Why Choose Small Sugar Spheres?

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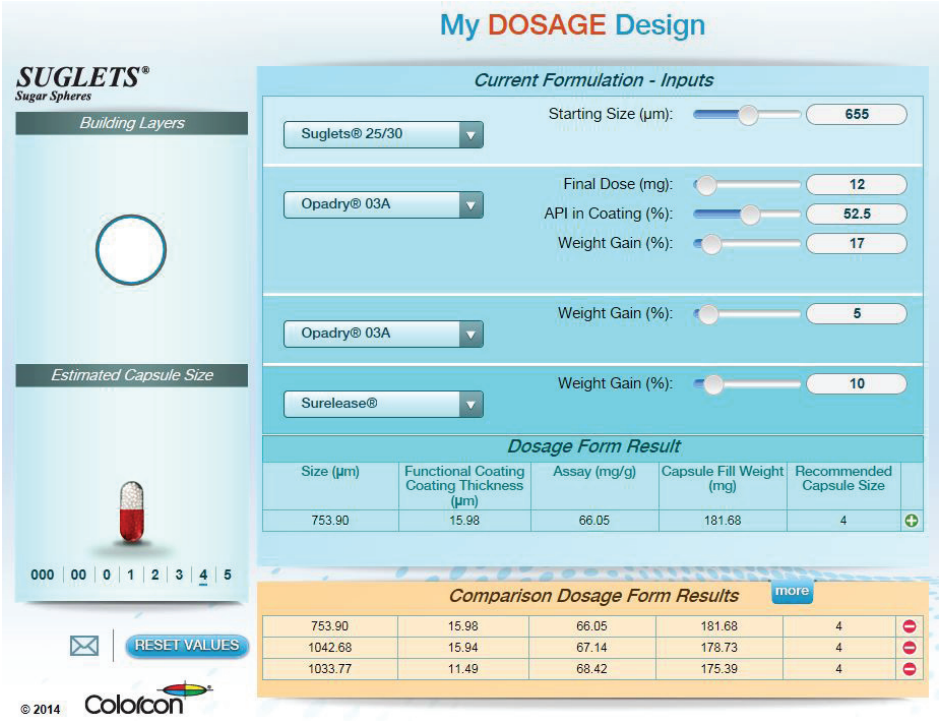
Purpose

This study shows the benefits of choosing a larger sugar sphere as the starting substrate when developing a modified release multiparticulate dosage form. It also demonstrates that similar drug release can be obtained regardless of the size of the starting substrate, ease of processing when coating larger spheres and that the starting size of the sphere does not impact the capsule fill volume.

Methods

Suglets® Sugar Spheres of two different sizes were drug loaded with chlorpheniramine maleate (CPM) (75.9 mg/mg dose) utilizing a hypromellose-based Opadry®, Complete Film Coating System as a binder (17% weight gain), seal-coated with the same Opadry formulation (5% weight gain) and subsequently coated with Surelease®, Aqueous Ethylcellulose Dispersion Type B NF (10% weight gain) to produce sustained release multiparticulates. All drug layering and coating was carried out using a Glatt GPCG-2 with 7" Wurster insert and 2 kg batch size. Samples were taken at various weight gains during the Surelease coating process. Particle size analysis was performed using a Camsizer dynamic image analyzer. The initial batch utilized Suglets size 25/30 mesh (600/710 µm). A proprietary modelling tool developed by Colorcon to help formulators develop multiparticulate dosage forms, *My Dosage Design*, was used to calculate film thickness of the barrier membrane with different size Suglets as the starter core, Figure 1. Through *My Dosage Design*, many variables relating to the multiparticulate dosage form can be theoretically calculated at different stages of the process; this includes particle size, surface area, film thickness, the volume of the final dose and the capsule size required to fill. A subsequent batch of multiparticulates was prepared using a larger sphere size, Suglets 18/20 mesh (850/1000 µm). The same properties, including drug release, capsule fill size etc, were also calculated.

