Comparative evaluation of Compritol® HD5 ATO with Sodium Stearyl Fumarate and PEG 6000 as amphiphilic, hydrodispersible pharmaceutical lubricants.

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ABSTRACT

Hydrophobic lubricants are commonly used to reduce the frictional forces generated during tableting but impart a hydrophobic film on the surface of the powder or granules. This affects negatively the performance properties of the resultant tablets by slowing disintegration and dissolution. This is especially problematic in the case of orally disintegrating tablets. In the present study the lubricant capacity of Compritol® HD5 ATO was compared with commonly used amphiphilic lubricants, sodium stearyl fumarate and PEG 6000. The effect of the concentration and mixing time of Compritol® HD5 ATO with the granulation, on material flow properties, tablet ejection force, hardness, disintegration time and rate of dissolution of paracetamol tablets was evaluated. The physical properties of the lubricants such as crystallinity, wettability, thermal behaviour and surface area were also measured. Compritol® HD5 ATO is crystalline, hydrodispersible and thermostable. It reduced the tablet ejection force, the desired hardness range was obtained at significantly lower compression forces and no significant effect of lubricant mixing time and concentration on the hardness and disintegration time of the tablets was observed when compared with Sodium stearyl fumarate and PEG 6000. Compritol® HD5 ATO was found to be an as effective a lubricant for a fast disintegrating paracetamol formulation containing microcrystalline cellulose, lactose and PVP prepared by wet granulation in comparison with sodium stearyl fumarate and PEG 6000.

KEY WORDS: Behenoylpolyoxyl – 8 glycerides, PEG 6000, Sodium Stearyl Fumarate, Contact Angle, Ejection force, crushing force

INTRODUCTION

Friction occurs during many pharmaceutical operations, such as blending, die-filling, compaction, capsule-filling, and compression at either the powder-tool interfaces or the particle-particle interfaces. The interaction between powder particles and the wall of the equipment is commonly known as wall friction and the particle-particle interactions are known as internal friction (1). Lubricants are added to

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reduce the friction between the surfaces of the manufacturing equipment and the pharmaceutical solids to ensure the continuation of the operation. Although lubricants are only a small proportion by weight of the granulation blend they play important roles such as a)decreasing the friction at the interface between a tablet's surface and the die wall during ejection so that the wear on punches and dies is reduced, b) preventing the sticking of the tablets to the punch faces and c) preventing sticking of capsule fills to dosators and tamping pins.

Lubricants improve the flow properties of powder or granule blends, for instance, for the blending of active pharmaceutical ingredients (APIs) of small particle size with other excipients, the adhesion force between particles can significantly reduce the powder flowability by increasing inter-particle friction. Lubricants cannot improve content uniformity and rat-holing in the hopper of a tablet press (segregation issue), affecting both product quality and operation. To overcome these issues, lubricants are added to enhance powder flow by reducing the inter-particle friction.

Magnesium stearate is the most commonly used lubricant because it reduces friction efficiently even at low concentrations of < 0.5 % and it also exhibits good anti-adherent properties. Despite its excellent lubricant performance, magnesium stearate have been reported to have a negative effect on the compactibility of powder blends. Depending on the deformation behaviour of the powder particles in a tablet formulation, magnesium stearate can reduce the physical strength of the tablets significantly. This is attributed to the formation of a thin lubricant film around each of the individual particles during blending and as a result the interparticulate bonding strength between the particles is weakened. Therefore, tablets consisting of excipients that undergo plastic deformation are greatly affected, while brittle materials are found to be less susceptible. In addition to the decreased bonding properties, magnesium stearate is also known to decrease the wettability due to its pronounced hydrophobic nature, and thus it can cause delayed tablet disintegration and prolong dissolution rate.

Sodium stearyl fumarate is widely used in the pharmaceutical industry as a relatively less hydrophobic lubricant alternative to magnesium stearate, especially in formulations where faster disintegration is desired. It has been shown that sodium stearyl fumarate has fewer negative effects on tablet strength and dissolution rate than magnesium stearate. If tablets are intended to be dissolved in water prior to ingestion, e.g., effervescent tablets, lubrication of the tablet formulation with water soluble excipients is preferable. For this purpose, solid polyethylene glycols, e.g., PEG 4000 and PEG 6000 have been used as lubricants (2-4).

Several new, less hydrophobic, lubricants such as 'Compritol® HD5 ATO' (Behenoyl-polyoxyl-8 glycerides NF), a mixture of glyceryl and polyethylene glycol behenate have become available. Owing to its amphiphilic nature, Compritol® HD5 ATO can also be used to enhance the wettability and/or dissolution characteristics of poorly soluble compounds when making solid dispersions. Compritol® HD5 ATO conforms to USP38/NF33 and is formed through an esterification reaction between PEG-8, glycerol and behenic acid followed by atomization. No solvent or catalyst is used during the manufacturing process thus ensuring lower levels of impurities and a better product.

In the work published by N'Diaye *et. al.*, the lubricant capacity of Compritol® HD5 ATO was compared to Compritol® 888 ATO (Glyceryl dibehenate) with respect to granular

characteristics, structural differences, compressibility and cohesiveness when blended with Lactopress™ (6). In this study, Compritol® HD5 ATO was compared with sodium stearyl fumarate (SSF) and polyethyleneglycol (PEG) 6000 by studying the effect of its concentration and mixing time on material flow properties, tablet ejection force, hardness, disintegration time and rate of dissolution. PEG 6000 was selected owing to its known hydrophilic nature and was used as a positive control while SSF was selected as it is a widely used alternative to magnesium stearate in the pharmaceutical industry in formulations where a faster disintegration is desired.

MATERIALS AND METHODS

Microcrystalline Cellulose (Avicel® PH 101, FMC Bioploymers), Lactose (Pharmatose® 200M, DMV) PVP K30 (Kollidon® K30, BASF), sodium stearyl fumarate (SSF) (Novalube™, Nitika Pharmaceutical Specialities Pvt. Ltd.), Behenoyl polyoxyl-8-glycerides (Compritol® HD5 ATO, Gattefosse India Pvt. Ltd.), Poylethylene glycol 6000 (S. D. Fine Chemicals Ltd.) were used in this study.

