Drug Development and Industrial Pharmacy, 34:199–205, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701539974

informa
healthcare

Masking of Unpleasant Gustatory Sensation by Cross-Linking of Dehydrated Paracetamol Alginate Pellets Produced by Extrusion-Spheronization

Rajesh B. Kulkarni and Purnima D. Amin

Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, University of Mumbai, Mumbai, India

Alginate paracetamol pellets were prepared by extrusion-spheronization process. The process variables studied were wet mass mixing time, feed rate, die opening diameter, spheronization residence time, feed rate, disk speed, and drying. The formulation variables studied were granulation fluid composition and level and drug-to-excipient ratios. The dried pellets were cross-linked with calcium chloride solution. The cross-linked pellets were evaluated for dissolution test, friability test, sphericity, flow behavior, particle size distribution, aggregation, water uptake, drug entrapment, and yield. Gustatory sensation test exhibited successful taste-masking of paracetamol by present approach.

Keywords taste masking; gustatory sensation test; paracetamol; sodium alginate

INTRODUCTION

Pellets as a drug delivery system offer therapeutic advantages, such as less irritation of the gastrointestinal tract (GIT); lowered risk of adverse effects due to dose dumping in modified release products; targeted delivery to a particular site(s) within the GIT; improved absorption through GIT (as it disperses freely in the GIT); reduced harmful effects of certain drugs by making a small amount of drug available in a single pellet; reproducibility of the drug blood levels; and reduced inter- and intrasubject variability. They offer technological advantages such as better flow properties, less friable dosage form, narrow particle size distribution, and uniform packing. They also possesses advantages over granules, such as reduced particle agglomeration, higher mechanical strength, suitability for coating due to spherical shape of pellets, and achieving a specific dissolution profile (Erkoboni, 2003; Vervaet, Baert, & Remon, 1995).

Address correspondence to Purnima D. Amin, Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, N. P. Marg, Matunga, Mumbai-400 019, India. E-mail: kulkarnirajeshb@yahoo.co.in

Pellets are evaluated for parameters like mechanical properties (like viscoelasticity and deformability) (Bashaiwoldu, Podczeck, & Newton, 2004); influence of formulation variables on strength, density, sphericity (Chopra, Alderborn, Podczeck, & Newton, 2002; Eriksson, Alderborn, Nystrom, Podczeck, & Newton, 1997; Hileman, Goskonda, Spalitto, & Upadrashta, 1993; Newton, Chapman, & Rowe, 1995; Santos, Veiga, Pina, Podczeck, & Sousa, 2002), and surface roughness (Podczeck & Newton, 1995); and friability (Howard, Neau, & Sack, 2006).

Drug and calcium alginate matrices are currently prepared by spraying or dropping an alginate drug aqueous dispersion into a bath of calcium chloride solution for cross-linking (Bodmeier & Wang, 1993; Rubio & Ghaly, 1994). However, the method has many drawbacks, which have been reported by Mukhopadhyay, Reid, Saville, and Tucker (2005). The authors have also reported cross-linking of dried drug alginate granules using calcium chloride and applicability of the method to industrial scale-up. However, flow behavior, particle size distribution, and mechanical strength need to be studied, as they are essential parameters for industrial scale-up. Sriamornsak and colleagues (Sriamornsak & Kennedy, 2006; Sriamornsak, Burton, & Kennedy, 2006) have developed calcium alginate gel–coated pellets by forming insoluble gel coat with emphasis on sustained dissolution. This differs from present work in that, in the reported work, calcium salt was incorporated in pellets for the purpose of coating with polysaccharide, while in the present work a bath of calcium salt solution was employed externally as a cross-linking agent for dried sodium alginate pellets. The purpose of the present study was not to coat pellets with gel but to use them as a matrix for taste-masking. Cham, Huey, and Heng (2006) have investigated mechanisms of external and internal gelation of alginate for coating and encapsulation purposes. Cross-linking mechanism of sodium alginate using calcium ion has been reported (Chan, Jin, & Heng, 2002). Chatchawalsaisin, Podczeck, and Newton (2004) have studied the influence of chitosan and sodium alginate on the properties of uncross-linked pellets. Takeuchi, Yasuji,

Yamamoto, and Kawashima (2000) have reported dry-coated tablets with sodium alginate as a release-retarding agent for formulating controlled-release dosage form. Effect of cross-linking with calcium on diffusion of paracetamol in alginate gels has been reported (Aslani & Kennedy, 1996). Amidated low methoxylated pectin has been used, similar to present study, for cross-linking in dried state with calcium ion solution (Tho, Sande, & Kleinebudde, 2005).

