Improvement of the stability of doxycycline hydrochloride pellet-containing tablets through a novel granulation technique and proper excipients

Tingting Peng a,1, Chune Zhu a,1, Ying Huang a, Guilan Quan a, Linchong Huang b, Linna Wu a, Xin Pan a,b, Ge Li c, Chuanbin Wu d

a School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510006, China
b School of Engineering, Sun Yat-Sen University, Guangzhou 510275, China
c Guangzhou Neworld Pharm. Co. Ltd., Guangzhou 510006, China
d Guangdong Research Center for Drug Delivery Systems, Guangzhou 510006, China

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ABSTRACT

Objective: Granulated pellet-containing tablets (GPCT) prepared by a novel granulation technique showed better uniformity and compressibility over traditional pellet-containing tablets (PCT). The superiority of GPCT was mainly due to the excipient layer, which was laid over the coated pellets and modified the surface of pellets with increased roughness. Microcrystalline cellulose (MCC) was the main layering component which greatly influenced the stability of GPCT in storage, so was the additional excipients. The purpose of this study was to investigate the influence of excipient layer on the stability of GPCT.

Methods: GP were prepared by layering the combination of various excipients with MCC over the coated pellets, and further compressed into GPCT. The drug release profiles from the coated pellets, GP, and GPCT were compared, and the drug degradation rate in GP and GPCT were evaluated under high temperature, strong light, and high humidity conditions for up to 10 days.

Results: The drug content in GP and GPCT was above 97% after storage under high temperature and strong light, but dropped to 93–96% under high humidity. The drug degradation rate in GP followed the order of excipient hygroscopicity as PVPP > CMC-Na > Lactose, while GPCT with PVPP showed the least drug degradation, suggesting the stability of GPCT was mainly determined by the excipient compressibility.

Conclusions: All formulations under high temperature and strong light were stable, indicating the influence of temperature and light could be ignored. Under high humidity conditions, the drug degradation in GP was in accordance with the excipient hygroscopicity, while it was dominated by excipient compressibility in GPCT. Therefore, the binary mixture of MCC and PVPP with the best compressibility may be ideal layering excipients to prepare acceptable GPCT for humidity sensitive drugs.

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1. Introduction

Multi-unit pellet systems (MUPS) have received considerable attention as one of the leading technologies for drug controlled release [1]. Compared to single-unit dosage forms, MUPS offer outstanding therapeutic advantages, such as less variable plasma profiles, reduced local irritation, and avoidable dose dumping [1–4]. With small particle size (<2 mm) and large surface area, pellets could enhance drug distribution, dissolution and absorption, resulting in fewer adverse effects. Generally, pellets are either filled in capsules or compressed into tablets. Recently, pellet-containing tablets have gained more popularity due to numerous superiorities, such as lower manufacturing cost, higher drug loading, improved patient compliance, divisible dose, etc. [1,4]. However, the compression of pellets into tablets creates several challenges: (1) to achieve non-segregated mixture of pellets and fillers/binders to ensure uniform distribution of pellets in tablets and multi-particulate function of the system [5,6]; (2) to form flexible polymeric film with elongation value greater than 75%, so it can withstand the compaction pressure without damage and neutralize the pellet deformation to ensure the designed release profiles of the pellets [7,8]. These challenges have constrained the development of traditional pellet-containing tablets (PCT).

Abbreviations: GP, Granulated pellets; GPCT, Granulated pellet-containing tablets; PCT, Traditional pellet-containing tablets; Doxy, Doxycycline hydrochloride; PVPP, Polylactosan® XL; Lactose, α-lactose monohydrate; CMC-Na, Sodium carboxy methyl cellulose; CMS-Na, Carboxy methyl starch sodium; DCP, Dihyphrogen phosphate calcium.

⁎ Corresponding author. Tel.: +86 2039943427; fax: +86 2039943115.
E-mail address: pxin_1385@163.com (X. Pan).

The first two authors contributed equally to this work.

