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STABILITY STUDIES OF PHARMACEUTICAL PRODUCTS

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ABSTRACT

The stability studies of pharmaceutical products are one of the very important parameter for development of new drugs as well as new formulations. The shelf-life prediction is a major role for the pharmaceutical product development of all the dosage forms and also it is utilized to determine the particular storage conditions and to suggest label instructions. Stability studies of pharmaceutical products ensuring the maintenance of product quality, safety and efficacy throughout the shelf life are considered as pre-requisite for the acceptance and approval of any pharmaceutical products. These studies are required to be conducted in a planned way following the guidelines issued by ICH, WHO or other agencies.

KEYWORDS: Stability Studies, Pharmaceutical Products and Stability Testing.

1. INTRODUCTION

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture. Shelf life of the product can be defined as the substance reduces to 90% of its original concentration. Shelf life is a technical term used to denote the stability of the product and it is expressed as expiry date. Expiration varies for each pharmaceutical preparations. The expiry of the pharmaceutical dosage form depends on various environmental factors such as temperature, humidity, light, radiations etc. and many physical and chemical active substances in the formulation, the nature of container-closures used and the storage conditions. Literature data on the decomposition process and degradability of active substances are generally available together with adequate analytical methods. Thus, stability

studies may be restricted to the dosage form. The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products.[1] Stability of a pharmaceutical product can also be affected because of microbiological changes like growth of microorganisms in non sterile products and changes in preservative efficacy.[2] Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation.[3]

2. IMPORTANCE OF STABILITY STUDIES

- ✓ Product instability of active drug may lead to under medication due to the lowering of the drug in dosage form.
- ✓ During the decomposition of the drug or product it may lead to toxic products.
- ✓ During the marketing from one place to another during the transportation the drug has the compatibility to change its physical properties.
- ✓ Instability may be due to changing in physical appearance through the principles of kinetics are used in predicting the stability of drug there different between kinetics and stability study.[4]

3. TYPES OF STABILITY STUDIES ON DRUG SUBSTANCES[4,5]

A comprehensive pharmacopoeial protocol (USP) prescribes the criteria for acceptable levels of physical, chemical, microbiological, therapeutic and toxicological stability studies.

Physical stability

The original physical properties such as appearance, colour, dissolution, palatability, suspendability are retained. The physical stability may affect the uniformity and release rate, hence it is important for the efficacy and safety of the product.

Chemical stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness

within specified limits. This microbiological instability could be hazardous to the sterile drug product.

Therapeutic stability

The therapeutic effect (Drug Action) remains unchanged.

Toxicological stability

Toxicological stability has no significant increase in the toxicity occurs.

Types of stability studies

Stability studies are used for testing the drug product for longer periods under varying conditions of temperature and Relative Humidity (RH). If the drug is to be distributed in different geographical regions and if shipping is required for transportation, in that case long term stability studies are of prime importance. Long term stability studies are performed by testing the sample at specific time intervals and conditions of external parameters are changed accordingly. Main objective of this study is to determine shelf-life of the drug product. Stability studies are mainly four types, they are Long term stability, Intermediate stability, Accelerated stability and In-use stability Studies. The type of stability studies and its storage conditions with respective time period were shown in Table 1.

Table 1: Types of Stability Studies.

Types of Stability Studies	Storage Conditions	Minimum Time Period (Months)
Long Term	25±2°C and 60±5% RH or 30±2°C and 65±5% RH	12
Intermediate	30±2°C and 65±5% RH	6
Accelerated	40±2°C and 75±5% RH	6

4. STABILITY TESTING METHODS

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development. In the early stages, the stability testing is performed by the accelerated stability studies which mainly are performed at high temperature\ humidity. The accelerated stability studies is easy to predict the degradation of the drug within short period of time. In the accelerated stability studies mainly the drug is performed at long-term storage. During this elevated temperatures are used to determine the products shelf-life. The main aim for the stability testing is to provide the acceptance level of fitness/ quality throughout the period during which they are available for the patience and should be fit for

the acceptance of the drug by the patient. This helps the patient to be cured easily and the acceptance of the drug would be easy and the known therapeutic uses of the pharmaceutical products manufactured.[6] Depending upon the aim, steps followed, the stability testing procedures have been categorized into four types and they are

1. Real-time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing.

1. Real-time stability testing

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time from inter-assay variation. While, testing the samples are collected at regular intervals such that the data is collected at the appropriate frequency such that the analyst is able to distinguish the degradation day-to-day. The data can be increased by including the single batch of reference material for which stability characteristics have been established. In this the reagents and the instruments used should be in the consistency throughout the stability testing. The control of drift and discontinuity results in the changes of both reagents and instruments should be monitored.[7]

2. Accelerated stability testing

This type of stability testing is done at higher temperatures and that decomposition the product is determined. The information is used to predict the shelf life or used to compare the relative stability of alternative formulations. The accelerated stability studies is easy to predict the shelf life thus reduces the duration to know the stability of the substance. In addition to temperature, stress conditions are applied such as moisture, light, pH and gravity. Due to the measurement of instability time is also reduced in comparison to the real-time testing. For the accelerated stability studies the stability projections are done at four different stress temperatures. However, projections are obtained when denaturing stress temperatures are avoided. The accelerated stability studies are easily predicted by the Arrhenius equation[8,9]**:**

$$K = Ae^{-Ea/RT}$$

Where:

