

Formulation and In Vitro Evaluation of Oxcarbazepine Conventional and Hollow-Type Rectal Suppositories

(Short Note)

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ABSTRACT

Oxcarbazepine (OXC) is one of the recent antiepileptic and anticonvulsant drugs. The purpose of the present study was to optimize the best formula for rectal suppositories of OXC. The suppositories were formulated successfully, using different types of witepsol, polyethylene glycols (PEGs) and glycerinated gelatin bases, at different ratios and types of suppositories (conventional and hollow-type). The prepared suppositories were evaluated for physical properties like softening, melting time, hardness and dissolution profiles. The study revealed that hollow-type suppositories of witepsol H35, base loaded with oxcarbazepine solution is the most promising formula compared with other rectal suppositories formulas prepared from different hydrophilic bases and mixtures. The selected formula, which contains 100 milligrams oxcarbazepine loaded as a solution in a witepsol H35 hollow-type suppository base, has a softening and melting time of 4 and 12 minutes, respectively. Besides that, 94% of the drug was released within one hour and had a shelf life of 3.1 years.

Keywords: hollow-type suppositories, oxcarbazepine, witepsols H35 and H37.

INTRODUCTION

Suppositories are solid dosage forms, intended for insertion into body orifices where they melt, soften or dissolve and exert local or systemic effects.¹ Their action depends on the nature of the drug, concentration, vehicle and the rate of absorption.

Many arguments were indicated for choosing the rectal route for drug administration, among them, to avoid patient gastro intestinal tract problems, unpleasant tasting or

bad smelling drugs, first pass effect² and their convenience for children and unconscious patients.³ A hollow-type suppository, which has a hollow cavity to accommodate drugs in various forms such as a powder

or solution, is very effective as a rapid pain reliever⁴ or an anxiolytic and tranquillizer therapy.⁵ Vaginal administration of hollow-type suppositories containing Ulinastatin was found to be effective in the prevention of imminent abortion in combination with the oral administration of uterine relaxing therapy.⁶ In addition, hollow-type suppositories have some advantages over conventional suppositories as they can carry either powdered or solution forms of drugs, and they eliminate the effect of the heating process on the nature of the drug during the preparation of the conventional suppositories.⁷

Oxcarbazepine is an antiepileptic drug used in many diseases including convulsion disorders; it is rapidly and completely absorbed from the GIT. The oral bioavailability is affected by food.⁸ This investigation was concerned with the preparation of oxcarbazepine as conventional and hollow-type suppositories for rectal administration to achieve the rapid and complete release of the drug.

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Received on 30/9/2012 and Accepted for Publication on 17/1/2013.

EXPERIMENTAL

Materials

The materials that were used in this study are listed below:

- Oxcarbazepine powder BP was from Mission Viva Care Limited, Mumbai, India.
- Witepsol H35 and witepsol H37 were supplied by Samarra Drug Industry SDI.
- Polyethylene glycols PEG (400,1000 and 4000), ethyl oleate and glycerin were supplied by BDH Chemicals Limited, England.
- Tween 80 and propylene glycol were supplied by Merck-Schuchardt, Germany.
- Lactose, gelatin and liquid paraffin were supplied by Fluka-AG, Switzerland.

Instruments

The instruments used in this study are as follows:

- UV-visible spectrophotometer, Apel UV-VIS PD-303UV, Japan.
- Water bath, Memmert Schwabach, Germany.
- Dissolution apparatus, Kavosh dissolution tester DUT-69, Germany.
- Balance, Sartorius AG Gottingen, Germany.
- Suppository moulds (2gm.), stainless steel, ERBO Prazision-Forminbau, GMPH D-7470, Albstadt 3, Germany.
- Electrical melting point apparatus, Thomas Hoover, England.
- Softening time and hardness tester, Erweka apparatus GMBH, SBT, Germany.
- Thermostat, Labsco Laboratory Supply Company, Ollman and Co KG, Germany.
- Vortex mixer, Stuart Scientific auto vortex SA6, United Kingdom.

Methods

Preparation of Oxcarbazepine Suppositories

Two types of oxcarbazepine suppositories were prepared:

1. Conventional oxcarbazepine suppositories
2. Hollow-type suppositories containing

oxcarbazepine in either solution or powder form

Preparation of Oxcarbazepine Conventional Suppositories

The above suppositories were prepared by the fusion method using different types of suppository bases. The fusion method involved the melting of the base by gentle heating in a water bath, followed by the addition of the equivalent weight of 100mg oxcarbazepine for each suppository. The melted mass was stirred constantly but slowly to avoid air entrapment, and then the mixture was poured into 2 gram suppository moulds. The moulds were allowed to cool thoroughly using a refrigerator, and any excess suppository mass was removed from the moulds by scraping. Then the moulds were opened and the suppositories were removed.⁹ For suppositories containing the mixture of polyethylene glycol (PEG), the higher molecular weight PEG was first melted, and the lower molecular weight one was added after and mixed well.¹⁰

The glycerinated gelatin base was prepared by heating the mixture of gelatin, glycerin

and distilled water at 70°C to dissolve the gelatin, and the mixture was stored in a water bath for 48 hours at 50°C, and then the mixture was used as a base after the removal of the bubbles.¹¹

Preparation of Hollow-type Suppositories Containing Oxcarbazepine in Solution or Powder Form

These types of suppositories were prepared by melting various suppository bases using gentle heat in a water bath. The melted bases were poured into 2 gram suppository moulds equipped with a cylindrical tube in the center and allowed to stand for 2 hours at room temperature to solidify.

