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CA 2420712 C 2009/07/07

(11)(21) **2 420 712**

(12) **BREVET CANADIEN
CANADIAN PATENT**

(13) **C**

(22) Date de dépôt/Filing Date: 2003/03/03

(41) Mise à la disp. pub./Open to Public Insp.: 2003/09/04

(45) Date de délivrance/Issue Date: 2009/07/07

(30) Priorité/Priority: 2002/03/04 (EP02386005.9)

(51) Cl.Int./Int.Cl. *A61K 31/546* (2006.01),
A61K 9/20 (2006.01), *A61K 9/22* (2006.01),
A61K 9/46 (2006.01), *A61K 9/28* (2006.01)

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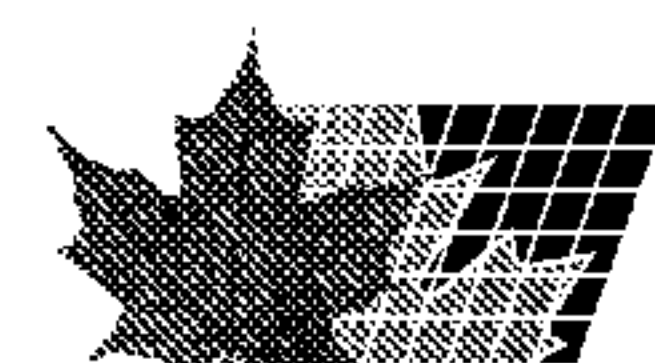
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(54) Titre : COMPOSES DE CEFUROXIME AXETIL A LIBERATION RAPIDE

(54) Title: FAST RELEASE CEFUROXIME AXETIL COMPOSITIONS

(57) Abrégé/Abstract:

Fast release formulations of CefuroximeAxetil based on agents effecting channel formation through the matrix in order to avoid gelatination, and rapidly dissolved coating effected by incorporation of a surfactant into a water-soluble polymer.



ABSTRACT

Fast release formulations of CefuroximeAxetil based on agents effecting channel formation through the matrix in order to avoid gelatination, and rapidly dissolved coating effected by incorporation of a surfactant into a water-soluble polymer.

TITLE

FAST RELEASE CEFUROXIME AXETIL COMPOSITIONS

5 **FIELD OF THE INVENTION**

This innovation concerns a formulation of a fast release dosage form of Cefuroxime Axetil, which provides optimized release of the drug according to the dissolution profile limits of the USP

10

In treatment of the respiratory tract infections fast release dosage formulations are particularly necessary in order to achieve high plasma therapeutic levels in as short a time as possible.

15 Specifically, the innovation constitutes a fast release pharmaceutical composition comprising an effective amount of Cefuroxime Axetil, as an active ingredient, an alkaline carbonate, a polycarboxylic acid as a buffering agent, and at least one excipient, wherein said composition is in a tablet form and comprises from 20 % to 90 % by weight of said Cefuroxime Axetil and from 0,1 % to 10 % by weight of said alkaline
20 carbonate.

BACKGROUND OF THE INVENTION:

Cefuroxime Axetil, the 1-acetoxyethyl ester of Cefuroxime (1-acetoxyethyl-(6R,7R)-3-carbamoyloxymethyl-157-[(Z)-2-(fur-2-yl)-2-methoxyiminoacetamido]ceph-3-em-4-carboxylate), is the orally bioavailable form of the broad spectrum antibiotic Cefuroxime.

Prior art reveals substantial difficulties in producing oral solid formulations of
30 Cefuroxime Axetil providing high bioavailability. Amorphous Cefuroxime Axetil, which has been disclosed in patent EP 0107256, is more soluble in aqueous media than the crystalline form, but shows a strong tendency to gel formation, leading to low dissolution profiles. Several innovations in order to overcome this problem include controlling of the film coat rupture time and using a tablet core rich in a super disintegrant (EP
35 0223365), converting Cefuroxime Axetil to a "non-gelatinous" form of solid solution or

dispersion (WO 0030647), or to a co precipitate with a water-soluble excipient (WO 9908683) etc.

WO-A-9962559 discloses a tablet made by compression of granules comprising
5 Cefuroxime Axetil and sorbitol mixed with crospovidone, sodium carbonate, magnesium stearate and colloidal silicon dioxide.

As mentioned above the critical factor for the bioavailability of the active material, Cefuroxime Axetil tablet compositions is the disintegration of tablet core leading to a
10 poor dissolution of drug in the medium.

The reasons for this are the physical properties of Cefuroxime Axetil. The drug forms a gelatinous mass at 37°C, which does not allow aqueous media to penetrate into the tablet matrix. This mechanism leads to a long disintegration time and thus, to
15 poor dissolution, and poor absorption of Cefuroxime Axetil by gasrtointestinal tract. Moreover, coatings applied on tablet core, in order to mask bitter taste of drug, intensify slow release of Cefuroxime Axetil as well.

