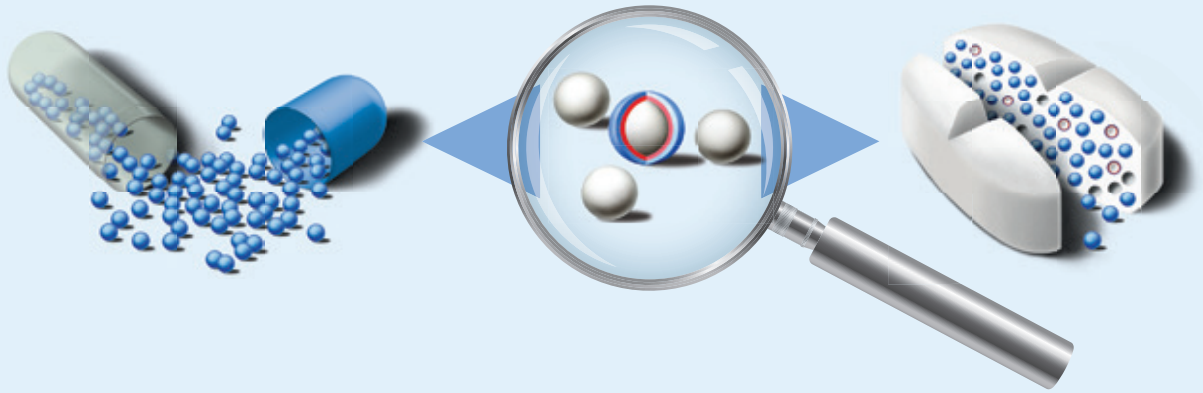
pharm-a-spheres®

Sugar spheres

Sugar spheres: a versatile excipient for oral pellet medications with modified release kinetics



Sugar spheres are a widely used excipient for sustained-release pellet formulations.[1] This paper reviews their development in the last decades, informs about the state of the art and provides the user with the necessary information for further processing. Finally, the article focuses on the possibilities of characterization related to the technological properties of the sugar spheres.

Pellets are a multiparticle, solid form of medication. The individual pellets are almost spherical with diameters usually between 100 and 2000 µm.

Their history is related to two important development trends in pharmaceutical technology: the hard gelatine capsule as an alternative to tablets, and biopharmacy and its concept of modified release.

The hard gelatine capsule provided a method of oral medication, which made it possible to put powders or granules directly in a patient-friendly form with specific dosage.[2] By mixing various components before filling the capsules or with sequential filling of the capsule with these components, it was possible to combine partial quantities that differ in appearance, are incompatible with each other, or have differing release behaviour, in one single dose. Pellets with their almost ideal spherical shape offer optimum mixing and flow behaviour, making them ideal for this application.

At the same time, since the 1950s, biopharmacy has developed concepts for optimum control of active pharmaceutical ingredient (API) release in the gastrointestinal tract, in terms of location and time.[3,4] In particular, the sustained release from a single application over a longer period of time (during the day) resulted in the development of mixtures whose individual components were given different quantities of a sustained release coating to ensure that the active substances are released accordingly at different points in time. Pellets with their reproducible, smooth surface were again the solution of choice.

These two developments together resulted in numerous pellet preparations. There were suitable pellet solutions for nearly all requirements, with a rapid increase in the market share of corresponding products. Formulas with pellets are still a modern form of medication, which offers an elegant solution even for new requirements.

Production technology

There are numerous procedures for pelletization, with two fundamentally competing concepts.[5] On the one hand, the use of sugar spheres, which are then coated with the active substance, and on the other, direct pelletization of active substance/excipient mixtures.

Figure 1 illustrates these two alternatives.

