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TO STUDY FOUR OLD MEDICATIONS: DOXOFYLLINE, NITAZAXONIDE, FENOPROFEN CALCIUM DIHYDRATE, AND TINIDAZOLE

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ABSTRACT

Crystal polymorphism has been known and studied since the early days of solid-state chemistry and crystallography, but it is only in the recent past that it has emerged as a strategic research area involving the use of molecular crystalline materials (pharmaceuticals, nutraceuticals, fertilizers, pigments, high-energy materials, etc.).

Although the unexpected appearance of a new crystal form of a known active principle is often a threat for an API on the market, it is also true that the urge for a careful pre-screening and form selection is a potent stimulus for research in various areas, and provides opportunities for innovation and new discoveries, especially in the burgeoning subfield of molecular co-crystals. This latter class of crystalline compounds is proving particularly apt to innovation and the development of new drugs and/or of new formulations of old ones.

In order to help the reader to put the current academic and industrial interest on crystal forms into a wide perspective, this review will move from the early days awareness of the importance of searching for crystal forms to the current impact and consequences for the scientific community and for the industrial sector of the discovery of polymorphs, solvates, and co-crystals of APIs.

KEYWORD: Crystal Polymorphism, Appearance, Industrial, Innovation

1. INTRODUCTION

The most complex process is drug discovery, which includes several important steps from research labs to the pharmacy shelf1. Out of 10,000 substances under investigation, only one is making it to the pharmacy shelf to treat patients. Typically, it takes 15 years of research and development, costing over USD 1.8 billion, to introduce a new medication. Many studies are currently being conducted on outdated medications for new uses due to high costs and lengthy R&D times.

In order to address issues with inadequate solubility, dissolution, bioavailability, dosage, stability, and toxicity, pharmaceutical research professionals have recently made significant efforts to prefabricate existing old drugs2,3. This inspired us to start a study on outdated medications for novel uses. Therefore, by identifying specific prefabrication parameters, such as pharmaceutically acceptable salts, new polymorphs, and new crystalline forms, we tried to address issues for a small number of chosen old medications.

The current chapter provides a summary of the key subjects related to the prefabrication processes (used in this thesis), including polymorphism, crystal forms, and salts that are appropriate for pharmaceutical use. There is also a thorough discussion of the various techniques for preparing and characterizing salts, polymorphs, and crystal forms. A brief explanation of the Biopharmaceutics Classification System, aqueous solubility, and solvent classification is also stressed in addition to the previously mentioned subjects.

2. AIMS AND OBJECTIVES OF THE PRESENT INVESTIGATION

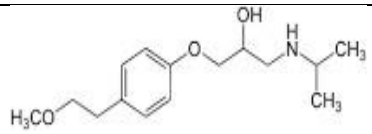
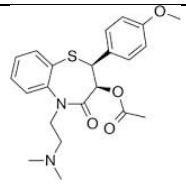
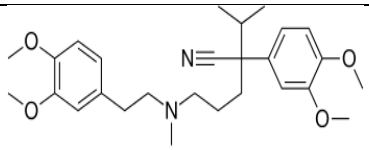
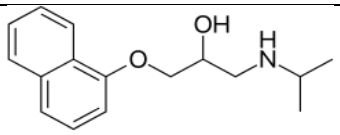
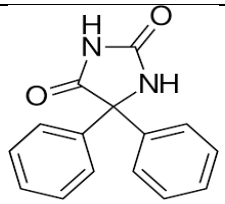
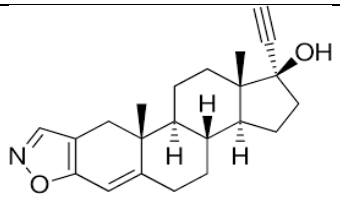
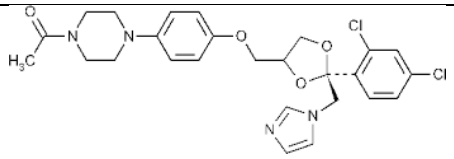
- This work identifies new salts, polymorphs, and crystalline forms to investigate new uses.
- The study will focus on the following four old medications: doxofylline, nitazaxonide, fenoprofen calcium dihydrate, and tinidazole.

