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Physical properties of chitosan pellets produced by extrusion–spheronisation: influence of formulation variables

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Abstract

Pellets comprising chitosan, cellulose microcrystalline, povidone, filler excipient and diclofenac sodium as model drug were prepared by extrusion–spheronisation. The effects of chitosan load (zero, 0%, low, 4% and high, 16% levels), type of filler (lactose, tribasic calcium phosphate and β-cyclodextrin) and composition of the binding liquid (ethanol/water mixtures 20 and 50%) on physical characteristics of pellets were evaluated. A three-factor factorial design was employed in the study. Analysis of variance (ANOVA) indicated that single factors had significant effect on the physical characteristics of the pellets. The type of filler followed by polymer load markedly affected the density. The type of binding liquid had negligible effect on the shape and surface roughness of the pellets. Increase in the chitosan load resulted in pellets of lower porosity values. This could be attributed to the binding capacity of chitosan and povidone leading to more compacted structures. Chitosan load and type of filler had significant influence on the surface roughness. The surface of pellets became rougher as the chitosan load increased, however, there was no significant difference between zero and low contents of chitosan. Pellets prepared using tribasic calcium phosphate showed a smoother surface when compared with formulations including lactose or β-cyclodextrin. Chitosan was useful to provide pellets of acceptable physical characteristics when employing an alcohol/water mixture 50% (v/v) as binding liquid for the extrusion–spheronisation process.

Keywords: Chitosan; Extrusion–spheronisation; Pellets; Shape factor; Surface roughness; Tensile strength

1. Introduction

The oral administration of pharmaceutical dosage forms is the more usual, convenient and comfortable way of active drug delivery to the body. Thus, for the development of dosage forms this route has received much more attention than, for instance, the parenteral route, mainly because of its great flexibility in the design.

Many attempts have been made concerning the conception and optimisation of pharmaceutical systems that could promote drug release control.

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Among many oral dosage forms that could be conceived as drug release system the pellets are still gaining interest due to their technological and therapeutic advantages such as the size/volume ratio, spherical shape, which is ideal for powder layering or film coating, the possibility for incorporating high drug load, the dispersion throughout the gastrointestinal tract decreasing the risk of gastric mucosa irritation and dose dumping (Reynolds, 1970; Bechgaard and Hegermann Nielsen, 1978).

The pelletisation process consists of the agglomeration of fine powders of active drug and excipients into small spherical units. Pellets are commonly prepared applying the extrusion–spheronisation pelletisation process. Extrusion–spheronisation consists of the compaction of a wet powder mass leading to an intermediate spaghetti-like product, which is promptly spheronised obtaining a final spherical product (Conine and Hadley, 1970; Reynolds, 1970; Ghebre-Sellassie, 1989). The physical characteristics of the pellets highly influence further manufacturing processes such as film coating, capsule filling or tabletting, which are directly affected by process and formulation variables (Fekete, 1998), and consequently the properties of the final dosage form and its biological performance.

Chitosan, a cationic polymer combined by β1-4 glicosidic linkage, is the main product obtained by the alkaline deacetylation of chitin, a major structural polysaccharide found in crustaceans, insects and lower plants (Felt et al., 1998; Paul and Sharma, 2000). Structurally similar to cellulose, chitosan has been mainly used as a pharmaceutical excipient (Upadrashta et al., 1992; Kristmundsdóttir et al., 1995; Illum, 1998) and has also been assessed for its potentiality in the development of controlled-release systems and for its propensity for targeting drugs to specific sites (Felt et al., 1998; Paul and Sharma, 2000).

Miyazaki et al., 1981; Sawayanagi et al., 1982 noticed the usefulness of chitosan as a sustained release vehicle when tablets including this polymer were submitted to dissolution test in acid medium. Goskonda and Upadrashta, 1993 showed that spherical beads could be produced by a combination of Avicel RC-591 and different viscosity grades of chitosan raising the possibility of designing beads with release modifying properties.

The potentiality of chitosan in sustained release systems has been assigned to its polymeric character including its gel and film forming properties. It has to be mentioned that chitosan demonstrates slow release properties due to its swelling nature in acid medium; on the other hand, it has been found to act as a disintegrant when in medium pH 6.8 or higher. Attempts have been made to diminish the medium dependent disintegrant activity of chitosan. Nigalaye et al., 1990 reported the successful use of carbomer 934P in association with chitosan reducing the disintegrant property of this polymer in tablets. Concerning chitosan inclusion in pellets, (Tapia et al., 1993) described the potentiality of this polymer to retard drug release from a sphere by use of a hydrophilic gel.

All the possible applications of chitosan are due to its biodegradability, biocompatibility and non-toxicity including its insolubility at neutral and alkaline pH values, which is influenced by its degree of deacetylation (DDAC), molecular structure, physical state and ionic strength of the medium. Chitosan with DDAC higher than 85% have been found to be soluble up to pH of 6.5. Furthermore, chitosan viscosity is also influenced by the DDAC (Knapczyk et al., 1989; Felt et al., 1998; Paul and Sharma, 2000).

The objective of this work was to investigate the application of chitosan as a binder in the production of pellets by the process of extrusion–spheronisation, evaluating its implication on the final physical characteristics of the pellets. For that purpose, the formulation parameters chitosan load level, type of filler and type of binding liquid were assessed for their influence on the density, porosity, tensile strength, size, shape, surface roughness and surface appearance of the pellets. Moreover, taking into account previous reports, which attributed a disintegrant property to chitosan when presented at concentration less than 10% in tablet formulations, the present work intended to verify this property of chitosan when included at a level of 4 or 16% in pellet formulations, which were subjected to the action of an aqueous medium of pH 7.4.

2. Materials and methods

2.1. Materials

Diclofenac sodium (BP grade) was purchased from Capsifar, Lisbon, Portugal and used as the model drug. Chitosan (90.5% deacetylation degree, viscosity 80 mPa × s), purchased from Exquim, Barcelona, Spain, was employed as the main binder. Microcrystalline cellulose powder (Microcel® 101) obtained from Sagran, Milan, Italy, was the support excipient. Lactose monohydrate (Granulac® 200, Meggle, Wasserburg, Germany), tribasic calcium phosphate (Lusifar, Lisbon, Portugal) and β-cyclodextrin (Kleptose®, Roquette, Lestrem, France) were used as filler excipients. Povidone (Kolidon® K30, BASF) was purchased from Lusifar, and employed as a secondary binder in the formulation. All the materials were used as received without further treatment. Mixtures of distilled water and alcohol 95% commercial grade were used as granulation liquid.

2.2. Extrusion–spheronisation

The extrusion–spheronisation process was used for the preparation of the pellets. Pellet formulations are presented in Table 1. Ethanol/water mixtures 20 and 50% v/v were used as the binding liquids. Two hundred gram of dry powder mixtures were blended in a planetary mixer for 20 min. Povidone was included in the formulations as a solution in the binding liquid. The appropriate total quantity of the liquid, which gave the suitable wet mass for extrusion thus the best pellets in terms of roundness (visual inspection), was determined by trial and error. The wet masses were extruded in a screen extruder (Caleva model 10, Dorset, England) equipped with a standard screen 1 mm aperture at 60 rpm extrusion rate. The extrudates were then transferred to a spheroniser (Caleva model 250, Dorset, England) equipped with a crosshatch plate and processed at 1000 rpm rotating speed. The resultant pellets were dried in a fluid bed processor (Uni-Glatt, Glatt GmbH, Binzen, Germany) at 50 °C during 20 min.

2.3. Characterisation of the pellets

The characterisation of the pellets was performed on the 1000–1400 μm sieve fraction obtained using a set of British standard sieves following a $\sqrt{2}$ progression from 500 to 2000 μm of mesh diameter.