Figure 1: *My Dosage Design* Tool



Results

Using My Dosage Design the average size of the beads was calculated for each batch, as well as the resulting film thickness based on the weight gain of Surelease applied. Table 1 shows some of the outputs from the design tool. With larger beads, there is less surface area to be coated and to achieve equivalent film thickness of the barrier membrane, less weight gain is applied.

Table 1: *My Dosage Design* Output

Starting Suglet Size (mesh)	Average Starting Size (µm)	WG of Surelease (%)	Final Coated Size (µm)	Film Thickness (µm)	SA / Film Thickness Ratio (cm^2/µm)
25 / 30	655	10	754	16.0	6.37
18 / 20	925	7	1043	15.9	4.49
18 / 20	925	5	1034	11.5	6.13

By matching only film thickness, a difference in dissolution was seen, Fig 2. This is due to the batch with larger spheres having less surface area exposed to the dissolution media; which results in a decrease of the release rate of the drug. The f_2 value for these batches is 60.3, but there is clearly a difference in the profiles. The design tool will calculate the surface area and allow for the production of similar surface area (SA) to film thickness (FT) values with the larger spheres, resulting in similar drug release. A third batch of 18/20 spheres were prepared to match SA: FT, Fig 3. The f_2 value for these two batches is 80.3.

Figure 2: Dissolution with Equal Film Thickness

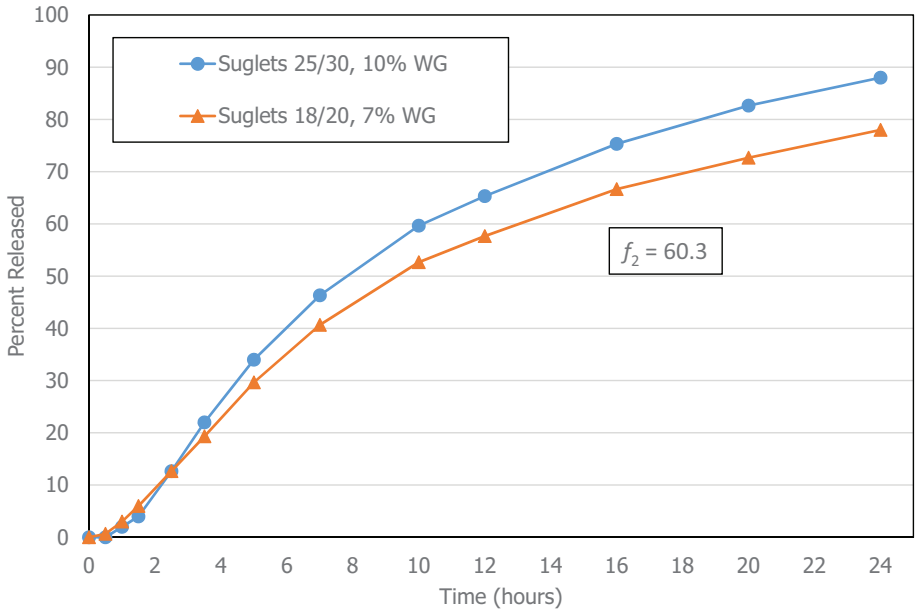
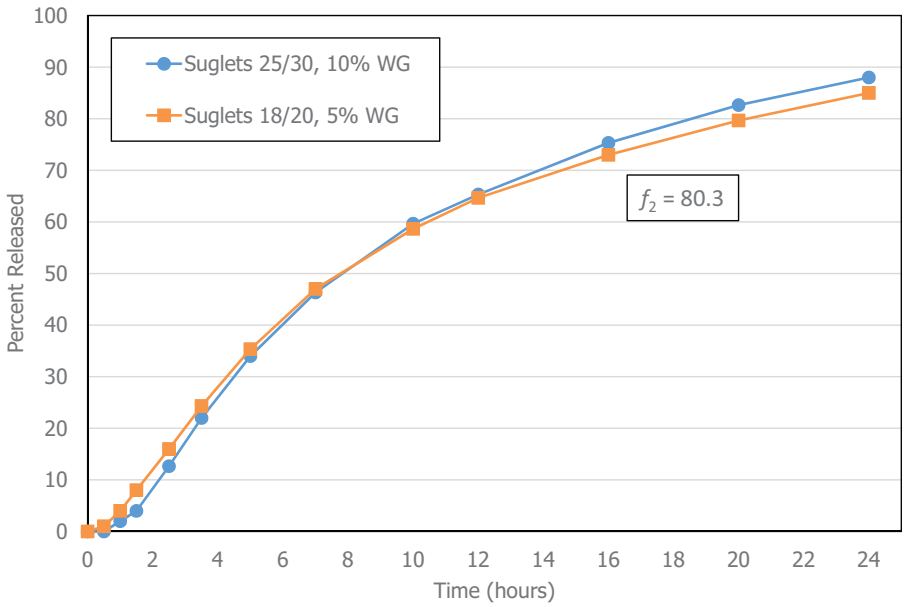
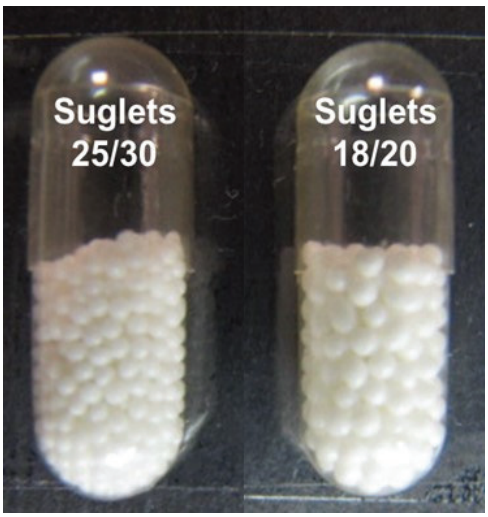


