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RESEARCH ARTICLE

THE IMPORTANCE OF STABILITY TESTING IN PHARMACEUTICAL DEVELOPMENT OF CEFTRIAXONE IMPLANT BIODEGRADABLE TABLETS

Mahmoud Mahyoob Alburyhi, Abdalwali Ahmed Saif, Maged Alwan Noman, Randa Mohammed Saif*

Faculty of Pharmacy, Pharmaceutics and Industrial Pharmacy, Sana'a University, Sana'a, Yemen.
Corresponding Author Email: randa.m.saif@gmail.com

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ABSTRACT

The Ceftriaxone given by the systemic route of administration that utilized to administer antibiotic for prevention of postoperative infection. It ensures uniform antibiotic distribution in the body, therefore, to stop an infection from occurring, a stable dosage form that delivers medications to the infection site at an effective concentration is required. The present study aimed to develop a biodegradable lipid implant for site administration, evaluate various formulations, and examine the stability of an optimum formulation. The different formulations were developed by molding technique and studied for their physical properties, swelling ratio, friability, weight variation, content uniformity, dissolution, gel method, and stability of optimized formulation. This study indicated that all formulations were passed all the tests successfully, and the kinetic study after dissolution, and gel method of formulations were followed Korsmeyer and Peppas model. Among the all formulations Ceftriaxone1 was found to be the best formula because it passed all the tests successfully and had less flocculation in release profile. Accordingly, this formula subjected to stability studies. Based on the results obtained from stability studies, Ceftriaxone1 showed no significant difference of the drug content. From the value of similarity factor, it can be concluded that the release pattern of Ceftriaxone1 among period of stability studied are similar. In conclusion, lipid base biodegradable Ceftriaxone was prepared successfully, and they passed all the tests. The optimized formulations are stable after stability studies as per ICH guidelines.

KEYWORDS

Ceftriaxone; lipid base biodegradable; Implant formulations; Stability studies.

1. INTRODUCTION

Systemic side effects of many therapeutic candidates prevent them from advancing past the initial stage of clinical trials in the field of drug development. Due to these difficulties, there is a need for alternate drug delivery methods that overcome biological and psychological barriers on the path to precision medicine (Fayzullin et al., 2021). The implanted drug delivery system (IDDS) is a formulation or surgically implantable device that introduces a therapeutic material in patient tissues in order to increase the medicine's safety and effectiveness by regulating the rate of release. A drug delivery system (DDS) serves as a conduit between a patient and a medication. It could be a drug formulation for use in a therapeutic setting or a delivery system for the drug. The drug or medicine control agency will use this distinction between the drug and the device as the standard for regulatory control of the delivery method (Jain and Kewal, 2008). Because antibiotics are evenly distributed throughout the body through the circulatory system, only a small portion of a given dose reaches the infection site (Firsov et al., 1987).

One of the dose types utilized to obtain effective concentrations (Conc) over a long time is implanted. Implant base materials must meet biocompatible standards. Polymers, both biodegradable and not, are frequently used as a basis material (Firsov et al., 1987; Kunou et al., 2000; Takahashi et al., 2004). Patients must have surgery to remove non-biodegradable polymers when the medication release is complete, which is painful and burdensome. However, because biodegradable polymers naturally leave the body during or after medication release, these implants are superior in easing patient stress (Okada et al., 1994). To successfully get over physical and biological limitations relating to poor water solubility and stability, membrane permeability, drug efflux, and availability, lipid-based systems are increasingly being studied (Westesen and Siekmann, 1998).

The variety and adaptability of pharmaceutical grade lipid excipients and drug formulations, as well as their compatibility with liquid, semi-solid, and solid dosage forms, are the main causes of the rapidly expanding use of lipid-based drug delivery systems (Attama and Nkemnele, 2005). The third-generation cephalosporin Ceftriaxone (CTX) is used to prevent postoperative infection (POI), and according to the biopharmaceutical classification, it is in the third class (William and Petri, 2011; Reynolds 1982; Singh and Gupta, 2012). The apparent volume of distribution is from 5.78 to 13.5L, and Highly protein-bound, CTX will only have a small fraction of free drug circulating in the blood at any given time (Patel et al., 1981; Heather et al., 2003). This study is concerned with the development of dosage forms for delivery of CTX to the site of infection in effective Conc, and stability study of optimized formulation.

