DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(14), 1485-1503 (1992)

INFLUENCE OF EXTRUSION-SPHERONIZATION PROCESSING ON THE PHYSICAL PROPERTIES OF d-INDOBUFEN PELLETS CONTAINING pH ADJUSTERS

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ABSTRACT

d-Indobufen pellets containing pH adjusters (acids, buffer, salt) were prepared by extrusion-spheronization technology.
The interaction effect between some processing variables (feeding/agitator speeds of extruder, plate speed and residence time of spheronizer) was evaluated by comparing the basic formulation pellets with the pellets in which the soluble filler (lactose) was substituted by fumaric, tartaric and citric acids and also sodium citrate.
The criteria of formulation and process evaluation were the reproducibility of the particle size distribution, the density, the hardness and morphological properties, in addition to the reproducibility of the drug dissolution rates.
In all cases, the physical/technological characteristics were not influenced very much by pH adjuster incorporation, but the drug dissolution profiles showed some significant variations in the first hour. As a logical extension of this work, wet granulations with aqueous ethylcellulose and acrylic resin dispersions instead of only water were tested to

evaluate the wetting effect of the release modifier inclusion. The results confirmed the validity of polymeric systems in the preparation of pellets and their ability to produce a further delay of d-Indobufen release.

INTRODUCTION

The high quality and excellent reproducibility of pellet preparation by the extrusion-spheronization process is widely recognized (1-5).
This process is capable of producing pellets containing more than 80% w/w of the drug, provided that its physico-chemical properties and other formulation components are amenable to processing (5). Moreover the presence of a spheronization enhancer, such as microcrystalline cellulose, is essential for conferring plasticity to the wetted mass and also for imparting binding properties that are fundamental for pellet strength and integrity. On the other hand, pH adjusters are substances that are incorporated in pellet formulations to influence the microenvironment of the drug molecule by modifying its solubility (3). Usually pH adjustment is applied in pellet formulations whose release rates are membrane-controlled and the solubility of the drug plays a major role in determining the rate of release. Acid systems may be introduced in the core containing acid drug to maintain the pH in a favourable range to slow the drug release rate.
The aims of this work were to investigate the extrusion-spheronization processing of pellet formulations including pH adjusters as well as release modifiers, and to evaluate the influence of these substances on the drug release profiles.
d-Indobufen, a carboxylic acid used as an inhibitor of ADP-induced platelet aggregation, was chosen as the model drug. The basic pellet formulation was based on drug, cellulose microcrystalline and lactose; some food acids, a buffer and a salt were used instead of lactose to influence the microenvironment of the drug molecules. In addition, ethylcellulose (Aquacoat) or acrylic resin (Eudragit RL/RS 30D) aqueous dispersions were also included to obtain pellets showing, prolonged release of the drug in a single step without the coating processing.

MATERIALS AND METHODS

Preparation method for d-Indobufen pellets

Active standard pellets, composed of d-Indobufen (Farmitalia Carlo Erba), microcrystalline cellulose (Avicel PH 101, FMC Corporation) and lactose (DMV, Veghel) (ratio 55:30:15 by weight) were prepared by multistage processing consisting of blending, wet granulation, extrusion, spheronization and drying. 3 kg of dry powders were blended in a high-speed granulator (Solid Processor, Lab 4, Patterson Kelley, USA) to prepare a uniform mixture prior to the wet granulation operation. The mass wetting was obtained by adding 1.570 kg of water and the end point was determined by the behaviour of the wetted mass during the extrusion operation (formation of rods, similar to short strands of spaghetti). All batches of the wetted mass were divided in three parts of 1 kg and processed at different conditions.

The wetted granulate was passed through the radial screen extruder (NICA, type E4, Sweden) to form cylindrical extrudates using a screen opening size of 1.0 mm. The wet extrudates were then processed in the spheronizer (NICA type S2-450) to produce pellets. The interaction between the feeding and agitator speeds of the extruder, the plate rotational speed and the residence time of the spheronizer was analysed.

The resulting spherical granules were dried on a fluidized bed (AEROMATIC STREA) at inlet air temperature of 70 ˆC for 30 minutes. Citric and sodium citrate/citric acid (1:1), sodium citrate, tartaric acid and fumaric acid (Farmitalia Carlo Erba) were included in the standard formulation as pH adjusters instead of lactose. Acrylic resins (Eudragit RS/RL 30D (1/1), Rohm Pharma) and ethylcellulose (Aquacoat ECD30, FMC Corporation) were incorporated in fumaric acid formulation as liquid of granulation; the amount of the polymers in the final pellets was 9%.

All preparations were processed at the same operative conditions and procedures.

Testing Methods

Physical tests on uncoated pellets included the following:

- Sieve analysis: utilizing a JEL 200 sieve shaker; 6 setting for 5 minutes with 100 g sample size

- Bulk density: weighting the pellets poured gently and slowly through a glass funnel into a stainless steel cilinder (volume 97.36 ml)
- Granule density: measuring the true volume occupied by exactly weighted pellets using a mercury picnometer (Carlo Erba Mod. 230)
- Friability: rotating 10 g of the pellets along with 25 glass spheres of 7 mm diameter in a Roche friabilator for 10 min; the pellets were placed on a 0.250 mm sieve and shaken for 5 min on JEL 200 sieve shaker and the value was recorded as a percentage
- Dissolution testing: performed by USP/NF Method I in a phosphate buffer solution with a paddle rotational speed of 200 rpm. Dissolution test sample was assayed by UV spectroscopy at 280 nm (Perkin Elmer, Lambda 15)
- Moisture content: determining the weight loss by thermobalance at 100 ^C for 20 min (Mettler PC 440 with IR ray oven)

All tests were performed in triplicate.

