

One-dimensional filtration of pharmaceutical grade phyllosilicate dispersions

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Abstract

The filtration behaviour of some clay–water dispersions was studied. Two Spanish fibrous phyllosilicates (sepiolite from Vicálvaro and palygorskite from Turón) and a commercial bentonite (Bentopharm®, UK) with similar sizes and different morphologies (fibrous and/or laminar) were selected as model clays. Sepiolite from Vicálvaro is an almost pure fibrous sample, Bentopharm® presents a high amount of laminar particles and palygorskite from Turón is made up of similar percentages of laminar and fibrous particles. The disperse systems were made up using a rotor-stator mixer working at two different mixing rates (1000 and 8000 rpm), for periods of 1 and 10 min. Filtration measurements were taken and the corresponding filtration curves obtained. Finally, the desorptivity (*S*) of the filtration cakes was calculated and correlated to the textural characteristics of the materials, the solid fraction and mixing conditions. Filtration behaviour of the dispersions depended on all three of these factors. Laminar dispersions presented lower *S* values than fibrous dispersions. In the 2% w/v dispersions the bridging forces between particles did not permit formation of an interconnected network as in 10% w/v dispersions and, consequently, filtration times increased with the solid fraction (i.e. *S* values decreased). Regarding stability to pH changes, the results showed that filtration behaviour was highly sensitive to basic pH in the fibrous clay dispersions and almost insensitive in the laminar clay dispersions. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Laminar (smectite, illite) and fibrous (palygorskite, sepiolite) clays are widely used in the

preparation of stable pharmaceutical disperse systems as a result of the colloidal dimensions and anisotropy of their particles (Alvarez, 1984; Galán et al., 1985). When laminar clays are dispersed in a polar medium, face–edge and face–face interactions are the two major mechanisms implied in the formation of a rigid network (Van Olphen, 1963; Permien and Lagaly, 1994a,b, 1995). Fi-

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brous clays dispersed in water form a three-dimensional structure composed of interconnecting

fibres (Simonton et al., 1988). Viseras et al. (1999) assessed effects of shear history on the rheology

