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Tabletability assessment of conventional formulations containing Vitamin E tocopheryl polyethylene glycol succinate

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ABSTRACT

Vitamin E tocopheryl polyethylene glycol succinate (TPGS) is known to enhance the bioavailability of poorly water-soluble drugs via solubility and permeability enhancement. Few studies have evaluated feasibility of formulating TPGS in conventional solid dosage forms such as tablets due to processing challenges resulting from its waxy nature and low melting point (~37 °C). The objective of this study is to systematically investigate the tabletability of conventional high shear wet granulation (WG) formulations incorporated with Vitamin E TPGS. Impact of critical formulation variables such as levels of TPGS, hydroxypropyl cellulose (binder) and Prosolv (extragranular filler) on product quality attributes was studied using a full factorial experimental design. The potential influence of temperature elevation during processing was assessed through a heated die fitted onto a compaction simulator. Bilayer tabletability of the TPGS formulation was also assessed in combination with a secondary non-TPGS formulation. TPGS levels significantly impacted tensile strength (TS), disintegration time and dissolution. Heat sensitivity studies indicated that TS reduction upon exposure to heat was minimized by higher levels of extragranular fillers. Acceptable interfacial strength of bilayer tablets was achieved and tablets could be coated without the need for hydroalcoholic solutions. The study demonstrates preliminary feasibility to develop monolithic and bilayer coated tablet formulations containing up to 10% (w/w) TPGS for the given compound and drug load. Further studies are required to validate these findings at larger scales.

1. Introduction

According to a recent report (Junghanns and Müller, 2008), the number of poorly water-soluble drugs and drug candidates is steadily increasing over the last 10 years. About 40% of the drugs in the pipeline and up to 60% of molecules coming from synthesis have solubility issues and consequently poor oral bioavailability and delivery problems, which poses a significant challenge to the development of these compounds. Surfactants have historically been used for enhancing solubility and bioavailability of lipophilic compounds. Vitamin E d-alpha tocopheryl polyethylene glycol succinate (Vitamin E TPGS), a nonionic surfactant, has been reported to increase the bioavailability of poorly water-soluble drugs by enhancing solubility and permeability (Sokol et al., 1991; Dintaman and Silverman, 1999; Yu et al., 1999; Wacher et al., 2002; Varma and Panchagnula, 2005; Ho et al., 2008). In a clinical study, Sokol et al. (1991) showed that Vitamin E TPGS can enhance the absorption of the highly lipophilic drug cyclosporine, leading to 40–72% reduction in the cyclosporine dosage which was required to maintain therapeutic plasma concentrations. The enhancement of cyclosporine bioavailability was explained based on the formation of micelles and p-glycoprotein (P-gp) inhibition by TPGS (Sokol et al., 1991; Dintaman and Silverman, 1999). Yu's study demonstrated that without TPGS there was no absorption of amprenavir in dogs, while 69% was absorbed in a 20% TPGS formulation by inhibiting P-gp (Yu et al., 1999). Several studies of paclitaxel have indicated that TPGS enhanced the bioavailability of paclitaxel in vivo resulting from increased solubility and permeability (Varma and Panchagnula, 2005; Ho et al., 2008). For the active pharmaceutical ingredient (MK-A) used in the current study, plasma exposures were doubled in a dog model with the use of Vitamin E TPGS. The aqueous solubility of MK-A is low at <0.15 mg/ml at room temperature.

The application of TPGS to improve the bioavailability of poorly water-soluble drugs has been investigated for over 20 years. However, formulating with Vitamin E TPGS has been mainly focused on solid dispersions (Shin and Kim, 2003; Sethia and Squillante, 2004; Goddeeris et al., 2008), emulsions and nano-delivery systems (Mu and Feng, 2003a,b; Ke et al., 2005; Zhang and Feng,

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2006; Zhang et al., 2007; Feng et al., 2007, 2009; Pan and Feng, 2008). Very few studies have evaluated conventional solid dosage forms such as tablets containing TPGS. In the few studies that have been reported in this area, TPGS was used as a melt binder (Wu et al., 2003; Yuan and Clipse, 2004; Yuan et al., 2006). These studies concluded that 2–10% of TPGS could be used as a melt binder/lubricant in the granulation and tableting process (Wu et al., 2003). No studies have been reported on the tabletability of drugs incorporated with TPGS through conventional wet granulation process. To our knowledge, this is the first study to explore this space. The wet granulation process using an aqueous solution of Vitamin E TPGS is also made more challenging by the rheological behavior of aqueous solutions in that these solutions exhibit gelation at ~23% (w/w) and hence aqueous TPGS solutions used as granulating fluids are limited to a concentration of ~20% (w/w). Though, higher solution concentrations leading to higher TPGS levels can be achieved using hydroalcoholic solutions, this is not a desirable route from an environmental standpoint and also the downstream issues are exacerbated by the higher TPGS levels.

