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International Journal of Pharmaceutics 281 (2004) 119–127

international journal of pharmaceutics

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Determination of tackiness of chitosan film-coated pellets exploiting minimum fluidization velocity

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Received 22 January 2004; received in revised form 27 May 2004; accepted 3 June 2004

Abstract

The tackiness of aqueous chitosan film coatings and effects of anti-sticking agents on sticking tendency, were evaluated. A novel rapid method exploiting minimum fluidization velocity to determine tackiness was introduced and tested. The pressure difference over the miniaturized fluidized-bed was precisely recorded as a function of velocity of fluidization air. High molecular weight chitosan plasticized with glycerol was used as a film-forming agent. Magnesium stearate, titanium dioxide, colloidal silicon dioxide and glyceryl-1-monostearate (GMS) were studied as anti-sticking agents. Film coatings were performed in a miniaturized top-spray coater. The incorporation of anti-sticking agents led to a clear decrease in tackiness of the chitosan films, and magnesium stearate and GMS were shown the most effective. Film-coated pellets containing magnesium stearate and GMS as an anti-sticking agent were very easily fluidized (showing very low values of minimum fluidization velocity) and were thus classified as the best flowing and the least sticking samples. Both these additives were found anti-sticking agents of choice for aqueous chitosan film coatings. Determination of the experimental minimum fluidization velocity in a fluidized bed, is a useful and sensitive method of measuring the tackiness tendency of film-coated pellets.

Keywords: Chitosan; Aqueous film coating; Pellets; Tackiness; Anti-sticking agents; Minimum fluidization velocity

1. Introduction

Chitosan, a polysaccharide derived by partial deacetylation of chitin, has been reported as an excipient of choice for a number of pharmaceutical applications (Illum, 1998; Paul and Sharma, 2000). Due to the unique dissolution and gelation characteristics, chitosan has been succesfully exploited in wet granulation as a binding agent, in direct compression as a diluent, in tabletting as a disintegrating agent and in sustained-release matrices as a retarding agent. Its use in novel drug delivery of, e.g., gene and peptide-type drugs and in colon targeting, has been described in recent review articles (Dodane and Vilivalam, 1998; Singla and Chawla, 2001). In spite of well-known gel and film forming characteristics of chitosan, little attention has been paid so far to the potential film coating applications of this poly-

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doi:10.1016/j.ijpharm.2004.06.004

meric material (Ritthidej et al., 2000; Koizumi et al., 2001).

The tackiness of films during coating procedure is a material- and process-related limitation that can result in extensive agglomeration of substrates. This may increase the number of coating defects and impair the yield and quality of the coated batch. Since chitosan has been reported to possess strong binding and mucoadhesive potential (Upadrashtra et al., 1992; Patel et al., 1999), it can be expected that the tackiness or sticking behaviour of this polymer during film coating is evident. It is also known that positive charges of chitosan could give rise to strong electrostatic interactions with negatively charged surfaces (He et al., 1998). During coating with other cellulosic or acrylic polymers, unwanted and irreversible agglomeration due to tackiness of the batch has been reported. This phenomenon was mainly due to the influences of the type of polymer as well as type and concentration of plasticizer (Wesseling et al., 1999). Therefore, effective anti-sticking agents are needed to improve the film coating (Petereit et al., 1995; Wesseling et al., 1999).

Little work has been done on methods that can be used for determining the tackiness or sticking behavior of pharmaceutical polymer films. Wesseling et al. (1999) developed a method, in which force-displacement curves of the detachment process of polymer films were used as a measure for tackiness. The method was suitable to measure the tackiness of cellulosic and acrylic polymer films.

The aim of the present study was to investigate aqueous chitosan film coating of pellets in a miniaturized top-spray coating system with special reference to the effects of anti-sticking agents on tackiness of film coatings. The sticking tendency of the chitosan films was evaluated using a novel rapid method which exploits minimum fluidization velocity.

