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FLOWABILITY TESTING OF DIRECTLY COMPRESSIBLE EXCIPIENTS ACCORDING TO BRITISH PHARMACOPOEIA

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ABSTRACT

Flowability and packability of thirteen commercially available, direct compression excipients, Avicel® CE-15, Prosolv SMCC® HD-90, Prosolv SMCC™ -90, Tablettose 80, Flowlac 100, Cellactose 80, Microcelac 100, Ludipress, Ludipress® LCE, Emcompress®, Starch 1500® G, Era Tab and Maize starch-B were examined according to the technical procedure described in the current British Pharmacopoeia. Results revealed unfavorable properties for Ludipress compared to other substances. Ludipress, however, appeared macroscopically to be of extremely pronounced free flowing properties. This contraindication was studied in more detail, proposing to express powder flow in terms of volume per time unit rather than mass time unit (Volume-flowability). Avicel® CE-15, Starch 1500® G, Era Tab and Maize starch B exhibited “poor” flow property.

Keywords: *Compressibility; Volume Flowability; Kawakita Constant; Directly Compressible Excipients.*

INTRODUCTION

Many factors influence the choice of the directly compressible adjuvant to be used in a tablet formulation. These factors vary from the primary properties of powder (particle size, shape, bulk density, solubility) to the characteristic needed for making compacts (compressibility and flowability) to factors affecting stability (water) to cost, availability and pharmacopoeial acceptability[1]. Optimum flowability of powders is crucial in the manufacturing process of solid single dose preparations. The British Pharmacopoeia therefore contains a test on “Flowability” which examines the ability of a powder to flow vertically out of a funnel[2]. The results are expressed in unit time per mass. In the manufacturing processes both for tablets and capsules, dosing for single dosage forms takes place after the volume rather than the mass. However, bulk densities of commonly used materials differ widely, considering that both organic substances like cellulose derivatives and inorganic substances like calcium phosphates are typical tableting excipients.

The aim of the present experiment was to study flowability and packability of directly compressible excipients with respect to usefulness for practical applications.

MATERIALS AND METHODS

Thirteen commonly used tableting excipients were utilized in this experiment:

Avicel® CE-15, (Lot. No. RH428), was obtained as generous gift from FMC Biopolymer, Newark, USA. Prosolv SMCC® HD-90, (Batch No. P9S5110) and Prosolv SMCC™ -90, (Batch No. D9S6016) were obtained generous gifts from JRS Pharma, Nastola, Finland. Tablettose 80, (Lot. No. L0514 A4003), Flowlac 100, (Lot. No. L0535 A4921), Cellactose 80, (Lot. No. L0541 A4901) and Microcelac 100, (Lot. No. L0541 A4931) were obtained as generous gifts from Meggle Gmbh, Wasserburg, Germany. Ludipress, (Lot. No. 56884216K0), and Ludipress® LCE, (Lot. No. 04479068E0), were obtained generous gifts from BASF Aktiengesellschaft, Germany Emcompress®, (Batch No. F12D), was obtained as generous gift from JRS Pharma, West Midlands, UK. Starch 1500® G, (Batch No. IN507543), was obtained as generous gift from Colorcon Ltd., Indianapolis, USA Era Tab, (Lot. No. 490425), was obtained as generous gift from Erawan pharmaceutical research & laboratory Co., Ltd., Bangkok, Thailand. Maize starch B, (Batch No. E4073), was obtained as generous gift from Roquette Freres, Lestrem, France.

Bulk Density and Tapped Density

Densities of bulk and settled product were examined as suggested by the British Pharmacopoeia’s Technical Procedure “Apparent Volume[3]” using a Tap density tester EDT-1020 (Electrolab, Mumbai, India). Deviating from the instructions, a 100 ml graduated cylinder was used for better accuracy of reading volumes, which is in accordance to the respective USP procedure[4]. The cylinder was filled up to at least 3/4 height of deagglomerated powder (Modified analytical balance, accuracy±1 mg) carefully level the powder without compacting, if necessary[5]. The unsettled apparent volume (Vo) was quotient in three parallels and bulk densities (mass/Vo) calculated. Unless, otherwise specified, tap the cylinder 100, 500, 1250 and 2500

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times initially and quotient the tapped volume (Va) after 1250 taps, to the nearest graduated unit. Repeat the tapping an additional 1250 times and quotient the tapped volume (Vb), to the nearest graduated unit[3]. As the difference in all cases between *V*1250 and *V*2500 was smaller than 2ml[3,4] and 2%, respectively *V*2500 was used to calculate tapped density (mass/Vb) in g/ml.