Post-wet granulation process steps such as milling, tableting and coating are energy intensive processes and pose a significant challenge due to the waxy, low melting (~37 °C) nature of TPGS. Studies have reported that tableting difficulties, such as sticking and picking, tablet softening or even localized melting may occur for materials with low melting points (Danjo et al., 1993). Furthermore, the waxy nature of TPGS can compromise the mechanical properties of the tablets. The objective of the current study is to systematically investigate the tabletability of conventional high shear wet granulation formulations incorporated with Vitamin E TPGS. The study consists of evaluating tabletability at room temperature using a multivariate design of experiments, evaluating the impact of temperature using a heated die fitted to a compaction simulator, potential for bilayer tabletability with a secondary non-TPGS formulation and evaluating feasibility of coating the TPGS laden tablets.

2. Materials and methods

2.1. Materials

Vitamin E TPGS was obtained from Eastman Chemical Company (Kingsport, TN). Microcrystalline cellulose (Avicel PH101 and PH102) and Croscarmellose sodium (CCNa) were obtained from FMC Biopolymer. Lactose monohydrate-312 from Foremost farms, hydroxypropyl cellulose (HPC) – Klucel EXF from Hercules Inc., magnesium stearate (MgStr) from Mallinckrodt Chemical Inc. and silicified microcrystalline cellulose – Prosolv 50 and Prosolv 90 from FMC were other excipients used. Active compounds, MK-A and MK-B were internal Merck compounds.

2.2. Methods

2.2.1. Tablet preparation methodology

The exploratory small scale batches differed from the DOE and scale up batches in the equipment used due to the different batch sizes. However, the experimental procedure was very similar. All the components in the formulation except the extragranular (EG) filler and the lubricant were added to the granulator bowl (BMG or Diosna P1-6) and dry mixed for 3 min. A 20% (w/w) TPGS solution was prepared by dissolving TPGS in USP water using a lightnin® mixer. Required amount of this solution was added (drop wise or sprayed depending on the granulator set up) to the dry mixture. The granulation was dried in the oven at 30 °C for 20 h. The dried granules were screened using a 750 μm sieve or a Quadro Comil; medium (50G screen/1000 rpm) and blended with extragranular fillers for 10 min, followed by the lubricant, magnesium stearate for 3 min using either a Turbula blender (Type T2f) or a V-shell blender (PK blendmaster, model B, East Stroudsburgh, PA). It has to be noted that Avicel PH101 was used as the intragranular filler for all formulations. Avicel PH102 was used as the extragranular filler, where specified. The blend was then compressed on a Carver press (Carver Inc., Wabash, IN) or Korsch XP-1 and Korsch XL-100 tablet presses (Korsch, Germany) with a target weight of 450 mg.

2.2.2. Particle sizing

The particle size distributions (PSDs) of the granules were determined by a laser diffraction particle size analyzer HELOS (Sympatec Inc., Germany) equipped with dry disperser RODOS/L with vibratory feeder VIBRI. A preliminary study showed that an air pressure of 0.5 bars was sufficient to disperse granules with minimal particle attrition. So an air pressure of 0.5 bars and a feed rate of 40% were used for all analyses.

2.2.3. Flowability measurement

The flowability of granules was measured using a Flodex™ flowability tester (Hanson research, CA). This method relies on the principle of 'flow through an orifice'. The Flodex number assigned to a powder or granulation is the diameter in millimeters of the smallest orifice through which the sample falls freely three consecutive times. Thirty grams of granules was charged into the apparatus from a hopper. Approximately 30 s after loading, the lever was gently released and the powder flow observed. If powder flow was observed to be poor such that the orifice remained obstructed after powder flow occurred, then the test was repeated using a disc with a larger orifice. The minimum orifice diameter was recorded upon three successful runs.

2.2.4. Tensile strength

The tensile strength of flat faced tablets was calculated using the following equation and a modified version of this equation was used for round biconvex tablets:

$$\sigma = \frac{2F}{\pi DT}$$

In the equation, σ is the tensile strength (MPa), F is the breaking force (N), D is the tablet diameter (m) and T is the thickness of tablet (m) (Fell and Newton, 1970). The diameter and the thickness of the tablet were determined by a micrometer (Mitutoyo digimatic indicator IDF-1030E). The breaking force of the tablet was measured using a Key hardness tester (HT-300S).

2.2.5. Friability

The friability of tablets was measured using a USP Friability Tester (Vankel model 45-2100). About 6.5 grams of tablets were carefully dedusted before the test. The tablets were accurately weighed, loaded into the drums and then subjected to the friability test. After 200 revolutions, any chipped material or powder was removed and the tablets were re-weighed. The weight loss was recorded. The process was repeated and the friability was calculated as percent weight loss with respect to the initial weight after 400 revolutions.

2.2.6. Sticking evaluation

A set of embossed, round concave 13/32″ tooling was used to evaluate tablet sticking. The punch faces of clean tooling were imaged using a Nikon E4100 optical microscope. Formulations with different levels of magnesium stearate were compressed on Korsch XP-1 single station tablet press. After 150 compaction events, the punch faces and the tablets were imaged using the

microscope and conclusions regarding sticking tendency were drawn.

2.2.7. Disintegration

The disintegration testing of tablets was conducted in Varian VK 100 Automated Disintegration Apparatus (Varian Inc., Palo Alto, CA). Simulated gastric fluid (SGF, without enzymes) was used as the disintegration medium. Nine hundred milliliter of SGF solution was heated to 37 °C and disintegration time was recorded.

