

# Performance of MCC Spheres and Sugar Spheres in a Multi-particulate Omeprazole Formulation

## Abstract

Robust and inert, spherical carriers are a prerequisite for the manufacture of multi-particulate dosage forms.

In this study, spheres composed of microcrystalline cellulose (**VIVAPUR® MCC SPHERES**) were compared with sugar spheres.

The spheres were evaluated in terms of their mechanical robustness and ease of drug-layering and coating, as well as the finished product's gastro-resistance and dissolution behavior. **VIVAPUR® MCC SPHERES** exhibited an overall superior performance compared to equally sized sugar spheres.

Furthermore, they enable a more predictable and reproducible drug release timeline. Large particles, such as monolithic tablets, show high variability in terms of their residence time in the stomach. Smaller particles, by contrast, have been shown to move to the intestine with almost no inter-individual variation and minimal influence of fed or fasted conditions [1].

API-containing pellets can be produced by extrusion-spheronization of the active ingredient(s) together with suitable excipients, such as microcrystalline cellulose. Drug-layering inert starter spheres is the other widely used option. Traditionally, sugar-based spheres have prevailed in this technology.

More recently, MCC carrier spheres have gained importance in this field of application. The scope of this study was, therefore, to compare the performance of MCC spheres and non-pareil sugar seeds in an omeprazole formulation, closely following the composition of a marketed omeprazole product.

## Introduction

Many active ingredients must be administered in a gastro-resistant form in order to protect the stomach against irritating properties of the active ingredient, or -vice versa- to protect the active ingredient against the acidic conditions in the stomach.

Gastro-resistance can easily be achieved using coating materials which are insoluble in the acidic conditions of the stomach and soluble in the closer-to-neutral pH of the intestines.

As opposed to conventionally coated tablets, multi-particulate systems contain the active ingredient in a subdivided form. Each of the individual units carries its own functional coating and acts as an independent modified release system.

Although multi-particulate systems are technically more demanding than monolithic tablets, there are some substantial advantages, which explain the wide acceptance of multi-particulate systems in the health science industry. Dividing the total API dose into individually coated subunits reduces the risk of immediate and uncontrolled release of the API in the case of a single coating defect. Multi-particulate systems, therefore, improve the safety of dosage forms.

## Study Design

First, the carrier spheres (**VIVAPUR® MCC SPHERES** of 350 and 700  $\mu\text{m}$  average particle size respectively), and sugar spheres with an average particle size of about 700  $\mu\text{m}$  were examined with a Scanning Electron Microscope (SEM) regarding their sphericity and surface structure before and after 60 minutes of dry processing in a fluid bed coater.

Next, the spheres were drug-layered and covered with an enteric coating.

The resulting spheres were tested for their API load and bulk density in order to determine the minimum capsule size to accommodate the target API dose of 20 mg.

Finally, the capsules were tested for gastro-resistance and drug dissolution according to the European Pharmacopoeia.

## Materials and Methods

### Equipment List

Fluid Bed Coater: Glatt AG (LF1)  
 Blender: Heidolph  
 Stainless steel sieves  
 Scanning electron microscope: Hitachi 2300  
 Dissolution Tester: Agilent Technologies 708 DS

### Ingredient List

#### VIVAPUR® MCC SPHERES 350

#### VIVAPUR® MCC SPHERES 700

Sugar spheres  
 Omeprazole, micronized  
 Hypromellose, 2910, 6m Pa.s  
 Low-substituted Hydroxypropyl Cellulose L-HPC LH11  
 Disodium Phosphate x 12 H<sub>2</sub>O  
 Lactose monohydrate  
 Sodium Lauryl Sulphate  
 Eudragit® L 30 D55  
 Sodium hydroxide, 1 N  
 Titanium dioxide  
 Talc  
 Hard gelatin capsules, n° 2, 3 and 4  
 Sodium chloride

Concentrated hydrochloric acid

### Preparation of API-loaded Pellets

Process conditions:

Inlet air temperature: 60 – 65 °C  
 Outlet air temperature: 45 – 50 °C  
 Atomisation air pressure: 2 bar

Lab-scale Glatt Wurster coater

## Results and Discussion

### SEM-based evaluation of spheres before and after mechanical stress in the fluid bed coater.

The evaluation of the SEM pictures showed that all types of spheres in this study had particle sizes according to their respective specifications and showed a high degree of sphericity. Some sugar spheres tended to appear slightly aspherical in shape compared to the more uniformly spherical MCC spheres.

The mechanical robustness of the spheres was tested by processing them in the fluid bed coater under drying conditions. That is – with the inlet air heater switched on, but without any liquid addition.

SEM pictures were taken after 15, 30, 45, and 60 minutes.

The sugar-based carrier showed visible signs of erosion even after 15 minutes, whereas both types of MCC spheres remained stable throughout the process.

