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SPRAY DRIED POLYLACTIDE MICROSPHERE PREPARATION: INFLUENCE OF THE TECHNOLOGICAL PARAMETERS.

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ABSTRACT

Spray drying technique has been widely used in the pharmaceutical technological field with different applications. Recently it has been also successfully employed in the preparation of microparticulate drug delivery systems. The structure of the microparticles obtained is different according whether the drug is dispersed or dissolved in the polymeric solution to be spray dried.

Microcapsules are obtained by spraying a drug suspension in a solution of the polymeric coating, while polymeric matrices (microspheres), in which the

drug is embedded, are obtained by spraying a solution of the drug and of the polymer.

The aim of this work is the investigation of several technological parameters that can affect the preparation and therefore the characteristics of the microparticles obtained by spray drying method.

The effect of the inlet/outlet temperatures, spray rate of feed and of concentration of the starting polymeric solution on the characteristics of diazepam loaded poly-D,L-lactide microparticles are studied and evaluated with respect to yield of production, shape, size, and in vitro drug release behaviours.

INTRODUCTION

Spray drying has been widely used for the drying of substances. It finds common applications in different areas as pharmaceutical, chemical, biochemical and food industries.

It is a one step process to convert a liquid into a powder by spraying a solution or a liquid dispersion through a nozzle in a drying chamber, where it comes in contact with hot air.

The pharmaceutical industry utilizes this technique since a long time to obtain powders, granulates, drying of heat sensitive substances and other more

recent applications like microencapsulation and microsphere preparation (1).

When spray drying is used in the preparation of microparticulate drug delivery systems, the structure of the system obtained is different according whether the drug is dispersed or dissolved in the polymeric solution to be sprayed. Microcapsules are obtained by spraying a suspension of drug in a solution of the polymeric coating, while polymeric matrices (microspheres), in which the drug is embedded, are obtained by spraying a solution of drug and polymer. In both cases spray drying appears to be an attractive technique as it is a one step, fast method, suitable for heat sensitive drugs (2,3).

The use of this technique in the preparation of biodegradable polylactide microspheres has recently been studied and, when compared to traditional techniques (emulsification solvent evaporation, emulsification solvent extraction), spray drying always gave excellent results (2,4,5).

The process involves assessing of technological parameters such as: concentration of the polymeric solution to be sprayed, inlet and outlet air temperatures, spray rate of feed, air flow rate, heating, exhausting. In this work an attempt is made

to investigate several of these process parameters and to evaluate in which extent they affect microsphere preparation and characteristics.

Poly-D,L-lactide has been chosen as the model polymer as this class of polymers is widely used in the preparation of biodegradable microspheres.

Diazepam is used as lipophilic model drug as it can be usefully embedded in a controlled release system (6).

Concentration of the polymeric solution, inlet air temperature and spray rate of feed are analysed as independent variables of the process, and their influence on microsphere characteristics is evaluated.

MATERIALS

Poly-D,L-lactide (PDLLA) Res 203R 16000 Mw, 0.3 i.v., was supplied by Boehringer Ingelheim (Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany).

Diazepam, Mw 284.7, mp 131 - 135°C, dvs 41.0 um (Coulter counter mod TAII Coulter Electr. ltd, Luton UK), water solubility 0.05 mg/ml at 25°C, was supplied by F.I.S. (Fabbrica Italiana Sintetici) SpA , Alte di Montecchio Maggiore, Vicenza, Italia.

Methanol, methylene chloride, chloroform, KH_2PO_4 HPLC grade were supplied by Carlo Erba (Farmitalia-Carlo

Erba srl, Milano, Italy) and Merck (Merck Bracco SpA, Milano, Italia).

All other chemicals used were of reagent grade.

0.8 μm, 0.45 μm and 0.22 μm membrane filters were supplied by Millipore (Millipore SpA, Milano, Italia).

METHODS

Microsphere preparation

Microsphere preparation was performed by spray drying with a spray dryer apparatus Mini Buchi 190 (BUCHI Laboratoriums-Tecknik AG, Flawil CH).

PDLLA and diazepam in a 70:30 w/w ratio were solubilized in a 1:1 w/w mixture of methylene chloride and chloroform. The composition of the solid phase (polymer and drug) and the total concentration of polymer and drug in the organic solution (3% w/w) were kept constant. 100 g of the solution containing polymer and drug were sprayed through a 2 fluids pressure standard nozzle (0.7 mm diameter). The flow type was co-current with the mixing of air and liquid with the nozzle head (Fig.1).

At first inlet air temperature and spray rate of feed, considered as independent variables, were varied following the process conditions listed in Table 1.

