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COMMUNICATIONS

MICROMERITIC PROPERTIES OF NITROFURANTOIN MICROCAPSULES

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ABSTRACT

In our previous study, we have prepared nitrofurantoin microcapsules using carboxymethylcellulose (CMC) and aluminium sulphate by a coacervation technique. In the present study, the micromeritics of these microcapsules were investigated in terms of standardization of the crude materials employed, the microcapsules product and the dosage forms prepared from these microcapsules. The microcapsules were prepared with a 1:1 core:wall ratio and sieved into three particle sizes. Both the micromeritic properties of the pure drug and the polymer were studied by determining their bulk volume and weight, tapping volume and weight, fluidity, angle of repose, weight deviation, particle size distribution, density and porosity. The particle size range went from approximately 250μm to 3000μm with a peak between 900μm and 1350μm. The results indicate that the flowability and the particle size of the resultant microcapsules were much increased compared with the raw materials. As the microcapsule size increases the porosity also increases but the density decreases.

The weight deviation of the microcapsules first sieved then filled into hard gelatin capsules was carried on according to the USP XXII. Hard gelatin capsule size was found by Lindenwald-Tawashi nomogram as number 3. The geometric mean diameters and the geometric standard deviation of microcapsules were calculated as 750μm for number distribution and 1275μm for weight distribution and 1.52 for number and weight distribution respectively.

In addition to evaluate whether some kind of glidant will be needed during tableting of microcapsules and filling of them into hard gelatines, "Hausner ratio and consolidation indexes" were calculated.

The results obtained suggest that sustained release dosage forms of nitrofurantoin can be prepared from the obtained microcapsules as far as the micromeritic properties is concerned and the microencapsulation changed the micromeritic proporties of the crude materials significantly.

INTRODUCTION

A previous article reports that, a pharmacist today must possess a sound knowledge of micromeritic [1]. Of primary importance to a formulator, when handling drug powder is an assessment of flow properties [2]. These can be evaluated simply from bulk density and angle of repose measurements. From this point of view, some reports were identical about the micromeritic parameters of the microcapsules such as particle density, porosity, particle size, particle size distribution and wall thickness [3-9].

Nitrofurantoin is an urinary tract antiseptic [10]. CMC microcapsules with nitrofurantoin were prepared by means of a coacervation-phase separation technique [11]. The microcapsules with a 1:1 core:wall ratio were separated into three size fractions. The 3 size fractions of microcapsules, the pure drug and the CMC were studied micromeritically.

Bulk volume and weight, tapping volume and weight, fluidity, angle of repose, weight deviation, particle size distribution, density and porosity were determined because these parameters can be used to standardize the microcapsule product and to optimize the pilot production of dosage forms with these microcapsules. Sometimes in order to obtain the required sustained release, the microcapsules are tableted or filled into hard gelatin capsules. From the powder flow therefore the Hausner ratio and consolidation index were calculated to determine whether sufficient flowability is present [8,12].

MATERIALS AND METHODS

Materials

Nitrofurantoin was supplied by Eaton Co. Switzerland, sieved through a 248 μm mesh before use. Carboxymethylcellulose, low viscosity grade, with viscosity of 1% solution at 27°C of 7.1 cps, was obtained from Serva Co. Germany and cyclohexane and N,N dimethylformamide (DMF) from Merck Co. Germany.

Methods

The particle size of the microcapsules was determined by a microscopic method using a particle size measurer (OMO , MOB-1-15[X]). Not less than 600 particles were measured. The geometric mean diameter and geometric standard deviation were calculated .

The bulk volume and weight, tapping volume and weight of the sieved microcapsules and the raw materials were determined [13]. The porosity of the microcapsules were calculated from the density of the materials [5] . The porosity of the raw materials was calculated from the true volume and the bulk volume values [1] .

The fluidity and angle of repose of microcapsules and raw materials were determined according to the Eczacılık Teknolojisi [14] .

The sieved fractions of microcapules were extracted with DMF and drug amounts were determined spectrophotometrically at 370 nm. The fractions of the microcapsules were filled into hard gelatin capsules (size 3) and weighed and drug contents of the filled gelatin capsules were calculated. The size of the hard gelatin capsules needed was estimated from the Lindenwald-Tawashi nomogram [14] . The USP XXII method was used for the determination of the weight deviations of hard gelatin capsules.

The particle densities of sieved microcapsules and other materials were determined with a pycnometer by using cyclohexane . Pharmaceutical preformulation equations were used to calculate the consolidation index and the Hausner ratio [2] .

RESULTS AND DISCUSSION

The particle size of microcapsules varied from approximately 250μm to 3000μm with a peak value between 900μm and 1350μm.

The weight of microcapsules less than 625μm is approximately 10%, less than 1300μm is 50% and less than 2250μm is 95%. The number of particles less than 225μm is approximately 10%, less than 750μm is 50% and less than 1500μm is 95%.

