TECHNOLOGICAL CHARACTERIZATION OF CARBOXYMETHYLSTARCH METHYL METHACRYLATE COPOLYMERS UNDER HUMID CONDITIONS

Irene Bravo Osuna, Carmen Ferrero Rodríguez y Mª Rosa Jiménez-Castellanos Ballesteros

Dpto. Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, C/ Prof. García González nº 2, 41012 Sevilla, Spain. (e-mail: mrosa@us.es)

Introduction

The presence of water molecules in pharmaceutical solids promotes deep changes in their technological properties (flowability, compressional characteristics, etc.), due to the ability of water to act as lubricant, plasticizer, surfacial contaminant…, depending on its total amount and specific distribution in the solid.

The aim of this work is to analyze the influence of the amount and distribution of water in the flow and compressional behaviour of a carboxymethylstarch methyl methacrylate copolymer (CSMMA), used as direct compression excipient (1).

Materials and Methods

CSMMA was synthetised by free radical copolymerization and dried by vacuum oven (OD) or freeze-drying (FD) (2). The OD derivative was milled (Retsch, Haan, Germany) to obtain powdery samples. The 25-500 μm size fraction of both copolymers was kept in vacuum dessicators to obtain products dried to constant weight. They were subsequently equilibrated over sulphuric acid solutions at four levels of relative humidities (RH) with a temperature of 25 ºC (Table 1). Both copolymers showed a similar water distribution, with a proportional increment of water internally absorbed with RH. On the contrary, the water externally adsorbed was mainly important at RH higher than 80% (3).

The *flow rate* was determined by a data acquisition flowmeter system (4) using a glass and a stainless-steel funnel with several sized holes (5, 10, 15, 20 mm). Data were statistically analysed (ANOVA) and results quoted significant when $p < 0.05$.

Table 1. % weight gained due to sorbed water.

RH (%)	*0*	*25*	*50*	*75*	*100*
OD	*0.0*	*2.3*	*4.7*	*9.1*	*19.6*
FD	*0.0*	*2.0*	*3.9*	*7.6*	*17.2*

The *evaluation of the consolidation mechanism* of powders was made on the basis of Heckel equation, using both the tablet-in-die and ejected-tablet methods. Copolymers stored at different RHs were also compacted into tablets of 500 mg weight, 12 mm diameter and 70-80 N breaking force to analyse compression parameters and physical properties.

Results and Discussion

OD-CSMMA samples showed free flow (values higher than 10 g/s) when tested with the *glass funnel* (10 mm diameter). Moreover, the flow rate increased from 0 to 25%RH, due to the lubricant effect of water. The increase in powder cohesiveness observed at RH>25% was due to the liquid bridge formation in the contact points of particles, caused by the presence of externally adsorbed water. FD-CSMMA was more independent with RH, offering poor flow characteristics in the whole range of RH, because of its higher particle size and irregular surface (1). Only at 75%RH the lubricant effect of externally adsorbed water was observed. The influence of RH was more evident when using the *stainless-steel funnel* (20 mm diameter), revealing in all cases a better flow behaviour for OD-CSMMA.

Table 2. Heckel parameters: mean yield pressures of total deformation (K_d), plastic deformation (K_p), total elastic deformation (K_{et}).

RH (%)		K_d (MPa)	K_p (MPa)	K_{et} (MPa)
OD	0	77.77 (7.28)	157.95	153.21
	25	82.01 (8.30)	140.65	196.73
	50	91.32 (4.21)	111.30	508.80
	75	62.06 (4.82)	98.58	167.51
FD	0	78.44 (6.28)	105.05	309.66
	25	87.77 (4.85)	81.88	*****
	50	56.24 (2.09)	76.12	215.41
	75	50.10 (2.51)	95.70	105.17

*****K_d value was higher than K_p value.

Heckel analysis demonstrated a plastic consolidation mechanism for both copolymers (Table 2), being this tendency even improved by the plasticizing effect of absorbed water according with K_p values, especially for the OD derivative. A diminish in the total elastic deformation for OD-CSMMA at 50%RH and the total absence of elasticity for FD-CSMMA at 25%RH confirmed these intermediate conditions as the best to improve the consolidation mechanism of these copolymers.

Table 3. Compression parameters: maximum applied upper punch pressure (P), maximum ejection force (F_e), Juslin's friction work (W_f)

	RH(%)	P (MPa)	F_e (N)	W_f (J)
OD	0	123.79 (0.01)	822.25 (31.68)	2.95 (0.17)
	25	140.71 (0.01)	855.72 (18.77)	3.31 (0.23)
	50	99.09 (0.01)	767.67 (64.61)	3.20 (0.30)
	75	263.57 (0.08)	1693.81 (216.53)	5.13 (1.55)
FD	0	65.62 (0.01)	529.43 (71.45)	3.04 (0.47)
	25	63.69 (0.01)	202.13 (22.40)	2.01 (0.21)
	50	50.64 (0.01)	302.86 (34.16)	2.68 (0.25)
	75	82.72 (0.00)	139.72 (5.92)	1.69 (0.06)

The positive effect of water in interparticulate unions at intermediate RH was also seen in *the maximum applied upper punch pressure (P)* values (Table 3). The surfacial contaminant and hydrodinamic effects of water made difficult the tablets elaboration at 75%RH and impossible at 100%RH.

The increment in adhesion and cohesion forces promoted by the presence of externally adsorbed water onto the OD-CSMMA particles was the cause of the rise in the *maximum ejection force (F_e)* and *Juslin's friction work (W_f)* observed at 75%RH, which was already noticed in flow studies. FD-CSMMA samples showed a completely different behaviour, with a decrease in the value of both parameters especially at high RH conditions. This might be the result of the presence of adsorbed water molecules (lubricant effect), as was also detected when studying the copolymer flow behaviour.

A decrease in *tablet thickness* was observed at 75%RH due to the plasticizing effect of water. In the same trend, the *friability* percentage of tablets diminished at RH≥50%. The results of these two tests revealed the cohesive effect of water, which made that only OD-CSMMA at 50% and 75%RH and FD-CSMMA at 75%RH batches had friability percentages lower than 1% (5). Related with the *disintegration study*, all batches showed disintegration times larger than 30 min, remaining the tablets nearly intact after the test.

In conclusion, these new products must be stored and manipulated at 25-50%RH, in order to maximize their technological characteristics and guarantee their use as direct compression excipients.

References

1. Ferrero C. and Jiménez-Castellanos, Int. J. Pharm., 248, 157 (2002).

2. Castellano I. et al., Carbohyd. Polym., 34, 83 (1997).

3. Bravo-Osuna I. et al., Eur. J. Pharm. Biopharm. (in press).

4. Muñoz-Ruiz A. and Jiménez-Castellanos, M.R., Pharm. Techn. Int. Biopharm., 8(4), 21 (1993).

5. European Pharmacopeia 3ª Ed., Council of Europe, Strasbourg, France, 1997.

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