2.3.1. Apparent particle density and porosity

The apparent particle density of each powder and pellets was determined using a gas pycnometer (Multipycnometer, Quantachrome Co., UK) with helium as the test gas. All powders and pellet batches were analysed in triplicate. The porosity of pellets was calculated according to Eq. (1).

$$\varepsilon = 1 - \left(\frac{\text{pellet density}}{\text{powder density}}\right) \quad (1)$$

Table 1
Pellet compositions

Formulation code*	Diclofenac sodium	Microcrystalline cellulose	Povidone	Lactose	Tribasic calcium phosphate	β-Cyclodextrin	Chitosan
Z1	10	50	2	38	–	–	0
Z2	10	50	2	–	38	–	0
Z3	10	50	2	–	–	38	0
L1	10	50	2	34	–	–	4
L2	10	50	2	–	34	–	4
L3	10	50	2	–	–	34	4
H1	10	50	8	16	–	–	16
H2	10	50	8	–	16	–	16
H3	10	50	8	–	–	16	16

*All in % w/w.

where ε stands for porosity and the powder density is the value of the sum of each component's proportion by weight multiplied by its density.

2.3.2. Tensile strength

The tensile strength of pellets of different formulations (Table 1) was assessed using a universal testing instrument with a 5 kg load cell (CT-5, Engineering Systems, Nottingham, UK). The pellets were strained until failure occurred. The load was recorded and the tensile strength was calculated applying Eq. (2) (Shipway and Hutchings, 1993; Salako et al., 1998).

$$\sigma_f(s) = \frac{(0.4F)}{(\pi R^2)} \quad (2)$$

where $\sigma_f(s)$ is the surface tensile strength, F is the failure load, and R is the radius of the pellet. Fifty pellets of each batch were analysed.

2.3.3. Image analysis

Size and shape of the pellets were concomitantly derived using an image analysis system (Seescan solitaire 512, Seescan, Cambridge, UK) connected to a black and white camera (CCD-4 miniature video camera module, Rengo Co. Ltd, Toyohashi, Japan), zoom lens (18–108/2.5, Olympus Co., Hamburg, Germany), and top position cold light source (Olympus Co). One hundred pellets of each batch were analysed. Aspect ratio, Ferret diameter and shape factor e_R were derived from image analysis and used for statistical analysis. The aspect ratio is here defined as the ratio between the longest Feret diameter and the Feret diameter perpendicular to this measure, and the shape factor e_R (Podczeck and Newton, 1994), is based on a two-dimensional outline analysis and considers both the geometrical shape and the surface texture of the agglomerate. A value of aspect ratio deviating from unity indicates the degree of spheroid elongation. For the shape factor e_R a value of unity considers a perfect spheroid although a value close to 0.6 describes a particle of good sphericity.

2.3.4. Surface roughness

Six pellets of each batch were assessed applying a non-contacting laser profilometer (UBM Microfocus Measurement System, UBM Messtechnik GmbH, Ettlingen, Germany). The roughness parameters were determined using the UBSOFT software, which also provides a three-dimensional profile of the surface of the analysed particle. The laser spot size was 1 μm, and the aperture angle was 53°. The measured area was 0.25×0.25 mm with a resolution of 500 points per mm in the X- and Y-directions. The scanning speed was 100 points per s. Among all the parameters derived from the measurements the 'mean peak to valley ratio' (R_{tm}) was chosen for the statistical analysis. It describes the arithmetic average of the largest height difference in each of 25 rectangles obtained by splitting the surface into a 5×5 grid, and provides information about the surface that a two-dimensional line scan would not detect.

2.3.5. Microscopy

Photomicrographs of the pellets were taken with a scanning electron microscope (SEM) (Philips XL20, Philips, Eindhoven, The Netherlands) for visual inspection of the shape and the surface texture of pellets. The visual assessment SEM conjugated with the quantitative assessment (R_{tm} parameter) of the surface was helpful to elucidate the effects of the formulation variables on the surface characteristics of the pellets.

2.3.6. Dissolution testing

In vitro dissolution tests were performed according to the USP basket method USP 24/NF 19, 2000 using a dissolution apparatus (VK 7000 dissolution testing station, Vankel, Essex, England). The test employed used 1000 ml pH 7.4 phosphate buffer at 37 °C and baskets rotating at 100 rpm. Samples were continuously collected and analysed by UV–Visible spectrophotometer (UV-1603 Shimadzu, Shimadzu Co., Kyoto, Japan) at 277.5 nm. Each batch was analysed in triplicate.

2.4. Experimental design

A $3 \times 3 \times 2$ factorial design was employed in this study (Table 2). The chitosan load and type of

Table 2
Factors for the 3 × 3 × 2 statistical factorial design

Chitosan loading	Level	Strength (% w/w)	
	Zero	0	
	Low	4	
	High	16	
Filler	Type	Density (g/cm^3)	Solubility in water (g/l)
	Lactose	1.540	200
	Tribasic calcium phosphate	3.140	<1
	β-cyclodextrin	1.490	18.5
Granulation liquid	Type	Strength (% v/v)	
	Alcoholic solution A	20	
	Alcoholic solution B	50	

filler varied at three levels each and the binding liquid type varied at two levels. Analysis of variance (ANOVA) was performed using SPSS version 10.0 for WINDOWS (SPSS Inc., Chicago, USA) employing an error probability of $P = 0.05$.

3. Results and discussion

Preliminary trials to process wet masses with no addition of povidone revealed poor consistency of the masses and consequently low yield of spherical agglomerates during spheronisation. Wet masses turned into powder or produced large amounts of dust even when applying low spheronisation rates. Povidone was then included in the formulation to impart consistency of wet masses thus improving yield of pellets. Goskonda and Upadrashta, 1993 observed a similar behaviour when acceptable beads were not possible to be produced using a ternary mixture of chitosan, theophyline and Avicel PH-101 by the extrusion–spheronisation process. Alternatively they employed Avicel RC-591 and the success was attributed to the binding ability due to addition of sodium corboximethylcellulose to Avicel RC-591. Here, the success in the extrusion–spheronisation of wet masses could be assigned to the povidone in the formulation. Due to the binding action of povidone, high yield of pellets of the nominal size fraction and low production of dust was possible to achieve.

The results for the physical properties of the pellets and the ANOVA are presented in Tables 3 and 4, respectively. The analysis of the density revealed that chitosan load and the type of filler were the influence factors on this property. The type of filler determined the density of the pellets. Interactions between all factors were also relevant. The major interaction was found between chitosan load and type of filler. This interaction explains why the density of pellets comprising high concentration of chitosan was lower than the density of pellets comprising low concentration of chitosan and simultaneously higher than that of pellets with no added chitosan. The partial substitution of filler by an equal amount of chitosan led to an increase in the density although, simultaneously, as the amount of chitosan increased in replacement of the filler in the formulation the density of the pellets decreased despite still remaining higher than that of pellets with no added chitosan. Goskonda and Upadrashta, 1993 reported a similar behaviour for beads containing chitosan, Avicel RC-591 and model drug. Density decreased with an increase of chitosan content in the formulation.

