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Analytical Review of the Modern Range of Suppository Bases

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ABSTRACT
The analysis of modern suppository bases is carried out depending on their physicochemical properties, classification of excipients from various pharmacopoeias of the world is given. The advantages and disadvantages of various suppository bases for the rational choice for the development of future drugs in the form of suppositories, in particular extemporal drugs, are given.
Keywords: extemporal medicines, suppository, suppository bases.

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INTRODUCTION

Despite the long history of the use of drugs in the form of rectal and vaginal suppositories, the global suppository market is currently limited due to certain inconveniences for the patient. Therefore, the development of new drugs in this dosage form was insufficient. However, suppositories have several advantages over other dosage forms and is one of the most common dosage forms used for the treatment of gynecological, proctological diseases, etc [1, 2].

It is known that the therapeutic effect of suppositories is due to the interaction of the medicinal substance and the base, which provides the necessary structural and mechanical properties and is one of the most important characteristics, determines the stability of connected-dispersed systems.

The suppository base has certain physical and chemical properties and has a significant effect on the biopharmaceutical characteristics of the drug, dosing accuracy and uniformity of API distribution etc [3].

AIM

The aim of this work is to review the current assortment of suppository bases, which are used for the manufacture of both rectal and vaginal suppositories.

MATERIALS AND METHODS

Methods of structural, logical and systematic analysis of literary sources were used.

RESULTS AND THEIR DISCUSSION

According to State Pharmacopoeia of Ukraine 2.0 and European Pharmacopoeia 8.0, suppositories (rectal) are solid single-dose drugs intended for administration into the rectum in order to obtain systemic or local effects; pessaries (vaginal) – solid single-dose drugs are intended for insertion into the vagina to provide local action [4, 5].

In USP35, the definition of suppository is as follows: suppository is a solid dosage form of various weights and shapes, intended for rectal, vaginal administration or introduction into the urethral ostium of the human body, usually melts, softens, dissolves at body temperature. The suppository can act as a protective or palliative agent for local tissues at the introduction place or as a carrier of therapeutic agents for systemic or local action [6].

According to State Pharmacopoeia of Ukraine and the European Pharmacopoeia, suppository bases used for the manufacture of this dosage form are divided into hydrophobic, hydrophilic and diphilic. And according to USP, there are six main classes of suppository bases [4-9]:

1. Cocoa butter.
2. Cocoa butter substitutes.
3. Glycerin gelatin.
4. Polyethylene glycol.
5. Surfactant basis.
6. Tablet suppositories or inserts.

But in some sources you can find the following classification of bases, which is based on their properties of melting or dissolution:

- suppository base such as fat or oil, melts at body temperature;
- a glycerol-gelatin base that absorbs water and dissolves to release API;
- water-soluble or water-miscible polymers or surfactants;
- a group of bases which contains disintegrating agents, natural resins, effervescent agents, collagen, fibrin, hydrogels, etc.

The requirements for suppository bases are the same all over the world and are listed in the State Pharmacopoeia of Ukraine and in other pharmacopoeias. They are as follows:

- chemical and physical resistance during storage and use;
- compatibility with a wide range of active pharmaceutical ingredients and excipients;
- no odor;
- aesthetically appealing appearance;
- non-toxicity, lack of sensitivity and irritation to sensitive tissues of the body;
- expansion-compression characteristics such that when cooled, suppositories must be compressed enough to be easily released from the molds;
- to melt and dissolve in the intended cavity of the body to release a medicinal substance;
- mixing and absorbing a small amount of water;
- the viscosity should be low enough in the melt for easy casting of the suppository mass into molds, but high enough for the suspending of the API solid particles.

- possessing wetting and/or emulsifying properties for maximum release of API.

In order to develop drugs, it is necessary to choose a suppository base, which would be appropriate in a certain case, depending on the physical and chemical properties of the APIs which are present in suppositories. For this purpose, it is necessary to conduct a more detailed study of the assortment of suppository bases, their properties, advantages and disadvantages. Of course, today a large number of suppository bases are known, but newer and more modern carriers appear every day. Therefore, some of them are worth pausing.

