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RESEARCH PAPER

The Development of a Modified Dissolution Method Suitable for Investigating Powder Mixtures

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ABSTRACT

A novel dissolution method was developed, suitable for powder mixtures, based on the USP basket apparatus. The baskets were modified such that the powder mixtures were retained within the baskets and not dispersed, a potential difficulty that may arise when using conventional USP basket and paddle apparatus. The advantages of this method were that the components of the mixtures were maintained in close proximity, maximizing any drug:excipient interaction and leading to more linear dissolution profiles. Two weakly acidic model drugs, ibuprofen and acetaminophen, and a selection of pharmaceutical excipients, including potential dissolution-enhancing alkalizing agents, were chosen for investigation. Dissolution profiles were obtained for simple physical mixtures. The f_1 *fit factor values, calculated using pure drug as the reference material, demonstrated a trend in line with expectations, with several dissolution enhancers apparent for both drugs. Also, the dissolution rates were linear over substantial parts of the profiles.*

For both drugs, a rank order comparison between the f_1 *fit factor and calculated dissolution rate, obtained from the linear section of the dissolution profile, demonstrated a correlation using a significance level of* $P = 0.05$*. The method was proven to be suitable for discriminating between the effects of*

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excipients on the dissolution of the model drugs. The method design produced dissolution profiles where the dissolution rate was linear for a substantial time, allowing determination of the dissolution rate without mathematical transformation of the data. This method may be suitable as a preliminary excipient-screening tool in the drug formulation development process.

Key Words: *Dissolution; Ibuprofen; Acetaminophen; Excipient*

INTRODUCTION

Two processes by which an excipient may affect the dissolution rate of a drug are through modification of the microenvironment around a drug particle, in terms of modified pH or increased solute concentration, and through changes in the apparent surface area of the drug. One approach to characterize these processes is an extension of the rotating disk apparatus,[1] involving the co-compression of the drug with the excipient of interest into a disk. While this method simulates tablet formulation, it complicates the study as other factors have been demonstrated to be significant. For example, it has been shown that the particle size of an excipient affects the dissolution rate of the drug and this may be attributed to several different mechanisms. One such mechanism is the percolation theory, in which pores of sufficient size and number are able to form networks, which allow the solvent to penetrate and increase the contact area. Also, an increase in excipient particle size produces more pores similar in dimensions to, or larger than, the boundary layer, whereby the diffusion layer can curve into the pores, effectively increasing surface area. Finally, the larger the excipient particle size, the less uniform the mix, leaving areas of the disk unexposed to the effect of the excipient.[2] These phenomena are unlikely to be predictable. Also, during the disk formation process, the energy input may affect the morphology of both the drug and excipient. Whilst these properties are clearly of interest, without full characterization of the processes involved, it would be difficult to attribute any changes in the dissolution rate of the drug to any specific property of the excipient under investigation.

A second approach can be demonstrated in the powder method used by Hendriksen,[3] where weighed samples of pure fenoprofen were rapidly tipped from a glass vial onto the surface of the stirred dissolution medium. Disadvantages of this method could include variation in addition technique, variable distribution of the material throughout the flask, a short period of linearity and, where mixtures are used, separation of the drug from the excipient.

Therefore a primary objective of this work was to develop a dissolution procedure which maintained and maximized drug:excipient interaction, without the necessity of subjecting the mixtures to non-optimized processing, and produced a linearized dissolution profile. On this basis, a novel method based on the USP basket apparatus was developed.[4] This involved sealing the lower part of the baskets, creating a well in which powder could be held and maintained. A second aim was to determine the discriminating power of the method and suitability as a screening method by comparing a large selection of excipients with contrasting properties, including soluble and insoluble alkalizing compounds, diluents, effervescing compounds, and soluble and insoluble pH neutral compounds, for their effects on the dissolution of two weakly acidic model drugs. The selected drugs were acetaminophen, pK_a summarized as being between 9.0 and 10.2[5] and ibuprofen, pK_a reported as 4.4 and 5.2.[6] Excipient selection included potential dissolution enhancers which, if found to demonstrate this property, could be considered for further study.

