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EFFECT OF DRUG SOLUBILITY IN WET GRANULATION FLUIDS ON THE DISSOLUTION RATES OF THE RESULTING TABLETS

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ABSTRACT

One factor in wet granulation processes which affects dissolution rates of the final tablets is shown to be the solubility of the drug substance in the granulating liquid. The relationship is not a direct correlation and a feasible explanation is offered.

INTRODUCTION

A fair amount of literature exists which addresses the area of wet granulation for flow enhancement and the improvement of binding in tablet manufacture (1-6). Much attention has also been focused on the physics of the process (7-8) and the effect that various parameters of granulation have on the mechanical properties of the tablets made from the agglomerates. It has been reported (2) that wet granulation ameliorates the wetting properties of hydrophobic drugs, but aside from that only a limited number of articles deal with wet granulation parameters which can potentially affect dissolution.

The article to follow describes an investigation of the dissolution characteristics of a wet granulated drug as a function of the solubility of the drug in the granulating liquid.

MATERIAL AND METHODS

The tablets used in this study were made using the following mg amounts per tablets: zindotrine 100 mg, lactose 57.4 mg, microcrystalline cellulose 30 mg, amorphous silicon dioxide 0.6 mg, sodium starch glycolate 10 mg, magnesium stearate, 2 mg, for a total tablet weight of 200 mg.

The tablets were made in the following fashion: the zindotrine, the lactose and the microcrystalline cellulose were passed through a 30 mesh hand screen, and then blended for 3 minutes in a Hobart mixer. The granulating liquid, the composition of which will be discussed further below, was then added, and mixing was carried out for an additional two minutes. The wet granulation was then passed through an oscillating granulator equipped with a 12 mesh screen. The wet granulation was then dried at 43^{o}C to a moisture content (loss on drying at 80^{o}C) of less than 12%. The dried granulation was passed through the oscillator equipped with a 16 mesh screeen. The dry, milled granulation was then mixed with the sodium starch glycolate, the amorphous silicon dioxide, and the magnesium stearate in a V-blender for 5 minutes. Tableting was carried out on a rotary tablet machine (Stokes Model RB2 rotary tableting machine). The tablets were produced so as to have a hardness of 8 kp, measured on a diametral hardness tester, (Schleuniger, Vector Corporation, Iowa) and a thickness of 2.9-3.1 mm.

The tablets were subjected to dissoluiton tests using USP method II at 37^{o}C with 0.1 N HCl as dissoluiton medium and an agitation speed of 50 rpm. Each dissolution curve was carried out in triplicate.

The granulation liquids used were hydroalcoholic solutions containing 0, 10, 20, 50 and 100% ethanol.

Solubilities of zindotrine in the various media were determined at 25^{o}C. The reason for testing at this temperature rather than 37^{o}C as is traditionally the case, was that the important parameter was the solubility of zindotrine under the granulating conditions, i.e. at 25^{o}C. The solubility determinations were carried out by placing an excess of

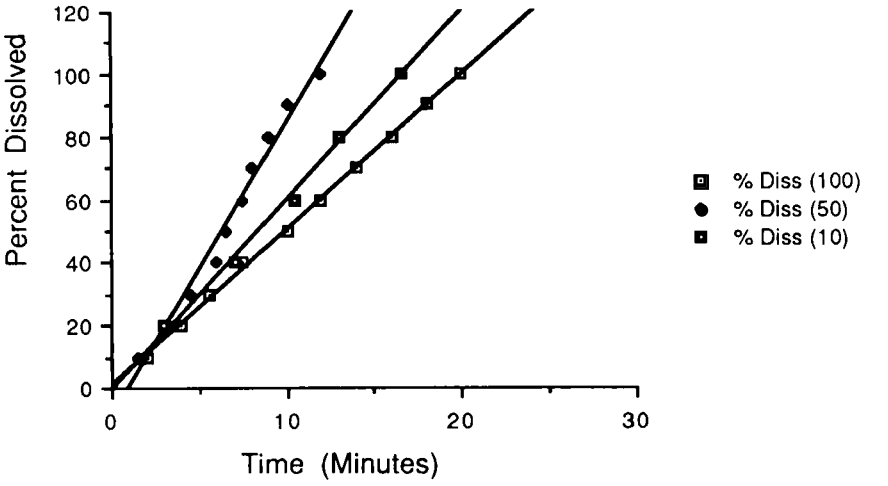

Fig. 1 Dissolution profiles in 0.1 N HCl of tablets made with varying granulation liquids. Water and 20% ethanol are not shown to avoid graphical clutter.

zindotrine in contact with the granulation liquid, agitating for 72 hours in a closed container, and assaying the supernatant. The assay method was spectrophotometric. Water was used as a diluent, and the measurement was carried out at 276 nm.

RESULTS AND DISCUSSION.

Dissolution rates of tablets made with the different granulation liquids are shown in Fig. 1.

It is seen that the curves are quite linear, showing that sink conditions are maintained. There is no lag time, so differences in disintegration times are not responsible for differences in the curves. The slopes, k (mg/mL/min), of the curves are of a type of dissolution constant. Fig. 2 is a plot of the values of k as a function of ethanol content of the granulation liquid. It is seen that there is a maximum in the curve.

