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Research Article

Fabrication and Evaluation of Cetrizine Hydrochloride Suppositories

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ABSTRACT
Objective: This present study aimed to formulate and evaluate Cetrizine hydrochloride in a rectal dosage form, suppositories. The drug release properties, hardness, disintegration time, melting range, as well as their weight variation, were assessed in various formulations.
Methods: Cocoa butter suppositories and Polyethylene Glycol Suppositories were prepared using standard methods with some modifications. In the preparation of polyethylene Glycol Suppositories, PEG-400, PEG-600, PEG-4000 and PEG-6000 were utilised in different ratios. The various suppository formulations were evaluated for weight variation, hardness, melting range, disintegration time as well as drug release properties.
Results: The findings demonstrated successful formulation of the Cetrizine hydrochloride suppositories as evident by the various evaluation parameters. Growing concentration of solid PEGs (6000 and 4000) with reducing the concentration of PEG 600 and PEG 600 resulted in increasing the melting point and increasing hardness of the base as well as other parameters of concern such as the hydration by water uptake followed by formation of gelatinous layers.
Conclusion: In the obtained results, the formulation containing PEG-400 and PEG-6000 in the ratio of 4:6 exhibited the highest release of the drug with a better profile.

Keywords: Suppositories, Cocoa butter, Polyethylene Glycol, Cetrizine hydrochloride, Rectal dosage form

1. INTRODUCTION

The effectiveness of cetirizine on eosinophil chemotaxis has been described in several reports. Histamine-induced wheal and flare responses were markedly reduced by cetirizine in clinical pharmacological tests. Fast-acting, long-lasting, potent inhibition was observed [1, 2]. Cetirizine was more effective than other antihistamines in inhibiting wheal response than terfenadine, loratadine, epinastine and ebastine. Furthermore, after a clinical dose of 10 mg, cetirizine inhibited eosinophil chemotaxis in vitro. Additionally, in vivo infiltration of allergic eosinophils into sites would be inhibited. Cetirizine provides fast and strong relief from histamine-induced symptoms, such as sneezing and rhinorrhoea in allergic rhinitis, and itchy feeling in idiopathic chronic urticaria [3, 4]. Cetirizine reduces minimal persistent inflammation caused by a faint but repeated exposure to allergens because of its inhibitory effect on eosinophil chemotaxis. Cetirizine may reduce hypersensitivity to normalize upper respiratory tract and eosinophil-induced skin inflammations by reducing inflammation in the upper respiratory tract [5].

The rectal route has advantages over other routes of administration due to its reduced side effects such as gastrointestinal irritation and the avoidance of both unpleasant taste and first pass effects. Patients who can't swallow medication or who are experiencing vomiting may benefit from the rectal route [6-8]. As a result, the rectal administration of Cetrizine in suppository form may prove to be more effective for increasing its bioavailability than oral administration. Many studies have shown that the release characteristics of many suppositories are dependent on physicochemical properties of the drug, the suppository base, and the formulation additives [6-8] and in order to achieve the maximum properties of suppository preparations, a lot of formulations are usually necessary. In order to prepare proper formulations for suppository preparation, it is imperative to select the right bases. The ideal base should not irritate the sensitive tissues of the rectum. Several suppository formulations, particularly those prepared with polyethylene glycol bases, have been reported to cause mucous membrane irritation [9, 10]. Therefore, the main objective of this study was to formulate and evaluate Cetrizine

in a rectal dosage form, suppositories. Various formulations were prepared with water-soluble PEG, gelatin, fatty, and emulsion-based bases, and the drug release properties, hardness, disintegration time, melting range, as well as their weight variation, were examined.

2. MATERIALS AND METHODS

2.1. Materials

KAPL of Bangalore, India generously supplied the cetirizine. Other chemicals and reagents were of analytical grade and sourced only from reputable vendors. Among the chemicals and reagents used were polyethylene glycol 400, 600, 4000, 6000, and cocoa butter (AIC Enterprises Bangalore, India), Zinc sulphate, Methanol, Propylene glycol, EDTA, Sodium alginate (S.D. Fine Chem. Ltd, Mumbai, India), Glacial acetic acid, Glycerin, Paraffin liquid light, Gelatine, Potassium di hydrogen phosphate, Sodium hydroxide (Bharath scientific Bangalore, India). As far as the other chemicals were concerned, they were analytical grade and used as received.

