Acta Poloniae Pharmaceutica – Drug Research, Vol. 70 No. 6 pp. 1087–1096, 2013 ISSN 0001-6837
Polish Pharmaceutical Society

A STUDY OF MICRONIZED POLOXAMERS AS LUBRICANTS IN DIRECT COMPRESSION OF TABLETS

JITKA MUŽÍKOVÁ[1*], BARBORA VYHLÍDALOVÁ[1] and TOMÁŠ PEKÁREK[2]

[1] Department of Pharmaceutical Technology, Charles University in Prague,
Faculty of Pharmacy in Hradec Králové, Heyrovského 1203, 500 05 Hradec Králové, Czech Republic
[2] Zentiva, k.s., Prague, Czech Republic

Abstract: The study evaluates the micronized poloxamers Lμtrol®micro127 (poloxamer 407) and Lμtrol®micro 68 (poloxamer 188) as lubricants in combination with the dry binders microcrystalline cellulose and spray-dried lactose. Magnesium stearate was employed as the comparative lubricant. The parameters under study included energy for friction, plasticity, ejection force, tensile strength of tablets, and disintegration time of tablets. The factors of influence were the concentration of lubricants, compression force, and mixing parameters. The lubricating effect of micronized poloxamers was smaller than that of magnesium stearate. Higher concentrations of poloxamers decreased the tensile strength of tablets from microcrystalline cellulose, shortened the disintegration time, and slightly prolonged the disintegration time in the case of spray-dried lactose. Parameters of mixing of dry binders with poloxamers influenced the tested parameters of compression more in the case of spray-dried lactose. In microcrystalline cellulose, they influenced more the tensile strength and disintegration time of tablets.

Key words: micronized poloxamers, lubricants, spray-dried lactose, microcrystalline cellulose, energy profile of compression, ejection force, tensile strength of tablets, disintegration time of tablets

Lubricants are necessary auxiliary substances for the production of tablets. Their function is to decrease friction during compression and to prevent sticking of tableting material to the upper and lower punch and the die, to facilitate easy pushing up of tablets from the press after compression. These auxiliary substances are used to manufacture tablets from granules also in the technology of direct compression, where in some cases their presence decreases the final strength of tablets. (1). Lubricants are most frequently hydrophobic substances, such as fatty acids and alcohols, salts and esters of fatty acids and oils. Examples are magnesium stearate, calcium stearate, zinc stearate, stearic acid, palmitic acid, stearyl alcohol, hydrogenated castor oil. The most widely used and the verifiably most effective lubricant is magnesium stearate, which generally serves as the reference lubricant for comparison with the effects of other lubricants. Magnesium stearate is not employed in the case of possible incompatibility with the active ingredient or if its hydrophobicity or great influence on the strength of tablets is detrimental. Hydrophobic lubricants cannot be used e.g., in effervescent tablets, where it would prolong the disintegration time too much. In this case water-soluble lubricants are used, e.g., some polyethylene glycols, fumaric acid, and sodium lauryl sulfate (2). More recently the water-soluble micronized poloxamers poloxamer 188 and poloxamer 407, firm names being Lμtrol®micro 68 and Lμtrol®micro 127, are also employed. They are block copolymers of polyoxyethylene – polyoxypropylene, which are micronized to the average particle size of ca. 50 μm (3, 4). The study aimed to investigate these poloxamers in the role of lubricants in combination with two dry binders, spray-dried lactose and microcrystalline cellulose. The parameters under examination were energy for friction, plasticity, ejection force, tensile strength of tablets, and disintegration time of tablets. The factors of influence were compression force, concentration of lubricants and time period and frequency of mixing. All parameters tested were compared with magnesium stearate.

* Corresponding author: e-mail: muzikova@faf.cuni.cz

EXPERIMENTAL

Materials

The dry binders used in the study were the microcrystalline cellulose Microcel® MC-102 (Blanver, Brazil) and spray-dried lactose Flowlac®100 (Meggle-Pharma, Germany). The lubricants were magnesium stearate (Acros Organics, USA), poloxamer 407 - Lμtrol®micro 127 and poloxamer 188 - Lμtrol®micro 68 (BASF, Germany).

Preparation of tableting compositions

A mixing cube KB 15S (Erweka GmbH, Germany) was employed to prepare tableting mixtures of Flowlac 100 and Microcel MC-102 with the lubricants magnesium stearate and micronized poloxamers 407 and 188 in concentrations of 1 and 2%. The time period of mixing for these tableting materials was 2.5 min, frequency of mixing of 17 rpm. Both dry binders were then mixed with 1% of all lubricants using a double frequency of mixing (34 rpm) for a period of 2.5 min and also a double time period of mixing (5 min) with a frequency of 17 rpm. Altogether 24 tableting mixtures in an amount of 20 g were prepared.

