

Original Article

ASSESSMENT OF THE TABLETING CHARACTERISTICS OF A NOVEL SORBITOL AND CALCIUM DIPHOSPHATE COMPOSITES

EDWARD ECHEVERRI^{a*}, JOHN ROJAS^a, MARCEL YEPES^a

^aDepartment of Pharmacy, School of Pharmaceutical Chemistry, University of Antioquia, Medellin, Columbia
Email: edwardecheverri@gmail.com

Received: 14 Jun 2015 Revised and Accepted: 08 Aug 2015

ABSTRACT

Objective: To improve the tableting properties of sorbitol (SOR) via particle engineering through agglomeration with anhydrous calcium diphosphate (ACD) employing a house-made agglomerator.

Methods: A novel SOR: ACD composites were produced by agglomeration at the 95:5; 80:20, 50:50, 20:80 and 6:94 SOR to ACD. The resulting tableting properties such as densification, compressibility, compactibility, ejection force, elastic recovery, sensitivity to lubricants, compression speed and disintegration time were then evaluated.

Results: The new agglomerated excipient had better flow, compressibility and compactibility than the physical mixture of SOR and ACD being the 95:5 SOR: ACD ratio the composite that exhibited the best tableting properties.

Conclusion: This novel excipient has a potential use as a pharmaceutical aid for direct compression applications.

Keywords: Sorbitol, Calcium diphosphate, Composites, Tableting, Direct compression.

INTRODUCTION

In recent years, no new chemical entities have been introduced in the market as novel pharmaceutical aid. This is explained by the extreme costs for the required toxicological and clinical studies demanded by the regulatory agencies. Nevertheless, the market has been fulfilled by the introduction of new grades of materials and co-processing of two or more already approved excipients produced at a fixed ratio. Co-processing implies the combination of two or more materials using an adequate technology to improve the particle and functional properties in comparison to the parent materials. Therefore, the undesired properties are removed and the co-processed product has also a superior functionality as compared to the physical mixture [1]. Spray-drying, co-precipitation, hot-melt extrusion and agglomeration are the most widely used technologies to generate co-processed products.

Sorbitol (SOR) and anhydrous calcium diphosphate (ACD) are commonly used as excipients for the production of solid dosage forms [2]. However, SOR is liquefied if stored at relative humidities larger than 65%, whereas it crystallizes at lower relative humidities forming harder compacts, especially if mixed with moisture sensitive drugs [3]. Further, when compression is executed at RH<50% it forms lumps in the hopper and a sticky residue is generated between the punches and die system [4]. On the other hand, ACD is an inexpensive excipient, which is virtually insensitive to alkaline lubricants. However, it causes a substantial tooling wearing and its compacts require a disintegrant since they suffer from hardening once stored leading to prolong dissolution times [5].

A possible alternative to solve the aforementioned issues and improve the tableting performance of these excipients is by co-processing. In this scenario, the study of the synergy between the plasticity of SOR and brittle behavior of ACD during the compression process is essential to understand their tableting characteristics. Thus, combination of these two excipients could generate a robust material with a less tendency for capping or lamination [6, 7].

Recently, the spray-drying, co-precipitation, hot-melt granulation and agglomeration technologies were employed to study the effect of processing technology on the resulting particle properties of the new co-processed SOR: ACD material. Particle density and porosity were mainly dependent on the technology used. Further, hot-melt granulation rendered particles with an excessive compatibility. On

the other hand, spray-drying generated the most porous materials having the lowest yield, whereas, the agglomeration technology produced the best yield (~90%) and had the least scale-up issues [8].

Die filling, particle deformation, decompression and ejection are the basic events which occur during the compression of powders. Therefore, knowledge of the fundamental mechanisms taking place during compression is essential to understand the performance and suitability of a material for tableting purposes [9]. Usually, compression and compaction phenomena of powders can be described as a function of porosity or compact tensile strength and compression pressure, respectively [10].

The goal of this study is to assess the tableting performance of a new co-processed SOR: ACD excipients produced by agglomeration, and determine the best SOR: ACD ratio which has the best functionality as compared to their physical mixtures.

