food Science* **45**, 1669-1674

Blaszczak W, Valverde S, Fornal J (2005) Effect of high pressure on the structure of potato starch. *Carbohydrate Polymers* **59**, 377-383

Bolhuis GK, Amstrong A (2006) Excipients for direct compaction – an update. *Pharmaceutical Development and Technology* **11**, 111-124

Bravo-Osuna I, Ferrero C, Jimenez-Castellanos RM (2005) Water sorption-desorption behaviour of methyl methacrylate-starch copolymers: effect of hydrophobic graft and drying method. *European Journal of Pharmaceutics and Biopharmaceutics* **59**, 537-548

Buléon A, Colonna P, Planchot V, Ball S (1998) Starch granules: structure and biosynthesis. *International Journal of Biological Macromolecules* **23**, 85-112

Burns SJ, Corness D, Hay G, Higginbottom S, Whelan I, Attwood D, Barnwell SG (1996) An in vitro assessment of liquid-filled Capill® potato starch capsules with biphasic release characteristics. *International Journal of Pharmaceutics* **134**, 223-230

Challa R, Ahuja A, Ali j, Khar RK (2005) Cyclodextrins in drug delivery: An updated review. *AAPS PharmSciTech* **6**, Article 43

Caramella C, Colombo P, Bettinetti G, Giordano F, Conte U, Manna AL (1984) Swelling properties of disintegrants. *Acta Pharmacologica et Technologica* **30**, 132-139

Chowdary KPR, Rao S (2000) Investigation of dissolution enhancement of itraconazole by solid dispersion in superdisintegrants. *Drug Development and Industrial Pharmacy* **26**, 1207-1211

Corveleyn S, Remon JP (1998) Formulation of lyophilized dry emulsion tablet for the delivery of poorly soluble drugs. *International Journal of Pharmaceutics* **166**, 65-74

Cotrell JE, Duffus CM, Paterson L, Mackay GR (1995) Properties of potato starch: effects of genotype and growing conditions. *Phytochemistry* **40**, 1057-1064

Cui D, Liu M, Liang R, Bi Y (2007) Synthesis and optimization of the reaction conditions of starch sulfates in aqueous solution. *Starch/Stärke* **59**, 91-98

de Brabander C, Vervaet C, Fiermans L, Remon JP (2000) Matrix mini-tablets based on starch/microcrystalline wax mixtures. *International Journal of Pharmaceutics* **199**, 195-203

Genta MT, Villa C, Mariani E, Loupy A, Petit A, Rizetto R, Mascarotti A, Morini F, Ferro M (2002) Microwave-assisted preparation of cyclic ketals from a cineole ketone as potential cosmetic ingredients: solvent-free synthesis, odour evaluation, *in vitro* cytotoxicity and antimicrobial assays. *International Journal of Pharmaceutics* **231**, 11-20

Geresh S, Gdalevsky GY, Gilboa I, Voorspoels J, Remon JP, Kost J (2004) Bioadhesive grafted starch copolymers as platforms for peroral drug delivery: a study of theophylline release. *Journal of Controlled Release* **94**, 391-399

Goni I, Ferrero MC, Jimenez-Castellanos RM, Gurruchaga M (2002) Synthesis of hydroxypropyl methacrylate/polysaccharide graft copolymers as matrices for controlled release tablets. *Drug Development and Industrial Pharmacy* **28**, 1101-1115

Gonnissen Y, Remon JP, Vervaet C (2008) Effect of maltodextrin and superdisintegrant in directly compressible powder mixtures prepared via co-spry drying. *European Journal of Pharmaceutics and Biopharmaceutics* **68**, 277-282

Guyot-Herman AM, Guyot JC, Ringard J (1983) Carboxymethylstarches in wet granulation. *Pharmaceutical Development and Industrial Pharmacy* **9**, 159-177

Hendrickx MEG, Knorr D (2003) *Ultra High Pressure Treatments of Foods*, Kluwer Academic/Plenum Publishers, New York, pp 1-210

Herman J, Remon JP, de Vilder J (1989a) Modified starches as hydrophilic matrices for controlled oral delivery. I. Production and characterisation of thermally modified starches. *International Journal of Pharmaceutics* **56**, 51-63

Herman J, Remon JP (1989b) Modified starches as hydrophilic matrices for controlled oral delivery. II. *In vitro* drug release evaluation of thermally modified starches. *International Journal of Pharmaceutics* **56**, 65-70

