



# Sugar coating sweetens the pill

**Table 1: NPTab grades**

NPTab 200	(180/250µm)
NPTab 250	(200/300µm)
NPTab 300	(250/355µm)
NPTab 350	(300/400µm)

dependent on the quality of the initial mixture and of the intermediate particle size, the goal is to obtain the best dispersion of active within the excipients at every process level.

The industry has already shown a large interest in spheroids in terms of their free-flowing properties and available surface area for layering and coating. Moreover, with a growing interest toward direct compression processes for solid dosage forms, there is an increasing need for novel excipients that provide good flowability and compactibility.

NPTab technology, utilising a direct compression process for guaranteed homogeneity and reproducibility, has been designed to ensure a very low dosage of the active drug in a tablet form. It is also free from the problems inherent in the stages of mixtures and segregation phenomena.

## layering process

The process comprises two steps, (see figure 1): layering with traditional coating equipments that spray a drug solution (homogeneous molecular dispersion by definition) onto a carrier consisting of sugar spheres (homogeneous particle size and texture), followed by direct compression of the layered sugar spheres. The mechanical resistance of the resulting tablets is related to both textural and compactibility properties of the sugar spheres.

The spraying process ensures pellets of defined technical properties: spherical with an homogeneous particle size and regular texture.

Particle size distribution (analysed by laser diffraction) shows the character of the distribution to be symmetrical, while the single modal profile, associated with low standard deviations reveals an homogeneous population of sugar spheres. These particles are available in four grades (see table 1).

Many factors favour segregation in the case of physical mixing, including differences in particles sizes, densities,

**Dr Christine Delesalle**, Pharm.D from NPPharm discusses the content uniformity of solid low-dosage forms, and how these are a challenge to the drug industry

In the pharmaceutical industry, drug homogeneity has become more important in recent years as the efficiency of actives has increased and their concentrations in solid unit forms decreased.

Within the European, Japanese and US Pharmacopeias' harmonisation context, the requirements concerning the uniformity of the dosage unit have become increasingly stringent and difficult to meet using conventional formulation technology.

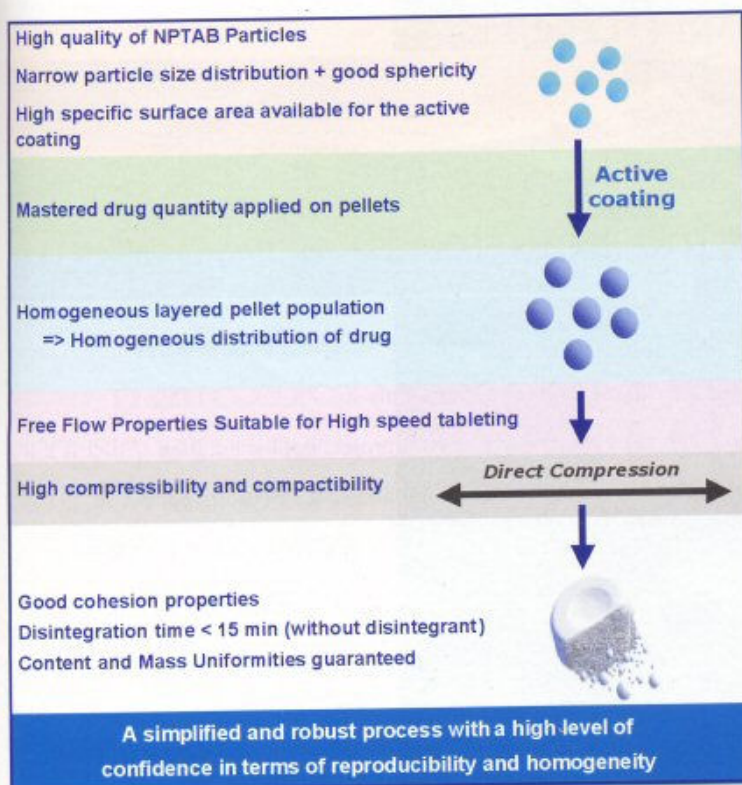
For several years French company NPPharm has worked in alongside Ethypharm and the Laboratoire de

Tablets formed using direct compression display a smooth appearance with a glossy surface

Physique Pharmaceutique (University of Pharmacy, Paris XI, France) in a collaboration dedicated to the development of a new technology concept that fulfils the essential need of the pharmaceutical industry to improve content uniformity of low dosage solid unit form. From that collaboration NPTab technology, which is covered by a European granted patent (EP 1 200 071), was developed.

## uniformity challenge

The content uniformity of solid low-dosage forms is a major challenge in the pharmaceutical industry. Highly



and proportions.

By means of the layering process, stabilisation between drug and carrier is attained, while the tendency towards segregation is definitively avoided.

Textural analysis results indicated that the spraying of a solution of drug on to the spherical and monodispersed carrier, led to an homogeneous layered particle population.

