RESEARCH ARTICLE

Development of Novel Directly Compressible Isomalt-based Co-processed Excipient

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ABSTRACT

Objective: The study aims to improve the tableting qualities by coprocessing isomalt with PEG 4000 and crospovidone.

Methodology: The melt granulation method was adopted for coprocessing isomalt with PEG 4000 and crospovidone. The proportion of constituents was optimized using full factorial design. Particle size distribution, true density, moisture content, flowability, flow rate, SEM analysis, dilution potential, and tablet ability were all examined for optimized co-processed isomalt-based excipient and compared with isomalt.

Result and Discussion: Co-processed isomalt-based excipients had 40% dilution potential for paracetamol as compared with 20% for isomalt. Co-processed isomalt-based excipient showed 30% dilution potential for mefenamic acid and aspirin. Co-processed isomalt overcomes the lamination and sticking problem, which has better tablet ability, binding, disintegration, and lubricating potential.

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

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INTRODUCTION

A multifunctional excipient is required for direct compression because it can replace two or more excipients in a formulation, greatly reducing the need for fillers, binders, disintegrants, lubricants, glidants, etc.[1] However, the selection of excipients is restricted because discovering and developing new excipients is exceedingly expensive. As a result, efforts are undertaken to alter the essential characteristics of existing excipients, such as particle size, shape, surface area, porosity, and density. It is evident in such modifications that while one may get the desired property, it does so at the expense of another similarly crucial property. Coprocessing has thus been investigated as an additional method of influencing the characteristics of excipients.[2] In coprocessing, two or more established excipients are made to physically interact with one another using a specific method (such as granulation, spray drying, milling, co-crystallization, melting, etc.) in order to enhance functionality and cover up unwanted characteristics of the individual components.[3] In this the components interact at the sub-particle level. Since no chemical changes take place during co-processing, the resulting product can be viewed as a combination of the excipients already in use, negating the need for substantial toxicological research.

Polyols such as sorbitol and mannitol are established multifunctional excipients in tablet manufacturing. However, the use of isomalt, the only polyol derived from sucrose, has not been very illustrious yet as a multifunctional excipient, despite being described in each of the major pharmacopoeias.

The enzymatic transglucosidation of sucrose produces isomaltulose that on hydrogenation gives stereoisomer disaccharide alcohol, α-D-glucopyranosyl-1,1-D-mannitol dihydrate (GPM) and α-D-glucopyranosyl-1,6-D-sorbitol (GPS) in an approximate equimolecular mixture called as isomalt. The ratio between the main components GPS and GPM can be varied employing an additional special crystallization process. This allows the development of isomalt with different solubilities since the water solubility of GPS is higher than that of GPM. The commercial isomalt GalenIQ 721 has a ratio of GPS:GPM of 3:1 that has water solubility of 42% w/w whereas Galen IQ 720 has GPS:GPM of 1:1 and solubility 25% w/w.[4] These materials are agglomerates prepared by milling the sieved isomalt followed by agglomeration using fluid bed process.

Isomalt has a sweet taste and a low negative heat of solution. It has certain advantages when compared with conventional saccharides like glucose, lactose, and sucrose. Its sweetening

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ability is half that of sucrose. It is resistant to hydrolysis by acid and enzyme. It has very good microbiological stability and doesn't serve as a substrate for microbial growth.[5] In contrast to traditional saccharides like glucose, lactose, and sucrose, it allows diabetic individuals to ingest it without experiencing any appreciable rise in body glucose, insulin, or lactic acid levels. The lack of a carbonyl group in the isomalt molecule makes it resistant to chemical degradation and resistant to the Maillard reaction. Compared to sucrose, isomalt is less hygroscopic. With these organoleptic, physicochemical, and metabolic properties, isomalt has several advantages over most sugars and sugar alcohols when used as a tablet excipient, including sweetness and mouthfeel, non-carcinogenicity, low glycemic index, suitability for diabetics, and low hygroscopicity. Besides its use as a sweetening agent, isomalt has been employed as filler for orally disintegrating tablets,[6,7] as binary excipient[8], as solid dispersion carrier[9,10] and core or layer material for pellets.[11,12]

Since isomalt is a low-glycemic, non-hygroscopic, non-cariogenic sweetener, it is the most suited excipient for the manufacture of tablets and lozenges. The main issues with isomalt as an excipient for direct compression of tablets are lamination and sticking,[4] hence isomalt's characteristics need to be improved. Coprocessing is an effective method for modifying isomalt at the particle level. Thus, this study aimed to coprocess isomalt using appropriate method (melt granulation) and assess the co-processed isomalt's tableting characteristics, including particle shape and size distribution, flowability, dilution potential, and tablet ability.