After the construction of the hollow-cavity in the solidified bases, oxcarbazepine was added to the cavity in the following forms:

1. Two grams of mixture powder prepared by mixing oxcarbazepine and lactose in a percentage 5%(w/w).
2. Four hundred micro liters of (A) oxcarbazepine solution prepared by dissolving the drug in ethyl oleate

and then mixed with Tween 80 in a ratio 70:30 w/w, and (B) oxcarbazepine aqueous solution of 4% v/v Tween 80 and the resultant solution was mixed with propylene glycol in a percentage of 50% v/v for oleaginous bases.

Each suppository contained an amount of solution or powder equivalent to 100 mg oxcarbazepine (Table 1). The openings at the back part of the suppositories were sealed with melted bases.

Physical Properties of the Suppositories

Melting Time Estimation

The suppositories were placed in a glass tube (2.5 cm in diameter), 2 milliliters of phosphate buffer (pH 7.4) was added, and then the tube was placed in a water bath at 37°C. The time required for each suppository to melt completely or to disintegrate was estimated.¹²

Rupture Test (Hardness)

This test determined under defined conditions the resistance to rupture of suppositories measured by the mass needed to rupture them by crushing the hardness tester inside the testing chamber maintained at 25°C by means of circulating water. The suppository was placed into the holding device with the tip upward and the testing chamber was then closed with a glass plate. At this point the initial load which was given by the entire suspended block was 600 grams. After one minute, a disc of 200 grams was added, and this weight addition was continued every minute until the suppository's collapse under the load of the weight. The mass required to crush the suppository was calculated by the sum of the masses weighing on the suppository when it was collapsed, and this was assessed as follows:

- If the suppository collapsed within 20 seconds of placing the last disk, then this mass was not taken into account.

- If the suppository collapsed within 20-40 seconds of placing the last disk, then half of this mass was used in the calculation, i.e., 100 grams.

- If the suppository remained uncrushed for more than 40 seconds, then all the mass was used in the calculation.¹³

Softening Time Test of Lipophilic Suppositories

The softening time was done by inserting the suppository in the spiral shaped glass basket of the test tube. A thermostat connected to the tester provided circulating distilled water inside the test tube at a temperature of 37°C and constant rate flow. The time required for the first drop of the suppository base to appear floating on the surface was considered as the softening time.¹⁴

In Vitro Drug Release

The release rates of oxcarbazepine from conventional and hollow-type suppositories were determined using the basket dissolution apparatus maintained at 50 rpm and temperature 37 °C. The medium was 500 ml of Sorensen phosphate buffer at pH 7.4.

The time intervals were 0,5,10,15,20,25,30,40,50 and 60 minutes. Four ml samples were withdrawn through a Millipore syringe filter. The amount of oxcarbazepine was determined using a UV-spectrophotometer at λ max 256.5 nm.

The removed volume of the medium was replaced by the same volume of the buffer solution. The released amount of oxcarbazepine was calculated as a percentage of drugs released with time.¹⁵

Factors Affecting Formulations

Effect of Suppository Type

Three types of suppositories were formulated; the first one was a conventional type while the second and the third type were a hollow-type containing oxcarbazepine powder and solution form, respectively.

Formula 1, 6 and 11 besides formulas 2, 7 and 12 were selected to demonstrate this effect by using Witepsol H35 and Witepsol H37 as an oleaginous base, respectively. Meanwhile formulas 3, 8 and 13 and formulas 4, 9 and 14 were selected as hydrophilic bases. Furthermore, formulas 5, 10 and 15 were selected to investigate this effect on glycerinated gelatin based suppositories.

Effect of Suppository Base Type

Lipophilic bases formula 1,2 and hydrophilic bases

formula 3, 4 and 5 were used to investigate the effect of the nature of the suppository base on the physical properties and the *in vitro* release of oxcarbazepine from the prepared suppositories. The investigations were estimated for hollow-type suppositories containing powder and solution as in formulas 6 to 10 and formulas 13 to 15, respectively.

On the other hand, formulas 11 and 12 were studied to show the influence of oleaginous bases on hollow-type suppository bases.

Effect of Storage Time and Temperature on Oxcarbazepine Release from Suppositories

The study was carried out using suppositories stored

for 1, 15, 30 and 45 days at 25°C.

Formula 11 was wrapped with aluminum foil and placed in a lightly closed container stored at previous mentioned temperature.¹⁰ Another sample of formula 11 was stored for 30, 60, 120 and 180 days at 25°C to determine the shelflife.