MATERIALS AND METHODS

Materials

SOR (lot 20140405) was purchased from Shandong Ruiyang Pharmaceutical Technology (Longwood, USA). ACD (lot BCU250711) was obtained from Innophos (Cranbury, NJ, USA). Talc (lot S321/11), magnesium stearate (lot lot 25654) and stearic acid (lot 413F120922A) were obtained from Rio Tinto minerals (Luzenac Val Chisone SA), Disan Columbia and Pacific Olechemical SDNB, respectively.

Preparation of SOR and ACD composites

Approximately, 100g of ACD and SOR were blended at a 5:95, 20:80, 50:50, 80:20 and 94:6 ratio and wetted with an appropriate amount of distilled water to form aggregates. These particles were then passed through a # 14 mesh and put in an agglomerator (Model 1LA7 080-6YC60, Medellin, Colombia) for 5 min operated at 30 degrees angle and ~100 rpm. Subsequently, these materials were dried at 60 °C for 24h and passed through a # 60 mesh sieve.

Powder X-Ray (PXRD) characterization

Powder X-Ray diffractions were obtained on a PANalytical diffractometer (Model, Empyrean 2012, Westborough, MA) at 45 kV and 40 mA, equipped with a monochromatic CuK α ($\alpha_1 = 1.540598 \text{ \AA}$, α_2

=1.544426 Å) X-Ray radiation. Diffractograms were obtained over a 5 to 45 ° range at a scan step and step time of 0.039 and 38.2 s, respectively. The Peak Fit software (V. 4.12, Sea solve, Inc, Framingham, MA) was used for the data analysis.

Preparation of compacts

Cylindrical compacts of ~300 mg were manufactured on an instrumented single station tablet press (Compact 060804, Indemec, Columbia) equipped with a 6.5-mm flat-faced punches and die tooling at a dwell time of 1 and 30s and compression pressures ranging from ~10 to ~300 MPa. The compaction and ejection forces were measured directly from a load cell (LCGD-10k, Omega Engineering, Inc, Stamford, CT) coupled to a strain gauge

(Model DP25B-S, Omega Engineering, Inc., Stamford, CT). Compacts were analyzed immediately after ejection.

Compact porosity and elastic recovery measurements

Compact thickness and diameters were measured with an electronic digital caliper (Titer; measuring range 0-150 mm and readability of 0.01 mm). The tablet thickness was measured at three different points around the compact and the average was taken. The compact volume was then determined and its porosity was calculated by subtracting the unity from the ratio of apparent compact density and true density of the sample determined on a Helium displacement micropycnometer (Accu Pyc II 1340, Micromeritics Corp., Norcross, GA, U. S. A.).

Compact tensile strength

The data, of breaking strength values obtained on a hardness tester (UK 200, Vankel, Manasquan, NJ, U. S. A.) were transformed to radial tensile strength using the Fell and Newton equation for cylindrical compacts. The crosshead speed of the left moving platen was 3.5 mm/s.

Compressibility and compactibility analyses

The natural logarithm of the inverse of compact porosity, $\ln(1/\epsilon)$, was plotted against compression pressure to construct the Heckel plots [11, 12]. The slope (m) of the linear region of this curve is inversely related to the material yield pressure (P_y), which is a measure of its plasticity [7]. Thus, a low P_y value (<100 MPa) indicates a high ductile deformation mechanism upon compression. The Heckel model is given by:

$$-\ln(\epsilon) = kP + A \quad (1)$$

Where, A is the intercept obtained by extrapolating the linear region to zero pressure. Other parameters useful in assessing compressibility are D_0 , D_a , and D_b , which are related to initial powder packing/densification, total compact densification, and particle rearrangement/fragmentation at the initial compaction stage, respectively. The compatibility analysis was performed by fitting the tensile strength data to the Leuenberger model:

$$\sigma t = \frac{\sigma_t}{T_{max}} \left(1 - \exp(-\gamma P^\rho) \right) \quad (2)$$

Where, σ_t , T_{max} , γ , P and ρ correspond to the compact tensile strength, tensile strength at infinite pressure, compression susceptibility, compression pressure and the solid fraction, respectively [13, 14].

