The Effect of Particle Size on the Intrinsic Dissolution of Acetylsalicylic Acid

Kristina Darmanin [1], Hans Helmut Frey [2] and Claude Farrugia [1]

[1] Department of Chemistry, University of Malta, Msida MSD2080, Malta
[2] Development Division, Actavis Ltd., Bulebel Industrial Estate, Zejtun ZTN3000, Malta

Introduction

Dissolution has an important role in the release of active ingredients from pharmaceutical preparations. The main focus of dissolution testing is in the area of quality control and product development, since the test yields information related to the composition and manufacturing variables. Moreover, the rate of dissolution is studied during the course of a new chemical entity development since it predicts potential bioavailability. The research objective of this study was to examine the dissolution rate of acetylsalicylic acid non-disintegrating compacts made up from four different particle sizes while exposing only a fixed surface area to the dissolution medium. This is also known as the rate of intrinsic dissolution, which is regarded as a characterization study and is therefore not referenced in individual monographs.

Methodology

Coarse acetylsalicylic acid powder (125 – 1000 µm) was milled using a Quadro C-mill U5 and then sieved; powder was retained on the 90, 125, 180 and 250-µm sieves. Fine acetylsalicylic powder (45 – 355 µm) was also sieved and powder retained on the 45, 90, 125 and 180-µm sieves. All powders were compacted at 200 psi for 2 minutes to form a 500-mg nondisintegrating compact, and tested for intrinsic dissolution at 37 °C, and 75 rpm in 0.1 M HCl using an Agilent Pharmatest Automatic Dissolution Tester. The compacts formed from the fine acetylsalicylic acid powders were also tested by conventional dissolution analysis using the paddle dissolution apparatus. The concentration of acetylsalicylic acid in solution was determined using by UV-Vis spectrophotometry at a wavelength of 276 nm, and a set of values of the percentage API dissolved for each time point set during the 3 hour test was automatically given by the software. The data were fitted using nonlinear regression analysis to the function $C=kt^n$, and the variation in parameters *k* and *n* examined statistically.

Results

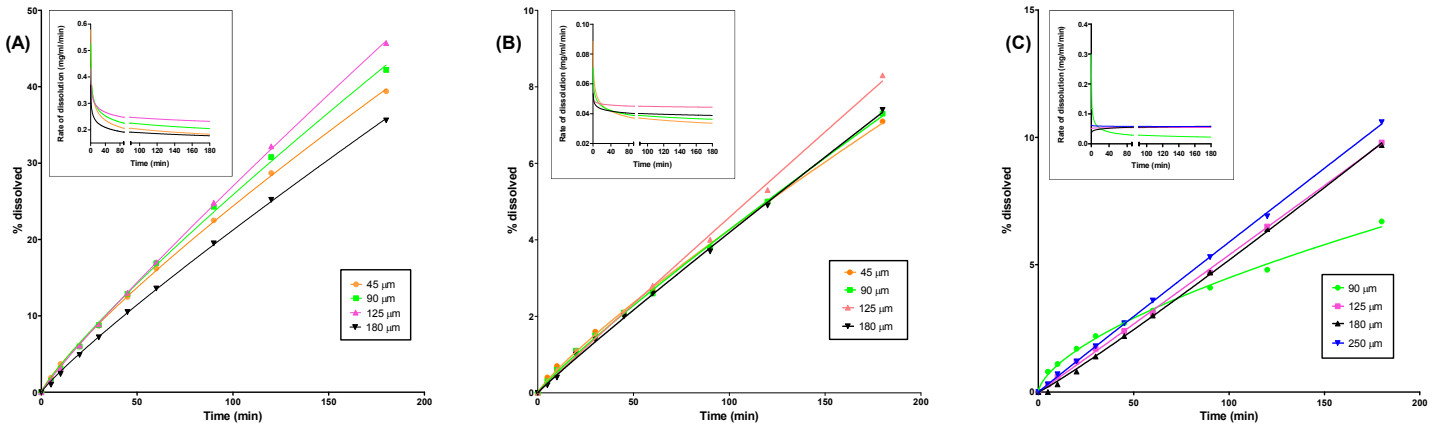

Figure 1: Nonlinear regression analysis of time dependent % dissolution of acetylsalicylic acid (with rate of dissolution computed as a differential function in inset) from compacts of (A) fine powder in paddle dissolution apparatus, (B) fine powder in intrinsic dissolution apparatus, and (C) coarse powder in intrinsic dissolution apparatus.

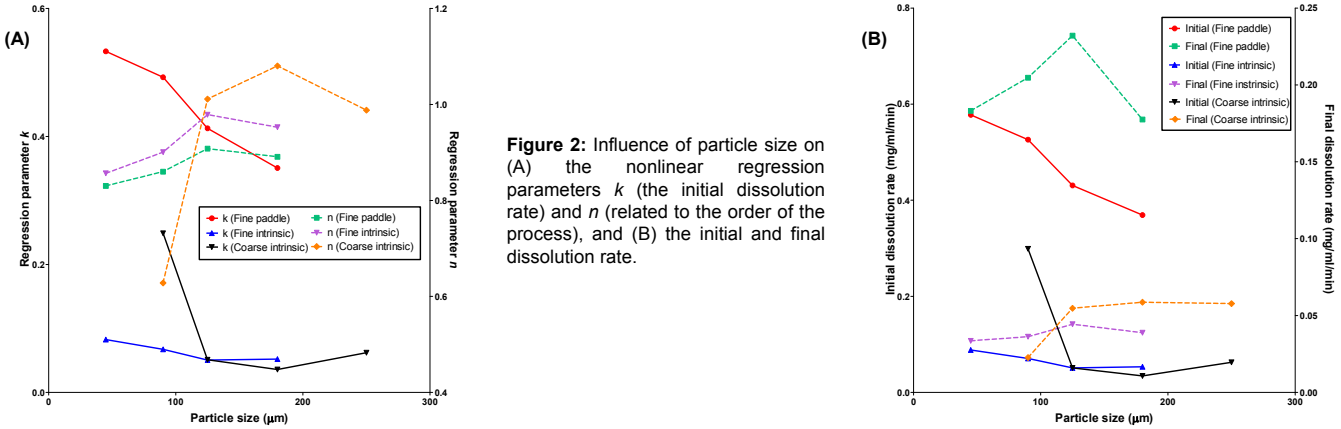

Figure 2: Influence of particle size on (A) the nonlinear regression parameters *k* (the initial dissolution rate) and *n* (related to the order of the process), and (B) the initial and final dissolution rate.

Conclusions

The initial dissolution rates for the paddle method showed an expected dependence on particle size, with the highest initial dissolution rate for 45 µm followed by the 90 µm, 125 µm and 180 µm respectively. However, the final dissolution rate showed no statistically significant trend. The intrinsic dissolution experiments showed no distinct correlation with particle size either for the initial or final dissolution rate, with the 90-µm powder showing an elevated initial dissolution rate following by a reduced final dissolution rate, presumably due to exhaustion of the drug reservoir. Moreover, *in vitro-in vivo* correlation considerations require dissolution tests to be carried out under sink, or zero order, conditions, which correspond to a theoretical value of *n* of 1; the results obtained appear to indicate that sink conditions were reasonably well attained. There appears to be conformity with previous investigations[1] that intrinsic dissolution enjoys the advantage of monitoring the dissolution rate in a manner uncomplicated by the particle size of the starting material.

References

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