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Influence of microphysical structure on in vitro activity of new synthetic antacids

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Summary

The microphysical structure of 5 new synthetic antacids (almagate, magaldrate, hydrotalcite, almagcit and aluminium hydroxide–magnesium carbonate co-gel) has been determined by laser light scattering. Almagate was shown to consist of unique particles and to have a large specific surface area whereas the other antacids contained agglomerates of various sizes which could be broken down in aqueous and acid suspensions. The speed of neutralisation of these antacids correlates well with their microphysical structure.

Introduction

In spite of the development of new systemically acting drugs, particularly histamine H_2-blocking agents, antacids continue to be widely used in the treatment of gastrointestinal disorders related to secretion of excess gastric acid (Marks, 1980). Recently a new group of synthetic antacids (Baur et al., 1981; Moragues et al., 1984) has been introduced, with advantageous therapeutic properties over the classical aluminium hydroxide gels and aluminium magnesium hydroxide co-gels.

In practice, antacid activity is directly related to wettability and surface area. The wettability of powders is an important parameter, since wetting is often the first step in dispersion, and the area of the product exposed to the solvent determines the dissolution rate (La Manna, 1985). In the case of antacids, this relationship between neutralizing velocity and efficacy has been amply demonstrated (Hem, 1975; Pattanhi et al., 1981; Ritschel and Koeleman, 1979; Svensson and Wiser, 1981).

In most of the standard dynamic methods for particle size determination erosion of the particles occurs, and the information obtained corresponds to the size of the elemental particles of a powder (true particle size). However, for very cohesive materials which are usually supplied as more or less consistent agglomerates, a method capable of measuring the distribution of these unaltered agglomerates is required. The laser light scattering technique of suspensions of antacids described below is an approach to measure this parameter which we suggest is the effective particle size of particles of a cohesive material.

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The true and effective particle size, and the specific surface area of 5 new synthetic antacids, i.e. almagate, magaldrate, aluminium magnesium carbonate co-gel, hydrotalcite, and almagcit have been determined by laser light scattering, and the microphysical structures determined by this method help to explain the performance in the pH-stat test carried out previously (Beneyto and Fábregas, 1984) on samples of the antacids (possessing identical specifications to those used in the experiments described below).

Materials and Methods

Materials

Almagate (Laboratorios Almirall, S.A., Spain), aluminium hydroxide–magnesium carbonate co-gel (Reheis, Ireland), hydrotalcite and almagcit (Giulini, F.R.G.) and hydrochloric acid (E. Merck, F.R.G.) were used.

Samples of magaldrate from two different manufacturers (Reheis and Giulini), identified in this work as I and II, respectively, have also been studied.

Apparatus

Particle size analysis was performed using a Malvern 2600 LBD laser light scattering powder particle analyzer. The instrument was fitted with a 63 mm focal length lens and the analyses were carried out with a dry powder feeder, or with a solid in suspension conversion unit (PS64 and PS14 cells, respectively).

True density was obtained using an air comparison pycnometer (Beckman, model 930). The apparent and tapped density were measured with an Engelsmann volumometer.

Test methods

Particle size analysis of dry powders was undertaken directly using the PS64 feeder, at a nitrogen pressure of 1.05 $kg \cdot cm^{-2}$ to impel the powder through the laser beam.

In disaggregation and dissolution experiments, the antacid sample (0.5 g) was dispersed in a constant volume (800 ml) of the selected fluid (distilled water or 0.003 M hydrochloric acid). Two stirring systems with different energy inputs have been compared on dispersions of each antacid material (propeller stirring with and without additional ultrasonic agitation).

At the selected time intervals samples were pumped through the flow cell of the instrument to measure particle size.

Results

The 6 antacid compounds studied exhibited different physical characteristics (Table 1). In particular the variation in specific surface area sug-

TABLE 1

Physical characteristics of antacid compounds

	Almagate	Magaldrate I	Magaldrate II	Hydrotalcite	Almagcit	Co-gel
Apparent density ($g \cdot ml^{-1}$)	0.20	0.46	0.31	0.26	0.21	0.24
Tapped density ($g \cdot ml^{-1}$)	0.32	0.62	0.46	0.38	0.29	0.39
Hausner's number	1.60	1.35	1.49	1.47	1.38	1.65
Particle size [a] (μm)						
$D_{10\%}$	1.92	10.57	4.93	7.99	3.11	6.33
$D_{50\%}$	5.84	39.72	11.90	32.10	15.30	23.03
$D_{90\%}$	11.47	91.10	38.82	77.44	47.27	49.90
VMD [b]	6.70	46.74	17.60	37.00	21.56	27.00
True density ($g \cdot ml^{-1}$)	2.28	2.16	2.08	2.08	2.16	2.22
Specific surface area ($cm^2 \cdot g^{-1}$)	4506	699	2424	898	1815	1173

[a] By using the PS64 cell.

