DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(14-16), 2653-2673 (1989)

STUDIES RELATING TO THE CONTENT UNIFORMITY OF SUPPOSITORIES. PART ONE: USE OF LACTOSE AS A DRUG CARRIER TO HINDER SEDIMENTATION

E. Sallam*, H. Ibrahim**, M. Takieddin***,
M. Saket, R. Awad, T. Arafat and M. Othman.

A.P.M. Co.*, ACDIMA**, J.P.M. Co.***, and Faculty of Pharmacy, University of Jordan, Jordan.

ABSTRACT

Little attention has been given to the content uniformity of dispersed solid drugs in suppositories. Problems like sedimentation and/or incomplete dispersion of drug agglomerates may result in poor content uniformity, particularly when drug is formulated in minute amounts. Addition of lactose, as an inert

(*) For Correspondence: Arab Pharm. Manuf. Co., P.O. Box 42, Sult, Jordan.

(**) Arab Company for Drug Industries and Medical Appliances, Amman, Jordan.

(***) Jordanian Pharm. Manuf. Co., Naor, Jordan.

carrier to a drug, at an optimal drug-carrier ratio has shown to improve content uniformity of suppositories. Time of mixing is another parameter which has also been optimized. In addition to the coefficient of variation a sedimentation Index 'SI' has been proposed as in-process control parameter to evaluate the content uniformity of suppositories. Value of unity for 'SI' indicates absence of sedimentation; a problem which is mainly encountered with mixing of solids in liquids or melted suppository bases.

INTRODUCTION

Little attention was given to the content uniformity of drug in suppositories. Few studies dealt with the aspects of attaining good homogeneity in suppositories (1-7). In studies concerning homogeneity in semi-solid preparations, problems like sedimentation and/or incomplete dispersion of drug agglomerates were suggested by several authors to produce poor content uniformity of durgs in suppositories (8-10). Such problems become more serious when the drug is formulated in minute amounts, e.g. potent drugs. The random mixing theory shows that at high level of dilution of drug in a dosage form, i.e.1% or less, to attain acceptable content uniformity, the drug must be very fine. Fine particles will be slowly sedimented, therefore; better homogeneity of drug in suppositories is produced. However, very fine particles are characterized by cohesiveness, a property which promotes presence of agglomerates (10). The latter behave like large particles, sediment rapidly, and produce unit doses with high drug content,

i.e. positively skewed distribution which is pharmaceutically unacceptable (11).

It is well documented that if the ratio of durg to base is high, for example 1 to 4; controlling content uniformity becomes manageable (12). Consequently, it is proposed that in cases where the drug content of the suppository is low, the proportion of solid content relative to the base can be increaed by loading the drug particles on an inert solid carrier. Thus, the new total solid content (drug and carrier) is expected to produce good content uniformity when mixed with the melted suppository base. It is a required condition that, the drug/carrier premix should attain good homogeneity. The present study has been undertaken to investigate the use of lactose as a drug carrier and define the mixing conditions, in order to improve content uniformity of suppositories having low drug content.

MATERIALS

Paracetamol powder, pharmaceutical grade, supplied by A.P.M.Co., Sult Jordan. Fine lactose monohydrate powder, B.P. 1980 grade, obtained from Merck, West Germany. Suppository base Witepsol H15 was purchased from Dynamit Nobel, West Germany. Methanol analytical grade (Merck, West Germany) was used for extraction of paracetamol from suppositories.

METHODS

Paracetamol was used as a model drug at a concentration of 10 mg per approximately 2.0 g suppository. While it is acknowledged that paracetamol is therapeutically used at higher levels than 10mg/2g, the used concentration was selected to represent the

normal strength of a potent drug in a suppository, e.g. commercial hyoscine butylbromide suppositories.

To arrive at the optimal ratio of drug to carrier for formulation of suppositories, preliminary experiments were done in duplicate using the following drug-carrier ratio: 1:0, 1:1, 1:2, 1:5, 1:10, 1:20, 1:30, 1:40, 1:50 and 1:60. Powder mixtures were prepared by trituration in a porcelain mortar using geometrical dilution procedure. The powder mixture was then mixed well with the melted base at two different temperatures 40° and 50°c, then poured into plastic cylinders (14.2cc) and left standing vertically at room temperature to congeal. Samples ammroximately 3 g each taken from top and bottom of the cylinders were analysed for paracetamol content. The analysis procedure was based on the extraction of paracetamol from the base with 70% v/v aqueous methanol at 40°c using shaking waterbath. After adjusting to the required volume and carrying out the proper dilution, the absorbance was measured at 249 nm (Kontron Spectrophotometer, Kontron, Sweden). Lactose powder did not interfer with the absorbance measurements. The extractability was determined and validated using known amounts of paracetamol in known quantities of melted suppository base and found to be 96.6% w/w with coefficient of varation 0.45% (n = 6).