2. MATERIALS AND METHODS

2.1 Materials

Ceftriaxone sodium as raw materials (Gift sample from Medical Union Pharmaceuticals / Egypt), Ceftriaxone sodium as working standard (Gift from Modern Pharma & Global Pharma Companies / Yemen), all the other ingredients were of analytical grads. Spectrophotometric Lasany ® advanced microprocessor UV-VIS-L1-295, Oven Gallenkamb, England, 3A 5048, Refrigerator LG, Indonesia, GN-B262SLCL, Water bath Clifton,

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England, NE2-56D, Micrometer DN-863/II, Friability test apparatus Campbell Electrinics, India, C-07-60, Electrical Shaker Hedioiph, Promax2020, Germany, Dissolution test apparatus type 2 Erweka, DT126 light, Germany, Centrifuge P-selecta, Spain, Mixtasel.

2.2 Preparation Method

The formulation of lipid based biodegradable implants contained, a suitable core as glyceryl mono-stereate (GMS), erosion and biodegradation enhancer like polyethylene glycol 6000 (PEG 6000), surfactant (Tween 20), and any drug can be included in the core composition that one wishes to deliver through the implants. A CTX as active pharmaceutical ingredient used for preparation lipid base biodegradable antibiotic as they used in the prevention of POI, generally all formulations appeared in table (1) (Shah and Allababidi, 1999).

In the study, GMS, PEG 6000, and tween 20 in specified quantities as represented in Table (1) were heated to 70 °C on a water bath under stirring with a glass rod. The weighed quantity of the CTX was dispersed uniformly. The molten mass was drawn up into a 10 ml-syringe and poured into round stainless-steel mold. The mold was allowed to cool at 2 – 8 ˚C. Different formulations were prepared. A blend was prepared in the same manner but without CTX (Mathur et al., 2010; Roy et al., 2012).

Table 1: Composition of lipid based biodegradable Ceftriaxone used in formulation.

No	Formula	CTX %	GMS %	PEG 6000 %	Tween 20 %
1	CTX1	20	40	35	5
2	CTX2	20	40	30	10
3	CTX3	20	40	25	15
4	CTX4	20	40	20	20

2.3 Evaluation Methods

2.3.1 Physical properties (color, shape, diameter, thickness)

The prepared tablets of each formula CTX were subjected to examination of their color, shape by visual inspection. The diameter and thickness measured by micrometer, the mean and SD were calculated with an acceptable variation of ± 5% (Pawar et al., 2013; Anand et al., 2009).

2.3.2 Friability

Friability was measured by introducing twenty tablets of each formula CTX in a drum as described by the British Pharmacopoeia (BP), a maximum weight loss of not more than 1 % of the tested tablets, generally is acceptable (Singh and Gupta, 2012).

2.3.3 Weight variation

Twenty tablets were selected randomly from each CTX formula and weighed individually. The average weight (X) of each formula of tablets was calculated. Individual weights of the tablets were compared with X. Since the tablets weighed over 250 mg, the tablets pass the test if not more than two of the individual weights deviate from the (X) by more than 5 % (Pani et al, 2010).

2.3.4 Content uniformity test

From each CTX formula ten tablets were randomly taken and grained separately by using glass mortar and pestle then, powder equivalent to 10 mg of CTX were accurately weighed and transfer to 50 ml of phosphate buffer solution (PBS) with pH 7.4 and stirred at 80 rpm for 1 h. The resulting solution was filtered and the final volume adjusted with PBS (pH 7.4) up to 100 ml. Then, suitable dilutions were prepared, and samples were analyzed by using validated U-V spectroscopic method of CTX at λ_{max} = 240 nm. The polymeric solution without CTX serves as a blank. Means and RSD were calculated. Tablets pass a test if content uniformity lies between 90 – 110 % of the label claim & the RSD is not greater than 6% (Pawar et al., 2013; Babu et al., 2011).

2.3.5 Water up takes

Water absorbed of tablets of each CTX formula determined by immersing weighed tablets (No=3) in 25ml PBS with pH 7.4 at 37 ˚C. At specified times (10, 20, 30, and 40 min) samples were removed and the tablets were blotted dry by using filter paper and weighed. Water absorbed (Q_s) of test sample was calculated using following equation:

$$Q_s = (W_s - W_d) / W_d$$

Where W_s is the weight of tablet after test sample and W_d is the initial weight of the test sample (Takahashi et al., 2004; Pawar et al., 2013; Babu et al., 2011).

