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Research Article

Stability Enhancement of Drug Layered Pellets in a Fixed Dose Combination Tablet

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Abstract. The purpose of this research was to develop a stable fixed dose combination tablet for a model DPP-IV inhibitor and metformin hydrochloride. The dipeptidyl peptidase IV (DPP-IV) inhibitor was particularly challenging to formulate due to its significant chemical instability and moisture sensitivity. Various formulation strategies were investigated and placed on accelerated stability to determine the lead approach and critical quality attributes. The lead formulation investigated was a drug layered pellet containing the DPP-IV inhibitor, which was further coated with various seal coats and moisture barriers, then compressed into a tablet with compression aids and granulated metformin hydrochloride. The investigations revealed that the drug layered pellets compressed into a fixed dose combination tablet yielded a unique stability enhancement. The stability was highly dependent on the final tablet water content and could be further improved by the addition of moisture barrier coatings. A fundamental understanding of the key critical quality attributes for the fixed dose combination product containing a DPP-IV inhibitor and metformin hydrochloride as an oral solid dosage form were established. This research identified a formulation approach to enable a successful commercial product to be developed.

KEY WORDS: DPP-IV; drug layered pellets; hydrolysis; moisture barrier; stability.

INTRODUCTION

An emerging class of molecules to improve glycemic control in type 2 diabetics is dipeptidyl peptidase IV (DPP-IV) inhibitors (1,2). This class of molecules is based on prolonging the beneficial effects of circulating glucagon-like peptide-1 (GLP-1) in the blood by inhibiting the degradation of GLP-1 by the DPP-IV enzyme. GLP-1 is an insulinotropic hormone that is released postprandially and has various physiological actions such as stimulation of insulin biosynthesis and inhibition of glucagon secretion (3). Several small molecule DPP-IV inhibitors have been discovered which have also achieved positive proof-of-concept (1,3–5). In addition, a recent 1-year efficacy study where a DPP-IV inhibitor was added to ongoing metformin therapy produced an initial reduction in HbA1c levels followed by an essentially flat HbA1c profile from week 12 to week 52 suggesting that the combination of metformin and a DPP-IV inhibitor may influence the underlying mechanism of disease progression. This efficacy study warrants longer term investigation of DPP-IV inhibitor and metformin combination therapy, and suggests that DPP-IV combination products may dominate future disease management (6).

A key structural attribute reported on a number of DPP-IV inhibitors is the nitrile moiety found on a pyrrolidine ring, which is often in close proximity to a basic amine group (Fig. 1). The nitrile moiety has a key interaction with the catalytic serine of the DPP-IV enzyme and achieves the desired pharmacological inhibition. However, the proximity of the nitrile moiety to a basic amine on the molecule allows it to undergo an intramolecular cyclization reaction to form a cyclic amidine which can subsequently be hydrolyzed to form a diketopiperazine (5). The reactivity of the nitrile and amine groups presents a stability challenge when formulating the compound into a commercial product. In addition, if a fixed dose combination product with metformin is pursued, the basic amine groups on metformin's structure may also pose additional stability issues (Fig. 2).

While stability challenges will most likely need to be overcome in the development of a fixed dose combination product, the pharmacological evidence points to substantial benefits for patients. As an additional patient benefit, a recent study concluded that a combination product improved the medication compliance rate *versus* dual therapy regimens (7). This may be due to the large dose of metformin which may result in patients taking multiple tablets. Based on the factors listed above, the goal of this paper was to investigate the possibility of formulating a stable fixed dose combination

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ABBREVIATIONS: GI, Gastrointestinal; AMB, Aqueous moisture barrier; DPP-IV, Dipeptidyl peptidase IV; GLP-1, Glucagon-like peptide-1; PVA, Partially hydrolyzed polyvinyl alcohol; HPMC, Hypromellose (hydroxypropylmethylcellulose).

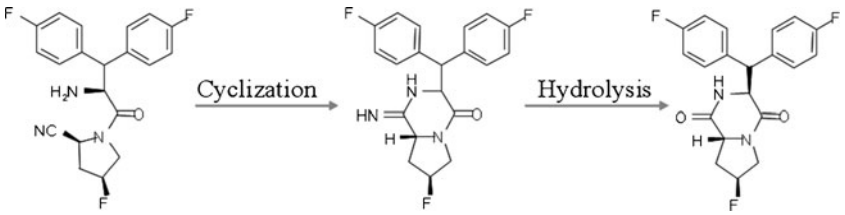

Fig. 1. Predicted degradation pathway for the model DDP-IV inhibitor (denagliptin). The proximity of the nitrile moiety to the basic amine on the molecule allows it to undergo an intramolecular cyclization reaction to form a cyclic amidine which can subsequently be hydrolyzed to form a diketopiperazine

product using a model DPP-IV inhibitor and metformin hydrochloride. The main formulation approach that was selected for development was drug layered pellets blended with metformin granule and compressed into a tablet. Compression of coated pellets into a tablet has been investigated in the past for various reasons, but most commonly to achieve a modified release profile; however, in this case we used coated pellets as a stability enhancement tool (8,9). Blending and segregation issues were avoided by using coated pellets that were the same particle size as the other key tablet components.