Testing of homogeneity of tableting materials:

Homogeneity of mixtures with 1% of lubricants obtained under different mixing conditions was tested on a FTIR spectrometer Nicolet iN10 MX (Thermo, USA), by means of which maps of distribution of the lubricant in the tablet were obtained. In each mixture, two tablets were compressed using a compression force of 17 kN for Flowlac 100 and 5 kN for Microcel MC-102. Tablets were cut by a surgeon blade. No polishing was applied prior to measurement. Cut tablets were placed on a microscopic glass cross-section side up and analyzed. Each spectrum was accumulated by acquisition of 1 scan. The image was acquired from an area of 200 × 200 pts. with 30 micrometer step.

Preparation of tablets, energy evaluation of compression process and ejection force

All tableting materials were used to produce tablets compressed with the use of a special die with an upper and a lower punch on a material testing equipment T1-FRO 50 TH.A1K Zwick/Roell (Zwick GmbH&Co., Germany). Proper compaction took place by applying the pressure on the upper punch. The tablets were of a cylindrical shape without facets with a diameter of 13 mm and weight of 0.5 ± 0.0010 g. Compression velocity was 40 mm/min. Flowlac 100 with lubricants was compacted with the use of compression forces of 12 and 17 kN, for Microcel MC-102 with lubricants compression forces of 4 and 5 kN were used. When the parameters of mixing were changed, tablets were compacted only from mixtures of dry binders with 1% of lubricants and in this case the compression forces of 17 kN for Flowlac 100 and 5 kN for Microcel MC-102 were used. At each compression force 12 tablets were compacted. In the first six tablets, using the computer programme testXpert V 9.01, energy evaluation of compression process was carried out, focusing on the energy consumed for friction and the value of plasticity (5). After the removal of the locking component of the lower punch from the die, ejection force was also evaluated in these tablets.

Measurement of tensile strength of tablets

Tensile strength was always evaluated in 6 tablets, no sooner than 24 h after compaction. Measurements were performed on a Schleuniger apparatus (Dr. Schleuniger Pharmatron AG, Switzerland), which measured tablet sizes accurate to 0.01 mm and destruction force in N. Tensile strength of tablets was calculated according to Eq. [1]:

$$P = \frac{2F}{\pi.d.h}, \qquad (1)$$

where P is the tensile strength of tablets [MPa], F is the destruction force [N], d is the tablet diameter [mm], and h is the thickness of the tablet [mm] (6).

Measurement of disintegration time of tablets

Disintegration times of tablets were evaluated earliest 24 h after compaction always in 6 tablets. Measurements were performed on an apparatus for the determination of disintegration time of tablets Erweka ZT 301 (Erweka GmbH, Germany) following the method described in the chapter *Pharmaceutical Technical Procedures* in (7). The test was carried out without discs in the medium of purified water tempered to 37 ± 1°C.

Statistical processing of results

The results of tensile strengths and disintegration times were statistically processed by means of the computer programmes Excel and Qcexpert. The values of the energy of friction, plasticity and ejection force were statistically processed by the computer programme testXpert V 9.01 directly during compaction. Elementary data analysis yielded the mean values with standard deviations. In the cases of unclear significance of differences in the values,

unpaired *t*-test at a level of significance of 0.05 was employed.

RESULTS AND DISCUSSION

This study aimed to evaluate the micronized poloxamers Lμtrol®micro127 (poloxamer 407) and Lμtrol®micro 68 (poloxamer 188) as lubricants in combination with selected dry binders. Magnesium stearate was employed as the comparative lubricant. Poloxamers were tested in concentrations of 1 and 2%. The dry binders were the spray-dried lactose Flowlac® 100 and microcrystalline cellulose Microcel MC®-102. The two types of fillers were selected on purpose; one is compressed mainly by crushing the particles (Flowlac 100) and the other by plastic deformation (Microcel MC-102). Compression forces were set in such a way as to make the tensile strengths of tablets oscillate about the lower and upper limits of the optimal strength, which is 0.56-1.11 MPa (8). For the mixtures of Flowlac 100 with lubricants, compression forces of 12 and 17 kN and for the mixtures of Microcel MC-102 with lubricants the compression forces of 4 and 5 kN were selected. In tableting materials containing 1% of the lubricant also the influence of the time period and frequency of mixing on the parameters under study were evaluated. The parameters under study were the energy for friction E_1 and plasticity Pl, which are the components of the energy profile of compression. Ejection force and subsequently tensile strength and disintegration time were also evaluated.

Table 1 shows the values of the energy for friction E_1, plasticity Pl and ejection force F_e for mixtures of dry binders with lubricants in concentrations

Table 1. Values of energie for friction, plasticity and ejection force.