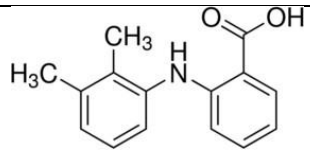
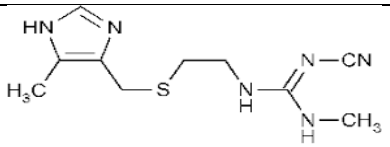
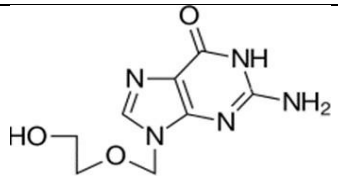
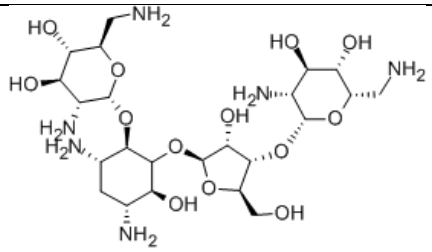
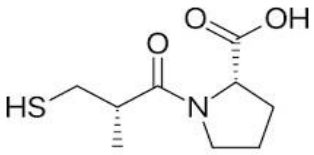
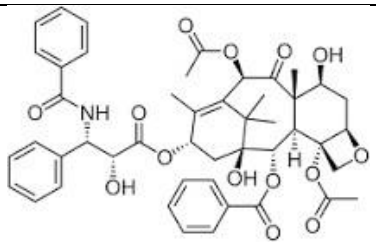
3. RESEARCH METHODOLOGY

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

Glabridin:

Physicochemical characterization of Glabridin

Table 4.1: Physicochemical characterization of Glabridin

Tests	Specifications	Results
Description	Yellowish brown to reddish brown colored powder	Complied
Solubility	soluble in ethanol (95%), methanol, insoluble in water	Complied
Melting point	Melts between 154^0C and 155^0C	154ºC
Loss on Drying	Not more than 5%w/w, determined on 1.0 g by drying in an oven at 105^0C $\pm$ 2^0Cfor 3 hours	0.68%w/w
Assay	Contains not less than 97.0%w/w Glabridin	95.52%w/w
Total Viable Bacterial Count	Not more than 100cfu/gm	20cfu/gm

The testing results showed that the Glabridin utilized in the formulation complied with all standards.

Differential Scanning Calorimetry

The drug's thermogram was characterized by a single melting endotherm at 155.40C. The thermogram, which was verified to be consistent with the specifications.