MATERIALS

Acetaminophen, ibuprofen, starch, lactose (Pharmatose DCL 11), sodium bicarbonate (extra fine grade), and microcrystalline cellulose (PH) were obtained from GSK Pharmaceuticals (Weybridge, U.K.). Calcium carbonate, citric acid, sodium chloride, magnesium hydroxide, calcium hydrogen phosphate, hydrochloric acid, potassium chloride, methanol, acetic acid, L-arginine, glycine, L-lysine, tribasic sodium phosphate, magnesium hydroxide,

sodium carbonate, potassium bicarbonate, aluminum hydroxide, sodium hydroxide, mono-basic potassium phosphate, and paraffin wax were purchased from Aldrich (Poole, U.K.). All materials were of pharmaceutical, analytical grade, AVS or HPLC grade as appropriate.

EQUIPMENT

The dissolution system consisted of a Caleva Model 7ST dissolution bath, equipped with 1-L round-bottomed flasks and with baskets conforming to Apparatus I—USP.[4] Sampling was performed on a continuous loop basis, using 10-μm filters (Caleva), using a Watson Marlow 5025 peristaltic pump set with a flow rate of $5\,mL\,min^{-1}$. Analysis was performed automatically at desired time intervals using a LKB Biochrom Ultrospec II multi-cell UV/VIS spectrometer Quartz cell with 10-mm pathlength. Data was collected by a PC running Tablet Dissolution Software V1.12 supplied by LKB Biochrom. Data printouts (absorbances) were collected and converted to quantity dissolved by comparison to a five-point standard curve.

METHOD

Initially, standard baskets as described in the USP were dipped in a fixed volume of molten paraffin, sealing the base and extending 10 mm up the sides of the basket. These adapted baskets were air-dried, visually inspected to ensure coverage was even and complete, and used throughout the experimental series. Pure acetaminophen, ibuprofen, or 1:1 mixtures (prepared by physical mixing) were weighed into the basket. The weights added were appropriate to give 300±3 mg of drug. The baskets were gently tapped until the powder was below the upper limit of the paraffin-coated mesh. Dissolution medium (900 mL per flask) (0.05 M HCl for acetaminophen and USP buffer 6.8 for ibuprofen, selected to ensure "sink" conditions) was prepared and thoroughly degassed. Dissolution fluid temperature was controlled at 37±0.5°C. After equilibration of dissolution medium temperature and sampling flow-through system, each sampling station was background zeroed. The baskets were lowered slowly into the dissolution bath, and after a brief holding period (seconds), to allow entrapped air to exit from the powder, the rotational speed of the baskets was set to 100 rpm. The data collection system was initiated, collecting absorbances at the appropriate wavelength, i.e., 237 nm for ibuprofen and 295 nm for acetaminophen. As a control, dissolution profiles were also obtained by adding the same quantities of acetaminophen and ibuprofen alone, and in the presence of the potentially modifiying excipients, directly to the vessel using the standard apparatus.

Values of f_1 were calculated according to a modification of the equation of Moore and Flanner:[7]

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100\%$$

where R_t is the percentage drug dissolved for the reference product, at time t, T_t is the percentage drug dissolved for the test product, at time t, and n is the number of time points, using the pure drug profile as reference. As this study's aims require the measurement of differences in terms of magnitude but also in terms of inhibition or promotion of dissolution, the equation was therefore modified as shown below. Thus, the sign of f_1 indicated either dissolution promotion (+) or dissolution inhibition (−), with the magnitude indicating the difference from the reference. This modification was used throughout for dissolution profile comparisons, recognizing that crossover of curves would cause a canceling of the differences:

$$f_1 = -\left\{ \frac{\sum_{t=1}^{n} R_t - T_t}{\sum_{t=1}^{n} R_t} \right\} \times 100\%$$

For acetaminophen the experiment was conducted over 90 min, sampling at least every 6 min. The f_1 values were calculated using data obtained at 6-min intervals from 6 to 84 min or until one interval after a minimum of 85% of the test mix had dissolved and five data pairs had been collected. For ibuprofen, the experiment was conducted over 240 min, sampling at least every 12 min. The f_1 values were calculated using data at 12-min intervals from 12 to 240 min or until one interval after a minimum of 85% of the test mix had dissolved and five data pairs had been collected.

The second method of analysis involved measuring the drug dissolution rate from the linear section of each dissolution profile by use of linear regression analysis. At least five replicates were used. All mathematical analysis was conducted

using the average dissolution profiles of at least five replicates.