RESULTS AND DISCUSSION

Extrusion-spheronization processing proved to be an effective technology for the preparation of d-Indobufen pellets. The cores obtained were approximately of spherical shape, uniform size, adeguate hardness and sufficient heaviness. All these factors are essential to facilitate blending, to ensure minimum variation in coating thickness, to keep out the presence of active fine in the coating and the segregation of granules during capsule-filling operations and to improve the reproducibility in gastric emptying. The results of physical testing are reported in tables I, II, III and IV for the pellets containing soluble filler, pH adjusters and release modifiers respectively. A higher amount of water content for wet granulation brought about a larger growth of the granules, which were more porous and less homogeneous in size. An extended residence time in the spheronizer made the product more homogeneous; a narrow granule size distribution was therefore obtained(Fig.1).

A simultaneous increase of feeding and agitation speeds determined only a slight decrease of both porosity and mean particle-size of the pellets.

TABLE I

PHYSICO-TECHNOLOGICAL PROPERTIES OF BASIC FORMULATION PELLETS OBTAINED BY EXTRUSION-SPHERONIZATION TECHNOLOGY

Extruder speed, rpm		(*)					(*)
- feeding	75	75	75	75	75	170	75
- agitator	50	50	50	50	50	100	50
Spheronizer speed, rpm	580	580	580	580	780	580	580
Residence time, min	3	6	3	6	3	6	6
Powder/water ratio	1.91	1.91	1.82	1.82	1.91	1.91	1.91
Mean granule diameter, mm	0.904	0.887	0.931	0.914	0.887	0.863	0.874
Bulk density, g/L	669	673	672	680	684	677	665
Granule density, g/L	1.23	1.25	1.14	1.14	1.16	1.46	1.26
Friability, %	0.3	0.3	0.1	0.3	0.5	1.1	0.8
Moisture content, %	2.2	2.3	1.7	2.2	2.2	2.4	2.2

Formulation: d-Indobufen/Microcrystalline Cellulose/Lactose, 55:30:15
(*) Two batches of preparation

TABLE II

PHYSICO-TECHNOLOGICAL PROPERTIES OF FORMULATION PELLETS OBTAINED BY EXTRUSION-SPHERONIZATION TECHNOLOGY

pH adjusters	Fumaric acid			Citric acid			Tartaric acid		
Extruder speed, rpm									
- feeding	75	75	170	75	75	170	75	75	170
- agitator	50	50	100	50	50	100	50	50	100
Spheronizer speed, rpm	580	780	580	580	780	580	580	780	580
Residence time, min	6	3	6	6	3	6	6	3	6
Powder/water ratio	1.71	1.71	1.71	2.03	2.03	2.03	2.13	2.13	2.13
Mean granule diameter, mm	0.846	0.894	0.790	0.947	0.827	0.805	0.964	0.898	0.891
Bulk density, g/L	667	682	671	750	771	773	719	738	737
Granule density, g/L	1.20	1.39	1.29	1.31	1.44	1.49	1.20	1.52	1.40
Friability, %	0.7	0.8	1.2	0.1	0.1	0.1	0.3	0.2	0.4
Moisture content, %	1.4	1.9	1.8	2.1	2.0	2.4	2.1	1.9	2.5

Formulation: d-Indobufen / Microcrystalline Cellulose / Acid, 55:30:15

TABLE III

PHYSICO-TECHNOLOGICAL PROPERTIES OF FORMULATION PELLETS OBTAINED BY EXTRUSION-SPHERONIZATION TECHNOLOGY

pH adjusters	Sodium citrate			Citric acid/Sodium citrate		
Extruder speed, rpm						
- feeding	75	75	170	75	75	170
- agitator	50	50	100	50	50	100
Spheronizer speed, rpm	580	780	580	580	780	580
Residence time, min	6	3	6	6	3	6
Powder/water ratio	2.28	2.28	2.28	2.01	2.01	2.01
Mean granule diameter, mm	0.899	1.004	0.985	1.151	0.980	0.927
Bulk density, g/L	761	765	730	729	735	707
Granule density, g/L	1.24	1.42	1.40	1.34	1.35	1.32
Friability, %	0.4	0.3	0.9	0.6	0.4	0.5
Moisture content, %	2.6	2.8	2.9	3.1	4.3	3.6

Formulation:d-Indobufen / Microcrystalline Cellulose / Salt or Buffer, 55:30:15

TABLE IV

PHYSICO-TECHNOLOGICAL PROPERTIES OF FORMULATION PELLETS OBTAINED BY EXTRUSION-SPHERONIZATION TECHNOLOGY

pH adjusters/release modifier	Fumaric acid/Eudragit RS/RL			Fumaric acid/Aquacoat		
Extruder speed, rpm						
- feeding	75	75	170	75	75	170
- agitator	50	50	100	50	50	100
Spheronizer speed, rpm	580	780	580	580	780	580
Residence time, min	6	3	6	6	3	6
Powder/water ratio	1.21	1.21	1.21	1.69	1.69	1.69
Mean granule diameter, mm	0.945	1.145	1.046	0.963	0.937	0.934
Bulk density, g/L	661	675	658	612	632	611
Granule density, g/L	1.28	1.28	1.37	1.21	1.23	1.21
Friability, %	0.0	0.0	0.0	10.0	10.0	10.0
Moisture content, %	1.5	1.5	1.4	1.2	1.5	1.5

