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CHARACTERIZATION OF COMPRESSION BEHAVIOR OF CO-PROCESSED EXCIPIENT FOR PRODUCTION OF ORALLY DISPERSABLE TABLETS AND OF THEIR BLENDS WITH ACTIVE INGREDIENT

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PURPOSE

Orally Dispersable Tablets (ODTs) are designed to disintegrate or dissolve rapidly in the mouth on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids.
Therefore ODTs can allow to improve treatment compliance and comfort of patients suffering dysphagia or other kinds of impaired swallowing [1].
Co-processed excipients suitable for compression into fast disintegrating tablets (CPE-ODT) are available on the market from several manufacturers. Usually they comprise a soluble filler and a superdisintegrant, possibly combined with other excipients functional to the applied co-processing technique (i.e. granulation, spray drying) [2].
CPE-ODT can be directly blended with active ingredient and lubricant and compressed into tablets, resulting in cost and time efficient development and manufacturing process.
Investigation of relationships among compaction stress (i.e. pressure), compacts solid fraction or porosity and compacts mechanical strength (i.e.tensile strength) is fundamental to optimize and speed-up tablets composition screening and tableting process development [3].
Reaching a good balance between strength of inter-particles bonding and porosity is particularly important for ODTs that must quickly disintegrate maintaining mechanical resistance suitable for downstream operations (i.e. packaging) and handling.
This work aimed to establish a general (pre)formulation screening method based on generation of compressibility, compactibility and tablettability profiles of selected CPE-ODTs blended with increasing amounts of target drug. These data should provide useful indication about drug load impact on compression behavior and on key properties (friability, disintegration time) of the obtained ODTs.

METHODS

The CPE-ODTs selected for this work were: Ludiflash (BASF, D), Pharmaburst 500 (SPI Pharma, F), F-MeltType C (Fuji Health Science, J),Smart EX (ShinEtsu, J). Ludipress (BASF, D) CPE was selected as non-ODT comparison reference.

All these materials were kindly provided by the manufacturers.

Target drug was niacin fine powder with d=20 µm as per supplier CoA (Lonza Europe, CH).

Blends of CPE-ODTs and niacin listed in Table 1 have been prepared in a free fall blender (MB015, Pharmatech, England) equipped with 1 liter bin. Batch size was 250 g. Pre-blending of all components other than lubricant was conducted at 15 rpm for 15 minutes. Blending with lubricant was conducted at 15 rpm for 3 minutes.

Blends were compacted using an instrumented single punch tablet press (EK0, Korsch, D) equipped with one round flat faced punch of 11.28 mm diameter. Fifteen tablets were prepared at each compaction pressure: 40, 80, 120 and 160 MPa.

Co-processed excipient name	Blend code	Niacin (%w/w)	CDE (%w/w)	CPVP (%w/w)	Mg stearate (%w/w)
Ludiflash®	C1-0	0	99	-	1
	C1-10	10	89	-	1
	C1-50	50	49	-	1
Ludipress®	C2-0	0	99	-	1
	C2-10	10	89	-	1
	C2-50	50	49	-	1
Pharmaburst® 500	C3-0	0	99	-	1
	C3-10	10	89	-	1
	C3-50	*50*	*49*	-	*1*
F-Melt® Type C	C4a-0	0	99	-	1
	C4a-10	10	89	-	1
	C4a-50	50	49	-	1
F-Melt® Type C+crospovidone	C4b-0	0	94	5	1
	C4b-10	10	84	5	1
	C4b-50	*50*	*44*	*5*	*1*
SmartEx®	C5-0	0	99	-	1
	C5-10	10	89	-	1
	C5-50	50	49	-	1

Table1 – Composition of the blend tested for each excipient.

Each tablet was characterized for weight (analytical balance Sartorius Secura125-1s), thickness (digital caliper 0.01 mm, Mitutoyo Ltd, J), hardness(hardness tester M8-Dr.Schleuniger Pharmatron), friability (USP-NF tester Erweka-TAR) and disintegration time (USP-NF Erweka ZT-3). Tensile strength, solid fraction and porosity values were derived from the measured properties of blends and tablets [3-5].