As observed for the density, the binding liquid had no statistical effect on the porosity of the pellets. Conversely, the solubility of fillers seemed to play an important role, taking into account that all three fillers are practically insoluble in alcohol though lactose is the most soluble in water ($\sim$200 g/l), followed by β-cyclodextrin ($\sim$18.5 g/l) and

Table 3
Physical properties mean values for pellets comprising chitosan at different loading levels, different types of filler and prepared with different binding liquids

Chitosan loading	Filler	Granulation liquid	True density (g/cm^3)	Porosity	Tensile strength (MPa)	Aspect ratio	Shape factor e_R	Roughness R_{tm} (μm)
Zero	Lactose	A	1.306	0.342	1.617	1.145	0.501	9.715
		B	1.407	0.290	1.188	1.076	0.606	11.842
	Tribasic calcium phosphate	A	1.765	0.319	1.614	1.214	0.401	5.390
		B	1.700	0.344	1.445	1.077	0.617	7.380
	β-cyclodextrin	A	1.305	0.336	1.374	1.076	0.598	13.022
		B	1.257	0.360	1.208	1.077	0.600	13.750
Low	Lactose	A	1.473	0.257	1.622	1.254	0.388	13.135
		B	1.447	0.270	2.319	1.074	0.626	11.318
	Tribasic calcium phosphate	A	1.750	0.307	2.179	1.171	0.478	7.527
		B	1.695	0.329	1.007	1.083	0.605	6.930
	β-cyclodextrin	A	1.412	0.281	1.991	1.094	0.578	14.870
		B	1.427	0.273	1.709	1.073	0.626	9.997
High	Lactose	A	1.438	0.262	1.761	1.168	0.486	17.918
		B	1.466	0.248	1.392	1.095	0.587	10.242
	Tribasic calcium phosphate	A	1.531	0.306	1.991	1.121	0.538	11.918
		B	1.552	0.296	1.377	1.094	0.590	10.795
	β-cyclodextrin	A	1.427	0.265	1.490	1.139	0.516	15.628
		B	1.431	0.263	1.271	1.100	0.576	11.483

Table 4
ANOVA[ψ] results for the physical properties of pellets comprising chitosan at different loading levels, different types of filler and prepared with different binding liquids

Source	True density		Porosity		Tensile strength		Aspect ratio		Shape factor e_R		Roughness	R_{tm}
	F-value	P-value	F-value	P-value	F-value	P-value	F-value	P-value	F-value	P-value	F-value	P-value
% chitosan	122.298	<0.001	378.967	<0.001	151.110	0.255	0.208	0.813	0.005	0.995	5.687	0.005
Type filler	1802.430	<0.001	149.021	<0.001	19.611	0.043	0.418	0.661	0.568	0.568	16.547	<0.001
Type liquid	0.355	0.555	0.006	0.937	256.182	0.225	0.528	0.472	6.326	0.013	5.448	0.022
% chitosan *filler	209.664	<0.001	35.852	<0.001	36.896	0.143	0.325	0.860	0.290	0.884	1.375	0.249
% chitosan *liquid	7.444	0.002	7.958	0.001	6.759	0.015	0.305	0.739	0.211	0.810	5.703	0.005
Filler *liquid	21.907	<0.001	24.086	<0.001	93.515	0.175	0.140	0.870	0.685	0.506	1.524	0.223
% chitosan *filler *liquid	19.580	<0.001	24.478	<0.001	98.671	0.309	0.106	0.980	0.331	0.857	0.916	0.458

[ψ] Alpha = 0.05.

tribasic calcium phosphate is very slightly soluble in water (< 1 g/l). Pellets comprising tribasic calcium phosphate, here the less soluble filler in both components of the binding liquid were found to be the most porous. This could be the result of the low solubility of the filler in the binding liquid, although a discrepancy is observed for pellets at zero chitosan load as seen in Fig. 1.

In Fig. 2, the relationship between the porosity and tensile strength of the pellets as a function of the filler solubility can be seen. Contrary to the results for density and porosity, the type of binding liquid also played an important role with respect to the tensile strength. Pellets prepared employing binding liquid type A gave tensile strength values statistically higher than those prepared with liquid type B. In this case, the greater fraction of water in liquid type A (ethanol/water mixture 20%) led to stronger agglomerates. As the fraction of water increased in the binding liquid pellets became stronger, which is in agreement with findings by Millili and Schwartz, 1990; Elbers et al., 1992. Pellets including high content of chitosan in their formulation were reported to be mechanically stronger than those not including the polymer and, at the same time, less strong than pellets comprising low chitosan content. Once again, as observed for the density of pellets, an explanation can be found from a balance between chitosan and filler contents in the formulation, the most important factors affecting this property. When lactose or tribasic calcium phosphate were employed, pellets were mechanically stronger than those comprising β-cyclodextrin. This finding appeared to be inconsistent in relation with the solubility of the fillers. It would be expected that the pellets were less strong when comprising tribasic calcium phosphate, the less soluble filler. However, other literature report confirmed this finding (Sousa et al., 2002). The solubility of the filler affected the degree of solute migration during the drying process. For a water soluble filler like lactose, crystallisation of the dissolved particles led to greater degree of close interparticulate contact

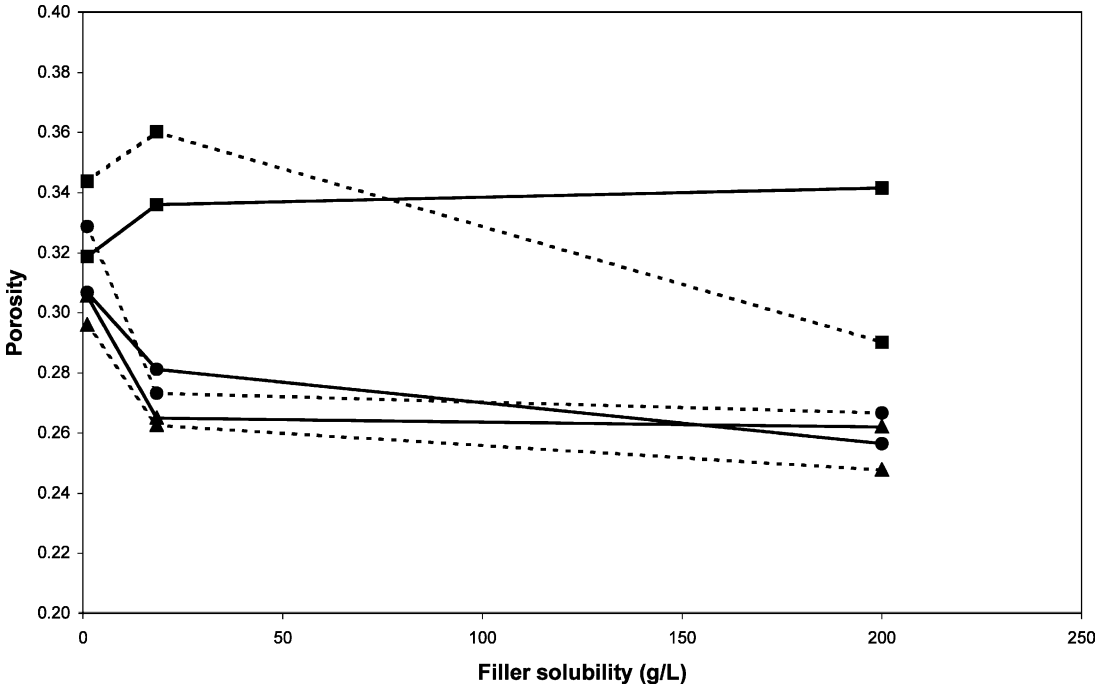


Fig. 1. Mean Porosity of pellets produced with different binding liquids (type A —; type B ····) and comprising different chitosan loads (zero ■; low ● and high ▲).

