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Investigation of the applicability of a titration method to determine parameters related to porosity in pharmaceutical suspension dosage forms

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Abstract

The purpose of this study was to find a more efficient method for determining the porosity, or voids, using an insoluble powder in a pharmaceutical suspension. In a random arrangement of uniform spheres the only concern is with the limits of porosity existing within that collection. Theoretically, no equation can completely describe the physical properties of a sediment in a liquid medium without considering its particle size, size distribution, shape features, surface characteristics, etc. For the ideal case dealing with uniform spherical particles, it is expected that the plot of the weight of solid versus the volume of liquid used to fill the voids should be a straight line with zero intercept.

A new titration method has been proposed to directly measure the immediate pore volume between particles in the suspension. Further investigation is required to determine its sensitivity such that it may provide a means of differentiating the nature of the particle–particle and particle–liquid attractive forces within a given pharmaceutical suspension system.

Keywords: Suspension porosity; Void volume; Bulk volume; Pharmaceutical powders; Pharmaceutical solvent systems

1. Introduction

This study was designed to investigate the wetting and associated behaviors exhibited by various powders which are commonly used in pharmaceutical dosage forms (e.g., aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium oxide, and zinc oxide). The study is an integral part of a project related to the investigation of an improved bulk volume determination method for pharmaceutical suspension.

Voidage or sediment porosity is the deviation of the volume exhibited by a solid when it is wetted (true volume) and when it is settled in an aqueous medium [1–3]. In other words, voidage is the difference between the volume of the solid and its final volume of sedimentation in a suspension. When the solid is in an aqueous medium, it undergoes certain physical changes, even though it may not react chemically with the medium. These changes include the formation of aggregates, preferential adsorption of a part of the liquid medium onto the solid. Moreover, the characteristics of the aqueous medium may dictate the overall physical changes in the solid.

In this study, three different solvents (i.e., glycerin, propylene glycol and syrup) were used at various

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concentrations and titrated dropwise into a weighed quantity of powder until the powder began to collapse into a suspension. The volume of the liquid used was noted along with the quantity of the respective powder. The data collected were then utilized to produce plots of the weight of the solid (x-axis) versus the volume of the liquid used (y-axis). It was expected that the theoretical plots would yield a straight line which would pass through the origin. Experimentally, the plots gave straight lines, which exhibited some minor deviations from ideality, but did not go through the origin.

2. Theory

In practice, general concern is for the behavior of irregularly shaped particles which are capable of packing in different ways. The arrangement assumed for these particles, when haphazardly dropped in a container of liquid medium, cannot be predetermined. The porosity of the dispersed suspension is related to the sediment porosity, voidage, by an equation using the true and bulk densities of the solid in the liquid medium. When the solid is in an aqueous medium, it undergoes some physical changes, even though it may not interact or react chemically with the medium. The surface area of the particles vary due to the cracks and crevices that may exist on and within this irregularly shaped particle. The aqueous solvents, namely various concentrations of glycerin (5–70% v/v), propylene glycol (5–70% v/v) and sucrose (5–85% w/v), were titrated into a known weight of powder until it collapsed into a concentrated suspension which was considered the end point [4]. The end point was shown to be constant and reproducible for a specific weight of powder, namely USP grades of $CaCO_3$, $Al(OH)_3$, $Mg(OH)_2$, MgO and activated charcoal. The data revealed that a straight line function exists between the volume of medium used and the weight of solid. The least squares analysis provided an intercept that was approximately zero.

It is hypothesized that the physical changes as well as variances in the surface area, size and shape of the solid particles may be responsible for the deviations observed for the experimental solid [5]. Traditional bulk volume determinations for concentrated suspensions are usually calculated from its final settled volume in a specific medium at time infinity, which is usually taken as 24–48 h after cessation of agitation. The traditional method is compared to the proposed titration method. The comparison was made with $CaCO_3$ which has been previously investigated in our laboratory.

Differences between these methods could be explained. The traditional final settled volume method allows the powder particles to associate into aggregates within the suspension by interacting with the medium to produce a hybrid particle which then settles to provide a new volume, the ''association volume''. The titration method is instantaneous, and only allows the liquid media to fill the voids within the powder. This method does not provide the time for particle–particle-suspending medium association nor for equilibrium to be established in this system.

This new method appears to directly measure the immediate pore volume between particles in the suspension. Further investigation is required to determine its sensitivity such that it may provide a means of differentiating the nature of the particle–particle and particle–liquid attractive forces within a given pharmaceutical suspension system.

3. Materials

Glycerin (Lot No. 22680) Humco Laboratory, Texarkana, TX, USA.
Propylene glycol (Lot No. C1089) Ruger Chemical, Patterson, NJ, USA.
Syrup was produced in the laboratory by using Big Chief Sugar produced by the Monitor Sugar, Baycity, MI, USA (no Lot number was provided).
Aluminum hydroxide (Lot No. 901900A) Fisher Scientific, Fairlawn, NJ, USA.
Magnesium hydroxide (Lot No. 915497) Fisher Scientific, Fairlawn, NJ, USA.
Calcium carbonate (Lot No. 923690) Fisher Scientific, Fairlawn, NJ, USA.
Activated charcoal was provided by Sigma Chemical, St. Louis, MO, USA.
Magnesium oxide (Lot No. 1105-6) J.T. Baker Chemical, Phillipsburg, NJ, USA.
Zinc oxide (no Lot number. provided) Sherman Research Laboratories, Toledo, OH, USA.

4. Method

Various concentrations of the stated liquids were used, namely the glycerin and propylene glycol concentrations ranged from 0% (purified water) to 70% (v/v) while the Sucrose USP concentrations ranged from 0% to 85% (w/v). Different quantities of the investigative powders, namely aluminum hydroxide, calcium carbonate, activated charcoal, magnesium hydroxide, magnesium oxide and zinc oxide were weighed and placed into appropriate sized beakers. The specific liquid was titrated dropwise into the powder until the end point was reached. The end point was considered to be when the wetted powder collapsed into a suspension. Above this point the powder acts as if it was a solid.

Most of the wetted powders (the prepared suspensions), except magnesium oxide, were allowed to stand overnight to reach saturation of the liquid medium. In prolonged contact, magnesium oxide will react with water in the liquid mixture to form a hard cake of magnesium hydroxide which makes clean up difficult. Necessary adjustments in volume, by adding more liquid, were made to ensure that the end point considered was truly obtained. The volume of liquid used to wet the powder was recorded along with the respective weight of the initial unwetted powder. These steps were repeated for all the concentrations for all three liquids.

The collected data were then plotted using the volume of the liquid for the *y*-axis and the weight of unwetted powder for the *x*-axis. The sedimentation method utilized a 250 ml graduated cylinder with the same quantity of solid in 150 ml of the appropriate suspended medium. The mixture was shaken 20–40 times then allowed to settle. The final settled volume was observed two days later.

5. Discussion

Theoretically, any given quantity of powder, regardless of its characteristics, should take up a specific volume of liquid. This is true provided that no chemical interaction and reaction occurred. As the mass of the solid increases, each additional unit of solid should require an additional unit of liquid. Therefore, it is expected that the graph of the weight of the solid versus the volume of liquid should be a straight line and go through the origin. The equation for a straight line is given as follows:

$$Y = mX + c \tag{1}$$

where Y is the Bulk volume, m the slope, X the Weight of the solid and c is the intercept.