The particles exhibit a high surface area (about 0.2 m<sup>2</sup>/g), which is beneficial for the active coating and allows a high quality application of the active and excipients on the surface. In comparison with non-layered NPTAB particles, the specific surface area decreases when the particles are layered (drug with conventional binder).

### surface properties

This is the result of a reduction in surface roughness through the complete coverage of carrier asperities by the binder. These results are confirmed by observation using SEM, (figures 2 and 3). The narrow distribution range of the particles, as well as the regular solution spraying, contribute to uniformity of layering, which in turn guarantees an homogeneous distribution of drug.

Solid dosage forms such as tablets are the most desired types of medication and represent the majority in the market place. The ease and cost-effectiveness of direct-compression techniques have positioned it as an attractive alternative to traditional granulation technologies. It is highly influenced by powder properties, while

the physico-mechanical properties of NPTAB particles, such as their spherical shape, excellent flow properties, reproducible die-filling, compressibility and compactibility, all ensure a robust process.

NPTAB particles exhibit the following properties, whether coated with active or not:

- free flow properties (Carr index < 10%, flow time < 10s);
- highly efficient and regular die-filling of tableting machine ensuring trouble-free high-speed tableting;
- the powder bed weight and the tablet weight are constant throughout the tableting process. Mean weight values with low standard deviations reflect weight uniformity;
- highly satisfactory compressibility: the yield pressure value (determined with the Heckel model) shows that pellets undergo plastic deformation during compaction (yield stress around 80 to 90MPa). This property increases with binder in coating and is favourable for the cohesion acquisition of tablets;
- are highly compressible with very little lubricant (Magnesium Stearate : 0.125% recommended).

Direct compression parameters (compaction force transmission > 90%, low ejection and residual forces) provide evidence of low stress heterogeneity inside the tablet, which in turn results in reduced sensitivity to lamination and capping incidents.

The tablets are perfectly smooth with a glossy surface, and layering with

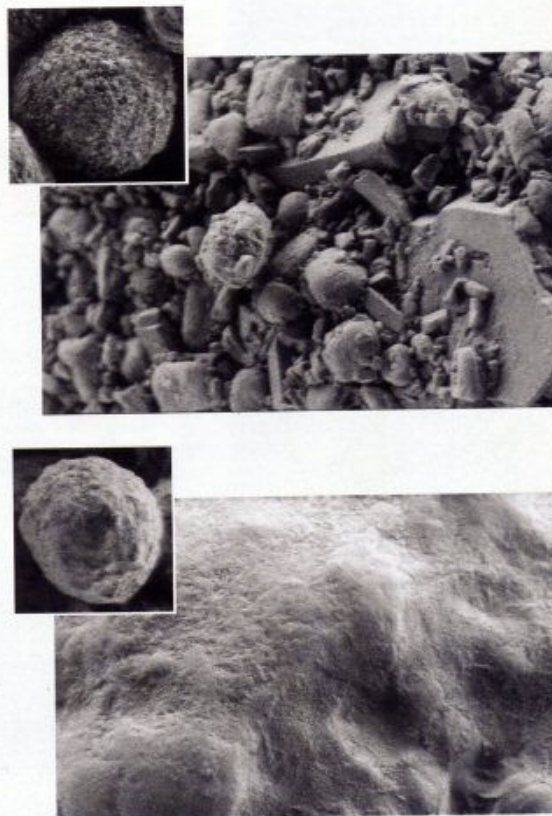


Figure 1 (Top left): The low dosage process comprises two steps

Figure 2 (Top right) and 3 (bottom right): The pictures show scanning electron micrographs of the NPTAB spherical particles (2a – non-coated and 3a – coated) and the surfaces (2b – non-coated and 3b – coated)

binder doesn't disturb the excellent compression characteristics.

Moreover, disintegration times are very short (< 600s), even in the presence of the binder layer and despite the absence of a disintegrant. This result is not surprising, considering that the particles are highly soluble in water and that erosion occurs from the outside.

### cohesion properties

Thanks to the plastic behaviour and high specific surface area of the pellets, tablets produced in this fashion exhibit good cohesion properties. Cohesion has been demonstrated at low stress levels (approximately 20MPa), which means that energy supplied during compression will be specifically used to create effective cohesion. Hardness levels, consistent with industrial production requirement (approximately 1MPa), are obtained with intermediate pressures (150MPa).

In summary, the process that NPPHarm has developed enables the pharmaceutical industry to develop cost-effective direct compression formulae for low dosage and/or narrow therapeutic range drugs with excellent content uniformity. It is a simplified process that provides a high level of confidence in terms of reproducibility and homogeneity. ■

### contact

NPPHarm is an excipient company. It is one of the world leader for manufacturing sugar spheres (SUGLETS) for the exclusive use of pharmaceutical industry.

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