ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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TECHNOLOGICAL PECULIARITIES FOR OBTAINING OF MEDICATED CHEWING GUMS

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Key words: medicated chewing gum; technology; direct compression; Health in gum compositions

A medicated chewing gum (MCG) is a new alternative solid dosage form for oral application, which is used for the delivery of a great number of active pharmaceutical ingredients. Monographs for this dosage form are introduced in the SPhU, European Pharmacopoeia and United States Pharmacopoeia. But to date, domestic manufacturers do not produce preparations in the form of medicated chewing gums. This is primarily due to the complexity of the equipment applied and the absence of appropriate legal documentation for MCG manufacture, which limited the introduction of this dosage form in pharmaceutical companies of Ukraine. We have analyzed the literature data on the methods of obtaining a medicated chewing gum, as well as the basic technological aspects and the equipment applied have been considered. This allowed us to conclude that with development of compositions for obtaining chewing gums by direct compression Pharmagum® (SPI Pharma, USA) and Health in gum® (Cafosa, Spain) the possibility of production of this dosage form in domestic enterprises has increased and is promising to date. Chemically, they are a mixture of polyols (sorbitol/xylitol/mannitol) and of sugars with gum bases, plasticizers and anti-caking agents. Chewing gums made by these compositions give faster release of drugs than conventional methods owing to lower binding of the medicinal substance with the gum base and can be directly compressed on a conventional tablet machine.

Nowadays, a chewing gum is part of daily life of many people [1, 5, 8, 9]. The SPhU and European Pharmacopoeia contain a monograph "Chewing gums, medicated", according to which they are "solid preparations containing one or more active substances and a base consisting mainly of a gum that are intended to be chewed but not swallowed. They are intended to be used for local treatment of mouth diseases, systemic drug delivery after absorption through the buccal mucosa or from the gastrointestinal tract" [2, 6-11]. That is, a medicated chewing gum (MCG) is a new alternative solid dosage form for oral application, which is used for the delivery of a great number of active pharmaceutical ingredients [3, 5, 8, 10, 11].

A medicated chewing gum has several advantages over other solid dosage forms for application in the mouth. This is, first of all:

- innovation and modernity;
- better perception by the patient and a pleasant way to introduction of drugs, especially for children;
- it is not required to use water, i.e. it is possible to use it in any convenient place for the patient;
- there is no need to swallow, it is important for children and people who have problems with swallowing of drugs;
- providing a rapid effect;
- fewer side effects and others [4, 5, 8, 9].

Unfortunately, due to the absence of the corresponding regulatory documentation, which controls the production of drugs, and because of the complexity of equipment required for production of MCG, current domestic drugs in the form of medicated chewing gums are absent at the pharmaceutical market of Ukraine.

The aim of this work is to characterize the methods for obtaining of medicated chewing gums and consider their main technological aspects.

Experimental Part

When developing a medicated chewing gum, only if there is a correct selection of active substances and excipients, the rational technology and storage conditions can provide the desired therapeutic effect.

Besides active pharmaceutical ingredients (API) and the base, MCGs contain excipients, which type and amount depend on the method of the gum obtaining. During chewing a medicated gum does almost not decrease in the volume, but the active substances and excipients are dissolved or dispersed gradually in saliva, then the base becomes tasteless and thrown away [5, 7, 8, 10, 11].

Methods employed for manufacturing of a chewing gum can be classified into three main classes [8, 10, 11]:

1. Conventional / traditional method (Melting method).
2. Freezing, grinding and tabletting method.
3. Direct compression method.

Results and Discussion

The traditional method is the previous melting or softening of the gum base (butadiene-styrene-like basic copolymer, isobutylene-isoprene copolymer (butyl

rubber), polyvinyl acetate and identical polymers) and subsequent mixing with the desired active substances and excipients. The mixture obtained is then sent through a series of rollers for obtaining a thin, wide ribbon. During this process a light coating of finely powdered sugar or sugar substitutes is added to enhance the flavour and to keep the gum away from sticking. In a carefully controlled room, the gum is cooled for 48 hours, after that it is cut to the desired size and cooled at a controlled temperature and humidity. If it is necessary for obtaining of the desired appearance of the product, then MCG is further processed (coating, glossing, etc.).

However, this method has several disadvantages: elevated temperature used in melting restricts the use of this method for thermosensitive ingredients; melting and mixing of a highly viscous gum mass makes controlling of accuracy and uniformity of drug dose difficult; there is a risk of providing an inaccurate form, shape or weight of the dosage form; because of the complexity of the equipment (extrusion and rolled lines) and facilities involving hot-melt and cool processers the technology itself is not so easily adaptable to incorporate the manufacturing conditions required for production of pharmaceutical products. In addition, such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%); if attempted to grind and tablet such a composition would jam the grinding machine, stick to blades, screens adhere to punches and would be difficult to compress [8, 10, 11].

