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Research Article

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Preformulation Considerations for Controlled Release Dosage Forms: Part II—Selected Candidate Support

Frank Chrzanowski[1,2]

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Abstract. Practical examples of preformulation support of the form selected for formulation development are provided using several drug substances (DSs). The examples include determination of the solubilities *vs*. pH particularly for the range pH 1 to 8 because of its relationship to gastrointestinal (GI) conditions and dissolution method development. The advantages of equilibrium solubility and trial solubility methods are described. The equilibrium method is related to detecting polymorphism and the trial solubility method, to simplifying difficult solubility problems. An example of two polymorphs existing in mixtures of DS is presented in which one of the forms is very unstable. Accelerating stability studies are used in conjunction with HPLC and quantitative X-ray powder diffraction (QXRD) to demonstrate the differences in chemical and polymorphic stabilities. The results from two model excipient compatibility methods are compared to determine which has better predictive accuracy for room temperature stability. A DSC (calorimetric) method and an isothermal stress with quantitative analysis (ISQA) method that simulates wet granulation conditions were compared using a 2 year room temperature sample set as reference. An example of a pH stability profile for understanding stability and extrapolating stability to other environments is provided. The pH-stability of omeprazole and lansoprazole, which are extremely unstable in acidic and even mildly acidic conditions, are related to the formulation of delayed release dosage forms and the resolution of the problem associated with free carboxyl groups from the enteric coating polymers reacting with the DSs. Dissolution method requirements for CR dosage forms are discussed. The applicability of a modified disintegration time (DT) apparatus for supporting CR dosage form development of a pH sensitive DS at a specific pH such as duodenal pH 5.6 is related. This method is applicable for DSs such as peptides, proteins, enzymes and natural products where physical observation can be used in place of a difficult to perform analytical method, saving resources and providing rapid preformulation support.

KEY WORDS: dissolution methodology; excipient compatibility; polymorphism; preformulation; solubility methods.

INTRODUCTION

This section deals with preformulation support after selection of a final candidate form. This phase of pharmaceutical development begins with the scaling up of the synthesis and recrystallization of the selected DS form in order to provide adequate supplies for preclinical, dosage form, and clinical development. These activities increase the availability of DS for additional preformulation support as described in Table I. Controlled release CR dosage form development may require modification or remediation of DS properties. Preclinical, dosage form, dissolution method, and analytical method development are dependent upon the physical–chemical properties and characterizations described in Table I.

A complete review of all of the preformulation activities in Table I is impractical. However most of the important considerations supporting development are reviewed. The presentation of examples of preformulation support in this phase of development continues with determination of the pH-solubility profile of Mc-5707 free base (Fig. 1), demonstrating how the solubilities of McN-5707 are expanded beyond the original determinations during the previous phase of candidate form selection. Additional examples of preformulation support are provided using other DSs because they provide better opportunities to present a topic. Three novel methodologies for characterizing DS properties such as solubilities, drug-excipient compatibilities, and dosage form dissolution testing are also reviewed. A complete description of the methods used is also impractical. However, they are available upon request.

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[1] FA Chrzanowski, Inc., Marlton, New Jersey 08053-1320, USA.
[2] To whom correspondence should be addressed. (e-mail: frankchrzan@comcast.net)

Table I. Physical–chemical properties of NCE/API applicable to CR dosage form development after final form selection

Physical–chemical Properties
Property
Solubility
vs. pH
Pharmaceutical and chemical solvents
Adjustment
Polymorphic (crystallinity)
Excipient compatibilities
Stabilities
Solid state (temp, temp/RH, [O], light, acid and base)
Solution state (pH, temp, [O], and light)
Ionization properties, p*K*a and partitioning
Wettability
Particle size distribution
Dissolution
Dosage form method development
Intrinsic
Permeability

Preformulation Considerations

The properties of a DS form such as its solubilities *vs*. pH and solvents, pH-stability profile, compatibilities with excipients, polymorphic behaviors, actual *vs*. expected dosage form dissolution behavior affect the selection and design of appropriate mechanisms for creating CR dosage forms.

Solubilities

Identifying a suitable mechanism for creation of CR or applying a DS to a proposed CR mechanism may depend upon a DS having suitable solubility *vs*. pH or in pharmaceutical solvents. pH-solubility data can also be used to estimate the p*K*a of a DS in the absence of more reliable titration methods, or as a supportive estimate of the results of titration methods.