The volume of liquid needed to wet solid particles depends on several characteristics of the solid such as size and surface area of the particle. When the particles are suspended in a medium, they undergo certain physical changes which include aggregation and preferential adsorption in which part of the liquid mixture is adsorbed onto the solid and is bound or associated with the solid and settles as if it were a part of the solid phase.

Powder is composed of finely divided particles, all of which may not have the same size and shape. Irregularly sized and shaped particles pack in different ways. The random arrangement increases the voidage or sediment porosity in the system. The porosity of the final settled bed, called voidage, can be expressed as

$$\text{Voidage} = \text{Volume of the sediment} - \text{Volume of the solid}, \tag{2}$$

$$\text{Voidage} = \text{Bulk volume} - \text{True volume}, \tag{3}$$

$$\text{Voidage} = \frac{(\text{Weight of solid})}{\text{Bulk density (pb)}} - \frac{(\text{Weight of solid})}{\text{True density (ps)}}. \tag{4}$$

The particles may be porous and the surface of the particle may include many tiny cracks and crevices (increasing the surface area of the particles) which cause and allow the particles to contain an extra volume of liquid when immersed in an aqueous medium. Some particles may be more solid, have smaller surface area and may require a smaller amount of liquid to reach equilibrium. Therefore, the same mass of powder may require different volumes of liquid to make a suspension. As a consequence, the experimental plots may give straight lines which do not pass through the origin as expected.

The reaction of $Al(OH)_3$, $CaCO_3$, activated charcoal, MgO, $Mg(OH)_2$, ZnO, with glycerin, propylene glycol and syrup have been studied. The results have been presented in Tables 1–18 and displayed in Figs. 1–18.

Table 1
$Al(OH)_3$ versus glycerin

Weight (g) of $Al(OH)_3$	Volume (ml) of glycerin used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
3	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
5	1.550	1.550	1.600	1.550	1.800	1.700	1.650	1.650
10	3.300	3.350	3.300	3.330	3.350	3.400	3.300	3.350
20	6.650	6.6550	6.750	6.750	6.700	6.800	6.600	6.700
30	9.950	9.950	9.950	9.950	10.050	10.150	9.950	10.050
50	15.600	15.600	15.600	15.600	16.750	16.950	16.550	17.750
70	23.250	23.250	23.250	23.250	23.450	23.700	23.200	23.450

Table 2
$Al(OH)_3$ versus propylene glycol

Weight (g) of $Al(OH)_3$	Volume (ml) of propylene glycol used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
5	1.550	1.700	1.650	1.700	1.600	1.700	1.800	1.750
10	3.300	3.300	3.300	3.500	3.400	3.500	3.400	3.600
20	6.650	6.500	6.300	6.300	6.400	6.300	6.900	6.600
30	9.950	9.800	9.800	9.800	9.600	10.10	9.800	10.50
50	15.600	16.100	16.200	16.000	16.400	16.200	16.950	16.500
70	23.250	22.500	22.500	22.450	22.600	22.500	23.400	22.700

Table 3
$Al(OH)_3$ versus syrup

Weight (g) of $Al(OH)_3$	Volume of syrup used at the specified concentration								
	Water (0%)	5%	10%	15%	20%	40%	50%	70%	85%
5	1.550	1.600	1.600	1.600	1.600	1.650	1.600	1.650	1.650
10	3.300	3.200	3.200	3.200	3.250	3.150	3.100	3.200	3.200
20	6.650	6.100	6.100	6.150	6.150	6.300	6.100	6.000	6.400
30	9.950	9.450	9.300	9.400	9.400	9.300	9.300	9.400	9.500
50	15.600	15.450	15.400	15.450	15.550	15.400	15.300	15.500	15.950
70	23.250	21.700	21.800	21.800	21.900	22.900	21.900	22.000	22.300

Table 4
Calcium carbonate versus glycerin

Weight (g) of $CaCO_3$	Volume of syrup used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
1	1.400	1.050	1.100	1.100	1.200	1.200	1.100	1.150
2	2.500	2.100	2.200	2.200	2.300	2.400	2.200	2.300
5	5.900	5.300	5.400	5.500	5.400	5.200	5.450	5.300
10	11.900	10.500	10.500	10.800	10.800	10.500	10.900	11.400
20	21.200	20.950	21.300	21.300	21.600	21.000	21.950	22.500
30	32.200	31.800	31.400	33.600	31.350	33.000	31.250	35.000
50	50.100	52.300	53.200	54.500	54.100	54.000	56.150	53.600

Table 5
$CaCO_3$ versus propylene glycol

Weight (g) of $CaCO_3$	Volume of syrup used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
1	1.400	0.900	0.950	0.900	0.950	0.950	0.950	0.950
2	2.500	1.850	1.850	1.800	1.850	1.850	1.850	1.850
5	5.900	4.650	4.650	4.650	4.700	4.650	4.650	4.750
10	11.900	9.300	9.300	9.300	9.300	9.350	9.300	9.400
20	21.200	18.600	18.600	18.600	18.600	18.600	18.600	18.800
30	32.200	27.900	27.900	27.900	28.000	27.900	27.900	28.200
50	50.100	46.500	46.500	46.500	46.500	46.500	46.500	47.000

Table 6
$CaCO_3$ versus syrup

Weight (g) of $CaCO_3$	Volume (ml) of syrup used at the specified concentration								
	Water (0%)	5%	10%	15%	20%	40%	50%	70%	85%
1	1.400	1.100	1.100	1.100	1.100	1.100	1.100	1.100	1.100
2	2.500	2.200	2.200	2.200	2.200	2.200	2.200	2.200	2.250
5	5.900	5.500	5.500	5.500	5.500	5.500	5.550	5.550	15.300
10	11.900	10.950	11.000	11.000	11.000	11.100	11.050	11.050	11.050
20	21.200	22.000	22.000	22.000	22.050	22.200	22.050	22.000	22.050
30	32.200	32.950	32.950	31.100	33.000	33.000	33.100	32.800	33.100
50	50.100	54.800	54.800	55.000	55.000	55.000	55.200	55.200	55.200

Table 7
Activated charcoal versus glycerin

Weight (g) of charcoal	Volume (ml) of glycerin used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
1	1.500	1.400	1.450	1.500	1.500	1.400	1.450	1.350
2	2.800	2.800	2.850	2.850	2.850	2.800	2.800	2.650
3	4.300	4.300	4.200	4.300	4.200	4.200	4.200	4.100
5	7.300	7.100	7.200	7.200	7.200	7.200	7.150	6.850
10	14.350	14.150	14.150	14.100	14.200	14.200	14.200	13.500
20	28.400	28.300	28.300	28.100	28.100	28.050	28.200	26.500
30	42.100	42.200	42.200	42.200	42.150	42.250	42.250	41.000

