HNSJ Humanitarian & Natural Sciences Journal
ISSN: (e) 2709-0833
www.hnjournal.net
Peer-Reviewed Journal
Indexed at: NSP - SJIF
Arabic Impact Factor 2020 = 0.44

RESEARCH ARTICLE

FORMULATION AND IN-VITRO EVALUATION OF DICLOFENAC SODIUM CONVENTIONAL SUPPOSITORIES

Rajaa A. Dahash* and Balkis A. Kamal**

**Ministry of Health and Environment, Baghdad*
Email: shamscarla88@gmail.com
***The Osol Aldeen University Collage , Pharmacy department*

Published at 01/08/2021 **Accepted at 24/07/2021**

Abstract

Diclofenac sodium is a non steroidal anti- inflammatory agent used in the treatment of many diseases including rheumatoid arthritis and ankylosing spondylitis . This investigation concerned with the preparation and evaluation of diclofenac sodium as conventional suppositories to achieve optimum drug release at a rectal route.

The influence of suppository base type on the in vitro release of the drug and the physical properties was studied using various hydrophilic and lipophilic bases in the preparation of conventional type suppositories.

Moreover the influence of storage time and storage temperature was investigated. One formula with optimum and uniform release profile were selected and stored at 4˚C and 25˚C for 1, 15, 30, 45 days.

The result revealed that the effect of storage of suppositories prepared from polyethylene glycol base was found to cause decrease in the melting time, hardness and slight increase in the release rate because of the brittleness of these bases, while the storage of the suppositories prepared from Witepsol bases cause a slight increase in the softening time, melting time and hardness, as well as decrease in the percent of the drug release.

Introduction

Drugs are often administered in to the rectum in the form of solutions, suppositories and ointments for both local and systemic effects. Rectum and colon are capable of absorbing many drugs [1].

Several categories of rectal preparations may be distinguished [2, 3]:

1-Rectal Capsule

2-Rectal Solutions, Emulsions and Suspensions

3-Powders and Tablets for Rectal Solutions and Suspensions

4- Semi-Solid Rectal Preparations

5- Rectal Foams

6- Rectal Tampons

Therapeutic Uses of Suppositories:

The suppository is a rational form of medication for treatment of local conditions, such as hemorrhoids as well as constipation [4]. However, it may also be used for systemic effect include antiemetics, antipsychotics, drugs used in the treatment of migraine, and non-steroidal anti-inflammatory agents [5] .

Factors Affecting Rectal Absorption of Therapeutic Agents

Physiological Factors :

The site of absorption will affect the fate of the therapeutic agent within the blood stream therefore the metabolism of therapeutic agents will depend on the location of the dosage form [6].

Physicochemical Factors of the Drug and Suppository Base

The selection of a physicochemically suitable base for the drug is essential for the preparation of the suppositories [7].

Lipid-Water Solubility of the Drug

Some rectal bases of suppositories are lipophilic and therefore if the therapeutic agent is also lipophilic, the release of the drug will be slow and the solubility of the drug in the rectal fluids will be low (a factor that is compounded by the low volume of the latter) [8] .

Particle Size and Concentration of the Drug

The rate of dissolution of a drug is influenced by the particle size of the solid particle of drug, so control of the particle size is important and can effect dissolution and subsequent absorption and bioavailability [9].

Nature of the Base

The nature of the base used in the suppository formulations need to carefully chosen during formulation in order to obtain suppositories of desired mechanical and drug release properties [10].

Experimental work

Methods

Determination of Diclofenac Sodium Melting Point

The melting point of Diclofenac sodium was measured by the electrical melting point apparatus using capillary method [11].

Determination of λ_{max} of Diclofenac Sodium

Diclofenac sodium solution of 30 µg/ml in Sorensen's phosphate buffer pH 7.4 was prepared, then the solution was scanned by spectrophotometer from 200-400 nm, and then the λ_{max} of the drug was determined .

Preparation of Diclofenac Sodium Conventional Suppositories

Diclofenac sodium conventional suppositories were prepared by fusion method using different types of suppository bases.

In general, the melting method involved melting of the base by gentle seating on water bath, followed by addition of the drug (100 mg for each suppository) with continuous and gentle stirring until a homogenous preparation was achieved. The mixture was poured into a 2 gram suppository mould and the suppositories were allowed to solidify over a night in a refrigerator [12].

Formulations:

Different formulas were prepared as shown in table (1).