2.3.6 In -vitro drug release

The release profile of different CTX formulation was estimated by placing tablets (No=3) selected randomly in dissolution apparatus (paddle method at 50 rpm) and 37 ± 1 °C in 900 ml of PBS pH 7.4. At pre-set time, 10 ml solution was taken and replaced with fresh PBS, the samples were filtered and analyzed spectrophotometrically at λ_{max} of CTX = 240 nm. In order to determine the mode of release from the tablets, the release data were analyzed with the following: zero order ($Q_t = Q_0 + K_0t$), first order ($\log Q_t = \log Q_0 + K_1t/2.303$), Higuchi ($Q_t = K_H.t^{½}$), and Korsmeyer Peppas model ($M_t/M_\infty = K.t^n$) (Mathur et al., 2010; Roy et al., 2012; Pawar et al., 2013; Onishi et al., 2005).

2.3.7 Gel simulating in-vitro implantation (gel method)

In-vitro release was followed by placing CTX tablet in agar gel simulating subcutaneous tissue conditions with respect to viscosity and water content. Agar crystals were dissolved in boiling 0.1 mol l^{-1} PBS with a pH of 7.4 to prepare 1.5 % an agar solution, which was poured into a Petri dish and left to congeal. A hole (depend on size of tablets) was drilled in the center of the agar plate and the tablet was placed in the hole. Sufficient quantity of the hot agar solution was poured on the top to cover the implants and left to congeal. The plate was covered and placed in the oven (37°C). Several agar plates implanted with CTX tablets were prepared at the same time, and the samples were collected at 6, 24, 48, 72, 96 h. At each sampling time, one plate was removed from the oven. The plate was divided into four sampling zones and three samples were removed from each zone. The samples were accurately weighed and dissolved in boiling PBS containing 25 % NaCl. The solution was cooled in an ice bath to precipitate the agar. The resulting suspension was weighed and then centrifuged to obtain a clear supernatant containing CTX. The supernatant solution was analyzed by UV spectrophotometer (Mathur et al., 2010; Roy et al., 2012; Allababidi and Shah, 1998).

2.3.8 Stability Studies

The best formula from CTX formulations were chosen, and each tablet wrapped in aluminum foil, then placed in a glass bottle, sealed and kept for stability studies as per ICH guidelines, under conditions (5 ± 3 ˚C, with monitoring, but not control of humidity), and under conditions (40 ± 2°C/75 ± 5 % relative humidity (RH)) for six months. Every month, one sample from each formulation was withdrawn and evaluated for drug concentration and study dissolution profile by similarity factor f2 = 50. Log $\{[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5}.100\}$, and difference factor f1 = $\{[\sum_{t=1}^{n} |R_t - T_t|] / \sum_{t=1}^{n} R_t\}.100$, where R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively (Roy et al., 2012; Pawar et al., 2013; Babu et al., 2011; Pawar and Khandelwal, 2019; Bajaj et al., 2012).

3. Results and Discussion

3.1 Preparation of biodegradable lipid base CTX

In this study, the formulations of biodegradable lipid base implant tablet were prepared successfully by molding method.

3.2 Evaluation of different CTX formulations

In the evaluation of prepared formulations, the color of CTX table was pale yellow, and the shape was round. The results of diameter were 12.83 ± 0.14, 12.71 ± 0.16, 12.83 ± 0.15, and 12.73 ± 0.16 mm for CTX1, CTX2, CTX3, and CTX4 respectively, whereas the thickness of different formulations was 4.93 ± 0.15, 4.94 ± 0.14, 4.95 ± 0.12, 4.89 ± 0.13 mm for CTX1, CTX2, CTX3, and CTX4 respectively, these results showed that, there was no significant change (at p = 0.05) in diameter or thickness, as data treated by ANOVA. The results of friability of different formulations were 0.83, 0.89, 0.77, 0.69 for CTX1, CTX2, CTX3, and CTX4 respectively, as calculated, the weight loss was less than 1% so all formulations pass the test successfully, and there was no significant difference (at p = 0.05) between different formulations when tested by ANOVA. The weight variation results of different formulations were 0.5154, 0.5082, 0.5106, and 0.5148 g for CTX1, CTX2, CTX3, and CTX4 respectively.

