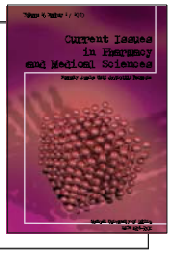
2013 © Curr. Issues Pharm. Med. Sci. Vol. 26, No. 3, Pages 339–343

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA
on-line: www.umlub.pl/pharmacy



Dimethicone impact on aeration of suppository mass in Unguator mixing machine

ANDRZEJ MAREK WINNICKI*, DANUTA PARTYKA, KATARZYNA JACHOWICZ, TOMASZ MACHEROWSKI, ŁUKASZ MARCHWIŃSKI, PAULINA NĘDZA, MARTYNA STEBNICKA, JOANNA SULEJEWSKA

Chair of Pharmaceutical Technology, Faculty of Pharmacy, Ludwig Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń

ABSTRACT

Suppository mass foaming is an important technological problem when making suppositories in an Unguator mixing machine that has an impact on the final quality and the decreased content of an active ingredient in suppositories. Dimethicone is commonly used as antifoam reducing the surface tension of liquid, which forms walls of gas bubbles. The study shows that using dimethicone results in the reduction of aeration of the suppository mass from 10.5% to 20.1%.

Keywords: aeration, suppository, dimethicone, Unguator mixing machine

INTRODUCTION

The foam is most often a dispersion of a gas in a liquid, stabilized by surfactants absorbed on the gas/liquid interface or high viscosity of the dispersing liquid [8]. Foaming can occur in the process of distillation, filtration, fermentation or mixing and it adversely affects the final quality of a pharmaceutical product [1]. Because of that, antifoams or defoamers are excipients/additives commonly used in the cosmetic and pharmaceutical industry. Addition of capryl or amyl alcohols, flaxseed, castor or rapeseed oils to the water-based mixtures was the past antifoam procedure [6]. Nowadays the most common antifoams are polydimethylsiloxanes (PDMS), used in water or oil dispersions. PDMS are produced as preparations of various viscosity, sometimes with addition of micronized silicon dioxide having the particle size of 0.1-10 μm. Through the synergism of silicone oil and the hydrophobic particles of silicon dioxide, the silicone oil decreases the surface tension of the liquid, which forms walls of gas bubbles while the silicon dioxide pinches off the weakened structure [3, 9]. One of the most frequently used representatives of polydimethylsiloxanes in the pharmaceutical industry is dimethicone. The properties of dimethicone decreasing the surface tension are mainly used in pharmaceutical preparations applied in tympanites (it enables break-up of gas bubbles in the intestines, followed by its resorption and elimination).

Dimethicone is also used in anti-inflammatory rectal suppositories. These suppositories contain silicone emulsion consisting of 0.01-85% dimethicone and 0.01-45% dimethyl sulfoxide (DMSO). The mechanism of action of such a system consists in the gradual absorption of DMSO by the anal mucosa to the systemic circulation; dimethyl sulfoxide reaches the organs in which a great concentration of reactive oxygen species (ROS) occurs, binds the ROS, transfers them to the silicone emulsion where they are neutralized, and then is excreted in the feces. A decrease in pain is already observed after 15 minutes. No medicinal effect is observed after using DMSO on its own [4].

In suppositories for hemorrhoid treatment dimethicone adsorbed in the porous polystyrene divinylbenzene layer is used; it inhibits the elution of the drug substance (benzocaine, bismuth subgallate or hydrocortisone) from the affected area [7].

The introduction of the Unguator mixing machine to the Polish market in 2001 greatly simplified the preparation of ointments and suppositories in chemists. Suppositories made in the Unguator mixing machine are characterized by better homogeneity compared to the preparations made by traditional methods.

Corresponding author
* Chair of Pharmaceutical Technology, Ludwig Rydygier Collegium Medicum in Bydgoszcz, Faculty of Pharmacy,
2 Jurasza Str., 85-089 Bydgoszcz
e-mail:andrzej.winnicki@cm.umk.pl

DOI: 10.12923/j.2084-980X/26.3/a.22

However, the possibility of aeration (foaming) of the suppository mass that occurs while mixing, which leads to great deviations in the mass of suppositories and thereby to a decrease in the content of the active ingredient below its declared value [2], should be considered. Some authors recommend in such cases correcting of the aeration of suppositories by changing mixing parameters of the suppository mass [5]. Thus considering the literature data on the anti-foaming properties of silicone [9], as well as its use in suppositories [4, 7], the aim of this study was to examine the possibility of reducing the aeration of the suppository mass by adding dimethicone to suppositories made in chemists.