The EP 0223365 describes a method of preparation of film coated tablets, in order to
20 avoid slow release profiles of the drug. According to this patent, a super disintegrant (cross-carmellose sodium) is used in the matrix, whilst the tablets are coated with a specific polymer (hydroxypropylmethylcellulose 5 cps or 6 cps) which is ruptured in less than 40 seconds from tablet core.

25 The release profile of formulation in the EP 0223365 is according to dissolution profile limits mentioned in USP for Cefuroxime Axetil tablets.

SUMMARY OF THE INVENTION

30 The present invention, has been made in view of the foregoing circumstances and is intended to provide, at least, a matrix with an optimum disintegration time, avoiding the formation of gelantinous layer, and a coating based on soluble polymers and surfactants in order to improve water penetration, and capable of masking the bitter taste of Cefuroxime Axetil.

35

A preferred embodiment according to the present invention relates to a fast release formulation of Cefuroxime Axetil tablet formulation comprising approximately 20% to 90% Cefuroxime Axetil by weight in a combination with approximately 0.1% to 10% of alkaline carbonates, buffered at pH less than 6.5 using a polycarboxylic acid from
5 approximately 1% to 30% for the justification of the galenical formulation.

In a particular case, the fast release formulation may also contain a quantity of an insoluble disintegrant from approximately 3% to 50% by weight. In particular, the insoluble disintegrant may be cross linked polyvinyl-pyrrolidone (Crospovidone).

10

In this particular case, tablets may be coated with from approximately 2% to 4% of total formulation weight of film coating comprising from approximately 65% to 85% by weight of film coating of soluble polymers and from approximately 2% to 6% surfactant.

15

In another particular case, the fast release formulation may include from approximately 20% to 90% Cefuroxime Axetil by weight, from approximately 0.1% to 10% alkaline carbonate (e.g. Sodium Bicarbonate), from approximately 5% to 40% sugar alcohol (e.g. Mannitol, Sorbitol), from approximately 3% to 50% disintegrant (Crospovidone),
20 from approximately 1% to 30% polycarboxylic acid (e.g. citric acid or tartaric acid) and from approximately 1% to 10% surfactants (e.g. Sodium Lauryl Sulfate).

In another particular case, a fast release formulation Cefuroxime Axetil tablet may be coated with a film comprising from approximately 20% to 99% by weight of soluble
25 polymers (e.g. PVA, PEG etc.) and from approximately 1% to 20% surfactant (e.g. Sodium Docusate), and the said coating represents from approximately 1% to 5% of the total formulation weight.

In another particular case, the fast release formulation includes from approximately
30 55% to 75% Cefuroxime Axetil by weight, from approximately 8% to 15% sugar alcohol, from approximately 10% to 20% disintegrant, from approximately 1% to 5% alkaline carbonates and from approximately 1% to 5% surfactants.

In another particular case, a fast release formulation of Cefuroxime Axetil tablet may use a type of sugar disintegrant such as Polyvinylpyrrolidone, Sodium Carboxymethylcellulose, Sodium Carboxymethyl Starch, etc.

- 5 In a particular case, a fast release formulation of Cefuroxime Axetil tablet may include a composition using alkaline carbonates such as Sodium Bicarbonate, Potassium Bicarbonate, etc.

10 In a particular case, a fast release formulation of Cefuroxime Axetil tablet may use surfactants such as Sodium Lauryl Sulfate, Sodium Docusate, etc.

In a particular case, a fast release formulation Cefuroxime Axetil tablet may be coated with water soluble polymers such as Polyvinylpyrrolidone, Polyethylenglycol, Polyvinylalcohol, etc.

15

In a particular case, a fast release formulation Cefuroxime Axetil tablet may be coated with soluble polymers in combination with surfactants such as Sodium docusate, Tween, etc.

- 20 In a particular case, a fast release formulation of Cefuroxime Axetil tablet may include the dissolution of tablets according to the USP Pharmacopoeia.

Another preferred embodiment according to the present invention relates to fast release formulation of Cefuroxime Axetil tablet using all types of sugar alcohols such as
25 Mannitol, Sorbitol etc.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a chromatogram showing the No Buffered Composition after 3 days.
30

Figure 2 is a chromatogram showing the Buffered Composition after 6 months.

Figure 3 is a graph showing Mean plasma concentrations.

- 35 Figure 4 is a graph showing the Dissolution Profile of Example 1.

Figure 5 is a graph showing the Dissolution Profile of Example 2.

DETAILED DESCRIPTION OF THE INVENTION

5

The present invention, concerning a fast release formulation containing Cefuroxime Axetil as the active drug component, was focused on:

- 10 1) Preparation of a matrix with an optimum disintegration time, avoiding the formation of the gelatinous layer.
- 2) Preparation of a coating based on soluble polymers and surfactants in order to improve water penetration, and being capable to mask the bitter taste of Cefuroxime Axetil.

