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Research paper

Development and characterisation of interactive mixtures with a fine-particulate mucoadhesive carrier for nasal drug delivery

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Abstract

The aim of this study was to investigate whether mucoadhesive interactive mixtures can be created using carrier particles in a size range appropriate for nasal administration, i.e. 10–50 μm. We also used theoretical models to investigate if homogeneity measurements can be used to evaluate the formation of interactive mixtures containing carrier particles in this size range. Sodium starch glycolate (SSG) was used as carrier material and sodium salicylate (SS) as the model fine-particulate drug. The size ranges of SSG particles and amounts of SS were varied to find the smallest carrier particle size and highest amount of drug that still resulted in an interactive mixture. Visual inspection of the mixtures by scanning electron microscopy showed that interactive mixtures could be formed with carrier particles as small as 30 μm and containing up to 4% (w/w) of SS. Comparisons with theoretical models highlighted the difficulties of using homogeneity measurements to determine if interactive mixtures were formed. The measured coefficients of variation (CV) for the amount of drug in the samples were low and inferior mixtures were associated with only a slight increase. It was thus concluded that mucoadhesive interactive mixtures can be created in an appropriate size range for nasal administration, but that visual inspection of these mixtures is initially necessary to confirm the formation of an interactive mixture.

Keywords: Interactive mixtures; Ordered mixtures; Mucoadhesion; Nasal drug delivery; Sodium starch glycolate; Primojel®

1. Introduction

Nasal administration of medication is advantageous for drugs that are required to have a fast onset of effect or that have poor oral bioavailability. The relatively large absorption area in the nasal cavity (approximately 160 cm^2) is covered by a highly vascularised, porous epithelial cell layer through which molecules can be quickly transported to the systemic blood circulation without first-pass metabolism in the liver.

Most nasal formulations on the pharmaceutical market today are in the form of liquid sprays, although dry powder formulations resulted in a higher drug bioavailability in several studies e.g. [1,2], possibly as a result of increased residence time and improved deposition. The deposition of a dry powder formulation is determined by the particle size: particles smaller than 10 μm in diameter risk pulmonary deposition while those exceeding 50 μm might be deposited in the anterior part of the nose, which is covered by non-ciliated, stratified squamous epithelium and is unfavourable for absorption [3].

The usual method of production of bioadhesive microspheres involves dissolution of the drug to incorporate it into the carrier, followed by lyophilisation or spray-drying. Although spray drying is less expensive than lyophilisation, both still have associated disadvantages with respect to drug stability, solvent residues and the size range of the resulting particles. An alternative could be to create interactive mixtures with a mucoadhesive carrier, if such mixtures can be obtained in the appropriate size range. Interactive, or ordered, mixtures are binary mixtures in

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which fine drug particles are adhered to coarse carrier particles to form interactive units, resulting in a highly homogeneous mixture. The fine particles are attached to the surface of the carrier particles mainly by van der Waals and electrostatic forces [4]. For successful attachment, the carrier particles must be able to exert enough force to break up agglomerates of the small particles during the dry mixing process. This ability will primarily be determined by the density, surface roughness, shape, flowability and size of the carrier particles.

The concept of interactive mixing has been applied to formulations administered by inhalation, as an alternative to metered-dose inhalers. Because of the strong adhesive forces between the fine drug particles and the carrier particles, one of the main research objectives in this field has been to increase detachment of fine particles during inhalation. As a result of this, mixing times have been limited to prevent the strong attachment to the carrier particles resulting from adhesion to "active sites" [5]. Many attempts e.g. [5–7] have also been made to increase the detachment by decreasing the size of the lactose carrier particles below 70–100 μm originally suggested by Bell et al. [8]. However, it cannot automatically be assumed that the mixtures created in this smaller size range will be interactive, especially when mixing times are short. Dickhoff et al. have shown scanning electron micrographs of interactive units with carrier particles in the size range of 32–45 μm [5], but the use of homogeneity measurements alone could be insufficient for determining whether a mixture is interactive. Thorough investigation into the formation of an interactive mixture and absence of free drug aggregates is required to reliably interpret the results of such studies.