MATERIALS AND METHODS

Active ingredients and excipients. Oleum Cacao – lot no. D031371, Ziaja Ltd Zakład Produkcji Leków Sp. z o.o.; *Aminophyllinum* – lot no. 010307, PPH Galfarm Sp. z o.o.; *Papaverini hydrochloridum* – lot no. 011209, PPH Galfarm Sp. z o.o.; *Luminalum natricum* – lot no. 011010, Farmaceutyczno-Chemiczna Spółdzielnia Pracy "Galenus"; *Acidum acetylsalicylicum* – lot no. 010810, PPH Galfarm Sp. z o.o.; *Metamizolum natricum* – lot no. 010908, PPH Galfarm Sp. z o.o.; *Hydrocortisonum* – lot no. 270509BG, Zakłady Farmaceutyczne "Amara"; *Ephedrini hydrochloridum* – lot no. 139806, Zakłady Farmaceutyczne "Amara"; *Prednisolonum* tabl. 20 mg – lot no. 00080310 Pabianickie Zakłady Farmaceutyczne Polfa S.A.; *Dimethiconum* 350 – lot no. 10205, Łódzkie Przedsiębiorstwo Farmaceutyczne "Polon".

screwed. When the cocoa butter melted, it was poured to the plastic 1-gram suppository molds. After the cocoa butter had been partly-congealed at room temperature, the suppositories were placed in the fridge. After the cocoa butter had been solidified, the suppositories were taken from the molds and weighed. An analogical procedure was carried out for the next working parameters of the machine.

Making suppositories. Suppositories with drug substances were made according to the prescriptions presented in Table 1.

The calculated appropriate amount of cocoa butter was weighed to the tared 100 ml jar, then drug substances earlier pulverized and mixed in the mortar were added. The jar was closed with the lid with the fixed spindle, and the jar was attached to the Unguator mixing machine. On the operation panel the rotation level (2) and mixing time (9 minutes) were set. After the mixing was completed, the jar was unscrewed from the support of the mixing machine, the lid with the mixing blade was removed, and the content was poured into ten 1-gram plastic molds. The procedure was repeated three times and 30 suppositories were obtained. The molds with the suppositories after partial congealing were placed in the fridge. After solidifying, the suppositories were taken from the molds and weighed.

Making suppositories with the addition of dimethicone. For each prescription two additional formulations were prepared which varied from the initial content with the addition of 1% of dimethicone (marked 1%D) and 5% of dimethicone (marked 5%D). The anti-foam was added to

Table 1. Contents of prescriptions for rectal suppositories

1 Rp.	2 Rp.	3 Rp.	4 Rp.	5 Rp.
Aminophyllini 0.1	Aspirini	Hydrocortisoni 0.05	Ephedrini hydrochloridi	Metamizoli natrici 0.25
Papaverini mur. 0.03	Metamizoli natrici aa 0.1	Cacao ol. q.s.	Encortoni aa 0.005	Cacao ol. q.s.
Luminali natrici 0.02	Cacao ol. q.s.	M.f.supp.anal. D.t.d. No 10	Cacao ol. q.s.	M.f.supp.anal. D.t.d. No 10
Cacao ol. q.s.	M.f.supp.anal. D.t.d. No 10	S. Once a day. Child 10 years old.	M.f.supp.anal. D.t.d. No 10	S. 3 x a day. Child 5 years old.
M.f.supp.anal. D.t.d. No 10	S. 3 x a day. Child 6 years old.		S. 2 x a day. Child 5 years old.	
S. 2 x a day. Child 7 years old.				

Equipment. Suppository molds 1 g – lot no. 21100711, Alfelder Kunstoffwerke; precision balance 110g Radwag WPS/10/C/2 max=110 g, d=0.001 g, e=0.010 g; UNGUATOR e/s mixing machine with accessories.

Making suppositories

Selection of mixing parameters of the Unguator mixing machine. A portion of 10.0 g of cocoa butter was weighed to the tared 100 ml jar. A reusable mixing blade was inserted into the opening in the lid. The lid with mixing blade was screwed on the jar, and using the spindle the jar was attached to the mixing unit. Working parameters of the mixing machine were set on the operation panel (e.g. level 9, time 1 minute). After the completion of mixing, the jar was detached and the lid with the mixing blade unthe tared jar with the cocoa butter and pulverized drug substances. The next steps were as in the section "Making suppositories".