Preparation of Paracetamol Suppositories:

In each run, the total weight of the final suppository mix, was 500 g including drug, carrier and suppository base. This amount constituted a batch. Premixing of paracetamol with the required amount of lactose powder (passed through 250 μm mesh) was attained by using stainless steel cube mixer (Erweka, West Germany). Mixing was proceeded until the content uniformity of 20 samples was within an acceptable

range, with a coefficient of variation of 1.77%. The required amount of the premix was added to a known quantity of the base heated at 50°c in a suppository machine (Erweka Suppository-Dosing Unit Type SG 3W, Erweka Co., West Germany) then mixing continued to the required time (without levigation process). When levigation was required, 50 g of melted base was used to levigate the required amount of paracetamol premix and the levigating container was then rinsed with another 50 g of melted base which was added to the rest of the base in the mixing vessel. Mixing was then proceeded according to the subsequently given scheduled time. The speed of rotation was kept constant through out the study at 25 rpm. Suppositories were filled into rows of suppository cavities. Analysis was then performed on 20 suppositories taken from the first the middle and the last rows of the filled batch. Each suppository was individually analysed.

Particle Size Analysis:

Microscope countiong was used with a British Standard Graticule fitted in the eyepiece. A representative sample of the powder under ivestigation was dispersed well in liquid paraffin. A small but, representative portion was transferred to a glass microscope slide and examined in order to count not less than 1000 particles randomly chosen from different fields. Drug/lactose particles from 5 suppositories sampled either from the first or the last rows, were obtained by extracting the suppository base with chloroform, washing well with the same solvent and then dried and mixed well. Representative sample was then taken for microscope counting as described above.

RESULTS AND DISCUSSION

A sedimentation index 'SI' is proposed to evaluate the effect of lactose as a drug carrier, which is supposed to hinder or minimize drug sedimentation in suppositories.

$$'SI' = \frac{X_1}{X_2}$$

X_1 = drug content per g of sample obtained from the bottom of the cylinder, or mean drug content per g of 5 or more consecutive suppositories sampled from the first rows.

X_2 = drug content per g of sample obtained from the top of the cylinder, or mean drg content per g of 5 or more consecutive suppositories sampled from the last rows.

A value of "one" for 'SI' indicates absence of sedimentation.

Particle size analysis of either paracetamol powder or lactose powder indicates log-normal distributions of particles. Paracetamol powder has an average diameter, d_{ave} = 17.5 μm (d_g = 10 μm, σg = 2.857); mean volume diameter, d_{vn} = 52.0 μm (Hatch and Choate Equation, Reference 13) and true density of 1.29 g / cc. Lactose powder has an average diameter, d_{ave} = 8 μm (d_g = 7 μm, σg = 1.667); mean volume diameter, d_{vn} = 10.5 μm and true density of 1.54 g/ cc. Particle size analysis data indicates that lactose powder has more close size distribution (σg of lactose powder $<$ σg of paracetamol powder) and more fine fraction than paracetamol powder. For comparative study; assumption of spherical particles is considered, the 'N' and 'S_w' parameters have been calculated (14)

for each powder 'N'; the particle number per unit weight for lactose powder is approximately 100 times of 'N' for paracetamol powder. In the mean time, 'S_W' the surface area per unit weight for lactose powder is approximately 9.7 times of 'S_W' for paracetamol powder.

Preliminary experiments to assess effects of carrier in hindering sedimentation were conducted using cylinders of size 14.2 cc. This work indicated that, under the experimental conditions, the sedimentation behaviour after mixing at 40° and 50°c then congealing at room temperature is similar at both temperatures (Table 1 and Fig. 1). With increasing carrier ratios 'SI' value starts to increase until it reaches a maximum at a paracetamol-lactose ratio of 1:10, then drops to a more or less a minimum value at ratios of 1:40, 1:50 and 1:60. At the ratio of 1:60 'SI' is very close to the theoretical or ideal value; i.e. unity.

