Comparative Study of Isomalt and Co-processed Isomalt

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RESEARCH ARTICLE

Comparative Study of Isomalt and Co-processed Isomalt

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ABSTRACT

Objective: The study aims to compare the tableting qualities of isomalt and co-processed isomalt.

Methodology: Co-processed isomalt prepared by melt granulation method evaluated for flow property, dilution potential, Kawakita plot, consolidation index, tabletability, Heckel plot and elastic recovery and compared with isomalt.

Result and Discussion: The co-processed isomalt demonstrated superior packing ability compared to isomalt and got rearranged in the early compression stage, as per modified Kawakita equation. Co-processed isomalt had 40% dilution potential for paracetamol as compared with 20% for isomalt. Co-processed isomalt showed 40% dilution potential for ascorbic acid, and nimesulide, whereas mefenamic acid and aspirin showed 30% dilution potential. Co-processed isomalt overcomes the lamination and sticking problem of isomalt which has better tabletability.

Keywords: Isomalt, Co-processed excipient, Melt granulation, Tableting ability, Flowability, Kawakita plot.

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INTRODUCTION

Direct compression is most suitable technique for manufacturing of tablets due its simplicity and cost-effectiveness. However, DC process is highly influenced by powder characteristics such as flowability and compressibility. Flowability and compressibility of powder is mainly depends upon the properties of drug and excipients.[1] Scientists must now create excipients promptly with minimal expenses associated with manufacturing, scaling up, and the environment. However, seeking for new excipients necessitates expensive and time-consuming toxicological investigations. Because of this, only a small number of unique excipients have been released to the market in the past three decades, compared to new grades of existing excipients. An excipient is deemed novel if it contains an entirely novel chemical entity, is physically modified, is a co-processed mixture of current excipients, is directed toward a new route of administration. The advantage of co-processed material is improved flow properties (e.g. Fujicalin®[2] and Cellactose), compressibility (Ludipress, Cellactose and SMCC), better dilution potential (Cellactose), and reduced lubricant sensitivity.[3] The above functionality of the excipient are determined by fundamental parameters such as morphology, particle size, shape, surface area, porosity, and density. To improve functioning, user could alter the powder's particle size and density.[4]

Directly compressible co-processed excipients have been available in the market include Ludipress, Cellactose, Microlac, StarLac, and Prosolv.[5] A comparison of functional property of co-processed excipients like Cellactose[6] and LubriTose SD[7] with its physical mixture shows the co-processed excipient has better functionality than its physical mixture.

Isomalt was co-processed by melt granulation method with PEG 4000 and crospovidone. The purpose of study is to check whether the flowability and tabletability of co-processed isomalt is better than isomalt by evaluating its flow property, dilution potential tabletability, heckle plot and elastic recovery.

MATERIALS AND METHODS

Isomalt (GalenIQ 721, BENEO-Palatinit GmbH, Germany) was a generous gift sample from SPA Food and PharmaIngredients Pvt. Ltd., (Thane, Maharashtra, India). Aspirin was purchased from Modern Industries Nashik, ascorbic acid from Loba Chemie Pvt. Ltd. Mumbai, paracetamol was purchased from Research-Lab Fine Chem Industries (Mumbai, Maharashtra, India). All other laboratory chemicals were of analytical grade.

Method

Co-processed isomalt was prepared by using isomalt (45.8%), PEG 4000 (43.7%) and crospovidone (10.5%). Melt granulation method was adopted for coprocessing by maintaining 60°C temperature. Co-processed material was stored in tightly closed containers and evaluated for the following parameters.

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Flow Property

Flow characteristic of powder (isomalt, physical mixture and co-processed isomalt) was predicted by determining angle of repose, carr's index and hausner ratio. The angle of repose was determined by measuring the angle of a static pile of powder using a fixed funnel.[8,9] It was calculated by measuring the radius (r) of pile and height (h) of pile using formula; $\theta=\tan^{-1}$ (h/r). Carr's index and hausner ratio was determined by measuring bulk density and tapped density. Bulk density is a mass of powder by pour volume of powder and tapped density is a mass by tapped volume of powder.

$$Carr's\ index = \frac{(tapped\ density - bulk\ density)}{tapped\ density} * 100$$

$$Hausner\ ratio = \frac{tapped\ density}{bulk\ density}$$

Note: physical mixture is the blend of isomalt, crospovidone and PEG 4000.

