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Effect of commercial and high purity magnesium stearates on in-vitro dissolution of paracetamol DC tablets

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Summary

The effects of several commercial grades and a high-purity magnesium stearate on in vitro dissolution of paracetamol DC tablets have been studied. In each case, 0.5% w/w concentration of the lubricant was added to the paracetamol DC granules and mixed for a pre-determined time interval. Tablets of equivalent weight and dimensions were prepared from paracetamol DC and the lubricated mixtures for direct comparison of in vitro dissolution. Whilst the commercial magnesium stearates show marked differences in dissolution between the various grades, all retarded dissolution to a greater extent than the high-purity sample. The in vitro dissolution of unlubricated and lubricated paracetamol DC tablets has been compared. The role of hydrophobic lubricant films has been discussed in terms of magnesium stearate influence on in vitro dissolution. The superior dissolution data for tablets lubricated with high-purity magnesium stearate confirmed the hypothesis that the hydrophobic film formation propensity of commercial and high-purity magnesium stearate is different.

Introduction

There are three fundamental processes which contribute to the dissolution of a solid immersed in a solvent, regardless of the mechanism by which dissolution may occur (Hsia et al., 1977). According to these authors the processes are:

(a) the primary surface interaction leading to the continuous production of a new surface at the solid-liquid interface;
(b) solvation of the solid at the solid surface or solid-liquid interface;
(c) mass transfer of the dissolved solid into the bulk of the solution.

Magnesium stearate is thought to interfere with these processes and thus is held responsible for retardation of the dissolution rate in solid dose formulations. Several workers (Levy and Gumtow, 1963; Samyn and Jung, 1970; Leeson and

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Carstensen, 1974; Bolhuis et al., 1975; Lerk and Bolhuis, 1977; Iranloye and Parrott, 1978; Ahmed and Enever, 1978; Nicklasson and Brodin, 1982; Itai et al., 1985; Johansson, 1985; Chowhan and Chi, 1986; Van Kamp et al., 1986) have investigated the deleterious effects of magnesium stearate on dissolution and attempted to explain its role in the dissolution process retardation. The mechanism by which magnesium stearate causes its negative effects is not yet fully understood. However, the involvement of the magnesium stearate hydrophobic film on the host particle is always envisaged.

The objective of this study was to examine the effects of magnesium stearate on tablet dissolution and assess the influence of different grades of lubricants and mixing times on in vitro dissolution. Since it has been shown that when lubricating sodium chloride commercial magnesium stearates form a far more extensive surface coverage of host than high-purity material (Hussain, 1988), the dissolution studies will also test the hypothesis that the hydrophobic film formation propensity of the commercial and high-purity lubricants is different. Relatively inferior drug dissolution profiles for lubricated paracetamol DC tablets with commercial lubricants would support this hypothesis.

Materials and Methods

Methods

Paracetamol DC granules, commercial magnesium stearates (MSD, MSH, MSJ, MSM and MSW) and the high-purity magnesium stearate MSZ were used in this study as reported earlier (Hussain et al., 1991). AnalaR grade of hydrochloric acid (BDH Chemicals Ltd, Poole) was diluted and used as dissolution medium.

Mixing and tabletting

The details of the mixing process of paracetamol DC with appropriate quantities of the lubricant and tablet manufacturing methods were identical to those previously reported (Hussain et al., 1991).

Specific surface area (SSA) measurement

The BET (Brunauer, Emmett, Teller) surface area was measured with an Orr Surface Area, Pore Volume Analyser Model 2100 (Micromeritics Instruments Corp., U.S.A.), using liquid nitrogen as the adsorbing gas. For surface area determinations, 2–5 g of material was accurately weighed and the adsorption of nitrogen gas at liquid nitrogen temperature (−196°C) at a range of pressures was measured and SSA calculated. Data recorded are means of three runs.

Particle size analysis

The particle size distribution was measured on a Laser Diffraction Particle Size Analyser, Series 2600 (Malvern Instruments Ltd, Malvern, Worcs., U.K.). Powder materials were suspended in ethanol and sonicated before analysis. In each case, particle size distribution and volume mean diameter were recorded.

Dissolution method and apparatus

The dissolution apparatus consisted of a single vessel Erweka dissolution tester Type DT (Erweka Apparatebau GmbH, Heusenstamm, Germany). The instrument was based on the USP XXII paddle method 2, and linked to an ultraviolet spectrophotometer for continuous flow of dissolution fluid.

