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Research Article

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Optimization of Direct Compression's Co-Processed Excpient Mannitol-Polyethylene Glicol (PEG) 6000 in Manufacture of Vitamin C Tablets

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ABSTRACT

Tablet excipients for direct compression should have a good flowability and compactibility. Mannitol commonly used as tablet diluents is less hygroscopicity, brittle and poor flowability and compactibility. The aim of this research was to improve the flowability and compactibility of mannitol by co-processing mannitol-PEG 6000 fabricated by wet milling technique. Optimum co-processed Mannitol-PEG 6000 were used in manufacture of vitamin C tablets. The co-processed material obtained were evaluated; particle size distribution, average diameter, density, porosity, flowability, compactibility, SEM, PXRD and DTA. Optimum co-processed Mannitol-PEG 6000 generates tablets of vitamin C model drug that meet the USP requirements of tablet dosage, which include hardness, friability, disintegration time and dissolution test. The flowability of co-processed mannitol-PEG was increased in the range of 6.92±0.64 to 6.91±0.74 g/second and the tensile strength of co-processed mannitol-PEG was increased which were 2.77±0.07 Mpa was higher than its physical mixture 2.15±0.07 MPa. X-ray diffraction analysis result of co-processed had similiar pattern with mannitol. SEM the tablet made by co-processing technique was more compact. In manufacture vitamin C tablets showed that formulation vitamin C by co-processed mannitol-PEG was great tablet. The co-processed mannitol-PEG is more promising to use as direct compression material.

Keywords: Mannitol; PEG 6000; Co-processed; Wet milling; Vitamin C

INTRODUCTION

Tablet is pharmaceutical preparations which most widely used and most favored than other preparations, because it is more convenient and practice. Nowadays more than 60 % all pharmaceutical preparations in the market available as a tablet preparation. Meanwhile, the efficient method to manufacture of tablet is direct compression. This methode is practical and quick easy process, so that industry can minimize the costs of productions. Direct compression is primarily for hygroscopic compound and sensitive to heat (1). Direct compression according to the powder mixture that has the good flowability, compressibility dan compactibility (2). Compactibility parameters mechanically is power of tablet, hardness deformation and bonding index (3).

Mannitol is polyol (alcohol sugar), hecsitol that is widely available in nature. It is isomer of sorbitol, less hygroscopicity, and brittle. There are currently three polymorphic form of mannitol which consist of α, β, and δ. The commonly polymorphic form is β (4). The polymorphism of mannitol indicate differences in the characteristics compression of mannitol (5). Mannitol is feels good in the mouth, so often used in formulations of chewable tablet. Formulation by mannitol has poor flowability and thus require many lubricants. Mannitol has less compressibility and readily reacts with metal (6). This causes direct compression methode can not be used in the manufacture of tablets by mannitol as filler.

Co-process is a mixing method the plastis and brittle excipients by a certain process with the composition of many brittle materials and less plastis materials (7). Co-process is a development concept that changes the functionality of excipient by mixing an excipient with other excipient (7). Some co-processed mannitol with other materials have been patented including MCC-Mannitol (Avicel®HFE), mannitol-kolidon-polivinil acetat (LudFlash®), mannitol-sorbitol (Compresol®). Besdides it has a lot of research to make coprocessed mannitol with other excipient, like mannitol and chitin (8), mannitol dan cellulose (9), mannitol : lactosa with PVP K 30 and with PEG 4000 (10).

The method have been developed in manufacture of co-processed excipients like spray drying, fluid bed spray granulation, roller compaction, wet milling (slurry), melt granulation, roller drying (11). Wet milling (slurry) is establishment of solid mass into a paste that is suspending a solid in the water becomes like's slurry. Water adsorption on the surface of solids can enchance reactivity with the action as a medium or plasticizer in certain reaction. Their water in the mixture of solid component will be help the moleculer movement in the reaction among two or more solid components (12). Drying without heating the slurry can maintain a stable polimorfic form because high temperature can make the fase transition. The aims of this research is to improve compactibility of mannitol by co-processed mannitol-PEG 6000.

