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Prevention of the sticking tendency of floating minitablets filled into hard gelatin capsules

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Abstract

Hydrophillic minimatrices filled into hard gelatin capsules should be able to disperse and float on the contents of the stomach. However, these floating minitablets exhibit a strong tendency to adhere to one another due to the gelatin capsule shell and to the earlier hydration of the minitablets. Two different procedures were investigated to circumvent this problem: (i) addition of a protective filler excipient into the capsule; and (ii) coating the minitablets. For this latter approach, the type and amount of coating agent and the presence of coating additives were assessed. The degree of dispersion of the minitablets was described using an equation based on the actual area generated by the individual or aggregated minitablets upon contact with the dissolution medium. We demonstrate that it is possible to prevent floating minitablets from aggregating in vitro by using either a protective filler or a polymeric coating insoluble in gastric juice but permeable and swellable. © 1997 Elsevier Science B.V.

Keywords: Multiple-unit dosage form; Minitablets; Floating dosage form; Hard gelatin capsule; Hydrophilic matrix; Film coating; Protective filler

1. Introduction

Floating dosage forms with sustained release characteristics can be expected to prolong the gastric residence time of active compounds and reduce the variability of transit performance [1]. They are supposedly capable of increasing the bioavailability of drugs which are mainly absorbed in the upper part of the gastrointestinal tract. Hydroxypropylmethylcellulose was previously selected after a comprehensive screening of potential excipients [2]. Water-soluble cellulose derivatives allow the formulation of matrices with prolonged drug delivery for oral application [3–6]. Furthermore, tablets made with these cellulose ether polymers have a bulk density of less than unity in gastric fluids [7–9].

Floating dosage forms administered in a single-unit are unreliable in prolonging the gastric residence time owing to their 'all or nothing' emptying process [10]. Multiple-unit dosage forms would appear better suited since they are claimed to reduce the intersubject variability in absorption and lower the probability of dose-dumping. A literature survey demonstrated, however, that the differences in behaviour of single and multiple-units are controversial [11].

According to Moës [12], it is not desirable to produce a capsule containing hydrophilic minimatrices because in vivo they would quickly form a single mass due to the hydration and to the swelling of the polymer and thus, would be emptied from the stomach as such. Indeed, hydrophilic minimatrices introduced into a capsule already exhibit a strong tendency to adhere to one another due to the presence of the gelatin capsule and to the earlier hydration of the minitablets. Moreover, the incomplete dispersion of minitablets decreases the surface of tablets in contact with the medium and this may decrease the drug release.

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To our knowledge, methods for reducing the adherence of minitablets to one another have not yet been described. In this work, two different procedures, based on prevention of contact between the minitablets either by using a protective filler excipient or a polymeric coating, were evaluated in vitro in order to prevent this sticking tendency during the dissolution of the capsule shell. Various types of fillers and coating agents were compared.

2. Materials and methods

2.1. Materials

USP type 2906 hydroxypropylmethylcellulose (Methocel® F4M, Colorcon, GB-Kent) and magnesium stearate (Siegfried, CH-Zofingen) were chosen as minitablet excipient and lubricant, respectively. Disintegrating agents used as protective fillers were: microcrystalline cellulose (Avicel® PH-102 and PH-200) and croscarmellose sodium (Ac-Di-Sol®, FMC, Philadelphia, USA-PY). Polymeric film coating agents tested were: methacrylic acid copolymers (Eudragit® E 100 and NE30D, Röhm GmbH, D-Darmstadt); poly(1-vinyl-2-pyrrolidone) (PVP K25 and K90, Fluka, CH-Buchs); vinylpyrrolidone/vinyl acetate copolymers (Kollidon® VA64) and poloxamer 108 (Pluronic® F38, BASF, Wyandotte, USA-MI); polyethylene glycols (1000 and 6000, Hoechst, D-Frankfurt am Main); hydroxypropylcellulose (Klucel® EF, Aqualon, F-Rueil-Malmaison); sodium carboxymethylcellulose (Blanose® 7LFD, Hercules, R-Rueil-Malmaison). Diethyl phthalate (Siegfried, CH-Zofingen) was used as a plasticizer. Coating additives used were: lactose (Hänseler AG, CH-Herisau), titanium dioxide (Siegfried, CH-Zofingen), colloidal silicon dioxide (Aerosil® R972, Degussa, D-Frankfurt). Transparent size 1 hard gelatin capsules (Coni Snap®, Capsugel, B-Bornem) were used for the study.