The experimental work was divided into two parts a) a physical characterization of the lubricants used in this study and b) a functional evaluation of the lubricants used in this study.

The physical characterization of the lubricants

Physical characterization of the lubricants in this study, that is, Compritol® HD5 ATO, sodium stearyl fumarate and PEG 6000 was performed with respect to specific surface area, thermal behaviour, extent of crystallinity and wetting behavior.

Surface area analysis

The surface area analysis was carried out by the Brunauer, Emmett and Teller (BET) Isotherm method using the Surface Area Analyzer, SA 3100, Beckman Coulter, USA under vacuum (7-10).

Particle Size Measurement

Particle size distribution analysis was carried out using a Beckman Coulter LS Particle Size Analyzer, Beckman Coulter LS 13 320, Beckman Coulter, USA.

Differential Scanning Calorimetry

The thermal behavior of the lubricants were studied using Differential Scanning Calorimetry (DSC) (Pyris 6, Perkin Elmer, USA).

The extent of crystallinity

The extent of crystallinity of the lubricants was examined using X-Ray diffraction analysis. The crystallinity was measured using a Miniflex apparatus (Rigaku, Japan) with Cu Kα radiation. Samples were held on a quartz frame. The diffraction patterns were obtained at a voltage of 40 kV and at a current of 20 mA. The slide was then placed vertically at a 0° angle in the X-ray diffractometer so that the X-ray beam was completely incident on the sample. The results were recorded over a range of 5 – 50° (2θ) using the Cu-target X-ray tube and Xe-filled detector. The instrument operating conditions were voltage 40 kV and current 20 mA. Temperature of acquisition was room temperature and the detector used was a scintillation counter detector. The percent crystallinity was calculated using Equation 1 (11).

$$\frac{Total\ area\ of\ crystalline\ peak \times 100}{Total\ area\ of\ all\ peaks} \qquad \text{Eq. 1}$$

Contact angle analysis

The wetting behavior of the lubricants was evaluated by measuring the contact angle made by the compressed lubricant surface with a

drop of water placed on its surface (Wilhelmy Plate Method) using a Kruss Contact angle meter (Model no. G10), Germany (12-13).

Scanning Electron Microscopy

The Microscopic imaging of the three lubricants were obtained using a JSM-5200 (JEOL, Japan) operated at 20 KV with Platinum sputtering for 20 seconds. The samples were mounted on carbon tape and placed inside the SEM instrument.

The functional evaluation of the lubricants in this study

The functional evaluation was performed by studying the effect of concentration and mixing time of the lubricants on ejection force, hardness and disintegration time of placebo tablets and the impact of concentration of the lubricants on the dissolution rate of paracetamol tablets.

Placebo granules of Avicel® 101(40%) and Pharmatose® 200M (55%) were prepared using dispersion of Kollidon® 30 (5%) as binder in a 2 litre bowl of a rapid mixer granulator (Saizonizer Mixer Granulator SAI 10L, Tapasya Engineering Works Pvt. Ltd., India) and were dried at 50°C in a hot air oven until reaching 2% moisture. The drying process was stopped when the moisture content was 1.58%.

The granules (200 g) and the lubricants (Compritol® HD5 ATO, SSF and PEG 6000) were blended in an interchangeable octagonal blender with a 1 litre attachment (Gansons Engineers Pvt. Ltd., India) at the following concentrations of lubricant 1, 1.5, 2 and 3% (w/w) at 20 RPM for 5 minutes. The mixing process was repeated at 2% (w/w) concentration of each of the lubricant for 3 minutes and 10 minutes in order to study the effect of mixing time.

The bulk and tap density of the lubricated granules were determined using an automated tap density tester ETD 1020 (Electrolab India Pvt. Ltd., India) from which the flow properties, *viz.* Compressibility Index (CI) and Hausners Ratio (HR) were calculated (14-19).

Force monitoring study

The effect of lubricant concentration and the mixing time on tablet compaction, ejection profile from the die cavity, hardness, disintegration time and dissolution was studied. The friction generated during compression and ejection of the tablets was measured using a tablet press with a load cell.

The friction parameters of the unlubricated and lubricated granules were investigated using a tablet rotary press (XL 100 Pro, Korsch, Berlin, Germany) equipped load cells, 8 mm diameter B tooling, round flat-faced punches and 8 mm high die walls during the filling phase. For all the different concentration variants, tablets of 200 mg weight, were compressed to a hardness value of 100 N $\pm$ 20 N. For each concentration and mixing time variant, 100 tablets were produced with a turret speed of 25 RPM. During the compression phase, real-time acquisition of press force data, automated analysis of force peaks, area under the compression curve, rate of force application, rate of force decay, and contact time were recorded with the help of specific software PharmaResearch® SE and LE versions, Korsch, Germany included with the tablet press (20-28).

Statistical analysis

The data from the force monitoring study was statistically analyzed using GraphPad Prism® software (3.02 version, 2000) by performing (unpaired) t test to evaluate the influence of the lubricant concentration on ejection force. The results were considered significantly different at p-values < 0.05.

The effect on tablet strength and disintegration time

After compression, the diameter (at a precision of 0.01 mm), thickness (at a precision of 0.01 mm), and hardness (at a precision of 0.01 N) of the tablets were measured using a breaking force tester EBT- 2PRL (Electrolab India Pvt Ltd., India). The value for tensile strength of the tablet was calculated using the Equation 2.

$$\text{Tensile strength } (\text{N}/\text{mm}^2) = \frac{2N}{\pi\theta h} \qquad \text{Eq. 2}$$

where; N = tablet hardness (N), θ = tablet diameter (mm) and h = tablet thickness (mm). The disintegration time was measured using a semi-automatic disintegration tester ED 2SAPO (Electrolab India Pvt Ltd., India) (29-33).

