Lacagpregs- a group of novel multifunctional excipients: development and solid state characterization

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Abstract

Background: The need for multifunctional excipients useful in wet granulation and direct compression informed the quest for this study.

Objective: This study was aimed at developing multifunctional excipient series from which product(s) with suitable characteristics for application in tablet production may be harnessed.

Method: A mixture of lactose and cashew gum solutions at 50 C was co-precipitated with chilled ethanol. A dispersion of partially pregelatinized starch in ethanol was added to the co-precipitate and agitated using a planetary mixer operated at three arbitrary speed levels (L, L, L) and time intervals (10, 30, 60 min) at 10±1 C to generate the products. Granule size was homogenized by double screening through 600 µm sieve. The granules were characterized and the best product was used to formulate tablets by direct compression and wet granulation.

Results: Agitating at the arbitrary speed, L, for 30 min was the optimum condition for generating the highest excipient yield. FTIR revealed that interactions between primary constituents during the production process were physical. X-ray powder diffraction and DSC showed that higher agitation's speed and/or longer agitation time generated less crystalline products. The products differed in moisture sorption characteristics but the differences were not statistically significant. The less crystalline products displayed better deformation upon compaction with little or no voids. Tablets formulated with lacagpregs met official requirements on quality and compared without significant difference to those of similar tablets formulated with standard excipients.

Conclusion: Lacagpregs, the products of this simple technique, may function as multifunctional excipients in tablet formulation via wet granulation or direct compression.

Keywords: Lacagpregs; Particle engineering; Novel multifunctional excipient; Direct compression; Wet granulation.
Lacagpregs- un groupe de nouveaux excipients multifonctionnels: le développement et la caractérisation de l’état solide

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RÉSUMÉ

Contexte: La nécessité d’excipients multifonctionnels utilisables dans la granulation humide et compression directe informé la quête de cette étude.

Objectif: Cette étude visait à développer multifonctionnel série d’excipient à partir de laquelle le produit(s) avec des caractéristiques appropriées pour une application dans la production de comprimés peut être exploitée.

Méthode: Un mélange de solutions de lactose et de noix de cajou gomme à 50 °C a été co-précipité avec de l’éthanol froid. Une dispersion de l’amidon partiellement prégélatinisé dans de l’éthanol a été ajouté au co-précipité et on l’agitait avec l’aide d’un mélangeur planétaire fonctionnant à trois niveaux arbitraires de vitesse (L1, L2, L3) et les intervalles de temps (10, 30, 60 min) à 10 ± 1 °C à générer les produits. Granulométrie a été homogénisé par un double blindage à 600 µm tamis. Les granulés ont été caractérisés et le meilleur produit a été utilisé pour formuler des comprimés par compression directe et granulation humide.

Résultats: L’agitation à la vitesse arbitraire, L2, pendant 30 min est la condition optimale pour la production, le rendement le plus élevé de l’excipient. FTIR a révélé que les interactions entre les constituants de base au cours du processus de production étaient physiques. X-ray diffraction de poudre et de DSC a montré que la vitesse d’agitation plus élevée et / ou plus le temps d’agitation des produits générés moins cristallins. Les produits diffèrent des caractéristiques de sorption d’humidité, mais les différences n’étaient pas statistiquement significatives. Les produits cristallins moins affichées mieux la déformation sous compression avec peu ou pas de vides. Comprimés formulés avec lacagpregs répondaient aux exigences officielles en matière de qualité et comparées sans différence significative à celles des comprimés semblables formulé avec des excipients standards.

Conclusion: Lacagpregs, les produits de cette technique simple, peut fonctionner comme excipients multifonctionnels de formulation de comprimé par granulation humide ou par compression directe.

Mots-clés: Lacagpregs; Ingénierie particule; Excipient multifonctionnel roman; La compression directe; Granulation humide
INTRODUCTION

In pharmaceutical industries, active ingredients are formulated into desirable dosage forms by incorporating materials referred to as excipients. Some excipients influence the biopharmaceutical properties of the active ingredients contained in different dosage forms, thus they are no longer regarded as inert components of dosage forms. Consequently, excipient materials or excipient-drug composites are currently designed to acquire desirable and predictable characteristics. Some multifunctional excipients are available for the production of solid dosage forms, but few of them can actually function under various manufacturing conditions (for example, in wet or dry granulation and direct compression). Almost all multifunctional excipients in the portfolio of pharmaceutical manufacturers are produced via particle engineering. Particle engineering is a term coined to encompass means of producing particles that have defined morphology, particle size distribution, and composition. Particle engineering is also associated with particle size reduction techniques, such as milling, grinding, homogenization, and micro- or nanoparticle formation techniques, such as spray-drying, supercritical fluid technologies, and precipitation. By this definition, particle engineering is practicable in all aspects of material science. The goal of particle engineering is to incorporate desirable attributes, such as narrow size distribution, enhanced protein stability, improved dispersability, sustained release, or enhanced targeting, into the particles. Many researchers have reported various particle engineering methods that actualised tailor made excipients (especially multifunctional ones) or excipient-drug composites. Alpha lactose monohydrate is a very popular diluent in the manufacture of oral solid dosage forms. It possesses brittle or fragmenting compaction characteristics that whenever used without modification in tableting requires the addition of a good binder to achieve a reasonably satisfactory compact. Starch is a well known disintegrant in tablet and granules formulations. Partial pregelatinization of starch improves its disintegrant activity and also imparts some level of binding ability to it. Purified cashew gum has been extensively characterised and its safety and effectiveness as a binder have also been evaluated. The purpose of this study was therefore to develop a multifunctional excipient that contains these three excellent excipients using an affordable/accessible particle engineering technique and to evaluate the new excipient for both wet granulation and direct compression applications as a diluent-binder-disintegrant composite.