Dilution Potential

Dilution potential refers to a drug's ability to load when combined with an excipient that compacts into a tablet. Paracetamol, mefenamic acid, nimesulide, ascorbic acid, and aspirin were selected as model drugs. All drugs were selected, having various flowability and compressibility. Paracetamol and mefenamic acid are poorly soluble, poorly compressible, brittle with poor flow property[10-12] and required in high dose.[13] Mefenamic acid has higher sticking tendency.[10] Nimesulide has poor flow property and compressibility.[14,15] Ascorbic acid and aspirin are moisture-sensitive and difficult to compress by wet granulation so direct compression is a suitable method for this drug. Compression of aspirin is by plastic deformation whereas ascorbic acid is by fragmentation.[16] Ascorbic acid has sticking property and capping tendency.[17]

Blend of Co-processed isomalt and drugs in 90:10, 80:20, 70:30, 60:40, 50:50, and 40:60 proportions were evaluated for flow property. Tablets were compressed with a rotary tablet compression machine and evaluated for dimension, hardness, weight variation, disintegration time, and friability study.[18]

Packing Ability

The packing ability of powder was determined by Kawakita equation.[19] The 30 gm of powder (isomalt, physical mixture and co-processed isomalt) was weighed and poured into measuring cylinder attached to tapped density apparatus (Shital scientific industries, Bombay). The initial powder volume was recorded and then the cylinder was tapped for 20, 40, 60, 80, 100 taps and respective volume were recorded.

$$N/C = N/a + 1/ab$$

Where, a and b are the constants, N is the number of taps and C denotes the degree of volume reduction due to tapping.

$$C = (Vo - Vn)/Vo$$

Where Vo and Vn are the volume of powder at initial and n^{th} tapped, respectively.[20]

Consolidation Index and Rate of Consolidation

The comparative decrease in volume and density of the powder bed was studied as a function of applied load (tapping) by using Neumann *et al.* method.[21]

$$Log(\rho td - \rho bd) = K \log N + CI \quad (1)$$

where K and CI are constants denoting the rate of consolidation and consolidation index, respectively, N is the number of taps, while ρ_{td} and ρ_{bd} are the density of the powder bed after N^{th} tap and initial bulk density, respectively.

Tableting Ability of Isomalt

Tabletting ability of isomalt was checked with paracetamol and followed the procedure as per the evaluation parameter 'dilution potential.[7, 21, 22]

Tabletability

Tabletability of isomalt, Co-processed isomalt and the physical mixture was performed on Gamlen D1000 powder compaction analyser. Gamlen D1000 powder compaction analyser was used to manufacture 15 tablets per sample using a 6 mm punch and die. Five compaction loads (100, 200, 300, 400, 500 kg) were employed with 3 tablets being compacted at each load. Tablet mass and thickness were measured using an automated balance and micrometer. Finally, tablet diameter and fractured load were measured with a Gamlen TTA (tablet tensile analyzer).

Heckel Plot

Heckels plot is one of the most useful equation to measure compaction properties of pharmaceutical powders.[23] Heckel plot is based on first order of kinetics reaction, the concentration and time is replaced with porosity and pressure.[24]

$$ln(1/(1-D)) = kP + A$$

Where D is relative density of tablet (tablet density to the true density of powder). P is applied pressure and k is slope of the straight-line portion of Heckel plot (ln(1/1-D) Vs pressure applied). Mean yield pressure (Py) is obtained by reciprocally transforming the slope, and the densification of powder as a result of initial particle rearrangement is shown by Y-intercept (A).

Elastic Recovery

Elastic recovery is used to study powder compactibility which relates to powder's ability to produce adequate compact strength. During the compression cycle, the dimension of tablet changes between the compression and ejection phase due to expansion. This change is referred to as elastic recovery of material. If the elastic recovery (ER) of tablet is large then it prone to manufacturing defect like capping, lamination, etc. Hence the minimum elastic recovery is required to produce adequate strength of the tablet.[7]

$$ER = [(Ht - H0)/H0] * 100$$

Where, H_0 and H_t are the thickness of tablet during compression and after ejection.

RESULT AND DISCUSSION

Flow Property

Bulk density and tapped density of co-processed isomalt (0.55 ± 0.006 gm/mL and 0.61 ± 0.007 gm/mL) is higher than physical mixture (0.50 ± 0.004 and 0.66 ± 0.008 gm/mL) and isomalt (0.45 ± 0.007 and 0.50 ± 0.0093 gm/mL).