Cacao butter NF24

Cocoa butter is the fat from Theobroma cocoa seeds (chocolate beans) that is obtained by squeezing the seed oil or by solvent extraction. From the chemistry side, cocoa butter is a mixture of triglycerides of saturated and unsaturated fatty acids, especially stearic, palmitic, oleic, lauric and linoleic. In appearance, it is a yellow substance with a pungent specific odor, solid at room temperature but melting at body temperature ($t_{melting}$ 31-34 °C).

Cocoa butter does not contain emulsifiers, so it does not absorb a significant amount of water. But, if necessary, can be added Tween-61, in an amount of from 5% to 10%, which is a tan, waxy, solid, nonionic surfactant. Its introduction provides an increase in the water-absorbing ability of cocoa butter, although the addition of nonionic surfactants leads to instability of suppositories during storage [10].

One of the significant disadvantages of cocoa butter is the effect of some APIs on its melting point. In particular, with the introduction of chloral hydrate, phenol or thymol in the composition of suppositories, a decrease in the melting point of cocoa butter is observed. This can be eliminated by adding from 4% to 6% white wax or from 18% to 28% cetyl ester wax. But you need to clearly calculate their amount [11, 12]. In addition, due to the low melting point, cocoa butter and suppositories based on it should be stored only in the refrigerator. It is very important to take into account another significant drawback, namely, that this basis is characterized by the existence of polymorphic forms having even lower melting points: 18, 24 and from 28 ° C to 31 ° C. That is why there are difficulties in the manufacture of suppositories based on cocoa butter , because this base can easily overheat and, as a result, turn into a form that has a lower melting point. This means that suppositories made improperly can melt already at room temperature, or when the patient tries to administer the drug.

However, cocoa butter has a number of real advantages, in particular, it is a soft base that does not irritate sensitive membrane tissues, easily accessible and convenient to use in the manufacture of suppositories in the absence of the necessary equipment [10].

Given this property, it is necessary to clearly control the manufacturing process of the drug. When melting, the base should have a slightly opalescent appearance. As soon as the melted cocoa butter has completely turned into a transparent, straw-colored liquid, this indicates that the desired melting point was exceeded, all stable crystals were destroyed, and the suppositories would melt at a temperature below the desired, namely 34 ° C.

As with other fatty bases, cocoa butter suppositories may have an incomplete or somewhat erroneous release of certain APIs. The release of substances from the fat base for suppositories, such as cocoa butter, into the aqueous medium of the body cavity depends on the water / base distribution coefficient in the medicine, because many organic molecules of the medicinal substance are insoluble in water and are lipophilic. An exception is the use of this substance in suppositories in the form of an ionized salt. That is why, in order to increase the bioavailability of APIs, it is advisable to use them in the form of water-soluble ionized (salt) forms, because they have high water / base distribution coefficients. For example, if it is necessary to prepare suppositories with phenobarbital, it is advisable to use the sodium salt of phenobarbital. If the medicinal substance does not have a water-soluble form, in this case, cocoa butter is not a rational choice as the basis for suppositories [13].

In addition to cocoa butter, other hydrophobic bases are also known such as Kuva-300, Kuva-500, GHM-3T, GHM-5T, Supporin-M, Butyrol, Salomas, Confectionery Solid Fat, Novata, etc.

These bases are already well studied and described in various literary sources, therefore it is advisable to study suppository bases, which are widely used in modern pharmaceutical practice, but their description and properties are not sufficiently disclosed in the literature.

Cocoa butter substitutes

As for this group of bases, these are the bases that are obtained from various vegetable oils, such as coconut or palm kernels, which are modified by etherification, hydrogenation and fractionation to obtain products of various compositions and melting points (for example, hydrogenated vegetable oil and solid fat). They can be designed so that rancidity is minimized during long-term storage. At the same time, the desired characteristics can be created, such as narrow intervals between the melting and solidification temperatures, melting ranges, in order to adapt to various warehouses and climatic conditions. It should be noted that the vast majority of representatives of this group of bases can be attributed to diphilic ones due to the presence of emulsifying agents in their composition.