Strain rate sensitivity (SRS)

The SRS was obtained by the percentage of P_y change of the materials compressed at dwelling times of 30 and 1 sec, respectively. The powder P_y was obtained from the Heckel model previously described.

Elastic recovery (ER)

Compacts of ~300 mg were made on a single punch tablet press equipped with a flat-faced 6.5 mm diameter tooling at a 20% porosity. Tablet thickness was measured immediately after ejection (0.01 mm sensitivity) and after 15 d of storage. The ER was calculated as reported previously [15].

Water uptake (WU)

Compacts were made as described for ER. The compact WU was obtained by the percentage of weight increase once stored in a 100% RH chamber for 15 d.

Lubricant sensitivity (LS)

Magnesium stearate, stearic acid and talc were selected as model lubricants. Batches of ~10g of an excipient: lubricant (99:1 ratio) were passed freely through a number 60 mesh sieve (250 μ m) and blended separately in a V-blender (Riddhi Pharma Machinery, Gulabnagar, India) for 5 min. Tablets were prepared at a dwell time of 1 s. The compression pressures varied so compacts of ~20% porosity were obtained. The LS was expressed as the lubricant sensitivity ratio (LSR):

$$LSR = (H_0 - H_{lub})/H_0 \quad (3)$$

Where, H_0 and H_{lub} are the compact tensile strength of tablets prepared without and with lubricant, respectively. Samples were analyzed in triplicates.

Compact disintegration

Tablets, each weighing ~300 mg, were made as described under ER in triplicate. It was performed in distilled water at 37 °C employing an Erweka GmbH disintegration apparatus (39-133-115, Hanson Research Corporation, Northridge, CA) at 30 strokes/min.

Statistical analysis

A principal Component Analysis (PCA) was the multivariate analysis employed. It identifies patterns in the compact properties and expresses them in such a way as to highlight their similarities and differences in the PC1 and PC2 axes. The Minitab® software (v.16, Minitab®, State College, U. S. A.) was used for the data analysis. The independent variables were the type of processing employed (agglomeration or blending) and ACD level (5, 20, 50, 80 and 94%). The response variables were the ER, SRS, LS, WU, compact disintegration and the parameters obtained from the Heckel and Leuenberger models.

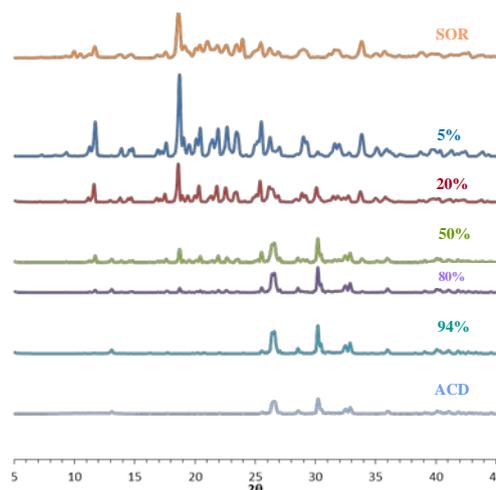


Fig. 1: Powder XRD of the new SOR: ACD composites

RESULTS AND DISCUSSION

Powder XRD characterization

There are 6 types SOR polymorphs known in nature (forms α , β , γ , Δ , ϵ and the crystallized melt with subforms E' and E). Commercially, the γ form is the most readily available [16]. Fig. 1 depicts the diffractograms of the aggregate composites. In the long spacing region of the SOR diffractogram (low values of 2θ angles) there were five main diffraction peaks at ~12, 14, 16, 18 and 26 ° 2θ , which corresponded to the typical reflections for the polymorph γ [17]. On the other hand, ACD exists as a dihydrate and anhydrous form. In this case, the diffractogram showed the main diffraction peaks at 26, 28, 30, 32 and 36 ° 2θ , corresponding to the typical reflections of the anhydrous form. The typical diffractions peaks at 12, 21 and 23 ° 2θ

characteristics of calcium diphosphate dihydrate were absent indicating the anhydrous nature of the composites [5]. As the level of ACD increased the magnitude of the SOR peaks at 12 and 18 ° 2θ decreased and that of 26 ° 2θ increased. On the other hand, the process of agglomeration *per se* did not cause any polymorphic transformation of the γ form of SOR.