Formulation:d-Indobufen / Microcrystalline Cellulose / Acid / Polymer, 55:30:15:9

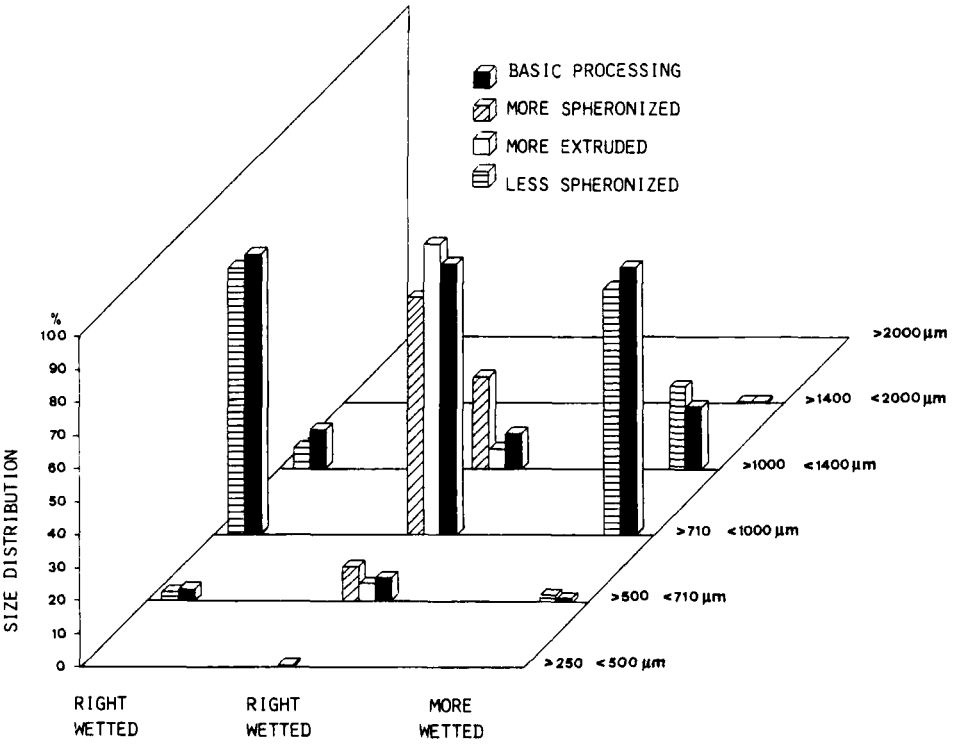

Figure 1: Size distribution of d-Indobufen pellets prepared by extrusion-spheronization: basic formulation consisting of d-Indobufen, cellulose and lactose (55:66:15) at different processing conditions

An increase of the spheronizer plate speed was found to produce a dishomogeneous growth of granules, which were more porous, generally smaller and less spherical.
The very promising reproducibility of the process was supported by all parameters relevant to the second batch of preparation (Table I).
In the preparation of pellets which contain pH adjusters, extruder and spheronizer speeds led to a decrease in the mean particle-size of the final pellets, sufficient abrasive resistance and higher granule density. The residence time in the spheronizer was found, as expected, to produce more homogeneous products in terms of a relatively narrow particle-size