METHODS

Materials

Primary excipients that were particle engineered included: D (+) – lactose monohydrate (Fluka, Netherlands), a diluent which fragments under compressive force; Corn starch B.P. (Sigma-Aldrich, Germany), a disintegrant; and cashew gum, a binder whose safety has been extensively studied, extracted from Anacardium occidentale L family Anacardiaceae exudates using previously reported method, Avicel PH 101 (Fluka, Switzerland), polyvinyl pyrrolidone K 15 (Fluka, USA ), paracetamol powder (Mallirickrot Inc., USA), metronidazole powder (Zhejiang chemical, China). Other reagents used were of analytical grade.

Particle engineering of the new excipients

The corn starch BP was partially pregelatinized using a standard method. Lactose and cashew gum powders were separately passed through sieve of 150 μm aperture size. Then 50 g of the sieved lactose was dispersed in 250 ml of water at 70°C and stirred at selected agitation-speed level (L, L, or L) for 10 min to enhance dissolution using a planetary mixer (Kenwood, model OWHM400020, Japan). Also, 1, 2, 3, 4, or 5 %w/w of cashew gum powder based on lactose weight were separately weighed and each dispersed in 25 ml of water at 50°C and stirred to hydrate completely. The cashew gum dispersion was then poured into the lactose dispersion with continuous stirring using the mixer. The mixture was stirred for 10 min and then co-precipitated with thrice its volume of chilled ethanol 96% (at -5°C) with continuous stirring. After another 10 min, a dispersion of under 150 μm size partially pregelatinized starch (PGS) (10 %w/w with respect to the weight of lactose and cashew gum) in 25 ml of chilled ethanol 96% was poured into the mixture as stirring was going on. The remaining PGS in the container was carefully rinsed with 10 ml of the ethanol and added to the mixture. The ternary mixture was further stirred for another 10 min and then transferred to an ice bath where stirring was continued until the mixture attained a stable temperature of 8°C – 10°C (about 15 min of stirring) and then stirring was continued for another 10, 30, or 60 min. Thereafter, it was left in the ice bath undisturbed for 8 h. After 8 h, the supernatant was carefully decanted and the sediment stirred at the selected speed for 10 min and allowed to
air dry for 6 h. The resulting wet mass was screened through sieve of aperture size 1000 µm and dried in a hot-air oven (Unitemp LTE Scientific Ltd Great Britain, Greenfield Oldham OL37EN) at 60°C for 1 h. Dry screening was done using sieve of aperture size 600 µm and the final granules were dried at 60°C for 1 h. The resulting granules' moisture content was determined and it ranged between 4.95% - 5.05% and they were then stored in air tight containers over silica gel. The process was repeated three times for each batch of engineered product. This procedure was carried out in accordance with the experimental design shown below and Fig. 1 is a schematic representation of the stages involved in the process.

**Preparation of the physical mixtures (PM) of the components of the new multifunctional excipients**

One hundred grams (100 g) of under 150 µm sized lactose, cashew gum (1, 2, 3, 4, or 5 %w/w based on lactose weight), and under 150 µm sized partially pregelatinized starch (10 %w/w based on lactose and cashew gum weight) were mixed for 15 min using a tumbler mixer (Karl Kolb, D. 6072 Dreieich, Germany) to generate the physical mixtures equivalent of the new multifunctional excipient. Thereafter, the physical mixtures were stored in air tight containers over silica gel.