EXPERIMENTAL SECTION

Materials

The following materials were used: mannitol, poliethylen glycol (PEG) 6000, aquadest, vitamin C and all other solvents were analytical grade.

Methods

Preparation and Evaluation co-processed excipient mannitol: PEG 6000

Made some a mixture of different composition mannitol-peg 6000 (see table 1)

Table 1: Composition a mixture of Mannitol-PEG 6000

Excipient	Formula (%w/w)			
	I	II	III	IV
Mannitol	100	90	94	98
PEG 600	-	10	6	2
Innitial (Co-porcessed)	CM	CMPEG1	CMPEG2	CMPEG3
Innitial (Physical mixture)		FMPEG1	FMPEG2	FMPEG3

Part of PEG dissolved in 60 % water then added with the part of mannitol and stirred by ball milling at speed 105 rpm for 30 minutes to make reaction both materials so can form the paste (slurry). A mixture of prepared then dried in an oven temperature 40 ^{O}C network for 6 hours. The drying stored on the room temperature. The result of dry sifted and an evaluation, including distribution size of particles and diameter of averge, the specific gravity , porosity, flowability, compressibility and compactibility, then it was identified by using DTA (Differential Thermal Analysis) and PXRD (Powder X-Ray Diffraction). Identification now over and compare polimorf form of co-processed mannitol-PEG 6000 against a physical mixture and pure mannitol.

Next make the tablet by compressed the powder, in which every sample compressed on same parameter the use of a machine tablet that is driven manually with variation power compressing such as 0.5; 1; 1.5; 2; 2.5; 3; 3.5; four tons. Tablets their compressed identified with Scanning Electron Microscopy (SEM) and evaluated that compactibility by means of measured diameter and thickness expressed in cm then measured violence hardness tablets using a tester 24 hours after compressed (time to stress relaxation compression) expressed in kg. By the value of diameter, thickness (l,cm) and violent (p,kg) can be calculated tensile strength (MPA) with the equations (12) :

$$F=\frac{0,0624\times P}{D\times L}$$

Tensile strength tablet desired is around 1 – 4 MPa (12).

Formulation and evaluation of vitamin c tablets

Made formulations vitamin C as a model medicine to optimize the co-processed mannitol-PEG 6000 as fillers tablet by the direct compression. The formula seen in Table 2.

Table 2: Formula vitamin C with some variation co-processed mannitol-PEG 6000 as a filler

	Compotition						
Formula	**Vitamin C**	**Starch 15000**	**Talk**	**Mg. Stearat**	**CMPEG1**	**CMPEG2**	**CMPEG3**
A	50 mg	10%	2%	1%	-	-	ad 300 mg
B	50 mg	10%	2%	1%	-	ad 300 mg	-
C	50 mg	10%	2%	1%	ad 300 mg	-	-

All of their mixed until homogeneous for 15 minutes according to a formula made except magnesium stearate and talk. Then added magnesium stearate and talk, stirred for 5 minutes. A mixture of made tablet by direct compression and evaluated including violence, friabilitas, time destroyed, uniformity size, uniformity weight, and dissolution test.

RESULT AND DISCUSSION

Early testing the physical properties of material co-processed was about the density of granule, and that compressibility (table 3), the average size of the diameters of minute particles and distribution size of particles (table 4).

Table 3: Evaluation data of powder

Initial	Granul Densitiy (g/mL)	Flowability (g/second)	Hausner	Compressibility (%)
M	1.64 ± 0.052	1.37 ± 0.3	1.31 ± 0.016	23.4 ± 0.9
CM	1.74 ± 0.005	1.02 ± 0.06	1.27 ± 0.017	21.2 ± 0.0
CMPEG1	1.71 ± 0.012	6.92 ± 0.64	1.36 ± 0.16	22.3 ± 0.8
CMPEG2	1.77 ± 0.044	6.40 ± 0.39	1.44 ± 0.00	30.7 ± 0.0
CMPEG3	1.82 ± 0.017	6.91 ± 0.74	1.36 ± 0.04	26.4 ± 2.2

On the outcome of the measurement of the granul density shows that there is no difference for each of. In addition, in testing compressibility also indicated no increase compressibility mannitol after co-processed. But in flowability test was increase in the results co-processed mannitol-PEG 6000.

