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CHARACTERIZING THE INHERENT PROPERTIES OF PLURONIC F-127 IN CARBAMAZEPINE SUPPOSITORIES

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ABSTRACT

The main goal of rectal administration, as opposed to oral administration, is to provide an effective method of delivering medication to pediatric and geriatric patients. There is a significant need for new non-oral formulations for antiepileptic drugs when oral administration is not possible when the person is unconscious or has swallowing difficulties. The present study aims to formulate Carbamazepine suppositories with Pluronic F127 base by fusion method. Pluronic F127 is an amphiphilic polymer that possesses unique thermo-responsive properties. Prepared suppositories were evaluated for general appearance, weight variation, drug content, and dissolution. Drug release was found in the range of 38.46% -56.93%, for F1- F5 respectively. Drug release was subjected to different kinetic models from the formulation, out of those models it was found that drug release followed the Higuchi model. The present study shows F1 (50:50) as a better formulation among the other four in terms of appearance, content between 61.36% and 97.44%, weight variation, and drug release showing purely by dissolution-controlled release.

KEYWORDS: Carbamazepine, Antiepileptic drug, Pluronic F127, suppositories.

INTRODUCTION

Epilepsy is a disorder of the brain characterized by repeated seizures that cause sudden changes in behavior due to temporary alterations in the brain's electrical functioning.[1] Epilepsy is one of the most common neurological conditions, with an incidence of approximately 50 new cases per year per 1,00,000 population. About 1% of the population uffers from epilepsy, and roughly one-third of patients have refractory epilepsy.[2]

Normally Epilepsy is treated by the administration of antiepileptic drugs. These are divided into first, second, and third generation AEDs. The common caused first generation AEDs are phenytoin, carbamazepine.[3]

Carbamazepine is a medication that belongs to the group of drugs known as Benzodiazepines which modulates voltage gated sodium channels causing inhibition of action potential and decrease synaptic transmission.[4] It works by calming abnormal over activity in the brain. Carbamazepine is commonly used broad spectrum antiepileptic drugs, suitable for the most epileptic seizure types.[5]

The oral route is the most convenient route for drug administration there are a number of drug circumstances where this is not possible from either a clinical or pharmaceutical perspective like unconscious patient, difficulty in swallowing.[6] In these cases, rectal route is followed to administer drugs for both local and systemic actions hence the environment in the rectum is relatively constant and stable and has low enzymatic activities when compared to other sections of GIT which avoid first pass metabolism.[7]

The main goal of rectal administration over oral administration which is effective in pediatric and geriatric patient.[8] This route can also useful in delivering drugs to prevent pre and postoperative systemic infectious. Research and development on rectal drug delivery focus on two areas: The enhancement of patient compliance and the design of mucoadhesive formulations that can provide better control of dosage form's positioning in the rectal cavity.[9]

Suppositories are a dosage form designed to delivery drug through rectal and vaginal routes of administration. The term *suppositorium* comes from latin word *supponere*, meaning 'substitute'. While commonly perceived to be for rectal administration and vaginal administration. Suppositories have classically been cylindrical in geometry, longer than wide, with a most common shape being the 'bullet' or 'torpedo' shape. Other commonly used shapes for suppositories include round and elongated ovals, tampon and 'teardrop' or 'cone'. Suppositories are of two types: lipophilic based or hydrophilic based.[10]

Lipophilic base such as cocoa butter can be used in the formulations of suppositories. As cocoa butter suppositories may have an incomplete or some erroneous release of certain APIs[11] so the hydrophilic bases such as PEG and Pluronic F127 combination are used in the

suppository formulation. PEG blends are effective vehicles for the drug release by means of suppositories. The release rate for the drugs can be predicted from the knowledge of molecular weights of PEG blends and is affected by the presence of high and low molecular weight PEG.[12]

Pluronic polymers have been approved by the FDA for pharmaceutical use and have been investigated for different therapeutic applications due to their PEG hydrophilic chains and PPO hydrophobic units. Due to their amphiphilic properties, these copolymers exhibit surfactant properties, including the ability to interact with hydrophobic surfaces and biofilms.[13]

USP dissolution apparatus II was used as a device to determine the release profile of active pharmaceutical ingredients.[14]

MATERIALS AND METHODS

Materials and Methods

Carbamazepine, Pluronic F-127, PEG 4000, Liquid Paraffin, Methyl Paraben, Butylated hydroxytoluene were used in the preparation of suppositories. All the ingredients were obtained from Yarrow chem products, Mumbai. The ingredients used in the preparation were of analytical grade.