Hibi Y, Matsumoto T, Hagiwara S (1993) Effect of high pressure on the crystalline structure of various starch granules. *Cereal Chemistry* **70**, 671-676

Hódi K, Révész P, Miseta M (1992) Measurement of the swelling pressure and its significance in producing tablets. *Gyógyszerészet* **36**, 623-627

Hulse JD, Yacobi A (1983) Hetastarch: an overview of the colloid and its metabolism. *Drug Intelligence and Clinical Pharmacy* **17**, 334-341

Illum L, Fisher AN, Jabbal-Gill I, Davis SS (2001) Bioadhesive starch microspheres and absorption enhancing agents act synergistically to enhance the nasal absorption of polypeptides. *International Journal of Pharmaceutics* **222**, 109-119

Ingram JT, Lowenthal W (1966) Mechanism of action of starch as a tablet disintegrant I. factors that affect the swelling of starch grains at 37º. *International Journal of Pharmaceutics* **55**, 614-617

Jantas R, Draczynski Z, Stawski D (2007) Starch functionalized by chloroacetate group coupling of bioactive salicylic acid. *Starch/Stärke* **59**, 366-370

Jenkins PJ, Donald AM (1995) The influence of amylose on starch granule structure. *International Journal of Biological Macromolecules* **17**, 315-321

Jiang G, Qiu W, DeLuca PP (2003) Preparation and in vitro/in vivo evaluation of insulin-loaded Poly(Acryloyl Hydroxyethyl Starch) – PLGA composite microspheres. *Pharmaceutical Research* **20**, 452-459

Jobling S (2004) Improving starch for food and industrial applications. *Current Opinion in Plant Biology* **7**, 210-218

Joshi HN, Kral MA, Topp EM (1989) Microwave drying of aqueous tablet film coatings: a study on free films. *International Journal of Pharmaceutics* **51**, 19-25

Karhu D, El-Jammal A, Dupain T, Gaulin D, Bouchard S (2007) Pharmacokinetics and dose proportionality of three Tramadol Contramid® OAD tablet strengths. *Biopharmaceutics and Drug Disposition* **28**, 323-330

Katopo H, Song Y, Jane J (2002) Effect and mechanism of ultrahigh hydrostatic pressure on the structure and properties of starches. *Carbohydrate Polymers* **47**, 233-244

Kelen Á, Ress S, Nagy T, Pallai E, Pintye-Hódi K (2006) Mapping of temperature distribution in pharmaceutical microwave vacuum drying. *Powder Technology* **162**, 133-137

Knorr D, Heinz V, Buckow R (2006) High pressure application for food biopolymers. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **1764**, 619-631

Korhonen O, Raatikainen P, Harjunen P, Nakri J, Suihko E, Peltonen S, Vidgren M, Paronen P (2000) Starch acetates – multifunctional direct compression excipients. *Pharmaceutical Research* **17**, 1138-1143

Kuentz M, Egloff P, Röthlisberger D (2006) A technical feasibility study of surfactant-free drug suspensions using octenyl succinate-modified starches. *European Journal of Pharmaceutics and Biopharmaceutics* **63**, 37-43

List PH, Muazzam UA (1979) Quellung – die treibende Kraft beim Tablettenzerfall. *Pharmazeutische Industrie* **41**, 459-464

Liu X, Heng WS, Li PQ, Chan LW (2006) Novel polymeric microspheres containing norcantharidin for chemoembolization. *Journal of Controlled Release* **116**, 35-41

Lowenthal W (1973) Mechanism of action of tablet disintegrants. *Pharmaceutica Acta Helvetiae* **48**, 589-609

Manelius R, Nurmi K, Bertoft E (2005) Characterization of dextrins obtained by enzymatic treatment of cationic potato starch. *Starch/Stärke* **57**, 291-300

Mao S, Chen J, Wei Z, Liu H, Bi D (2004) Intranasal administration of melatonin starch microspheres. *International Journal of Pharmaceutics* **272**, 37-43

McMinn WAM, McLoughlin CM, Magee TRA (2005) Microwave-convective drying characteristics of pharmaceutical powders. *Powder Technology* **153**, 23-33

Miles MJ, Morris VJ, Oxford PD, Ring SG (1985) The roles of amylose and amylopectin in the gelation and retrogradation of starch. *Carbohydrate Research* **135**, 271-281