Dry binder	Lubricant	CF /kN/	E_1 /J/ (s_{E1} /J/)	Pl /%/(s_{Pl}/%/)	F_e /N/ (s_{Fe})
Flowlac 100	1% Mgst	12	10.94 (0.44)	65.86 (0.22)	53.53 (2.48)
	1% P407		10.41 (0.23)	66.84 (0.27)	209.90 (3.76)
	1% P188		10.17 (0.27)	67.17 (0.43)	204.41 (6.63)
	2% Mgst		10.03 (0.40)	65.41 (0.40)	50.27 (1.27)
	2% P407		9.84 (0.16)	66.89 (0.23)	108.51 (2.26)
	2% P188		10.24 (0.25)	66.25 (0.32)	119.50 (2.83)
	1% Mgst	17	16.12 (0.44)	58.43 (0.26)	74.03 (3.88)
	1% P407		16.95 (0.44)	59.28 (0.35)	295.77 (19.53)
	1% P188		15.46 (0.49)	59.50 (0.37)	239.05 (5.98)
	2% Mgst		14.94 (0.31)	57.38 (0.41)	67.56 (2.41)
	2% P407		16.14 (0.44)	58.43 (0.31)	123.72 (4.15)
	2% P188		15.68 (0.39)	58.24 (0.52)	177.23 (2.35)
Microcel MC-102	1% Mgst	4	4.54 (0.28)	88.94 (0.15)	11.05 (0.37)
	1% P407		4.61 (0.18)	89.20 (0.13)	12.42 (0.27)
	1% P188		4.52 (0.10)	89.14 (0.12)	21.24 (0.35)
	2% Mgst		4.26 (0.08)	88.74 (0.14)	9.20 (0.34)
	2% P407		4.54 (0.05)	89.11 (0.09)	16.53 (0.55)
	2% P188		4.59 (0.12)	88.91 (0.16)	23.01 (0.43)
	1% Mgst	5	6.20 (0.10)	87.96 (0.09)	11.77 (0.36)
	1% P407		6.37 (0.08)	88.22 (0.10)	15.46 (0.35)
	1% P188		6.35 (0.14)	88.08 (0.09)	26.33 (0.41)
	2% Mgst		5.90 (0.17)	87.73 (0.10)	10.46 (0.21)
	2% P407		6.36 (0.15)	88.21 (0.19)	24.86 (0.64)
	2% P188		6.27 (0.12)	87.98 (0.20)	26.95 (0.40)

Explanations: Mgst – magnesium stearate; P407 – poloxamer 407; P188 – poloxamer 188; CF – compression force; E_1 – energy for friction; s – standard deviation; Pl – plasticity; F_e – ejection force.

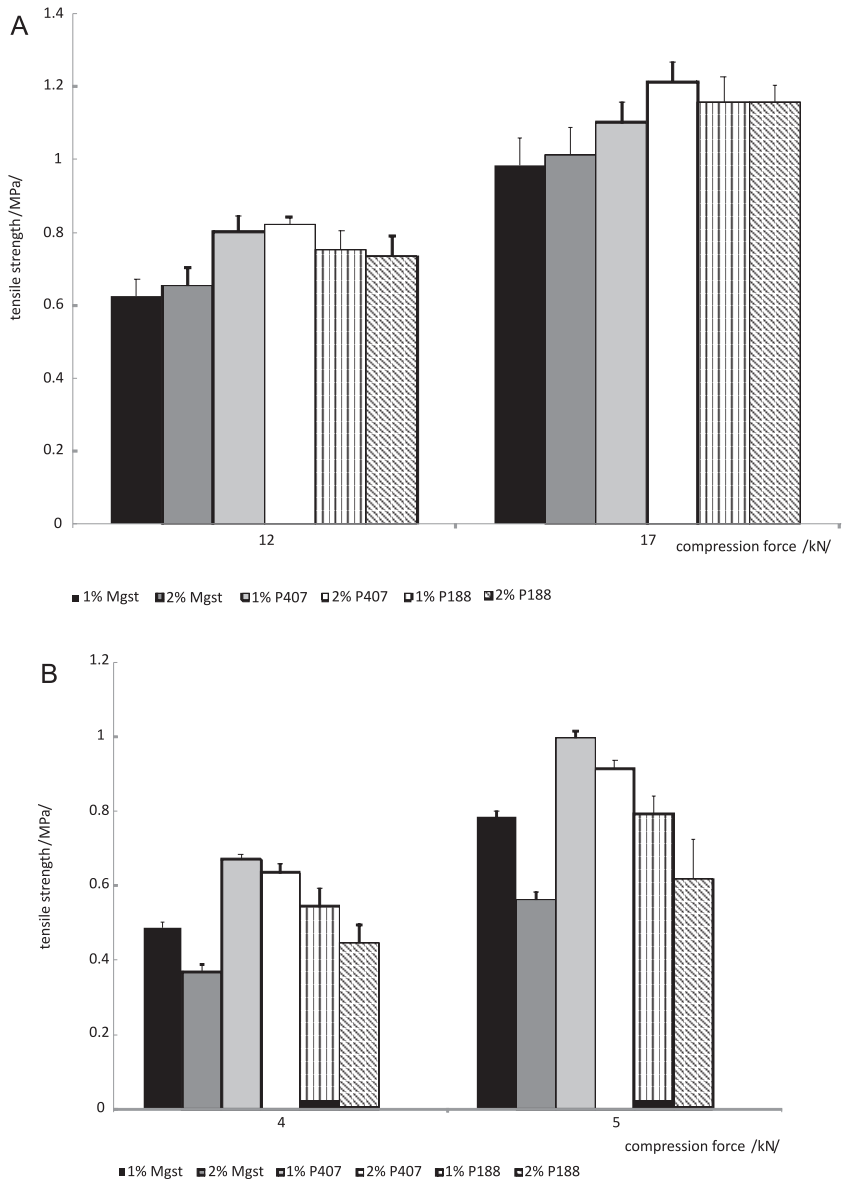

Figure 1. Tensile strength of tablets. **A**: Flowlac 100 with lubricants; **B**: Microcel MC-102 with lubricants. Mgst – magnesium stearate; P407 – poloxamer 407; P188 – poloxamer 188