All CTX formulations were passed the test successfully, that was no tablet deviates from the upper and lower limit by more than 5%. There was no significant difference between formulations (at p = 0.05). In addition, the content uniformity test that designed to ensure that the amount of CTX was in the permitted level for ten tablets assayed individually were 99.11 ± 2.60, 100.8 ± 7.89, 97.70 ± 7.62, and 100.7 ± 2.63 % with a relative standard deviation of 2.63, 7.82, 7.80, and 2.61 for CTX1, CTX2, CTX3, and CTX4 respectively. It was found that, formulations (CTX1, CTX4) were passing the test whereas formulations (CTX2, CTX3) were filled to meet

requirement as the relative standard deviation was more than 6%, this variation could be attributed to non-uniform distribution of CTX. The data were treated by ANOVA and there was no significant difference (at p = 0.05) between different formulations. The results of water absorbed of different formulations were represented in table 2.

Table 2: Percentage w/w of water up take of Ceftriaxone formulations

Formula Time	CTX1	CTX2	CTX3	CTX4
After 10 min	19.11±0.17	23.51±1.16	26.36±0.32	28.51±0.24
After 20 min	22.94±0.99	25.01±0.76	27.03±1.72	31.31±1.24
After 30 min	29.57±0.91	32.13±0.76	35.94±3.20	39.43±0.50
After 40 min	29.88±0.82	32.31±1.06	35.32±0.58	39.66±0.98

It was represented as mean ± SD. The data were tested by ANOVA, there was a significant difference (at p > 0.05) for each formula which means that the water uptake was increased with time as the concentration of tween 20 increase but the differences became non-significant at the end of the test. The release of CTX was studied in triplicate under sink condition. From the result obtained, the release rate was high due to higher erosion during dissolution. The formulations CTX1 (containing 35% PEG 6000, 5% tween 20), CTX2 (containing 30 % PEG 6000, 10 % tween 20), CTX3 (containing 25% PEG 6000, 15% tween 20), and CTX4 (containing 20% PEG 6000, 20% tween20) showed 99.78 %, 102.21%, 111.46, and 111.45% Cum drug release in 35 minutes respectively as represented in table 3.

Table 3: Percentage cumulative (Cum) drug release of Ceftriaxone formulations.

Time (min)	CTX1 % Cum drug release	CTX2 % Cum drug release	CTX3 % Cum drug release	CTX4 % Cum drug release
0	0	0	0	0
5	11.063	15.546	14.426	14.633
10	20.33	34.364	37.251	33.223
15	45.376	56.499	55.708	59.619
20	63.058	71.467	83.468	79.944
25	81.956	96.781	101.01	99.537
30	96.43	102.86	110.71	111.61
35	99.785	102.21	111.46	111.45

The release of CTX was slightly increased as the amount of tween 20 increase and the amount of PEG 6000 decrease among formulations as represented in figure 1- A, that facilitate the penetration of dissolution medium which in turn enhances solubility and dissolution. All formulations (CTX1, CTX2, CTX3, and CTX4) were followed Korsmeyer Peppas model with the R^2 value (0.98, 0.979, 0.976, and 0.979) respectively. The results indicate biphasic CTX release pattern, which includes the initial burst release of CTX followed by the release of the drug within 35 minutes. The diffusion exponent (n) for CTX formulations were more than 1 which followed supper case II diffusion mechanism, that referred to the erosion drug release. The biodegradable lipid base antibiotic was not designed to be in direct contact with liquids as in case of dissolution test, in this case the result that obtained from dissolution could not be represented the real state as the dosage form came in direct contact with tissue. According to this fact the dissolution test usually followed by a gel simulating method in which the tablets surrounded by tissues rather than liquid. CTX formulations showed prolonged release in gel method, they released 47.08%, 47.973%, 48.601%, and 30.73% within 96 h for CTX1, CTX2, CTX3, and CTX4 respectively, as shown in table 4, and figure 1- B.

Table 4: Percentage of release in gel method for Ceftriaxone formulations.