15

More details are described below: Cefuroxime Axetil possesses poor flow properties and the fact that it has to be present in the final composition in high amounts relatively to the other excipients suggests that a process of improving the flow properties of the whole mixture is necessary. The manufacturing process of dry granulation, which includes slugging and dry granulation through sieve, and secondly compression was selected so that the active substance is not exposed to conditions that could have a negative impact on the stability such as kneading and drying.

20

25 1) CORE - FORMULATIONS

30

In the course of this investigation it was found that partially water-soluble disintegrants (e.g. starch 1500, Primogel™ etc.) lead directly to the formation of a gelatinous mass, thus intensifying disintegration times to more than 30 min. and resulting in slow dissolution profiles.

35

The use of extra quantities of a surfactant such as Sodium Laurul Sulphate (SLS) did not improve the disintegration of prepared tablets. The disintegration time was more than 12 min.

The combination of disintegrants partially soluble and insoluble in water (Primogel™ - Crospovidone,1:1) improved disintegration time (7 min.), but gel formation still occurred.

- 5 The use of water insoluble Crospovidone as a disintegrant in combination with a sugar alcohol(e.g. mannitol, sorbitol etc) as a filler reduced disintegration time to 5 minutes.

All of the above compositions contained Aerosil™, Sodium Lauryl Sulphate and Magnesium Stearate as lubricants. However, Magnesium Stearate was found to have a
 10 negative effect on the disintegration and dissolution properties due to its hydrophobic character. For this reason it was avoided from the remainder of the trials and was replaced by Talc.

Although the disintegration time was satisfactory, the dissolution profile was not
 15 acceptable because a gel layer continued to form, preventing water penetration throughout the whole mass of the matrix. Therefore the quantity of the disintegrant in the center of the matrix was not working, as insufficient contact with the water was occurring, in order for it to swell and consequently act in the desired manner.

- 20 The formation of channels throughout the matrix, following contact of the matrix with water, is necessary for water penetration throughout the whole mass of the matrix. This mechanism leads to rapid action of the disintegrant and rapid disintegration time.

For the formation of these channels, alkaline carbonate salts (e.g. sodium
 25 bicarbonate, potassium bicarbonate) have been used in quantities from 0.1% to 10 %. Their effect is based on the following indicative reaction:



- 30 The produced CO₂ is the factor, which forms the above-mentioned channels. The use of the surfactant Sodium Lauryl Sulphate improves water penetration by reducing surface tensions.

The use of carbonates in oral pharmaceutical formulations belongs to prior art.
 35 Nevertheless, it was found that the drug substance is not compatible with the

carbonates. Specifically, when the formulation was exposed under accelerated (40%, 75% RH) stability conditions a high degree of decomposition was observed. As it is clearly shown in the chromatogram (fig.1) extended degradation in quite short time occurs under accelerated conditions when the composition is not pH buffered. On the contrary, the formulation proves to be very stable for long time under accelerated conditions (fig.2) when buffering agents are incorporated. The same results came also for normal stability conditions.

The chemical explanation of the decomposition is that Cefuroxime Axetil is sensitive in alkaline conditions. More specifically, under alkaline pH conditions hydrolysis of the β -lactamic ring and of the carbamide group in C3 position. When alkaline carbonates are added in the formulation, the environment of the Cefuroxime Axetil becomes alkaline, which results in poor stability of Cefuroxime Axetil over time. A pharmaceutical composition has to be stable over time so that the pharmacological activity is maintained and no degradation products that may be dangerous or toxic for human are formed. As the above results are unacceptable, more investigation in different pH values were performed. For the achievement of these different pH values a buffering agent was added in the formulation. Polycarboxylic acids such as citric or tartaric acid and other pharmaceutically acceptable acids such as ascorbic acid were incorporated as a buffering agent. The target was a pH $\approx$ 4.5, when one tablet is diluted in 10mL of water. This pH value, achieved by the combination of alkaline carbonate salts with polycarboxylic or other pharmaceutically acceptable acids, is well within the region of pH where the hydrolysis constant of Cefuroxime shows its lowest value resulting in maximum stability. Furthermore this combination enhance the mode of action of the carbonate salts in the formation of channels. This reaction is very critical for the vivo repeatability of the disintegration of the product. Specifically, pH value for the gastric fluid varies up to a limited pH of 8 in the patients with active ulcer. In this case the action of carbonates is limited and the repeatability of the product is not acceptable. This matrix shows an autonomous action, independent of the gastrointestinal pH conditions and this autonomy in action is classified as very critical for the quality of the product. The resume of the present invention is firstly the achievement compatibility between cefuroxime Axetyl and carbonate salts using the suitable quantities of polycarboxylic acids and secondly the combination of the said substances with the suitable ingredients as described above in order to form a stabilized bioavailable, fast release composition.

Additionally, a novel coating mixture was investigated as described in the next paragraph in order to eliminate the negative effect of the coating material to the disintegration of the product.