2.2. Compatibility study

The compatibility study was carried out for the Cetirizine Hcl, PEG-4000, 6000, Gelatin and Cocoa Butter alone and combinations at ambient condition and 40°C / 75% RH for a period of one month and samples were subjected for FTIR for their characterization of possible interaction between drug and career in solid state.

2.3. Preparation of cocoa butter suppositories (SF-1)

In a China dish over a water bath at 33^{0}C, a small amount of grated cocoa butter is liquefied and transferred to the warmed tile. The finely powdered drug is mixed with the base by levigation, and then the remaining grated cocoa butter is added to achieve homogenous dispersion. The dispersion should appear cream rather than clear. The creamy melt is poured continuously into the mould at room temperature to avoid layering. It is recommended that the suppositories congeal and harden in the refrigerator for 30 minutes. After trimming and unmoulding, they are packaged in aluminium foil. Soft soap, glycerine, and alcohol (90%) served as lubricants in this method [11-13].

2.4. Procedure For Polyethylene Glycol Suppositories (SF-2-SF-8)

Using a China dish, PEG 6000 and PEG 400 were melted together and then vigorously stirred into a homogeneous mixture. Mixing the finely micronized drug in the base resulted in its complete dissolution. After the mixture was poured into the mould cavities at a stretch excessively and allowed to cool on ice, the excess was trimmed off and chilled for 15 minutes. Suppositories were removed from the mould, opened, and wrapped in aluminium foil. In the case the formula contains water, the melted base should be incorporated with hot water and the process outlined above should be followed. PEG-4000 and PEG-600 were used in other formulations, respectively [14-17].

Table 1. Formulation code of Cetirizine hydrochloride suppositories

Formulation code	SF-1	SF-2	SF-3	SF-4	SF-5	SF-6	SF-7	SF-8
Drug (mg)	5	5	5	5	5	5	5	5
Cocoa butter	100	-	-	-	-	-	-	-
Water	-	-	-	-	-	20	20	20
PEG-400	-	40	40	-	-	60	-	-
PEG-4000	-	-	60	-	40		20	40
PEG-600	-	-	-	40	60	-	-	-
PEG-6000	-	60	-	60	-	20	60	40

2.5. Evaluation of plain and medicated suppositories

2.5.1. Weight Variation

According to the British Pharmacopoeia 2007, the weight variation test was estimated [18]. The average weight of twenty suppositories was calculated by weighing each one individually. In no case does an individual weight deviate more than 5% from the average and none more than 10% [19].

2.5.2. Disintegration time

In this experiment, suppositories are placed in a liquid medium, under a prescribed experimental condition, to see if they disintegrate or soften within a prescribed time. A special container with perforated ends is used to keep suppositories in an immersion bath at 37 °C. Every ten minutes,

the container is inverted below the surface. Disintegration is evidenced by

- Complete solution except for insoluble powders.
- Disintegration products trivial enough to sink or rise through the perforation.
- Complete softening with considerable alteration in shape and the mass has no solid core, which cannot be pressed with a glass rod.

Three suppositories are tested and all must disintegrate within 30 minutes (BP) [18].

2.5.3. Hardness (Fracture point) Determination

Suppositories are tested to determine whether they are brittle or elastic, and the amount of force required to break them is measured. This test is done using the Erweka method, and it measures the mass (in kgs) that a suppository can hold without breaking; for satisfactory results. At least 1.8 to 2 kilograms of mechanical strength should always be present.

2.5.4. Melting range determination

With a non-destructive U tube method, it can be evaluated. There are several techniques which cause the suppository to melt before measurement can be taken. There are two types of melting range tests: macro melting range tests which measure the time taken for an entire suppository to melt when immersed in a constant water bath and micro melting range tests which measure the melting range in capillary tubes for the fat base alone. As a general rule, a finished suppository's melting point shouldn't exceed 37 °C.