2.2.8. Dissolution

Dissolution testing was performed using USP II apparatus (Varian Inc., Palo Alto, CA) with a paddle speed of 75 rpm. The dissolution media consisted of 900 ml of 0.5% SDS maintained at 37 ± 1 °C. Samples were withdrawn from the dissolution vessels at time intervals of 15 min, 30 min, 45 min and 60 min and were analyzed with a reverse phase HPLC method using a Waters Xterra RP18 column (4.6 mm × 50 mm ID, 3.5 μm) with an SDS scavenger guard column. The mobile phase consisted of 0.1% phosphoric acid/acetonitrile (67/33) and the compound was detected by UV at 220 nm.

2.2.9. Heat sensitivity studies

A set of 10/32″ round flat-faced tooling was used for compaction simulation. The die fitted onto the ESH compaction simulator (Huxley Bertram, Cambridge, UK) was externally heated to a target temperature of 35 °C and 45 °C using a temperature controller (Betta tech controls, model CU400-RS232). This was done to simulate temperature elevation that occurs during compression on a high speed press. About 300 mg of granulation was compressed and tablet weight, dimensions and breaking force were measured. Also, tolerability of the TPGS tablets to higher temperatures was evaluated by subjecting the tablets (both placebo and MK-A) in an oven to a temperature of 45 °C for 5 h to understand impact on physical integrity during the coating process. The tablets were imaged before and after the study using an optical microscope.

2.2.10. Bilayer tabletability study

Two formulations were used to make bilayer tablets. The bottom layer contained MK-A and 6% TPGS while the top layer contained a non-TPGS wet granulated formulation of MK-B. The bilayer tablets were compressed using the compaction simulator with the first layer compression pressure fixed at about 5 MPa. The tablet weight ratios of two formulations were 30:70, 50:50 and 70:30 respectively. The forces required to shear the bilayer tablets apart were measured using a tablet hardness tester retrofitted for bilayer tablets.

2.2.11. Scale up

Two formulations with batch size of 1 kg were compacted on a Korsch XL 100 rotary press for tabletability evaluation. One was placebo with 9% TPGS. The other one was MK-A with 10% TPGS. Standard round concave, 13/32′. tooling was used to achieve a target tablet weight of 450 mg. The press speed was 20 rpm and the compression pressure was ~200 MPa.

2.2.12. Tablet coating

Film-coating was done in a Vector pan coater with Opadry II suspension (15%, w/w). Inlet temperature was modulated to result in an exhaust temperature of ~38.0 °C. The pan speed was maintained at 20 rpm and the atomization pressure was set at 20.0 psi. Weight of 10 tablets was measured before and during the coating process at different intervals. The process was stopped when a target weight gain of 3% (w/w) was achieved.

3. Results and discussion

3.1. Understanding critical formulation factors and selection of DOE variables

As discussed in previous sections, tabletability of conventional TPGS formulations is inherently challenging. Additionally, the model API (MK-A) used in the current study had very poor compaction properties and the neat API tablets delaminated at all compression pressures tested. This resulted in further significant challenges towards development of tablet formulations. TPGS was chosen as one of the factors in the DOE. The presence of Vitamin E TPGS presents two major complications in the tablet development process. As mentioned previously, the low melting nature can present challenges due to the potential for localized melting during energy intensive processes such as milling, compaction, etc. Secondly, there exists an inverse correlation between the level of TPGS in the formulation and the tensile strength of the tablet. TPGS imparts plasticity to the formulation and reduces tensile strength significantly. This is strongly supported by preliminary data as well as results of the DOE in the current study. Hence when designing TPGS formulations, low tensile strength can be a critical factor that needs to be addressed. One possible approach to potentially increase tensile strength would be to increase the level of binder. Hence, HPC level was chosen as the second factor in the DOE. Preliminary studies also revealed that the disintegration of TPGS tablets was significantly slow due to potential gelation in the media. Disintegration time of tablets containing 3% intragranular Croscarmellose Na was much longer than 1 h. The disintegration testing was stopped at 1 h at which point 40–50% of the tablet was yet to be disintegrated. Even with the addition of extragranular CCNa, disintegration times were still longer than desired at ~30 min. Inclusion of an extragranular filler was hypothesized to have a three pronged effect. Firstly, it was expected that presence of EG filler would interfere with the gelation and provide rapid disintegration. Additionally, it was hypothesized to provide a 'shielding effect' to TPGS against elevated temperatures and lastly, the EG filler was also expected to increase tensile strength via greater bonding. Before including extragranular filler as one of the design factors, preliminary studies were conducted wherein three types of fillers were evaluated based on there relative ability to enhance tablet tensile strength and facilitate disintegration (Table 1).

Three EG fillers, Avicel PH102, Prosolv 50 (silicified microcrystalline cellulose) and Prosolv 90 were compared. The tensile strength of tablets with Prosolv 50 (2.37 ± 0.05 MPa) and Prosolv 90 (2.26 ± 0.12 MPa) was significantly higher than Avicel PH102 (1.93 ± 0.13 MPa). With the addition of EG fillers, the disintegration time was significantly reduced to about 15 min. Prosolv 90 has an average particle size of 110 μm, whereas Prosolv 50 has average

Table 1
Selection of extragranular filler based on tablet tensile strength and disintegration.

