THE CONTRIBUTION OF BIO-POLYMERS TO PHARMACEUTICAL INDUSTRY 2. EVALUATION OF SAS-LUB, A NEW BI-FUNCTIONAL TABLETTING EXCIPIENT

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Abstract

SAS-Lub, a new bi-functional excipient co-processed from micro-crystalline cellulose and olive oil was evaluated as a lubricant against magnesium stearate, MS, in a model direct compression tablet formulation compressed from micro-crystalline cellulose, MCC at a fixed compressional pressure. The result showed SAS-Lub decreased the plastic deformation of MCC and generated a higher decompression index, k_c which was determined from: $(1-D) = (1-D)^o e^{kc.C}$ where D, D^o and C stand for the relative densities of a tablet batch before and after lubrication and the concentration of the added lubricant material, respectively. Unfortunately, SAS-Lub imported a higher adverse effect on the tablet tensile strength and friability. Unlike MS, SAS-Lub showed a disintegration activity. The disintegration rate constant, k_d, was fairly correlate to C in a tablet batch by the relation: $k_d = k^O_d e^{kx.C}$ where k^O_d and k_x stand for the disintegration rate constant of the tablet batch before lubrication and the disintegration inducing index, DII, respectively.

Keywords: SAS-Lub, decompression index, inducing disintegration index

Introduction

Excipients in tablets service different functions complying with their physico-chemical properties. Long ago, naturally occurring polymers such as celluloses, starches and gums were applied as binders and disintegrants. Celluloses served as bulking agents, direct compression excipients[1,2] and disintegrants[3]. Lubricants are essential additives in tablet making[1]. They enhance the flow of powders and granules and facilitate their compression into tablets. Reports evaluating the lubricant potentiality of vegetable oils and hydrogenated oils and fats[4-6].

Several parameters such as punch force and displacement, die-wall stress, die-wall friction, temperature changes, and yield stress[7] are monitored

during compression process to assess the lubricants functionality. Dika fat was reported to decrease the unit ejection force and increase the plasto-elasticity ratio of the tested powders[6]. The effects of a material on the tensile strength, friability, disintegration and dissolution rates of the finished tablets were the parameters employed to assess the lubricant property of the material[4-6]. Co-processed excipients possess improved physico-chemical properties and functionality. At subparticle level, co-processed excipients are a mixtures of two or more existing excipients that may offer their desired multipurpose effects and minimize their adverse actions. Thus, the number of formulation excipients in a tablet would be reduced.

The objective of this study was to design and evaluate a bi-functional tabletting excipient serving as a lubricant and as a disintegrant from olive oil and MCC.

2. Experimental

2.1. Materials and methods

2.1.1. Materials

Authentic olive oil sample was purchased from LOBA Chemie Ltd. Mumbai- 400005, India. MCC PH101 was obtained from Krishna Chemicals, Mumbai-40078, Maharashtra, India. Magnesium stearate and the analytical grades hydrochloric acid (37.5%), absolute ethanol, and acetone were purchased from Scharalab, S.L., Gato Prez, Spain.

2.1.2. Methods

2.1.2.1. Processing SAS-Lub

A 50 g MCC sample was pulverized, passed through 63 um stainless sieve and placed into a porcelain dish over a thermostatically controlled water maintained at 50^{O}C. A precisely weighed 5.0 g oil sample was dissolved in 30 ml water free acetone. The MCC was at first wet with appropriate volume (40ml) of acetone. The wet MCC received the oil/acetone solution and the slurry was mechanically stirred for 15 min. to ensure the efficient distribution of the oil. The obtained sample was dried at 40^{O}C for 12 h in a laboratory oven. The dried powder was thoroughly washed from the free oil by shaking with sufficient quantity (200 ml) of absolute ethanol for 2 h and then dried at 40^{O} C for 1 h using the laboratory oven. The dried mass was boiled in a sufficient quantity of distilled water (200ml). The mass was re-washed by boiled in distilled water for 1h. The mass was filtered, dried, pulverized and stored in a screw capped powder bottle till use .

2.1.2.2. Physico-chemical properties of SAS-Lub

2.1.2. 2.1. Chemical properties

2.1.2. 2.1.1. FTIR and DSC

IR spectra for MCC, and for SAS-Lub were carried out using the earlier reported technique[8] . KBr pellets containing 1 mg a given material were prepared on a portable press at a dwell time of 5 min and at a force of 10,000 pounds. The infrared spectrum was run between 650 and 4000/ cm using a Perkin Elmer IR Spectrometer (Spectrum BX, PerKin Elmer, CA, USA) equipped with the Ommic software (Nicolet Corp., Madison, WI, USA). The resolution, the interval length, and the number of scans employed were 16, 2, and 16/ cm, respectively.