**Experimental design:**

<table>
<thead>
<tr>
<th>L:Mi:T</th>
<th>L:Mi:T</th>
<th>L:Mi:T</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>


PM – M:PM – M:PM – M:PM

L – Agitator speed level: 1, 2, 3.
M – Cashew gum concentration: 1, 2, 3, 4, 5 %w/w.
T – Duration of stirring: 10 min, 30 min, 60 min.
PM – Physical mixture of the excipients at cashew gum concentrations: 1, 2, 3, 4, 5 %w/w.
Lacagpregs- multifunctional excipients: development and characterization

Fig. 1: Schematic representation of the engineering process
Solid state characterization of the novel multifunctional excipients and the physical mixtures of their components

Particle size analysis
The sieve method was used and each sieve was tarred to the nearest 0.001 g. Thereafter, 20 g of each powder sample was carefully loaded on the coarsest sieve of the assembled stack (1000 µm to 150 µm) and the lid was replaced. The nest was subjected to a 5 min cycle of mechanical vibration using the Shaker (AS 400 Retsch, Germany) for a total of 25 min. Thereafter, the sieves were carefully separated and each sieve was carefully reweighed with its content. The weights of powder retained on each sieve and the collecting pan were determined by difference. The values were used to calculate (equation 1) the percent of sample retained on each sieve, and a frequency distribution curve generated for each powder sample.20-29

\[
\% \text{ Retained} = \frac{W_{\text{sample}}} {W_{\text{total}}} \times 100 \quad \text{(1)}
\]

where \( W_{\text{sample}} \) is the weight of powder in the sieve and \( W_{\text{total}} \) is the total weight of the powder.

Thereafter, the mean particle diameter (\( d_m \)) for each powder sample was evaluated using the formula 30:

\[
d_m = \left( \frac{\text{percent retained} \times \text{mean aperture size}}{100} \right) \quad \text{(2)}
\]

The particle size distribution for the new multifunctional excipient was evaluated by calculating their spans using equation 3:

\[
\text{Span} = \frac{d_{90} - d_{10}}{d_{50}} \quad \text{(3)}
\]

Moisture sorption
The moisture sorption properties of the engineered products and the physical mixtures of their components were determined using the static gravimetric method. Samples were dried at 105 C until constant weight and stored in a desiccator over anhydrous silica gel before use. One gram of each sample was quickly weighed in a petri dish of known weight and exposed to six relative humidity conditions in desiccators containing saturated salt solutions: 29% (CaCl₂.2H₂O), 53% (Mg(NO₃)₂), 60% (NaBr), 75% (NaCl), 90% (KNO₃) and 100% (distilled water) at 32 C and allowed to equilibrate in the different relative humidity conditions for two weeks. Changes in weights were measured after the period. Triplicate determinations were conducted on each sample and the water sorption behaviours of the samples were evaluated from the average weight increases and expressed as percentage moisture uptake with respect to the starting weight.31-34

Differential scanning calorimetric (DSC) analyses
DSC characterization of each powder sample was carried out using the apparatus Netzsch DSC 204 F1 Phoenix (Nietzsche Germany). Four milligrams (4 mg) of each sample was carefully weighed using the analytical balance (Mettler Toledo AB54, Switzerland) and sealed in an aluminium pan. Calibration of the calorimeter was done with indium and the purge gas was nitrogen. Heating of the sample was carried out at the rate of 10°C/min from 30 C to 400 C under nitrogen flow rate of 20 ml/min, followed by cooling back to 30 C at the same rate. Percentage crystallinity of the new excipients was evaluated by comparing their heats of fusion to that of lactose using equation 4:

\[
\% \text{ Crystallinity} = \frac{\text{H}_f(\text{excipient})}{\text{H}_f(\text{lactose})} \times 100 \quad \text{(4)}
\]

X-ray powder diffraction (XRPD) analyses
X-ray diffraction pattern tests were conducted on the samples using the Diffractometer XRD PANalytical (X’Pert PRO, Netherlands). About 1 g of each powder sample was finely ground and thinly spread in the sample holder of diameter 10 mm. The latter with its content was then placed on the stage of the instrument and scanned continuously at a step time of 10.16 sec, temperature of 25°C, using an anode material of Cu with Kα1 and Kα2 equal to 1.54060 Å and 1.54443 Å respectively at 40 kV and 10 mA. Scanning of samples was initiated at 5.0251° 2θ and ended at 119.9751° 2θ at step size of 0.05° 2θ. A nickel filter was used to reduce the Kα contribution to the X-ray signal. The relevant parameters (peak position, peak height, FWHM, d-spacing, and relative intensity) for the interpretation of the diffractograms were evaluated using Bragg’s law (equation 5) of diffraction in conjunction with values automatically generated by the instrument.

\[
\text{n} \cdot \text{\bar{e}} = 2d \cdot \text{sina} \quad \text{(5)}
\]

where \( \text{\bar{e}} \) is angle of incidence of an X-ray of wavelength \( \text{\bar{e}} \). The variable \( d \) is the distance (d-spacing) between atomic layers in a crystal, and \( n \) is an integer.

Fourier transform Infrared (FTIR) spectroscopy
The FTIR analyses of the powder samples were conducted using the apparatus FTIR-8400S spectrometer (Shimadzu, Japan). Two milligrams (2 mg)
of each sample and 200 mg of KBr were powdered with an agate mortar and pestle, and compressed into a pellet using the pellet press. The resulting tablet was mounted on the sample holder and the system was purged with nitrogen gas. Scanning was conducted in the range of 400 to 4000 cm$^{-1}$ with a resolution of 1 cm$^{-1}$.