Statistical Analysis

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

Table 1. Composition and physical properties of oxcarbazepine conventional and hollow-type suppository formulas(*)

Formula Number	Content of The Base	Type of The Suppository	Melting Time (min.)	Softening Time (min.)	Hardness (Kg.)
F1	Witepsol H35	Conventional	14 (±0.10)	6(±0.53)	3.4(±0.11)
F2	Witepsol H37	Conventional	15(±0.14)	7(±0.31)	3.8(±0.27)
F3	PEG400:PEG4000 (70:30)w/w	Conventional	26(±0.26)	-----	2.8(±0.32)
F4	PEG1000:PEG4000 (70:30)w/w	Conventional	35(±0.32)	-----	3.19(±0.62)
F5	Glycerin:Gelatin:Water (4:2:4) w/w	Conventional	42(±0.87)	-----	-----
F6	Witepsol H35	Hollow-Type (Oxcarbazepine-powder)	13(±0.21)	4(±0.41)	3.0(±0.18)
F7	Witepsol H37	Hollow-Type(Oxcarbazepine-powder)	12(±0.44)	5(±0.12)	3.3(±0.23)
F8	PEG400:PEG4000(70:30) w/w	Hollow-Type (Oxcarbazepine-powder)	22(±0.19)	-----	2.4(±0.64)
F9	PEG1000:PEG4000(70:30) w/w	Hollow-Type(Oxcarbazepine-powder)	29(±0.55)	-----	2.8(±0.73)
F10	Glycerin: Gelatin :Water (4:2:4) w/w	Hollow-Type(Oxcarbazepine-powder)	36(±0.47)	-----	-----
F11	Witepsol H35	Hollow-Type(Oxcarbazepine-	12(±0.16)	4(±0.48)	3.0(±0.22)

Formula Number	Content of The Base	Type of The Suppository	Melting Time (min.)	Softening Time (min.)	Hardness (Kg.)
		solution)			
F12	Witepsol H37	Hollow-Type(Oxcarbazepine-solution)	12(\pm 0.23)	5(\pm 0.21)	3.1(\pm 0.40)
F13	PEG400:PEG4000(70:30) w\w	Hollow-Type(Oxcarbazepine-solution)	23(\pm 0.16)	-----	2.2(\pm 0.44)
F14	PEG1000:PEG4000(70:30) w\w	Hollow-Type(Oxcarbazepine-solution)	31(\pm 0.51)	-----	2.7(\pm 0.34)
F15	Glycerin: Gelatin :Water (4:2:4) w\w	Hollow-Type(Oxcarbazepine-solution)	36(\pm 0.47)	-----	-----

* (\pm SD) each represented for three values

RESULTS AND DISCUSSIONS

Effect of Suppository Type on the Physical Properties and Oxcarbazepine Release of the Prepared Suppositories

Table 1 shows the effect of changing the type of suppositories on the physical properties of oxcarbazepine suppositories. It was found that the melting time, softening time and hardness for both the hollow-type suppositories (powder and solution) form, as in formulas 6 and 11, were less than those obtained for the conventional type, formula 1. This reduction may be attributed to the presence of oxcarbazepine containing cavities which might affect the skeletal structure of the hollow-type suppositories.¹⁰

Figure 1 illustrates a significant increase in the release of oxcarbazepine (94%) from solution hollow-type suppositories, formula 11, compared with 3% and 22% for powder hollow-type and conventional suppository base, formulas 6 and 1, respectively. This increase may be in reference to the fast melting of the suppository base and release of the drug faster from the base loaded with the drug solution form.¹⁵

The effect of changing the suppository type on the

physical properties and release profile of oxcarbazepine suppositories prepared from witepsol H37 revealed that a reduction in the melting time, softening time and hardness in both hollow-type suppositories, formulas 7 and 12, compared with the conventional type, formula 2. This reduction may be attributed to the presence of air cavities within the skeleton of the suppository which may affect the physical properties of the suppository base.¹⁰ There was a significant increase ($p < 0.05$) in the percentage of the drug release from the solution hollow-type suppository, formula 12, compared with the conventional and powdered hollow-type, formulas 2 and 7, respectively as shown in figure 2. This result may be due to the same effect of the fast dissolution of oxcarbazepine from the solution compared with the drug dispersed or powder forms.

On the other hand, the table and figure 3 show the effect of changing the suppository type on the physical properties and in vitro dissolution rate of the resultant suppositories using PEG400 and PEG4000 in a ratio of 70 : 30 as hydrophilic suppository bases as shown in formulas 3, 8 and 13.

The results indicated that the melting time and hardness of the hollow-type suppositories, formulas 8 and 13, were

less than those of the conventional type, formula 3. This effect may be attributed to the compact backbone of the conventional type with the more rigid and consolidated structure than the hollow-type.¹¹

In addition, the release profiles of the drug from these suppositories revealed no significant ($p > 0.05$) change in 100% of the drug release from these types. The result is quietly referring to the solubility and partitioning of the drug in the buffered media, and the partition coefficient of the drug with the base used, respectively.¹⁶ Meanwhile the times for 50% (T50%) of the drug release were 10, 13 and 4 minutes for formulas 3, 8 and 13, respectively.¹⁷

The same results were obtained when PEG400 was replaced by PEG 4000 in the suppository base with the same ratio formulas 4, 9 and 14, as shown in table 1 and figure 4 since the T50% of drug release for these formulas were 12, 14 and 7 minutes, respectively.

In addition, the glycerinated gelatin base when changing the suppository type, the effect in physical properties and the release profile are shown in figure 5. The results revealed that a decrease in the melting time was an insignificant ($p > 0.05$) increase in 100% oxcarbazepine release from both the hollow-types compared with the conventional one. The T50% drug release illustrated that the solution containing hollow-type suppositories are faster than those prepared from powder containing hollow-type and conventional suppositories, corresponding to 20, 25 and 13 minutes, respectively.