In the first option, sugar spheres (also called neutral pellets, nonpareil seeds, microgranules or sugar beads) are produced, preferably using a layered sugar-coating structure.[6] The result is sugar spheres with sufficient mechanical stability for further processing. The ideally rounded sugar spheres classed in closely graduated particle sizes are then coated with the active substance and sustained release additives. The core of the finished pellet contains no active substance itself so that this solution is used for low-dose substances or substances with a high effect/dose relation. But the use of small sugar spheres and corresponding procedures also makes it possible to use this method to produce pellets containing more than 75% active substance.

In the second concept, pelletization already includes the active substance itself. The procedures developed here consist of fluidized bed granulation, rotor granulation, or extrusion followed by spheronization, whereby the initially cylindrical particles are then rounded out in a second step.[7-9] The advantage of this procedure is that the whole pellet contains the active substance.

There are numerous applications for both alternatives on the market,

so it is still not possible to ascertain any clear preference of one over the other. Each solution offers its own pros and cons, depending on the specific product. The following points outline certain aspects where the two concepts differ, to make it easier for the user to decide which one to choose:

- The use of sugar spheres means that the drug producer can outsource pelletization to a specialist and concentrate on processing the API. This will produce sugar spheres as a spherical excipient of uniform size.
- The shaping process involved in pelletization entails thermal load and contact with a solvent (usually water). This can cause stability problems, depending on the susceptibility of the active substance.
- Pelletization and classification produces fractions (attrition or agglomerates): recycling these in the production process often causes quality, batch homogeneity and traceability problems. If active substances are already involved in the pelletization process, fraction disposal is often not possible for cost reasons, whereas in the case of sugar spheres, only low-cost excipients are affected.
- Pellets produced by direct pelletization often only show moderate mechanical stability. But subsequent coating procedures demand adequate abrasion and crushing resistance.

The use of sugar spheres results in a layered structure of the subsequent sustained release pellets, as shown in Figure 2.

Qualitative characteristics

The qualitative requirements for sugar spheres are meanwhile described in monographs in the major pharmacopoeias. Here it is worth giving a special mention to the longstanding monograph „Sugar Spheres"of the National Formulary and the more recent monograph „Sugar Spheres"of the European Pharmacopoeia (EP), both of which have already been extensively harmonized.[11, 12]

Sugar spheres characteristically consist of sucrose and corn starch, which are pharmacologically indifferent, digestible excipients frequently occurring in the normal diet. These are also described in the pharmacopoeias (for example the United States Pharmacopeia and EP). Other auxiliary substances are not explicitly ruled out and can be used to achieve certain desirable properties, as long as their pharmaceutical quality is verified. But they should not replace the a fore said main ingredients.

The tests for identity, purity and content stated in the mentioned monographs contain no special aspects worth mentioning. Only definition of the sucrose content by polarimetry means that no other optically active excipient can be used as an ingredient. When other sugars or starch hydrolysates are used, alternative methods are required (e.g., specific enzymatic methods) to obtain correct results.

By containing corn starch, the sugar spheres also contain water. On the condition that this is not surplus water from the production process, it should be noted that this water is not available in free state, and our experience shows that it cannot interfere with active substances susceptible to hydrolysis. This water is permanently bound to the starch molecules and required for their technological properties. An attempt to remove this water from the sugar spheres would result in very complicated drying procedures; the sugar spheres would become hygroscopic and absorb moisture again from the air. This means that the success of this procedure would be in doubt. It is only important that the water activity (the aW value) as a measure for water bonding remains below 0.65 so that any microbial growth is reliably prevented. These interpretations are based on the water vapour absorption isotherms, which are available for sugar spheres, and which should also be ascertained on the same basis for active substance pellets.[13, 14]

The technological properties of the sugar spheres are particularly important for the user; their main details are discussed below.

Flow properties

Sugar spheres are normally purchased in bulk, therefore, the rheological properties are important for handling and also for filling in the capsules later on.[15] There are a number of suitable methods for obtaining reproducible values here.

Flowability is analysed using the EP method, which is identical with international standards.[16] Thanks to the frequently obtained ideal spherical form of the sugar together with a smooth surface, the flowability is so high that there is no need to define the angle of response after being poured in bulk.