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (Avicel PH 102) was sourced from FMC International (Philadelphia, PA, USA). Microcrystalline cellulose sphere (Celphere CP-102) was sourced from Asahi Kasei Corporation in Tokyo, Japan. Hypromellose 2910 (Methocel E5) was sourced from Univar USA, a distributor for Dow Chemical. Magnesium stearate was sourced from Peter Greven (Vista, CA, USA). A common metformin granule (93.5% potency) was manufactured for GSK *via* an external company with a median particle size of 150 μm. Opadry® II film coat, Opadry® AMB film coat, and Opadry® clear film coat were sourced from Colorcon (Westpoint, PA, USA). Acetonitrile and hydrochloric acid were obtained from Sigma.

Model DDP-IV Inhibitor

Denagliptin, GW823093C, is a white, crystalline powder manufactured as the tosylate salt by GlaxoSmithKline (GSK). It is classified as a BCS 1 compound (high solubility/high permeability) with a solubility of 2.7 mg/mL in water. The dose utilized in this study was 15 mg, but the expected dose range was 7.5 mg to 45 mg. Micronization of the drug substance was performed by Micron Technologies (Exton, PA, USA) which generated two particle sizes: 50 μm and 2 μm median particle size.

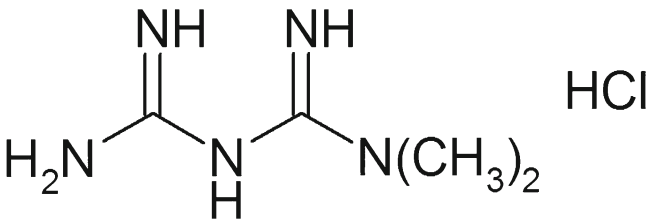

Fig. 2. Metformin hydrochloride molecular structure

Drug Layered Pellets

Coated pellets were manufactured in a Glatt GPCG 1.1 fluid bed granulator equipped with a 3.5 in. Wurster column and 1.0-mm nozzle. Microcrystalline cellulose (MCC) spheres (Celphere CP-102) were fluidized and sprayed with an aqueous suspension containing the DDP-IV inhibitor, hypromellose, and water (drug coat), followed by spraying another aqueous solution containing hypromellose (seal coat). Optionally, an additional Opadry® seal coat was sprayed onto the pellets from an aqueous solution of Opadry®. All coating solutions were prepared by mixing the appropriate amount of excipient in water for 1 h. When preparing the drug suspension, the suspension was further homogenized for 10 min with an IKA50 homogenizer and mixed continually while spraying. After application of the coating materials, the pellets were dried with fluidizing air until the pellet water content was less than 1%. The pellet water content was determined by placing approximately 3–4 g of pellets in a loss on drying balance (Mettler Toledo HR 73). The pellets were dried at 90°C for 4 min. The percent weight loss at the end of the test was used to reflect the pellet's water content.

Blending, Compression, and Tablet Coating

The coated pellets were passed through a 425-μm screen to remove any agglomerated pellets and blended with metformin granules and microcrystalline cellulose. The mixture was blended for 10 min in a V-shell blender. Magnesium stearate was added to the blend. The final mixture was blended for an additional 2 min. The blend was compressed into tablets using a Korsch EKO single station press. The tooling used was a standard capsule-shaped tablet with a length of 23 mm and a width of 9.5 mm, and the tablets were compressed to a hardness of ~25 kp. Tablet hardness was tested with a Schleuniger Model 6D hardness tester. The core tablets were then coated in a Vector LDCS-5 pan coater using a 1.3-L pan and a single spray gun with a 1.0-mm nozzle. The core tablets were coated with a hypromellose-based Opadry® clear film coat. To quantify tablet water content, a tablet was ground to reduce the tablet into a powder. The ground tablet was placed in a loss on drying balance (Mettler Toledo HR 73) at 130°C for 2 min. The percent weight loss at the end of the test was used to reflect the tablet's water content.

Stability Packaging and Storage

Ten tablets were placed in a 45-cm^3 high-density polyethylene bottle with the appropriate amount of desiccant

(silica gel in pre-packaged 0.5-g or 1-g canisters) with a child-resistant closure cap containing a liner suitable for induction sealing. The bottles were then induction sealed and placed in a 50°C oven at ambient relative humidity for 2 weeks. ICH conditions were not utilized because the DPP-IV inhibitor's poor chemical stability and rapid degradation allowed formulation assessments to be made using the aforementioned storage conditions.

High-Pressure Liquid Chromatography Method for Stability Testing of the DDP-IV Inhibitor

Two tablets were placed in 60 mL of a mixture of acetonitrile/0.1 N HCl in the ratio 50:50 by volume, then placed on a platform shaker for 45 min, and the flask was allowed to equilibrate to room temperature. An additional 60 mL of the acetonitrile/0.1 N HCl mixture was added and mixed thoroughly. A portion of this solution was centrifuged for 10 min at 3,500 rpm to obtain a clear supernatant. A 5-μL sample of the supernatant was injected on a Zorbax SB-Phenyl, 150×4.6 mm, 3.5 μm particle size (column temperature 40°C, flow rate 1.5 mL/min, detector wavelength 215 μm, run time 20 min). Mobile phase A was a mixture of water, methanol, and trifluoroacetic acid in a ratio of 90:10:0.05. Mobile phase B was a mixture of water, methanol, and trifluoroacetic acid in a ratio of 10:90:0.05. An initial 3 min of 70% mobile phase A/30% mobile phase B was used followed by a linear gradient from 70% mobile phase A to 5% mobile phase A over 12 min, then a 1-min gradient back to 70% mobile phase A followed by 4 min at 70% mobile phase A was utilized. This gradient elution method successfully separated all key degradation products identified during prior stress testing (10).