Inlet temperature is the temperature of air at the entrance of drying chamber, it was varied between 44°C

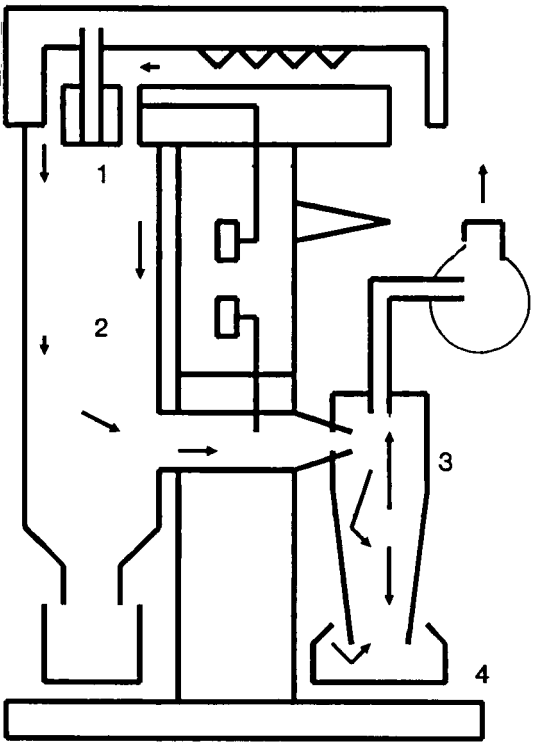


FIGURE 1

Scheme of a two fluids co-current spray dryer apparatus.

1) Nozzle, 2) Spray chamber, 3) Cyclone, 4) Collector.

and 63°C: outlet air temperature depends on the values chosen for this variable (Table 1).

Spray rate of feed represents the rate the polymer and drug solution is sprayed through the nozzle by a peristaltic pump, it varied among 2 ml/min and 7 ml/min: it corresponds to the flow rate of product

TABLE 1

PROCESS CONDITIONS

	INDEPENDENT VARIABLES		DEPENDENT VARIABLES
BATCH #	INLET AIR TEMP. °C	SPRAY RATE FEED ml/min	OUTLET AIR TEMP. °C
1	44-45	2	37
2	44-45	5	36
3	44-45	7	36
4	53-54	2	46
5	53-54	5	43
6	53-54	7	42
7	62-63	2	51
8	62-63	5	45
9	62-63	7	51

CONSTANTS:
air flow rate = 600 liter/h;
conc. of polymer plus drug in $CH_2Cl_2/CHCl_3$ solution = 3% w/w.

through the nozzle when the concentration of polymer in the solution to be sprayed is kept constant (Table 1).

In a second step the concentration of polymer and drug in the organic solution was considered as independent variable, and it was varied between 1.25% and 5% w/w, while PDLLA and diazepam ratio (70:30) and all other process parameters were kept constant (Table 2). In these conditions flow rate of product does not correspond anymore to spray rate of feed, but it

TABLE 2

PROCESS CONDITIONS

	INDEPENDENT VARIABLE	DEPENDENT VARIABLE
BATCH #	POLYMER AND DRUG CONC. % w/w IN ORGANIC SOL.	FLOW RATE ml/min.
10	1.25	6.03
5	3.00	4.57
11	5.00	3.94

CONSTANTS:
inlet air temperature = 52°C - 53°C;
outlet air temperature = 43°C;
spray rate of feed = 5 ml/min;
air flow rate = 600 liter/h.

becomes a variable depending on concentration of the polymeric solution to be sprayed.

The values of the independent variables tested were chosen according to the technical characteristics of the apparatus, to the solvent boiling points (39°C CH_2Cl_2 b.p.; 60°C $CHCl_3$ b.p.) and to the polymer characteristics.

The microspheres were collected in two different fractions: from the spray dryer cyclone (fraction A) and from the harvesting collector (fraction B) (Fig.1). Fractions A and B of each batch were always kept separated and separately analyzed to highlight differences in microsphere properties.

Microsphere characterization

Microspheres were charaterized for their shape, size, yield of preparation and drug content.

Scanning electron microscopy

Scanning electron microscopy was carried out on all batches of microspheres by a Jeol JXA 840A (Jeol Italia SpA, Pieve Emanuele, Italy) at 15 kv acceleration voltage, with $1x10^{-9}$ probe current, 1500 and 3000 magnifications. Samples were analyzed after they had been gold sputtered (25 nm gold film thickness).

Particle size distribution

Particle size distribution was analyzed by light blockage method with an HIAC/ROYCO model 3000 (Pacific Scientific, Silver Spring, Maryland, U.S.A.). Small amounts of product were suspended in 50 ml of bi-distilled filtered water; 1 ml suspension was withdrawan and analyzed in a 2-30 μm size range. Results are the average of 5 withdrawals for each sample tested.

