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THE COMPARATIVE ANALYTICAL METHOD DEVELOPMENT STUDY OF GENERIC VS BRANDED DRUGS

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Abstract: The current goal of the project is to build a comparative analytical methodology for studying generic versus branded medications utilizing various brands, such as Micardis. By using the system's 0.98-m axial resolution to discriminate between GSK's branded Panadol tablets and generic paracetamol using UHROCT apparatus, we were able to demonstrate its usefulness and capacity. The method employed in this study demonstrates how FMEA may be used to screen possible variables for PBD study in order to reduce the overall number of tests carried out for the development of analytical methods. For the estimation of the above-mentioned anti-cancer drugs (Imtanib Mesylate, Nilotinib, Dasatinib) in pharmaceutical dosage forms, human plasma, rabbit plasma, serum, urine, culture medium, cell preparations, etc., sensitive and accurate RP-HPLC methods, stability-indicating HPLC, HPLC-PDA, HPLC-UV, stability-indicating HPTLC and HPLC-MS, and solid phase extraction methods were developed. It is evident from this work that it is feasible to create a novel sensitive and precise HPLC approach for anti-cancer medications. Regular testing of generic medicinal items can greatly benefit from the use of UPLC technology, which can boost sample throughput and reduce solvent use (and eventual disposal). The systematic procedures described in this work will be useful for streamlining the production of generic AmpB liposomal formulations and verifying the similarity between generic and reference goods.

Keywords: Generic, Branded, HPLC, UPLC

I. INTRODUCTION

The pharmacokinetic and pharmacodynamic parameters are the strong predictors of the therapeutic response of the drug. Pharmacodynamics is a link relating dosage forms with pharmacological effects, especially how solid dosage forms are absorbed in vivo. In the process many complicated factors are involved, among which, drug disintegration and dissolution are very important ones Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers such as Telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. The pharmacokinetics of orally administered Telmisartan is nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. The solubility of telmisartan in aqueous solutions is strongly pH-dependent, with maximum solubility observed at high and low pH. In the range of pH 3–9 it is only poorly soluble. Telmisartan is active as such: it is not a prodrug. The Telmisartan molecule is unusually stable. Formulations of different brands have different types and/or amount of diluents, disintegrants, lubricants, or other excipients. They may be also subjected to different compression forces which affect the disintegration and dissolution rate of a given formulation. Apart from this, feedback from doctors that some Telmisartan brands need to be given more than the recommended once daily dose or that doses higher than the recommended 80 mg are required to produce the desirable clinical effects necessitated a study comparing the dissolution profiles and other parameters of these generic Telmisartan brands with that of the innovator brand Micardis.[(Gosse, 2006)] Systems for ultra-high performance liquid chromatography benefit from advances in particle chemistry performance, system optimisation, detector design, and data collection. processing. When all of these accomplishments are considered, chromatographic performance has improved. UPLC boosts the overall connected qualities of speed, sensitivity, and resolution while maintaining the usefulness and principles of HPLC. The evolution of the packing materials employed to produce the separation was the driving force behind the creation of the UPLC technology. The van Dee metre equation, which explains the relationship between linear velocity and plate height, governs the underlying principles of this evolution [(Eswarudu et al., 2012)]. An organised method for identifying potential issues, failures, and their impacts on the system or process before a negative event takes place is called a Failure Mode and impacts Analysis (FMEA). In contrast, root cause analysis (RCA) is a methodical method for dealing with issues after they arise. FMEA involves finding and fixing process flaws to stop an undesirable event from happening. [(QAPI., 2011)]

Method validation: (Rina, R., Baile, M., & Jain, A., 1998)

- Validation is concerned with assuring that a measurement process produces valid measurements;
- Results from method validation can be used to judge the quality, reliability and consistency of analytical results. It is an integral part of any good analytical practice.
- A measurement process producing valid measurements for an intended application is fit for purpose.
- Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice.