Six types of bases were used during the preparation of diclofenac sodium suppositories .The displacement values (the number of parts by weight of the medicament that

displaces one part by weight of the base) of diclofenac sodium in these six bases was first determined and the amount of the base needed was calculated [13].

The displacement values of the drug in different bases are listed in table (2).

Table (1) :Composition of Diclofenac Sodium Conventional Suppositories

Formula No.	Quantity of Diclofenac Sodium(mg)	Type of the Base
1	100	Hydrogenated palm kernel Glycel
2	100	Witepsol H35
3	100	Witepsol H37
4	100	Polyethylene Glycols 400:6000 (70:30)
5	100	Polyethylene Glycols 1000:6000 (70:30)
6	100	Glycerinated gelatin base (glycerine, gelatin and water) (70: 20 : 10)

Table (2):Calculated Displacement Values of Diclofenac Sodium in Different Bases

Base	Displacement Value
Hydrogenated Palm Kernel Glycel	1
Witepsol H 35	1.158
Witepsol H 37	1.1
Polyethylene Glycols 400:6000 (70:30)	1.2
Polyethylene Glycols 1000:6000 (70:30)	1.7
Glycerinated gelatin base	1.4

Physical Properties of the Suppositories Breaking Strength Test

Determination of the mechanical strength of suppositories can be valuable to avoid problems with formulations [14] .

The breaking strength test was carried out using the Erweka hardness tester. This test determines, under defined conditions, the resistance of suppositories to rupture, and it is measured by the mass needed to rupture them by crushing. This test is not suited to suppositories based on excipients such as gelatin-glycerol mixture (2).

Determination of the Melting Time

The release of the active ingredient from the vehicle is related to the melting point of the vehicle and the solubility of the drug in the vehicle. Suppositories undergo three changes in phase during their "life". First, they are melted and then solidified; upon administration, they are again melted. An understanding of these factors and their relationships is critical for evaluating the bioavailability of the final suppository formulation. The higher the melting point, the later the drug effects appear. If too high, the drug effect does not appear [15,16] .

Softening Time Determination (for lipophilic suppositories)

The softening time test indicates how long certain preparation takes to lose its physical in the spiral shaped b glass basket of the test tube with the tip pointed upwards and the tube was then closed , A thermostat connected to the tester provided circulating distilled water inside the test tube at the constant temperature 37 ˚C structure and constant flow rate . The time required for the first drop of the suppository base to appear floating on the surface of the water inside the testing tube was considered softening time [17].

In Vitro Drug Release

The release rates of diclofenac sodium from conventional suppositories were determined.

The suppository placed in a jar containing 1 liter Sorensen's phosphate buffer (7.4), with a paddle rotating at 100 rpm at a constant

temperature of 37˚C ± 0.5˚C [111] .The dissolution test was carried out for 60 minutes .

At appropriate time intervals (0, 5, 10, 15, 20, 25, 30, 40, 50 and 60 minutes), 5-ml samples were withdrawn through syringe Millipore filter, the removed volume of the medium was replaced by the same volume of the buffer withdrawn at each time. Samples were diluted when necessary and assayed for diclofenac sodium content spectrophotometrically at λ max of the drug [18] .

Factors Affecting Formulation

Effect of Nature of Suppository Base Used

The effect of base type on the release of diclofenac sodium from conventional containing the drug in a powder or solution form was studied [19] .

Lipophilic bases (Hydrogenated palm kernel Glycel, Witepsol H 35 and Witepsol H 37) formula (1) , formula (2) and formula (3) respectively and hydrophilic bases {formula (4) [PEG $_{400:6000}$ (70:30)], formula (5) [PEG $_{1000:6000}$ (70:30)] and formula (6) (glycerinated gelatin base)} were used to investigate the effect of nature of suppository base on in vitro release of diclofenac sodium and the physical properties of the prepared conventional suppositories.

Effects of Changing the Type of Polyethylene Glycols (PEGs)

The effect of changing the type of polyethylene glycols as suppository base on the physical properties and the rate of release was demonstrated [113]. This was done by changing the type of polyethylene glycol as in formula (4) [PEG $_{400:6000}$ (70:30)] and formula (5) [PEG $_{1000:6000}$ (70:30)].