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). PEG 4000 was purchased from Research-Lab Fine Chem Industries, (Mumbai, Maharashtra, India). Crospovidone (Kollidone CL-M) was obtained from BASF, (Ludwigshafen, Germany). All other laboratory chemicals were of analytical grade.

Method

Preparation of co-processed excipients

Isomalt, PEG 4000, and crospovidone were weighed accurately and passed through 180 µm mesh. The ingredients were mixed intimately and transferred to a previously heated porcelain dish at 60°C. The mixture was heated with a continuous stirring for 15 minutes to develop agglomerates and mixture of 1% talc and silicon dioxide (1:1) was added and blended for another 5 minutes. The agglomerates were cooled to room temperature with continuous stirring to avoid the formation of large lumps. The agglomerates were passed through 250 µm mesh and kept in a tightly closed container till further use.[13]

Experimental design

A two-factor, three-level full factorial design (response surface technique) was utilized to formulate an optimized co-processed excipient and to investigate the impact of experimental variables on the functionality of the developed co-processed excipient. Table 1 displays the chosen independent and dependent variables. The level of independent variables was chosen to range from -1 to +1. The five center points (40% PEG 4000 and 10% crospovidone) were included in a total of 13 experimental runs (Table 2), which were then assessed using Design-Expert software.

Preparation of placebo tablet by using co-processed excipient

The placebo tablets of co-processed excipients (batch F1 to F13) were compressed using 9 mm concave-faced punches on a rotary tablet press (Rimek Minipress II MT).

Evaluation of placebo tablets of co-processed excipients

The dimension of tablets was determined by using a vernier caliper and the weight of the tablet was measured on digital balance (Shimadzu AUX220).[14] Using the Monsanto hardness tester, the crushing strength of six tablets from each batch was assessed.

Friability (F) of tablets were determined by using Roche friability apparatus (Remi equipments) and calculated by using formula; F=(Iw-Fw)/Iw*100, where, Iw is initial weight of tablets, Fw is final weight of tablets. Disintegration time was determined by utilizing a USP tablet disintegration testing instrument (Bio-Technics India) in distilled water at 37 ± 2°C.

Based on this study, optimized batch was selected from hardness and disintegration time by using response surface methodology.

Characterization of optimized co-processed isomalt

The optimized co-processed isomalt was characterized on the following parameter.

Particle size distribution

A mechanical sieve shaker was used to assess the particle size distribution of isomalt and optimized co-processed isomalt. A nest of standard sieves was used. The weight of the agglomerates retained on each sieve was recorded after the sample was put onto the upper sieve and the sieves were shaken for 10 minutes.[13,15,16]

Moisture content

One gram of optimized co-processed isomalt and isomalt powder was added to a petri plate, which was then dried at 105°C until the weight remained constant. The percentage weight loss was then utilized to determine the moisture content.[17]

Table 1: Level of independent variable

Variables	*Level, actual (Coded value)*		
	Low (-1)	*Medium (0)*	*High (+1)*
Independent variables			
X_1: PEG 4000 (%)	30	40	50
X_2: Crospovidone (%)	5	10	15
Dependent variables (response)			
Y1: Hardness	Maximum		
Y2: Disintegration time	Minimum		

