FORMULATION OF DIAZEPAM SUPPOSITORIES WITH HYDROPHILIC AND LIPOPHILIC BASES

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Abstract: Diazepam belongs to a class of a long-acting benzodiazepine with anticonvulsant, sedative, and anxiolytic properties. Because of its rapid absorption it is a commonly used drug for the treatment of acute recurrent epileptic seizures that occur at children.
It is also used for the treatment of acute febrile convulsions and as the drug of choice diazepam is given intravenously to produce the effect more quickly. But the intravenous method of application requires professional competence from medical personnel. Due to the difficult swallowing during a seizures, the oral and sublingual administration of diazepam in that case is impossible. Rectal formulations with diazepam stand out as a type of drug administration that achieves rapid application and timely action. Diazepam rectal solutions are not widely used because of the possibility of incorrect dosing and rectal leakage. Suppositories as a pharmaceutical dosage form are the drug of choice for administering diazepam. Absorption of the active component after rectal administration depends on: the melting or dissolution of the suppository and the diffusion of the active substance and the penetration of the dissolved molecules through the epithelial cells of the mucous membrane of the rectum. In the formulation of suppositories, the solubility of the active component in the base plays a major role. The bases used in manufacturing the suppositories can be hydrophilic or lipophilic.
The aim of this study is to define a base of choice for the manufacture of diazepam suppositories, following the pharmaceutical-technological manufacturing process and the physico-chemical properties of the obtained suppositories. Suppositories were made with two types of bases, hydrophilic and lipophilic. Macrogol (Polyethylene glycol-PEG) with a different molecular weight is used as a hydrophilic base. During the technological development, three different formulations of suppositories were made with diazepam and a hydrophilic base Macrogol (PEG) with different molecular mass in different ratio.
The first formulation consists of diazepam and Macrogol 6000, the second diazepam and Macrogol 6000- 40% and PEG 1500- 60% and the third of diazepam and Macrogol 6000 - 40%, Macrogol 1500 - 40% and Macrogol 400 - 20%. Lipophilic base Withepsol H15 was used in the other formulations, and one formulation was made with diazepam and Withepsol H15, and one formulation with diazepam and Withepsol H15 + Tween 80.
Based on the obtained results, it is estimated that the third developed formulation, which in its composition has diazepam and a hydrophilic base in the following ratio Macrogol 6000 - 40%, Macrogol 1500 - 40% and Macrogol 400 - 20%, shows the best physico-chemical characteristics in relation to the rest.
Keywords: diazepam, suppositories, formulations

1. INTRODUCTION

Rectal dosage forms are forms that are intend to insert into the body through the rectum for local or systematic effect. The environment in rectum is constant in comparison to gastrointestinal tract, but because of small surface of absorption of the rectum, the drug absorption is lower that the oral administration. The absorption of drug given by rectal administration is by passive diffusion. (Aulton, M. and Taylor, K., 2017). Rectal forms can be classified into conventional and novel delivery systems. The conventional delivery system includes suppositories, gels, suspensions, and tablets, whereas the novel drug delivery system includes microspheres, liposomes, polymeric micelles and nanoparticles. (Rathi & Sanshita, 2022). Rectal dosage forms should be non-irritable, should be suitable enough to be accepted by the patient and should show good retention in the lower region of the large intestine patient (Capra et al, 2013). Suppositories are solid-dosage forms that are inserted into the rectum where they undergo softening, melting or dissolution to liberate the therapeutic agent.
Suppositories as a rectal dosage form contain one or more active ingredient that can be dispersed or dissolved in a suitable base. The base may be soluble or dispersible in water or may melt at body temperature. (Ham & Buckheit, 2017)
An ideal suppository base should melt, dissolve or disperse at body temperature. It should be non-irritating, physically and chemically stable, and pharmacologically inert. (Alton, M. and Taylor, K., 2017)

There are two main classes of bases for manifacture suppositories: fatty bases and water-soluble bases. In the formulation of suppositories, the solubility of the active component in the base plays a major role. 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 (Melnyk et al., 2020). There is not found an ideal base for suppositories, but the large number of natural, synthetics and semi-synthetics bases which are available enables a well-considered choice for every drug that has to be formulated into a suppository. The factors affecting the absorption of the drug in the rectum can be divided into two groups. The first group includes the characteristics of the pharmaceutical formulation, such as, partition coefficient, degree of ionization and particle size of the active substance, as well as the physical and chemical characteristics of the formulation base. The second group includes physiological factors, i.e. factors determined by the rectum: the amount of fluid available in the rectum, the properties of the rectal mucus, the contents of the rectum and the mobility of the rectal wall (Jones, D. 2008).