Carr's Index

The bulk density was the quotient of weight to the volume of the sample. Tapped density was determined as the quotient of weight of the sample to the volume after tapping a measuring cylinder for 500 times from a height of 2 inch. The percentage compressibility (carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density[6,7].

Hausner Ratio

Hausner Ratio is the ratio of tapped density to bulk density. Lower the value of Hausner ratio better is the flow property. Powder with Hausner ratio less than 1.18, 1.19-1.25, 1.3-1.5, and greater than 1.5 indicates excellent, good, passable and very poor, respectively[8,9].

Angle of Repose

Angle of repose was measured by the fixed funnel method[10]. A reposograph (model 640; Enar Foundation Research Center, Navsari, India) was used to measure angle of repose. Per the manufacturer's instruction the samples were graded as excellent, good, fair, or poor if the angle of repose found to be in the range of 30–32º, 32–35º, 35–37º, or 37–45º, respectively.

Volume Flowability[11]

A glass funnel as described in the British Pharmacopoeia's flowability test[10] was fixed in a strictly vertical position. The bottom opening was blocked impermeably. Test samples were weighed (Modified analytical balance) and introduced carefully into the dry funnel in order to avoid dusting and compaction. The funnel was unblocked and the time the entire powder needed to flow out of the funnel measured (n=3). Flowability was expressed in seconds per 100 gm of sample[10]. The values show that the flowability can be measured reproducibly.

Kawakita's and Ludde's Equation[12]

The packability was evaluated by tapping the agglomerates in a measuring cylinder. The data were analyzed by using Kawakita and Ludde's equations 3 and 4, respectively. Where a and b are the constant, n is the tap number, Vo, Vn, and Vinf are the powder bed volumes at initial, after nth tapping and at equilibrium state, respectively. In this method agglomerates/ granules was filled in 50 ml capacity measuring cylinder. The cylinder was tapped from a height of 2 inch. Volume of the powder bed was recorded after 5, 10, 15, 25, 50, 75, 100, 200, 300, 400 and 500 taps. Slope was obtained from the plot between ratio of number of taps "n" to "c" (Equation 1) against numbers of taps. The reciprocal of slope gives the value of Kawakita's constant "a" and from the value intercept and "a" the value of "b" was calculated.

$$n/C = n/a + 1/ab \quad \text{——————} \quad (1)$$

$$C = (V_0 - Vn) / V_0 \quad \text{——————} \quad (2)$$

The constant "a" represents the proportion of consolidation as closest packing is attained. The smaller value of constant "a" for the granules indicates good packing even without tapping. The "b" represents the packing velocity. The larger value "b" for the agglomerates/powder indicates that the packing velocity of the batch is rapid than that of corresponding powder[13].

Kuno's Equation[14]

Similar experimental observations can used to calculate the Kuno's constant "k" by following Equation 3.

$$\tilde{n}_f - \tilde{n}_n = (\tilde{n}_f - \tilde{n}_o)\, e^{-kn} \quad \text{——————} \quad (3)$$

$\tilde{n}_o$, $\tilde{n}_n$, and $\tilde{n}_f$, is the apparent densities an initial state, after nth tapping (5, 10,15, 20, 25, 50, 75, 100, 200, 300, and 400) and at equilibrium (500th tap) respectively, and k is a constant. Smaller value of kuno's parameter "k" indicates the slower packaging velocity of the powder or agglomerates.