Effect of Storage Time and Temperature on the Release and Physical Properties of Diclofenac Sodium of the Selected Formulas

To study the effect of storage time and temperature on drug release and physical properties of different suppositories formulas , the prepared suppositories were stored at 4˚C and 25˚C for 1, 15, 30, 45 days . Two formulas were selected for this study {formula (1) and formula (2)}. The suppositories were wrapped with aluminium foil, placed in tightly closed containers and stored at the mentioned temperatures for periods indicated [20] .

Statistical Analysis

The results obtained were statistically analyzed by using one way analysis of variance (ANOVA). Differences of ($p < 0.05$) were considered to be significant.

Physical Properties of Diclofenac Sodium

Determination of Diclofenac Sodium Melting Point

The measured melting point of diclofenac sodium was found to be 280 ˚C with decomposition. This result is the same as reported in references, which indicates the purity of the supplied drug powder [21].

Determination of λ max of Diclofenac Sodium

The UV scan the solution which contains (30 µg/ml) of diclofenac sodium in solution of Sorensen's phosphate buffer pH 7.4 by UV spectrophotometer at 200-400 nm gave the spectrum shown in figure (1) with a λ max. at 275 nm .

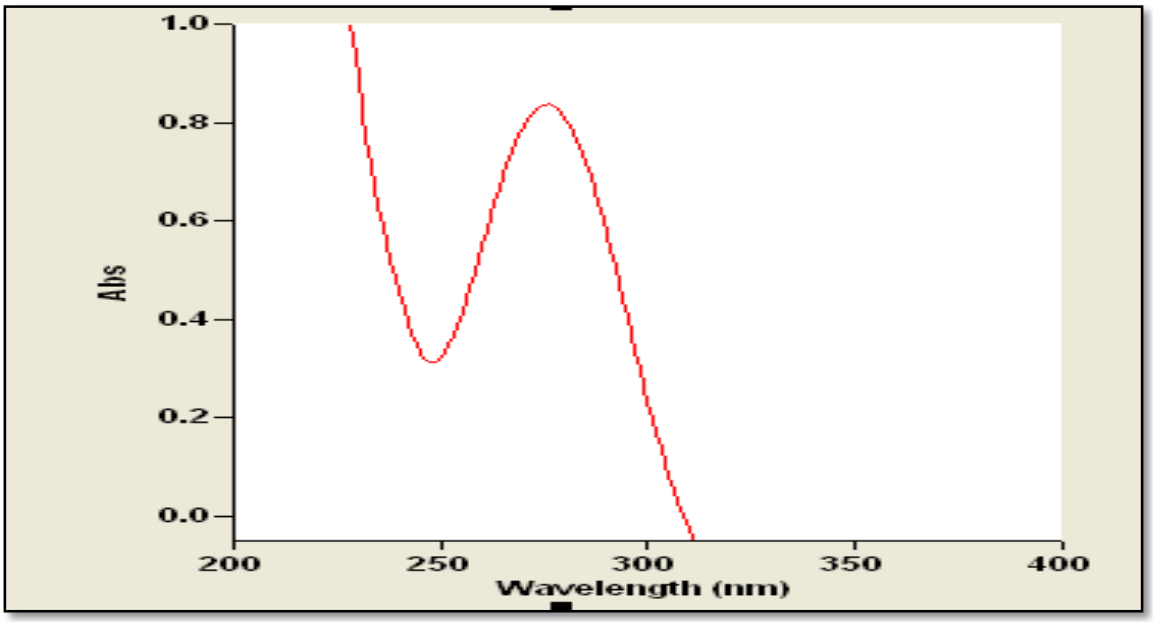

Figure 1 : The UV spectrum of Diclofenac Sodium in Sorensen's Phosphate Buffer pH 7.4 at 37ºC.

Physical Properties of the Suppositories

Effect of Nature of Suppository Base Used

Table (3) represent the effect of changing the type of suppository base on the softening, melting time and hardness of the conventional prepared suppositories. It was found that the melting time for hydrophilic bases (glycerinated gelatin and polyethylene glycols) was found to be longer compared to that of lipophilic bases. The dissolution behavior of diclofenac sodium from these oleaginous and hydrophilic base was shown in figure (5) . It was seen that the drug release was increased significantly ($P< 0.05$) from Witpsol H35 and Witpsol H37 when compared with Hydrogenated Palm Kernel Glycel this may be attributed due to the presence of monoglycerides in the Witpsol H35 and Witpsol H37 bases which act as emulsifying agent, thus fascilitating the dispersion of the medicament to the surrounding media [121] . Moreover the release of diclofenac sodium increased significantly ($P< 0.05$) from polyethylene glycols mixture and glycerinated gelatin base compared with Hydrogenated Palm Kernel Glycel, Witepsol H35, and Witepsol H37, this behavior may be due to the low water solubility of diclofenac sodium , so the affinity of the drug to lipophilic bases is higher than hydrophilic bases since the drug has relatively a high partition coefficient of 13.4 [22], so it have better solubility in a lipophilic bases than in aqueous environment of the rectal fluid and tend to stay in a lipophilic base longer than in a hydrophilic base [23] .