2. Materials and methods

2.1. Materials

The coating solutions contained high molecular weight chitosan (HMW-chitosan, Sigma–Aldrich, USA), hydroxypropyl methylcellulose (HPMC, Methocel E5, Dow Chemical, USA), acetic acid (Riedel-de Haën, Germany) and glycerol (Ph. Eur.) in purified water. Magnesium stearate (Ph. Eur.), titanium dioxide (TiO_2, Ph. Eur.), colloidal silicon dioxide, Aerosil (SiO_2, Ph. Eur.) and glyceryl-1-monostearate (GMS, Genay, France) were used in the film coating formulations as anti-sticking agents. Polyoxyethylenesorbitan monooleate 80 (Tween 80, Ph. Eur.) was used to enhance the dispersability of GMS in water. The pellet cores for film coatings were prepared by using microcrystalline cellulose (MCC, Emcocel, type 90M, E. Mendell, Nastola, Finland) and lactose monohydrate (LM, Pharmatose, type 80M, DMV International, Veghel, The Netherlands) as fillers, theophylline anhydrous (Ph. Eur.) as a model drug, and purified water as a granulation liquid. For preparing core tablets for contact angle measurements, the following excipients were used: microcrystalline cellulose (MCC, Emcocel, type 90M, E. Mendell, Nastola, Finland), lactose monohydrate (LM, Pharmatose, type 80M, DMV International, Veghel, The Netherlands) as filler materials and magnesium stearate (Ph. Eur.) as a pre-lubricating agent in the die.

2.2. Contact angle measurements

For contact angle measurements, both unplasticized and plasticized aqueous solutions of chitosan at concentrations of 0.5, 1.0 and 1.5% were prepared by dissolving chitosan in diluted acetic acid solution with glycerol. HPMC at 10% (w/w) aqueous solution plasticized with glycerol was used as a reference solution. Two types of tablet preparations with a qualitative composition identical to that of pellet cores were compressed in a Korsch EK-0 single-punch tablet machine (Erweka Apparatebau, Germany) equipped with 13 mm flat-faced-punches and a compression force of 20 kN (Table 1). The tablet height under load was kept constant.

Table 1
Compositions of substrates (core tablets) used in contact angle measurements

Formulation	Composition of core tablets (%)	
	Formulation I	Formulation II
Lactose monohydrate (LM)	99.0	49.5
Microcrystalline cellulose (MCC)	–	49.5
Magnesium stearate	1.0	1.0

Table 2
Matrix of the experimental design and results of contact angles

Experiment no.	Chitosan (%)	Plasticizer[a] (%)	Contact angles (°)	
			Formulation I	Formulation II
1	0.5	0	44.0 ± 2.3	36.1 ± 2.4
2	1.5	0	54.6 ± 1.9	53.1 ± 1.4
3	0.5	20	44.2 ± 2.6	35.9 ± 2.2
4	1.5	20	53.7 ± 0. 9	52.6 ± 1.8
5	1	0	47.6 ± 2.2	43.2 ± 2.1
6	1	20	51.6 ± 1.3	47.4 ± 0.8
7	1	20	54.7 ± 2.5	51.5 ± 2.7
8	1	20	53.7 ± 2.1	49.1 ± 2.0
9	1	20	53.7 ± 1.8	51.5 ± 1.8
Reference solution (HPMC/glycerol)		20	59.7 ± 3.5	53.8 ± 2.7

[a] Percentage (w/w) of the polymer weight.

The contact angles between the solutions and the core tablets were determined by the sessile drop method (Optical Contact Angle Meter CAM 200, KSV Instruments Ltd.). The measurements were repeated ten times for each experiment according to the complete two factorial experimental design (Table 2).

2.3. Film coating of pellets

2.3.1. Preparation of core pellets

The composition of core pellets was as follow: 5% (w/w) theophylline anhydrous, 60% (w/w) MCC and 35% (w/w) LM. Pellets were made with the extrusion/spheronization technique (Nica M6L mixer/granulator; Nica E170 extruder; Nica S320 spheronizer; Nica System AB, Mölndal, Sweden). The pellets were dried for 48 h at room temperature (21 ± 2 °C), and the size fraction ranging from 1.0 to 1.25 mm was used in the subsequent coating experiments. The physical properties of the core pellets are shown in Table 3.