The flow property of powder is described by angle of repose, Carr's index and flow rate. The Carr's index and Hausner ratio of co-processed isomalt is 9.203 ± 0.097 and 1.10 ± 0.0011, which is lower than the physical mixture (24.86 ± 0.23 and 1.33 ± 0.004) whereas, similar with isomalt (9.43 ± 2.17 and 1.10 ± 0.026). Per Carr's index and hausner ratio, the co-processed isomalt and isomalt show similar flow property and are better than a physical mixture.

Angle of repose is not robust method for flowability detection. Flow rate is usually measured by flow of powder mass per unit time through an orifice of funnel or, cylinder or hopper. Flow rate is a direct measure flow of powder.[8] The flow rate of co-processed isomalt is higher than isomalt at different orifice diameters as shown in Figure 1. This confirms the co-processed isomalt has good flowability as compared to isomalt.

Dilution Potential

The immediately compressible excipients ought to have a high dilution potential, which calls for compressing more medication per tablet to achieve the appropriate level of strength.[25] Dilution potential of the co-processed isomalt was studied using paracetamol, mefenamic acid, ascorbic acid, nimesulide, and aspirin as drugs. The blend of co-processed isomalt and model drugs in various proportions were compressed into tablets. Co-processed isomalt showed 40% dilution potential for ascorbic acid, paracetamol, and nimesulide whereas, mefenamic acid and aspirin showed 30% dilution potential Table 1.

Packing Ability

The modified Kawakita equation[19] was used to determine the packing ability of the physical mixture and co-processed isomalt. In the Kawakita equation, 'a' is the maximum volume of reduction and 'b' is the apparent packing velocity or cohesiveness of powder. The value of 'a' was calculated from the slope and 'b' from the y-intercept of the N vs N/C plot Figure 2. The isomalt and co-processed isomalt show very low 'a' values of 0.13 and 0.0846, respectively. This indicates particles were packed more densely at the initial stage of tapping. The apparent packing velocity (b) of co-processed isomalt confirms that it has better packing ability and that particles are reorganized at the initial stage of compression. Powder with a low value of 'a' has superior packing ability. The particles are rearranged without changing their shape and size and this process removes void space in the powder bed.[25]

Isomalt and co-processed isomalt have coarse particle sizes and wider size distribution. Later one indicates better packing ability and spherical particles have better packing ability than a plate or irregular shaped particles.[26]

Consolidation Index and Rate of Consolidation

Neumann *et al.*,[21] method was used to calculate the consolidation index (which measures the effect of packing on flow) and rate of consolidation (which measures the powder packing rate). The values of K and C (Table 2) were calculated from the slope and y-intercept of a plot of log (ρt-ρb)/ρt vs log N Figure 3. The co-processed isomalt's consolidation index was higher than the isomalt's. A higher consolidation index indicates a higher flow of powder. A low value of K and a high value of consolidation index of co-processed isomalt is mainly due to particle shape and particle size distribution.

Heckle Plot

Heckle plot is the relationship between logarithm of reciprocal porosity and compaction pressure (Figure 4). The slope K is determined from linear portion of plot and inverse of slope is yield pressure (Py). The yield pressure indicates the plastic