5

2) COATING

The EP 0223365 claims the use of a coating material, specifically Hydroxypropylmethylellulose 5 or 6. Apparently the patent uses the term "rupture" because the mentioned polymers are slowly dispersed in water, giving colloidal
10 dispersions so the polymer is "ruptured" before their solubilization.

In order to obtain more rapid disintegration of tablets, several other water-soluble coating polymers have been tested instead of Hydroxypropylmethylcellulose, such as
15 PEG, PVA and PVP. These soluble polymers in combination with a surfactant have been used, in order to improve water penetration.

Specifically a coating based on soluble polymers such as Polyvinylpyrrolidone (PVP K 30) has been developed in combination with a surfactant such as Sodium Docusate. The
20 surfactants work in two ways:

- Lead to a rapid dissolution (not "rupture") of the coating (less than 10 sec).
- Improve water penetration directly to the mass of the core. In this way the problem of the formation of the gelatinous mass, which is observed in
25 conventional coatings, is completely avoided.

The dissolution time of the films prepared as above is less than 10 seconds.

IN VITRO TESTS-Dissolution of the coated tablets

30

The dissolution characteristics of the coated tablets prepared according to the present invention, as described above and further exemplified hereafter in the examples, were tested according to the method set forth in the monograph of Cefuroxime Axetil tablets in USP 23. Average results of dissolution tests of the coated tableted prepared according
35 to the present invention are the following.

Dissolution According to USPXXII I: 75% in 15 min(USP Limit: at least 60%)
 85% in 30min
 91 % in 45 min (USP Limit: at least 75 %)

5

The other tests, such as assay, impurities, friability, compressibility and stability are acceptable.

IN VIVO TESTS- Bioavailability of the coated tablets

10

All the in vitro tests (disintegration, dissolution) concerning or related to the ability of Cefuroxime Axetil to be released from the tablet core and to be available in the gastrointestinal tract to be absorbed, were confirmed by in vivo study in healthy volunteers. In specific, the study was designed and conducted in compliance with the EMEA (European Agency for the Evaluation of Medicinal Products) guidelines, subsection CPMP/EWP/QWP/1401/98, on the investigation of bioavailability and bioequivalence (London 26 2001).

In this bioavailability assessment study, the objective was to determine bioavailability and pharmacokinetic variables of the said formulation following oral administration. Twenty-four male and female volunteers participated in the study while cefuroxime concentrations were determined in blood samples drawn after administration.

Pharmacokinetic variables under study were:

1. Maximum concentration of cefuroxime, $C_{\max}$
2. Time of maximum concentration of cefuroxime, $T_{\max}$
3. The area under the cefuroxime plasma concentration versus time curve (AUC)
4. Elimination half-life of cefuroxime, $T_{1/2}$
5. k_{el} : constant of the terminal elimination rate, estimated after In-linear regression of the points following $T_{\max}$

Bioavailability was assessed based on the results of AUC and $C_{\max}$. Means plasma concentrations versus time are shown in fig 3.

All the variables measured were found not statistically different from known published values from respective studies while the variability was found to be acceptable after statistical evaluation.

5

Example 1 (Mannitol Formula)

CEFUROXIME 500 mg/TAB

	Cefuroxime Axetil	602.0 mg
10	Mannitol	76.0 mg
	Citric acid	20.0 mg
	Crospovidone	140.0 mg
	Talc	24.0 mg
	Sodium Lauryl Sulphate	20.0 mg
15	Sodium Bicarbonate	20.0 mg
	Aerosil™	<u>2.0 mg</u>
	Total weight	904.0 mg

The other strengths are linear to the above.

20

Manufacturing process is described below.

This formulation gave the following results:

25	Hardness	112 Nt
	Disintegration (uncoated tablets)	40 seconds

Coating:

	PVP	24.0 mg
30	Sodium Docusate	1.2 mg
	Propylene Glycol	0.021 mg
	Titanium Dioxide	6.4 mg
	Solvent	<u>Ethanol</u>
	Total coating weight per 500 mg tablet	31.62 mg

35

Coating Dissolution < 10 seconds.

Total Tablet Weight 935.62 mg

- 5 Dissolution Profile of Example 1 is shown in Figure 4 to have the following profile:

	<u>TIME(min)</u>	<u>% RELEASED</u>
	5	70.13
	10	84.06
10	15	88.57
	20	89.64
	30	92.8
	45	93.17

- 15 Example 2 (Sorbitol Formula)

CEFUROXIME 500 mg/TAB

	Cefuroxime Axetil	602.0 mg
	Sorbitol	76.0 mg
20	Tartaric acid	20.0 mg
	Crospovidone	140.0 mg
	Talc	24.0 mg
	Sodium Lauryl Sulphate	20.0 mg
	Sodium Bicarbonate	20.0 mg
25	Aerosil™	<u>2.0 mg</u>
	Total weight	904.0 mg

The other strengths are linear to the above.

