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THE INFLUENCE OF GRANULATION PROCESS AND SURFACTANTS ON THE BIOPHARMACEUTICAL PROPERTIES OF PHENYLBUTAZONE TABLETS

F.Carli(x), P.Iamartino(*) and E.Ciranni Signoretti(°)

(x)(*) A.F.I. Via Ranzoni, 1 - 20149 Milano (Italy)
(x) Biopharm. Group, (*) Pharm. Technol. Group

(°) Istituto Superiore di Sanità - Drug Chemistry Laboratory
Viale Regina Elena, 299 - 00161 Roma (Italy)

ABSTRACT

The influence of granulation process on the biopharmaceutical properties of experimental tablets has been studied, using phenylbutazone as a model substance. Four wet granulation procedures were compared. Moreover, in order to assess the influence of some surfactants, four different formulations were investigated.

INTRODUCTION

It is well known that the granulation process has a great influence on technological and biopharmaceutical properties of granules and tablets [1-8].

Partecipants to the Groups and co-authors of the present work:
(x) D.Ceriani, T.Crimella, P.De Filippis, D.Locati, G.Maffione, L.Moro, G.Scarpetti.
(*) A.Binda, F.Delucchi, G.Kauten, C.Miliano, M.Pedrani, E.Pisoni, T.Prato, G.Ponti, C.Ronchi, F.Stroppolo.

In a previous study we compared the effects of different wet granulation procedures on the technological characteristics of granules and tablets [8]. The study is now extended pointing out the biopharmaceutical aspects related to these different granulation conditions. In order to make these phenomena more evident, phenylbutazone tablets were taken as a model in our investigation because of the slight solubility and low wettability of the active ingredient. Moreover, the dissolution rate variability of phenylbutazone from tablets, and the variation in bioavailability, both in tablets from different manufacturers and different batches of the same producer have been reported by many authors [9-21].

Due to the very low superficial wettability of phenylbutazone, we thought it would be important to add surfactants to our experimental tablets. In fact, the role of surfactants in solid oral dosage form with known bioavailability problems, and the most likely mechanisms by which they could affect the release of the drug (wetting, micellar solubilization and deflocculation [22-25]) are well known.

In conclusion, we studied the influence of both the granulation process and surfactants on the biopharmaceutical properties of phenylbutazone tablets.

EXPERIMENTAL

Composition of tablets

Four different formulations of phenylbutazone, with and without surfactants, were studied.

The composition of the experimental tablets is reported in Table 1.

The following ingredients were used: Phenylbutazone (Coop. Farmac. Milanese), Maize starch (SPAD), Polyvinylpyrrolidone K25 (BASF), Silicon dioxide colloidal (Aerosil 200 - Degussa), Magnesium stearate (FACI), Polysorbate 20 (Tween 20 - ICI Pharma), Polysorbate 80 (Tween 80 - ICI Pharma), Triton X-100 (BDH).

TABLE 1

Composition of tablets (mg)

Ingredients	A	B	C	D
Phenylbutazone	200	200	200	200
Maize starch	214	211,5	211,5	211,5
Polyvinylpyrrolidone K 25	14	14	14	14
Silicon dioxide colloidal	8	8	8	8
Magnesium stearate	4	4	4	4
Tween 20	-	2,5	-	-
Tween 80	-	-	2,5	-
Triton X-100	-	-	-	2,5

All the ingredients were in accordance with U.S.P. and/or the Official Italian Pharmacopoeia specifications.

Compatibility between the active ingredient and the excipients was verified by Differential Scanning Calorimetry [26-32].

Dissolved surfactants were added to a 4-7% starch solution employed during the wet granulation process.

Granulation method

Four different manufacturing processes were compared. They are reported in Table 2.

Physical measurements

- Wettability. Contact angles of dissolved surfactants with phenylbutazone and of water with surfactant-coated phenylbutazone were determined by means of a wettability tester (Lorentzen-Wettre, Sweden) using the Mack method [33]. The contact angle measurements were used to estimate the solid surface polarity [34].

TABLE 2

Granulation methods

Apparatus	1	2	3	4
Mixer	high-speed (a)	fluid-bed (b)	traditional (sigma blade) (c)	traditional (high-speed) (d)
Granulator	oscillating	fluid-bed	oscillating	rotating extruder
(lumen)	2,5 mm (f)	(b)	4 mm (f)	2 mm (e)
Drier	fluid-bed (b)	fluid-bed (b)	air oven 12h - 30°C	fluid-bed (b)

(a) Diosna P_{50}; (b) Glatt WSG 15; (c) Olsa; (d) Viani ST 25
(e) Viani GC/300; (f) Erweka FGS

- Dissolution tests. The intrinsic dissolution rate of phenylbutazone and surfactant-coated phenylbutazone, in a 6.5 pH phosphate buffer, was measured by the rotating disk method [35]. The rotating velocity of the disk was 150 rpm.
  Release rates of phenylbutazone from granules and tablets were also determined by means of the U.S.P. paddle method [36], using 900 ml of 7.0 pH phosphate buffer as dissolution medium. The rotation speed of the paddle was 50 rpm.
  In both methods the temperature was 37 ± 0,1°C.
  Phenylbutazone was determined by ultraviolet absorption at 263 nm.