Sedimentation rate of particles in liquid is a function of many parameters; the particle diameter, the density difference between particles and liquid and the vistosity of the liquid. In the absence of lactose carrier, the 'SI' is relatively high which indicates rapid sedimentation of paracetamol particles. Sedimentation rate increases by adding lactose, but the ratios 1:1, 1:2 and 1:5 donot differ significantly. Lactose being a fine powder is expected to be cohesive and adhere strongly to paracetamol particles. Up to a drug-carrier ratio of 1:5 (3.0% w/w solid content) it seems that, the adhered units of paracetamol-lactose are small in size and number. Consequently, small changes in the particle diameter and density difference occur with only little apparent changes in 'SI' values. Lactose particles in the adhered units will

TABLE 1

Sedimentation Index 'SI' of Melted Base Containing Different Ratios of Paracetamol and Lactose Poured Into Cylinders at Different Temperatures.

Paracetamol Lactose Ratio	Solid % w/w	'SI' at 40°c	'SI'at 50°c
1:0	0.5	5.2	6.3
1:1	1.0	7.4	7.5
1:2	1.5	7.7	7.0
1:5	3.0	7.7	7.5
1:10	5.5	10.5	10.8
1:15	8.0	9.0	8.4
1:20	10.5	6.7	6.7
1:30	15.5	1.69	1.92
1:40	20.5	1.26	1.29
1:50	25.5	1.03	1.16
1:60	30.5	1.03	1.07

N.B. The concentration of paracetamol per g suppository base is kept constant for all preparations (0.5% w/w).

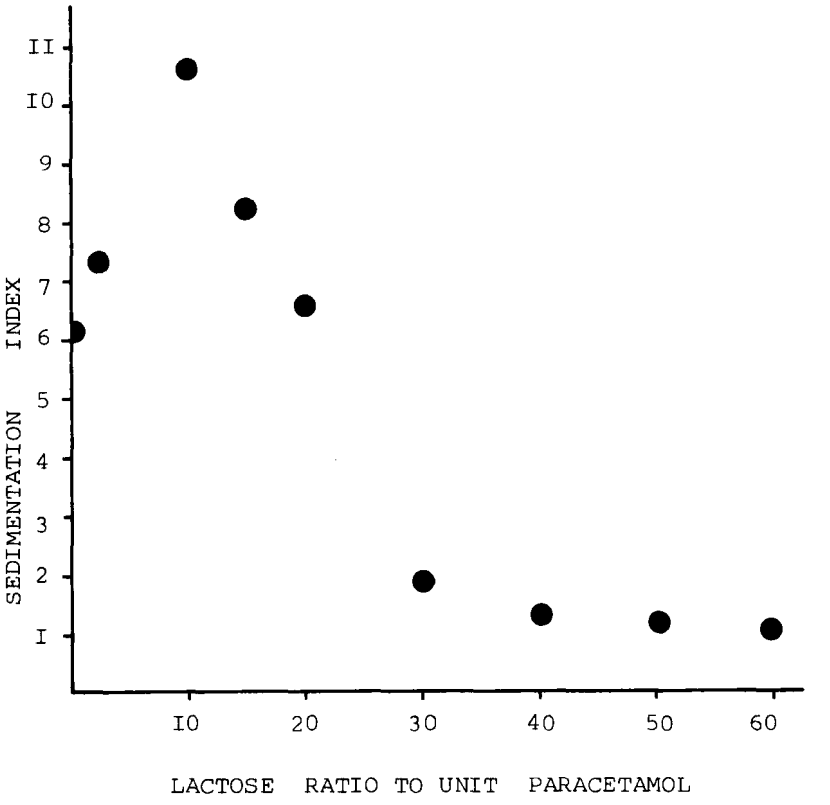

FIGURE 1

Relationship between Sedimentation Index 'SI' of Paracetamol in Suppository Base and Ratio of Lactose as a Drug Carrier.