The method of freezing (cooling), grinding and tabletting has been developed with an attempt to decrease the moisture content and alleviate the problems of the conventional method mentioned above.

In this method the gum base is cooled to a temperature, at which the composition is sufficiently brittle and will remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. The temperature required for cooling is determined in part by the composition of the chewing gum. Generally, the temperatures of the cooled mixture are around -15°C or lower. As coolants a liquid nitrogen, hydrocarbon slush are used; solid carbon dioxide is preferred as it can give low temperatures (up to -78.5°C), sublimes readily on warming the mixture, is not absorbed by the chewing gum composition, does not interact adversely with the processing apparatus and does not leave behind any residue, which may be undesirable or potentially hazardous.

To facilitate cooling, grinding and to achieve the desired properties of a chewing gum some excipients such as a grinding agent and an anti-caking agent can be added to the composition.

An anti-caking agent such as precipitated silicon dioxide can be mixed with the chewing gum composition and solid carbon dioxide prior to grinding. It helps to prevent agglomeration of the subsequently ground chewing gum particles.

To prevent the gum from sticking to the grinding apparatus the grinding auxiliary substance can be incorporated (in the amount of 2-8%): alkaline metal phosphate, an alkaline earth metal phosphate or maltodextrin. However, the practical use of these substances is limited because these substances are highly alkaline and, therefore, will be incompatible with acidic ionisable therapeutic agents. They also tend to remain in the composition of the final chewing gum, and it may be problematic for therapeutic and safety point of view.

After the composition is ground to a powder, the coolant is removed by allowing the coolant to evaporate. After that the powder is mixed in a suitable mixer (sigma mill, high shear mixer or fluidized bed reactor) with other ingredients. The resulting mixture is transferred to the stage of pressing, which can be carried out by any conventional process like punching on a tablet machine.

However, this method has several disadvantages such as a large number of the equipment applied; careful monitoring of moisture during the tabletting process [8, 10, 11].

The manufacturing process can be accelerated, and the above-mentioned disadvantages are excluded using compositions for obtaining chewing gums by direct compression *Pharmagum*® (SPI Pharma, USA) and *Health in gum*® (Cafosa, Spain) [4, 8, 10, 11]. These compositions are manufactured under GMP conditions, comply with food chemical specifications and are "generally regarded as safe" (GRAS), regulated by FDA title 21 C.F.R Section 172.615 [4, 11]. A chewing gum made by these gum compositions can be directly compressed on a conventional tablet machine, which enables rapid and low-cost development of medicated chewing gums. As it does not require high temperature, this method is also suitable for thermosensitive and water-sensitive APIs.

Medicated chewing gums made with *Pharmagum* and *Health in gum* compositions are similar to tablets in appearance and give faster release of drugs than conventional methods owing to lower binding of the medicinal substance with the gum base [8, 10, 11].

Last years the *Health in gum*® composition has gained widespread, the advantages of which are, above all, homogeneity and simplicity of manufacture, so that to work with a single elastic base is difficult and it requires additional equipment. Chemically, *Health in gum* compositions are a mixture of polyols (sorbitol/xylitol/mannitol/isomalt) or of sugars with gum bases (elastomers), plasticizers and anti-caking agents. Depending on the percentage of the elastic base and the type of polyols that are included in the composition 3 types of *Health in Gum* are produced such as HiG PWD 01, HiG PWD 03, HiG PWD 04 [4, 10].

Obtaining of chewing gums with *Health in gum* lies in mixing of this composition, the active substance and flavourings in the mixer; after adding an anti-caking agent and a lubricant the resulting mass is sent to direct compression. If necessary, for protection from moisture and providing additional external characteristics the finished product can be covered with a film or coated with sugar [4, 10].

CONCLUSIONS

The analysis of possible technologies of medicated chewing gums manufacture conducted has allowed to determine that the use of *Health in gum* compositions provides an easy and rapid obtaining of MCG by direct compression without purchasing and installation of sophisticated technological equipment, which, in turn, will make this dosage form more promising for introduction into industrial production of Ukraine.

