Effect of processing methods on xylitol-starch base co-processed adjuvant for orally disintegrating tablet application

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Abstract: Orally disintegrating tablet (ODT) is a friendly dosage form that requires no access to water and serves as a solution to non-compliance. There are many co-processed adjuvants available in the market. However, there is no single product possesses all the ideal characteristics such as good compressibility, fast disintegration and good palatability for ODT application. The aim of this research was to produce a xylitol-starch base co-processed adjuvant which is suitable for ODT application. Two processing methods namely wet granulation and freeze drying were used to compare the characteristics of co-processed adjuvant comprising of xylitol, starch and crospovidone XL-10 mixed at various ratios. The co-processed excipients were compressed into ODT and physically characterized for powder flow, particle size, hardness, thickness, weight, friability, in-vitro disintegration time and in-situ disintegration time, lubricant sensitivity, dilution potential, Fourier transform infrared spectroscopy, scanning electronic microscopy and x-ray diffraction analysis. Formulation F6 was selected as the optimum formulation due to the fastest in-vitro (135.33±11.52 s) and in-situ disintegration time (88.67±13.56s) among all the formulations (p<0.05). Increase in starch component decreases disintegration time of ODT. The powder flow fell under the category of fair flow. Generally, it was observed that freeze drying method produced smaller particle size granules compared to wet granulation method. ODT produced from freeze drying method had shorter disintegration time compared to ODT from wet granulation batch. In conclusion, a novel co-processed excipient comprised of xylitol, starch and crospovidone XL-10, produced using freeze drying method with fast disintegration time, good compressibility and palatability was developed and characterized. The co-processed excipient is suitable for ODT application.

Keywords: Co-processed adjuvant, xylitol, starch, crospovidone, freeze drying.

INTRODUCTION

Orally disintegrating tablets (ODT) are also called as orodispersible tablet, mouth dissolving tablets, fast melt tablets, rapid dissolving tablets and quick dissolving (Hirani et al., 2009). It was first invented in 1970 to solve the issue of non-compliance. The ideal characteristics of an ODT are (a) fast disintegration time, (b) require no access to water, (c) good palatability and mouth feel, (d) robust and less friable, (e) stable, (f) simple manufacturing method such as direct compression, (g) consists of highly compressible excipients which allow high drug loading and (h) cost effective (Badgujar and Mundada, 2011).

One of the simplest methods to produce ODT is through direct compression (Akram et al., 2011). However, there is no single pharmaceutical excipient possesses all the properties for direct compression. Co-processing is a technique to mix two or more excipients to produce an end product with functionality improvement and masking the undesirable properties of individual (Ambore et al., 2014). A successful co-processing excipient has superior properties compared with physical mixtures of components or individual components in terms of flow properties, compressibility, dilution potential, fill weight uniformity, and reduced lubricant sensitivity (Nachaegari and Bansal, 2004).

Although there is a number of commercial co-processed adjuvants in the market now, but not all are suitable for ODT application. Moreover, the available co-processed adjuvants have certain limitations. To summarize, the co-processed adjuvant for ODT application must have good compressibility, achieving fast disintegration, good palatability and economical.

Xylitol has excellent compressibility (Olinger and Karhunen, 1991). Moreover, it has intense sweet taste which will improve the palatability of ODT products (Lyn, 2012). Starch, apart from its low cost, is also an excellent disintegrant for which the disintegration mechanism depends majorly on swelling (Desai et al., 2016). Crospovidone XL-10 is a super disintegrant which is effective at very small percentage to promote disintegration of ODT through wicking process (Desai et al., 2016). The aim of this research was to produce and characterize a co-processed adjuvant comprising of
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xylitol, starch and crospovidone XL-10. Two manufacturing methods namely wet granulation and freeze drying were compared to produce the xylitol-starch base co-processed adjuvant.