Morise Z, Sugioka A, Kato R, Fujita J, Hoshimoto S, Kato T (2006) Transarterial chemoembolization with degradable starch microspheres, irinotecan, and mitomycin-C in patients with liver metastases. *Journal of Gastrointestinal Surgery* **10**, 249-258

Papadimitriou SA, Bikiaris D, Avgoustakis K (2008) Microwave-induced enhancement of the dissolution rate of poorly water-soluble tibolone from poly (ethylene glycol) solid dispersions. *Journal of Applied Polymer Science* **108**, 1249-1258

Patel NR, Hopponen RE (1966) Mechanism of action of starch as a disintegrating agent in aspirin tablets. *Journal of Pharmaceutical Sciences* **55**, 1065-

1068

Rahmouni M, Chouinard F, Nekka F, Lenaerts V, Leroux J-C (2001) Enzymatic degradation of cross-linked high amylase starch tablets and its effect on *in vitro* release of sodium diclofenac. *European Journal of Pharmaceutics and Biopharmaceutics* **51**, 191-198

Rahmouni M, Lenaerts V, Massuelle D, Doelker E, Leroux J-C (2002) Influence of physical parameters and lubricants on the compaction properties of granulated and non-granulated cross-linked high amylase starch. *Chemical and Pharmaceutical Bulletin* **50**, 1155-1162

Rowe RC, Sheskey PJ, Weller PJ (2003) *Handbook of Pharmaceutical Excipients* (4th Edn), Pharmaceutical Press and American Pharmaceutical Association, pp 603-608

Rudnic EM, Rhodes CT, Welch S, Bernardo P (1982) Evaluation of the mechanism of disintegrant action. *Drug Development and Industrial Pharmacy* **8**, 87-109

Sanghvi PP, Collins CC, Shukla AJ (1993) Evaluation of Preflo® modified starches as new direct compression excipients. I. Tabletting characteristic. *Pharmaceutical Research* **10**, 1597-4603

Selek H, Sahin S, Suheyla Kas H, Hincal A, Ponchel G, Ercan MT, Sargon M (2007) Formulation and characterization of formaldehyde cross-linked degradable starch microspheres containing terbutaline sulfate. *Pharmaceutical Development and Industrial Pharmacy* **33**, 147-154

Sintzel MB, Schwach-Abdellaoui K, Mäder K, Stösser R, Heller J, Tabatabay C, Gurny R (1998) Influence of irradiation sterilization on a semisolid poly(ortho ester) *International Journal of Pharmaceutics* **175**, 165-176

Sourbaji M, Pintye-Hódi K, Novák Cs, Szabó-Révész P, Kása Jr. P, Erős I (2000) A study of sulfadimindin-β-cyclodextrin mixtures. *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **37**, 299-307

Steendam R, Frijlink HW, Lerk CF (2001) Plasticisation of amylodextrin by moisture. Consequences for compaction behaviour and tablet properties. *European Journal of Pharmaceutics Sciences* **14**, 245-254

Stepto RFT (1997) Thermoplastic starch and drug delivery capsules. *Polymer International* **43**, 155-158

Stepto RFT (2006) Understanding the processing of thermoplastic starch. *Macromolecular Symposia* **245-246**, 571-577

Stute R, Klingler RW, Boguslawski S, Eshtiaghi MN, Knorr D (1996) Effects of high pressure treatment on starches. *Starch/Stärke* **48**, 399-408

Swarbrick J, Boylan JC (2002) *Encyclopedia of Pharmaceutical Technology* (Vol 2), Marcel Dekker, New York, pp 223-248, 2574-2581

Szabó-Révész P, Pető K, Pintye-Hódi K (1986) Untersuchung der Verwandbarkeit von mikrokristallinen Cellulosen bei der Herstellung von Phenobarbital-Tabletten. *Pharmazeutische Industrie* **48**, 289-291

Szepes A, Hasznos-Nezdei M, Kovács J, Funke Z, Ulrich J, Szabó-Révész P (2005) Microwave processing of natural biopolymers – studies on the properties of different starches. *International Journal of Pharmaceutics* **302**, 166-171

Szepes A, Fehér A, Erős I, Szabó-Révész P (2007a) Determination of the gelatinization temperature of starches via thermoanalytical and rheological methods. *Acta Pharmaceutica Hungarica* **77**, 90-96