REFERENCES

1. *Эрлихман В. // Gala Биография. – 2009. – №5. – С. 71-80.*
2. *Державна фармакопея України / ДП «Науково-експертний фармакопейний центр». – 1-е вид. – Доп. 2. – Х.: РІРЕГ, 2008. – С. 291.*
3. *Basani G., Venkata D.R., Madhusudan Y.R. // Intern. J. of Res. in Pharmac. and Biomed. Sci. – 2011. – Vol. 2, №1. – P. 23-32.*
4. *Belmar J., Ribé M. Eye on excipients. Health in Gum by Cafosa. – Barcelona, Spain, 2013.*
5. *Ezhumalai K. // Intern. J. of Pharmacy and Technol. – 2011. – Vol. 3, №1. – P. 725-744.*
6. *General Monograph on Dosage Forms. Chewing gums, Medicated. In European Pharmacopoeia, 6-th ed.; European Directorate for the Quality of Medicines, Council of Europe: Strasbourg, France, 2008. – P. 719.*
7. *Heema N., Stuti G. // Intern. J. of Pharmac. Res. and Development. – 2010. – Vol. 2, №11. – P. 66-76.*
8. *Khanekar P., Mhatre S., Momin M. // Intern. J. of Pharmac. Frontier Res. – 2012. – Vol. 2, №4. – P. 64-75.*
9. *Khatun S., Bishwajit K. // Intern. Current Pharmac. J. – 2012. – Vol. 1, №4. – P. 86-91.*
10. *Kinjal R. Shah, Tejal A. // Intern. J. Pharm. Technol. Res. – 2014. – Vol. 6, №1. – P. 35-48.*
11. *Shivang A. Chaudhary, Aliasgar F. Shahiwala // Expert Opin. Drug Deliv. – 2010. – Vol. 7, №7. – P. 871-885.*

ТЕХНОЛОГІЧНІ ОСОБЛИВОСТІ ОТРИМАННЯ МЕДИЧНИХ ЖУВАЛЬНИХ ГУМОК

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Ключові слова: *медичні жувальні гумки; технологія; пряме пресування; композиції Health in gum*

Медична жувальна гумка (МЖГ) – нова альтернативна тверда лікарська форма для орального застосування, яка використовується для доставки великої кількості активних компонентів. Статті на дану лікарську форму введені у ДФУ, Європейську Фармакопею та Фармакопею США. Однак на сьогоднішній день препарати у формі медичних жувальних гумок не виробляються вітчизняними виробниками. Це пов'язано насамперед зі складністю використовуваного обладнання та відсутністю відповідної нормативної документації на виробництво МЖГ, що обмежує впровадження даної лікарської форми у виробництво фармацевтичних підприємств України. Нами був проведений аналіз літературних даних відносно методів отримання медичних жувальних гумок та основних технологічних аспектів, а також обладнання, що використовується. Це дозволило зробити висновок, що з розробкою композицій для отримання жувальних гумок методом прямого пресування Pharmagum® (SPI Pharma, США) і Health in gum® (Cafosa, Іспанія) можливість виробництва даної лікарської форми на вітчизняних підприємствах зросла і є перспективною на теперішній час. Хімічно вони являють собою суміш поліолів (сорбіту/ксиліту/маніту) та цукрів з жувальними основами, пластифікаторами і антизлежувальними агентами. Жувальні гумки, виготовлені за допомогою цих композицій, забезпечують більш швидке вивільнення лікарських речовин, ніж МЖГ, отримані традиційними методами, внаслідок більш низького зв'язування лікарської речовини з жувальною основою та можуть бути безпосередньо спресовані на звичайній таблетковій машині.

ТЕХНОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ПОЛУЧЕНИЯ МЕДИЦИНСКИХ ЖЕВАТЕЛЬНЫХ РЕЗИНОК

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Ключевые слова: *медицинские жевательные резинки; технология; прямое прессование; композиции Health in gum*

Медицинская жевательная резинка (МЖР) – новая альтернативная твердая лекарственная форма для орального применения, которая применяется для доставки большого количества активных компонентов. Статьи на данную лекарственную форму введены в ГФУ, Европейскую Фармакопею и Фармакопею США. Однако на сегодняшний день препараты в форме медицинских жевательных резинок не производятся отечественными производителями. Это связано, прежде всего, со сложностью используемого оборудования и отсутствием соответствующей нормативной документации на производство МЖР, что ограничивает внедрение данной лекарственной формы в производство фармацевтических предприятий Украины. Нами был проведен анализ литературных данных относительно методов получения медицинских жевательных резинок, раскрыты основные технологические аспекты, а также рассмотрены виды используемого оборудования. Это позволило сделать вывод, что с разработкой композиций для получения жевательных резинок методом прямого прессования Pharmagum® (SPI Pharma, США) и Health in gum® (Cafosa, Испания) возможность производства данной лекарственной формы на отечественных предприятиях возросла и является перспективной в настоящее время. Химически они представляют собой смесь полиолов (сорбита/ксилита/маннита) и сахаров с жевательными основами, пластификаторами и антислеживающими агентами. Жевательные резинки, полученные с помощью этих композиций, обеспечивают более быстрое высвобождение лекарственных веществ, чем МЖР, полученные традиционными методами, вследствие более низкого связывания лекарственного вещества с жевательной основой и могут быть непосредственно спрессованы на обычной таблеточной машине.