The PC1 vector is the direction on the abscissa along which projections that has the largest variance. The PC2 is the direction, which maximizes variance among all directions orthogonal to the PC1. In this study, the PC1 and PC2, had a variance of 8.9, and 3.3 respectively, and accounted for ~75.8 % of the total variance indicating that most data structure was captured into the two underlying dimensions studied. The loading plot of measured properties is shown in fig. 2. The lines show projections of the processing conditions and the resulting tableting properties from the models onto the PC1 and PC2 plot. The loadings can be understood as weights for each original property when calculating the principal component.

This plot is the result of the linear combination of original data that maximizes data variance. Further, each point in the graph indicates the contribution of this property in defining these components. A factor contributing very little to the components such as LS and SRS had small loading value and appear plotted near the center and thus, they had a little effect on the overall properties studied. On the other hand, properties shown further away from the center (appearing dispersed around the borders of the plot) such as processing type, compressibility, compactibility and powder P_y had a major effect on the overall tableting behavior suggesting the processing type as the most important variable that affected all the tableting parameters. Moreover, the strain rate sensitivity (SRS), which is related to plastic deformation due to a reduction in the time available for stress relaxation and bond formation and the ER was highly affected by the processing employed during the composite manufacture. Thus, prolongation of the time available for deformation increased tablet densification for the agglomerate composites with respect to the physical mixtures. This is explained by the larger plasticity observed for the agglomerated composites. Further, processing had some effect on the elastic recovery of the resulting composites as compared to the physical mixtures. This is explained, by the formation of weaker and brittle compacts as compared to the strong bonds formed during the agglomeration process. As a result, compacts made from the physical mixtures had virtually no tendency for elastic relaxation or capping.

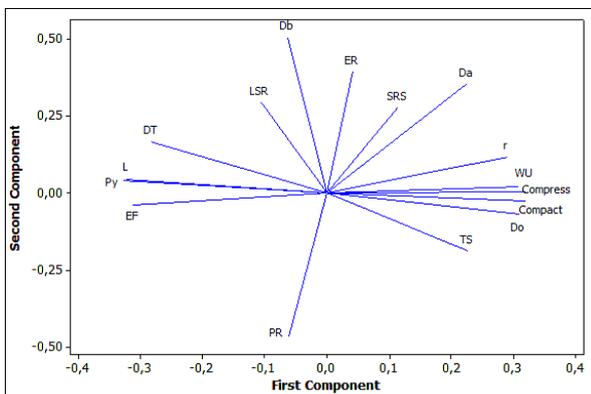


Fig. 2: Loading plot of the effect of processing and ACD level on the tableting properties of the new composites

Factors such as compressibility, compactability, compact tensile strength and powder densification by die filling formed a large cluster to the right side of the plot indicating they are highly correlated. This means that composites having low levels of ACD (<20%) presented a large magnitude of these variables. On the other hand, factors such as level of ACD, P_y and ejection forces formed a cluster that was directly opposite to the first cluster indicating an

inverse correlation. This indicates that composites having high levels of ACD showed a large brittle deforming behavior, ejection forces and formed compacts having a low compactibility, compressibility and tensile strength. Conversely, materials with ACD levels lower than 50% showed an extensive ductile tendency resulting in compacts having a large compressibility, compactibility and low ejection forces. Moreover, independent of the process employed water uptake and disintegration time decreased as the level of ACD increased. This is due to the reduction of the hygroscopicity and dissolving ability of SOR in the composites. The scores for PC1 and PC2 are:

$$PC1 = -0.322 \text{ ACD level} + 0.319 \text{ Compact} + 0.319 \text{ Compress} - 0.327 P_y - 0.311 \text{ EF}$$

$$PC2 = -0.465 \text{ Process} + 0.355 D_a + 0.504 D_b + 0.357 \text{ SRS} + 0.392 \text{ ER}$$

The PC1 model was dominated by the level of ACD and represents a connection between the levels of ACD in the composites with the resulting compressibility and compactibility. On the other hand, the ACD level had a negative effect on the resulting plasticity and compact ejection forces from the die. Conversely, The PC2 component, showed an inverse relationship between processing, and powder densification and compact ER. For instance, opposed to the agglomerate composites, the physical mixtures had a low sensitivity to the compression speed and low powder densification.