[b] Volume mean diameter.

gests there could be substantial differences in antacid activity. For this reason the microphysical structure was examined in more detail, and showed that almagate consisted of individual particles whilst the other antacids were detected as more or less complete agglomerates. The level of aggregation of the latter compounds (ca. 65% and 80% for magaldrate I and hydrotalcite, respectively) was established by measuring the mean particle size variations as a function of the residence time in an

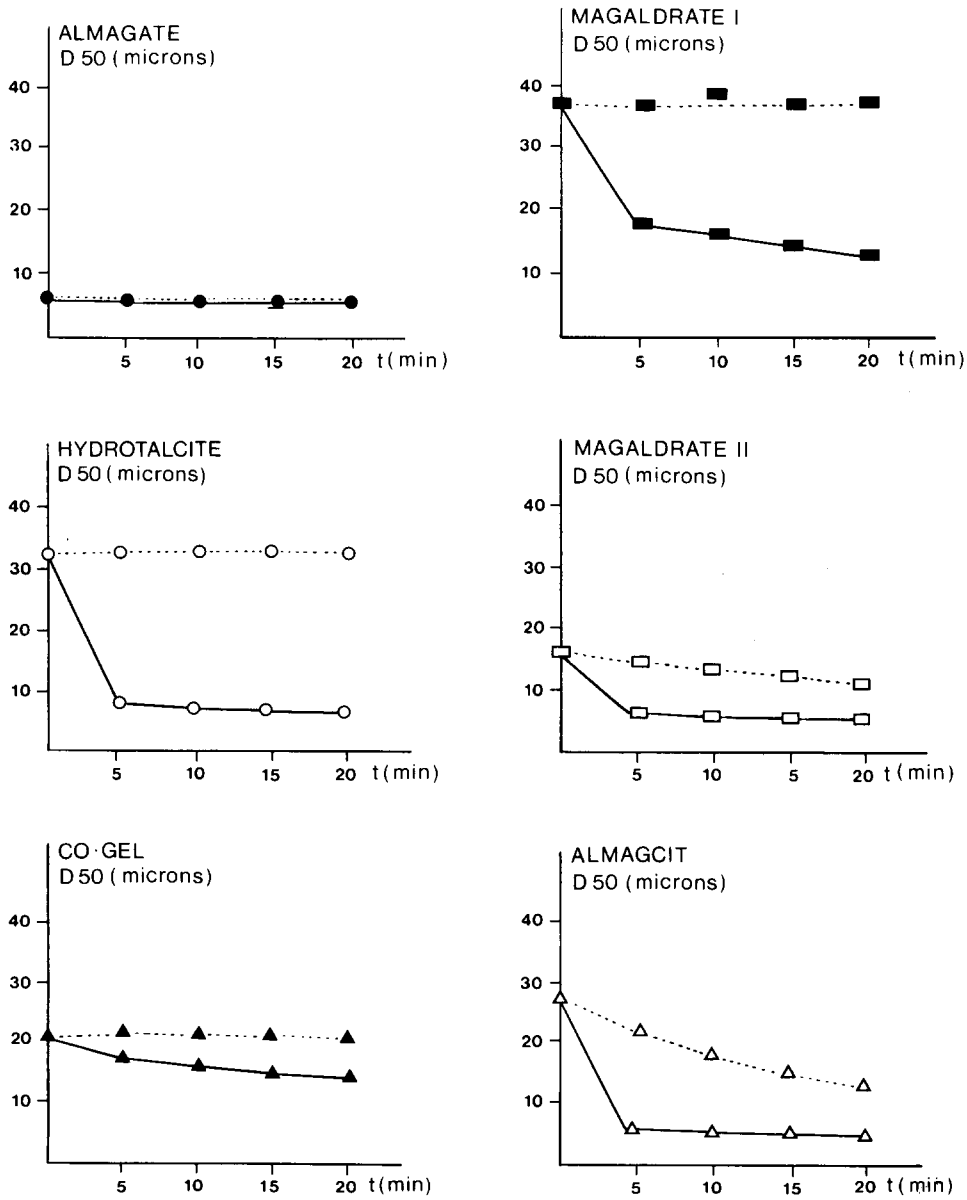

Fig. 1. Particle size variations versus residence time in a stirred aqueous suspension. ●, almagate; ■, magaldrate I; ▲, co-gel; ○, hydrotalcite; □, magaldrate II; △, almagcit. Effective and true particle size (broken and continuous lines, respectively) corresponds to simple recirculation or with ultrasonic agitation.