The effect on the dissolution rate of immediate release paracetamol tablets

The effect on the dissolution rate of each variant was measured for immediate release paracetamol tablets using dissolution test specified in USP 29/NF 24 in apparatus equipped with an auto sampler (Electrolab India Pvt. Ltd.). Immediate release tablets of paracetamol weighing 500 mg were prepared by compressing granules containing 150 mg of Paracetamol, Avicel® PH 101, Pharmatose® 200M used as diluents and Kollidon® 30 used as a binder. Each lubricant was added at 2% (w/w) concentration and mixed for 5 minutes. The test was performed in phosphate buffer of pH 5.8 using USP apparatus 2 at 50 RPM. Aliquots were withdrawn at 5, 10, 15, 20, 30, 45 and 60 minutes and the release profile for the unlubricated and the tablets with the three different lubricants were compared by recording the absorbance at the maximum wavelength of 243 nm using a spectrophotometer (UV 1800, Shimadzu) (34-36). All measurements were performed 3 times and in no case was RSD > 10%.

RESULTS AND DISCUSSION

The BET surface area values derived from the BET isotherm indicated that SSF had larger surface area in comparison to Compritol® HD5 ATO and PEG 6000. The observed surface area values along with the corresponding mean particle size values of the lubricants are shown in Table 1.

Table 1 Specific Surface area values and mean particle size

LUBRICANT	OBSERVED SURFACE AREA	MEAN PARTICLE SIZE
Compritol HD5 ATO	0.228 Sq. m/g	50.57 µm
Sodium Stearyl Fumarate	4.045 Sq. m/g	22.43 µm
PEG 6000	0.350 Sq. m/g	100.00 µm

The specific surface area of a powder was estimated from the amount of nitrogen adsorbed in relationship with its pressure, at the boiling temperature of liquid nitrogen under normal atmospheric pressure. The observations were interpreted following the model of Brunauer, Emmett and Teller (BET Method). The smaller surface area of Compritol® HD5 ATO can be attributed to the atomization step involved during the manufacturing process. This results in formation of spherical shaped particles of uniform, controlled particle size (7-10).

The DSC thermogram for Compritol® HD5 ATO was broad as a melting point range of 56°-64°C was observed, PEG 6000 showed a sharp endotherm at its melting point while multiple endotherms were observed in case of SSF. The thermograms for the lubricants obtained from the differential scanning calorimetric analysis are shown in Figure 1.

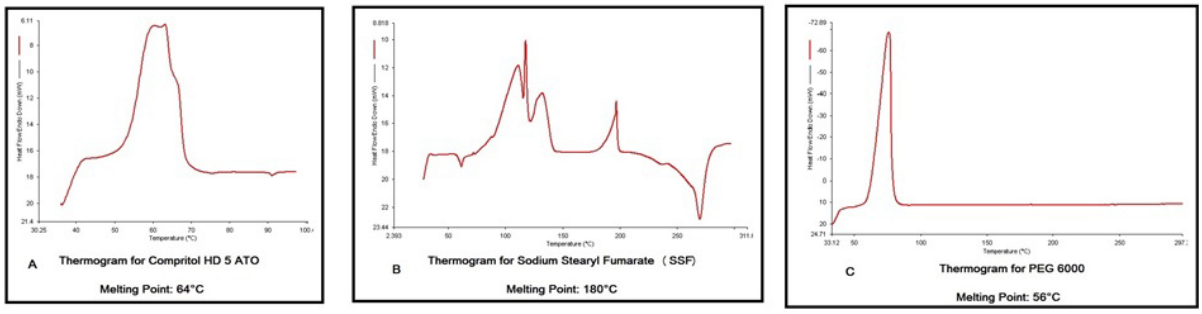

Figure 1 DSC thermograms and their melting points for the three lubricants used in this study A) Compritol® HD5 ATO, B) Sodium Stearyl Fumarate and C) PEG 6000.

The diffractograms observed in the X-Ray diffraction analysis and the sharp endotherms observed for Compritol® HD5 ATO and PEG 6000 confirmed their crystalline nature. The percent crystallinity values obtained by incorporating the data obtained from XRD diffractograms into the equation indicated that Compritol® HD5 ATO and PEG 6000 were crystalline while SSF exhibited a partial crystalline structure. The XRD diffractograms are shown in Figure 2.

The observations for the wetting behaviour of the lubricants evaluated by measuring the contact angle between water and the lubricant surface measured using the Wilhelmy Plate Method are summarized in Table 2.

Table 2 Contact angle observed for the lubricants

LUBRICANT	CONTACT ANGLE BETWEEN WATER AND LUBRICANT SURFACE
Compritol® HD5 ATO	70°
Sodium stearyl fumarate	115°
PEG – 6000	5°

From the contact angle measurement, it can be inferred that Compritol® HD5 ATO is more hydrophilic than SSF and thus may be more effective in improving the wettability of tablet formulations. PEG 6000, being a hydrophilic solubilizer, displayed a contact angle of 5°. The contact angle (wetting angle) is a measure of the wettability of a solid by a liquid. When an interface exists between a liquid and a solid, the angle between the surface of the liquid and the outline of the contact surface is described as the contact angle θ. In the case of complete wetting, the contact angle is 0°. Between 0° and 90°, the solid is considered wettable and above 90° it is considered as not being wettable. In the case of ultrahydrophobic materials with the so-called lotus effect, the contact angle approaches the theoretical limit of 180°. Compritol® HD5 ATO (70°) and PEG 6000 (5°) can be classified as water wettable solids with their contact angles ranging between 0° and 90°. While SSF with a contact angle value of 115° can be considered as not wettable. Wettability may affect the tablet disintegration time and dissolution (12-13).

The spherical particle structure of Compritol® HD5 ATO as indicated in the SEM images can be attributed to the atomization step in the manufacturing process. The results are shown in Figure 3. Thus the physical characterisation of the lubricants indicates that Compritol® HD5 ATO has a spherical, crystalline structure, due to which it exhibits smaller surface area. It is more wettable than SSF.