The same results were obtained when diazepam was incorporated as a liquid and powder state drug in hollow-type rectal suppositories.¹⁵

According to all the above results, Formula 11 was selected as a promised rectal suppository preparation for further pharmaceutical studies.

Effect of Storage Time and Temperature on Oxcarbazepine Release From Selected Formula 11

Figure 6 shows the effect of the storage period at 25°C on the release behavior of oxcarbazepine. It was clearly revealed that there was no significant change ($p > 0.05$) in 100% of the drug release. This effect may be attributed to the presence of oxcarbazepine in a hole separated liquid state in the backbone of the hollow suppository that protects the drug itself from any storage environment that affects the base itself since the witepsol base when stored at room temperature for a prolonged time may undergo crystallization.¹²

Shelf Life of the Selected Formula 11

The selected formula of oxcarbazepine rectal suppositories were introduced for their shelf life estimation. The suppositories were stored at 25°C, and the samples were analyzed for the drug content at 30, 60, 120 and 180 days where the results indicated that the oxcarbazepine degradation followed the first order kinetic with a rate constant $K_1(25^\circ\text{C}) = 0.093 \times 10^{-3} \text{ day}^{-1}$, as shown in figure 7. The shelf life calculation was found to be 3.1 years.

CONCLUSION

Based on the results obtained from this study, one can conclude the following:

- Oxcarbazepine can be formulated successfully as conventional and hollow-type rectal suppositories.
- Best results were obtained when a combination of PEG400 and PEG4000 were used as a water soluble base.

For fast release of oxcarbazepine, hollow-type selected formula 11 was the most promising candidate to be a rectal dosage form with acceptable physical properties and estimated shelf life of 3.1 years.

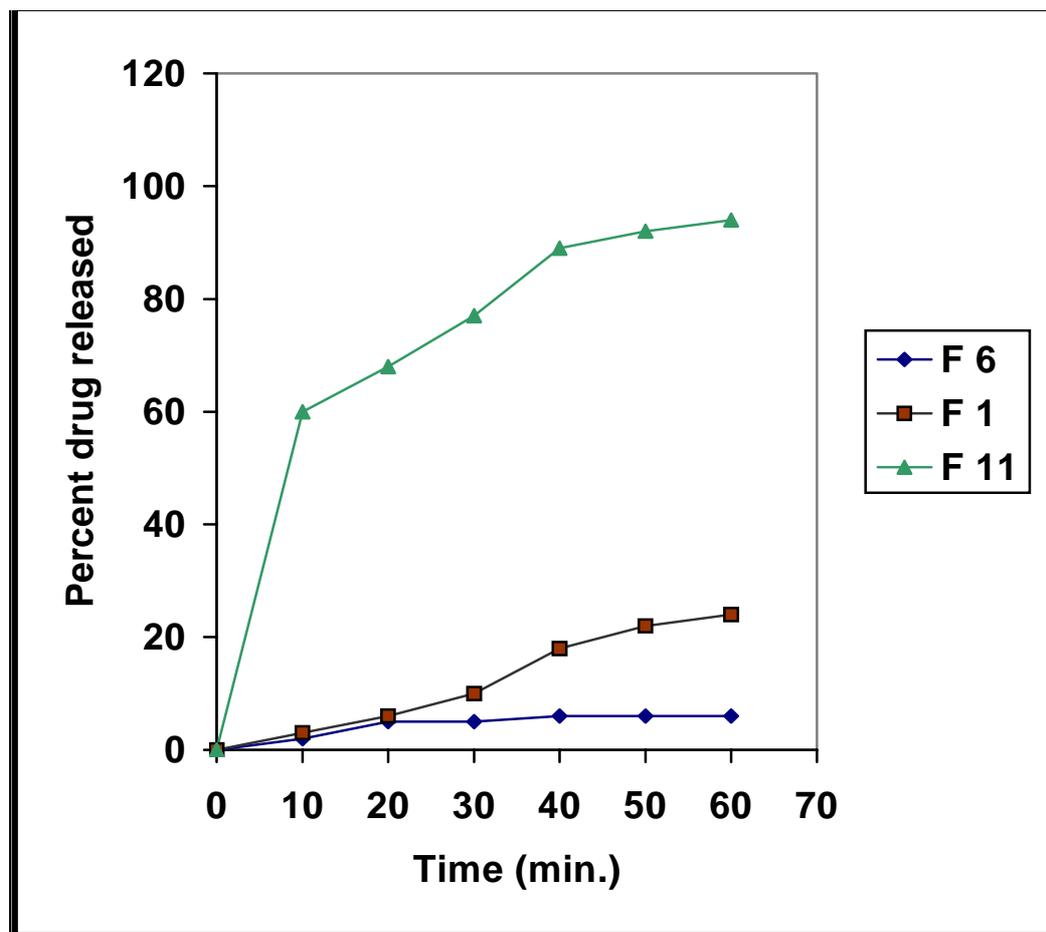


Figure 1. The effect of the suppository type on the in vitro release of oxcarbazepine from witepsol H35 in Sorenson's phosphate buffer pH7.4 at 37 °C temperature.