### Preparation of Omeprazole Pellets

Omeprazole-layered pellets could be produced with all three types of starter spheres without any apparent problems. In order to obtain comparable results, the same process conditions, as well as the same qualitative and quantitative formulations, were used for all three types of pellets, with the exception of the seal coat, which was only necessary with the sugar spheres to prevent erosion during the fluid bed process.

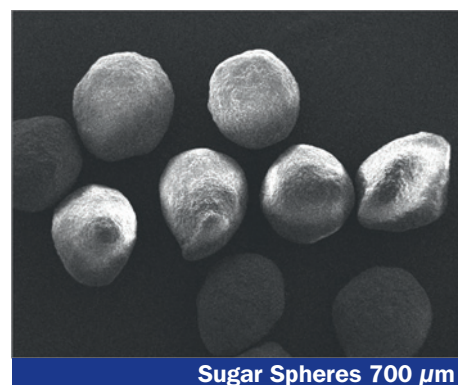
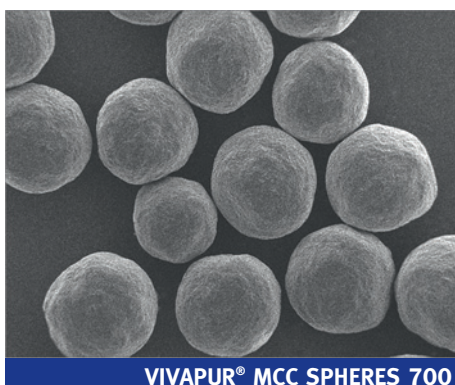
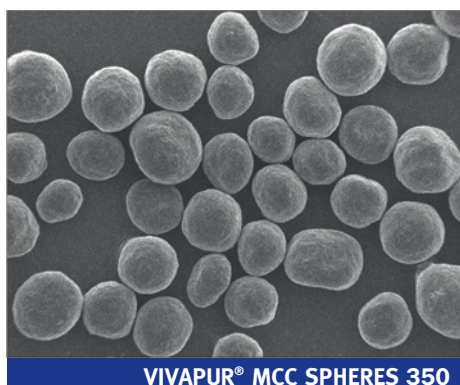
As a result, the duration of the process was extended for the sugar-based formulation.

When using MCC spheres with a mean diameter of 350 μm, the processing time almost doubled compared to the 700 μm spheres, as a result of the increase in specific surface area.

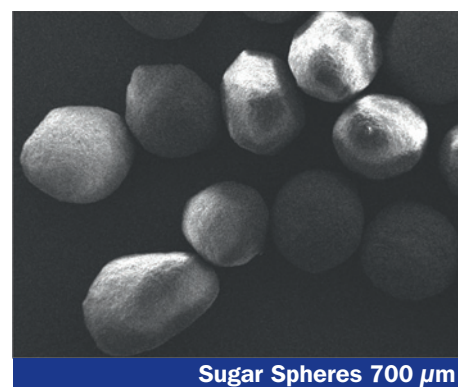
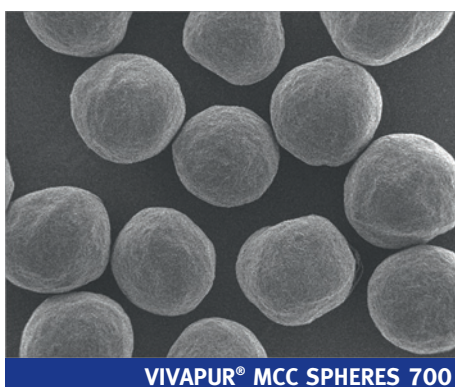
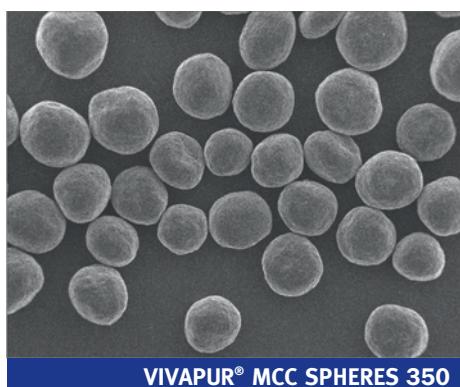
Table 1 shows the process duration for each of the coating and layering steps.

	Seal Coat	API Layer	Seal Coat	Enteric Coating	Total Duration
<b>VIVAPUR® MCC SPHERES 350</b>	-	135 min	285 min	195 min	615 min
<b>VIVAPUR® MCC SPHERES 700</b>	-	165 min	85 min	135 min	385 min
Sugar Spheres 700 μm	115 min	120 min	75 min	180 min	490 min

Tab.1: Duration of the Individual Process Steps



Pic. 1: Spheres after 15 Minutes of Fluid Bed Drying at 40 °C



Pic. 2: Spheres after 60 Minutes of Fluid Bed Drying at 40 °C

The formation of sharp edges and irregularities on the surface of the sugar spheres through erosion is disadvantageous for subsequent drug-layering and functional coating. The effect of erosion becomes more obvious with increasing processing time, as illustrated in Picture 2. The sugar spheres, therefore, needed to be seal-coated prior to further processing.