**Scanning electron microscopy (SEM) studies**

These were carried out using the scanning electron microscope (EVO/MAIO. Carl Zeiss Germany). Briefly, each sample powder was placed on the sample holder and vacuum was created using the vacuum pump. The electron gun equipped with a variable pressure aperture was then aligned to finely focus the electron beam on the sample and different magnifications (x100, x200, x500, and x1000) were employed to examine the sample. The magnification that gave the best resolution was selected and the image saved. The operating voltage was limited to 5 kV since at higher voltage, charging effect would negatively affect the resolution of the image.

**Compaction studies**

Seven hundred and fifty milligrams (750 mg) of each particle engineered sample or its equivalent physical mixture was accurately weighed and manually filled into one pre-lubricated die of a twelve station rotary press (JC – RT - 24H, Jenn Chiang Machinery Co., LTD, Feng – Yuan, Taiwan) equipped with 13 mm flat faced punches, after eleven of the dies were blinded. The excipients were compacted into tablets with a force of 30 KN. At this pressure, the porosities of the resulting tablets ranged from 7.5% - 8.5% based on the calculations made using their weights, dimensions and particle densities (of the powders from which they were compacted) 30 days after compaction. The tablets were subsequently broken into half diametrically and subjected to scanning electron microscopy at x 100 and x 1000 magnifications.

**Tablet formulation**

The novel excipient (L.M.T$_{a}$), selected based on results from percentage yield and its characteristics, or Avicel PH 101 was used to formulate metronidazole tablets by direct compression at excipient-drug ratio of 1:1. Lubrication of powder mix was done with 0.5 %w/w magnesium stearate and 100 mg of the mixture was compressed using the tableting machine (Manesty Type F3, Poole, England) fitted with concave punches of diameter 6 mm at an arbitrary force sufficient to yield tablets of hardness in the range of 60 N to 80 N. The tablets were then stored in air tight containers over silica gel for 7 days before relevant tests were carried out on them.

Tablet formulation by wet granulation was conducted with 5 g of paracetamol and 2 g of the novel excipient (L.M.T$_{a}$); and the control, 5 g of paracetamol, 680 mg of lactose, 285 mg of PVP, and 600 mg of partially pregelatinized starch. Each powder mix was granulated with 2 ml of distilled water at 32°C by kneading with pestle until a homogeneous mass was formed. Wet screening was conducted with a 1000 m stainless steel sieve and the resulting granules dried in the hot air oven at 60°C for 1 h. The dry granules were finally screened through a 600 m stainless steel sieve, and dried again at 60°C for 1 h before they were stored in air tight containers over silica gel prior to tableting. The tablets were produced by lubricating the granules with magnesium stearate (0.5% w/w) in a powder bottle and accurately weighing 150 mg of granules and compressing using the tableting machine (Manesty Type F3, Poole, England) fitted with concave punches of diameter 6 mm at an arbitrary force sufficient to yield tablets of hardness in the range of 60 N to 80 N. The tablets were then stored in air tight containers over silica gel for 7 days before relevant tests were carried out on them.

**Tests conducted on the tablets**

The quality control tests conducted on the tablets were hardness, friability and disintegration time. These tests were conducted using Eweca hardness tester (Karl Kolb, Erweka Germany), Roche friabilator (Copley/Erweka GmbH Type: TAR 20 Heusenstamm Germany), disintegration test unit (Manesty Mk 4 Machine, UK) respectively in accordance with standard protocols.

**Statistical analysis**

The results of the experiment were analyzed with one way ANOVA (Excel 2007) set at 0.05% level of significance.
RESULTS

Percentage yield of new excipient
The various parameters (agitator speed level, L, amount of binder, M, and duration of stirring, T) utilized in engineering lacagpregs influenced the amount of excipient generated in the process. The mean percentage yield of lacagpregs from the process ranged from 49.01 ± 1.29% (L3M2T60) to 80.08 ± 0.39% (L2M3T30) as shown in Table 1. Generally, increase in binder concentration resulted in decreased percentage yield at all speed levels and duration of stirring. Duration of stirring produced a sort of anomalous result on the percentage yield. From Table 1, it is evident that stirring for 30 min yielded the highest amount of product followed by 10 min, while 60 min gave the least amount of the product at every level of stirring and binder concentration. Agitation for 30 min probably is the optimal stirring time to generate the highest amount of the novel excipient, lacagpregs. At the highest agitator’s speed level (L3), percentage yield was highest at 10 min duration and least at 60 min, while at L2, product yield was highest at 30 min stirring time and least at 60 min. The lowest stirring speed, L1, generated the highest product yield in 30 min and the least in 60 min.

