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FORMULATION AND CHARACTERIZATION OF SUPPOSITORIES OF HESPERIDIN

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ABSTRACT

Rectal drug delivery has several advantages such as reduced hepatic first pass elimination of high clearance drug, avoidance of gastric irritation associated with certain drugs in case of nausea, vomiting, and when the patient is unconscious. The objective of this work is to formulate suppositories of hesperidin obtained from peels of citrus fruit to treat hemorrhoids. Method: For the preparation of the suppository we use the hot melt method. In this method, hesperidin is used as an active ingredient. polyethylene glycol 400, polyethylene glycol 6000 as a water-soluble base. The macro melting range, liquefaction time, mechanical strength, and content uniformity test are characterized. All the suppositories were free from pits, fissures, and cracks. The longitudinal section of the suppository was plain and clear, indicating the dissolution of the drug in the base. The drug content was found to be 97.34 % which is within the acceptable range liquefaction time was found to be 17 minutes at 37^0c. The temperature for macro melting was found to be 32ºC. The hesperidin suppository prepared by this method meets the quality requirement of the suppository and may be developed as a new formulation of hesperidin.

KEYWORD:- Hesperidin suppository, Hemorrhoid, Anti-inflammatory, Anti-microbial, Polyethylene Glycol, Hot melt method.

INTRODUCTION

The use of the medicinal substance of herbal origin is the perspective direction for the development of pharmaceutical science. Even though increased demand for synthetic medicines. There was also a growing interest in using that substance from its wide range, of therapeutic effects, and low toxicity. One of the most numeral classes of herbal substances is flavonoids which are contained in almost all medicinal plants and have growing demand among patients.

Flavonoids are a class of compounds found in plant cells. These phenolic compounds are generally nontoxic and belong to the natural pigment family. In food, flavonoids are responsible for taste and color. Existing research confirms that a no. of positive health effects of flavonoids primarily results from their antioxidant activity.[1]

Hesperidin is a plant chemical that is classified as a bioflavonoid. It is most commonly found in citrus fruits. Its aglycone form is called hesperetin. Its name is derived from the word 'hesperidium' for fruit produced by citrus trees.[2]

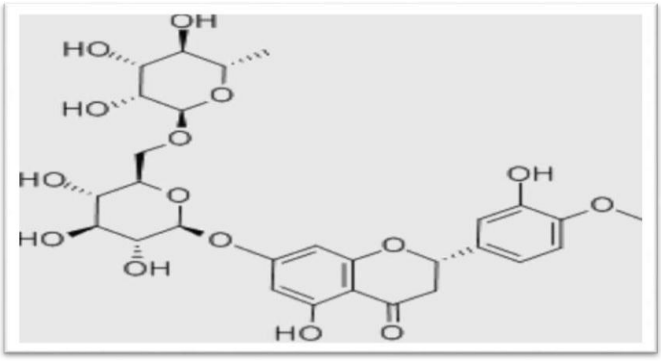


Figure no. 1: Hesperidin structure.

Hesperidin has demonstrated efficacy in the treatment of hemorrhoids. Hesperidin exhibits phlebotonic activity, vasculo-protective effects, and antagonism of the biochemical mediators of inflammation. Hesperidin has been the subject of numerous clinical trials on efficacy and safety in the treatment of haemorrhoids.[4]

The Merck Manual defines hemorrhoids as "varicosities of the veins of the hemorrhoid plexus, often complicated by inflammation, thrombosis, and bleeding. "It has been suggested this is an oversimplification of the nature of hemorrhoids. A more recent definition is, "Vascular cushions, consisting of thick sub-mucosa containing both venous and arterial blood vessels, smooth muscle, and elastic connective tissue." While everyone has this tissue, the enlargement, bleeding, and protrusion creates pathology. Considering the combined prevalence of varicose veins and hemorrhoids, venous insufficiency and its manifestations are an extremely common medical problem that every physician should be prepared to treat.[5]