Table (3) :Effect of Nature of Suppository Base Used on the Physical Properties

Formula no.	Base type	Time Softening (minutes)	Melting Time (minutes)	Hardness
1	Hydrogenated Palm Kernel Glycel	8	12	2.4
2	Witepsol H 35	10	13	3
3	Witepsol H37	13	18	3.2
4	$PEG_{400:6000}$ (70:30)	-	25	3.6
5	$PEG_{1000:6000}$ (70:30)	-	36	3.8
6	Glycerinated gelatin	-	42	-

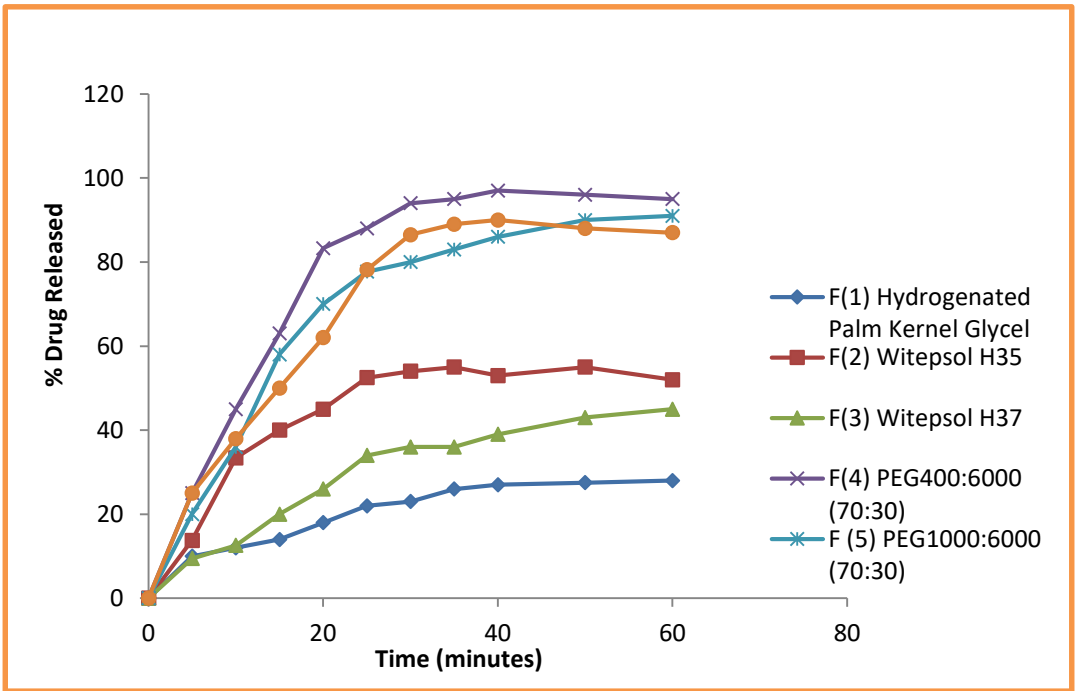

Figure (2) : Effect of Suppository Base Type on the In Vitro Release of Diclofenac Sodium from Conventional Suppositories in Sorensen's Phosphate Buffer pH7.4 at 37 °C .

Effect of Changing the Type of Polyethylene Glycols

Concerning the effects of changing the type of polyethylene glycols on the physical properties of conventional suppositories formula (4) {PEG $_{400:6000}$ (70:30)} shows lower melting time (25 minutes) as compared with formula (5){ PEG $_{1000: 6000}$ (70:30 } (36 minutes) as shown in table (4) . This may be related mainly to the fact that the melting point of polyethylene glycols increase as a function of increasing of polymerization of polymer used, that increase with increasing the molecular weight used [24].