Compression pressure (MPa)	EG component (30%)	Tensile strength (MPa)	Disintegration time (min)
200	Prosolv 90	2.26 ± 0.12	16.5
200	Prosolv 50	2.37 ± 0.05	13.5
200	Avicel pH102	1.93 ± 0.13	15.5

Table 2
A three factor, full factorial design.

Run	Factor A, TPGS (%, w/w)	Factor B, HPC	Factor C, extragranular Prosolv (%, w/w)	GFL (%)
1	6	5	30	50.0
2	6	5	0	58.3
3	4	4	15	55.5
4	2	3	0	58.3
5	4	4	15	55.5
6	2	3	30	55.5
7	6	3	30	55.5
8	2	5	30	52.8
9	6	3	0	58.3
10	2	5	0	58.3

particle size of 60 μm. The mean particle size of the DOE granulations ranged from 120 μm to 280 μm. Prosolv 90 was selected over Prosolv 50 due to relatively low susceptibility to segregation issues.

3.2. Results from the DOE

Based on the preliminary screening, the factors that were included in the DOE were (1) level of TPGS, (2) level of the binder, HPC-EXF and (3) level of extragranular filler, Prosolv 90. A three factor full factorial experimental design with two mid point replicates was used (Table 2). The granulation fluid (GFL) levels in Table 2 represent a sum total of the TPGS solution and additional free water required to reach granulation end point. The response factors that were studied included granule flow, tensile strength (TS), friability, tablet disintegration and dissolution.

The readouts on the various response factors (flowability, friability, tensile strength, disintegration and dissolution) from the DOE are tabulated in Table 3. The flow of all 10 granulations was in the 14–18 flodex range indicating good flow properties. The friability of the tablets was expected to be low due to the plasticity imparted by TPGS. The results indicate that the maximum friability was 0.18% after 400 revolutions which is very low. Tensile strength of the formulations ranged from 1.64 MPa to 2.58 MPa. The requirement on tensile strength is less stringent for tablets with low friability resulting from formulations that tend to exhibit higher levels of plasticity. For all the DOE runs, except #2 and #9 which had the highest level of TPGS in the design and no extragranular Prosolv, the disintegration time was less than 15 min and 100% drug release was achieved within 30 min for all the runs. Hence, percent drug released in 15 min (Q15) was chosen to perform statistical analysis since there was good differentiation at this time point.

A statistical analysis of the DOE results suggests that all three independent variables have significant impact on one or more of the response factors. Tensile strength, disintegration and dissolution were key response factors that were of primary interest. TPGS levels are most critical in that they significantly impact all three of these response factors. Higher levels of TPGS resulted in a decrease in tensile strength and a slow down in tablet disintegration and dissolution. Interestingly, binder levels had no significant impact on tablet tensile strength. Though impact of extragranular filler, Prosolv 90 on tablet tensile strength was not statistically significant over the entire design space, there was a significant increase in tensile strength ($p < 0.01$) with inclusion of Prosolv at the higher TPGS level of 6% (w/w). This is in agreement with the pre-DOE data. Binder level, however, significantly slowed down disintegration and dissolution and Prosolv levels significantly accelerated tablet disintegration as hypothesized earlier. Fig. 1 depicts Pareto charts for tensile strength, disintegration and dissolution. The top horizontal line is the cut off for statistically significant effect and A, B and C are TPGS levels, HPC levels and extragranular Prosolv levels respectively with the combinations of these being interactions i.e., AC is the interaction of TPGS levels and extragranular Prosolv levels. It is interesting to note from the results in Fig. 1 that though extragranular Prosolv had a statistically significant impact on tablet disintegration, its effect on dissolution was not statistically significant. In addition when considering the entire DOE there is not a strong correlation between disintegration time and percent drug dissolved. This discrepancy arises from an interesting phenomenon taking place in special scenarios with higher levels of TPGS and extragranular Prosolv. For DOE runs 1 and 7 where we have 6% TPGS and 30% extragranular Prosolv, the higher Prosolv levels result in rapid tablet disintegration. However, due to the higher levels of TPGS, drug dissolution from the granular level is still slow due to the gelation at the granular level. Fig. 2 shows correlation plots between disintegration time and percent drug dissolved (Q15) for the entire DOE (3a) and for the DOE with runs no. 1 and 7 excluded (3b). The r^2 value for the latter scenario is much higher at 0.98 compared to 0.67 for the former scenario, thus further illustrating the hypothesis.

3.3. Lubrication optimization and lubricating effect of TPGS

The sticking of formulation to punch faces during tablet production is a significant concern and the condition exacerbates with the presence of engravings on the tooling surface. Several papers have studied this phenomenon with conventional formulations

Table 3
Flow, friability, tensile strength, disintegration and dissolution data for the DOE runs.