- Solubility. Phenylbutazone solubility with or without surfactants, in a 6.5 pH phosphate buffer, was measured spectrophotometrically at 263 nm.
- Porosity. Pore volume and pore size distribution of granules and tablets were measured by a mercury porosimeter (Model 225, C.Erba), with intrusion pressures ranging from 0 to 2000 Kg/cm^2.
- Thermal analysis. Differential scanning calorimeter (TA 3000, TA 10 cell, Mettler) was employed for thermal analysis of phenylbutazone and of its mixtures with the excipients. Samples were heated at a temperature range of 50-250°C, with a heating rate of 10°/min., in a nitrogen atmosphere.
- Powder density. A helium picnometer (Beckman) was used to measure the real density of the powders.
- Particle size and surface area distributions. Mercury porosimetry was used to determine the particle size of powders.The surface area distribution was derived from these data [37]. Particle size analyses were also made with an electrical sensing zone apparatus (Coulter-Counter Model TA II, Coulter Electronics).

Tableting. The granules were mixed with magnesium stearate (sized through 0,25 mm screen) and compressed on a single-punch tablet press (Fette) to tablets of 11,3 mm in diameter with a 1 cm^2 area.

Testing of dried granules

- Residual moisture content. Weight loss on drying at 105°C was determined.
- Bulk density, tapped density, Hausner ratio (H.R.), compactibility index (C.I.). Determinations were carried out on 100 g granules with a volumeter presser (Stamp, Volumeter Staw 2003)

that dropped 10 and 2000 times for the bulk and the tapped density determinations, respectively.

The bulk density is given by: $d_{10} = \frac{g}{v_{10}}$;

tapped density is: $d_{2000} = \frac{g}{v_{2000}}$; H.R. $= \frac{d}{d_{10}}$;

I.C. $= \frac{d_{2000} - d_{10}}{d_{2000}} 100.$

- Repose angle. A steel funnel with a 1 cm stem lumen was used, set at a distance of 10 cm from a steel plate.
  The angle of repose is the tangent

$$\alpha = \frac{\text{height of the cone}}{\text{radius of the cone base}}$$

  expressed in degrees.
- Size distribution. A set of sieves (63, 100, 140, 200, 400, 500, 710 μ) connected to a vibrating apparatus (Analysette - Fritsch) was used.

Testing of the tablets

- Dose uniformity. 30 tablets were randomly selected and weighed on a Mettler PC 360 balance. Average weight was then determined.
- Thickness. Determined on 30 tablets by means of a Borletti micrometer.
- Hardness. We used the Schleuniger-2E apparatus. 20 tablets per test were examined.
- Friability. Measured on 10 tablets, with the Engelsmann apparatus, after 4 min.
- Disintegration time. Determined on six tablets using water at 37°C, according to the Official Italian Pharmacopoeia.

TABLE 3

Properties of phenylbutazone utilized.

Melting point	106,6°C
Enthalpy	91.2 J/g
Powder density	1.19 g/ml
Mean particle size ($d_{50\%}$)	2.3 μm
Surface area	0.71 m^2/g
Solubility (pH 6,5)	1.245 g/l
Intrinsic dissolution rate (pH 6,5)	8.21×10^{-4} mg $cm^{-2} sec^{-1}$
Contact angle (water)	82°37'
Solid surface polarity	15.7%

RESULTS AND DISCUSSION

Table 3 shows the properties of phenylbutazone used in our investigation. Low values of solubility, dissolution rate and wettability are evident. Surface area value was derived from a particle size ranging between 30 and 5 μm in 75% of the total. A single polymorph, with the same characteristics as that reported in literature, was revealed by thermal analysis[10,12,16,17,38,39].

Phenylbutazone dissolution and wettability properties were examined by different means, for a better evaluation of the efficency of each surfactant.

Table 4 reports the contact angles of some surfactant solutions with phenylbutazone. The present data, as well as technological and toxicological considerations indicated Tween 20, Tween 80 and Triton X-100 as the most suitable surfactants for our purpose, in particular Triton X-100 seemed the most adequate.

TABLE 4

Contact angles for surfactant solutions with phenylbutazone.