Suppositories[8][9][10]

Rectal drug delivery has several advantages such as reduced hepatic first-pass elimination of high clearance drugs, avoidance of gastric irritation associated with certain drugs in case of nausea, vomiting, and when the patient is unconscious. The rectal route of administration is specifically useful for infants and children who have difficulty in swallowing oral medicine. Drugs administered in suppository form can produce local effects and systemic therapeutic action. Suppositories can be prepared using lipophilic bases like cocoa butter or hydrophilic bases such as PEGs. These suppositories melt or dissolve in body fluids and release the drug, but are unstable at higher temperatures. This study aimed to formulate and characterize suppositories containing hesperidin. Suppositories are solid dosage forms of various sizes, shapes, and weights intended for insertion into body orifices where they melt, soften or dissolve to exert their effect.

Suppository bases[8][10]

Ideal suppository bases should be easily formed by compression or molding; release any medicament readily; melt at body temperature or dissolve or disperse in body fluids; keep their shape when handled; compatible with the drugs, non-irritant and non-toxic. It is convenient to classify them according to their physical characteristics into:

1. Fatty or oleaginous bases (ex. Cocoa butter.)
2. Water-soluble or miscible base (ex. Polyethylene glycol, glycerinated gelatin)
3 Miscellaneous bases.

Methods of preparation[8][9][10]

1. Hot-Melt Method
2. Compression Method
3. Hand rolling and shaping Method

The first method is most commonly used for the preparation of suppositories.

Advantages of suppositories

- The drug may be administered in suppository form for either local or systemic effects.
- Emollients, astringents, antibacterial agents, hormones, steroids, and local anesthetics are dispensed in suppository form for treating local conditions of the rectum.
- Rectal suppositories are primarily intended for the treatment of constipation and hemorrhoids. A wide variety of drugs are employed, e.g., analgesics, antispasmodics, sedatives, tranquilizers, and antibacterial agents.

MATERIAL AND METHOD

Soxhlet extraction:[11]

800 mL petroleum ether (40 – 60°C) is filled in a 250 mL round bottom flask with a magnetic stir bar. 250g dried and powdered orange peel are placed in the extraction sleeve of a Soxhlet extractor and covered with a little glass wool. A reflux condenser is put on the Soxhlet extraction unit, and then the reaction mixture is stirred and heated for 4 hours under strong reflux. The petroleum ether extract is discarded. To remove the adherent petroleum ether, the content of the extraction sleeve is laid out in an extensive crystallization dish.

Figure no. 2: Soxhlet apparatus.

Afterward, the substance is placed again in an extraction sleeve and, like before, but with 800 mL methanol, extracted unless the solvent leaving the extraction sleeve is colorless (1 to 2 hours). After complete Soxhlet extraction and maceration, the filtrate was then acidifed (pH 3-4) with 6%acetic acid, Keep the concentrated residual liquid in the refrigerator (4-6◦C) overnight when a solid crystalline substance appears. It was again filtered and the crude hesperidin was separated on the Buchner funnel as an amorphous powder. The hesperidin was further characterized and identified according to various physicochemical parameters. The compound was characterized according to various factors. The yield of hesperidin was analyzed by graphical representation. [11]

Figure no. 3: Drug obtained.

1. Identification test[14]

Test for hesperidin:

a) Ferric chloride test:

Addition of Ferric Chloride Solution to Hesperidin Produces a Wine Red Colour.

b) Magnesium –Hydrochloric acid reduction test:

Dropwise addition of Concentrated Hcl to an Ethanolic Solution of hesperidin Containing Magnesium Develops a Bright Violet Colour.