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Fortunately, several strategies have been proposed to overcome these restrictions. It was reported that pellets with rougher surface showed more similarity in shape with cushioning granules, which advantage to circumvent segregation problems associated with mixing [59, Altaf and coworkers constructed multilayered pellets by spray-layering excipients such as Avicel and mannitol onto beads in a fluid bed to increase pellet roughness [9]. A centrifugal granulation technique was also adopted by our group to prepare granulated pellets (GP) by laying excipients onto the coating film to increase the surface roughness of pellets [5,10,11]. The diminished roughness differences between granulated pellets and cushioning granules could ensure more uniform mixture. Furthermore, the excipient layer could absorb the compression force during the tablet compaction, thus reducing film rupture. Therefore, compression of GP into granulated pellet-containing tablets (GPCT) might be a promising approach in preparing acceptable pellet-containing tablets.

Based on our previous study, excipients play an essential role in the granulated pellets technology, and there are several basic principles for selection of appropriate granulating excipients. First, the excipients should be moldable but not adhere to the chassis and inner wall of the equipment, so that a high actual granulating ratio and good batch homogeneity could be achieved. Besides, the excipients should possess excellent disintegration properties to ensure quick disintegration upon dissolution but no influence on drug-release profiles [2]. Further, the excipients may assist the compaction process and prevent film abrasion/rapture [2]. Up till now, various excipients have been used to construct GP and act as excipient layer materials [2,5,12], such as microcrystalline cellulose (MCC), Polyplasdone® XL (PVPP), lactose, sodium carboxy methyl cellulose (CMC-Na), dihydrogen phosphate calcium (DCP), and carboxy methyl starch sodium (CMS-Na), etc. In this study, microcrystalline cellulose (MCC), Polyplasdone® XL (PVPP), lactose, sodium carboxy methyl cellulose (CMC-Na), dihydrogen phosphate calcium (DCP), and carboxy methyl starch sodium (CMS-Na), etc. In this study, microcrystalline cellulose (MCC) was used as the main layering excipient, and additional excipients, such as PVPP, lactose, CMC-Na, DCP and CMS-Na to MCC was introduced to modify the physical properties of pellets. Previous study also showed that a small amount of additional excipients could influence the storage stability of GPCT. The purpose of this study was to investigate the influence of excipient layer on the stability of GPCT. Doxycycline hydrochloride (Doxy) was selected as a model drug due to its sensitivity to heat, light and humidity, which would keenly reflect the integrity of coating films and the stability of the preparations.

2. Materials and methods

2.1. Materials

Doxycycline hydrochloride was employed as a model drug (Doxy, 99.2%, Suhai Co., Ltd., China). Eudragit® FS 30D and Eudragit®L 30D-55 were donated by EvonikRohmGmbH (Darmstadt, Germany) as coating materials. Triethyl citrate (TEC, Jingqiu Co., Ltd., China) and glyceryl monostearate (GMS, Xilong Co., Ltd., China) were incorporated in the coating suspension to act as a plasticizer and anti-tack agent, respectively. Methocel®E3 (HPMC-E3, Colorcon, USA) was used for subcoating to prevent drug immigration. Microcrystalline cellulose (MCC, Hopetop Co., Ltd., China), Polylasdone® XL (PVPP, ISP, USA), α-lactose monohydrate (Lactose, DMV, Veghel, The Netherlands), sodium carboxy methyl cellulose (CMC-Na, Zth Biological Engineering Co., Ltd., China), carboxy methyl starch sodium (CMS-Na, Shandong Liaocheng Pharm Co., Ltd., China) and dihydrogen phosphate calcium (DCP, Tianjin Guangfu Chemical Industry Research Institute, China) were used as layer excipients to prepare GP. Polyvinylpyrrolidone K-30 and K-90 (PVK K-30, PVK K-90, ISP, USA) were used as adhesives during granulation. Other chemicals were used as received.

