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Glyceryl Laurate Tablets: Effect of the Excipients and Granule Size on the Tablet Quality

Special Issue Article

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Abstract Glyceryl laurate (GL) is a natural or synthetic surfactant with antiviral and antimicrobial activity and is not only effective in common colds or flu, but also against swine flu, herpes simplex, shingles, or chronic fatigue. The study aimed to formulate the GL granules as a semi-product for the compression of tablets and evaluate the influence of the substitution of sucrose laurate (Ryoto®) with sucrose ester (Sisterna®) in the composition of the granules and the effect of granule size on the quality of the compressed tablets. Four types of granules, varying in grain size and the type of additional surfactant, were prepared by melt granulation. The traditional pharmacopoeia tests were used to assess tablets' quality. The granule size significantly affected all evaluated parameters: hardness, uniformity of mass, friability, and disintegration. The replacement of sucrose laurate with sucrose ester caused a slight decrease in tablet strength and a shortening of disintegration. However, it did not significantly impact friability and uniformity of mass. For this reason, the excipient, sucrose ester, can be evaluated as an adequate replacement in the composition of GL tablets.

Keywords *glyceryl laurate – monolaurin – melt granulation – granules – quality tests*

INTRODUCTION

Glyceryl laurate (GL), also known as glycerol monolaurate or monolaurin, is a naturally occurring compound. It was first available as a dietary formulation in the mid-60s of the 20th century and today it is known as a dietary supplement suitable for supporting the immune system, a healthy balance of intestinal microflora, or as a product to maintain beneficial yeast levels (Barker et al., 2019; Fosdick et al., 2022; Luo et al., 2022). The richest source is coconut oil, but GL is also found in breast milk and palm oil. In addition to natural sources, it is produced by partial esterification of pure glycerol, chemical glycerolysis of fats and oils by inorganic catalysts, or enzymatic glycerolysis (Nandi et al., 2004; Nitbani et al., 2022; Serri and Muhammad Shahrin, 2019). The formation of an ester bond between lauric acid and glycerol occurs in two isoforms, that is, α-glyceryl laurate and β-glyceryl laurate. However, chemically synthesized α-monolaurin seems to be more active (Dayrit, 2015). It does not have an irritating effect, is nontoxic, and can be used as a food additive or taken as a nutritional supplement daily. GL belong to substances generally recognized as safe (Feltes et al., 2013). It acts as a nonionic, hydrophilic–lipophilic surfactant with excellent emulsifying properties, which is the reason for its wide application in the food, cosmetic, and pharmaceutical industries (Feltes et al., 2013). Due to its antimicrobial activity, it is also used as a preservative and can extend the shelf life of food. Oh and Marshall (1992) compared the minimal inhibitory concentration (MIC) of GL and other common food antimicrobials (e.g., propyl parahydroxybenzoate, butylated hydroxyanisole, etc.) against *Listeria monocytogenes* and found the lowest MIC of GL (10 μg mL^{-1} at pH 7.00).

Generally, the mechanism of action of surfactants on the intestinal microbiota may consist in modifying the viscosity and motility of mucin or the cytoplasmic membrane of bacteria colonizing the intestine. Alternatively, they reduce adhesion and thus the ability of bacteria to adhere to the surface. It is assumed that the antimicrobial activity of GL with different mechanisms of action is determined precisely by its nature, which is described by several works (Churchward et al., 2018; Yoon et al., 2018; 2015).

GL is incorporated into the cell membrane and causes its damage by solubilizing lipids and phospholipids. It disrupts signal transduction and transcription in the cell and

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prevents replication, thus preventing the spread of bacteria. In addition, GL stabilizes the human host cell membrane (Dayrit, 2015; Projan et al., 1994). It is proved that GL inhibits the production of exotoxin and other proteins at the level of bacterial DNA. Besides that, it blocks the production of beta-lactamases that are responsible for resistance to penicillins and cephalosporins (Subroto and Indiarto, 2020).

GL-inactivated lipid coat bacteria include *L. monocytogenes*, *Helicobacter pylori*, *Hemophilus influenzae, Staphylococcus aureus*, *Streptococcus agalactiae,* and streptococci (group A, B, F, and G) (Lieberman et al., 2006). Besides that, it acts on the species *Bacillus cereus/stearothermophillus/subtilis* and *Enterococcus faecalis* (Subroto and Indiarto, 2020).

In addition, a beneficial effect of GL on maintaining healthy vaginal microflora has been demonstrated as it can inhibit the pathogens *Candida vaginalis* and *Gardenella vaginalis* without adversely affecting the beneficial bacterial strains of *Lactobacillus* and altering the vaginal pH (Strandberg et al., 2010). Besides *Candida albicans*, GL exhibits antifungal activity against *Aspergillus* sp.*, Penicillium* sp.*, Cladosporium* sp.*, Fusarium* sp., *Alternaria* sp.*, Fonsecaea pedrosoi,* and *Cryptococcus neoformans* (Nitbani et al., 2022).