Valuable information is also provided by the parameters obtained after measuring the bulk and tap density using the stamping volumeter.[17] It is then possible to calculate the Hausner factor and Carr index as a measure of compressibility.[18] Top quality sugar spheres show low compressibility and, therefore, scarcely cause any problems in the handling and dosing stages, for example from so-called bridging.

Figure 1 Pelletization of active substances and sugar sphere coatings.

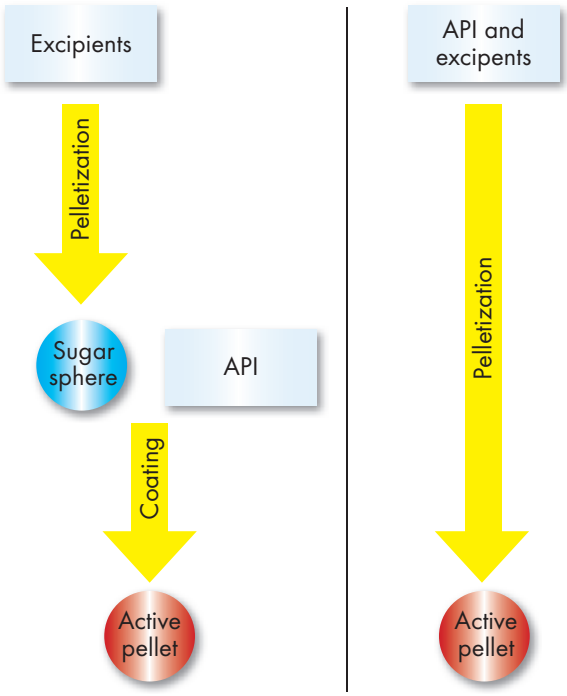
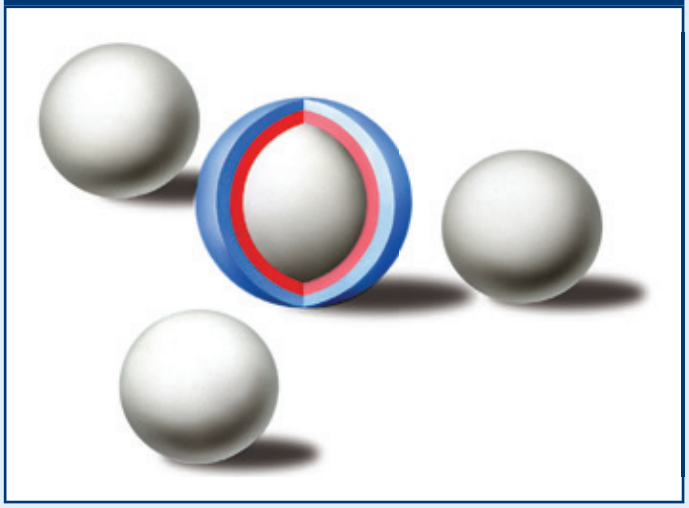


Figure 2 Diagram to show the structure of a sustained release pellet with sugar sphere care (grey), active substance layer (red) and film coating (blue). [10]



Particle size

One important requirement is for the closest possible distribution of the sugar sphere's particle size. This is a vital prerequisite for uniform application of the active substance in subsequent coating. Calculating the surface-per-input quantity also depends on a uniform particle size, as well as a spherical shape.

The particle size is defined according to the international sieve series, whereby the partly uneven numbers of the nominal mesh widths come from conversion from the still common ASTM standard sieves. Table 1 shows the µm limits and corresponding ASTM mesh values.

Usually a specification defines an upper and lower limit within which at least 90% of the particles must lie. This type of close particle size spectrum is normally produced using sieves. The corresponding sieve fabrics must comply with the international standard.[19] Table 2 shows the requirements of this standard, clearly indicating how far the effective and nominal mesh width can differ in specific cases.