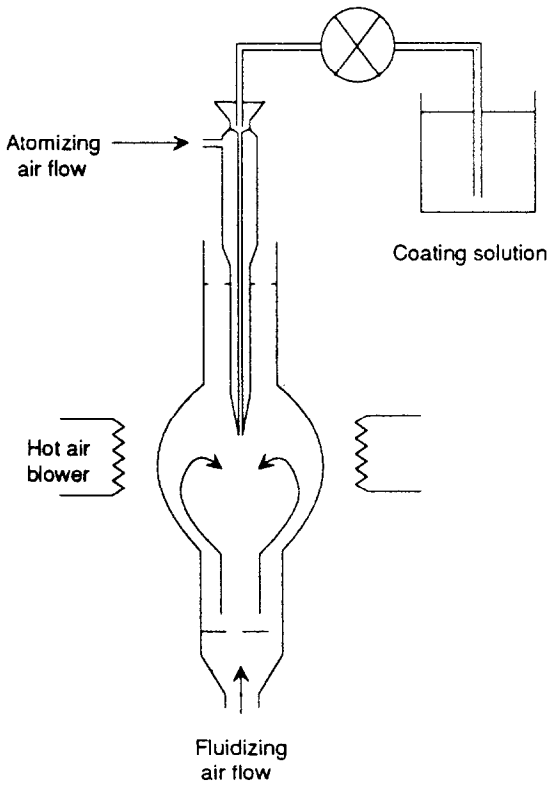

Fig. 1. Miniature coating apparatus (adapted from [14]).

Table 1
Process parameters for minitablet coating

Batch size (g)	1
Coating solution (ml of 1% (V/w) polymer solution	0.9–5.7
Solution delivery rate (ml/min)	0.5–0.8
Nozzle (mm fluid aperture)	0.5
Atomizing pressure (bar)	0.7
Fluidizing air flow pressure (bar)	0–0.05
Drying temperature (°C)	40–45

2.2. Methods

2.2.1. Preparation of minitablets

A 6-punch die 3 mm in diameter was specially manufactured in our laboratory [2]. The compression force was applied using a hydraulic press (Specac®) and equal distribution of force between the six punches was achieved by means of a ball bearing on the upper part of the device. Minitablets of Methocel® F4M with 0.25% (w/w) magnesium stearate were prepared at a compaction pressure of 900 MPa. Each minitablet weighed 20 mg.

2.2.2. Protective filler excipient

Capsules were filled with 10 minitablets previously mixed with half of the amount of protective filler. Then, the empty space within the capsule was filled with the same excipient. The total amount of the protective filler was about 100 mg. The flow rate of Ac-Di-Sol® and Avicel® PH-200 through an orifice of 15 mm was measured using a strain gauge balance and the flow rate was calculated for Avicel® PH-200 from the recorded curve. The angle of repose of Avicel® PH-200 was determined using the apparatus described by Jones and Pilpel [13].

2.2.3. Coating of minitablets

The minitablets were coated using the miniature air suspension coating apparatus shown in Fig. 1. This apparatus, first described by Ranga Rao et al. [14], was adapted for the coating of a small number of minitablets. The coating process parameters and the composition of coating solutions are given in Tables 1

and 2, respectively. Unless otherwise stated, an usual amount of plasticizer (19% (w/w) total dried mass) was added. Methylene blue was added to the coating solution in order to check for film homogeneity. Coating additives were also added to the coating solution containing either PVP K25 + K90 1:1 or PEG 1000 (3.8 ml solution at 1% (w/V)) at a ratio of 10% based on the dry weight of the film coating agent. The amount of diethyl phthalate was 44% (w/w) of the total dried mass for the PVP coating.