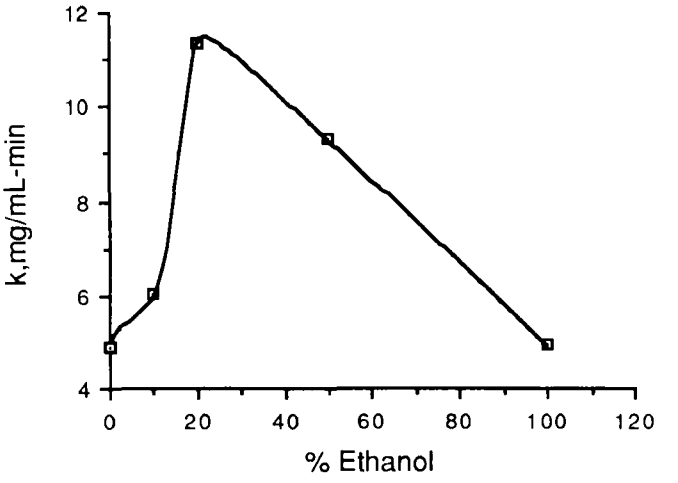

Fig. 2. Dissoluiton rate constants in 0.1 N HCl, *k* (mg/mL/min) from Fig. 1 plotted as a function of ethanol concentration in the granulation fluid.

The solubilities of the drug substance in hydroalcoholic solutions are shown in Fig. 3. This type of solubility curve is not unusual (9-10).

Comparison of the slopes of the profiles in Figures 2 and 3 suggests that the eventual dissolution rate is a function of the solubility of zindotrine in the granulaiton liquid. The correlation is, however, not a direct one, since the maximum in Fig. 2 occurs at a different ethanol concentration than that exhibited in Fig. 3.

The essential steps of the wet granulation process are (a) mixing the dry powders, (b) adding the granulating fluid, (c) kneading for a period of time, and (d) drying the wet mass.

During step (c) a certain mass of drug (m_1 grams) will dissolve in the granulating liquid, leaving [m_0-m_1] grams of undissolved drug. During the drying step, the m_1 grams of dissolved drug will precipitate, presumably in a fine state, hence increasing the overall surface area, *A*. The specific surface area of the undissolved and precipitated parts of the drug substance are denoted A_0 and A_1 (cm^2/g) respectively.

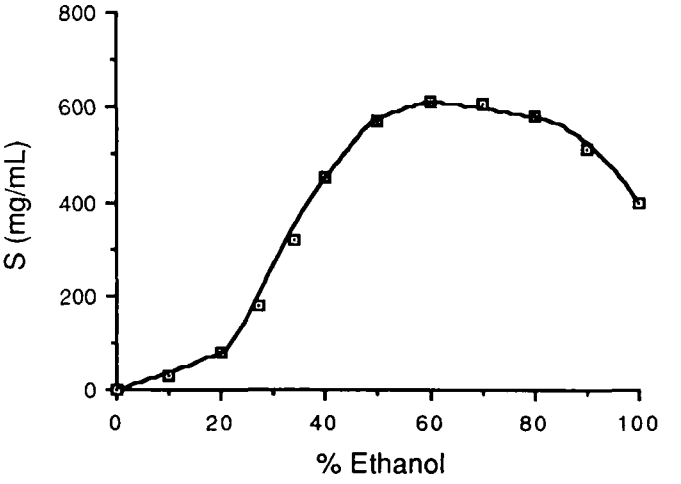

Fig. 3 Solubility of zindotrine in hydroethanolic solutions plotted as a function of ethanol concentration.

m_1 grams of material with *specific* surface area A_1 cm^2/gram will have a total surface area of $m_1 \cdot A_1$ cm^2 and $[m_0 - m_1] \cdot A_0$ cm^2, so the total surface area of the two fractions will be:

$$A = [m_0 - m_1] \cdot A_0 + m_1 \cdot A_1 \qquad \text{(Eq. 1)}$$

When material precipitates out by rapid evaporation, it usually is quite fine having a large *specific* surface area, so it is assumed here that A_1 is larger than A_0. In this case, Eq. 1 predicts that there will be an increase in *A*, with increasing solubility of the drug substance in the granulation medium. If the specific surface area of the precipitated drug substance were independent of the ethanol concentration, then the maxima in Fig. 2 and Fig. 3 would be identical, but since evaporation rates (and hence the particle sizes upon precipitation) differ with ethanol concentration, a general specific surface area cannot be assigned to the precipiated drug substance. The maximum in the two figures can, therfore, not be expected to necessarilay coincide.

The above is, of course, one explanation of many, but is deemed to be the most reasonable. Other explanations such as lactose salting-in (or at high ethanol concentration salting-out) the zindotrine could be visualized. Another factor which may play a part is that lactose is solubilized by the granulation fluid, but will be less solubilized at the higher concentrations of ethanol. This may, for instance, affect the porosity of the prime granules and hence, indirectly, the dissolution rate.

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