of 1 and 2%, which were obtained under the identical conditions of mixing, i.e., the time period of mixing was 2.5 min and frequency 17 rpm. In Flowlac 100 the energy for friction was decreased by a double concentration of the lubricant in the case of magnesium stearate and poloxamer 407; in the case of poloxamer 188 there was no statistically significant difference between the values. In microcrystalline cellulose a lower value of energy for friction was recorded for a higher concentration of the lubricant only in the case of magnesium stearate, the other values of this energy for both poloxamers and both concentrations did not show a statistically significant difference with the mixture containing 1% of magnesium stearate. In the case of both dry binders the values of the energy for friction were logically increased with the compression force. On the other hand, the values of plasticity decreased with the compression force as the result of decreased porosity of tablets (9). In the case of Flowlac 100, the lowest values of plasticity were recorded for the mixture with 2% of magnesium stearate; increased

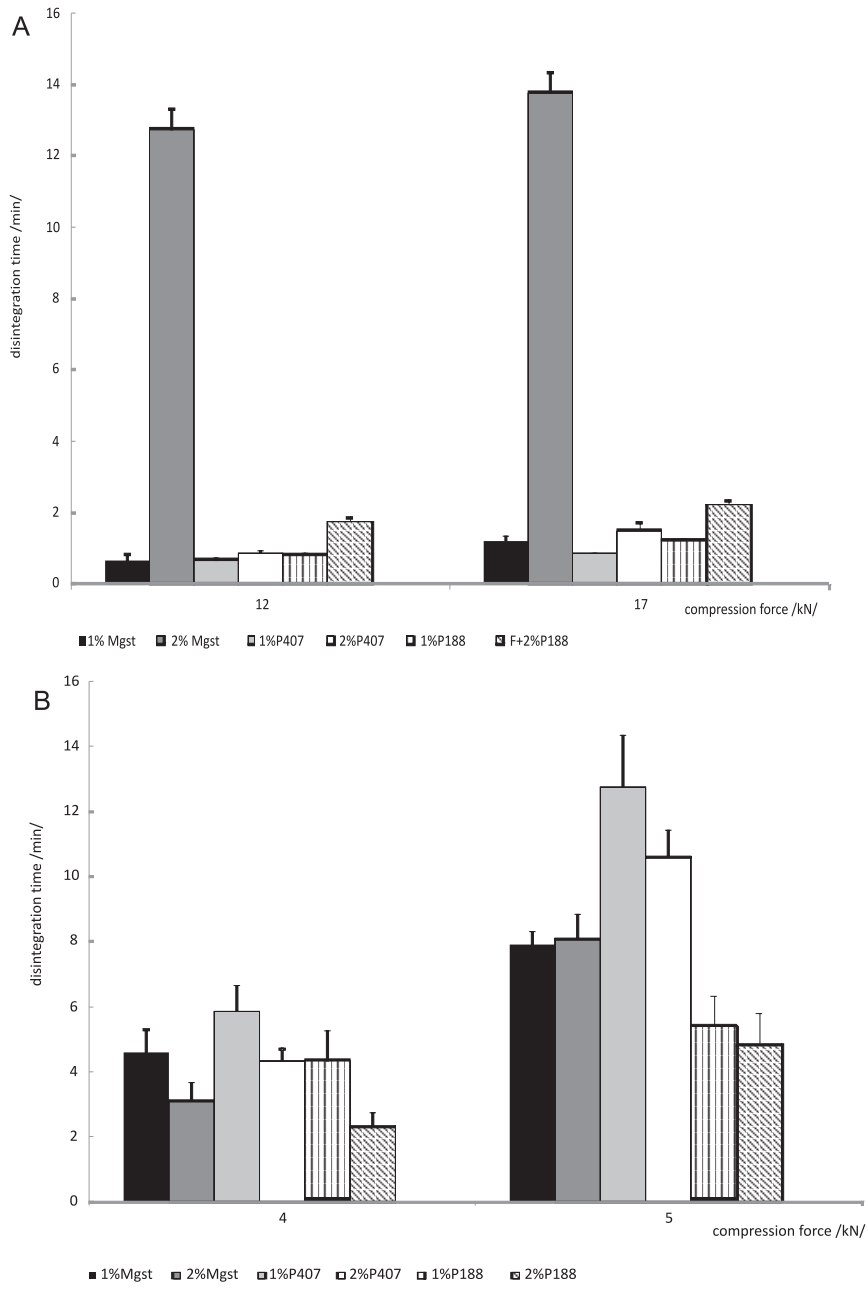

Figure 2. Disintegration time of tablets. **A**: Flowlac 100 with lubricants; B: Microcel MC-102 with lubricants. Mgst – magnesium stearate; P407 – poloxamer 407; P188 – poloxamer 188

