

Formulation of cefuroxime axetil oral suspension and investigation of its pharmaceutical properties

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ABSTRACT

Purpose: Cefuroxime is the second generation cephalosporin, which its intravenous and oral dosage forms are available. Oral route is the selective method for administration of most of the drugs. The aim of this study was formulating 'for oral' cefuroxime axetil suspensions. **Methods:** Minitab (ver.15) was used to design the formulations containing 125 mg of cefuroxime in 5 ml vehicle. After selecting the acceptable preparations, physical stability tests and other tests such as dissolution rate, pH, zeta potential and viscosity measurement of formulations were performed. **Results:** From all 33 formulations, only 9 were selected to further investigation. Considering no sedimentation, the sedimentation volume was determined to be 1. The degrees of flocculation were also equal to 1. All selected formulations released the drug between 81-100% in 30 minutes which was acceptable according to the USP32 criteria. The results of assay test also proved that all formulations contain the drug in acceptable range (91-106%). The viscosity curves showed that the systems were pseudo plastic and thixotrop. **Conclusion:** Designed cefuroxime axetil formulations had good qualities and could be added as a new product to Iran drug marketing.

Introduction

Cefuroxime is 1-acetoxyethyl ester of a β -lactamase-stable cephalosporin [1]. This second generation-cephalosporin is active against a wide range of Gram-positive and Gram-negative organisms [2] which makes it useful in treating a variety of infections caused by β -lactam-producing strains of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus*. An advantage of cefuroxime over other second-generation cephalosporins is that it is effective in the treatment of *Neisseria gonorrhoea* and *H influenzae*. It is characterized by being the only second-generation cephalosporin which adequately penetrates into the cerebrospinal fluid (CSF) [3]. The use of Cefuroxime by the oral route requires its administration in the form of prodrug, cefuroxime axetil. Since cefuroxime is not absorbed orally, the 1-acetoxyethyl (axetil) ester of cefuroxime was used to improve its gastrointestinal absorption [4]. Oral route is the selective method for administration of most of the

drugs because of its ease and patient compliance [5A]. Because of the advantages of using a suspension and high bioavailability in comparison to other dosage forms (except solutions), in this investigation the aim was formulating oral cefuroxime axetil suspensions.

Materials and Methods

Materials

Cefuroxime axetil was purchased from Dana Pharmaceutical Company, Tabriz, Iran. Avicel, Colloidal silicon dioxide, Silloidal silicon dioxide were purchased from Exir Pharmaceutical Company, Boroujerd, Iran. Xanthan, Ploxamer were purchased from Sigma-Aldrich, Basal, Switzerland. All other chemicals were purchased from Merck, Darmstadt, Germany.

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Formulation of suspensions

One of the methods for making the suspension, is the dispersion of a particle in a vehicle that can be done by mechanical instruments or by the use of surfactants that contains three steps: a) wetting of particles, b) disintegration of aggregated particles, and c) prevention of re-aggregation of particles in the vehicle [6].

For suspension formulation equivalent to 125 mg of cefuroxime was suspended in 5 ml vehicle, after selecting the type and concentration of wetting agent, other ingredients such as flocculating agents, suspending agents, preservatives and flavors were added [6]. Minitab (ver.15) software was used to design the formulations.

Evaluation of physical stability

Made formulations are then evaluated for physical stability tests in which the sedimentation volume (the ratio of the final volume of the sediment to the original volume of the suspension) and degree of flocculation (the ratio of the ultimate sediment volume of flocculated suspension to the ultimate sediment volume of deflocculated suspension) were conducted [7].

Assay test

Prepared formulations were evaluated by UV system in 281 wavelengths, for the standard solution 20 mg of the drug was dissolved in 50 ml methanol and 10.61 concentration of it was made by dilution and the absorbance was read. For the assay solution 5 ml of suspension was dissolved in 50 ml methanol and after shaking for 5 minutes 200 ml of medium was added and after achieving 10.61 concentrations the absorbance was read.

Dissolution test

For 3 of each formulation, dissolution test was performed with USP 2 apparatus (Paddle) in 50 rpm for 30 minutes. 900 ml of medium (3.7 g of monobasic sodium phosphate and 5.7 g of anhydrous dibasic sodium phosphate) was transferred to each vessel and the absorbances of the samples were read in maximum absorption wavelength of 281. Then using equation derived from calibration curve ($y = 0.0344x + 0.0233$, $R^2 = 0.9991$) the percentage of drug release was calculated [8].