METHODS

Preparation of suppository by fusion method

In this process the bases are melted with drug to form solid dispersion and then additives are mixed in bases.

The following methods are involved in this process

a. Melting the bases

Pluronic F-127 and PEG 4000 are melted together with Carbamazepine followed by uniform stirring to form solid dispersion of poorly soluble drug Carbamazepine.

b. Incorporation of additives

Additives such as preservative- methyl paraben and Antioxidant- butylated hydroxytoluene was then mixed in solid dispersion.

c. Filling of molds

First lubricant such as liquid paraffin was applied to the molds. Then the above masses were poured into the molds. During introducing the masses in molds, the stirring should be done to prevent the sedimentation of insoluble solids, if they present. Overfilling is required to prevent depression in suppositories.

d. Cooling and collection of suppositories

After the 2-3 min, the mass was left to set. Then remove the excess mass with warm spatula. Cool the suppositories for 10-15 min, in the refrigerators. Then open the mold and collect the suppositories and packed. Store the suppositories in the refrigerators.

Table 1: Formulation of sustained release suppositories.

Ingredients (% w/w)	F1	F2	F3	F4	F5
Carbamazepine (mg)	200	200	200	200	200
Pluronic F-127	50	30	70	60	40
PEG 4000	50	70	30	40	60
BHT	0.01	0.01	0.01	0.01	0.01
Methyl Paraben	0.01	0.01	0.01	0.01	0.01

Figure No. 1: Carbamazepine suppositories.

Evaluation of suppositories

- **Appearance**

The prepared suppositories were characterized for their general appearance like color, shape and physical characters.

- **Weight variation**

All the suppositories (made by respective bases), were weighed and average weight was calculated. Then all the suppositories were individually weighed and the variation from the

average was calculated. No suppositories should deviate from average weight by more than 5% except two which may deviate not more than 7.5%.

Table 2: Weight variation observation table

Average weight of suppository	% Deviation
80 mg or less	10
More than 80mg but less than 250mg	7.5
250mg or more	5

- **Drug content**

A suppository taken randomly from each batch was weighed and placed in a beaker containing 100ml phosphate buffer solution (pH 7.4). The suppository was melted by heating the beaker on a water bath maintained at 45-50^{0}C. The beaker was shaken in ultra sonicator for 5-10mins until the suppository had been completely dispersed. Then the solution was filtered; and the filtrate was diluted suitably and absorbance was measured against blank at determined λ max.

- **Dissolution studies**

In this study, the in vitro dissolution rate of carbamazepine from the suppositories was examined using the basket method (Apparatus I). The temperature was maintained at 37^{0}C and stirring rate was kept constant at 50rpm. 900 milliliter phosphate buffers (p^H 7.4), was used as a dissolution medium, and samples of 5ml test solution were collected manually at specified time intervals for up to 5h for hydrophilic bases. The withdrawn volume of the sample was replaced with the equal volume of fresh dissolution medium contained at the same temperature. The samples were analyzed for carbamazepine concentration after appropriate dilution. In this study, the amount of dissolved carbamazepine was detected at obtained λmax on a UV spectrophotometer.

- **Stability studies**

Short term stability studies were performed at a room temperature and refrigeration temperature (4^{0}C) was kept for 6w on the promising formulation. The suppositories were individually wrapped in aluminum foil and packed in card board boxes. Samples are taken after 6 w and checked for drug content estimation and dissolution test was performed.