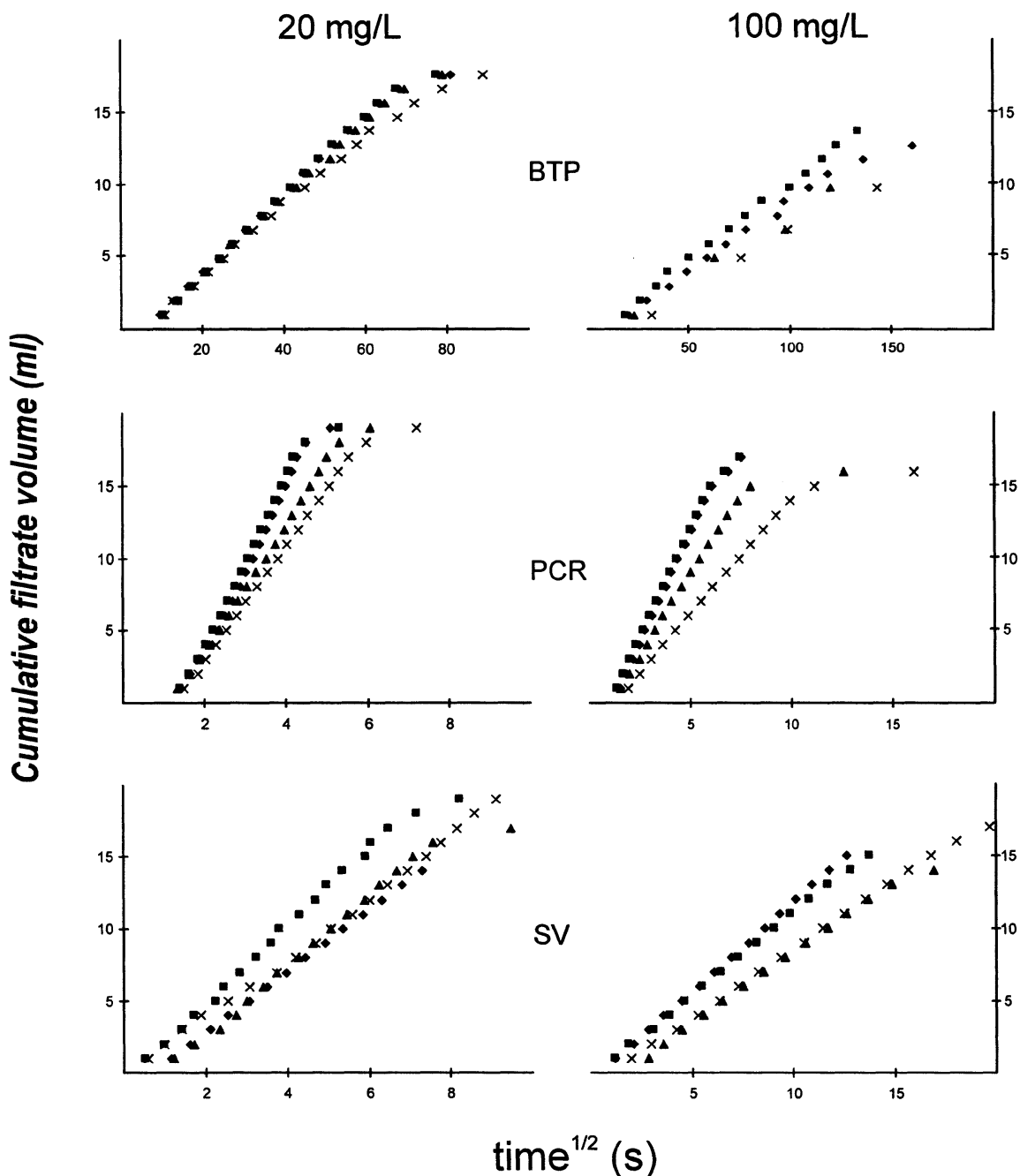


Fig. 1. Effect of mineral type, solid fractions and initial interposition conditions (◆ = 1000 rpm × 1 min, ■ = 1000 rpm × 10 min, ▲ = 8000 rpm × 1 min, X = 8000 rpm × 10 min) on the filtration curves of the systems.

Table 1

Pseudoequilibrium pH of the systems after 2 h of addition of the three different pH solutions

Medium pH	BTP		PCR		SV	
	10% w/v	2% w/v	10% w/v	2% w/v	10% w/v	2% w/v
1.20	7.35	7.42	7.55	7.82	6.98	6.31
5.80	8.15	8.61	8.12	8.65	7.54	7.78
13.10	10.12	10.58	9.06	10.24	10.61	11.62

of laminar and fibrous clay dispersions. The results showed that the degree of dispersion and the structural changes resulting from differences in particle shapes had significant influence on the rheology of the systems. A linear relation was found between mixing energy and apparent viscosity in the laminar systems, while apparent viscosity in the fibrous samples was related to mixing power, with minor influence of mixing times. The differences were explained assuming that gel structure in fibrous clay suspensions resulted mainly from hydrodynamic forces that depend on the mixing power applied to the system.

The aim of this study was to fully characterise these systems by means of one-dimensional filtration measures. Filtration behaviour depends on the structure and degree of flocculation of a suspension (Smellie and La Mer, 1958; La Mer, 1966). Filterability of dispersions is a measure of the ease with which the continuous and discontinuous phases may be separated. Lee and Hsu (1994) suggested measuring filterability by the average specific resistance α_{av} of a filter cake, according to:

$$\alpha_{av} = 2P/S\eta C_o \quad (1)$$

where C_o is the mass density of the dewatered filter cake, η is the viscosity of the filtrate and S is the desorptivity. In particular, for a constant filtration pressure (P), desorptivity obeys Terzaghi's law (Terzaghi and Peck, 1948; Terzaghi, 1965) described by:

$$V = S(P)t^{1/2} \quad (2)$$

in which V is the volume of filtrate per unit area of a filter, produced in time t , and caused by a

pressure difference P applied at $t = 0$. Desorptivity is related to the permeability (K) of the filter cake, the volume G of the cake and the viscosity η of the filtrate (Akers and Ward, 1977) by:

$$S^2 = 2PK/\eta G. \quad (3)$$

In order to obtain the corresponding filtration curves, one-dimensional filtration measurements were made. Desorptivity (S) of the filtration cakes was then calculated according to Eq. (2). Information of the state of aggregation of the particles forming the discontinuous phase was obtained and correlated to the textural characteristics of the solid fraction and mixing conditions used in the interposition. Finally, the results obtained were compared with those of a previous rheological study of the same systems (Viseras et al., 1999).

2. Materials and methods

2.1. Materials

Laminar sample: benthopharm© (BTP), Bromhead and Denison, UK. Fibrous sample: sepiolite from Vicálvaro, Madrid (SV). Fibrous/laminar sample: palygorskite from Turón, Ciudad Real (PCR).

Their mineralogical and chemical contents had been previously quantified (Viseras et al., 1999). In these materials, particle morphology is related to mineral composition (Viseras and Lopez-Galindo, 2000). BTP particles are mainly laminar (80% w/w of smectite–illite), SV particles mainly

fibrous (> 90% w/w of sepiolite) and PCR particles fibrous–laminar (53% w/w of palygorskite

and > 25% w/w of smectite–illite). The 75–125 μm fraction of each sample was selected by dry