Apart from cross-linking of dried drug-alginate granules (Mukhopadhyay et al., 2005) there has been no work dealing with cross-linking of pellets containing drug produced by extrusion-spheronization technique. This article describes research on the cross-linking of dried paracetamol sodium alginate pellets produced by extrusion-spheronization process. The cross-linked pellets were evaluated in terms of aggregation behavior, water uptake during cross-linking, yield, drug entrapment, dissolution test, friability, roundness (sphericity), flow properties, and extent of unpleasant gustatory sensation–masking test.

MATERIALS AND METHODS

Materials

Paracetamol (sodium: absent; calcium: absent) was obtained as a gift sample from Bajaj Healthcare Ltd., Mumbai, India. Manugel® LBA (sodium alginate, 400 mPas, calcium 0.1%, sodium 12% based on dry weight) was gifted by Anshul, Mumbai, India. Microcrystalline cellulose (Avicel® PH 101) and colloidal microcrystalline cellulose (95%) and sodium carboxymethylcellulose (5%) combination (Avicel® RC 591) were gifted by Signet Chemical Corporation, Mumbai, India. Calcium chloride dihydrate was purchased from Ranbaxy Laboratories Ltd., S. A. S. Nagar, India. All other materials used were of analytical grade.

Methods

Pre-Treatment Pellets Preparation

The extrusion-spheronization process parameters were optimized in terms of granulation fluid level, wet mass mixing time, feed rate, die opening diameter, spheronization residence time, disk speed, and drying (use of fluidized bed dryer, tray dryer, and oven drying). The formulation variables like drug:Avicel® PH101:Avicel® RC 591 ratio and granulation fluid composition, that is, water:polysorbate 80 ratio, were also optimized (data not shown). The optimized process and formula are described below.

Paracetamol (25%), Manugel® LBA (25%), Avicel® PH 101 (35%), and Avicel® RC 591 (15%) were dry mixed in a Hobart planetary mixer for 5 minutes. Avicel® PH 101 was used as a spheronizing aid. A mixture of purified water and polysorbate 80 (as a lubricant for extrusion) (Mesiha & Valles, 1993) (99.8:0.2) was added as the wet massing fluid (0.4 mL/g) to form wetted mass for extrusion. The wetted mass was further mixed for 1 minute and then passed through axial single screw extruder (Naomi Enterprise, Mumbai, India) equipped with 0.8-mm aperture diameter screen with L/R ratio of 1.7, where L is thickness of screen and R is radius of screen aperture (Vervaet et al., 1995). The extruder rate was maintained at 50 rpm. The extrudates were collected on butcher paper. The extrudates were spheronized for 300 seconds in a spheronizer (R. R. Enterprises, Thane, India) fitted with a cross-hatched plate with length of each groove of 2 mm. The spheronizer rate was maintained at 750 rpm. The contents emptied from the spheronizer were dried in an Aeromatic fluidized bed dryer at 50°C for 30 minutes. All experiments were carried out in triplicate.

Cross-Linking Treatment of Pellets

The cross-linking of pellets was carried out in a beaker of 250 mL capacity with a paddle-type stirrer shaft dipped in it at 25° to 30°C. The stirrer blade was 2.5 cm above the bottom of the vessel. The pellets (W_3 = 100 g) were immersed in 5% calcium chloride solution (100 mL) at a stirrer speed of 25 rpm for 30 seconds (these parameters were considered to be optimum in the previous study by Mukhopadhyay and colleagues [2005]). At the end of the treatment process, the wet pellets were filtered through 0.2-mm nylon membrane filter under suction for 60 seconds. Cross-linked pellets were dried at 60°C for 12 hours. The weights of the wet pellets before (W_1) and after drying (W_2) were determined. All experiments were carried out in triplicate.