Functional evaluation of the lubricants under consideration was performed so as to demonstrate a) their ability to reduce friction

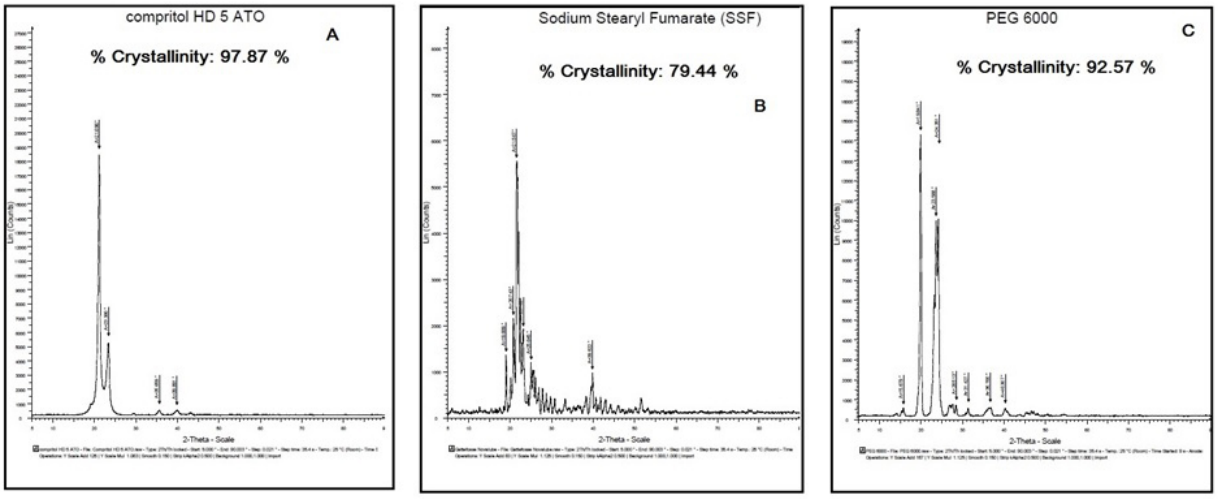

Figure 2 XRD diffractograms for the three lubricants used in this study A) Compritol® HD5 ATO, B) Sodium Stearyl Fumarate and C) PEG 6000.

and adhesion to the punches, b) the influence of their concentration and the mixing time on tablet hardness and disintegration time and c) their effect on release profile of paracetamol from immediate release tablets.

The flow properties of the granules after addition of Compritol® HD5 ATO, SSF and PEG 6000 were found to be comparable, improved with increase in concentration level from 1% and 1.5% to 2 % and were optimum at 2.0 % concentration level for Compritol® HD5 ATO. The flow properties of the lubricated granules improved when the mixing

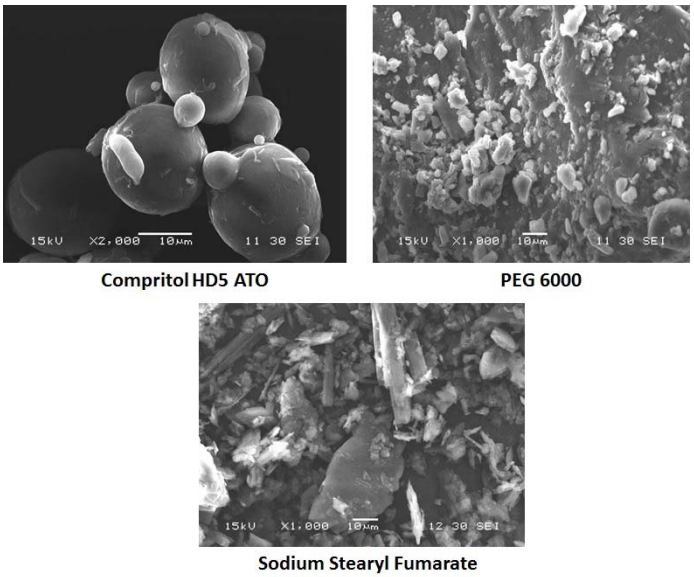

Figure 3 SEM images for the three lubricants used in this study.

time was increased from 3 minutes to 5 minutes, while no significant effect was observed after further increasing the mixing time to 10 minutes in the case of Compritol® HD5 ATO. The observations on the flow properties of the lubricated granules are summarized in Tables 3 and 4.

Table 3 USP specifications for evaluating flow properties

USP SPECIFICATIONS		
CI* (%)	Flow Characteristics	HR#
≤ 10	Excellent	1.00 - 1.11
11 - 15	Good	1.12 - 1.18
16 - 20	Fair	1.19 - 1.25
21 - 25	Passable	1.26 - 1.34
26 - 31	Poor	1.35 - 1.45
32 - 37	Very poor	1.46 - 1.59
> 38	Very very poor	> 1.60

*CI: Compressibility Index; #HR: Hausners Ratio

Among the three lubricants, SSF was better able to improve the flow properties in comparison to Compritol® HD5 ATO & PEG 6000. This is likely due to its larger surface area and partial crystalline structure which allows it to coat the granular surface and reduce the intragranular friction.

Force monitoring study

Ejection force is the force necessary for the lower punch to eject the tablet from the die. The lower the ejection force, the better the antifriction effect of the lubricant.

During compression the hardness range of the tablets was set between 80 to 120 N. The main compression force and the ejection force generated to achieve and maintain this hardness range was measured and evaluated.

Table 4 The effect of flow properties of the lubricated granules

CONCENTRATION (Mixing time 5 minutes)		1%			1.5%			2%			3%		
	Granules without lubricant	HD5 ATO	SSF	PEG - 6000	HD5 ATO	SSF	PEG 6000	HD5 ATO	SSF	PEG 6000	HD5 ATO	SSF	PEG - 6000
HR	1.43	1.37	1.32	1.33	1.34	1.18	1.30	1.24	1.21	1.27	1.29	1.24	1.21
CI (%)	30.14	27.08	24.44	25.00	25.5	15	23.26	19.51	17.07	21.43	22.2	19.05	17.50

MIXING TIME (at 2% concentration)	3 Minutes			5 Minutes			10 Minutes		
	HD5 ATO	SSF	PEG 6000	HD5 ATO	SSF	PEG 6000	HD5 ATO	SSF	PEG - 6000
HR	1.37	1.24	1.27	1.2	1.21	1.27	1.26	1.2	1.27
CI (%)	27.08	19.05	21.43	20	17.07	21.4	20.46	18	21.43

HR = Hausner's Ratio; CI = Compressibility Index; HD5 ATO: Compritol HD5 ATO; SSF: Sodium stearyl fumarate

In the absence of any of the lubricants the granules had a maximum ejection force of 636 N. As the granules were lubricated and as the lubricant concentration increased the ejection force decreased. As the concentration of Compritol® HD5 ATO increased from 1% to 3 % the ejection force decreased from 55 N to 47.3N.