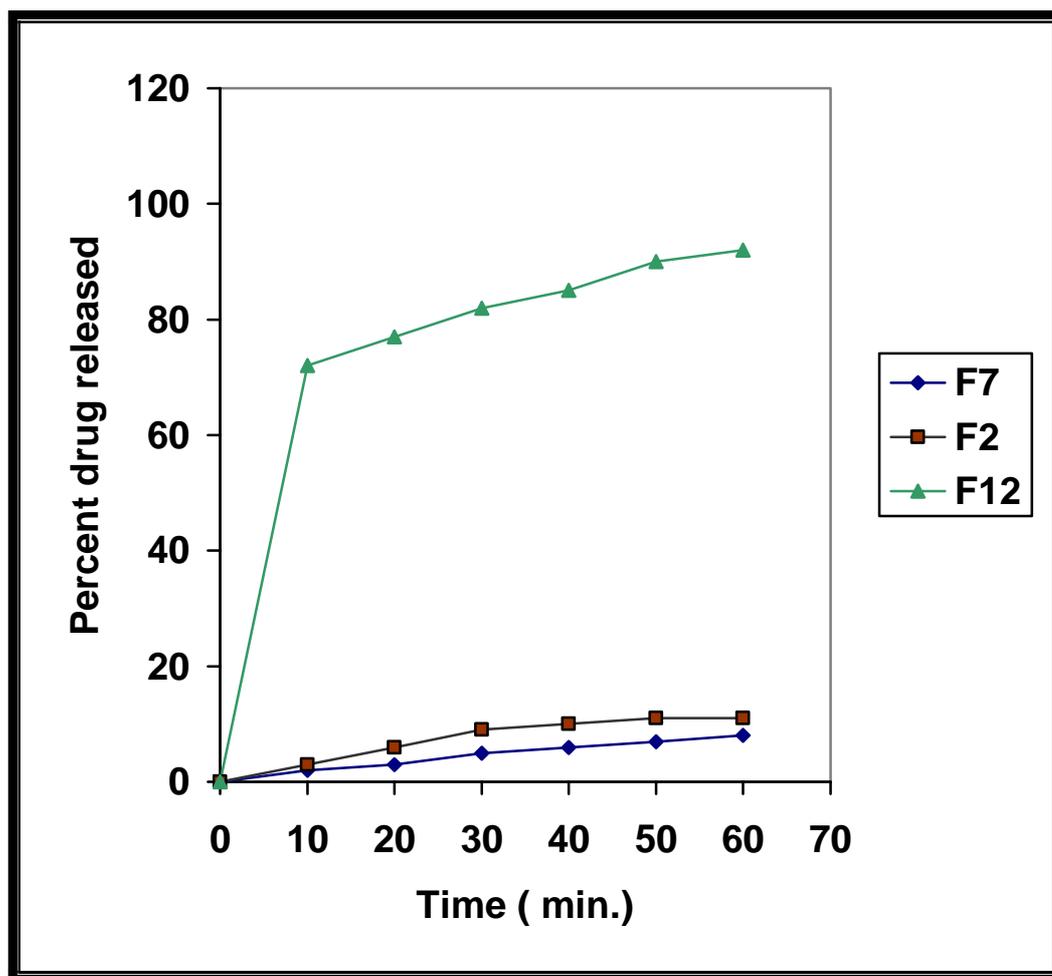


Figure 2. The effect of the suppository type on the in vitro release of oxcarbazepine from witepsol H37 in Sorensen's phosphate buffer pH 7.4 at 37°C temperature.

