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Compressibility of alginate microparticles made by emulsification

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INTRODUCTION AND OBJECTIVES

Oral administration of peptidic drugs is of great interest, but difficulties associated with its pharmacokinetics characteristics have thwarted efforts to achieve an efficient formulation.(Allemann 1998)

Emulsification/internal gelation is a scaling-up method used to microencapsulate peptidic drugs where the microparticle diameter can be easily controlled (Poncelet 1992). In this method, gelled alginate microparticles are recovered as an aqueous dispersion which can be freeze-dried, so a solid dosage form can be obtained.

The production of tablets from microparticles is of great interest to the pharmaceutical industry. Mycrocrystalline cellulose (MCC) and lactose are both useful adjuvants in the formulation of tablets by giving plastic and elastic characteristics. Due to the reduced size of these substances, they penetrate through the freeze-dried microparticles network and reduce the particles mechanic forces that could difficult the flow and, consequently, promotes a better compressibility. Thus, main objectives of this work are the set-up of technique to assess the flow properties of dried microparticles, compare obtained results to those obtained with excipients, alone and mixed with microparticles, by determining the Carr index (CI).

MATERIALS AND METHODS

Materials

Alginic acid sodium salt (supplier's specifications: viscosity of 2% solution at 25 ◦C, 250 cps) were purchased from Sigma Chemical Co. (St. Louis, MO, USA) and dextran sulphate sodium salt from Fluka BioChemika (France; approximately MW 5 kDa). calcium carbonate was obtained from Omya (Orgon, France). Paraffin oil was supplied by Vaz Pereira (Lisbon, Portugal). The emulsifier, Span® 80, was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Nebulised lactose and MCC were purchased from Vaz Pereira (Lisboa, Portugal). All other chemicals (Acetone, Hexane, Acetic acid) were of reagent grade or equivalent.

Methods

An aqueous solution of low viscosity sodium alginate (2%, w/v) and dextran sulfate (0,94%, w/v). An aqueous suspension of ultrafine calcium carbonate (5%, w/v) was sonicated for 30 min to break up crystal aggregates, and then dispersed into the alginate–dextran water solution (calcium–alginate ratio, 7%, w/w). Apart from this a mixture of paraffin oil and Span 80® (3%, v/v) was stirred using a mixing impeller at 200 rpm for 15 min. This mixture was used to emulsify the first one with the mixing impeller at 600 rpm. After 15 min emulsification, gelation was triggered by addition of 40mL paraffin oil containing 1mL of acetic acid. After 60 min at 600 rpm, an acetate buffer solution (140mL at pH 4.7, United States Pharmacopeia, USP 30) with dehydrating solvents (acetone, isopropanol and hexane, 30mL:20 mL:10 mL, respectively) was added to the oil-particle suspension and stirred for 5 min at 500 rpm. Then, this mixture was put on an orbital shaker for 15 min. Microparticles-containing biphasic medium was stored at 2ºC for at least 8h followed by the residual oil elimination with a vacuum pump. Aqueous-dispersed microparticles were freeze-dried by using a Freeze Dry System (Labconco™).

Clustered freeze-dried microparticles demand a previous desaglomeration step in order to obtain reproducible results. The Index Carr of formulations, which composition is showed in table 1, was determined according to (Johanson 2009).

Table 1: Composition of tested formulations

Components	Formulation (%) (w/w)					
	F1	F2[a]	F3[b]	F4	F5	F6
Freeze-dried microspheres	100	-	-	3,23	3,23	3,23
Nebulized lactose	-	100	-	96,77	-	-
MCC	-	-	100	-	96,77	-
Nebulized lactose+MCC (1/1)(w/w)	-	-	-	-	-	96,77

[a] Compressibility index of isolated nebulized lactose
[b] Compressibility index of isolated MCC

RESULTS AND DISCUSSION

Results obtained for freeze-dried microparticles without adjuvants, with a Carr Index (CI) of 27,9, classify them with bad flow properties. Nebulized lactose shows

excellent flow properties and the CI of MCC is between acceptable and bad flow properties. It must be emphasized that MCC is used for formulation of tablets, not by it flow properties but rather by its excellent compressibility behaviour, adequate for cores like alginate microparticles, with lower density, not appropriate for compression.

The microparticles-containing formulation having shown the best flowing properties is composed by the mixture of microparticles with nebulized lactose, which gives an acceptable flow property. The MCC improves flowing properties of microparticles, yet still between the bad and acceptable. The CI of the mixture of microparticles and both excipients simultaneously is the worst result obtained. Possibly, it can be explained by the fact that different excipients have different densities, and it could have lead to the segregation of powders during testing and therefore compactation was affected.

Table 2: Compaction and compressibility results obtained for tested formulations

Flow property	Formulation					
	F1	F2	F3	F4	F5	F6
Ability to settle (mL)	43,13	5,82	41,25	10,00	33,75	22,95
Índex Carr (%)	27,92	7,82	25,74	19,00	25,60	26,50
Poured density (mg/mL)	0,02	0,70	0,33	0,50	0,33	0,41
Tapped density (mg/mL)	0,02	0,77	0,45	0,61	0,44	0,56

CONCLUSIONS

Microparticles obtained by emulsification/internal gelation are mainly composed by hydrogels-like materials which lose their water-dependant structure followed a freeze-dried process. Obtained freeze-dried microparticles showed a clustered macroscopic aspect requiring a disaggregation step to obtain more individualized microparticles.

Bad flowing properties obtained for alginate microparticles were improved when they were formulated with nebulised lactose leading to an acceptable flow property.

The set-up of this technique to determinate the Carr's index for microparticles has revealed some obstacles due to the difference of apparent densities between microparticles and excipients.

Studies still being performed and other excipients or formulations will provide better flowing properties of microparticles.

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