# CHAPTER – 1

# INTRODUCTION

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## 1.0 INTRODUCTION

In the world of pharmaceutical analysis, the analyst's job mainly revolves around analysis of the Active Pharmaceutical Ingredient (API) or the finished formulation.
The API is also known as "Drug Substance" whereas the final formulated material is known as "Drug Product". The other analytical field involves the analysis of the intermediates, in process or inactive ingredients.

Getz Pharma Research (GPR) is a contract research organization (CRO) dealing in formulation development for worldwide markets. The work presented in this thesis has been carried out at GPR on the drug products developed at GPR.

In the modern world of Pharmaceutical analytical sciences, developing a good stability indicating analytical method in a short time is an ever challenging job. Even if there are official methods available in internationally accepted pharmacopeia, often these methods need optimization and in some cases substantial changes. The method development scientist has to face mainly two types of challenges as mentioned below:

- The Drug Substance: Different sources of a single Active Pharmaceutical Ingredient (API), in the sphere of intellectual property protection, results in different API manufacturing process. This, in turn generates new process impurities; thus analytical methods need to be modified to accommodate these ever changing processes.
- Drug Product: In drug product, patent circumvention often leads to changes in excipients wherein the analyst has to go about changing the method once again to suite the placebo behaviour. The drug substances, often, reacts with new excipients to form additional products which may not be covered in the official methods.

The real challenges, however, come from the drug products which do not have any official methods. In today's therapeutic culture very often more than one drug is being given to patients to fight against an ailment. This is often, we are realizing that a single

symptom may be caused by a number of factors and the treatment has to be likewise, attacking a number of targets.

In some cases two or more drugs complement each other in their activities. Taking a single drug does not yield the expected result. In some other cases another drug or supplement may be given to reduce the side effect of the other drug. Thus there has been a significant surge in launch of multi-therapy drug products (formulations containing more than one drug substance) instead of mono-therapy ones (containing one drug substance).

Apart from the therapeutic reasoning, there are two practical and very relevant advantages of combination drug therapies, if these are combined into a single formulation.

- The patient needs to take only one pill of the drug product wherein he/ she gets all the medicines. Thus missing a pill becomes less of an occurrence.
- From manufacturers' point of view, this translates into less manufacturing cost (in terms of time and manpower) and thus lowers the cost of the finished product for the patient. Additionally this also becomes a good marketing strategy to have more brand-following for the manufacturing company.

However, these activities of adding more than one API in a single drug product give rise to monumental challenges for the formulator and the analyst. While the formulator struggles to find a stable combination of drugs and excipients, the analyst tries to ensure that the method is flexible enough to accommodate and understand the frequent changes in the formulation development trials.

The factor one tends to forget a lot is "Time". The time taken for analysis and thus the release of results, directly affects the formulation development cycle and production at large. For multi-drug products this is of paramount importance since the analysis time, more often than not, is directly proportional to the number of drug substances in the drug product. Thus special importance is given to development of single method which can detect two or more actives in a single HPLC run. In other words "Simultaneous Determination" is the ideal choice for any organization.

Among the analytical methods to be developed, the most difficult obviously, is the one for related substances, followed by assay and then dissolution. These three tests are essentially the most critical part of any drug development.

Apart from multi-dose drug products, one of the other challenges that are faced by an analytical method developer is on new molecules, or molecules on which information is not readily available. Molecules developed at Japan are notorious for lack of available information. The main reason behind this is the language barrier which is now slowly but steadily dissipating.

This PhD thesis entails the development work for stability indicating analytical methods for a combination tablet of Telmisartan and Hydrochlorothiazide. The methods include related substances, assay and dissolution.
The second formulation on which similar work has been conducted is Nicorandil tablet.

All the above developed analytical methods have been fully validated as per ICH guidelines.

## 1.1 PRELUDE TO THE THESIS

This thesis is divided into ten chapters

**Chapter 1: Introduction**

It highlights challenges faced for analytical method development for drug products in the new world scenario.

**Chapter 2: General Literature Survey**

It provides information and importance of stress studies in method development and validation. It also emphasizes on development and validation of stability indicating method by HPLC and degradant product characterization, whenever required.

**Chapter 3: Research Envisage**

This part highlights aim and comprehensive plan of the present research work.

**Chapter 4, Chapter 5 and Chapter 6:**

Chapters 4 to 6 describe experimental and development work carried out on the combination drug product of Telmisartan and Hydrochlorothiazide (two different strengths) and the subsequent validation of methods.

**Chapter 7, Chapter 8 and Chapter 9:**

Chapters 7 to 9 describe experimental and development work carried out on the drug product of Nicorandil and the subsequent validation of methods.

**Chapter 10:**

References