Surfactant	Concentration (μg/ml)	Contact angle
Tween 20	10	76° 25'
	100	78° 13'
	1000	54° 57'
	5000	45° 10'
Tween 21	10	81° 20'
	100	87° 4'
	5000	27° 32'
Tween 80	10	94° 28'
	100	75° 11'
	1000	64° 59'
	5000	56° 23'
Sodium Lauryl Sulfate	10	93° 33'
	100	90° 58'
	1000	48° 10'
	5000	27° 13'
Mirj 51	10	98° 49'
	100	77° 53'
	1000	63° 11'
	5000	63° 31'
Triton X-100	10	87° 11'
	100	47° 7'
	1000	0°
	5000	0°
Pluronic F 68	10	87° 54'
	100	82° 14'
	1000	80° 24'
	5000	73°

TABLE 5

Contact angles of water with surfactant-coated phenylbutazone

Surfactant	Concentration % (w/w)	Contact angle
Tween 80	0.125	81° 8'
"	0.50	78° 17'
"	1.25	37° 58'
Triton X-100	0.125	81° 13'
"	0.50	68° 2'
"	1.25	0°
Tween 20	0.125	79° 59'
"	0.50	71° 44'
"	1.25	0°
Phenylbutazone		82° 37'

TABLE 6

Phenylbutazone solubility in solutions (pH 6,5) containing surfactants (24 hrs)

Surfactant	Concentration (µg/ml)	Solubility (µg/ml)
Tween 20	10	3.36
"	100	3.32
"	1000	3.19
Tween 80	10	1.30
"	100	1.25
"	1000	1.28
Triton X-100	10	1.20
"	100	1.21
"	1000	1.29
Without surfactant		1.245

TABLE 7

Intrinsic dissolution rate (pH 6,5) of surfactant-coated phenylbutazone

Product	Intrinsic dissolution rate (10^4 mg $cm^{-2}sec^{-1}$)
Ph. + Triton X-100 (0,125°% w/w)	8,00
" + Tween 20 (")	10,00
" + Tween 80 (")	10,93
Phenylbutazone	8,21

Table 5 shows the contact angles of water with surfactant-coated phenylbutazone, suitable for a more direct evaluation of the influence of the surfactants on the phenylbutazone surface polarity. In this case, both Triton X-100 and Tween 20, more than Tween 80, were equally efficient in decreasing the contact angle of water on phenylbutazone.

Solubility of phenylbutazone in solutions with surfactants is reported in Table 6. Only Tween 20 increased (three times) the drug solubility even at higher concentrations than the critical micellar one.

Table 7 shows the intrinsic dissolution rates of phenylbutazone wet with the three surfactants. During the dissolution, contact surface between the dissolution medium and phenylbutazone remained unchanged. This permitted us to evidence the eventual influence of surfactants on the diffusion layer and the diffusion coefficient rather than on the wettability. Triton X-100 seemed not to influence these parameters. Instead, Tween 20 and Tween 80 changed the parameters, in such a way as to cause only a small increase of the intrinsic dissolution rate of phenylbutazone.

TABLE 8

Residual moisture content of granules (%) (*)

Formula	Method			
	1	2	3	4
A	4,95	4,5	5,9	4,2
B	5,35	5,55	6,3	5,8
C	4,90	4,3	7,2	4,6
D	5,0	4,15	5,2	4,1

(*) average of 3 determinations

TABLE 9

Bulk density (d_{10})(1) - Tapped density (d_{2000})(2) (g/l), Compactibility index (I.C.) (%) (*)

Formula	Method											
	1			2			3			4		
	(1)	(2)	I.C.	(1)	(2)	I.C.	(1)	(2)	I.C.	(1)	(2)	I.C.
A	526	577	8,84	395	467	10,43	417	526	20,72	405	454	10,79
B	454	548	17,15	430	469	8,32	398	506	21,34	385	492	21,79
C	375	508	26,18	434	508	14,56	353	461	23,43	306	395	22,53
D	410	526	26,05	422	480	12,08	385	469	17,91	375	491	23,62

(*) average of three determinations.

TABLE 10

Size distribution (%) (*)

$\geq 710/u$ (1); $710\text{-}200/u$ (2); $\leq 200/u$ (3)

Formula	Method											
	1			2			3			4		
	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
A	14,7	71,4	13,9	0,9	69,5	29,6	2,6	48,2	49,2	7,4	34,2	58,4
B	10,1	69,8	20,1	1,3	76,5	22,2	1,8	45,0	53,2	4,7	66,2	29,1
C	16,5	74,0	9,5	4,6	62,8	32,6	-	46,9	53,1	5,7	41,9	52,4
D	11,7	75,6	12,7	7,3	69,2	23,5	3,5	61,6	34,9	13,0	41,0	46,0

(*) average of three determinations.