2.2. Preparation of Doxy coated pellets

Microcrystalline cellulose pellets of 210–250 μm were prepared using a centrifugal granulation apparatus (BZJ-360MII, Beijing Long March Tianmin Hi-Tech Co., Ltd., China). Then the pellets were laid in a fluidized bed coater (Glatt GPCG-1.1, Germany, bottom spraying) and sprayed with drug solution containing 32% (w/v) Doxy and 7.5% (w/v) PVK K-30 to form Doxy loaded pellets. Subsequently, the drug loaded pellets were sub-coated with 6% (w/v) HPMC-E3 to prevent the immigration of drug into the outer enteric coating and/or the potential interaction between drug and enteric polymer. Finally, the pellets were coated with a combination of Eudragit® FS 30D and Eudragit®L 30D-55 at a ratio of 2:1 to 30% coating weight gain to achieve enteric dissolution and good flexibility. TEC (5% base on dry polymer, w/w) as a plasticizer and CMS (5% based on dry polymer, w/w) as an anti-sticking agent were also incorporated in the enteric coating suspension, of which the total solid content was adjusted to approximately 20% (w/w) using distilled water. During the coating process, the inlet air temperature and the spraying rate were adjusted as necessary to maintain the product temperature at 30 °C. At last, the coated pellets were sieved manually to collect those in a size range of 250–300 μm and stored in a desiccator at room temperature for study.

2.3. Preparation of granulated pellets (GP)

The above Doxy coated pellets (30 g per batch) were granulated with five excipient formulations (Table 1) using a centrifugal granulator (BZJ-360MII, Beijing Long March Tianmin Hi-tech Co., Ltd., China) to prepare GP, which were correspondingly labeled as G1–G5 (Fig. 1). For each formulation, the proportion of MCC and additional excipients was 90% and 10%, respectively. During the granulation process, the central rotary speed was set at 60 rpm, the spraying rate was 5 g/min, and the mixed powder was fed at 9 g/min. Adhesive solution containing 5% (w/w) PVK K-90 in pH 1.0 HCl was used to ensure the enteric film integrity. The obtained GP were oven-dried at 40 °C for 4 h and sieved manually to collect granules in a size range of 350–550 μm for further investigation. The yield of GP is the proportion of the weight of GP with a designed size to the total weight of coated pellets, granulating excipients and dry adhesive, which is an indicator of the potential of excipients to form GP under the set conditions. And it is calculated as follows:

\[
\text{Yield} = \frac{\text{weight of coated pellets}}{\text{weight of excipients + weight of coated pellets}} \times 100\%
\]

(1)

Since the weight of dry PVK K-90 was in a relatively small proportion, the above equation could be simplified as:

\[
\text{Yield} = \frac{\text{weight of coated pellets}}{\text{weight of excipients}} \times 100\%
\]

(2)

The drug amount in the pellets remained constant before and after granulation, so the following equation exists:

\[
c_1 \times m = c_2 (m + x)
\]

(3)

Where \(c_1\) and \(c_2\) are the drug contents in coated pellets and GP, respectively. \(m\), \(x\) and \((m + x)\) represent the weight of coated pellets,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Excipient formulations of GP preparation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td>MCC (g)</td>
</tr>
<tr>
<td>F1</td>
<td>27.0</td>
</tr>
<tr>
<td>F2</td>
<td>27.0</td>
</tr>
<tr>
<td>F3</td>
<td>27.0</td>
</tr>
<tr>
<td>F4</td>
<td>27.0</td>
</tr>
<tr>
<td>F5</td>
<td>27.0</td>
</tr>
</tbody>
</table>
excipients, and GP, respectively. And Eq. (3) can be transformed as follows to calculate the actual granulating ratio:

\[
\text{Actual granulating ratio (\%) = } \frac{x}{m} \times 100\% = \frac{c_1 - c_2}{c_2} \times 100\%.
\] (4)

The actual drug content was determined by HPLC method with UV detection at 208 nm.

2.4. Preparation of fluidized bed-cushioning granules

MCC and PVPP were blended at a ratio of 19:1 (a total of 400 g) in a fluidized bed granulator (Glatt GPCG-1.1, top spraying) for 5 min. Then 240 g of 10% (w/w) PVP K-30 binder solution was added at the rate of 10 g/min with the air flow of 15 m³/h, the inlet temperature of 35 °C, the outlet temperature of 25 °C, and the product temperature around 27 °C. Upon completion of spraying, the granules were dried at 40 °C for 5 min in the fluidized bed and then oven-dried at 60 °C for 4 h. The dry granules were sieved, and collected in the size range of 350–550 μm for follow-up studies.

2.5. Characterization of the excipients

2.5.1. Particle size distribution

The size distribution of the excipient powder was measured in triplicate by means of dry laser diffraction (Mastersizer 2000 with a Scirocco dry module, Malvern Instruments Ltd., UK).