Fig. 3 shows the PCA score plot for the tableting properties studied. The score plot of the two principal components contains the original data in a rotated coordinate system. This plot was able to classify and mainly attribute data variability to the ACD level in the composites. The first component separates composites having low levels of ACD (<50%) from those having levels higher than 50%. Since the PC1 was mainly influenced by the compressibility and compactibility characteristics, data stratification was mainly dependent on the plasticity of the materials. For this reason, highly compactable and compressible composites are illustrated on the right side of the PC1 axis, whereas, poorly compactable and compressible composites are shown on the left side of the plot. On the other hand, the PC2 separated the overall properties of the agglomerates from the physical mixtures shown in the upper and lower parts of the plot, respectively. In this case, composite stratification was essentially due to the processing type. The initial high data scattering at low levels of ACD is mainly attributed to the differences in ER, SRS and densification by particle rearrangement (D_b). As the level of ACD increases data appear closer to the zero value in the ordinate axis indicating small differences between the two processes, especially for the composites having an ACD level of 94%.

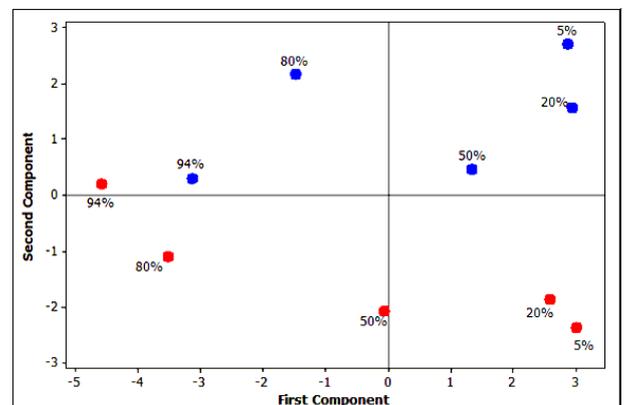


Fig. 3: PCA Score plot showing the effect of processing and ACD level on the tableting properties of the new composites. Blue and red dots correspond to the agglomerates and physical mixtures, respectively

Further, the correlation matrix among the parameters studies showed a good inverse correlation between the level of ACD with D_0 and compressibility (r^2 of 0.955 and 0.957, respectively). As a result,

materials having a large concentration of ACD are expected to have a low compressibility and densification by die filling due to the low densification characteristics of ACD. Likewise, compressibility and compactibility were highly correlated (r^2 of 0.958) since composites that had a large densification such as those having a ACD level <20% were also able to form strong compacts. On the other hand, P_y which is an indicator of the ductile characteristics of a material was inversely related (r^2 of 0.930) to compactibility indicating the strong correlation between the P_y parameter of the Heckel model and the AUC obtained from the Leuenberger model. Further, as seen by the Heckel model, composites that were highly plastic deforming (having a low P_y) also showed a high volume reduction ability. Further, a high plasticity was essential for having low compact ejection forces from the die. This means that composites having a large level of SOR also possessed self-lubricant characteristics preventing the formation of frictional forces between the powder bed and the die wall.

Table 1 lists the overall properties of the composites studied. According to Leuenberger [14], a compression susceptibility parameter (γ) < 0.01 MPa^{-1} is indicative of a plasticity of a material. This implies that composites having ACD levels <20% can be

considered as ductile in nature. In fact, composites having ACD levels <20% required lower compression forces to rapidly form cohesive compacts with a large volume reduction ability. As explained previously, independent of the process employed, the increase in the ACD level caused a reduction in compressibility, densification, and compactibility of the composites. The brittle nature and low porosity of ACD are responsible for this phenomenon. In one exceptional case, the agglomerate having a 5% ACD presented a larger densification and compressibility than the physical mixtures and the parent materials (SOR and ACD). This is explained by the aggregated nature of the composites, where ACD is embedded inside the granular matrix. Once the compression process takes place sliding and rearrangement of the crystal planes within the agglomerates is boosted, leading to superior volume reduction ability keeping the plastic behavior of the parent SOR almost intact. Nevertheless, this high plasticity also creates a slight increase in susceptibility to lubricants and the SRS. On the other hand, the simple physical mixture of the SOR: ACD composites rendered more brittle products with a larger compact ER and ejection force. This is explained by the larger surface area of the powders in the blend, which gives a large contact area between the powder bed and machine tooling.