Analytical methods need to be validated or revalidated

- Before their introduction into routine use;
- Whenever the conditions change for which, the method has been validated (e.g., an instrument with different characteristics or samples with a different matrix); and
- Whenever the method is changed and the change is outside the original scope of the method.

Nowadays, there are several international renowned organizations offering guidelines on method validation and related topics.

- American Society for Testing and Material (ASTM)
- Codex Committee on Methods of Analysis and Sampling (CCMAS)
- European Committee for Normalization (CEN)
- Cooperation on International Traceability in Analytical Chemistry (CITAC)
- European Cooperation for Accreditation (EA)
- Food and Agricultural Organization (FAO)
- United States Food and Drug Administration (FDA)
- International Conference on Harmonization (ICH)

ICH Guidelines (ICH Q2R1) for Analytical Procedure and Validation: The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc. (Harron, D. W. G. 2013)

Following are the Validation Parameters: (Raja & Ganesan, 2012)

1. Accuracy: The accuracy of an analytical method is the degree of closeness between the 'true' value of analytes in the sample and the value determined by the method. Accuracy is often determined by measuring samples with known concentrations and comparing the measured values with the 'true' values. At least 9 conclusions of minimum 3 concentration levels could be performed which should cover the predetermined range is known as accuracy. For instance, three replications each from three concentrations could be performed to analytical procedure. Either the percent recovery or the difference between the mean and the accepted true value together with the confidence intervals should be recorded as the result of accuracy. (ICH harmonized tripartite guideline).

2.Precision: Precision of a method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings. Precision is measured by injecting a series of standards or analyzing series of samples from multiple samplings from a homogeneous lot. For the homogeneous sample, sampling should be done for the multiple time. Measurement series are gained. Precision is performed in predetermined condition. The result i. e. scattering of the result must be very close.

3.Repeatability: Repeatability is the phenomenon where tests are conducted by identical test subjects with the same method, with the same method in short span of time. The type of precision which are performed within equivalent working environment and parameter. It must be completed in small interval of time. Intra-assay precision is another term given for it. Evaluation of this test is done from nine conclusions. It should cover the specific range while preparing the sample. For example, at least three replications each from three concentrations can be performed. Another way of analysis is examining minimum six 100% samples.

4.Intermediate Precision: Intermediate precision (also called within-laboratory or within-device) is a measure of precision under a defined set of conditions: same measurement procedure, same measuring system, same location, and replicate measurements on the same or similar objects over an extended period of time. Intermediate precision is a measure of the ruggedness of the method, i.e., reliability when performed in different environments. Demonstration of intermediate precision requires that the method be run on multiple days by different analysts and on different instruments. At a minimum, such studies should be run on at least two separate occasions. This type of precision can be performed by variation in laboratory condition. The Specificity test can be done in alternate days, by another person, by other machine, etc

5.Detection Limit: The detection limit in a particular analytical procedure is the most minimal measure of chemical in a sample which could be identified yet not really evaluated as the accurate measurement i. e. quantification cannot be exact. From instrumental or non-instrumental process basis, a few methodologies for deciding the detection limit are possible. Some approaches for determination are explained below

- Visual Evaluation basis.
- Signal-to-Noise basis:
- Standard Deviation of the Response and the Slope basis.
- Standard Deviation of the Blank basis

6.Quantitation Limit: the lowest analyte concentration that can be quantitatively detected with a stated accuracy and precision. The quantification limits in the particular analysis methods are the most minimum quantity of sample chemical from which quantitative assay of component can be calculated. The result should be within the acceptable range. Few methodologies in deciding the limit of quantitation can be performed based on non-instrumental or instrumental procedure.

7.Linearity: Capability to elicit check consequences which might be at once, or with the aid of well described mathematical adjustments, proportional to the concentration of analytes in within a given range. Linearity is determined by creating a minimum 5 level calibration curve using the analyte(s) of interest. The resulting plot of detector response versus analyte concentration should have a regression coefficient of at least 0.999, and should be visually inspected for areas of non-linearity. Linearity is generally indicated by the calibration curve, which shows that the measurement or data of the testing substance is directly proportional with the quantity of the testing chemical in the sample. Such capacity is the knows as linearity. It should be performed within the rang. The value of R2 is studied in the linearity. It must be within the range i.e near to one. Samples are prepared either by diluting the

standard stock solution or weighing different amount of sample as per the protocol. Solution of different concentration should be prepared. At least five concentrations must be prepared for analysis.