TABLE 11

Repose angle (*)

Formula	Method			
	1	2	3	4
A	39° 52'	37° 17'	45° 46'	43° 02'
B	54° 35'	36° 24'	54° 29'	53° 06'
C	44° 30'	45°	52° 76'	54° 46'
D	46° 21'	45° 16'	53° 27'	56° 60'

(*) average of three determinations.

In conclusion, the three examined surfactants seemed to influence the phenylbutazone properties in a different way. Thus, the importance of their employment in the granule preparation and the individuation of their role in the dissolution mechanism is evident.

TABLE 12

Thickness (mm) - (compression force: 4,5 KN, 16 KN)

Formula	Method							
	1		2		3		4	
	4,5	16	4,5	16	4,5	16	4,5	16
A	4.25	3.64	4.37	3.69	4.20	3.67	4.35	3.68
B	4.20	3.60	4.30	3.65	4.30	3.70	4.30	3.70
C	4.22	3.82	4.33	3.73	4.37	3.80	4.40	3.80
D	4.32	3.74	4.38	3.72	4.46	3.84	4.30	3.90

TABLE 13

Hardness (Kp) - (compression force: 4,5 KN,16 KN)

Formula	Method							
	1		2		3		4	
	4,5	16	4,5	16	4,5	16	4,5	16
A	4	13	4.3	17	3.95	14	4.1	12.15
B	3.1	10.3	4.8	11.4	5.5	13.1	4.15	20
C	2.2	8	2.64	10.7	2.6	7.3	2.32	7.7
D	2.14	7.7	2.70	10.2	1.36	7.4	2.12	7.8

In Tables 8 to 11 the results of the technological tests carried out on the dried granules obtained with the different granulation methods are reported, for the examined formulas.

Table 8 shows the residual moisture content after the drying process. The values fell within the variability due to the different drying conditions.

TABLE 14

Disintegration time

1) Compression force: 4,5 KN

Formula	Method			
	1	2	3	4
A	6'30"-7'	1'30"-4'15"	1'45"-2'30"	3'30"
B	1'50"-2'40"	1'30"-7'10"	1'45"-2'30"	2'30"
C	5'15"-7'30"	5'-5'30"	1'20"-2'	2'-3'
D	6'15"-9'	9'30"-11"	2'15"-2'45"	3'30"-5'

2) Compression force: 16 KN

Formula	Method			
	1	2	3	4
A	30'	15'30"-16'30"	6'-7'45"	8'30"-9'
B	5'45"	8'10"	6'40"	5'30"
C	5'30"- 6'45"	9'-10'15"	3'-3'30"	6'30"-7'
D	10'-11'30"	14'30"-15''	6'15"-7'15"	4'-7'

Table 9 shows the bulk and tapped densities (d_{10}, d_{2000}) and the compactibility index (I.C.). Granules obtained with the traditional (at high-speed rotation) granulation process and fluid-bed drying method presented the lowest bulk density.

A more homogeneous size distribution and a lower amount of small particles were observed in granules obtained with fluid-bed and high-speed granulation methods, as reported in Table 10.

Table 11 shows the repose angle values. Lower values were obtained with fluid-bed granulation and fluid-bed drying as well as with granules without surfactants.

TABLE 15

Porosity

(Pen.vol.: ml/g) (a); (R50%: Angstrom) (b)

For- mula	Comp. force (KN)	Method							
		1		2		3		4	
		(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
A	4,5	0,1875	4249	0,2089	5311	0,2035	4871	0,2166	5686
	16	0,0822	2173	0,0913	2915	0,0831	2052	0,0960	3562
B	4,5	0,2183	6909	0,1994	5383	0,1756	5636	0,2024	6730
	16	0,1002	4159	0,0954	3426	0,0653	2606	0,0972	4315
C	4,5	0,2381	7890	0,2445	6052	0,2505	9876	0,2356	8050
	16	0,1277	5161	0,1146	3844	0,1375	6326	0,1269	5600
D	4,5	0,2512	8630	0,2513	6577	0,2711	8916	0,2518	9013
	16	0,1240	5500	0,1113	3900	0,1331	5703	0,1271	5730

In Tables 12 to 15 and in Figures 1 to 8 the results of the tests on the tablets are reported.

The average weight of the tablets was in accordance with the Italian Official Pharmacopoeia.

Table 12 shows thickness in relation to two different compression force values.

Table 13 evidences higher hardness values both for products without surfactants and products with Tween 20. A large variability of values was noted with the various technologies used.

The increase of disintegration time in relation to the compression force was within 15', except for the formulation without surfactant, obtained by means of the high-speed granulation method (Table 14).