- 30 Manufacturing process is described below.

This formulation gave the following results:

	Hardness	128 Nt
35	Disintegration (uncoated tablets)	42 seconds

Coating:

	PVP	24.0 mg
	Sodium Docusate	1.2 mg
	Propylene Glycol	0.021 mg
5	Titanium Dioxide	6.4 mg
	Solvent	<u>Ethanol</u>
	Total coating weight per 500 mg tablet	31.62 mg

Coating Dissolution < 10 seconds.

10

Total Tablet Weight 935.62 mg

Dissolution Profile of Example 2 is shown in Figure 5 to have the following profile:

15	<u>TIME(min)</u>	<u>% RELEASED</u>
	5	66.8
	10	81.4
	15	90.2
	20	91.8
20	30	93.8
	45	94.2

Manufacturing Process

25 Manufacturing Process

• Weighing

	Cefuroxime Axetil	602 mg
	Mannitol or Sorbitol	76 mg
30	Citric or Tartaric acid	20 mg
	Crospovidone	100 mg
	Talc	12 mg
	Sodium Bicarbonate	12 mg
	Sodium Lauryl Sulphate	10 mg

35

- Sieving and Mixing
- Slugging
- Granulation

5 This product is the INTERNAL phase

- Weighing

10	Crospovidone	40 mg
	Talc	12 mg
	NaHCO ₃	8 mg
	Sodium Lauryl Sulphate	10 mg
	Aerosil™	2 mg

- Sieving and Mixing

- 15
- This product is the EXTERNAL phase
 - Mixing of INTERNAL AND EXTERNAL PHASE
 - Tableting
 - Coating

20 In the following examples several coating materials based on soluble polymers in combination with a surfactant were applied on the cores described above in the examples 1 and 2.

Example 3 (PVA coating)

25

The cores were produced according to Example 1

30	PVA	24 mg
	Sodium Docusate	1.2 mg
	Propylene Glycol	0.021 mg
	Titanium Dioxide	6.4 mg
	Solvent	Ethanol
	Total coating weight per 500 mg tablet	31.62 mg

35 COATING DISSOLUTION <10 sec

Example 4 (PEG coating)

The cores were produced according to Example 1

5

	PEG	24 mg
	Sodium Docusate	1.2 mg
	Propylene Glycol	0.021 mg
	Titanium Dioxide	6.4 mg
10	Solvent	Ethanol
	Total coating weight per 500 mg tablet	31.62 mg

COATING DISSOLUTION <10 sec

15 Example 5 (TWEEN™ 80 coating)

The cares were produced according to Example 1

	PVP	24 mg
20	TWEEN™ 80	1.2 mg
	Propylene Glycol	0.021 mg
	Titanium Dioxide	6.4 mg
	Solvent	Ethanol
	Total coating weight per 500 mg tablet	31.62 mg

25

COATING DISSOLUTION <10 sec

Example 6 (Poloxamer coating)

30 The cores were produced according to Example 1

	PVP	24 mg
	Poloxamer (F 68)	1.2 mg
	Propylene Glycol	0.021 mg
35	Titanium Dioxide	6.4 mg

Solvent Ethanol
Total coating weight per 500 mg tablet 31.62 mg

COATING DISSOLUTION <10 sec

5

CLAIMS

We claim:

- 5 1. A fast release pharmaceutical composition comprising an effective amount of cefuroxime axetil, as an active ingredient, an alkaline carbonate, a polycarboxylic acid as a buffering agent, and at least one excipient, wherein said composition is in a tablet form and comprises from 20 % to 90 % by weight of said cefuroxime axetil and from 0.1 % to 10 % by weight of said alkaline carbonate.
- 10 2. The fast release pharmaceutical composition according to claim 1, wherein it further comprises a disintegrant.
3. The fast release pharmaceutical composition according to claim 2, wherein said
15 disintegrant is selected from the group of polyvinylpyrrolidone, sodium carboxymethylcellulose and sodium carboxymethyl starch.
4. The fast release pharmaceutical composition according to claim 2, wherein said disintegrant is water-insoluble.
- 20 5. The fast release pharmaceutical composition according to claim 4, wherein said disintegrant is crospovidone.
6. The fast release pharmaceutical composition according to claim 2, wherein it
25 further comprises a filler.
7. The fast release pharmaceutical composition according to claim 6, wherein the filler is a sugar alcohol.
- 30 8. The fast release pharmaceutical composition according to claim 7, wherein said filler is chosen from the group consisting of mannitol and sorbitol.
9. The fast release pharmaceutical composition according to claim 1, wherein said alkaline carbonate is selected from the group consisting of sodium bicarbonate and
35 potassium bicarbonate.