The DSC thermo-gram for CCR was obtained by heating a given CCR sample from 30 to 500°C at a rate of 10°C min^{-1} under inert nitrogen dynamic atmosphere. The transition temperatures for water loss and the thermal decomposition of CCR were determined.

2.1.2. 2.1.2. Estimation of the loaded oil

An accurately weighed 3.0 g SAS-Lub sample was placed in a 100 ml capacity screw capped bottle. An excess quantity of water free acetone (50ml) was added onto the sample and the bottle was mechanically shaken for 1h to wash out the oil. Washing was carried out 5 times and the sample was dried at $50^{O}C$ for three h. The dried sample was desiccated over silica gel for 6 h and precisely weighed. The percent of oil loading the cellulose was determined. The mean of such three determination was taken as the percent of the oil loading the cellulose. It was found 10 ± 0.35% w/w.

2.1.2. 2.2. Physical properties

2.1.2. 2.2.1. Morphology and flow properties

The color, taste, odor, and the touch of the processed SAS-Lub were examined. The flow rate, repose angle, bulk and tap densities of SAS-Lub and MCC powders were measured using the early described techniques[9].

2.1.2. 2.2.2. Study of moisture sorption isotherm

Moisture adsorption isotherms exhibited by SAS-Lub, MCC and the corresponding tablets at $40^{O}C$- 74.7% RH (using a saturated. at $40^{O}C$- 100% RH water were studied.

2.1.2. 2.2.3. Swelling index determination

The swelling index, S_w, was determined as follows[10]: One gram sample of the dried SAS-Lub powder was placed into 100ml graduate screw capped bottle. The powder was suspended in 30 ml distilled water. The suspension was shaken vigorously shake every 10 min. The powder was

allowed to settle and the bottle was protected from disturbance overnight. The sediment volume was precisely recorded as $S_{w.}$ The mean of such three determination was recorded as mean $S_{w.}$

2.1.3 Compression of cellulose tablets

Simple mixing technique using a laboratory drum mixer of suitable capacity was adopted to lubricate cellulose batches with increasing concentrations (0-5% w/w) of a given lubricant. Lubrication was just carried out before compression. A single punch tabletting machine (F3 Manesty, Manesty Machines ltd., UK) fitted to flat faced punches was employed to compress the prepared cellulose tablets. The machine settings were adjusted to compress tablets of 9.0 ±0.1 mm mean diameter, 0.380g mean weight, 10 kg mean tensile strength and of 0.1 mean friability from the un-lubricated cellulose batch. The machine settings were kept constant throughout compressing the batches lubricated with increasing concentrations of MS.

2.1.4. Evaluation of lubricants

The effect of SAS-Lub on the mechanical properties of the compressed cellulose tablet batches mainly the tensile strength H, friability, F, and porosity, ε, and on the percent reduction in the height of a cellulose powder column due to compression
were studied as shown earlier[11] to evaluate its lubricant property. The effect of SAS-Lub on the disintegration behavior of the tested tablets was also studied. MS was used as a reference lubricant.

3. Result

3.1. FTIR and DSC of SAS-Lub

IR spectrum and DSC thermo-gram of SAS-Lub are shown in Figs.1 (a,b). The peaks characterizing the cellulose molecule are clearly shown in the charts. There is no evidence of a chemical interaction taken place between olive oil and MCC.

3.2. Physical properties of SAS-Lub

The off whit to faint yellow SAS-Lub powder was sluggish, cohesive and fluffy and had a high repose angle ($\geq 56^{o}$). At a concentration level ≥ 4.0%, SAS-Lub showed a glidant effect equal to that of MS. it positively affected the flow rate and decreased the repose angle of MCC powder as shown in Table 1. It has large loose density and small packing fraction.

3.3. Moisture sorption isotherm study

Figs. 2 (a,b) shows that the SAS-Lub powder and corresponding tablets exhibited small moisture sorption character. Generally, as the

lubricant concentration increased the amount of absorbed moisture decreased in a given tablet formulation. Tablet batches lubricated with MS exhibited smaller moisture sorption.