MATERIALS AND METHODS

Materials
Soluble starch was purchased from Systerm Chemicals (Malaysia). Xylitol was obtained from Sigma Aldrich Chemical Co. (USA). Polyplasdone XL-10 was bought from ISP Technologies INC (USA). Microcrystalline cellulose was obtained from FMC Corporation (USA). Magnesium stearate was purchased from Peter Grevan (Holland). Paracetamol powder was purchased from Zulat Pharmacy Sdn Bhd (Malaysia). Tablettose was a free gift from Meggle Group (Germany).

Development or co-processed adjuvant
The co-processed adjuvant was consisted of three components which were xylitol, starch and crospovidone XL-10. Two processing methods were used to produce the co-processed adjuvant namely freeze drying and wet granulation. The formulations are presented in table 1.

Freeze drying
The three components at various compositions were weighed. Xylitol was dissolved in 200g of distilled water in a beaker. Starch and crospovidone XL-10 were dispersed in 200g of distilled water in another beaker. The two portions were mixed and the final weight of the mixture was adjusted to 800g. The mixture was homogenized using a homogenizer for 15 minutes. The homogenized mixture was transferred to a freezer at -20°C for freezing. The frozen sample was dried in a freeze dryer (Alpha 1-4 LD Plus) to freeze dry under vacuum suction for 24 hrs at -55°C. The dried granules were sieved through 1 mm mesh and stored for further evaluation (Dey et al., 2010). Co-processed adjuvant of 200g per batch was produced.

Wet granulation
The three components at various compositions were weighed. Xylitol was dissolved in 200g of distilled water in a beaker. Starch and crospovidone XL-10 were dispersed in 200g of distilled water in another beaker. The two portions were mixed and the final weight of the mixture was adjusted to 800g. The mixture was homogenized using a homogenizer for 15 minutes. The homogenized mixture was transferred to a freezer at -20°C for freezing. The frozen sample was dried in a freeze dryer (Alpha 1-4 LD Plus) to freeze dry under vacuum suction for 24 hrs at -55°C. The dried granules were sieved through 1 mm mesh and stored for further evaluation. Co-processed adjuvant of 200g per batch was produced.

Powder characterization
Angle of repose
Cone forming method with fixed base was applied to determine the angle of repose. Powder sample or granule, devoid of any aggregation, was poured from a fixed height of about 10 cm to a fixed base with diameter of 2.4 cm, through a funnel supported by stand to form a symmetrical cone of powder mass. The hypotenuse of the powder mass (h) was measured in triplicate to calculate the angle of repose.

Particle size determination
A stack of sieves with diameters from 0.1-1.0 mm was arranged in descending order. The sample was placed on the top sieve and the entire system was agitated at a speed of 50 amplitudes for 15min. The granules remained on each sieve were collected at the end of the test and weighed using a Metler Toledo B-204-S analytical balance (USA).

The samples retained on each sieve was collected, weighed and calculated for the % retained using the equation below:

\[
\text{Retained(%) } = \frac{W_{\text{sieve}}}{W_{\text{total}}} \times 100\%
\]

Where \(W_{\text{sieve}}\) is the weight of aggregates retained on a sieve and \(W_{\text{total}}\) is the total weight of the powder.

The average particle size was calculated using the equation (Jagdale et al., 2010) below:

\[
\text{Average particle size } = \frac{\sum n d}{\sum n}
\]

Where \(n\) is the weight retained (in gram), \(d\) is the aperture size (in \(\mu\)m).

Compression of co-processed adjuvant and physical characterization
The co-processed adjuvant was weighed and compressed using a STC ZP17 (Y112M-6B7) rotary tableting press (China) fitted with round, concave faced, 1 cm diameter punches and die assembly. The weight of each tablet was 400 mg.

Physical characterization of co-processed adjuvant
Evaluation of hardness
The hardness was determined using a Tab-Machines T-MNT-20 hardness tester (India). Ten tablets were used and the hardness of tablet was controlled within 3-5kg \((n = 10)\).