Moisture Absorption Studies for the Pellets

Approximately 400 mg of pellets was placed into labeled glass vials. The vials were weighed initially using a Mettler Toledo balance and placed in a 75% relative humidity glass desiccation chamber containing a saturated sodium chloride solution. The vials were removed every week and weighed to determine any weight gain due to moisture absorption. Each experiment was performed in duplicate.

Scanning Electron Microscopy of Pellets

The drug layered pellets were coated with a layer of gold (~10 nm) and observed with a Zeiss DSM-960 scanning electron microscope (Thornwood, NY, USA) at a voltage of 15 kV. To evaluate the pellets inside the core of a compressed tablet, the tablet was carefully broken by hand and small sections were coated with a layer of gold (~10 nm) and observed in a similar fashion to the coated pellets.

RESULTS AND DISCUSSION

Drug Layered Pellets Compressed Into a Tablet

Initial stability investigations revealed significant incompatibility of the model DPP-IV, denagliptin, drug substance, and most excipients. The second drug substance in this fixed dose combination product, metformin hydrochloride, did not show any major excipient compatibility issues. Therefore, the primary focus of this work was ensuring optimal stability of the DPP-IV inhibitor. The first step was to evaluate a simple approach which was a direct compression tablet using metformin granule, the model DPP-IV inhibitor, and two excipients to ensure a suitable tablet was produced. Microcrystalline cellulose was added as a compression aid and magnesium stearate was added as the lubricant. Attempts were made to minimize the quantity of microcrystalline cellulose to reduce total tablet weight; however, lower levels of microcrystalline cellulose had led to compression problems at commercial scale for a similar fixed dose combination tablet. The suitable range of microcrystalline cellulose for this product was 13–18% of the total tablet weight to ensure manufacturing robustness. The stability result from the direct compression formulation was very poor and rapidly degraded the DPP-IV inhibitor. This approach was quickly abandoned.

In an effort to reduce the physical interaction of the drug substance and other tablet components, an alternative formulation approach was utilized by incorporating drug layered pellets into the compressed tablet. The DPP-IV inhibitor was first coated onto microcrystalline cellulose spheres of a particle size between 106 and 212 μm followed by a seal coat of hypromellose to act as a physical barrier. Then drug layered pellets were blended with microcrystalline cellulose and magnesium stearate, and compressed into a tablet. It is important to note that the particle size of the drug substance is critical when spraying onto such small microcrystalline cellulose spheres. In this case, the median particle size was 2 μm and yielded excellent coating efficiency. Tables I and II list the formulation of the coated pellets compressed into a tablet (Pellet Tab-1 and Pellet Tab-2) compared to the initial direct compression tablet (DC Tablet) which had poor stability.

Due to the model DPP-IV inhibitor's poor chemical stability and thus rapid degradation, we could evaluate if a formulation modification improved the stability in a relatively short amount of time. It was determined that storing the formulations for 2 weeks at 50°C/ambient conditions was sufficient to judge if a formulation change improved stability. To evaluate the concept of using drug layered pellets to improve the stability of the DDP-IV inhibitor, three formulations were placed on stability. The DC Tablet which revealed poor chemical stability was used as a reference and formulations containing two different levels

Table I. Fixed Dose Combination Tablets

Tablet ingredient	Direct compression (DC) tablet (mg/tablet)	Pellet Tab-1 (mg/tablet)	Pellet Tab-2 (mg/tablet)
DPP-IV inhibitor[a] (median particle size 50 μm)	22	–	–
Standard pellet	–	50	–
Pellets-10%	–	–	53.7
Metformin granule[b]	1,070	1,070	1,070
Microcrystalline cellulose	163	235	231.3
Magnesium stearate	5	5	5
Total tablet weight (mg)	1,260	1,360	1,360

[a] The dose for the model DPP-IV inhibitor is 15 mg free base (or 22 mg including the salt)

[b] The metformin hydrochloride dose is 1,000 mg

Table II. DPP-IV Inhibitor Drug Layered Pellet Formulations

Ingredient	Std Pellets (% w/w)	Pellets-10% (% w/w)
Pellet base		
Microcrystalline cellulose sphere	49.9	46.1
Drug layer		
DPP-IV inhibitor[a] (median particle size 2 μm)	43.8	40.5
Hypromellose	3.65	3.4
Seal coat		
Hypromellose	2.65	10
Total	100	100

[a] The potency of the pellets is 30% and 27.9% w/w free base for the standard pellets and Pellets-10%, respectively

of hypromellose seal coat on the pellets were investigated to help identify the proper level of seal coat to ensure there was no physical interaction between the drug coating on the pellets and the other tablet excipients. Pellet Tab-1 has a 2.65% hypromellose seal coat and Pellet Tab-2 has a 10.0% hypromellose seal coat. Shown in Fig. 3 is the change in total degradation after 2 weeks at 50°C/ambient for the formulations mentioned above.

When drug substance (median particle size 50 μm) was included as a direct compression formulation, it is clear that rapid degradation occurs. Most likely this is due to chemical interactions with various tablet components. The moisture level of the those components could also have an impact; however, to reduce the chance of degradation due to higher moisture levels of components in the tablet, tablet coating conditions were selected to produce a final tablet water content of approximately 1.0% and the tablets were immediately packaged. When a coated pellet with a 2.65% hypromellose seal coat is utilized, the amount of degradation decreases approximately 3.5-fold. As the amount of hypromellose seal coat increases to 10%, there only appears to be a limited improvement in the stability suggesting that a 2.65% hypromellose weight gain is sufficient to prevent physical interaction of the drug substance and the other tablet components. Although the chemical stability data using the drug layered pellet approach revealed a substantial improvement in chemical stability, it was important to verify that the 2.65% hypromellose seal coat could retain its integrity when compressed into a tablet at the upper limit of compression forces. Scanning electron microscopy (Fig. 4) was performed to inspect the drug layered pellets before and after compression when a high compression force was used (tablet hardness was ~30 kp).

