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TO STUDY A VARIETY OF ANALYTICAL TECHNIQUES, INCLUDING 1H NMR, FT-IR, POWDER X-RAY DIFFRACTION, POLARIZED MICROSCOPY, DIFFERENTIAL SCANNING CALORIMETER, AND THERMOGRAVIMETRIC ANALYSIS

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ABSTRACT

The existence of a substance in more than one crystal form has been known since 1822, but we have to wait until 1962 for Walter McCrone, unanimously recognized as the father of this field of research, to provide the definition of a polymorph as "a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state …every compound has different polymorphic forms…" He also opinioned that "the number of forms known for a given compound is proportional to the time and money spent in research on that compound". This "prediction" was published in 1962, but it took more than three decades before the phenomenon of polymorphism would hit the pharmaceutical field in a rather shocking way. In addition to polymorphs, i.e., crystals having the same chemical composition but different structures, the term "crystal forms" nowadays encompasses not only the association of the molecule of interest with solvents (solvates), but also the association with molecules that form solids at room temperature (co-crystals) or with salts (ionic co-crystals). The effort is by no means only theoretical or academic and has important implications both in terms of the drug ultimate efficacy and of the protection of the intellectual property rights associated with the final pharmaceutical product.

KEYWORD: Polymorphs, Crystalline, Intellectual Property, Association

1. INTRODUCTION

By combining an acidic or basic drug molecule with a counter ion to form a salt, one can overcome the inferior physicochemical or biopharmaceutic qualities of a therapeutic substance. The biopharmaceutic properties of poorly soluble and weakly bioavailable pharmaceuticals are significantly altered by this technique, which increases the drug's solubility. One strategy for getting around the parent drug's unfavorable characteristics with ionizable functional groups is the salt production method. A drug's chemical stability is increased and its pharmacokinetic profile can be altered by turning it into a salt. As a result, the number of medications made in salt form has increased quickly; currently, salts make up over half of all medications used in clinical settings.

Salt production is essential for creating safe and efficient dose forms for a variety of medications. The use of a salt yields a larger concentration in solution than the free acid or free base (nonionized forms), regardless of whether the drug products are solids or liquids. Salts usually crystallize easily, and the resulting substance makes further processing easier. As a result, the salt is frequently the best form for drug isolation and purification. Apart from manufacture and solubility, the salt is usually a more stable version of the medication5.

Drugs in salt form have a major impact on the physicochemical characteristics of the drug, which affects its performance, safety, and quality. Crucially, the pharmacological characteristics of drugs are rarely altered by different salt forms. The drug's improved solubility and rate of dissolution are among its primary effects. Because of its buffering effect, salt production for weak bases and weak acids will enhance solubility and dissolving rate in the gut (pH: 7.0). For instance, it is well known that the sodium salt version of the oral hypoglycemic drug tolbutamide dissolves in acidic environments 5,000 times quicker than the free acid. Similarly, compared to the free acid form, the sodium salt of the non-steroidal anti-inflammatory medication Naproxen has a higher solubility profile. When compared to the free base forms, strong acid salt forms (hydrochloride) improved the solubility profiles of weak basic medications like ranitidine and chlorpromazine in the stomach and intestinal media.

Additional favorable physicochemical outcomes of salt production include greater compatibility6, improved hydrolytic and thermal properties, improved photo-stability, and improved organoleptic properties.

2. AIMS AND OBJECTIVES OF THE PRESENT INVESTIGATION

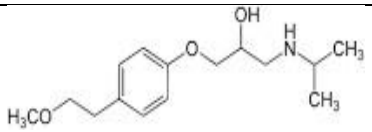
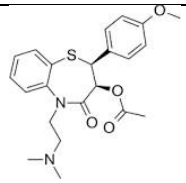
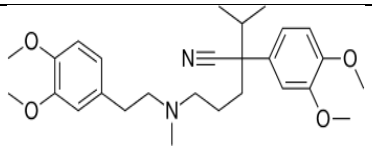
- Making and characterizing salts (in the case of tinidazole), polymorphs (in the case of nitazoxanide and doxofylline), and new crystalline forms (in the case of fenoprofen calcium dihydrate) are the goals of the current thesis.
- A variety of analytical techniques, including 1H NMR, FT-IR, powder X-ray diffraction, polarized microscopy, differential scanning calorimeter, and thermogravimetric analysis, were used to characterize the novel solid forms.

