SOLUBILITY DETERMINATION OF CARBAMAZEPINE CO-CRYSTALS IN ETHANOLIC SOLUTION AT VARIOUS TEMPERATURE

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SUPERVISOR'S DECLARATION

We hereby declare that we have checked this thesis and in our opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Master of Engineering in Chemical.

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STUDENT'S DECLARATION

I hereby declare that the work in this thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at University Malaysia Pahang or any other institutions.

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DEDICATION

This thesis were dedicated to my beloved husband Azim,
my precious daughter Raisya, my lovely parents and parents-in-law,
family, in laws and for those who made this possible.

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A	Surface area of the crystal
A, B	Complex temperature-dependent constant
a, b, c	Spatial dimensions of unit lattice
B	Number of nuclei
C	y-intercept
C_P	Heat capacity
c	Instantaneous solute concentration
c^*	Solute concentration at saturation
d	Interplanar spacing
dH/dt	Changes of heat flow over time
dT/dt	Heating rate
$f(T,t)$	Heat flow that is function of time at an absolute temperature
k_n	Rate constant
L	Characteristic dimension
M_T	Suspension density
m	Slope of linear equation
N	Number of nuclei per unit volume
n	Order of reflection
n, j, b	Empirical exponent
R	Gas constant (8.314 J/molK)
R_G	Crystal growth rate
R_{B+S}	Crystal growth rate based Birth and Spread model
R^2	Value of linear regression
r	Solute radius

r_c	Critical solute radius
S	Solubility ratio
S	Supersaturation ratio
T	Temperature
T_f	Temperature of melting or fusion
T_m	Temperature of melting
T_{sat}	Saturation temperature
t	Time
x	Mole fraction of solute
x_{ideal}	Mole fraction of solute in ideal system
Y, X	Intercepts on the plane axes
ΔG	Gibb's free energy
ΔG_s	Free energy change as the formation of unit surface
ΔG_v	Free energy change as the formation of unit volume
$\Delta H°$	Enthalpy
ΔH_d	Enthalpy of dissolution
ΔH_f	Enthalpy of melting or fusion
$\Delta S°$	Entropy
ΔS_d	Entropy of dissolution
℃	Degree Celsius
α, β, γ	Angles of the point lattice
α	Volume of the shape features
β	Area shape features
γ	Interfacial energy
γ	Activity coefficient

γx	Activity coefficient
λ	Wavelength of the incident x-ray beam
θ	Diffraction or scattering angle /angle
ρ	Crystal density
σ	Relative supersaturation
π	Radian

LIST OF ABBREVIATIONS

A, B, C	Lattice point at the centre of each pair of the cell lattice
ACN	Acetonitrile
ADHD	Attention-deficit hyperactivity disorder
API	Active pharmaceutical ingredient
BCF	Burton, Cabrera and Frank model
BCS	Biopharmaceutical classification system
B+S	Birth and spread
C	Base centered / Diamond
CBZ	Carbamazepine
CCFs	Co-crystal formers
CH_2Cl_2	Dichloromethane
CH_4	Methane
CO_2	Carbon dioxide
COO^-	Carboxylic group
CSD	Crystal size distribution
DF	Dilution Factor
DSC	Diffraction scanning calorimetry
F	Face centered / Flourine molecule
FDA	Food and Drug Administration
Fe	Iron
FTIR	Fourier transforms infrared spectroscopy
FUM	Fumaric acid
GA	Glutaric acid
GRAS	Generally recognized as safe

Hg	Mercury
HPLC	High performance liquid chromatography
H_2	Hydrogen gas
H_2O	Water
I	Body centered
KBr	Potassium bromide
MA	Maleic acid
Mg	Magnesium
MgO	Magnesium oxide
MW	Molecular weight
N	Nitrogen molecule
NaCl	Sodium chloride
NH_2	Amidogen
NH_3	Ammonia
NH_3^+	Amino group
NIC	Nicotinamide
NT	Nicotinamide
O	Oxygen molecule
P	Primitive cells
PXRD	Powder X-ray diffraction
RCS	Refrigerated cooling system
SAC	Saccharin
SCA	Succinic acid
SEM	Scanning electron microscope
SiO_2	Silicon dioxide

SUC	Succinic acid
TA	Thermal analysis
TA	Thermogravimetric analyser
UV	Ultraviolet
W	Tungsten
XRD	X-ray diffraction