The mechanism of antiviral action consists in damaging the lipid envelope of the virus. Since GL is of the same size as the lipid molecules of the virus, it is absorbed into its fat layer. The virus thus loses its binding ability, is unable to enter the host cells, and continues to infect and replicate. When GL attaches to the virus envelope, the virus becomes more sensitive to the immune system. It also disrupts virus replication by blocking DNA replication signals and the process of maturation and spread of viruses (Arora et al., 2010; Peterson and Schlievert, 2006; Projan et al., 1994). GL works against various viruses, especially enveloped lipid sheaths (human immunodeficiency virus, measles virus, herpes simplex virus, herpes viridae, human lymphotropic virus, vesicular stomatitis virus, visna virus, cytomegalovirus, Epstein–Barr virus, influenza virus, pneumovirus, sarcoma virus, syncitial virus, rubeola virus) (Lieberman et al., 2006). It also inhibits various influenza and respiratory viruses (RSV, HP1V2, H1N1, paramyxo and myxoviruses). GL-like, monocaprine and monocapryline, also have good results against influenza viruses, Their virucidal activity increases at lower pH (about 4.2) (Arora et al., 2010). Welch et al. reported that GL inhibits the replication of enveloped mumps, yellow fever, and Zika virus at concentrations of 80 µg/mL (Welch et al., 2020). Since the chemical structure of GL is similar to the structure of soaps, it could be equally effective against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), destroying viral membranes and preventing RNA synthesis, binding to the host cell, and virus maturation (Subroto and Indiarto, 20 20).

GL also plays a particularly important role in the development of infants' immune systems and their ability to resist various infections. It occurs naturally in breast milk. At an amount of about 3 mg mL^{-1}, it forms an important part of its lipid composition (Nitbani et al., 2022; Subroto and Indiarto, 2020). The support for the immune system happens through modulating lymphocyte production and controlling immune cell proliferation. GL may also play a role in inhibiting the production of proinflammatory cytokines (Subroto and Indiarto, 2020). GL has another benefit for the human body. It is a so-called bioactive lipid able to reduce serum cholesterol levels and thus prevent cardiovascular disease (Eyres et al., 2016).

The study aimed to evaluate the influence of the substitution of sucrose laurate with sucrose ester in the composition of GL granules and the effect of the excipients and the granule size on the quality of the compressed tablets. Through melt granulation, the excipients were effectively agglomerated with a meltable binder. There was no need of water, other organic solvents, or subsequent drying of the material. It is a time- and energy-saving technique. The principle of the granule preparation consisted in creating a solid solution from components of suitable properties and subsequent disaggregation of this solution using a high-shear mixer. The rest of the powder components were added to the solid solution, which, due to heat and mixing, formed the final granules, which were then pressed through various sieves.

MATERIALS AND METHODS

Ryoto® sugar ester L1695 (sucrose laurate) and GL were obtained from K2pharm s.r.o. (Opava, Czech Republic). Sucrose ester Sisterna® SP70 (E473) (sucrose stearate/palmitate) was purchased from Sisterna (Roosendaal, the Netherlands). Sorbitol and microcrystalline cellulose were obtained from CentralChem (Bratislava, Slovakia). (+)-Lactic acid 80% liquid was obtained from PENTA s.r.o. (Prague, Czech Republic). Talc was purchased from Galvex (Banská Bystrica, Slovakia). Magnesium stearate and aminoacetic acid were obtained from Sigma-Aldrich/Merck KgaA (Darmstadt, Germany).

Formulation of granules

The granules were prepared by melt granulation. The solid ingredients (see Table 1) were sieved through a sieve (250 µm). After homogenization of the ingredients, both mixtures (A_1/A_2) were spread on a baking pan in a thin layer and left to melt in the oven heated to 105°C for 1 h during occasional stirring. Subsequently, the molten mass was allowed to cool at room temperature. The solid solution A_1/A_2 was homogenized with the mixture B in a blender for 15 min at a maximum speed. Then the mixture was transferred to a granulator (Frewitt, Germany), where the mass was extruded through the sieve (1.25 or 4 mm). In this way, four types of granules were prepared, in which sucrose laurate was replaced by sucrose ester (Sisterna) and which varied in granule size as the scheme explains.

Table 1. The preparation of the granules.

Ingredient	Mixture A_1	Mixture A_2	Mixture B
Glyceryl laurate (g)	54.75	54.75	54.75
Sucrose laurate/Ryoto (g)	7.50	-	-
Sucrose ester/Sisterna (g)	-	7.50	-
Sorbitol (g)	15.00	15.00	15.00
Lactic acid (g)	-	-	1.50
Amino acetic acid (g)	-	-	1.50

Table 2. The final composition of the tablets.