2.5.5. Uniformity of drug content

Only after the active ingredients in a pooled sample of the suppositories have been shown to be within the accepted limits for their stated contents should the test for uniformity of content be performed.

2.6. In-vitro drug release in phosphate buffer pH 7.4 by dialysis method

An earlier phosphate buffer pH 7.4-soaked cellophane membrane was stretched tight over a 15 cm long glass tube (with an internal diameter of 20 mm). The tube was suspended in phosphate buffer pH 7.4 in a 100-milliliter glass beaker containing 50 milliliters of phosphate buffer. The glass tube was filled with 10 ml of phosphate buffer. One suppository was introduced into the tube and the system was placed in a constant temperature shaker water bath (37=0.5°C, 100 rpm). At regular intervals, samples of 5 mL were withdrawn from the release medium and replaced with fresh buffer. Spectrophotometric analysis of the samples was conducted at λmax 280 nm after they were filtered through a 0.45-mm membrane filter [20] against a blank of plain suppositories treated by the same procedure for medicated suppository. Throughout the experiment, sink conditions are maintained. Based on three release experiments, the results are reported as mean values. Graphs of cumulative drug release over time were plotted.

2.7. Kinetics of the drug release from suppositories

In order to determine the drug release mechanism, the in-vitro release data were fitted into different kinetic models of zero order, first order, Hixon-Crowell and Korsmeyer-Peppas models. The correlation coefficient values (R^2) were calculated for all the models.

2.8. Statistical analysis

All experiments were carried out in three independent experiments, and the results were recorded as mean ± standard deviation (SD). Statistical analysis of all the data was performed using Graph pad prism program, version 5, San Diego, USA. All statistically significant differences were anticipated when $p<0.05$.

3. RESULTS AND DISCUSSION

3.1. Compatibility study

The compatibility study was carried out for the Cetirizine hydrochloride, PEG-4000, 6000, and Cocoa Butter alone and combinations at ambient condition and 40°C / 75% RH by FTIR for their characterization of possible interaction between drug and polymers in solid state. The results suggested no interaction observed between the rug and the excipient as evident from the FTIR spectra.