8.Range: interval from the upper to the lower concentration of the analyte in the sample e.g. drugs for which the analytical method has been demonstrated to work with acceptable level of trueness, precision, and linearity. The linearity studies for a method usually define the range for it. The criteria of ranges that should be followed are given below:

1) Normally the range of assay of the finished good of drug lies between 80 to 120 percent of label claim.

2) While performing the content uniformity, it should be within the range of 70 to 130 percent of label claim. Proper justification should be example given if broad range has to be set for metered dose inhalers.

3) Plus minus 20 percent is recommended in case of dissolution test.

II. Materials and Method:

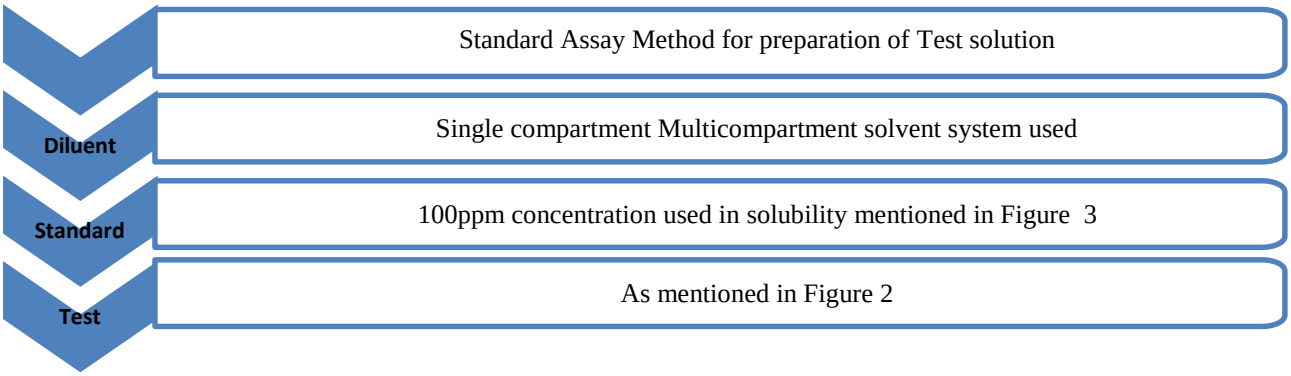

Fig. No.1: Method to follow to performed assay

