PHARMACEUTICAL AND TECHNOLOGICALCHARACTERISTICS OF BARIUM SULPHATE TABLETS -THE SCREENING OF VARIOUSFORMULATION FACTORS

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Introduction

The study examined the development of barium sulphate tablets that do not dissolve in the digestive tract and are used as a contrasting agent for measuring transit time through the column. Several different formulations were tested in which they were varied: the presence of different polymers Eudragit ® RS PO and/or PMMA, wet granulation and direct compression procedure, different granulation of filler calcium hydrogen phosphate dihydrate, and the time of sintering in a pair of organic solvent s of acetone or IPA at different time intervals. The results of the tensile strength of the tablets that are important for the further sintering process and the degradability of sintered tablets were monitored as the output parameter. In the final manufact uring process - tablet sintering, only formulations in which the tensile strength of the tablet was ≥20 MPa were used. For this reason, direct compression tablets, as well as wet granulation formulations with PMMA, are not sintered. The tensile strength of the tablet before and after sintering indicates that the "wet" granulation is more efficient with IPA because it produces better compacted granules (higher tensile strengths), while acetone is more efficient in the sintering process at 35 °C , which is exp ected due to the higher vapor pressure at that temperature compared to the IPA.

Materials and Methods

The tablets are made by the wet granulation process, and the direct compression process, and the pharmaceutical and technological characteristics of t he tablets have been compared. The API Barium sulphate (Merck, Germany) was used. The essence of the formulation is based on the use of two polymers: polymethyl methacrylate (PMMA DP 300 U) and copolymers of ammonium methacrylic acid (Eudragit® RS PO). The formulation composition is presented in table 1.

Table 1. Composition of the tested barium sulfate tablet formulations

Formulation	**A**	**B**	**C**	**D**	**E**	**F**	**G**
Barium sulfate	100,00	100,00	100,00	100,00	100,00	100,00	100,00
Calcium hydrogen phosphate dihydrate powder	75,00	75,00	75,00	75,00	75,00	75,00	0
Calcium hydrogen phosphate dihydrate (Emcopress®)	0	0	0	0	0	0	75,00
Eudragit RS PO	45,00	90,00	0	45,00	45,00	45,00	45,00
PMMA DP 300 U	45,00	0	90,00	45,00	45,00	45,00	45,00
Purified water	45,00	45,00	45,00	45,00	45,00	0	0
Acetone	6,00	6,00	6,00	0	0	0	0
Isopropyl alcohol	0	0	0	0	6,00	0	0
Ethanol conc. (96%)	15,00	15,00	15,00	15,00	15,00	0	0
Magnesium stearate	3,00	3,00	3,00	3,00	3,00	3,00	3,00
Tablet mass	**268,00**	**268,00**	**268,00**	**268,00**	**268,00**	**268,00**	**268,00**

Wet granulation

In laboratory tests, mixing and wet granulation were carried out in a high shear mixer and dried at 50 ° C in a fluidization oven. A vacuum processor was used for the pilot test. In the vacuum processor homogeneous mixing of the previously measured barium sulphate, calcium hydrogen phosphate dihydrate, Eudragit RS PO, and PMMA DP 300 U. The granulation solution is a mixture of acetone or isopropanol, concentrated ethanol, and purified water, i.e. isopropanol and purified water and purified water. The wet ag glomerated mass is dried in a vacuum processor by heating to a temperature of 50 °C., and the vacuum is included with occasional stirring until is achieved loss on drying of not more than 1% (at 105 °C). Magnesium stearate was added to the diluted granulate and further stirred.

Tableting

Compression of laboratory trials was performed on an eccentric tablet press EKO type, and pilot trials were performed on a Kilian rotary tablet press Synthesis 500. For the 80 mg dose, the characteristics of the tablets were: mass: 0.268 g, diameter: 8.8 - 9.2 mm, and hardness: at least 20.0 MPa.

Sintering

Tablets were sintered in a sealed chamber saturated with either acetone vapor or isopropanol vapor at 35°C (± 2°C) for 8h, 16h, 24h, 32h, and 40h.

Drying

After sintering, the tablets were dried or residual acetone or isopropanol is removed to a maximum of 2.5 mg/tablet. The sintered tablets were dried according to the scheme: 1) Temperatures 22°C for 16 h, 2) 40°C for 24 h, 3) 50°C for 8 h and 4) 55°C for 8 h.

Results and discussion

Formulation (C) made with PMMA DP 300 U, without the addition of Eudragit® RS PO polymer could not be compressed due to the spherical shape of PMMA DP 300 U cones which is extremel y unfavorable for compression. Better results were achieved with formulation F made by direct compression of powdered calcium hydrogen phosphate dihydrate. Tablets were obtained, but their hardness was lower than the minimum necessary for further manipulat ion (sintering).