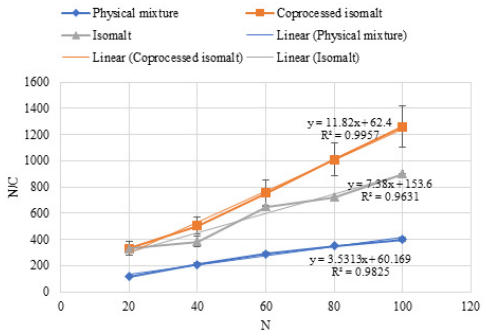

Figure 2: Kawakita plot of physical mixture, co-processed isomalt, isomalt

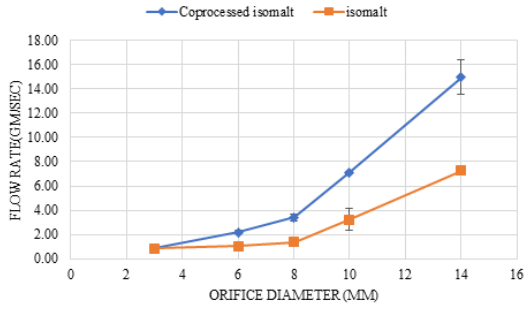

Figure 1: Flow rate of isomalt and co-processed isomalt

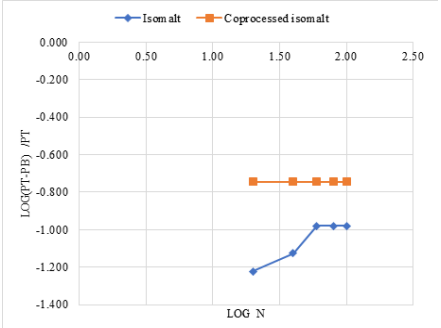

Figure 3: Consolidation behaviour of isomalt and co-processed isomalt

Table 1: Dilution potential of co-processed isomalt for paracetamol, mefenamic acid, ascorbic acid, nimesulide, aspirin

Parameter	(90:10)	(80:20)	(70:30)	(60:40)	(50:50)
Paracetamol	DP1	DP2	DP3	DP4	DP5
Dimension (mm)	9.6 x 4.4	9.6 x 4.4	9.6 x 4.4	9.6 x 4.5	9.8 x 4.6
Hardness (kg/cm^2)	8.16 ± 0.75	6.83 ± 0.40	5.5 ± 0.54	4.66 ± 0.51	2 ± 0.0
Disintegration time (min*)	6.31 ± 0.05	6.69 ± 0.25	6.825 ± 0.68	7.82 ± 1.23	10.95 ± 0.72
Friability (%)	0.0735	0.1873	0.2931	0.5677	0.6326
Mefenamic acid	DM1	DM2	DM3	DM4	-
Dimension (mm)	9.6 x 4.4	9.6 x 4.4	9.6 x 4.4	9.6 x 4.5	-
Hardness (kg/cm^2)	5.41 ± 0.37	4.41 ± 0.20	3 ± 0.44	0.66 ± 0.25	-
Disintegration time (min*)	5.23 ± 0.71	8.74 ± 0.30	15.73 ± 0.97	15.33 ± 0.18	-
Friability (%)	0.3122	0.5598	0.5256	10.988	-
Ascorbic acid	DA1	DA2	DA3	DA4	DA5
Dimension (mm)	9.6 x 4.4	9.6 x 4.4	9.6 x 4.4	9.6 x 4.4	9.6 x 4.3
Hardness (kg/cm^2)	6.66 ± 0.25	4.83 ± 0.25	3.83 ± 0.25	2.91 ± 0.20	1.16 ± 0.60
Disintegration time (min*)	5.11 ± 0.02	3.67 ± 0.35	4.25 ± 0.16	2.56 ± 0.67	1.29 ± 0.40
Friability (%)	0.2408	0.1663	0.0866	0.1665	1.6279
Nimesulide	DN1	DN2	DN3	DN4	DN5
Dimension (mm)	9.6 x 4.4	9.6 x 4.4	9.6 x 4.4	9.6 x 4.4	9.6 x 4.3
Hardness (kg/cm^2)	6.75 ± 0.41	4.41 ± 0.49	3.41 ± 0.73	2.25 ± 0.27	1.25 ± 0.41
Disintegration time (min*)	6.78 ± 0.50	7.96 ± 0.31	8.96 ± 0.54	8.93 ± 0.83	5.42 ± 0.36
Friability (%)	0.3786	0.4718	0.5578	0.804	0.6911
Aspirin	DS1	DS2	DS3	-	-
Dimension (mm)	9.6 x 4.4	9.6 x 4.4	9.6 x 4.4	-	-
Hardness (kg/cm^2)	3.75 ± 0.61	1.75 ± 0.27	1.08 ± 0.20	-	-
Disintegration time (min*)	5.15 ± 0.16	6.77 ± 0.6	9.12 ± 0.06	-	-
Friability (%)	0.026	0.08	0.9032	-	-

Mean ± SD *n=3, SD: standard deviation. * Disintegration time is in minute decimal of average.

Table 2: Kawakita parameter of physical mixture and co-processed isomalt

Material	*Rate of consolidation (K)*	*CI*
Isomalt	0.38674	-1.7228
Co-processed isomalt	0	-0.7439

deformation of powder. Yield pressure of powder is in order of isomalt < co-processed isomalt < physical mixture (Table 3). Yield pressure of co-processed isomalt is lower than physical mixture. Coprocessing of material lowers the yield pressure. Isomalt and co-processed isomalt shows compaction by initial fragmentation and then plastic deformation.

Elastic Recovery

Elastic recovery of co-processed isomalt is lower than physical mixture and isomalt at high compaction pressure as shown in Figure 5. This indicates that co-processed isomalt has good compatibility.