RESULTS

In the present study characterizing the inherent properties of Pluronic F-127 in Carbamazepine suppositories containing its solid dispersion by fusion method was done successfully. The results for the following experiment conducted are as follows.

Determination of λ_{max} of Carbamazepine in PBS 7.4

The spectrum of Carbamazepine in buffer showed the peak at 285nm**.** The absorption spectrum of Carbamazepine was scanned between 200-400nm. The of drug λ_{max} was found to be 285nm in phosphate buffer pH 7.4. The curve obtained is shown in figure 7.

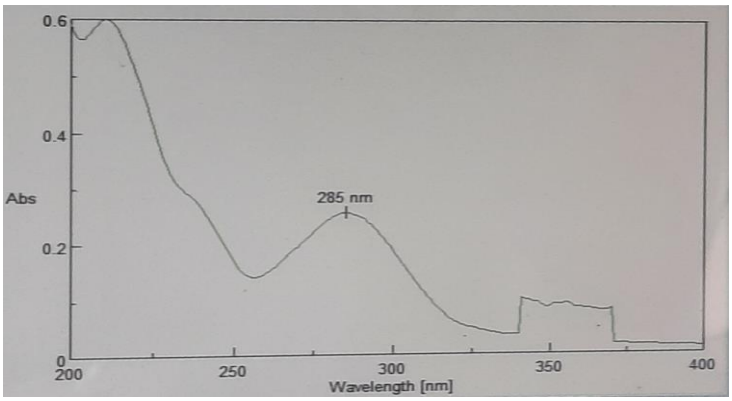

Figure No. 2: UV spectrum of Carbamazepine.

a) Preparation of Standard Plot of Carbamazepine

The values of absorbance at different concentrations (µg/ml) in phosphate buffer pH 7.4 are given in the table 6 and the standard plot is shown in the fig no.8. The absorbance value retained linear and obeyed Beer's Lamberts law in the range of 2-12µg/ml with the R^2 0.9943 and slope of 0.029.

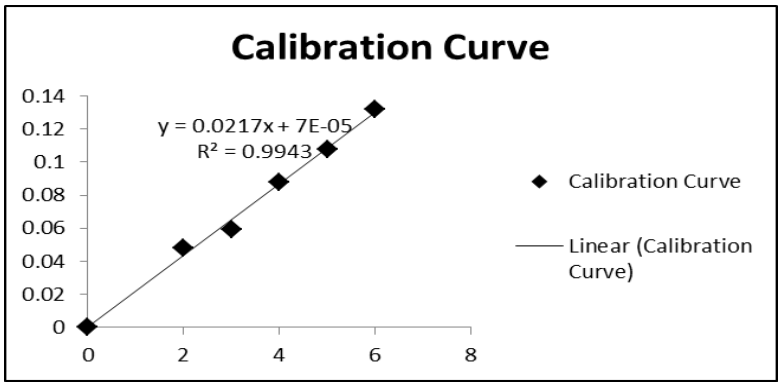

Figure No. 3: Calibration curve of Carbamazepine.

EVALUATION OF SUPPOSITORY CONTAINING CARBAMAZEPINE:

Weight variation

The average weight of all suppositories were weighed and calculated for each formulation and weight variation for all suppositories were found to be within the acceptable range of <5%, indicating a well-calibrated mold and uniformity in the weights of different suppository base combinations.

Table 3: Weight variation data.

Product code	Average wt.	Maximum wt. (mg)	Minimum wt. (mg)	(%±SD) *
F_1	970	980	960	4.03±0.0128
F_2	960	990	950	3.12±0.0448
F_3	970	990	960	2.06±0.0208
F_4	960	980	950	2.04±0.02
F_5	950	980	920	3.15±0.0264

Drug Content Study

The results were reported in table 9. The percentage drug content of all the formulation was found to be between 61.36% and 97.44% indicating that uniform distribution of the drug in all the formulation as per the monograph.

Table 4: Drug content study of F1 to F5.