To our knowledge, interactive mixtures have not so far been used for nasal administration of drugs. Sodium starch glycolate (SSG), which is a cross-linked derivative of starch, is commonly used as a superdisintegrant in tablet formulations and is generally regarded as a non-toxic and non-irritant material. The dry powder has an excellent capacity for absorbing water; attachment to mucous membranes would thus occur by water transport from the mucosa. The work of te Wierik et al. on the effect of SSG on the dissolution of a poorly soluble drug [9] indicated that SSG has good deagglomerating characteristics and that it could be a suitable candidate for a mucoadhesive carrier material.

The objective of this study was to investigate whether interactive mixtures can be formed with a mucoadhesive carrier material (SSG) in a particle size range appropriate for nasal administration, i.e. 10–50 μm. We also used theoretical models to investigate how the formation of interactive mixtures in this particle range can be evaluated.

2. Theoretical models

The homogeneity of the mixtures in this report is described as the coefficient of variation (CV) of the drug amount in the various powder samples [10]. Theoretically, the optimal homogeneity can be described according to three models: (I) random mixtures, in which the primary particles are optimally mixed but still appear as free, non-interactive units (the least homogeneous state of the three theoretical models); (II) interactive mixtures, in which polydispersed fine particles adhere to larger carrier particles to form interactive units (each interactive unit may include a different number of fine drug particles, which will cause some degree of disorder in the mixture [11,12]); and (III) ordered mixtures, which consist of carrier particles with exactly the same number of monodispersed particles attached to each one [13]. The third model will result in a mixture with an absolute homogeneity, i.e. a CV equal to nil; as this is unlikely to occur in practice, only models (I) and (II) are included in the theoretical comparisons. The definitions of perfectly randomised or interactive mixtures do not allow the presence of free agglomerates of fine particles. If such agglomerates are still present after dry mixing this will result in a more heterogeneous mixture than predicted by any of the theoretical models.

2.1. Random mixtures

The homogeneity of a perfectly randomised mixture of two powder materials can be calculated according to Eq. (1), here expressed as the coefficient of variation (CV_{RM}) [14]:

$$CV_{RM} = 100 \cdot \sqrt{\frac{q}{p} \cdot \frac{p\overline{w_q} + q\overline{w_p}}{M}} \quad (1)$$

where p and q are the proportions by weight of fine and coarse particles, respectively. The weight of the mixture sample is represented by M and the mean particle weights of the two components by $\overline{w_p}$ and $\overline{w_q}$. Poole et al. [14] defined this factor as:

$$\bar{w} = \sum \left(f_r \cdot \alpha_v \cdot \rho \cdot \frac{d_{r1}^3 + d_{r2}^3}{2} \right) \quad (2)$$

where α_v is the volume shape factor [15], which in this investigation was given a value equal to that of a sphere, ρ is the particle density and d_{r1} and d_{r2} are the lower and upper limits, respectively, of the particle diameter in size range r. The fraction of particles in size range r is represented by f_r. According to Kristensen [16], the fraction based on particle weight, i.e. the volume distribution, achieves more accurate results in this context than the fraction based on particle number. By accounting for the different weight distributions of the powders the CV can be calculated for polydispersed powders, assuming that no segregation occurs.

2.2. Interactive mixtures

As the fine particles become attached to carrier particles, the homogeneity of the mixture will increase and the amount of disorder will primarily depend on the amount

and size of the fine drug particles. The homogeneity of an interactive mixture, expressed by the coefficient of variation (CV_{IM}), can be described by Johnson's equation [17], as modified by Egerman [12,18], who also confirmed it valid for polydispersed fine particles [19]:

$$CV_{IM} = 100 \cdot \sqrt{\frac{1}{p} \cdot \frac{\overline{w_p}}{M}} \quad (3)$$

in which the parameters are as described above.