DOE run number	Flodex number	% Friability (400 rev)	Tensile strength (MPa, mean ± SD)	Disintegration time (min, mean ± SD)	Dissolution Q15 (% dissolved in 15 min)
1	16	0.16	1.87 ± 0.15	13.67 ± 0.55	58.8
2	14	0.14	1.66 ± 0.12	27.28 ± 0.08	59.6
3	16	0.10	2.02 ± 0.11	13.37 ± 0.16	78.6
4	14	0.11	2.58 ± 0.20	02.87 ± 0.25	98.6
5	16	0.14	1.99 ± 0.11	14.42 ± 0.13	75.6
6	16	0.15	2.57 ± 0.05	05.41 ± 0.04	95.1
7	14	0.18	1.82 ± 0.12	11.80 ± 0.54	70.0
8	14	0.15	2.37 ± 0.04	08.98 ± 0.45	86.6
9	18	0.08	1.64 ± 0.09	18.43 ± 0.12	71.6
10	14	0.12	2.41 ± 0.05	11.25 ± 0.05	85.0

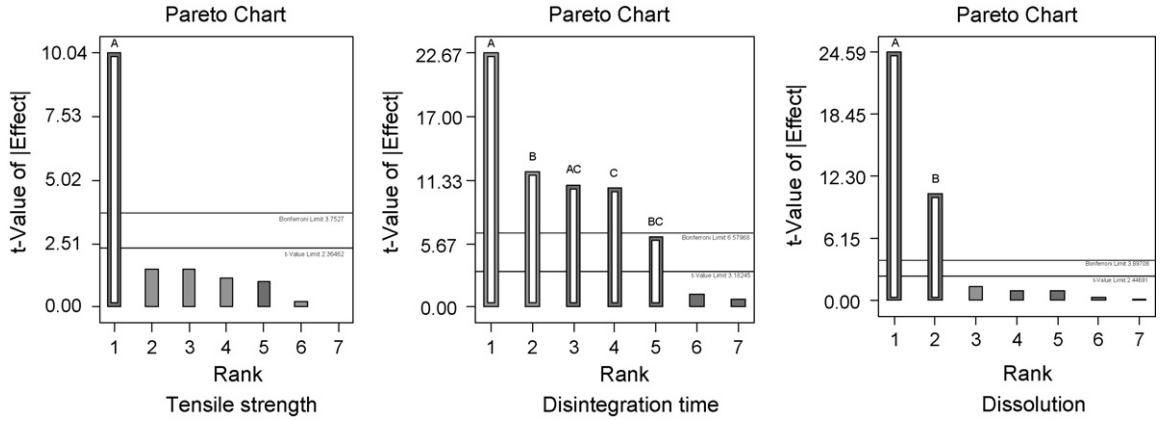

Fig. 1. Pareto charts for tensile strength, disintegration and dissolution.

and instrumented upper punches by measuring adhesion forces (Waimer et al., 1999a,b; Roberts et al., 2004). Though, with the presence of a waxy material such as TPGS, one can expect some lubricating capacity which generally mitigates the sticking effects; it is not clear whether a potential localized melt of TPGS can exacerbate this effect in which case need for traditional lubricants such as magnesium stearate can be critical. As noted in previous sections, the application of Vitamin E TPGS is in the enhancement of wetting and dissolution of poorly soluble drugs. Since these compounds are intrinsically lipophilic, attention must be given to the amounts of hydrophobic lubricants that can potentially adversely impact dissolution. Also, since higher levels of magnesium stearate can adversely impact tensile strength and since TPGS is also shown to have a negative impact on tensile strength, an unoptimized combination of the two can result in tablets with inferior mechanical properties.

Optimization of external lubricant (magnesium stearate) levels was conducted as a result of early indications of sticking from preliminary studies. Typically sticking issues result from the adhesion forces generated between the API and the punch surface. For the placebo tablets containing 10% (w/w) TPGS and 0.75% magnesium stearate, there was no significant sticking on the punch and no obvious defects on the scoring of tablet were observed after a diagnostic test. This diagnostic test involves using an optical microscope to image the surface of a scored tooling before and after ~150 compaction events at ~200 MPa compression pressure (Fig. 3). For MK-A tablets (40% DL) with 4% TPGS and 0.75% MgStr, significant in filling of the scoring on punch surface was seen. The resulting tablets also had defects indicating a sticking issue. In order to alleviate the sticking problem, the level of MgStr was increased to 1.5%. This alleviated the sticking issue without a considerable drop in tensile strength and disintegration time of tablets was unchanged. The potential lubricating effect of TPGS was evaluated on a compaction simulator where the ejection forces were monitored as a function of TPGS levels. Formulations with 40% MK-A and no external lubrication (i.e., magnesium stearate) and with increasing levels of TPGS (2%, 6% and 10%) were tested for ejection forces. As shown in Fig. 4, ejection forces for the 2% TPGS formulation at a modest compression pressure of 100 MPa were very high at >1000 N and the simulator was unable to eject the tablets. However with both the 6% and 10% TPGS formulations, ejection forces dropped significantly to ~250 N thus clearly illustrating the lubricative properties of Vitamin E TPGS. Hence, when optimizing lubricant levels for TPGS formulations, drug levels, TPGS levels and external lubricant levels must be taken into account. For formulations containing high TPGS levels, relatively low external lubrication should be sufficient.