The preferred range for evaluation is pH 1 to 14; however, the range pH 1 to 8 is adequate and critical because it provides insight relevant to gastro intestinal (GI) behavior. Two practical solubility methods have been used in our laboratories, equilibrium and trial. The equilibrium method requires multiple analyses over time to establish an exact value. It has added value because it can detect polymorphic behavior. Figure 2 presents hypothetical solubility *vs*. time profiles for a DS that exists as two polymorphs. The equilibrium solubility of the DS is that of the more stable polymorph. Not allowing sufficient time for equilibration would result in an over estimation of the actual equilibrium solubility of the DS.

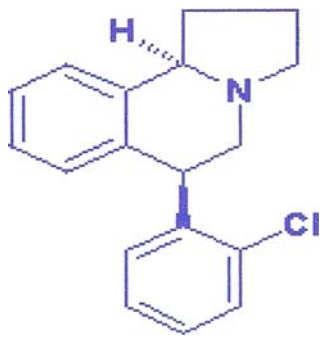

Fig. 1. McN-5707 (free base)

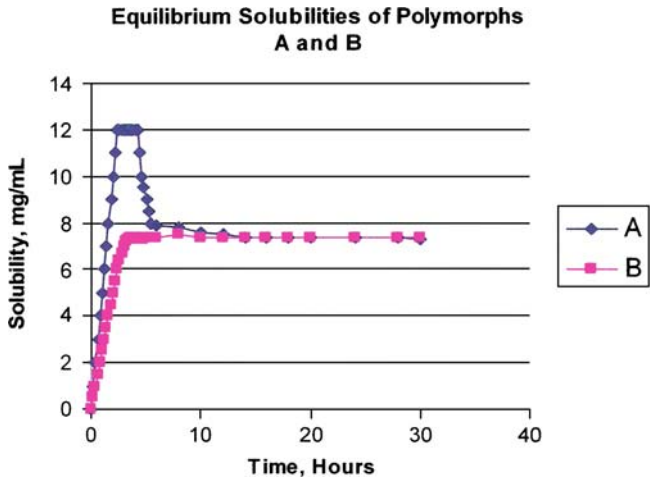

Fig. 2. Hypothetical solubility profiles for polymorphs A and B

Equilibrium Solubilities

The first example is a routine determination of the pH solubility profile of McN-5707 free base at 25°C (Table II). There were no signs of polymorphic behavior. The data show that the pH range 1 to 8 is adequate for the characterization of this DS.

The second example is related to the investigation of potentially less soluble forms of linogliride (Fig. 3) for development of a CR line extension. Linogliride fumarate was in development as an immediate release (IR) dosage form to treat Type 2 Diabetes. Its solubility over the pH 1 to 8 range exceeds 150 mg/mL (Table III). The free base and four salts, pamoate, *p*-hydroxybenzoate, 3-hydroxy-2-naphthoate

Table II. McN-5707 pH solubility[a] profile in citrate–phosphate buffers, μ=0.5 M, at 25°

pH		Solubility
Initial	Final	mg/mL
2	3.2	12.9
3	3.8	10.5
4	4.4	7.1
5	5.1	1.5
6	6.0	0.18
7	7.0	0.020
8	8.2	0.0005

[a] Expressed as free base equivalent

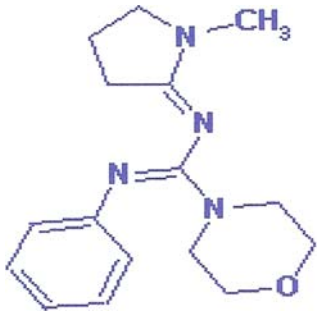

Fig. 3. Linogliride (free base)

and the 1-napsylate, were prepared and their solubilities *vs.* pH were determined (Table III).

The solubilities of the four new salts are appreciably lower than the fumarate and the free base and meet the initial requirement of reduced solubility. Interestingly, the solubility of the 1-napsylate salt is independent of pH, and might provide zero-order release.