2.5.2. Bulk and tapped density of the excipients

The bulk (ρb) and tapped density (ρt) of the excipients were determined by a powder comprehensive tester (BT-1000, Dandong city Baxter instrument co., Ltd, China). Each determination was performed in triplicate. The Carr’s compressibility index (C%) was calculated according to the following equation based on the mean bulk and tapped density.

\[
\text{Carr’s index (\%) = } \frac{\rho_t - \rho_b}{\rho_b} \times 100.
\] (5)

2.5.3. True density of the excipients

The true density (ρ) of the excipients was measured by Helium-pycnometry (Accupyc 1330 Pycnometer, Micrometrics, Norcross, USA). A total of ten runs and ten purges were performed per experiment with a purge fill pressure of 19.5 psig.

2.5.4. Hygroscopicity of the excipients

The excipients were stored individually in open vials and enclosed in a dryer at elevated humidity (RH 90 ± 10%, 25 °C) for 10 days. Hygroscopic weight gain was measured in triplicate on the fifth and tenth day [13].

2.6. Characterization of the particles

The bulk (ρb) and tapped density (ρt), together with the angle of re-pose of coated pellets, cushioning granules and GP were measured in triplicate by a powder comprehensive tester (BT-1000, Dandong city Baxter instrument co., Ltd, China). The corresponding Carr’s compressibility index (C%) was calculated according to Eq. (5).

2.7. Scanning electron microscopy (SEM)

The coated pellets and GP prepared from PVPP formulation were sputtered with gold palladium, and then observed using a scanning electron microscope (SEM JSM-6330 F, JEOL, Japan). The SEM photographs were magnified 100 times.

2.8. Preparation of granulated pellet-containing tablets (GPCT)

An essential tablet compres machine (ZYD-8, Shanghai Fareast Pharmaceutical Machinery General Factory, China) was utilized to prepare GPCT. Four formulations of GP (G1–G4) were mixed separately with an equivalent amount of fluidized bed-cushioning granules and then compressed into GPCT (T1–T4 in Fig. 2). The diameter of GPCT was set to 10 mm and the compression force was adjusted based on the properties of granulating excipients to achieve a desirable and consistent tablet hardness (30 N ± 3 N). The prepared GPCT were stored at 40% relative humidity and room temperature for at least four days before characterization.

2.9. In vitro drug-release studies

Doxy release from coated pellets, GP and GPCT was evaluated according to the USP 34 paddle method (VK 8000, Vankel, New Jersey, USA) at a rotational speed of 50 rpm and temperature of 37.0 ±
Fig. 2. The schematic presentation of preparing GPCT.

0.5 °C. The release study was carried out initially in 900 ml of pH 1.0 HCl for 2 h, followed by up to 6 h of release in pH 5.5 potassium acid phthalate buffer. Samples were withdrawn at predetermined time intervals and kept frozen at 4 °C prior to analysis by a HPLC method. Each batch was analyzed in triplicate. The similarity factor \( f_2 \) was introduced to evaluate the dissolution profiles of GP and GPCT, with the coated pellets as a control, and calculated according to Eq. (6):

\[
f_2 = 50 \log \left(1 + \frac{1}{n} \sum_{i=1}^{n} \left(\frac{R_t - T_t}{T_t}\right)^2 \right)^{-0.5} \times 100
\]

where \( n \) is the number of sampling points, \( R_t \) and \( T_t \) are the percentages of dissolved drug for the reference and the test product at each time interval.

2.10. HPLC analysis for drug content

Samples were analyzed by HPLC method according to requirements of “Chinese Pharmacopoeia” 2005 edition, using a 4.6 × 250-mm Phenomenex Luna C18 5-\( \mu \)m ODS column with UV detection at 208 nm. The mobile phase was composed of 0.05 M ammonium oxalate solution, N,N-dimethylformamide, and 0.2 M diammonium hydrogen phosphate solution (65:30:5). The pH of the salt eluent was adjusted to 7.8 ± 0.2 using ammonia solution. Before examination, the sample was degassed and filtered through 0.2 \( \mu \)m microporous membrane. The injection volume was 20 \( \mu \)l, the flow rate was set at 1.0 ml/min, and the column temperature was set at 35 °C.