An ejection force of 46.85 N was obtained at the optimum concentration of 2%. In comparison to Compritol® HD5 ATO, SSF was less effective in reducing the ejection force with values ranging between 59.25 to 58.2 N for concentrations from 1% to 3%. PEG 6000 was found to be most efficient in reducing the ejection force among the three lubricants, although the absolute values of the ejection force were significantly greater than those obtained with the other two lubricants. At a 1% concentration, the ejection force was 320.5 N which decreased to 149 N at 2% concentration and to 97.05 N at 3% concentration.

Among the three lubricants, PEG 6000 was the most effective in reducing the ejection force followed by Compritol® HD5 ATO while SSF was least effective. The least absolute values of the ejection force were obtained with Compritol® HD5 ATO The effect of varying the concentration and lubrication mixing time of the three lubricants on the ejection force and main compression force is summarized in Figures 4 and 5 respectively.

Statistical Analysis

The p values observed from the unpaired t test performed for evaluating the effect of concentration of the lubricants on tablet ejection force was less than 0.05 indicating a significant effect of a particular lubricant concentration on the observed ejection force.

The effect of lubricant concentration on tablet strength and disintegration time

The desired hardness range of 80 to 120 N was achieved at all concentrations of Compritol® HD5 ATO & PEG 6000 while SSF failed to provide the desired hardness range at 1%, the lowest concentration studied. The hardness range for tablets prepared using SSF as lubricant varied between 71.7-60.8 N and was achieved after increasing the main compression force 13.1 kN (for 1% concentration) to 31 kN (for 3 % concentration). With increase in concentration levels of Compritol® HD5 ATO the desired hardness range was achieved by lowering the main compression force from 13.1 kN (for 1% concentration) to 8.5 kN (for 2% concentration level). PEG – 6000 was most effective in achieving the desired hardness range at minimum main compression force value of 9 kN for minimum as well as maximum hardness levels. The effect of varying the concentration and lubrication mixing time on tablet hardness and disintegration time is shown in Figures 6 and 7 respectively.

The derived tensile strength values for the tablets with the corresponding main compression force values required to achieve the same are shown in Table 5. Table 5 shows that the tensile strength of Compritol® lubricated tablets increased with the concentration when mixed for 5 minutes. This was not the case for SSF and PEG 6000 lubricated tablets where the tensile strength decreased with an increase in concentration from 1 to 3%. A similar pattern was observed when the mixing time was increased from 3 to 10 minutes at a constant concentration (2%) for each of the lubricants. Tablets prepared using Compritol® HD5 ATO and PEG 6000 showed greater tensile strengths at lower main compression force values.

Table 5 Tensile strength values with the corresponding main compression force

IMPACT OF CONCENTRATION (Mixing time 5minutes)	Granules without lubricant	Compritol HD 5			SSF			PEG - 6000		
		1%	2%	3%	1%	2%	3%	1%	2%	3%
Main Compression force (kN)	10	13.35	8.5	11.25	13.1	13.85	30.9	9	9	8.95
Hardness (N)	84.3	85.8	90.6	122.1	71.7	60.8	66.3	89.5	89.4	74.4
Tensile strength (N/mm^2)	1.71	1.74	1.86	2.59	1.56	1.32	1.47	1.85	1.85	1.54
IMPACT OF MIXING TIME (at 2% concentration)	**Granules without lubricant**	**3 minutes**	**5 minutes**	**10 minutes**	**3 minutes**	**5 minutes**	**10 minutes**	**3 minutes**	**5 minutes**	**10 minutes**
Main Compression force (kN)	10	9.35	8.5	9.65	17.35	13.85	18.8	9.65	9	10.35
Hardness (N)	84.3	83.2	90.6	95.9	82.7	60.8	64.6	100.3	89.4	111.9
Tensile strength (N/mm^2)	1.71	1.73	1.86	2.01	1.84	1.32	1.41	2.08	1.85	2.31

The disintegration time for Compritol® HD5 ATO and PEG 6000 were comparable and were within the USP specification of not more than 15 minutes for immediate release tablets, times ranging between 1.17 minutes at a 1% concentration to 9.12 minutes, at 3% concentration of Compritol® HD5 ATO, and 2.27 minutes (at 1% concentration of PEG – 6000) to 4.48 minutes (at 3% concentration of PEG 6000). Tablets compressed using SSF as lubricant disintegrated with times ranging between 4.13 minutes (at 1% concentration) to 21.29 minutes (at 3% concentration). The increase in disintegration time for SSF at 3% concentration could be attributed to the relatively higher hydrophobic nature and more coverage of the granular surface by SSF.