Relative rate of reduction of the suppository mass aeration. The relative rate of reduction of aeration of the suppository mass was calculated using the following formula:

$$AR\%_{rel} = \frac{m_d - m_0}{m_d} \quad (1)$$

where:
$AR\%_{rel}$ – rate of reduction of aeration of suppository mass
m_0 – average mass of a suppository made in the Unguator mixing machine without dimethicone
m_d – average mass of a suppository made in the Unguator mixing machine after adding dimethicone.

Statistical analysis. The statistical analysis of results was carried out using Statistica software with the significance level of α=0.05. To determine the average mass of a suppository, measures of location (quartile) were used because the mass distribution of some lots of suppositories differed from the normal distribution, and the application of classical measures (e.g. arithmetic mean) in such a case would result in falsifying the results of statistical analysis.

The Kruskal-Wallis one-way analysis was performed to test statistical significance of differences between average suppository masses measured for various formulations.

RESULTS AND DISCUSSION

In the preliminary studies, the influence of the mixing parameters in the Unguator mixing machine on the average weight of a suppository (Tab. 2) was examined. It should be stressed that for obtaining suppositories, a choice of appropriate mixing parameters is necessary. Selection of too low rotation speed and too short time of mixing did not cause the melting of cocoa butter (e.g. level 4, time 3 minutes), which made it impossible to pour the suppository mass into the molds or the melted suppository mass was not liquid enough to pour all the suppositories (e.g. level 2, time 7 minutes) (Tab. 2). Suppositories obtained with appropriate parameters of work of the mixing machine were characterized by varied average weight, e.g. when setting level 9 for 9 minutes suppositories with the weight of 1.065±0.008 g were obtained, whereas when setting level 2 for 7 minutes – 0.680±0.015 g. This divergence in average suppository weight was caused by the aeration of the suppository mass while mixing. With the fixed capacity of the suppository mold, density of the suppository mass has an influence on the final weight of a suppository. Comparing the weight of suppositories, it is possible to determine the aeration of the suppository mass. The smaller the weight of a suppository, the smaller the density of the suppository mass and the greater aeration.

In order to study the impact of dimethicone on the aeration of the suppository mass for the further part of the experiment, working parameters of the mixing machine were chosen with which the greatest number of suppositories of the smallest average weight (the greatest aeration) were obtained, i.e. rotation level 2, mixing time 9 minutes (Tab. 2). The user's guide of the Unguator mixing machine suggests making the suppository mass for 8 minutes on level 4. However, suppositories obtained that way were aerated (average weight of 0.934±0.010 g) (Tab. 2).

In the next part of the study the impact of dimethicone on the aeration of suppositories containing typical drug substances and made on the basis of five selected pediatric prescriptions was studied (Tab. 1). Suppositories of a determined content were made in three formulations: first – without dimethicone, second – with 1% dimethicone, third – with 5% dimethicone. All formulations were made in the Unguator mixing machine on rotation level 2 with mixing time of 9 minutes. Statistical calculations for prepared suppositories are presented in Tab. 3. In Figure 1 differences in average weights of suppositories depending on dimethicone content are presented. The average weight of suppositories without dimethicone was always lower than the weight of suppositories with dimethicone, e.g. 3Rp. – 0.830±0.020 g, 3Rp1%D – 1.039±0.022 g; 3Rp.5%RpD – 1.027±0.014 g. Moreover, in the case of suppositories with dimethicone, significantly lower variability of results (smaller interquartile range) than in suppositories without dimethicone was observed.

Table 2. Median weight of suppositories in grams (median±quartile deviation) depending on the rotation speed level of the Unguator mixing machine and its working time (in brackets there is the number of casted suppositories with appropriate parameters of work of the Unguator e/s mixing machine)