cause changes in the density difference. At the ratio 1:10, the number of lactose particles become approximately 1000 times of paracetamol particles. Furthermore, the surface area of lactose particles multiplies 10 times. At this ratio it seems that, the paracetamol particles are surrounded completely by the carrier particles thus form adhered units with larger diameter and the density difference increases significantly. Consequently, 'SI' attains its

maximum value. Above this ratio, 'SI' starts to decrease as a consequence of two possible effects, the first is mechanical hindrance to motion of adhered units and the second is the increase in viscosity of the medium due to high solid content. The voids which allow free motion for sedimentation become less available. These factors become more prominent by increasing the proportion of the lactose, until 'SI' approaches its ideal value of unity, at the drug-carrier ratio of 1:60. At this ratio; the distribution of adhered units along the cylinder is homogeneous, i.e. the top portion has solid content including drug similar to the bottom portion. This conclusion is arrived at from the fact that 'SI' value of system is one. Thus, lactose powder is distributed to fill the whole volume of the cylinder (14.2 cc) although the true volume of total solids determined experimentally compromises 22% of cylinder volume. Calculation based on d_{vn} , N , weight and density of solids, and suppository volume give a value of 31.0% v/v occupied by lactose and paracetamol. Flowability of the melted suppository mixture is significantly reduced at 1:60 ratio, a factor which should be optimized to have a successful system.

Content Uniformity of Suppositories:

Results (Table 2) of paracetamol suppositories prepared without lactose, B1 - B3 indicate poor content uniformity. The problem could not be attributed to the presence of drug agglomerates, because levigation has been used to guarantee maximum breakdown of drug agglomerates and complete dispersion of individual drug particles. It is very likely that sedimentation plays a major role in causing the problem, even when the mixing time has been shortened to 5 minutes. During filling, the apparatus allows mixing to continue at the

TABLE 2

Results of Paracetamol Suppositories (10 mg / Suppository) Prepared Without Lactose Under Different Mixing Conditions. .

Batch No	Time of Mixing, Minutes	Mixing Condition	Mean mg/Supp.	CV %	Range mg/Supp.	'SI'
B1	60	Without Levigation	9.9	76.3	2.2-45.2	7.75
B2	60	With Levigation	9.7	75.5	3.9-45.5	6.63
B3	5	With Levigation	12.5	86.5	4.2-39.3	5.90

CV = Coefficient of Variation of Drug Content in Suppositores; n = 30 for B1, n = 20 for B2 and B3. 'SI' = Sedimentation Index.

same time. However, the results clearly point out that long time mixing, e.g, up to one hour does not prevent sedimentation of paracetamol particles. This is because the mixer is operating as a paddle mixer without any tangential or turbulent mixing. Figure 2 shows diagramatically the distribution of drug content in individual suppositories according to their sequence number during filling. All batches B1, B2 and B3 show high drug content in the first 20 suppositories. This indicates high sedimentation rate of paracetamol which is followed by depletion of drug from portion producing last suppositories. Accordingly, 'SI' values are very high as shown in Table 2.

Results shown in Table 3 indicate significant improvement of content uniformity of paracetamol in suppositories where the drug-lactose ratio is 1:60. Sedimentation rate has been reduced to a great extent, 'SI' values have been decreased from a level of 5.90 - 7.75 to a level approaching unity 0.76 - 1.12. Levigation process appears to be benefetial in batches containing lactose as the coefficient of variation decreased significantly, 21.5% for B4 prepared without prior levigation compared to 15.3% for B5 prepared with levigation (Table 3). It is obvious that, levigation has helped in breaking down agglomerates and subsequent dispersion of individual particles as indicated by smaller assay range 8.4 - 12.8 mg per suppository. Time of mixing in case of B1-B3; i.e. paracetamol mixed alone with suppository base, does not make any significant contribution to improvement of content uniformity (Table 2). On contrary, it becomes an important parameter when the carrier lactose is in the formulation (Table 3). By decreasing time of mixing content uniformity improved; B8 (5 minutes mixing)