## Evaluation of Dosage Volume

The target dose of 20 mg omeprazole was contained in 222 mg of pellets in the MCC sphere formulations and in 225 mg of the sugar sphere formulation, respectively.

The highlighted fields in the table below show the required capsule sizes for each formulation.

	Size 4	Size 3	Size 2
VIVAPUR® MCC SPHERES 350	135 mg	230 mg	315 mg
VIVAPUR® MCC SPHERES 700	165 mg	225 mg	300 mg
Sugar Spheres 700 µm	120 mg	215 mg	290 mg

Tab. 2: Formulation dependence of the maximum capsule fill by weight. Highlighted fields indicate the necessary capsule size for the target dose of 20 mg Omeprazole

## Dissolution Testing

Dissolution testing of the omeprazole pellets produced with MCC spheres resulted in compliance with the Ph. Eur. requirements for gastro-resistant dosage forms, meaning not more than 10 % of the API released after 2 hours in an acidic medium (pH 1.2) and not less than 80 % released within 60 minutes in a neutral dissolution medium (pH 6.8) (See Fig. 1). The pellets produced with the 350  $\mu\text{m}$  spheres exhibited a much faster release than the ones made with 700  $\mu\text{m}$  spheres. While the former released 96 % of the API after 15 minutes in a neutral pH, the latter only liberated 78 % in the same time interval. This observation can easily be explained by the larger surface area of the smaller pellets.

Since omeprazole is a BCS class II drug (poorly soluble but sufficiently permeable), the use of smaller pellets, which accelerate the dissolution, may be favorable in terms of enhancing bioavailability. This theoretical consideration, however, would have to be backed up by bioavailability studies.

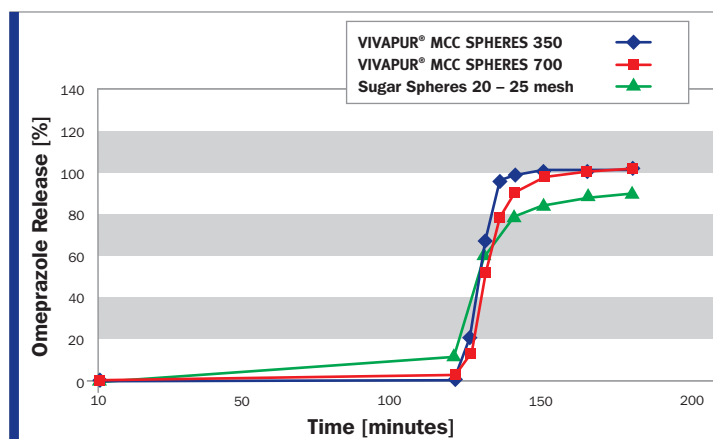


Fig. 1: Dissolution curves for MCC and sugar spheres respectively. The sugar spheres show non-compliant API release in the acidic phase of the test.

By contrast, dissolution testing of the sugar-based pellets revealed non-compliance with the Ph. Eur. in terms of resistance to acidic conditions, whereas the requirements for dissolution in a neutral medium were met, as shown in Fig. 1.

The process conditions and coating quantities, as defined in the scope of the study, were kept constant throughout the different sets of experiments. While these conditions were suitable for achieving good pellet properties with the MCC spheres they turned out to be insufficient in case of sugar spheres. Even though a seal coat was applied to prevent erosion, the irregular shapes formed during the early phase of the process, when the seal coat was not yet fully built, led to shapes which prevented the formation of a coherent and evenly thick gastric coating.

In order to achieve gastro-resistance, the sugar spheres would have required additional quantities of enteric coating.

Interestingly, the liberation in neutral conditions was slower for the sugar spheres than for the equally sized MCC spheres. This may be a result of the thickness variation of the API layer resulting from the effect described above.

## Summary and Conclusion

Initially, all tested spheres had smooth surfaces and a high sphericity. Sugar-based spheres showed erosion after mechanical stress, thus requiring an additional seal coat prior to API-layering. Between MCC spheres and sugar spheres of the same particle size, the total process duration was longer for sugar spheres due to the application of an additional seal coat.

Because of their larger surface area, smaller spheres required far longer coating times than their larger counterparts.

The target dosage of 20 mg omeprazole fit into size 3 (smaller) capsules for MCC spheres, while sugar spheres required size 2 (larger) capsules.

The sugar spheres formulation did not comply with gastro-resistance according to the pharmacopoeia. More enteric coating would have been necessary to cover the irregular surface.

MCC 350 spheres took longer to produce, but showed faster dissolution of the API than MCC 700 spheres due to the increased surface area.

### Disclaimer:

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