Trial Solubility

This method is particularly applicable if a specific target or minimum solubility is required, there are a number of DSs and/or media to evaluate, an exact solubility would require the expenditure of appreciable resources, and trial solubility would take appreciably less time. The trial solubility method involves the complete or serial addition of the required weight of DS to the solvent and observing for complete solubility. A practical example of the trial solubility method is presented in Table IV using palmoxiric acid, its sodium salt and methyl ester (Fig. 4). Palmoxiric acid is a fatty acid epoxide, with properties and structure similar to stearic acid. The acid and methyl ester are inhibitors of fatty acid metabolism. An intravenous (IV) dosage form containing 30 to 40 mg/mL was needed for a preclinical bioavailability and pharmacokinetics study. An oil in water emulsion modeled after Intralipid® was considered for use if there were sufficient solubility in an oleaginous medium. The only quantitative analytical method for palmoxiric acid forms was gas chromatographic with on column derivatization of the acid form to an ester. The method was not intended or validated for use in fatty acid rich vegetable oils or liquid esters such as glyceryl acetate or benzyl benzoate. Assay development would have taken much longer with no guarantee of success for all of the trial media. The trial solubility method took one analyst one day to complete (Table IV). A 160 mg/mL solution of the methyl ester was prepared in sesame oil. This oily solution was emulsified in a ratio of 20:80 with water to give a 32 mg/mL sesame oil in water dosage form for IV administration.

Polymorphism

New polymorphic and the amorphic forms may be encountered through deliberate or accidental discovery. Deliberate discovery comes from attempts to create new forms by recrystallization of the DS in a number of solvents. Accidental discovery can result from exposure of the DS to a new solvent, a new process especially processes that apply energy to the DS. These include changes in solvents of recrystallization and synthetic method, wet granulation and solvent deposition, milling, drying or heating, compaction, and changes in processing equipment. DS properties such as color, hardness, thermal behavior, solubility, physical and chemical stability, and bioavailability can be affected by changes in crystalline form.

X-ray powder Diffraction (XRD) and solid state nuclear magnetic resonance (NMR) are the best methods for detection, identification and quantitative analysis of individual polymorphs and mixtures. Our laboratories used XRD to characterize each new DS and screen each new lot of DS to ensure continuity of crystalline form during development. If necessary, a quantitative XRD (QXRD) method was developed for mixtures of polymorphs. QXRD, DSC, TGA, hot stage microscopy, equilibrium solubilities *vs.* time, and intrinsic dissolution rates were used to provide additional data regarding the properties of polymorphic and amorphic forms and possible conversion of forms.

Solubility

Figure 2 illustrates the differences in solubilities that can be observed with two polymorphs. The conversion of polymorph A to B in solution is demonstrated by the drop in solubility of Form A to the solubility of Form B.

Table III. pH solubility[a] profiles of linogiride free base, fumarate, and four less soluble salts, mg/mL (1)

Initial pH	Free base	Fumarate	Pamoate	*p*-Hydroxy benzoate	3-Hydroxy-2-naphthoate	1-Napsylate
1.4	74.2	186	27.0	34.4	28.2	8.6
2.3	129.0	173	40.0	29.2	15.8	8.8
3.1	129.0	187	25.5	24.4	6.8	8.8
4.1	89.8	175	1.7	18.8	1.2	7.9
5.1	75.0	284	1.6	16.2	1.1	8.4
6.2	65.8	293	1.3	19.2	1.0	8.9
7.2	41.4	>251	1.0	31.2	1.0	6.7
7.5	33.4	154	1.1	24.4	1.2	8.7
8.3	25.8	290	0.8	41.8	0.9	6.2

[a] Expressed as free base equivalent

Table IV. Trial solubilities data for aliphatic epoxide forms (Fig. 4), mg/mL

Solvent	Free acid	Sodium salt	Methyl ester
Glyceryl acetate	ND	<2	8 to 28
Ethyl oleate	8–12	<2	>100
Peanut oil	4–6	ND	>160
Cottonseed oil	8–10	ND	>160
Corn oil	12–14	ND	>160
Safflower oil	10–12	ND	>180
Sesame oil	8–10	ND	>200
Benzyl benzoate	4–6	>2	>100

ND Not determined

Stability

Differences in stability are demonstrated with fenretinide (Fig. 5) a clinical candidate with potential antineoplastic and chemopreventive activities. Bulk fenretinide DS lots frequently contained mixtures of polymorphic Forms I and II. Stability data from DS storage at 4° to 80°C showed (Table V) that Form II is much less more stable than Form I with only 91.2% Form II remaining after 2 weeks at 25°C. The instability of Form II required investigation and resolution.