2.11. Drug degradation rate

To thoroughly investigate the effect of excipients on the stability of Doxy, the coated pellets, GP and GPCT were stored under high temperature (60 ± 2 °C), strong light (4500 ± 500 lx, 25 ± 2 °C) and high humidity (RH 90 ± 10%, 25 ± 2 °C) conditions. Since degradation of Doxy might occur in such conditions, drug contents varied with time and were reported as an indication of the stability of the formulations. The samples were withdrawn at predetermined time intervals to determine drug contents.

3. Results and discussion

3.1. Characterization of the powders

3.1.1. Powder characteristics

According to the literatures, the variations of the excipient powder, such as the particle size distribution, and the flowability of the excipient powder, have considerable effects on characteristics of both granules and tablets [14,15]. Smaller particle size generally leads to poor flowability, which is problematic for tableting [14]. The Carr’s index is commonly used as an indication of the flowability of powder/particles in pharmaceutical industry [16,17]. The Carr’s index above 23 is an indication of poor flowability, and below 12 of excellence [16].

As shown in Table 2, values of \( d_{50} \), the particle diameter value corresponding to the cumulative distribution percentage of 50%, for these excipients differ greatly, leading to diverse properties of the powder. It was noted that excipient with smaller size exhibited larger bulk/tapped density and poorer flowability, which is consistent with the results reported by Wolfgang [14]. DCP with the Carr’s index of 30.70 shows poor flowability [18], so it may constrain the movement of G4 during compaction process and potentially cause film ruptures [19]. However, PVPP with the Carr’s index of 10.42 was expected to have a good flowability and benefit for tableting [14]. Additionally, the true density of the excipients ranges from 1174.8 mg/ml to 1964.0 mg/ml.

3.1.2. Hygroscopicity of the excipients

It is well known that hygroscopicity of the coating film may stir the drug degradation in the coated pellets. For the GPT, the excipient layer wrapped around the coating film also preformed as a coating layer. Based on this hypothesis, the stability of Doxy could be affected by the excipient hygroscopicity during storage as it is a humidity sensitive drug. Fig. 3 showed the amount of moisture absorption weight gain
for the excipients recorded on the fifth and tenth day. The hygroscopicity of these excipients is in the order of CMS-Na > PVPP > CMC-Na > DCP > MCC > Lactose. CMS-Na and PVPP are commonly used as superdisintegrants due to their strong hygroscopicity. CMS-Na is the sodium salt of a carboxymethyl ether of starch, which absorbs moisture through disruption of the hydrogen bonding within the polymer structure by the large hydrophilic carboxymethyl group [20], so it may assist to break GPCT/GP into individual coated pellets. PVPP also showed a strong hygroscopicity due to its porous structure and capillary force [1] and might perform a similar function as CMS-Na. CMC-Na exhibited a moderate hygroscopicity, but it can prevent the immigration of water into the coating film due to its gelating property, and potentially suppressed the degradation of Doxy. DCP with certain hygroscopicity can be used as a diluent in tablets to modify the compaction properties of the GP. Lactose almost showed no hygroscopicity even under such high humidity. Addition of lactose to MCC not only protect Doxy against degradation more effectively due to its minor hygroscopicity, but also the water-soluble lactose prevent the swellable MCC from adhering to the coating film to affect drug release.

3.2. Characterization of the particles

The characteristics of coated pellets, cushioning granules, and GP (G1–G5) were summarized in Table 3. The bulk density of GP decreased from 726.5 mg/ml to 426.5 mg/ml and the tapped density declined from 772.8 mg/ml to 475.6 mg/ml. It is known that the bulk and tapped density is affected by particle properties such as size [21], shape and surface roughness [5]. Since the granules were more irregular in shape than the coated pellets, GP are more liable for a looser packing structure, resulting in a smaller bulk and tapped density. Also, GP showed a larger angle of repose, suggesting a poorer flowability in comparison with coated pellets. The marked increase in the Carr’s index of GP as compared to those of coated pellets, further demonstrates that a rougher surface was formed around the coated pellets after granulation. For the GP (G1–G5), the Carr’s index was less than 12, indicating that all of them had good flowability, which is advantageous to tableting process [14]. In addition, these values were smaller than those of powdery excipients, suggesting an improvement of flowability through granulation, during which powdery excipients formed granules with smooth surface by water-uptake [15]. Overall, the characteristics of GP were closer to those of cushioning granules, suggesting similar surface textures between them, which may lead to a more uniform mixing. Therefore, the modification of surface and geometry of the coated pellets was intended to obtain a non-segregated blend of coated pellets and cushioning granules in order to produce acceptable tablets [5]. And the excipient layer surrounding the coated pellets may first crack, and then fill the space between the particles during compaction process, it could protect the internal coated pellets from film ruptures [5].