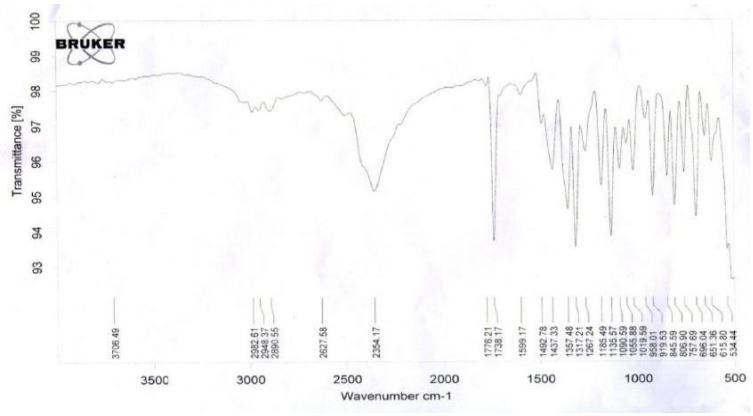

Fig.1: FTIR spectra of pure Cetrizine

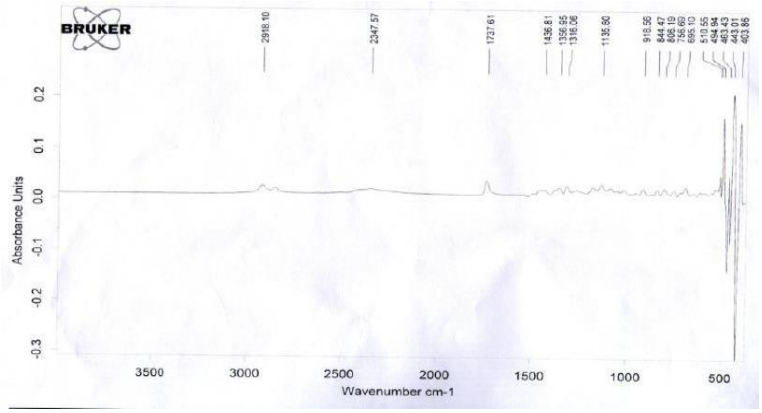

Fig.2: FTIR spectra of pure Cetrizine and Cocoa Butter

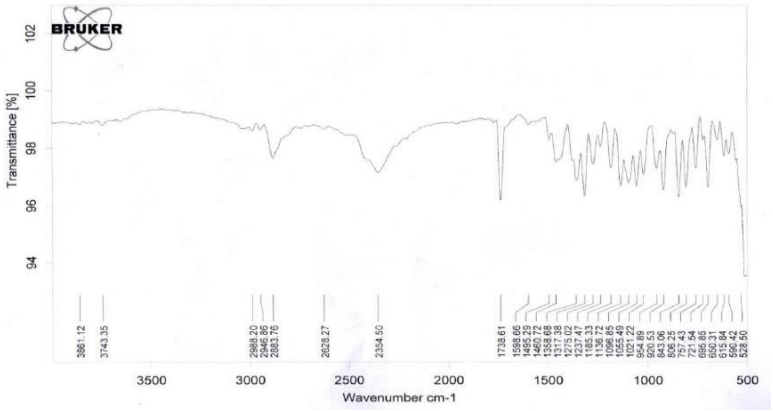

Fig.3: FTIR spectra of pure Cetrizine and PEG-4000

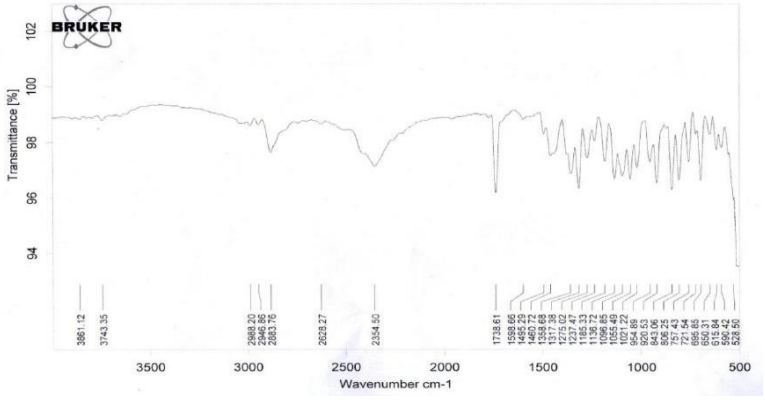

Fig.4: FTIR spectra of pure Cetrizine and PEG-6000

3.2 Weight Variation, Disintegration time, Hardness (Fracture point) Determination, Melting range determination and Uniformity of drug content

PEGs, fats, and emulsion bases produced white or whitish coloured suppositories. Suppositories containing gelatin appeared yellow. Transversely cutting the suppositories did not reveal any fissures, cracks, or holes. It was found that, the weight variation for all tested suppositories within the acceptable range of < 5 % (Table 2), that indicated ideal standardization of mould. Table 2 showed the disintegration times for different suppository formulations. In the case of cocoa butter and polyethylene glycol suppository formulations, they either dissolve or soften and melt within 7.23 min and 6.27-13.32 min, respectively. For the different formulations of suppository, the melting time ranged from 42 to 112 minutes. Mechanical strength for the formulated suppositories ranged from 2.5 to 4.6 kg/cm2, demonstrating optimum hardness for handling, shipping, and insertion (Table 2). The melting point determination of the tested formulations varied considerably. In order to preserve the shape of the suppository at room temperature and to control the melting time after insertion, a narrow melting range is critical. The melting range of the SF-2 formulation is the lowest among all the other formulations (Table 2). According to results, polyethylene glycol-based suppositories (SF-2-SF-8) had a higher melting range than cocoa butter-based suppositories (SF-1). It was established that drug content be in compliance with B.P. (2007), the range was from 98.44 – 101.63 % of the incorporated amount. (Table 2) No differences were found between plain suppositories and medicated suppositories in any of the previous studies.

