IJBPAS, March, 2023, 12(3): 1378-1388

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

METHOD ADJUSTMENTS, CHANGES, REVALIDATION AND VERIFICATION OF STANDARD AND COMPENDIAL METHODS

NEELIMA K, RAVISANKAR P*, DIVYA B, MUJAHID IMRAN MD, LAKSHMI ABHIGNA M, HARISH G AND SRINIVASA BABU P

Department of Pharmaceutical Analysis, Vignan Pharmacy College, Vadlamudi, Guntur-522213, Andhra Pradesh, India

***Corresponding Author: Dr. Ravisankar P: E Mail: banuman35@gmail.com**

Received 11th May 2022; Revised 15th June 2022; Accepted 18th Aug. 2022; Available online 1st March 2023

https://doi.org/10.31032/IJBPAS/2023/12.3.6988

ABSTRACT

The goal of any analytical measurement is to attain consistent, reliable, and accurate data. Validated analytical methods play a key role in achieving this goal. Most likely analytical methods have to be changed or altered at some stage in the life of the method. Sometimes method parameters may need modification back to their original specifications if the method is no longer meeting performance requirements. Method revision would also be necessary if the scope of a method modifies, such as the addition of new target compounds or a change of the sample matrix. The results from method validation can be used to judge the quality, reliability, and consistency of analytical results, which is an integral part of any good analytical practice. This review paper discusses method adjustments, changes, revalidation, verification of standard methods, and how method validation helps to achieve high-quality data.

Keywords: Revalidation, Accurate, Reliable, Method of adjustment, Analytical methods

INTRODUCTION

Analytical methods **[1]** have to be validated and revalidated in the following instances. When transferred to another laboratory. Before initial use in routine testing.

Whenever the method parameters for which the method has been validated **[2]** change. The change is outside the original scope of the method. An instrument with different samples with a different matrix. Validation of compendial methods gives the validation of analytical methods with all validation parameters from the introduction. The result is a validated method for a specific sample. Verification of compendial methods gives recommendations of compendial methods **[3]** that demonstrate a laboratory's ability to

successfully run the method. Methods are also verified during method transfer by the receiving laboratory.

METHOD ADJUSTMENTS

Most likely analytical methods should be distorted or adjusted **[4]** during the lifetime of the method. As an example, method parameters might need to change back to their new specifications if the tactic is not any longer meeting performance requirements. Method adjustment would even be required if the scope somehow changes, rather like the addition of the latest target compounds or altering- the action of the sample matrix. This chapter discusses both scenarios and recommends when revalidation is required and therefore the way its documented. Frequently, validated analytical methods don't perform as evidently. As an example, chromatographic **[5]** peaks aren't separated because the tactic predicts. This might happen when a method is transferred from a development laboratory to a routine lab or between routine laboratories.

Typically, analysts try and change method parameters like mobile phase composition, column temperature, or flow, to bring the performance back to original specifications. It's unclear if the method has to be revalidated after these kinds of changes.

Answers to the present are addressed for chromatographic methods by Pharmacopeias in Europe and therefore the United States. The article list performance characteristics for liquid and gas chromatography with changes that don't require revalidation **[6]** as long as system suitability parameters are met. There commendations from USP and EP for HPLC **[7-8]** and GC are shown side by side. Recommendations from USP and EP are identical or similar. As an example, the parameters for the column are identical for USP and EP. comparison of HPLC **[9-10]** parameters according to USP& EP.

Table 1: Comparison of HPLC Parameters according to USP&EP

High-performance liquid chromatography		
Property	**USP**	**EP**
Column length	**± 70 %**	**± 70 %**
Particle size	**Reduction by 50%, No increase**	**Reduction by 50 %**
Internal diameter	**Can be adapted as long as the inear flow velocity remains the same**	**± 25 %**
Flow rate	**± 50 % or more, provided the linear flow velocity remains the same**	**± 50 %**
Column temperature	**± 10 °C**	**± 10 °C, maximum 60 °C**
Injection volume	**Reduction allowed as far as precision and detection limit acceptable. No increase**	**Reduction allowed as far as precision and detection limit acceptable. No increase.**
pH of the mobile phase	**± 0.2 units**	**± 0.2 units**
The salt concentration of the buffer	**± 10 %, as far because the allowed change in pH value**	**± 10 %**
Composition of mobile phase	**Minor components ± 30 %, if not more than ± 10 % absolute**	**Minor components ± 30 %,if not more than ± 2 % absolute**

Table 2: Allowed modifications for HPLC and GC

Gas chromatography	USP	EP
Column length	± 70 %	± 70 %
Column internal diameter	± 50 %	± 50 %
Particle size	changes allowed SST must pass	-50%, no increase
Film thickness	-50 to +100%	-50 to +100%
Flow rate	± 50 %	± 50 %
Oven temperature	± 10 %	± 10 %
Injection volume	It May be decreased (if LOD and repeatability ok.)	