Particle size analysis
The results of particle size analysis of the novel excipients - lacagpregs as shown in Table 1 revealed that the mean particle diameter (dav) ranged from 232 µm (L1M2T60) – 320 µm (L3M3T30) with corresponding median particle diameter (d50) of 210 µm and 330 µm. The particle size distributions (PSDs) of the excipients were however similar as can be observed from the values of the span which is an index of PSD.
### Table 1: Percentage yield and particle size analysis results of the new excipients

<table>
<thead>
<tr>
<th>Product</th>
<th>Mean yield (%)</th>
<th>d₅₀(μm)</th>
<th>d₉₀(μm)</th>
<th>Span</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiM₁T₁₀</td>
<td>60.08±2.72</td>
<td>292</td>
<td>300</td>
<td>1.70</td>
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<tr>
<td>LiM₂T₁₀</td>
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<td>300</td>
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<td>260</td>
<td>2.00</td>
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<td>340</td>
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<td>58.67±2.85</td>
<td>296</td>
<td>305</td>
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</tr>
<tr>
<td>LiM₅T₁₀</td>
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</tr>
<tr>
<td>LiM₁T₃₀</td>
<td>66.57±0.70</td>
<td>310</td>
<td>310</td>
<td>1.60</td>
</tr>
<tr>
<td>LiM₂T₃₀</td>
<td>63.54±1.68</td>
<td>295</td>
<td>310</td>
<td>1.63</td>
</tr>
<tr>
<td>LiM₃T₃₀</td>
<td>61.16±0.96</td>
<td>305</td>
<td>315</td>
<td>1.59</td>
</tr>
<tr>
<td>LiM₄T₃₀</td>
<td>60.41±0.13</td>
<td>284</td>
<td>295</td>
<td>1.71</td>
</tr>
<tr>
<td>LiM₅T₃₀</td>
<td>60.05±0.77</td>
<td>286</td>
<td>300</td>
<td>1.70</td>
</tr>
<tr>
<td>LiM₁T₆₀</td>
<td>60.94±1.36</td>
<td>273</td>
<td>265</td>
<td>1.94</td>
</tr>
<tr>
<td>LiM₂T₆₀</td>
<td>59.68±1.40</td>
<td>290</td>
<td>305</td>
<td>1.66</td>
</tr>
<tr>
<td>LiM₃T₆₀</td>
<td>54.98±1.01</td>
<td>287</td>
<td>300</td>
<td>1.70</td>
</tr>
<tr>
<td>LiM₄T₆₀</td>
<td>50.53±1.69</td>
<td>296</td>
<td>315</td>
<td>1.62</td>
</tr>
<tr>
<td>LiM₅T₆₀</td>
<td>49.01±1.29</td>
<td>280</td>
<td>285</td>
<td>1.79</td>
</tr>
</tbody>
</table>
Moisture sorption
Results of the moisture sorption characteristics of the novel excipients and the physical mixtures of their constituents are shown in Table 2. The percentage change in weight of the excipients, represented as the percentage moisture sorbed was influenced by the different processing conditions employed in the particle engineering of the novel excipients. The physical mixture sorbed the lowest amount of moisture at all relative humidity conditions to which the powders were exposed. On the other hand, among the lacagpregs, less crystalline excipients sorbed more moisture (Table 2).

Table 2: Result of moisture sorption test on some of the products

<table>
<thead>
<tr>
<th>RH* (%)</th>
<th>Sample % moisture uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PM-M5</td>
</tr>
<tr>
<td>29</td>
<td>0.18±0.03</td>
</tr>
<tr>
<td>53</td>
<td>0.28±0.02</td>
</tr>
<tr>
<td>74</td>
<td>0.52±0.03</td>
</tr>
<tr>
<td>84</td>
<td>0.59±0.04</td>
</tr>
<tr>
<td>92</td>
<td>1.76±0.15</td>
</tr>
<tr>
<td>100</td>
<td>8.22±0.03</td>
</tr>
</tbody>
</table>

RH* = relative humidity at 32°C.

Differential scanning calorimetry
The DSC thermogram of the primary excipient, lactose, revealed two sharp endothermic peaks corresponding to dehydration (150.6°C) and melting point (220.1°C) (Fig. 2 A). On the other hand, from Figs. 2 B and 2 C which are the thermograms of the physical mixture (PM-M5) and one of the lacagpregs (L1M5T60) respectively, it is obvious that the physical mixture has very similar thermal characteristics (endothermic peaks for dehydration and melting lie at 152.7°C and 220.4°C respectively) to lactose, while L1M5T60, displayed perceivable deviations (endothermic peaks for dehydration and melting lie at 145.9°C and 216.4°C respectively). The heat of fusion of lactose in comparison to those of the physical mixture and L1M5T60 also showed marked differences which point to the fact that crystallinity decreased in the order: lactose > physical mixture > L1M5T60.
Lacagregs—multifunctional excipients: development and characterization