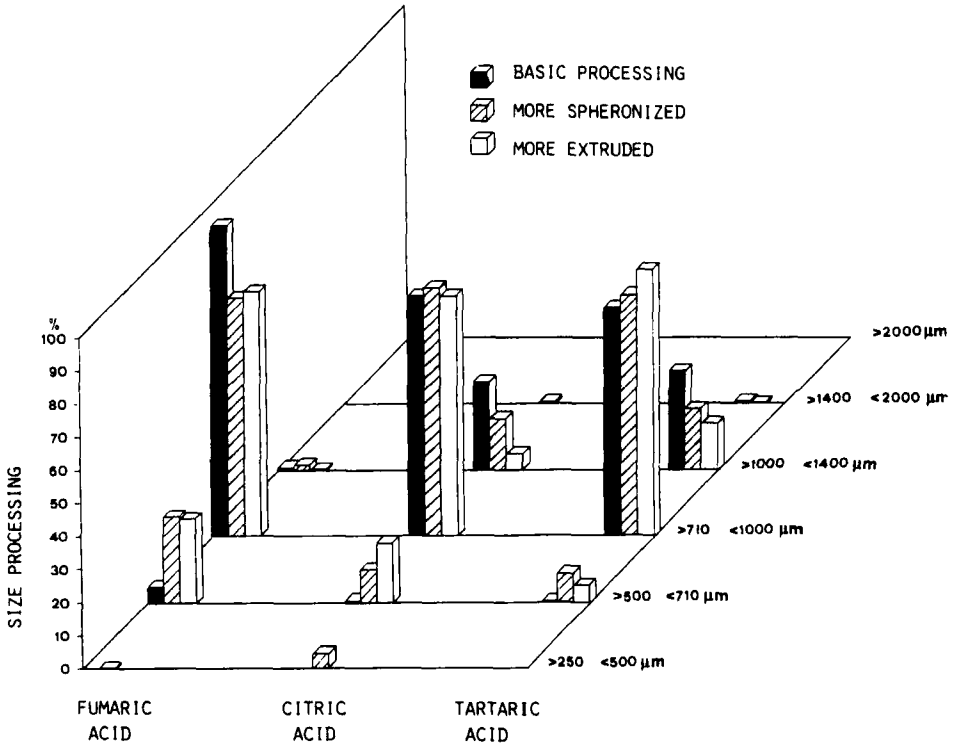

Figure 2: Size distribution of d-Indobufen pellets prepared by extrusion-spheronization: formulations containing d-Indobufen, cellulose, food acid (55:30:15) at different processing conditions

distribution (Fig.2). The incorporation of the salt, that dissolves more rapidly, determined a dishomogeneous pellet growth with a wider particle-size distribution (Fig.3), but did not influence the densities of the granules.

The inclusion of water insoluble polymers such as ethylcellulose (Aquacoat) and acrylic resins (Eudragit RS/RL 30D, 1:1) was found not to affect the extrusion-spheronization processing making it possible to obtain granules spherical in shape and smooth in surface. The ethylcellulose pellets were generally smaller, less uniform , softer and more friable than the acrylic resin pellets (Table IV and Fig.4).

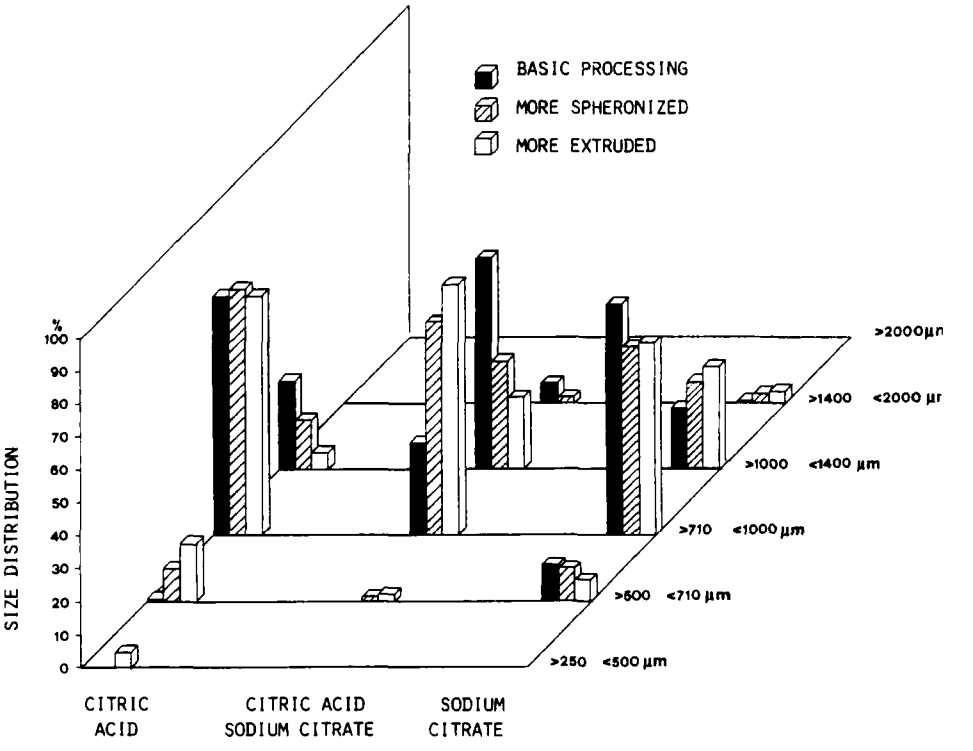

Figure 3: Size distribution of d-Indobufen pellets prepared by extrusion-spheronization: formulations containing d-Indobufen, cellulose, pH adjuster (55:30:15) at different processing conditions

Moreover the most spherical granules were found to be the pellets obtained in processing conditions of lower extruder and spheronizer speeds as well as longer spheronizer residence.

The morphological shapes and the surface which are dependent on the formula components are shown in figure 5 and 6.

The "in vitro" release data are presented in figures 7, 8, 9 and 10.

The release profiles of d-Indobufen pellets, obtained by the basic formulation, were found to be substantially independent on the processing conditions.