RESULTS AND DISCUSSION

Flowability Testing

Bulk densities of the substances (Table 1) range from 0.36 gm/ml (Prosolv SMCC™ -90) to 0.83 gm/ml (Emcompress®) and tapped densities from 0.43 gm/ml (Prosolv SMCC™ -90) to 1.01 gm/ml (Emcompress®). The powder bed density of Prosolv SMCC™ -90 is much smaller compared to other substances (Table 1), which is due to the porous structure of the particle. In contrast to this, Emcompress®, consisting of compact agglomerates of inorganic crystals, has a particularly high density. This would mean that flowability expressed in terms of mass per time necessarily is much higher in the case of Emcompress® compared to others substances if the speed of flow of individual particles is equal.

Carr's index between 5 to 15 and 15 to 20 indicates excellent and good flowability, respectively. Although value >21 indicates poor flow[6,7]. Among all samples Flowlac 100, Ludipress and Ludipress LCE exhibited Carr's index <15 %, indicating excellent flow (Table 1). The Avicel CE-15, Starch 1500-G and Maize starch B exhibited Carr's index >21% indicating poor flow (Figure 1) may be due to the presence of guar gum in Avicel CE-15 and starch compounds contains little amount of moisture. The remaining samples were exhibited Carr's index between 15 to 20 %, indicating

***Table 1**. Results of density measurement and powder compressibility*

Sample	Sample mass (gm)	Bulk Volume (ml)	Tapped Volume (ml)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner Ratio
Avicel® CE-15	45	97	67	0.46	0.67	31.34	1.45
Prosolv SMCC® HD-90	45	99	79	0.45	0.56	19.64	1.24
Prosolv SMCC™-90	35	97	80	0.36	0.43	16.27	1.19
Tablettose 80	50	79	64	0.63	0.78	19.23	1.23
Flowlac 100	45	71	61	0.63	0.74	14.86	1.17
Cellactose 80,	40	91	73	0.43	0.54	20.37	1.25
Microcelac 100	40	78	65	0.51	0.61	16.39	1.19
Ludipress	45	86	77	0.52	0.58	10.34	1.11
Ludipress® LCE	45	87	77	0.51	0.58	12.06	1.13
Emcompress®	60	72	59	0.83	1.01	17.82	1.21
Starch 1500® G	45	72	54	0.62	0.83	25.30	1.33
EraTab	40	78	65	0.51	0.61	16.39	1.19
Maize starch-B	35	79	49	0.44	0.71	38.02	1.61

Data shows averages of three measurements, standard deviation is within ±0.5 ml for volume and ±0.1 gm for mass

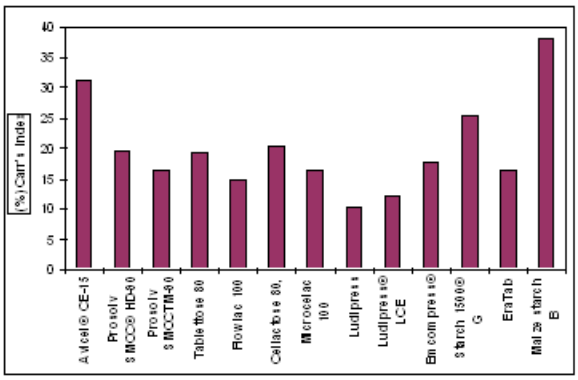

***Fig. 1:** Comparison of Carr's Index of Different Directly Compressible Excipients*

good flow (Table 1). Hausner ratios (Table 1) differ from 1.11 (Ludipress) to 1.61 (Maize starch B), with a variability of ± 0.2 between repetitions. According to commonly accepted criteria of Hausner factors[8,9], Ludipress, Ludipress® LCE and Flowlac have excellent flowability, Avicel CE 15, Starch 1500 G and Maize starch-B have poor flow property (HR>1.5), remaining sample have good flow property (HR values between 1.5 to 1.25). Flow of the samples is ranked as "good" if the value of angle of repose falls within 30-35Ú. All samples were exhibited good flow according to angle of repose values except Maize starch B (angle of repose > 40Ú) was exhibited "poor" flow (Table 2)[10].