Water Uptake, Yield, and Drug Entrapment in Cross-Linked Pellets

Water uptake (WU) was determined as:

$$WU = [(W_1 - W_2) / W_2] \times 100$$

The yield as a percentage was determined as:

$$\text{Yield} = (W_2 / W_3) \times 100$$

Drug entrapment was estimated by spectrophotometric assay (λ_{max} = 247 nm) after extraction of drug from pellets (n = 3) in methanol under stirring followed by suitable dilution in methanol to concentration of 5 ppm. The quantity of drug entrapped (DE) was given by:

$$DE = 100 \times ([\text{amount of drug in } W_2 \text{ g pellets}] / [\text{amount of drug in } W_3 \text{ g pellets}])$$

Aggregation Behavior

Aggregation behavior was determined as described previously in the literature (Mukhopadhyay et al., 2005). In short, a

weighed quantity of cross-linked pellets was pressed with a spatula on a glass slide to determine whether individual pellets could be separated. All experiments were carried out in triplicate.

Dissolution, Friability, Roundness (Sphericity), Flow Behavior, and Particle Size Analysis of Cross-Linked Pellets

Dissolution test of cross-linked pellets was carried out as per USP 29 procedure for acetaminophen capsules. USP II dissolution test apparatus (Electrolab, Mumbai, India) was used for the test. Pellets equivalent to containing 500 mg drug (2.105 g) (calculated from percent drug entrapment after cross-linking) was taken as unit dose. The dissolution test for pellets was carried out using 900 mL water as the medium and rotating the paddle at 50 rpm for 45 minutes.

Friability test ($n = 3$) was performed using a Roche friabilator. A pre-weighed sample (5 g, 16/25 mesh fraction) was placed in the friabilator along with 25 steel balls, each 2 mm in diameter. After 100 revolutions at 25 rpm the mass retained on the 25-mesh sieve was weighed and the friability was calculated as the percentage loss of mass between the initial and final weights of each bead sample (Howard et al., 2006).

Sphericity of the pellets was determined as described in the literature (Hileman et al., 1993). Briefly, it was determined by assigning a rank score, with 1.0 being very spherical and 12 being a cylinder. When two different scores were obtained, rank scores were averaged.

Flow behavior was assessed in terms of parameters like angle of repose, fluffy bulk density, tapped bulk density (Woodruff & Nuessle, 1972), Carr's index, and Hausner ratio (Stainforth, 1988), as reported previously.

Particle size analysis was carried out by sieve analysis (Woodruff & Nuessle, 1972).

Gustatory Sensation Test

Gustatory sensation test was performed by modifying a previously described method (Tokuyama et al., 2006). In brief, quinine hydrochloride solution 1 mM was considered as a standard for bitterness with a bitterness score of 5 and purified water as 0. The human volunteer study was done according to ethical guidelines for biomedical research on human subjects by the Indian Council of Medical Research (ICMR) (http://www.icmr.nic.in/ethical.pdf). The protocol for the test was approved by the institutional ethical committee. The test was performed with 10 well-trained volunteers. The cross-linked paracetamol pellets were rated between 0 and 5 depending upon the intensity of bitterness, 0 being tasteless and 5 very bitter. After tasting each sample, volunteers gargled well and waited for at least 20 minutes before tasting the next sample.

Statistical Analysis

The results were expressed as mean values ± SD. The Student t-test was applied to examine significance of difference. In all cases $p < .05$ was considered to be significant.

RESULTS AND DISCUSSION

Introduction

In the present work, steps in the pellet manufacturing process were: (1) dry mixing; (2) wet granulation; (3) extrusion; (4) spheronization; (5) drying; and (6) cross-linking (including immersing pellets in calcium chloride solution, filtration, and drying).