3. Materials and methods

3.1. Materials

Sodium starch glycolate (SSG, Primojel®), kindly donated by DMV International GmbH, The Netherlands, was used as carrier material. Sodium salicylate (SS; Sigma–Aldrich Sweden AB, Sweden) was used as a model fine-particulate drug. SSG was dry sieved (Retsch, Germany) between 63–45 and 45–32 μm to provide the two larger size fractions (A and B). The two finer carrier particle size fractions (C and D) were obtained using an air classifier (100 MZR, Alpine, Germany). SS was milled in a mortar grinder (Retsch, Germany) for 10 min and the coarsest fraction was removed by air elutriation. All materials and mixtures were stored in desiccators below 18% RH.

3.2. Methods

3.2.1. Primary characterisation of materials

A helium pycnometer (AccuPyc 1330 Pycnometer, Micromeretics, USA) was used to determine the apparent particle densities of SSG and SS. The external specific surface area of SS was measured with Blaine permeametry [20] and corrected for slip flow [21]. The specific surface areas of the SSG size fractions were measured using steady-state permeametry [22,23] and calculations were made according to Eriksson et al. [24]. The particle size distributions of the test materials were determined using laser diffraction analysis, 100 mm lens and Fraunhofer theory (Sympatec Helos H0321, Sympatec GmbH, Germany). A Sympatec RODOS dry dispersing system at 3 bar was used to feed the particles to the laser beam.

3.2.2. Preparation of mixtures

Mixtures were prepared in batches of 50 g using glass jars of 250 mL capacity, which were placed in a Turbula mixer (2L W.A. Bachofen, Switzerland); the materials were mixed at 67 rpm for 50 h. If visible aggregates were still present thereafter, the mixing time was prolonged to 74 h. Because of the small carrier particles and the small batches, long mixing times were chosen to optimise deagglomeration [25] and adhesion stability [5]. The theoretical surface coverage of the carrier particles was calculated according to Nyström et al. [26] by dividing a quarter of the external surface area of the amount of SS by the external surface area of the amount of SSG in each mixture.

3.2.3. Evaluation of mixture quality

Powder thieves in three different sizes (15, 40 and 60 mg) were used to evaluate the mixture homogeneity [27,28]. As described by the theoretical models, the sample size will have no effect on an ordered mixture, whereas the homogeneity will increase slightly with sample size for interactive mixtures and more markedly for random mixtures. Thirty samples of each sample size were collected from random sites in the powder bed, as required for accurate statistical analysis [10,29,30]. The samples were dissolved in water, vigorously shaken and allowed to rest for 15 min, during which SSG formed a sediment. The UV absorption of the clear supernatant was measured at 295 nm (U1100, Hitachi, Japan). The standard deviations of the content of SS were assumed to follow a χ^2-distribution and the confidence limits were calculated for the 95% probability level [29].

The visual appearance of the compounds and mixtures was examined by means of scanning electron microscopy (SEM) (LEO 1530 Gemini, Leo, UK). The powders were prepared for microscopy at the Department of Medical Cell Biology, Uppsala University, Sweden.

4. Results and discussion

4.1. Primary characteristics of test materials

The primary characteristics of the test materials are summarised in Table 1. The SSG particles had a favourable particle size distribution and the investigated size fractions were easily obtained without pre-treatments such as granulation or milling. The powder flowed well, probably as a result of the nearly spherical shape of the carrier particles. However, it should be borne in mind that other brands of SSG may not have the same primary characteristics as Primojel®. Other superdisintegrants such as croscarmellose sodium or crospovidone should have comparable mucoadhesive properties to those of SSG [31], but these could not be used as carrier particles because of difficulties in obtaining particles with appropriate size range, shape and/or flowability.