3.4. Evaluation of lubricant property of SAS Lub

The lubricant property of a material is normally evaluated by measuring the negative effect of the material on the compression behaviors of a powder or a granules bed using different documented expressions[12-15]. In the present study, the effect of SAS-Lub on tablet tensile strength, H, friability, F, porosity fraction, (1-D), and disintegration rate constant, k_d was studied. Fig.3 shows that H generally decreased as the C of the added lubricant increased in a given tablet batch. H fairly correlated to C in the given tablet batch by the relation: $H = H^o$ Exp.- $K_H C$ where H^o and K_H stand for the tensile strength of the batch before lubrication and a parameter indicative of the degree of reduction in strength of bond between the compressed particles (isolation intensity factor). MS generated smaller (- K_H) value see Table1. Generally, friability, F, increased (parallel to the decrease in H) as C increased in a tablet batch. Lubrication with SAS-Lub produced more friable tablets.

Fig. 4 shows that (1-D) is fairly positively correlated to C in a given tablet batch. The decompression index, k_c, (elasticity factor) was calculated from the relation:

$$(1-D) = (1-D)^o \ e^{kc.C} \qquad \text{Eq.1}$$

where $(1-D)^o$ stands for porosity fraction of the tablet at 0% lubricant. SAS-Lub generated higher k_c value. Fig. 5 shows that tablets lubricated with SAS-Lub disintegrated within short times. The disintegration rate constant, k_d, was a function of C of the lubricant in a tablet batch. The disintegration inducing index DII (or k_x) was calculated from:

$$k_d = k^O_d \ e^{kx.C} \qquad \text{Eq.2}$$

where k^O_d stands for the disintegration rate constant of the tablet batch before lubrication.

4. Discussion

4.1. Chemical characterization of SAS-Lub

FTIR spectrum and DSC thermo-gram of SAS-Lub seen in Figs.1(a,b) clearly shows the existence of the peaks characterizing the cellulose molecule i.e. there was no chemical interaction taken place between olive oil and cellulose.

4.2. Physical properties of SAS-Lub

4.2.2 Morphology, flow rate and repose angle

Morphologically, the processed SAS-Lub powder had off whit to faint yellow color, oily taste and a faint olive oil odor. The powder was greasy to the touch and adhered to the skin but did not adhere to the smooth surfaces like glass. The powder was agglomerating, cohesive and sluggish to flow. It possessed a high repose angle ($\geq 56^{o}$). The agglomeration of SAS-Lub may be due to the cohesion bond between the particles. Table 1 shows that, at a concentration level exceeding 1%, SAS-Lub and MS showed more or/ or less equal glidant effects on MCC powder. The adsorption of lubricant particles onto MCC surface reduced the inter-particulate friction force and facilitate particles movement.

4.2.2 Moisture sorption isotherm

SAS-Lub free powder exhibited less moisture sorption than MCC powder. A hydrophobic film layer of the oil used in processing contributed to reduce moisture sorption exhibited by SAS-Lub. The hydrophobicity of a lubricant in tablets effectively contribute to delay the disintegration and dissolution of the tablets. Tablets lubricated efficient hydrophobic material like MS would absorbed small quantity of moisture and delay the disintegration and dissolution of the tablets. Since SAS-Lub was co-processed from MCC which has a disintegration effect, it is expected to have a disintegration effect.

4.2.3. Lubricant property of SAS-Lub

The incorporation of SAS-Lub or MS to tablet formulation reduced the tensile strengths of the finished tablets. The sound reduction was effected by SAS-Lub. The mode of action of the studied lubricants is explained on the basis of the formation of lubricant isolating monolayer films around the substrate (MCC) particle. These films isolated the aspirities (sites of bonding) available on particles surface. It seems that SAS-Lub films were thick and complete and therefore, the reduction in tablet strength was sound.

The porosity fraction, (1-D), of a tablet batch was found to increase as C of the added lubricant increased in the tablet batch. This is due to the fact that lubricant increases powder elasticity. by Lubrication generally increased powder elasticity. The decompression indexes, k_c , or elasticity factors of the powder formulations lubricated with SAS-Lub and MS were determined. SAS-Lub generated higher k_c value i.e. it sharply decreased the compactibility of MCC powder.

As expected, SAS-Lub showed disintegration activity. It accelerated the disinteg- ration of the tested tablets. This is due to its cellulosic nature. SAS-Lub generated positive DII value. Contrary, due its hydrophobicity,

MS generated smaller DII value i.e, it retarded the disintegration of the tested tablets.