Figure 1 shows the log-probability plots for the side of the microcapsules. The geometric number and weight mean diameters (dg and d'g) and the corresponding geometric standard deviations (σg and σ'g) were calculated from these plots. The geometric mean diameter is the logarithm of the particle size equivalent to 50% on the probability scale and the slope of the straight line is the geometric standard deviation which is the quotient of the ratio (84% undersize or 16% oversize)/(50% size) or (50% size)/(16% undersize or 84% oversize).

In figure 1 for the number and weight distribution dg=750 microns and d'g=1275 microns and $\sigma g = \frac{750}{495} = 1.52$ *and* $\sigma' g = \frac{1275}{840} = 1.52$

The bulk volume and weight, tapping volume and weight, angle of repose, flowing time, standard deviations, relatif deviations, density and porosity values of the materials are

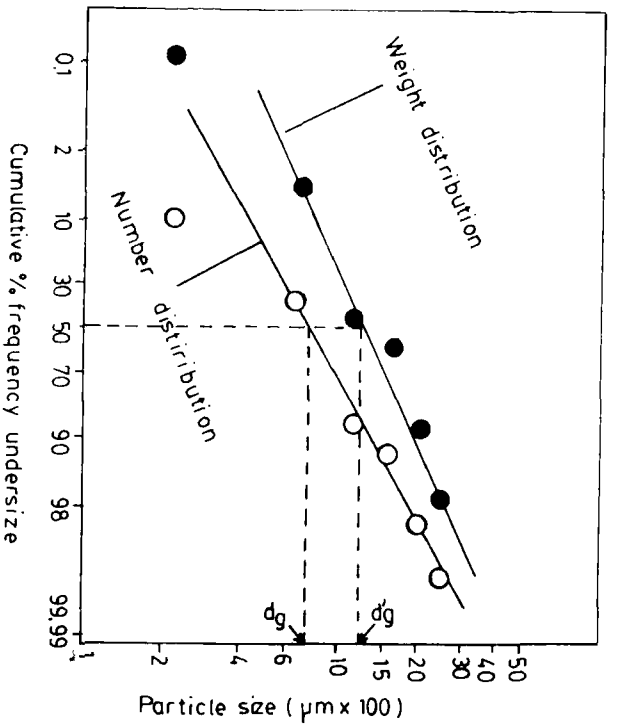

FIGURE 1
Log-probability plots of microcapsules

given in table 1.The order of the bulk volume and weight of the materials is: Pure drug < 476-248μm < 840-476μm < > 840μm < CMC for bulk volume (ml/g) and CMC < > 840μm < 840-476μm <476-248μm < pure drug for bulk weight (g/ml) so drug is the heaviest and CMC is the lightest.When the particle size of microcapsules increases, the bulk weight decreases.

It was found that, drug < CMC < 476-248μm <840-476μm < > 840μm for tapping volume (ml/g) and > 840μm < 840-476μm < 476-248μm < CMC < drug for tapping weight (g/ml). Normally, the tapping volumes of all materials decrease according to the bulk volumes. The largest volume decrease was observed from CMC.

The particle size of microcapsules is bigger than that of crude materials so the volume decrease is very small for microcapsules. The volume decrease is less when the mean particle size of the microcapsules increases.

The density of the materials is given in the following order: > 840μm < 840-476μm < CMC <476-248μm < drug. Normally, when the size of microcapsules increases, the density decreases. Nitrofurantoin has the highest density and this is supported by the data of the bulk density but the density of the CMC was found to be less.

The highest porosity was observed for CMC and the porosity of the drug was higher than that of the microcapsules. When the size of microcapsules increases, the porosity also increases.

TABLE 1
Micromeritic Properties of Powders and Microcapsules (mean ± SE)

		Pure Drug	CMC	>840μm	840-476μm	476-248μm
Bulk Volume (ml/g)		2.22 ± 0.04	3.53 ± 0.16	3.41 ± 0.12	2.99 ± 0.05	2.88 ± 0.08
Bulk Weight (g/ml)		0.457 ± 0.015	0.248 ± 0.013	0.293 ± 0.009	0.335 ± 0.006	0.348 ± 0.06
Tapping Volume (ml/g)		1.46 ± 0.03	2.18 ± 0.05	3.27 ± 0.01	2.8 ± 0.0	2.3 ± 0
Tapping Weight (g/ml)		0.683 ± 0.016	0.47 ± 0.01	0.306 ± 0.001	0.357 ± 0.006	0.420 ± 0
	Amount					
Angle of repose (°)	1g	39°,9′ ± 0.4	46°,8′ ± 0.0	17°,8′ ± 0.2	19°,6′ ± 0.2	20°,7′ ± 0.2
	2g	44°,7′ ± 0.3	47°,3′ ± 0.2	24°,7′ ± 0.3	28°,3′ ± 0.2	32°,2′ ± 0.3
Flow time (sec)	1g	2 ± 0	6± 1	1±0	1± 0	1± 0
	2g	5 ±0	10 ±1	2.5±0.5	1± 0	1± 0
	Volume (ml)					
Weight deviation (± mg)	1	5.08	20.3	11.7	7.31	8.06
	2	27.5	11.1	5.95	11	7.38
	4	14.1	41	8.42	20.6	-
	5	55.3	39.5	12.2	15.9	-
	6	8.85	26.1	25.4	28.5	-
Relative deviation ±%	1	1.00	6.9	3.94	2.15	2
	2	2.8	1.86	0.926	1.54	2.95
	4	0.716	3.57	1.6	1.45	-
	5	2.34	2.75	0.758	0.87	-
	6	0.31	1.51	1.27	1.31	-
True Density (g/ml)		1.49 ± 0.02	1.39 ± 0.01	1.26 ± 0.01	1.36 ± 0.00	1.42 ± 0.00
Porosity		0.66 ± 0.02	0.76 ± 0.03	0.139 ± 0.005	0.063 ± 0.001	0.022 ± 0.001