Pre-Treatment Pellets Preparation

The mixing time of the powder blend with granulating fluid was optimized. The amount of granulating fluid needed was also optimized (0.4 mL/g of dry blend) in terms of extrudate desirable characteristics (discussed later), and was found to be greater than that used for tabletting granulation. Overgranulation (when the amount of granulating fluid used was more than 0.4 mL/g of the dry blend) caused sticking of the extrudates to each other that could not be processed further, and employing lesser granulating fluid (less than 0.4 mL/g of the dry blend) formed extrudates of poor mechanical strength and consequently low pellet yield. Granulating fluid at the extrudate and die interface acted as a lubricant and facilitated the movement of the extrudates through the die, which was evident from lesser extrusion force required when granulating fluid level was increased. Granulation time was kept longer during the initial stages of formulation development, prior to optimization, as recommended by Erkoboni (2003). The granulation time was optimized in terms of desirable properties of extrudates (like length, reduced shark-skin effect, and low extrusion force). The optimum granulation time was found to be 1 minute. The extrudates produced were plastic enough to deform and did not adhere to each other when collected or rolled in the spheronizer. The surface impairments of extrudates like roughness and shark skinning have been reported to increase at a higher extrusion speed as well as when the stress at the wall of the die perforations increases with increasing thickness (i.e., higher L/R ratio) of the extrusion screen or as the granulating fluid content of the formulation decreases (Harrison, Newton, & Rowe, 1985a, 1985b). It was indeed found to be the situation and therefore the lower L/R ratio (1.7) screen was found to be suitable for getting extrudates with desirable properties, which have been mentioned above. However, this observation was contradictory to that reported by Baert, Remon, Elbers, and Van Bommel (1993). Further, employing extrusion speed of 50 rpm and granulating fluid content of 0.4 mL/g of dry blend produced extrudates with no surface roughness as well as shark skin effect. Harrison and colleagues (1984, 1985a) have reported that under high stress, that is, more requirement of extrusion force associated with low granulating fluid content, high L/R ratio and absence of lubricant (like polysorbate 80 used in the present study), causes rough surface in moderate cases and shark skinning in more severe cases, which is further in agreement with the results of the

present study. Some researchers (O'Conner & Schwartz, 1989) have indicated that pellets having acceptable properties can be produced from extrudates having shark skinning, attributed to the fact that shark skinning facilitates the breakage of the extrudates during the spheronization step. This is in agreement with our observation of pellet qualities produced in various batches (data pertaining to optimized batch only has been shown). Higher granulating fluid content caused agglomeration of pellets and no product roping effect during spheronization process was observed. Lesser granulating fluid reduced the yield of the pellets. Increase in spheronization speed (800 to 1,200 rpm) and spheronization residence time (more than 300 seconds) also caused agglomeration, specifically increased pellet diameter. Higher disk speed and longer residence time during spheronization increased the coarser fraction and the mean diameter and decreased the fine fraction. Conversely, lower disk speed and shorter residence time during spheronization produced cylindrical- or dumbbell-shaped particles. Therefore, disk speed of 750 rpm and spheronization residence time of 300 seconds were considered to be optimum conditions for spheronization, which produced spherical pellets with narrow particle size distribution (Figure 1). Friability (1.5% to 12%) of pellets decreased with increasing spheronization residence time. The effect was similar to that reported by O'Conner and Schwartz (1989). Fluidized bed dryer was used for drying due to its efficient processing and its requiring less time than a hot air oven.

Cross-Linking Treatment of Pellets

No studies have been reported so far to cross-link dry drug alginate pellets produced by extrusion-spheronization technology. In this study, the parameters found optimal in the previous work by Mukhopadhyay and colleagues (2005) for cross-linking paracetamol alginate granules in dehydrated state were kept constant, as studying these parameters (like calcium concentration, agitation rate during cross-linking, temperature during cross-linking, and moisture content of uncross-linked granules) would be repetitive and obvious. Instead, emphasis was on other parameters, like masking of unpleasant gustatory sensation, water uptake, yield, drug entrapment, and dissolution (to be discussed later). Briefly, during cross-linking treatment of dried drug alginate pellets, an insoluble calcium alginate layer is formed when pellets first come in contact with cross-linking agent (calcium chloride in present case). Calcium ion cross-links the polymer chains by its bond to polycarboxylic acid group present in sodium alginate. Conformational changes of polymer chain due to the cross-linking slow the diffusion of calcium ion into the interior of the matrix and thus leading to stoppage of cross-linking process (Julian, Radebaugh, & Wisniewski, 1988). This also supports the finding that longer cross-linking time is unnecessary and that it may further reduce drug entrapment by promoting diffusion of the drug through matrix into calcium chloride solution bath. Dried alginate pellets treated with calcium chloride solution for 30 seconds for cross-linking showed satisfactory taste masking and dissolution. The drug loss during treatment weakens the matrix and thereby reduces the yield due to erosion of the porous polymer mass (Mukhopadhyay et al.). The use of optimized concentration of cross-linking agent (5% calcium chloride) also reduced pellet aggregation.

