Starch based excipients for pharmaceutical tablets

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In today's pharmaceutical industry, excipients must have more functional properties than being just inert filler. Excipients are now essential parts of the drug delivery system in pharmaceutical tablets. They are generally used as diluent, binder, disintegrant, gliding agent, lubricant or release control agent. At a time when synthetic polymers and animal-based products are creating some concerns amongst the users, the need for natural excipients that are safe and versatile becomes more acute.

Starch is one of the most traditional excipients used for solid dosage formulations. Depending on the application, maize starch acts as a diluent, disintegrant or binder. Native starch is a classic tablet disintegrant whereas pregelatinised starch is often used as a binder. Starch also offers a wide range of possibilities and can be one of the preferred functional excipients of the future. It can undergo a wide range of physical or chemical modification in order to modify its properties (Table I).

The specific advantages brought by special starches can be better illustrated by three examples.

DIRECTLY COMPRESSIBLE STARCH

Tablets containing regular maize starch easily allow water to penetrate into the tablet, softening it for fast disintegration. Pregelatinised or cold water soluble starches act as strong binders resulting in stronger, but also slower, disintegrating tablets.

Both starches can be used in wet granulation and direct compression processes, although granulation is frequently favored, due to their poor compressibility (1).

The way starch acts in a tablet formulation is related to different starch characteristics. Among these parameters, the crystalline structure or crystallinity of the starch plays an important role. Native starch has a crystallinity of approximately 45%. By gelatinisation of the starch the crystal structure is melted, resulting in a crystallinity of barely 5% (2). Maize starch with an increased amorphous structure will have a larger tendency to solubilise, i.e. reduced tablet disintegration, and the higher its binding strength, the stronger tablets will be.

Figure 1 - Scanning electron microscope picture of C☆Pharm DC 93000

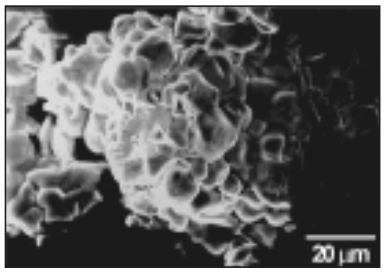
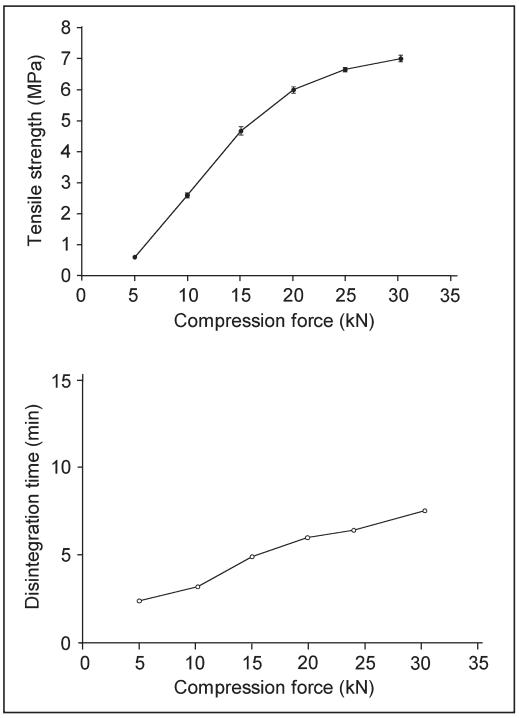


Table I

Chemical modification	Physical modification
- Oxidation	- Extrusion
- Substitution	- Roll drying
- Cross-bonding	- Spray drying
	- Granulation / agglomeration
Advantages:	**Advantages:**
- New functionality	- Versatility
- Innovation	- Existing monographs

Figure 2 - Compression profile of C☆Pharm 93000



A direct compressible starch that has to be both a binder and a disintegrant, therefore needs to possess the correct ratio of both a crystalline to amorphous structure.

As direct compression is a shorter, less complex and also cheaper production process, the interest to provide a starch which is suitable for direct compression is high (3). C☆Pharm DC 93000 combines the two main properties of both pregelatinised and native starch: strong binding and fast disintegration (4). This new directly compressible starch appears as a white free-flowing powder composed of partly gelatinised agglomerated starch granules (Figure 1).