4.2. Mixture characteristics

The homogeneity measurements showed that very homogeneous mixtures were formed (Table 2 and Fig. 1). The Pharmacopoeial specifications for low dose nasal powders state that a maximum of 3 out of 30 samples in the correct scale of scrutiny may diverge by over 15% of the mean content but none may deviate by more than 25% [32]. As can be seen by the low CV obtained with the small sized powder thief (Table 2), only the mixture with the smallest carrier fraction (D) did not pass the Pharmacopoeial regulations.

Table 1
Primary characteristics of mixture components

Material[a]	Apparent particle density[b] (g/cm^3)	Particle size[c] (μm)	Surface area[b] (m^2/g)	Heywood surface-volume shape factor[d]	Particle weight[e] (ng)
SSG	1.511 (0.0001)	36.7 (14.6, 62.2)			
A		59.0 (44.1, 73.0)	0.075 (0.002)	6.6	183
B		44.8 (34.0, 58.0)	0.092 (0.003)	6.2	86.7
C		29.5 (21.2, 40.7)	0.13 (0.00)	5.8	29.4
D		16.2 (6.38, 24.6)	0.24 (0.01)	5.8	5.89
SS	1.563 (0.0005)	3.17 (0.840, 10.8)	1.8 (0.1)[e]	8.8	0.442

[a] Letters A–D represent the SSG size range.
[b] Results are shown as mean values of three measurements, standard deviation in parentheses.
[c] Median values based on volume distribution. The values in parentheses indicate the particle diameters below which 10% and 90%, respectively, of the particles fell.
[d] Calculated according to Heywood [15].
[e] Mean value, calculated according to Eq. (2).

Table 2
Summary of mixture characteristics

Mixture[a]	Amount of SS (%)	Theoretical surface coverage (%)	CV (%)[b]
A:1	0.992	5.9	1.77
B:1	1.01	4.9	1.32
C:1	1.01	3.5	1.29
D:1	1.01	1.9	8.15
B:2	2.01	9.8	0.917
B:4	3.83	19	1.18
B:6	6.01	29	3.04

[a] Letters represent the SSG particle size class and numbers represent the theoretical percentage of SS.
[b] The CV was calculated from the 15 mg powder samples.

4.3. Visual appearance

Scanning electron microscopy confirmed that interactive mixtures had been formed in 5 of the 7 mixtures. Representative micrographs are shown in Fig. 2. Interactive mixtures were formed with carrier particles as small as 30 μm and containing up to 4% SS. The bulk properties of the powders were unaffected by the addition of SS, except in the mixtures containing the two highest concentrations where the flowability appeared to be somewhat negatively affected. SEM showed that the mixture with the smallest carrier particle size range (D:1) contained drug agglomerates, which would explain its high CV. The decrease in homogeneity was most probably caused by inadequate deagglomeration forces of the small carrier particles, whose flowability was visibly not as good as that of the other size fractions. Visible drug agglomerates also remained in the mixture with the highest amount of SS (B:6), despite its rather low CV. Interestingly, its surface coverage was not as high as that of the 4% mixture, which indicates that the poor mixture quality was a result of insufficient deagglomeration rather than oversaturation of the binding capacity of the carrier particles. It is therefore possible that this mixture could be improved by prolonging the mixing time [33], or increasing the batch size [25]. Total surface coverage of SSG in size range B would theoretically be

