

# Pharmaceutical applications of sucrose

## or

### “Does a spoonful of sugar really help the medicine go down?”

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#### *Abstract*

The unique, multi-functional properties of sugar find many applications in the pharmaceutical sector. Sugar is combined with other ingredients to provide palatable dosage forms of many drugs, thus aiding compliance. The techniques to produce the dosage forms (e.g. medicated confectionery and tablets) are similar to those employed in the confectionery industry. Sugar companies have developed specific sugar-based products (Directly Compressible (DC) sugars and sugar spheres) to meet the needs of the pharmaceutical formulator. Pharmacopoeial monographs specify the analytical parameters for sugars that can be used in pharmaceutical applications.

#### *Introduction*

The anecdotes “a spoonful of sugar helps the medicine go down” and “sugaring the pill” refer to the sweetening property of sugar and its ability to help the palatability of pharmaceutical preparations.

In addition to sweetness, sugar also provides desirable functional properties. The low toxicity, high purity and diverse physicochemical properties of sugar account for its popularity in pharmaceutical applications.

Sugar and other ingredients used in

the food industry (e.g. starches, bulk sweeteners, thickeners, flavours etc) are used in the pharmaceutical and nutraceutical (functional foods) industries as excipients in dosage forms. Typical dosage forms include syrups, suspensions, capsules, tablets and creams. The dosage form acts as a vehicle by which the active ingredient is introduced to the body, and almost invariably contains excipients in addition to the active ingredient.

A medicine should be safe and efficacious, and the primary function of formulation is to ensure that the active ingredient is delivered to its site of action at an appropriate concentration. An important aspect of this is to ensure patient compliance i.e. the medicine is taken as prescribed. For example many drugs have a bitter taste, so taste masking is an important aid to compliance. Sugar provides the sweetness required for the taste-masking role and thus ensures patient compliance. In addition to the sweetness sucrose performs many functions in a range of products in the pharmaceutical sector. These are summarised in Table 1 and reviewed in more detail below

In the past, excipients were thought of as ‘inert’, but this has now been shown not to be the case. Improper formulation using inappropriate excipients can seriously compromise or even inhibit drug activity. More recent-

ly the excipients have been found to perform other functions in addition to the traditional ones described above (e.g. taste masking, diluent). The correct formulation of excipient and active can provide accurate delivery of the required dose with a reduction of side effects and targeted/controlled release to the site of therapeutic need. The development of particular sugar based products meeting these specific requirements (e.g. sugar spheres) has expanded the application of sugar products in the pharmaceutical sector.

The volumes of sugar used in the pharmaceutical sector are not great when compared to the other, routinely used binders and fillers like cellulose, polyols, starches and lactose (Rogers, 1999). Sugar does have some unique and desirable properties e.g. sweetness, preservative properties, which are hard to replicate with other products (cf. the food sector) and thus there will always be opportunities for sugar-based products in this sector.

#### *Dosage forms*

##### *Medicated Confectionery*

Medicated confectionery is an area where confectionery crosses over into the pharmaceutical sector. The production techniques employed are essentially the same in both applications (e.g. high boiling of carbohydrate mixtures to produce stable glasses) (Cummings, 1995). In medicated confectionery the main objective is to produce pleasant tasting confectionery that delivers specific actives targeted at alleviation of symptoms. Products are typically high boil sweets, but could also be lozenges and more recently liquid filled high boils. The key targets are the symptoms associated with coughs and colds: - blocked nose, sore throat, congestion etc. The flavours associated with these products are usually those associated with cold remedies e.g. honey and lemon, blackcurrant etc. The main actives typically employed are menthol and oil of eucalyptus to provide the desired therapeutic action. Due to their volatile nature these ingredients are usually added at the end of processing to

**Table 1.** Functionality of Sugar Ingredients in Pharmaceutical Dosage Forms

Pharmaceutical Dosage forms	Sugar Products	Desired functionality
Medicated Confectionery	Liquid sugars, granulated sugars, invert syrups, (glucose syrups)	Glass forming, diluent, controlled dissolving, stability, sweetness, taste masking
Blended Powders e.g. cold and flu remedies	Powdered sugars, screened sugars	Diluent, rapid dissolving, complementary particle size, sweetness, taste masking
Syrups, Elixirs	Liquid sugars, Inverts	Diluent, Sweetness, preservative, demulcent, wetting agent, prevention of crystallisation, viscosity (body, mouthfeel), taste masking
Suspensions	Liquid sugars, Inverts	Diluent, Sweetness, viscosity (body, mouthfeel), taste masking, demulcent, wetting agent, prevention of crystallisation, suspending agent
Tablets, Lozenges	Liquid sugars, powdered sugars, Directly compressible sugars	Compressibility (tablet forming), binder, diluent, dissolution, texture, coating, protection, sweetness, taste masking
Capsules	Sugar spheres	Diluent, Uniformity, ability to coat, controlled dissolving, stability