Slight differences were observed with the product more

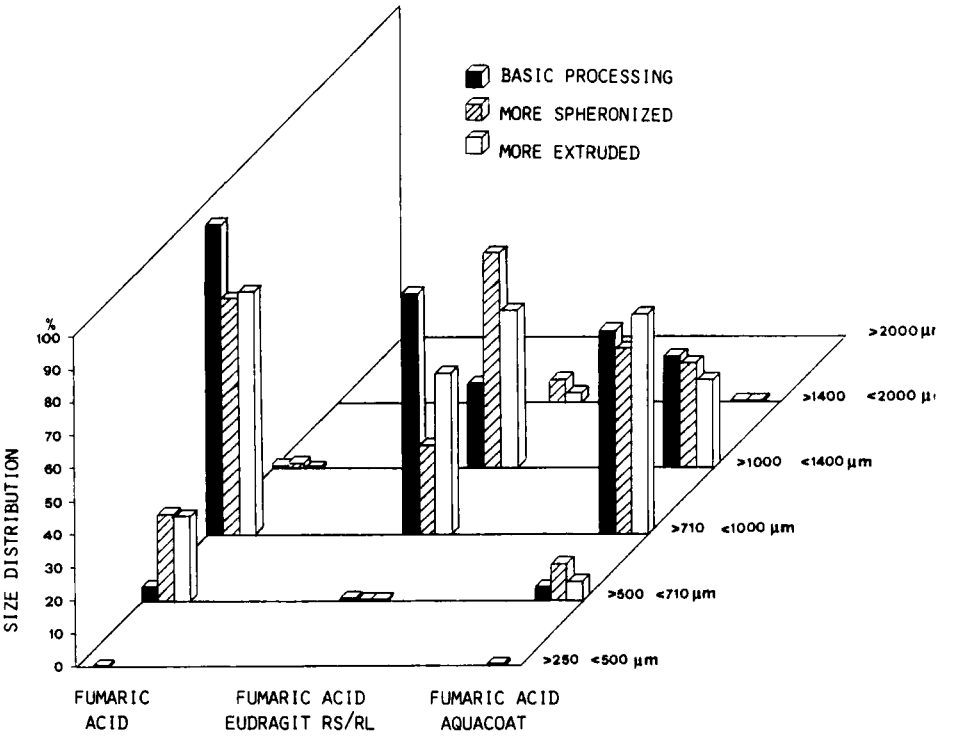

Figure 4: Size distribution of d-Indobufen pellets prepared by extrusion-spheronization: formulations containing d-Indobufen, cellulose, fumaric acid and insoluble polymer (55:30:15:9) at different processing conditions

wetted during the granulation operation. The time needed to release 50 percent of the dose (t_{50}) was about 30 minutes (the amounts released varied from 52 to 59 percent); complete release was reached within 3 hours. The presence of both acids and buffer in the pellets instead of lactose seemed to slow the drug release rate in the early release period; particularly the fumaric acid appeared to be more effective.
On the contrary the sodium citrate improved the drug release rate so that complete release took place after 2 hours. Finally the incorporation of insoluble polymers in the fumaric acid containing formulation de-

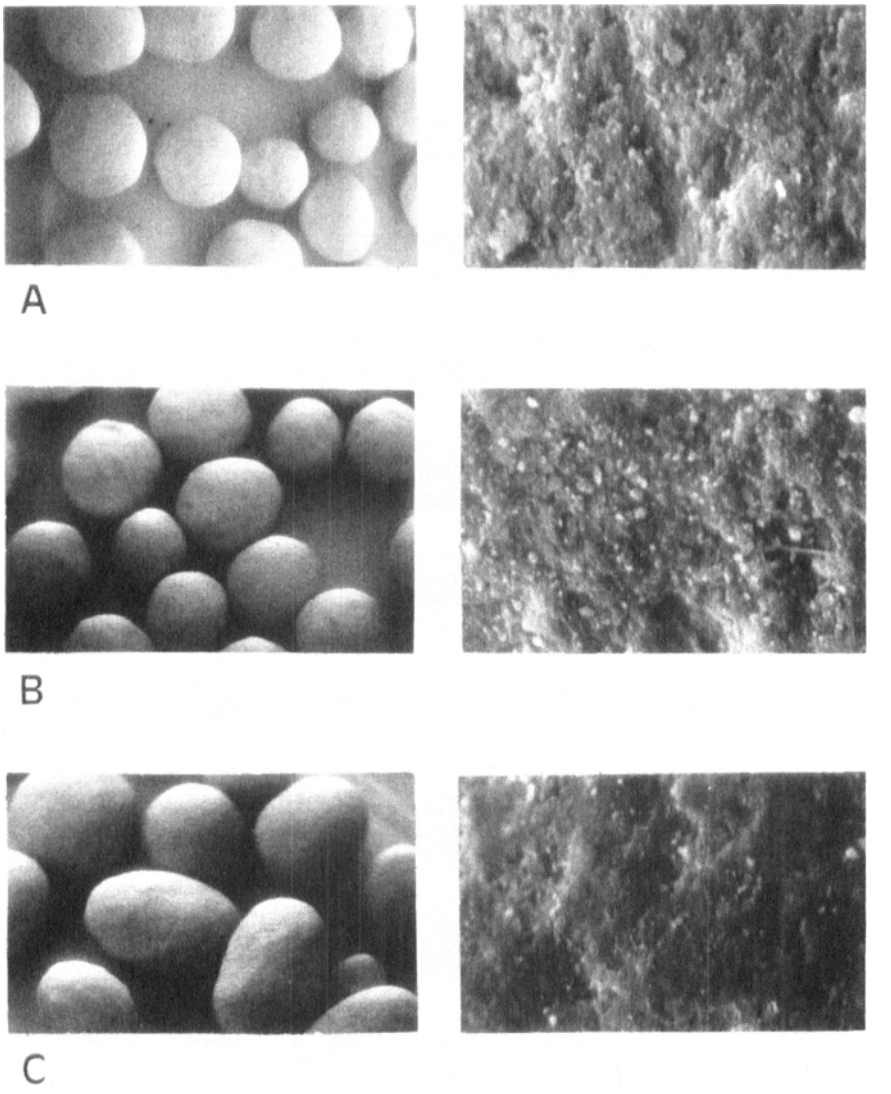

Figure 5: Scanning electron photomicrographs of pellets containing different excipients (Magnification 15x and 1500x). A) Lactose, B) Fumaric acid, C) Sodium citrate.