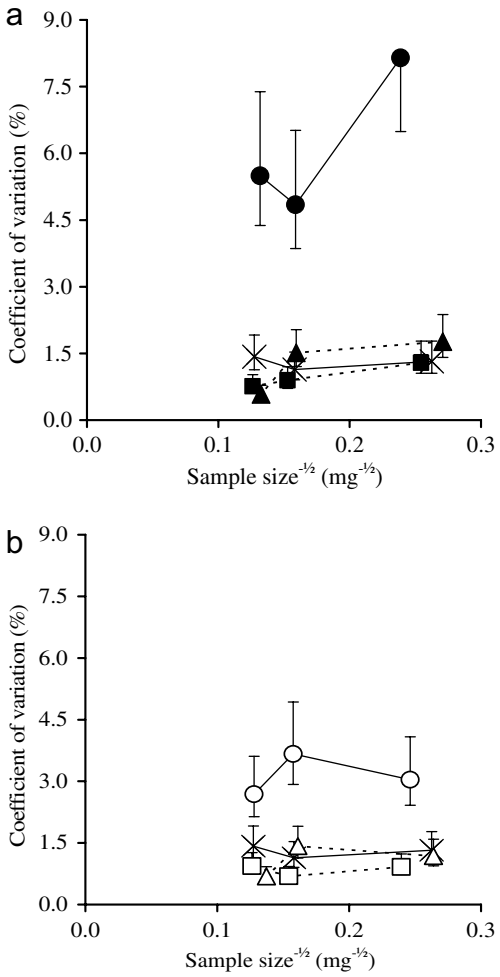

Fig. 1. The effect of carrier particle size and drug content on mixture homogeneity. The figures show experimental results (CV) of 30 samples in 3 sample sizes. (a) The effect of carrier particle size in mixtures containing 1% SS. The symbols denote the size fractions as follows: A (▲); B (×); C (■) and D (●). (b) The effect of drug amount in mixtures containing carrier particles of size fraction B. The symbols denote the content of SS as follows: 1% (×); 2% (□); 4% (△) and 6% (○). Error bars represent confidence limits following a χ^2 distribution at 95% probability level [29]; one upper limit exceeded 9% and was removed to improve the figure clarity.

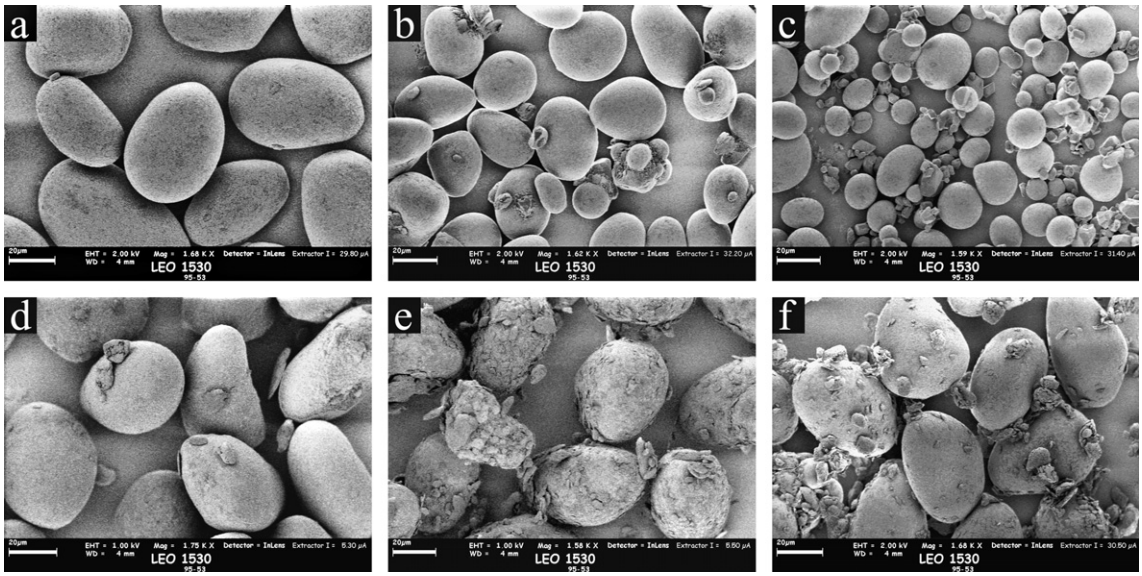

Fig. 2. Representative scanning electron micrographs. (a) SSG size class B; (b) mixture C:1; (c) mixture D:1; (d) mixture B:1; (e) mixture B:4; (f) mixture B:6. Pictures (c and f) show the presence of free aggregates of SS, demonstrating that interactive mixtures were not formed. Scale bars represent 20 μm.

created by the addition of 20% (w/w) SS. As can be seen in Table 2, the amounts applied resulted in much lower theoretical surface area ratios. The maximum amount of fine particles that can be added is dependent on the drug and its particle size and may be increased in some cases, although the surface coverage cannot automatically be expected to be as high as for coarser carrier particles.