Formulation code	Drug content (%±SD) *
F1	97.44±0.005
F2	89.64±0.01
F3	61.36±0.025
F4	88.96±0.01
F5	72.48±0.015

In vitro drug release study

From the dissolution studies, it was observed that the release rate of drug from suppositories varied. Table 10 and figure 11 shows the cumulative percentage drug release from formulation F1, F2, F3, F4 and F5 containing different concentration of bases at the end of 5 hour was found to be 56.93%, 38.46%, 48.92%, 50.03%, 54.08% respectively.

Through analysis of all suppository formulations made with hydrophilic bases, we determined that the formulation of choice is F1, which contains 200 mg Carbamazepine, PEG-4000, and Pluronic F-127 in the ratio of 50:50. This formulation has the best physical

properties in terms of appearance and consistency. Formulations made with Pluronic F-127 show good physical properties.

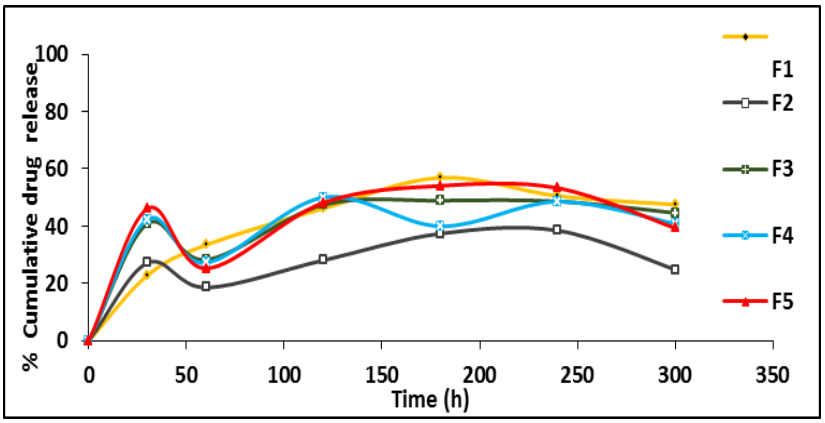

Figure No. 4: *In vitro* drug release study.

Mathematical Model showing Release Kinetics

Table 5: Mathematical model showing Release kinetics.

Time (Hr)	Log Time	SQRT Time	% CDR	Log % Release	% Drug remaining	Log % Drug remaining
0		0	0		100	2
0.5	0.301	0.707	22.85	1.359	77.15	1.887
1	0.000	1.000	33.42	1.5240	66.58	1.823
2	0.301	1.414	46.19	1.6645	53.81	1.731
3	0.477	1.732	47.53	1.6770	52.47	1.720
4	0.602	2.000	50.55	1.7037	49.45	1.694
5	0.699	2.236	56.93	1.7553	43.07	1.634

Table 6: Drug release kinetics.

Order	Graphs
Zero Order	Time vs Drug release
First Order	Time vs log% drug remaining
Peppas Model	log Time vs log% drug remaining
Higuchi Model	SQR Time vs % drug remaining

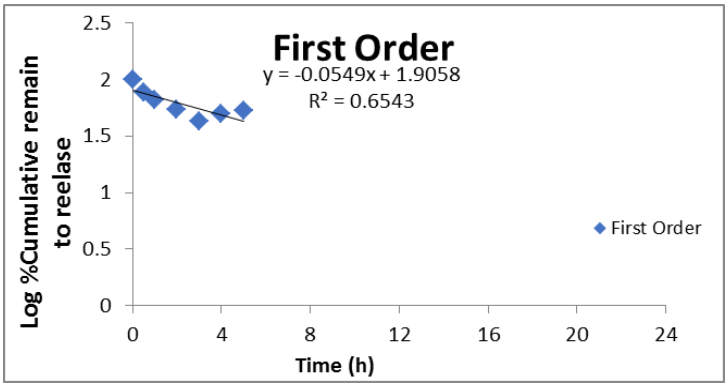

Figure No. 6: First order Kinetics release model of F1.

