

COMPARATIVE IN-VITRO STUDY OF IMMEDIATE AND MODIFIED RELEASED ORAL DOSAGE FORMS OF CEFACLOR

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Abstract

The paper presents the results of *in vitro* dissolution testing for various immediate and controlled release formulations of cefaclor, based on compendial recommendations and specific methodological adaption. The data suggest a rapid and complete release for capsules and suspensions dosage forms, the profiles being independent on dose-strength. The sinkers used for preventing the floating phenomenon did not influence significantly the dissolution pattern. For modified release film-coated tablets, the paddle apparatus provided similar results compared to USP30 pharmacopoeial conditions.

Rezumat

Lucrarea prezintă rezultatele testelor de cedare *in vitro* pentru cefaclor, din diferite forme farmaceutice cu cedare imediată sau modificată, pe baza recomandărilor compendiale sau prin adaptarea unor metodologii specifice. Datele obținute indică o eliberare completă și rapidă a cefaclorului din suspensii și capsule, profilele de cedare fiind independente de doză. Sinker-ele folosite pentru prevenirea fenomenului de flotare nu influențează semnificativ profilul de dizolvare. În cazul comprimatelor filmate cu cedare modificată, folosirea aparatului cu paletă a condus la rezultate similare celor generate de condițiile de testare indicate în farmacopeea Statelor Unite ale Americii (USP30).

Keywords: cefaclor, tablets, capsules, suspension, dissolution test.

Introduction

The application of current recommendations for dissolution testing frequently determines adaption to the particularities of the dosage forms, release mechanism or physico-chemical properties of the active pharmaceutical ingredient (API). When no official monographs are

available, minor changes in the testing conditions (media, hydrodynamics, apparatus etc.) can be implemented only after the accurate evaluation of the discriminatory character for the intended use. For example, although a particular drug is used in the clinical practice in various dosage forms, only few of them have specific dissolution specification in either United States Pharmacopoeia (USP) or Food and Drug Administration (FDA) Dissolution Methods Database [1].

A prudent approach for the development of new dissolution methodologies is to adapt the available monograph. The solubility profile of the API is one of the critical issues, but several other general principles of *in-vitro* tests must be approached. For the capsule formulation, USP1 (basket) apparatus seems to be the method of choice, but USP2 (paddle) apparatus can also be selected, with additional use of sinkers that prevent the floating phenomenon. The design of the sinkers can vary largely, according to the manufacturer or compendial specifications, the selection criteria being based on the ability to induce an unconstrained opening of the capsules shell, without entrapping any fraction of content [2].

Concerning the pharmaceutical suspensions, there is a high variability in terms of testing conditions, especially the rotation speed and the procedures for introduction of the dosage form in the dissolution vessels [3]. In this particular case, the release rate is dependent on the viscosity of the vehicle, controlling the access of the dissolution media to the dispersed particles of API.

In this context, cefaclor is a highly relevant case, since it is available as immediate or modified release oral dosage forms [4], covering a considerable interval of dose strengths (125 - 750 mg). Previous reports indicated a variable solubility throughout the physiological range of the gastro-intestinal pH (simulated by compendial buffer systems, [5]). Two USP monographs are available, none of which address the case of suspensions. The current paper presents the results of dissolution tests performed on available formulations according to the current recommendations and by implementing specific adaptations, based on the particularities of the vehicle. We focused our analysis on the ability of *in vitro* methodologies to discriminate the difference in both composition and drug release mechanism.

Materials and Methods

The compendial recommendations [6, 7] were initially applied for *in vitro* dissolution testing of available oral formulation of cefaclor. The set of 7 hard-gelatine capsule formulations (250, 500 mg), 8 suspensions (125, 250

mg) and 4 modified-release, film coated tablets (375, 500 and 750 mg) is presented in table I. In a second stage, alternative methodological approaches were implemented. For capsules, helix (23 x 12 mm) and Japanese Pharmacopoeia sinkers were used, for preventing the floating phenomenon, but also for comparing of data variability. The dissolution media was water for immediate release formulations, while tablets were evaluated on USP1 and 2 apparatus, in acidic condition (hydrochloric acid 0.1N). Due to the lack of official monograph, the *in vitro* drug release conditions for suspensions were selected by simple extension of the parameters implemented previously for capsules (media, stirring rate). The powder was dispersed in the indicated volume of water, then the package was shaken for 5 minutes. 5mL of suspension were slowly introduced at the bottom of vessels, using a 10 cm syringe with 2 mm wide orifice. All tests were performed in triplicate, at 37°C, in 900 mL of degassed media, using a Hanson SR8Plus dissolution tester (Hanson Research Inc., USA). Samples of 5 mL were collected and filtrated through immersed cannula filters (10 µm pore size). The sample volume was replaced with fresh media.

