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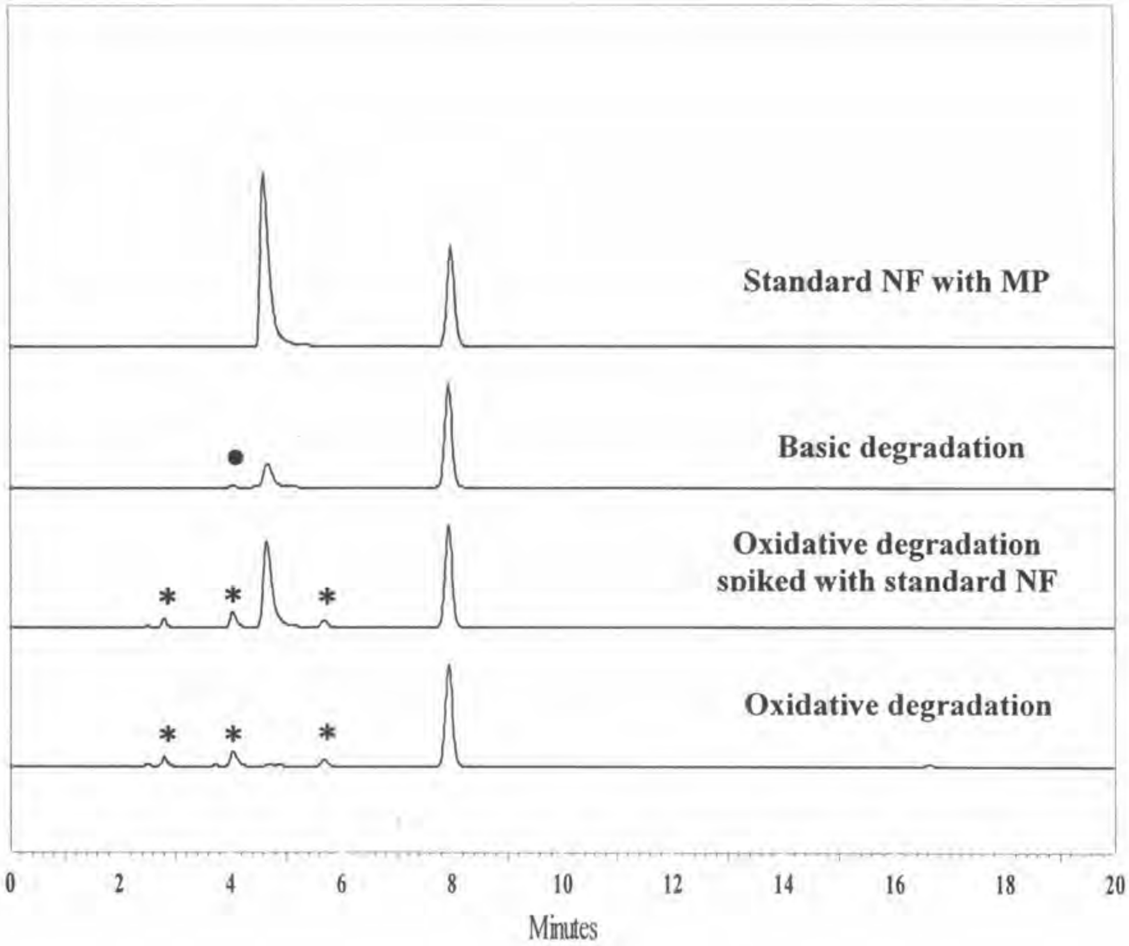
APPENDICES

APPENDIX A

SI-HPLC



Comparative HPLC chromatograms of standard NF with methyl paraben (MP) as internal standard by SI-HPLC method. (* degradant from oxidative reaction and • degradant from basic reaction)

APPENDIX B

THE RATE LAW

Classical chemical reaction of desolvation pharmaceutically follows the reaction schemes below:

$$A_{(s)} \longrightarrow B_{(s)} + C_{(g)}$$

So the rate of reaction usually declares as a function of the concentration of reactant or products. It should be derived as follows.

$$\text{Rate} = \frac{d[A]}{dt} = -\frac{d[B]}{dt} = -\frac{d[C]}{dt}$$

In general, rate of reaction, k, is commonly monitored with respect to the decrease of reactant or the increase of product in term of amount or concentration. Thus, it will be presents here.

$$\text{Rate} = -k[A]^n = k([A]_0 - [B])^n = k([A]_0 - [C])^n$$

Where A_0 is initial concentration of A and n is order of reaction.