Time (h)	CTX1 % release	CTX2 % release	CTX3 % release	CTX4 % release
0	0	0	0	0
6	2.0759	2.2083	2.279	1.1511
24	5.8971	5.8227	6.4222	4.2045
48	11.556	7.4397	11.833	6.1183
72	36.535	20.324	38.126	10.81
96	47.08	47.973	48.601	30.73

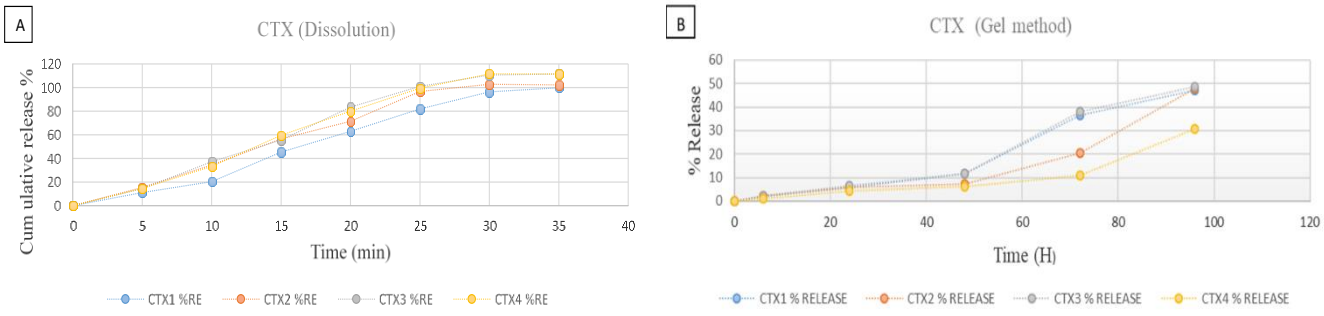


Figure 1: Cumulative percentage release of Ceftriaxone formulations (A) in Dissolution, (B) in Gel method

These results give an idea of the possibility to use developed formulations to prolong the release of CTX from lipid base biodegradable antibiotics. Since the kinetic release of CTX from lipid base biodegradable antibiotic by gel method, the formulations (CTX1, CTX2, CTX3, and CTX4) were followed Korsmeyer Peppas model with the R^2 value (0.9354, 0.8617, 0.9314, and 0.9189) respectively. These prolonged CTX release patterns,

which includes a slow release of CTX a prolonged period of time. The (n) for CTX formulations was in the range 0.9955 – 1.1316, for CTX2 it was followed by super case II diffusion mechanism time independent zero order release, and for CTX1, CTX3, CTX4 were super case II relaxation/ erosion.

3.3 Stability Studies

In the stability studies, formulations CTX1 (containing 20 % of CTX, 40 % GMS, 35% of PEG 6000, and 20% Tween 20) were chosen as the optimized formulation because had passed all the test successfully and had highest R^2 value.

The results of CTX1 content stored at (5 ± 3 ˚C, with monitoring, but not control of humidity) were examined after three months and after six months, and they were 99.52 ± 5.87, and 98.67 ± 2.15 % after three and six months respectively. Whereas the samples of CTX1 that stored at (40 ± 2°C/75 ± 5 % RH) conditions were examined monthly for six months, and the results were 99.76 ± 2.92, 97.73 ± 3.73, 97.57 ± 6.60, 97.78 ± 1.79, 96.59 ± 6.33, 96.95 ± 4.03 % for the first, second, third, fourth, fifth, and sixth month respectively. From the obtained results of CTX1 content, there was no significant change in the amount of CTX1 after storage at (5 ± 3 ˚C, with monitoring, but not control of humidity) after three and sixth months when compared with the amount of CTX in the beginning of the analysis (at p = 0.05), that mean the drug remain stable during these periods of storage. Also, the previous results of CTX1 content that stored at (40 ± 2°C/75 ± 5 % RH) shown that there was no significant change in the amount of drug after first, second, third, fourth, fifth and sixth months when compared with that in the beginning of the analysis (at p = 0.05), that mean the drug remain stable during these periods of storage. The release profile studied over three, and six months of the CTX1 stored at (5 ± 3 ˚C, with monitoring, but not control of humidity) and monthly for the CTX1 stored at (40 ± 2°C/75 ± 5 % RH) for six months. The results were represented in tables 5 and 6, and figure 2 (A & B).