Besides, all formulations except G5 showed a high granulating yield. CMS-Na in G5 with the most capable disintegrating properties absorbed enough water in a short time, and thus the formulation adhered to the inner wall of the granulator or formed self-aggregation [5], resulting in a low granulating yield of 42.28%. So G5 was removed from the follow-up study.

The SEM photographs of coated pellets and G1 were presented in Fig. 4. A complete, smooth coating film was obtained for coated pellets (A), and the subsequent granulating process modified the smooth surface of the coated pellets to rough surface with the addition of an excipient layer. As the proportion of additional excipients to MCC was small, the differences in SEM morphology of G1–G5 were invisible. Therefore, the SEM photographs of G2–G5 were not shown.

3.3. In vitro drug dissolution studies

The drug release from pellet containing tablets is influenced by various factors, such as type and amount of excipients, pellet hardness, compression force, thickness and elasticity of the film [7]. An acceptable

<table>
<thead>
<tr>
<th>Particles</th>
<th>Bulk density (mg/ml)</th>
<th>Tapped density (mg/ml)</th>
<th>Angle of repose (°)</th>
<th>Actual granulating ratio (%)</th>
<th>Yield (%)</th>
<th>Carr’s index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coated pellets</td>
<td>726.5 ± 3.4</td>
<td>772.8 ± 1.6</td>
<td>20.7 ± 0.8</td>
<td>–</td>
<td>–</td>
<td>5.99</td>
</tr>
<tr>
<td>Cushioning granules</td>
<td>297.6 ± 4.2</td>
<td>334.1 ± 3.4</td>
<td>42.3 ± 0.2</td>
<td>77.56</td>
<td>74.07</td>
<td>11.34</td>
</tr>
<tr>
<td>G1</td>
<td>432.2 ± 1.8</td>
<td>487.5 ± 1.3</td>
<td>28.3 ± 0.1</td>
<td>85.77</td>
<td>78.03</td>
<td>9.87</td>
</tr>
<tr>
<td>G2</td>
<td>445.8 ± 0.3</td>
<td>494.6 ± 0.9</td>
<td>28.7 ± 0.5</td>
<td>84.10</td>
<td>77.07</td>
<td>8.01</td>
</tr>
<tr>
<td>G3</td>
<td>437.5 ± 0.2</td>
<td>475.6 ± 0.4</td>
<td>28.2 ± 0.5</td>
<td>84.10</td>
<td>78.03</td>
<td>9.87</td>
</tr>
<tr>
<td>G4</td>
<td>446.3 ± 0.6</td>
<td>496.5 ± 0.5</td>
<td>30.2 ± 0.5</td>
<td>80.05</td>
<td>74.16</td>
<td>10.11</td>
</tr>
<tr>
<td>G5</td>
<td>426.5 ± 0.5</td>
<td>475.6 ± 0.4</td>
<td>30.5 ± 0.1</td>
<td>84.74</td>
<td>42.28</td>
<td>10.32</td>
</tr>
</tbody>
</table>