ensure the requisite amount is present in the final product. These actives can be declared as flavours, however, if a therapeutic action or relief of symptoms are claimed the products must be licensed with the relevant authority (Medicines Control Agency (MCA) in the UK; Food and Drug Administration (FDA) in the United States).

#### *Blended powders*

Blended powders are dry mixes which contain actives e.g. paracetamol, phenylephedrine and vitamins which are self-administered to alleviate the symptoms of colds and flu. Sucrose typically powdered or milled sugars, with other flavours and sweeteners, are added to provide a pleasant tasting remedy. In these applications the sugar provides a taste-masking role to hide the bitterness of the actives (paracetamol and phenylephedrine) and improve the dispersability and resultant solubility of the ingredients.

#### *Liquid Products (Syrups, Elixirs, Suspensions)*

Sugar has been used to sweeten liquid medicines and make them more palatable and thus aid and ensure compliance. Sugar is used because of its multifunctional properties (see Table 1). In these applications sweetness is important and sucrose is considered to be

more acceptable than some artificial sweeteners that have a bitter after taste that can affect patient compliance (anon, 1996). Sucrose also controls Ostwald Ripening and thus prevents the crystallisation of actives in suspension. Paracetamol suspensions are particularly prone to this (Sugden and Jolliffe, 1994). Use of artificial sweeteners and polyols is increasing due to concerns about 'medication caries' particularly in the treatment of chronically sick children. These products are usually launched as line extensions rather than direct replacements and the sugar variants are seen as the 'gold standard' for taste and functionality against which the sugar-free alternatives have to compete (Sugden and Jolliffe, 1994).

#### *Tablets (DC, coatings etc)*

The techniques used in the pharmaceutical industry to make tablets and lozenges are essentially the same as those used in the confectionery industry (Beacham, 1995).

The processes used to make tablets rely on a combination of different physical processes (mixing, drying, granulation etc) to integrate several ingredients to provide the desired physical properties of the tablet. Outlines of two processes – wet granulation and direct compression are provided in Figure 1.

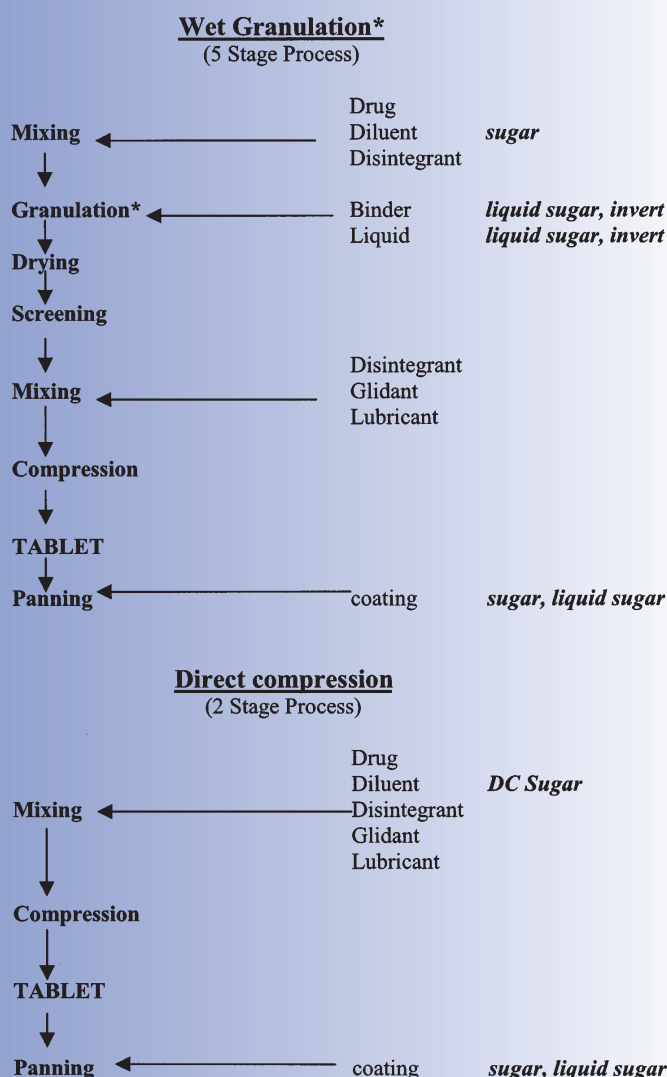
Sugar and sugar based products e.g. liquid sugar and inverts can be used to provide different functions in the tableting process (Figure 1.).