Yields and drug content

Yields of preparation, intended as the weight percent of product obtained with respect to the weight of polymer and drug added to the solvent mixture to be sprayed, were determined by weighing all batches of

microspheres (respectevely fractions A and B) after they have been kept 24 hours in dessicator.

Drug content was determined by HPLC. Amounts of microspheres resulting in a final theoretical diazepam concentration between 20 and 30 ug/ml were weighed, they were dissolved in methylene chloride and analyzed with an HPLC Varian model 9010 coupled with a variable U.V. detector Varian model 9050 at 230 nm (Varian instruments, Milano, Italia). A Lichrosorb RP8 column 125x4 (Merck-Bracco SpA, Milano, Italia) and a mobile phase of methanol/KH_2PO_4 0.025 M aqueous solution 60:40 v/v were used. Drug loading is expressed as encapsulation efficiency, i.e. as the ratio of actual to theoretical drug content percentage.

Release tests

Release tests on all batches of microspheres were carried out with a rotating bottle method.

The microspheres and the reference samples were suspended in 100 ml of saline phosphate buffer solution F.U.I.IX ed. (pH 7.4) at 37°C and rotated at 100 rpm for 81 hours; the tests were performed in sink conditions. Dissolution profiles were obtained measuring diazepam concentration by HPLC (Varian model 9010) analysis at predetermined time intervals.

RESULTS AND DISCUSSION

Scanning electron microscopy performed on all batches of microspheres, prepared with the process conditions listed in Table 1, reveals completely formed microspheres with spherical shape and smooth surfaces; no crystals of drug are evident. Figs. 2,3 show as an example the photomicrographs of batch # 1 A,B and batch # 9 A,B produced with dramatically different process conditions. In both preparations a difference is highlighted between the microspheres collected from the cyclone (Samples # 1A, 9A) and those collected from the collector (Samples # 1B, 9B). As expected fractions B are always made of smaller particles more homogeneous in size than those belonging to fraction A. No difference is evident between microparticles of different batches but coming from the same harvesting area (Figs. 2a, 3a, 1b, 2b).

Scanning electron microscopy performed on batches # 5B, 10B, 11B (Fig. 4 a,b,c), obtained spraying organic solutions with different concentrations of polymer and drug, shows that this parameter greatly affects microsphere formation. In the tested conditions, the best results in term of microsphere shape are achieved with 3% w/w concentration (Fig. 4b). Very diluted solutions (1.25%, Fig. 4a) result in not completely

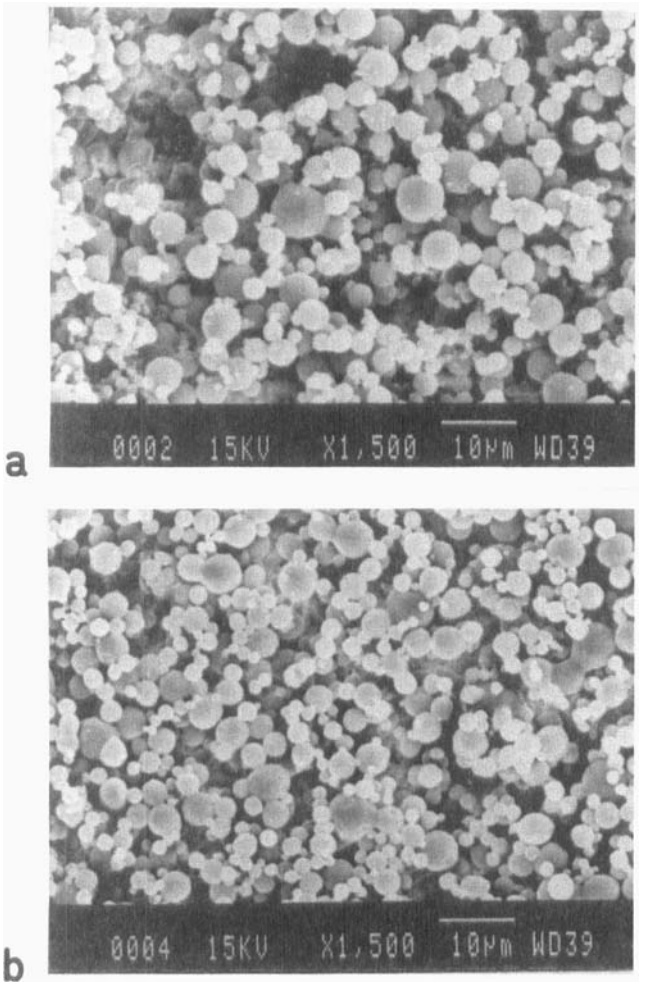


FIGURE 2

Photomicrographs of batch # 1 of microspheres obtained at 44°C inlet air temperature and 2 ml/min spray rate of feed: (a) fraction A, (b) fraction B.

