ABSTRACT

Kalbag, Arjun V., Ph.D., Purdue University, August 2009. Modeling Inter- and Intra-tablet Coating Variability of Pan Coated Tablets. Major Professor: Carl R. Wassgren Jr.

This thesis work is focused on the modeling of inter- and intra-tablet coating variability of pan coated tablets. Tablets are coated for a number of reasons such as controlling the bioavailability and release profile of the drug (functional coatings), ensuring product identification and aesthetics, masking odor and taste and protecting the tablet core. Due to the critical nature of functional film coating, significant variations in coating between tablet-to-tablet (inter-tablet coating variation) and between different regions of a tablet, such as the cap and the band of a biconvex tablet (intra-tablet coating variation) will adversely affect product efficacy. Therefore, modeling the process is an important tool towards predicting and controlling variability and can help eliminate some of the problems caused by poor coating uniformity.

The thesis work uses first principles analysis, Discrete Element Method (DEM) simulations, and experiments to determine the variables that control coating uniformity. The parameters that can potentially affect inter-tablet coating variability and studied in this work are the pan speed, the tablet load, coefficient of friction, and spray zone size and location. The parameters that can potentially affect intra-tablet coating variability and studied in this work are the pan speed, the tablet load, tablet aspect ratio (and sphericity), and the effect of baffles. DEM models used to study intra-tablet coating variability are restricted to simple glued sphere particles instead of modeling true geometric primitives such as cylinders as this requires the implementation of prohibitively difficult contact detection algorithms and development of new force models.

The combination of DEM simulations, experiments and analysis provides a comprehensive framework for the understanding of the processes that control coating variability and serves as a platform from which more complex models of coating processes can be developed and implemented.

The thesis work investigates inter-tablet coating variability, specifically, tablet residence times within the spray zone. DEM computer simulations, experiments, and analytical investigations are performed to measure the residence time per pass, the circulation time, and appearance frequency of spherical shaped

tablets for a range of pan speeds and tablet loads. In addition, the fractional residence time, defined as the ratio of time spent by a tablet in the spray zone to the total coating time, is measured. The average fractional residence time (averaged over all the tablets in the bed) is found to be equal to the ratio of the time-averaged number of tablets exposed to the spray to the total number of tablets in the pan, a result that is consistent with analyses. The average fractional residence time is observed to be independent of pan speed and total coating time. Furthermore, the fractional residence time is shown to be related to the residence time per pass and circulation time per pass. Circulation time per pass for a tablet is defined as the average time between successive appearances in the spray zone and residence time per pass is defined as the average time spent in the spray zone per pass. Appearance frequency is defined as the number of appearances a tablet makes in the spray zone per pan rotation. Simulations and analyses show that appearance frequency decreases with increasing pan speed. These various measures of residence time are all related, but from the standpoint of developing an analytical model for coating variability, fractional residence time is a more useful and intuitive parameter as it determines the fraction of total run time that a tablet spends in the spray.

To study the coefficient of variation of the coating mass distribution, the variation in tablet residence times is studied, as both quantities are directly related. The DEM simulations indicate that the coefficient of variation of tablet residence times, and subsequently, of coating mass, decreases with time following a power law relation. The theoretical model demonstrates that the coefficient of variation of residence time for a randomly mixed tablet bed is inversely proportional to the square root of the number of coating "trials." DEM simulations show that during each pan revolution, tablets in the spray zone remain in a quasi-segregated state from tablets located outside the spray zone for some time period termed Δt_{seg}. Increasing the pan's Froude number (to ensure the tablet bed operates in the well-mixed rolling regime), the spanwise-to-streamwise spray zone aspect ratio, and the tablet-tablet and tablet-pan friction coefficient all act to decrease Δt_{seg}, leading to more uniform residence times and less inter-tablet coating variability for a given operating time. The relationship between Δt_{seg} and tablet load is more complex due changes in bed dynamics. In addition to the variability studies, a model is developed that relates coating fraction, effective mass flow rate, Δt_{seg}, and the desired average coating mass to the allowable fraction of tablets with a coating mass lying outside of a specified range of coating masses.

When studying intra-tablet coating mass variation, an indirect approach is taken. Since tablet shape strongly influences intra-tablet coating variability, the preferred orientation of non-spherical tablet shapes within a coater is studied. The motion of a bed of biconvex tablets with black caps and white bands with three different aspect ratios were recorded in a drum. The ratio of white-to-black pixels in the video stream provides the band-to-cap exposure times. The orientation index is defined as the measured band-to-cap exposure ratio divided by the ideal band-to-cap exposure ratio. The ideal band-to-cap exposure ratio would be in the same proportion as the band-to-cap area ratio, to ensure a uniform coating. Three different pan speeds and two fill levels were used for the tablets. The orientation index experiments results indicate that more cap than ideal was exposed for all operating conditions.

From the orientation index experiments, it was generally observed that increased pan speed improved the value of preferred orientation index. Qualitatively these results agree well with the orientation index experiments conducted by Pérez-Ramos (2007). Direct numerical comparisons cannot be made due to the absence of baffles and anti-slip bars in the current study, the use of a different coating drum and dissimilar lighting conditions. Increased tablet sphericity, in general also improved orientation index, a result similar to that reported by Wilson and Crossman, (1997) where they found variability to be a minimum for round tablets. The effect of fill level on the orientation index was hardest to discern, with the overall behavior indicating that the orientation index was only a weak increasing function of the fill level.

Finally, the thesis work describes the use of a spray coating algorithm to quantify the accumulation of coating on the surface of individual tablets. The ray tracing algorithm describes the spray as a continuous stream of coating mass, originating at a point source. Once a DEM simulation provides tablet states, *i.e.* tablet positions, orientations, translational, and angular velocities, the ray tracing algorithm computes the coating mass accumulation on the surface of the tablets by checking which regions of individual tablets have an unoccluded line of sight to the spray source. The coating mass on a small unoccluded region on the surface of the tablet is then computed by knowing the surface area's local outward point unit normal, local spray velocity, spray mass flow rate. In this manner the coating mass can be tracked over all particles.