Fig. 2 A. DSC of lactose

Fig. 2 B. DSC of PM – M$_5$

Fig. 2 C. DSC of L3M5T60
X-ray powder diffraction

Fig. 3 A shows the diffraction pattern of lactose powder. It exhibited 39 peaks, with the most prominent peaks of heights: 6249.74, 5770.18, 1980.82, 1758.44, 1484.35, 879.58, 665.09, 636.68, 586.33, 578.94, etc, counts per second at 20.02 °, 20.91 °, 18.81 °, 21.22 °, 36.59 °, 38.02 °, 21.06 °, 18.95 °, 37.42 °, 38.07 °, etc, per second at 19.79 °, 20.05 °, 21.06 °, 18.95 °, 37.42 °, 38.07 °, etc, respectively. The physical mixture (PM-M) manifested a diffraction pattern that is very similar to that of lactose. Fig 3 B revealed that it exhibited 37 peaks, with the prominent ones having heights: 6180.04, 3462.13, 2253.99, 1738.80, 1733.72, 1689.73, 861.47, 823.79, 625.69, 498.01, etc, counts per second at 19.66 °, 19.13 °, 20.02 °, 37.33 °, 20.91 °, 18.81 °, 38.02 °, 21.22 °, 36.59 °, 39.77 ° respectively. The number of peaks present in the diffraction patterns of lacagpregs decreased with increase in duration of stirring, and increase in stirrer's speed. From Fig. 3 C for example it is evident that L:M:T displayed 26 peaks. The lacagpregs, L:M:T and L:M:T, displayed 29 peaks and 32 peaks respectively (diffractograms not shown). The d-spacing (distance between the lattice planes in a crystal) of all the lactose–based excipients remained virtually similar for similar peaks at the same positions. The full width at half maximum (FWHM) ranged from 0.1476 ° to 0.9840 ° for lactose and lactose-based excipients.
Fourier transform infrared spectroscopy

Fig. 4 shows the FTIR spectra of the excipients with the fingerprint region for lactose, physical mixture and lacagregs lying between 377 cm\(^{-1}\) and 1046 cm\(^{-1}\). It is within this region that the characteristic functional groups (alcohol OH out-of-plane bend, hydrogen bonded OH out-of-plane bend, and C–O stretch) are located. The alcohol OH in-plane bend lies between 1260 cm\(^{-1}\) and 1379 cm\(^{-1}\), this is followed by the narrow peaks: methyl C–H asymmetric bend at 1407 cm\(^{-1}\) to 1438 cm\(^{-1}\), aldehyde C=O stretch at 1643 cm\(^{-1}\) to 1654 cm\(^{-1}\), and aldehyde C–H asymmetric stretch at 2897 cm\(^{-1}\) to 2933 cm\(^{-1}\). The broad band which is diagnostic for alcohols occurred between 3208 cm\(^{-1}\) and 3531 cm\(^{-1}\).
SEM of powders

Figs. 5 E and 5 G are the micrographs of L1M5T60 and L2M5T30 respectively at x 500. They show very good continuity of one in the other between the primary excipients in that none of them could be distinguished from the others. The almost round shape of the particles of L1M5T60 and hollow nature of the particle of L2M5T30 are obvious. These two features do enhance the compaction properties of powders.
SEM of tablets
The micrographs prepared at x 1000 magnification shown in Fig. 6 are those of the various excipients compacted into tablets with a force of 30 KN. At this pressure, the porosities of the resulting compacts ranged from 7.5% - 8.5% based on the calculations made using their weights, dimensions and particle densities (of the powders from which they were formulated) 30 days after compaction. Fig.6 A shows the micrograph of PM – M₃ tablet with the presence of many pores, fissures or furrows in the tablet matrix very visible (indicated by the arrows in the micrograph), suggesting that the tablet will fail under tension. The lacagpregs also manifested striking differences in their compaction properties. From their SEMs one can easily notice the progression in plasticity of the excipients as stirring speed and duration were increased. Deformation, an index of plasticity, increased in the order \( \text{L.M.T}_{10} < \text{L.M.T}_{30} < \text{L.M.T}_{60} \) as shown in Fig 6.
Fig. 6. SEMs of tablets: (A) PM-M5, (C) L2M5T30, (E) L2M5T60 and (F) L3M5T60
Qualities of the formulated metronidazole and paracetamol tablets

The hardness, friability and disintegration time of paracetamol tablets formulated with the novel excipient (L.M.Tₐ₋₀) were respectively 66.70 ± 0.57 N, 0.02% and 4.40 ± 0.13 min; while those of tablets formulated with PVP-partially pregelatinized starch were 73.30 ± 0.57 N, 0.17% and 4.48 ± 0.46 min respectively. Metronidazole tablets formulated with the novel excipient (L.M.Tₐ₋₀) displayed hardness, friability and disintegration time of 70 ± 0 N, 0.01% and 2.01 ± 0.14 min respectively; while their Avicel® PH 101 counterpart’s properties were respectively 66.7 ± 1.53 N, 2.47 ± 0.45 min, and 0.02%. Statistical analyses on the hardness values and the disintegration times of the various formulations revealed that there was no significant difference in these properties for tablets formulated with the lacagpregs and those formulated with the standard excipients. This suggests that the lacagpregs functioned as binder-filler-disintegrant in both wet granulation and direct compression methods of tablet formulation. This is because all the values are within the standards stipulated by various pharmacopeia for conventional tablets.  