The given limits should not be interpreted as saying that any method may be changed up to the limit as long as it meets all performance characteristics. The recommendations are that system suitability tests be performed after any modification. Revalidation **[11]** is not required if all system suitability criteria are met. In other words, the performance of the strategy should be established but doesn't have to be revalidated. The baseline point is usually the last revalidation, not the last parameters before the method changes are implemented, for example, if the flow rate at initial validation was 1.0 min, 1.4 at the primary modification (40 %) and then 1.7 (20 % from last change but70 % from baseline point) the scheme must be revalidated even if the system suitability test (SST) passed. The flow chart that can be followed for the chromatographic method that requires modification is exhibited in **Figure 1**.

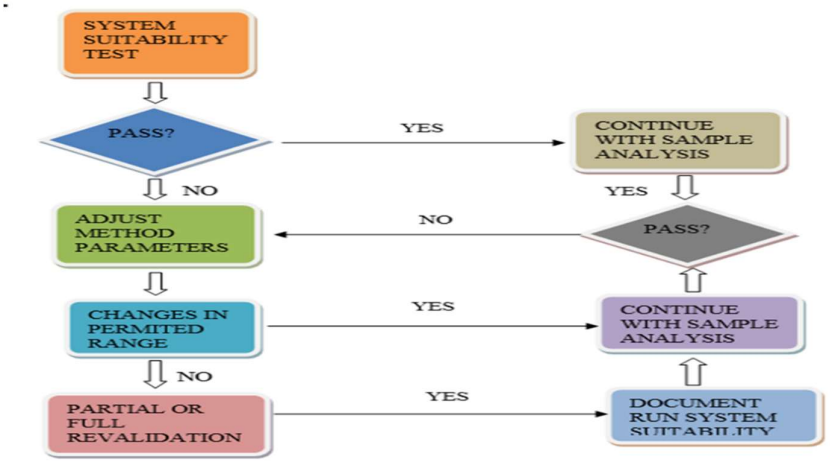

Figure 1: Flow chart for method modification

The USP originally defined the same variations for the inner diameter of the HPLC as the EP (±25%). The USP has changed this with USP 32 Second Supplement (Dec1, 2009). The column diameter changes are allowed, provided that the linear velocity is kept constant according to the formula:

$$F_2 = F_1 \frac{l_2 d_2^2}{l_1 d_1^2}$$

Where,

F = flow rate, l = Column length , d = Column diameter

This allows a reduction in mobile phase consumption through reduced column

diameters and flow rates, as long as the method's performance is verified under the new conditions.

Otherwise, the division doesn't allow changes to the column per the monograph. For example, switching to a column with different particle sizes and dimensions may provide a more rapid separation with equivalent, chromatographic performances. However, both these situations currently require revalidation. USP is tuned into this and will edit their requirements to feature resist. A committee, led by USP's H. Pappa, published a stimuli paper in the Pharmacopeial Forum 26. The article proposes a new approach that may both preserve the quality of the Separation as well as expand the changes in particle size beyond the present two-fold decrease.

REVALIDATION PROCESS:

Revalidation of any process is a vital part of the validation. It improves the standard of the product and increases the smoothness of the method.

Revalidation can be done in two conditions.

A. Periodic Revalidation, B. Revalidation after any change

A. Periodic Revalidation: Periodic revalidation is ended to get the change in process that will happen over some time.

B. Revalidation after any change: Revalidation should be done after any change that may affect the standard of the merchandise. Following changes should be followed by revalidation.

1. Any change in raw material including the physical properties as changing the bulk density, viscosity, and the particle size of the material because these can alter the dissolution and the disintegration of the product manufactured.