Evaluation of Pellets

The pellets were complying with limit of at least 75% of dissolution of the drug in 45 minutes as mentioned in USP 29 monograph for acetaminophen capsules (Figure 2). Relatively low dissolution of the drug (93.854% ± 4.215% in 45 minutes) was considered to be due to the incorporation of Avicel® RC 591. This finding is in conformity with that described by Ghali, Klinger, and Schwartz (1989), who stated that because of the

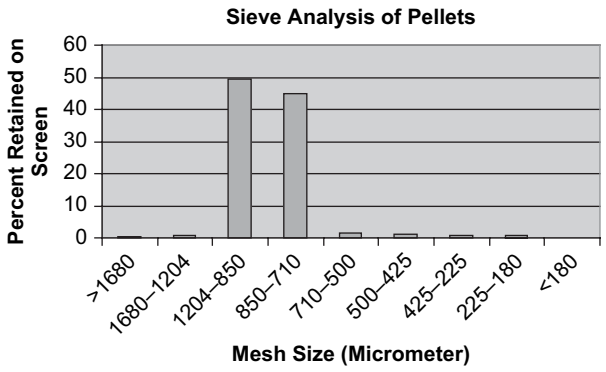

FIGURE 1. Sieve analysis of cross-linked paracetamol alginate pellets expressed as weight percent retained on screen of optimized batch.

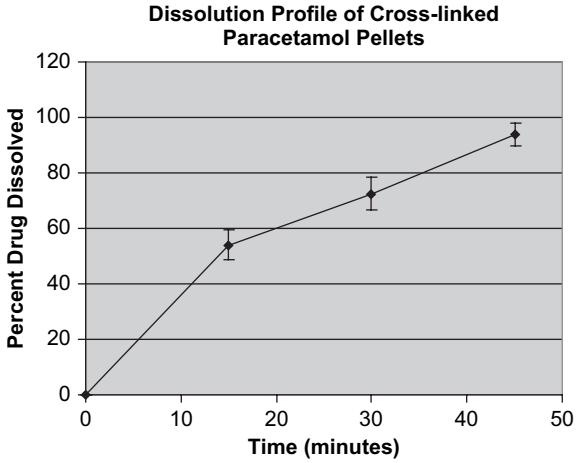

FIGURE 2. Dissolution profile of cross-linked paracetamol pellets. The error bars represent the SD of the mean.

formation of gel-like structure in water due to the presence of sodium carboxymethylcellulose in the RC and CL types of Avicel® slowed the he dissolution of the drugs. However, in the present study, Avicel® RC 591 was incorporated in pellets to reduce diffusion of drug (the drug having 14.28 mg/mL solubility in water [El-Obeid & Al-Badr, 1985]) into calcium chloride solution bath during cross-linking.

Water uptake by the pellets was 150% ± 3.05%. The water uptake during treatment was reproducible. The average pellet yield was found to be 96% ± 2.1%. The drug entrapment was 95% ± 4.2%, which was higher than previously reported data for granules (Mukhopadhyay et al., 2005). It might be due to the incorporation of Avicel® RC 591 retarding drug diffusion from pellets (Ghali et al., 1989) to calcium chloride bath, and thus retaining drug within pellet as microcrystalline cellulose has been reported to have binding action (Chilamkurti, Rhodes, & Schwartz, 1982).

Aggregation value of 1% ± 0.05% of pellets was observed, which was not significant. Aggregated pellets could be separated easily so it is unlikely to pose any practical separation problems during preparation.

