Cases where polymorph plays a vital role?

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Abstract- The polymorph of final compound plays a vital role in the dissolution and solubility of the drug. The research paper highlights some of the landmark cases in which polymorph have gained high attention and the market was affected due the changing of polymorphs. The shelf life of the drug is based on the polymorph and many a times the entire strategy of drug designing is changed including the formulation due to the polymorphic changes and transitions during the process of formulation.

Key words: Ritonavir, Polymorph, crystalline, amorphous.

Introduction

Some case studies are presented here to illustrate how drug formulations had to be changed due to alteration in properties of active pharmaceutical ingredients (API) resulting from polymorphic transformations. The development of new polymorphs is thus an important patent strategy in the pharma industry. Control on polymorphism is used to optimize the API- physical properties, both for processing as well as drug deliveries [1].

1 Ritonavir

Ritonavir (**1**) is an anti retroviral drug used to treat HIV infections. It is marketed by Abbott Labs.

The drug was introduced in the market in 1995, as semi solid capsule having one polymorph only melting at 122^{o}C. Literature survey reveals that this drug was withdrawn from the market by the company in the summers of

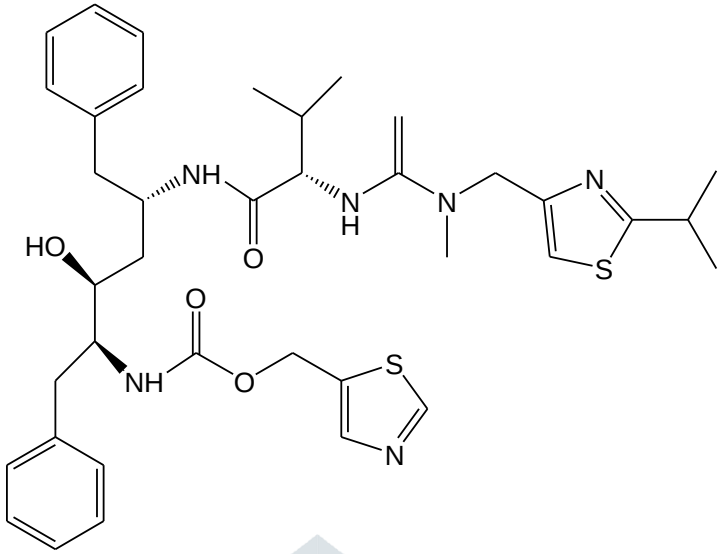

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Fig 1.5 Structure of ritonavir

1998, on changes shown in the dissolution profile. On investigation by the innovator, it was found that a polymorphic transformation had occurred due to high temperature resulting into another polymorph having higher melting point i.e., 125ºC. Further research on the molecule resulted in reporting of three additional polymorphs having melting points 80ºC, 97ºC and 116ºC, respectively. In this specific case, the temperature had affected the polymorphic transformation and the new polymorph changed the bioavailability of the drug. To overcome this problem, the formulation of the drug was replaced by refrigerated gelcaps, instead of capsules. Recently, ritonavir has been reformulated into a white oblong solid tablet that no longer requires refrigeration [2].

2 Enalapril maleate

Enalapril (**2**) is an antihypertensive drug which functions against chronic heart failure. It is one of the first members of the group of angiotensin converting enzyme (ACE) inhibitors. It is marketed under the brand name of vasotec as its maleate salt by Valeant International.

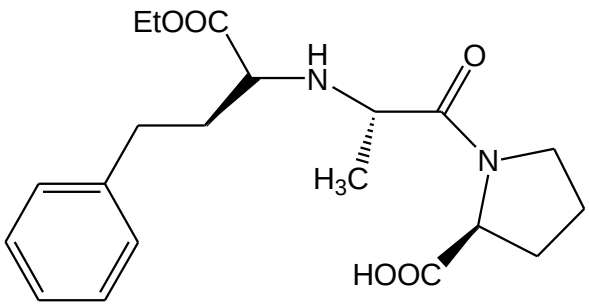

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Fig 1.6 Structure of enalapril

Two polymorphs Form I and Form II have been reported for enalapril. Both forms exhibit similar properties, like solubilities, dissolution characteristics, heats of solution, Raman and IR spectra, and DSC thermograms. Although Form II has been reported to be thermodynamically more stable, than Form I but at the same time it is more prone to degradation to the diketopiperazine derivative [3]. The potential difference in degradation rate of the two polymorphs has been minimized by addition of sodium bicarbonate or some other suitable stabilizer to the tablet formulation of Form II [4]. Both forms of enalapril are being marketed now.

3 Ranitidine hydrochloride

Rantidine (**3**) is a H_2-receptor antagonist used to treat peptic ulcer and gastroesophageal reflux disease (GERD). It is marketed under the trade name of zantac as its hydrochloride salt by Glaxo Smithkline.