From table 4 shows that mannitol having distribution size of particles not homogeneous, in contrast to the co-processed mannitol with PEG sowed to the distribution of particles high at every the range of sizes have left adequate weight. It could also be determined diameter average particles point to a difference size diameter particles between the co-processed mannitol-PEG tend to be less than pure mannitol and co-processed mannitol without PEG.

Table 4: Distribution size of particle

Initial	% Lagging Weights					Diameter Average (mm)
	35/40	**40/60**	**60/120**	**120/170**	**170/230**	
M	96.6±1.1	1.6±0.7	0.9±0.3	0.7±0.2	0.1±0.1	0.453±0.002
CM	93.0±0.3	2.4±0.2	2.4±0.0	1.9±0.2	0.2±0.1	0.443±0.001
CMPEG1	21.91±0.73	9.51±1.28	17.34±1.08	29.70±0.36	21.54±0.58	0.213±0.001
CMPEG2	24.43±5.10	14.76±6.92	27.98±7.47	14.96±3.26	14.96±3.26	0.236±0.026
CMPEG3	21.39±0.19	10.93±0.18	27.25±1.84	28.28±2.40	12.15±4.39	0.225±0.005

An increase in rate of flowability is associate with size of particles on each of. Although in general, the less size of particles will cause the decline in their flowability compared with bigger particles (13). But in the research indicated that increased flowability rate on the size of smaller particles. The same have been reviewed by other researcher (14). The results of co-processed are increased the lowability although have small particle, it is because of the co-processed shaped more homogenous and having high cohesivity high compared to before co-processed.

The analysis of mannitol by PXRD showing that there are peak 10.56 top relatively intense in 14.71 denoting the polymorph β, the summit also present in the polymorph α and δ but very weak (15). Meanwhile for all powder analyzed wheter it is physical mixture and co-processed having pattern PXRD similar to mannitol. This is because the composition of PEG is very small that does not affect mannitol. The absence of a shift in a pattern demonstrate that there is no new crystal formation.

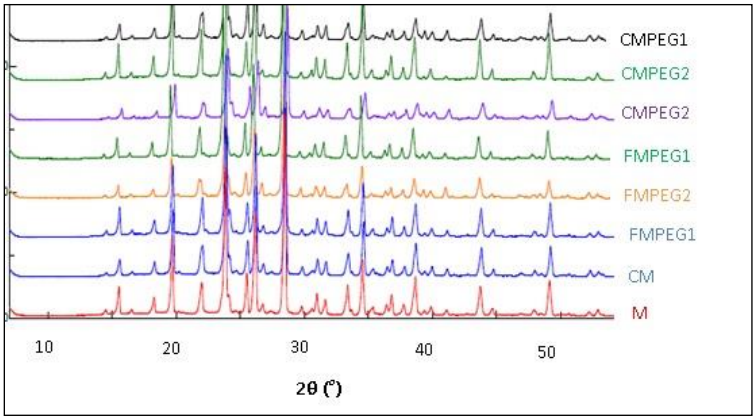

Figure 1: Difractoghram X rays

Identification for the rest of mannitol, physical mixture mannitol-PEG and co-processed mannitol-PEG by the thermal analysis using DTA. On a curve to mannitol shows that there has been the top of an endothermic at a temperature 171.8 ^{o}C which is of mannitol melt down, while in co-processed mannitol without PEG endothermic show the top of that is almost the same first at the top of 169.9 ^{o}C endoterrmik namely at a temperature 170.7 ^{o}C but suddenly appeared to some endothermic the top of which is not too sharp at a temperature 66.3 ^{o}C, by the same to co-processed mannitol-PEG that shows the top of an endothermic at a temperature 170.3 ^{o}C then also appeared the top of an endothermic other sharp at the temperature 52.0 ^{o}C. Therefrom this result shows that a shift in the top of an endothermic was not that much different is the melting point of mannitol , while at the height of the new endothermic shown on a physical mixture and co-processed mannitol-PEG is the melting point of PEG. In addition there is no new the tops of which means that does not happen the transformation of polymorphic.