The results of the friability, roundness, and flow behavior are depicted in Table 1. Friability of pellets is influenced by spheronization residence time, speed (Erkoboni, 2003), calcium cross-linking treatment time, and calcium concentration (Mukhopadhyay et al., 2005). The optimized formulation showed lower friability values than those that have been reported abundantly in the literature (Bianchini, Bruni, Gazzaniga, & Vecchio, 1992; Howard et al., 2006; Malinowski & Smith, 1975; Mesiha & Valles, 1993; O'Connor & Schwartz, 1985; Zhang, Schwartz, Schnaare, Wigent, & Sugita, 1991) and which may also be attributed to the presence of Avicel® RC 591 having strong binding property.

Free surface of the static heap of powder, when gravity is the only external force acting upon it, can assume various forms, but one limitation persists: the angle to the horizontal cannot exceed a certain value, which is known as angle of repose. Difference between tapped bulk density and aerated bulk density indicates cohesiveness of the powder and the greater the difference, the more cohesive the powder and poorer the flow and vice versa (Stainforth, 1988). However, in this study the flow properties, as evident from the values shown in Table 1, indicate that flow behavior of the optimized formulation is good and thus aids in downstream pharmaceutical processes like filling in sachet or capsule and further reduces weight variation.

TABLE 1
Measurement of Angle of Repose, Aerated Bulk Density, Tapped Bulk Density, Carr's Index, Hausner Ratio, and Sphericity of Cross-Linked Pellets

Parameter	Values
Angle of repose	27° 22′
Aerated bulk density	0.71 g/cm^3
Tapped bulk density	0.82 g/cm^3
Carr's index	13.41
Hausner ratio	1.15
Friability	1.5% ± 0.05%
Sphericity (n = 30)	2 ± 0.15

Sphericity is one of the most important properties of the pellet and is also related to flow properties (Woodruff & Nuessle, 1972). Determination of sphericity by visual inspection, the simplest and most economical method, even though it lacks sharpness and sensitivity (Hileman et al., 1993), was used in the present study. The sphericity value of about 2 (Table 1) indicates excellent sphericity of the optimized formulation, and thus the formulation was found to be suitable for coating process, as compared with other formulations (sphericity values between 2 and 12).

Particle size distribution by sieve analysis of pellets was as shown in Figure 1. The histogram (Figure 1) of sieve analysis of pellets indicates Gaussian distribution without skewness. It also indicates that the particles produced had narrow particle size distribution, major percentage of pellets being in the range of 1,204 to 710 micrometers, which is the usable yield size range (Howard et al., 2006). The factors determining particle size distribution of pellets produced by extrusion-spheronization have been reviewed previously (Vervaet et al., 1995).

Gustatory Sensation Test

Table 2 shows the gustatory sensation–masking effect in human volunteers. Masking of unpleasant taste by using a matrix-type system has been studied previously (Albertini et al., 2004). However, in the study, matrices were prepared by wet granulation without employing the cross-linking process. In the current study, cross-linked pellets showed no bitter taste as evident from bitterness score (Table 2). The mean bitterness score of 0.3 of the pellets was not significant ($p < .001$). Further, pellets were soft to chew, which may be due to the formation of sodium carboxymethylcellulose gel in presence of saliva. The pellets produced can be coated with sweeteners and flavors to improve palatability. Further, spherical nature of the pellets would produce uniformly coated pellets.

CONCLUSION

Cross-linking of dehydrated paracetamol sodium alginate pellets produced by extrusion-spheronization technique can mask unpleasant taste. The process is simple and can be easily scaled up. The pellets as a drug delivery system can provide additional benefits over granules especially in terms of flow behavior and reduced friability. The pellets produced can be coated uniformly due to their sphericity with flavors and sweeteners so as to improve taste, palatability, and mouthfeel.

TABLE 2
Bitterness Scores Obtained in Human Gustatory Sensation Test of Cross-linked Paracetamol Pellets

Volunteer No.	Bitterness Score
1	1
2	0
3	0
4	1
5	0
6	1
7	0
8	0
9	0
10	0
Mean score	0.3

REFERENCES

Albertini, B., Cavallari, C., Passerini, N., Voinovich, D., Gonzalez-Rodriguez, M. L., Magarotto, L., et al. (2004). Characterization and taste-masking evaluation of acetaminophen granules: Comparison between different preparation methods in a high shear mixer. *Eur. J. Pharm. Sci., 21*, 295–303.