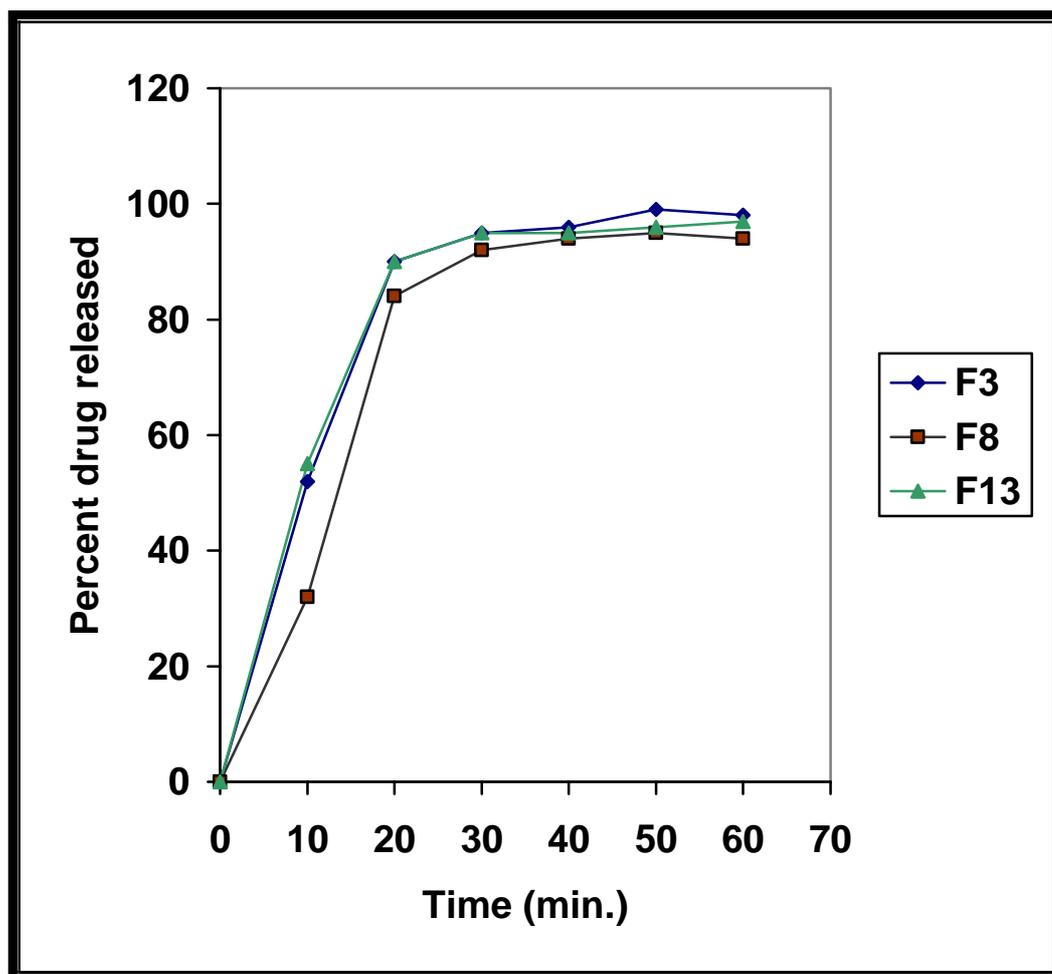


Figure 3. The effect of the suppository type on the in vitro release of oxcarbazepine from PEG 400 : PEG4000 (70:30) w/w in Sorensen's phosphate buffer pH 7.4 at 37 °C temperature.

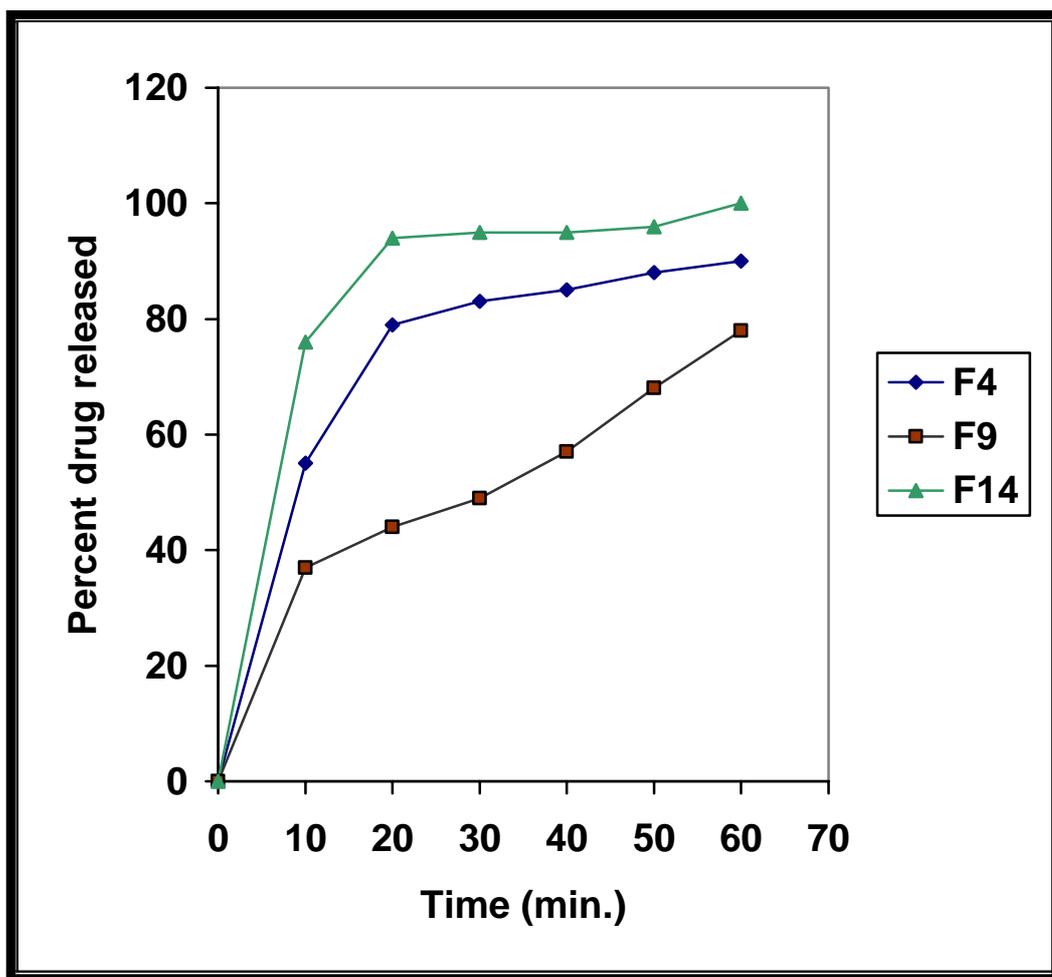


Figure 4. The effect of the suppository type on the in vitro release of oxcarbazepine from PEG₁₀₀₀ : PEG₄₀₀₀ (70:30) w/w in Sorensen's phosphate buffer pH 7.4 at 37 °C temperature.