Quantitative evaluations of cefaclor performed after the appropriate dilution of samples with the corresponding media, using validated spectrophotometric methods ($\lambda=264$ nm for water and 267 nm for hydrochloric acid 0.1N; 8453 Pharmaceutical UV-visible system, Agilent Technologies, with Multicell Transport systems and General Purpose UV-Vis Software, Rev.B.04.01).

Hydrochloric acid 37% and cefaclor were purchased from Sigma-Aldrich. The purified water was generated by a SGW Ultraclear UV PlusTM system.

The dissolution profiles were analyzed using official dissolution metrics (difference and similarity factors, f1 and f2 [8]). The impact of various methodological parameters was assessed by calculating the dissolution efficiency, DE [9]:

$$DE_t = \frac{\int_0^t y dt}{y_{100} \cdot t} \cdot 100\%$$

where y is the fraction dissolved and t is the time

Table I
Identification of dosage forms and description of dissolution test parameters

Formula	A	B	C	D	E	F	G	H	I	J
Dosage form	capsules				suspension				film coated tablets	
Mechanism of release	immediate				modified					
Dose (as monohydrate, mg)	250	500	500	500	125	250	125	250	375	500
Batch	7081211	7071211	792L	414M	AX5885	AT6238	*	500411	550411	BG2398
microcrystalline cellulose PH 101	V	V	V	V	V	V	V	V	V	V
talcum	V	V	V	V	V	V	V	V	V	V
anhydrous colloidal silicon dioxide	V	V	V	V	V	V	V	V	V	V
stearic acid	V	V	V	V	V	V	V	V	V	V
magnesium stearate	V	V	V	V	V	V	V	V	V	V
dimethicone	V	V	V	V	V	V	V	V	V	V
sodium croscarmellose	V	V	V	V	V	V	V	V	V	V
sodium laurylsulphate	V	V	V	V	V	V	V	V	V	V
methyl-cellulose	V	V	V	V	V	V	V	V	V	V
corn starch	V	V	V	V	V	V	V	V	V	V
guar galactomannan	V	V	V	V	V	V	V	V	V	V
xanthan gum	V	V	V	V	V	V	V	V	V	V
simethicone emulsion	V	V	V	V	V	V	V	V	V	V
citric acid, anhydrous	V	V	V	V	V	V	V	V	V	V
sucrose	V	V	V	V	V	V	V	V	V	V
sugar	V	V	V	V	V	V	V	V	V	V
yellow iron oxide	V	V	V	V	V	V	V	V	V	V
quinoline yellow	V	V	V	V	V	V	V	V	V	V
erythrosine aluminum lake	V	V	V	V	V	V	V	V	V	V
flavor	V	V	V	V	V	V	V	V	V	V
lactose monohydrate	V	V	V	V	V	V	V	V	V	V
hydroxypropyl cellulose	V	V	V	V	V	V	V	V	V	V
hydroxypropyl methylcellulose	V	V	V	V	V	V	V	V	V	V
manitol	V	V	V	V	V	V	V	V	V	V
methacrylic acid copolymer type C	V	V	V	V	V	V	V	V	V	V
Stirring rate (rpm)	50				50 / 100					
Equipment	USP 2 (lateral stainless steel helix / Japanese sinker)				USP 2					
Media composition (900 mL)	water				USP 2 / USP 1 (40 mesh)					
Sampling (minutes from beginning)	5, 10, 15, 20, 30, 45, 60				hydrochloric acid 0.1N					
Test duration (min)	60				30, 60, 90, 120, 150, 180, 240					

* - pilot scale capsule formulation, developed in our laboratory.