2.2.4. Sticking evaluation and dispersion coefficient

The capsule was placed in the USP XXIII paddle apparatus at 37°C and containing 900 ml of artificial pepsin-free gastric juice with 0.05% (V/V) Tween® 80 as a surface tension lowering agent, because it is recognized that the composition of the medium influences the time of rupture of the hard gelatin capsules [15]. Stirring rate was set at 60 rpm. Dispersion of the minitablets after the dissolution of the capsule was evaluated using Eq. (1) (see Appendix A):

$$f_d = \frac{1}{1 - n^{-1/3}} \left(\frac{\sum_{i=1}^{n'} m_i m_i'^{2/3}}{n} - n^{-1/3} \right) \quad (1)$$

where f_d is a normalized dispersion coefficient and varies between 0 and 1 (1 corresponds to a fully dispersed formulation), n is the number of minitablets in a capsule, m_i is the number of agglomerates containing an identical amount of minitablets and m_i' is the number of minitablets in the agglomerate.

The lag time before tablet buoyancy occurred was assessed under the same conditions.

Table 2
Composition of coating solutions

Coating agent	Solvent	Amount of plasticizer (diethyl phthalate) % (w/w) total dried mass
Eudragit® E	Isopropanol:acetone (1:2)	—
Eudragit® NE30D	Ethanol	—
PVP K25 + K90 (1:1)	Ethanol	19
PVP K25 + K90 (1:1)	Ethanol	44
Kollidon® VA64	Ethanol	19
Pluronic® F38	Water:acetone (1:2)	19
PEG 1000	Water:acetone (1:2)	19
PEG 1000	Water:acetone (1:2)	44
PEG 6000	Water:acetone (1:2)	19
Klucel® EF	Isopropanol:acetone (1:2)	19
Blanose® 7LFD	Acetone:water (1:2)	19

3. Results and discussion

Photographs 1(A, B) (Fig. 2) illustrate the sticking tendency of the minitablets when filled into a capsule without any protective filler or polymeric coating, before and after the dissolution of the capsule shell, respectively. All minitablets adhered to one another, which corresponds to a dispersion coefficient of 0. These tablets floated immediately in the medium, probably because of the adherence of the minitablets to the gelatin of the capsule shell. The capsule shell is maintained buoyant by the air entrapped in it. The gelatin capsule after immersion in the liquid opened within 1–2 min at the shoulders and was completely dissolved after about 10 min, as already observed by Ludwig et al. [16]. The relatively long time required for the total dissolution of the capsule shell may favour the aggregation of the hydrated minitablets.

3.1. Use of protective fillers

Photographs 2(A, B) show the total separation of the minitablets when filled into a capsule with 100 mg of the superdisintegrant Ac-Di-Sol® (coefficient of dispersion of 1). The dispersion coefficients (Table 3) show that common disintegrants such as microcrystalline cellulose allowed an almost total separation of the tablets, regardless of the particle size (Avicel® PH-102 and PH-200).

Most minitablets sank one after the other following the opening of the capsule. They floated after less than 10 min. As already mentioned, the presence of the gelatin of the capsule was not favorable for a good dispersion, which was governed by the rate of opening of the capsule and the dissolution of the capsule shell. The shell of the capsules filled with Ac-Di-Sol®, Avicel® PH-102 and PH-200 opened generally in less t/han 1 min. It appears that the hydrophilic nature of Ac-Di-Sol® and Avicel® favours the dissolution of the capsule shell. Furthermore, the swelling of these insoluble disintegrants keeps the minitablets separated during the dissolution of the capsule shell and thus helps the dispersion of the minitablets. Avicel® exhibits low and Ac-Di-Sol® high swelling characteristics [17]. This difference may explain the better results obtained with Ac-Di-Sol®. It may be favourable to mix Avicel® PH-200 with Ac-Di-Sol® since Avicel® PH-200 is cheaper and has better flow properties than Ac-Di-Sol®. Ac-Di-Sol® is a non free-flowing powder, while the flow rate