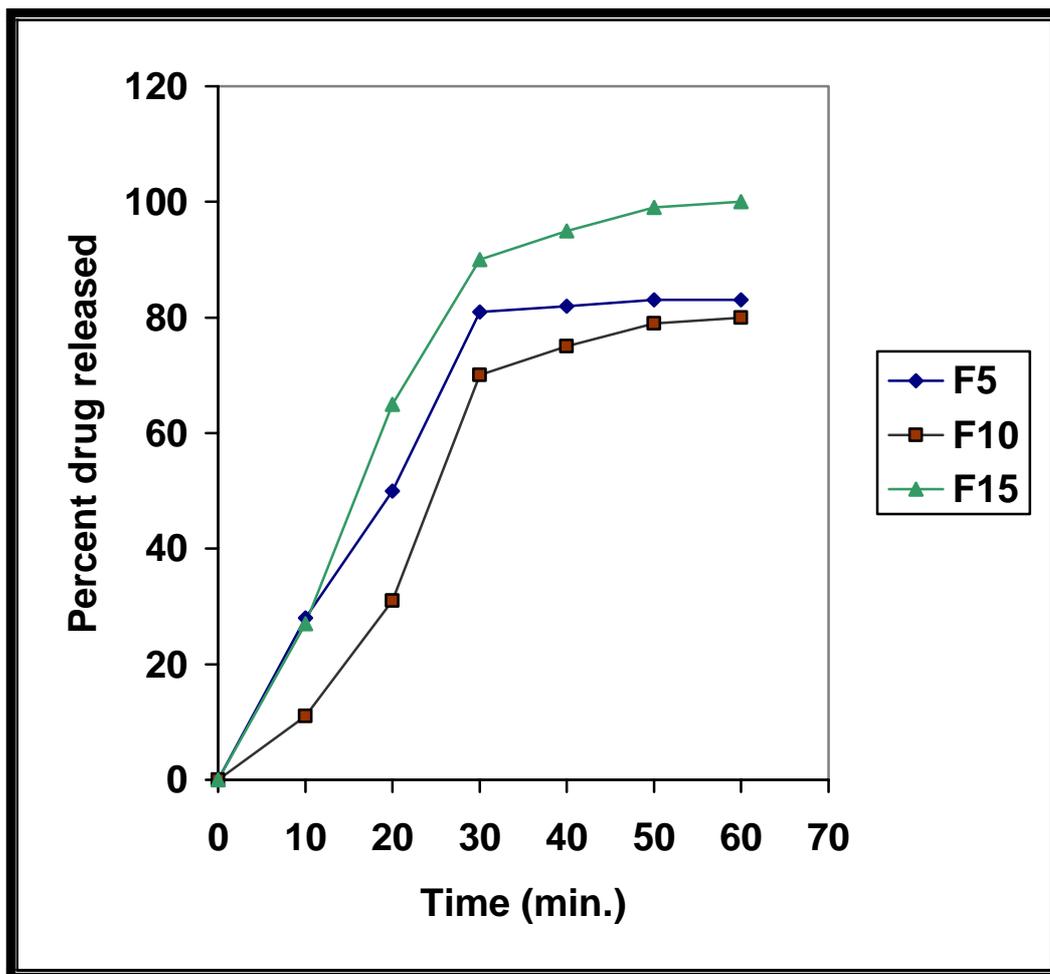


Figure 5. The effect of the suppository type on the in vitro release of oxcarbazepine from glycerin : gelatin : water (4:2:4) w/w base in Sorensen’s phosphate buffer pH 7.4 at 37 °C temperature.