Other tests, including measurement of pH, viscosity and zeta potential measurements were performed and finally the best formulations were selected.

Results

From all 33 formulations designed in Minitab software, only 9 was selected to further investigation that are listed in the Table 1. The sedimentation volume was calculated to be 1 in all the suspensions, therefore there was no need to re-dispersion test and the degree of flocculation value was also 1. All selected formulations released more than 60% of the drug (81-100%) that was acceptable according to the USP32 criteria. In Fig.1, the percentage of release in all the formulations are presented. Assay tests also show that the amount of drug in all formulations are in the range of 91-106% and all are acceptable (Table 2). After calculating the viscosity, the curves of viscosity against shear rate were plotted. A sample of these curves is shown in Fig.2.

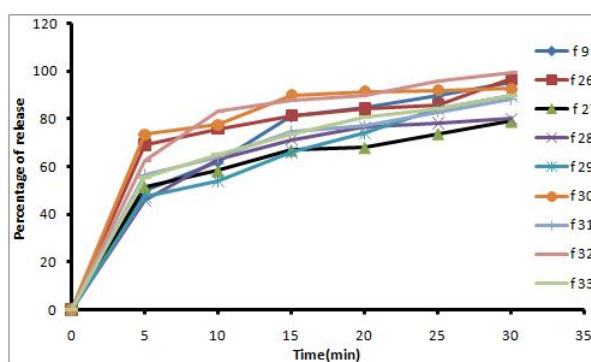


Fig1. Percentage of release for all selected formulations

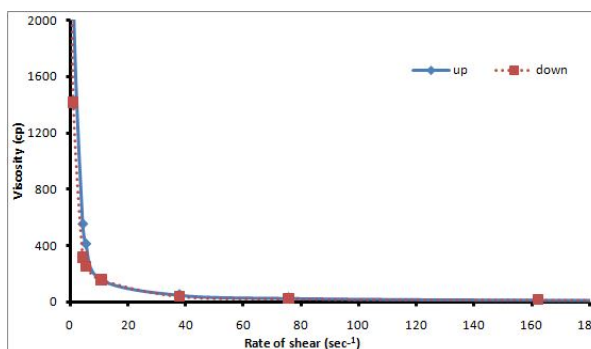


Fig 2. A sample viscosity curve for formulated suspension

Table 1: Composition of selected formulations designed in Minitab (ver.15)

Formulations	Drug%	Glucose%	Avicel%	Polaxamer%	Siloidal silicon dioxide%	Xanthan%	Colloidal silicon dioxide%
9	20	50	12.5	0.55	0.275	0.175	16.5
26	20	50	5	1	0.05	0.05	23.9
27	20	50	5	1	0.5	0.3	23.2
28	20	50	5	0.1	0.05	0.05	24.35
29	20	50	5	0.1	0.05	0.3	24.55
30	20	50	5	1	0.05	0.3	23.65
31	20	50	5	0.1	0.05	0.05	24.8
32	20	50	5	1	0.5	0.05	23.45
33	20	50	5	0.1	0.5	0.3	24.1

Table 2: Results of assay test

Formulations	concentration ($\mu\text{g/ml}$) sample 1	concentration ($\mu\text{g/ml}$) sample 2	concentration ($\mu\text{g/ml}$) sample 3	Percent of labeled amount
9	9.97	11.05	10.29	98.36
26	13.26	9.77	10.29	104.66
27	10.03	9.53	9.68	91.87
28	9.26	10.11	10.48	93.78
29	10.35	10.93	10.46	99.73
30	10.48	10.44	10.67	100.37
31	11.08	10.7	10.81	102.37
32	11.54	11.19	11.25	106.76
33	11.1	10.58	10.76	101.92

Discussion

General criteria for selecting a suitable suspension can be considered as proper appearance of uniformity and homogeneity, the number of low-frequency shaking for the complete distribution, the high volume of sediment, no crystal growth and appropriate pour ability. According to these properties a general discussion is presented. 33 formulations were designed with Minitab (ver.15) software and only 9 were pourable and had ideal characteristics to continue more other tests. There was no sediment in selected formulations and the sediment volume was 1 for all of them so there was no need for re-dispersion test and the degree of the flocculation was also 1 that was probably because of the high viscosity of the system. pH measurement indicated that all the suspensions' pH were between 5 - 6 that was acceptable according to the pharmacopeia. Release test approved that all the formulations released drug more than 60% in 30 minutes. According to the curve each formulation released 95.44, 96.82, 79.10, 81.10, 89.69, 92.62, 88.14, 99.28, and 89.69 in 30 minutes. The assay test showed that all the formulations contain drug in acceptable range according to the pharmacopeia and all contains between 91-106%.