Results and Discussion

The general aspect of the dissolution profiles indicates a rapid release of cefaclor (more than 85% of the labeled amount in 30 minutes) for capsules and suspensions, independent of the dose and testing conditions. There is an obvious similarity between the two strengths of the same product and a reduced variability of the data (coefficient of variation, lower than 10% for all sampling times). This indicates that the two types of sinkers used for preventing the floating phenomenon of hard-gelatin capsules generated a comparable, homogenous distribution of the powder content into the dissolution vessels (figure 1). The rapid release rates induced high values of dissolution efficiency in 60 minutes - DE_{60} (77 to 99%).

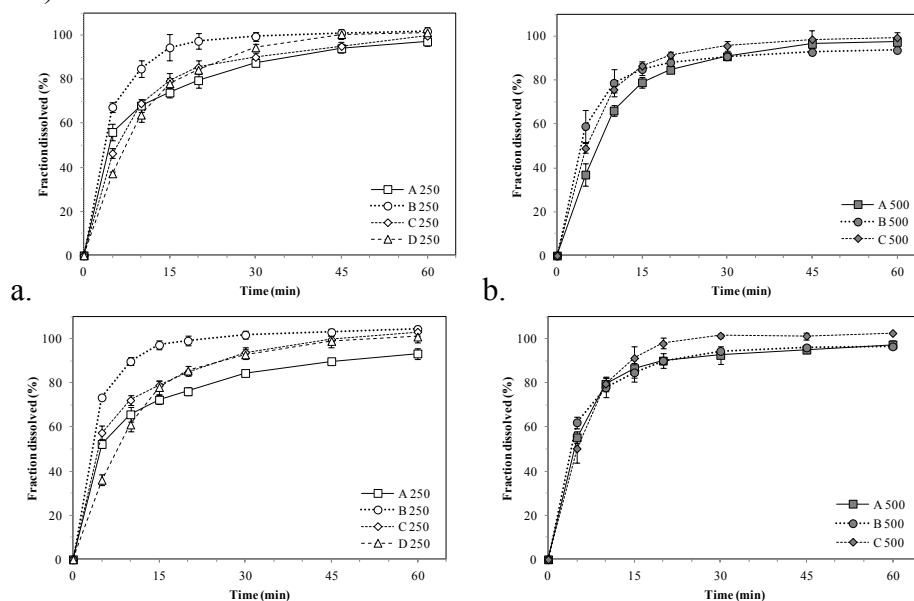


Figure 1.

Dissolution profiles of cefaclor from immediate release capsules
 a. stainless steel helix sinkers; b. Japanese sinkers.

For suspensions, the selection of an intermediate stirring rate provided an accurate discriminatory power for the detection of composition differences (the lowest value of similarity factor, f_2 , being 21.61). For example, the fraction released after 10 minutes varied between 50 and 100% (Figure 2). The mean profiles indicate a complete dissolution after 30 minutes, theoretically complying with the compendial recommendations for capsules. According to the visual observations, the viscosity of the vehicle controls the *in vitro* drug release, the API presenting a high solubility in

water. The dispersion of the semisolid vehicle is the limiting step for the dissolution of cefaclor. Formulation H and G behave as fast and, respectively, slow release dosage forms, independent on strength.

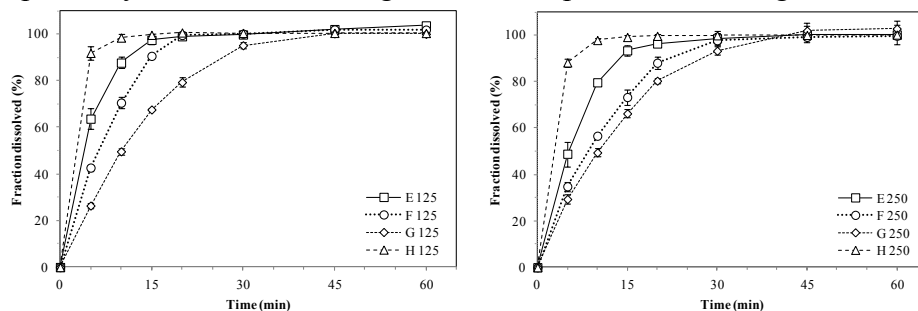


Figure 2.