Heckel (HK) and Ryshkewitch-Duckworth (RD) equations [3-5] were used to fit experimental data and obtain respectively mean yield pressure(P), indicator of blend compressibility, and slope of RD linear regression (k), indicator of blend compactibility.

Slope of linear regression of tensile strength versus compaction force (TA) values was used as tabletability indicator (k) [3-5].

RESULTS

The correlation coefficients (R, Table 2) of the compressibility, compactibility and tabletability regressions range from 0.950 to 0.999 indicating reliability of the linear fitting and of the derived parameters for all the tested materials.

The analysis of regression parameters (Table 2) suggest that Ludiflash®, F-Melt® and SmartEx® compressibility is significantly higher (Py values difference of 40-50 MPa [6]) than that of Pharmaburst® and Ludipress®; whilst F-Melt® C showed the highest value of ka, significantly different (about 100 MPa) than that of other tested CPEs, suggesting the best tabletability. According with values of kr (ranging between 0.1150 to 0.1222) the evaluated CPE-ODTs have comparable comapctibility.

The value of porosity at similar compaction pressure are comparable for all the CPE-ODTs, and reflect very fast disintegration time ranging from 4-8 seconds to 60 seconds with increase of pressure from about 40 to about 170 MPa.

On the other hand friability values below the Pharmacopoeial standard of 1% were obtained at low compaction pressure (80 MPa) for Ludiflash® and F.Melt® C only; other tested CPEs required 160 MPa or more to comply with that limit.
Niacin seems to impact negatively the compression performance and to increase disintegration time and friability when blended with CPE-ODTSs, with a very significant effect at 50% drug load, and minor impact at 10% drug load.