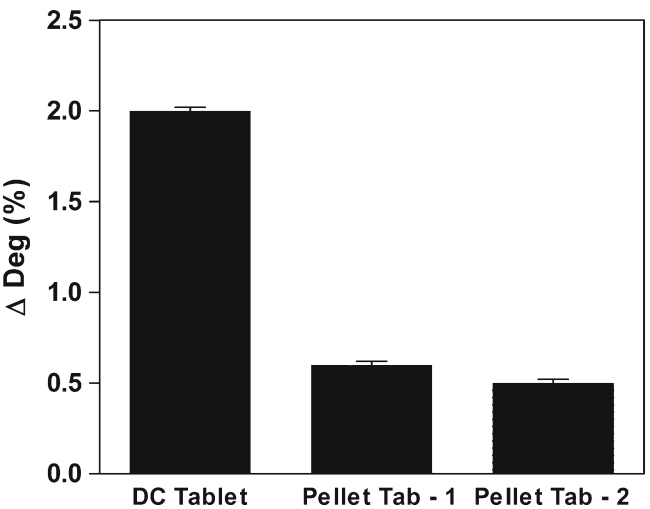

Fig. 3. The percent change in DPP-IV inhibitor degradants for three prototype fixed dose combination formulations are shown. The formulations were stored for 2 weeks at 50°C/ambient RH in a 45-cc HDPE bottle, induction sealed with 2 g of desiccant

Figure 4a and b displays the drug layered pellets before compression which have a smooth surface morphology and generally spherical or oval shape with an approximate diameter of 250 μm. Figure 4c and d shows the pellets after compression and removal from the tablet core. Based on these SEM images, it does not appear that the hypromellose pellet coating is compromised during tablet compression. However, if the integrity of the hypromellose pellet coating was compromised, it would have been difficult to discern if the damage occurred while attempting to remove the pellets from the core. In contrast, it may be possible that the tablet components which remain on the pellet surface after removal from the tablet core may be covering a crack or fissure in the hypromellose coating. Although SEM information is very important to understand gross physical integrity of the hypromellose coating, the ultimate data driving the final formulation decision is the chemical stability data for the DDP-IV inhibitor.

Impact of Moisture of DPP-IV Inhibitor Stability

Another important aspect of the DPP-IV inhibitor investigated in this work is the moisture sensitivity. When performing Wurster coating of the drug layered pellets, the pellet base is dried prior to coating and the pellets are also dried at the end of coating to a loss on drying (*i.e.*, water content) of less than 1.0%. However, when compressing the pellets into a tablet, moisture can migrate from other tablet components, such as the metformin granule which has up to 1.3% water content, or a significant amount of moisture can be absorbed by the tablet core during the application of aqueous film coatings. To quantify the effect of tablet water content on the DDP-IV inhibitor stability, various coating conditions were chosen to create Pellet Tab-1 formulations with different final tablet water content. Shown in Fig. 5 is the effect of water on the stability of the formulation based on the final tablet water content. As the water content of the coated tablet is increased, the level of degradation also increases. The tablet water content is clearly a critical quality attribute of the product and controls should be implemented to ensure that an appropriate water content is obtained after coating.

Another source of water during stability testing is ambient water, which is typically mitigated by the addition of desiccant. All of the stability information obtained to this point utilized 2 g of desiccant to minimize the impact of water ingress into the bottle; however, the level of desiccant can also have a significant impact on the stability of the formulation for "wetter" formulations. Figure 6 displays the impact of different desiccant levels on the chemical stability of the DDP-IV inhibitor, in the Pellet Tab-1 formulation, when the final tablet water content is 2.0%. The desiccant can rapidly remove water from the formulation and reduce the degradation. When stored for 2 weeks with 2 g of desiccant, the tablet water content was reduced to 1.1%, and when 4 g of desiccant was used, the tablet water content was 0.9%. The tablet water content remained constant after 2 weeks