2. Calculation of replacement factor or displacement value:

Replacement factor (American system) is the amount of base that is replaced by active ingredients in the suppository formulation (f) and given by the following formulation:

$$F = [100(EG)/(G)(X)] +1$$

Where E is the weight of pure base suppositories and G is the weight of medicated suppository with X% active ingredient

3. Formulation of suppository

A suppository is prepared by the hot-melt method. 20g PEG400 and 15g PEG 6000 are mixed and melted at 50^0C to form a homogenous blend. Subsequently, 1.25g hesperidin was dissolved in this melt. The resultant melt of drug-containing bases was then poured into a 1g capacity suppository mold. The suppositories are allowed to be set at room temperature for 5-10min and further refrigerated for 30min at 10^0C.

Table 1: Formula used to prepare suppositories

Sr. No.	Ingredients	Quantity taken
1.	PEG 400	20g
2.	PEG 6000	15g
3.	Hesperidin	1.25g

Figure no. 4: Suppositories.

4. Characterization of suppository:[8][9][11]

a) Macro melting range test

The formulation was filled to about 1cm height in capillary tubes of 10 cm length and dipped in a beaker containing water the temperature was raised slowly and the temperature at which the mass liquefies was recorded.

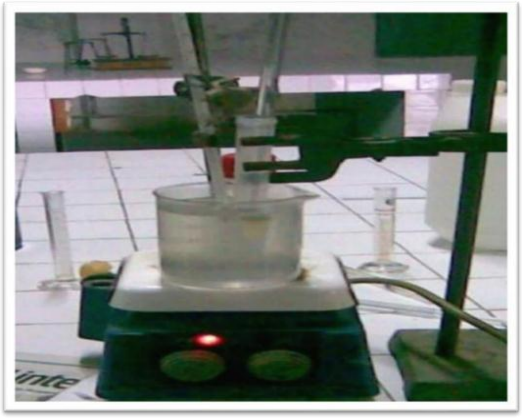


Figure no. 5: Macro melting test.

***b)* Liquefaction time:**

A burette was with a broken stop-cock was taken and cut suitably so that it has a narrow opening on one side and a d broad opening on another side. The burette was dipped in a hot water maintained at 37^0C so that the narrow end faces towards hot water. The suppository was introduced from the top of the burette through a broad end and carefully pushed down in length until it aches a narrow end. A glass rod weighing 30g and 45cm in length was then inserted so that it rest over the suppository. The time at which the glass rod reaches the narrow end after complete melting of the suppository represents the narrow end complete melting of the suppository represents the liquefaction time.

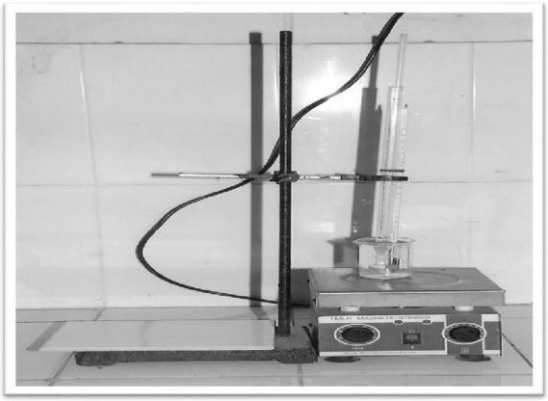


Figure no. 06 Fabricated instrument.

c) Mechanical Strength/Crushing test:

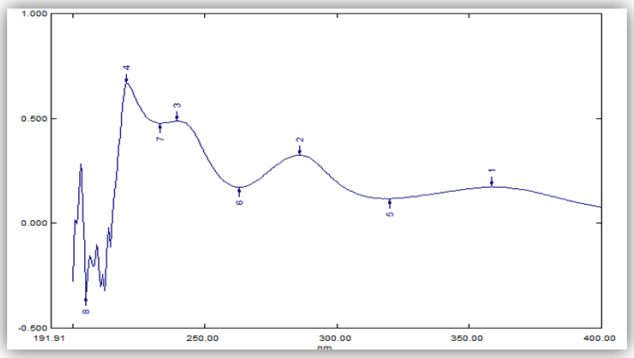
For determining the mechanical strength of suppositories a suppository was kept horizontally between two fiber slabs of smooth surfaces and pressure was slowly increased on the upper slab till it was crushed. The weight required for crushing the suppository was calculated and the procedure was repeated thrice.