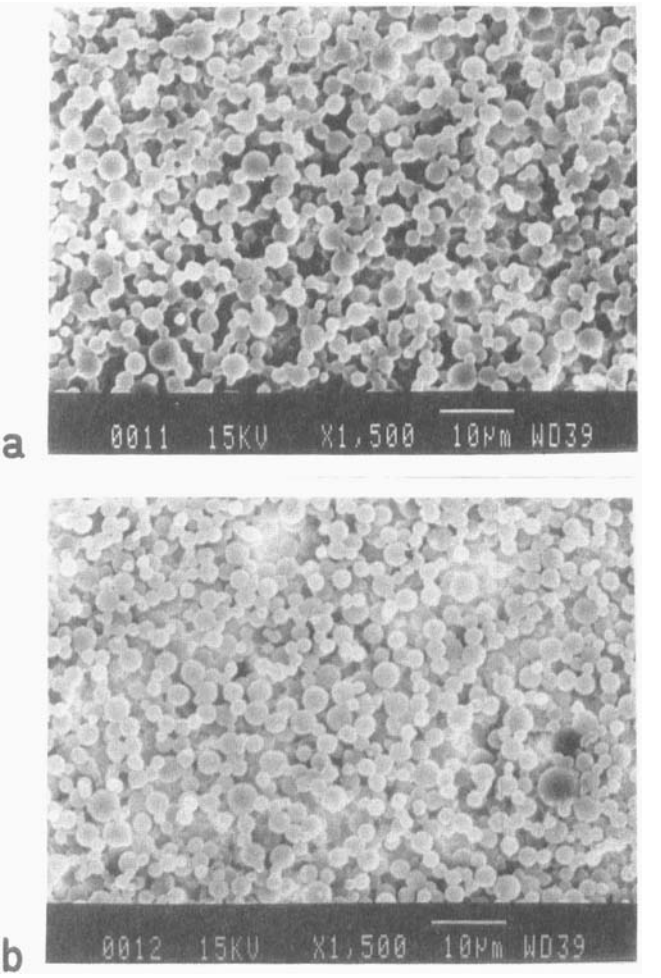


FIGURE 3

Photomicrographs of batch # 9 of microspheres obtained at 62°C inlet air temperature and 7ml/min spray rate of feed: (a) fraction A, (b) fraction B.

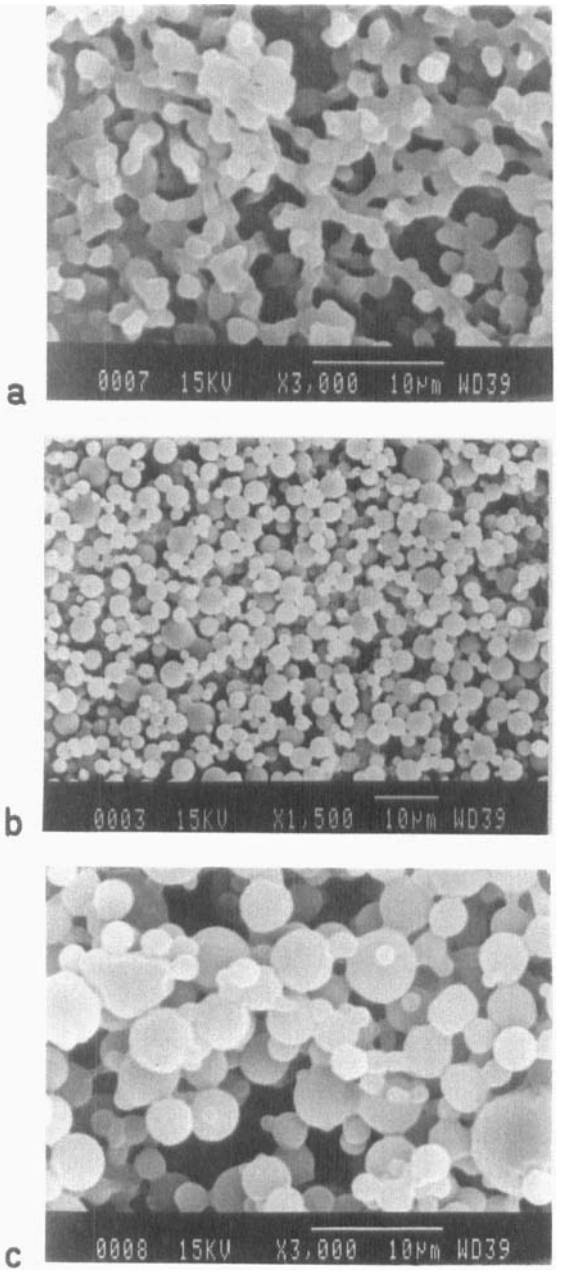


FIGURE 4

Photomicrographs of microspheres obtained from different polymer and drug concentrations in the spraying solutions: (a) 1.25 %, (b) 3 %, (c) 5 %.