***Table 2.** Results of Angle of repose and Flowability measurement (n=3)*

Sample	Angle of repose	Mass of sample (g) ± S.D.	Flow time (s) ± S.D.	Flow time per mass (s/100 gm) ± range	Poured density (g/ml) ± range	Flow time per volume (s/100 ml) ± S.D.
Avicel® CE-15	30.70	301 ± 0.4	No flow	No flow	0.46 ± 0.1	No flow
Prosolv SMCC® HD-90	27.03	250 ± 0.2	5.18 ± 0.1	2.59 ± 0.1	0.45 ± 0.1	1.59 ± 0.1
Prosolv SMCC™-90	32.32	250 ± 0.2	4.52 ± 0.1	2.26 ± 0.1	0.36 ± 0.1	1.26 ± 0.1
Tablettose 80	32.25	250 ± 0.3	4.6 ± 0.1	2.30 ± 0.1	0.59 ± 0.1	1.30 ± 0.1
Flowlac 100	32.62	250 ± 0.3	4.9 ± 0.1	2.50 ± 0.1	0.63 ± 0.1	1.50 ± 0.1
Cellactose 80,	30.78	200 ± 0.2	5.1 ± 0.1	2.55 ± 0.1	0.43 ± 0.1	1.55 ± 0.1
Microcelac 100	31.10	200 ± 0.2	5.34 ± 0.1	2.67 ± 0.1	0.51 ± 0.1	1.67 ± 0.1
Ludipress	30.76	350 ± 0.3	4.32 ± 0.1	2.16 ± 0.1	0.52 ± 0.1	1.16 ± 0.1
Ludipress® LCE	31.24	350 ± 0.2	4.41 ± 0.1	2.21 ± 0.1	0.51 ± 0.1	1.21 ± 0.1
Emcompress®	30.76	350 ± 0.3	5.4 ± 0.1	2.70 ± 0.1	0.83 ± 0.1	1.70 ± 0.1
Starch 1500® G	28.67	250 ± 0.2	No flow	No flow	0.62 ± 0.1	No flow
EraTab	30.16	90 ± 0.1	2.78 ± 0.1	2.64 ± 0.1	0.51 ± 0.1	1.64 ± 0.1
Maize starch-B	+2.92	151 ± 0.1	No flow	No flow	0.44 ± 0.1	No flow

The time consumed for flow of a certain volume of the bulk powder was calculated using poured density (Table 2). The "volume flowability" reveals that Ludipress and Ludipress® LCE consumed 2.16±0.1 and 2.21±0.1 sec/100 ml volume means these substances consumed minimum time for flowing 100 ml sample from the funnel and the results reveal that these two directly compressible materials may provide good uniformity during production of solid dosage form than other samples (Prosolv SMCC® HD-90, Flowlac 100, Microcelac 100, Emcompress® and EraTab). Avicel CE-15, Starch 1500-G and Maize starch-B exhibited no flow, due to irregular particle size and contains little amount of moisture in it (Figure 2). Ludipress exhibited highest flowability followed by Avicel CE-15, Prosolv SMCC, Tablettose, Flowlac, Cellactose, Microcelac, Emcompress, Starch 1500, Era Tab and Maize starch as demonstrated by angle of repose and volume flowability.

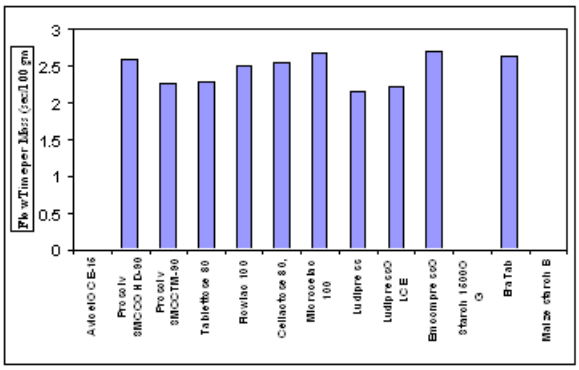

***Fig. 2:** Comparison of Flow Time of Different Directly Compressible Excipients*

Packability Testing

The packability of samples were ascertained by comparing the constants a, b, and k, in Kawakita's and Kuno's equations, respectively (Table 3). The constant "a" represents the proportion of consolidation as closest packing is attained. The reciprocal of "b" and "k" represent the packing velocity. The constant "a" for the Ludipress (0.100) was smaller than for the other samples. The result indicates that the agglomerates of Ludipress show good packing even without tapping. The larger value of "b" for the agglomerates of Ludipress (0.0928) proved that the packing velocity of the Ludipress was faster than that of the other samples. The "k" for Ludipress was found 0.0049. The smaller value of k in the Kuno's equation supports the above findings. The slow packing velocity corresponds with