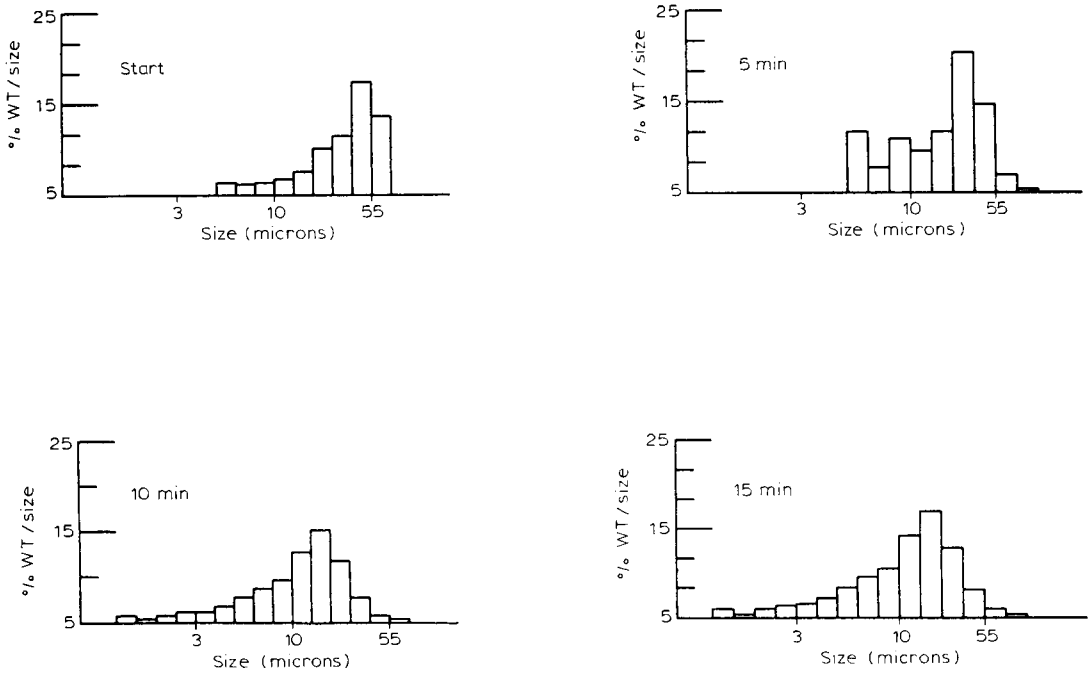

Fig. 2. Changes in size distribution of magaldrate I particles under ultrasonic agitation.

aqueous stirred suspension (PS 14 cell), with or without ultrasonic destruction of aggregates (Fig. 1).

When the suspension is agitated ultrasonically there is a change in particle size distribution in all the antacids with the exception of almagate. This redistribution of size values for magaldrate I particles in experiments with ultrasonic agitation are recorded as frequency histograms in Fig. 2, showing a considerable rearrangement of size values during the first 10 min. It appears therefore that the redistribution of particle size, which occurs more intensely during ultrasonic agitation, is caused by the breakdown of powder agglomerates.

In order to study the effect of variations in particle size on neutralization velocity, the 6 antacid samples were evaluated in the presence of a volume of 0.003 M hydrochloric acid under the conditions described in the experimental section without ultrasonic agitation. The initial concentration of hydrochloric acid was selected as the physiological value (pH 2.5) when antacid therapy is considered to be advisable. During the neutralization process, the particle size and pH variations were measured at the same intervals until a buffered suspension of residual antacid remained. The results are shown graphically in Figs. 3 and 4. A rapid initial breakdown of larger agglomerates was observed for magaldrate I, almagcit, and hydrotalcite, while the variation of particle size of