TABLE 2

Drug contents of the microcapsules and the filled gelatin capsules (mean ± SE)

	>840μm	840-476μm	476-248μm
Per cent of drug	68.4	61.6	56.7
Microcapsule amount equivalent to 50 mg drug	0.073g	0.081g	0.088g
Weight of empty gelatin capsules	0.050 ± 0.000	0.050 ± 0.000	0.050 ± 0.000
Weight of filled gelatin capsules	0.135 ± 0.002	0.142 ± 0.001	0.155 ± 0.001
Weight of microcapsules in gelatin capsules	0.085 ± 0.002	0.092 ± 0.001	0.105 ± 0.001
Drug content of the filled gelatin capsules	0.058	0.055	0.059

TABLE 3

Interpretation of Carr's Index and Hausner Ratio for Powders and Microcapsule Flow

	Consolidation index (Carr)		Hausner ratio	
	%	Flow		Flow
Nitrofurantoin	31.5	Poor	1.46	Poor
CMC	40.4	Very very poor	1.68	Poor
>840μm	4.25	Excellent	1.04	Good
840-476μm	7.84	Excellent	1.09	Good
476-248μm	17.1	Good	1.21	Good

It was observed from the calculated standard deviations and relative deviations that the standard error is less than 5% when filling the microcapsules into hard gelatin capsules. For all microcapsule size fractions the a size 3 gelatin capsules could be used to fill the microcapsules. The weight deviation of the microcapsules in which sieved and filled into the hard gelatin capsules, was found to be 90-110% of the capsule's weight which fits the USPXXII. This data was supported by the calculations of the relative deviations of the microcapsules. Drug contents of the microcapsules and the filled gelatin capsules are shown in table 2.

Table 3 shows the consolidation index (Carr index or compressibility) and Hausner ratio of the materials. The flowability of the microcapsules are found excellent and good respectively. These results were conformed by the angle of repose values.

From these results, it may concluded that the tabletting and filling into the hard gelatin capsules of the microcapsules don't need any glidant.

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REFERENCES

1. A.N. Martin, J. Swarbrick, A. Cammarata, in "Physical Pharmacy," Lea and Febiger, Philadelphia, 1969, 2nd. edn., p. 467.
2. J.I. Wells, in "Pharmaceutical Preformulation:The physicochemical Properties of Drug Substances," Ellis Horwood, Chicester , 1988 , p. 209.
3. H. Takenaka, Y. Kawashima and S.Y. Lin, Chem. Pharm. Bull., 27, 3054, (1979).
4. H. Takenaka, Y. Kawashima, Y. Chikamatsu and Y. Ando, Chem. Pharm. Bull., 30, 2189 (1982).
5. H. Takenaka, Y. Kawashima and S.Y. Lin, J. Pharm. Sci., 69, 513 (1980).
6. J. R. Nixon and S.E. Walker, J. Pharm. Pharmac., 23, Suppl., 147S (1971).
7. J.R Nixon, Saleh A.H.Khalil and J.E. Carless, J. Pharm. Pharmac., 20, 528 (1968).
8. C. Dubernet, J. P. Benoit, G. Couarraze and D. Duchêne, Int. J. Pharm., 35 , 145 (1987).
9. P.L. Madan, L.A. Luzzi and J.C. Price, J. Pharm. Sci., 63, 280 (1974).
10.E.D. Cadwallader and W.H. Jun, Analytical Profiles of Drug Substances, 5, 346 (1976).

11. G.Ertan, I. Sarıgüllü, Y. Karasulu, K. Erçakır and T. Güneri, J. Microencapsulation, 11, No.2, 127 (1993).
12. L. Kırılmaz, A. Kendirci and T. Güneri, J. Microencapsulation, 9, 167 (1992).
13. R. Voigt, M. Bornschein, "Lehrbuch der Pharmazeutischen Technologie," Verlag Chemie, Weinheim, 1982.
14. K.C. Güven, "Eczacılık Teknolojisi," Modern Röprodüksiyon, İstanbul, 1987.