3.4. Heat sensitivity assessment

It is widely known that there is significant increase in press temperatures during production mainly resulting from frictional forces. This increase in press temperature can translate into a rise in tablet temperature, the extent of which is dependent on material composition, compression pressure and the use of lubricant. The susceptibility of TPGS formulations to increase in press temperatures was studied using a compaction simulator wherein the die was heated to controlled conditions using an external temperature controller. Impact of 10 °C increments in die temperature on tablet tensile strength was evaluated. Fig. 5 shows compaction profile of 6% TPGS formulations at 25 °C, 35 °C and 45 °C temperatures. It is clearly evident that the tensile strength of the formulation decreases as the die temperature increases from 25–35 °C to 45 °C. This downward trend in tensile strength with an increase in temperature clearly illustrates that there is softening of the tablet matrix at temperatures that are close to or higher than the TPGS melting point (~37 °C). At a macroscopic level there are no signs of

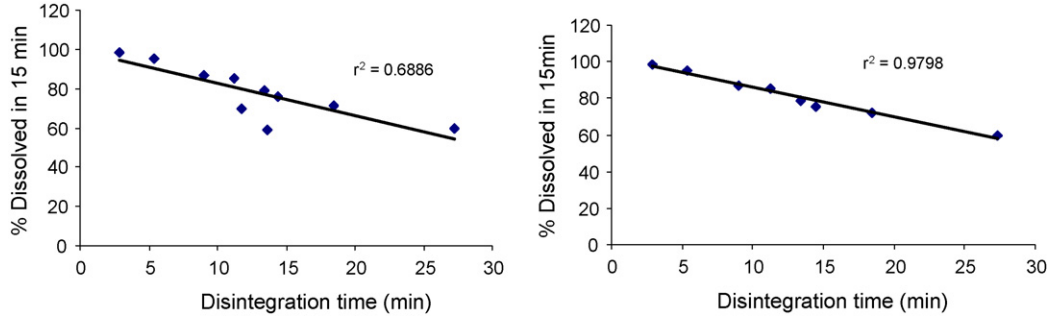

Fig. 2. Correlation plots between disintegration and dissolution, (a) complete DOE; (b) DOE excluding runs 1 and 7 (high TPGS and extragranular Prosolv).

Fig. 3. Sticking assessment of placebo and MK-A tablets with TPGS. (A) Punch image post-compaction of placebo tablets with 10% TPGS and 0.75% MgStr; (B) Placebo tablet with 10% TPGS and 0.75% MgStr; (C) Punch surface post-compaction of MK-A tablets with 4% TPGS and 0.75% MgStr; (D) MK-A tablet with 4% TPGS and 0.75% MgStr; (E) Punch surface post-compaction of MK-A tablets with 4% TPGS and 1.5% MgStr; (F) MK-A tablet with 4% TPGS and 1.5% MgStr.

physical failure of the tablets. However at a microscopic level one can anticipate localized softening or melting of the TPGS. This is further supported by some additional data where the tablet tensile strength is partially regained after equilibration to room temperature. For formulations with 4% TPGS and 15% EG Prosolv 90 (DOE #3) that were compacted at 45 °C, there was a 13% increase in TS after 48 h of re-equilibration. This data suggests that post-ejection resolidification of TPGS results in a regain of tablet tensile strength.

As mentioned previously, one of the expected applications of the extragranular component was in providing a 'shielding effect' to TPGS against the high temperatures. As discussed above, since the higher temperatures resulted in tensile strength reduction due to softening/melting of TPGS, the role of extragranular Prosolv in this regard was assessed by measuring the TS reduction across a range of formulations with different extragranular Prosolv levels.

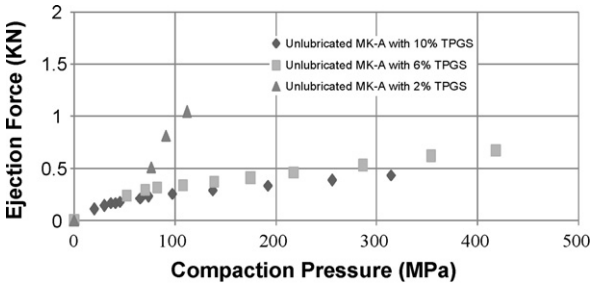

Fig. 4. Lubricating effect of TPGS.

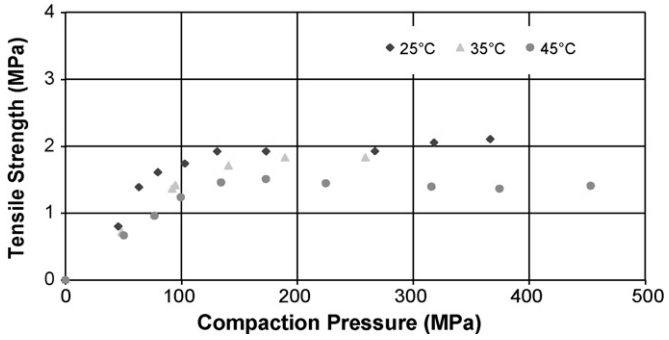

Fig. 5. Compaction profiles of MK-A tablets with 6% TPGS at 25 °C, 35 °C and 45 °C.