Table 2: Experimental runs as per 3^2 full factorial design

Batch	*PEG 4000 (%)*	*Crospovidone (%)*	*Isomalt*	*Hardness (Kg/cm^2)*	*Disintegration time (min.)*	*Friability (%)*	*Weight variation (%)*
F1	30	5	65	5.17 ± 0.61	4.67 ± 0.15	0.065	± 2.69
F2	40	5	55	5.75 ± 0.27	7.01 ± 0.06	0.131	± 1.99
F3	50	5	45	6.08 ± 0.38	5.50 ± 0.25	0.000	± 2.20
F4	30	10	60	5.00 ± 0.32	6.61 ± 0.10	0.131	± 3.16
F5	40	10	50	6.00 ± 0.63	6.00 ± 0.00	0.131	± 2.84
F6	50	10	40	6.50 ± 0.45	7.00 ± 0.25	0.197	± 2.79
F7	30	15	55	6.33 ± 0.26	6.28 ± 0.05	0.265	± 4.29
F8	40	15	45	6.92 ± 0.38	6.92 ± 0.14	0.327	± 3.73
F9	50	15	35	8.42 ± 0.49	9.17 ± 0.58	0.195	± 2.81
F10	40	10	50	5.50 ± 0.32	6.06 ± 0.05	0.131	± 1.98
F11	40	10	50	5.75 ± 0.27	6.13 ± 0.04	0.131	± 1.65
F12	40	10	50	5.67 ± 0.41	6.15 ± 0.02	0.130	± 1.93
F13	40	10	50	5.58 ± 0.38	6.00 ± 0.13	0.130	± 2.25

Mean ± SD *n=3, SD: standard deviation

True density (Dt)

The true density of isomalt and optimized co-processed isomalt was determined by the liquid pycnometer (specific gravity bottle) by using xylene. A clean and dry pycnometer was filled up with xylene and weighed. 1-gm of powder was put in a pycnometer and filled with xylene taking care to remove excess of xylene and weighed. The following equation determined the Dt of powder:

$$\rho t = \frac{w}{a+w-b} \times SG \qquad (1)$$

where is the true density of powder, w is the weight of powder, is the weight of the pycnometer filled with xylene, is the weight of the pycnometer filled with powder and xylene , and SG is the specific gravity of xylene.[17-19]

Flowability

The flowability of isomalt and optimized co-processed isomalt was assessed by calculating Carr's index, Hausner ratio, angle of repose, and flow rate.[13]

The powder was assessed for flow rate using a 3, 6, 8, 10, and 14 mm opening diameter funnel. A 100 mL graduated cylinder fixed on a tapper supported this funnel. The funnel's orifice opening was blocked when the sample was poured into it. The tapper initiates motion when unlocked. The powder is forced through the funnel's aperture and then drops to the cylinder's base. The amount of time needed to funnel the entire volume of powder down the funnel was recorded. The flow rate was determined by dividing the sample mass by the flow rate.[20]

Scanning electron microscopy (SEM)

SEM image was used to determine the sample's morphology (Jeol, JSM 6390LA). The sample was applied to a small piece of carbon tape that was attached to a brass stub with adhesive. A sputtering apparatus (model: JFC1600) was used to apply gold coating to the sample for 10 seconds at a current of 10 mA. The gold-coated sample's secondary electron/back scattered electron images were captured in a SEM chamber.

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, 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[23-25] and required in high dose.[26] Mefenamic acid has higher sticking tendency.[23] Aspirin are moisture sensitive and difficult to compress by wet granulation so direct compression is a suitable method for this drug. The compression of aspirin is by plastic deformation.[27]

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

Tablet ability

Tabletability of isomalt, optimized co-processed isomalt and 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 micrometre. Finally, tablet diameter and fractured load were measured with a Gamlen TTA (tablet tensile analyser).

Tableting ability of isomalt

The tabletting ability of isomalt was checked with paracetamol and followed procedure as per the evaluation parameter' dilution potential.[18,21,22]

RESULT AND DISCUSSION

Co-processed isomalt was prepared by melt granulation method using PEG 4000 and crospovidone. PEG 4000 is hydrophilic, semicrystalline, less hygroscopic and having low melting range 58 to 60°C.[29,30] It also acts as a binding agent and impart plasticity to agglomerates.[4] PEG 4000 is suitable polymer for coprocessing of isomalt because of its melting range (58–60°C) is less than the glass transition temperature of isomalt (63°C). Crospovidone is cross-linked homopolymer of N-vinyl-2-pyrrolidinone, water-insoluble, hygroscopic excipient.[31] It acts as a disintegrant and help to enhance solubility of poorly soluble drug.[4,32]

Statistical Analysis

The Design-Expert software gives 13 runs for 3^2 full factorial designs

Table 2, all formulations' weight variations were within the pharmacopoeial limit of 7.5% and their hardness ranged from 5 to 8.42 kg/cm^2. These responses of all experiments were fitted into a quadratic model. Analysis of variance show model is significant for hardness (*p-value* < 0.0001, α=0.05) (Table 3). Compared to the significance level of 0.05, the *p-value* for the lack of fit for hardness was higher (0.4398). As a result, it demonstrated the non-significant lack of fit value desired for a suitable model.[33] Therefore, it is argued that the quadratic model fits the response well based on its p-value and lack of fits (hardness; $R^2 = 0.9707$).