RESULTS

There was rapid dissolution when the uncontrolled powders were added to the dissolution medium. Figure 1 shows the dissolution of acetaminophen alone and in the presence of magnesium hydroxide and calcium carbonate. Rapid dissolution of acetaminophen alone and in the presence of magnesium hydroxide results in no difference between the curves ($f_1 = 7.3$). Although the dissolution of acetaminophen is retarded in the presence of calcium carbonate ($f_1 = -40.7$), the data is very variable (%RSD up to 40%), indicating the variable distribution of the material throughout the flask (Fig. 1).

Generally, for the dissolution profiles generated using the modified method three distinct phases were observed. The first phase corresponded to a "dispersal" phase where some of the powdered material was lost from the basket during the initiation of the experiment, for example through the release of entrapped air bubbles. This led to an increase in the initial rate. The second, most relevant phase was the "linear" phase that corresponded to a steady dissolution rate from the surface of the powder mix. The third phase was apparent for the experiments where the dissolution rate was high, corresponding to a decrease in the quantity of drug still to dissolve and therefore a decreasing dissolution rate. Typical dissolution profiles for both drugs and selected excipients using the modified method are illustrated in Figs. 2 and 3. The Spearman rank order correlation method was applied to compare the f_1 and dissolution rate derivation methods, with a correlation found at the $P = 0.05$ level, $\rho = 0.93$ and $\rho = 0.85$ for acetaminophen and ibuprofen, respectively. The calculated f_1 fit factors and dissolution rates obtained from the linear section of the profiles are detailed in Table 1.

DISCUSSION

For both drugs, modification of the drug dissolution rate by the addition of excipients could be characterized as either significantly inhibiting, marginal, or significantly enhancing. For acetaminophen, compounds showing significant negative effects on the dissolution rate consisted of generally insoluble excipients, e.g., starch and microcrystalline cellulose, or soluble excipients with a slow dissolution rate, e.g., magnesium oxide and hydroxide, aluminum hydroxide, and calcium carbonate, which are all completely soluble under these conditions (unpublished data), but where residue was observed

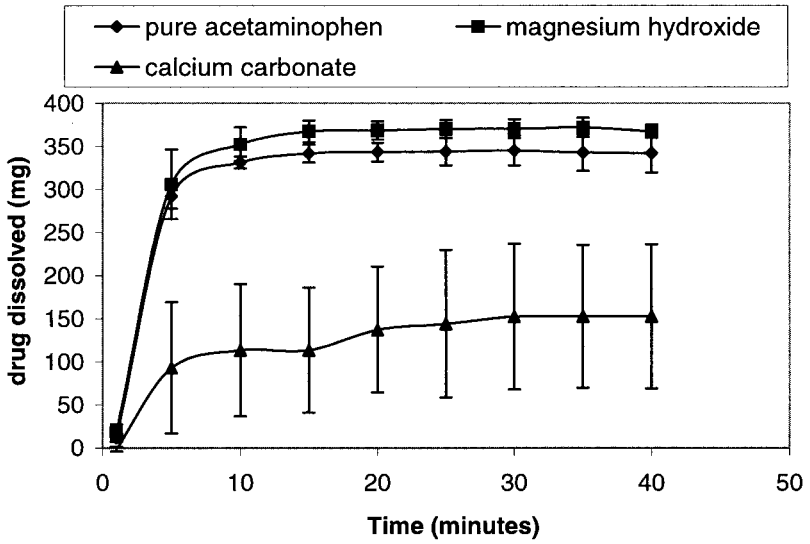

Figure 1. Illustrating typical dissolution profiles for uncontrolled acetaminophen:excipient powder mixtures. Results are mean of six replicates ± SD. Legend indicates excipient used.