In order to assess the degradation in mixtures of the forms, determine if degradation of the less stable form affected stability of the stable form, and establish limits for the amount of Form II in bulk DS, physical mixtures containing 5% increments of the unstable Form II with Form I were stored at 60°C for 4 weeks and at 40°C for 2 weeks. The 60°C samples were analyzed weekly by HPLC, and the 40°C samples were analyzed after 2 weeks by HPLC and QXRD methods for polymorphs I and II (3). In another experiment Form II was stored at 50°C and analyzed by QXRD over a 1 week period. The HPLC method is stability indicating and the QXRD method is specific for the two forms.

The HPLC data in Tables VI and VII show that the amount of degradation is related to the amount of unstable

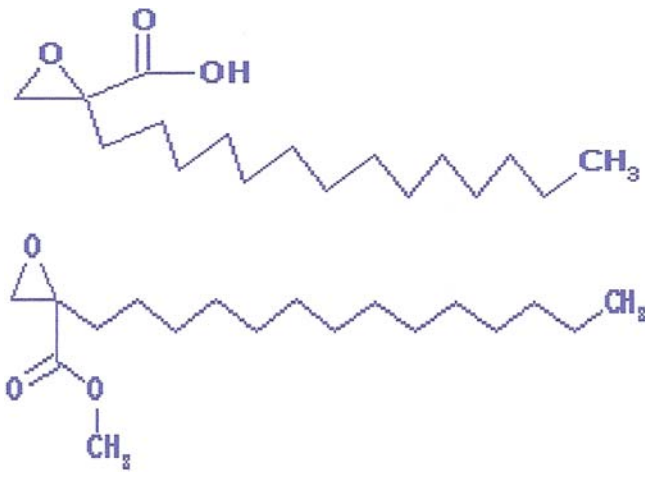

Fig. 4. Palmoxiric acid (*top*) and methyl palmoxirate ester (*bottom*)

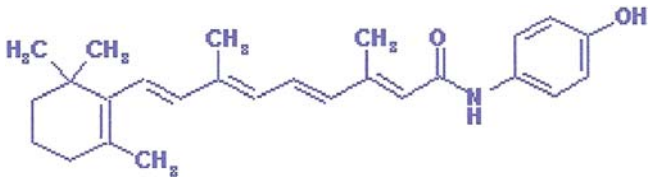

Fig. 5. Fenretinide

Form II in each mixture. However, the data in Table VII show that Form II is disappearing faster from XRD detection than from HPLC detection suggesting that Form II is converting to an amorphic form which is then degrading. In the 50°C QXRD study of Form II, no new peaks were detected, only a decrease in Form II peaks and an increase in the typical amorphic curve were observed. Fig. 6 shows that the conversion of Form II to an amorphic form follows first order kinetics and has a half-life of about 230 h at 50°C. It is the instability of the amorphic form formed by Form II that accounts for the difference in chemical stabilities of the two polymorphic forms.

Drug Excipient Compatibilities

Excipient compatibility studies facilitate dosage form development by identifying excipients which are compatible with the DS. These studies generally precede formulation development, and are performed at laboratory scale. The most frequently used methods are quantitative analysis after isothermal stress under accelerating conditions (QAIS), and thermal calorimetry of the components and mixtures.

We compared a DSC method proposed by El Shatawy *et al*., (4,5) with a QAIS method that included addition of water and drying to simulate wet granulation/drying (6) to determine which method was more predictive. The test materials were fenretinide and six excipients in a fixed ratio of 100:150. The DSC method required calculation of the differences in the heats of melting of fenretinide alone and in each binary mixture and took one analyst one day to complete. The QAIS method required preparation, storage for 2 months at 60°C, and HPLC analysis at three time points. An additional sample set stored at 25°C for 2 years provided an actual time reference. The results are presented in Tables VIII and IX. The predicted stability from QAIS matched the results for 2 years at 25°C. The DCS method did not.