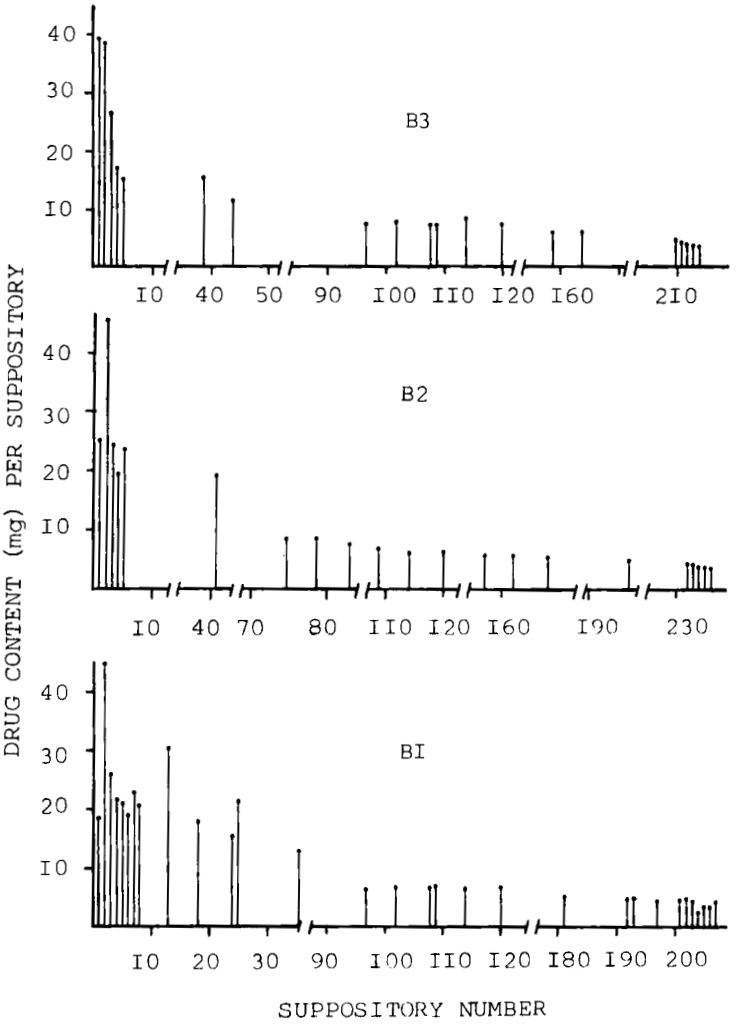

FIGURE 2

Diagramatic Presentation of Drug Content Per Suppository in mg according to the Sequence of Filling for B1, B2 and B3.

TABLE 3

Results of Paracetamol Suppositories (10 mg / Suppository) Prepared With Lactose Under Different Mixing Conditions.

Batch No	PA/LA	Time of Mixing, Minutes	Mixing Conditions	Mean mg/Supp.	CV%	Range mg/Supp.	'SI'
B4	1:60	60	Without Levigation	9.9	21.6	8.0-15.1	0.76
B5	1:60	60	With Levigation	9.1	15.3	8.4-12.8	0.83
B6	1:60	25	With Levigation	9.2	10.3	7.9-11.9	1.04
B7	1:60	15	With Levigation	9.3	8.9	8.4-10.3	1.12
B8	1:60	5	With Levigation	9.3	6.2	8.4-11.1	1.01

PA = Paracetamol; LA = Lactose. CV = Coefficient of Variation of Drug Content in Suppositories; n = 20. 'SI' = Sedimentation Index.