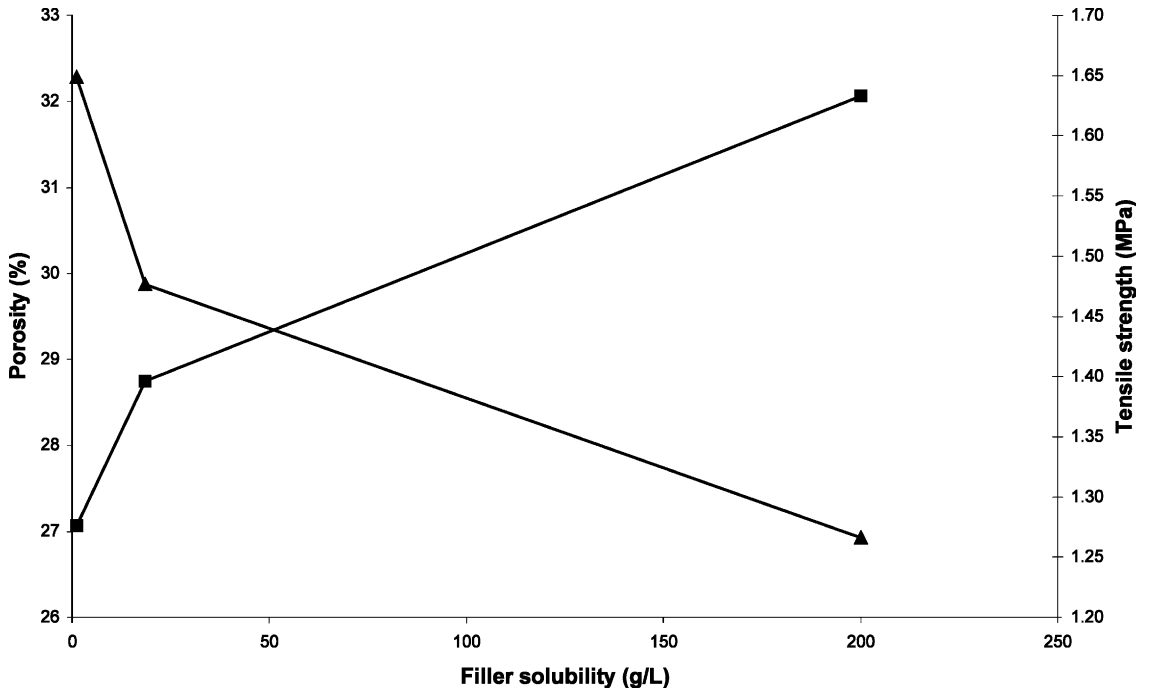


Fig. 2. Mean porosity (▲) and tensile strength (■) of pellets obtained with binding liquid type B according to filler solubility.

and hence less elastic and brittle agglomerates (Dyer et al., 1994). Such fact was well observed for pellets made with binding liquid type B (Fig. 2).

Chitosan load and type of filler could not be identified as major influence factors on the shape factor e_R (ANOVA). On the other hand, the type of binding liquid was the only single factor leading to differences in the shape factor e_R of the pellets ($P = 0.013$). When pellets were prepared applying binding liquid type A they appeared to be less spherical than those obtained applying binding liquid type B as revealed by the shape factor e_R. It has to be taken into account that when employing binding liquid type A the process of extrusion–spheronisation was more difficult to handle because of the tackiness of the wet masses. In these cases, the ideal quantity of liquid necessary to give masses of proper consistency to be processed was harder to achieve thus influencing the quality of the spheroids. Considering a lower limit of 0.6 for the shape factor e_R of agglomerates, pellets prepared applying binding liquid type B could be accepted as nearly spherical, whereas those pellets prepared applying liquid type A were clearly not round (Fig. 3). From Fig. 3 it could also be seen that shape factor e_R and surface roughness were not clearly correlated. Nevertheless, for pellets prepared with binding liquid type B, the results of shape factor e_R were accompanied by surface roughness values not as scattered as those obtained when applying binding liquid type A. Although chitosan load and filler type gave no statistically different shape factor e_R, it has to be mentioned that, considering only the product of liquid type B, values of the shape factor e_R of pellets comprising zero or low chitosan load were equal to or higher than the recommended threshold limit for pellets to be accepted as round. However, pellets comprising high chitosan load showed values of the shape factor e_R close to but below 0.6. It is inferred from the experiment that the greater the fraction of water in the binding liquid and the higher the chitosan content in the formulation, less spherical is the product of the process. This deduction is reasonably supported by the hydrophilicity of the chitosan which made it difficult to obtain wet masses of good quality that could be extruded and, consequently, to obtain

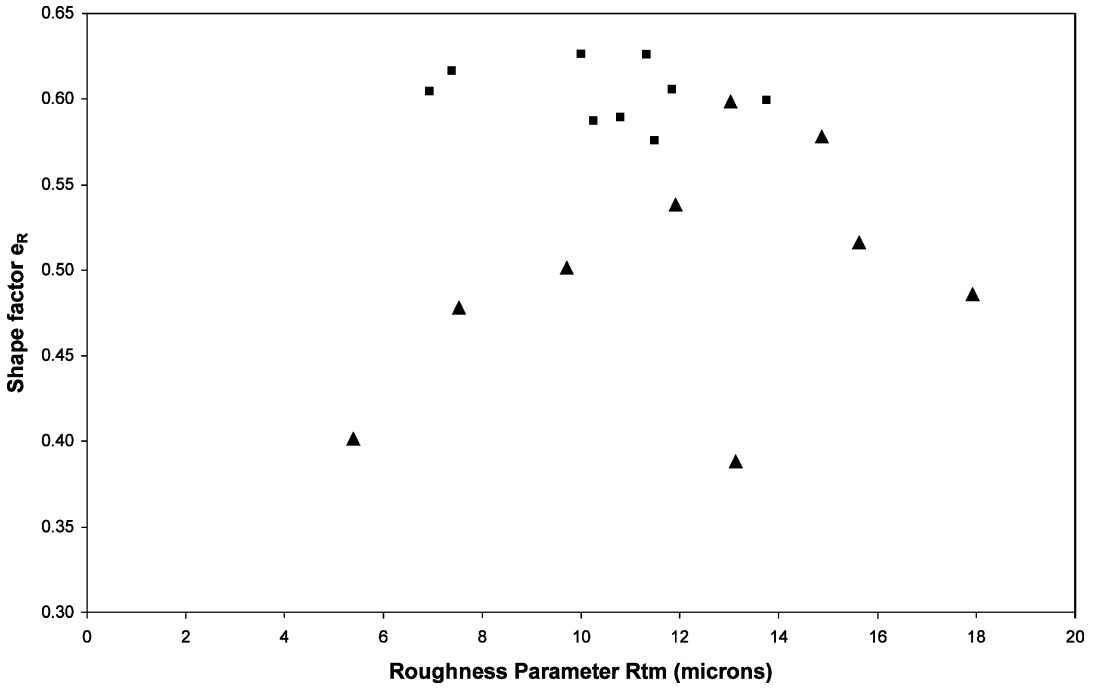


Fig. 3. Shape factor e_R of pellets obtained with binding liquids type A (▲) and type B (■) as a function of the surface roughness.

extrudates of reasonable plasticity to be spheronised.

ANOVA could not identify a significant difference between the results for the aspect ratio of the different pellet formulations. Assuming 1.1 as the upper limit recommended for aspect ratio to be accepted as an indication of round shape (Podczeck et al., 1999), only pellets prepared with binding liquid type A gave values of the aspect ratio higher than this threshold limit. The results for sphericity confirm the usefulness of the shape factor e_R to describe this property revealing to be more sensitive than the aspect ratio in detecting small differences and deviations.