Table 8
Activated charcoal versus propylene glycol

Weight (g) of charcoal	Volume (ml) of propylene glycol at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
1	1.500	1.400	1.450	1.450	1.400	1.400	1.400	1.400
2	2.800	2.900	2.800	2.900	2.950	2.800	2.850	2.800
3	4.300	4.300	4.200	4.100	4.200	4.200	4.300	4.200
5	7.300	7.150	7.200	7.100	7.050	7.000	7.050	6.950
10	14.350	14.100	14.150	14.100	14.050	14.150	14.300	13.950
20	28.400	28.150	28.200	28.150	28.200	28.100	28.150	28.000
30	42.100	42.200	42.500	42.250	42.250	42.200	41.850	41.950

Table 9
Activated charcoal versus syrup

Weight (g) of charcoal.	Volume (ml) of syrup used at the specified concentration								
	Water (0%)	5%	10%	15%	20%	40%	50%	70%	85%
1	1.500	1.400	1.450	1.500	1.450	1.400	1.400	1.400	1.400
2	2.800	2.850	2.850	2.950	2.800	2.900	2.800	2.800	2.850
3	4.300	4.200	4.350	4.500	4.200	4.200	4.250	4.300	4.450
5	7.300	7.300	7.200	7.250	7.200	7.200	7.250	7.200	7.500
10	14.350	14.100	14.200	14.100	14.300	14.100	14.200	14.400	14.450
20	28.400	28.300	28.000	28.500	28.400	28.400	28.300	28.650	29.250
30	42.100	42.500	42.500	42.650	42.350	42.200	42.250	43.100	43.600

Table 10
Magnesium oxide versus glycerin

Weight (g) of MgO	Volume (ml) of glycerin used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
1	2.700	2.700	2.650	2.550	2.450	2.300	2.200	2.100
2	5.500	5.400	5.300	5.150	4.900	4.700	4.400	4.200
3	8.200	8.050	7.900	8.250	7.350	7.050	6.500	6.300
5	13.700	13.400	13.200	12.850	12.550	11.850	10.650	10.450
10	27.300	26.850	26.400	25.750	24.000	23.500	21.350	21.000
20	54.600	53.650	52.800	51.500	49.000	47.000	42.650	42.000
30	82.000	80.500	79.250	77.250	73.500	70.500	65.950	63.050

Table 11
Magnesium oxide versus propylene glycol

Weight (g) of MgO	Volume (ml) of propylene glycol used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
1	2.700	2.350	2.350	2.350	2.350	2.300	2.300	2.200
2	5.500	4.800	4.700	4.750	4.700	4.550	4.500	4.500
3	8.200	7.000	7.050	7.000	7.000	6.900	6.800	6.700
5	13.700	11.700	11.700	11.700	11.700	11.400	11.300	11.200
10	27.300	23.400	23.600	23.400	23.400	22.850	22.600	22.400
20	54.600	46.800	46.800	46.800	46.800	45.700	45.250	44.800
30	82.000	71.250	70.450	70.250	70.250	68.850	67.900	67.200

Table 12
Magnesium oxide versus syrup

	Volume (ml) of syrup used at the specified concentration								
Weight of MgO	Water (0%)	5%	10%	15%	20%	40%	50%	70%	85%
1	2.700	2.500	2.500	2.550	2.650	2.650	2.650	2.600	2.600
2	5.500	5.000	5.000	4.650	5.350	5.300	5.300	5.300	5.350
3	8.200	7.350	7.450	6.600	8.000	8.000	8.000	8.050	8.000
5	13.700	12.550	12.400	12.550	13.300	13.500	13.300	13.350	13.350
10	27.300	25.100	24.900	24.200	26.800	26.750	26.550	26.750	27.000
20	54.600	49.900	49.800	48.450	53.250	53.350	53.150	53.250	53.500
30	82.000	77.250	78.500	79.000	80.000	80.000	80.100	80.100	80.250

Table 13
Magnesium hydroxide versus glycerin

Weight (g) of $Mg(OH)_2$	Volume (ml) of glycerin used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
3	1.900	1.850	1.800	1.800	1.750	1.750	1.700	1.600
5	3.150	3.100	3.050	2.9500	2.900	2.900	2.800	2.700
10	6.300	6.150	6.050	5.950	5.850	5.800	5.600	5.400
20	12.600	12.500	12.100	11.900	11.700	11.550	11.250	10.850
30	18.900	18.600	18.200	17.800	17.650	17.350	16.850	16.300
50	31.500	31.000	30.300	29.700	29.250	28.900	28.100	27.150

Table 14
Magnesium hydroxide versus propylene glycol

Weight (g) of $Mg(OH)_2$	Volume (ml) of propylene glycol used at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
3	1.900	1.650	1.650	1.650	1.550	1.500	1.550	1.500
5	3.150	2.750	2.750	2.750	2.750	2.550	2.550	2.500
10	6.300	5.400	5.400	5.500	5.400	5.100	5.000	5.000
20	12.600	10.850	10.800	10.800	10.850	10.250	10.250	9.950
30	18.900	16.300	16.300	16.300	16.300	15.350	15.350	14.950
50	31.500	27.150	27.150	27.150	27.150	25.600	25.600	24.900

Table 15
Magnesium hydroxide versus syrup

Weight (g) of $Mg(OH)_2$	Volume (ml) of syrup used at the specified concentration							
	Water (0%)	10%	15%	20%	40%	50%	70%	85%
3	1.900	1.800	1.750	1.750	1.800	1.750	1.800	1.900
5	3.150	3.100	2.800	2.900	3.050	3.050	3.000	3.150
10	6.300	5.400	5.600	5.650	5.550	5.500	5.550	5.600
20	12.600	11.800	11.500	10.650	11.300	11.050	11.350	12.550
30	18.900	17.750	17.850	17.700	17.700	17.800	18.400	17.850
50	31.500	29.200	29.350	29.200	28.900	29.100	30.100	29.750

Table 16
Zinc oxide versus glycerin

Weight (g) of ZnO	Volume (ml) of used glycerin at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
2	0.700	0.700	0.750	0.700	0.700	0.700	0.750	0.700
3	1.100	1.100	1.050	1.050	1.100	1.100	1.100	1.100
5	1.800	1.800	1.800	1.750	1.800	1.800	1.800	1.750
10	3.550	3.550	3.600	3.650	3.650	3.550	3.500	3.550
20	7.100	7.100	7.100	7.100	7.100	7.100	7.100	7.100
30	10.650	10.650	10.700	10.650	10.650	10.600	10.600	10.600
50	17.750	17.750	17.800	17.750	17.800	17.700	17.700	17.700

Table 17
Zinc oxide versus propylene glycol

Weight (g) of ZnO	Volume (ml) of used propylene glycol at the specified concentration							
	Water (0%)	5%	10%	15%	20%	40%	50%	70%
2	0.700	0.600	0.650	0.650	0.650	0.600	0.650	0.600
3	1.100	0.900	0.900	0.900	0.950	0.950	0.950	1.000
5	1.800	1.650	1.700	1.600	1.650	1.650	1.650	1.650
10	3.550	3.200	3.000	3.200	3.200	3.200	3.200	3.200
20	7.100	6.450	6.500	6.450	6.450	6.450	6.450	6.450
30	10.650	9.700	9.700	9.700	9.700	9.700	9.700	9.700
50	17.750	16.150	16.000	16.250	16.150	16.250	16.150	16.150