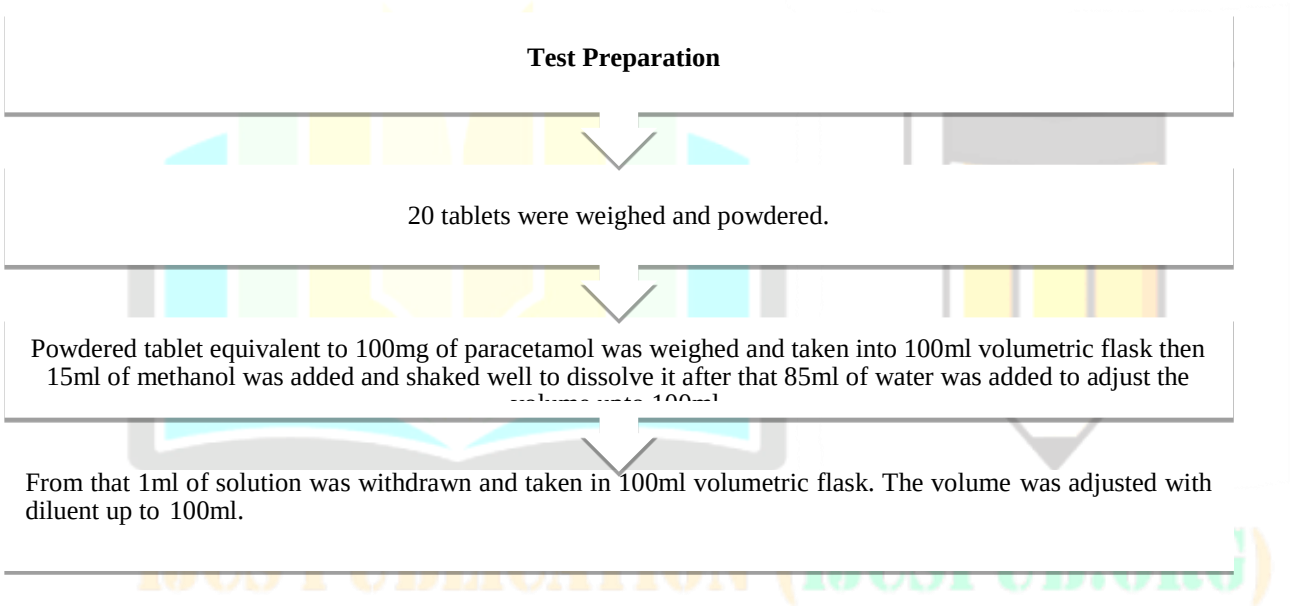

Fig. No.2: Standard Assay Method for preparation of Test solution

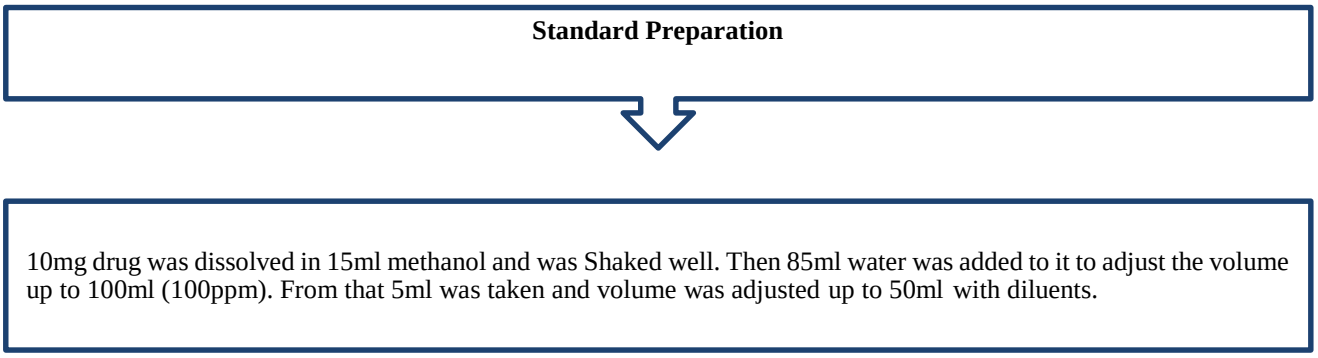

Fig. No.3: Standard Assay Method for preparation of Standard solution

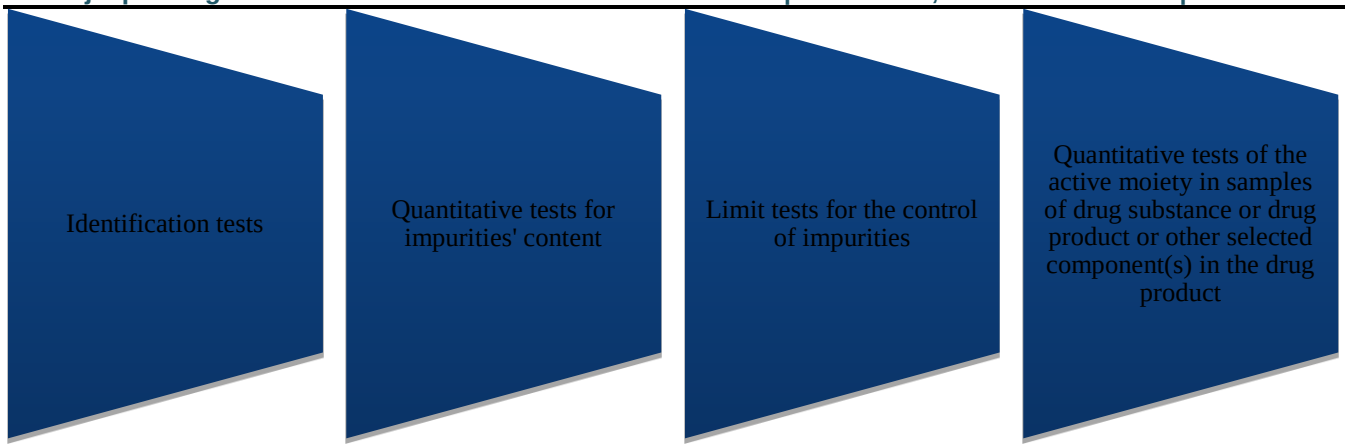

Fig. No.4: Analytical Procedures to be validated

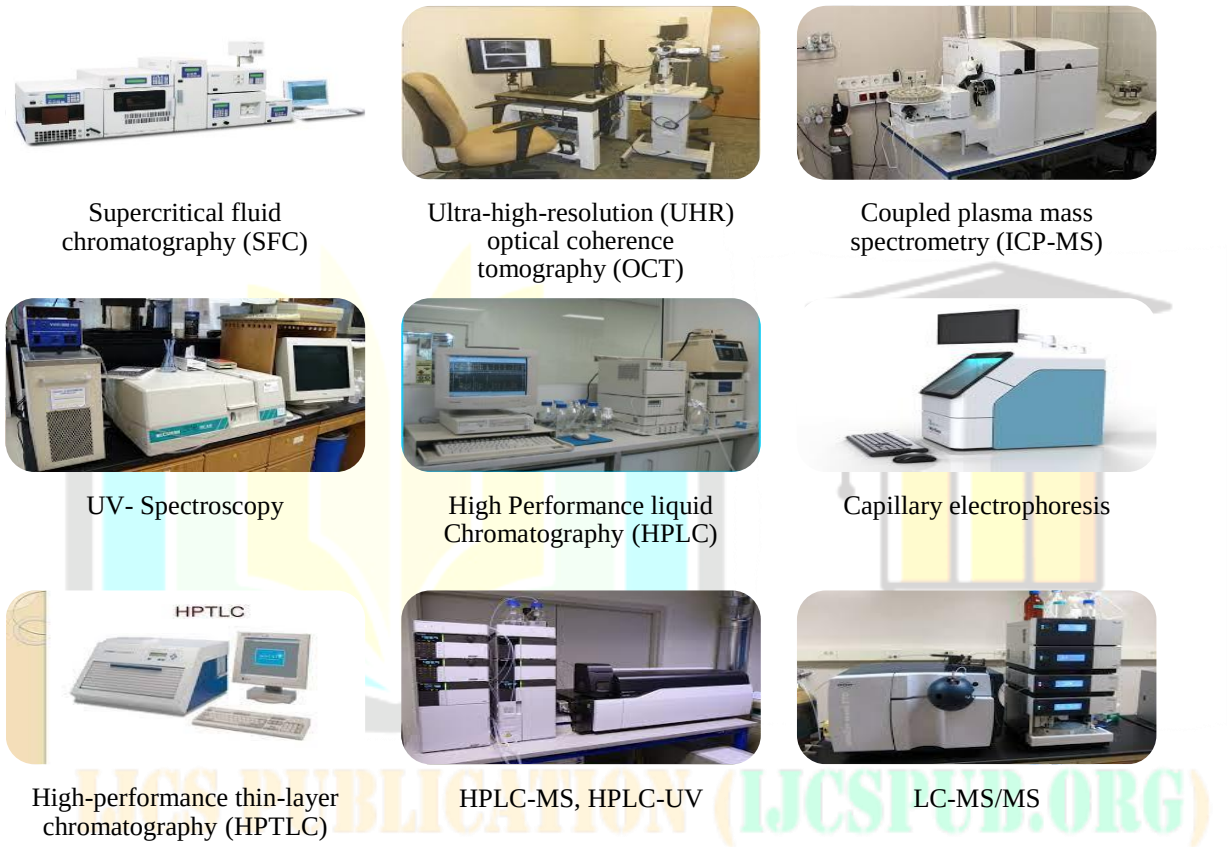

Fig. No.5: Instruments used in Analytical Method Development

III. Result and Discussion:

For branded Panadol, the associated A-scan wave patterns confirm a weak air/coating contact, but not for generic Panadol. Both branded and generic products failed under these conditions, and we found that generics were released later (that is, had a longer half-life) than brands. It can be seen that the typical particle size is smaller than the brand's particle size, and the simple and ideal