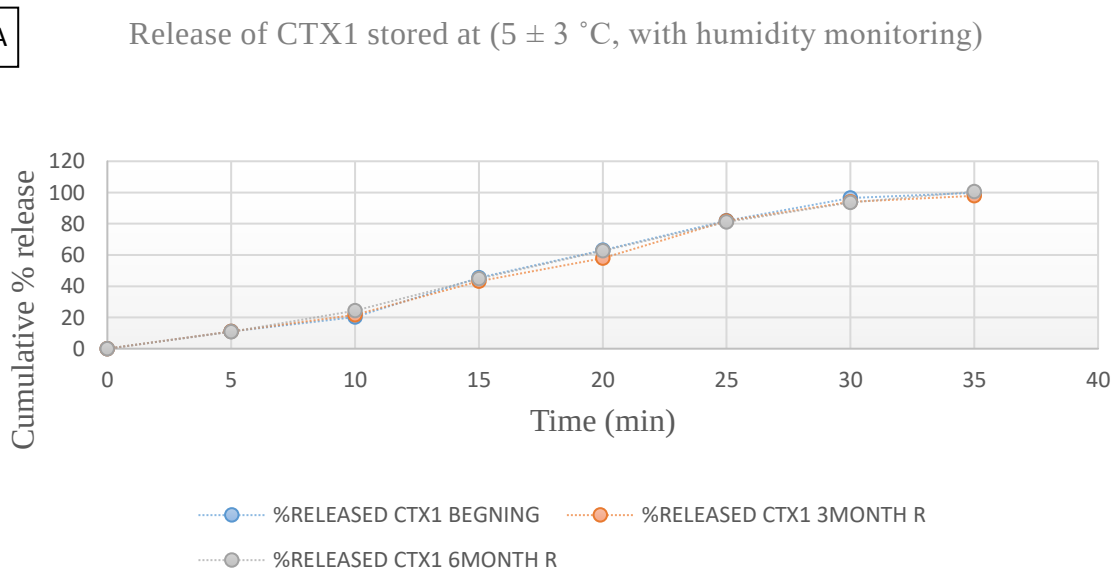
Table 5: Percentage of Cum release of Ceftriaxone 1 after stored at (5±3 ˚C, with humidity monitoring).

Percentage Cum Release of CTX1 after Storage at (5 ± 3 ˚C, with Humidity Monitoring)			
Month Min	**0 Month**	**3 Month**	**6 Month**
0	0	0	0
5	11.06	11.11	10.82
10	20.33	21.72	24.42
15	45.38	43.2	44.86
20	63.06	57.91	62.66
25	81.96	81.8	81.1
30	96.43	94.07	93.57
35	99.78	97.89	100.55

Table 6: Percentage of Cum release of Ceftriaxone 1 after stored at (40±2 ˚C / 75±5 % RH).

Percentage of Cum Release of CTX1 after Stored at (40 ± 2°C/75 ± 5 % RH)						
Month Min	**0 Month**	**1 Month**	**2 Month**	**3 Month**	**4 Month**	**6 Month**
0	0	0	0	0	0	0
5	11.06	17.54	12.58	10.15	12.44	12.5
10	20.33	26.26	23.46	25.65	26.7	25.26
15	45.38	44.46	46.8	45.04	36.85	42.85
20	63.06	69.47	64.91	61.71	57.86	63.92
25	81.96	77.52	80.69	75.2	87.9	79.11
30	96.43	100.97	95.77	99.22	97.64	99.59
35	99.78	99.09	100.9	97.45	98.26	99.48