Table 3: Drug content of the suppository formulations (SF-1-SF-8)

Formulation Code	Drug content (mg)	Drug content (%)
SF-1	4.41±0.58	98.44
SF-2	4.61±0.33	97.58
SF-3	4.91±1.79	98.65
SF-4	4.0±0.25	101.63
SF-5	4.68±1.01	101.23
SF-6	4..68±0.58	100.52
SF-7	4.42±0.67	99.11
SF-8	4.91±1.69	98.79

3.2. In-vitro drug release in phosphate buffer pH 7.4 by dialysis method

Since there is no standard method or apparatus design for studying the release of drugs from suppositories, many studies have been conducted. Dialysis as well as direct contact methods have been utilized with varying modifications. Suppository dissolution testing methods without membrane have been developed by adjusting the USP tablet dissolution apparatus. The dialysis technique was used in this study since the drug release will be similar to that of the rectum.

Table 2:Characterization of the suppository formulations (SF-1-SF-8)

Formulation code	Colour	Surface Condition	Uniformity of mix	Weight variation (mg)	Melting point	Melting range (^{0}C)	Melting range (min)	Mechanical strength (kg/cm^2)	Disintegration time(min/sec)
SF-1	CREAM	GRITTY	++	883 + 0.1	36.5 +1.1	36.5 _ 41.5	66	3.1 + 0.4	7, 23,,+ 0.351
SF-2	WHITE	SMOOTH	++	959.1 +1.0	38.8 +1.4	37 _ 38	42	2.5 + 0.5	13, 32,,+ 0.4
SF-3	WHITE	SMOOTH	++	976 + 1.3	39 + 1.5	38 _ 41	48	3.4 + 0.5	7, 08,,+ 0.674
SF-4	WHITE	SMOOTH	++	945.6 +2.06	43 +1.0	40 _ 42	64	4 + 0.706	9, 44,,+ 0.16
SF-5	WHITE	SMOOTH	++	993.1 + 1.2	38.8+ 1.5	37 _ 41	81	4.6 + 0.351	6, 34,,+ 0.342
SF-6	WHITE	SMOOTH	++	995.75	37+1.46	45 _ 49	110	3.4 + 0.435	6, 27,,+ 0.2

				+1.0					
SF-7	WHITE	SMOOTH	++	989.56+ 1.2	36.3+1. 5	38 _ 41	87	3.7 + 1.000	9,+ 0.65
SF-8	WHITE	SMOOTH	++	964.5+1.08	43+1.16 7	41 _ 46	112	3.2 + 0.384	9, 09,,+ 3.6

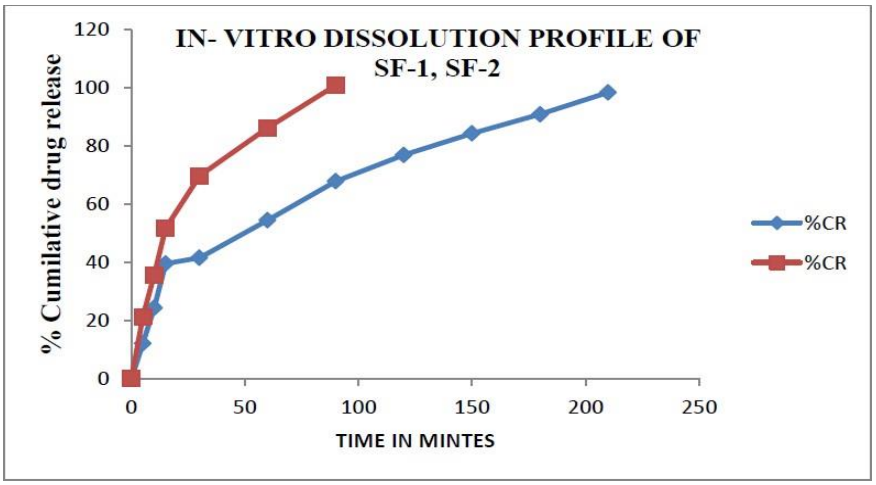

Fig.5: In vitro dissolution profile of the suppository formulations (SF-1-SF-2)