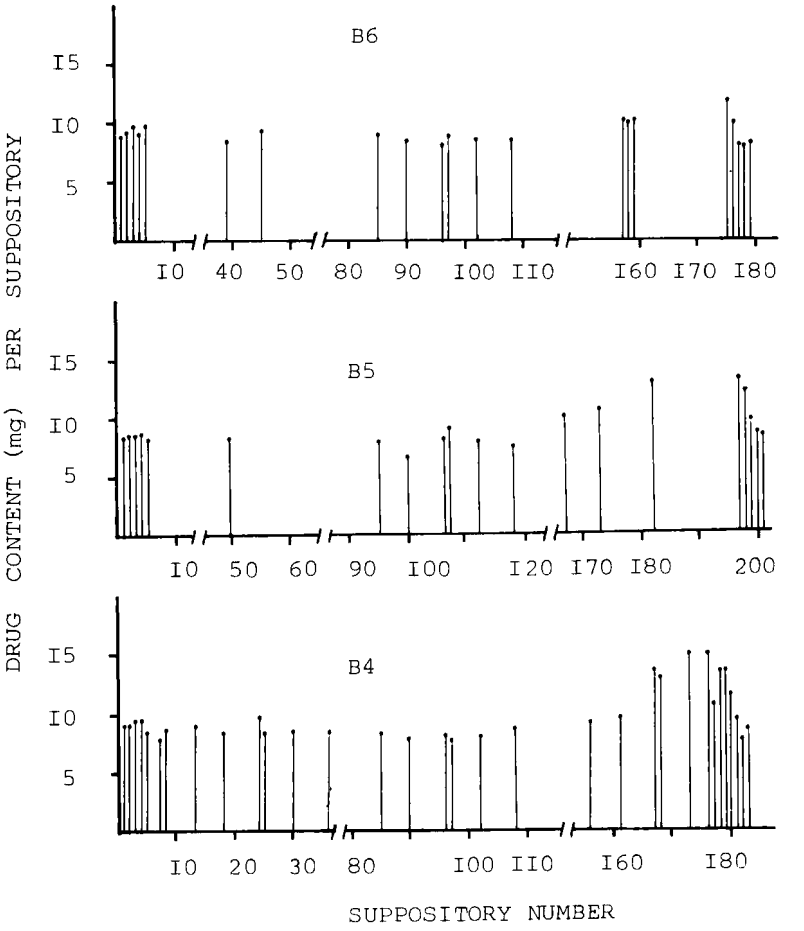

FIGURE 3

Diagramatic Presentation of Drug Content Per Suppository in mg according to the Sequence of Filling for B4, B5 and B6.

as can be judged by a coefficient of variation 6.2%, while B5 (60 minutes mixing) produced coefficient of variation 15.3%. 'SI' values could explain the mechanism. For 5 minutes mixing time, 'SI' value approaches unity, which indicates a homogeneous distribution of drug through the whole mixture as

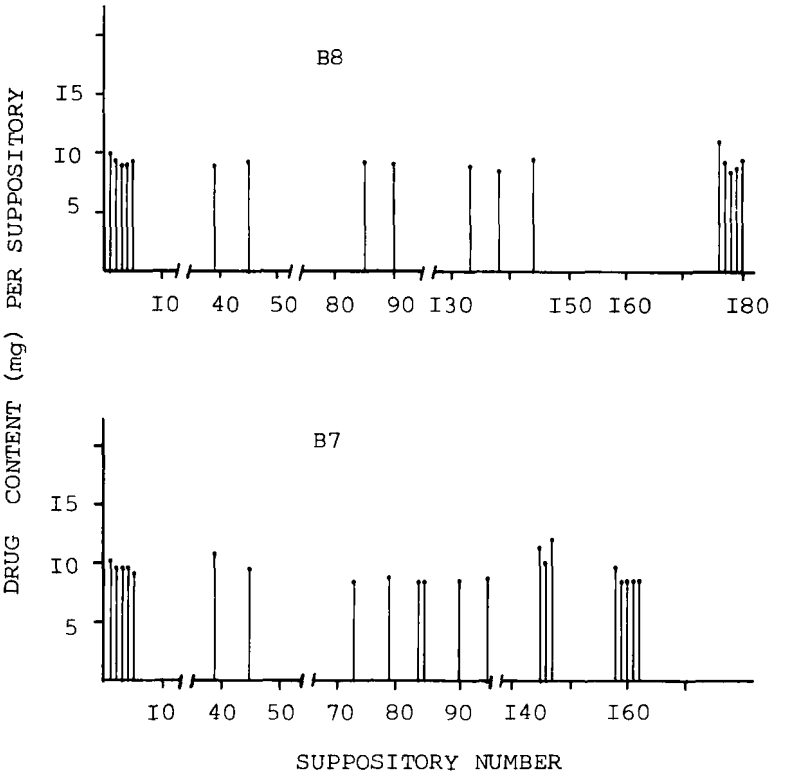

FIGURE 4

Diagramatic Presentation of Drug Content Per Suppository in mg according to the Sequence of Filling for B7 and B8.

shown in Fig. 4. By increasing time of mixing, coefficient of variation and range of drug content in suppositories increase. Figure 3 shows that the last suppositories of B5 (60 minutes mixing) have high mean drug content which is reflected on 'SI' value, i.e. less than unity (0.84). It seems that, this phenomenon is related to the type of particle size distribution after a prolonged time of mixing. The particle size distribution of the solid contents in 5 consequetive suppositories taken from the first