Table 3
Physical properties of core pellets

Property	
Mean size (mm)	0.940
Bulk density (g/cm^3)	0.802 ± 0.001
Tap density (g/cm^3)	0.837 ± 0.007
Carr index (%)	4.2
Hausner ratio	1.0
Moisture content (%)	1.1 ± 0.2

The size and size distribution of the core pellets were determined by sieve analysis with a set of sieves with 1250, 1000, 710, 500, 315, 250 and 125 μm screens and a collector. The moisture content of pellet cores was determined as a loss of weight using an infrared apparatus (Sartorius Thermol Control, Sartorius GmbH, Germany). All measurements were made in triplicate. The Carr index and Hausner ratio were calculated from the tap and bulk densities (Wells and Aulton, 1998).

2.3.2. Film coating experiments

The basic composition of the coating solution was 1.0% of chitosan in aqueous acetic acid (1%) plasticized with glycerol (20% (w/w) of the polymer weight). The coating solutions were applied using a miniaturized top-spray air-suspension coating apparatus (Caleva Mini Coater, Caleva Process Solutions Ltd., UK). Each small-scale batch coated comprised 8.0 g of pellets.

A full 3^2 factorial design was used as a study design (Table 4). The levels of position (height) of spraying nozzle, X_1 (120, 140 and 160 mm) and inlet air temperature, X_2 (50, 60 and 70 °C) were varied. The levels of coating solution flow rate, inlet air flow and atomizing air pressure were adjusted to 15 ml/h, 6.0 m/s and 0.5 bar, respectively. The theoretical amount of coating was 3% (w/w) of the total weight of the pellets. The present film coating batches of pellets prepared without any anti-sticking agents were used as a reference

Table 4
Matrix of the complete 3^2 experimental design and results

Experiment no.	Coating parameter		Response	
	X_1	X_2	A	B
1	−1	−1	29.8	5
2	+1	−1	36.5	4
3	−1	+1	24.6	6
4	+1	+1	41.3	7
5	−1	0	18.2	5
6	+1	0	39.4	6
7	0	−1	19.4	6
8	0	+1	30.1	6
9	0	0	22.8	6
10	0	0	24.3	6
11	0	0	17.4	5

Key: (A) Expected yield (%) and (B) batch quality rank score.

batches for those obtained by applying anti-sticking agents.

Eight coating batches were prepared to investigate the effects of four anti-sticking agents on the tackiness of pellets during the coating process. Magnesium stearate, titanium dioxide, colloidal silicon dioxide and GMS (0.1 and 0.3%) were added to the plasticized solution of chitosan. GMS was added in the form of suspension in an aqueous 0.08% Tween 80 solution. The polymer dispersions were sprayed according to the conditions of central level used in the experimental design described above. After spraying the same temperature (60 °C) was maintained for an additional 10 min in the drying phase. Film-coated pellets were placed in plastic bottles for further evaluation.

Expected yield and quality (i.e. film coating appearance) were used as indicators of film tackiness. The expected yield was obtained by gently sieving the film-coated batches through a 1.8 mm and weighing the mass of the pellets passing this sieve. The physical appearance of the coated pellets (batch quality) was determined by visual inspection (assigning rank scores from 1 to 10 based on visual inspection). Furthermore, the in vitro release test for uncoated and coated pellets was performed using a USP apparatus I (basket method). The dissolution medium was 900 ml of phosphate buffer pH 6.8 or 7.4 maintained at 37.0 ± 0.1 °C. The basket rotation speed was kept at 50 rpm. The samples were filtered through a filter and assayed by UV spectrophotometry (Perkin-Elmer, Perkin-Elmer GmbH, Germany) at 273 nm for theophylline.

2.4. Film tackiness measurements

2.4.1. Theoretical considerations of minimum fluidization velocity

The minimum or incipient fluidization velocity (u_{mf}) represents the point of transition between the fixed and the fluidized states. Several authors have published models for predicting the u_{mf} in different conditions (Wen and Yu, 1966; Saxena and Vogel, 1977; Chitester et al., 1984; Noda et al., 1986; Lippens and Mulder, 1993; Rao and Bheemarasetti, 2001). The u_{mf} describes universally the velocity when the buoyancy of the upward moving gas counterbalances the weight of the bed of solid particles. For design and scaling-up purposes it is important to be able to calculate the value of u_{mf} precisely and thus to keep the number of experiments low.