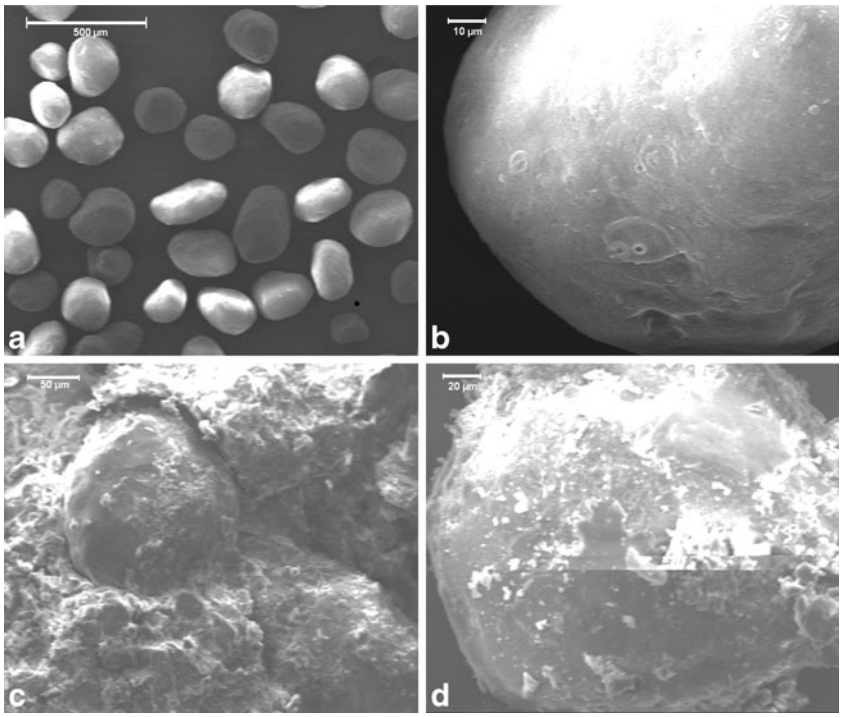

Fig. 4. Figure 4a (×50 magnification) and 4b (×750 magnification) show the standard pellets before compression which have a smooth surface morphology and generally spherical or oval shape with an approximate diameter of 250 µm. Figure 4c (×200 magnification) shows the pellets inside the Pellet Tab-1 tablet core after the tablet was broken in half. Figure 4d (×350 magnification) is a picture of a pellet carefully removed from the Pellet Tab-1 tablet core

and appeared to reach an equilibrium value. There is a complex interplay of desiccant level, tablet water content, and chemical stability when the initial tablet water content is high. If the rate of tablet water removal by the desiccant is faster than the rate of chemical hydrolysis of the DDP-IV inhibitor, it can improve the stability. However, this approach utilizes the desiccant as a formulation aid rather than as a tool to reduce the effect of water ingress into the HDPE bottle.

In contrast, when the water content of the coated tablet is controlled during the coating operation, the impact of desiccant is less significant. Shown in Fig. 7 is DDP-IV inhibitor stability data using tablets with an initial tablet water content of 1.1%. It is clear from Fig. 7 that a certain amount of desiccant is beneficial. Subsequent studies identified that 0.5 g of desiccant in a 45-cm^3 HPDE induction sealed bottle with 10 tablets is the most representative package to screen formulation and process modifications. This packaging configuration has been shown to

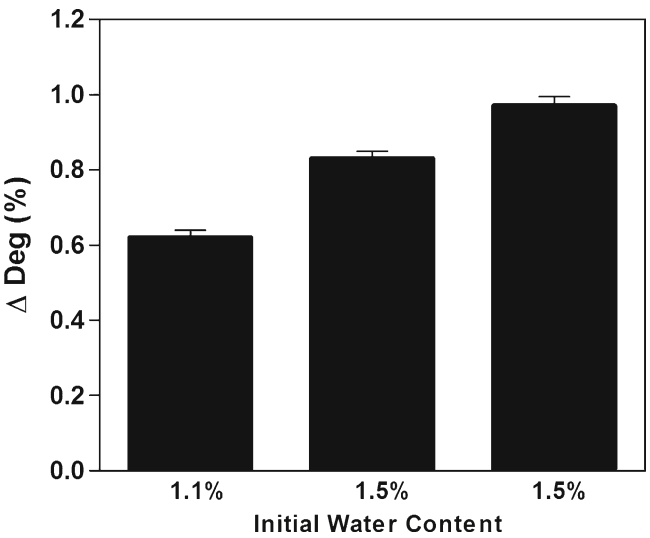

Fig. 5. The percent change in DPP-IV inhibitor degradation for three versions of Pellet Tab-1 which were manufactured to three different final product water content of 1.1%, 1.5%, and 2.0%. The formulations were stored for 2 weeks at 50°C/ambient RH in a 45-cc HDPE bottle, induction sealed with 2 g of desiccant

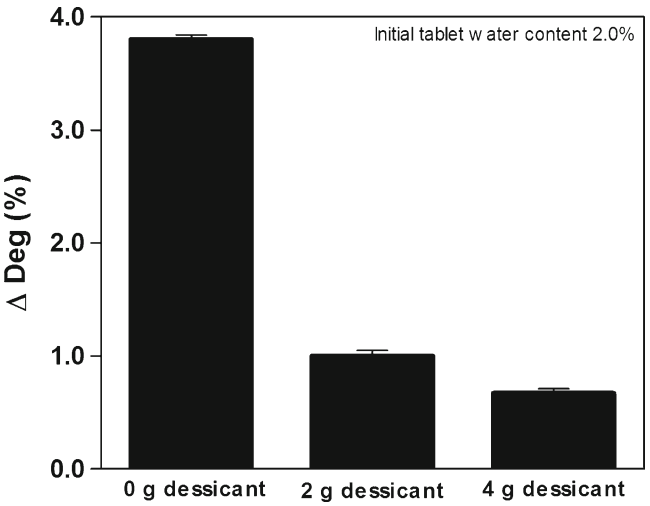

Fig. 6. The percent change in DPP-IV inhibitor degradation for Pellet Tab-1 with a final product water content of 2.0% is shown when stored at three desiccant levels, 0, 2, and 4 g, for 2 weeks at 50°C/ambient RH in an induction-sealed 45-cc HDPE bottle