Table 18
Zinc oxide versus syrup

Weight of ZnO	Volume (ml) of syrup used at the specified concentration								
	Water (0%)	5%	10%	15%	20%	40%	50%	70%	85%
3	1.100	1.050	1.050	1.050	1.050	1.050	1.050	1.050	1.050
5	1.800	1.800	1.850	1.800	1.800	1.850	1.800	1.850	1.800
10	3.550	3.550	3.500	3.500	3.550	3.600	3.550	3.500	3.550
20	7.100	7.100	7.000	7.150	7.100	7.000	7.100	7.000	7.100
30	10.650	10.700	10.750	10.700	10.750	10.700	10.700	10.600	10.700
50	17.750	23.200	17.900	17.900	17.800	17.800	17.800	17.900	17.800

Comparing the filtration method to the sedimentation method, it should be realized that the powder particles take up more water in the sedimentation method than in the titration method as seen in Table 19. Solid particles can undergo certain physical changes which includes particle aggregation and preferential absorption. In an aqueous medium, the solid particles aggregate and interact with the medium to produce a hybrid particle which then settles to provide a new volume, the ''association volume.'' On the other hand, the filtration method only allows the medium time to fill in the voids between and within the particles. The particles do not have enough time to interact nor establish equilibrium among themselves and with

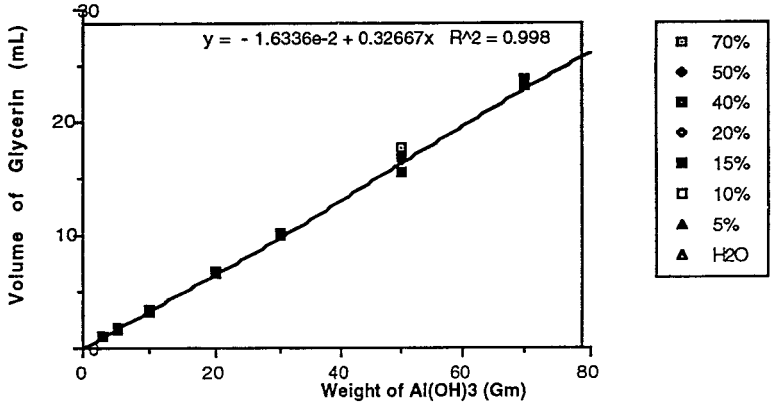

Fig. 1. $Al(OH)_3$ versus glycerin plot.

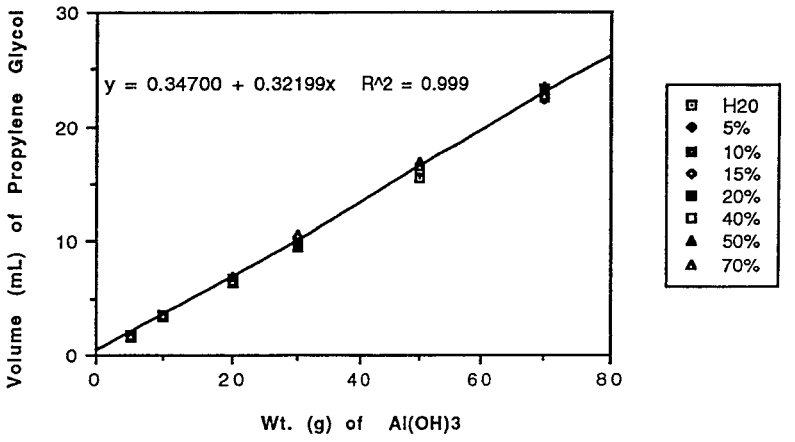

Fig. 2. $Al(OH)_3$ versus propylene glycol plot.

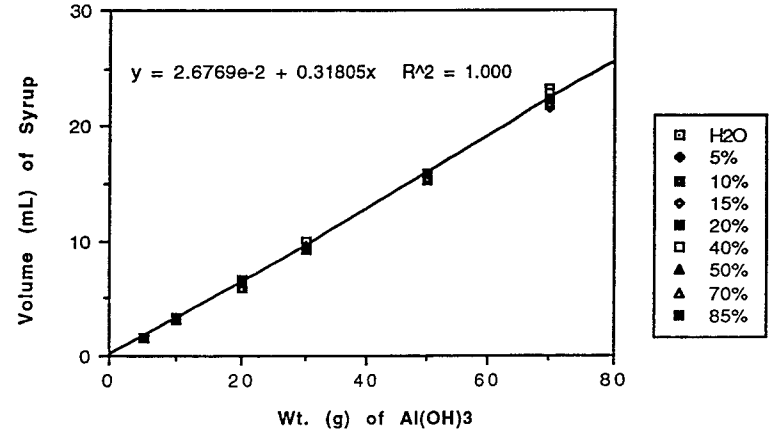

Fig. 3. $Al(OH)_3$ versus syrup plot.

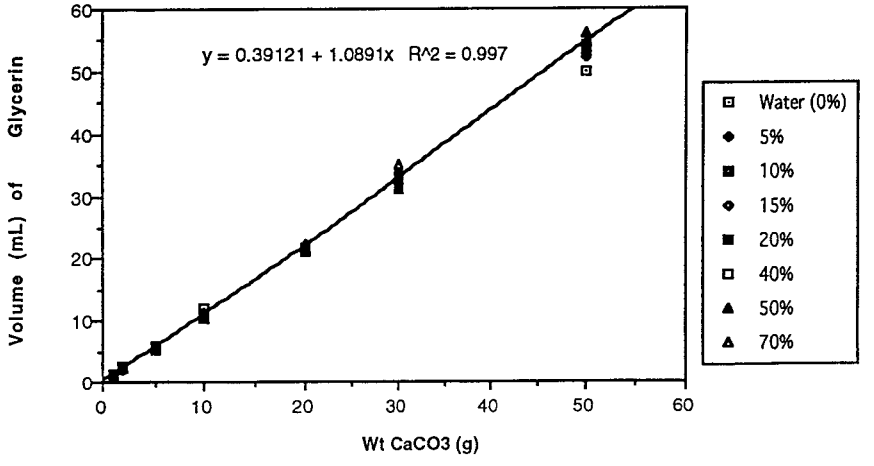

Fig. 4. $CaCO_3$ versus glycerin plot.

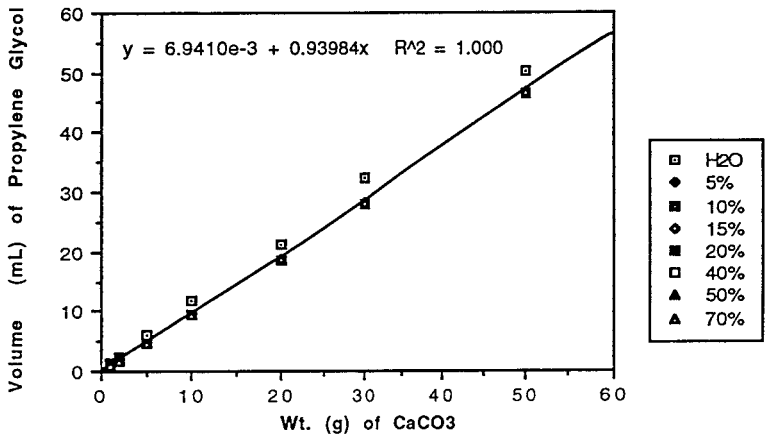

Fig. 5. $CaCO_3$ versus propylene glycol plot.