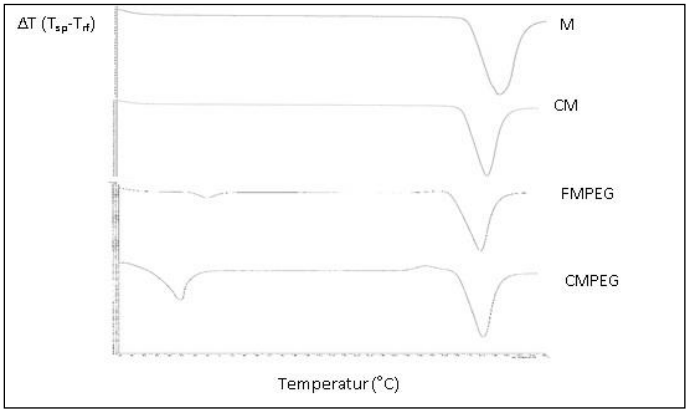

Figure 2: Thermogram DTA

The measurement result compactibility of co-processed mannitol-PEG (see figure 3). The results of tensile strength to co-processed mannitol and PEG with various concentration 90:10, 94:6, and 98:2 each with value tensile strength highest is 2.34±0.4; 2.77±0.07; 2.43±0.25. While on a physical mixture mannitol and PEG to concentration 90:10, 94:6, and 98:2 having value tensile strength that are 1.79±0.13; 1.69±0.04; 1.93±1.03. It shows that there were increase in value tensile strength after co-processed mannitol and PEG

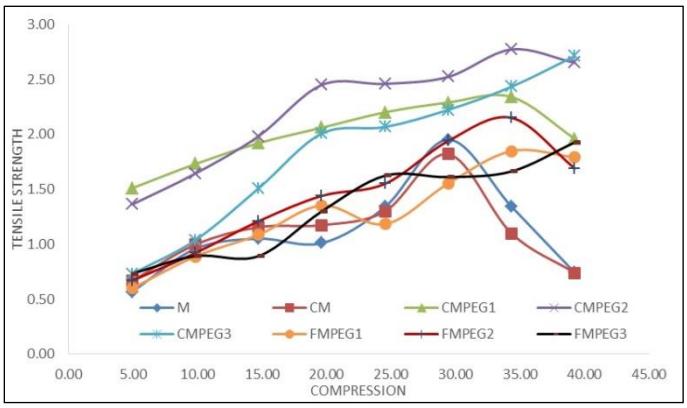

Figure 3: Curve the relationship of *tensile strength* and compression mannitol-PEG

compared with mannitol and also compared with a physical physical mannitol and PEG that tends to smaller.

Compactibility profile of mannitol show in pretty any force compressing from 3.5 to 4 tons a decline in compactibility. This phenomenon means that samples to that power experienced vulnerability (brittle fracture). This process characterized by the presence of cracks along the surface of the material. Tablet fragile when testing violence indicates has happened vulnerability (brittle fracture) (12).

Based on the determination of porosity (table 4), mannitol have about 68,3±0,0% of that particle pore. Thus, in was conducted co-processed mannitol-PEG caused entrapment polymer chains PEG formerly dissolved in water and so carried away by water into pore mannitol. By the presence of water as a medium can hasten reactivity between mannitol with PEG, in addition done stirring use ball milling to help reduction in size of solid particles at the time is suspended in water and can be achieved that homogeunity. Diminution size of particles also aims to improve the carrier compactibility, because with the small size of particles the more surface area available for binding in particles each other.