10. The fast release pharmaceutical composition according to claim 1, wherein said polycarboxylic acid is selected from the group of consisting of citric acid and tartaric acid.
- 5 11. The fast release pharmaceutical composition according to any one of claims 1 to 10, wherein said at least one excipient is selected from the group consisting of surfactants and lubricants.
- 10 12. The fast release pharmaceutical composition according to claim 11, wherein said surfactant is selected from the group consisting of sodium lauryl sulphate and sodium docusate.
- 15 13. The fast release pharmaceutical composition according to any one of claims 1 to 12, wherein it comprises from 20% to 90% by weight of said cefuroxime axetil, from 0.1 % to 10% by weight of said alkaline carbonate, from 5% to 40%, by weight of said sugar alcohol, from 3% to 50% by weight of said disintegrant, from 1% to 30% by weight of said polycarboxylic acid and from 1 % to 10% by weight of said surfactant.
- 20 14. The fast release pharmaceutical composition according to any one of claims 1 to 13, wherein it comprises from 55% to 75% by weight of said cefuroxime axetil, from 8% to 15% by weight of said sugar alcohol, from 10% to 20% by weight of said disintegrant, from 1 % to 5% by weight of alkaline carbonate and from 1 %, to 5% by weight of said surfactant.
- 25 15. The fast release pharmaceutical composition according to any one of claims 1 to 14, wherein said composition is in a tablet form and it further comprises a film coat which serves to improve the water penetration and to mask the bitter tastes of said cefuroxime axetil.
- 30 16. The fast release pharmaceutical composition according to claim 15, wherein said film coating being from 1% to 5% by weight of said total pharmaceutical compositions.

17. The fast release pharmaceutical composition according to claim 15, wherein said film coating comprises from 20% to 99% by weight of a soluble polymer and from 1 % to 20% by weight of a surfactant.
- 5 18. The fast release pharmaceutical composition according to claim 17, wherein said soluble polymer is chosen from the group consisting of PVA and PEG.
19. The fast release pharmaceutical composition according to claim 17, wherein said surfactant is sodium docusate.
- 10 20. The fast release pharmaceutical composition according to claim 15 wherein said film coating comprises a water soluble polymer.
21. The fast release pharmaceutical composition according to claim 20 wherein
15 said water soluble polymer is chosen from the group consisting of polyvinylpyrrolidone, polyethylenglycol and polyvinylalcohol.
22. The fast release pharmaceutical composition according to claim 15, wherein said film coating comprises a water soluble polymer in combination with a
20 surfactant.
23. The fast release pharmaceutical composition according to claim 22, wherein said surfactant is sodium docusate.

Pk#	Name	Retention Time	Area	Area Percent	ESTD concentration
	(Unknown(Cel. Acid))		0.000	BDL	
1	Unknown	4.400	16510	0.27	0.000
	(Unknown)		0.000	BDL	
2	Diastereoisomer B	9.233	3007409	19.23	11.1334
3	Diastereoisomer A	9.255	3061897	50.12	71.6378
	(D3 isomer 1&2)		0.000	BDL	
4	E isomer 1	13.942	11467	0.19	0.000
5	E isomer 2	15.725	9225	0.15	0.000