As per response surface plot Figure 1 hardness of the tablet is more influenced by the concentration of PEG 4000 than crospovidone in a co-processed excipient. Hardness of tablets increases proportionally as PEG 4000. Polyethylene glycol is a ductile material and is also used as a binder in the tablet dosage form. PEG 4000 improves the plastic behavior of co-processed excipient, thereby improving the tablet ability of material and tablet strength.

Equation 4 and equation 5 illustrate the final model equation in terms of coded factors and actual factors, respectively.

$$\text{Hardness} = 5.68 + 0.75A + 0.77B + 0.29AB + 0.10A^2 + 0.68B^2 \quad (4)$$

$$\text{Hardness} = 17.90 - 0.068\times\text{PEG4000} - 0.6259\times\text{Crospovidone} + 0.0058\times\text{PEG4000}\times\text{Crospovidone} + 0.001\times\text{PEG4000}^2 + 0.027\times\text{Crospovidone}^2 \quad (5)$$

The disintegration time of all formulation was in the range of 4.67 to 9.17 minutes (Table 2). These responses of all experiment were fitted into a linear model. Analysis of variance show model is significant (*p-value* < 0.0169, α=0.05) for disintegration time Table 3. The disintegration time lack of fit has a p-value of 0.0001, with a significance threshold of 0.05. As a result, it demonstrated a significant lack of fit value, which is poor for a good model. The F-value for the lack of fit is 204.57, which indicates a 0.01% possibility that noise may be the cause of a number this significant. As a result, the linear model was fitted for the disintegration time at a correlation coefficient R2=0.5578 based on the model's p-value and lack of fit.

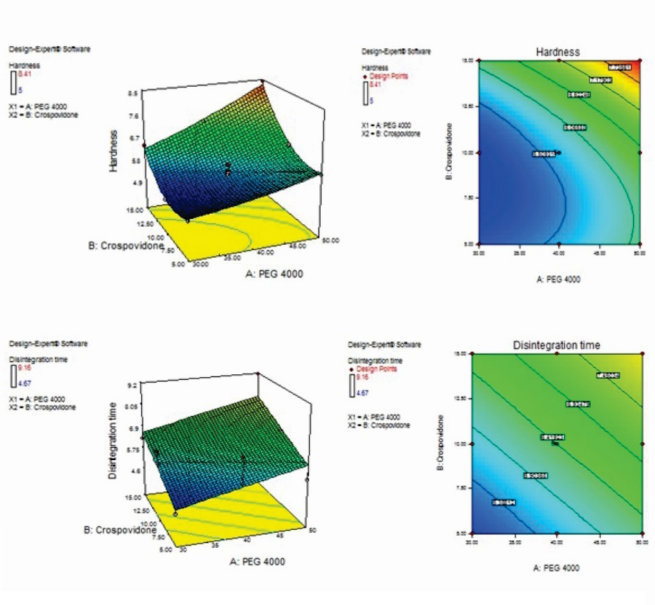

Figure 1: Response surface and contour plot surface of hardness and disintegration time

A linear relationship was observed in independent variables and disintegration time. Both crospovidone and PEG 4000 concentrations have shown a linear increase in the disintegration time. Since PEG 4000 acts as a binding agent, it prolongs the disintegration at higher concentrations.

Equation in terms of coded factors

$$\text{Disintegration time} = 6.419230769 + 0.685\times A + 0.861666667\times B \quad (6)$$

Equation in terms of Actual Factors:

$$\text{Disintegration time} = 1.955897436 + 0.0685\times\text{PEG 4000} + 0.172333333\times\text{Crospovidone} \quad (7)$$

Optimization

For independent variables criteria set was crospovidone (5 to 15%) and PEG 4000 (30 to 50%). For dependent variables criteria set was hardness (6 to 8 Kg/cm^2) and disintegration time (5–8 minutes). Design-Expert 7.0.0 software gives 30 solutions. A solution with crospovidone 10.5% & PEG 4000 43.7% and a desirability value of 1 was selected. The selected solution showed predicted response of hardness 6.06 kg and a disintegration time 6.75 minutes. If a solution has a desirability value of 1, it means that all of the variables' requirements were satisfied.[34] The observed values (hardness=5.66 ± 0.87 kg, disintegration time=6.46 ± 0.50 minutes) of this co-processed excipient, compared with the responses predicted by software, exhibited close similarity. Thus, the selected solution was considered as optimized and it concluded that the model used in optimizing composition of the co-processed excipient is valid. Selected optimized formulation was further evaluated and compared with isomalt.