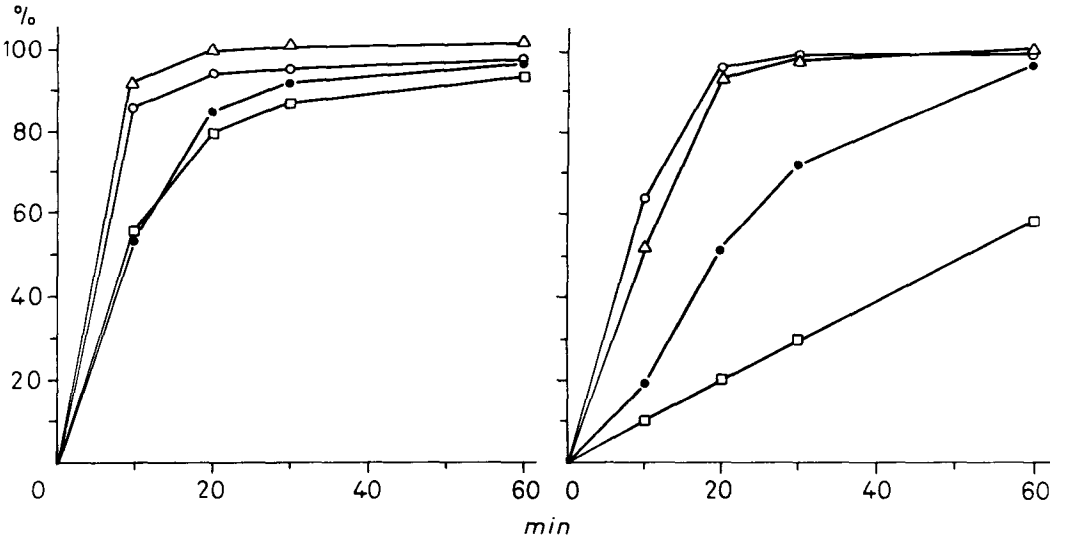

FIGURE 1

Release rate profiles of phenylbutazone from tablets without surfactant (A); 4,5 KN and 16 KN compression force. Granulation methods: □ 1, ● 2, o 3, Δ 4.

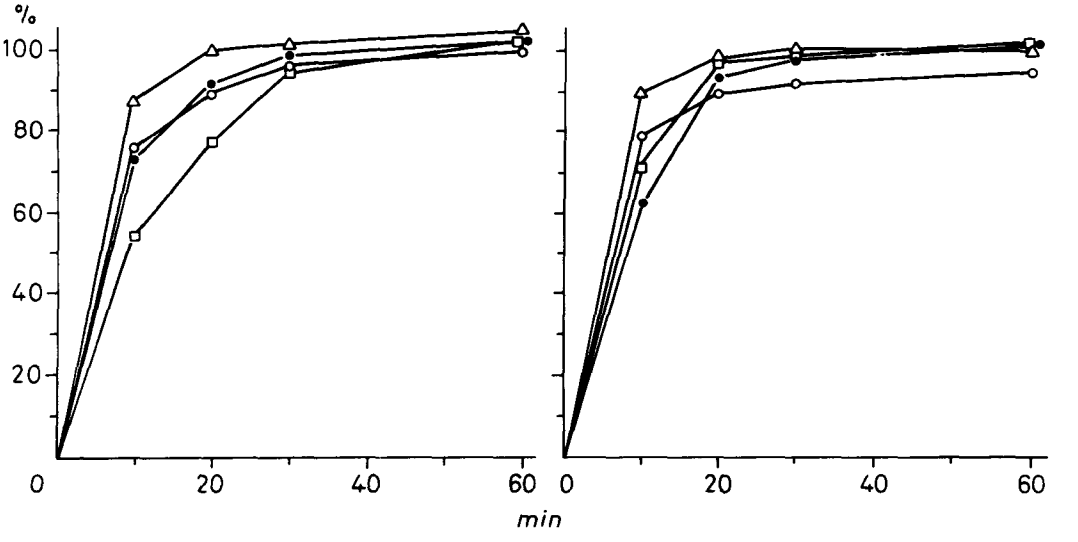

FIGURE 2

Release rate profiles of phenylbutazone from tablets containing Tween 80 (C); 4,5 KN and 16 KN compression force. Granulation methods: □ 1, ● 2, o 3, ▲ 4.