For the surface roughness, all single factors were identified to be important in determining differences within the results, but the type of binding liquid was less important ($P = 0.022$) than the other parameters. A significant statistical difference of the surface roughness values was observed only between chitosan load and type of binding liquid. As expected, the type of filler was very important in determining the surface roughness of pellets. Pellets comprising lactose or β-cyclodextrin gave surface roughness parameter R_{tm} values statistically not different from one another. On the other hand, they were both different from and higher than that of the pellets comprising tribasic calcium phosphate. Chitosan load demonstrated a related behaviour, i.e. pellets comprising zero or low content of the polymer showed surface roughness parameter R_{tm} lower than that of pellets comprising high content of the binder. Hence the higher the polymer load the higher was the surface roughness of the pellets.

The shape and the surface structure of the pellets were observed by scanning electron microscopy. The three-dimensional representations of the surface of the pellets derived from the surface roughness analysis (not presented) were also an important tool supporting the visual analysis. Pellets comprising low chitosan load prepared with binding liquid type A (Fig. 4) were dumbbells except for pellets L3A that demonstrated an improvement in shape although still ellipsoid, probably because of some resistance to be spheronized. The surfaces of pellets L1A and L3A were visually rough showing macropores and fissures,

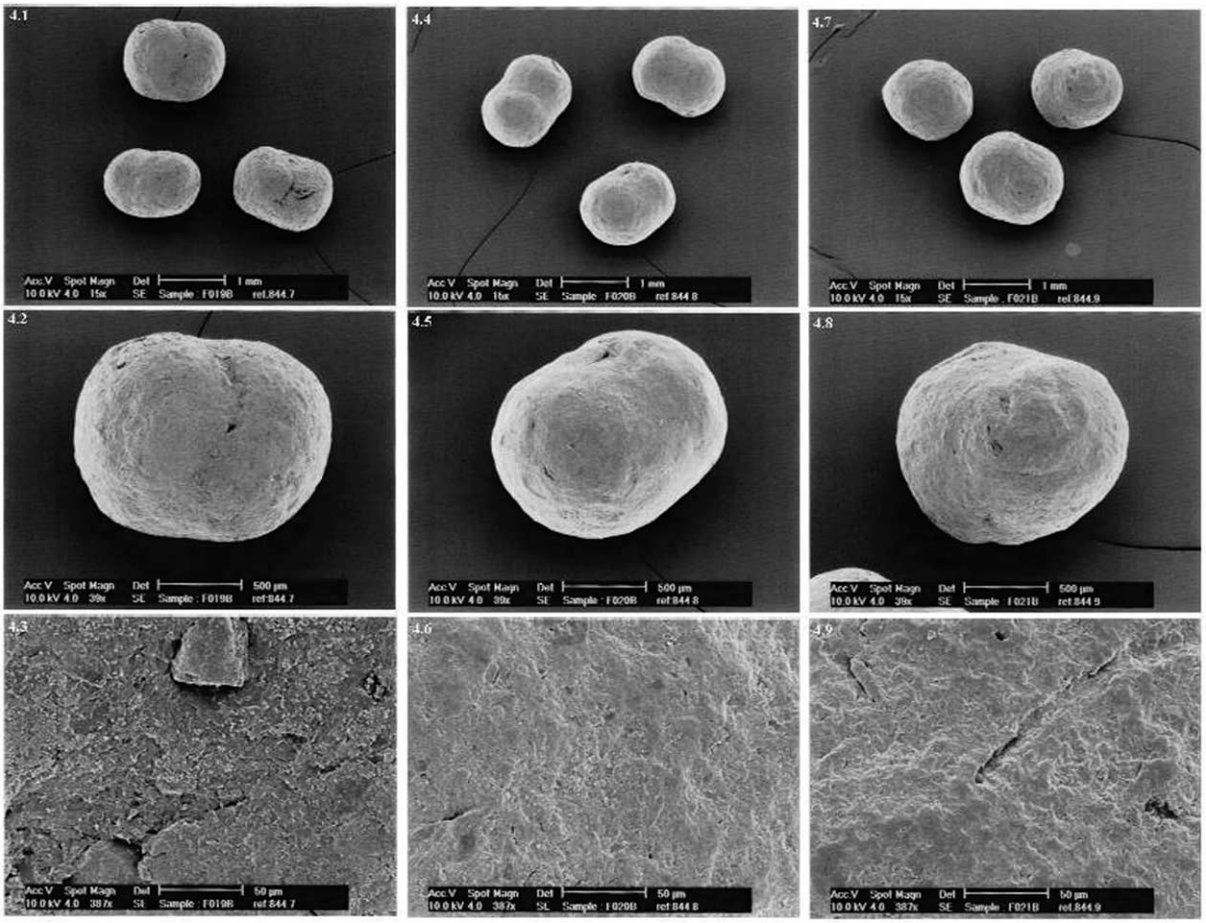


Fig. 4. SEM micrographs of pellets comprising low chitosan load level prepared with binding liquid type A, comprising lactose (4.1–4.3), tribasic calcium phosphate (4.4–4.6), β-cyclodextrin (4.7–4.9) at different magnifications (15 × —4.1; 4.4; 4.7; 39 × —4.2; 4.5; 4.8 and 387 × —4.3; 4.6; 4.9).

which accounted for the high surface roughness parameter R_{tm} (13.135 and 14.870 μm, respectively). The micrographs of pellets L1A revealed signs of coalescence of smaller particles on the surface. This could have yielded not only high surface roughness but also deviation of the shape factor e_R from the ideal round shape. Pellets L2A showed an improvement in the smoothness and contrary to what was observed for pellets comprising lactose, smaller particles composed the surface structure of these pellets. Such observations have enabled confirmation of the differences in surface roughness parameter R_{tm}. Micrographs of the pellets comprising low chitosan loading prepared with binding liquid B (Fig. 5) revealed an enhancement in shape and roughness. Pellets L2B were visually more spherical than pellets L1B and L3B despite their lower shape factor. The surface structures of these pellets L1B, L2B and L3B resembled each other although the surface of pellets L2B was regularly uniform thus supporting its surface roughness parameter R_{tm}. Pellets comprising high chitosan load prepared with binding liquid type A (Fig. 6) were more spherical. Micrographs showed shape irregularities that probably led to the deviation of the shape factor e_R. Nevertheless, pellets H2A were visually rounder although pellets H3A gave higher values