Particle surface and particle size distribution

Both isomalt and optimized co-processed isomalt exhibited excellent flowability. The particle size of isomalt was in the range of 75 to 350 µm and over 53% of particles were

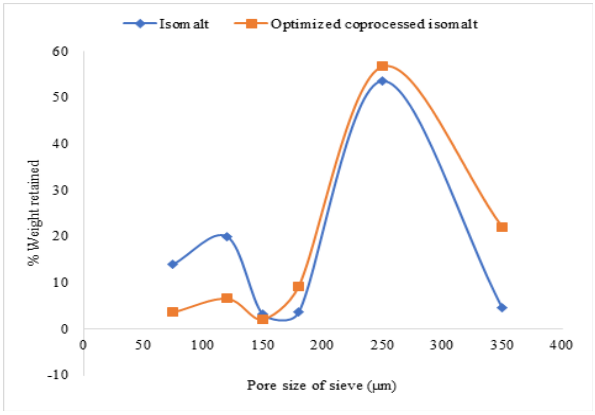

Figure 2: Particle size distribution of isomalt and optimized co-processed isomalt by sieve method

Table 3: Statistical data of ANOVA

Hardness of tablet					
Term	*Sum of Square*	*Degree of freedom*	*F-value*	*p-value (α=0.05)*	*Inference*
Model	9.07	5	46.45	< 0.0001	Significant
Lack of fit	0.12	3	1.12	0.4398	Not significant
R2 value	0.9707				
Disintegration time of tablet					
Model	7.27	2	6.30	0.0169	Significant
Lack of fit	5.74	6	204.57	< 0.0001	Significant
R2 value	0.5578				

α = significance level

distributed in 250 to 350 µm. The optimized co-processed isomalt particle size was 75 to 350 µm and 56% of particles were distributed in 180 to 350 µm range (Figure 2).

Scanning electron microscopy showed isomalt in agglomerate form having a rough and highly porous surface (Figure 3). In contrast, SEM image of optimized co-processed isomalt displayed a smoother and less porous surface, indicating coating of isomalt by PEG 4000 in co-processed isomalt.

Physical characterization of material

The physical characteristics of isomalt and the optimized co-processed isomalt are given in Table 4. The moisture content in optimized co-processed isomalt is higher than in isomalt, enabling optimized co-processed isomalt to act as a plasticizer.

According to the flowability parameter, isomalt and optimized co-processed isomalt exhibit good flow properties.

Flowability

Excipients used for direct compression tablet manufacturing must have good flow characteristics. Flow rate of isomalt & optimized co-processed isomalt increased proportionally as the orifice diameter as given in Figure 4. Optimized co-processed isomalt shows better flowability as compared to isomalt. This flowability was calculated for a 6 mm orifice. Isomalt has 1051.2 mg sec^{-1} and the optimized co-processed isomalt has 2172.09 mg sec^{-1} flow rate. Flow rate of the optimized co-processed isomalt is 2.066 times greater than that of isomalt.

Table 4: Physical characterization of isomalt and optimized co-processed isomalt

Parameter	*Result*	
	Isomalt	*Optimized co-processed isomalt*
Moisture Content (%)	0.0843 ± 0.02	0.1159 ± 0.01
Bulk density (gm mL^{-1})	0.4478 ± 0.00	0.5521 ± 0.00
Tapped density (gm mL^{-1})	0.4946 ± 0.00	0.6081 ± 0.00
True density (gm mL-1)	1.5037 ± 0.00	1.3825 ± 0.29
Angle of repose (θ)	30.88 ± 3.39	33.83 ± 0.53
Hausner ratio	1.10 ± 0.02	1.1013 ± 0.00
Carr's index	9.43 ± 2.17	9.20 ± 0.09