Table 5: Determination of porosity

Initial	Bulk Density (g/mL)	Granul Density (g/mL)	Porosity
M	0.52 ± 0.00	1.64 ± 0.052	68.3 ± 0.0
CM	0.51 ± 0.00	1.74 ± 0.005	70.5 ± 0.0
CMPEG1	0.48 ± 0.01	1.71 ± 0.012	71.8 ± 0.0
CMPEG2	0.48 ± 0.02	1.77 ± 0.044	73.5 ± 0.0
CMPEG3	0.48 ± 0.00	1.82 ± 0.017	72.9 ± 0.0

Equation:

$$\text{Porosity} = 1 - \frac{\text{Bulk density}}{\text{Granul density}} \text{x } 100\%$$

In addition, an increase in porosity after co-processed so that this can be increase compactibility. The higher the porosity of the more plenty of room interpartikel available for bonding. Morphology tablet were analyzed use SEM. The results of SEM (figure 4) between mannitol, co-processed mannitol-PEG compared with a physical mixture of mannitol-PEG look distinction density morphology on the surface of tablet .Tablet mannitol looks more slack, on the surface there are of fractures so density tablet as if not continuous. Compared by tablets co-processed mannitol:PEG, the results of mikrofoto who seems so much homogeneous and compact, than by tablets from the a mixture of physical who looked a little more loose. When look at the level compacty and homogeneity the surface tablets, so tablet from the co-processed manitol-PEG is look better.

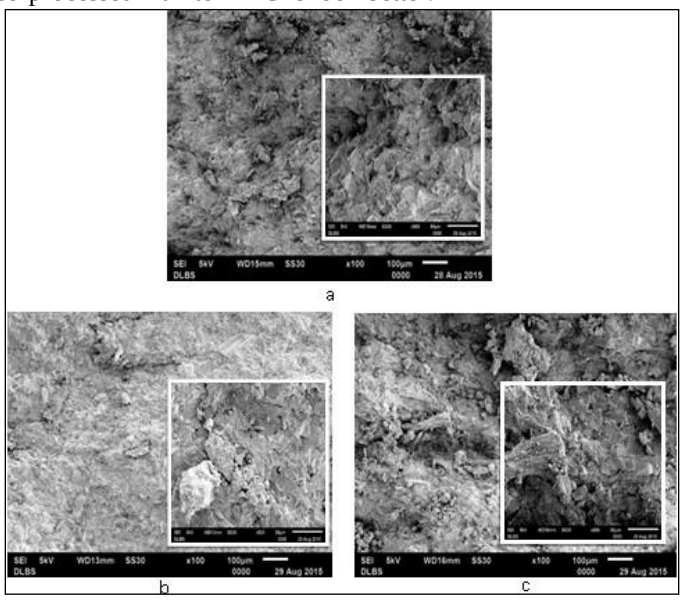

Figure 4: Mikrofoto SEM event 100x (insert 500x); mannitol (a), co-processed mannitol-PEG (b), physical mixture mannitol-PEG (c)

The evaluation formulations of vitamin C on some variation filler by the co-processed mannitol-PEG (formula A, B and C) has a good flowability of about 5 g/seconds even without the granulation process first. The use of talk have also been increasing the speed of a the formula A, B and C. Visually tablet resulting from any formula invisible happened not homogeneity colour and free from freckles or stain disturbing appearance tablet. Homogeneity size and violence tablet for all formula also meet the requirements usp. In addition, in testing firiabilitas no tablet Disintegration or split after the testing, lost weight no more than 10 % for each 20 tablet tested of any formula. While in testing Disintegration time and disolution tablet formula A, B and C seen in table 6 and 7. Disintegration tablet time and the disolusi adequate indicated from formula A.

Table 6 The disintegration time tablet vitamin C

Formula	Disintegration (second)
A	00:08:10
B	0.0100463
C	00:12:20

Table 7: Dissolution test of tablet vitamin C

Time (minutes)	Absorbent (A)		
	Formula A	Formula B	Formula C
5	0.3569	0.0686	0.0531
10	0.7098	0.8464	0.119
15	1.0955	1.2017	0.3245
20	1.1509	1.3971	0.6409
25	1.4	1.4617	0.7151
30	0.4175	1.5708	0.972

CONCLUSSION

The present research showed that combination of mannitol-PEG 6000 can be developed as filler binder co-processed excipient. It was found that mixture of mannitol-PEG 6000 generates fluctuating co-processed excipients in terms of flowability, while the compactibility increased with the additional proportion of PEG 6000. Optimum co-processed excipients proportion is generated at 90:10 (mannitol-PEG 6000).

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