		Time [min]								
		1	2	3	4	5	6	7	8	9
		Median weight of suppositories ±quartile deviation [g] (number of casted suppositories)								
Level of rotation speed of Unguator mixing machine	9	(0)	0.922±0.008 (9)	0.968±0.017 (9)	1.035±0.027 (9)	1.025±0.031 (9)	1.053±0.006 (8)	1.048±0.005 (9)	1.063±0.040 (7)	1.065±0.008 (8)
	8	(0)	(0)	0.883±0.008 (8)	0.994±0.009 (9)	0.983±0.016 (9)	1.031±0.022 (9)	1.041±0.009 (8)	1.041±0.070 (9)	1.055±0.010 (9)
	7	(0)	(0)	(0)	0.897±0.008 (8)	1.010±0.018 (9)	1.024±0.011 (8)	1.037±0.014 (8)	1.047±0.003 (9)	1.051±0.007 (9)
	6	(0)	(0)	(0)	(0)	0.877±0.004 (7)	0.980±0.015 (9)	1.003±0.009 (8)	1.032±0.029 (9)	0.996±0.009 (8)
	5	(0)	(0)	(0)	(0)	(0)	0.850±0.009 (9)	0.942±0.015 (9)	0.949±0.010 (9)	0.993±0.019 (9)
	4	(0)	(0)	(0)	(0)	0.789±0.006 (10)	0.813±0.012 (10)	0.857±0.026 (10)	0.934±0.010 (9)	0.982±0.020 (10)
	3	(0)	(0)	(0)	(0)	(0)	(0)	0.735±0.013 (8)	0.760±0.010 (10)	0.845±0.035 (10)
	2	(0)	(0)	(0)	(0)	(0)	(0)	0.680±0.015 (7)	0.690±0.005 (9)	0.740±0.015 (10)
	1	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Table 3. Basic descriptive statistics of studied suppositories

Type of suppository	Me	Q_1	Q_3	IQR	Q	Min	Max
1Rp.	0.919	0.867	0.954	0.087	0.043	0.997	0.833
1Rp.1%D	1.106	1.096	1.113	0.017	0.008	1.137	1.074
1Rp.5%D	1.101	1.098	1.118	0.020	0.010	1.133	1.077
2Rp.	0.907	0.800	0.927	0.127	0.064	1.008	0.776
2Rp.1%D	1.117	1.109	1.122	0.013	0.007	1.140	1.094
2Rp.5%D	1.134	1.108	1.145	0.037	0.018	1.172	1.096
3Rp.	0.830	0.816	0.856	0.040	0.020	0.887	0.794
3Rp.1%D	1.039	1.024	1.068	0.044	0.022	1.083	1.006
3Rp.5%D	1.027	1.014	1.043	0.029	0.014	1.072	0.992
4Rp.	0.869	0.834	0.932	0.098	0.049	0.964	0.810
4Rp.1%D	1.021	1.006	1.034	0.028	0.014	1.071	0.992
4Rp.5%D	1.045	1.036	1.064	0.028	0.014	1.091	1.012
5Rp.	1.003	0.976	1.022	0.046	0.023	1.058	0.965
5Rp.1%D	1.121	1.112	1.132	0.020	0.010	1.148	1.101
5Rp.5%D	1.135	1.126	1.150	0.024	0.012	1.186	1.114

Notes: Me – median, Q1 – first quartile, Q3 – third quartile, IQR – interquartile range, Q – quartile deviation, Min – minimum, Max – maximum.

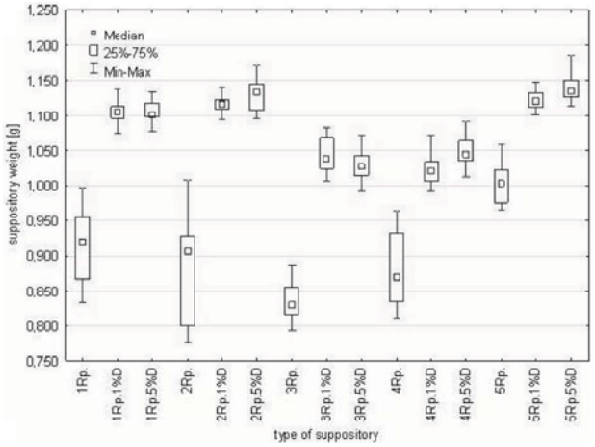


Fig. 1. Graphical presentation of the differences in the average weight of the suppositories

Statistically significant differences in the average weight of a suppository between formulations without dimethicone and formulations containing dimethicone were found (p-value below 0.05, marked red in Tab. 4). No statistically significant differences in the average weight of a suppository between formulations containing 1% dimethicone and 5% dimethicone were found.

For a quantitative determination of the impact of dimethicone on the aeration of the suppository mass the rela0-tive rate of reduction of aeration was calculated according to formula 1. In this method, the point of reference was the average weight of suppositories made with the addition of dimethicone. The positive relative rate of aeration means that there was a decrease in aeration by a given percentage value. A zero value means that the excipient has no impact on the decrease in aeration. A negative value means that the excipient causes an increase in aeration by a given percentage value. The relative rate of reduction of aeration of suppositories with dimethicone is significant and depending on the formulation ranges from 10.5% (5Rp.1%D) to 20.1% (3Rp.1%D) (Tab. 5).