Tablet characterization of isomalt

Isomalt was able to compress up to 40% of paracetamol as a model drug. However, the tablets failed friability and broke down into two parts. The tablet containing 20% paracetamol showed acceptable tablet strength and disintegration time.

Tabletability

The tabletability of isomalt, physical mixture, and co-processed isomalt is shown in Figure 6. Co-processed isomalt has good tabletability as compare to physical mixture and isomalt.

For pressure-sensitive drugs (such as candesartan cilexetil), which exhibit polymorphism instability at higher compaction pressure, compacting powder to a lower compaction pressure

Table 3: Yield pressure of isomalt, physical mixture, and co-processed isomalt

Sr. no.	*Sample*	*Slope (K)*	*Yield pressure (Py)*
1	Isomalt	0.0058	172.41
2	Physical mixture	0.0013	769.23
3	Co-processed isomalt	0.0017	588.23

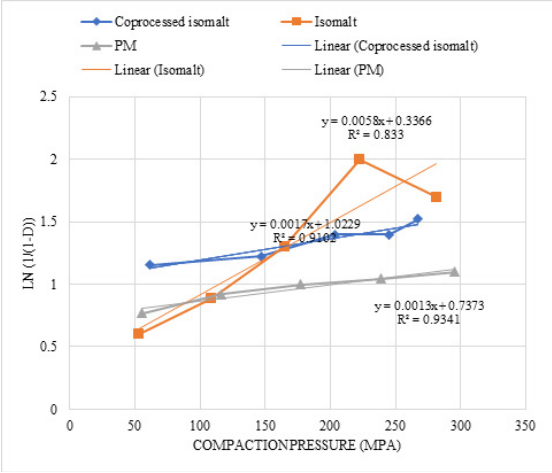

Figure 4: Heckel plot of isomalt, co-processed isomalt and physical mixture

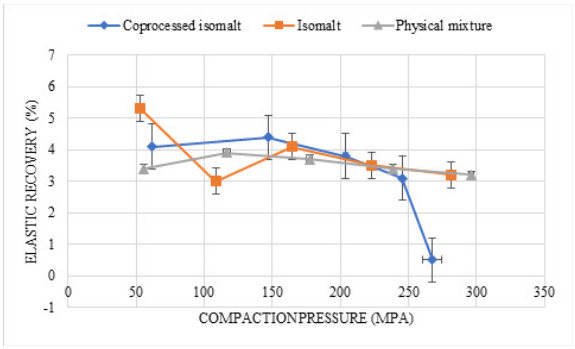

Figure 5: Elastic recovery of isomalt, physical mixture, and co-processed isomalt

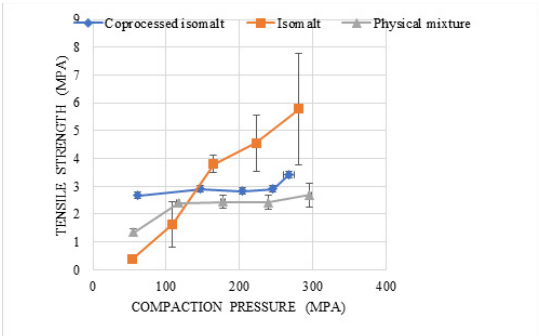

Figure 6: Tabletability of isomalt, co-processed isomalt and physical mixture

is preferable. Compression of tablets at low compaction pressure also increases the manufacturing capacity of tableting machines by consuming less energy. At lower compression pressure, tensile strength of the co-processed isomalt tablet is significantly higher than physical mixture and isomalt at *p-value* 0.0007 ($\alpha = 0.05$). The tensile strength of co-processed isomalt and physical mixture is increased parallelly as effect of compression pressure whereas, tensile strength of isomalt is increase suddenly as compression pressure increases with higher standard deviation.

CONCLUSION

Isomalt and co-processed isomalt have a similar particle size distribution and exhibit good flow properties. The flow rate of co-processed isomalt is better than isomalt. The dilution potential of isomalt is 20% for paracetamol (poorly compressible), which was improved to 40% with co-processed isomalt. Co-processed isomalt has better packing ability; particles are packed more densely at the initial stage of tapping without changing their shape and size. Co-processed isomalt has good tabletability as compared to physical mixture and isomalt. Isomalt and co-processed isomalt shows compaction by initial fragmentation and then plastic deformation.

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