Diazepam is the most widely used drug for treatment of insomnia, febrile convulsions, status epilepticus and alcohol withdrawal symptoms. Diazepam belongs to a class of a long-acting benzodiazepine with anticonvulsant, anxiolytic, sedative muscle relaxant and amnesic properties .(Alsamman, A., & Othman, M. 2017). Because of his short duration of action, should be given intravenously or rectally. Oral and sublingual administration is difficult or hazardous when the patient is actively having a seizure. Absorption of the diazepam after parenteral or rectal administration is faster than oral administration of tablets (O. Henriksen, 1998). Rectal administration of diazepam is now widely used because could be as effective as the intravenous administration. One more advantages using diazepam as suppositories is their easily and safely administration by the patient. (Dodov, M et al, 2005).

The objectives of this paper are:

- to manifacture diazepam suppositories with hydrophilic and lipophilic bases
- to determine which formulation would show better results, in terms of the production process and the physical-chemical characteristics

2. MATERIALS AND METHODS

Materials

Raw materials for making diazepam suppositories

- Diazepam, micronized powder that corresponds to pharmacopoeial regulations (FIS)
- Polyethylene glycol (PEG) - 6000, polyethylene glycol (PEG) - 400, polyethylene glycol (PEG) - 1500 - (Clariant GmbH, Division Functional Chemicals, Sulzbach, Germany
-Witepsol H-15 (Sasol Germany)
-Polysorbate 80- Omnichem - Farm Skopje

Equipment for making suppositories

- Plastic suppository shells of 1.4 ml
- Analytical weighting scale
- Dropper
- Water bath
- Analytical cups

Methods

Prepration of Diazepam suppositories :

The fusion method was used to prepare the conventional suppositories (table 1.), by mixing 5 mg.equivalent weight of diazepam in each suppository base. After calculation the displacement value, using water bath the bases were melted with continous stirring until homogenous mixture was produced. Then, the melted mixture was poured into plastic suppository shells and cooled to a room temperature.

Table No.1 Composition of solid suppository formulation

	Composition of solid suppository formulation	
Formulation	*Diazepam (mg)*	*Bases*
F1	5mg	PEG 6000
F2	5mg	PEG 6000 - 40% , PEG 400 – 60 %
F3	5mg	PEG 6000 - 40%, PEG 1500 - 40% , PEG 400 - 20%
F4	5mg	Witepsol H 15
F5	5mg	Witepsol H 15 + Tween 80

3. RESULTS AND DISSCUSION

- The formulation of the different PEG suppositories proceeded without any problems and no instabilities, such as separation, were observed.
- The formulations with PEG-6000 are white in color and there are no cracks or migration of the active ingridient, but there are irregularities on the surface, and in some cases, depressions. The surface is dry to the touch. In this formulation, the excessive hardness(plastic) of the suppository and the possibility of fragility when taking the suppository out of the package can be observed.
- Formulations with PEG-6000 и PEG-400 are white in color and there are no cracks or migration of the active ingridient, no irregularities on the surface. The surface is dry to the touch and the hardness is reduced compared to the previous formulation.
- Formulations with PEG-6000, PEG-1500 и PEG-400 have the best consistency and the best properties compared to the other formulations. They are white, dry and smooth to the touch. No cracks, migration of the active ingredient or other irregularities are observed. They have the desired consistency with reduced hardness and brittleness.
- During the formulation of the suppositories with Tween 80, as a result of the instability of the used nonionic surfactant, a separation of the suppository phases was observed.
- Both of the lipophilic suppositories, the first ones containing only Witepsol H15 and the second ones containing combination of Witepsol H15 and Tween 80, are yellow, soft and greasy to the touch. Their surface is smooth and no unevenness are observed.

Picture No. 1 Suppositories with different bases
(F3, F2,F1, F4, F5 formulation)

4. CONCLUSION

Through analysis of all suppository formulations made with hydrophilic and lipophilic bases, we determined that the formulation of choice is F3, which contains 5 mg Diazepam, PEG-6000, PEG-1500 and PEG-400. This formulations has the best physical properties in terms of appearance and consistency.
Formulations made with Witepsol H15 show good physical properties. However, in the formulations with Tween 80, instead of enhancing the release of the active ingredient, the emulsifier is responsible for the occurrence of

instability in the form of separation of the phases. In order to overcome this problem, it is necessary to carry out additional analyses in the future.

The main objective of this study was to develop a diazepam suppository formulation with specific physical properties, which will enable quick and easy release of the active ingredient from the suppository base.

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