										Compressibility estimation				Tabletability estimation		Compactibility estimation	
	Niacin amount	Compaction Pressure (P)	Weight	Thickness	Hardness	Tensile strength (σ)	Porosity (ε)	Friability	Disintegration time	Heckel equation parameters				Tensile strength (σ) Compaction pressure (P) equation parameters		Ryshkewitch-Duckworth equation parameters	
Excipient	%w/w	MPa	mg	mm	N	MPa	%	%	seconds		R Square	K	Py	R Square	Ka	R Square	Kr
Niacin	-	41	454.6	3.62	37.7	0.56	33.8	Not measured	>1200								
		80	456.6	3.59	64.0	1.01	14.5	Not measured	>1200								
		117	455.8	3.43	91.3	1.50	10.7	Not measured	>1200								
		175	457.8	3.38	156.3	1.77	8.9	Not measured	>1200								
Ludiflash	0	39	444.7	4.25	25.9	0.34	28.9	3.05	17	LN(1 / ε) = 0.0076P + 0.0075	0.9585	0.0075	133	σ = 0.0179P - 0.2883	0.9937	0.0179	LN(σ) = -0.115εK + 2.2594	0.9981	-0.115
		79	443.1	3.69	80.3	1.23	18.3	1.07	24										
		120	440.9	3.49	114.8	1.86	13.9	0.84	24										
		161	440.5	3.38	153.1	2.56	11.5	0.77	22										
	10	45	426	4.12	33.5	0.46	31.0	2.55	12	LN(1 / ε) = 0.0079P + 0.0079	0.9568	0.0079	127	σ = 0.0189P - 0.4051	0.9999	0.0189	LN(σ) = -0.0923εK + 2.053	0.9908	-0.0923
		90	452	3.70	84.8	1.29	16.4	1.19	18										
		120	454.1	3.59	118.5	1.87	15.5	0.84	24										
		157	454.5	3.48	159.1	2.58	12.7	0.69	60										
	50	46	456.7	3.95	26.7	0.38	23.3	3.72	25	LN(1 / ε) = 0.0055P + 0.0055	0.9597	0.0055	182	σ = 0.0133P - 0.1527	0.9807	0.0133	LN(σ) = -0.1425εK + 2.3712	0.9981	-0.1425
		89	451.2	3.57	70.2	1.11	16.2	1.69	114										
		138	442.7	3.35	109.1	1.83	12.5	1.17	185										
		184	446	3.32	130.4	2.22	10.8	1.01	313										
Ludipress	0	37	463.1	4.40	17.1	0.22	31.8	5.29	80	LN(1 / ε) = 0.0061P + 0.0061	0.9927	0.0061	164	σ = 0.0153P - 0.399	0.9955	0.0153	LN(σ) = -0.1346εK + 2.7968	0.9979	-0.1346
		78	456.1	3.87	49.4	0.72	23.6	1.23	60										
		122	458.9	3.63	94.7	1.47	18.1	0.65	108										
		162	461.2	3.51	131.1	2.11	14.9	0.42	191										
	10	44	459.2	4.16	19.4	0.26	28.8	4.29	90	LN(1 / ε) = 0.0061P + 0.0061	0.9934	0.0061	164	σ = 0.0154P - 0.4448	0.9989	0.0154	LN(σ) = -0.1399εK + 2.7176	0.9971	-0.1399
		79	458.4	3.83	49.8	0.74	22.0	1.48	107										
		128	454.2	3.55	95.2	1.52	16.6	0.84	212										
		162	450.2	3.40	124.6	2.07	13.9	0.62	176										
	50	40	Compacts not sufficiently bound to be tested																
		80	439.2	3.55	38.2	0.61	21.8	2.44	37	LN(1 / ε) = 0.0039P + 0.0039	0.9907	0.0039	256	σ = 0.0127P - 0.3684	0.9936	0.0127	LN(σ) = -0.1567εK + 2.9458	0.9934	-0.1567
		131	437.2	3.33	80.2	1.36	17.2	1.06	44										
		193	431.3	3.16	113.0	2.05	14.0	0.34	198										
Pharmaburst 500	0	39	438.3	4.78	15.8	0.19	37.6	5.79	4	LN(1 / ε) = 0.0057P + 0.0057	0.9989	0.0057	175	σ = 0.0147P - 0.4983	0.9737	0.0147	LN(σ) = -0.122εK + 2.9832	0.9954	-0.122
		81	460.8	4.41	48.7	0.62	29.0	3.51	10										
		116	457.9	4.11	77.3	1.06	24.3	1.76	18										
		170	463.4	3.84	144.3	2.12	17.8	1.01	26										
	10	45	469.4	4.69	23.6	0.28	32.4	2.95	5	LN(1 / ε) = 0.005P + 0.005	0.9514	0.005	200	σ = 0.0147P - 0.3491	0.9969	0.0147	LN(σ) = -0.1396εK + 3.2552	0.9995	-0.1396
		98	458.1	3.99	79.6	1.13	22.4	1.00	7										
		116	456.5	3.86	94.1	1.38	21.2	1.13	12										
