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Designing disintegration into oral dosage

An ageing global population, consumer demand for greater convenience and the need to improve patient compliance are driving the development of new platforms for orally disintegrating dosage forms. Roquette shares its latest innovations and the connection to growing popularity in the industry.

The convenience and consumer appeal of medication that can be taken 'on the go' has led to a rise in the popularity of Oral Disintegrating Tablets (ODTs). This dosage form has expanded from over-the-counter preparations, such as nutraceuticals and vitamins, into the realm of prescription-only (Rx) drugs.

From a consumer point of view, the availability of a tablet that disintegrates rapidly in saliva and can therefore be taken without water makes ODTs an easy and convenient solution for today's pressured lifestyle. A pleasant taste and smooth mouth feel are also crucial to consumer acceptance.

The format is also popular with hospitals and other healthcare providers, because it increases patient compliance, particularly among psychiatric, pediatric and geriatric patient populations and those with dysphagia who are unable to swallow conventional solid dosage forms.

Offering products that benefit both patients and healthcare providers give a clear competitive advantage to pharmaceutical manufacturers. ODTs can also offer improved lifecycle management and an opportunity to create strong brands through innovation and differentiation in a crowded market.

The benefits of ODTs go much further than mere convenience and palatability. In particular, ODTs are suitable for drugs with medium or high potency active ingredients; low potency drugs with a high proportion of API do not result in a good ODT. Furthermore, for some drugs, the orodispersible formulation may result in greater bioavailability through buccal and pre-gastric absorption, thereby reducing first-pass gastric and liver metabolism.

Market growth will also be driven by the introduction of new manufacturing processes. Spritam (levetiracetem), the first orally dispersible tablet produced by 3D printing, has been approved by the US FDA; this technology opens the way to the personalized drug delivery, tailoring treatments to suit individual patients.

The increased popularity of ODTs on the market has been the main driver behind the creation of ready-to-use platforms by the excipients industry. The challenge for manufacturers is to create a tablet that will satisfy the requirement for fast disintegration but at the same time have the mechanical properties that enable it to be produced efficiently.

The need for prompt disintegration is met by formulating the ODT with mannitol, one of the only water soluble excipients that presents a delay in water adsorption. During this delay, saliva is fully available to enter the porous structure and for disintegrants or superdisintegrants to act. Furthermore, mannitol is non-hygroscopic, and protects the stability of the active ingredients.

The consumer requirement for palatability and pleasant mouth feel also works in favor of mannitol, which has a mild, natural sweet taste and cooling effect in the mouth. Other diluents may have a less acceptable mouth feel; they are also known to contain reactive groups and impurities that can reduce the shelf life of ODT formulations.

There are a variety of methods that can be used to manufacture ODTs, including freeze-drying, spray-drying, direct compression, moulding sublimation and mass extrusion. However, direct compression is the method that is most cost-effective and easy to carry out on standard equipment, producing a tablet that combines the targeted rapid disintegration and meets pharmaceutical friability requirements.

The main challenge in ODT formulation is to find the excipients that will offer the right balance between disintegration time, friability, API stability and mouth

feel. To meet these requirements, a number of companies have developed ready-to-use ODT platforms by co-processing the filler, usually mannitol, with a superdisintegrant. Although these excipients can offer fast disintegration, they also contain traces of the reagents used in their synthesis that can lead to drug degradation. Furthermore, at the levels of inclusion needed for rapid oral disintegration, their taste and texture can make them unpleasant to consumers.

Roquette is the world's leading producer of mannitol for pharmaceutical applications, and has developed PEARLITOL® Flash, a patented compound that offers the compactability, friability and disintegration properties required to manufacture optimal ODTs.

Japanese Pharmacopeia JPE has recently published the monograph "D-Mannitol and Corn Starch Granules", describing PEARLITOL® FLASH (1).The listing of PEARLITOL® Flash in JPE is significant: it means it is now recognized by the Ministry of Health, Labor and Welfare (MHLW) as an important product for the Japanese market in tablet formulation. Pharmaceutical companies prefer to use excipients compliant with the JPE monograph whenever possible because it can speed up formulation registration.

The superior wettability of PEARLITOL® Flash compared with other platforms results in rapid self-disintegration without the need to add a superdisintegrant. Mannitol used in conventional ODT formulations requires a porous structure of tablet to reach target disintegration time whereas PEARLITOL® Flash disintegration time is independent of the tablet porosity.

PEARLITOL® Flash has a simple composition based on mannitol and maize starch for direct compression, achieves good flow properties, and requires only a low level of lubricant (0.4% magnesium stearate). It melts in the mouth in seconds and has a smooth, creamy mouth feel with a sweet taste. The use of native starch, which is neutral and requires no reagent, offers taste and stability advantages over the use of a superdisintegrant.

A paper published in PharmSciTech (2) examined whether four commercially available ODT platforms, including PEARLITOL® Flash, induce degradation of active pharmaceutical ingredients under standard and accelerated conditions. Benzocaine was selected as the model API due to known degradation through ester and primary amino groups. The ODTs were formulated with 6% benzocaine, 1.5% magnesium stearate, and 92.5% of the respective ODT platform and were investigated under ICH conditions at 25°C and 60% relative humidity (RH) and 40°C and 75% RH for up to six months. No degradation was observed in the tablets exposed to subtropical conditions (25°C and 60% RH), but under accelerated degradation conditions, benzocaine decomposition was identified in the tablets made using an ODT platform containing microcrystalline cellulose, colloidal silicon dioxide, fructose and crospovidone, in addition to mannitol. The researchers felt that the silicified MCC and crospovidone in the platform could be potential sources of organic acid and aldehyde impurities, which caused the degradation.

Although degradation of the API was detected in only one of the four ODT platforms, the physical appearance of the tablets varied greatly, especially under accelerated conditions. Mannitol is not hygroscopic and does not absorb water even under accelerated conditions, and the shape changes in the tablets was attributed to the propensity of the disintegrants to absorb water. Crospovidone, used in two of the platforms as a disintegrant, swells when it comes into contact with water. Tablets made with three of the platforms maintained a shiny and relatively smooth surface for the 6-month period under subtropical conditions (25°C/ 60% RH). However, after storage under accelerated degradation conditions (40°C/75% RH) the tablets made using PEARLITOL® Flash were the only ones to maintain a satisfactory aesthetic appearance, the research found.

It is clear that the ODT platform plays a significant role in the success of the formulation. Making the wrong choice can compromise the stability of the API and reduce the shelf-life of the medicine. PEARLITOL® Flash was shown to have excellent shelf-life and consistent stability under standard and accelerated conditions over six months of storage. It also offers rapid disintegration and superior organoleptic properties compared with other ODT formulation platforms.

REFERENCES

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