Dissolution tests were carried out under the following experimental conditions: volume and dissolution medium, 1000 ml of 0.1 M HCl, at 37°C; paddle speed, 25 rpm; reference solution, 0.1 M HCl; cell width and type, 1 mm, silica. The absorbance of the paracetamol reference standard solution (100 mg l^{-1}) was measured at 242 nm and stored for calculations. During the test runs a sample was continuously taken from the dissolution vessel at a rate of 9.6 ml min^{-1}, filtered through a Millipore filter and the absorbance measured every minute on a 841A Diode Array Spectrophotometer (Hewlett Packard, San Diego, U.S.A.) returning the sample to the dissolution beaker. The spectrophotometer was connected to a microcomputer and the data were collected and stored.

From a knowledge of drug absorbance at a particular time, the total quantity of the drug in

solution was calculated. At least five tablets were tested and the dissolution data were expressed as plots of mean drug release against time; runs were generally discontinued after 20 min, since dissolution after this time was considered to be outside the region of influence of the lubricant film.

Results and Discussion

Effects of lubricants on dissolution

Fig. 1 shows the relative drug release from paracetamol DC tablets prepared from 0.5% w/w concentration of commercial, high-purity magnesium stearates blended for 30 min and unlubricated tablets. Drug release has been lowered for all lubricated samples. Moreover, all commercial magnesium stearates cause an appreciable decrease in the dissolution rate. MSH shows the maximum negative influence on dissolution whilst MSM exerts least effect on drug dissolution.

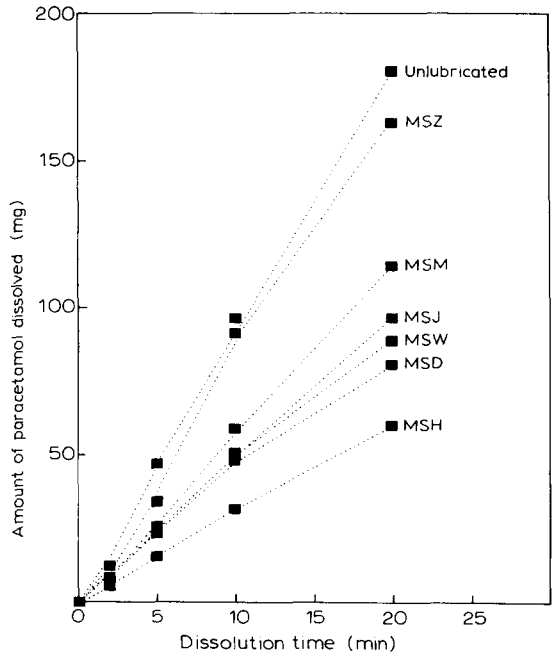

Fig. 1. Dissolution profiles of paracetamol DC prepared from blends containing 0. 5% w/w of various grades of magnesium stearates, after mixing for 30 min.

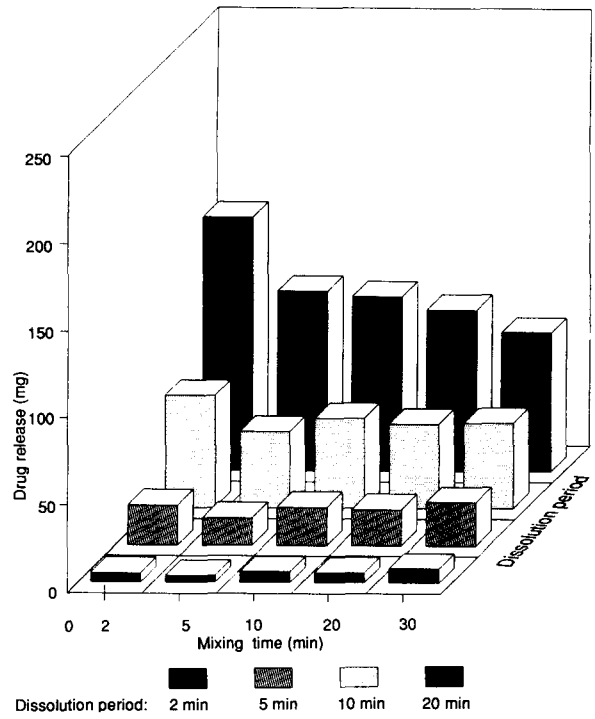

Fig. 2. Effect of 0.5% w/w MSD on drug release as a function of lubricant mixing time and dissolution time.