Conclusion

Multi-functional excipients meeting the pharmacopoeal standards can be locally manufactured from a mixture of two or more excipients. Such excipients offer substantial benefits of the incorporated excipients and minimize their drawbacks. The use of a multi-functional excipient may reduce the number of excipients in tablet formulations. Reducing the number of formulation excipient would reduce the capital costs and achieve stable formulations.

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Table 1 Physical properties of lubricants used in the study

Parameter measured	Lubricant Material SAS-Lub	MS
Repose angle, degree	≥ 56	-
Flow rate, g/sec	1.70	-
Density, g/cc		
loose	1.20	-
tap	0.30	-
S_w	1.80	-
Isolation intensity Factor	-32.70	-13.620
Elasticity Factor	0.051	0.027
Disint. Inducing Index, DII	-0.380	0.746

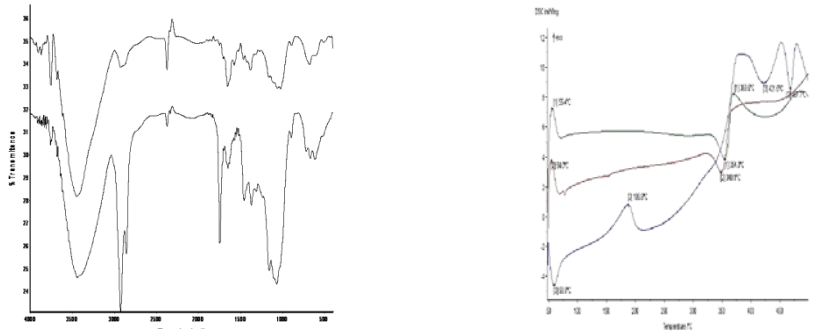
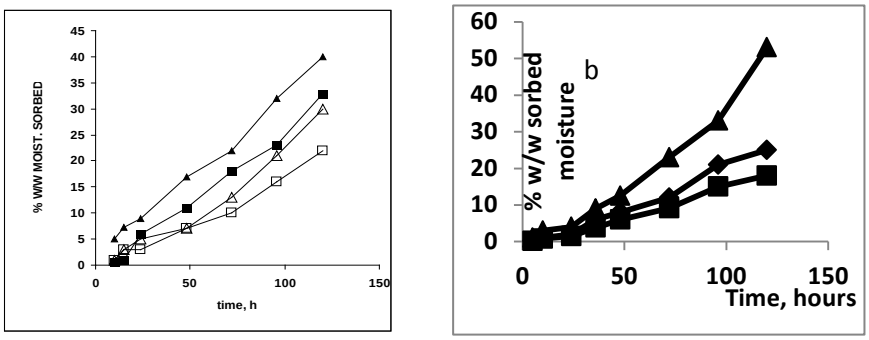


Fig.2 FTIR spectrum and DSC thermo-gram for MCC and oil loaded MCC the blue color curve is for oil.



Figs.3 Moisture sorption isotherm for MCC powder (a) and tablets (b) lubricated with SAS-Lub and MS and stored at 40°C- RH 74%, key: (a) ▲, 0; ■, 1.0, Δ, 2 and □, 3 % w/w SAS-Lub and (b) ▲ un-lubricated and lubricated with 5% w/w ♦, SAS-Lub and ■, MS, respectively

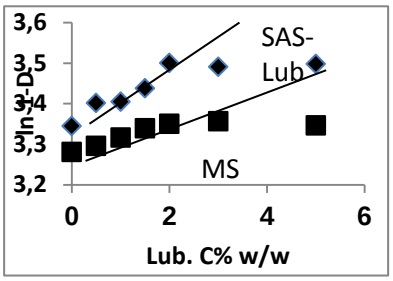


Fig. 5 Effect of the tried lubricants on (1-D) of MCC tablets

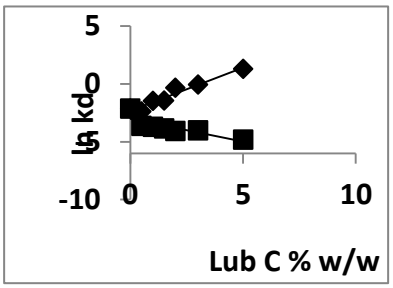


Fig. 6 Effect of the tried lubricants on K_d of the tested MCC tablets