Tensile strength
The diameter and thickness of the tablets were determined with a Mitaka vernier calliper (Japan) as well as their hardness using hardness tester as mentioned above. Their radial tensile strengths was evaluated using the formula below:

\[
T = \frac{2F}{\pi dt}
\]

Where \(T\) is the radial tensile strength, \(F\) is the hardness of the tablet and \(d\) and \(t\) are the diameter and thickness respectively. Ten tablets were used in the study \((n=10)\).
Table 1: Various formulations of xylitol-starch base co-processed adjuvant prepared using wet granulation and freeze drying method

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Formulation (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Xylitol</td>
<td>5</td>
</tr>
<tr>
<td>Starch</td>
<td>4</td>
</tr>
<tr>
<td>CPV XL-10</td>
<td>1</td>
</tr>
<tr>
<td>Manufacturing method</td>
<td>WG</td>
</tr>
</tbody>
</table>

WG = Wet granulation, FD = Freeze drying

Table 2: Results of angle of repose (N = 3) and average particle size of various xylitol-starch base co-processed adjuvant formulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Angle of repose (˚)*</td>
<td>45.35±2.27</td>
</tr>
<tr>
<td>Ave particle size (µm)**</td>
<td>728.04</td>
</tr>
</tbody>
</table>

*P = 0.04; **P = 0.01

Table 3: Results of physical characterization of various xylitol-starch base co-processed adjuvant formulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Hardness (kg)*</td>
<td>4.68±0.50</td>
</tr>
<tr>
<td>Thickness (cm)*</td>
<td>0.42±0.01</td>
</tr>
<tr>
<td>Tensile strength (kg/cm²)*</td>
<td>7.20±0.78</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>0.41±0.01</td>
</tr>
<tr>
<td>Friability (%)*</td>
<td>0.71±0.02</td>
</tr>
<tr>
<td>In-vitro disintegration time (s)**</td>
<td>190.1±25.58</td>
</tr>
<tr>
<td>In-situ disintegration time (s)**</td>
<td>129.17±11.43</td>
</tr>
</tbody>
</table>

*Parameter using 10 tablets for evaluation; **Parameter using 6 tablets for evaluation

Table 4: Lubricant sensitivity ratio values for different concentration of magnesium stearate

<table>
<thead>
<tr>
<th>Percentage of magnesium stearate used (%)</th>
<th>Lubricant sensitivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Co-processed adjuvant F6</td>
</tr>
<tr>
<td>0.25%</td>
<td>20.83</td>
</tr>
<tr>
<td>0.5%</td>
<td>41.96</td>
</tr>
<tr>
<td>1%</td>
<td>58.93</td>
</tr>
<tr>
<td>2%</td>
<td>60.42</td>
</tr>
</tbody>
</table>

Table 5: Results of palatability study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F6</td>
</tr>
<tr>
<td>Taste</td>
<td>3.00±0.00</td>
</tr>
<tr>
<td>After taste</td>
<td>3.00±0.00</td>
</tr>
<tr>
<td>Mouth feel</td>
<td>2.67±0.52</td>
</tr>
</tbody>
</table>

Mean ± SD, N=10
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Evaluation of weight
The weight was determined using a Metler Toledo B-204-S analytical balance (USA). Ten tablets were selected at random, weighed individually and the average weight of the tablets was calculated from the total weight. The weight variation of individual tablet compared with the average weight should not exceed 5% (n=10).

Evaluation of thickness
The thickness was evaluated using a Mitaka vernier calliper (Japan). Ten tablets were used and the thickness variation of individual tablet compared with the average thickness should not exceed 5% (n=10).

Friability
The friability was evaluated using a Guoming CS-2 friabilator (China). Ten tablets were weighed, put into the friabilator and ran for 4 minutes at 25 rpm (n=10). During each revolution, the tablets were subjected to fall from a height of 6 inches. After completion, tablets were cleaned to make them free from any adhered dust and reweighed. The test was acceptable under the pharmacopoeia limit of less than 1% weight loss.