***Table 3**. Results of Packability Testing (n = 1)*

Sample	Kawakita's Constant "a"	Kawakita's Constant "b"	Kuno's Constant "k"
Avicel® CE-15	0.311	0.0416	0.0112
Prosolv SMCC® HD-90	0.209	0.0362	0.0157
Prosolv SMCC™-90	0.164	0.0766	0.0394
Tablettose 80	0.264	0.0287	0.0099
Flowlac 100	0.269	0.0097	0.0097
Cellactose 80,	0.188	0.0900	0.0721
Microcelac 100	0.185	0.0730	0.0219
Ludipress	0.100	0.0928	0.0049
Ludipress® LCE	0.112	0.0505	0.0081
Emcompress®	0.178	0.0511	0.0269
Starch 1500® G	0.253	0.0405	0.0120
EraTab	0.163	0.0957	0.0197
Maize starch-B	0.382	0.0448	0.0079

proportion of the consolidation of the powder bed per tap. The kawakita plot of Ludipress LCE and Ludipress represent in Figure 3. Ludipress is the co-processed multifunctional product, consists of 93.4 % á-lactose monohydrate, 3.2 % polyvinyl pyrrolidone (Kollidon 30) and 3.4 % crospovidone (Kollidon CL). The agglomerates of Ludipress showed good compression property compared with other samples.

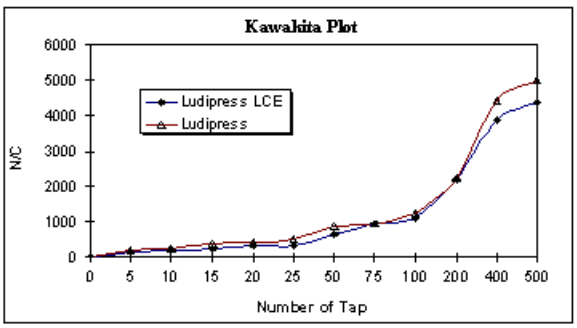

Fig. 3: *Kawakita plot of Ludipress LCE and Ludipress*

CONCLUSION

It can be concluded that the flowability test is reproducible, quick and cheap. Neither the United States Pharmacopoeia 28 NF-23 nor the Japanese Pharmacopoeia (14th Edition) contain any method for measuring flow properties of powders. *USP 29–NF 24,* effective as from 1st Jan. 2006, is the first *USP* edition to include the recently harmonized General Information Chapter "‹1174› Powder Flow[14]. The chapter identifies experimental considerations for four methods: angle of repose, compressibility index or hausner ratio, flow rate through an orifice, and shear-cell methods. Some of the traditional flowability test methods described in the new *USP* chapter have been used for at least 40 years, and their advantages and limitations are well known[15]. Each method reveals something different about the powder or its flowability, but more than one is needed. No single and simple test method can adequately characterize the flow properties of pharmaceutical powders. Instead, most scientists advocate using multiple standardized test methods to characterize various aspects of powder flow. Some tests yield information about the physical properties to predict what may happen during manufacture, and others serve as a ranking or correlation tool. The usefulness of the flowability test in the British Pharmacopoeia (2005)–with respect to manufacture of solid dosage forms - may be up to discussion. However, due to widely different densities of powders, the expression of flowability in terms of time per mass may in some cases not match the macroscopic flow qualities. It is proposed that "Volume-Flowability" is a better description for production of uniform solid dosage form. According to data Ludipress and Ludipress® LCE exhibited satisfactory flow property and compression characteristics than other samples.

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