Table 2. Tensile strengths of formulation A tablets before (A^0) and after sintering in isopropanol (A_{IPA}) and acetone (A_A): 7 h -A^1, 14 h -A^2, 21 h -A^3, 28 h -A^4 and 35 h -A^5.

Tablet	Tensile strength (MPa)										
	IPA						Aceton e				
	A^0	A^1_{IPA}	A^2_{IPA}	A^3_{IPA}	A^4_{IPA}	A^5_{IPA}	A^1_A	A^2_A	A^3_A	A^4_A	A^5_A
1	23	25	41	40	44	69	180	289	307	293	344
2	25	44	46	47	93	70	187	296	295	329	318
3	25	47	88	78	92	61	165	308	334	297	326
4	27	25	70	67	49	95	132	274	296	318	313
5	26	23	70	71	65	101	154	303	310	308	320
6	25	46	75	78	73	90	128	298	297	282	336
7	29	35	69	52	79	99	195	322	319	333	315
8	29	43	56	93	62	68	125	302	311	289	308
9	26	49	76	92	90	86	133	319	291	301	310
10	24	45	69	69	97	87	140	299	282	308	324
Average value	**25,9**	**38,2**	**66,0**	**68,7**	**74,4**	**82,6**	**153,9**	**301,0**	**304,2**	**305,8**	**321,5**
RSD (%)	***1,50***	***9,0***	***11,0***	***13,8***	***15,8***	***12,5***	***22,3***	***8,9***	***10,9***	***12,2***	***8,1***

Table 3. Tensile strengths of formulation B tablets before (B^0) and after sintering in isopropanol (B_{IPA}) and acetone (B_A): 7 h -B^1, 14 h -B^2, 21 h -B^3, 28 h -B^4 and 35 h -B^5.

Tablet	Tensile strength (MPa)										
	IPA						Aceton e				
	B^0	B^1_{IPA}	B^2_{IPA}	B^3_{IPA}	B^4_{IPA}	B^5_{IPA}	B^1_A	B^2_A	B^3_A	B^4_A	B^5_A
1	38	42	76	79	81	97	111	258	240	242	265
2	25	57	90	67	91	79	197	237	289	231	332
3	30	43	104	80	87	93	127	276	277	295	265
4	36	56	74	91	79	89	196	216	238	277	329
5	35	49	68	87	128	94	168	299	223	272	283
6	33	75	89	94	86	66	152	259	287	343	271
7	20	47	80	89	79	103	154	236	255	330	334
8	33	54	92	102	82	104	139	318	239	286	336
9	30	66	88	93	91	95	193	219	280	243	274
10	35	61	58	85	82	103	151	233	291	330	269
Average value	**31,5**	**55,0**	**81,9**	**86,7**	**88,6**	**92,3**	**158,8**	**255,1**	**261,9**	**284,9**	**295,8**
RSD (%)	***4,2***	***8,0***	***10,7***	***7,2***	***8,8***	***8,6***	***23,8***	***26,9***	***22,9***	***31,9***	***29,6***

Table 4. Tensile strengths of formulation D tablets before (D^0) and after sintering in isopropanol (D_{IPA}) and acetone (D_A): 7 h -D^1, 14 h -D^2, 21 h -D^3, 28 h -D^4 and 35h -D^5.

Tablet	Tensile strength (MPa)										
	IPA						Aceton e				
	D^0	D^1_{IPA}	D^2_{IPA}	D^3_{IPA}	D^4_{IPA}	D^5_{IPA}	D^1_A	D^2_A	D^3_A	D^4_A	D^5_A
1	26	29	37	52	138	145	89	211	234	250	288
2	25	22	52	55	87	71	164	235	246	250	273
3	25	24	34	38	50	65	216	249	237	243	261
4	23	28	55	52	141	64	126	242	242	256	280
5	24	28	46	52	80	109	139	221	250	261	291
6	24	29	43	52	87	102	126	236	264	249	279
7	22	22	34	55	67	145	138	244	269	268	278
8	22	24	58	41	56	86	191	243	224	232	270
9	23	21	48	42	60	74	151	223	269	241	276
10	22	30	52	44	116	88	95	255	252	251	273
Average value	**23,6**	**25,7**	**45,9**	**48,3**	**88,2**	**94,9**	**143,5**	**235,9**	**248,7**	**250,1**	**276,9**
RSD (%)	***1,2***	***3,1***	***7,1***	***5,6***	***26,1***	***24,3***	***29,6***	***10,7***	***12,1***	***7,1***	***6,3***

Table 5. Tensile strengths of formulation E tablets before (E^0) and after sintering in isopropanol (E_{IPA}) and acetone (E_A): 7 h -E^1, 14 h -E^2, 21 h -E^3, 28 h -E^4 and 35h -E^5 .