In-vitro disintegration time
The in-vitro disintegration time was determined using an Electro Lab ED-2L disintegration tester (India) with distilled water at 37°C as disintegration medium. Six tablets of each formulation were used in the study (n = 6). The in-vitro disintegration time of ODT should not exceed 3 minutes.

In-situ disintegration time test
The in-situ disintegration time was determined using six human volunteers (n=6). The time of completely disintegration of ODT in mouth was determined as the in-situ disintegration time using a stop watch to measure. The in-situ disintegration time of ODT should not exceed 3 minutes.

Selection of optimum formulation
The optimum formulation was selected based on the shortest in-vitro disintegration time. The optimum formulation was carried forward for the remaining tests.

Dilution capacity
A poorly compressible drug (paracetamol) was chosen as model drug. The drug was mixed with co-processed adjuvant at four different ratios (1:4; 2:3; 3:2; 4:1). The controlled formulation was the co-processed adjuvant without mixing with drug (0% drug mixture). For every category, the mixture was sub-divided into 5 batches and compressed using five different compression forces. The tensile strength of the tablet was plotted against the compression force used (n=6). Area under curve was calculated using trapezoidal method. The sum of area under the curve (AUCsum) of each mixture was divided by the AUC of the “0% drug mixture” to obtain Minchom and Armstrong (MA's) working potential (Habib et al., 1996). The equation is listed below.

Dilution capacity index = M. A.’s working potential x AUCsum (0% drug mixture)

The dilution capacity optimum formulation was compared with microcrystalline cellulose, which is a common excipient used as filler in tablet formulation.

Lubricant sensitivity
Co-processed adjuvant and each individual excipient were mixed with magnesium stearate at 4 different concentrations (0.25, 0.50, 1 and 2%). The mixture was compressed into tablet and hardness of the tablet was determined. Five replicates of each formulation was conducted (n=5). Lubricant sensitivity ratio was also calculated using the equation below (Almaya and Aburub, 2008):

\[
\text{LSR} \% = \frac{\text{Hardness of tablet without lubricant} - \text{Hardness of tablet with lubricant}}{\text{Hardness of tablet without lubricant}} \times 100\%
\]

Physico-chemical study
Fourier Transformed Infra Red (FTIR)
IR spectra of starch, xylitol, crospovidone XL-10 as well as the optimum co-processed adjuvant formulation were recorded using the Thermo Fisher Scientific Nicolet™ iS5 FTIR spectrophotometer (USA) in the range of 4000-500 cm⁻¹ using potassium bromide discs (Gangude et al., 2013).

Scanning electronic microscopy (SEM)
The samples of optimum co-processed adjuvant formulation and all the single component were observed using the SEM technique to study the morphology of particles. SEM images were obtained using Zeiss Supra 55VP scanning electron microscope (Germany). The samples were mounted on a metal stub with double-sided
adhesive tapes. The samples were sputtered with a thin layer of platinum to improve the electrical conductivity prior to imaging (Garg et al., 2015).

**X-Ray diffraction analysis**

X-ray diffraction (XRD) patterns was obtained using a Siemens D 5000 diffractometer (Germany) for optimum co-processed adjuvant formulation and the single component. The X-ray source was Kα radiation from a copper target with graphite monochromater. The X-ray tube was operated at a potential of 40 Kv and a current of 30 Ma. The range (2θ) of scans was from 2˚-50˚. The data were collected at room temperature (26˚C) and scanned with a step size of 0.03° 2θ and a dwell time of 38 seconds each step (Patel and Bhavsar, 2009).

**Palatability study**

The palatability of the optimum co-processed adjuvant formulation was evaluated by human panel. Six human volunteers were invited to participate in the study to evaluate the taste, aftertaste and mouth feel of the test samples. The 3-points Likert scale was used for the evaluation (Liew and Peh, 2015). The optimum formulation was compared with tablet compressed using Tablettose®.