Table 1: Tableting properties of the new SOR: ACD composites

P^a	L^d (%)	TS^e (MPa)	γ^f (MPa^{-1})	Compact ^g (MPa^2)	D_{a^h}	D_{o^i}	D_{b^j}	Compress ^k (MPa^2)	Py^l (MPa^{-1})	SRS ^m (%)	DT ⁿ (Min)	ER ^o (%)	LSR ^p	EF ^q (N)	WU ^r (%)
A ^b	5	4.1	0.02	268	0.85	0.39	0.47	862	60.5	30.2	1.5	1	0.49	33.3	14
A	20	3.2	0.03	269	0.77	0.3	0.47	760	82.7	41.2	1.6	0	0.22	45.7	24.6
A	50	4.8	0.01	252	0.63	0.29	0.33	560	91.6	45.3	5.9	0	0.39	47.3	16.7
A	80	3.7	0.01	155	0.63	0.13	0.49	509	195.1	15.7	30	1	0.33	239	9.8
A	94	4	0	83.4	0.54	0.14	0.4	347	354.8	21.9	30	0	0.23	400	1.3
PM ^c	5	4.9	0.02	330	0.61	0.39	0.22	867	42	4.2	1.03	0	0.15	38.7	18.2
PM	20	5.3	0.02	347	0.52	0.3	0.22	874	30.4	35.4	1.6	0	0.27	33.3	16
PM	50	5.2	0	117	0.59	0.29	0.3	480	143.4	2.1	3.4	0	0.17	153	10.9
PM	80	2.3	0	44.8	0.5	0.13	0.37	320	298.6	2.9	12.2	0	0.28	749	5.5
PM	94	1.5	0	33.2	0.48	0.14	0.35	303	394.8	27.4	30	0	0.6	726	2.5
SOR ^s	0	4.9	0.03	421	0.67	0.31	0.35	768	71.8	49.6	2.2	5.51	0.64	74.3	35.7
ACD ^t	100	1.7	0.01	48.9	0.44	0.17	0.27	260	383.1	14.3	30	0.31	0.14	648	1.1

a. process, b. agglomeration, c. physical mixture, d. phosphate level, e. compact tensile strength, f. compression susceptibility, g. compactibility, h. Total compact densification, i. compact densification by die filling, j. compact densification by rearrangement/fragmentation, k. Compressibility, l. Powder yield pressure, m. strain rate sensitivity, n. compact disintegration time, o. Elastic recovery, p. Lubricant sensitivity, q. Ejection force, r. water uptake, s. sorbitol, t. anhydrous calcium diphosphate