concentrations of poloxamers decreased plasticity excepting Poloxamer 407 at the compression force of 12 kN, where no statistically significant difference was found between the values within the range of the concentration. In the case of microcrystalline cellulose, the values of plasticity were generally higher, because the substance is plastically deformable. The lowest values were found again in the mixtures with stearate, where they again decreased with its increasing concentration. In the mixtures with poloxamers no statistically significant differences were recorded within the range of the concentration used. The values of the ejection force in Flowlac 100 increased with the compression force

and were multiple times lower in the mixtures with magnesium stearate; at the same time, its higher concentration did not exert more marked influence on ejection force, which means that the 1% concentration was sufficient. On the other hand, increased concentrations of poloxamers exerted marked influence on a decrease in ejection force; this decrease was the most markedly manifested in the case of poloxamer 407 at the compression force 17 kN. In the case of Microcel MC-102, the values of ejection force were much smaller, because microcrystalline cellulose itself possesses a certain lubricating effect and its lowest values were found again in the mixtures with magnesium stearate; the values were decreased also in the case of its higher concentration. With the use of poloxamers, a contrary phenomenon appeared than in Flowlac 100, i.e., there was an increase in ejection force due to their higher concentrations excepting poloxamer 188 at the compression force of 5 kN, where no statistically significant difference between the values was found. It is necessary to state that this increase in the values is not marked, yet in this case a 2% concentration of poloxamers is useless. Table 2 shows the identical evaluation parameters for the mixtures of dry binders with 1% lubricants, which are mixed under different conditions (double time period and frequency of mixing). The presented results show higher dependence of E_1 on the parameters of mixing and the lubricant used for the substance Flowlac 100. The lowest value of energy for friction was achieved in the mixture with magnesium stearate with twofold frequency of mixing, and in the mixture with poloxamer 188 at the time period of mixing of 2.5 min and the frequency of 17 rpm. The smallest influence on the parameters of mixing was shown by poloxamer 407 and at twofold frequency of mixing in the range of lubricants there was no statistically significant difference between the values. In Microcel MC-102 there were no marked differences in the values of energy for friction within different parameters of mixing; the values decreased only slightly with the time period and frequency of mixing in magnesium stearate, in poloxamers they were slightly increased. There was no statistically significant difference between the individual poloxamers. In the mixtures of Flowlac 100 with magnesium stearate, plasticity was not changed with changes in

Table 2. Values of energy for friction , plasticity and ejection force at diferent parameters of mixing.

Tableting material	TM/min/; SM /rpm/	CF /kN/	E_1 /J/ (s_{E1} /J/)	Pl/%/(s_{Pl}/%/)	F_e /N/ (s_{Fe})
F100 + 1% Mgst	2.5; 17	17	16.12 (0.44)	58.43 (0.26)	74.03 (3.88)
F100 + 1% P407			16.95 (0.44)	59.28 (0.35)	295.77 (19.53)
F100 + 1% P188			15.46 (0.49)	59.50 (0.37)	239.05 (5.98)
F100 + 1% Mgst	5; 17		14.99 (0.44)	58.25 (0.26)	63.10 (1.71)
F100 + 1% P407			16.56 (0.31)	58.09 (0.45)	161.27 (2.52)
F100 + 1% P188			16.76 (0.30)	58.12 (0.23)	230.15 (3.51)
F100 + 1% Mgst	2.5; 34		15.8 (0.552)	58.11 (0.30)	61.29 (0.93)
F100 + 1% P407			16.24 (0.19)	58.63 (0.36)	162.49 (2.54)
F100 + 1% P188			15.89 (0.39)	59.09 (0.32)	189.75 (5.63)
MCC + 1% Mgst	2.5; 17	5	6.20 (0.10)	87.96 (0.09)	11.77 (0.36)
MCC + 1% P407			6.37 (0.08)	88.22 (0.10)	15.46 (0.35)
MCC + 1% P188			6.35 (0.14)	88.08 (0.09)	26.33 (0.41)
MCC + 1% Mgst	5; 17		5.92 (0.15)	88.00 (0.10)	12.10 (0.51)
MCC + 1% P407			6.75 (0.17)	88.47 (0.11)	20.65 (1.33)
MCC + 1% P188			6.71 (0.13)	88.42 (0.06)	23.36 (0.55)
MCC + 1% Mgst	2.5; 34		5.69 (0.16)	87.63 (0.11)	10.67 (0.37)
MCC + 1% P407			6.60 (0.20)	88.24 (0.08)	16.66 (0.34)
MCC + 1% P188			6.47 (0.10)	88.26 (0.08)	18.88 (0.27)

Explanations: F100 – Flowlac 100; MCC – Microcel MC-102; Mgst – magnesium stearate; P407 – poloxamer 407; P188 – poloxamer 188; CF – compression force; E_1 – energy for friction; s – standard deviation; Pl – plasticity; F_e – ejection force; TM – time of mixing; SM – speed of mixing.