DISCUSSION

Generally, percentage yield of the lacagpregs decreased with increase in binder concentration at all speed levels and duration of stirring. This observation may be tied to preferential precipitation of cashew gum to lactose upon the addition of ethanol. Since the amount of ethanol was kept constant, with increase in gum concentration, more ethanol was used in precipitating the gum which is less soluble than lactose. This explanation was corroborated by the gravimetric estimation of the amount of precipitate formed after the supernatant layer from various reaction mixtures were allowed to stand undisturbed for 72 h. The amount of residual precipitate was found to increase with increase in cashew gum concentration. In precipitation reaction involving agitation, post nucleation and growth phases, continued agitation leads to breakdown of crystal and re-dissolution of the precipitated material back into the solvent phase in order to establish equilibrium at the operating temperature of the reaction. But if agitation is stopped at the point of maximum precipitation, re-dissolution of the precipitate would be minimized or avoided, whereas terminating agitation before the formation of maximum amount of precipitates leads to decreased yield because nucleation which agitation enhances is suddenly interrupted. These results may be explained based on onset of nucleation, crystal growth and crystal break-down with respect to strength of agitation and duration. It has been reported that the faster the stirring rate the shorter the onset of nucleation in precipitate formation. However, extended agitation has also been implicated in the break-down of formed crystals into their primary particles. These two processes must have taken place in the reaction mixture at L₁ beyond 10 min duration, hence the progressive reduction in yield at 30 min and 60 min. Speed level L₂ and duration of 30 min may therefore be the optimal conditions for the generation of the highest amount of product.

In the particle size analysis, the similarity in the PSDs of the various products may be attributed to screening with sieve of aperture size of 600 μm which was reported to produce granules with narrow PSDs. A small span value indicates a narrow particle size distribution as evident in the span: 1.43 (L.M.Tₐ₋₀) – 2.45 (L.M.Tₐ₋₀), of the products. The diversity of the particle size and size distribution might have resulted from the different compositions of the excipients and the different processing conditions under which they were generated.

The moisture sorption pattern observed in the excipients can be explained by the fact that crystalline lactose is marginally hygroscopic, the main adsorbing components being partially pregelatinized starch and cashew gum which constitute a maximum of 15.5 % of excipient mixtures. The novel excipients adsorbed more moisture because the engineering processes reduced their degrees of crystallinity in comparison to that of the physical mixture. Stirring speed, duration of stirring, and the amount of binder, which were the variables introduced during the particle engineering processes influenced their moisture sorption properties. Although differences in the amounts of moisture sorbed by the various excipients were evident, they were not statistically significant. It is obvious from Table 2 that at faster stirring speed and longer duration of stirring, excipients with higher affinity for moisture were generated especially as the amount of binder increased to 5% w/w. These findings are consistent with previous reports which explained that such behaviour was due to reduction in the crystallinity and increase in the amorphous nature of the excipient. The sharp peaks observed in the DSC thermogram of lactose are indicative of the purity and crystalline nature of lactose. The thermogram of the physical
mixture in Fig. 2 B, unlike that of lacagpregs has a very close resemblance to lactose thermogram, which implies that there was no form of interaction between the primary excipients in the physical mixture. The dehydration and melting point endothermic events for L1M3T60 occurred at 145.9°C and 216.4°C respectively. Depression of melting point in DSC study of materials has been shown by Van't Hoff 46 , 47 to result from the presence of impurities. In theory, a melting transition of an absolutely pure crystalline material should occur within a narrow range whereas an impurity, when present, could broaden the melting range. 48-50 In order to estimate the levels of crystallinity of some of the excipients, their enthalpies of fusion (ΔHf) were compared to those of the “pure” lactose and expressed in percentage.51-53 Table 3 shows the estimated percentage crystallinity of some of the excipients and it is evident that crystallinity decreased with increase in stirrer’s speed from level 1 to level 3. Previous workers used enthalpies of fusion to quantify crystallinity 44 , and amorphization.13,55