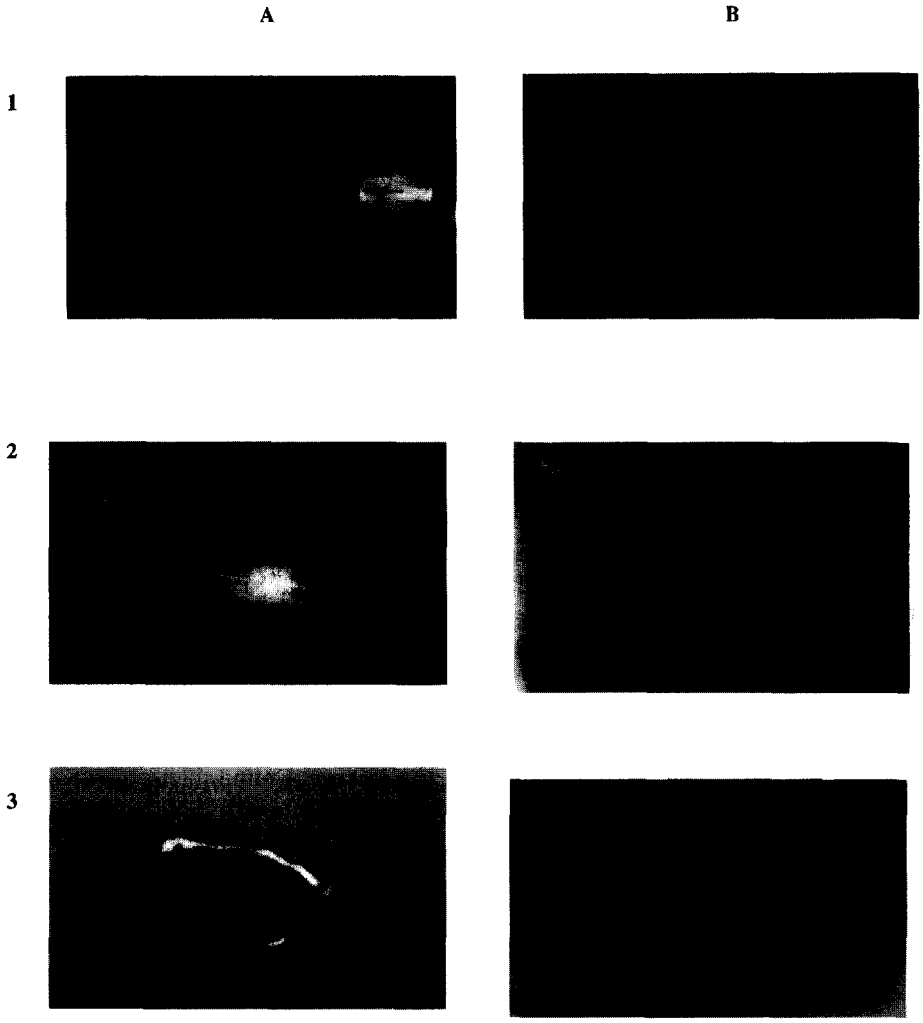

Fig. 2. Photographs of minitablets (A) before (at 1 min) and (B) after (at 3 min) the dissolution of the capsule shell. The minitablets floated after less than 10 min and during more than 8 h. Key: (1) without protective filler or coating; (2) protective filler; (3) coating with Eudragit® NE30D.

of Avicel® PH-200 is 2.4 g/s through an orifice of 15 mm. Avicel® PH-200 is, however, slightly cohesive considering the angle of repose which is of 53°. It should be noted that Avicel® PH-102 is a non free-flowing powder according to Doelker et al. [18,19]. It would be expected that Avicel® with a coarser particle size would mix better with the minitablets and as the ratio of Avicel® PH200/Ac-Di-Sol® does not have a great influence on the dispersion factor, the combination of the two is recommended.