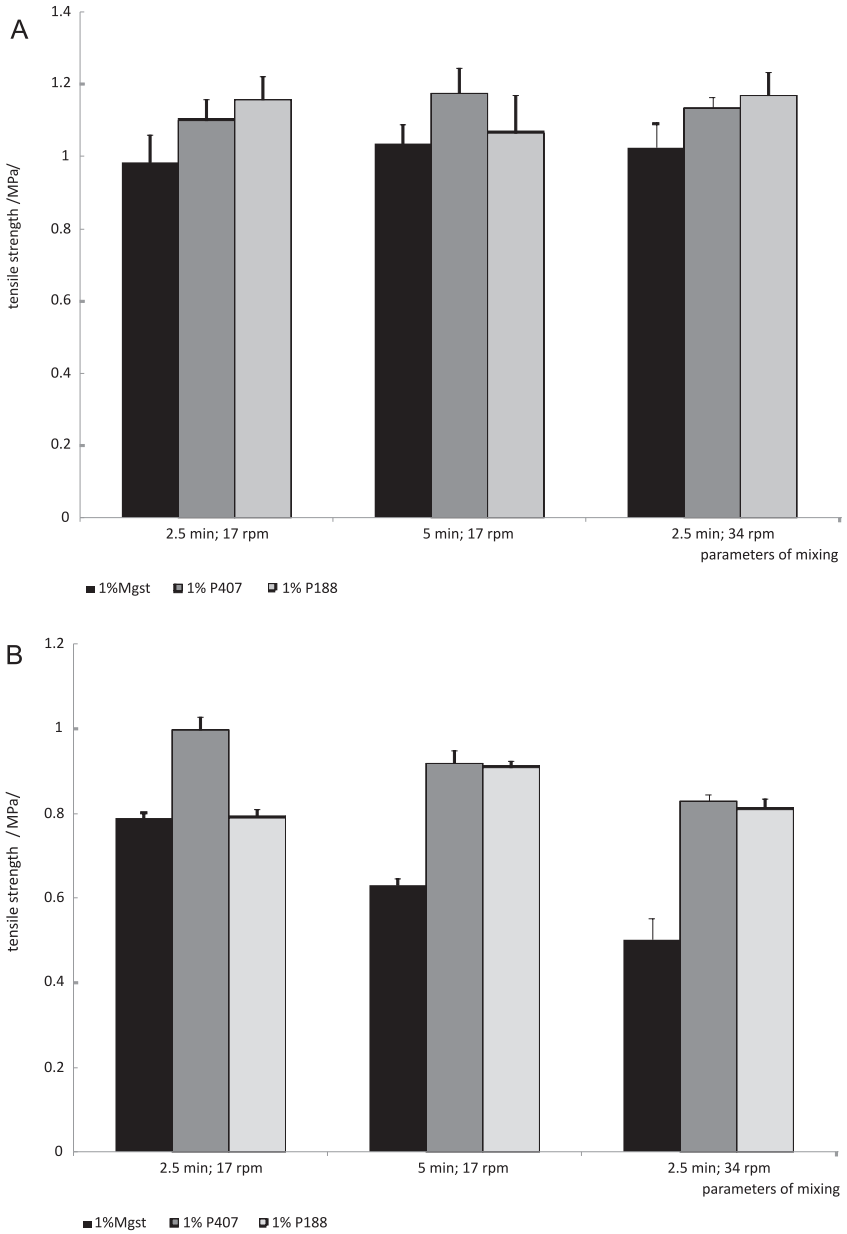

Figure 3. Tensile strength of tablets at diferent parameters of mixing. **A**: Flowlac 100 + 1% of lubricant; **B**: Microcel MC-102 + 1% of lubricant. Mgst – magnesium stearate; P407 – poloxamer 407; P188 – poloxamer 188

the parameters of mixing and the values in this type of the lubricant were the lowest, excepting the twofold time period of mixing, where there was no statistically significant difference between the values. Plasticity of the mixtures of Microcel MC-102 with lubricants was the lowest again in the case of magnesium stearate, where it was decreased to the lowest value with the twofold frequency of mixing. There was no statistically significant difference between poloxamers. The values of ejection force in the mixtures of Flowlac 100 with magnesium stearate were the lowest and were not influenced by the parameters of mixing. With the use of poloxamer 407, the lowest value of ejection force was observed at the twofold time period of mixing, in poloxamer 188 at the twofold frequency of mixing. The values of ejection force of the mixtures of Microcel MC-102 with magnesium stearate were the