Aslani, P., & Kennedy, R. A. (1996). Studies on diffusion in alginate gels: I. Effect of cross-linking with calcium or zinc ions on diffusion of acetaminophen. *J. Control. Release, 42*, 75–82.

Baert, L., Remon, J. P., Elbers, J. A. C., & Van Bommel, E. M. G. (1993). Comparison between a gravity feed extruder and a twin screw extruder. *Int. J. Pharm., 99*, 7–12.

Bashaiwoldu, A. B., Podczeck, F., & Newton, J. M. (2004). Application of dynamic mechanical analysis (DMA) to determine the mechanical properties of pellets. *Int. J. Pharm., 269*, 329–342.

Bianchini, R., Bruni, G., Gazzaniga, A. and Vecchio, C. (1992). Influence of extrusion-spheronization processing on the physical properties of d-indobufen pellets containing pH adjusters. *Drug Dev. Ind. Pharm., 18*, 1485–15.

Bodmeier, R., & Wang, J. (1993). Microencapsulation of drugs with aqueous colloidal polymer dispersions. *J. Pharm. Sci., 82*, 191–194.

Cham, L. W., Huey, Y. L., & Heng, P. W. S. (2006). Mechanisms of external and internal gelation and their impact on the functions of alginate as a coat and delivery system. *Carbohydrate Polymers, 63*, 176–187.

Chan, L. W., Jin,Y., & Heng, P. W. S. (2002). Cross-linking mechanisms of calcium and zinc in production of alginate microspheres. *Int. J. Pharm., 242*, 255–258.

Chatchawalsaisin, J., Podczeck, F., & Newton, J. M. (2004). The influence of chitosan and sodium alginate and formulation variables on the formation and dissolution from pellets prepared by extrusion/spheronisation. *Int. J. Pharm., 275*, 41–65.

Chilamkurti, R. N., Rhodes, C. T., & Schwartz, J. B. (1982). Some studies on compression properties of tablet matrices using a computerized instrumented press. *Drug. Dev. Ind. Pharm., 8*, 63–86.

Chopra, R., Alderborn, G., Podczeck, F., & Newton, J. M. (2002). The influence of pellet shape and surface properties on the dissolution from uncoated and coated pellets. *Int. J. Pharm., 239*, 171–178.

El-Obeid, H. A., & Al-Badr, A. A. (1985). Profile supplements: Acetaminophen. In: K. Florey, (Ed.), *Analytical profiles of drug substances*, Vol. 14 (pp. 551–596). Academic Press, Inc.

Eriksson, M., Alderborn, G., Nystrom, C., Podczeck, F., & Newton, J. M. (1997). Comparison between and evaluation of some methods for the assessment of the sphericity of pellets. *Int. J. Pharm., 148*, 149–154.

Erkoboni, D. F. (2003). Extrusion/spheronization. In: I. Ghebre-Sellasie and C. Martin (Eds.), *Pharmaceutical extrusion technology* (pp. 277–322). New York: Marcel Dekker.

Ghali, E. S., Klinger, G. H., & Schwartz, J. B. (1989). Modified dissolution from beads prepared with combinations of two grades of microcrystalline cellulose. *Drug Dev. Ind. Pharm., 15*, 1455–1473.

Harrison, P. J., Newton, J. M., & Rowe, R. C. (1984). Convergent flow analysis in the extrusion of wet powder masses. *J. Pharm. Pharmacol., 36*, 796–798.

Harrison, P. J., Newton, J. M., & Rowe, R. C. (1985a). The characterization of wet powder masses suitable for extrusion/spheronisation. *J. Pharm. Pharmacol., 37*, 686–691.

Harrison, P. J., Newton, J. M., & Rowe, R. C. (1985b). Flow defects in wet powder mass extrusion. *J. Pharm. Pharmacol., 37*, 81–83.

Hileman, G. A., Goskonda, S. R., Spalitto, A. J., & Upadrashta, S. M. (1993). A factorial approach to high dose product development by an extrusion-spheronization process. *Drug Dev. Ind. Pharm., 19*, 483–491.

Howard, M. A., Neau, S. H., & Sack, M. J. (2006). PEO and MPEG in high drug load extruded and spheronized beads that are devoid of MCC. *Int. J. Pharm., 307*, 66–76.