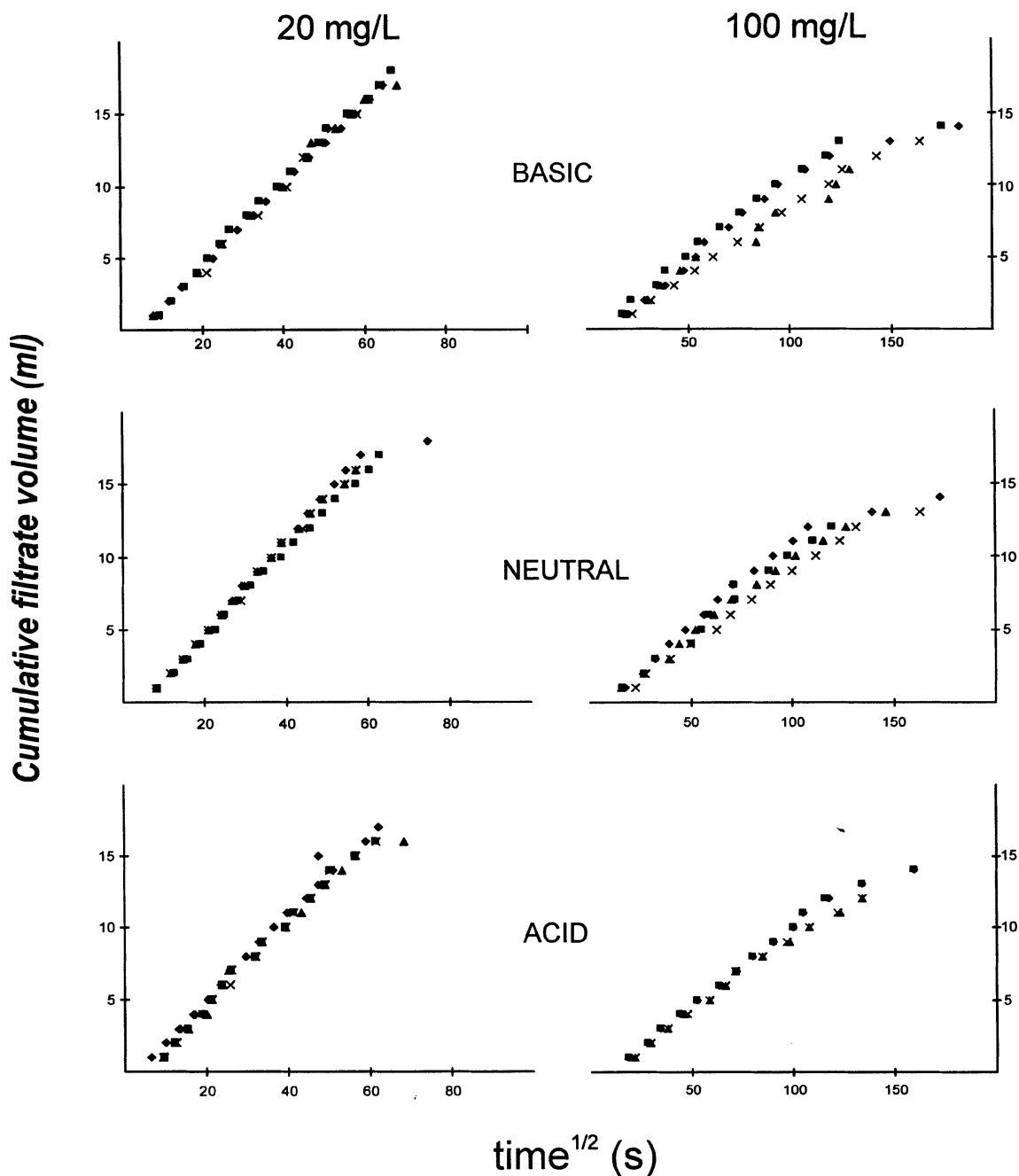


Fig. 2. Effect of pH modifications on the filtration curves of the BTP dispersions as a function of their solid fraction and initial interposition conditions (\diamond = 1000 rpm \times 1 min, \blacksquare = 1000 rpm \times 10 min, \blacktriangle = 8000 rpm \times 1 min, \times = 8000 rpm \times 10 min).