Many potent drugs have doses of only a few milligrams or less. Since tablets weighing less than 50mg are difficult for patients to handle, tablets containing potent actives need a suitable diluent to make up the bulk. Lubricants and glidants are added to improve the tableting efficiency e.g. lubricant, typically magnesium stearate is added to tableting mixtures to aid removal/ejection from the tableting die. Other ingredients are added to aid dispersion and dissolution of the tablet once it is inside the body eg. disintegrants; carboxymethyl cellulose is added to increase the rate at which a tablet breaks up on contact with water or other fluids (Shah *et al* 1981).

Granulated sugar alone does not tablet effectively so manufacturers use powdered sugars e.g. icing or confectioners grades in wet granulation processes (Figure 1.). Sugar companies around the world have developed a range of directly compressible (DC) sugars that can be used in the two-stage process outlined in Figure 1.

Compressible sugars contain not less than 95% and not more than 98% sugar. They may also contain starch, maltodextrin, glucose syrup or invert sugar and can contain a suitable lubricant (e.g. magnesium stearate) and

Figure 1. Tablet production processes



\* Granulation = formation of granules (not sugar granulation)

colours (United States Pharmacopoeia (USP) & British Pharmacopoeia (BP), see below).

Tablets and other solid dosage forms can be panned or spray coated to provide a uniform surface, protection to the main core and a pleasant tasting sugar coat. Once again confectionery techniques (Beacham, 1995) can be used to provide an attractive, functional finish to pharmaceutical dosage forms.

Recent developments in technology have been applied to provide viable delivery systems for people who may have difficulty in swallowing tablets or liquids. Several companies have designed fast dissolving tablets. These

are rapidly dissolved in the mouth in several seconds thus delivering the active into the oral cavity. In these instances taste masking becomes vital to achieve compliance. This type of delivery system has recently been reviewed (Bogner & Wilkosz, 2002). The Flashdose products from Fuisz Technologies are based on sugar which is melted/spun like candy floss to deliver a rapidly dissolving/compressible sugar which is formulated into oral delivery systems.

#### Capsules (sugar spheres)

The ability to deliver drug actives in a controlled manner is becoming a main

aim of the pharmaceutical industry. Precise delivery of an accurate dose to the designated target area in the body at the correct time is highly desirable. It reduces side effects, minimises drug overload and ensures effective 'cost in use' for expensive actives. Sugar spheres are solid dosage forms for sustained and controlled release pharmaceutical products. They have been developed in connection with hard gelatine capsules. The sugar spheres are defined particle sizes and are essentially spherical. They can be coated (sprayed) with drug actives at precise levels, they can then be further coated with materials that change the solubility of the sphere and thus provide control/delay of the release of the active from the matrix. Several different 'time-release' spheres can be combined to give a capsule that delivers the active(s) in a pre-determined manner with respect to time or conditions prevailing at the desired site of action.

Sugar spheres are produced by traditional panning/coating techniques found in the confectionery industry (Beacham, 1995). The sugar granules are coated in a mixture of sugar and starch to give a uniform sphere. The spheres are screened to give the required particle size range (defined ranges between 200µm and 2.0mm; e.g. 425 – 500µm). Sugar spheres contain not less than 62.5% and not more than 91.5% sucrose (USP/ National Formulary (NF)) (92% in European Pharmacopoeia (PhEur)) with the balance of the sphere being starch (usually maize starch).