When evaluated in a standard formulation with 0.25% silicon dioxide and 0.5% magnesium stearate, this starch shows outstanding performances compared to those of native and pregelatinised starch and also compared to those of standard compressible starches. The properties of the tablets produced at different compression forces show a very high resistance to crushing at the same time as a very fast disintegration in water (Figure 2).

One of the other very interesting properties of directly compressible starch is its aptitude to demonstrate synergies with other excipients such as lactose and micro-crystalline cellulose. These two products are certainly some of the most widely used excipients in pharmaceutical formulations besides starch (5).

Partly-pregelatinised starch and MCC will deform chiefly plastically whereas lactose will fragmentise (6). Both kinds of deformation will aid tablet formation and will increase the tablet hardness. The synergy becomes more visible when disintegration time of a ternary blend is investigated (Figure 3). Tablets that are made with both lactose and MCC keep very high disintegration times. Only when C☆Pharm DC 93000 is added to either lactose or MCC or for mixtures containing all three excipients, a lower disintegration time is obtained.

The fastest disintegration time is achieved when the formulation contains 35% to 70% directly compressible starch (7).

Figure 3 - The influence of the composition of the mixture on the disintegration time.
Tablets made with a compression force of 25 kN.
Type of fit: Special cubic smoothing ($R^2 = 0.8502$)

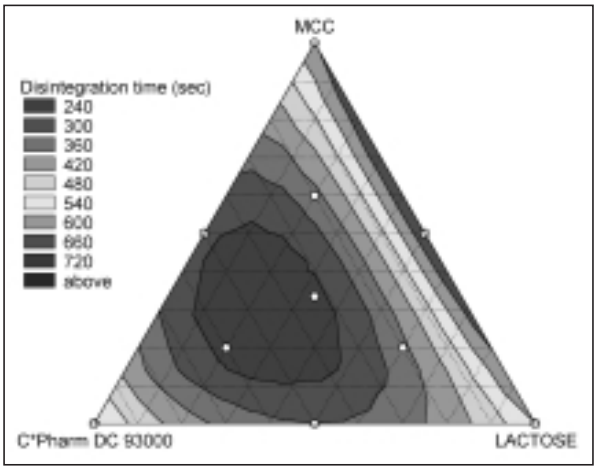
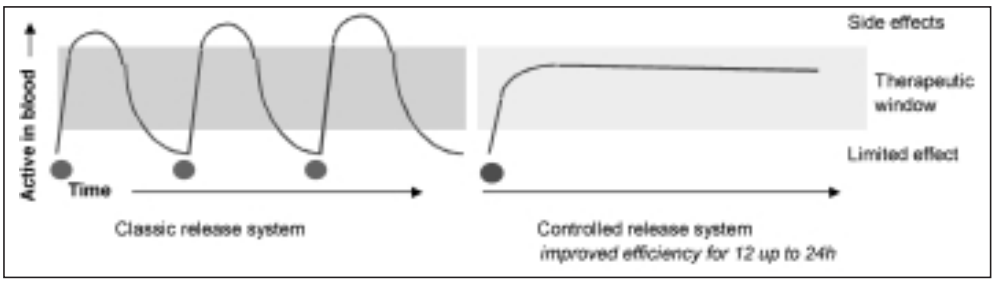


Figure 4 - Classic release versus controlled release



SLOW-RELEASE TABLETS

The immediate and fast delivery of an active ingredient is not always recommended. Delayed or prolonged release may be more effective or better tolerated in, for instance, the case of permanent treatment or when high peak dosage could have an adverse effect (Figure 4).

There are several systems known to do this but they are complex and rather expensive (8). This is the case with osmotic systems where the release is governed by the permeability of the drug through a porous membrane. Ion exchange systems are also used when ionic active is embedded in a matrix capable of exchanging ions. Another solution is multi-layer coating the tablets. In this case, the delivery of an active ingredient is delayed by the respective dissolution time of the different layers.