Table 3
Influence of the protective filler on the dispersion coefficient f_d of 10 minitablets filled into a hard gelatin capsule

Protective filler excipient	f_d
Avicel® PH-102	0.92 ± 0.05
Avicel® PH-200	0.97 ± 0.03
Ac-Di-Sol®	1.00 ± 0.00
Ac-Di-Sol® + 5% Avicel® PH-200	0.89 ± 0.03
Ac-Di-Sol® + 10% Avicel® PH-200	0.92 ± 0.05
Ac-Di-Sol® + 20% Avicel® PH-200	0.92 ± 0.00
Ac-Di-Sol® + 30% Avicel® PH-200	0.95 ± 0.03
Sodium bicarbonate	0.89 ± 0.07

Mean ± S.E.M.; $n = 3–6$.

The mechanism of action of sodium bicarbonate is different from that of common disintegrating agents. The carbon dioxide generated from the sodium bicarbonate in contact with gastric juice, formed bubbles around the minitablets and kept the minitablets separated from each other. In spite of the fact that an acceptable dispersion coefficient was obtained, sodium bicarbonate was not considered to be a suitable protective filler due to the fact that it also increased the disintegration of the minitablets themselves.

3.2. Coating of minitablets

The dispersion process of minitablets coated with gastrosoluble polymers can be divided into four successive steps: (1) capsule shell dissolution; (2) spreading of

Table 4
Influence of the volume of coating solution (1% polymer) on the dispersion coefficient (f_d) of 10 minitablets filled into hard gelatin capsule

Coating solution	0.9 ml	1.9 ml	3.8 ml	5.7 ml
Gastrosoluble polymers				
Eudragit® E	—	0.33 ± 0.01	0.18 ± 0.01	0.34 ± 0.21
Kollidon® K25+ K90 1:1	—	0.39 ± 0.03	0.21 ± 0.11	0.13 ± 0.07
Kollidon® K25+ K90 1:1[a]	0.46 ± 0.09	0.55 ± 0.07	0.54 ± 0.14	0.25 ± 0.08
Kollidon® VA64	—	0.50 ± 0.18	0.49 ± 0.13	0.38 ± 0.19
PEG 1000	—	0.53 ± 0.10	0.67 ± 0.06	0.64 ± 0.04
PEG 1000[a]	—	—	0.19 ± 0.06	—
PEG 6000	—	0.35 ± 0.12	0.48 ± 0.17	0.59 ± 0.07
Pluronic® F38		—	0.59 ± 0.06	—
Klucel® EF	—	0.54 ± 0.07	0.57 ± 0.06	0.35 ± 0.11
Blanose® 7LFD	0.23 ± 0.10	0.50 ± 0.07	0.18 ± 0.03	0.15 ± 0.09
Swellable, permeable polymer insoluble in gastric juice				
Eudragit® NE30D	0.57 ± 0.08	0.91 ± 0.04	0.99 ± 0.03	0.99 ± 0.03

Mean ± S.E.M.; $n = 3$–6.
[a] Contains 44% (w/w) of diethyl phthalate instead of 19% (w/w).

the minitablets; (3) film coating dissolution; and (4) hydration of the minitablets.

The coating of minitablets with gastrosoluble polymers reduced the sticking (Table 4) regardless of the amount of coating agent. However, the results were not entirely satisfactory. The lag time before buoyancy occurred was always less than 10 min but these values were highly variable (data not shown).