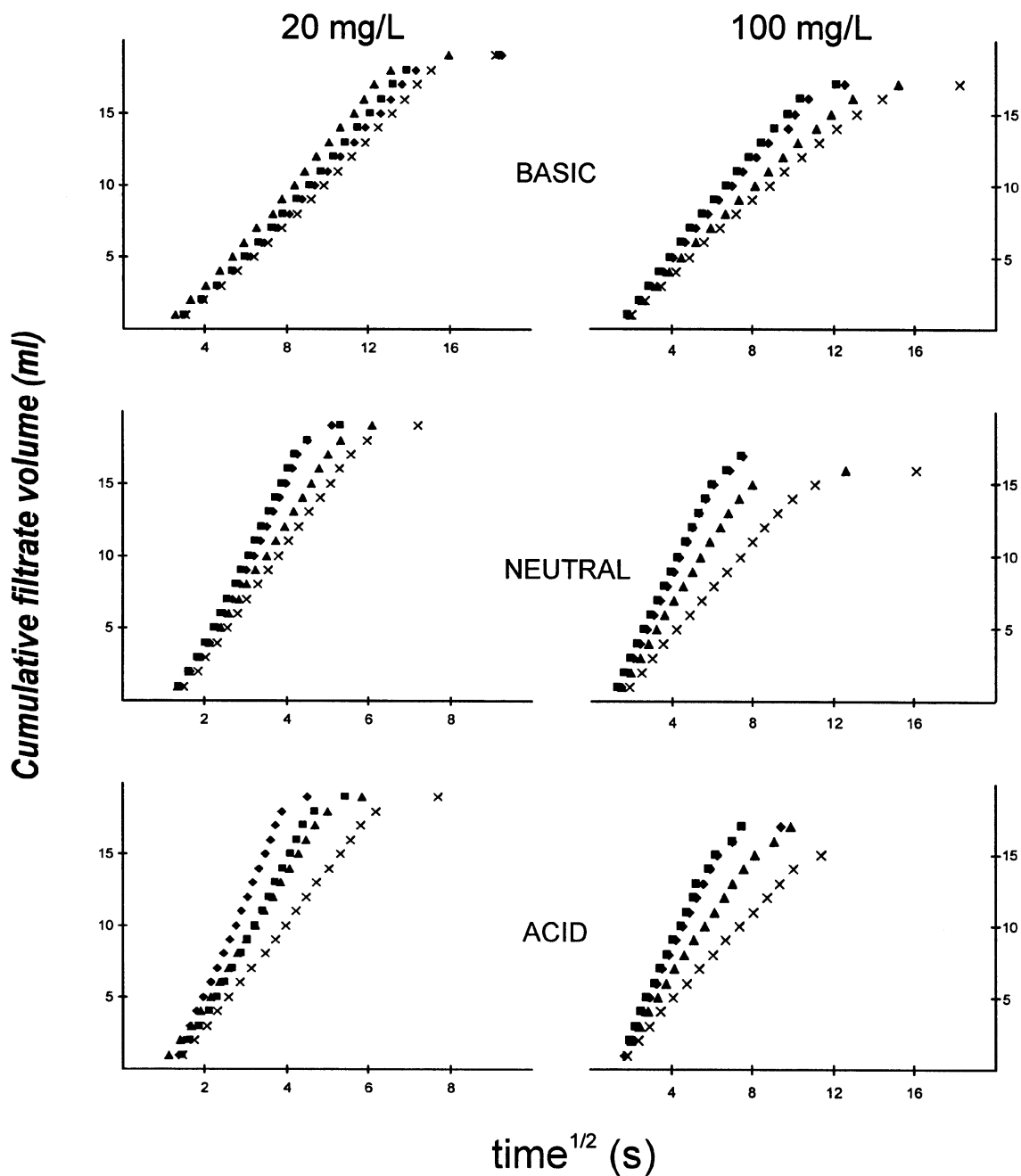


Fig. 3. Effect of pH modifications on the filtration curves of the PCR dispersions as a function of their solid fraction and initial interposition conditions (◆ = 1000 rpm × 1 min, ■ = 1000 rpm × 10 min, ▲ = 8000 rpm × 1 min, X = 8000 rpm × 10 min).

sieving and then stored at 40% relative humidity and room temperature (22–25°C) for at least 48 h before study.