Table 3
Characteristics of the particles (n = 3).
pellet containing tablet should disintegrate into individual pellets in the gastrointestinal fluids and the drug-release is not influenced by the compaction process [22]. For GPCT, there is an additional requirement that the granulating layer should not change the drug-release profile. The coating polymers used in this study were a blend of Eudragit® FS 30D and Eudragit® L 30D-55 at a ratio of 2:1. Eudragit® FS 30D is commonly used for colon-targeting with a dissolution above pH 7.0 [10,23], while Eudragit® L 30D-55 dissolves in media with pH above 5.5, and is not suitable to prepare GPCT because of its brittle nature [10]. Based on our previous study, major changes in the physical properties of free film were coincident with the increased amount of Eudragit® FS added to Eudragit® L 30D-55, including a lower tensile strength and modulus of elasticity, and a higher elongation at break. It is demonstrated that the addition of Eudragit® FS can improve the flexibility and elasticity of the film, but reduce strength of the film either. Therefore, the ratio of these two polymers should be kept at an appropriate level to obtain a qualified film with acceptable flexibility and strength, further to enhance resistance of the film to impact load and maintain integrity of the film. So the ratio of Eudragit® FS and Eudragit® L 30D-55 was set as 2:1 to form a sufficiently flexible coating film, which might potentially withstand the compression force and avoid ruptures [10]. According to USP 34, if the coated pellets could maintain their sustained release properties after compaction, the drug release from the compressed tablet within 2 h in pH 1.0 medium was expected to be lower than 10%.

The similarity factor $f_2$ was introduced to compare the drug-release profiles of GP/GPCT with that of coated pellets. The value of $f_2$ above 50 is an indication of similar dissolution curves [24]. Besides, the more closer to 100, the greater equivalence between the two profiles [25]. The drug release from T4 was more than 10% at initial 2 h (data were not shown). The enteric property of T4 indicated that the coating film cracked during compaction, which may be due to the poor compressibility of DCP as confirmed in the preliminary tests. In addition, a split of tablet, especially around the marginal region, was observed when DCP was directly compressed into tablet under a compression force of only 60 kPa. Further, the Carr’s index and Hausner ratio (data were not shown) of DCP also revealed that it is a kind of viscous powder and its movement could be constrained between particles, which is not suitable for tableting [18]. So, following G5 being removed from the study due to low granulating yield, G4 and T4 were also excluded from the further study.

The released drug amount from these GP and GPCT formulations (G1–G3 and T1–T3) in acidic medium for 2 h was less than 10% (Fig. 5), suggesting that the enteric property of the coating film was maintained after granulation and compaction processes [7]. Surprisingly, it is observed that the GP:lactose has a slightly higher drug release after 3 h as compared to GPCT:lactose and coated pellets (Fig. 5B). Considering that the excipients have been fully swollen/dissolved after 3 h of exposure to the release media, GP:lactose lost the protection by excipients against media. Besides, film abrasion/rupture could occur during granulation process, so GP:lactose showed a higher drug release as compared to coated pellets. Since more time and driving force were required to detach the granulating excipients from the coated pellets in GPCT, drug release from GP:lactose was also higher than that of GPCT: lactose.

As shown in Table 4, there is a decreasing trend from G1/T1 (PVPP), G2/T2 (lactose) to G3/T3 (CMC-Na), which is profoundly more or less attributed to the excipient properties. Among the GP, the $f_2$ values of G1 is the highest, implying that PVPP has the least effect on the drug-release behavior of G1 due to its most excellent disintegrating properties. G3 showed a lowest $f_2$ values because of the gelating properties of CMC-Na invoked upon water uptake. For the GPCT, it is in good agreement with the yield pressure of these excipients [2]. In other words, a least compression force was required to achieve a desirable tablet hardness for the excipient with the best compressibility, so T1 endured the least damage of coating film during compaction process and showed a highest $f_2$ value. Besides, the $f_2$ values of GP and GPCT, in comparison with the coated pellets, were all greater than 50, indicating that the drug-release was similar among all these formulations, and the granulation and compaction processes did not modify the dissolution performance of the coated pellets. Therefore, it can be concluded that the quality of these GPCT was acceptable and there was no statistical difference among them, and any effect of their quality differences on the follow-up study could be ignored.
3.4. Drug degradation rate studies

Since Doxy is sensitive to surroundings, drug degradation could occur when Doxy was incorporated in GP and GPCT, and stored under high temperature, strong light, and high humidity conditions. For example, drug degradation could be affected by hygroscopicity of excipients during storage under high humidity [26]. It is known that the hygroscopicity of these excipients is in the order of PVPP > CMC-

![Graph A: High temperature (60 ± 2 °C)](image)

- Coated pellets
- GP:PVPP
- GP:Lactose
- GP:CMC-Na
- GPCT:PVPP
- GPCT:Lactose
- GPCT:CMC-Na