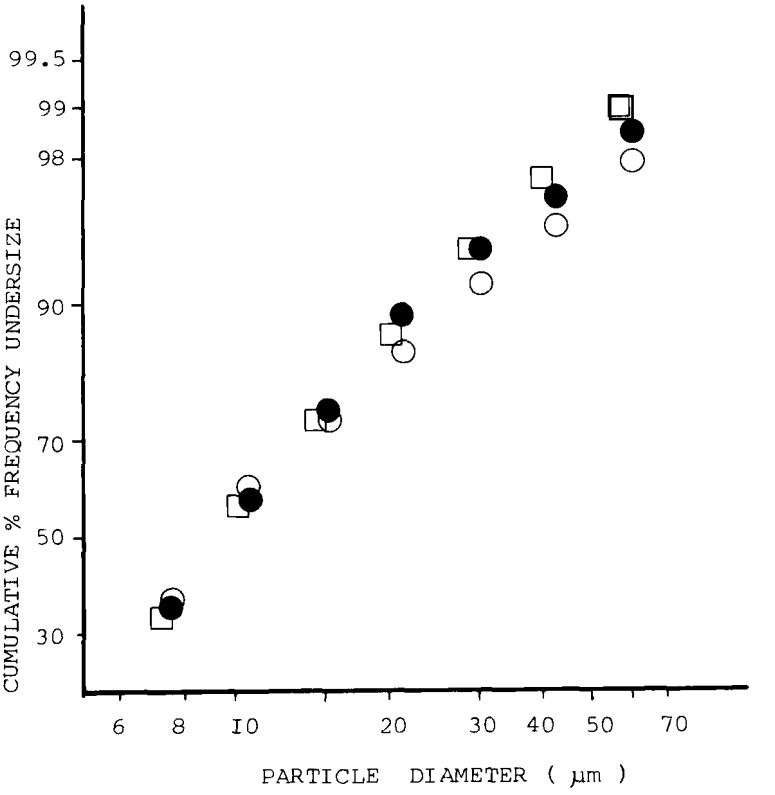

FIGURE 5

Plots of Cumulative Percentage Frequency Undersize Versus Particle Diameter on a Log-Probability Scale for: □ Lactose Powder, ○ Solid Content of Suppositories Sampled from the First Rows of B8, and ● Solid Content of Suppositories Sampled from the Last Rows of B8.

rows and others taken from the last rows of B5 and B8 were determined and compared to the original particle size distribution of lactose powder. Figure 5 shows the particle size distribution for solids of B8 (5 minutes mixing) and lactose powder. The figure shows that the particle size distribution of lactose powder, and solids obtained from the first and

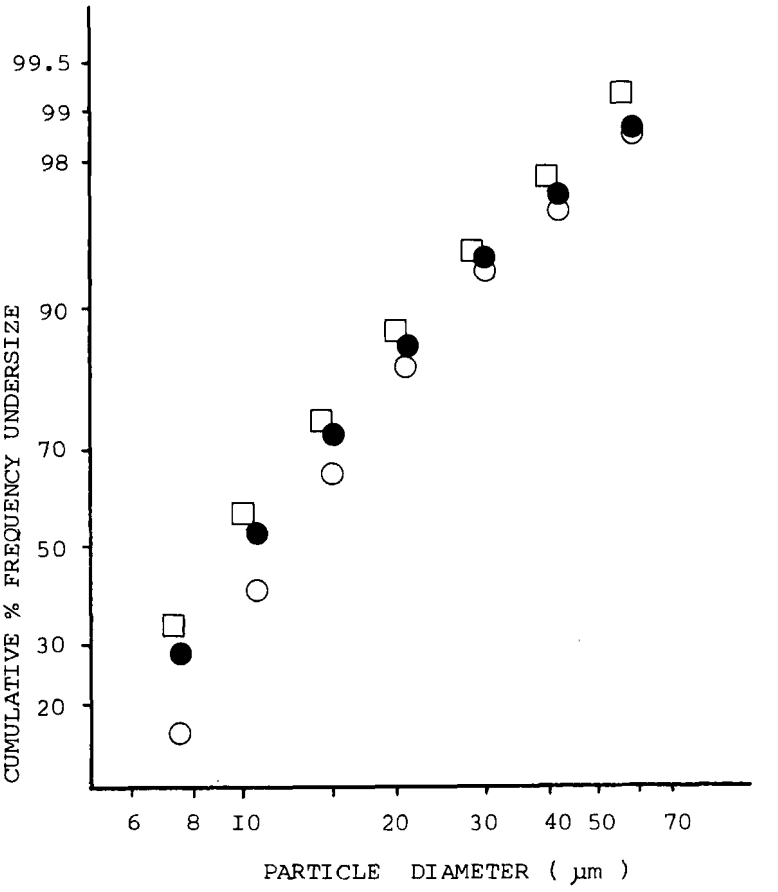

FIGURE 6

Plots of Cumulative Percentage Frequency Undersize Versus Particle Diameter on a Log-Probability Scale for: □ Lactose Powder, ○ Solid Content of Suppositories Sampled from the First Rows of B5, and ● Solid Content of Suppositories Sampled from the Last Rows of B5.