2.2. Preparation of disperse systems

Clay dispersions were made up at 2 and 10%

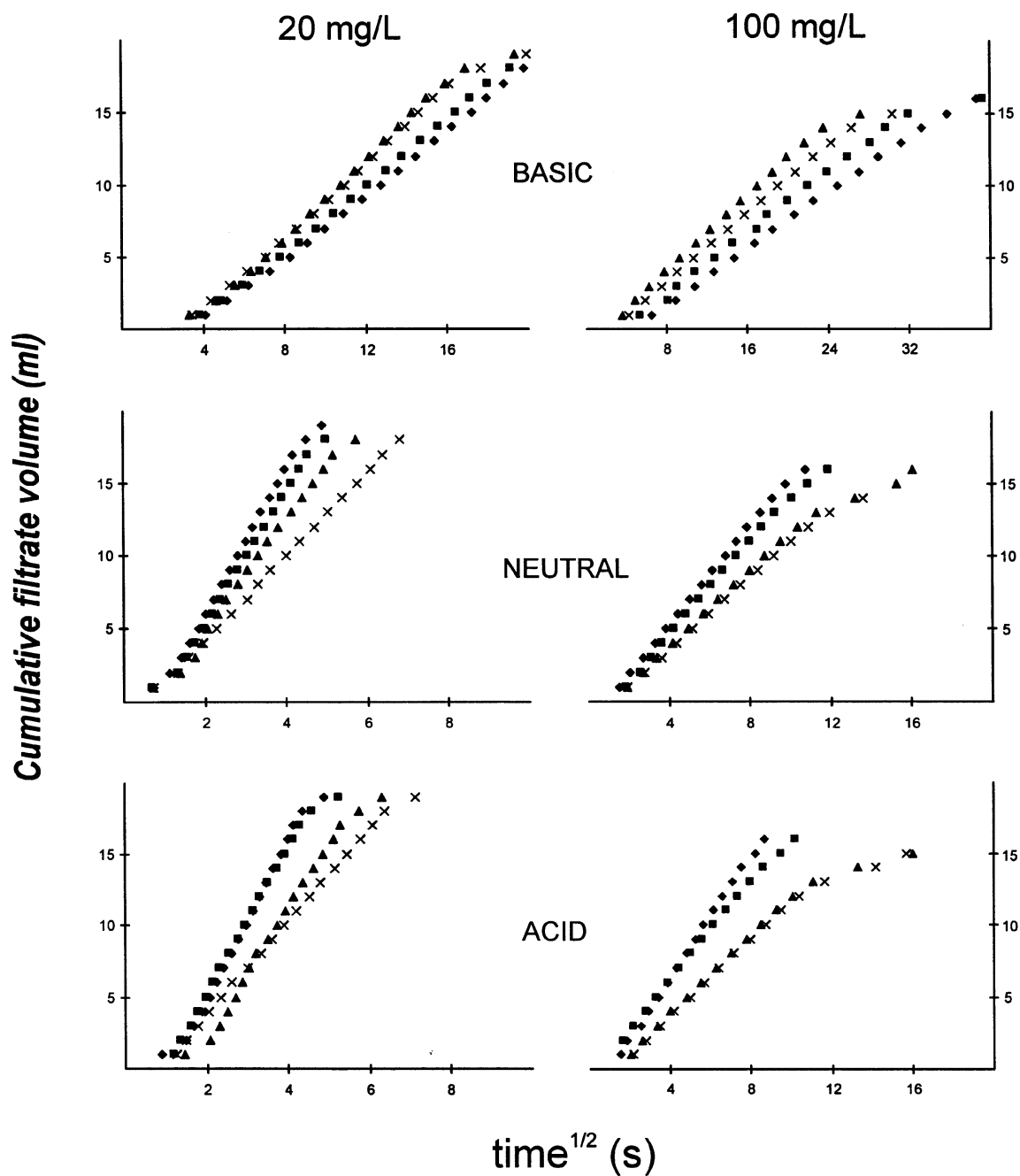


Fig. 4. Effect of pH modifications on the filtration curves of the SV dispersions as a function of their solid fraction and initial interposition conditions (◆ = 1000 rpm × 1 min, ■ = 1000 rpm × 10 min, ▲ = 8000 rpm × 1 min, X = 8000 rpm × 10 min).

Table 2

Desorptivity values of the disperse systems as function of mineral type, solid concentration and mixing conditions

Sample	Concentration (% w/v)	Agitation (rpm)	Time (min)	Desorptivity ($\text{ml mm}^{-2} \text{s}^{-1/2}$)
BTP	2	1000	1	665.51
			10	658.27
		8000	1	624.34
			10	567.30
	10	1000	1	256.54
			10	231.55
		8000	1	206.47
			10	188.10
			10	188.10
PCR	2	1000	1	13047.67
			10	12800.67
		8000	1	10013.07
			10	9159.36
	10	1000	1	7062.98
			10	6854.50
		8000	1	5110.02
			10	3601.75
			10	3601.75
SV	2	1000	1	4898.78
			10	6340.32
		8000	1	5637.57
			10	4602.60
	10	1000	1	2833.72
			10	2603.03
		8000	1	2192.66
			10	2190.36
			10	2190.36

w/v in distilled water using a high shear rotor-stator mixer (Silverson L4RT, Silverson Machines, UK). Rotor speeds (N) of 1000 rpm and 8000 rpm were used in the interposition for periods of time (t) of 1 and 10 min (i.e. four different mixing energies). The resultant suspensions were shaken in a roller at 30 rpm for 24 h (which was found to be necessary for the swelling of the laminar–clay dispersions).

As these kind of disperse systems are mainly used for oral administrations, it is important to assess the effect of drastic pH changes on their structural stability. The pH of the dispersions was altered by addition of 10 ml of three different pH solutions to 90 ml of the initial dispersions. The solutions used were obtained by dilution of suitable amounts of HCl 0.1 N or NaOH 0.1 N in water, the ionic strength being adjusted by adding

KCl 0.1 M. The pH values of the solutions used to bring about the pH changes (pH = 1.2, pH = 5.8, pH = 13.1) were selected following Dressman et al. (1993) and Viseras et al. (1999) to imitate those of gastric fluid in three extreme conditions (i.e. pH before lunch, after lunch, highly anomalous pH, respectively). The pH values of the disperse systems were then monitored until an equilibrium value was reached.