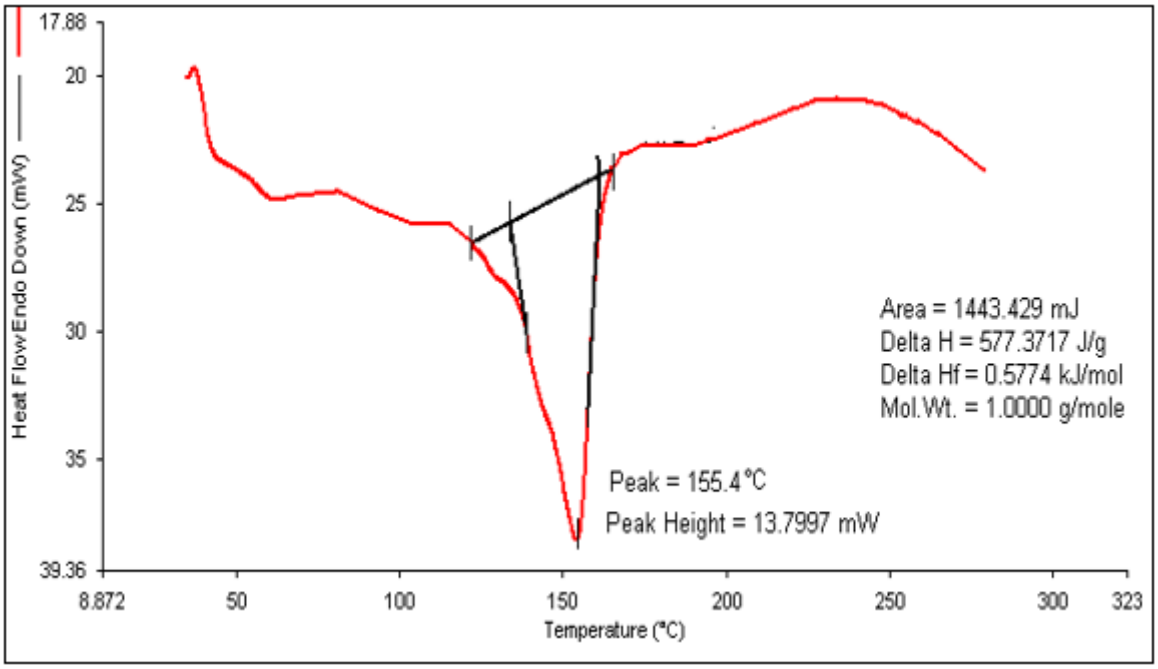


Figure 4.1: DSC graph of Glabridin

The presence of contaminants in a sample is known to lower the melting point and increase the melting range. There were no signs of the impurity, as shown by the prominent melting endothermic peak at 155.40C (H = 577.3717J/g) in Glabridin's DSC thermogram.

I.R. Spectrum of Glabridin

The sample (1.0 mg) was thoroughly mixed with 200.0 mg of dried KBr (kept at 100oC for 8 hours) after being coarsely powdered to a particle size of 2 m or less. A transparent disk in an evacuable die was then filled with the mixture under high pressure. A Shimazdu IR-8400S was used to scan the sample, and the entire process was conducted in a controlled setting. The graphic below shows the I.R. Spectrum.

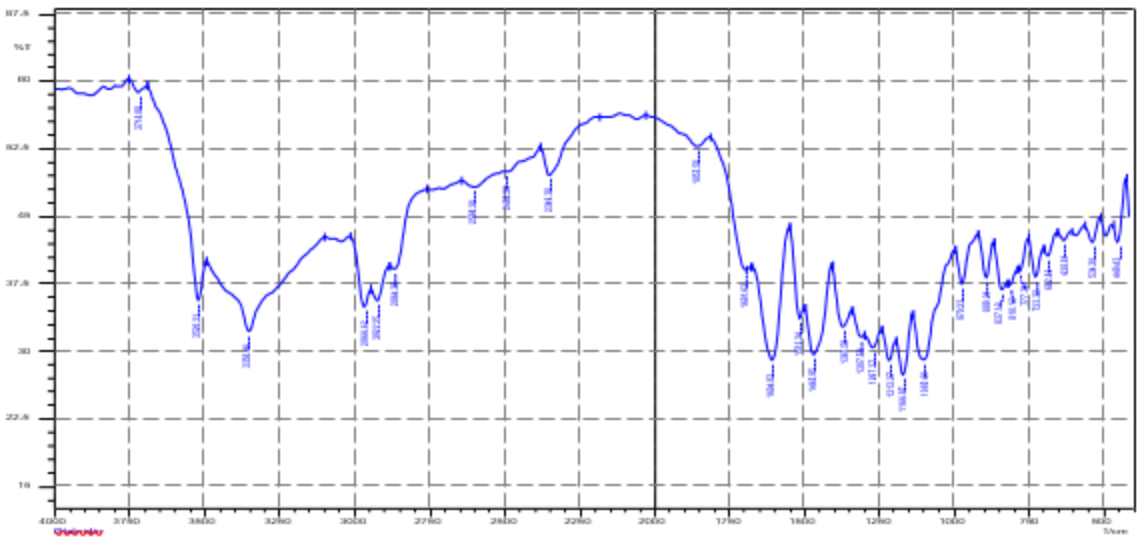


Figure 4.2: IR spectrum of Glabridin

Table 4.3: Results of IR interpretation of glabridin

Sr. no	Bond	Frequency range, cm^{-1}	Conclusion
1	O- H	3351 - 3528	Strong stretch
2	Benzene ring with C-H	2973, 2967, 2934, 2878	Medium stretch
3	C-O-C	1056, 1091, 1114, 1170	Strong stretch
4	C-H	1468, 1519	Strong bend

The IR spectrum of glabridin matches the criteria.

Determination of λmax for U.V absorption

A 10g Glabridin in ethanol solution was scanned in the 200–400 nm range.