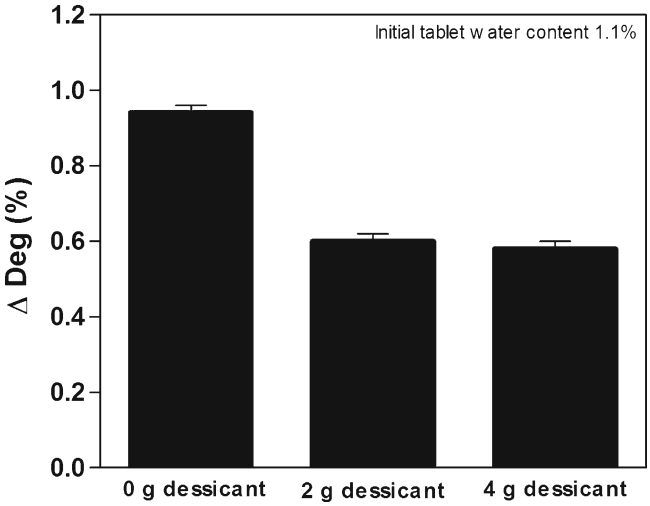

Fig. 7. The percent change in DPP-IV inhibitor degradation for Pellet Tab-1 with a final product water content of 1.1 is shown when stored at three desiccant levels, 0, 2, and 4 g, for 2 weeks at 50°C/ambient RH in an induction-sealed 45-cc HDPE bottle

be able to scale to larger packages for this formulation (data not shown). For all future studies, this pack will be used as the screening pack. The stability data up to this point has clearly identified that the final tablet water content is a critical quality attribute and the key processing step to control this value is the tablet coating process where water content needs to be monitored and controlled.

Optimization of Drug Layered Pellet Seal Coat

Previous drug layered pellet formulations investigated hypromellose seal coat levels of 2.65% and 10% weight gain and revealed minimal differences in DPP-IV inhibitor stability. In order to evaluate the impact of lower levels of hypromellose seal coat on the stability of the product, hypromellose coating levels between 0% and 2.65% were applied to the drug layered pellets and subsequently compressed into tablets, coated, and placed on stability. These new formulations are shown in Tables III and IV. Pellet Tab-3 and Pellet Tab-4 contain 0% and 1.3% hypromellose seal coat, respectively, on the drug layered pellets. The tablet water content was kept low during these evaluations (water content ~1.1%). Shown in Fig. 8 are the chemical stability results for the DDP-IV inhibitor.

Figure 8 revealed a surprising result that the hypromellose seal coat may not be required to enhance chemical stability. This result was in direct contrast to the previous work utilizing drug substance directly in a direct compression tablet with the same excipients. It is important to note that the tablet water content was 1.0% for the DC Tablet which confirms that the poor chemical stability was not due to excessive water. Clearly, there is a stability enhancement by utilizing the drug layered pellets that goes beyond water contents and physical interactions. Based on simple geometric calculations, there is a reduction in the exposed surface area of the drug when using drug layered pellets *versus* 50-μm particles, but this does not account for the ~3.5-fold decrease in percent change in degradation, after 2 weeks. The additional stability enhancement is unclear at this point; X-ray analysis (data not shown) of the drug coated pellet reveals the same crystal structure so a change in the molecular orientation of the drug did not occur. Based on prior stress testing of the model DPP-IV inhibitor, it could be hypothesized that the Wurster coating process with hypromellose allows the amino group to be more likely to remain protonated and trans to the cyano group thus improving stability (10). While the exact mechanism of stability enhancement is unknown, it was interesting to find that a similar result was obtained when using the fluid bed Wurster coating process to stabilize a chemically unstable compound in a fixed dose combination tablet. In this case, aspirin was granulated using a Wurster coating insert prior to compression into a tablet with ranitidine. This process yielded a stable combination product (11).

Alternative Drug Layered Pellet Water Barriers

While the exact mechanism for stability enhancement is difficult to elucidate, from a practical standpoint, a known contributor to DDP-IV inhibitor chemical degradation is the water contents in the tablet. It is also important to note that the drug layered pellets are dried to a water content below 1.0% prior to incorporation into the tablet, and it is only in the subsequent tableting and coating operations where additional water can enter the tablet core and becomes detrimental to the final product stability. In an effort to mitigate the impact of downstream processing and final tablet water, alternative seal coats for the pellets were investigated.

While hypromellose-based coatings are prevalent in the pharmaceutical industry, an alternative polymer coating material

Table III. Fixed Dose Combination Tablets with Alternative Input Pellets

Tablet ingredient	Pellet Tab-3 (mg/tablet)	Pellet Tab-4 (mg/tablet)	Pellet Tab-Op2 (mg/tablet)	Pellet Tab-OpAMB (mg/tablet)
Pellets-0%[a]	48.7	–	–	–
Pellets-1.3%[a]	–	49.3	–	–
Opadry II pellets[a]	–	–	53.7	–
Opadry AMB pellets[a]	–	–	–	53.7
Metformin granule[b]	1,075	1,074.4	1,070	1,070
Microcrystalline cellulose	231.3	231.3	231.3	231.3
Magnesium stearate	5	5	5	5
Total tablet weight (mg)	1,360	1,360	1,360	1,360

[a] The dose for the model DPP-IV inhibitor is 15 mg free base (or 22 mg including the salt)
[b] The metformin hydrochloride dose is 1,000 mg

Table IV. Alternative DPP-IV Inhibitor Drug Layered Pellet Formulations

Ingredient	Pellets-0% (% w/w)	Pellets-1.3% (% w/w)	Opadry II pellets (% w/w)	Opadry AMB pellets (% w/w)
Pellet base				
Microcrystalline cellulose sphere	51.2	50.6	46.1	46.1
Drug layer				
DPP-IV inhibitor[a]	45.0	44.4	40.5	40.5
Hypromellose	3.8	3.7	3.4	3.4
Seal coat				
Hypromellose	–	1.3	2.65	2.65
Opadry II	–	–	7.35	–
Opadry AMB	–	–	–	7.35
Total	100	100	100	100