A more recent development involves the encapsulation of an active ingredient in a modified starch matrix like a modified pregelatinised high amylose maize starch (9). In the case of Contramid® (10) a cross-linked amorphous high amylose starch forms a strong gelly/rubbery layer at the surface of the tablet on contact with water or gastric juice. This layer acts as an osmotic membrane that does not allow enzymes to penetrate and thus prevents the amylose network from being disrupted. At the same time the active ingredient can slowly diffuse through (Figure 5).

This product is being launched on the market and is likely to help in the design of many slow-release formulations.

Figure 5 - Drug release properties.
Dissolution profile of standard tablets of Contramid 92450 with 5% diclofenac Na as a model drug

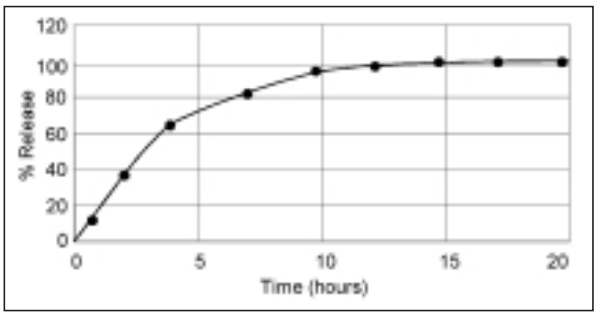
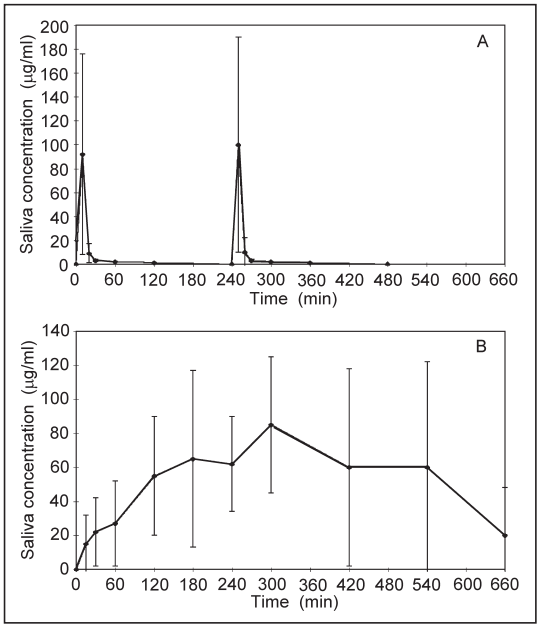


Figure 6 – Concentrations of salivary miconazole after administration of oral gel and of bio-adhesive tablet. Mean (SD; n=15) salivary miconazole concentrations after
A) repeated applications of 60 mg miconazole nitrate as Daktarin gel;
B) administration of 10 mg miconazole nitrate as bio-adhesive tablet



BIO-ADHESIVE TABLETS

Buccal gels containing miconazole nitrate are usually used for the treatment of conditions such as oral candidiasis. They must be applied several times a day. In order to increase the buccal residence time of miconazole, a bioadhesive buccal tablet with slow-release properties can be applied (11). The main advantages of this delivery system are a reduction in the frequency and amount of drug administered, which might improve patient compliance.

The bio-adhesive tablet formulation contained pregelatinised waxy maize starch. The salivary miconazole nitrate concentrations after administration of the bio-adhesive tablet and of oral gels were compared (Figure 6).

Although the amount of drug administered via the bio-adhesive tablet was six fold lower than when the gel was used, the salivary miconazole levels were higher and remained above the MIC value of *Candida albicans* for more than 10 hrs. The mean adhesive time of the tablet was 586 min. The gingiva seemed to be the best site for application of the buccal bioadhesive system (12).

CONCLUSION

Starch and modified starches are safe and well established excipients. It can be physically modified to enhance its properties and to improve its performances. It can also be chemically modified to obtain a very wide range of new properties that can play an important role in the formulation of complex delivery systems. Additional example (13) of such systems could be given as magnetic starch micro-spheres or starch based micro-capsules.

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