A



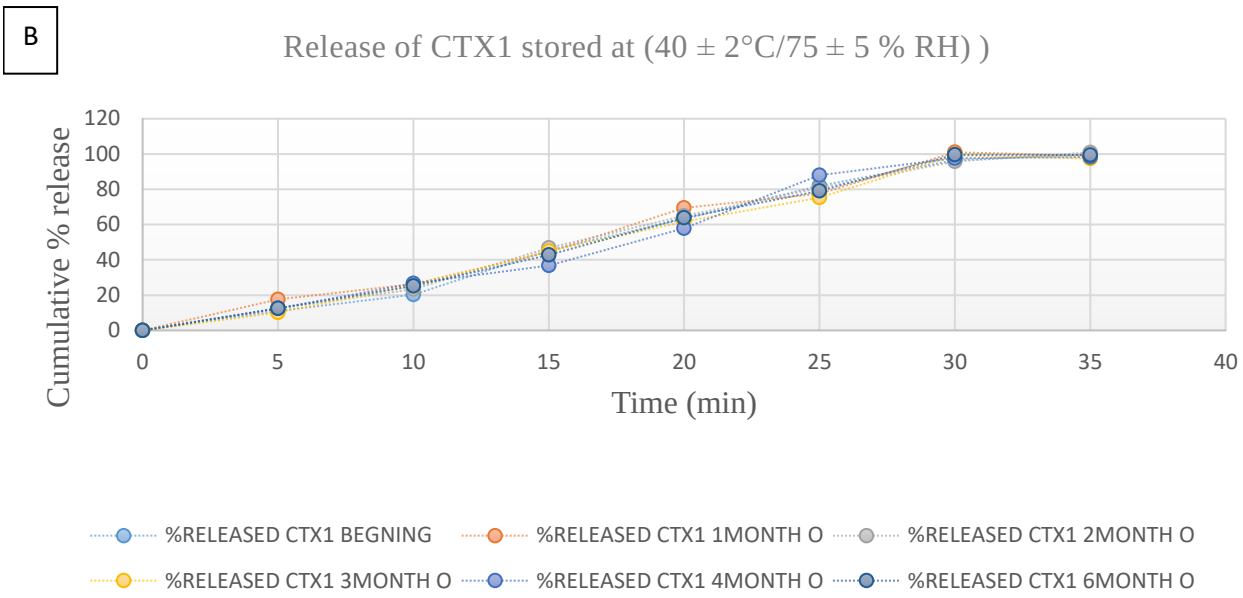


Figure 2: Cumulative percentage release of Ceftriaxone 1 after storage at, (A) 5±3˚C, with humidity monitoring, (B) 40 ± 2˚C/75 ± 5% RH.

The results of the Cum amount dissolved of the CTX are 99.78 %, 97.89 %, and 100.55 % within 35 minutes for zero, third, and sixth month respectively as appeared in table 5. The dissolution profile of CTX during period of storage at 5 ± 3 ˚C, with humidity monitoring could be regarded identical as shown in figure 2 - A. The results of the Cum amount dissolved of the CTX were 99.78 %, 99.09 %, 100.09 %, 97.45 %, 98.26 %, 121.98 %, and 99.48 % within 35 minutes for zero, first, second, third, fourth, and sixth month respectively as appeared in table 6. The dissolution profile of CTX during period of storage at 40 ± 2 ˚C/ 75 ± 5 % RH could be regarded identical as shown in figure 2 - B. The release of CTX studied by comparison of f2 and f1 factors of CTX to that of a reference. Analysis of CTX1 samples stored at (5 ± 3 ˚C, with humidity monitoring) shows that their release profile could be regarded similar to the release profile obtained at the beginning (zero month) as the value of f2 were (51.601 and 51.681) for third month and sixth month respectively.

These results fell in the accepted range of f2 (50 – 100). Also, the values of f1 were calculated for third and sixth months (3.149 and 2.325) respectively, they have also fallen in the accepted range of f1 (0 – 15). In addition, the results got from the in vitro dissolution of CTX1 stored at (40 ± 2°C/75 ± 5 % RH) for the six months were acceptable since the value of f2 (51.339, 51.721, 51.456, 51.313 and 51.564) for the first, second, third, fourth, and sixth month respectively, were in the accepted range (50 – 100), and the value of f1 (7.034, 2.623, 4.738, 7.211 and 3.841) for first, second, third, fourth, and sixth month respectively, were fallen in the limited range (0 – 15). The results obtained from the dissolution of tablets were satisfactory and show that the CTX1 formula was stable and retained their release pattern when stored at accelerated conditions. From all the above results CTX1 was stable formula.

4. Conclusion

The formulations of lipid base biodegradable Ceftriaxone were developed successfully. It was concluded that, all formulations for CTX with GMS, PEG 6000, and tween 20 showed physical properties, friability, and weight variation within the acceptable range. The in vitro dissolution results indicated an increase in release profile among formulations as the concentration of tween 20 increase and concentration of PEG 6000 decrease. The in vitro dissolution usually followed by gel method that simulates in vivo implantation conditions, and all formulations followed a Koresmyer Pepas model in both tests. Among the all formulations CTX1 formulation was found to be the best formulations because they passed all the tests successfully, and had less flocculation in release profile. Accordingly, these formulations subjected to stability studies. Based on the results obtained from stability studies, the formulations CTX1 showed no significant difference of the drug content. From the value of similarity factor, it can be concluded that the release pattern of formulation (CTX1) among period of stability studied are similar.

Recommendations

- The use of another method for the preparation should be studied carefully because it may change the release pattern of the drug.
- The preparation of different formulations should be studied under sterilization conditions, as the biodegradable lipid base antibiotic will be used during surgery to prevent post-operative infection.

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