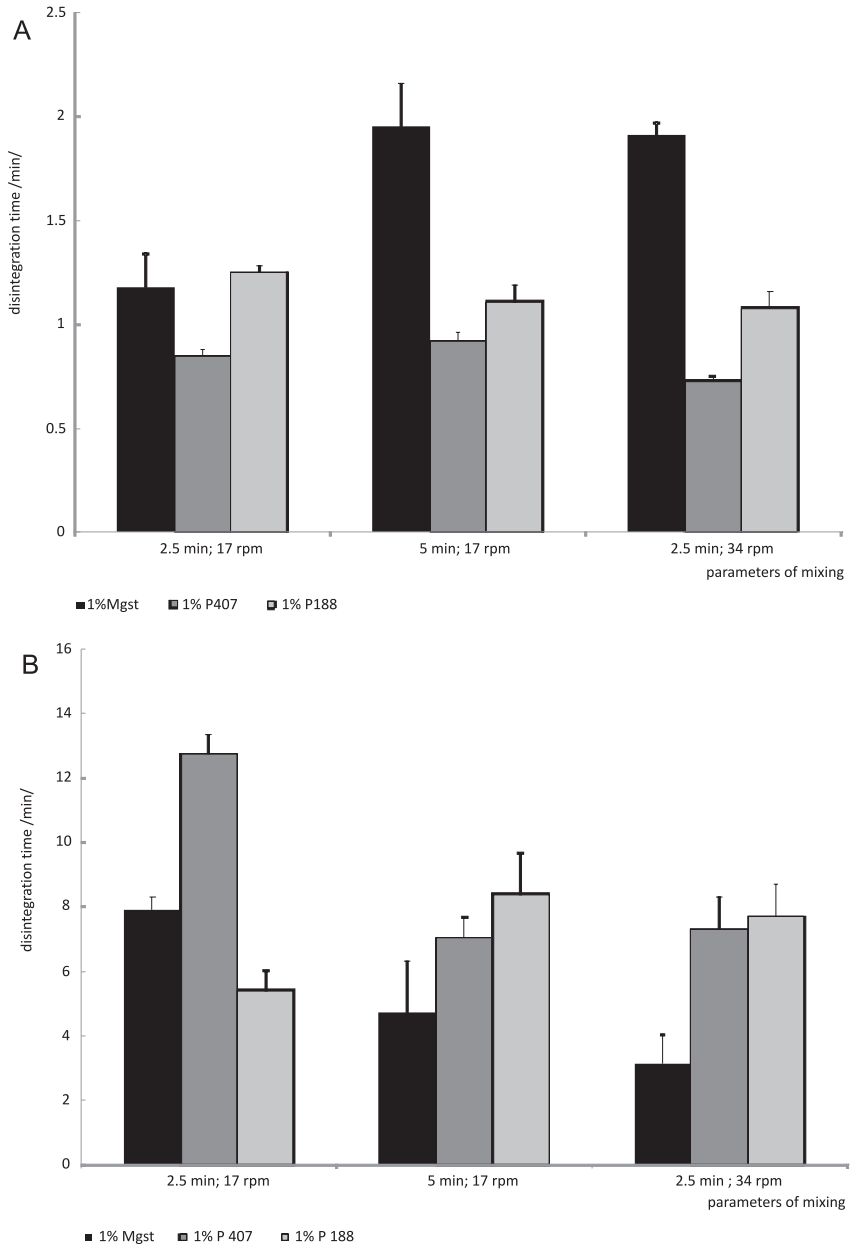

Figure 4. Disintegration time of tablets at diferent parameters of mixing. A: Flowlac 100 + 1% of lubricant; B: Microcel MC-102 + 1% of lubricant. Mgst – magnesium stearate; P407 – poloxamer 407; P188 – poloxamer 188

lowest and independent of the parameters of mixing. With the use of poloxamer 407 the most advantageous time period of mixing seemed to be 2.5 min with a frequency of 17 rpm, with the use of poloxamer 188 it was a twofold frequency of mixing. The tested properties of tablets included tensile strength and disintegration time. Figure. 1 (A, B) represents the values of tensile strength of tablets for dried binders with lubricants under study. In Flowlac 100 the lowest strength was recorded in the mixtures with magnesium stearate, no statistically significant difference being observed between the values for both concentrations. The strongest tablets were provided by the mixtures with 2% poloxamer 407, and