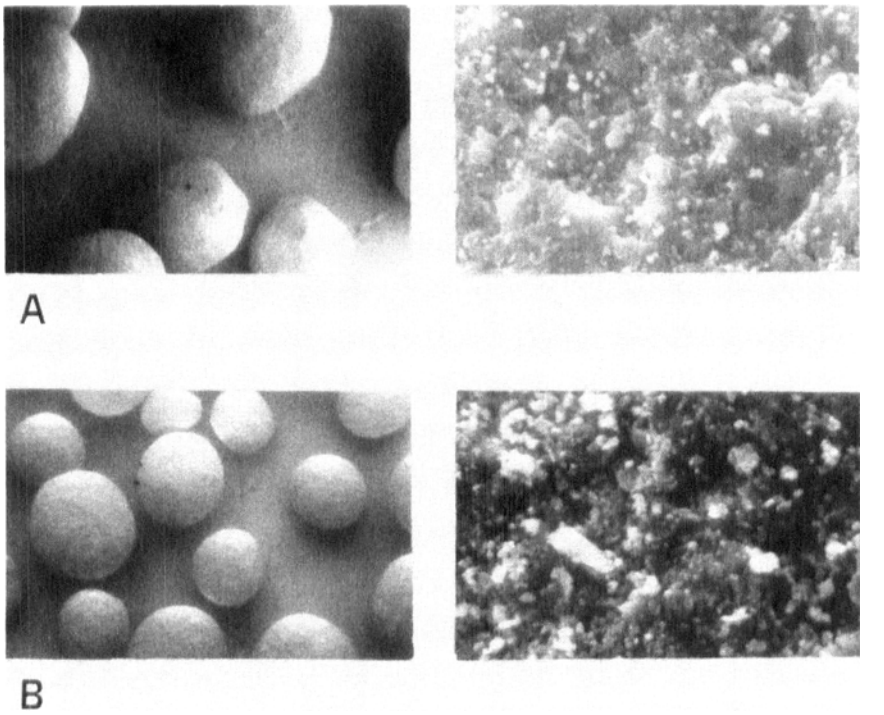

Figure 6.Scanning electron photomicrographs of pellets containing different excipients (Magnification 15x and 1500x).Fumaric acid with Eudragit RS/RL (1:1)(A) and Aquacoat (B).

termined a further decrease in the release rate of d-Indobufen.
The results of dissolution testing showed similar drug release profiles for both formulations containing the same amounts of acrylic resins or ethylcellulose.

CONCLUSIONS

It was verified that spheronization processing is an effective technology for the manufacturing of d-Indobufen pellets which contain different excipients such as pH adjusters and insoluble polymers.
The pellets obtained showed a good reproducibility of the technological properties such as spherical shape, size and hardness.

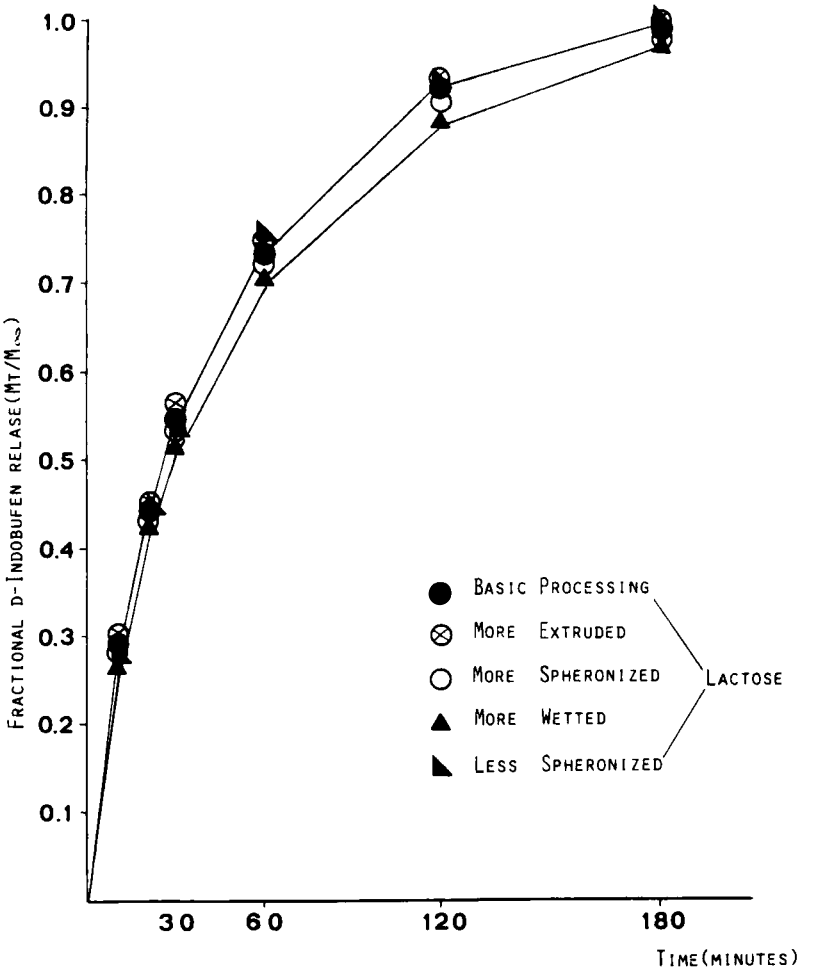

Figure 7: Drug release rate (USP XXII apparatus 2 in 900 ml of phosphate buffer solution, pH 7.5, 37 ˆC, 200 rpm) from pellets obtained by extrusion-spheronization technology. Basic formulation consisting of d-Indobufen, cellulose and lactose (55:30:15) at different processing conditions.