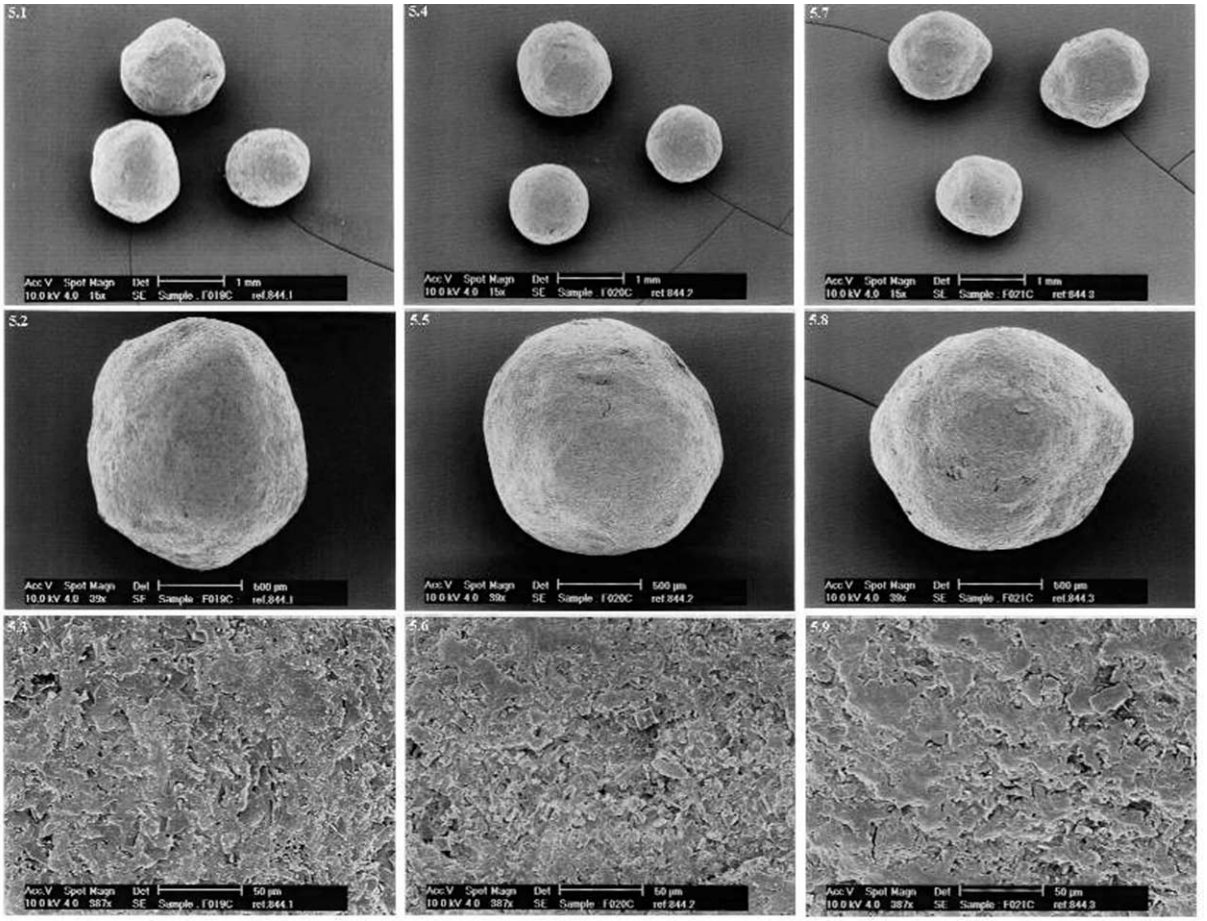


Fig. 5. SEM micrographs of pellets comprising low chitosan load level prepared with binding liquid type A, comprising lactose (5.1–5.3), tribasic calcium phosphate (5.4–5.6), β-cyclodextrin (5.7–5.9) at different magnifications (15 × —5.1; 5.4; 5.7; 39 × —5.2; 5.5; 5.8 and 387 × —5.3; 5.6; 5.9).

for the shape factor e_R. The surfaces of these pellets revealed to be rough showing fissures and cracks. The detailed picture in Fig. 6 shows the considerable dimension of such cracks. These features explained the high surface roughness parameter R_{tm} obtained for these pellets. Moreover, in large magnification view of this surface (Fig. 6), great particles possibly of lactose could be seen. The surfaces of these pellets were visually rougher and more uneven than those comprising low chitosan loading. This is probably due to the higher amount of chitosan in the formulation. Similar formulations prepared with binding liquid type B (Fig. 7) were slightly rounder. The surfaces of these pellets resembled each other; structurally they can be regarded to have the same features. Micrographs revealed that surface roughness also improved compared with former formulations. However, a closer examination of the surface revealed a myriad of tiny pores throughout the surface of the pellets. This unevenness was more apparent than in pellets comprising low chitosan load prepared with binding liquid type A. Once again, the surface unevenness seemed to be related to the amount of chitosan and to the type of binding liquid, which supported the significant statistical difference of surface roughness parameter R_{tm} observed between these two factors.

When pellets were subjected to dissolution testing (phosphate buffer pH 7.4 as the medium)

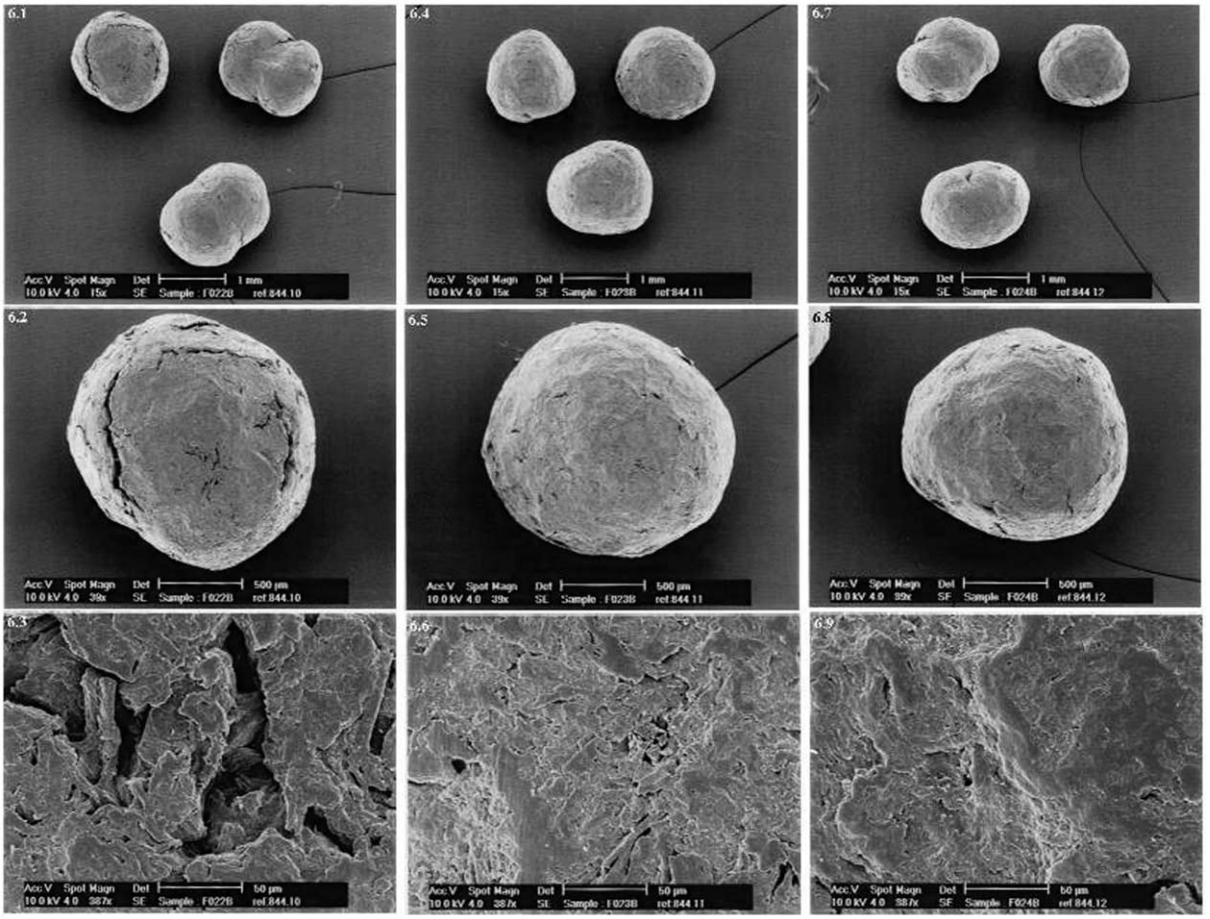


Fig. 6. SEM micrographs of pellets comprising low chitosan load level prepared with binding liquid type A, comprising lactose (6.1–6.3), tribasic calcium phosphate (6.4–6.6), β-cyclodextrin (6.7–6.9) at different magnifications (15 × —6.1; 6.4; 6.7; 39 × —6.2; 6.5; 6.8 and 387 × —6.3; 6.6; 6.9).