Table 5
Influence of coating additives on the dispersion coefficient f_d of 10 minitablets introduced into a hard gelatin capsule (mean ± SEM; $n = 3$)

Coating additive	Coating agent	
	Kollidon® K25+K90 1:1	Polyethylene glycol 1000
Without coating additives	0.54 ± 0.14	0.67 ± 0.06
Lactose	0.36 ± 0.12	0.60 ± 0.09
Magnesium stearate	0.21 ± 0.11	0.51 ± 0.08
Titanium dioxide	0.18 ± 0.18	0.49 ± 0.01
Avicel® PH-105	0.32 ± 0.04	0.63 ± 0.02
Ac-Di-Sol®	0.41 ± 0.06	0.69 ± 0.15
Aerosil® R972	0.35 ± 0.12	0.68 ± 0.10
Aerosil® R972[a]	0.36 ± 0.13	0.53 ± 0.17
Shellac	0.40 ± 0.07	0.60 ± 0.05

[a] 20% (w/w) instead of 10% (w/w).

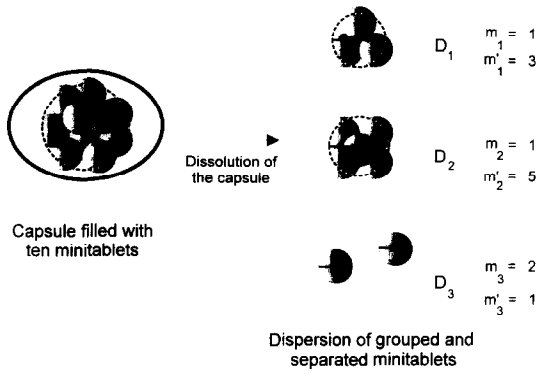

Fig. 3. Example of dispersion of 10 minitablets into 4 entities giving an f_d of 0.44: m_i = number agglomerates containing an identical amount of minitablets; m'_i = number of minitablets in the agglomerate.

Depending on the polymer used, the increase in the amount of coating agent had variable effects. The amount of Eudragit® E did not significantly affect the dispersion coefficient of the minitablets. Moreover, this polymeric coating was not an effective film coating agent for preventing the sticking of the minitablets as shown by the low value of f_d. Increasing the amount of polymeric coating agents such as Klucel® EF, Blanose® 7LFD, Kollidon® K25 + K90 and Kollidon® VA64 decreased the dispersion of the minitablets. These three coating agents became hydrated and gelified before dissolving. It can be anticipated that the gel around the minitablets is sticky, attracting the minitablets to each other and reducing the space between the minitablets in the gelatin capsule.

The PEG coatings are less sticky than the other film forming agents because they dissolve without forming a gel. However, the minitablets were never totally dispersed due to the viscosity of the PEGs. High molecular weight PEG chains may prevent contacts between the minitablets by steric hindrance [20], and indeed, increasing the amount of PEG 1000 and PEG 6000 increased the dispersion coefficient. If a layer of magnesium stearate is added to the coated minitablets (3.8 ml solution of PEG 1000, 1%), the dispersion coefficient is strongly diminished ($f_d = 0.2$ after 1 h), because magnesium stearate prevents the PEG chain from unfolding and hinders the wetting of the PEG.

It is interesting to note when considering the dispersion coefficient, that an increase in the amount of plasticizer is favorable for polyvinlylpyrrolidone coating but not for PEG 1000 coating. At this point, no explanation can be proposed.

The addition of coating additives did not reduce the tendency of the minitablets to stick to each other (Table

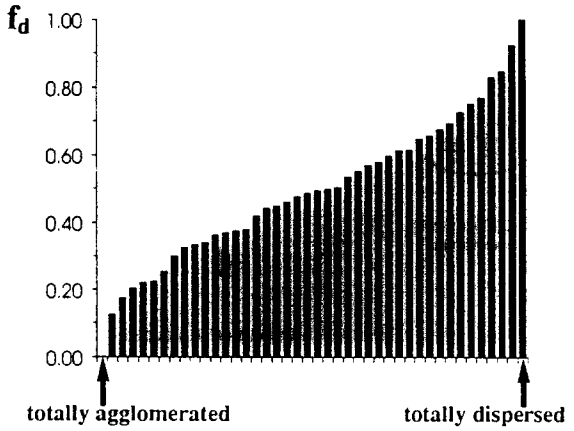

Fig. 4. Evolution of the dispersion coefficient for the possible 42 combinations of dispersed and agglomerated minitablets ($N = 10$).