		159	436.2	3.61	124.7	1.95	18.4	Not available	10										
F-Melt C	0	46	454.7	4.42	28.1	0.36	32.7	2.23	11	LN(1 / ε) = 0.0078P + 0.0078	0.9932	0.0078	128	σ = 0.0273P - 0.969	0.9968	0.0273	LN(σ) = -0.1178εK + 2.8536	0.9987	-0.1178
		81	453.2	3.88	78.7	1.15	23.4	0.08	10										
		122	455.5	3.60	148.2	2.33	17.2	0.10	18										
		159	456.2	3.45	208.9	3.42	13.5	0.03	163										
	10	40	459	4.56	20.1	0.25	33.8	5.16	3	LN(1 / ε) = 0.0074P + 0.0074	0.9867	0.0074	135	σ = 0.0222P - 0.7015	0.9957	0.0222	LN(σ) = -0.1227εK + 2.7755	0.9988	-0.1227
		77	466	3.99	66.9	0.95	23.1	0.81	7										
		123	457.1	3.64	126.3	1.96	17.5	0.36	11										
		159	454.5	3.46	177.5	2.90	13.6	0.22	15										
	50	46	446.9	3.95	14.9	0.21	25.4	6.05	7	LN(1 / ε) = 0.007P + 0.007	0.9801	0.007	143	σ = 0.0145P - 0.4429	0.9973	0.0145	LN(σ) = -0.1423εK + 2.5832	0.9975	-0.1423
		90	455.8	3.62	57.6	0.90	17.0	1.55	600										
		125	451.5	3.46	81.5	1.33	14.0	1.15	>1200										
		147	455	3.43	103.5	1.70	12.5	0.65	>1200										
F-Melt C + crospovidone	0	42	454.5	4.66	23.1	0.26	35.3	4.99	11	LN(1 / ε) = 0.0083P + 0.0083	0.9989	0.0083	120	σ = 0.0237P - 0.7774	0.9986	0.0237	LN(σ) = -0.1116εK + 2.6854	0.9844	-0.1116
		85	449.9	3.92	80.9	1.17	23.9	0.34	12										
		120	453.3	3.68	134.8	2.07	18.4	0.11	13										
		167	456.3	3.46	195.7	3.20	12.4	0.08	39										
	10	47	451.6	4.49	18.6	0.23	33.1	7.41	2	LN(1 / ε) = 0.0069P + 0.0069	0.9867	0.0069	145	σ = 0.0212P - 0.8248	0.9973	0.0212	LN(σ) = -0.1289εK + 2.8502	0.9959	-0.1289
		87	448.8	3.90	63.9	0.93	23.4	0.86	3										
		125	453.2	3.68	118.3	1.82	17.6	0.30	12										
		180	452.3	3.46	184.4	3.01	13.1	0.23	23										
SmartEx	0	45	4	4.05	34.4	0.48	27.2	3.18	12	LN(1 / ε) = 0.0059P + 0.0059	0.9881	0.0059	169	σ = 0.0168P - 0.2439	0.9986	0.0168	LN(σ) = -0.1189εK + 2.5376	0.9955	-0.1189
		81	446.5	3.67	75.6	1.16	20.6	1.39	17										
		113	436.6	3.44	103.1	1.66	17.2	1.16	17										
		166	444.6	3.35	149.9	2.53	13.2	0.95	18										
	10	47	454.8	4.05	37.0	0.52	26.5	3.33	5	LN(1 / ε) = 0.0053P + 0.0053	0.9837	0.0055	182	σ = 0.0159P - 0.1943	0.996	0.0159	LN(σ) = -0.1201εK + 2.5415	0.9976	-0.1201
		83	454.2	3.72	74.8	1.14	20.1	1.51	5										
		124	453.1	3.55	116.1	1.85	16.4	1.17	9										
		169	448.7	3.39	147.4	2.45	13.4	0.89	15										
	50	36	3.9	2.10	20.6	0.30	26.0	4.57	10	LN(1 / ε) = 0.0056P + 0.0056	0.9558	0.0056	179	σ = 0.0112P + 0.0083	0.9588	0.0112	LN(σ) = -0.1308εK + 2.2364	0.9917	-0.1308
		77	453.2	3.63	80.1	0.93	18.1	1.80	18										
		113	457.7	3.53	89.8	1.44	14.8	1.27	220										
		173	446.5	3.32	108.4	1.94	11.9	0.87	>600										

Table 2 – Summary of tablets characterization results and of the fitting of Heckel and Rishkewitch-Duckworth and tabelttability equations

CONCLUSIONS

The applied screening approach allowed to point out differences of blends compression depending on CPE-ODT type and on drug load. These differences could explain the observed changes of compacts porosity, tensile strength, friability and disintegration time values.

This approach will be further evaluated in new experimental works with other target drugs.

REFERENCES

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