2. If the source of the raw material is modified because the manufacturer of the material is changed because the quality of the raw material may change due to the change in the manufacturer. This could also affect the quality of the product.

3. If the type of the packing material is changed. As an example, if we modify the glass bottle to the plastic bottle or PVDC to Alu- Alu.

4. If manufacturing procedure is modified as any change in the mixing or blending time, change in RPM, change in the coating process, change in time for drying, etc.

5. Any change with in-process equipment because the automatic system is installed in place of manual, additional feature is added in any instrument, etc.

6. Any change in the production system or change within the utility used in the process as a major change in the HVAC system or any change within the water system, relocation of any equipment or instrument, etc.

7. Any change required within the process due to the change in the technology.The process validation is stated in **Figure 2**.

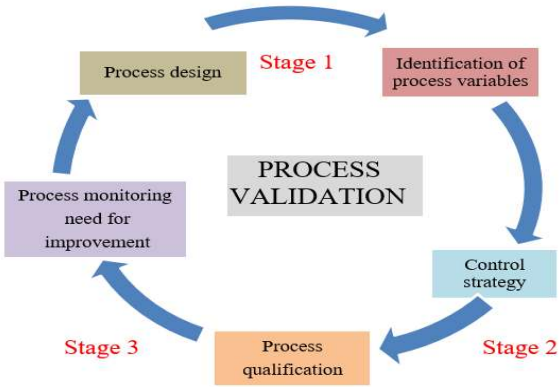

Figure 2: Stages of process validation parameters

Table 3: Parameters for method validation regarding ICH, USP, and ISO 17025

parameter	comment
Specificity	USP, ICH
Selectivity	ISO 17025
Precision	USP, ICH
Repeatability	ICH, ISO 17025
Intermediate precision	ICH
Reproducibility	ICH, defined as ruggedness in USP, ISO 17025
Accuracy	USP, ICH, ISO 17025
Linearity	USP, ICH, ISO 17025
Range	USP, ICH
Limit of detection	USP, ICH, ISO 17025
Limit of quantitation	USP, ICH, ISO 17025
Robustness	USP, Included in ICH as a method development activity, ISO
Ruggedness	USP, defined as reproducibility in ICH

VERIFICATION OF ORDINARY AND COMPENDIAL METHODS:

Laboratories working in regulated or quality standard environments **[12]** are recommended to use the official methods developed by organizations like the EPA, American Society for Testing and Materials (ASTM), AOAC, ISO, or the USP.

For example, the US Food, Drug, and Cosmetic Act requires FDA-regulated industries to use compendial methods or demonstrate equivalency.

ISO/IEC17025states: "Methods published in international, regional or national standards shall preferably be used." These methods are validated therefore many analysts incorrectly assume that the methods will be used as they're without any further validation, verification, or testing exhausted in the laboratory.

The US FDA cGMP regulation statesin21CFR211.194 (a)(2); "If the method employed within the current revision of the United States Pharmacopoeia, or in other recognized standard methods, or is detailed in an approved new drug application and therefore the reference method isn't modified, a statement indicating the strategy and reference will suffice.

This makes it clear that official methods don't have to be validated as long as they're not changed, but the laboratory should

demonstrate that it's capable of successfully running the method. Issues arise when determining the best thanks to trying this.

USP answers these questions in Chapter<1226>: Verification of compendial **[13]** methods. The given recommendations apply to the implementation of compendial methods and standard methods.

The key recommendations are:

1. Demonstrate the performance of the laboratory and system through system suitability tests. 2. Assess the criticality and complexity of the method. 3. Select the most crucial performance characteristics of the strategy. 4. Depending on the criticality and difficulty of the method, repeat one to a few most crucial validation experiments.

Similar to the validation **[14]** of methods developed internally, the evaluation and verification of ordinary methods should also follow a documented process like a validation plan or an SOP. Results should be documented within the validation **[15]** protocol. Both documents are going to be the key source for the validation report.