Figure 3: Dissolution with Equal Surface Area/Film Thickness Ratio



My Dosage Design determines the appropriate size capsule, filled to a maximum of 85% fill volume, based on the size of the final bead and the packing density. A drug dose of 12 mg of CPM would require approximately 180 mg of coated beads, representing a volume of 0.17 mL for each batch. Filling these batches into clear, size 4 capsules, also resulted in visually similar fill volumes in the capsule shells regardless of the starting sphere size, Figure 4. It is a common misconception that a shift in bead size will impact the fill volume in the capsule. As the bead size changes, the interstitial void volume also changes making the overall bulk volume change insignificant. In addition, with smaller beads, additional weight gain of polymer will be needed, adding to the overall size of the final bead.

Figure 4: Filled Capsules with Equivalent Drug Dose



Conclusions

Choosing a small sugar sphere for a modified release multi-particulate dosage form has many disadvantages[1]. Smaller spheres are more difficult to coat, due to higher incidence of agglomeration and the higher surface area requires higher weight gains of coatings to achieve similar film thickness. The smaller spheres required higher weight gain of barrier membrane coating to achieve the same dissolution profile; resulting in longer processing times for the final product. Dissolution profiles can be modulated regardless of the sphere size. This study showed that the dissolution of a product using a 25/30 mesh bead and a 10% WG of barrier membrane coating, can be matched using an 18/20 mesh bead with only 5% WG of barrier membrane coating. Using the *My Dosage Design* tool, film thickness and surface area to film thickness ratios can be determined in order to control drug release rates. To match the dissolution profile using a different size substrate, both the film thickness of the coating and the surface area need to be considered. Starting substrate size did not impact fill volume of the final capsule.

References

1. Augsberger & Hoag, Pharmaceutical Dosage Forms: Tablets, Third Edition, Volume 1 Unit Operations and Mechanical Properties. 2008, Informa Healthcare Inc

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