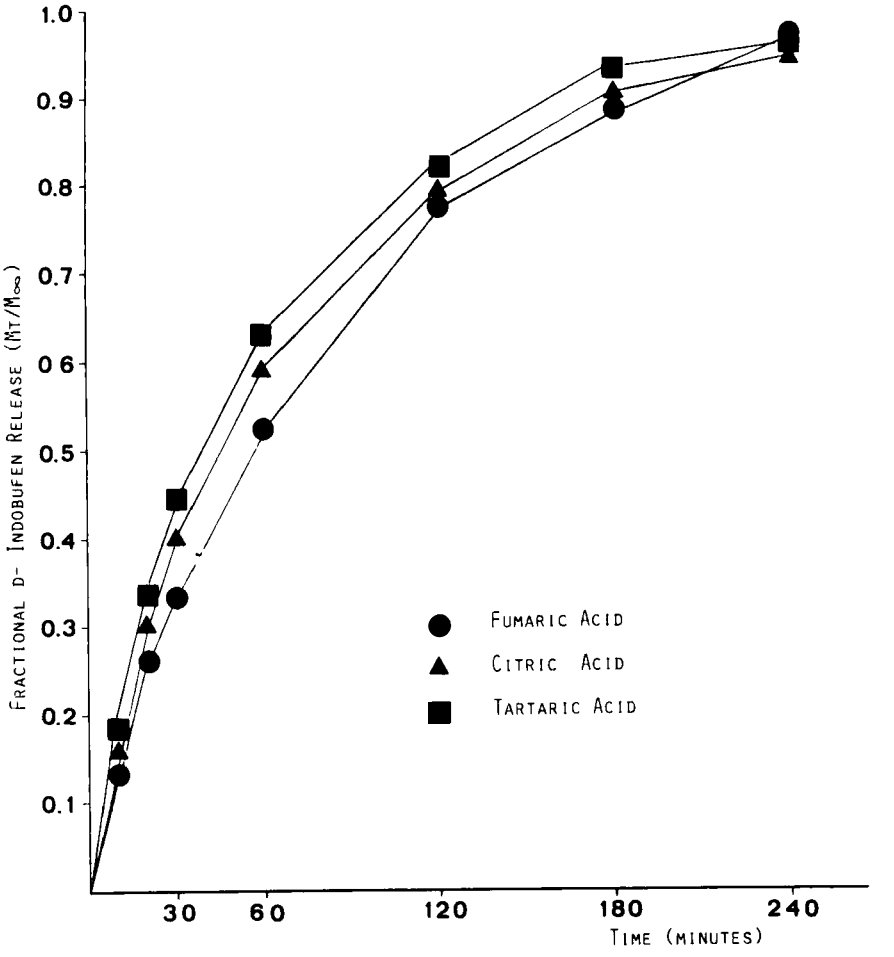

Figure 8: Drug release rate (USP XXII apparatus 2 in 900 ml of phosphate buffer solution, pH 7.5, 37 ˆC, 200 rpm) from pellets obtained by extrusion-spheronization technology. Formulations consisting of d-Indobufen, cellulose and acid (55:30:15) at different processing conditions.