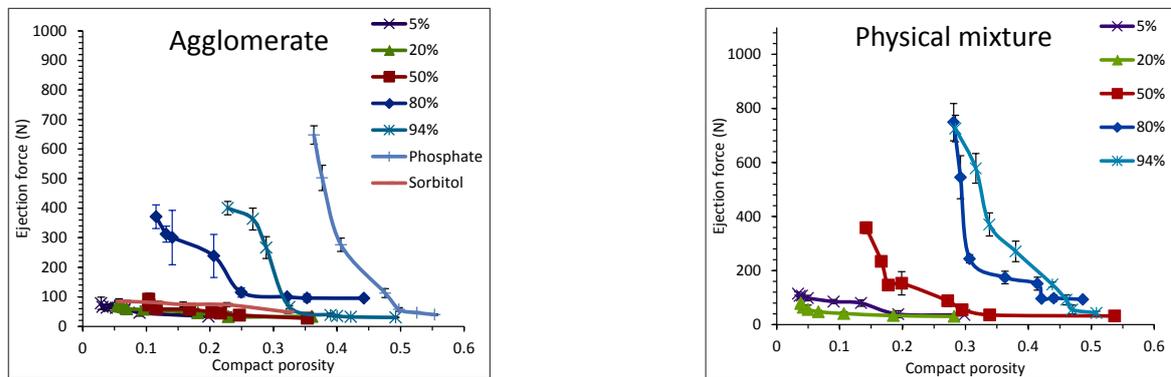


Fig. 4: Compact ejection force of the SOR: ACD composites

Further, no significant differences were observed among the hygroscopicity data of the compacts as reflected by the water uptake ability between the agglomerates and the physical mixtures. Likewise, compact disintegration times of agglomerates were comparable to those of the physical mixture, except for that having an ACD level of 80% in which the agglomerate showed a delayed disintegration due to the formation of strong compacts. Moreover, in all cases, composites were less hygroscopic than SOR, and required about seven days to reach equilibrium and liquefaction, except for

composites having a ACD level >80 which never liquefied. Conversely, SOR reached liquefaction within 24 h of storage ment at a relative humidity environment of 100%.

Fig. 4 shows data resulted from the compact ejection force as a function of compact porosity. As expected, ejection forces decreased as porosity increased. In fact, ejection forces of the physical mixtures were higher than those of agglomerate products independent of the level of ACD. The higher plasticity and low surface area of the agglomerates explained this phenomenon.

Fig. 5 depicts the lubricant sensitivity of the SOR: ACD composites and fig. 6 illustrate the lubricant sensitivity of pure materials. A low sensitivity to a lubricant is observed for composites having a LS near the center of the radial plot. The magnitude of the sensitivity varied with the ACD level and did not showed any trend. The area under the curve of each radial curve can be considered as indicative of the magnitude of the LS. In this case, the agglomerates showed the same LS for talc and magnesium stearate, but small LS to stearic acid than the physical mixtures. It is possible that stearic acid is able to form a complete particle coating for the physical mixtures and thus,

reduced the number of contact points required to form a strong compacts. On the other hand, pure materials, especially, SOR was highly sensitive to lubricants as compared to ACD. In this case, lubricants strongly interfered with bonding forces of SOR such as hydrogen bonding between particles and softened tablets. Therefore, the continuous lubricant film on SOR particles is not destroyed reducing the surface area and thus, weakening particle bonding. However, the contrasting result was found for the brittle deforming ACD. This is explained by the continuous formation of fresh surfaces not coated by lubricant, which bind together reducing slightly LS.

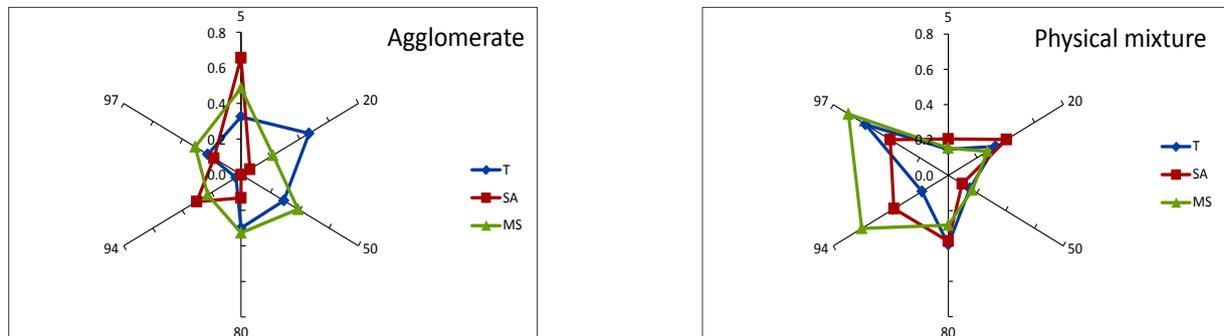


Fig. 5: Radial plots showing the effect of lubricant on composites having different levels of ACD. Batch size: 10 g. T: Talc, SA: Stearic acid, MS: Magnesium stearate