5). There seems to be no apparent correlation between the solubility or density of these substances and the dispersion coefficient obtained. According to Alam and Parrat [21] tablets coated with polyvinylpyrrolidone K25 + K90 1:1 and shellac are non tacky when they were held in the hand. It appears that the tackiness of the coating is not related to the sticking of the tablets in a solution.

Photographs 3(A, B) show the dispersion of the minitablets obtained by using Eudragit® NE30D as a coating agent (Fig. 2 and Table 4). This film forming agent is insoluble in gastric juice but permeable and elastic, allowing the minitablets to swell. However, the swelling pressure developed by the tablet core after a while overcomes the mechanical resistance of the coating and breaks it (Fig. 2, photograph 3B) [22]. Before rupture, this coating agent prevents the sticking of the minitablets during the dissolution of the capsule shell and thus, allows a total dispersion of the minitablets.

4. Conclusion

It is possible to prevent floating minitablets from aggregating in vitro by the two procedures tested: (i) the concomitant filling of the capsule with minitablets and a protective filler and (ii) coating the minitablets with the 'Polyacrylate dispersion 30%' USP/Ph.Eur (Eudragit® NE30D) which is insoluble in gastric juice but permeable and swellable. This latter approach is rather more complex because it requires an additional manufacturing step, but it can be more readily scaled up.

Acknowledgements

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Appendix A

The dispersion coefficient does not represent the increase in the surface area occurring, but it is a simple and useful way to measure the ability of a coating or filler to prevent the sticking of the minitablets. The agglomerate may have several arrangements. The easiest way to represent the shape of the agglomerate is a sphere. Then, the increase in area induced by the tablet separation can be expressed by the following ratio:

$$F_d = \frac{\text{Surface area created after dispersion of minitablets}}{\text{Total surface area of fully dispersed minitablets}} \quad \text{(A1)}$$

$$F_d = \frac{\sum_{i=1}^{n'} (m_i D_i^2 \pi)}{nD^2\pi} \quad \text{(A2)}$$

m_i = Number of agglomerates containing an identical amount of minitablets
D_i = Diameter of a spherical agglomerate of minitablets having a volume equivalent to the sum of the volume of each minitablet
D = Diameter of a single minitablet
n' = Number of distinct minitablet agglomerates
n = Number of minitablets in a capsule

Considering that

$$D_i = \left(\frac{6V_i}{\pi}\right)^{1/3}$$

and

$$V_i = m_i' V = m_i'\left(\frac{\pi D^3}{6}\right),$$

where V_i is the volume of the ith spherical agglomerate, V the volume of a single minitablet and m_i' the number of minitablets in the agglomerate, we obtain Eq. (A3) after appropriate substitution and rearrangement of Eq. (A2):

$$F_d = \frac{\sum_{i=1}^{n'} m_i m_i'^{2/3}}{n} \quad \text{(A3)}$$

In order to have the possibility to compare the dispersion coefficient of minitablets regardless the number of minitablets in a capsule, Eq. (A3) can be normalized on a 0–1 scale, where 1 corresponds to a fully dispersed formulation, resulting in Eq. (A4) after rearrangement:

$$f_d = \frac{F_d - F_{d\,min}}{F_{d\,max} - F_{d\,min}} \quad \text{(A4)}$$

Considering $F_{d\ min} = n^{-1/3}$ and $F_{d\ max} = 1\text{-}n^{-1/3}$, we finally obtain the dispersion coefficient f_d as:

$$f_d = \frac{1}{1 - n^{-1/3}} \left(\frac{\sum_{i=1}^{n'} m_i m_i'^{2/3}}{n} - n^{-1/3} \right) \quad \text{(A5)}$$

The example given in Fig. 3 illustrates the use of Eq. (A5) and the evolution of the dispersion coefficient for the possible combinations of dispersed and agglomerated minitablets is shown in Fig. 4.

References

[1] J. Timmermans, A.J. Moës, Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy, J. Pharm. Sci. 83 (1994) 18–24.