When a gas passes through a bed of solid particles at a low velocity, the gas fluid first percolates through the void spaces between the particles. This stage is called the fixed bed (Davidson et al., 1985; Kunii and Levenspiel, 1991). When the velocity is increased, particles begin to vibrate and the pressure drop across the bed increases. This is the expanded bed and at this stage the bed performance is fairly similar to that of a fixed bed. An insignificant increase in the void fraction in the bed is then observed. At a certain velocity the buoyancy of upward moving gas counterbalances the weight of the bed (interparticle forces denied). This stage is referred to as a bed at minimum fluidization or an incipiently fluidized bed. The bed starts to behave like a dense fluid. At this point the pressure drop across the bed equals the weight of the bed. After the bed has been fluidized and the velocity of air increase, the pressure drop across the bed remains constant but the height of the bed continues to increase.

2.4.2. Film tackiness measurements exploiting minimum fluidization velocity

A microscale fluid-bed apparatus (Ariacon Oy, Helsinki, Finland) was used to study the tackiness (sticking) tendency and flow properties of coated pellets. The present fluidized-bed system and experimental setup have been described earlier in detail (Räsänen et al., 2003). The accuracy of the method was improved using a rubber 0-ring just above the bed of pellets. In each test, the pressure difference over the bed was recorded as a function of velocity of fluidization air. Experimental minimum fluidization velocity (u_{mf}) was measured from increasing and decreasing flow rates. The sample size of the pellets was 5 ml equal to 2–4 g, and the pellets were fluidized by increasing air flow rate slowly up to 400 ml/s. The pellets were fluidized 1 min at constant velocity (400 ml/s) and the fluidization occurred mainly at the lower part of the chamber. Thereafter the velocity of the fluidization air was gradually decreased to zero. Uncoated pellets were used as a reference sample representing a readily flowing (unsticking) product. The measurements were identical. The reference sample was measured triplicate, other samples once.

3. Results and discussion

3.1. Wettability of MCC-containing substrates by chitosan solutions

In granulation, pelletization and film coating uniform wetting of the solids is necessary. In the present study, the contact angle measurements were used to characterize the wettability of MCC-containing substrates that were qualitatively identical with the core pellets used in subsequent film coatings. The contact angles between chitosan solutions and core tablets are shown in Table 2. Aqueous HPMC solution (10% (w/w)) was used as a reference solution.

The effect of chitosan concentrations on the contact angles of the substrates was evident. The results showed that the contact angle between the solutions and both types of MCC-containing substrates increases slightly with increasing amount of chitosan in the solutions. On the other hand, the effect of plasticizer (glycerol) on the contact angles measured was minimal (not statistically significant). On the basis of the present results, the solution with 1.0% (w/w) chitosan was selected for aqueous film coating of pellets.

3.2. Effect of position of spraying nozzle and inlet air temperature on film coating

Coating experiments were first performed with chitosan solutions without any anti-sticking agents. In these experiments, the coating efficiency expressed as amount of non-agglomerated coated pellets (expected yield) and batch quality was quantified. The position of the spraying nozzle was found an important parameter affecting both expected yield and batch quality and, consequently, tackiness of chitosan film-coated pellets (Fig. 1). It is obvious that by increasing the height of the spraying nozzle, excessive over-wetting and subsequent irreversible agglomeration (sticking) of pellets are avoided due to partial spray drying of the coating solution droplets. As shown in Fig. 1, increasing the air flow temperature improved slightly the batch quality.