2.3. Filtration of disperse systems

The various clay–water dispersions were filtered using a standard filter press (API, 1988), by Hilton Instruments, UK. The press had a 54.1 mm diameter (filter area = 2299 mm²), 254.0 mm long circular bore, one end of which held a What

man # 50 filter paper with ca. 2.7 μm retention size, while the other was attached to a compressed air source driving filtration (10 kPa at time = 0). Pressure was measured by an electronic pressure gauge (Druck, DPI 701). The ambient temperature was $21.5 \pm 0.5^\circ\text{C}$. The suspension volume in the bore was typically 20 ml. The filtrate was weighed using an electronic balance, and the filtrate volume V obtained, taking the filtrate density to be 1000 kg m^{-3} . S was obtained from a least-squares fit of filtrate volume (V) to $t^{1/2}$. Results are the mean of at least three filtration replicates, taken immediately after the swelling period, and after alteration of the pH.

Regression analysis of each set of data were carried out. Variations between replicates were found to be under 1% in all cases, except for the BTP dispersions after basic treatment ($\pm 5\%$). On the other hand, correlation coefficients of filtration curves (Figs. 2–4) were also calculated ($r^2 \geq 0.98$, except for BTP dispersions; $r^2 \geq 0.82$).

3. Results

3.1. Filtration curves

Four mechanical agitation energies (1000 rpm \times 1 min; 1000 rpm \times 10 min; 8000 rpm \times 1 min and 8000 rpm \times 10 min) were used to disperse two solid fractions (20 and 100 mg l^{-1}) of three samples (BTP, PCR and SV) in distilled water. The data obtained by the filtration study were plotted as cumulative filtrate volume V versus t and $t^{1/2}$.

3.1.1. Effect of mineral type, solid content and interposition conditions

As can be observed in Fig. 1, BTP dispersions showed the slowest filtration rates. Textural differences between the samples may help us to explain these differences. Cakes formed by laminar particles are more compacted and water pathways are more wandered, resulting in longer

Table 3
Desorptivity of the BTP dispersions after pH modification

Concentration (% w/v)	pH	Agitation (rpm)	Time (min)	Desorptivity ($\text{ml mm}^{-2} \text{ s}^{-1/2}$)
2	Basic	1000	1	650.87
			10	695.91
		8000	1	672.50
			10	688.30
	Neutral	1000	1	746.04
			10	687.89
		8000	1	731.37
			10	730.56
	Acid	1000	1	710.51
			10	694.29
		8000	1	678.85
			10	691.24
10	Basic	1000	1	264.22
			10	253.31
		8000	1	213.09
			10	194.60
	Neutral	1000	1	278.36
			10	251.86
		8000	1	234.82
			10	225.66
	Acid	1000	1	256.32
			10	258.02
		8000	1	225.30
			10	189.58

Table 4
Desorptivity of the PCR dispersions after pH modification

Concentration (% w/v)	pH	Agitation (rpm)	Time (min)	Desorptivity ($\text{ml mm}^{-2} \text{s}^{-1/2}$)
2	Basic	1000	1	3416.56
			10	3611.94
		8000	1	3763.92
			10	3229.39
	Neutral	1000	1	13055.08
			10	12807.80
		8000	1	10017.43
			10	9163.01
	Acid	1000	1	15065.53
			10	12274.43
		8000	1	10379.23
			10	8421.24
10	Basic	1000	1	3935.30
			10	4109.03
		8000	1	3254.99
			10	2922.33
	Neutral	1000	1	7078.20
			10	6870.89
		8000	1	5121.41
			10	3610.24
	Acid	1000	1	6973.01
			10	7164.23
		8000	1	4917.65
			10	3492.86

filtration times. The presence on PCR of a considerable amount of laminar particles did not seem to reduce the filtration rate as regards SV. This may be explained as the result of a decrease in cake homogeneity.

A five times increase in solid content resulted in a two times decrease in rate, regardless of particle texture (left to right plots).

Finally, mixing energy seemed to have a small effect on BTP dispersions. On the other hand, SV dispersions presented significant differences on the slope of the $V/t^{1/2}$ plots, mainly related to the mixing power used in the preparation (1000 vs. 8000 rpm). PCR plots seem to be affected both by mixing power and mixing times.

3.1.2. Effect of drastic pH changes

The pH levels of the suspensions were monitored until an equilibrium value was reached. Table 1 shows the equilibrium values of the dis-

pensions after two hours. Since longer times resulted in slight variations in the pH values, the two hour period was therefore chosen to estimate the effect of gastric pH on real residence times. Fig. 2 illustrates the filtration plots of BTP dispersions after pH change. As can be observed, BTP dispersions do not modify their filtration characteristics as a function of pH. Figs. 3 and 4 show the filtration curves obtained for PCR and SV dispersions, respectively. In general, basic pH increases filtration times for both samples, while they remain similar at neutral or acid pH, but otherwise, the effects of mixing conditions are more evident after pH modification. PCR dispersions showed an increase in filtration rate in all cases, and SV dispersions filtrated more slowly after dilution with the basic solution. Calculation of desorptivity values allowed a more compressive analysis of the induced changes.