[2] N. Rouge, E.T. Cole, P. Buri, E. Doelker, Screening of potentially floating excipients for minitablets, S.T.P. Pharma, submitted.

[3] P. Buri, E. Doelker, Formulation des comprimés à libération prolongée II. Matrices hydrophiles. Pharm. Acta Helv. 55 (1980) 189–196.

[4] D.A. Alderman, A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms, Int. J. Pharm. Tech. Prod. Manuf. 5 (3) (1984) 1–9.

[5] E. Doelker, Water-swollen cellulose derivatives in pharmacy, in: N.A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy vol. II polymers, CRC Press, Boca Raton, 1987, pp. 115–60.

[6] E. Doelker, Cellulose derivatives. Adv. Polym. Sci. 107 (1993) 199–265.

[7] Sheth P.R., Tossounian J. Novel sustained release tablet formulations. US Patent, 1979;4 167 558.

[8] A. Menon, A. Ritschel, A. Sakr, Development and evaluation of a monolithic floating dosage form for furoemide, J. Pharm. Sci. 83 (1994) 239–245.

[9] J. Timmermans, Floating hydrophilic matrix dosage forms for oral use: factors controlling their buoyancy and gastric residence capabilities, Ph.D. Thesis, University of Brussels, 1991.

[10] Y. Kawashima, T. Niwa, H. Takeuchi, T. Hino, Y. Itoh, Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (in vivo), J. Control. Release 16 (1991) 279–290.

[11] N. Follonier, E. Doelker, Biopharmaceutical comparison of oral multiple-unit and single-unit sustained-release dosage forms, S. T. P. Pharma 2 (1992) 141–158.

[12] A.J. Moës, Recherche et développement de formes orales à libération contrôlée, J. Pharm. Belg. 44 (1989) 60–70.

[13] T.M. Jones, N. Pilpel, The flow properties of granular magnesia, J. Pharm. Pharmacol. 18 (1966) 81–93.

[14] K.V. Ranga Rao, P. Buri, A novel laboratory model for the film coating of microparticles, Acta Pharm. Technol. 35 (1989) 256–257.

[15] A. Ludwig, M. Van Ooteghem, Disintegration of hard gelatin capsules Part 5: the influence of the composition of the test solution on the disintegration of hard gelatin capsules, Pharm. Ind. 43 (1980) 188–190.

[16] A. Ludwig, M. Van Ooteghem, Disintegration of hard gelatin capsules Part 2: disintegration mechanism of hard gelatin capsules investigated with stereoscopic microscope, Pharm. Ind. 42 (1980) 405–406.

[17] G.K. Bolhuis, H.V. van Kamp, C.F. Lerk, G.M. Sessink, On the mechanism of action of modern disintegrants, Acta Pharm. Technol. 28 (1982) 111–114.

[18] E. Doelker, D. Mordier, H. Iten, P. Humbert-Droz, Comparative tableting properties of sixteen microcrystalline celluloses, Drug Dev. Ind. Pharm. 13 (1987) 1847–1875.

[19] E. Doelker, D. Massuelle, F. Veuillez, P. Humbert-Droz, Morphological, packing, flow and tableting properties of new Avicel types, Drug Dev. Ind. Pharm. 21 (1995) 643–661.

[20] B. Wesslén, M. Kober, C. Freij-Larson, A. Ljungh, M. Paulsson, Protein adsorption of poly(ether urethane) surfaces modified by amphiphilic and hydrophillic polymers, Biomaterials 15 (1994) 278–284.

[21] A.S. Alam, E.L. Parrott, Effect of adjuvants on tackiness of polyvinylpyrrolidone film coating, J. Pharm. Sci. 61 (1972) 265–268.

[22] A. Gazzaniga, U. Conte, M.E. Sangalli, C. Caramella, A. La Manna, A multiple unit modified release system, in: C. Migliaresi et al. (Eds.), Polymers in Medicine III, Elsevier, Amsterdam, 1988, pp. 201–208.