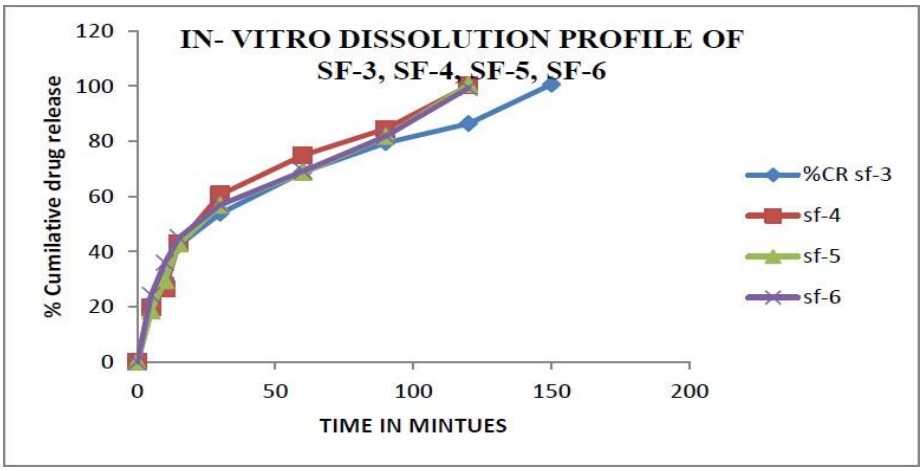

Fig.6: In vitro dissolution profile of the suppository formulations (SF-3-SF-6)

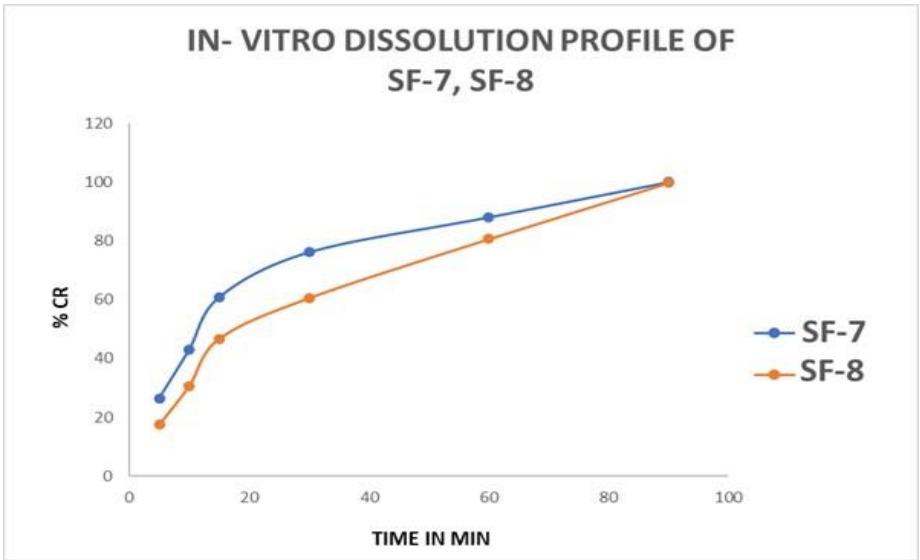

Fig.7: In vitro dissolution profile of the suppository formulations (SF-7-SF-8)

3.3. Kinetics of the drug release from suppositories

The in-vitro release of Cetrizine from formulations (SF-1-SF-8) is demonstrated in figure 5 to figure 7. It is clear that the release can be affected by the presence of propylene glycol and liquid PEGs (400 and 600) and the percent of solid PEGs (6000 and 4000) in the suppository base which contributed to enhance solubility and dissolution in the aqueous medium. Increasing concentration of solid PEGs (6000 and 4000) at the same time with decreasing the concentration used from PEG 600, PEG 600 or propylene glycol resulted in rising the melting point and increasing hardness of the base as well as the hydration process by water uptake followed by formation of gelatinous layers which leading to retardation in the in-vitro release of the drug and vice versa. According to the obtained results, (SF-2) which contained PEG-400 and PEG-6000 (4:6 ratio) showed the highest release of the drug among all.