The atomization process involved in the manufacturing of Compritol® HD5 ATO

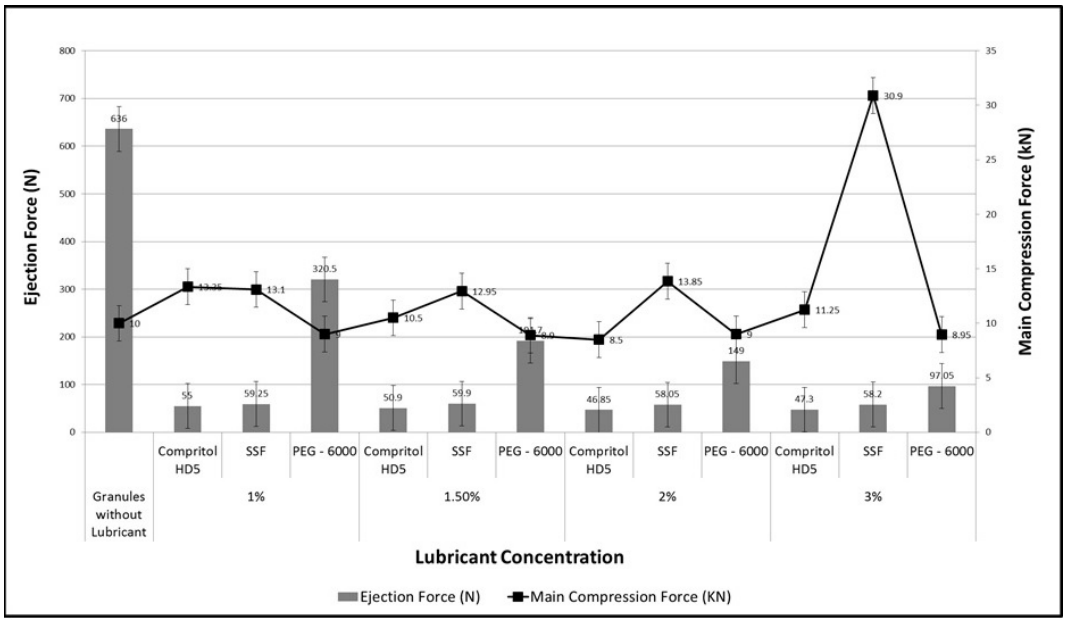

Figure 4 Plot indicating the effect of the lubricant concentration on tablet ejection and main compression forces.

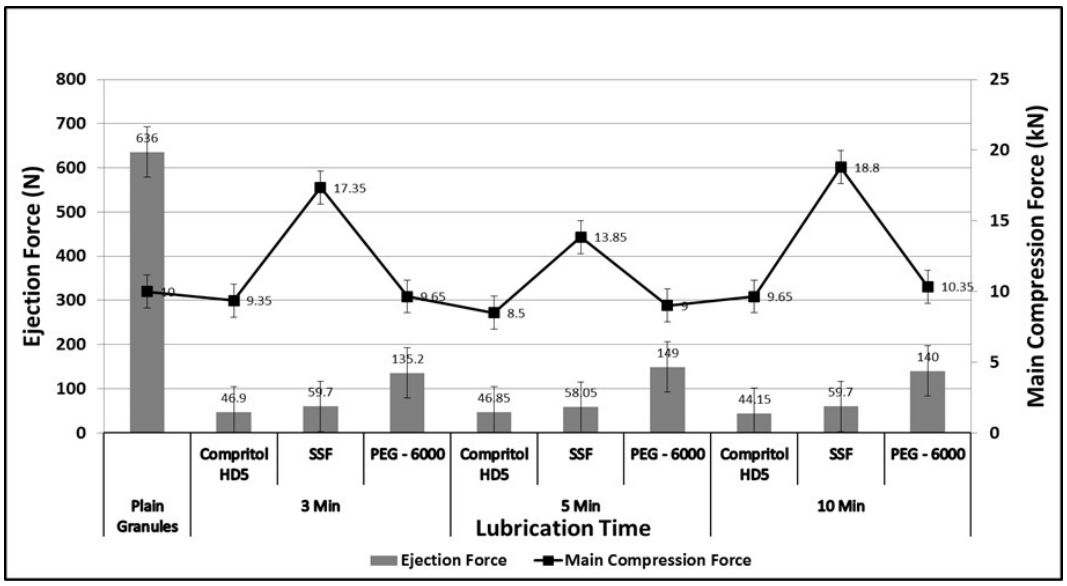

Figure 5 Plot indicating the effect of the lubrication mixing time on tablet ejection and main compression forces.

results in formation of spherical shaped particles with controlled particle size and crystalline structure. These spherical particles owing to their smaller surface area and crystalline structure do not coat the granule surface and occupy the intergranular spaces instead. Compritol® HD5 ATO also provides a larger design space for Quality by Design (QbD) attributes of particle size and surface area. These attributes do not affect the formulation characteristics such as tablet hardness, disintegration time and dissolution and hence can be excluded from critical material attributes (CMA). Since variation of

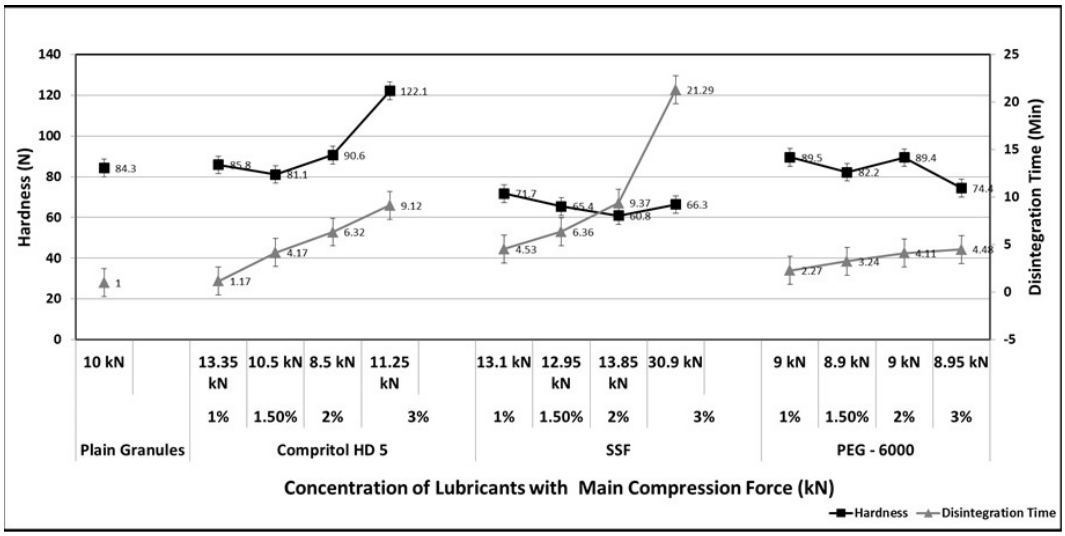

Figure 6 Plot indicating effect of the lubricant concentration on tablet hardness and disintegration time.