As shown in Fig. 6, for DOE #9 with 6% TPGS and no extragtranular Prosolv the TS reduction from 25 °C to 45 °C was 21.7% and for a placebo formulation with 9% TPGS and no extragranular Prosolv, the TS reduction was 22.5%. For 30% Prosolv formulations with 6–8% TPGS, the TS reduction is the least around 9.7% and 7.9% respectively. One anomaly is the case of DOE #3 with 4% TPGS and 15% Prosolv for which a TS reduction of 30% is observed. The TPGS levels are relatively low at 4% and the distribution of the TPGS could play a role in this case. Overall, two formulations with 30% Prosolv show ~50% less TS reduction compared to two formulations with 0% Prosolv thus supporting the proposed hypothesis of 'heat shielding' by the extragranular filler.

To further understand the thermal stability of these formulations, an oven study and a coating trial were conducted. The oven study was in fact a precursor study for the coating trial. Since tablets coated with aqueous polymeric dispersions can easily encounter coating bed temperatures of 40–45 °C which is well above the melting point of TPGS, placebo and active tablets with up to 10% TPGS were placed in the oven at 45 °C for 5 h. After the 5 h period the tablets were inspected for any defects and were imaged under an optical microscope. No significant change in tablet attributes was observed which provided evidence for the feasibility of a coating trial. 100 g of MK-A tablets containing 10% TPGS was coated using a 15% (w/w) Opadry-II coating suspension. The exhaust temperature was ~38 °C and the spray rate was ~1 g/min and a target coating

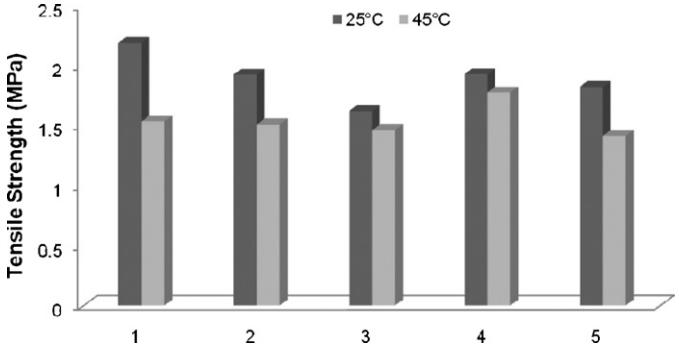

Fig. 6. Tensile strength of tablets with different formulations compacted at 25 °C and 45 °C. 1, DOE #3 (4% TPGS and 15% Prosolv 90); 2, DOE #9 (6% TPGS and 0% Prosolv 90); 3, DOE #7 (6% TPGS and 30% Prosolv 90); 4, MK-A (7.7% TPGS and 30% Prosolv 90); 5, placebo (9% TPGS and 0% Prosolv 90).

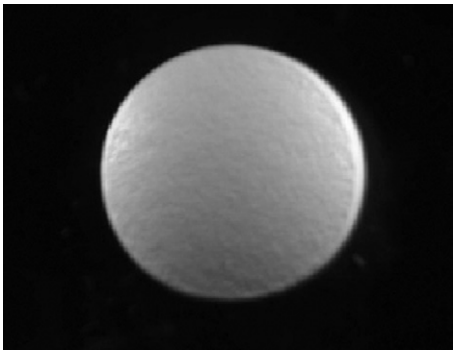

Fig. 7. Coated MK-A tablet (40% DL) containing 10% TPGS.

weight gain of 3% was achieved. No significant processing problems were observed during the coating process. The coated tablets were observed under the microscope and Fig. 7 illustrates a coated tablet with highly acceptable elegance. This suggest that formulations with up to 10% TPGS can be coated without the need for hydroalcoholic coating solutions.

3.5. Bilayer tabletability

Among many other applications, bilayer tablets have been increasingly used for both combination regimens to combine two different active compounds and also to generate multiple release profiles from different fractions of the tablet. A complete understanding of the tabletability behavior of TPGS formulations also involved feasibility of bilayer tabletability. This was assessed in combination with a non-TPGS wet granulation formulation of a different compound MK-B. Bilayer tablets are generated in a two step process where in first layer is compressed at a very low compression force to make a very low strength layer with a defined interface. The second layer is then filled onto the first lightly compressed layer and the two formulations are then compressed during a main compression event to form a bilayer tablet. The formation of a bilayer tablet with good interfacial strength is partly dependent on the optimization of the first layer compression. Fig. 8 shows a contour plot with a distribution of interfacial strength of bilayer tablets as a function of precompression force on the 1st layer (MK-A, TPGS layer) and the main compression force. A 1:1 blend of the MK-A TPGS formulation and MK-B non-TPGS formulation was used