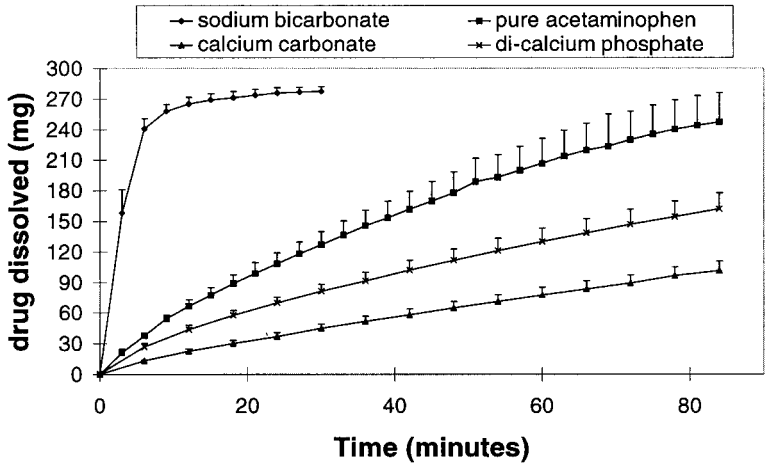

Figure 2. Illustrating typical dissolution profiles for acetaminophen:excipient powder mixtures. Results are mean of at least five replicates + SD. Legend indicates excipient used.

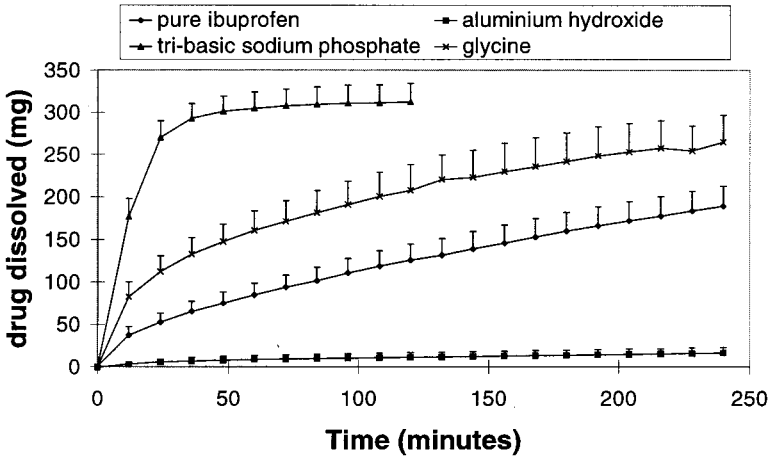

Figure 3. Illustrating typical dissolution profiles for ibuprofen:excipient powder mixtures. Results are mean of at least five replicates + SD. Legend indicates excipient used.

in each basket on completion of the experiment. In fact, the calcium carbonate mix appeared completely impervious to dissolution fluid penetration. The insolubility/slow dissolution rate and variable "wetting" characteristics may have contributed to an effect resulting in shielding of the drug from the dissolution medium and reducing the effective surface area. A surprising member of this group was sodium carbonate, being soluble with effervescence in dilute acids and producing a solution with pH 11.6,[8] significantly higher than the pK_a of acetaminophen, and considered as having potential as a dissolution enhancer.

For compounds having a marginal effect on dissolution, it is noted that all are water-soluble and neutral or acidic. The closeness of the data does not allow for assessment of the role of excipient solubility, but it is noted that all of these excipients are inhibitory, the likely mechanism being a reduction of the surface area of the drug in contact with the dissolution medium, due to the diluting effect of the excipient.

There were two subgroups of excipients having a positive effect on the dissolution of acetaminophen. The first subgroup consisted mainly of non-effervescing, alkalizing, soluble excipients. When

Table 1

Summary of f_1 *Fit Factors and Dissolution Rates for Drug:Excipient Mixtures Compared to Pure Drug as Reference* (f_1=0)

	Acetaminophen		Ibuprofen	
Excipient	f_1 Factor	Dissolution Rate (mg min^{-1})	f_1 Factor	Dissolution Rate (mg min^{-1})
Microcrystalline cellulose	−72.9	0.439	25.7	0.510
Calcium carbonate	−62.7	1.12	−54.1	0.294
Starch	−52.1	0.577	−48.2	0.333
Magnesium hydroxide	−47.8	0.901	−39.8	0.235
Sodium carbonate	−40.7	0.694	374	12.5
Magnesium oxide	−39.2	0.709	−23.8	0.235
Aluminum hydroxide	−37.0	0.901	−91.0	0.0432
Di-calcium phosphate	−36.2	1.69	−47.2	0.257
Sodium chloride	−20.0	2.37	19.0	1.06
Tartaric acid	−8.7	2.76	−70.7	0.268
Lactose	−6.8	2.47	72.3	0.452
Citric acid	−4.1	2.73	−61.8	0.340
Glycine	16.7	3.04	61.9	0.623
L-lysine	26.8	2.39	401	11.3
L-arginine	28.1	3.32	350	9.57
Tri-sodium phosphate	39.5	4.67	329	11.3
Sodium bicarbonate	210	40.1	389	12.7
Potassium bicarbonate	211	37.5	347	11.5