Table V. Chemical stabilities of fenretinide polymorphic Forms I and II (2)

		Fenretinide (%) Remaining *vs*. Temperature				
Form	Weeks	4°C	25°C	40°C	60°C	80°C
I/102.0%	1	100.6	100.8	99.0	98.8	–
	2	100.0	100.3	99.1	98.7	–
II/99.4%	1	97.6	–	90.3	77.6	35.8
	2	93.1	91.2	87.4	66.0	–

Table VI. Effect of polymorphic ratio on fenretinide chemical stability at 60°C for 2 weeks (2)

	Fenretinide (%) Remaining at Form I:Form II Ratio				
Weeks	100:0	95:5	90:10	85:15	80:20
1	99.4	99.1	96.3	97.6	95.8
2	99.6	98.6	98.2	97.5	96.6
3	96.7	98.3	97.2	96.3	94.8
4	97.6	91.7	86.6	81.3	76.0

Dissolution Testing Support

Guidance for development of dissolution methods for CR dosage forms is available from both the FDA and the USP. The specifications must include at least three sampling time points (T) with lower and higher limits (Q) at each time point. Methodologies have been devised that involve media and pH changes from low pH to mildly acidic, neutral or nearly neutral conditions to simulate passage through the GI tract. The USP lists four apparatuses for actual testing. It also lists seven dissolution methods for CR theophylline dosage forms that differ in media, method (apparatuses) and specifications (Q *vs*. T).

Dissolution method development actually begins with the determination of the DS solubilities in water, 0.1 N hydrochloric acid, simulated intestinal fluid (SIF) during candidate form selection and is refined with the pH 1 to 8 solubility profile providing clues to *in vivo* GI performance and *in vitro* sink conditions necessary for dissolution testing. Final media selection is based on DS solubility data in relevant media at 37°C. If equivalent dissolution can be demonstrated in appropriate media at several relevant pHs, a valid argument can be made for the adoption of a singe pH/medium for testing.

Applicability of the DT Apparatus in CR Dosage Form Development

The Disintegration Time (DT) apparatus mesh size can be changed from 10- to 40-mesh to create an apparatus suitable to support development of CR dosage forms containing beads, pellets, microspheres and mini-tabs by measuring their disappearance *vs*. time and pH without the need for assay. This is particularly advantageous for formulation development of pH sensitive and difficult to assay peptides, proteins, enzymes and natural source products formulated with pH sensitive coatings. Our laboratory used this modified DT apparatus to demonstrate the specificity of release of pancreatic lipase from microspheres intended for release at pH 5.6 for treatment of cystic fibrosis. A fixed number of beads were added to the apparatus for each media condition. The numbers of beads disappearing from the apparatus *vs*. time were determined at typical GI conditions and at small incremental pHs near 5.6 in support of optimizing the release near pH 5.6.

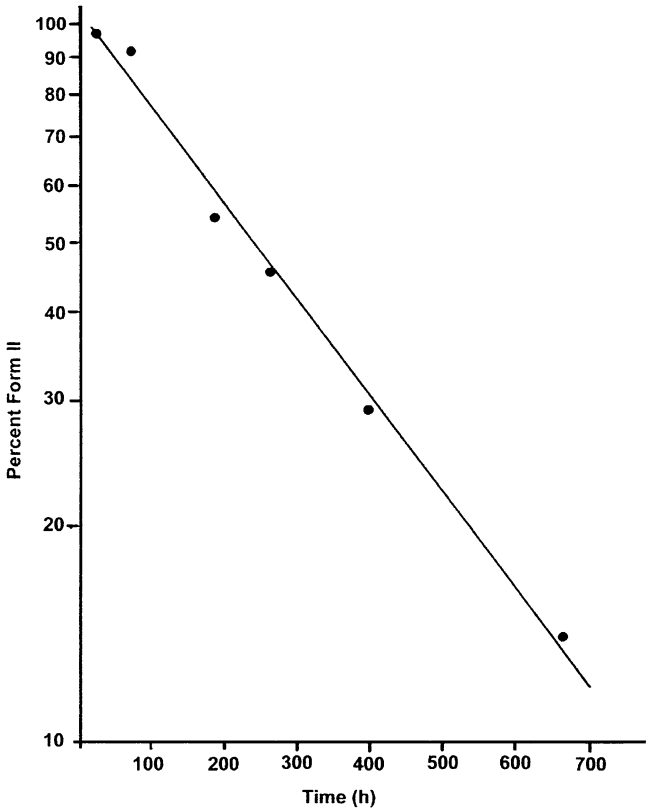

Fig. 6. Physical stability of fenretinide polymorph form II as measured by X-ray powder diffraction (2)

Table VII. Effect of polymorphic ratio on fenretinide chemical stability at 40°C for 2 weeks

	Ratio Form I:Form II				
Method	100:0	95:5	90:10	85:15	80:20
HPLC[a]	99.6	99.3	98.9	98.7	98.2
QXRD[b]	105:0	92:0	88:0	84:4	81:0