[a] API median particle size is 2 μm. The potency of the pellets is 30.76% and 30.37% for Pellets-0% and Pellets-1.3%, respectively. The potency is 27.9% for both Opadry II pellets and Opadry AMB pellets

is partially hydrolyzed polyvinyl alcohol (PVA). PVA-based coatings have been reported to have a lower water transmission rates and are sold as a formulated product called Opadry® II (12). In addition, there is a special formulation of Opadry® II, which provides an additional level of moisture protection sold as Opadry® AMB (12,13). Opadry® AMB has additional proprietary excipients which result in additional water protection. It is known that additives to PVA tablet coatings can reduce the water vapor diffusivity (14). A key factor when using water barriers is to ensure that water is not trapped inside the coating during processing; therefore, appropriate coating conditions must be selected to reduce water ingress. To investigate alternative seal coats on the pellets, the standard pellet formulation with 2.65% (w/w) hypromellose seal coat was further coated with either a 7.35% (w/w) Opadry® II or Opadry® AMB moisture barrier coat. These pellets were progressed through the same downstream operations of blending and tableting. The formulations were labeled as Pellet Tab-Op2 and Pellet Tab-OpAMB, respectively, and are shown in Tables III and IV. Finally, the batches were tablet coated with appropriate processing conditions to achieve two different final product water levels to better elucidate the impact of final tablet water content on the chemical stability when using drug layered pellet moisture barriers. In this example, we used a low tablet water content of ~1.4% instead of 1.0% because the coating parameters required to achieve a 1.0% tablet water content led to significant spray drying of the coating polymers and poor coat quality with small-scale coating equipment. This was another reason to use moisture barriers to allow for "wetter" coating conditions to ensure an optimal final tablet coat quality. The chemical stability results for the DDP-IV inhibitor are shown in Fig. 9 with the standard pellet formulation (Pellet Tab-1) at similar final tablet water content as a basis for comparison.

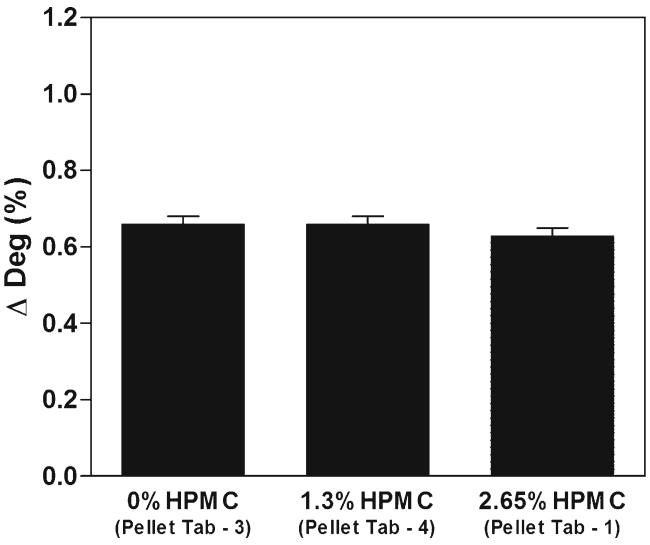

Fig. 8. The percent change in DPP-IV inhibitor degradation for three prototype fixed dose combination formulations are shown, Pellet Tab-3, -4, and -1. The % HPMC refers to the level of hypromellose seal coat on the pellets. The final product water content for all of the formulations was 1.1%. The formulations were stored for 2 weeks at 50°C/ambient RH in an induction-sealed 45-cc HDPE bottle with 0.5 g of desiccant

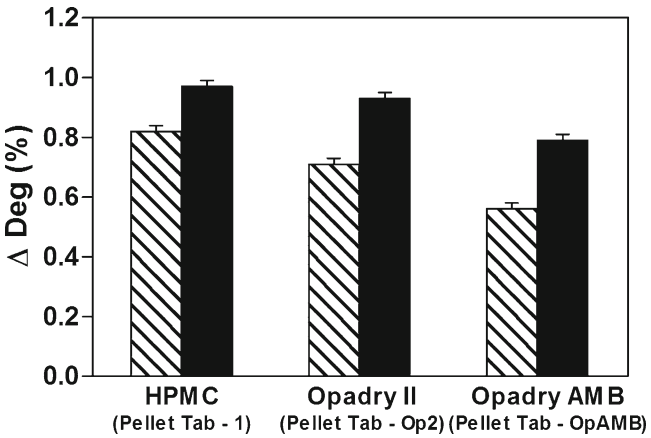

Fig. 9. The percent change in DPP-IV inhibitor degradation for three prototype fixed dose combination formulations are shown, Pellet Tab-1, -Op2, and -OpAMB, with the coating type used as the seal coat shown on the *x*-axis. The formulations were stored for 2 weeks at 50°C/ambient RH in an induction-sealed 45-cc HDPE bottle with 0.5 g of desiccant. *Dashed bars* are dry tablets (1.3–1.5% initial water content) and *solid bars* are wet tablets (1.9–2.0% initial water content)