#### Pharmacopoeial Specifications

Sugar and other food ingredients are used as excipients in pharmaceutical applications. Typically they are not produced under specific process conditions (unless they are for use in injectables or parenteral nutrition) they are however, subject to more detailed analytical requirements. These are detailed in the pharmacopoeial monographs. The main pharmacopoeias are in the United States (both USP and NF (National Formulary)), Europe (PhEur) and Japan (JP). In the United States excip-

**Table 2.** Pharmacopoeial Specifications for Sucrose  
(Adapted from Kibbe (2000))

Test	JP	PhEur*	USP
Identification	+	+	-
Characters	+	+	-
Appearance of solution	+	+	-
Acidity or Alkalinity	+	+/-]	-
Specific Optical Rotation	+66.3° to+67.0°	+66.3° to+67.0°	≤+65.9°
Conductivity	+	≤35μScm <sup>-1</sup>	-
Water	≤0.1%	≤0.1%	-
Endotoxins	≤0.25 IU/mg	≤0.25 IU/mg #	-
Colouring Matter	-	+/[≤45 ICUMSA units]	-
Dextrins	+	+#	-
Dextrose and Invert sugar	-	≤0.04%	-
Invert Sugar	+	-	+
Chloride	-	-	≤0.0035%
Sulphate	-	-	≤0.006%
Sulphites	+	≤15ppm/[≤10ppm]	-
Barium	-	-	-
Calcium	-	-	+
Heavy Metals	-	-	≤5ppm
Lead	≤0.5ppm	≤0.5ppm	-
Residue on ignition	-	-	≤0.05%
Sulphated Ash	-	-	-
Organic volatile impurities	-	-	+

Key: + required; - not required

# If intended for use in large-volume infusions

IU = International Units

\*PhEur European Pharmacopoeia 4th Edition 2002

[ ] Proposed changes to PhEur in Pharmeuropa Vol 13, 4 Oct 2001, 775 - 777

ients are usually covered in the National Formulary (NF) with actives compounds being in the USP, however most agencies refer to the USP/NF as one specification. In Europe most countries had separate national pharmacopoeias e.g. British Pharmacopoeia (BP). However most are now harmonising with PhEur.

Attempts to harmonise excipient standards on a global basis are now well advanced. The International Pharmaceutical Excipients Council (IPEC) has been set up and world-wide specifications for excipients and their test methods have been proposed. (Castle 2001 (2) & (3)).

The analytical specifications and test methods (including standards and reagents) for Sugar (Sucrose (JP, USP); Sucrose, Saccharum (PhEur)) are detailed in monographs in the pharmacopoeias; a comparison of the specific requirements is summarised in Table 2.

Included in the Table are the current PhEur details and proposed

amendments pending ratification (Pharmeuropa, 2001). Other sugar products that are routinely used in pharmaceutical applications, which have monographs in the pharmacopoeias, are compressible sugar (USP/NF, BP), Sugar Spheres (USP/NF, PhEur) and confectioners sugar (USP/NF). Conformance to pharmacopoeial specification is not essential for all pharmaceutical products, however; if a product is to be licensed the clearance procedures are simpler if all the components conform to the requisite pharmacopoeial specification. An alternative is for the manufacturer to prepare a drug master file that is held by the regulatory authorities and referred to by formulators in their clearance petition. (More details on Drug Master files can be obtained from the FDA website ([www.fda.gov](http://www.fda.gov))).

#### **Other uses of Sugar and sugar derivatives in pharmaceutical applications**

Sugar and other naturally occurring

carbohydrates (e.g. honey) have been reported in both folklore and medical journals for their wound healing properties. (Middleton and Seal, 1985; Thomas, 1990).

Sugar has been shown to possibly activate natural painkillers when given to newborn babies. Researchers found that newborn babies who were given sugar had a lower response to pain when they were subjected to routine blood tests. (Carbajal *et al*, 1999).

Another important role for sugar is in oral rehydration therapy to combat the effects of severe diarrhoea in patients suffering from cholera and other life threatening diseases in the developing world ([www.rehydrate.org](http://www.rehydrate.org)).

Sugar has also been applied to the treatment and cessation of prolonged hiccups (Engleman *et al*, 1971)

Sugar derivatives have been shown to have therapeutic action in some conditions. Sucralfate (aluminium salt of sucrose octasulphate) is used in treatment of peptic and stomach ulcers (Hough, 1972).

Platinum (bis and tris) complexes of sugar have demonstrated anti tumour activity. (Sachinvala *et al*, 1993).

Sugar esters have been used to improve the dissolution rate and thus the bioavailability of certain actives (Ntawukulilyayo *et al*, 1993) and also the stabilisation of suspensions and inhibition of crystal growth of actives (paracetamol) (Ntawukulilyayo *et al* 1996). Sucrose polyesters have also been used as contrast agents in magnetic resonance imaging (mri) (Ballinger *et al* 1991).

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