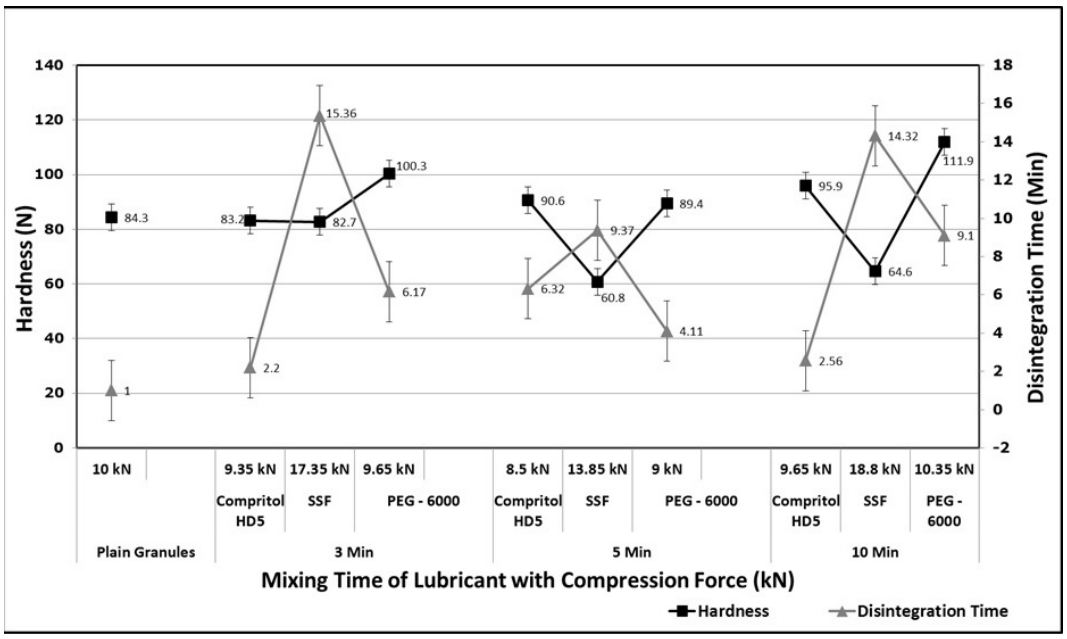

Figure 7 Plot indicating the effect of the lubrication mixing time on tablet hardness and disintegration time.

mixing time did not affect hardness and disintegration time for the granulation studied, the mixing time may be excluded as critical process parameter (CPP) for the QbD assessment (5).

Figure 8 shows the dissolution profiles of the paracetamol tablets prepared using the three lubricants showed comparable dissolution profile and none of the variant delayed the dissolution rate of paracetamol when compared with unlubricated granules.

CONCLUSIONS

Compritol® HD5 ATO is crystalline, hydrodispersible and thermostable. It was able to achieve tablet ejection to higher main compression force ratio values comparable to those of PEG 6000 and lesser ratios than those of SSF. Within the range of lubricant concentration and mixing time utilized in this paper, the lubricant effectiveness, as measured by disintegration time, of Compritol® HD5 ATO was insensitive to lubricant concentration and mixing time.

Compritol® HD5 ATO was found to be as effective a lubricant for a fast disintegrating paracetamol formulation containing microcrystalline cellulose, lactose and PVP prepared by wet granulation in comparison with sodium stearyl fumarate and PEG 6000.

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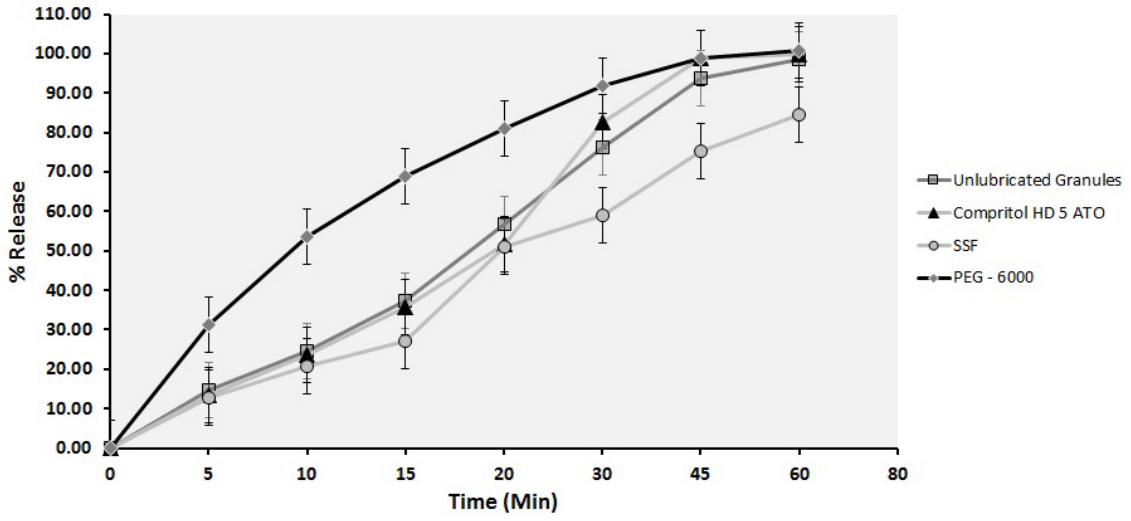

Figure 8 A comparison of the dissolution profiles for the three lubricants used in the paracetamol tablets.

DECLARATION OF INTEREST

The authors report no declarations of interest. The authors alone are responsible for the content and writing of this paper.

REFERENCES

1 Li J, Wu Y. Lubricants in Pharmaceutical Solid Dosage Forms. Lubricants 2014; 2: 21 - 43.

2 Saniocki I., et. al., Evaluation of the suitability of various lubricants for direct compaction of sorbitol tablet formulations. J. Excipients and Food Chem 2013; 4 (4): 169 - 182.

3 Holzer A, Sjogren J. Evaluation of Sodium Stearyl Fumarate as a tablet lubricant. Int J Pharm 1979; 2: 145 - 153.

4 Nelson D, Wu R, Wymbs K. Effects of magnesium stearate on tablet properties. International journal of advanced pharmaceutics [Internet]. 2012; 2(1): 1-4. Available from: http://www.ijapjournal.com

5 Gattefosse technical brochure on Compritol®: The Lubricant for Challenging Pharmaceutical Tablets.

6 N'Diaye A, Jannin V, Bérard V, Andrès C, Pourcelot Y. Comparative study of the lubricant performance of Compritol® HD5 ATO and Compritol® 888 ATO: effect of polyethylene glycol behenate on lubricant capacity. Int J Pharm 2003; 254: 263 - 269.