d) Content uniformity test:

10 suppositories were weighed and mixed properly. Accurately weighed quantity of mixed material equivalent to about 0.05 g of hesperidin was dissolved in 50 ml 0.1N NaOH in a mechanical shaker for 15 min and diluted to 100 ml with 0.1N NaOH. It was filtered to Whatman filter paper (no. 42). 2.0 ml of filtrate was transferred to a 100 ml volumetric flask and the volume was made up to 100 ml with 0.1N NaOH. The concentration of paracetamol was calculated from the absorbance taken its λ max 286 nm and the standard calibration curve.

1. Location of λmax of hesperidin in 0.1N NaOH

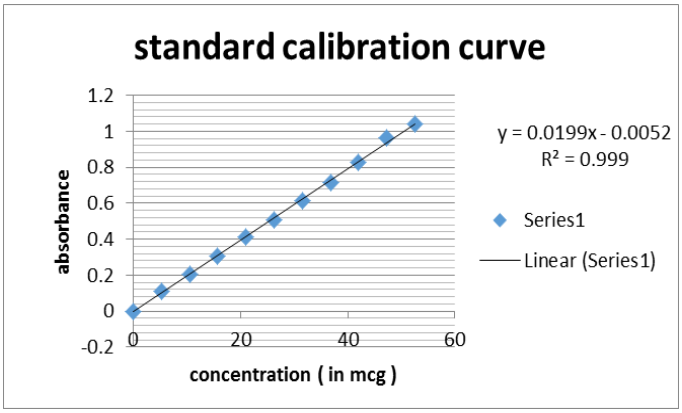
The stock standard solution of Hesperidin was appropriately diluted with 0.1N NaOH to obtain the concentration of 15 µg/mL and the solutions were scanned in the UV range (400-200 nm) in 1.0 cm cell against solvent blank. UV absorbance spectra of drugs are depicted in the following fig.



From the above spectra in λ max of hesperidin was found to be 286 nm.

2. **Standard calibration curve of hesperidin in λ max 286 nm**

The stock standards solution of Hesperidin was diluted with 0.1N NaOH to get a series of concentrations from 0-50 µg/ml. The absorbance of each of the solutions was measured at 286 nm in a 1.0 cm cell using a solvent blank. The graphs plotted as concentration vs absorbance are depicted in the following fig.



RESULT

Table no.02: Result- Characterization of suppository.

Sr. No.	Test		Observation	Standard
1	Visual examination	Colour	Yellowish-brown	-
		Odour	Odourless	
		Appearance	Dry	
		Texture	Mine smooth	
		Feel	hard(plastic)	
2	Macro melting determination		32ºC	≤ 37 °C
3	Liquefaction time		17minutes	Less than 30 min.
4	Mechanical strength/crushing test		1.8 kg pressure	0.5 – 5 kg pressure
5	Assay		97.81%	85 – 115%
6	Content uniformity		97.34%	85-115%

Displacement value:

1. Displacement value of hesperidin fo*r PEG 6000*

Displacement value = 0.05/0.0435 = 1.1495

DISCUSSION

Hesperidin tablets are insoluble in water and are easily affected by acid after oral administration. So hesperidin is made into a suppository, compared with oral administration, rectal administration has a rapid onset of action, and there is no difference in the concentration maintenance time after absorption, so orange peel Glycosides made into suppositories are more in line with the purpose of clinical treatment of hemorrhoids. In this experiment, polyethylene glycol was used as a water-soluble suppository base, which can make hesperidin release quickly in the body and exert its curative effect. obtained suppository had a good appearance, and its weight difference and content were uniforms.