The process for verification of compendial/standard methods **[16]** is illustrated

1. Define the scope of the analytical tests to be carried out in the laboratory.
2. Verify that the scope of the compendial/standard procedure is identical to the scope defined.
3. If the scope as defined is not identical, modify the existing method or develop a new method and validate for characteristics that don't seem to be identical.
4. If the strategy is identical, perform system suitability tests and run one to three validation experiments, depending upon the criticality of the tactic. If the tests pass acceptance criteria, document the scope, tests, and test results and write a press release that the strategy is prepared to be used.
5. If the test results aren't acceptable attempt to find the explanation or root reason for the problem. This might be inadequate equipment or reference material. If the cause is apparent, correct the matter and test again. This will be an iterative process.
6. If the root cause cannot be found change the tactic or develop a new one.
7. If the required changes are outside acceptable limits as defined in Pharmacopeias, the tactic must be revalidated.

The process for verification of analytical methods is shown in **Figure 3**.

The selected verification tests are application-specific. Recommended verification tests for selected pharmaceutical applications as exhibited in **Table 4**.

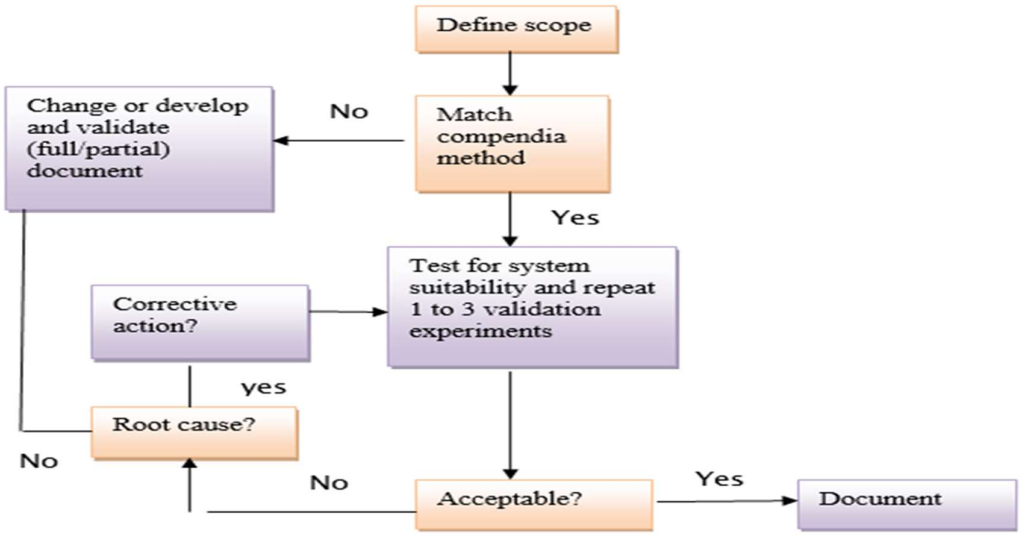

Figure 3: Process for verification of analytical methods

Table 4: Recommended verification tests for selected pharmaceutical applications.

Example #	Application	Recommended Tests
1	Quantization of major compounds of drug substances in finished drugs or APIs	Precision, Specificity, linearity
2	Quantitative determination of impurities in drug substances or degradation products in finished drugs	Precision, specificity, limit of quantification
3	Limit tests of impurities in drug substances or degradation products in finished drugs	specificity, the limit of detection

METHOD VALIDATION

Methods and procedures that are used to assess the standard of pharmaceuticals must meet certain standards of accuracy and reliability (USP, 2013).

The International Conference on Harmonization (ICH) published the Q2 (R1) **[17]** guideline which summarizes the principles and practices for analytical method validation **[18]** (ICH, 2005). The process of validation entails the execution of a set of analytical **[19]** tests and calculations to prove that the particular method is suitable for its purpose. Typical questions that should be answered during method validation **[20]** include.

TERMINOLOGY

Validation paramet**[21]** ers. The following section provides a brief overview of terminology associated with the analytical method **[22]** validation.

ACCURACY

An analytical method **[23]** is considered accurate when the experimental values correspond (within reasonable limits) to the particular true/known values, also referred to like the closeness of agreement (USP, 2013; Graham, 2011). The ICH Q2(R1) document (ICH, 2005) recommends covering the specified concentration range with a minimum of three concentrations with a minimum **[24]** of nine determinations .

PRECISION

Precision is defined because of the measurement of scatter or as the agreement between replicate measurements of a homogeneous sample (USP, 2013; Graham, 2011).