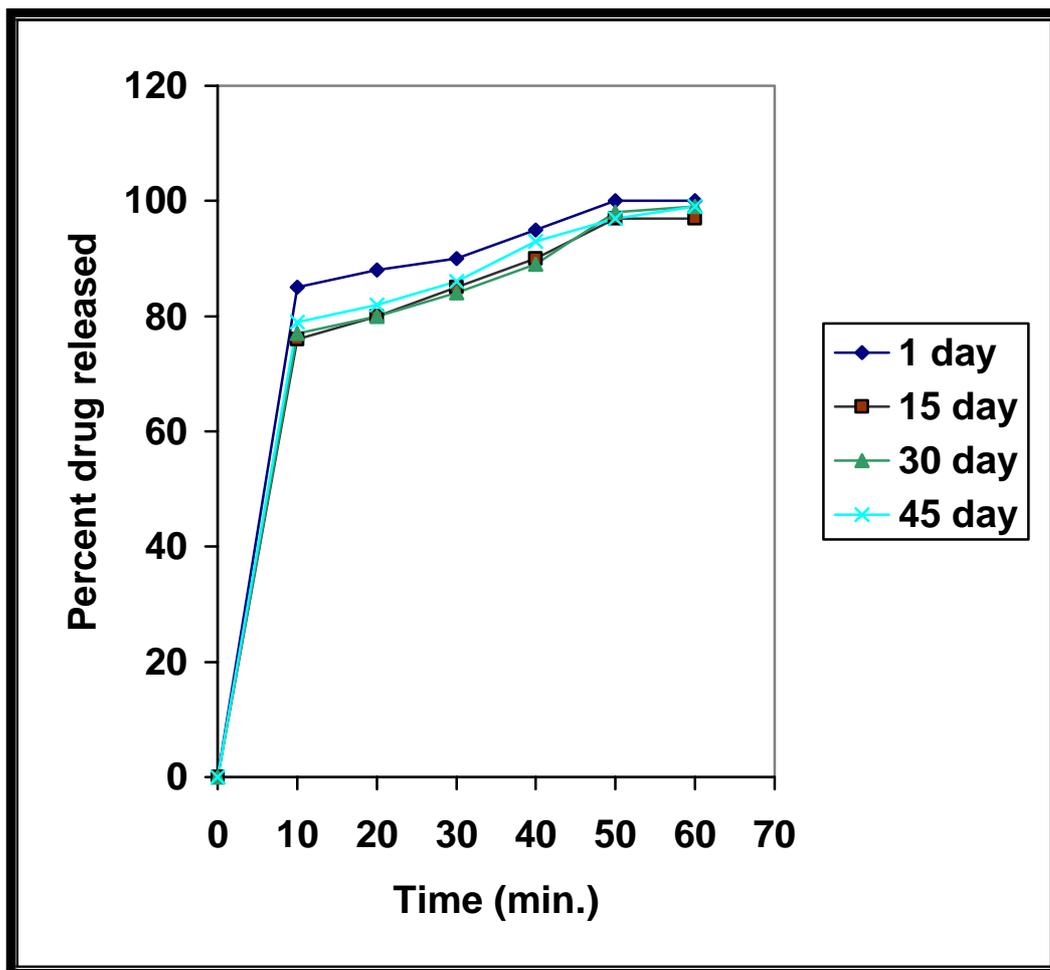


Figure 6. The effect of storage period at 25 °C on the release of oxcabazepine from witepsol H35 hollow-type suppository containing liquid drug state selected (formula 11) in Sorensen's phosphate buffer pH 7.4 at 37 °C temperature.

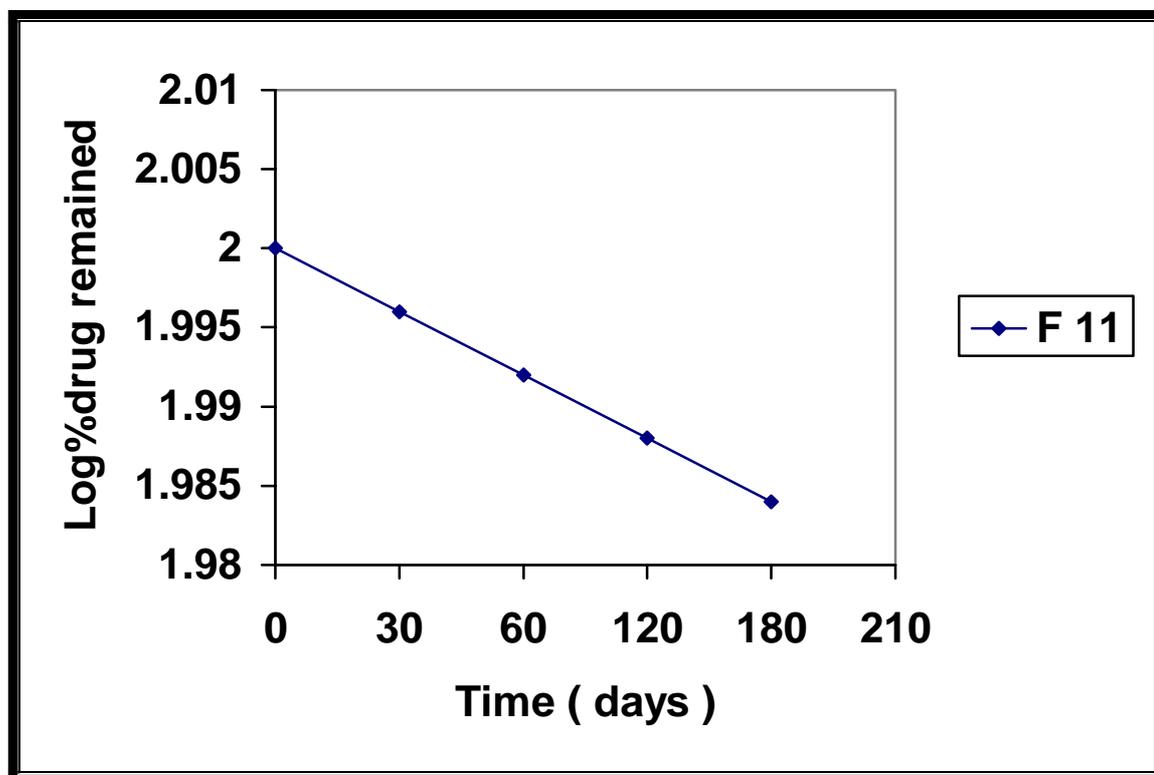


Figure 7. Determination of oxcabazepine degradation rate constant (k_1 25 °C) for formula 11 stored at 25 °C temperature.

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