Table (4) :Effect of Changing the Type of Polyethylene Glycols on the Physical Properties of the Conventional Suppositories

Formula no.	Base type	Melting Time (minutes)	Hardness (Kg)
4	PEG $_{400:6000}$ (70:30)	25	3.6
5	PEG$_{1000:6000}$ (70:30)	36	3.8

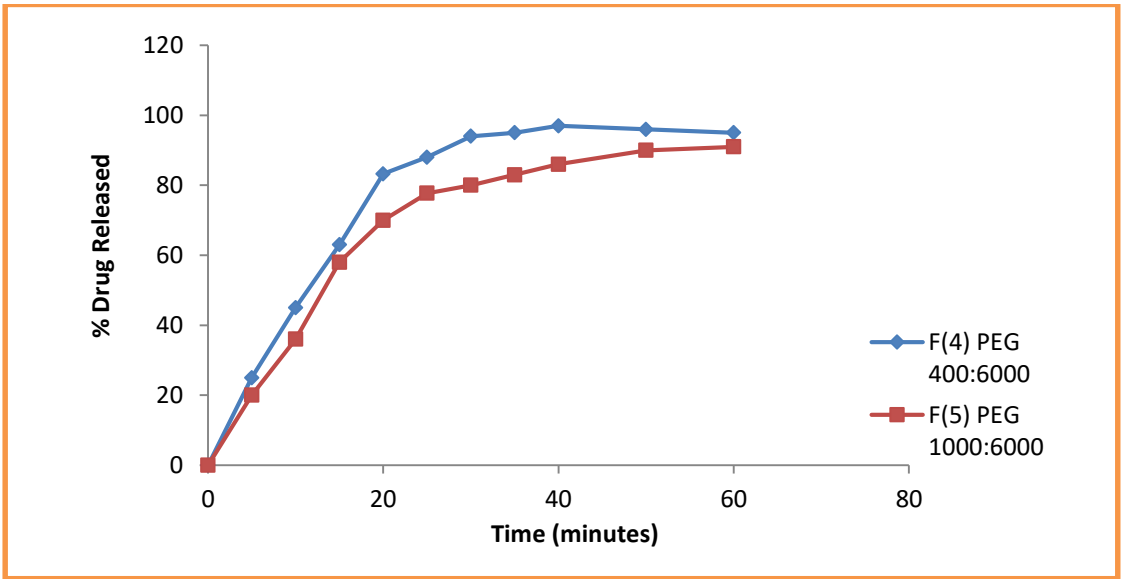

Figure (3): Effect of Changing of Type of Polyethylene Glycols on the In Vitro Release of Diclofenac Sodium in Sorensen's Phosphate Buffer pH 7.4 at 37 °C.

Effect of Storage Time and Temperature on Diclofenac Sodium Release and Physical Properties of the Selected Formulas

The effect of storage period and temperature on the physical properties and the release of diclofenac sodium for the selected formulas were studied .

Formula (4) was chosen because they gave optimum and uniform release profile. Samples were selected from these two formulas and stored for 1, 15, 30 and 45 days at 4˚C and 25˚C.

Table (5) shows that storage of formula (4) suppositories at 4˚C the melting time and hardness of these suppositories was decreased. Also there was a slight decrease in the values of these parameters on storage at 25˚C. The above results may be due to storage of polyethylene glycols at low temperature lead to their brittleness which may cause decrease in melting point and hardness [25] .

On the other hand, figure (4) shows the study of the dissolution behavior of the drug from these formulas during the storage conditions at a various temperatures, there was no significant change ($P > 0.05$) in the time of 100% of drug released from the formulas tested, but on the other hand, the $t_{50\%}$ of drug release showed that there was increase in the drug released when formula (4) stored at 4˚C and 25˚C after 30 days and 45 days when compared with those stored for one day . This is because this type of bases become brittle on storage [26]. This may be due to crystallization of Witepsol bases when stored prolonged period of time [4]. These findings are in consistent with

the results obtained by storage of metronidazole conventional suppositories made from Witepsol base [27] .