- **REPEATABILITY:** Represents precision under the same operating conditions over a short interval of time (ICH, 2005);
- **INTERMEDIATE PRECISION:** Precision is represented as within laboratory variations e.g., different days, different analysts, different equipment, etc.
- **REPRODUCIBILITY:** Represents precision between laboratories and is usually applied when standardizing methodology

SPECIFICITY

An analytical method is also considered specific when it can selectively distinguish between the analyte of interest within the presence of other components (impurities, degradation products, and matrix) especially components with closely related structures (ICH, 1999). 53 within the case of chromatographic **[25]** procedures representative chromatograms should indicate the separation and identification of peaks (USP, 2013).

LIMIT OF DETECTION:

The detection limit is defined because of the lowest amount of analyte during a sample that can be detected.

The LOD may be expressed as:

$$\mathbf{LOD = 3.3\ \sigma / S}$$

Where, σ = Standard deviation of Intercepts of calibration curves

S = Mean of slopes of the calibration curves

The slope S may be estimated from the calibration curve of the analyte.

QUANTITATION LIMIT:

The quantitation limit is the lowest amount of analyte which will be determined with acceptable precision and accuracy under the stated experimental conditions (USP, 2013). The quantitation limit may be calculated utilizing a signal-to-noise ratio with a ratio of 10:1 being acceptable (Graham, 2011; ICH, 2005).

The LOQ may be expressed as: $\mathbf{LOQ = 10\ \sigma / S}$

Where,

σ = Standard deviation of Intercepts of calibration curves, S = Mean of slopes of the calibration curves, The slope S may be estimated from the calibration curve of the analyte.

LINEARITY AND RANGE:

"The linearity of an analytical procedure is its ability to elicit test results that are directly, or by a well-defined mathematical transformation, proportional to the concentration of analyte in samples within a given range" (USP, 2013).

ROBUSTNESS:

The capacity of an analytical procedure to remain unaffected by small, but deliberate

variations in method parameters is observed as its robustness.

CHANGE CONTROL AND REVALIDATION

Changes to a validated cleaning process, and changes to a producing process or equipment that will affect a validated cleaning process, must be made following approved change control procedures.. A change evaluation process determines the extent of validation required.

CONCLUSION

In this manuscript, ruggedness as a validation parameter is considered in terms of its definition, appropriate evaluation procedures, and acceptance criteria. The applicability of using the United States Pharmacopeia (USP) method scaling approach in place of method re-validation using a column with a different L–designation to the original analytical column was investigated. Although USP method scaling is only permitted for columns within the same L-designation, these data suggest that it may also apply to columns of different designation.

REFERENCES

[1] V. P. Shah *et al*., Analytical methods validation: Bioavailability, bio-equivalence, and pharmacokinetic studies. Eur. J. Drug Metabolism and Pharmacokinetics 16 (4):249–255 (1991) and Pharm. Res.9:588–592, 1992

[2] V.P. Shah, *et al*., Bioanalytical Method Validation – a Revisit with a Decade of Progress. Pharm.Res. 17; 2000 1551-1667.

[3] Chung WL, Yin J, Messick S, Saggu M, Tschudi K, Woys A, Rahimi R, Azarias M, Kong C, Kabakoff B, Compendial Methods: Suitability Verification, Challenges and Recommendations for Proteins, PDA Journal of Pharmaceutical Science and Technology,74(5), 2020 Sep 1,581-91.

[4] Snyder LR, Dolan JW, Majors RE. Adjusting conditions for a routine reversed-phase HPLC assay, Part I: changing the column, LC-GC North America,22(12), 2004 Dec 1,1146-50.

[5] Epshtein NA, Revalidation of Procedures and Allowed Adjustments to Chromatography Conditions in Liquid Chromatography, Pharmaceutical Chemistry Journal,53(12), 2020 Mar 1174-83.

[6] Lavenda O, Mahat-Shamir M, Lorenz L, Hamama-Raz Y, Greenblatt-Kimron L, Pitcho-Prelorentzos S, Ring L, Bar-Shua E, Ben-Ezra M. Revalidation of Adjustment Disorder–New Module-4 screening of adjustment disorder in a non-clinical sample: Psychometric reevaluation and correlates with other ICD-11 mental disorders, PsyCh journal, 8(3), 2019 Sep,378-85.

[7] Schmidt AH, Stanic M, Molnár I, In silico robustness testing of a compendial HPLC purity method by using of a

multidimensional design space build by chromatography modeling—Case study pramipexole, Journal of Pharmaceutical and Biomedical Analysis,2014 Mar 25,91:97-107.