reviewing the relationship between the alkalinity of the compounds vs. the dissolution promotion, a trend was apparent, i.e., the more alkaline an excipient, the faster the dissolution rate. This is in line with expectations due to an increasing solubility of the drug in the diffusion layer, at and above the pK_a value, with increasing pH. The second subgroup consisted of alkalizing, soluble excipients that effervesce in the dissolution medium used, namely sodium bicarbonate and potassium bicarbonate in 0.05 M HCl. In acidic media, sodium bicarbonate and potassium bicarbonate react to form water and carbon dioxide. This gas generation is the basis of many effervescent formulations.[9] This has the effect of causing large changes in agitational force and increasing the surface area of the drug. These are likely to be the causes of the very significant differences in dissolution profile, i.e., difference factors f_1>200%, for both excipients.

For ibuprofen, the group of excipients found to significantly inhibit dissolution included four compounds commonly used in antacid formulations and also di-calcium phosphate (see Table 1). Of particular note was the presence of "solid cakes" in the baskets on completion of the experiment for the magnesium oxide and hydroxide:ibuprofen mixes, the calcium carbonate:ibuprofen mix, and particularly the aluminum hydroxide:ibuprofen mix, which was found to be the most inhibitory of the compounds under test, and which was also noted as completely dry and impervious to water on completion. The mode of action is likely to be as for acetaminophen, i.e., reduction of the apparent surface area by physical shielding and restriction of "wetting" of the drug. This group also contained both citric and tartaric acid, and the slightly acidic (laboratory measured) starch. It is postulated that these may retard the dissolution of ibuprofen by limiting the buffering capacity of the dissolution medium, i.e., act by maintaining the acidification of the boundary layer around each particle, in conjunction with the dissolving ibuprofen, hence reducing the concentration gradient, the driving force for dissolution.

The remaining excipients/antacids were all found to be dissolution promoters when compared to pure ibuprofen. The first subgroup, having a positive effect ($0<f_1<100$), was fairly diverse in nature, one

common property being their neutrality. The second subgroup (f_1>300) was found to have a major promoting effect on the dissolution of ibuprofen. This group consisted of the alkalizing, soluble compounds and also the two bicarbonates whose mode of action is likely to include modification of the dissolution hydrodynamics through effervescence (possibly reacting with the weakly acidic drug). Clearly, all of these compounds are likely to act by substantially increasing the solubility of ibuprofen by modification of the pH in both the bulk and diffusion layers above the pK_a of the drug.

The use of the method developed in this study yielded potential dissolution enhancing excipients for both model drugs, i.e., potassium and sodium bicarbonate, tri-sodium phosphate, L-arginine and L-lysine, and also sodium carbonate for ibuprofen. The promoting effect of sodium bicarbonate has been recognized previously, in an ibuprofen tablet development study,[10] where a formulation containing sodium bicarbonate exhibited the fastest dissolution rate, of the prepared formulations, but also exhibited unfavorable granulation properties, i.e., the formulation containing sodium bicarbonate: ibuprofen liquefied during the granulation stage and was not pursued to full tablet production. For acetaminophen, tablets formulated with sodium bicarbonate at a ratio of at least 0.74:1.00 have been demonstrated to significantly improve the rate of absorption compared to a commercially available tablet.[11] The development of formulations containing the excipients, alone and, in combination, with the aim of maximizing the drug dissolution rate and, in the case of ibuprofen, handling properties, may be worth investigating.

In conclusion, the developed method has demonstrated discriminatory power in terms of examination of the effect of an excipient on the dissolution rate of the model drugs. It was shown to be more discriminating and had less variability than a non-controlled method. The observed modification to the dissolution rate was generally in line with expectations, in terms of physicochemical properties of the excipient and observations during the study. Comparison of the dissolution rate from the linear section of each dissolution profile with the calculated f_1 fit factor produced a significant rank correlation. The method may be suitable as a rapid screening tool for the testing of pharmaceutical excipients in terms of their effect on the dissolution rate of the model drugs.

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