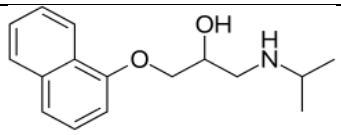
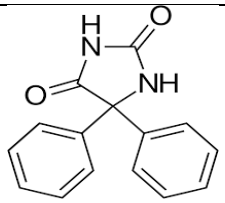
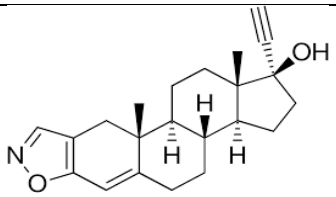
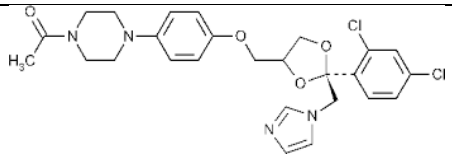
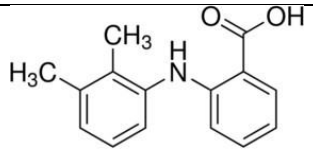
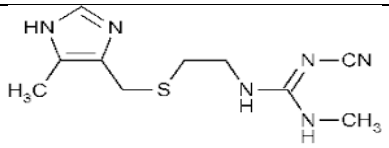
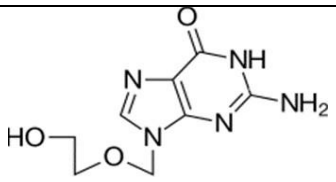
3. RESEARCH METHODOLOGY

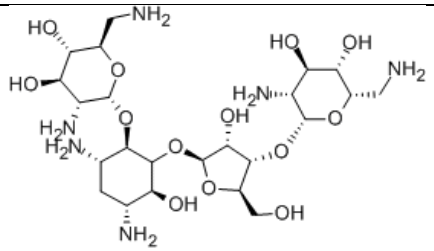
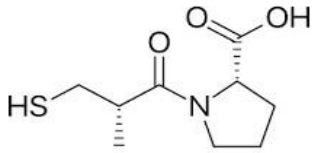
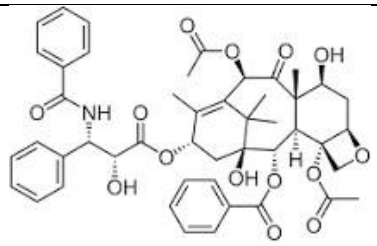
Classification of BCS

Based on permeability and solubility characteristics, BCS is divided into four groups.

Table 3.1: Some of the examples of API drugs categorized under BCS

Group	Solubility /Parmeability parameter	Name of the API drug	Structure of the API drug
Class I	High solubility, High permeability	Metoprolol	
		Diltiazem	
		Verapamil	

		Ropranolol	
Class II	Low solubility, High permeability	Phenytoin	
		Danazol	
		Ketoconazole	
		Mefenamic acid	
Class III	High solubility, Low permeability	Cimetidine	
		Acyclovir	

		Neomycin B	
		Captopril	
Class IV	Low solubility, Low permeability	Taxol	

4. RESULT AND DATA INTERPRETATION

Solubility of glabridin in water

An excess of medication was administered to a 5.0 mL vial that contained 2.0 mL of purified water. Following proper cyclomixer mixing, the vial was kept in an orbital shaker at 251 °C for 72 hours. The material was centrifuged for 15 minutes at 3000 rpm and filtered through a 0.45µ membrane filter in order to achieve symmetry. A UV-Visible spectrophotometer was used to detect the absorbance at 226.0 nm after the filtrate had been suitably diluted. Glabridin's saturation solubility in distilled water was determined and shown in table 6.3.