Mean ± SD *n=3, SD: standard deviation

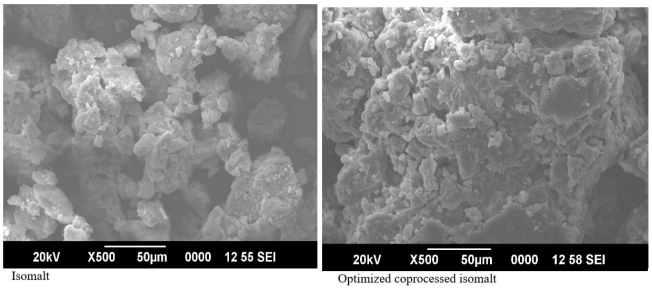

Figure 3: SEM image of isomalt and optimized co-processed isomalt

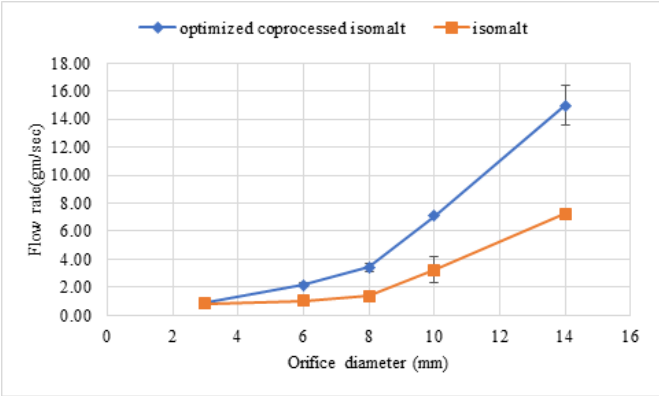

Figure 4: Flow rate of isomalt and optimized co-processed isomalt

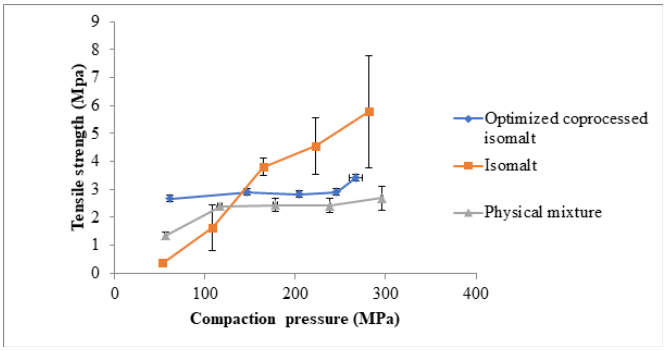

Figure 5: Tabletability of isomalt, optimized co-processed isomalt and physical mixture

Table 5: Dilution potential of optimized co-processed isomalt for paracetamol, mefenamic acid, 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	-
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

A similar relationship of flowability was observed for a 14 mm orifice diameter. The flow rate of the optimized co-processed isomalt is 2.06 times greater than that of isomalt.

Tabletability

The tabletability of isomalt, physical mixture, and co-processed isomalt is shown in Figure 5. Co-processed isomalt has good tablet ability as compare to physical mixture and 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.[35] Dilution potential of the optimized co-processed isomalt was studied using paracetamol, mefenamic acid, and aspirin as drugs. The blend of optimized co-processed isomalt and model drugs in various proportions were compressed into tablets. Co-processed isomalt based excipient showed 40% dilution potential for paracetamol whereas, mefenamic acid and aspirin showed 30% dilution potential Table 5.

Tablet characterization of isomalt

The isomalt has good compressibility and flowability as per the result of powder characteristics given in Table 4. 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 tablets strength and disintegration time.

CONCLUSION

3^2 full factorial design was used to optimize the constituents of co-processed isomalt. Co-processed isomalt having the composition of isomalt (45.80%), crospovidone (10.5%), and PEG 4000 (43.7%) was selected as optimized. Isomalt and optimized co-processed isomalt have a similar particle size distribution and exhibit good flow properties. The flow rate of optimized co-processed isomalt is better than isomalt. Optimized co-processed isomalt is non-hygroscopic; however, it absorbs 0.904% of moisture at 84% RH because of the polymer PEG 4000, which absorbs moisture above 80% RH. The dilution potential of isomalt is 20% for paracetamol (poorly compressible), which was improved to 40% with optimized co-processed isomalt. Co-processed isomalt has good tabletability as compared to physical mixture and isomalt.

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