[8] Makoni PA, Chikukwa MT, Khamanga SM, Walker RB, Stability indicating HPLC-ECD method for the analysis of clarithromycin in pharmaceutical dosage forms: method scaling versus re-validation, Scientia Pharmaceutica,87(4), 2019 Dec,31.

[9] P. Ravisankar, Sai Snehalatha, Tabasssum Firdose Shaik, P. Srinivasa Babu, Applications of HPLC in pharmaceutical analysis, Int. J. Pharm.Sci. Rev.Res, 59(1), 2019, 117-124.

[10] P. Ravisankar, B. Madhuri, A. Naga Lakshmi, A. Pooja, M. Bhargava Sai, K. Suresh, P. Srinivasa Babu, Selected HPLC applications-Quick separation Guide: A Review, Int. J. Pharm. Sci. Rev.Res, 60(2), 2020, 13-20.

[11] Chan CC, Saraswat P, Analytical Method Verification, Method Revalidation, and Method Transfer, Practical Approaches to Method Validation and Essential Instrument Qualification,2010 Aug 26,27-43.

[12] Swartz ME, Krull IS, Implementing new technology in a regulated environment, LC-GC North America. 24(8), 2006 Aug 1,770-5.

[13] United States Pharmacopoeia, 24, National formulary 19, section<1225' validation of compendial methods. US Pharmacopoeial Convention, Rockville, Validation of analytical procedures text and methodology Q2(R1), November, 2000: 2005.

[14] Rambla-Alegre M, Esteve-Romero J, Carda-Broch S, Is it really necessary to validate an analytical method or not? That is the question, Journal of Chromatography A, 12(32), 2012 Apr 6, 101-9.

[15] Swartz M, Krull I, Analytical method validation: Back to basics, part I, LC-GC North America, 27(11), 2009 Nov 1,989-995.

[16] USP 32 – NF 27, General Chapter 1225, Validation of Compendial Methods, **2009.**

[17] ICH Q2A, Validation of Analytical Procedures: Definitions and Terminology, Geneva, 1995, in 2005 incorporated in Q2(R1).

[18] Schofield T, Heuvel E, Weitzel J, Lansky D, Borman P, Distinguishing the analytical method from the analytical procedure to support the USP analytical procedure life cycle paradigm, InPharm Forum 2019 (Vol. 45, No. 6), 2019.

[19] Ravisankar P, Devala Rao G, A validated RP-HPLC method for quantitative determination of mirabegron in bulk and pharmaceutical

dosage form, Der Pharmacia Lettre, 8 (14),2016, 96-103.

[20] Olefir YN, Sakanyan EI, Luttseva AI, Babeshina LG, Shemeryankina TB, Validation of Methods and Procedures in Pharmacopoeial Monographs in the Framework of a drug standardization program, Pharmaceutical Chemistry Journal, 52(10), 2019 Jan 873-7.

[21] G. Lavanya Chowdary, P. Ravisankar, G. Akhil Kumar, K. Mounika, P. Srinivasa Babu, Analytical method validation parameters: An updated review, Int. J. Pharm. Sci.Rev.Res. 61(2), 2020, 1-7.

[22] Shah VP, Midha KK, Findlay JW, Hill HM, Hulse JD, McGilvery IJ, McKay G, Miller KJ, Patnaik RN, Powell ML, Tonelli A, Bioanalytical method validation—a revisit with a decade of progress, Pharmaceutical research17(12), . 2000 Dec 1551-7.

[23] Ravisankar P, Gowthami S, and Devala Rao G, A review on analytical method development Indian journal of research in pharmacy and biotechnology, 2 (3) 2014, 1183-1195.

[24] B. Divya, P. Ravisankar*, K. Neelima, E. Durga Gayathri, Jahnavi M, P. Srinivasa Babu, Fundamental chromatographic parameters: Accom-plishing optimum resolution and in the minimum amount of time for developing better HPLC methods: An updated review, volume 28, Issue 2,2022,155-176

[25] Panchumarthy Ravisankar, S. Anusha, Kommanaboina Supriya, U. Ajith Kumar, Fundamental chromatographic parameters, Int.J. Pharm, Sci.Rev. Res,55(2), 2019,46-50.