Figs 2 and 3 give detailed information on the influence of commercial (MSD), and the high-purity lubricant MSZ respectively in terms of mixing time and drug dissolution. The MSD dissolution profile in Fig. 2 indicates that maximum deleterious influence is exerted after 2 min of blending as indicated by the drug release after 2–20 min. Mixing for longer periods does not increase the negative effects on dissolution. The data and the corresponding dissolution profiles for MSZ confirm the influence of mixing time, however, the magnitude of the negative influence is markedly less than that for MSD. This difference in the effects on dissolution of the two lubricants on paracetamol DC may be explained by incomplete and quantitatively less hydrophobic film coverage on the individual granules particles and the formed tablets by MSZ than MSD and the other commercial lubricants. These dissolution observations are consistent with the secondary ion mass spectrometry (SIMS) surface

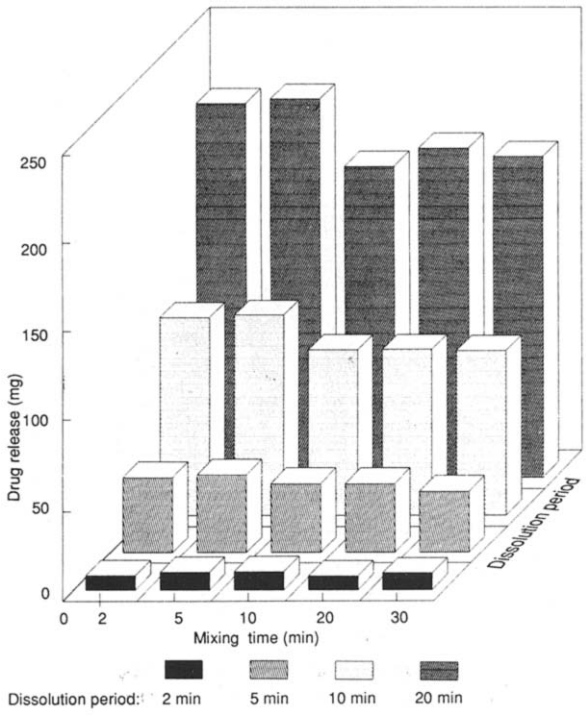

Fig. 3. Effect of 0.5% w/w MSZ on drug release as a function of lubricant mixing time and dissolution time.

analyses data reported recently (Hussain et al., 1990).

The lubricant physical properties such as specific surface area and particle size are recorded in Table 1. Attempts were made to relate dissolution data with the physical characteristics of the lubricants but no direct relationship or correlation was found. It is therefore reasonable to suggest that effects on dissolution are related to the hydrophobic film formation on the granules and the tablet.

TABLE 1

Specific surface area and particle size analysis data for commercial and the high-purity grades of magnesium stearate

Sample	SSA ($m^2\ g^{-1}$)	Volume mean diameter (μm)
MSD	7.30	7.0
MSH	8.92	10.0
MSJ	7.31	9.6
MSM	2.83	18.9
MSW	6.63	7.6
MSZ	7.68	10.2

Role of hydrophobic lubricant films

Drug dissolution essentially involves the release of drug molecules from the solid surface into solution and subsequent transfer to the liquid bulk. These two processes determine the rate of drug release. The hydrophobic nature of surface exposed to the dissolution fluid profoundly influences dissolution. Paracetamol, whilst containing polar functional groups and polar crystal faces, may become relatively more hydrophobic after blending with a lubricant. It is envisaged that commercial magnesium stearates retard dissolution due to hydrophobic film formation on granules. It has been suggested (Chowhan and Chi, 1986) that magnesium stearate flakes cover drug particles by particle-particle interactions, forming a physical barrier and decreasing the effective surface area for drug dissolution. The end result is a marked reduction in dissolution. Applying a similar argument, Levy and Gumtow (1963) had earlier stated that the dissolution rate retardation by magnesium stearate could be partially the result of delayed disintegration time and reduced contact between drug and solvent. Furthermore, since magnesium stearate powders are extremely hydrophobic, lubricant films would decrease the wettability of the lubricated powders and thus reduce dissolution. The wettability influences the disintegration time, dissolution and subsequently release of the drug. Igwilo and Pilpel (1987) reported that the decreased wettability of paraffin coated tablets was due to changes in contact angles with water and also showed reduced drug dissolution from these tablets.

From the dissolution results in this work it is evident that commercial lubricants adversely affect dissolution of paracetamol DC tablets whilst the high-purity sample MSZ has practically no influence on drug dissolution (see Fig. 1).

In addition, the findings from this work may be interpreted in terms of particle surface coverage and hydrophobic films. Therefore it is proposed that, at the blending stage, commercial lubricants form a more complete hydrophobic molecular and particulate film on the particles. Initially, the

film is of molecular dimensions with subsequent particulate and molecular form on prolonged mixing (Hussain et al., 1988). MSZ coverage is less extensive. Also, on compression of samples lubricated with commercial materials, the paracetamol particles fragment and deform, exposing a proportion of newly created surface so that tablets have a number of non-hydrophobic areas. Initially, the dissolution may begin from such centres. The presence of the hydrophobic films in the core of the tablet surrounding the majority of particles nevertheless retards dissolution. The high-purity magnesium stearate forms a much reduced hydrophobic film coverage of host powders and therefore will not interfere with the dissolution to the same extent.

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