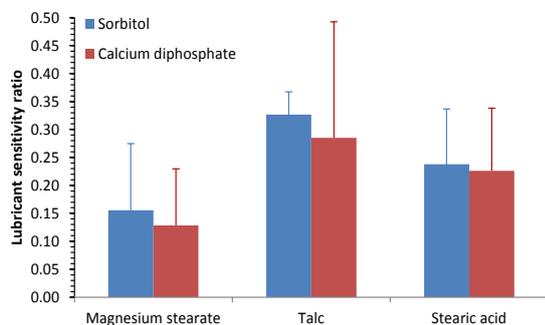


Fig. 6: Effect of lubricant on pure SOR and ACD. Batch size: 10 g

CONCLUSION

The agglomerated SOR: ACD composites showed improved characteristics such as good densification, low ejection forces, and better compressibility and compatibility than the plain physical mixture of the individual components. The agglomerate having a 5% ACD level was the composite that exhibited the best tableting properties.

ACKNOWLEDGEMENT

This work has been supported by the committee for the development of research (CODI) through its sustainability strategy (2015-2016).

CONFLICT OF INTERESTS

Declared None

REFERENCES

- Ramya K, Chowdary K. Preparation, characterization and evaluation of a new coprocessed excipient as directly compressible vehicle in tablet formulation. *J Global Trends Pharm Sci* 2013;4:1322-8.
- Guyot-Herman A, Draguet-Brughmans M. Gama sorbitol as a diluent in tablets. *Drug Dev Ind Pharm* 1985;11:551-64.
- Reiff F, Hartner H, Basedow A, Hugenbush HW, Schmidt PC, Bardonnier H. Sorbitol, process for its preparation and use thereof; 1986. p. 794.

- Lachman L, Lieberman HA, Kanig J. *The Theory and Practice of Industrial Pharmacy*. (Febiger, L. ed). 3rd ed. Philadelphia; 1986. p. 1317-8.
- Doldan C, Souto C, Concheiro A, Martinez-Pacheco R, Gomez-Amoza J. Dicalcium phosphate dihydrate and anhydrous dicalcium phosphate for direct compression: a comparative study. *Int J Pharm* 1995;124:69-74.
- Saha S, Shahiwala AF. Multifunctional coprocessed excipients for improved tableting performance. *Expert Opin Drug Delivery* 2009;6:197-208.
- Bolhuis CK, Chowham ZT. *Pharmaceutical Powder Compaction Technology* (Alderborn G, Nystrom, C. eds.) New York, Marcel Dekker; 1996.
- Echeverri E, Rojas J. Functionality enhancement of sorbitol and anhydrous calcium diphosphate composites for direct compression applications. *Int J Res Pharm Sci* 2014;5:299-303.
- Rojas J, Ciro Y, Correa L. Functionality of chitin as a direct compression excipient: An acetaminophen comparative study. *Carbohyd Polym* 2014;103:134-9.
- Paronem P, Ilkka J. *Pharmaceutical Powder Compaction Technology*. (Alderborn G, Nystrom C. eds.). Marcel Dekker, New York; 1996.
- Heckel RW. Density-pressure relationships in powder compaction. *Trans Metall Soc AIME* 1961a;221:671-5.
- Heckel RW. An analysis of powder compaction phenomena. *Trans Metall Soc AIME* 1961b;221:1001-8.
- Jetzwer W, Leuenberger H, Sucker H. The compressibility and compactibility of pharmaceutical powders. *Pharm Technol* 1983;74:33-9.
- Leuenberger H, Rohera BD. Fundamentals of powder compression 1. The compactibility and compressibility of Pharmaceutical powders. *Pharm Res* 1986;3:12-22.
- Armstrong NA, Haines-Nutt RF. Elastic recovery and surface area changes in compacted powder systems. *J Pharm Pharmacol* 1972;24:135-6.
- Nezzal A, Aerts Luc, Verspaille M, Henderickx G, Redl A. Polymorphism of sorbitol. *J Cryst Growth* 2009;311:3863-70.
- Willard JF, Lefebvre J, Danede F, Comini S, Looten P, Descamps M. Polymorphic transformation of Γ -form of D-sorbitol upon milling: structural and nanostructural analyses. *Solid State Commun* 2005;135:519-24.