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B1072

DEVELOPMENT AND ADAPTATION OF SUITABLE METHODOLOGY FOR QUALITY ASSURANCE OF CERTAIN DRUGS

A Thesis Presented By

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(Pharmaceutical Chemistry)

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بسم الله الرحمن الرحيم

(قالوا سبحانك لا علم لنا إلا ما علمتنا إنك

أنت العليم الحكيم)

صدق الله العظيم

سورة البقرة (٣٢)

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To My Father,

Mother and

My Sisters

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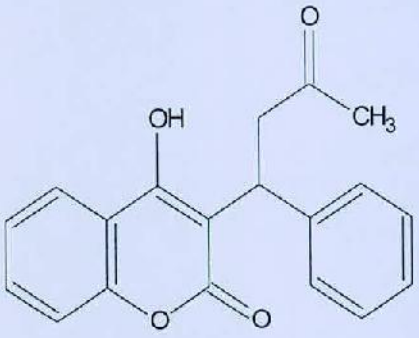
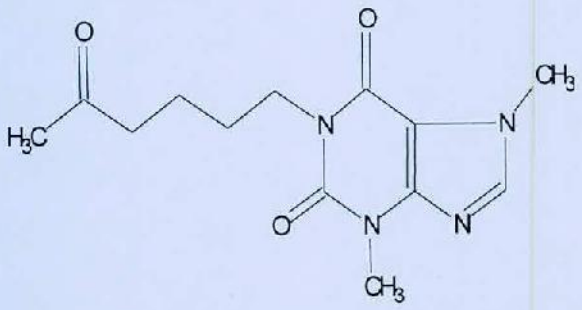
Scope of the Investigation

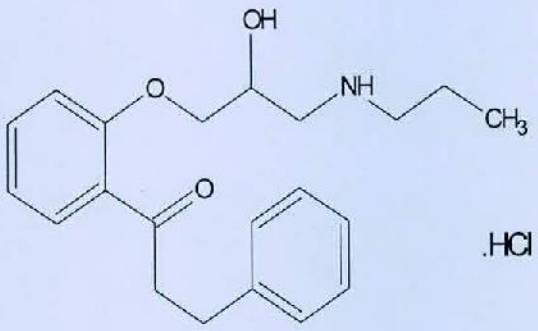
The thesis at hand constitutes a part of a program directed toward facing certain challenges that pharmacy practice encounters during both clinical and industrial settings [1-6]. The scope of this manuscript utilizes the built-in high sensitivity of spectrofluorimetric analysis technique to develop and adapt quality assurance (QA) algorithms to solve different problems imposed by said challenges. Life saving drugs, containing active methylene groups and having narrow therapeutic indices, namely warfarin sodium, pentoxifylline, propafenone hydrochloride and acebutolol hydrochloride, continue to face such problems during their manufacture and utilization. Accordingly, addressing these problems formulates the subject matter of this research project.



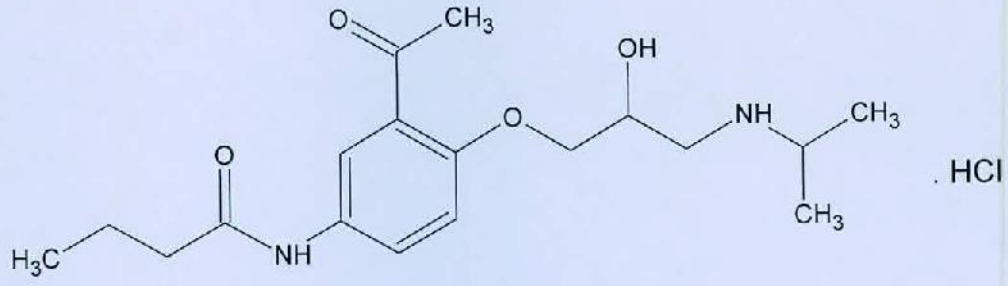
Warfarin



Pentoxifylline



Propafenone hydrochloride



Acebutolol hydrochloride

Warfarin is the most problematic of these drugs because of its marked low dose and its individualized pharmacokinetics. This calls upon finding a high sensitive analytical method that would be suitable for content uniformity and dissolution QA methods during manufacture. Further, the method to be developed will have to be suitable for titration of patients' response to anticoagulant therapy and minimization of the shortcomings of the international normalized ratio (INR) system in clinical settings. Furthermore, its wide use as a rodenticide requires the availability of validated method for determination of trace amounts as a pollutant and measurement of its blood level in case of suspected poisoning.

Pentoxifylline is marketed as controlled release dosage forms and propafenone is currently being studied for such dosage forms. Accordingly, the method to be developed for these two drugs will be adapted for rate of release measurements for such dosage forms.

All these drugs do not require dedicated line for their manufacture. Accordingly, there is a need for determination of ultra trace amounts of each drug during validation of equipment cleaning prior to line clearance, a mandatory regulation in order to avoid cross contamination.

The validity of the methods to be developed will be tested for compliance with current good laboratory practice (cGLP) as stipulated by leading regulatory competent authorities at national (e.g. EPA, FDA and OSHA), regional (e.g. EMEA), and international (e.g. ICH and WHO) levels.

List of Abbreviations

ADCo	: The Arab Drugs Company (Egypt).
AMP	: Adenosine Mono-Phosphate.
ATP	: Adenosine Tri-Phosphate.
BSA	: Bovine Serum Albumin.
cGLP	: Current Good Laboratory Practice.
CNS	: Central Nervous System.
CV	: Coefficient of Variation.
CZE	: Capillary Zone Electrophoresis.
DVT	: Deep Vein Thrombosis.
EIMS	: Electron Ionization Mass Spectrometry.
EMEA	: European Medicines Evaluation Agency (EU).
EPA	: Environmental Protection Agency (USA).
FDA	: Food and Drug Administration (USA).
GC	: Gas Chromatography.
Gm	: Gram.
GSK	: GlaxoSmithKline.
HPLC	: High Performance Liquid Chromatography.
Hr	: Hour.
HSA	: Human Serum Albumin.
ICH	: International Conference on Harmonization (EU, Japan, and USA).
INR	: International Normalized Ratio.
ISA	: Intrinsic Sympathomimetic Activity.
ISI	: International Sensitivity Index.
LC	: Liquid Chromatography.
LC-MS	: Liquid Chromatography-Mass Spectrometry.
LOD	: Limit of Detection.
LOQ	: Limit of Quantitation.