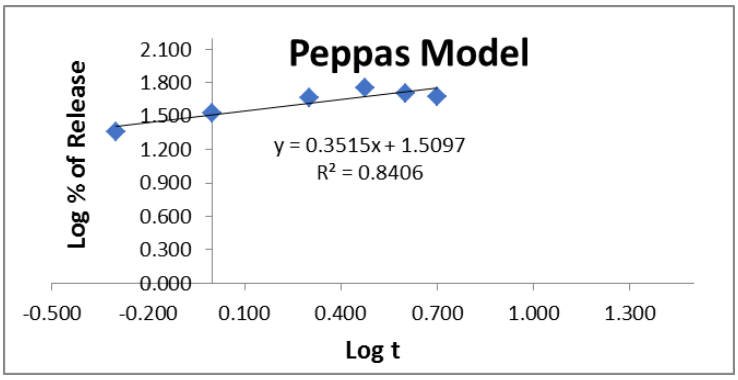

Figure No. 7: Peppas Kinetics release model of F1.

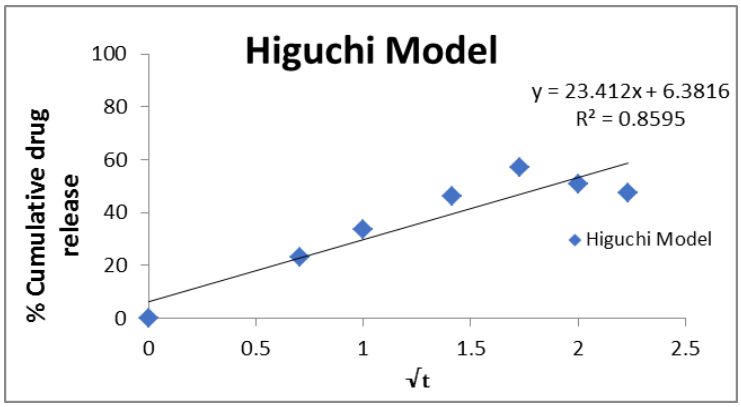

Figure No. 8: Higuchi Kinetics release model of F1.

SUMMARY AND CONCLUSION

The present study has been satisfactory to characterize the inherent properties of Pluronic F-127 in carbamazepine suppositories containing its solid dispersion by fusion method.

From the reproducible results of executed experiments, it can be concluded that

- The main objective of the present research work was to improve the solubility and dissolution properties of the poorly soluble drug Carbamazepine.

- Various techniques have been used to improve the solubility and dissolution rate of poorly soluble drugs; amongst these, one, solid dispersion of drug using Pluronic F-127 and PEG by fusion method improved solubility and dissolution rate.
- The λ max of drug was found to be 285nm, the absorbance value remains linear and obeyed Beer's Lamberts law in the range of 2-12µg/ml with the R^2 value of 0.994.
- The weight variation was found be within the prescribed limit as per IP indicating uniformity in the weights of all combinations of suppository bases.
- The drug content was uniform in all the formulation of prepared suppositories.
- At the end of 5-hour formulation F1 released 56.93% of drug and considered as best formulation.
- In this study, sustained release Carbamazepine suppositories, which is used in the treatment of epilepsy was prepared by solid dispersion using Pluronic F-127 and PEG by fusion method to improve the dissolution and controlled release.
- Solid dispersion by fusion methods improves the dissolution property.
- Among five formulations, F1 was selected as optimum formulation in comparison to other formulations which showed better drug content (97.44), dissolution rate (56.93%) at the end of 5 hours.
- It was confirmed from the stability studies that sustained release Carbamazepine suppositories containing its solid dispersion with Pluronic F-127 and PEG by fusion method remained stable at room temperature 27^0C and refrigeration temperature 4^0C.
- From the present investigation, it can be concluded that Carbamazepine suppository formulation can be potential novel drug dosage form for pediatrics, geriatrics and non-cooperative patient.

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