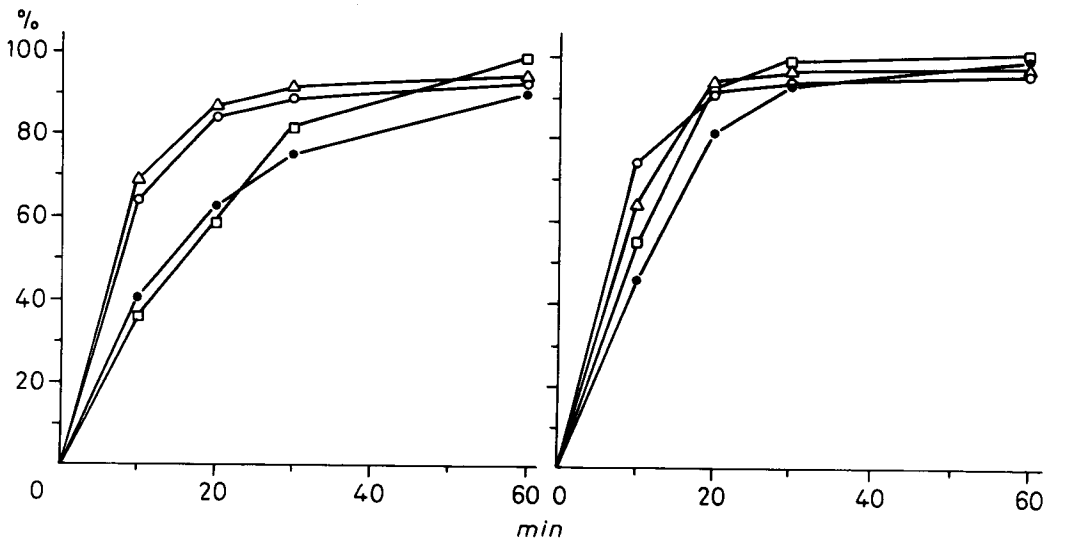

FIGURE 3

Release rate profiles of phenylbutazone from tablets containing Triton X-100 (D); 4,5 KN and 16 KN compression force. Granulation methods: □ 1, ● 2, ○ 3, △ 4.

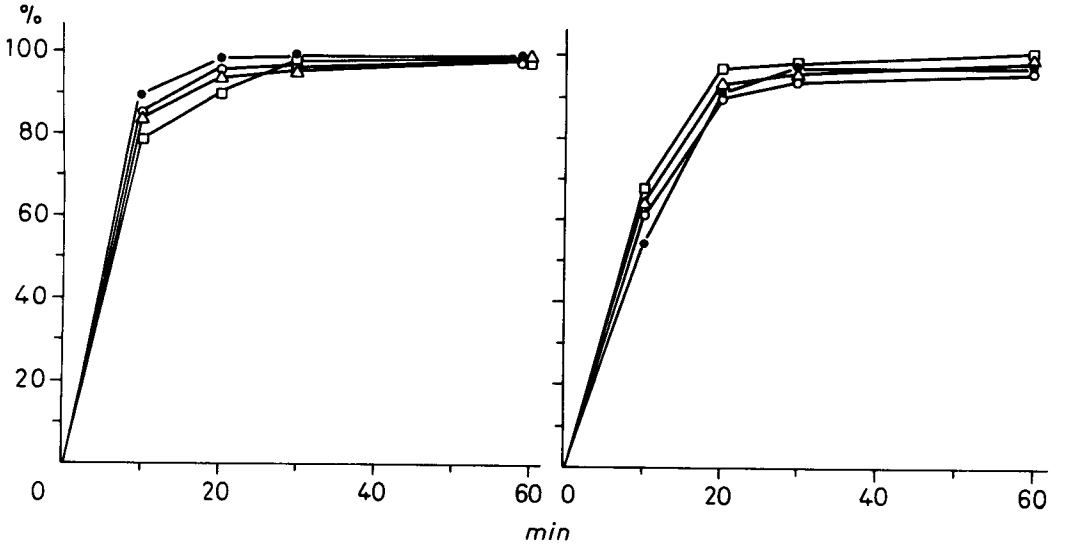

FIGURE 4

Release rate profiles of phenylbutazone from tablets containing Tween 20 (A); 4,5 KN and 16 KN compression force. Granulation methods: □ 1, ● 2, ○ 3, △ 4.