Julian, T. N., Radebaugh, G. W., & Wisniewski, S. J. (1988). Permeability characteristics of calcium alginate films. *J. Control. Release, 7*, 165–169.

Kubo, W., Miyazaki, S., & Attwood, D. (2003). Oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulations. *Int. J. Pharm., 258*, 55–64.

Malinowski, H. J., & Smith, W. E. (1975). Use of factorial design to evaluate granulations prepared by spheronization. *J. Pharm. Sci., 64*, 1688–1692.

Mesiha, M. S., & Valles, J. (1993). A screening study of lubricants in wet powder masses suitable for extrusion-spheronization. *Drug Dev. Ind. Pharm., 19*, 943–959.

Mukhopadhyay, D., Reid, M., Saville, D., & Tucker, I. G. (2005). Cross-linking of dried paracetamol alginate granules Part 1: The effect of cross-linking process variables. *Int. J. Pharm., 299*, 134–145.

Newton, J. M, Chapman, S. R., & Rowe, R. C. (1995). The influence of process variables on the preparation and properties of spherical granules by the process of extrusion and spheronisation. *Int. J. Pharm., 120*, 101–109.

O'Conner, R. E., & Schwartz, J. B. (1989). Extrusion and spheronization technology. In: I. Ghebre-Sellasie (Ed.), *Pharmaceutical pelletization technology* (pp. 187–216). New York: Marcel Dekker.

Podczeck, F., & Newton, J. M. (1995). The evaluation of a three-dimensional shape factor for the quantitative assessment of the sphericity and surface roughness of pellets. *Int. J. Pharm., 124*, 253–259.

Rubio, M. R., & Ghali, E. S. (1994). In-vitro release of acetaminophen from sodium alginate controlled release pellets. *Drug Dev. Ind. Pharm., 20*, 1239–1251.

Santos, H., Veiga, F., Pina, M., Podczeck, F., & Sousa, J. (2002). Physical properties of chitosan pellets produced by extrusion-spheronisation: Influence of formulation variables. *Int. J. Pharm., 246*, 153–169.

Sriamornsak, P. Burton, M. A., & Kennedy, R. A. (2006). Development of polysaccharide gel-coated pellets for oral administration 1. physico-mechanical properties. *Int. J. Pharm., 326*, 80–88.

Sriamornsak, P., & Kennedy, R. A. (2006). Development of polysaccharide gel-coated pellets for oral administration 2. Calcium alginate. *Eur. J. Pharm. Sci., 29*(2), 139–147.

Stainforth, J. N. (1988). Powder flow. In M. E. Aulton (Ed.) *Pharmaceutics: The science of dosage form design* (pp. 600–615). London: Churchill Livingstone, Inc.

Takeuchi, H., Yasuji, T., Yamamoto, H., & Kawashima, Y. (2000). Drug releasing properties and tensile strength of dry-coated tablets prepared with spray dried composite particles of lactose and sodium alginate. *STP Pharma. Sci., 10*, 173–179.

Tho, I., Sande, S. A., & Kleinebudde, P. (2005). Cross-linking of amidated low methoxylated pectin with calcium during extrusion/spheronisation: Effect on particle size and shape. *Chemical Engineering Science, 60*, 3899–3907.

Tokuyama, E., Shibasaki, T., Kawabe, H., Mukai, J., Okada, S., & Uchida, T. (2006). Bitterness suppression of BCAA solutions by L-ornithine. *Chem. Pharm. Bull., 54*(9), 1288–1292.

Vervaet, C., Baert, L., & Remon, J. P. (1995). Extrusion-spheronisation A literature review. *Int. J. Pharm., 116*, 131–146.

Woodruff, C. W., & Nuessle, N. O. (1972). Effect of processing variables on particles obtained by extrusion-spheronisation processing. *J. Pharm. Sci., 61*, 787–790.

Zhang, G., Schwartz, J. B., Schnaare, R. L., Wigent, R. J., & Sugita, E. T. (1991). Bead coating: II. Effect of spheronization technique on dissolution from coated spheres. *Drug Dev. Ind. Pharm., 17*, 817–830.