Table 4.1: Saturation solubility of Glabridin in Distilled water

Solvent system	Solubility of Glabridin at 25±1^{0}C (µg/mL)
Distilled water	3.80±0.0620

Analytical method Development by U.V. Spectrophotometry:

A) Standard plot of Glabridin in ethanol

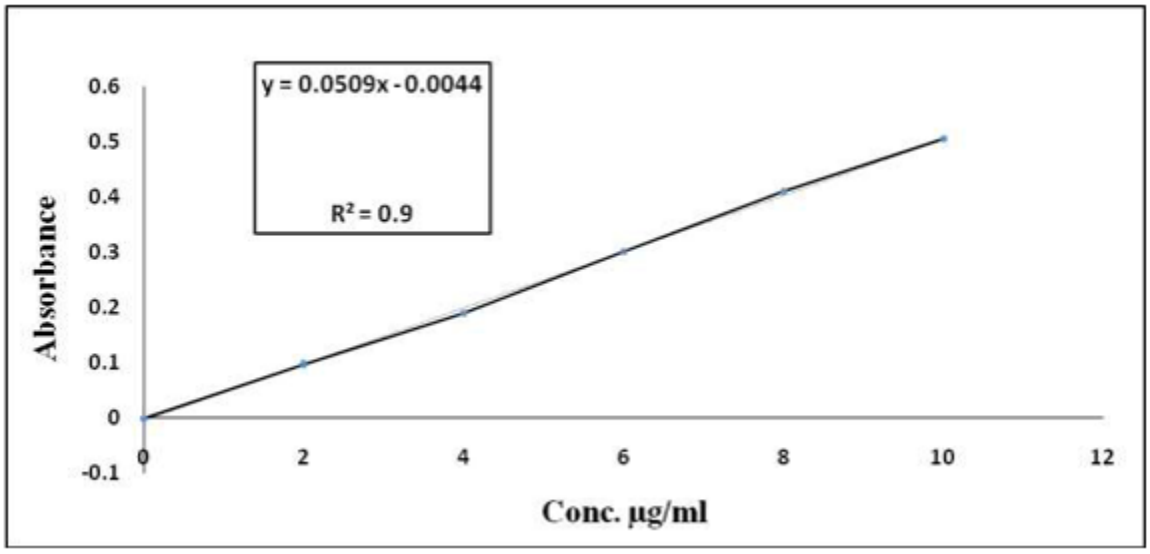


Figure 4.1: Standard plot of Glabridin in ethanol

A strong correlation of 0.9991 was observed between the Glabridin calibration curves in ethanol. The graph displayed linearity throughout the entire designated range of 2–10 µg/mL.

Y= 0.0509x + 0.0044

R^2= 0.9991

Where, y= Absorbance

X= Concentration

R^2= Correlation linearity coefficient.

B) Absorption spectrum of Glabridin in ethanol: phosphate buffer (pH 6.8) mixture (1:1)

The 200–400 nm range was used to scan a 10 mg glabridin solution in a phosphate buffer:ethanol mixture (1:1) pH 6.8. Figure 6.5 shows a UV scan of the medication. The -max of the medication was measured at 226.0 nm in phosphate buffer:ethanol.

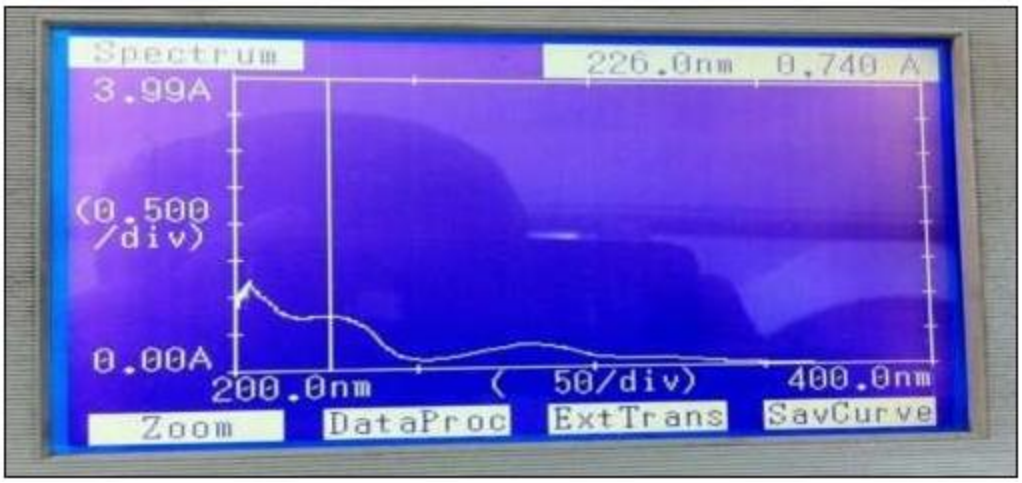


Figure 4.2: Absorption spectrum of Glabridin in ethanol: phosphate buffer (pH 6.8) mixture (1:1)