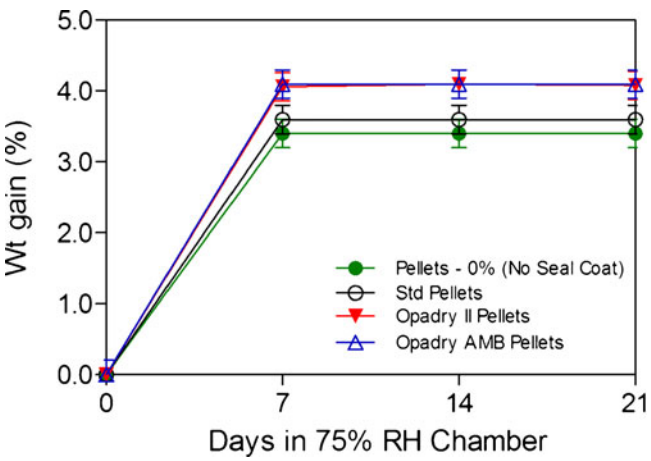

Fig. 10. The percent weight gain of four pellet formulations are shown when stored in an ambient temperature/75% relative humidity chamber for 21 days

Upon initial evaluation of the results in Fig. 9, there appears to be a clear trend as the moisture protection capability of the seal coat improves, the chemical stability improves for both "wet" and "dry" tablets. While this is consistent with the purpose of additional coatings, the sensitivity to tablet water content actually increases. The difference between the change in degradation for "wet" and "dry" tablets is 0.15% for the hypromellose seal coat but 0.22% and 0.23% for the Opadry® II and Opadry® AMB, respectively. Perhaps, this could be explained by the fact that at very low water content in the drug layered pellets, water is truly the rate-limiting step to degradation; however, as the water content increases above a certain threshold value, other factors also make significant contribution to the final degradation rate.

To further understand the mechanism of moisture protection of the various moisture barriers and seal coats, a moisture absorption study was performed by placing the coated pellets in a 75% relative humidity chamber and measuring the waters uptake *via* weight gain over time. The pellets at each stage of the coating process were investigated including (1) pellets coated with the drug layer only (Pellets-0%); (2) pellets with both the drug layer and the 2.65% hypromellose seal coat (Std Pellets); (3) pellets with the drug layer, 2.65% hypromellose seal coat, and 7.35% Opadry® II coating (Opadry II Pellets); and (4) pellets with the drug layer, 2.65% hypromellose seal coat, and 7.35% Opadry® AMB moisture barrier (Opadry AMB Pellets). The pellet formulations are shown in Tables II and IV, and the moisture uptake data is shown in Fig. 10.

All of the pellets appear to reach an equilibrium water content after 7 days, and interestingly, the pellets coated with only the drug layer had the lowest weight gain. The hypromellose coated pellets (Std Pellets) absorbed slightly more water than the drug coated pellets (Pellets-0%), and both Opadry® coated pellets absorbed the most water. An explanation for this result is simply the hygroscopicity of the exposed surface of the pellets. The drug substance itself is not hygroscopic, while hypromellose and partially hydrolyzed PVA are known to be hygroscopic, with PVA being the most hygroscopic and can retain as much as 9% water at ambient conditions (15). While this data was generated in a high moisture level environment (75% RH) in contrast to the relatively low water content of the tablet core (water content 1–2%), it does provide insight into the mechanism of moisture barrier protection of the Opadry® coatings when combined with the chemical stability data for the final product. The Opadry® AMB and Opadry® II coated pellets show similar absorption properties at high water content, suggesting that the partially hydrolyzed polyvinyl alcohol is the key ingredient in the coating, with the additional proprietary excipients in the AMB formulation possibly enhancing the stability at low water contents. The mechanism by which PVA-based Opadry® coating (AMB and II) act as a moisture barrier appears to be absorption of water followed by entrapment of the water by hydrogen bonding, preventing subsequent water penetration into the pellet core. This phenomenon is similar to the initial phase of water ingress that occurs with high molecular weight HPMC-based matrix tablets where water uptake occurs first by capillary action, then the porous channels are rapidly blocked by HPMC swelling and the newly formed swollen HPMC gel layer will act as a diffusion barrier (16). Therefore, a certain amount of water needs to enter the PVA-based film before closure of the porous network occurs. PVA has such a high density of hydrophilic alcohol groups that it can easily form hydrogen bonds with the penetrating water and therefore the water is referred to as "bound water" (17). While PVA may not form a true gel like hypromellose, water is neither a good solvent nor a theta solvent for PVA and it tends to form a swollen pseudo-micelle at higher molecular weights that can block moisture ingress (15). Thus, the bound water in Opadry® AMB and Opadry® II prevents further water migration deeper into the pellet, while for hypromellose and drug coated pellets moisture ingress can be rapid and migrate deeper into the pellets creating more potential for chemical instability of the DPP-IV inhibitor.

The true value of the moisture barrier seal coats must be balanced by the additional processing time; however, this study has shown that it is possible to reduce the degradation of the DDP-IV with moisture barriers. Process analytical tools utilized during the tablet coating process may allow appropriate monitoring and control of tablet water content to be precise enough to ensure appropriate stability of the final product.

CONCLUSION

The results of this study have shown a unique stability enhancement when the DPP-IV inhibitor was formulated as drug layered pellets in a fixed dose combination product with metformin hydrochloride. While the exact mechanism of stability enhancement has not been elucidated at a molecular level, the pellet coating process is able to reduce cyclization of the nitrile and amine group on the molecule. The stability enhancement of drug layered pellets goes beyond a simple reduction in moisture and preventing direct physical contact with other tablet components and suggests that the DDP-IV inhibitor molecule adopts a more favorable conformation which reduces degradation. In addition, an understanding of the impact of moisture barrier coatings has been established and can provide additional stability enhancement for moisture-sensitive drug substances.

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