File Name	Glabridin
Model	Shimadzu UV- 1700
Measurement Range	400-200 nm

Scanning Speed	100 nm/min
λ_{max}	226.0nm

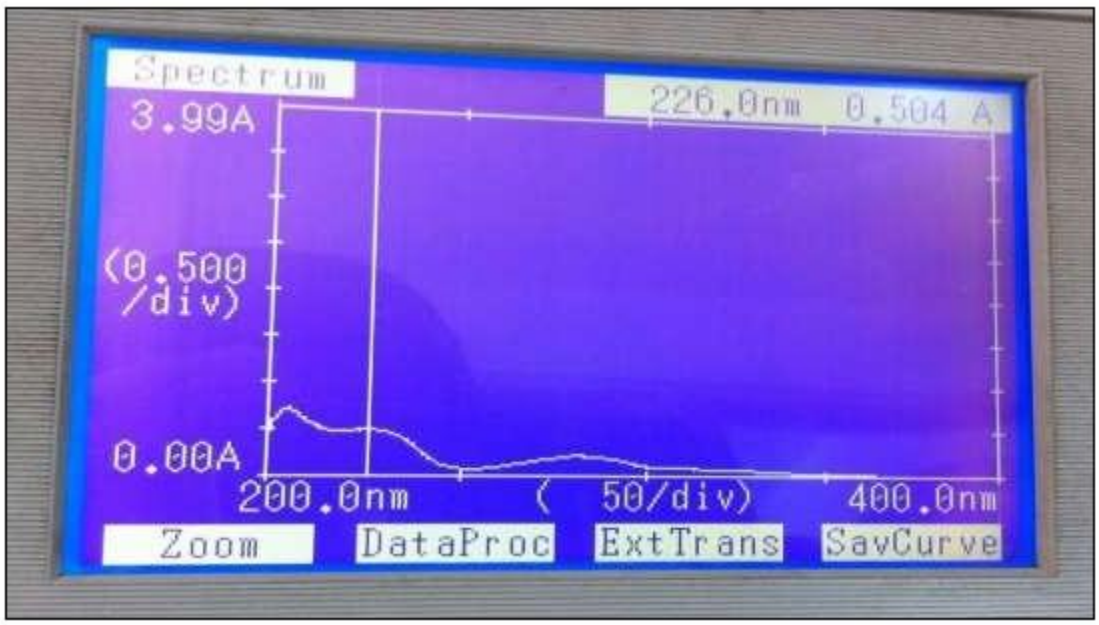


Figure 4.3: Absorption spectrum of Glabridin in ethanol

The λmax of the glabridin was found to be 226.0 nm in ethanol

5. CONCLUSION

An introduction of the key subjects related to the prefabrication processes used in this thesis is provided in chapter 1, including pharmaceutically acceptable salts, polymorphs, crystal shapes, solubility, and the significance of the biopharmaceutical classification system. There includes a thorough discussion of the various techniques for preparing and characterizing salts, polymorphs, and crystal forms. A brief explanation of the Biopharmaceutics Classification System, aqueous solubility, and solvent classification is also stressed, in addition to the previously mentioned subjects.

1H NMR, IR, PXRD, and DSC analyses were used to produce and characterize the novel tinidazole salts and molecular salts. The observed patterns of variation in TN and TN-PTSA's powder X-ray diffraction suggest that their crystal structures differ. TN-PTSA is a more physically stable molecule than TN, according to the DSC data. The DSC data agrees with the Karl Fisher titration and TGA results. In comparison to TN, the

solubility of TN-HCl was enhanced by 86.8 times, and TN-PTSA was enhanced by 49.7 times. In comparison to TN and TN-Hydroxybenzoic acids, TN-PTSA demonstrated notable antibacterial, anti-inflammatory, and analgesic properties. The TN-EBA, TN-DBA, and TN-VA were the TN-Hydroxy benzoicacids that shown the best antibacterial, anti-inflammatory, and analgesic properties in comparison to TN. The improvement in the aforementioned tested activities indicates that TN-PTSA, a pharmaceutical salt of tinidazole with p-toluene sulfonic acid, can be used as a substitute for tinidazole and has the potential to be developed as an oral formulation with better solubility and bioavailability than the poorly water-soluble TN. For filtration in manufacturing, rod-shaped crystals are typically preferred. The rod-shaped TN-PTSA crystals are simple to filter during manufacture. Thus, TN-PTSA can be utilized to conduct additional study with the goal of lowering the dosage of the medication tinidazole in order to treat infections caused by Gram-positive Bacillus bacteria. The pharmaceutical salt of tinidazole with p-toluene sulfonic acid (TN-PTSA) may also be a viable alternative to tinidazole, as evidenced by the enhanced antibacterial activity.

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