3.2. Cake desorptivity (*S*)

The desorptivity (*S*) of a dispersion is a measure of the feasibility of phase separation. It may be used as an indirect method to assess the degree of network formation of the particles forming the discontinuous solid phase.

3.2.1. Effect of mineral type, solid content and interposition conditions

Table 2 shows the calculated values of desorptivity of the initial dispersions as functions of mineral type, solid content and interposition conditions. Desorptivity values seem to be affected by all three factors, namely textural characteristics of the materials, solid fraction and mixing energy and/or power used in the preparation.

BTP dispersions (laminar particles) presented *S* values ten times lower than SV (fibrous particles). As indicated above, this difference may be explained on the basis of the intrinsic behaviour of

the laminar or fibrous particles during cake formation and resultant water pathways. PCR dispersions (mix of laminar and fibrous particles) presented the highest *S* values (around 50 times those of BTP). The presence of both laminae and fibres clearly prevented intimate particle compaction, resulting in heterogeneous cakes.

Desorptivity values invariably decreased with increase of solid percentage. Eberl et al. (1995) proposed that when the solid fraction of a dispersion falls below a percolation or gel point, filtration occurs in two stages: compact bed formation and subsequently consolidation of the compact. In view of this hypothesis, we inferred that in the 2% w/v dispersions the bridging forces between particles may be too weak to permit formation of an interconnected network able to transmit throughout the compressive stresses induced by the filtration pressure. At 10% w/v a fully networked dispersion with the solid structure proper-

Table 5
Desorptivity of the SV dispersions after pH modification

Concentration (% w/v)	pH	Agitation (rpm)	Time (min)	Desorptivity (ml mm ⁻² s ^{-1/2})
2	Basic	1000	1	2520.56
			10	2624.73
		8000	1	3070.66
			10	2943.66
	Neutral	1000	1	11225.59
			10	10267.98
		8000	1	8907.40
			10	6633.01
	Acid	1000	1	12151.16
			10	11838.31
		8000	1	10459.51
			10	7572.46
10	Basic	1000	1	1125.97
			10	1237.75
		8000	1	1519.50
			10	1377.06
	Neutral	1000	1	3956.97
			10	3709.26
		8000	1	2841.08
			10	2705.34
	Acid	1000	1	4965.44
			10	3980.95
		8000	1	3081.36
			10	2983.00