TABLE 3

MEAN DIAMETERS OF PDLLA MICROSPHERES

BATCH #	MEAN DIAMETER μm FRACTION A	FRACTION B
1	14.31	10.66
2	15.52	9.23
3	15.31	15.98
4	15.84	11.87
5	16.17	12.83
6	9.09	5.60
7	8.32	4.99
8	6.21	2.74
9	8.30	5.69
10	13.50	16.92
11	16.00	11.55

formed microspheres, while the most concentrated solution (5%, Fig. 4c) generates spherical particles, many of which are aggregates. Particle size analysis by light blockage method shows different particle size distribution for fraction A and fraction B of microspheres. The mean diameters of microspheres belonging to fractions B are generally smaller than those of fractions A, as shown in Table 3.

Particle size distributions are affected by process conditions as shown in Fig.5 for fractions B of microspheres. Temperature increase has great effect in reducing microsphere size : the granulometric

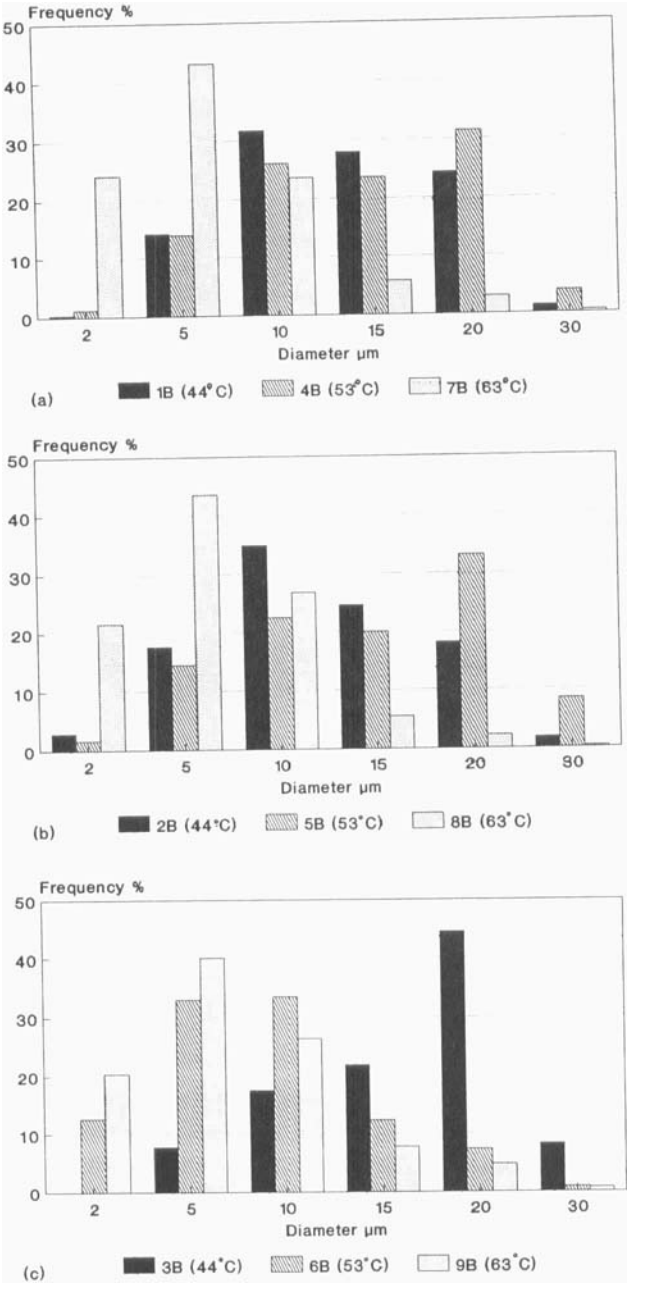


FIGURE 5

Particle size distribution of microspheres (fractions B) produced at (a) 2 ml/min, b) 5 ml/min, (c) 7 ml/min spray rate of feed, with increasing inlet air temperatures.

fraction ranging between 2-5 μm is 40-45% of total when microspheres are prepared at 62°C, while it reduces to 15-30% for microspheres prepared at 44°C. This behaviour repeats in fractions A even if with increased percentage of larger particles.