In the case of desolvation, liberated gas is carried out from the system and made the [C] became to zero. If unimolecular reaction, n is 1, is considered. By following the reactant point of view, the rate would be illustrated as

$$\text{Rate} = \frac{d[A]}{dt} = -k[A]$$

By intergration

$$-\ln\frac{[A]}{[A_0]} = kt$$

Solid state kinetics will be observed the progress of reaction by describing the fraction of conversion (α) instead of the reaction concentration. The rate is hence transformed based on above relation and expressed as

$$\text{Rate} = \frac{d\alpha}{dt} = k(1-\alpha)$$

then be integrated as

$$-\ln(1-\alpha)=kt$$

In addition, unlike solution state, solid state kinetics should be varied depend on several factors. It can be commonly illustrated as

$$\frac{d\alpha}{dt}=kf(\alpha)$$

and

$$g(\alpha)=kt$$

where f(α) is the differential reaction model and g(α) is the integral reaction model.

The temperature dependence of the rate constant (k) is normally described by the Arrhenius relationship.

$$k=Ae^{-\frac{E_a}{RT}}$$

where A is the frequency factor, E_a is activation energy, R is the gas constant and T is absolute temperature. Combining above equations yield the relationship below.

$$\frac{d\alpha}{dt}=Ae^{-\frac{E_a}{RT}}f(\alpha)$$

and

$$g(\alpha)=Ae^{-\frac{E_a}{RT}}t$$

APPENDIX C

SOLID STATE KINETIC EQUATION

(Byrn et al., 1999; Dong et al., 2002)