1 / 2

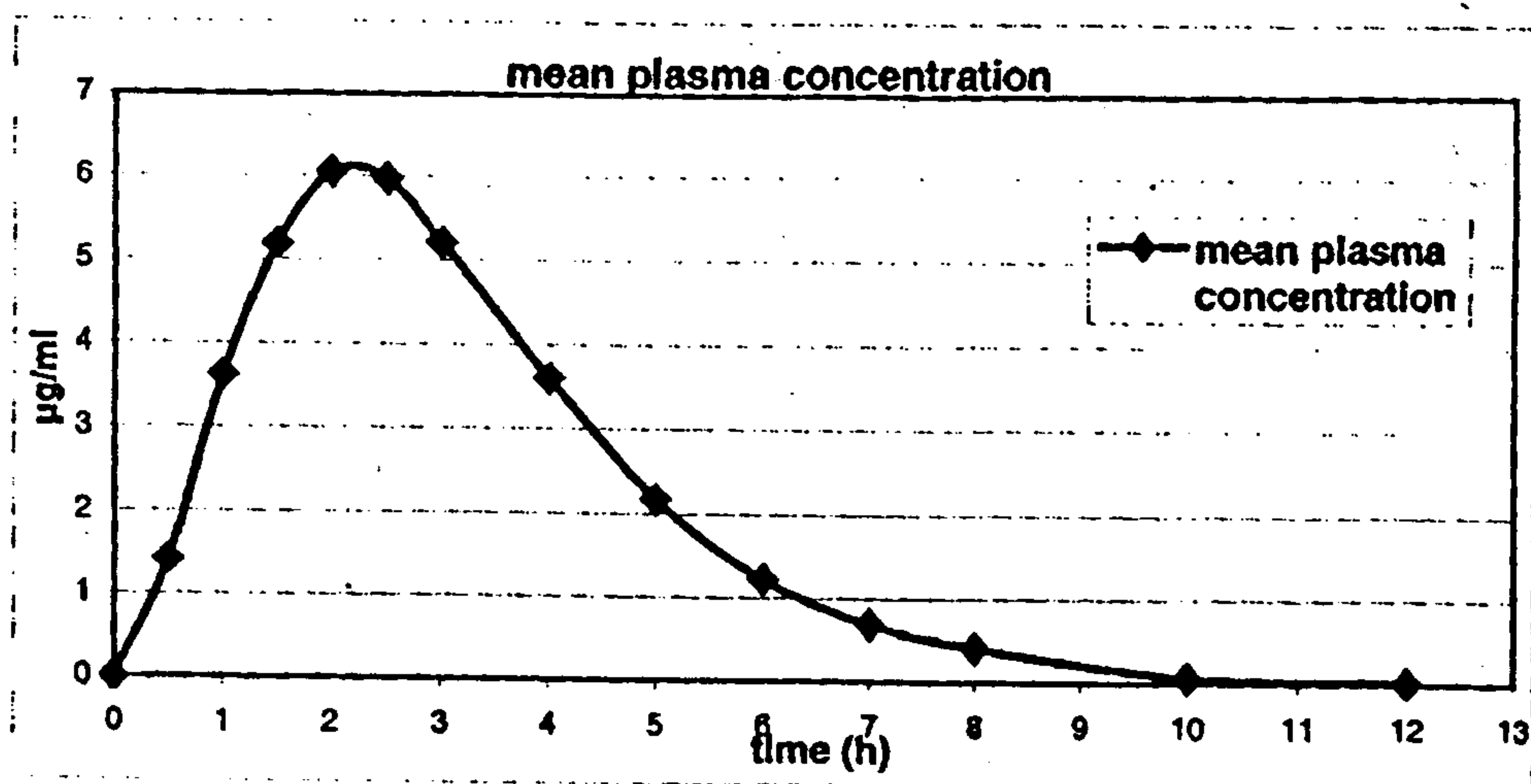


Fig. 3 Mean plasma concentrations