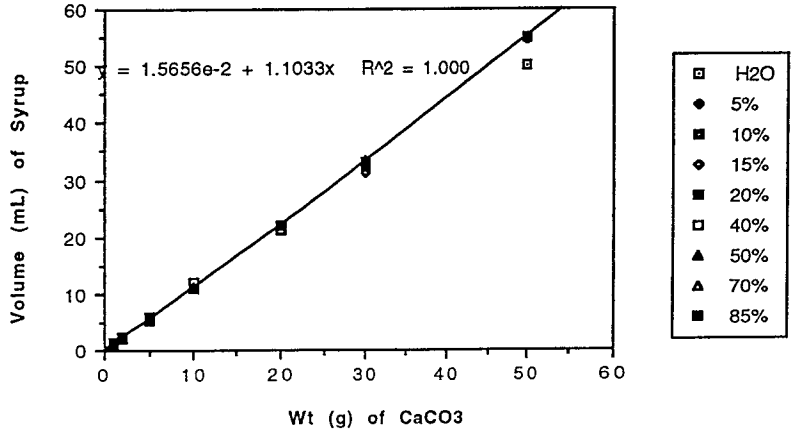

Fig. 6. $CaCO_3$ versus syrup plot.

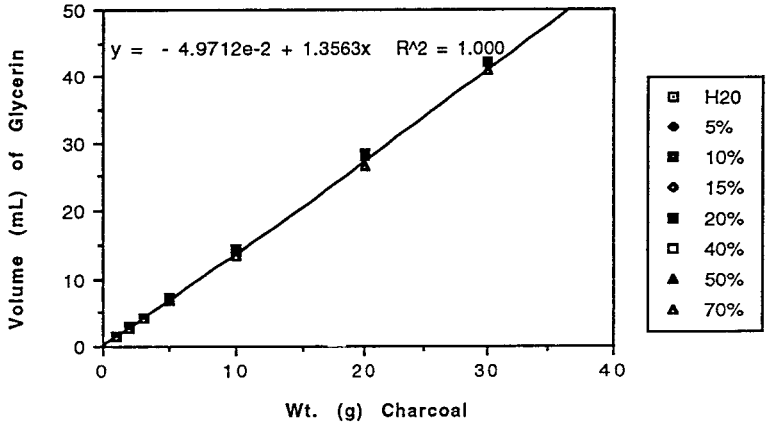

Fig. 7. Activated charcoal versus glycerin plot.

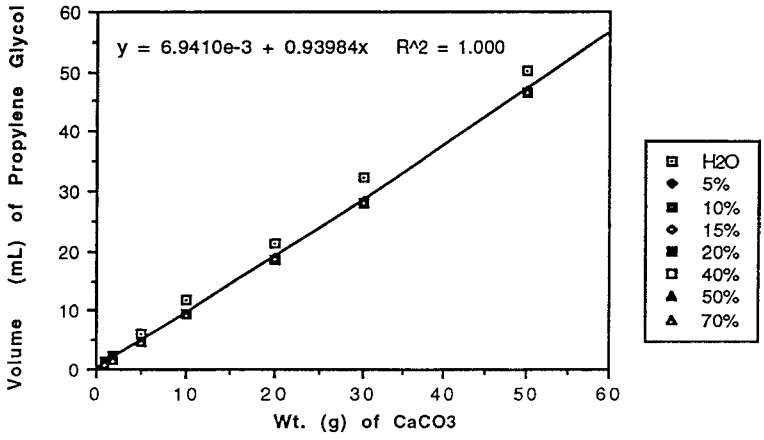

Fig. 8. Activated charcoal versus propylene glycol plot.

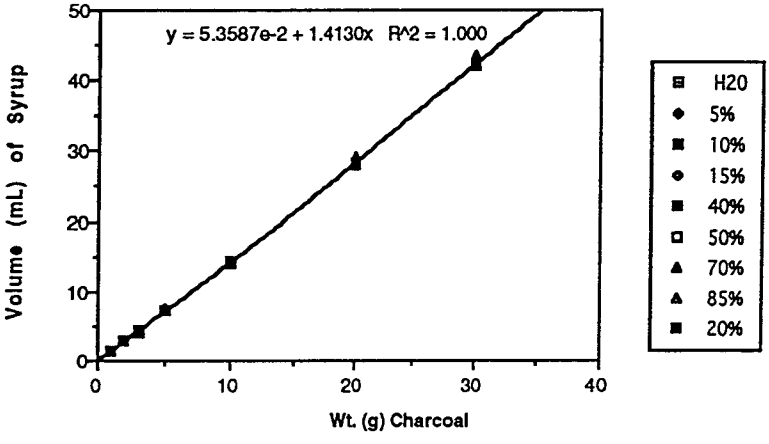

Fig. 9. Activated charcoal versus syrup plot.

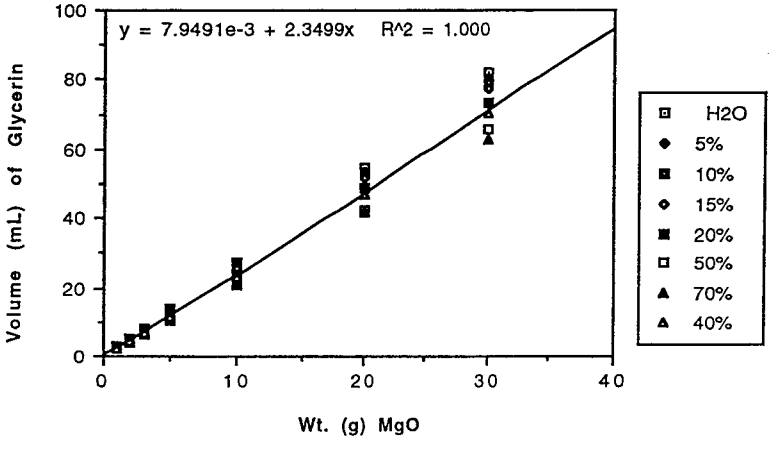

Fig. 10. MgO versus glycerin plot.

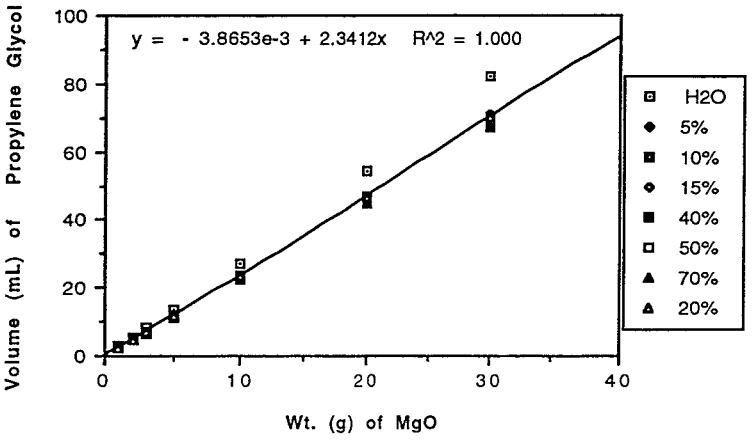

Fig. 11. MgO versus propylene glycol plot.