the model drug was promptly released, and no distinctive differences were noticed between control and chitosan formulations (Fig. 8). The experiment revealed no visible swelling or increase in size of the pellets. The most interesting finding was that the pellets did not disintegrate during dissolution. On the contrary, after completion of dissolution tests (720 min), pellets were observed to be intact, the integrity of the structure was visually maintained. In a previous work, Tapia et al., 1993 assessed the sustained release property of pellets with chitosan included in the formulation as a solution during the preparation of wet masses. The Sea Cure® 242 chitosan grade (Protan Ind., viscosity 20–200 mPa × s, although not mentioned in the text), a medium molecular weight chitosan was employed in the experiment and a significant retardant effect on the release of the model drug (diclofenac sodium) was observed due to the polymer when undertaking dissolution test in phosphate buffer pH 7.4. Similarly as observed in this present report, Tapia et al., 1993 noticed no visible increase in size or swelling of the pellets during dissolution (disintegration was not mentioned), which they ascribed to the small proportion of the polymer in the formulation. According to reports mentioned in this text a collapse of pellet structure would have been expected because

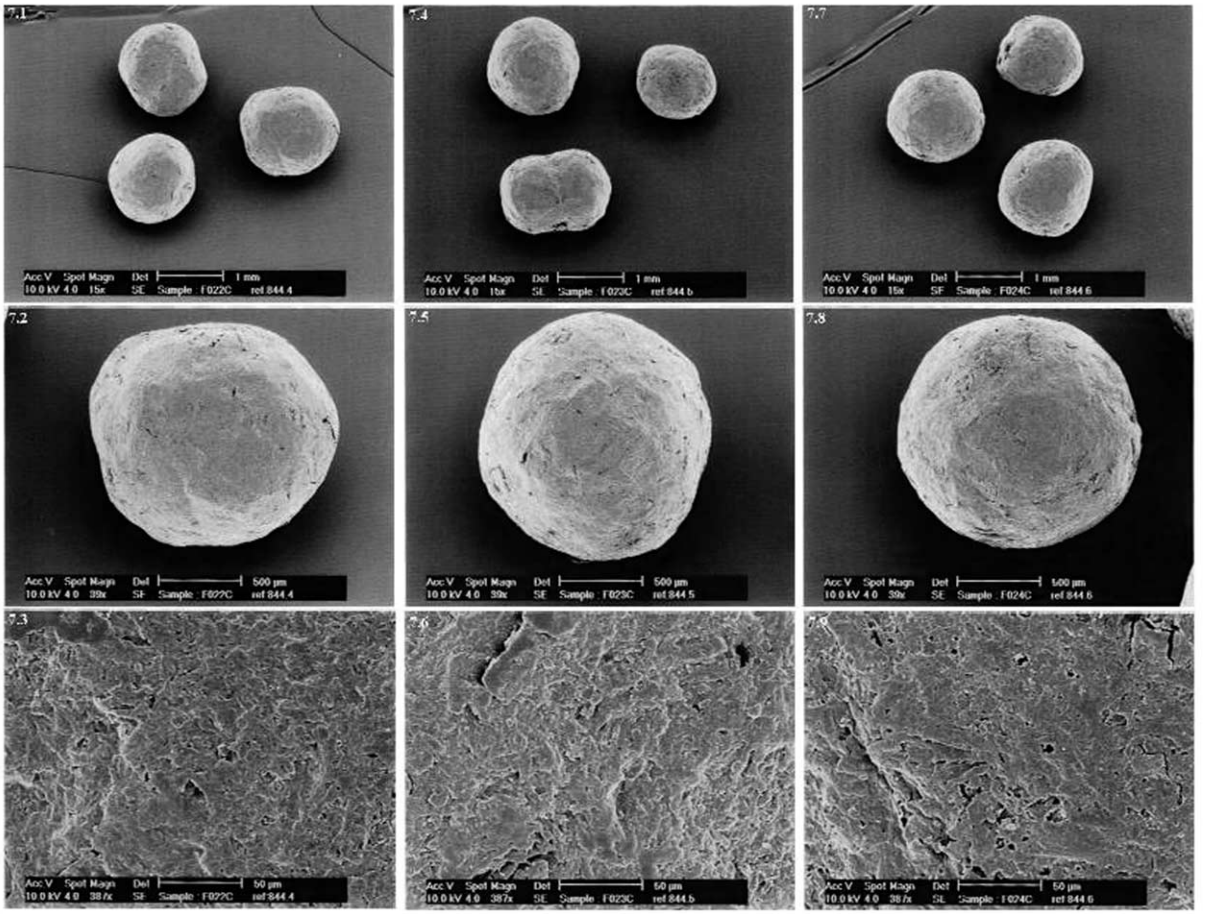


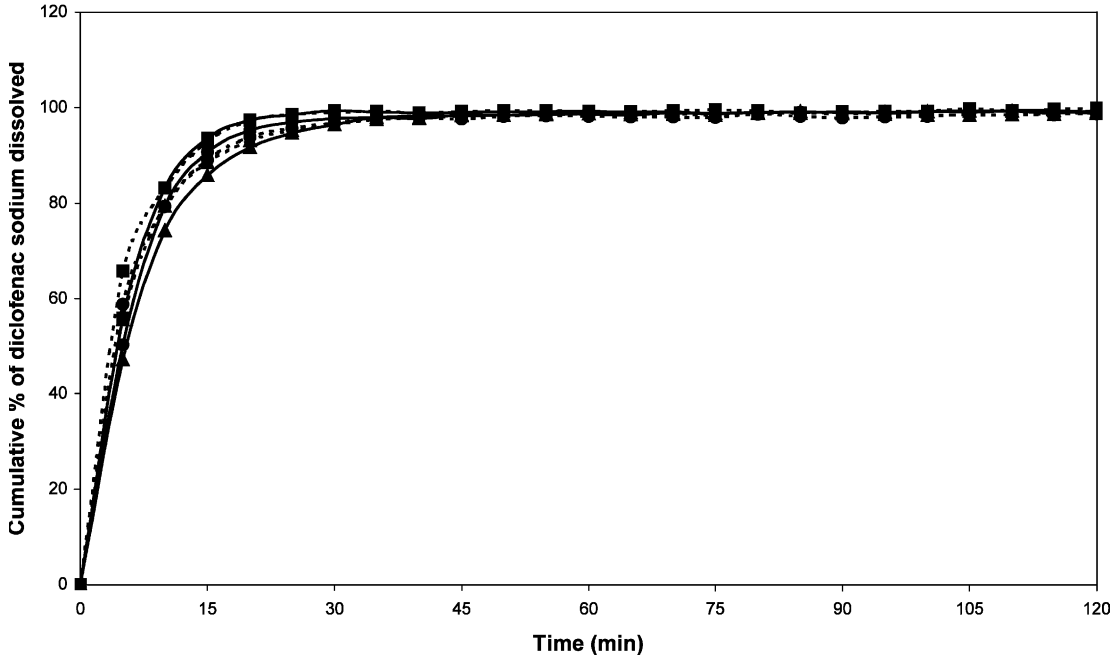
Fig. 7. SEM micrographs of pellets comprising high chitosan load level prepared with binding liquid type B, comprising lactose (7.1–7.3), tribasic calcium phosphate (7.4–7.6), β-cyclodextrin (7.7–7.9) at different magnifications (15 × —7.1; 7.4; 7.7; 39 × —7.2; 7.5; 7.8 and 387 × —7.3; 7.6; 7.9).

of the reported disintegrant effect of chitosan. However, this present report observed the maintenance of the multi unit dosage form. In order to reduce disintegration of the dosage form Nigalaye et al., 1990 suggested the use of the binder carbomer 934P in association with chitosan obtaining the intended results. Hereto, povidone was primarily included, as mentioned before, as a binder to impart consistency of wet mass allowing the extrusion–spheronisation process although according to what was observed during dissolution test, it could be inferred that povidone may also have led to the reduction of the disintegrating activity of chitosan, or even counteracted this property allowing the pellet structure to be preserved during dissolution.