File Name	Glabridin
Model	Shimadzu UV- 1700
Band width	2.0 nm
Measurement Range	400-200 nm
Scanning Speed	100 nm/min
λ_{max}	226.0 nm

Standard plot of Glabridin in ethanol: phosphate buffer (pH 6.8) mixture (1:1)

A 10 mg/ml solution of Glabridin in Phosphate buffer:Ethanol (1:1) was scanned in the 200–400 nm range using a Shimadzu UV-V 1700 spectrophotometer, with Phosphate buffer:Ethanol (1:1) serving as a blank. As shown in Figure

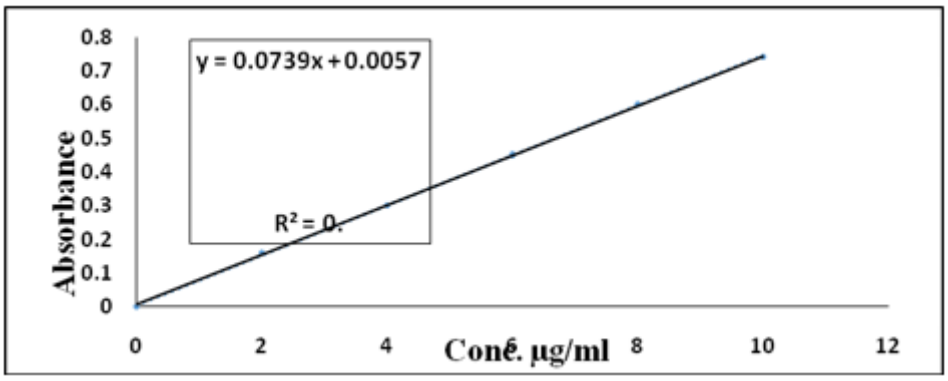


Figure 4 .2: Standard plot of Glabridin in ethanol: phosphate buffer (pH 6.8) mixture (1:1)

$Y = 0.0739x + 0.0057$

$R^2 = 0.9997$

A 0.9997 correlation was found using Glabridin calibration curves in ethanol:phosphate buffer (pH 6.8) (1:1). The curve showed linearity over the selected range of 2–8 µg/mL. Glabridin is almost water insoluble. Consequently, the phosphate buffer was mixed with a polar organic solvent, like ethyl alcohol.

Characterization of Excipients:

Physicochemical characterization of Phospholipon 90G

Table 4.3: Physicochemical characterization of Phospholipon 90G

Tests	Specifications	Results
Description	Yellowish waxy solid	Complied
Solubility	Soluble in ethanol, methanol and chloroform	Complied
LOD	Not more than 1.5 %	1.5%
Acid value	Not more than 0.5	0.5%

5. CONCLUSION

Nitazoxanide's new polymorph (Form II) has been found to have better water solubility. Form II is the most physically stable form of nitazoxanide, according to the DSC data. The polymorphs may be easily and quickly identified thanks to the significant differences between Form I and II's X-ray diffractogram and DSC thermogram. According to HPLC tests, Form II's water solubility increased by 2.76 times. Therefore, additional study aiming at lowering the dosage of the medicine in antiprotozoal treatment can be conducted using Form II of Nitazoxanide.

Fenoprofen calcium dihydrate has been found to exist in a novel crystal structure (structure II) that is monotropically more stable while maintaining its aqueous solubility. Form II is the most physically stable form of fenoprofen calcium dihydrate, according to the DSC data. The PXRD patterns of Form I and II did not alter in response to the X-ray diffraction patterns. Form II's water solubility remained unchanged, according to HPLC tests. Since there are no pediatric formulations of fenoprofen calcium dihydrate (Form I), Form II can be used to conduct additional exploratory research in order to create an appropriate pediatric formulation.

A rod-shaped polymorph of doxofylline, known as Form P, has been discovered. Polarized microscopy microphotographs show that Form P has a rod-shaped morphology, while all previously known forms had a needle-shaped morphology. The powder X-ray diffraction pattern provided additional evidence for the morphological difference. For filtration, drying, and particle size distribution, rod-shaped crystals are better than needle-shaped crystals. Doxofylline's recently discovered polymorph/crystal form (Form P), which has a rod-like morphology, is most suited for use in pharmaceutical production. Consequently, Form P can be used to conduct additional exploratory research in order to create an appropriate formulation of doxofylline.

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