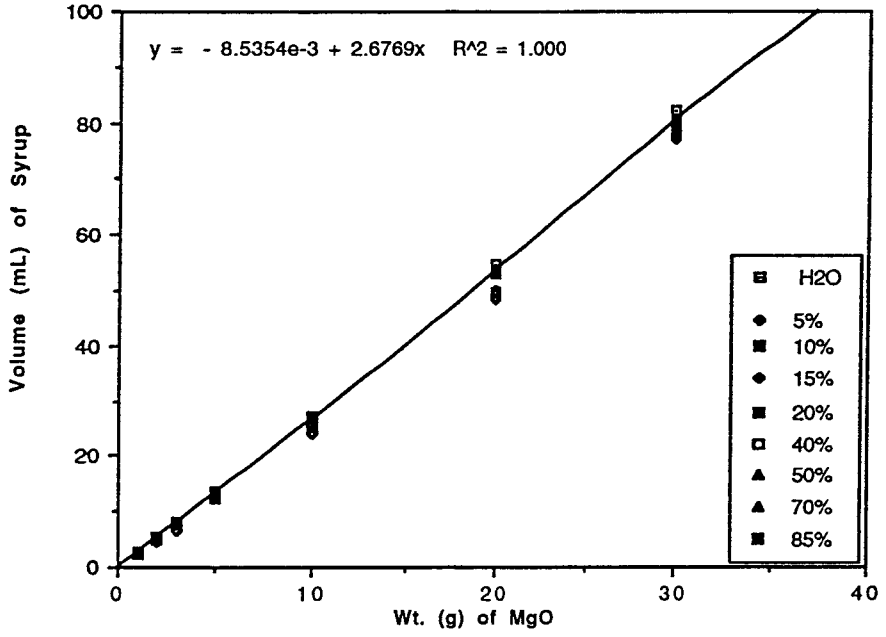

Fig. 12. MgO versus syrup plot.

the suspending medium. As a result, the sedimentation bulk volumes were different from that of the filtration bulk volumes.

6. Results

Experimentally, the plots of the weight of solid versus the volume of liquid used to reach the end point and to make a suspension should be and were relatively straight lines. Most of the plots had a coefficient of correlation (R^2) of one (1.000) as seen in Figs. 5–7, Figs. 12 and 16. The others had some minor deviations, possibly due to experimental errors, as seen in Figs. 1–3, Figs. 8 and 9. However, they did not pass through the origin. In other words, they had intercepts. All of the plots cross the y-axis at either positive or negative points. Positive intercepts indi-

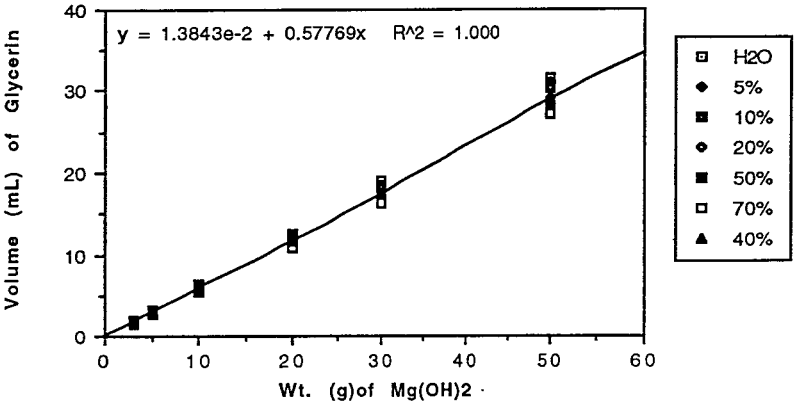

Fig. 13. $Mg(OH)_2$ versus glycerin plot.

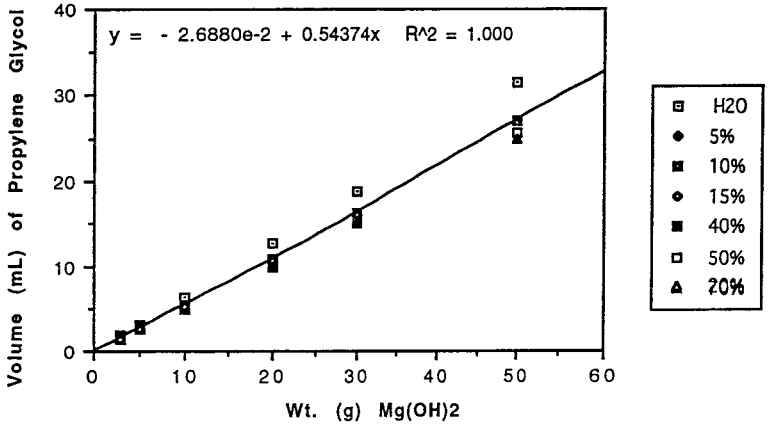

Fig. 14. $Mg(OH)_2$ versus propylene glycol plot.

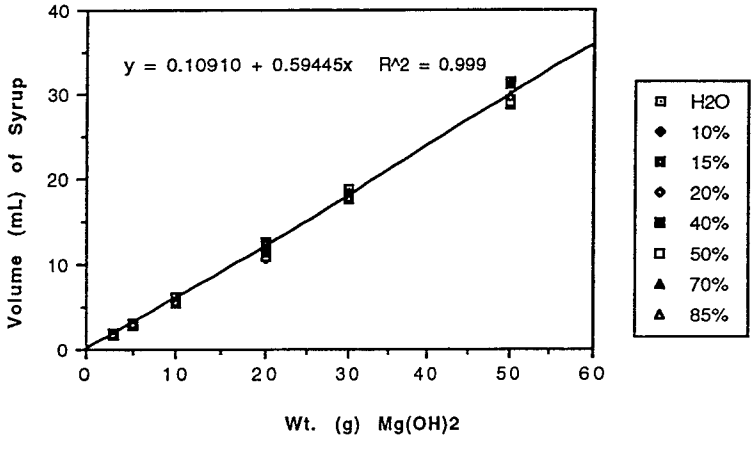

Fig. 15. $Mg(OH)_2$ versus syrup plot.

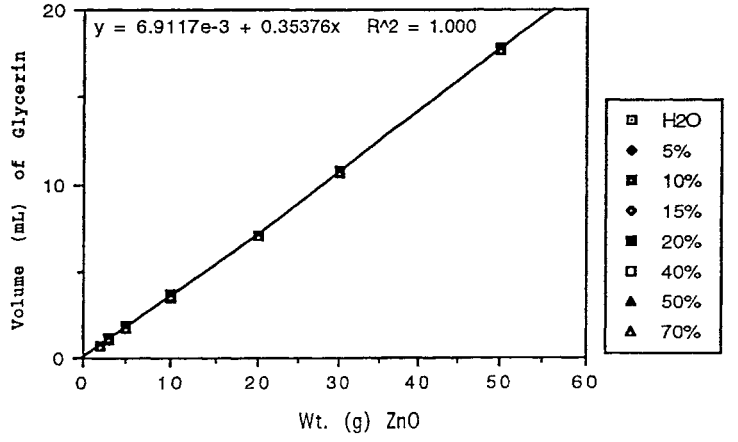

Fig. 16. ZnO versus glycerin plot.