4. Conclusion

The extrusion–spheronisation of wet masses comprising chitosan revealed the need of an additional binder to impart consistency thus improving the process. On that purpose, povidone was included as a secondary binder, which effectively allowed the production of pellets applying ethanolic solutions as the binding liquid. The use of chitosan in the formulations enhanced the

(8.1)



(8.2)

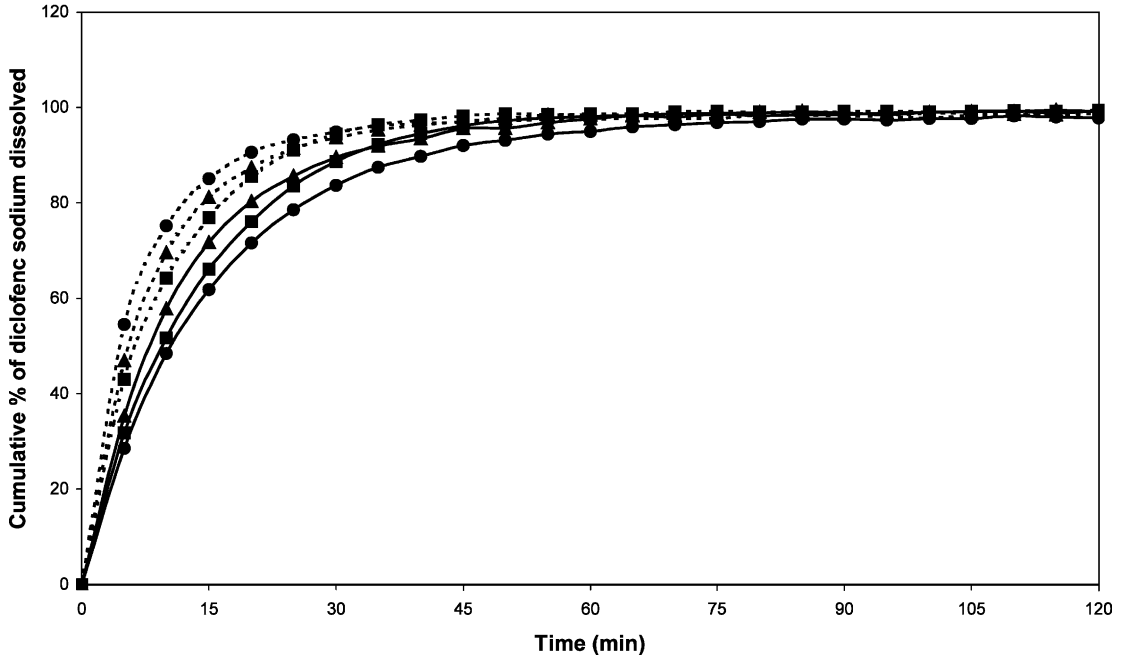


Fig. 8. Cumulative dissolution profile for pellets comprising lactose (8.1), tribasic calcium phosphate (8.2) and β-cyclodextrin (8.3) at different chitosan load levels (zero ■, low ●, and high ▲) and prepared with different binding liquids (type A —, and type B ····).

(8.3)

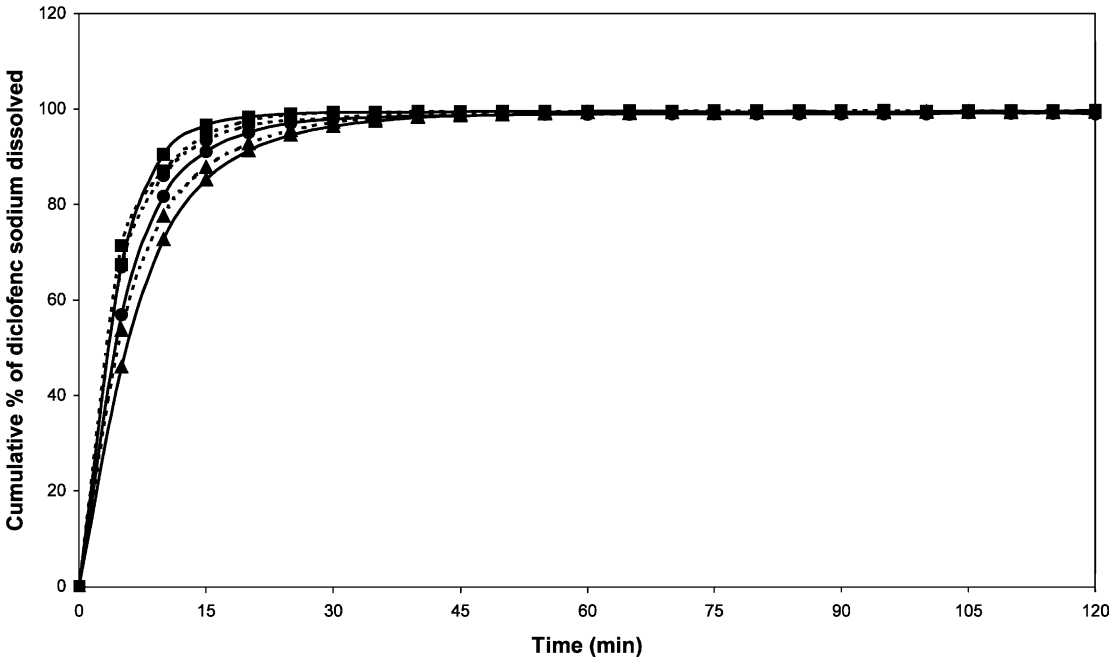


Fig. 8 (*Continued*)

strength of the resultant pellets and acceptable physical characteristics (e.g. shape factor e_R) were successfully achieved when using an ethanol/water mixture of 50% v/v. The composition of the binding liquid had no direct effect on the porosity of the pellets, however, the solubility of the filler excipients in the binding liquid influenced this property. The experiment revealed that as the fraction of water increased in the composition of the binding liquid, pellets were mechanically stronger. The increase in chitosan content in the formulation affected negatively the density and the tensile strength of the resultant pellets. Tribasic calcium phosphate, here the less soluble filler in the binding liquid resulted in most porous pellets. In terms of sphericity, only the composition of the binding liquid revealed to have an influence on the shape factor of the pellets. The best results were obtained when applying binding liquid type B (ethanol/water 50% v/v). The inclusion of povidone in the formulation was important not only for the production of pellets imparting the consistency of wet masses for extrusion–spheronisation, but also allowed the preservation of the structure of the pellets counteracting the disintegration properties of the hydrophilic polymer chitosan. Acceptable dissolution profiles meeting controlled release requirements were not achieved, even for high chitosan load the release of the active drug from the pellets was not retarded. It seemed that chitosan does not swell promptly in order to ensure formation of a gel-like structure that would sustain the release of the model drug. Other reasons could be that the concentrations of chitosan employed in the experiment were not sufficient to guarantee the formation of the gel layer. This could be related to the physical characteristics of chitosan used, such as its low molecular weight and viscosity (80 Mpa $\times$ s). Contrary to literature reports cited, the pellets produced remained intact during the dissolution studies in aqueous medium of pH 7.4.

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