The effect of spray rate of feed on particle size distribution varies depending on inlet air temperature and it repeats both for fractions A and B. Generally increased spray rate of feed at high temperatures (53°C, 62°C) seems to slightly reduce particle size, while the effect of spray rate of feed on particle size distribution reverses at low temperatures (Fig. 6).

The effect of concentration of the solution to be sprayed on particle size distribution, is highlighted in Fig.7: the smaller size of microspheres belonging to fractions B is confirmed independently to concentration of the starting solutions.Diluted solutions of polymer and drug leads to increase size of microspheres belonging to fraction B along with narrowing their size distribution. No remarkable changes in particle size are highlighted in fractions A depending on concentration of the solution to be sprayed.

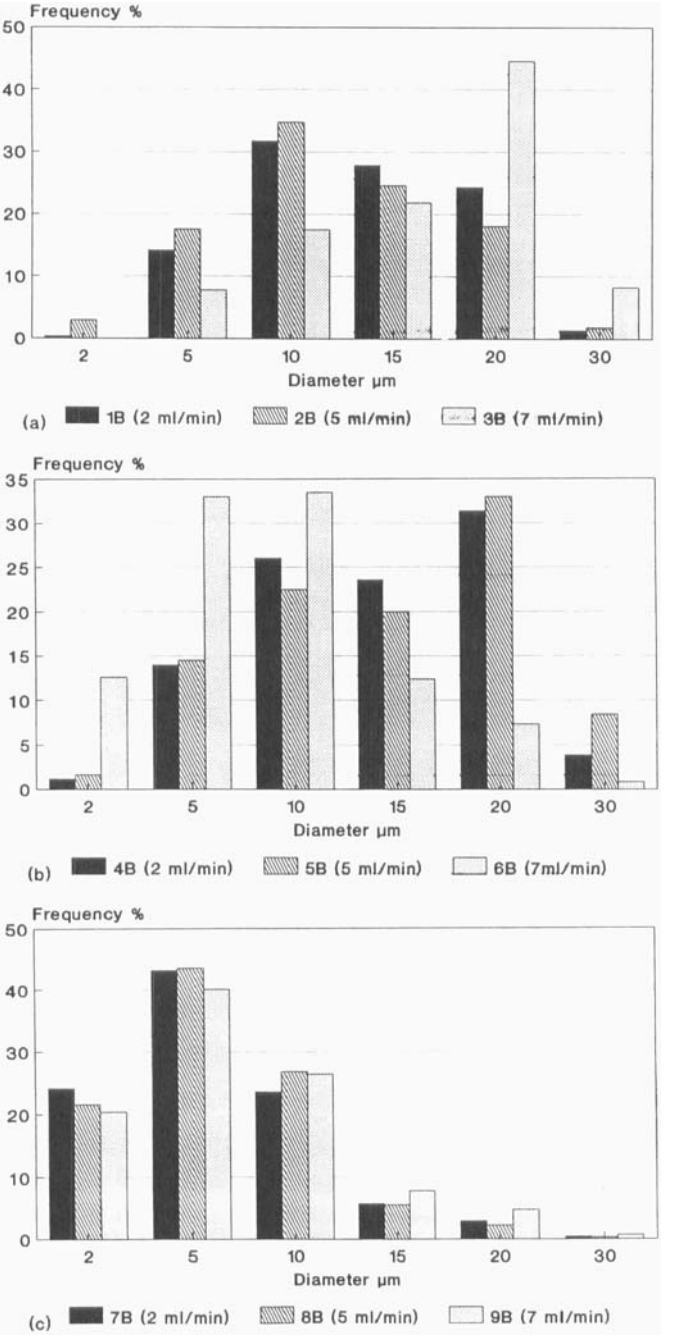
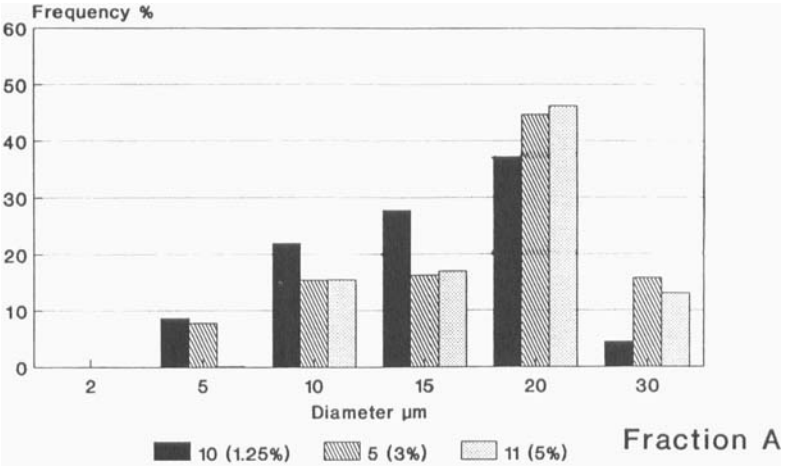