On the chemistry side, this type of suppository base consists mainly of mixtures of triglyceride esters of saturated fatty acids ranging from C-12 to C-18 with lesser amounts of mono- and diglycerides. Other additives include beeswax, lecithin, polysorbates, ethoxylated fatty alcohols, ethoxylated partial fatty glycerides. Cocoa butter substitutes were first developed in Europe during World War II due to the limited availability of natural cocoa butter. In recent years, suppliers of composite materials have developed additional products of this type, which are listed below [14-16].

Witepsol

Witepsol is a whitish, waxy, brittle, solid substance that melts into a clear or yellowish liquid with an almost absent odor and has a density of 0.95 to 0.98 at 20 ° C. It contains emulsifiers, due to which it absorbs a small amount of water.

There are about 20 different varieties of Witepsol, which are divided into the following series: H, W, S, E, but the most available for pharmaceutical practice is class H15. It has a range of melting points from 33.5 ° C to 35.5 ° C, which is close enough to its pour point from 32 ° C to 34 ° C [15, 17, 18].

Although most pharmacists value highly the Witepsol bases, they report some cases of poor-quality suppositories. In particular, there are cases of their destruction when trying to remove from forms.

Fattibase (producer Paddock Laboratories, USA)

Fattibase – opaque, white, waxy, odorless solid substance. Its specific gravity at 37 ° C is 0.89. This is a mixture of triglycerides from palm kernel and coconut oil together with glyceryl monostearate and polyoxyl stearate, which serve as emulsifiers and suspending agents [19]. This base has a range of melting temperature of 32 ° C to 36.5 ° C, but instructions from its manufacturer (Paddock Labs) state that before adding the active pharmaceutical ingredients, the base should be slowly and uniformly heated to 49-54 ° C, not exceeding the specified temperature. Suppositories should be poured when the mixture reaches a temperature of 43 ° C to 49 ° C.

Fattibase has the advantages of cocoa butter and does not have its disadvantages, namely, the sensitive range of melting points and polymorphism. Suppositories on this basis are well extracted from the molds [10, 19].

Fattyblend (producer Gallipot Inc., USA)

The Fattyblend basis for suppositories melts at body temperature, but as cocoa butter does not have a polymorphism. It provides uniformity, a mild odor and low irritation. It also has remarkable mold extraction properties compared to cocoa butter suppositories.

Fattyblend contains palm, palm kernel and coconut oil triglycerides, and emulsifying and suspending agents. This basis is also used in the manufacture of lip balms and lipsticks at the expense of mild taste [10, 14].

Supposiblend (producer Gallipot Inc., USA)

It is a granular form of the suppository base of triglycerides (a mixture of fatty acids), made from vegetable oils, preferably from palm kernel oil, which is resistant to oxidation and does not have a cocoa butter polymorphism. It has a melting temperature range from 34 ° C to 37 °C. Slightly compresses during cooling, which provides excellent mold removal characteristics. Contains emulsifiers to absorb small amounts of aqueous solutions [10].

Supposibase-F (producer, Hawkins, USA)

Like Supposiblend, Supposibase-F is a granule base that is made from refined, hydrogenated, deodorized vegetable oils, mainly palm kernel oil. It is reported that this base has good chemical stability, physical stability with minimal polymorphism and a slight tendency to oxidize. The range of melting points from 34 ° C to 37 ° C [10, 20].

If we talk about cocoa butter substitutes in general, they are practically insoluble in water; they have some difficulties in lowering the temperature, which are also observed when using cocoa butter. But, the advantages of these bases are that they are more suitable for use, because they have emollient properties and do not irritate sensitive membrane tissues. Some of the commercially available synthetic versions of cocoa butter are more convenient to use than cocoa butter because they are not so sensitive to slight fluctuations in the melting temperature, and, unlike cocoa butter, exhibit minimal problems with polymorphism. In addition, most of the specially designed synthetic fatty bases include surfactants that improve the release of APIs and their bioavailability [21-23].

But still, certain disadvantages of the synthetic bases overlap with the disadvantages of cocoa butter, namely, predominant storage in the refrigerator, the possibility of incomplete release of APIs.

