OBJECTIVES OF THE WORK

The number of drugs introduced into the market is increasing every year. These drugs may be either new entities or partial modifications of the existing ones. Very often, there is a time lag from the date of introduction of a drug into the market to the date of its inclusion in pharmacopoeias. This happens because of the possible uncertainties in the continuous and wider usage of these drugs, reports of new toxicities (resulting in their withdrawal from the market), development of patient resistance and introduction of better drugs by competitors. Under these conditions, standards and analytical procedures may not be available in pharmacopoeias. It becomes necessary therefore, to develop newer analytical methods for such drugs.

Market is flooded with combination of drugs in various dosage forms. The multicomponent formulations have gained a lot of importance nowadays due to greater patient acceptability, increased potency, multiple action, fewer side effects and quicker relief. There is a plethora of analysis of such formulations without prior separation. Simultaneous analysis procedures are now being used more frequently for estimation of drugs in multi-component pharmaceutical formulations due to their inherent advantages viz. avoid time consuming extraction and separation, economical in the sense that use of expensive reagents is minimized are equally accurate and precise. For the estimation of multi-component formulation, the instrumental techniques, which are commonly employed, are Spectrophotometry, HPLC, GLC, HPTLC, LCMS etc. These methods are based upon the measurement of specific and nonspecific physical properties of the substances.

The existing analytical procedures may require expensive reagents and solvents. It may also involve cumbersome extraction and separation procedures and
Most of the drugs in formulations forms and in biological samples can be analysed by UV Spectrophotometric, HPLC and HPTLC methods because of the several advantages like rapidity, specificity, accuracy, precision, and ease of automation. These methods eliminate tedious extraction and isolation procedures. Some of the advantages of these methods are speed (analysis can be accomplished in shorter time), greater sensitivity (various detectors can be employed), improved resolution (wide variety of stationary phase), reusable columns (expensive columns but can be used for many analysis), ideal for the substances of low volatility, easy sample recovery, handling and maintenance, instrumentation lends itself to automation and quantitation (less time and less labour), precise and reproducible, calculations are done by integrator itself etc.

In the early part of this century, colorimetric and Spectrophotometric methods were used for drug analysis due to reasons of economy and easy availability. These methods however are used to a lesser extent today because they lack specific, sensitivity and accuracy.

For the estimation of the drugs present in formulations or in biological fluids, HPLC and LC-MS, LC-MS/MS methods are considered to be most suitable.

- **Aim of the work is to develop new method which is simple, precise and economical UPLCMS/MS and HPLC method for simultaneous determination of antihypertensive and antidiabetic class of drugs in the pharmaceutical formulations using internal standard**

- **To validate the developed method in terms of specificity, sensitivity, linearity range, accuracy, precision and ruggedness, limit of detection and limit of...**
quantification following ICH guidelines

SELECTION OF DRUGS

Antihypertensive agents:

Antihypertensive agents are now widely used for the treatment of various forms of hypertension. Antihypertensive agents in the form of monotherapy make simple treatment schedules possible, only a limited number of hypertensive drugs can be used in this way. These drugs are Beta blockers, diuretics, calcium antagonists and Angiotensin-Converting Enzyme (ACE) inhibitors. All other antihypertensive drugs cause sodium and water retention during chronic application. Thus, their blood pressure lowering action decreases or even totally disappears.

It is known several patients with hypertension require two or more antihypertensive drugs with complementary mechanisms of action to lower their blood pressure. The angiotensin II type 1-receptor antagonist (Amlodipine, losartan, atenelol and Telmisartan) and the diuretic Hydrochlorothiazide are two antihypertensive agents that have a well recognized clinical efficacy. Their combination was shown in randomized, controlled trials to be more effective than each agent alone in lowering blood pressure, due to a dual and synergistic mechanism.

a. **Drugs used for monotherapy**

- Beta blockers
- Diuretics
- Calcium antagonists

b. **Combinations of two antihypertensive drugs**

- Beta blockers and Diuretic
- ACE inhibitor and Diuretic
- Calcium antagonist and Diuretic
Objectives

Betablocker and Calcium antagonist
ACE inhibitor and Calcium antagonist
c. Useful Combinations of three antihypertensive drugs
   Betablocker, Diuretic and Vasodilator
   ACE inhibitor, Diuretic and Calcium antagonist
d. Drugs selected for the study from their combined dosage forms
   Amlodipine, Losartan, Atenelol, Hydrochlorothiazide, Telmisartan,
   Bisoprolol and Ramipril
   Pharmaceutical dosage form:
   Teram-H5, Losar-Beta H, Nusar AHM

Antidiabetic agents:

Diabetes and its abnormalities constitute a major health problem in the modern society. It is characterized by disrupted insulin production, leading to high blood glucose concentration and other complications such as renal dysfunction, neuropathy and cardiopathy. Type II diabetes is a complex metabolic disorder with two major biochemical defects, namely impaired insulin secretion and impaired insulin action at the periphery. Chronic hyperglycemia results from these defects. Many oral antidiabetic drugs with different mechanisms of action have been developed to lower blood sugar and delay the occurrence of serious complications in patients with type II diabetes. For glycemic control in such cases, monotherapy with an oral antidiabetic agent is not adequate to achieve satisfactory blood glucose control. Thus, combination regimens which include drugs with different and complementary mechanisms of action are recommended. The combinational therapy for type II diabetes is frequently prescribed when mono therapy fails. The combination of metformin (MET) and voglibose (VOG) is approved by FDA for treatment of type II diabetes.
Chapter 2

Objectives

a. Drugs used in monotherapy
b. Combinations of two antidiabetic drugs
c. Useful Combinations of three antidiabetic drugs
d. Drugs selected for the study from their combined dosage forms

Triglycomet, Trilopace, Geoglit GM and Posmeal MET