the last set of suppositories are close to each other. Therefore; it could be concluded that, 5 minutes mixing time has not caused major changes in the particle size distribution of the solid portion of the suppository. Consequently, the homogeneity is judged good and is reflected in 'SI' value which becomes close

to unity. For B5 (60 minutes mixing) the particle size distribution of the solid portion of suppositories obtained from the first row (Supp. No. 6-10) exhibited significant deviation from the original distribution of lactose powder (Fig.6). This distribution is characterized by having more coarse fraction. Furthermore, the mean drug content of suppositories in this region is 8.6 mg / suppository which is lower than the target value of 10 mg / suppository. The voids available in suppository mixture with 30.5% w/w solids is around 78% which during 1 hour mixing, will allow sedimentation of adhered units of coarse lactose particles. Coarse lactose particles have smaller surface area and less number of interactive sites and hence, lower paracetamol content. Suppositories obtained from the last rows (Supp. No. 192-196) produced particle size distribution of solid portion close to that of lactose powder (Fig. 6). However, in this region of the suppository batch (Supp. No. 179-199), the drug content per suppository is high (12-12.8 mg). The drug content decreases on decreasing mixing time until it approaches the target value as shown in Figures 3 and 4. Since paracetamol powder has lower density than lactose and has a wider size distribution, then it is proposed that coarse drug particles tend to separate on longer time of mixing and concentrate in this region. However, further investigations are required to elucidate the mechanism more clearly.

CONCLUSION

In formulation of suppositories when the drug content is low, an inert carrier like lactose could be added as an agent to hinder sedimentation. A

sedimentation index, 'SI' is proposed as an in-process control parameter along with coefficient of variation to evaluate the content uniformity of the suppositories. Value of unity for 'SI' indicates absence of sedimentation, a problem which is mainly encountered with mixing of solids in liquids or melted suppository bases. The studied mixing conditions such as, percentage of carrier and time of mixing are found to significantly affect the value of 'SI'. A drug to carrier ratio of 1:60 and 5 minutes mixing produce good content uniformity and 'SI' value close to unity. It is suggested that such approach could be of value in solving content uniformity problems arising from sedimentation of active ingredient in potent drug containing suppositories.

REFERENCES

1. G. Regdon and G. Kedvessy, Gyogyszereszet, 6 , 452 (1962).
2. I. Setnikar and F. Fontani, J. Pharm. Sci, 59(9), 1319 (1970).
3. F. Fontani, Boll. Chim. Farm., 109(8) , 447 (1970).
4. H.L.M. Cox, R.P. Dessing and C.P. Scholten, Pharm. Weekbl., 113(16) , 398 (1978).
5. H.L.M. Cox, C. Hekket and L.A.P. Dekind, Pharm. Weekbl., 114(30) , 811 (1979).
6. W. Hening, Dtsch. Apoth. - Ztg., 119(26) , 1027 (1979).
7. H.L.M. Cox, J.J.M. Holthuis and L.A.P. Dekind, Pharm. Weekbl., 116(36) , 1101 (1981).
8. J.A. Hersey and P.C. Cook, J. Pharm. Pharmacol., 26 , 126 (1974).

9. N.A. Orr, E.A. Hill and J.F. Smith, Int. J. Pharm. Tech. & Prod. Mfr., 1(2) , 4 (1980).
10. N.A. Orr, E.A. Hill and E.A. Sallam, The Institution of Chemical Engineers, Symposium No. 64 , D1 (1981).
11. E. Sallam and N. Orr, Drug Devel. Ind. Pharm., 12 (11 - 13) , 2051 (1986).
12. D. Train, Pharm. J, 131 , 129 (1960).
13. T. Hatch and S.P. Choate, J. Franklin. Inst., 207 , 369 (1929).
14. A. Martin, J. Swarbrick and A. Cammarata, "Physical Pharmacy", Third Edition, Lea and Febiger, Philadelphia, 1983.