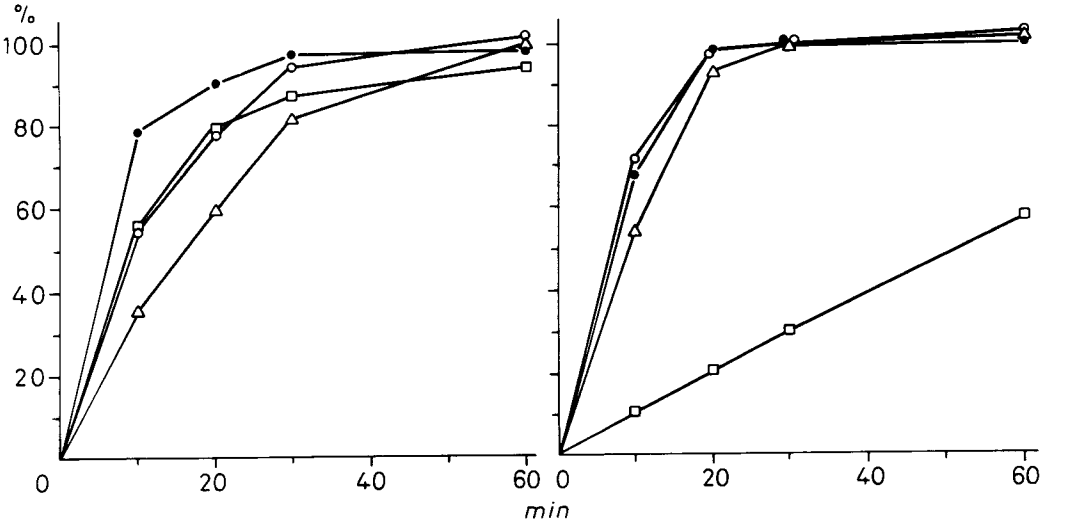

FIGURE 5

Release rate profiles of phenylbutazone from tablets obtained with high-speed granulation method (1); 4,5 KN and 16 KN compression force. Formulations: □ without surfactant (A), ● with Tween 20 (B), o with Tween 80 (C), ▲ with Triton X-100 (D).

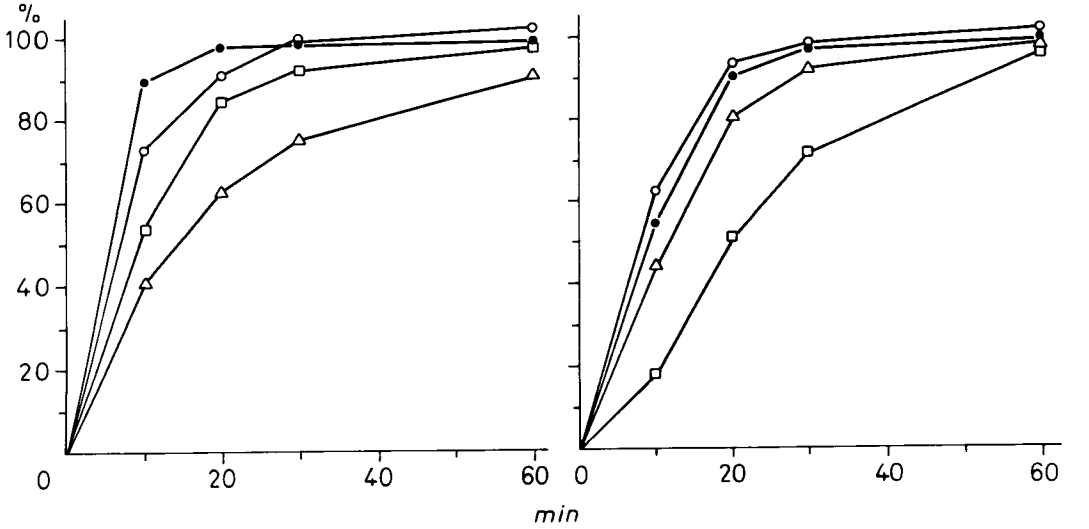

FIGURE 6

Release rate profiles of phenylbutazone from tablets obtained with fluid-bed granulation method (2); 4,5 KN and 16 KN compression force. Formulations: □ without surfactant (A), ● with Tween 20 (B), ○ with Tween 80 (C), ▲ with Triton X-100 (D).