Tablet	Tensile strength (MPa)										
	IPA						Aceton e				
	E^0	E^1_{IPA}	E^2_{IPA}	E^3_{IPA}	E^4_{IPA}	E^5_{IPA}	E^1_A	E^2_A	E^3_A	E^4_A	E^5_A
1	60	118	126	139	131	229	83	176	309	309	335
2	58	114	162	149	181	186	85	281	323	334	360
3	46	119	143	154	143	182	104	257	320	332	351
4	62	102	136	136	166	182	108	199	328	304	335
5	43	116	136	176	162	194	115	204	326	338	341
6	40	111	118	169	162	158	132	155	290	317	316
7	53	107	130	181	134	201	95	222	306	295	342
8	47	118	177	176	196	188	94	175	293	256	331
9	47	114	161	140	170	174	92	197	300	287	313
10	45	105	130	173	202	158	104	187	345	328	322
Average value	**50,1**	**110,4**	**141,9**	**159,3**	**164,7**	**185,2**	**101,2**	**205,3**	**314,0**	**310,0**	**334,6**
RSD (%)	***6,5***	***4,9***	***15,1***	***15,7***	***18,3***	***14,4***	***11,4***	***28,8***	***14,4***	***19,8***	***11,3***

The results of the tensile strengths of the tablets before and after sintering indicate, when it comes to the solvents IPA and acetone, that for "wet" granulation the solvent IPA is more effective because it gives granules that are better compacted (higher tensile strengths are obtained), while acetone in the sintering process at 35°C a more effective solvent, which is expected given the higher vapor pressure at that temperature compared to IPA. The intervals (days) during which the disintegration of the tablets did not occur during the disintegration test are shown with the sign √, while the time when the opalescence of the medium was observed due to the dissolution of the polymer matrix and the release of barium sulfate registered as the hour of the first appearance of opalescence.

Table 6. Examination of the disintegration of bariu m sulfate tablets sintered in an atmosphere of acetone and isopropanol in a phosphate buffer pH 7.4: 7 h - A^1, B^1, D^1 and E^1, 14 h - A^2, B^2, D^2 and E^2, 21 h - A^3, B^3, D^3 and E^3, 28 h – A^4, B^4, D^4 and E^4 and 35 h – A^5, B^5, D^5 and E^5

sample	Acetone							IPA						
	Disintegration time (h)													
	24 h	48 h	72 h	96 h	120 h	144 h	168 h	24 h	48 h	72 h	96 h	120 h	144 h	168 h
A^1	√	√	√	6 h	-	-	-	√	√	√	2 h	-	-	-
A^2	√	√	√	√	3 h	-	-	√	√	√	√	1 h	-	-
A^3	√	√	√	√	√	4 h	-	√	√	√	√	√	2 h	-
A^4	√	√	√	√	√	5 h	-	√	√	√	√	√	4 h	-
A^5	√	√	√	√	√	√	√	√	√	√	√	√	√	√
B^1	√	√	7 h	-	-	-	-	√	√	3 h	-	-	-	-
B^2	√	√	√	5 h	-	-	-	√	√	√	1 h	-	-	-
B^3	√	√	√	7 h	-	-	-	√	√	√	3 h	-	-	-
B^4	√	√	√	8 h	-	-	-	√	√	√	6 h	-	-	-
B^5	√	√	√	√	2 h	-	-	√	√	√	√	1 h	-	-
D^1	√	8 h	-	-	-	-	-	√	4 h	-	-	-	-	-
D^2	√	√	6 h	-	-	-	-	√	√	4 h	-	-	-	-
D^3	√	√	√	5 h	-	-	-	√	√	√	1 h	-	-	-
D^4	√	√	√	√	2 h	-	-	√	√	√	√	1 h	-	-
D^5	√	√	√	√	7 h	-	-	√	√	√	√	4 h	-	-
E^1	√	√	√	√	2 h	-	-	√	√	√	√	1 h	-	-
E^2	√	√	√	√	√	5 h	-	√	√	√	√	√	3 h	-
E^3	√	√	√	√	√	√	6 h	√	√	√	√	√	√	3 h
E^4	√	√	√	√	√	√	√	√	√	√	√	√	√	8 h
E^5	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Conclusion

Tests of different formulations and technological parameters in the production process showed that for obtaining a contrast agent for examining the functional radiology of the colon, rectum and anal canal, i.e. measuring the transit time through the colon, which meets the defined criteria, the most adequate formulation is that, apart from barium sulfate in its it contains calcium -hydrogen phosphate dihydrate powder, an equivalent amount of Eudragit RS PO and PMMA DP 300 U polymers, that in the process of wet granulation, isopropanol is used as a solvent, in addition to ethanol and water, and the sintering process is carried out in the vapor of the organic solvent acetone at 35 °C.