dissolution rate of drug particles is often inversely proportional to the particle size, resulting in faster dissolution. But this trend was not. The case here is probably because the iron-sodium gluconate complex in sucrose is a complex product and the comparison is cross-formation (i.e. generic and branded). Current comparative studies show that both linezolid branded and generic tablets are of the same quality and meet all the criteria set by the Pharmacopoeia standards. The following data show all comparative values for the linezolid 600 mg tablet formulation.

Formulation	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Drug content(mg/tablets)
Brand-A	102±0.93	5.8±0.2	0.98	98.11±0.4
Brand-B	107±0.98	6.1±0.2	0.98	99.45±0.2
Brand-C	138±0.72	6.8±0.2	0.98	100.75±0.2

Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice. This HPLC method for the determination of impurities of divalproex sodium is analyzed against external standard using HPLC with UV detector at 210 nm analytical wavelength. Test method is validated on Specificity,

Linearity/Range, LOD and LOQ, Accuracy, Precision (Repeatability and Intermediate Precision) the simultaneous estimation of imatinib, nilotinib and dasatinib in dried blood spot by HPLC- MS. The chromatographic separation of drugs achieved by C18 column and eluted with gradient mode through the mobile phase A was 0.1% formic acid in milliQ water and mobile phase B was 100% acetonitrile. The MS was operated in positive ESI mode and the drying temperature, flow rate were 275 c and 5L/min. Mass spectrometer was operated in MRM mode. This method was validated in terms of linearity, selectivity, specificity, accuracy, precision and stability.