The sieve fabrics consist of a large number of woven wire meshes whose size is distributed in statistical terms in both the warp and weft direction so that it is possible for the sieve results to differ considerably from the nominal value. This explains the technological difficulty of producing very narrow particle size ranges. When agreeing on a specification, it is, therefore, important to check in advance exactly which requirements are really necessary for later product quality.

The problems involved in the precision of sieve fabrics are also involved in the analytical determination of particle size. It is often possible for different laboratories to produce different results for the particle size for one and the same sample. There can, therefore, be considerable differences in the figures particularly for near-mesh grains, which is always the case for narrow particle size specifications.

Prerequisite for a uniform appraisal is, therefore, close consultation in terms of testing systems and the fabrics being used.[20]

Table 1 Common sieve series.

item-no.	mesh ASTM	diameter in µm
08001	170 - 100	90 - 150
08013	100 - 80	150 - 180
08023	80 - 70	180 - 212
08025	80 - 60	180 - 250
08033	70 - 60	212 - 250
08035	70 - 50	212 - 300
08043	60 - 50	250 - 300
08050	50 - 45	300 - 355
08051	60 - 45	250 - 355
08052	50 - 40	300 - 425
08053	60 - 40	250 - 425
08062	45 - 35	355 - 500
08063	45 - 40	355 - 425
08065	50 - 35	300 - 500
08073	40 - 35	425 - 500
08130	35 - 30	500 - 600
08150	35 - 25	500 - 710
08230	30 - 25	600 - 710
08250	30 - 20	600 - 850
08330	25 - 20	710 - 850
08350	25 - 18	710 - 1,000
08430	20 - 18	850 - 1,000
08450	20 - 16	850 - 1,180
08530	18 - 16	1,000 - 1,180
08630	16 - 14	1,180 - 1,400
08643	16 - 12	1,180 - 1,700
08653	14 - 12	1,400 - 1,700
08663	12 - 10	1,700 - 2,000

Table 2 Requirements for test sieves as per ISO 3310/1:2000, illustrated for mesh width of 850 µm.

W=850 µm	
X=127 µm 723-977 µm	Tolerance range for the individual mesh
Y=29 µm 821-879 µm	Tolerance range for the mean mesh width

Together with the different possibilities available for test sieve procedures (vibration sieving, airjet sieving, RoTap sieving), laser diffraction and image analysis have also become established methods in recent years.[21-23] Although these instruments have a far higher purchase price than test sieve machines, they do offer the advantage of automatic sieving, and of measuring a far larger quantity of samples. Image analysis also provides other important parameters, for example, particle roundness. But even when using these modern procedures, precise calibration and matching of the procedures is necessary to ensure that supplier and customer obtain coinciding results.

The results supplied by all methods consist either in the defined particle size range as a percentage or the calculated mean diameter derived from the primary data. The width of the distribution curve is crucial for estimating the risk of segregation or nonuniform behaviour during coating.

Mechanical stability

Robustness against mechanical stress is an important parameter for further processing of the sugar spheres. Sugar spheres must have adequate mechanical stability to withstand the loads during subsequent coating, including contact with solvents. Interesting parameters here are friability and crushing strength.

The Roche friabilator developed for tablets is not suitable for assessing the friability of sugar spheres; even if the test time is prolonged, no measurable attrition is obtained because of the high resistance. There have been numerous attempts to develop methods specially suited to pellets.[24] In all these instructions, there is doubt as to whether the mechanical stress corresponds to the actual loads involved in later processing. For example, methods recommending the use of steel or glass beads are dubious because the crushing of pellets caused by the impact of steel balls is in no way comparable with the forces involved, for example, in a fluidized bed procedure, where friction between the particles or tangential friction on the unit wall is typical.[25]

In our opinion, an instrument that has proven effective in detecting differences in the mechanical properties between different pellets or batches is the Born Friabimat.[26] Here, load is created by reproducibly shaking the pellets in a glass vessel, whereby the first pellets in every cycle do impact on the glass or lid surface, but this is followed essentially by friction or impact between the pellets.