FIGURE 6

Particle size distribution of microspheres (fractions B) produced at (a) 44°C, (b) 53°C, (c) 63°C inlet air temperatures, with increasing spray rates of feed.



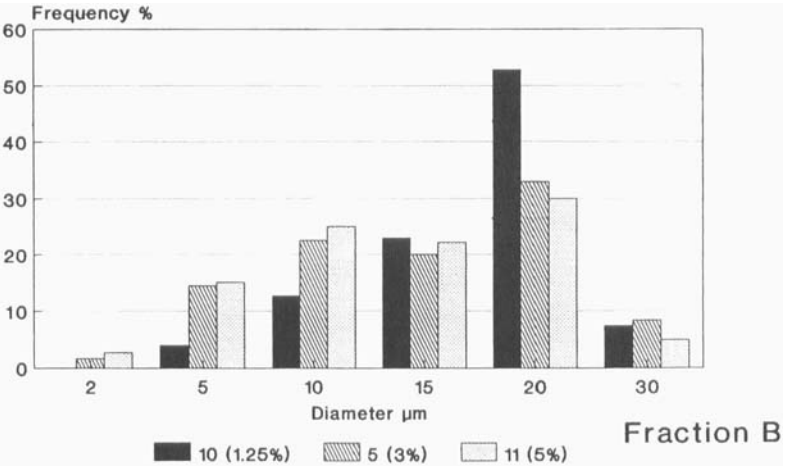


FIGURE 7

Particle size distribution of batch # 10, 5, 11 of microspheres prepared from solutions with different polymer and drug concentrations.

TABLE 4

ENCAPSULATION EFFICIENCY AND YIELD OF PRODUCTION OF SPRAY DRIED MICROSPHERES.

BATCH #	ENCAPS.EFFICIENCY % A	ENCAPS.EFFICIENCY % B	YIELD OF PRODUCTION % A	YIELD OF PRODUCTION % B
1	82.00	80.52	39.33	0.53
2	91.25	86.53	39.33	0.53
3	83.23	79.36	18.66	1.33
4	81.33	82.36	36.60	3.20
5	83.66	80.10	46.30	4.16
6	80.87	81.16	40.50	4.60
7	81.86	77.74	17.00	7.46
8	80.61	82.85	22.33	6.83
9	81.83	83.43	48.56	5.33
10	74.57	78.25	38.00	3.70
11	70.77	68.83	43.35	13.57
M (+-sd)	81.08 (5.15)	80.10 (4.50)	35.44 (10.99)	4.65 (3.75)

Drug encapsulation efficiency ranges between 70 - 85 % (Table 4); these data are not affected by process parameters. Moreover there is no remarkable difference in encapsulation efficiency between fraction A and B. Total yield of production (fraction A plus fraction B) is averagely about 40 %, where fraction A is prevalent.

As shown in Fig.8 the two process parameters tested cooperate in affecting the weight % of microspheres recovered. Increasing spray rate of feed leads to