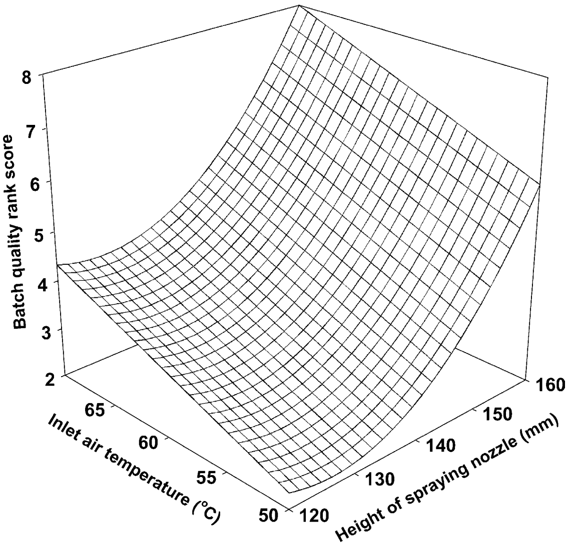

Fig. 1. Effect of height of spraying nozzle and inlet air temperature on batch quality of pellets coated with chitosan films.

In these preliminary experiments, expected yield and batch quality were far below the optimal. Thus, the batches were not very satisfactory (Table 4). The dissolution of the chitosan-coated pellets in phosphate buffer (pH 6.8) was rapid and unaffected by the coating process (t50% values for all batches were 10–12 min). It was concluded that chitosan film coatings lacking anti-sticking adjuvants are prone to evident irreversible agglomeration of pellets thus impairing the performance of film coating.

3.3. Effect of anti-sticking agents on the film coating

For various coating applications, a low stickiness is desirable. As seen in Fig. 2, the expected yield

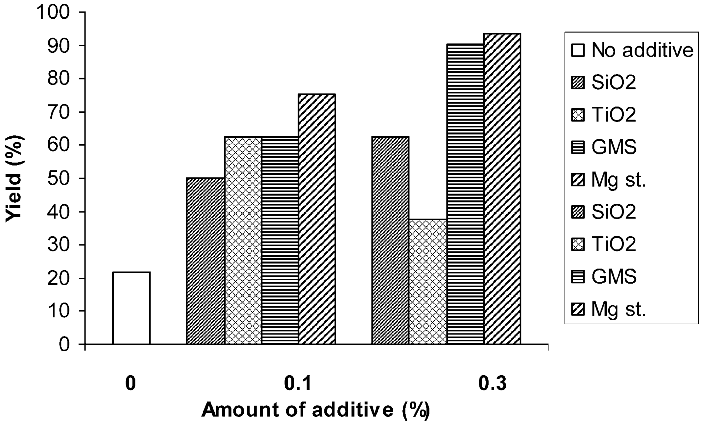

Fig. 2. Effect of anti-sticking agents on the yield of pellets coated with chitosan films.

values increased with increasing concentration of anti-sticking additives used. The incorporation of the anti-sticking agents led to a clear decrease in tackiness of films, and magnesium stearate and GMS were shown more effective than SiO_2 and TiO_2. In aqueous chitosan film coating, water-accelerated formation of hydrogen bonds is evident due to a great number of hydroxyl groups and protonated amino groups existing in chitosan molecule (primary amine) (Kienzle-Sterzer et al., 1982; Peng et al., 1994). Since hydrogen bonds are very strong covalent type of bondings, the films show a tendency for tackiness, resulting in irreversible agglomeration of the pellets. The mechanism of anti-sticking agents is obviously based on their strong capability to reduce hydrogen bonds existing in the wet film coatings (also to break water bridges) and to form simultaneously an increased number of competitive hydrophobic bondings in the coating system.

Traditionally, talc and magnesium stearate have been used as a glidants to reduce the sticking of cores during the coating process. Petereit et al. (1995) and Wesseling et al. (1999) were of the opinion that GMS is a promising alternative to talc in coating suspensions of acrylic and cellulosic polymer films and more effective and less toxic. The present results are in accordance with the earlier results obtained with GSM. High amounts of anti-sticking (solid) additives may block the nozzle.

In the present study this was observed especially with SiO_2 and TiO_2 at the concentration of 0.3%.