[a] % fenretinide Ref. (2)
[b] Ratio Form I:Form II Ref. (3)

Table VIII. Excipient compatibility predictions using a DSC method based on reduction of the heat of melting (5)

Excipient	Heat of melting difference %	Predicted stability
None (Fenretinide)	0	NA
Docusate sodium	53.2	Worst Case
Sodium laurylsulfate	17.9	Best
Lactose, hydrated	16.9	Best
Microcrystalline cellulose	38.0	Intermediate
Powdered cellulose	29.5	Intermediate
Dicalcium phosphate	54.2	Worst Case

All drug:excipient ratios, 100:150

Table IX. Comparison of DSC and simulated granulation with isothermal stress (5)

Excipient	DSC predictions	% Remaining			
		60°			25°
		0 months	1 month	2 months	24 months
None (fenretinide)	NA	100.0	96.4	92.6	96.7
Docusate sodium	Worst	100.2	94.5	91.8	97.6
Sodium laurylsulfate	Best	98.0	67.0	60.0	71.2
Lactose, hydrated	Best	99.0	95.4	93.4	97.8
Microcrystalline cellulose	Intermed.	99.0	92.8	88.7	94.2
Powdered cellulose	Intermed.	98.8	94.0	95.2	97.1
Dicalcium phosphate	Worst	102.0	96.8	98.0	97.8

All drug:excipient ratios, 100:150
NA Not applicable

Stability *versus* pH

The pH stability of a DS can affect the selection and development of a CR delivery system, manufacturing process, analytical method, and dissolution method development. The pH-rate profile of perindopril (Fig. 7) at three temperatures is presented in Fig. 8. Maximum stability is at the minima of the curves near pH 2 to 3, and least stability is at pHs >9. The kinetic rate constants from 40°, 60° and 80°C can be extrapolated to predict rates at lower environmental temperatures.

A second example related to pH stability of DSs comes from the proton pump inhibitors such as omeprazole and lansoprazole. They are extremely acid labile and are formulated as delayed release dosage forms to avoid exposure to stomach acidity. The half-life of omeprazole is less than 10 min at pHs ≤ 4 at ambient conditions and the half-life of lansoprazole is about 0.5 h at pH 5 and about 18 h at pH 7. Enteric coatings were proposed to resolve the instability and to delay the release in the GI until a more suitable pH was encountered. However, polymeric coating materials such as the methacrylic acid–acrylic acid co-polymer, hydroxylpropylmethylcellulose acetate succinate, and cellulose acid phthalate have residual carboxyl groups which create an acidic environment with the addition of water or moisture in the dosage form and result in color change and degradation. Prilosec® brand omeprazole capsules are formulated with one or more inert water soluble polymer layers separating omeprazole granule from the free carboxyl groups. An alkaline reacting substances such as a magnesium or calcium salt is added to the granule mixture as an additional stabilizing agent (7–9).

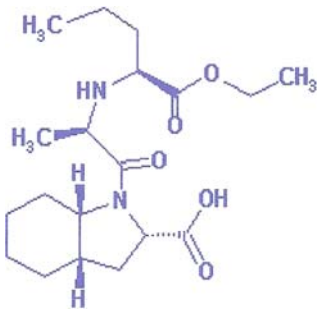

Fig. 7. Perindopril

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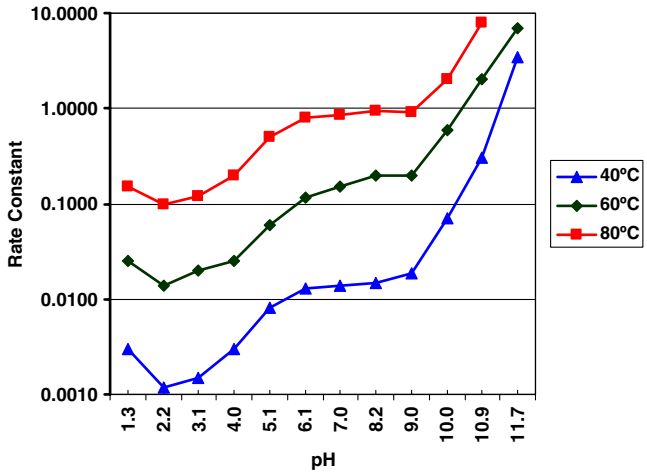

Fig. 8. The pH-rate profile of perindopril at 40°, 60° and 80°C

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