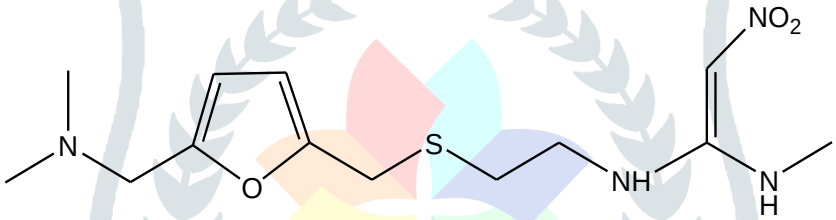

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Fig 1.7 Structure of ranitidine

Two polymorphs of ranitidine hydrochloride are reported in the literature, Form I and Form II. Form II is more stable than Form I and the melting points are in the range of 140-144^{o}C and 134-140^{o}C, respectively. Both polymorphs have been reported to be bioequivalent [5]. As a patent strategy, the innovator company (Glaxo Smithkline) patented Form II later than Form I but marketed Form II earlier than Form I. The generic companies were forced to use the less stable Form I for early entry in the market as product patent for ranitidine Form II was expiring later.

4 Terazosin hydrochloride

Terazosin (**4**) is a α_1-adrenoceptor receptor antagonist, used to treat enlarged prostrate along with hypertension by lowering blood pressure in men. It is marketed under the brand name of hytrin or zayasel and sold as its hydrochloride salt by Abbott Labs.

It has been reported in the literature that terazosin exists in three different anhydrous (I, II, III) [6], one monohydrate [7] and one dihydrate form [8]. The stable dihydrate form is found to be approximately 10 times lesser solubility than the anhydrous form [9], but both show the same dissolution profile. Both forms have been marketed keeping a check on the water content based upon the hydrate polymorph being used.

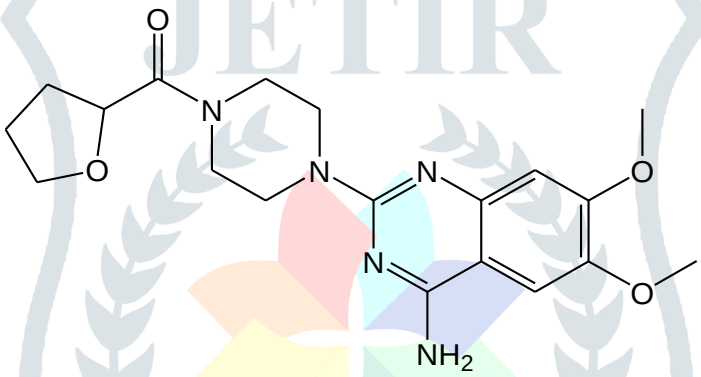

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Fig 1.8 Structure of terazosin

5 Torsemide

Torsemide (**5**) is a diuretic pyridine sulfonyl urea type compound. It is marketed under the brand name of demadex and diuver by Meda Pharms.

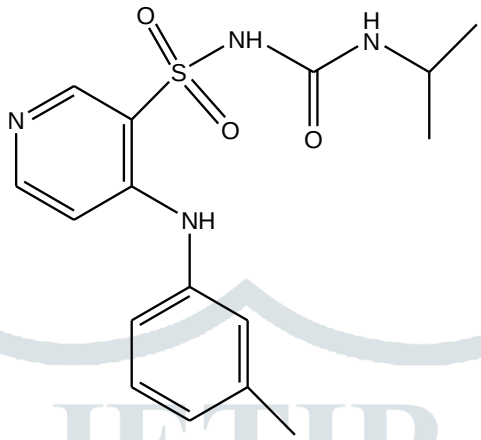

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Fig 1.9 Structure of torsemide

It is reported to exist in two modifications (Form I and Form II) and one solvate (Form A), the latter contains water and alcohol [10]. Out of the two marketed forms, Form II is 3 times more soluble than reported Form I and is not readily converted to latter. However an ANDA has been approved and currently marketed drug formulation of torsemide does not have the form reported in the reference listed drug (RLD). This case indicates that drug formulation and manufacturing process may also affect drug performance by masking any potential effect arising due to polymorphism.

6 Carbamazepine

Carbamazepine (**6**) is an anticonvulsant and a mood stabilizing drug which is used to treat epilepsy, bipolar disorders as well as trigeminal neuralgia. It is marketed under the brand name of tagretol by Novartis.

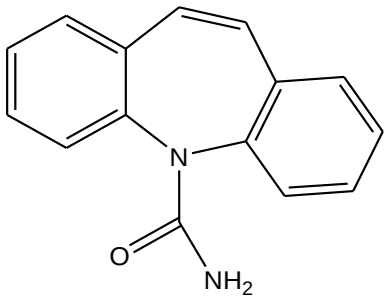

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Fig 1.10 Structure of carbamazepine

It has been seen to exist in 3 non-solvated Forms (α, β, γ) and in one dihydrate form, latter exhibiting the lowest solubility [11]. The β form and dihydrate form show the same bioavalibilty. In the case of tablets β form of carbamazepine is used due to its solubility and processibility characteristics, while the lesser soluble dihydrate form is used in supensions. This is a classic example of two different morphs being used in two different formulations of a drug [12].

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