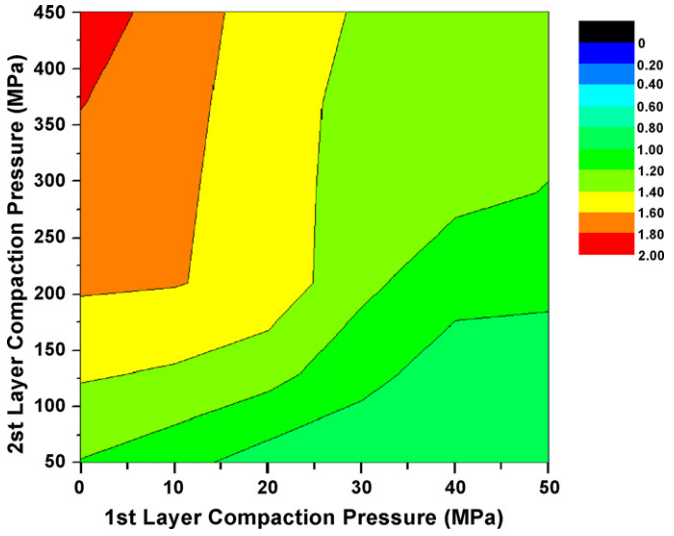

Fig. 8. Selection of 1st layer compaction pressure for bilayer tablets.

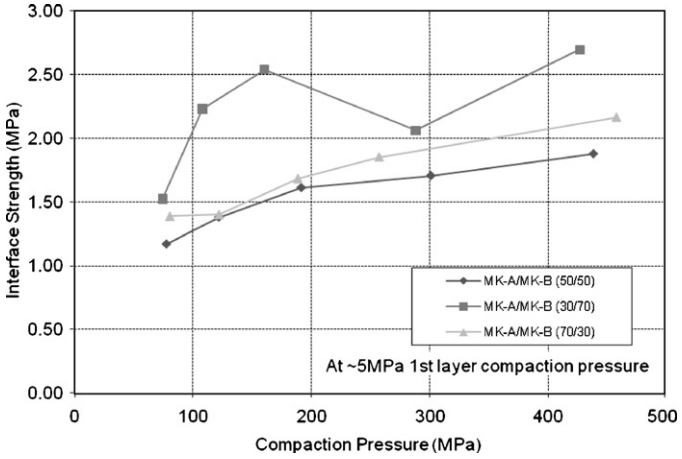

Fig. 9. Interfacial strength profiles of bilayer tablets at different interlayer ratios.

for optimizing the precompression force. As expected, the final tablet interfacial strength decreases as the first layer compression force increases though with a suboptimal first layer compression force, there is lack of interfacial definition. Specifically, for the two formulations studied, at a first layer compression pressure of less than 10 MPa and a final compression pressure of higher than 200 MPa, good interfacial strength of higher than 1.6 MPa was achieved.

Furthermore, impact of ratios of the two layers on interfacial strength was studied. As shown in Fig. 9, there is a decrease in the interfacial strength as the fraction of the TPGS formulation increased from 0.3 to 0.7. The measurement of interfacial strength of bilayer tablets is challenging primarily due to alignment of the shear planes with the interface and this could explain the scatter in the data. For all three formulations tested, interfacial strength higher than 1.5 MPa was achieved at main compression forces >200 MPa. Due to the low friability of the TPGS formulations, these interfacial strengths are considered acceptable and the data suggests preliminary feasibility for bilayer tabletability of TPGS formulations.

3.6. Scale up study

A scale up study with a moderate batch size of 1 kg was conducted with MK-A formulation containing 10% (w/w) TPGS and 40% DL on a Korsch XL100 Press. No significant issues were observed during the manufacturing process. However, temperature measurement using infrared equipment indicated that the press temperature did not exceed 40 °C. Though the current study demonstrates preliminary feasibility of tabletability of TPGS formulations, compression runs at much higher batch sizes and high press speeds need to be conducted to further understand and validate the feasibility of this process.

4. Conclusions

There are no published reports, to our knowledge, in the area of wet granulated TPGS tablet formulations. The goal of this work was to explore this space and gain preliminary understanding of this subject. The current study demonstrates preliminary feasibility of developing tablet dosage forms with TPGS wet granulation formulations for the given compound and drug load. The TPGS levels in these formulations were as high as 10% (w/w) and the results clearly indicate that the level of TPGS is the most significant formulation variable. Preliminary feasibility of both monolithic and bilayer tablets, with a secondary non-TPGS formulation, has been

demonstrated. Heat sensitivity studies demonstrate a noticeable impact of heat on critical tablet attributes such as tensile strength. However, the loss of tensile strength upon exposure to heat is partially regained after equilibration to ambient conditions. Also, subjecting TPGS tablets (with up to 10% TPGS) to temperatures well above the melting point for significant periods of time did not show any signs of physical failure. The susceptibility to heat can also be addressed via formulation options such as inclusion of extragranular fillers, which in addition to the above application also facilitate tablet disintegration and enhance tensile strength for high TPGS formulations. A tablet coating operation was also conducted without any significant issues and the resultant product was highly acceptable from a product quality standpoint. Though, all these results do point to feasibility of tabletability of TPGS formulations, this is clearly only a preliminary study and susceptibility to high temperatures and potential process complications occurring at manufacturing scales certainly need to be further evaluated.

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