**STATISTICAL ANALYSIS**

Statistical analysis was performed using Statistical Procedure for Social Science (SPSS) statistical software (version 16, SPSS Inc, US). The results obtained from the physical characterization were analysed statistically using one-way analysis of variance (ANOVA). When there was a statistically significant difference, post-hoc Tukey HSD test was performed. A statistically significant difference was considered at p<0.05. The palatability study results were analysed using Mann-Whitney test. A statistically significant difference was considered at p<0.05.

**RESULTS**

**Angle of repose and particle size**

The results of angle of repose and average particle size of co-processed adjuvant F1-F6 are presented in table 2. Formulation F1, F2, F4 and F5 were in the category of passable flow while formulation F3 and F6 were in the...
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category of fair flow. The flowability improved with the increase in starch amount in the formulation and the difference was statistically significant (p<0.05). The flowability improved following an ascending order: F1< F2< F3 and F4< F5< F6.

**Physical characterization of co-processed adjuvant**

The results of evaluation of hardness, thickness, tensile strength, weight, friability, in-vitro disintegration time and in-situ disintegration time are presented in table 3. There was no thickness and weight of individual tablet exceeds 5% of the average thickness and weight of the tablets measured. This shows that the co-processed adjuvant produced has consistency in contents.

The hardness of the tablets produced per batch was fixed at 3 – 5kg to assess the disintegration efficiency of the formulations. It was noticed that the tablets disintegrated faster when the amount of starch present in the formulation increased. F3 (60% starch) has shorter disintegration time compared to F2 (50% starch) and F1 (40% starch). The trend was similar for batches of tablets produced using freeze drying method. Furthermore, tablets produced using freeze drying method was found disintegrated faster compared to tablets produced using wet granulation method when the same composition formulations are compared and the difference was statistically significant (F6< F3; F5< F2; F4< F1).

Freeze dried co-processed adjuvant produced tablet with lower thickness in general compared to co-processed adjuvant prepared by wet granulation method. This might be attributed to the lower particle size of freeze dried co-processed adjuvant. Compression of the lower particle size granules pack the particles into more compact tablet structure.

**Dilution potential**

The tensile strength against compression force curves for various combinations of co-processed adjuvant Formulation F6 and PCM are shown in fig. 1. Dilution capacity index of F6 was 4630.45, whereas dilution capacity index of MCC was 2632.85. The finding showed that the co-processed adjuvant Formulation F6 could be readily compressed after mixing with drug with poor compressibility.

**Lubricant sensitivity**

The lubricant sensitivity ratio (LSR) is presented in Table 4. Increase in percentage of magnesium stearate decreased the hardness of the tablets. However, it was noticed that decrease in hardness of tablets produced from individual component was more prominent compared to F6 tablet.

**SEM**

The results of SEM are presented in fig. 2. Starch particle can be seen as spherical particles with smooth surface. Xylitol particles appeared as irregular crystal. The co-processed adjuvant appeared as an agglomerate of particles which was an effect of mixing in dispersion form followed by freeze drying. The three individual excipients were blended and merged to form a large agglomerated particle.

**FTIR**

FT-IR was used to check interaction between excipient (Patel and Patel, 2009). Starch, xylitol, crospovidone XL-10, and co-processed adjuvants and F6 were subjected to IR studies and the results are presented in fig. 3. The IR spectra of co-processed adjuvants was compared with the IR spectra of individual excipients. Characteristic bands of starch were observed at 1637 cm\(^{-1}\) (–C=O), 2932 cm\(^{-1}\) (–CH\(_2\)-cycloalkane) and 3385 cm\(^{-1}\) (–OH stretching). The spectra of xylitol showed the bands at 1637 cm\(^{-1}\) (–C=O), 2943 cm\(^{-1}\) (–CH\(_2\)-cycloalkane) and 3400 cm\(^{-1}\) (–OH stretching). The spectra of crospovidone XL-10 showed the bands at 1654 cm\(^{-1}\) (–C=O) and 2940 cm\(^{-1}\) (–CH\(_2\)-cycloalkane). The IR spectrum of the co-processed adjuvants F6 showed the respective characteristic bands of starch, xylitol and XL-10, since no new bands were observed it suggests that no chemical interaction took place between the excipients during the co-processing stage.