In vitro drug release of cefaclor from suspensions

In the case of modified release patterns, it is to be mentioned that compendial testing conditions provided a faster release, compared to the paddle apparatus at low stirring rates (Figure 3).

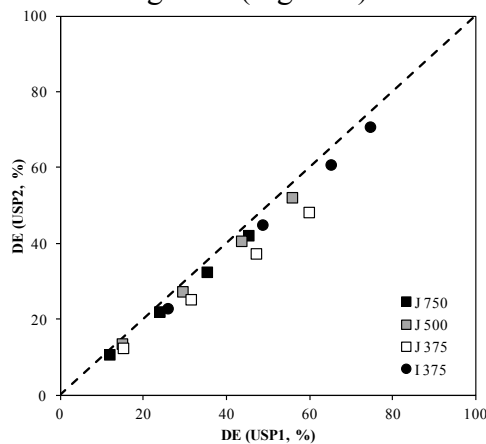


Figure 3.

Comparison of dissolution efficacy for modified-release film coated tablets
(time intervals: 60, 120, 180 and 240 minutes)

One of the formulations (I 375) presented an atypical profile, with disregard of the limits for the fraction released at the intermediate time point (51.2% of the labeled amount dissolved in 60 minutes, compared to the pharmacopoeial acceptance interval of 20 to 50%; Figure 4). Nevertheless, the differences induced by the two methodological approaches are minor, at the selected stirring rates, so it is reasonable to assume that, in this case, the

paddle apparatus can provide similar information on the quality and prospected performance.

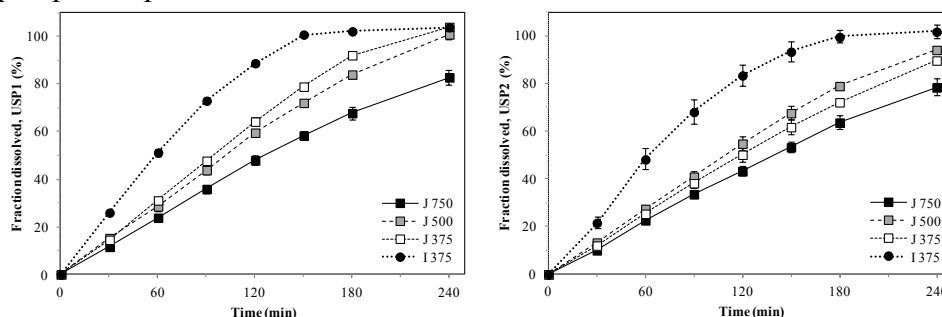


Figure 4.

In vitro drug release of cefaclor from modified release film-coated tablets

It is still controversial if cefaclor should be considered a high solubility, low permeability drug [5, 10]. The higher release rate of immediate release dosage forms, independent of the dose, indicates an *in vivo* biopharmaceutical behavior similar to solutions. Therefore, the absorption profile is dependent only on the permeability properties of the active entity, encoded by the structural (physico-chemical) characteristics. There are several reports addressing the biowaiver issues for Biopharmaceutical Classification System (BCS) class III drugs [11]. In the same time, this type of regulatory procedures can be presumably applied only if excipients display "uncritical" profiles [12], e.g. they don't affect physiological transit times of the gastro-intestinal segments, local permeability or metabolic processes. The composition of suspensions includes several tensioactive agents and poly-alcohols with proven impact on drug dissolution and/or active transport [13]. So, it seems to be more difficult to support the idea of *in vitro* testing as a surrogate for bioequivalence in case of suspensions, compared to capsule formulations. Nevertheless, the compendial recommendations must be implemented mainly as quality control procedures, with reduced biological relevance.

Conclusions

The tested immediate release formulations of cefaclor displayed a rapid and complete release, when tested according to compendial specifications. The dissolution profiles of hard gelatin capsules were independent on dose strength and were not dependant on the sinker design, with low variability of the data. Methodological adaptations for suspensions were implemented and provided accurate discriminatory power for the

obvious differences in the qualitative and quantitative composition. The viscosity of the vehicle could be considered as the main structural factor controlling the release rate. For the modified release film-coated tablets, the use of paddle apparatus at a lower stirring rate provided similar dissolution profiles, compared to official recommendations.

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