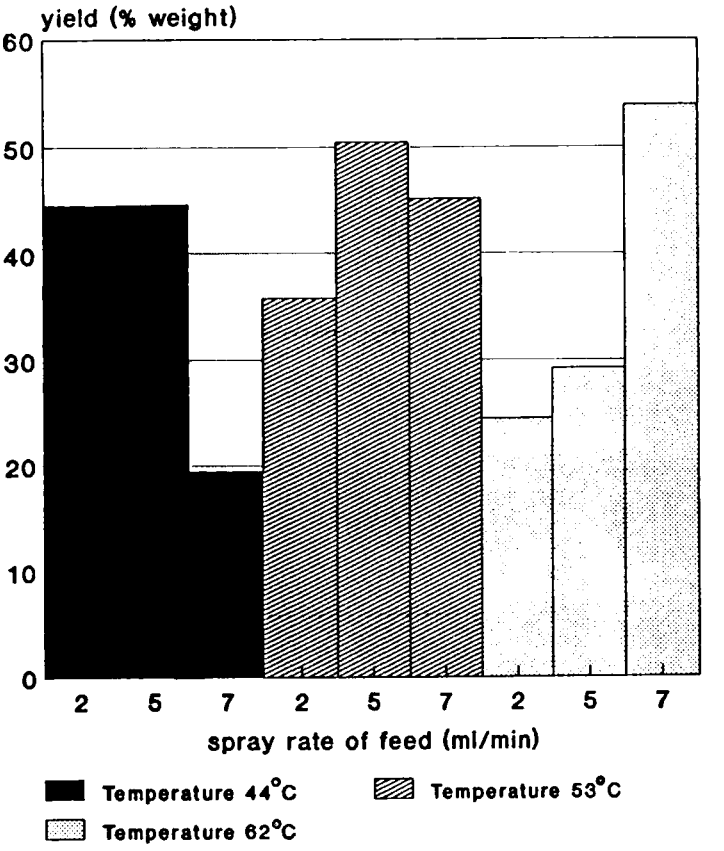


FIGURE 8

Influence of temperature and of spray rates of feed on yields of preparation.

increase yield of production when process take place at high temperatures (62°C), and to decrease yield of production when process is carried out at low temperatures (44°C) . The highest yield of production are obtained at 62°C with the highest value of spray rate of feed.

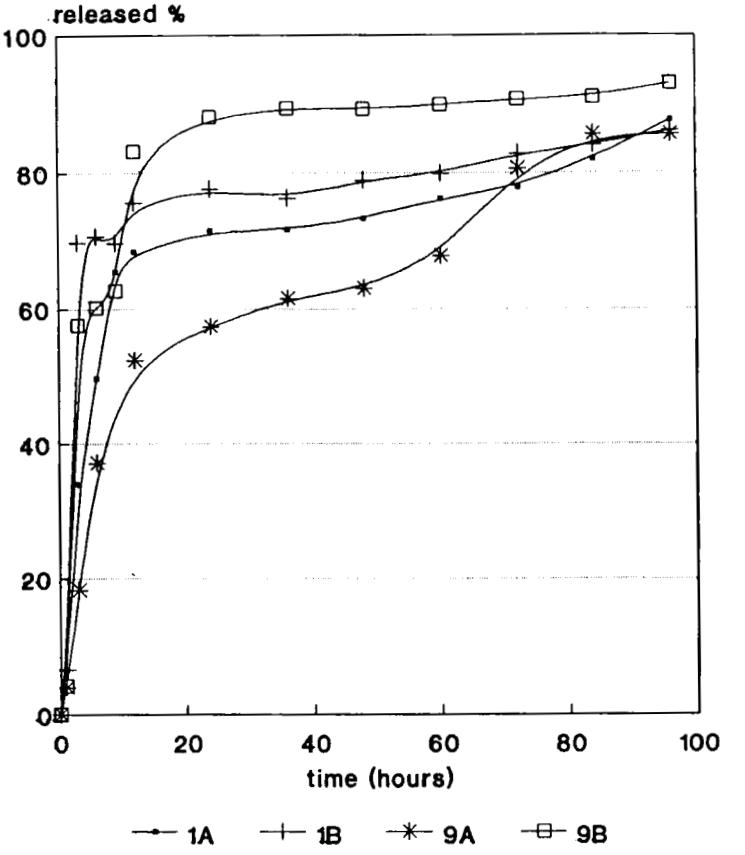


FIGURE 9

Dissolution behaviour of diazepam loaded PDLLA microspheres with the same drug content (about 25%) and prepared with different process conditions : 44°C, 2 ml/min spray rate of feed (batch # 1), 62°C, 7 ml/min spray rate of feed (batch # 9).

Fig. 9 shows as an example the release behaviours of batches # 1 A,B and # 9 A,B obtained with dramatically different process conditions. Since all batches bear almost the same values of drug content (about 25%), differences in release rate of drug depend on microspheres size and on the process conditions followed. Release rates from fractions B of both batches are faster, due to their smaller sizes (mean diameters 10.66 μm (1B) and 5.69 μm (9B), compared to 14.31 μm (1A) and 8.30 μm (9A))

When drug release from batches 1 and 9 is compared , with respect to the same fraction (A or B) the behaviour is inconsistent with their granulometry. This supports the influence of the two process parameters tested on release behaviour.

CONCLUSION

The parameters evaluated, related to the polymer utilized, prove to be effective in affecting particle shape , size and yield of production. In the tested conditions best results are obtained employing the highest spray rate of feed and temperatures.

Polymer concentration in the organic solution to be sprayed plays an important role in microsphere formation, hence it mainly affects the shape of microparticles.

The results obtained confirm that spray drying is a convenient technique to prepare microspheres. It is a one step fast method, and it allows processing of even small batches achieving good yields of production.

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