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ABSTRAK

Ko-penghabluran adalah salah satu teknik baru untuk reformasi hablur yang semakin diterima pakai kebelakangan ini apabila pendekatan tradisional seperti saringan garam tidak tidak dapat dicapai bagi satu-satu molekul khususnya molekul yang mempunyai ionisasi lemah. Teknik ini membolehkan penggabungan dua atau lebih komponen organik dari bahan aktif farmaseutikal (API) dan komponen hablur bersama (CCF), dimana kedua-duanya hadir dalam bentuk pepejal di dalam keadaan persekitaran, digabung dalam struktur hablur yang sama tanpa memecahkan atau membentuk ikatan -kovalen yang baru. Ini seterusnya dapat menambah baikkan sifat-sifat fizikal dan kestabilan API tanpa mengubah integriti struktur hablur dan fungsi pengubatannya. Carbamazepine (CBZ) adalah sejenis dadah yang digunapakai sebagai ubat penenang dan penstabilan yang mempunyai sifat-sifat lemah dari segi kadar keterlarutan, kestabilan, polimorfisme dan keterbiosediaan yang menyumbang kepada masalah dos penggunaannya dalam merawat pesakit telah digunakan dalam kajian ini. Kajian ini memberi tumpuan kepada kebolehlarutan ko-hablur CBZ yang dihasilkan dari gabungan empat jenis CCFs iaitu nikotinamide (NIC), sakarin (SAC), asid suksinik (SUC) dan asid fumarik (FUM) pada suhu 25-55 °C. Kajian kebolehlarutan sistem ko-hablur merupakan salah satu faktor penting dalam meningkatkan dan membangunkan bidang farmaseutikal ko-penghabluran. Mesin kromatografi cecair berprestasi tinggi (HPLC) dan kaedah gravimetrik telah digunakan untuk menentukan keterlarutan setiap kristal komponen manakala peralatan analitikal (Pembelauan X-Ray hablur, pengimbas kalorimeter, pengimbas sinar-merah Fourier, dan mikroskop optik) digunakan untuk mengkaji ciri-ciri hablur dan ko-hablur yang terhasil. Eksperimen keterlarutan dijalankan dengan penambahan hablur ke dalam larutan etanol pada suhu yang berbeza (25-55 °C) dan dibiarkan selama 72 jam (sehingga mencapai keseimbangan). Hasil eksperimen dan maklumat terkumpul membuktikan bahawa kesemua hablur baru yang terhasil adalah komponen hablur baru yang dipercayai ko-hablur kepada CBZ dimana ia menunjukan sifat-sifar yang berbeza seperti penurunan suhu takat lebur and bentuk morfologi yang berlainan. Hasil kajian juga menunjukkan profil kebolehlarutan semua komponen CBZ, CCFs dan ko-hablur CBZ meningkat selari dengan kadar peningkatan suhu. Situasi ini memenuhi 'Hukum Pertama Termodinamik' dimana haba yang dibekalkan menyumbang lebih banyak tenaga kepada sistem larutan dan secara tidak langsung memudahkan dan membantu proses pelarutan berlaku. Walau bagaimanapun, kebolehlarutan ko-hablur CBZ-NIC dan CBZ-FUM didapati lebih tinggi daripada hablur CBZ tulen, sementara kebolehlarutan ko-hablur CBZ-SUC lebih rendah daripada hablur CBZ tulen untuk julat suhu yang dikaji. Gaya yang berbeza diperolehi bagi ko-hablur CBZ-SAC, untuk suhu lebih rendah daripada 40 °C, kebolehlarutan hablur CBZ adalah lebih tinggi dan pada suhu yang lebih tinggi daripada 40 °C, ko-hablur CBZ-SAC mempunyai keterlarutan lebih tinggi daripada hablur CBZ. Plot kadar kelarutan van't Hoff pula menunjukkan sifat sisihan negatif untuk semua komponen hablur, ini menunjukkan kewujudan interaksi antara bahan larut dan pelarut dalam sistem tersebut. Hasil dapatan juga menunjukkan kepentingan proses pemilihan CCFs kerana setiap satu ko-hablur API-CCFs yang dihasilkan mempunyai sifat fisikokimia yang berbeza walaupun CCFs yang digunakan terdiri dari kumpulan berfungsi yang sama.

ABSTRACT

Co-crystallization is one of the new ways for crystal reformulation highlighted in recent years for weakly ionisable molecules when the traditional approaches, such as salt screening, cannot be achieved. This approach allows binding two or more organic components of an active pharmaceutical ingredient (API) and co-crystal former (CCF) that are, in their pure forms, solids under ambient conditions within one periodic crystalline lattice without breaking or making a new covalent bond. This, in turn, improves the API physicochemical properties and stability while maintaining its structural integrity and therapeutic functions. Carbamazepine (CBZ) is an anticonvulsant and mood-stabilizing drug known for its poor solubility, stability, polymorphism, and bioavailability, which causes problems in dosage consumption in treating patients, was used in this study. This study emphasis on a solubility study of CBZ co-crystals formed with nicotinamide (NIC), saccharin (SAC), succinic acid (SUC), and fumaric acid (FUM) as the CCFs at various temperatures (25-55 °C). Solubility study of the co-crystal system is an important factor in developing and improving the pharmaceutical co-crystallization pathway. High-Performance Liquid Chromatography (HPLC) and gravimetric methods were used to determine the solubility of each component while analytical equipment (X-Ray Powder Diffraction, Diffraction Scanning Calorimetry, Fourier Transform Infrared, and Optical Microscope) were used to characterize the solid crystals and co-crystals formed. The solubility experiment was conducted by the addition of a solid in ethanol solution at different temperatures (25-55 °C) and equilibrates at 72 hours. Based on the data collected, all the crystals formulated are characterized as new crystals believe to be CBZ co-crystals that show different physicochemical properties such as reduction of melting point and distinct morphology. The solubility profiles for all components of CBZ, CCFs and CBZ co-crystals shows the same trend where the solubility values increases as the temperature rises. This finding meets the First Law of Thermodynamics in which heat can facilitate the dissolution process by providing more energy to the system. In addition, the solubility of CBZ-NIC and CBZ-FUM co-crystals were found to be higher than that of pure CBZ crystal, while the solubility of the CBZ-SUC co-crystal was lower than that of pure CBZ crystal for the range of studied temperatures. A different trend was found for the CBZ-SAC co-crystal in which for temperatures lower than 40 °C, the solubility of CBZ crystal is higher, while at temperatures higher than 40 °C, the CBZ-SAC co-crystal has higher solubility than that of the CBZ crystal. The van't Hoff solubility plot indicates negative deviation behaviour for all crystal components, which shows the existence of an interaction between the solute and the solvent in the system. Findings of this study also show the significant of CCFs screening since different type of API-CCF co-crystals formulated produced different physicochemical properties even same functional group of CCFs is selected.

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