at the compression force of 12 kN there was no statistically significant difference with the value of 1% poloxamer 407. In the case of poloxamer 188, no statistically significant difference between the values was found within the range of the concentrations employed. A different situation was observed in Microcel MC-102, where higher concentrations of all lubricants decrease the strength of tablets, the least strong being those with magnesium stearate. In microcrystalline cellulose the lubricants decreased the strength of tablets, because the substance is plastically deformable and the produced film of the lubricant on the particles of the dry binder negatively intervenes into the strength of the bonds of the dry binder. In the case of spray-dried lactose the intervention of lubricants into tensile strength of tablets is not too marked, as the mechanism of compaction is mainly fragmentation. It means that during compaction new inter-surfaces originate, not coated with the lubricant, and the bonds thus become stronger (10). In both cases the tensile strength of tablets was increased with compression force. Figure 2 (A, B) shows the effect of lubricants on disintegration times of tablets from both dry binders. Disintegration time was increased with compression force. In Flowlac 100 a prolongation of disintegration time was observed due to the higher concentration of the lubricant, and a very long prolongation of disintegration time was recorded in magnesium stearate due to its hydrophobicity. In the case of poloxamers, it might be due to moderate gelation (11). In Microcel MC-102, the concentration of the lubricant exerted a contrary effect, excepting magnesium stearate at the compression force of 5 kN, where the hydrophobicity of the lubricant maintained an identical disintegration time. In other cases a higher concentration of the lubricant thus decreased disintegration time, and this fact is most probably connected with decreased tensile strength and the hydrophilic character of poloxamers. At the compression force of 5 kN, the longest disintegration time was observed in the tablets with poloxamer 407, which was most probably due to their higher strength, but again with possible gelation (11). The influence of the parameters of mixing was also evaluated in the mixtures of dry binders with 1% of lubricants on tensile strength and disintegration time of tablets (Figs. 3, 4). In Flowlac 100 in the individual lubricants no effect was observed of prolonged time period or increased frequency of mixing on tensile strength of tablets. In the case of Microcel MC-102 tensile strength of tablets decreased by the action of a prolonged time period and increased frequency of mixing very markedly in the case of magnesium stearate, and then in the case of poloxamer 407. In the case of poloxamer 188 the tablets were least strong at the time period of mixing of 2.5 min and the frequency of 17 rpm. The disintegration time in tablets in Flowlac 100 was prolonged due to a longer time period and higher frequency of mixing only in the case of the mixture with magnesium stearate. In Microcel MC-102 a contrary effect was observed, where the disintegration time was shortened by a change in the parameters of mixing, most probably as the result of decreased tensile strength of tablet. The disintegration time of tablets was shortened also in the presence of poloxamer 407 and, on the contrary, in the mixtures with poloxamer 188 it was prolonged. Also this finding is in agreement with tensile strength of tablets. Homogeneity testing of tableting materials for Flowlac 100 with lubricants showed the optimal time period of mixing to be 5 min using the frequency of 17 rpm. The shorter time of mixing produced lower homogeneity and at the higher frequency of mixing aggregates of the particles of the lubricant developed. In the case of microcrystalline cellulose, the best homogeneity was achieved under varying conditions of mixing in dependence on the lubricant employed. The results of homogeneity testing did not correlate in any significant manner with the measured parameters of compacting and properties of tablets.

CONCLUSION

Micronized poloxamers function in tablets as lubricants, even though their effect in the concentrations under study is markedly lower than that of magnesium stearate. Plasticity of mixtures of dry binders with micronized poloxamers is higher than that of the mixtures with magnesium stearate, and the same holds true for the strength of tablets made from these mixtures. A higher concentration of poloxamers decreases the strength of tablets from microcrystalline cellulose, shortens the disintegration time, and in the case of spray-dried lactose it slightly prolongs the disintegration time. The parameters of mixing influence the tested parameters of compression of mixtures of dry binders with micronized poloxamers more than those with magnesium stearate. This is more manifested in spray-dried lactose. The influence of the parameters of mixing on the properties of tablets is more evident in microcrystalline cellulose. The resulting influence of micronized poloxamers as lubricants on the process of compaction and the properties of tablets therefore depends on the dry binder employed.

Acknowledgments

The study was supported by the firms Meggle – Pharma and Blanver, which supplied the samples of the dry binders tested.

REFERENCES

1. Bolhuis G.K., Hőlzer A.W.: in Pharmaceutical powder compaction technology, 2nd edn., Çelik M. Ed., p. 205, Informa Healthcare, New York 2011.
2. Armstrong N. A..: in Pharmaceutical dosage forms: Tablets, 3rd edn., Vol. 2, Ausburger L.L., Hoag S.W. Eds., p. 251, Informa Healthcare USA, Inc, New York 2008.
3. Collett J. H., Popli H..: in Handbook of pharmaceutical excipients. 3rd edn., Kibbe A. H. Ed., p. 386, American Pharmaceutical Association and Pharmaceutical Press, Washington, London 2000.
4. BASF: Fir. lit.2012, http://ebookbrowse.com/basf-lutrolmicro-pdf-d58109473
5. Ragnarsson G.: in Pharmaceutical powder compaction technology, Alderborn G., Nyström Ch. Eds., p. 77, Marcel Dekker Inc., New York 1996.
6. Fell J.T., Newton J.M.: J. Pharm. Sci. 59, 688 (1970).
7. European Pharmacopoeia. 7th edn., Vol. 1, Council of Europe, Strasbourg 2010.
8. Belousov V.A.: Khim. Farm. Zh. 10, 105 (1976).
9. Picker-Freyer K.M.: in Pharmaceutical manufacturing handbook: Production and processes, Gad S.C. Ed., p. 1053, John Wiley and Sons, Inc., New Jersey 2008.
10. Jarosz P.J., Parrot E.L.: Drug Dev. Ind. Pharm. 10, 259 (1984).
11. Dumortier G., Grossiord J.L., Agnely F., Chaumeil J.C.: Pharm. Res. 23, 2709 (2006).

Received: 04. 03. 2013