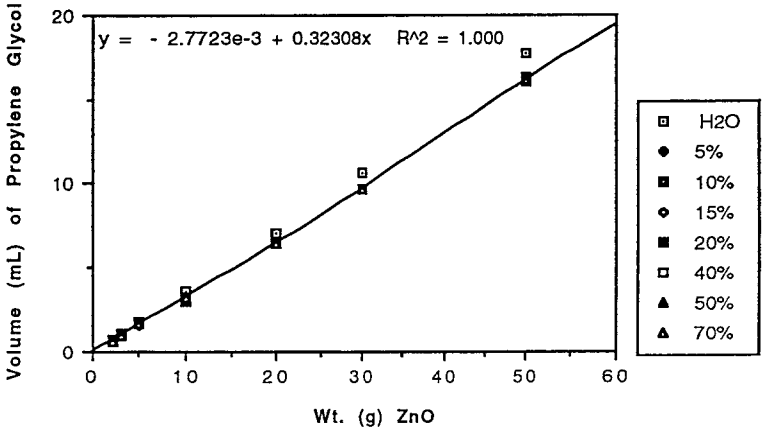

Fig. 17. ZnO versus propylene glycol plot.

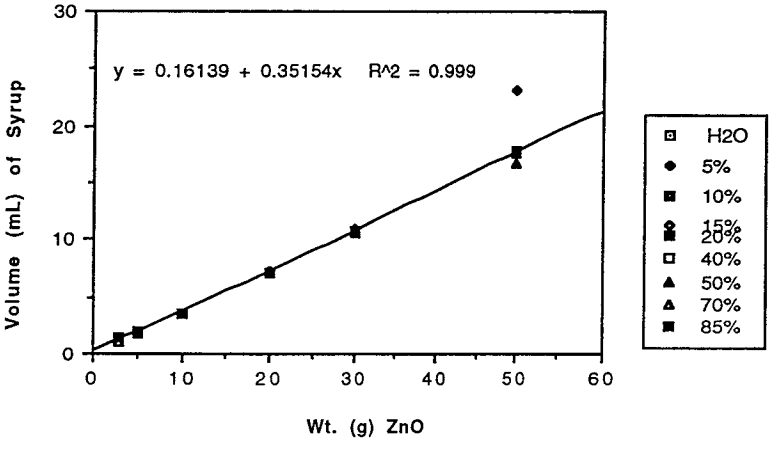

Fig. 18. ZnO versus syrup plot.

cated the volume of the liquid used was more than normal. Cracks and crevices on the particle surface cause some particles to have a larger surface area than others. Those that have a larger surface area would take up more liquid. Therefore, their plots had positive intercepts as seen in Figs. 2–6, Figs. 8–10, Figs. 13 and 15. Negative intercepts mean that the volume used was less than normal, as seen in Figs. 1 and 7, Figs. 11 and 12, Fig. 14. Solid particles have certain physical changes when they are immersed in an aqueous medium. These changes include aggregation and preferential absorption.

The attractive force between particles may also cause them to associate (stick together). This causes a decrease in the surface area of the particles. Particles with smaller surface area would require a smaller volume of liquid to make a suspension, and as a consequence, negative intercept plots were obtained. The comparison of the bulk volume of the traditional sedimentation method versus that of the titration method showed that the bulk volume for the titration method is relatively constant while those obtained for the sedimentation process varied. The compared data for the two methods are given in Tables 19–21 and displayed in Figs. 19–21.

The differences observed are hypothesized as being that of the volume of liquid attached to the aggregate of the solid and its association. This is like the example of a pea in a tennis ball which then is in association with the liquid as seen in Fig. 22. Similarly, we looked at the comparison of the titration and the sedimentation methods. The titration volume per gram is the volume of liquid plus the volume of one gram of solid which is also the voidage per gram of the solids, in this

Table 19
Comparison between the titration and sedimentation method for calcium carbonate in glycerin

Weight of solid (g)	Titration method		Sedimentation method	
	Volume added (ml)	Voidage per gram (ml/g)	Settling volume (ml)	Bulk density (g/ml)
5	5.2	0.962	15	0.303
10	10.5	0.952	22	0.454
20	21.0	0.952	42	0.476
30	33.0	0.909	62.0	0.484

Table 20
Comparison between the titration and sedimentation method for calcium carbonate in propylene glycol

Weight of solid (g)	Titration method		Sedimentation method	
	Volume added (ml)	Voidage per gram (ml/g)	Settled volume (ml)	Bulk density (g/ml)
5	4.65	0.930	16	0.313
10	9.3	0.935	28	0.357
20	18.6	0.930	45	0.444
30	27.9	0.930	–	–

Table 21
Comparison between the titration and sedimentation method for calcium carbonate in water

Weight of solid (g)	Titration method		Sedimentation method	
	Volume added (ml)	Voidage per gram (ml/g)	Settled volume (ml)	Bulk density (g/ml)
5	5.9	0.847	18	0.278
10	11.9	0.840	33	0.303
20	21.2	0.943	60	0.333
30	32.2	0.904	86	0.348

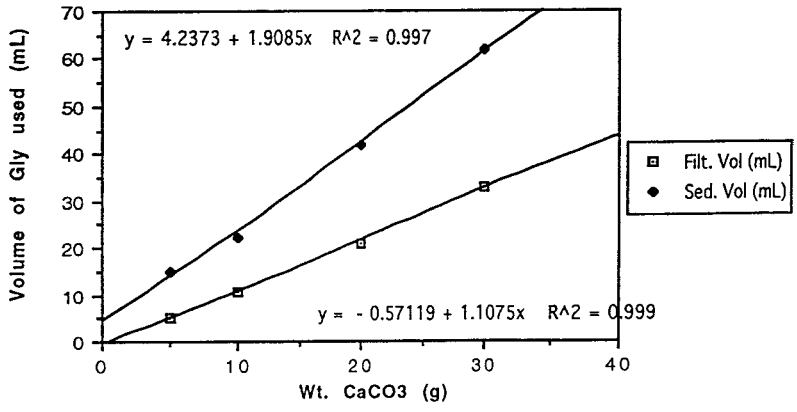

Fig. 19. Comparison between titration and sedimentation method for $CaCO_3$ in glycerin plot.

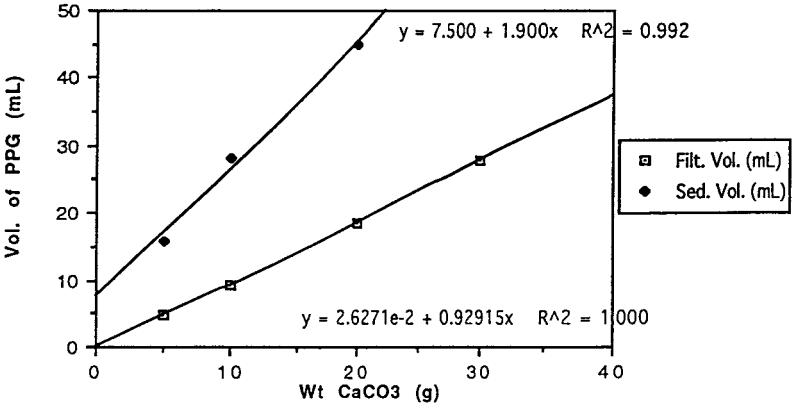

Fig. 20. Comparison between titration and sedimentation method for $CaCO_3$ in propylene glycol plot.