CONCLUSION

All the suppositories were free from pits, fissures, and cracks. The longitudinal section of the suppository was plain and clear, indicating the dissolution of the drug in the base. The drug content was found to be 97.34 %

which is within the acceptable range liquefaction time was found to be 17 minutes at 37^0c. The temperature for macro melting was found to be 32ºC. Maybe a suppository of hesperidin developed as a new formulation.

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REFERENCES

1. Binkowska, I., Hesperidin: synthesis and characterization of bioflavonoid complex. *SN Applied Sciences*, 2020; *2*(3): 1-9.
2. Daoud, S., Afifi, F.U., Al-Bakri, A.G., Kasabri, V. and Hamdan, I.I., Preparation, Physicochemical characterization, and biological evaluation of some hesperidin metal complexes. *Iranian Journal of Pharmaceutical Research: IJPR*, 2014; *13*(3): 909.
3. Roy JA, Azamthulla MO, Mukkerjee DH. Hesperidin and diosmin-a novel drug. International Journal of Pharmacy Research & Technology, 2020; 10(2): 25-33.
4. Gami, B., Hemorrhoids–a common ailment among adults, causes & treatment: a review. *Int J Pharm Pharm Sci*, 2011; *3*(5): 5-13.
5. Bharat, g., Hemorrhoids–A Review. *Indian Journal of Pharmaceutics*, 2014; *5*(1): 37-42.
6. MacKay, D., Hemorrhoids and varicose veins: a review of treatment options. *Alternative medicine review*, 2001; *6*(2): 126-126.
7. Suzuki, H., Asakawa, A., Kawamura, N., Yagi, T. and Inui, A., Hesperidin potentiates ghrelin signaling. *Recent Patents on Food, Nutrition & Agriculture*, 2014; *6*(1): 60-63.
8. Lachman. Lieberman et al. The Theory and Practice of Industrial Pharmacy CBS Publishers and Distributors. New Delhi, 2009; 564-588.
9. R. Mehta. Dispensing pharmacy, 2017; 6: 265-270.
10. Fairthorne RF. ON THE PREPARATION OF SUPPOSITORIES. American Journal of Pharmacy (1835-1907), 1871; 1: 488.
11. Sharma P, Pandey P, Gupta R, Roshan S, Garg A, Shulka A, Pasi A. Isolation and characterization of hesperidin from orange peel. Journal of Pharm Research, 2013; 3(4).
12. Belboukhari, N., Cheriti, A., Feddoul, A. and Bouanini, M., Chiral TLC resolution of Hesperidin diastereomers on silica gel plates. *EJEAFChe*, 2009; *8*(11): 1170-1172.
13. Garg, A., Garg, S., Zaneveld, L.J.D. and Singla, A.K., Chemistry and pharmacology of the citrus bioflavonoid hesperidin. *Phytotherapy Research*, 2001; *15*(8): 655-669.
14. Aushutoshkar.Pharmacognosy and pharmacobiotechnology New Delhi, 2003; 2007: 425-426.
15. Baria A. H., Patel R. P., Suthar A. M., Parmar R. B., Formulation Development and Evaluation of Sustained Release Aceclofenac Suppository, International Journal of Pharmaceutical Sciences and Drug Research, 2009; 1(2): 71-73.
16. Gold M, VePuri M, Block LM. Suppository development and production, in: H.A. Lieberman, Rieger M.M., Banker G.S. (Eds.). Production Pharmaceutical Dosage Forms: Disperse Systems, Marcel Dekker, New York, 1996; 447-496.
17. Hasan M, Otoom S, Najib N, Sallam E. Basic & Clinical Pharmacology & Toxicology, 2004; 95 (6): 1742-7843.
18. Azhgikhin IS. Determination of the hardness of suppository bases using Kaminskii's device. AptechnDelo, 1965; 14: 14–19.