The next group of suppository bases that must be considered is hydrophilic, in particular, *glycerol-gelatin base*, which is a mixture of glycerin, gelatin and purified water. This is one of the oldest hydrophilic suppository bases. The ratio of the ingredients of the base varies depending on the different country. For example, according to USP31 / NF26, this base consists of 70 parts of glycerin, 20 parts of gelatin and 10 parts of water, and in the British Pharmacopoeia 2009 the ratio of gelatin / glycerin / water is 14: 70: 16. In general, it is mainly found in European countries the ratio of gelatin, water and glycerin is 1: 2: 5. Today, this base is rarely used due to the time-consuming process of preparation and a small number of advantages. The resulting glycerol-gelatin-based suppositories have a soft, elastic consistency, which makes them suitable for vaginal use. They do not melt, but slowly dissolve in the mucous secretions of the vagina. That is why their use is recommended, if necessary, to slow the release of local antibacterial and antifungal drugs [5, 7]. It should also be noted that before using these suppositories must be moistened with water. One of the significant disadvantages of such suppositories is that they are a good medium for the reproduction of bacteria and other microorganisms, therefore, the introduction of preservatives is obligatory in their manufacture (for example, methyl paraben 0.18% or propyl paraben 0.02%) [5, 24, 25].

The next group of hydrophilic bases are *polyethylene glycol (PEG)*, which are mixtures of polyethylene glycol polymers with different molecular weights. The properties of some polyethylene glycol polymers most commonly used in pharmaceutical practice are shown in Table 1 [10, 26].

Table 1: Physical properties of polyethylene glycols

Class (molecular weight)	Molecular weight range	Physical form	Melting point range (°C)	Solubility in water (%)	pH of 5% solution
300	285-315	liquid	from -15 to -8	complete, 100	from 4,5 to 7,5
400	380-420	liquid	from 4 to 8	complete, 100	from 4,5 to 7,5

600	570-630	liquid	from 20 to 25	complete, 100	from 4,5 to 7,5
1000	950-1050	semi-solid	from 37 to 40	80	from 4,5 to 7,5
1450	1300-1600	semi-solid or flaky	from 43 to 46	72	from 4,5 to 7,5
3350	3000-3700	flaky or powder	from 54 to 58	67	from 4,5 to 7,5
4600	4400-4800	flaky or powder	from 57 to 61	65	from 4,5 to 7,5
8000	7000-9000	flaky or powder	from 60 to 63	63	from 4,5 to 7,5

The compositions of some polyethylene glycol alloys most commonly used in the production of suppositories are shown in Table 2 [10, 26].

Some commercial polyethylene glycol bases for suppositories also contain additional components, such as surfactants. One of the most used bases are *Polybase* (produced by Paddock Labs, USA) and *PEGblend* (produced by Gallipot Inc., USA), which contain a mixture of polyethylene glycols with the addition of polysorbate-80 emulsifier [7, 10, 19].

In general, polyethylene glycol bases are made in such a way that in the future they will not melt at body temperature, but dissolve in body fluids, so they must be moistened with water before use.

A significant advantage of such suppositories is the relatively high release of water- and fat-soluble substances compared to hydrophobic bases. In addition, due to the fact that their melting point is easily controlled by the appropriate mixing of certain PEGs with different molecular weights, these bases and suppositories based on them do not require a carefully controlled storage temperature [10].

Table 2: Polyethylene glycol bases

	Molecular weight	%
Base 1		
PEG	8000	50
PEG	1540	30
PEG	400	20
Base 1 – well water soluble suppository base for general purpose		
Base 2		
PEG	3350	60
PEG	1000	30
PEG	400	10
Base 2 – well-soluble general-purpose suppository base that is softer than base 1 and has better water-soluble properties		
Base 3		
PEG	8000	30
PEG	1540	70
Base 3 has a higher melting point		
Base 4		
PEG	8000	40
PEG	400	60
Base 5		
PEG	8000	20
PEG	400	80
Base 4 andi 5 used for progesterone suppositories		
Base 6		
PEG	8000	60
PEG	1540	25
Cetyl alcohol		5
Purified water		10
Base 6 used for suppositories, which include water-soluble API		

However, such suppositories irritate the tissues of the body, have osmotic properties, so the bases are used for the manufacture of vaginal suppositories. In addition, due to the fact that the polyethylene glycol bases are easily oxidized, the manufactured suppositories need to be wrapped in foil.