Table 5. Relative rate of reduction of aeration of suppositories after adding dimethicone

Type of suppository	Relative rate of reduction of aeration [%]	Type of suppository	Relative rate of reduction of aeration [%]
1Rp.	–	**4Rp.**	–
1Rp.1%D	16.9	**4Rp.1%D**	14.9
1Rp.5%D	16.5	**4Rp.5%D**	16.8
2Rp.	–	**5Rp.**	–
2Rp.1%D	18.8	**5Rp.1%D**	10.5
2Rp.5%D	20.0	**5Rp.5%D**	11.6
3Rp.	–		
3Rp.1%D	20.1		
3Rp.5%D	19.2		

In summary, it is possible to say that suppositories made using the Unguator mixing machine undergo the aeration process which depends on the time and the speed of mixing the suppository mass. The aeration of the suppository mass translates directly into a decrease in its density and the weight of suppositories. Due to the aeration of the suppository mass, it is inappropriate to apply standard methods for calculating the quantity of cocoa butter because it causes excess production of the suppository mass and thereby the suppositories can be characterized by a decreased content of drug substances [2]. The addition of dimethicone to the suppository mass significantly reduces the aeration of suppositories and can be one of the ways to prepare suppositories in chemists. The content of 1% dimethicone is sufficient to reduce the aeration of the mass suppositories.

Table 4. P-values for multiple comparisons carried out with the Kruskal-Wallis one-way analysis: H (14, N=450) =412.118 p=0.0000 (statistically significant p-values were marked red)

	Median weight of suppositories ±quartile deviation [g]														
	0.919± 0.043	1.106± 0.008	1.101± 0.010	0.907± 0.064	1.117± 0.007	1.134± 0.037	0.830± 0.020	1.039± 0.022	1.027± 0.014	0.869± 0.049	1.021± 0.014	1.045± 0.014	1.003± 0.023	1.121± 0.010	1.135± 0.012
	1Rp.			**2Rp.**			**3Rp.**			**4Rp.**			**5Rp.**		
p-value	0.0000	**1Rp. 1%D**		0.0000	**2Rp. 1%D**		0.0000	**3Rp. 1%D**		0.0433	**4Rp. 1%D**		0.0000	**5Rp. 1%D**	
	0.0000	1.0000	**1Rp. 5%D**	0.0000	1.0000	**2Rp. 5%D**	0.0003	1.0000	**3Rp. 5%D**	0.0000	1.0000	**4Rp. 5%D**	0.0000	1.0000	**5Rp. 5%D**

Acknowledgaments

The study was financed by a grant from Collegium Medicum in Bydgoszcz, Student Scientific Research "The impact of mixing parameters of the Unguator mixing machine and anti-foams on the suppository mass".

A poster of this work was presented at the 22nd Scientific Congress of Polish Pharmaceutical Society, Białystok, Poland.

REFERENCES

1. Bergeron V., et al.: Polydimethylsiloxane (PDMS)-based antifoams. Colloid. *Surface. A*., 122, 103, 1997.
2. Bill M., Allen L. (2008): Manufacturing suppositories. In: Allen L. Suppositories. *Pharmaceutical Press*, p. 99.
3. Denkov N.: Mechanisms of Foam Destruction by Oil-Based Antifoams. *Langmuir*, 22, p. 9463, 2004.
4. Exner H.: Method for producing of a preparation of a solid DMSO-containing silicone oil emulsion for binding of reactive oxygen compounds in human and animal bodies. Patent US 2009/0104235 A1, 2009.
5. Gold M., VePuri M., Block M. (1996).: Suppository Development and Production. In: Lieberman H., Rieger M., Banker G. Pharmaceutical Dosage Forms: Disperse Systems. Vol. 2., *Marcel Dekker*, p. 447.
6. Karakashev S., Grozdanova M.: Foams and antifoams. *Adv. Colloid. Interfac*., 176, 1, 2012.
7. Koral E., Oswald M.: *Multiphase pharmaceutical formulations.* Patent EP 0 486 117 B1, 1996.
8. Miller C.: Antifoaming in aqueous foams. Curr. *Opin. Colloid. In*., 13, 177, 2008.
9. Von Phul S., Stern L.: Antifoam. What is it? How does it work? Why do they say to limit its use? http://www.d-foam.com/files/Antifoam_What_Is_It.pdf (08.02.2013).