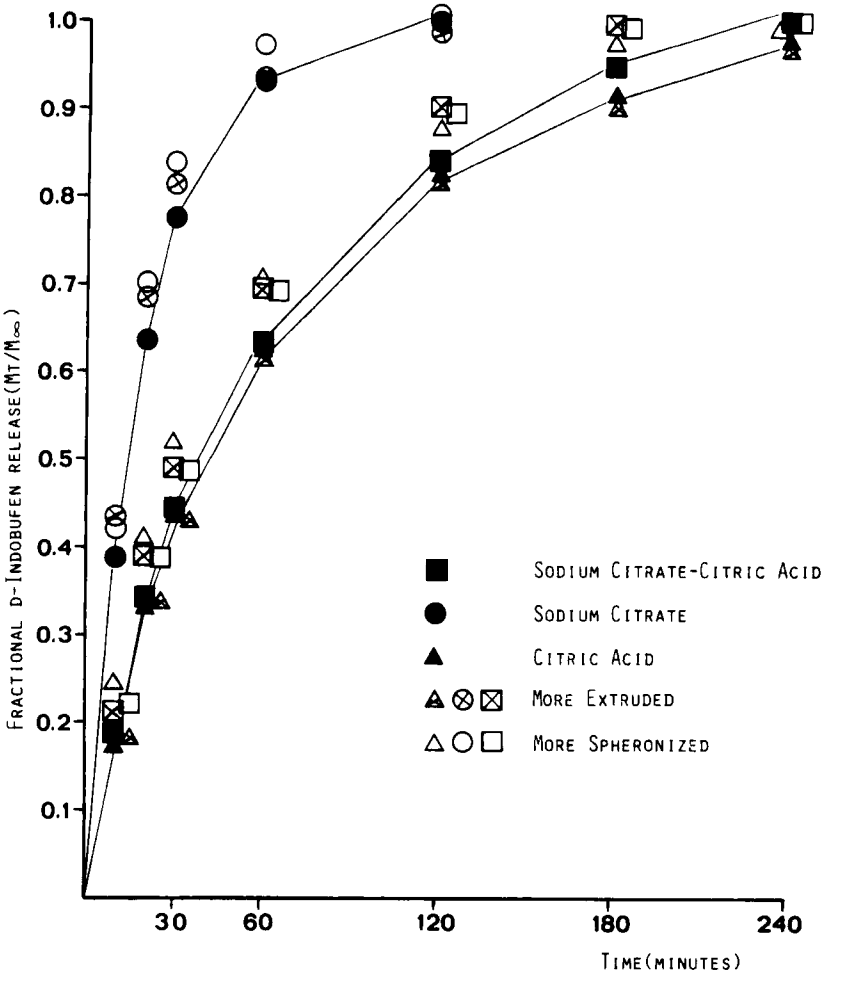

Figure 9: Drug release rate (USP XXII apparatus 2 in 900 ml of phosphate buffer solution, pH 7.5, 37 ˆC, 200 rpm) from pellets obtained by extrusion-spheronization technology. Formulations consisting of d-Indobufen, cellulose and pH adjusters (55:30:15) at basic processing conditions.

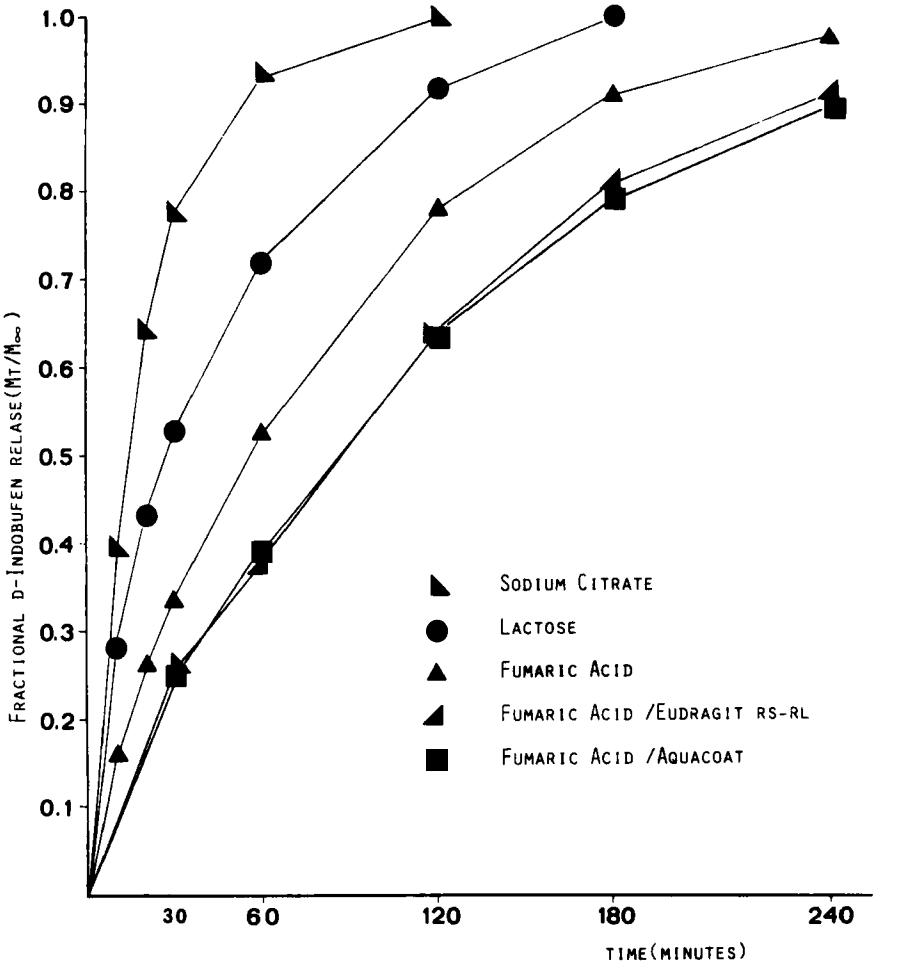

Figure 10: Drug release rate (USP XXII apparatus 2 in 900 ml of phosphate buffer solution, pH 7.5, 37 ˆC, 200 rpm) from pellets obtained by extrusion-spheronization technology. Formulations containing the soluble excipients in comparison with the formulations including the insoluble polymers.

The presence of pH adjusters in pellet formulation affects the microenvironment of drug molecules giving rise to different release profile patterns.
Incorporation of insoluble polymers brings out a homogeneous matrix system that leads to a prolonged drug release.

Acknowledgments

The authors appreciate the collaboration of De Luigi S., Cristina G., Fabiani F.,Motta A and Rossi G.
Thanks are due to Braglia R. and Morelli of Donegani Institut-Novara for the photomicrographs.

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