Component/formulation	F1	F2	F3	F4
Glyceryl laurate (%)	35.40	35.40	35.40	35.40
Sucrose laurate/Ryoto (g)	2.42	-	2.42	-
Sucrose ester/Sisterna (g)	-	2.42	-	2.42
Sorbitol (%)	9.70	9.70	9.70	9.70
Amino acetic acid (%)	0.49	0.49	0.49	0.49
Lactic acid (%)	0.49	0.49	0.49	0.49
Talc (%)	1.20	1.20	1.20	1.20
Magnesium stearate (%)	0.30	0.30	0.30	0.30
Microcryst. cellulose (%)	50.00	50.00	50.00	50.00
Granule size (mm)	<1.25	<1.25	<4	<4

Formulation of tablets

To the granules, talc, magnesium stearate, and microcrystalline cellulose were added and homogenized for 10 min. The tablets were compressed from the material by an eccentric tablet press machine (Korsch, Germany).

Quality assessment of tablets

The quality of tablets was assessed by the traditional pharmacopoeia tests: a) uniformity of mass (Ph. Eur. 10, 2019c), b) friability (Ph. Eur. 10, 2019a), c) resistance to crushing (Ph. Eur. 10, 2019b), and d) disintegration (Ph. Eur. 10, 2019a). Moreover, the four formulations of tablets ($n = 20$) were compared for their apparent density (g cm^{-3}).

RESULTS

DISCUSSION

Uniformity of mass

The tablets comply with the test of uniformity of mass if at the most, two of the individual masses deviate from the average mass by not more than ±5% and no tablet deviates by more

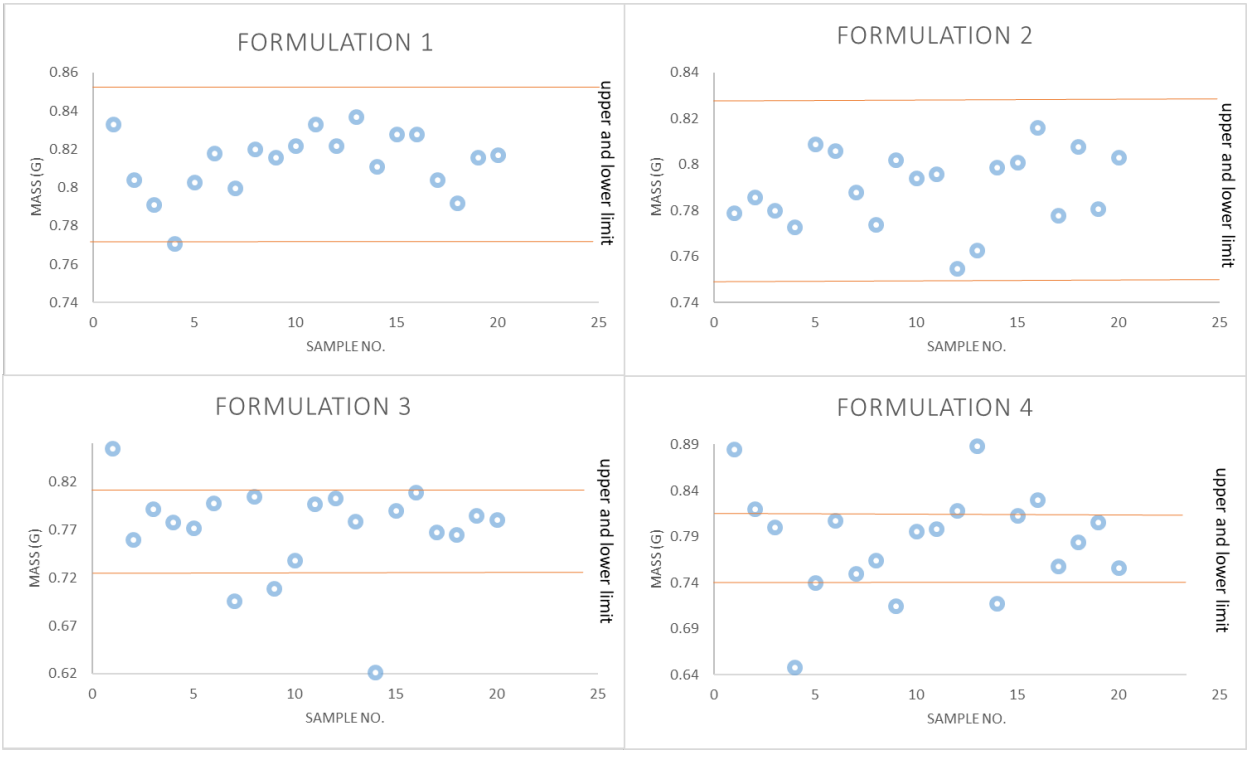

Figure 1. The uniformity of mass of the tablets with different composition (F1 vs. F2) or different granule size (F1 vs. F3/F2 vs. F4).