Table (5) :Effect of Storage and Temperature on the Physical Properties of Polyethylene Glycols 400:6000 (70:30) Conventional Suppositories(Formula 4) at 4˚C and 25˚C

Storage Period (days)	Physical Properties			
	4˚C		25˚C	
	Melting Time (minutes)	Hardness(Kg)	Melting Time (minutes)	Hardness(Kg)
1	25	3.6	25	3.6
15	23	3.4	23	3.4
30	21	3.2	23	3.2
45	22	3	22	3.2

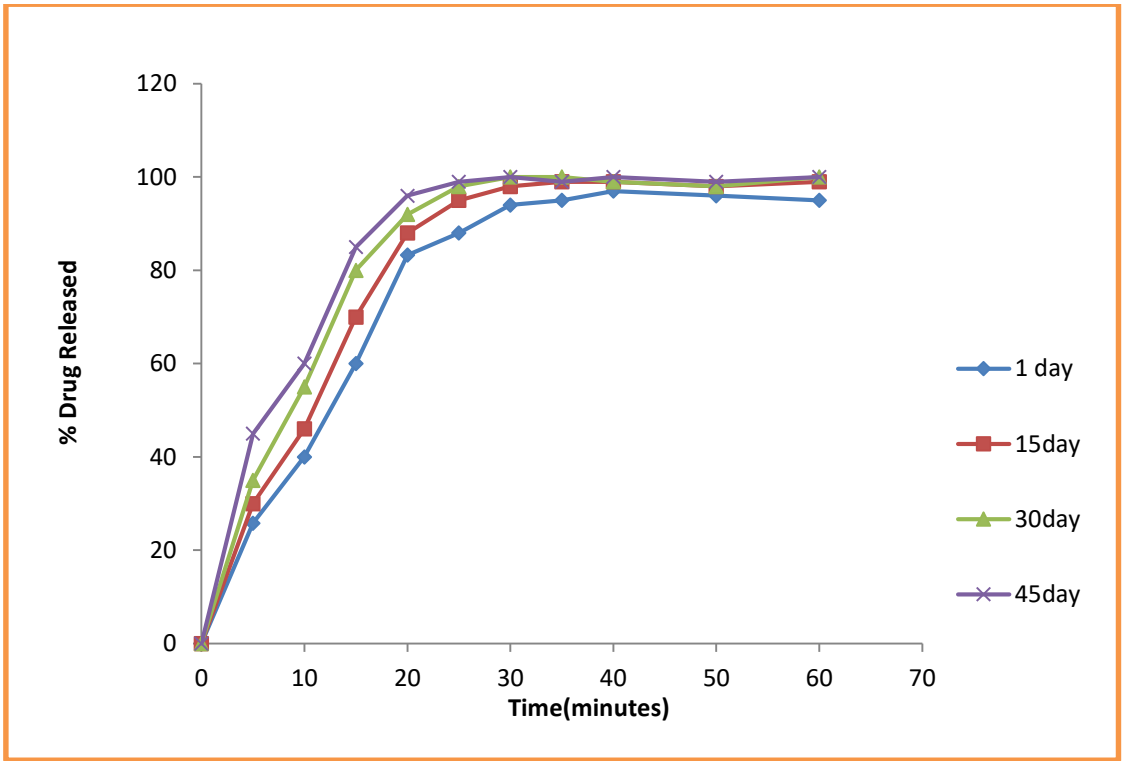

Figure (4): Effect of Storage Period and Temperature on the Release of Diclofenac Sodium from PEG 400:6000 (70:30) Conventional Suppositories (formula 4) Stored at 4˚C Using Sorensen's Phosphate Buffer pH 7.4 at 37 ˚C .

References

1. Biopharmaceutics. In: Gaud RS, Yeole PG,Yadav AV, Gokhale SB , editors. A Text book of pharmaceutics .10th edition. India: Nirali Prakashan, 2018; p. 84.
2. 2.British Pharmacopoeia, The stationary office, London; 2009.
3. 3.European Pharmacopoeia, Directorate for the Quality of Medicines & Health Care; 2018; p. 227-229 .
4. 4. Suppositories. In : Youngson RM, Arnot D, Evans D, Gary L, Griffon J , Harris T, editors. Encyclopedia of family health. 3th edition .Marshall Cavendish Corporation. 2015; p.2133.
5. Rectal and Vaginal products. In: Lund W, editors. The pharmaceutical codex. 12th edition. London: The Pharmaceutical Press. 2019; p.170-174.
6. Vaginal and Rectal Dosage Forms. In: Jones D, editors. Pharmaceutics Dosage Form and Design. London: Pharmaceutical Press, 2018; P. 157-171.
7. Hidaka N, Suemaru K, Aimoto T, Araki H. Effect of simultaneous insertion of oleaginous base on the absorption and on the anticonvulsant effect of diazepam suppository. Biol. Pharm. Bull. 2016; 29(4): 705-708.
8. Young C, Pallin KJ, Reid AS, Thomas NW, Gould PL. Formulation of fenbrufen suppositories. II. Selection of a suppository base using dissolution studies and histological studies in rats. Int J Pharm 2015; 40(3): 187-191.
9. Mahaguna V, McDermott JM, Zhang F, Ochoa F, Investigation of product quality between extemporaneously compounded progesterone vaginal suppositories and an approved progesterone vaginal gel. Drug Development and Industrial Pharmacy 2014; 30:1069-1078.
10. Okubanjo O, Odeku OA. Effect of interacting variables on the mechanical and release properties of chlorquine phosphate suppositories. Acta Pharmaceutica Sciencia 2019; 51: 281-288.
11. Ashford M. Bioavailability-physicochemical and dosage from factors. Tukker JJ. Rectal and vaginal drug delivery. In: Aulton ME, editors. Aulton's Pharmaceutics: The Design &Manufacture of Medicines. 3rd edition. London: Churchill Livingstone. 2018; p. 347, 606 - 614.
12. Block LH. Medicated topical. In: Tory DB, Hauber MJ, editors. Remington: The