**X-RD**

The X-RD diffractograms of co-processed adjuvant Formulation F6 and the individual components are presented in fig. 4. Xylitol is crystalline in nature whereas starch and crospovidone XL-10 are amorphous in nature. The intensity of the peaks in co-processed adjuvant was reduced when compared to individual component. The results showed that co-processing have changed the solid-state property of the individual components.

**Palatability study**

The results of palatability study are presented in Table 5. Optimum co-processed adjuvant formulation F6 and Tablettose® were compressed into ODT and tested for the palatability using human volunteer panel. Tablettose® was chosen as comparison because it is a common co-
processed adjuvant used in tablet formulation. The results showed that both are neutral in taste and after taste (no bitterness). However, in terms of mouthfeel, co-processed adjuvant F6 scored higher than Tablettose® tablets. A better mouth feel signifies lesser grittiness. Co-processed adjuvant F6 contains xylitol, which will leave a soothing effect on the tongue when it dissolves. This gives an added advantage of the newly invented xylitol-starch base co-processed adjuvant F6.

**DISCUSSION**

*Angle of repose and particle size*

The flowability is an important parameter concerning uniform feed from bulk storage containers or hoppers into the feed mechanism of tabletting. Proper flow is always desired to allow uniform particle packing and a constant volume-to-mass ratio, which maintains tablet weight uniformity (Staniforth and Aulton, 2002) Moreover, powder with good flowability reduces the inter-batch variation hence enhances the reproducibility. Powder with good flowability produces products of more consistent physicochemical properties. Uneven powder flow can result in excess entrapped air within powders, which in some high-speed tabletting conditions may promote capping or lamination (Sandler et al., 2010).

For particle size, it was observed that the average particle size increased with an increase in amount of starch in the formulation. The trend was the same for formulations produced using both methods. Moreover, it was also noticed that formulations produced using wet granulation had larger particle size compared to formulations produced using freeze drying method. As a result,
improvement in flowability can be correlated with the increase in average particle size.

The flowability of powder is a multifunctional parameter which depends on particle size and size distribution, shape, particle interactions and moisture content (Jiang et al., 2009). Moreover, in a study conducted by Hart (2015), it was found that the strength of the produced tablet was dependent on the particle size of the powder. Powder of smaller sizes showed higher tensile strength than larger particles because of their large surface area available for bonding (Hart, 2015). Mullarney and Leyva (2009) investigated the possibility of predicting powder flowability based on the particle size distribution data. It was reported that powder with larger particle size possesses better flowability in general.

**Physical characterization**
The tablets produced from co-processed adjuvant disintegrates through three mechanisms: wicking of crospovidone that causes capillary effect and draws water into the tablet structure, swelling of starch and dissolution of xylitol. Starch swells when it comes in contact with water promoting disintegration (Herbert et al., 1989). It is noticed that formulation with higher starch content disintegrates faster due to the swelling effect of starch.

**Dilution potential and lubricant sensitivity**
Magnesium stearate is reported to adversely affect the binding properties of tablet excipients when used as a lubricant in tablet formulation (Mužíková and Eimerová, 2011). A good co-processed adjuvant should have a lower lubricant sensitivity ratio.

**SEM**
Starch will swell and expand when it is dispersed in water (Zhou et al., 2007). The swelling property of starch enables the particle to expand and entangle with xylitol and crospovidone particles to form a large agglomerate.

**CONCLUSION**
In conclusion, a co-processed adjuvant suitable for ODT application was formulated and characterized. The co-processed adjuvant contains xylitol, starch and crospovidone XL-10 at a ratio of 3: 6: 1. Freeze drying is the preferred method. ODT produced from the co-processed adjuvant has good mechanical strength and fast disintegration time of less than 3 minutes. The co-processed adjuvant uses dissolution, swelling and wicking as the main disintegration mechanism respectively. The manufacturing method is easy and affordable.

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**REFERENCE**