Table 3: Percentage crystallinity of some of the excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Melting point(°C)</th>
<th>ΔHf (J/g)</th>
<th>% Crystallinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>220.1</td>
<td>538.1</td>
<td>100.0a</td>
</tr>
<tr>
<td>PM − M5</td>
<td>220.4</td>
<td>307.1</td>
<td>57.1</td>
</tr>
<tr>
<td>L1M3T60</td>
<td>217.2</td>
<td>177.1</td>
<td>32.9</td>
</tr>
<tr>
<td>L1M3T30</td>
<td>216.8</td>
<td>180.4</td>
<td>33.5</td>
</tr>
<tr>
<td>L1M3T60</td>
<td>215.5</td>
<td>136.4</td>
<td>25.3</td>
</tr>
<tr>
<td>L1M3T60</td>
<td>216.4</td>
<td>128.8</td>
<td>23.9</td>
</tr>
</tbody>
</table>

a – Lactose is arbitrarily assigned 100.0 % crystallinity

In X-ray powder diffractometric analysis, disappearance of peaks have been reported to imply loss or decrease in crystallinity of a material.56,57 Shift in peak positions, and variations in the relative intensities of the peaks of lactose, physical mixture and the lacagpregs, which ranged from 0.75% to 100.0%, reveal that these parameters decreased as processing conditions became more stringent (faster agitation rate and longer duration), and also points to the reduction in the crystallinity of the major excipient- lactose. This observation is in-line with the report that variations in intensity of major peaks reflect differences in the processing history of a material.58 Since the d−spacing of all the lactose−based excipients remained virtually similar for similar peaks at the same positions, it implies that the lattice planes in lactose crystals were not altered by the engineering method employed in this experiment. A shift in the d−spacing of a material is taken to be significant when there is a difference (Δd) of approximately 1.5 Å between similar peaks.59 The differences between the FWHM values are narrow since large broadening is said to have taken place when FWHM > 1°. 59 This narrow difference shows that the particle or grain size of lactose crystal was retained and that there was uniform (similar) strain in the lattice structure of lactose in both the physical mixture and the lacagpregs.50

In the FTIR spectra of the excipients, the wide range between 3208 cm−1 and 3531 cm−1 may be attributed to the little differences in the water content of the excipients since water also exhibits a broad band in this region.61,62 The functional groups present in the primary excipients were retained in both the physical mixture and the lacagpregs. This revelation confirms that there was no chemical interaction during the engineering process of the lacagpregs. The small differences in the positions and intensities of the peaks may be explained by entrapment of cashew gum and pregelatinized starch into lactose to form a complex63,64 or their concentrations were too low to be detected.

The almost round shape of the particles of L1M3T60 and hollow nature of the particle of L1M3T60 are among features that have been established to enhance the compaction properties of powders.35 Processing at
speed level 2 or 3 for 60 min as shown in Figs. 5 F and 5 H caused very good intimate interaction between the primary excipients as is evident in the matted and convoluted nature of their particles to form almost spherical shaped complex particles of the lacagpregs. A comparison of the micrographs of the lacagpregs resulting from stirring for 30 min to product from 60 min of stirring, as depicted in Fig. 5 G and 5 F reveals that the latter caused better matting and convolution than the former. Stirring for 60 min led to the formation of complex particles with much closer resemblance to a sphere than stirring for 30 min. The better intimacy that exists between lactose (brittle diluent), cashew gum (plastic binder) and pregelatinized starch (disintegrant) in the lacagpregs resulting from 30 min and 60 min of stirring impacted positively on the compaction properties of these excipients as is very evident in the micrographs of their tablets. The particles deformed most with sample L:M:T50, a product of high speed and long duration of stirring in the engineering process. It has been established that the ability of a material to retain its deformed shape upon the withdrawal of a compaction force qualifies the material to be classified as plastic. Furthermore, some points (arrows in the micrographs) from which propagation of crack that may eventually lead to tablet failure are visible in L:M:T30, much fewer in L:M:T50 and absent in L:M:T60 tablets as can be seen in Figs. 6 C, 6 E and 6 F respectively. These features give credence to the fact that L:M:T60 is the most plastic novel excipient generated by the method investigated in this research.

**CONCLUSION**

New multifunctional excipient series, lacagpregs that may serve as wet or dry filler-binder-disintegrant in tablet production were successfully developed via a new particle engineering method. Developing the excipient, lacagpregs using high agitation force or agitating for up to 60 min resulted in products with very good compaction properties, which in contrast need protection from moisture. The particle engineering method did not cause any chemical interaction between the components of the new excipient. The lacagpregs displayed much better compaction properties than the physical mixture of its components and there were no significant differences between its binding and disintegrant abilities in tablet formulation and those of polyvinylpyrrolidone and microcrystalline cellulose respectively.

**ACKNOWLEDGEMENT**

We are grateful to the following institutes where the instrumental characterization of the excipients was conducted: National institute for pharmaceutical research and development (NIPRD), Abuja; Shedda science and technology complex (SHESTCO), Abuja; National institute for chemical research technology, Zaria, Nigeria.
REFERENCES


Lacagpregs- multifunctional excipients: development and characterization

49. de Angelis N, Papariello G (1968). Differential scanning calorimetry: advantages and limitations for absolute purity determinations. *Journal of