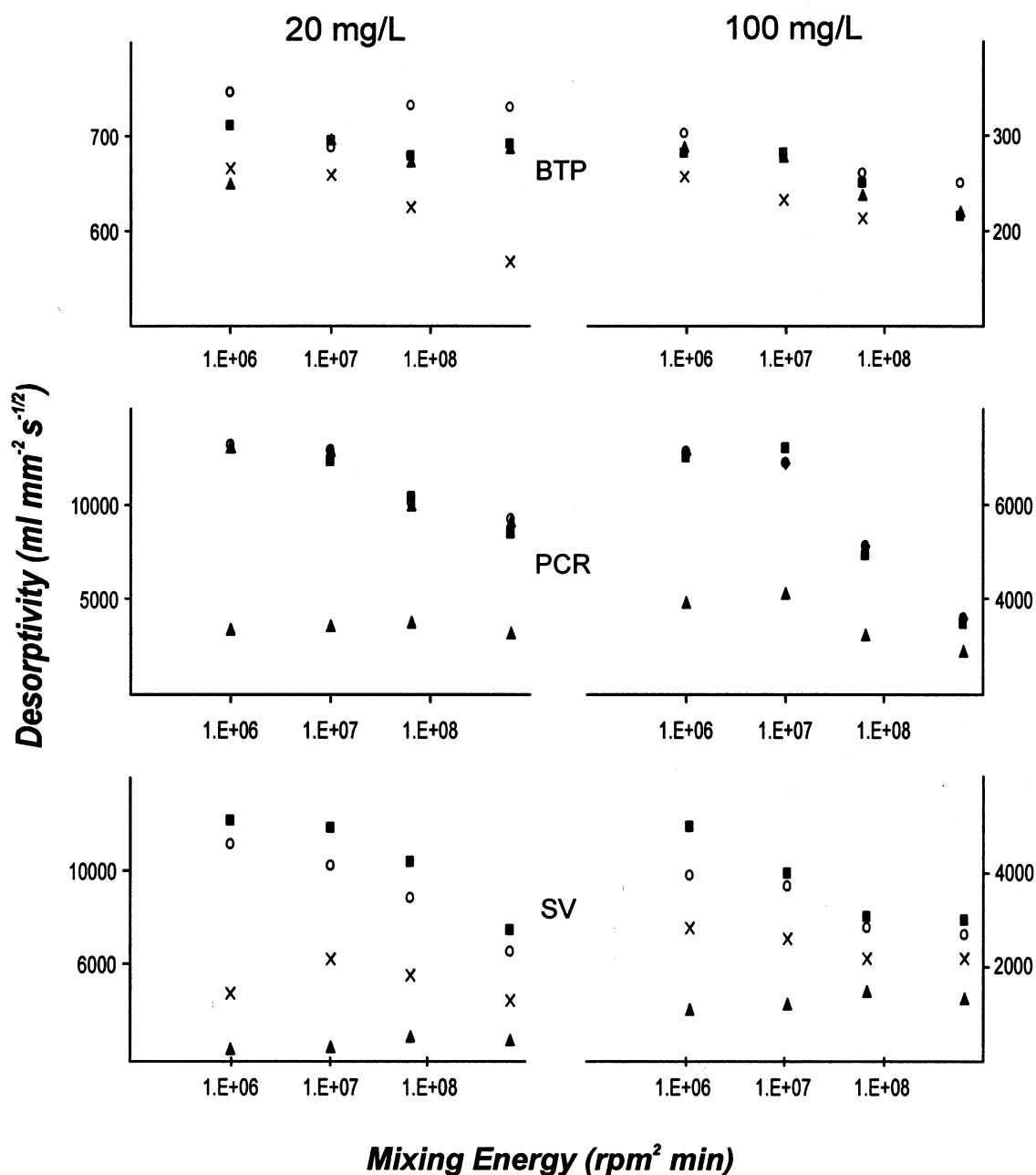


Fig. 5. Correlation study of mixing energies to desorptivity values of BTP, PCR and SV systems as a function of initial solid fractions and pH modifications (X = initial dispersion, ▲ = dispersion diluted with a solution of pH 13.10, ■ = dispersion diluted with a solution of pH 1.20, ○ = dispersion diluted with a solution of pH 5.8).

ties would be formed. In this situation, a consolidation process prior to compact bed formation

must occur and consequently filtration times increase (i.e. S values decrease).

In BTP and PCR samples, *S* values decreased with increase in mixing energy. Desorptivity of SV dispersions did not decrease linearly with the energy of interposition, but seemed to mainly depend on the mixing power applied.

3.2.2. Effect of drastic pH changes

Tables 3–5, respectively, show the calculated values of desorptivity after induction of pH changes in BTP, PCR and SV dispersions. The values were also correlated with mixing energy and compared with those obtained before any pH modification (Fig. 5).

Even in the case of a depreciable pH effect, *S* values should be slightly increased as a result of the induced dilution, which is, in general, what happened with BTP dispersions. Obviously, stability to the pH changes was more pronounced at 10% w/v. Basic dilution seems to affect only the low concentration, low mixing energy dispersion (i.e. the suspension with a lower degree of network formation). On the other hand, *S* values of PCR and SV dispersions decreased when diluted with the basic solution and increased (SV) or were similar (PCR) after dilution with the neutral or acid solutions. Finally we observed a reduction in the differences between basic-diluted dispersions and the other when mixing power increased, which we interpret as higher system stability with increased mixing power.

4. Discussion

In general terms the results presented here for one one-dimensional filtration coincide with those obtained by rheological measurement as reported in Viseras et al. (1999), where we suggested the need for aggregate breakdown and formation of a structure in both laminar and fibrous clays and provided a correlation study of mixing energy factors (N^3t or N^2t) and the apparent viscosities.

The same correlation was found between desorptivity values and these mixing factors (Fig. 5), confirming that network formation is a function of mixing energy for laminar particles

(BTP) and mainly depends on shaking power when the particles are rod-shaped (SV and PCR).

The gelling mechanisms of fibrous and laminar clays are clearly different. In our opinion, gel structure in fibrous clay suspensions may be formed by hydrodynamic forces, even when non-hydrodynamic forces could be involved in its final stability. Our results confirm the need for breakdown of aggregates and formation of a structure in both laminar and fibrous clays (which otherwise could not give rise to a gel by mere swelling). Once this open structure in which the particles are more or less isolated has been established, the system is sensitive to pH alteration, which demonstrates the importance of electrostatic equilibrium in its stability. In fact, after pH modifications, all samples showed differences in their filtration profiles. These changes were more pronounced after basic treatment. So, space network stability (floc formation/breakdown) in these systems firstly depends on the applied energy and, secondly, on medium pH.

5. Conclusions

Filtration measurements may be used to evaluate the degree of clay network formation in water dispersions. The results obtained after one-dimensional filtration and the rheological characteristics of the systems were found to be compatible.

Regarding the use of these dispersions for oral administration, only the presence in the stomach of a highly anomalous pH (i.e. $\text{pH} > 13$) resulted in system instability and affected their filtration properties.

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