The drug release profiles of chitosan film-coated pellets with anti-sticking additives in buffer 7.4 are illustrated in Fig. 3. Drug release from uncoated and coated pellets without additives was about 100% of the drug at approximately 30 min. Incorporation of additives possibly enhanced the hydrophobic nature of the film coat which reduces penetration of the dissolution medium and may prolong slightly drug release. The apparent reversal dissolution of the 0.1 and 0.3% magnesium stearate results may be due to the unhomogeneous dispersion of the solid (magnesium stearate) in the coating liquid.

The greater efficiency of the addition of magnesium stearate to prolong drug release compared with the other anti-sticking agents could be attributed to the ionic interaction between protonoted amino groups on chitosan and carbonyl groups of stearates in magnesium stearate molecule. This electrostatic charge interaction with further amide formation and its effect as a barrier to prolong drug release have been demonstrated previously (Ritthidej et al., 2000).

3.4. Determination of film tackiness using minimum fluidization velocity

A novel method based on determination of the experimental minimum fluidization velocity (u_{mf}) in a fluidized bed was used to evaluate the influence of anti-sticking agents on the tackiness of aqueous chitosan films. The pressure difference over the fluidized bed as a function of velocity represented the effect

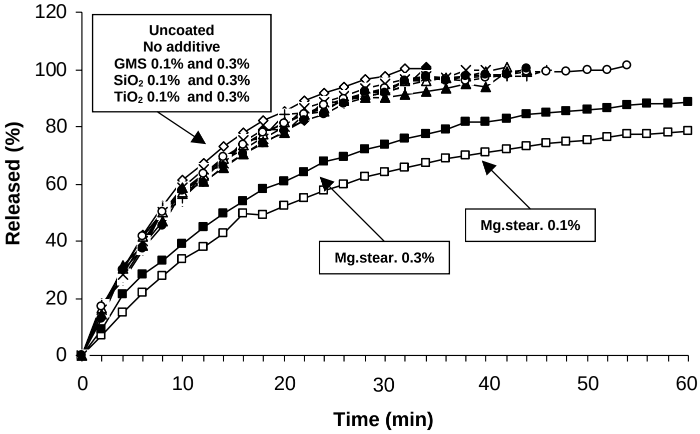

Fig. 3. Effect of anti-sticking agents on dissolution of chitosan film-coated pellets in phosphate buffer (pH 7.4) solution ($n = 6$). *Key*: Uncoated pellets (◇), film-coated pellets without antisticking agent (◆) and film-coated pellets with magnesium stearate (□, ■), titanium dioxide (○, ●), colloidal silicon dioxide (△, ▲) and GMS (+, ×) (0.1 and 0.3%).

of anti-sticking agents on the fluidization behavior of the coated pellets studied (Figs. 4 and 5). The shape of the pressure curve changed with the amount and type of anti-sticking agent used thus allowing to distinguish the anti-sticking efficiency of the adjuvants tested.

As seen in Fig. 4 and Table 5, the lowest values for experimental u_{mf} were obtained with uncoated

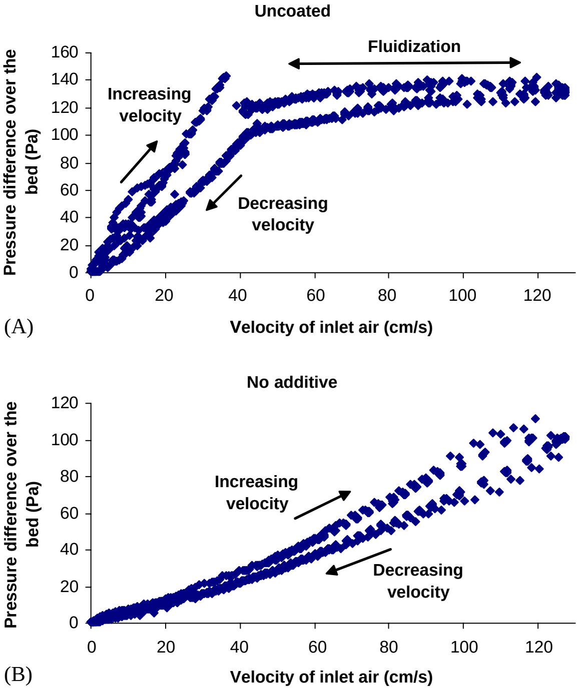

Fig. 4. Pressure difference over the bed profiles of (A) uncoated pellets (= reference sample representing non-sticking behaviour) and of (B) HMW-chitosan film-coated pellets without any anti-sticking agent.