Table 4: In vitro drug release data of different kinetic models

Formulation codes	Kinetic model	Equation	R^2
SF-1	Zero	y = 0.491x +22.164	0.8678
	First	y = 6.649x +3.4375	0.9845
	Hixon-Crowell	y = -0.008x + 2.006	0.9308
	Korsmeyer-Peppas	y = 0.4915x + 0.87	0.9448
SF-2	Zero	y = 1.557x + 15.50	0.9292
	First	y = 10.92x + 2.309	0.9781
	Hixon-Crowell	y = -0.029x + 2.1199	0.888
	Korsmeyer-Peppas	y = 0.521x + 1.0267	0.9576
SF-3	Zero	y = 0.752x + 21.99	0.8689
	First	y = 7.885x + 5.002	0.9826
	Hixon-Crowell	y = -0.014x + 2.0466	0.9045
	Korsmeyer-Peppas	y = 0.4583x + 1.015	0.9706
SF-4	Zero	y = 1.055x + 17.58	0.9043
	First	y = 9.112x + 2.307	0.981
	Hixon-Crowell	y = -0.0199x + 2.099	0.9172
	Korsmeyer-Peppas	y = 0.5041x + 0.974	0.9673
SF-5	Zero	y = 8.860x + 2.279	0.9847
	First	y = 1.034x + 16.86	0.9226
	Hixon-Crowell	y = -0.019x + 2.1086	0.8837
	Korsmeyer-Peppas	y = 0.495x + 0.9766	0.9701
SF-6	Zero	y = -0.020x + 2.11	0.8563
	First	y = 8.4468x + 6.27	0.9817
	Hixon-Crowell	y = -0.0207x + 2.113	0.8563
	Korsmeyer-Peppas	y = 0.4103x + 1.132	0.9843
SF-7	Zero	y = -0.029x + 2.07	0.9123
	First	y = 10.5x + 7.9786	0.9458
	Hixon-Crowell	y = -0.029x + 2.0709	0.9123
	Korsmeyer-Peppas	y = 0.438x + 1.1875	0.9305
SF-8	Zero	y = 1.543x + 11.61	0.9566
	First	y = 10.728x - 1.009	0.9885
	Hixon-Crowell	y = -0.0357x + 2.236	0.7636
	Korsmeyer-Peppas	y = 0.5747x + 0.901	0.9644

On the basis of linear regression coefficient (R^2) were used for the comparison between the formulations. All the Cetirizine suppository formulations were following best fitting for the first order release kinetics irrespective use of hydrophilic or lipophilic basses (Table 4). The 'n' values Korsmeyer-Peppas for the formulations (SF-2, SF-4, SF-8) were found in the range of 0.504 to 0.574 Log %, hence it may be following non-fickian mechanism and the formulations (SF1, SF3, SF5, SF6, SF7) 'n' value of Korsmeyer-Peppas was found between the range of 0.410 to 0.491 Log %, hence it may be following the fickian mechanism.

4. CONCLUSIONS

The present study attempted the formulation of Cetirizine hydrochloride suppositories using hydrophilic and hydrophobic polymers. FTIR studies revealed no chemical interaction between drug and polymers used for the Study. The physical parameters of all formulations showed good physical parameters of all formulations within limits. All the Cetirizine hydrochloride suppository formulations were found to be acceptable, however formulation SF-2 was found to be the best formulation among all. As a result of this study, it may be concluded that the Cetirizine hydrochloride rectal suppositories may be alternative dosage form with improved bioavailability.

Declaration of Interest

The authors declare that there is no financial or personal interest, as well as no any potential conflicts of interest. Additionally, the authors maintain that research validity has not been influenced by any secondary interest.

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