science and practice of pharmacy, 21 st edition, Philadelphia: Lippincot Williams & Wilkins 2016; p. 883-886.

13. Suppositories and Pessaries. In: Cooper JW, Gunn C, editors. Cooper and Gunn's Dispensing for Pharmaceutical Students. 12th edition. London: Churchill Livingstone 2014; p. 232-250.
14. Shargel L, MutnickAH, Souney PF, Swanson LN, Comprehensive pharmacy review. London: Lippincott Williams &Wilkins, 2011; p. 51.
15. Block LH. Medicated topical. In: Tory DB, Hauber MJ, editors. Remington: The science and practice of pharmacy, 21 st edition, Philadelphia: Lippincot Williams & Wilkins 2016; p. 883-886.
16. Rowe RC, Sheskey PJ, Quinn ME, Handbook of pharmaceutical excipients. 6 th edition. London: Pharmaceutical Press, 2019; p.517.
17. Analgesic-Antipyretic-Anti-inflammatory and Related drugs. In: Abrams AC, Ferguson SG, Goldsmith T, Hirnle CJ, Lammon CA, Pennington SS, Romanelli F, ed. Introduction to drug therapy.Canda: Bc Decker Inc., 2017; p. 106.
18. Kaew nopparst N, Kaewnopparat S, Rojanarat W, IngkatawornwongS. Enhanced release of diazepam from hollow type suppositories. International Journal of Pharmaceutical Compounding 2014; 8: 310-312.
19. Adegboye T, Itiola O. Physical and Release Properties of Metronidazole Suppositories. Topical Journal of Pharmaceutical Research. 2018; 7(1): 887-896.
20. Suppositories and inserts. In: Allen LV , Popovich NG, Ansel HA, ed. Ansel's Pharmaceutical Dosage Forms and Drug Delivery systems. 8th edition. London: Lippincott Williams & Wilkins, 2015; p. 316-335.
21. Ullmann F, Ullmann's encyclopedia of industrial chemistry. Wiley-VCH , 2003; p. 56 .
22. Sallmann AR, The history of diclofenac . Am J Med 2015 ; 80: 29-33.
23. Desai A. Rectal, Vaginal and Urethral Delivery. In: Desai A, Lee M, editors: Gibaldi's Drug Delivery Systems. Silverchair Science and Communications Inc. 2017. P. 96-101.

24. Suppositories and inserts. In: Allen LV , Popovich NG, Ansel HA, ed. Ansel's Pharmaceutical Dosage Forms and Drug Delivery systems. 8th edition. London: Lippincott Williams & Wilkins, 2015; p. 316-335.
25. Winfield AJ, Suppositories and pessaries. In: Winfield AJ, Richards RME, editors: Pharmaceutical practice. 3 th edition Churchill Livingstone, 2014; p. 219.
26. Wade A, Pharmaceutical hand book: incorporating the pharmaceutical pocket book. London: Pharmaceutical Press, 2017; p. 97.
27. Paek SH, Xuan JJ, Choi HG, Park BC, Lee YS, Jeong TC, Jin C H, Oh Y K, Kim JA, Poloxamer 188 and propylene glycol based rectal suppository enhances anticancer effect of 5- fluorouracil in mice, Biol. Pharm. Bull. 2016; 29: 1060-1063.