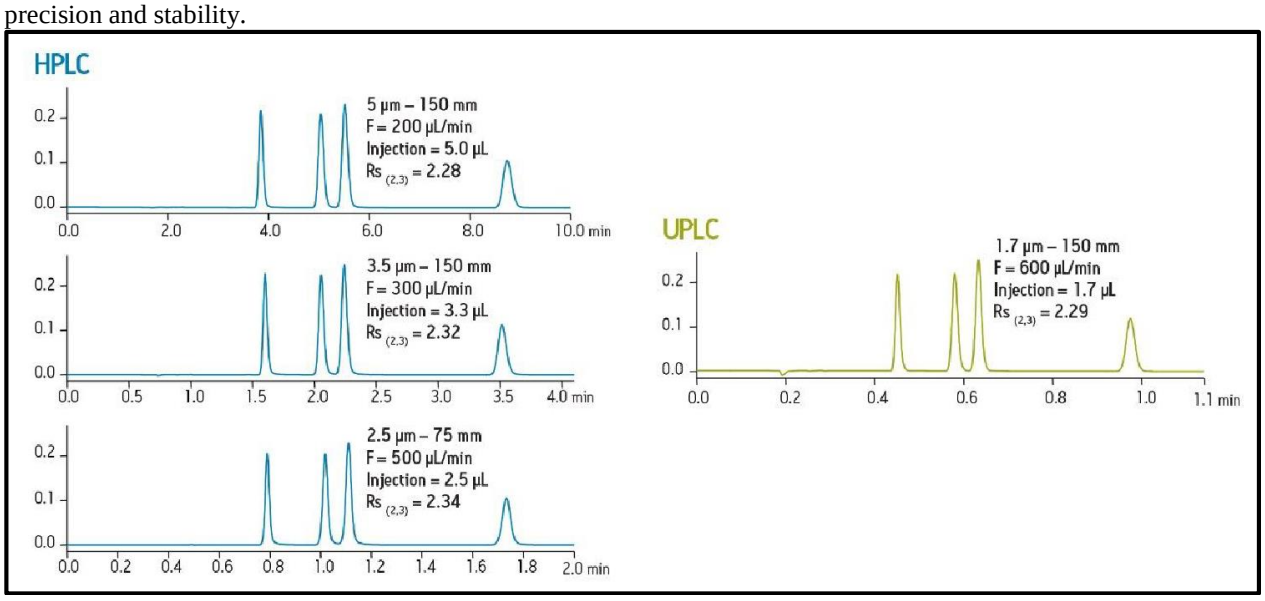

Fig. No.6: Schematic Graphical Representation of HPLC and UPLC

IV. Conclusion:

We created a UHROCT apparatus, as well as automated segmentation and analysis algorithms, for imaging pharmaceutical tablets with thin coatings in this study. We showed the system's capability and effectiveness by using its 0.98-m axial resolution to resolve 4-m thick pill coatings, allowing us to distinguish GSK's branded Panadol tablets from generic paracetamol. Identify some differences in the physicochemical properties of iron nanoparticles. These differences were (i) iron instability measured in acid release tests (faster iron release in branded products compared to general products (at least twice)), and (ii) measured in DLS. Particle size (particle size branded products were larger than generics and particle size was reduced by diluting the sample) and (iii) molecular weight by GPC (branded products were larger than generics). Validated UV-spectrophotometer methods for the determination of Losartan potassium in pharmaceutical dosage preparations (tablets) by the external standard method at 288 nm were applied. The process demonstrated in this study illustrates how FMEA can be used to screen potential variables for PBD study to minimize the total number of experiments conducted for the analytical method development. All potential factors and all critical responses are studied to determine the relationships and effects. It can be concluded from the results that the method is robust for most of the factors evaluated by FMEA. The analysis time is influenced by the flow rate and percentage of organic solvent in mobile phase. The original design was further modified through software optimizer and validated to be workable and efficient. A sensitive and accurate RP-HPLC methods, stability-indicating HPLC, HPLC-PDA, HPLC-UV, stability indicating HPTLC and HPLC-MS, with solid phase extraction methods was developed for the estimation of the above selected anti-cancer drugs (Imtanib Mesylate, Nilotinib, Dasatinib) in pharmaceutical dosage forms, human plasma, Rabbit plasma, serum, urine, culture medium, cell preparations etc. The above methods was evaluated for Specificity, Linearity, Accuracy, Precision, Ruggedness and Robustness as

per ICH&FDA guidelines. From this study it is clear that it is possible to develop a new sensitive and accurate HPLC method for anticancer drugs. Micardis tablets at both the strengths showed consistently higher release at pH 4.5 and 7.5 (i.e., pH conditions relevant to the intestine) suggesting its pharmacokinetic activity could be perhaps superior to other marketed brands as it would release the drug consistently irrespective of pH. UPLC Technology can provide tremendous benefits to routine testing of generic drug products, including increased sample throughput and decreased solvent consumption (including subsequent disposal). Analysis times can be reduced by 70 to 90%, and solvent consumption can be decreased by over 90%. This offers significant cost benefits associated with running more samples in less time, and can decrease the overall operating expenses in development and quality control laboratories. Most of all, it helps provide a competitive advantage to generic drug companies who leverage UPLC Technology to bring drugs to market faster and cheaper. The systematic methods outlined in this study will be helpful for optimizing the manufacturing process of generic AmpB liposomal formulations and confirming the similarity between generic and reference products.

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