0 day
5 days
10 days

![Graph B: Strong light (4500 ± 500 lx, 25 ± 2 °C)](image)

![Graph C: High humidity (RH 90 ± 10%, 25 ± 2 °C)](image)

0 day
5 days
10 days

Fig. 6. The drug content of coated pellets, GP and GPCT under A. high temperature (60 ± 2 °C), B. strong light (4500 ± 500 lx, 25 ± 2 °C), and C. high humidity (RH 90 ± 10%, 25 ± 2 °C) (n = 3).
Na > Lactose. The drug degradation rate could be affected by excipient hygroscopicity after storage in high humidity due to its sensitivity to water [26]. Besides, the film with Eudragit® L 30D-55 as a coating polymer exhibits certain moisture permeability and allows for water-uptake, which could potentially cause drug degradation under high moisture [8].

The drug contents under different extreme conditions were presented in Fig. 6. The amount of Doxy in all formulations on the tenth day was above 97% under high temperature (Fig. 6A) and strong light (Fig. 6B), indicating that the influence of temperature and light could be ignored. A possible reason was that the excipients laid over the pellet surface through granulating technique protect the drug from direct exposure to elevated temperature and strong light. Meanwhile, the drug degradation rate was in the order of GPCT > GP > coated pellets. This could be attributed to partial abrasion or rupture of the coating film created by granulation and compaction processes, and the extent of film damage was greater in GPCT due to the additional compaction than in GP. During compaction, deformation of pellets could occur when they are either at the tablet surface in contact with the punches on or in closer contact with each other inside the tablet [27].

The drug content of these formulations ranged from 93% to 96% under high humidity (Fig. 6C), suggesting that Doxy was oxidized or degraded to a certain extent as water absorption occurred under high humidity. It was noted that the drug degradation rate in GP on the tenth day was sequenced as PVPP > CMC-Na > Lactose, which was consistent with the order of hygroscopicity for these excipients. The stability of GP could be influenced by both coating film permeability and excipient hygroscopicity, as the polymer permeability remained constant among these GP before granulation, the least drug degradation for lactose GP was attributed to the lowest hygroscopicity of lactose. However, such relationship between excipient hygroscopicity and the drug degradation rate was not observed in GPC. The sequence of drug degradation rate in GPC on the tenth day was PVPP < CMC-Na ≈ Lactose, which was inversely proportional to the excipient compressibility. It is likely that the stability of GPCT is impacted by the permeability and rupture of coating film, and the hygroscopicity of auxiliary layers. Due to the compaction process, pellet coating film could have certain deformation and damage [28,29], resulting in a lower drug content in GPC compared to GP under high humidity, which was also verified under high temperature and strong light conditions. Since the excipient compressibility may directly impact the integrity and permeability of the coating film during compaction, it played a dominant role in stability of GPC. PVPP has the highest yield pressure, and best compressibility among these excipients [2], hence the film rupture in T1 with PVPP was the least under the same tabletting conditions. Additionally, PVPP with the best flowability, as above-mentioned, could effectively fill the spaces between particles and avoid aggregation and film fusion of the pellets during compacting process [5], thus providing an effective protection for the coating film. Furthermore, PVPP was laid denser in GPC after compaction than in GP, so it was less likely to contact directly with water in GPC, resulting in a lower drug degradation rate for T1 than G1. Therefore, the drug degradation rate of T1 was the lowest and lower than that of G1. Overall, it is speculated that the combination of MCC and PVPP with the best compressibility may be the most ideal excipients to maintain the integrity of the coating film and improve the stability of the humidity sensitive drugs.

4. Conclusions

The excipient layer in GP showed significance in improvement of the compressibility of coated pellets and maintaining the drug release properties of coated pellets after granulation and compaction. Not only did it provide an effective way to circumvent the segregation problems associated with mixing of coated pellets and powder, but also it could absorb the compression force to protect against film rupture. Though the granulation and compaction processes caused partial abrasion/rupture to the coating film, the GP and GPCT were stable under high temperature and strong light conditions, and the stability of GPCT under high humidity was dominated by the excipient compressibility. It is speculated that the binary mixture of MCC and PVPP with the best compressibility could be ideal leveling excipients to prepare GPC for humidity sensitive drugs.

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