Another subgroup of hydrophilic bases are s*urfactants or water dispersed bases*.

Several nonionic surfactants, such as fatty acid esters and polyoxyethylene sorbitan and polyoxyethylene stearates, are used alone or in combination with other suppository excipients to obtain new suppository bases [27-29]. Bases of this type are rarely used, because they require more complex technological operations. If they are combined correctly and suppositories are prepared on their basis, these bases have the desired melting points and consistencies. Since they contain surfactants, they dissolve easily in body fluids.

One easy-to-make mix in pharmacy contains 60 % Tween 61 and 40% Tween 60 [7]. Both of these compounds are solids at room temperature.

It is also necessary to indicate the existence of another group of suppository bases, namely, *tablet suppositories or inserts*. This group of suppository bases is described in USP. They are vaginal suppositories (now commonly referred to as vaginal inserts), which are prepared by compressing powdered materials into an appropriate form. They can also be prepared by encapsulation in soft gelatin [10]. The pressing method is suitable for suppositories containing heat-resistant preparations or contain a large proportion of insoluble ingredients. This method offers the ability to produce suppositories of various shapes and sizes. As a filler used in such suppositories, usually is lactose, which is combined with a disintegrant, a grinding agent and a lubricant.

The release of a medicinal substance from a suppository base is a complex and unpredictable process. The stage limiting the release rate of a drug is not only the rate at which the fatty bases melt or the hydrophilic bases dissolve, but also the time required for the disintegration of APIs and diffusion from the base into the rectal or vaginal lumen. In practice, since bioavailability studies are usually difficult to implement, it is important to monitor the effectiveness of the drug delivery system by frequently monitoring the results of therapy. That is why, the selection of a rational and appropriate suppository base at the stage of medicines creation is the most important task.

CONCLUSIONS

1. In this article, an analytical review of the assortment of modern suppository bases with a description of their physical and chemical properties, advantages and disadvantages was carried out, in the future it makes it possible to choose a suitable excipient in order to create new medicines in the form of suppositories.
2. The classification of excipients for suppositories not only in Ukraine but also abroad was analyzed and their influence on the physical and chemical, biopharmaceutical, pharmacological and technological properties of finished medicines was proved.