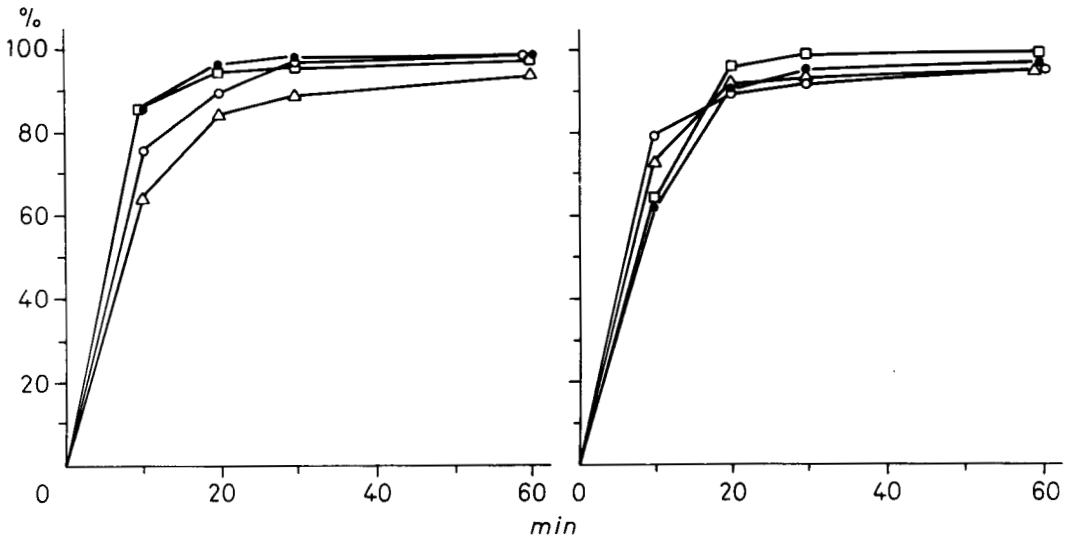

FIGURE 7

Release rate profiles of phenylbutazone from tablets obtained with traditional granulation method (3); 4,5 KN and 16 KN compression force. Formulations: □ without surfactant (A), ● with Tween 20 (B), ○ with Tween 80 (C), ▲ with Triton X-100 (D).

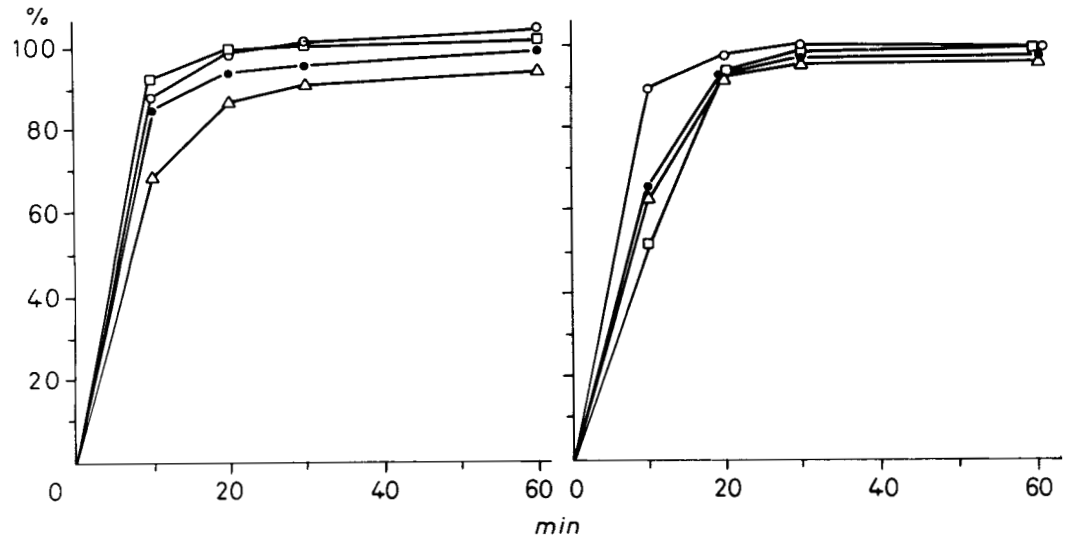

FIGURE 8

Release rate profiles of phenylbutazone from tablets obtained with high-speed traditional granulation method (4); 4,5 KN and 16 KN compression force. Formulations: □ without surfactant (A), ● with Tween 20 (B), ○ with Tween 80 (C), ▲ with Triton X-100 (D).

Table 15 shows pore volume and mean pore size of the tablets, measured with mercury porosimetry, at different compression forces. A significant relationship between porosity and the granulation process as well as the surfactants was difficult to determine. The difference in particle size of the granules seemed to disappear with the compression process due to their friability.

Release rate profiles of phenylbutazone from tablets prepared at a compression force of 4,5 KN and 16 KN, with the four different granulation methods, are reported in the following figures (Fig. 1 - 8).

A lower dissolution rate was observed in the tablets without surfactants (A), when high-speed (1) and fluid-bed (2) granulation methods were used. This phenomena, observed with both compression force levels, could be caused by a greater cohesion of the granules. Moreover, we noted higher dissolution profiles at the lower compression force (Fig.1). Instead, no significant difference was revealed among dissolution profiles of phenylbutazone tablets contaning Tween 80 (C), obtained with the different granulation methods and at different compression forces (Fig. 2). For the formulations with Triton X-100 (D), a difference between traditional (3,4) and high-speed and fluid-bed (1,2) methods was observed only at the lower compression force (Fig. 3). Tween 20 seemed to minimize any difference among the various methods, at the two compression forces (Fig.4). Finally, using different surfactants, no significant difference was noted with the same granulation process (Fig.5 - 8).

CONCLUSIONS

The influence of two variable parameters relative to formulation (wetting agent) and process (granulation) on the technological and biopharmaceutical properties of phenylbutazone tablets

was pointed out. Moreover, correlations between different control parameters were studied in order to explain the fundamental phenomena related to the biopharmaceutical characteristics of the examined formulations. Finally, an example of biopharmaceutical study in the formulation and manufacturing process of tablets was suggested.

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