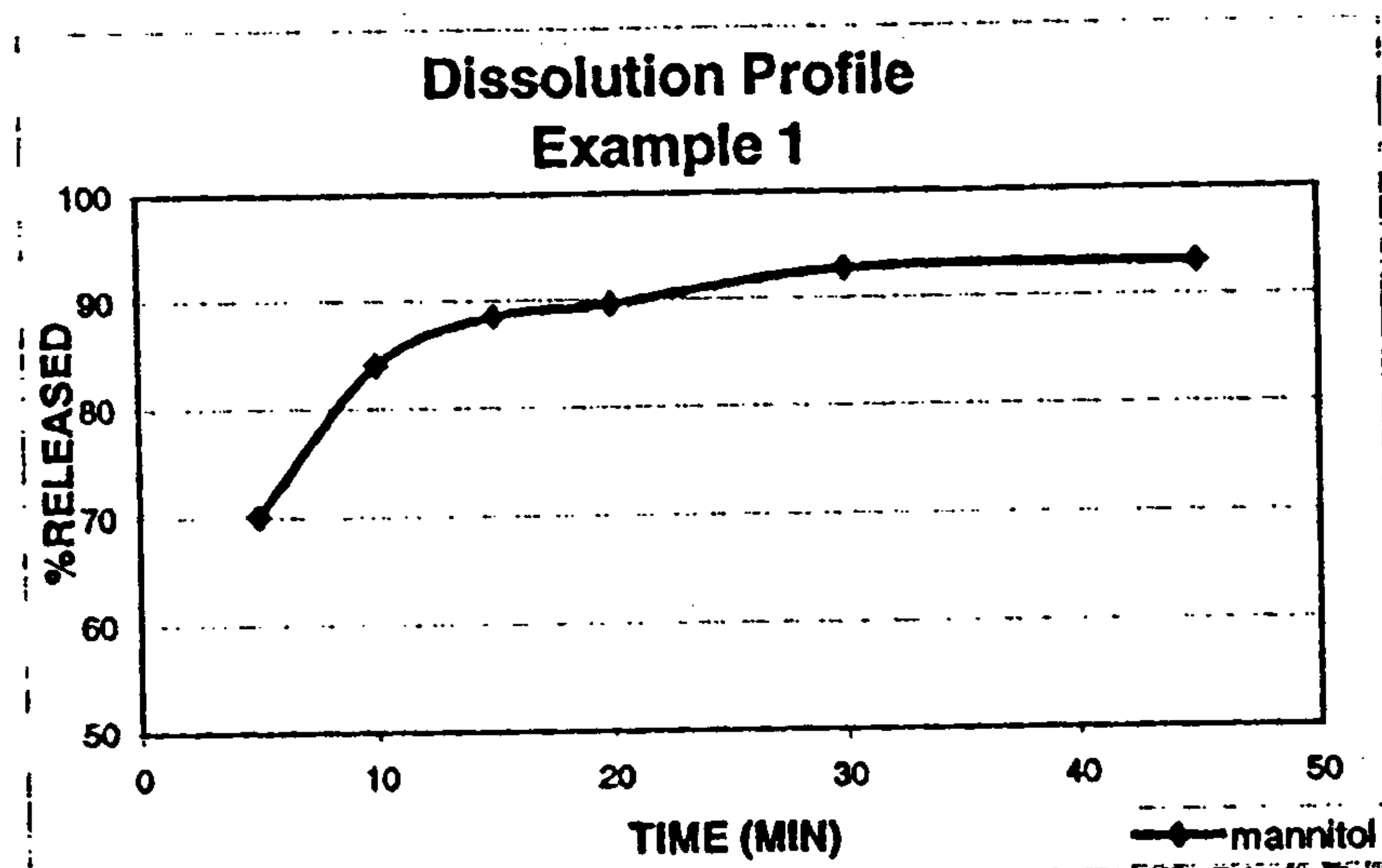


Fig. 4

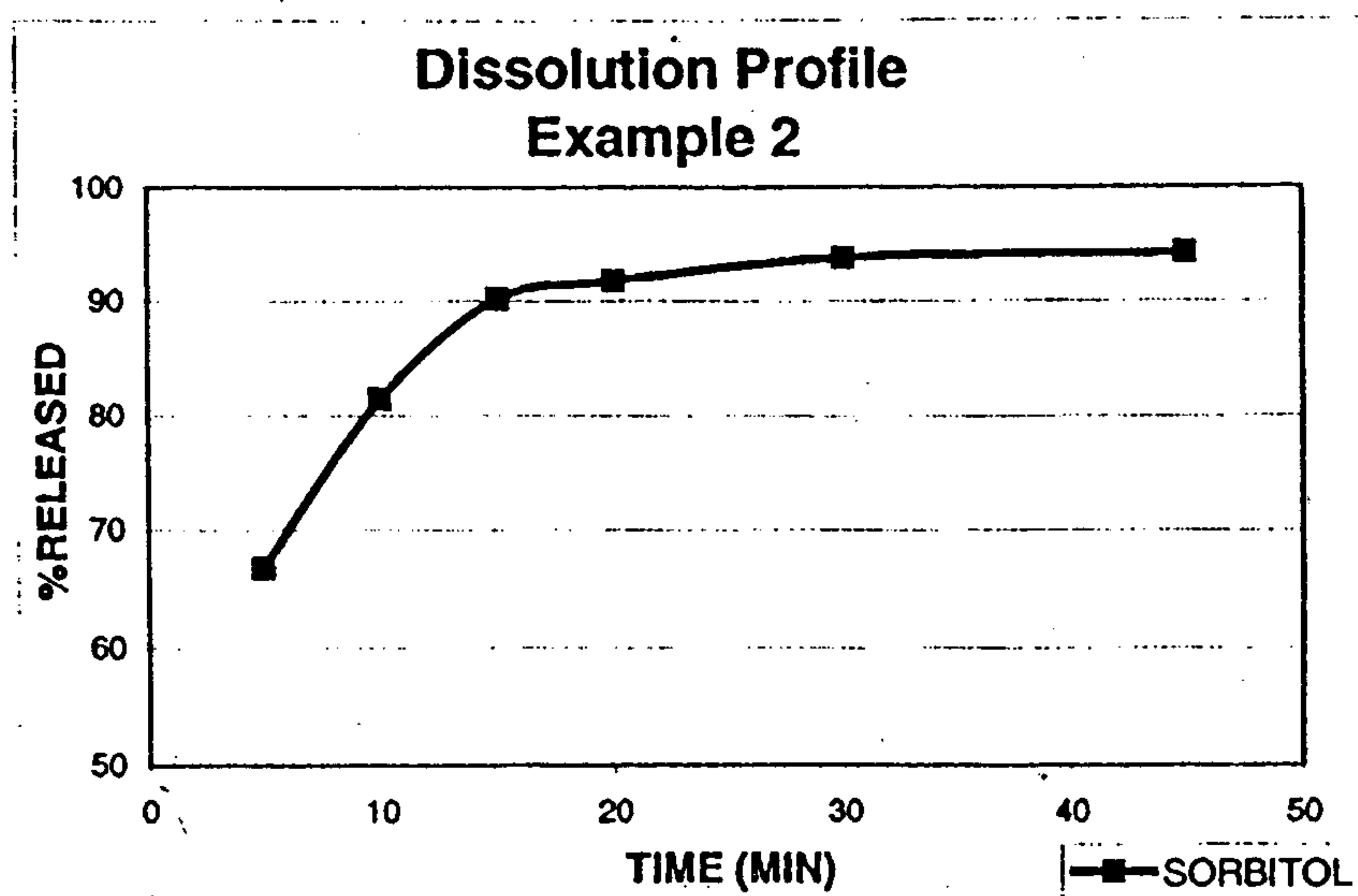


Fig. 5