REFERENCES

1. Block L. H. Medicated topicals. In: University of the Sciences in Philadelphia, ed. Remington: The science and practice of pharmacy, 21st ed. Baltimore, MD: Lippincott Williams & Wilkins, 2005.
2. Coben L. J., Lieberman H. A. Suppositories. In: Lieberman H. A., Lachman L., Kanig J., eds. The theory and practice of industrial pharmacy, 3rd ed. Philadelphia: Lea & Febiger, 1986.
3. Plaxco J. M. Suppositories. In: King R. E., ed. Dispensing of medication, 9th ed. Easton, PA: Mack Publishing Co., 1984.
4. European Pharmacopoeia, 8th ed. – Council of Europe, 67075 Stasbourg Cedex, France 2014.
5. Derzhavna Farmakopeya Ukrayini: v 3 t. Derzhavne pidpriemstvo «Ukrainskiy naukoviy farmakopeyniy tsentr yakosti likarskih zasobiv». – 2-e vid. – Harkiv: Derzhavne pidpriemstvo «Ukrayinskiy naukoviy farmakopeyniy tsentr yakosti likarskih zasobiv» 2014–2015.
6. USP 35-NF 30. General Chapter Pharmaceutical Dosage Forms, The United States Pharmacopeial Convention, Rockville, MD, 2009.
7. USP 31/NF 26. Inc. Chapter 1151, The United States Pharmacopeial Convention, Rockville, MD, 2008.
8. USP 30/NF 25. Inc. NF monographs,The United States Pharmacopeial Convention, Rockville, MD, 2007.
9. USP 29/NF 24. Inc. Front matter — NF: Excipients, The United States Pharmacopeial Convention, Rockville, MD, 2007.
10. Melgardt de Villiers. Suppository bases. Chapter 24. https://www.researchgate.net/publication/318380307_Suppository_Bases.
11. King J. C. Suppositories. In: Martin E. W., ed. Dispensing of medication, 7th ed. Easton, PA: Mack Publishing Co., 1971.
12. Schumacher G. F. Chloral hydrate suppositories. Am. J. Hosp. Pharm. 1966; 23, 110.
13. Feldman S. Bioavailability of acetaminophen suppositories. Am. J. Hosp. Pharm. 1975; 32, 1173–1174.
14. Yarnykh T. G., Tolochko E. V., Chushenko V. N. Studying an assortment of suppository bases (Review). Pharmaceutical Chemistry Journal. 2011; 44 (10), 551-556.
15. Rowe R., Sheskey P., Weller P., eds. Handbook of pharmaceutical excipients, 5th ed. Washington, DC: APhA Publications, 2005.
16. Rowe R., Sheskey P., Quinn M., eds. Handbook of pharmaceutical excipients, 6th ed. London-Chicago: APhA Publications, 2009.
17. Allen L. V. Compounding rectal dosage forms. Part II. Secundum Artem, 14(4). http://www.paddocklabs.com/forms/secundum/volume_14.4.pdf.
18. Yarnykh T. G., Tykhonov O. I., Hryzodub O. I., Chushenko V. M., Levachkova Yu. V. Technology of rectal suppositories and pessaries ex tempore — proposals for the supplement of the general monograph of SPU 5.N.1 «Ex tempore drugs». Pharmacom. 2010; 1, 68–73 (in Ukrainian).
19. Fattibase Product Data Sheet, Paddock Laboratories, Minneapolis, MN. https://msdsreport.com/ds.cfm?msds=CGJDS&name=FATTIBASE&mfg=PADDOCK%20LABORATORIES%20INC
20. Hawkins Inc. 2008 Hawkins Pharmacy Compounding Catalog. 3000 East Hennepin Avenue, Minneapolis, MN 55413. www.hawkinsinc.com/pharmaceutical).
21. Yamazaki M., Soichi I., Sasaki N., Uchiyama M. Comparison of three test methods for suppositories. Pharmacopeial forum. Rockville, MD: The United States Pharmacopeial Convention, Inc., 1991; Sept–Oct; 2427–2437.
22. Constantin I. O., Zelger G. L., Paroz A. L., Furrer P., Rudaz S., Messeiller C. P. Development of

Misoprostol suppositories for Postpartum hemorrhage. Pharmacology & Pharmacy. 2013; 4, 71-76.

23. Belniak P., Świąder K., Szumiło M., Hyla A., Poleszak E. Comparison of physicochemical properties of suppositories containing starch hydrolysates. Saudi Pharm. J. 2017; 25 (3), 365-369.
24. Japanese Pharmacopeia, 16th ed. The Ministry of Health, Labour and Welfare, Japan 2014.
25. British Pharmacopoeia, TSO, Great Britian, London 2009.
26. The Dow Chemical Company. Carbowax and Carbowax Sentry Product Data Sheets. http://www.dow.com/polyglycols/carbowax/ index.htm.
27. Chernykh V. P., Tykhonov A. I., Yarnykh T. G., Terno I. S., Tovmasyan E. K., Tykhonenko T. M., Bondarenko L. V., Hryzodub A. I., Georgievskiy V. V. General monographs of the State Pharmacopoeia of Ukraine to extemporaneous preparations. Pharmacom. 2007; 3, C. 8-16. (in Russian)
28. Rukhmakova O. A., Yarnykh T. G., Tykhonov O. I., Kotvitska A. A. Methodology for development of pediatric medicines for complex treatment of diseases of immune-dependent nature. Journal of Global Pharma Technology. 2018; 10 (12), 54-57.
29. Herasymova I. V., Tykhonov O. I., Shpychak O. S., Buryak M. V., Koval V. N. Pharmacological research of loravit suppositories. Asian Journal of Pharmaceutics. 2018; 12(1), 106-110