7 Busignies V, Leclerc B, Truchon S, Tchoreloff P. Changes in the specific surface area of tablets composed of pharmaceutical materials with various deformation behaviours. Drug Dev Ind Pharm 2011; 37(2): 225 - 233.

8 EP. 2.9.26. Specific surface area by gas adsorption. European Pharmacopoeia 5.1 (8th Edition).

9 JP. Specific surface area determination. Japanese Pharmacopoeia XIV.

10 Carter D, Mortland M, Kemper W. Specific Surface. 2nd ed. Madison, USA: American Society of Agronomy-Soil Science Society of America, 1986.

11 Mulla S, Phale P, Saraf M. Use of X-Ray Diffraction Technique for Polymer Characterization and Studying the Effect of Optical Accessories. AdMet 2012 Paper No. OM 006.

12 Yuan Y, Lee R. Contact Angle and Wetting Properties. In: Bracco G, Holst B. (eds.), Surface Science Techniques. Berlin Heidelberg: Springer-Verlag, 2013: 3 - 34.

13 Overview on Contact Angle [Internet]. Hamburg: Kruss - Advancing your surface science. Available from: http://www.kruss.de/services/education-theory/glossary/contact-angle/

14 United States. The United States Pharmacopeial Convention. Bulk density and tapped density of powders. 616. 2011.

15 Odeniyi M, Alfa J, Jaiyeoba K. Effect of Lubricants on Flow Properties and Tablet Strength of Silicified Microcrystalline Cellulose. FABAD J Pharm Sci 2008; 33: 71-75.

16 Shah R, Tawakkul M, Khan M. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS Pharm Sci Tech 2008; 9 (1): 250 - 258.

17 Navaneethan C, Missaghi S, Fassihi R. Application of powder rheometer to determine powder flow properties and lubrication efficiency of pharmaceutical particulate systems. AAPS Pharm Sci Tech 2005; 6 (3): E398 - E404.

18 Velasco M, Munozruiz A, Monedero M.C, Study of flowability of powders - effect of addition of lubricants, Drug Dev Ind Pharm. 1995; 21 (20): 2385 - 2391.

19 Hancock B, Colvin J, Mullarney M, Zinchuk A. The Relative Densities of Pharmaceutical Powders, Blends, Dry Granulations, and Immediate-Release Tablets. Pharmaceutical Technology 2003; 64 - 80.

20 Takeuchi H, Nagira S, Yamamoto H, Kawashima Y. Die wall pressure measurement for evaluation of compaction property of pharmaceutical materials. Int. J. Pharm. 2004; 274: 131 - 138.

21 Specialised techniques for developing ODT dosage forms. 2010. http://www.ondrugdelivery.com

22 Deveswaran R, Bharath S, Basavaraj BV, Abraham S , Furtado S and Madhavan V. Concepts and Techniques of Pharmaceutical Powder Mixing Process: A Current Update. Research J Pharm and Tech 2009; 2 (2): 245 - 249.

23 Al-muaikel N. The contribution of bio-polymers to pharmaceutical industry. 2. Evaluation of SAS - LUB, a new bifunctional tabletting excipient. European Scientific Journal. 2014; 10 (3): 356 - 364.

24 Faldu B, Zalavadiya B. Lubricants: Fundamentals of tablet manufacturing. IJRPC. 2012; 2 (4): 921 - 925.

25 Sheskey P, Robb R, Moore R. Effects of lubricant level, method of mixing, and duration of mixing on a controlled-release matrix tablet containing hydroxypropyl methylcellulose, Drug Dev Ind Pharm. 1995; 21 (19): 2151 - 2165.

26 Dietrich P, Bauer-Brandl A, Schubert R, Influence of tableting forces and lubricant concentration on the adhesion strength in complex layer tablets, Drug Dev Ind Pharm. 2000; 26 (7): 745 - 754.

27 Mollan M, Celik M. The effects of lubrication on the compaction and post-compaction properties of directly compressible maltodextrins. Int J Pharm. 1996; 144 (1): 1-9.

28 Muzikova J, Vyhlidalova B, Pekarek T. A study of micronized poloxamers as lubricants in direct compression of tablets. Acta Poloniae Pharmaceutica - Drug Research. 2013; 70 (6): 1087 - 1096.

29 Kushner J, Moore F. Scale-up model describing the impact of lubrication on tablet tensile strength. Int J Pharm. 2010; 399: 19 - 30.

30 Pabari R, Ramtoola Z. Application of face centred central composite design to optimise compression force and tablet diameter for the formulation of mechanically strong and fast disintegrating orodispersible tablets. Int J Pharm. 2012; 430 (1-2): 18 - 25.

31 Schwarz E, Fichtner V, Irlinger B, Haeusler O. Influence of lubricants on tableting and disintegration time of tablets made up of co - processed excipients vs. physical blends. Proc. 5th World meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Geneva 27 - 30 March 2006.

32 Cunningham C, Scattergood L. Optimizing lubricant usage in a direct compression hydrochlorothiazide formulation containing a plastically deforming excipient. Reprint of poster presented at AAPS, Indianapolis Nov.2000.

33 Häusler O, Brockmann Ch, Rein H. Comparison of native starches as tablet disintegrant. Roquette - Pharma. Available from: http://www.roquette-pharma.com

34 Alebiowu G, Adeagbo A. Disintegrant properties of a paracetamol tablet formulation lubricated with co - processed lubricants. FARMACIA 2009; 57(4): 500 - 510.

35 Uzunovic A, Vranic E. Effect of magnesium stearate concentration on dissolution properties of ranitidine hydrochloride coated tablets. Bosnian Journal of Basic Medical Sciences. 2007; 7 (3): 279 - 283.

36 Acetaminophen Tablets (2005) In: The United States Pharmacopoeial Convention USP NF 29, Inc., Rockville, Maryland, U.S.A.