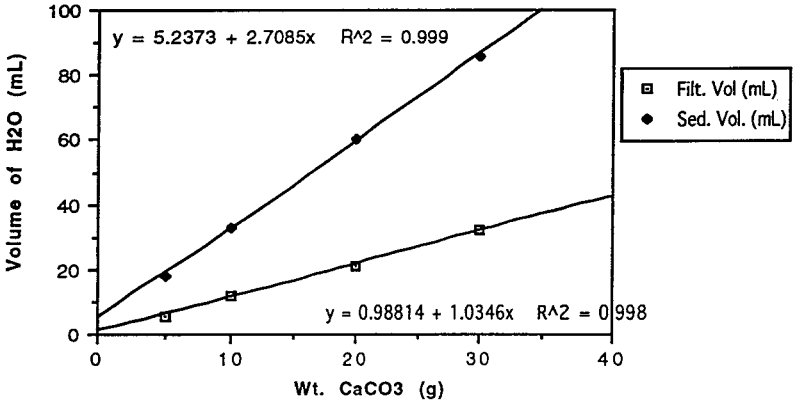

Fig. 21. Comparison between titration and sedimentation method for $CaCO_3$ in water plot.

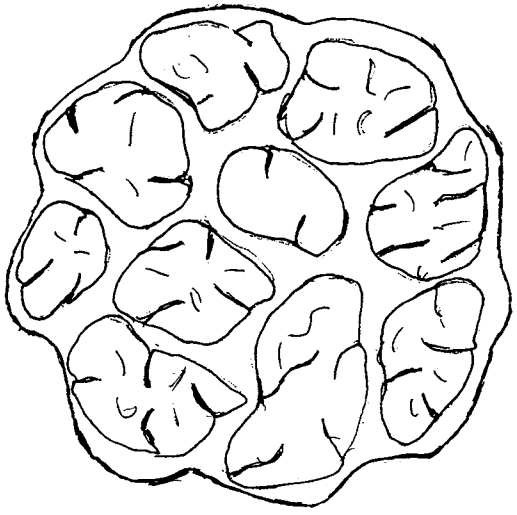

Fig. 22. Drawing of powder titrated with appropriate solvent depicting the ''pea-in-a-tennis-ball'' concept which allows for the calculation of the pore volume.

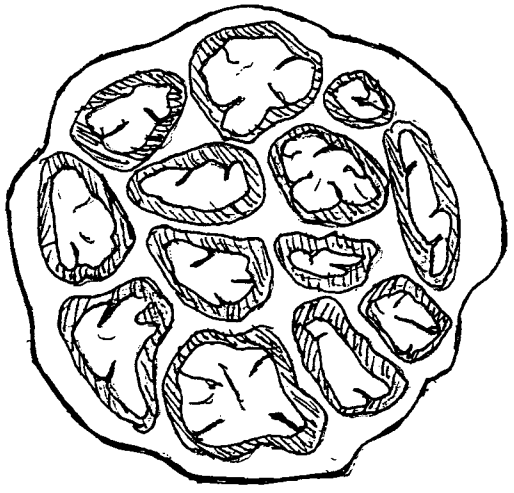

Fig. 23. Drawing of powder with its associated bound solvent as an aggregate, which falls in the solvent under hindered settling conditions to provide a measurement of the final settled volume.

case, $CaCO_3$.

$$\text{Density} = \text{weight/volume} \Rightarrow \text{Volume} = \text{weight/density}.$$

In this case, the weight is 1, therefore,

$$\text{Volume of 1 gm of } CaCO_3 = 1/\text{density of } CaCO_3 = 1/2.711 = 0.369\ \text{ml}$$

If we perform the calculation, we can find that the bulk volume per gram, voidage per gram, for $CaCO_3$ in association with the medium, in this example the medium was water, as seen in Table 21. Then

$$\text{Voidage per gram} = 0.848 + 0.369\ \text{ml} = 1.217\ \text{ml} \Rightarrow \text{Voidage of 5gm} = 1.217 \times 5\ \text{ml} = 6.08\ \text{ml}$$

Since the settled volume is the sum of the aggregated volume and the voidage, as seen in Fig. 21, then

$$\text{Aggregated volume} = \text{settled volume} - \text{voidage} = 18 - 6.08\ \text{ml} = 11.92\ \text{ml}.$$

The sedimentation method allows enough time for the powder particles to associate into aggregates by interacting with the medium to produce a hybrid particle which then settles to provide a new volume, the ''association volume'' as seen in Fig. 23. The aggregation volume, calculated as 11.92 ml, is the volume of the suspended medium interacting with the hybrid particles. The bulk volume comparison results for $CaCO_3$ versus H_2O, glycerin, propylene glycol are presented in Tables 22–24.

The titration method only allows the medium to fill the voids within the powder particles and does not

Table 22
$CaCO_3$ versus H_2O bulk volume comparison

Weight of $CaCO_3$ (g)	Titration method		Sedimentation method	
	Volume (ml)	Density (g/ml)	Volume (ml)	Bulk volume (g/ml)
5.000	5.900	0.847	18.000	0.278
10.000	11.900	0.840	33.000	0.303
20.000	21.200	0.943	60.000	0.333
30.000	32.200	0.904	86.000	0.348

Table 23
$CaCO_3$ versus glycerin bulk volume comparison

Weight of $CaCO_3$ (g)	Titration method		Sedimentation method	
	Volume (ml)	Density (g/ml)	Volume (ml)	Bulk volume (g/ml)
5.000	5.200	0.962	15.000	0.303
10.000	10.500	0.952	22.000	0.454
20.000	21.000	0.952	42.000	0.476
30.000	33.000	0.909	62.000	0.484

Table 24
$CaCO_3$ versus propylene glycol bulk volume comparison

Weight of $CaCO_3$ (g)	Titration method		Sedimentation method	
	Volume (ml)	Bulk volume (g/ml)	Volume (ml)	Bulk volume (g/ml)
5.000	4.650	1.075	16.000	0.313
10.000	9.350	1.070	28.000	0.357
20.000	18.600	1.075	45.000	0.444
30.000	27.900	1.075	[a]	[a]

[a] Data unobtainable.

allow time for particle–particle-suspending medium association nor for equilibrium to be established in the system. Therefore, the final settled volume of the sedimentation method is larger than that of the titration method.

7. Conclusion

Through the process of wetting, insoluble solid particles (i.e., aluminum hydoxide) exhibited certain physical changes even though no interaction or reaction occurred. In addition, the surface area and the variation of size and shape of the particles caused the experimental plots of the weight of solid versus the volume of the liquid used to deviate from the ideal plot.

In short, the experimental data gave plots that were relatively straight lines. However, they did not pass through the origin as theoretically expected. The differences between the traditional sedimentation method versus the titration method indicate that the titration method seems to directly measure the immediate pore volume between particles. Further investigation is required to determine its sensitivity such that it may provide a means of differentiating the nature of the particle–particle and particle–liquid attractive forces within a given suspension pharmaceutical system.

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