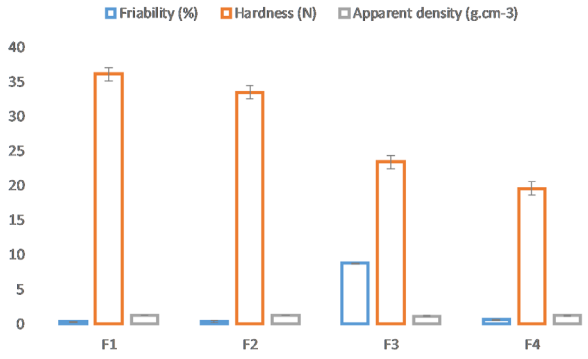

Figure 2. Physical parameters and mechanical resistance of the tablets.

than twice the permitted deviation (Ph. Eur. 10, 2019c) applying to all four tablet formulations, as the average mass is more than 250 g. As it is obvious from Fig. 1 representing the mass deviation of the permitted range (upper and lower limits) calculated for a specific batch of tablet formulation, only F1 and F2 met the requirement.

Apparent density

Simultaneously with the mass uniformity test, the height (*h*) and diameter (*r*) of the cylindrical tablets were determined. With the parameters, it was possible to express the volume (*V*) of the tablets and recalculate their apparent density (ρ) as a weight (*m*) to volume (*V*) ratio.

$$\rho = \frac{m}{\pi r^2 h} \ (\mathrm{g.cm^{-3}})$$

The apparent density was moving around 0.909 ± 0.013 g cm^{-3} for all batches. The differences caused by the replacement of sucrose laurate with sucrose ester (Sisterna) in the composition were statistically significant, as well the differences caused by the variability in granule size in the formulation F1 versus F3 (Student's *t*-test: $p < 0.05$). Conversely, the influence of the granule size on apparent density was not confirmed in formulation F2 versus F4 (Student's *t*-test: $p > 0.05$).

Friability

The maximum permissible loss on the tablet's weight after rotating is not more than 1%. If the tablets break, crack, or otherwise change their basic shape during the mechanical stress, the tablets automatically do not meet the requirement on the test of friability (Ph. Eur. 10, 2019a). The results are shown in Fig. 2. Only formulations F1, F2, and F4 met the pharmacopoeia requirement on friability. The tablets of the third batch (F3) disintegrated during rotation, which caused an increase in the percentage loss.

Hardness

As Fig. 2 shows, the hardness of the tablets increased in the following order: F4 < F3 < F2 < F1, that is, the strongest tablets contained sucrose laurate. Therefore, it can be concluded that the grain size significantly affects the hardness of the tablet. Smaller grain size favors the strength of the tablets. The substitution of sucrose laurate by sucrose ester (Sisterna) in the composition caused a negligible decrease in tablet hardness.

Disintegration

The uncoated tablets have to disintegrate within 15 min without leaving the rest on the sieve, as the European Pharmacopeia recommends. Only F2 met this limit with a disintegration time of about 14 min. F1 disintegrated within 19 min. The tablets compressed from granules with a larger grain size disintegrated within 30 min.

Both melts looked the same when removed from the drying oven. When processing the granules in a blender, both mixtures showed the same processing time. After homogenization of the granules with the excipients, the individual pairs of tablets could not be distinguished at the first glance. During compression, all four tablet formulations exhibited the same properties, which means that the excipient replacement or granule size does not have a significant effect on compression. The tablets had similar colors, smell, and the same shape. All four formulations were waxy to touch. Visually, they differed only in the granule size inside the tablet. Comparison of the quality parameters (F1 vs. F2) showed similar properties of tablets containing sucrose laurate and sucrose ester. It can be summarized that their substitution in the composition does not affect the visual and physical properties of the tablet.

CONCLUSION

Using melt granulation and addition of other excipients, especially microcrystalline cellulose, partial prevention of the adhesion of the material to the punches was achieved, resulting in the compression of the quality tablets when granules of smaller grain size (less than 1.25 mm) were used. Finally, it can be concluded that sucrose ester is a suitable substitute for sucrose laurate, without having a significant effect on the quality of pressed tablets, as long as a suitable granule size is used. The mentioned tablet production is not suitable for large-scale manufacture. During the manual pressing of the tablets by an eccentric press, it was possible to check the press punches during the process and possibly clean them, which is inadmissible and nonsecurable in the case of large-scale production. Therefore, it would be more appropriate to pack the final granules into hard capsules. Even in this case, the better flow properties of the granules

with a smaller size were demonstrated. The results of the comparison of GL granules containing various surfactants, as well as the influence of the modified granulation technique on the properties of the granules are the subject of another, more extensive study.

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