Szepes A, Ulrich J, Farkas Zs, Kovács J, Szabó-Révész P (2007b) Freeze-casting technique in the development of solid drug delivery systems. *Chemical Engineering and Processing* **46**, 230-238

Szepes A, Fehér A, Szabó-Révész P, Ulrich J (2007c) Influence of freezing temperature on product parameters of solid dosage forms prepared via the freeze-casting technique. *Chemical Engineering and Technology* **30**, 1-7

Szepes A, Mohnicke M, Szabó-Révész P (2007d) Water sorption behavior and swelling characteristics of starches subjected to dielectric heating. *Pharmaceutical Development and Technology* **12**, 555-561

Szepes A, Makai Zs, Blümer C, Mäder K, Kása Jr. P, Szabó-Révész P (2008) Characterization and drug delivery behaviour of starch-based hydrogels prepared via isostatic ultrahigh pressure. *Carbohydrate Polymers* **72**, 571-578

Talja RA, Peura M, Serimaa R, Jouppila K (2008) Effect of amylose content on physical and mechanical properties of potato-starch-based edible films. *Biomacromolecules* **9**, 658-663

Taneri F, Güneri T, Aigner Z, Kata M (2002) Improvement in the physicochemical properties of ketoconazole through complexation with cyclodextrin derivatives. *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **44**, 257-260

Tarvainen R, Sutinen R, Peltonen S, Tiihonen P, Paronen P (2002) Starch acetate – A novel film-forming polymer for pharmaceutical coatings. *Journal of Pharmaceutical Sciences* **91**, 282-289

Tarvainen R, Sutinen R, Peltonen S, Mikkonen H, Maunus J, Väha-Heikkilä K, Lehto V-P, Paronen P (2003) Enhanced film-forming properties for ethyl cellulose and starch acetate using *n*-alkenyl succinic anhydrides as novel plasticizers. *European Journal of Pharmaceutics Sciences* **19**, 363-371

Te Wierik GHP, Eissens AC, Bergsma J, Arends-Scholte AW, Lerk CF (1997a) A new generation starch product as excipient in pharmaceutical tablets II. High surface area retrograded pregelatinized potato starch products in sustained-release tablets. *Journal of Controlled Release* **45**, 25-33

Te Wierik GHP, Eissens AC, Bergsma J, Arends-Scholte AW, Bolhuis GK (1997b) A new generation starch product as excipient in pharmaceutical tablets III. Parameters affecting controlled drug release from tablets based on high surface area retrograded pregelatinized potato starch. *International Journal of Pharmaceutics* **157**, 181-187

Tomasik P, Zaranyika M (1995) Nonconventional methods of modification of starch. *Advances in Carbohydrate Chemistry and Biochemistry* **51**, 243-320

Tuovinen L, Peltonen S, Järvinen K (2003) Drug release from starch-acetate films. *Journal of Controlled Release* **91**, 345-354

Vermeire A, Kiekens F, Corveleyn S, Remon JP (1999) Evaluation of the emulsifying properties of some cationic starches. *Drug Development and Industrial Pharmacy* **25**, 367-371

Waigh TA, Donald AM, Heidelbach F, Riekel C, Gidley MJ (1999) The phase transformations in starch during gelatinisation: a liquid crystalline approach. *Biopolymers* **49**, 91-105

Walther N, Ulrich J (2005) Freeze casting or cold pressing – an alternative technology to form tablets. *16th International Symposium on Industrial Crystallization*, ISIC Dresden, *VDI-Berichte* **1901/1**, 343-348

Woo BH, Jiang G, Jo YW, DeLuca PP (2001) Preparation and characterization of a composite PLGA and Poly(Acryloyl Hydroxyethyl Starch) microsphere system for protein delivery. *Pharmaceutical Research* **18**, 1600-1606

York P (1980) Studies of the effect of powder moisture content on drug release from hard gelatin capsules. *Drug Development and Industrial Pharmacy* **6**, 605-627

Young PM, Edge S, Staniforth JN, Fraser Steele D, Price R (2005) Dynamic vapour sorption properties of sodium starch glycolate disintegrants. *Pharmaceutical Development and Technology* **10**, 249-259

Young PM, Edge S, Staniforth JN, Fraser Steele D, Traini D, Price R (2007) Effect of moisture on the compressibility and compactibility of sodium starch glycolate. *Pharmaceutical Development and Technology* **12**, 217-222