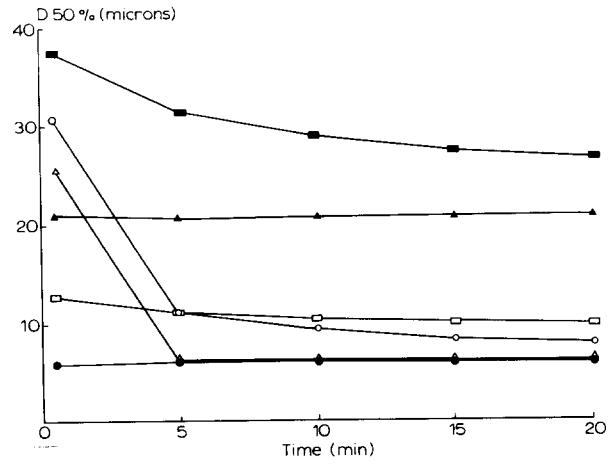

Fig. 3. Particle size variations versus residence time in a stirred acid suspension (initial pH value 2.5) with simple recirculation. Same key as Fig. 1.

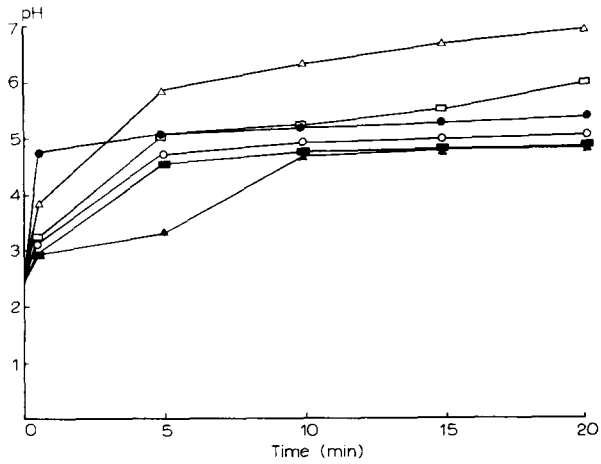

Fig. 4. pH variations versus residence time in a stirred acid suspension with simple recirculation. Same key as Fig. 1.

the other 3 antacids followed a similar pattern to that observed when the determinations were carried out in simple aqueous suspension, without ultrasonic agitation (see Figs. 1 and 3)

As expected, due to the absence of agglomerates, almagate rapidly neutralized the acid present in less than 1 min reaching a plateau at pH 5. The other 5 antacids neutralized the hydrochloric acid more slowly and in the case of almagcit, the pH of the buffered suspension was higher than pH 6 after the 10 min time interval.

These results correlated well with the neutralization performance of these substances in the pH-stat test at pH values 2 and 3. The special case of almagate with an almost immediate neutralization of acid together with its unique effective particle size is in agreement with the excellent in vitro properties of this product (Beneyto and Fábregas, 1984). Lower neutralization rates were observed with magaldrate, hydrotalcite and almagcit, and in the case of co-gel its amorphous structure also reduces long-term stability (Beckman, 1960).

Discussion

An antacid should rapidly neutralize the acid present in the stomach before it is removed by physiological gastric-emptying processes (OTC Panel on Antacids, 1974). The ratio of the real amount of acid neutralized by the antacid compared to the quantity that could be theoretically neutralized, during its residence time in the stomach, has been suggested (Hem et al., 1982) as a concept analogous to that of bioavailability applied to systemically active drugs. Consequently the neutralization velocity is synonymous with therapeutic efficacy.

The reaction velocity is directly related to particle size. The true particle size value, i.e. the size of non-agglomerated, particles of a powder as measured by most dynamic methods is not a very useful parameter if the material is only available as a more or less consistent agglomerate. This is particularly important in the case of antacids where therapeutic efficacy is critically related to the wettability and surface area of particles, and it is suggested that in addition to the current concept of true particle size, a new criterion should be introduced that reflects the effective particle size. This parameter represents the mean particle size of the discrete physical units of the antacid powder (individual particles or agglomerates), as supplied and will be utilized in pharmaceutical preparations.

In this sense an antacid will be therapeutically preferred if it exhibits similar values between true and effective particle sizes. Almagate complies with these requirements while important deviations were observed with the samples of magaldrate and hydrotalcite (Fig. 1).

The in vitro behaviour of almagate described in this report indicates that its favourable antacid properties are related to its unique microphysical structure and also helps to explain the evident therapeutic efficacy of almagate observed in clinical practice (Aran Suau et al., 1984). Studies are in progress to investigate the mechanism of action of pepsin on gastric acid neutralization by synthetic antacids under naturally occurring conditions.

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