According to the viscosity curves, the suspensions were pseudo plastic, i.e., the viscosity decreases as the shear rate increases. This is probably because of xanthan and sodium carboxymethyl cellulose (exists in the avicel RC-591 in the amount between 8-13%) [9] which give pseudo plastic property to the vehicle. Considering the differences of the viscosity in up and down curves the thixotropy of the system is obvious so the vehicle was pseudo plastic and thixotrop. Also the system was found to be time-dependent. That means after a while takes the stress off, the initial viscosity of the suspension is achieved and that's a good chance to pour the suspension after each re-dispersion which is one of the most important characteristics in suspensions, also because of the high viscosity of the system despite of having flocculated particles in the vehicle according to Stokes's law the sedimentation rate was low [4B].

The charge of the particles effects their distribution in the environment and increases the concentration of opposite charge on the surface close to them which produces electric double layer. The potential of the

moving layer around each particle is called zeta potential. Quantity of zeta potential can indicate the potential stability of the colloidal system, if the particles have a large positive or negative zeta potential they will have a tendency to repel each other and in too low zeta potentials particles will accumulate and attract each other. Overall, the borderline between stable and unstable suspensions is usually considered zeta potentials between + 30 mv or - 30 mv means those particles which have zeta potential more than +30 or lower than -30 mv considered stable [10]. In this investigation all the formulations had zeta potential lower than -30 mv but all of them were stable so it seems that mechanisms other than the zeta potential of the particles is involved in the formulation of stable formulations. In other words, polymer bridging was the main mechanism for controlled flocculation in the present work.

Conclusion

According to the obtained results and considering the ideal characteristics of prepared suspension formulations, this product can be added to drug market.

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Conflict of interest

The authors report no conflicts of interest.

References

1. Dhumal R, Biradar V, Yamamura SH, Paradkar R, York P. Preparation of amorphous cefuroxime axetil nanoparticles by sonoprecipitation for enhancement of bioavailability. *Eur. J. Pharm. Biopharm.* 2008;70(1): 109-115.
2. Jelinska A, Dudzinska I, Zajac M, Oszczypowicz I. The stability of the amorphous form of cefuroxime axetil in solid state. *J. Pharm. Biomed. Anal.* 2006;41(3): 1075-1081.
3. Al-Said MS, Al-Khamis KI, Niazy EM, El-Sayed YM, Al-Rashood KA, Al-Bella S, Al-Yamani MA, Al-Najjar TA, Alam SM, Dham R. Bioequivalence evaluation of

- two brands of cefuroxime 500 mg tablets (cefuzime and zinnat) in healthy volunteers. *Biopharm. Drug Dispos.* 2000;21(6): 205-210.
4. Ruiz-Carretero P, Merino-Sonjuan M, Casabo VG. Pharmacokinetic models for the saturable absorption of cefuroxime axetil and saturable elimination of cefuroxime axetil. *Eur. J. Pharm. Sci.* 2004;21(2-3): 217-223.
 5. Kulshreshtha AL, Singh, O.N Chandrasekar. Pharmaceutical suspensions from formulation to manufacturing. In: Chandrasekar M, Ashwin B, Jagdish S. ed. *Various Pharmaceutical Disperse System*; New York: Springer, 2010:1-38.
 6. Sinko JP, Singh YA. *Martin's Physical Pharmacy and Pharmaceutical Sciences*. USA: Courier Westford; 2011. A:410-414 , B:469-477
 7. Bowman JB, Mofner C, Schott H. Colloidal dispersion. In: *Remington's Pharmaceutical Sciences*. Easton: Mack Publishing Company; 2006:293-337.
 8. Tabibi S, Rhodes CH. Disperse system. In: Banker SG, Rhodes TC. *Modern Pharmaceutics*. CRC press; 1996:365-436.
 9. *The United States Pharmacopeia (USP)*. Port City Press; 2009; pp 1864-1865.
 10. Epshtein NA. A new approach to HPLC analysis of medicinal suspensions. *Pharm. Chem. J.* 2001; 35(12): 686-689.
 11. Benitez EI, Lozano JE. Influence of the soluble solids on the zeta potential of the cloudy apple juice. *Lat. Am. Appl.* 2006;36(3): 163-168.