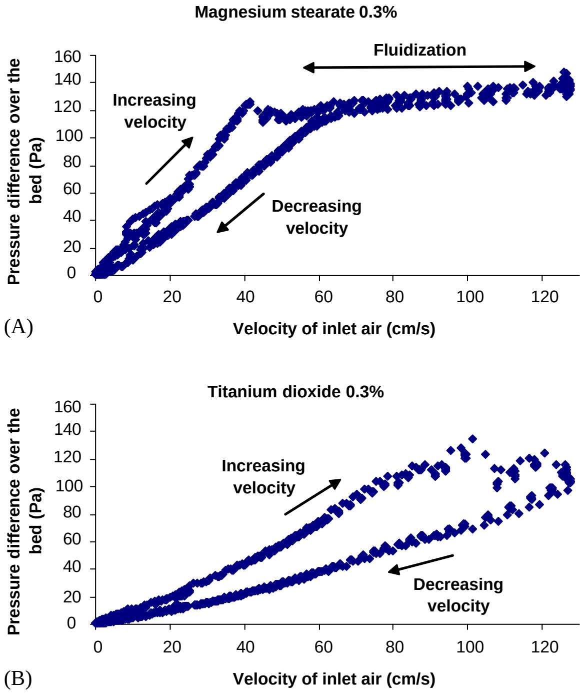

Fig. 5. Pressure difference over the bed profiles of HMW-chitosan film-coated pellets containing (A) magnesium stearate 0.3% (w/w) and (B) titanium dioxide 0.3% (w/w) as an anti-sticking agent.

Table 5
Values for minimum fluidization velocity (u_{mf})

Formulation	Increasing velocity u_{mf} (cm/s)	Decreasing velocity u_{mf} (cm/s)	Difference
Uncoated pellets	35	59	24
Film-coated pellets			
No anti-sticking agent	>130	>130	–
Colloidal silicon dioxide 0.1%	71	122	51
Colloidal silicon dioxide 0.3%	60	127	67
Titanium dioxide 0.1%	74	126	52
Titanium dioxide 0.3%	91	>130	–
Magnesium stearate 0.1%	63	120	57
Magnesium stearate 0.3%	41	71	30
GMS 0.1%	69	112	43
GMS 0.3%	44	94	50

reference pellets. With lower values of u_{mf} the fluidization capacity of the pellets increased and enhanced fluidization behavior and the non-sticking behaviour. This phenomenon was observed as the amount of anti-sticking agent was increased from 0.1 (w/w) to 0.3% (w/w) with exception of titanium dioxide. Film-coated pellets containing magnesium stearate as an anti-sticking agent were very easily fluidized (showing very low values of minimum fluidization velocity). The present film-coated pellets were more readily fluidized compared with those containing, e.g. titanium dioxide (Fig. 5). Since the film-coated pellets that contained no anti-sticking agent did not fluidize in the present testing system, values for u_{mf} could not be detected. In Table 5, the lowest and highest values for u_{mf} difference between increasing and decreasing velocity shows better fluidization (i.e. non-sticking tendency) and poorer fluidization (sticking tendency) of pellets, respectively.

Chitosan film-coated pellets without anti-sticking additives could not be fluidized and were thus classified as the worst flowing sample. Film-coated pellets containing magnesium stearate and GMS as anti-sticking agents (0.3% (w/w)) were easily fluidized and were classified as the best flowing and the least tacking sample. Both these additives are anti-sticking agents of choice for aqueous chitosan film coatings. The present method has interesting possibilities as a method for quantifying film tack.

Acknowledgements

The Centre for International Mobility for Foreign Students (CIMO) is gratefully acknowledged for financial support of the present study and Maria João Cravo Martins (University of Coimbra, Portugal) for assistance in the contact angle measurements.

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