Another interesting development is a unit simulating the conditions in a fluidized bed.[27] But the mechanical forces in this test are so low, even with a drastic increase in the flow of compressed air, that there is scarcely any abrasion of sugar spheres produced in the coating method. Both tests are decribed in the European pharmacopoeia now.[28]

In companies where sugar spheres are processed in a production machine, and which also have an identically designed, but smaller unit for test purposes, it is possible for the batches to be tested in this miniature version. These test conditions are then identical to the later conditions and scaling-up of the results is feasible.

Similarly, the instruments normally used to measure the crushing resistance (or pressure resistance) of tablets, such as the established Schleuniger tester, are usually not suitable for the far smaller pellets. As a substitute, an apparatus developed for testing the texture of food products equipped with a suitably formed transducer tool has proven effective.[29] The analysis of individual pellets gives a force-over-distance curve that can be evaluated according to the maximum or area under the curve (AUC) to obtain a detailed statement about the mechanical properties.

Surface

The properties of the surface are interesting in biopharmaceutical terms. It is important to know these properties to calculate the subsequent coating procedure, as well as the release kinetics. Ideally, the surface-per-pellet mass can be calculated as sphere surface from the mean diameter. In sugar spheres produced using a modified sugar-coating

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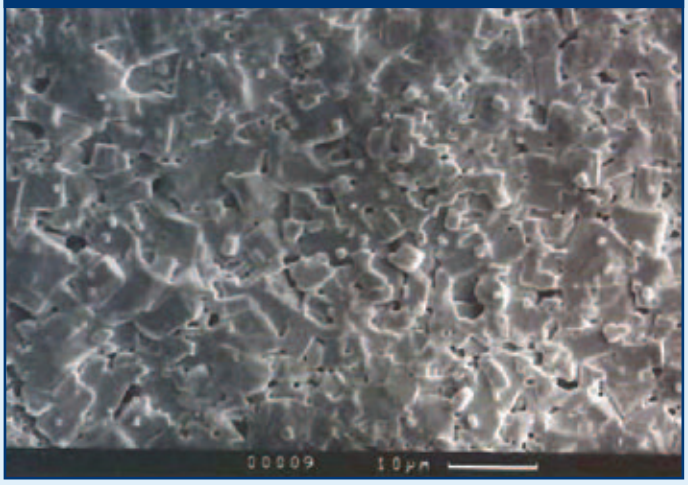
Figure 3 REM picture of the surface of a sugar sphere produced using the modified sugar-coating procedure.



procedure, the roundness of the individual particles resulting from the rolling motion in the production process is very high, so that this calculation is adequately precise in a first approximation.

On the one hand, direct optical methods are used for assessment, ranging from using a stereomicroscope through to automatic image analysis.[30]

Indirect methods are also used for certain aspects to define the specific surface area or porosity and pore size (porosimetry).[31-34] Sugar spheres with the layered structure obtained during the sugar-coating process have a low interstitial surface of sucrose crystals with extremely low porosity (Figure 3).

Future development

Thanks to their unique technological properties, sugar spheres are a key ingredient in numerous medications administered in pellet form, and have proven their worth even when compared with alternative concepts and medication forms. New applications continue to emerge, such as compressing coated pellets to produce sustained release tablets (multiple unit tablets). The mechanical stability of the pellets and the elasticity of the polymer auxiliary substances in the coating have an important function to play.[35]

The role of the tablet is to offer the pellets in a favourable, divisible form which is safe from manipulation and easy to use. In the gastrointestinal tract, it disintegrates into the partial pellets with differing sustained release rates, corresponding to the application of pellets in hard gelatine capsules.

There have been a large number of such developments in recent years.[36-40]

Sugar spheres can be expected to remain an important excipient for solid medications in future too, with the possibility of being used successfully as a tool for new developments.[41]