4.4. Comparison with theoretical models

The theoretical dependence of CV on the carrier particle size and amount of drug can be seen in Fig. 3. As the carrier particle size decreases, the theoretical homogeneity of a random mixture will approach that of an interactive system and differences will consequently be difficult to detect. An increase in drug amount will also theoretically lead to more homogeneous mixtures, but in this case the effect is more pronounced for interactive mixtures.

Fig. 4 shows the experimental values for the 1% mixture with medium-sized carrier particles (B:1) in comparison with theoretical results. Although the experimental CV is much higher than the theoretical values, it is still within the error range of the analytical procedure, which can be as high as 2% for studies with this type of experimental design [25,28]. However, SEM showed that an interactive mixture had been obtained and if this is used in combination with homogeneity measurements it may be possible to set a limit for an acceptable CV for other mixtures with the same components. New interactive systems will, however, need an initial visual inspection to ascertain the formation of interactive mixtures.

4.5. General discussion

It is important to note that the theoretical models display ideal situations and neither account for analytical errors nor for segregation of particles or ordered units. Furthermore, there is no consideration given to the altered ability of the carrier particles to form interactive units as their size decreases or to the formation of stable aggregates of fine particles. Although the theoretical homogeneity of a randomised mixture approaches that of an interactive mixture as the size of the particles decreases, it is unlikely that a cohesive fine-particulate substance will appear as single units rather than as aggregates or interactive units.

As a result of the difficulties in determining the true homogeneity of interactive mixtures without analytical errors, Crooks and Ho [34] proposed that an arbitrary maximum value of CV 5% could be used to assure good mixture quality in accordance with Pharmacopoeial specifications on tablet uniformity of content. This limit has also been used with respect to interactive mixtures with small carrier particles [6,35]. Only the mixture with the finest particle size (D:1) fell outside this limit in our study. However, as can be seen by the theoretical models, this only describes the mixture homogeneity and does not ensure that an interactive mixture has truly been achieved. Hence, a CV of 5% can only be used to distinguish between random and interactive mixtures for much coarser particle systems. This was also shown in a study by de Boer et al. [36] where, using SEM, the authors saw that no interactive mixtures were formed but nonetheless obtained a CV of 2.8%. It can thus be concluded that even if an appropriate homogeneity evaluation is performed, i.e. at least 30 samples collected from different places in the powder bed, the CV will only be an indication of the type of mixture. Since small carrier particles will result in a lower CV (because more particles are removed with each sample) and since the formation of interactive mixtures cannot automatically be expected in the relevant carrier particle size range, it is important to combine homogeneity measurements with visual inspection of the mixture.