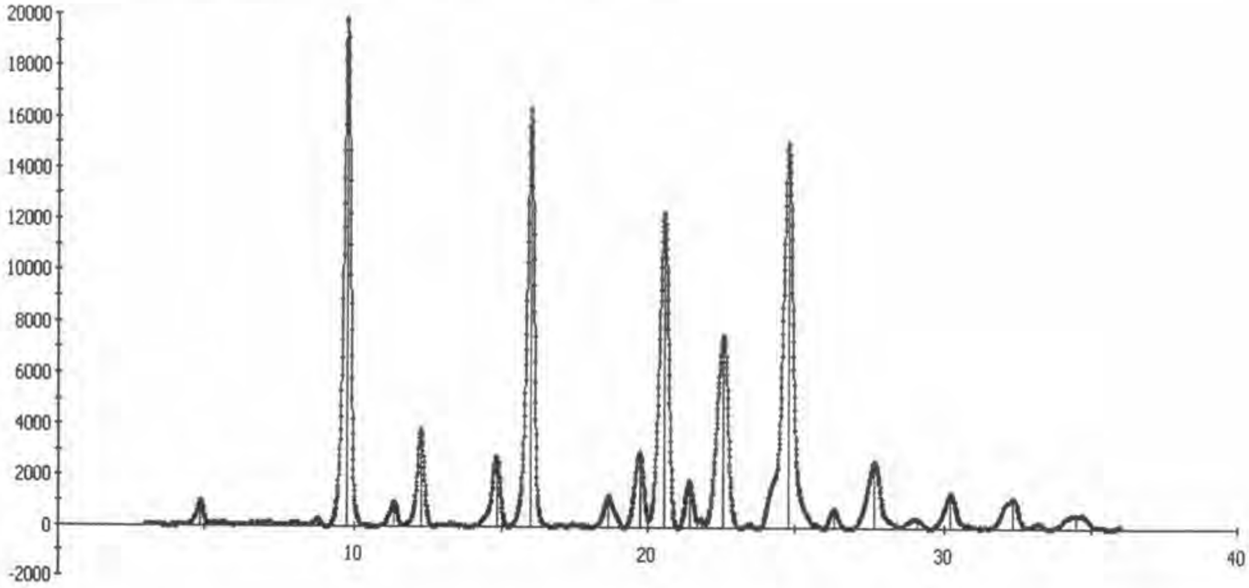
Model	Mechanism
$[-\ln(1-\alpha)]^{\frac{1}{2}} = kt$	One-dimensional growth of nuclei (Avrami-Erofe'ev equation, *n*=2)
$[-\ln(1-\alpha)]^{\frac{1}{3}} = kt$	Two-dimensional growth of nuclei (Avrami-Erofe'ev equation, *n*=3)
$[-\ln(1-\alpha)]^{\frac{1}{4}} = kt$	Three-dimensional growth of nuclei (Avrami-Erofe'ev equation, *n*=4)
$\alpha^2 = kt$	One-dimensional diffusion
$(1-\alpha)\ln(1-\alpha) + \alpha = kt$	Two-dimensional diffusion
$(1-(1-\alpha)^{\frac{1}{3}})^2 = kt$	Three-dimensional diffusion (Jander equation)
$1-\frac{2}{3}\alpha-(1-\alpha)^{\frac{2}{3}} = kt$	Three-dimensional diffusion (Ginstling-Brounshtein equation)
$-\ln(1-\alpha) = kt$	First order reaction (Mampel)
$\frac{1}{(1-\alpha)}-1 = kt$	Second order reaction
$\frac{1}{2}\left(\frac{1}{(1-\alpha)^2}-1\right) = kt$	Third order reaction
$\frac{1}{3}\left(\frac{1}{(1-\alpha)^3}-1\right) = kt$	Fourth order reaction
$\ln\left(\frac{\alpha}{(1-\alpha)}\right) = kt$	Random nucleation (Prout-Tompkins equation)
$\alpha^{\frac{1}{2}} = kt$	Power law (*n*=1/2)
$\alpha^{\frac{1}{3}} = kt$	Power law (*n*=1/3)
$\alpha^{\frac{1}{4}} = kt$	Power law (*n*=1/4)
$\alpha = kt$	One-dimensional phase boundary reaction (zero-order mechanism)
$1-(1-\alpha)^{\frac{1}{2}} = kt$	Two-dimensional phase boundary reaction (contracting cylinder)
$1-(1-\alpha)^{\frac{1}{3}} = kt$	Three-dimensional phase boundary reaction (contracting sphere)

APPENDIX D

List of Peaks Used for Indexing

Group of 22 peaks	Group of 23 peaks
4.855	4.855
8.810	8.810
9.770	9.770
11.360	11.360
12.290	12.290
14.840	14.840
15.995	15.995
18.680	18.680
19.725	19.725
20.560	20.560
21.420	21.420
21.835	21.835
22.580	22.580
24.775	24.222
26.335	24.775
27.660	26.335
29.003	27.660
30.235	29.003
30.840	30.235
32.282	30.840
33.230	32.282
34.493	33.230
	34.493

High refined XRPD of anhydrous NF Form A



VITA

Mr. Wanchai Chongcharoen was born on December 4^{th} in 1973. He graduated from Chulalongkorn University, Bangkok of Thailand and earned his Bachelor degree of Science in Pharmacy with second class honor. During the period of 1996 to 1998, He had been taken a responsibility as junior pharmacist in product formulation and development for local pharmaceutical product at M&H manufacturing Co., Ltd. Since a year of 2000, he obtained a Master's degree in Manufacturing Pharmacy from Faculty of Pharmaceutical Sciences, Chulalongkorn University. He immediately got a challenged opportunity to has a task on product development as manager position at T MAN Pharma., Ltd Part. He spent one and half years to focus a strategy of product development plan. Nowadays, he gained a grant from Graduate School of Chulalongkorn University and conducted the researches in the field of solid state chemistry of drug. He has presentation works at Global Pharmaceutical Educational Network (GPEN) and American Association Pharmaceutical Science (AAPS) Annual Meeting and Exposition in 2006. Nowadays, he will be reserved to play a role of senior scientist in pharmaceutical development at MEDICA INNOVA Company.