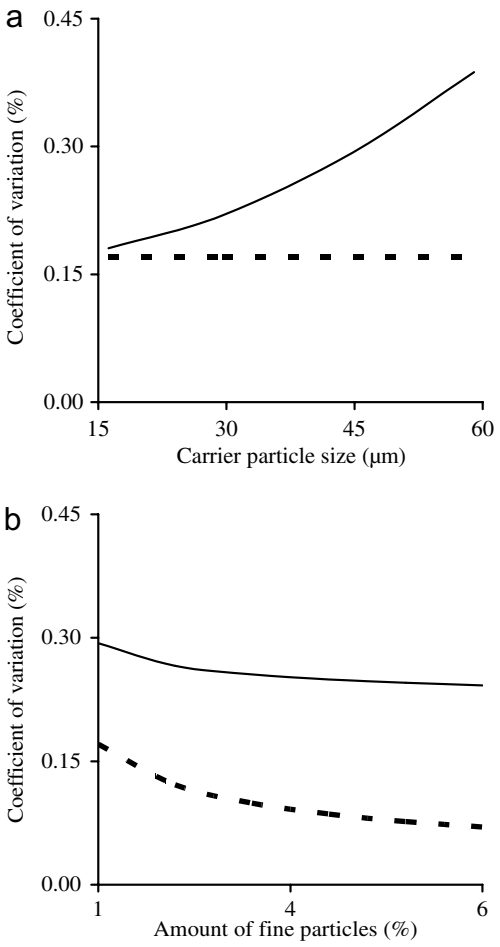

Fig. 3. The theoretical effect on homogeneity of (a) carrier particle size and (b) amount of fine (i.e. drug) particles calculated according to Eqs. (1) and (3) for a sample size of 15 mg. In (a), a drug content of 1% is assumed and, in (b), carrier size B is applied. The effect of carrier particle size is more pronounced for random mixtures (–) whereas the drug amount affects the interactive mixtures (---) to a greater extent.

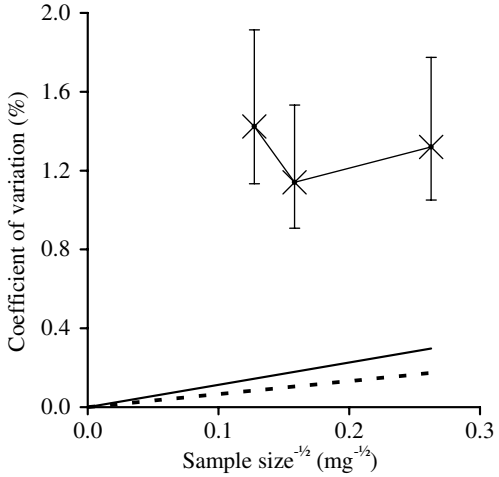

Fig. 4. Theoretical and experimental values of mixture homogeneity for mixture B:1. The figure shows experimental results (×) as well as theoretical values for a random mixture (–) according to Eq. (1) and an interactive mixture (---) according to Eq. (3). Error bars represent confidence limits following a χ^2 distribution at 95% probability level [29].

Interactive mixtures enable a fast absorption of the active component because of its small particle size and deposition on the surface of the carrier; the carrier does thus not need to be fully hydrated before the drug can be released. The extensive capacity for absorbing water that SSG has could, apart from causing mucoadhesion, also induce a temporary opening of the tight junctions in the epithelium and facilitate an instant paracellular drug absorption [37]. SSG proved to be a favourable small-particulate carrier material, probably owing to its good flowability that enables deagglomeration of the fine drug particles. It should be possible to apply the concept of interactive mixing to other mucoadhesive materials such as chitosan, which has already displayed positive effects even in a simple powder mixture [2], where the drug can easily be deposited separate from the mucoadhesive material in the nasal cavity. The prerequisite would be that microparticles with high density and good flowability can be obtained with the approximate size of 30–50 μm.

5. Conclusions

Because of its particle size and powder flowability, SSG (Primojel®) is a good candidate for a small-particulate mucoadhesive carrier material. Interactive mixtures were formed with mucoadhesive carrier particles as small as 30 μm, which is ably suited for nasal administration. This study thus offers a novel way of producing mucoadhesive delivery systems which can easily be used both in the laboratory and on an industrial scale.

CV values can be a good indicator of the formation of an interactive mixture with small carrier particles but, as shown by the theoretical models, these values alone are not sufficient to ensure that all fine particles are adhered to the carriers without remaining agglomerates. The homogeneity measurements will therefore initially need to be complemented with visual inspection of new interactive systems.

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