K= Specific rate constant

A= Frequency factor or Arrhenius factor

Ea= Energy of activation

R= Real gas constant 4.184 j/mol. k

T= Absolute temperature, k

In this method the drugs are stored at different temperatures such as 40°C, 60°C, 70°C, 80°C, 100°C etc. These studies are to be done at room temperature and at refrigerator temperatures. During different intervals the samples are collected and examined for the stability. The sampling is done at 3 months in the first year and 6 months interval the next year and yearly thereafter. The products which degrade very fast for them regular sampling at short duration of time should be done. When the temperature increases the decomposition of the substance is also very rapid. The stress tests used in the current ICH guidelines (40% for products are to be stored at controlled room temperature) were developed from a model that assumes energy of activation of about 83 KJ/mole. As per ICH and WHO the storage condition for accelerated stability studies is 40°C ± 2°C 75% RH ± 5% RH. If the product is unstable on the prescribed temperature and humidity intermediate conditions are used i.e. 30°C ± 2°C 65% RH ± 5% RH. FDA prescribes the sampling testing for 0, 2, 4, and 6 months respectively. WHO prescribes for 0, 1, 2, 3, 4, and 6 months. ICH prescribes the test to be performed for every 3 months in a year, 6 months in 2 years and yearly thereafter. These accelerated tests are mainly done for photochemical stability and moisture absorption. This test is performed for all the pharmaceutical preparations but mainly this is a test used for dispersed systems like pharmaceutical emulsions and suspensions.

3. Retained sample stability testing

This is a usual practice for every marketed product for which stability is needed. In this type of testing, the stability is done by selecting one batch for a year. If the number of samples exceeds more than 50 then they are divided into two batches. At the time of first introduction of the product into the market the samples of every batch are taken which may decrease from 2% to 5% of the marketed batches at the later stages. The samples stability studies help to predict the shelf life. The maximum shelf life of every product predicted could be 5 years which is conventional to the test samples at 3, 6. 9, 12, 18, 24, 36, 48 and 60 months. This method of testing is also known as constant interval method.[6,10] This type of stability

sampling testing is inherently more realistic since it challenges the product not just in the idealized retained sample storage conditions but also in the actual market place.

4. Cyclic temperature stress testing

This method is not so much used to the sampling of the products. In this method, cyclic temperature stress tests are designed knowledge of the product so as to mimic likely conditions in the market place storage. In this testing the sampling is considered to be conducted by a cycle of 24 hours which is known as the rhythm of the earth is 24 hours. For this the test of samples the minimum and maximum temperatures are noted for product by product by the basis of temperature, storage conditions, chemical and physical degradation of the product. For predicting the shelf life the cycles of 20 are recommended.[6,11]

5. GUIDANCE OF STABILITY STUDIES

The drug to be administered for wellbeing of the patient the pharmaceutical preparation should be optimally stable and products are manufactured according to the standard guidance which are proposed by WHO, FDA, ICH. ICH plays a key role in the preparation and marketing of the preparations. ICH stands for "International Conference of Harmonization" which is used for the register of the pharmaceuticals products for human use. The ICH was established in 1991, was a consortium formed inputs from both regulatory and industry from European commission, Japan, USA and various guidelines for drug substance and drug product came into existence regarding their quality, safety, efficacy and multidisciplinary (also known as Q, S, E, M). The secretariat of ICH is situated at Geneva, Switzerland. These guidelines include basic issues related to stability, the stability data requirements for application dossier and the steps for execution. Later in the year 1996 WHO (World Health Organization) has modified the guidelines proposed by ICH and WHO, in 2004 released the guidelines for stability studies in global environment.[6] As the ICH did not assess the extreme climatic conditions found in many countries and it only covered new drug substances and the products which were earlier established. In 1997, June the United States Food and Drug Administered (US FDA) situated at Silver Spring also issued the guidelines but they were not entitled. The CDSCO (Central Drug Standards Control Organization) is a drug regulating authority for India situated at New Delhi. The regulatory requirements vary from country to country. Thus, organizing the data and scrutinizing the application became difficult. Hence, there was an urgent need to rationalize and harmonize the regulations. The ICH Steering committee was established at the meeting and A decision was to be taken at

least twice a year. Series of guidelines related to stability testing have also been issued by the Committee for Proprietary Medicinal Products (CPMP) under the European agency for the Evaluation of Medicinal Products (EMEA) to assist the seeking marketing products. The Codes and Titles used in ICH[1,3] and CPMP.[1,3,12] Guidelines were tabulated in Table 2 and Table 3 respectively.

Table 2: Codes and Titles used in ICH Guidelines.

ICH Codes	Guideline Titles
Q1A	Stability testing of new drug substances and products (second revision)
Q1B	Photo stability testing of new drug substances and products
Q1C	Stability testing of new dosage form
Q1D	Bracketing and Matrixing Designs for the stability testing of drug substances and products
Q1E	Evaluation of stability data
Q1F	Stability data package for registration applications in climatic zones III and IV
Q5C	Stability testing for biotechnological/ biological products
Q6A	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
Q6B	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

Table 3: CPMP Guidelines for stability studies.

CPMP Codes	Guideline Titles
CPMP/QWP/576/96 Rev. 1	Guideline on Stability Testing for Applications for Variations to a Marketing Authorization
CPMP/QWP/6142/03	Guideline on Stability Testing for Active Substances and Medicinal Products Manufactured in Climatic Zone III and IV to be marketed in the EU
CPMP/QWP/609/96 Rev. 1	Note for Guidance on Declaration of Storage conditions for Medicinal Products particulars and Active Substances
CPMP/QWP/122/02 Rev. 1	Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products
CPMP/QWP/072/96	Note for Guidance on Start Shelf Life of the Finished Dosage Form
CPMP/QWP/2934/99	Note for the Guidance for In-Use Stability Testing of Human Medicinal Products
CPMP/QWP/576/96	Note for Guidance on Stability Testing for a Type 2 Variation to a Marketing Authorization

6. CLIMATIC ZONES FOR STABILITY STUDIES[1,3, 13, 14]

The stability studies are performed worldwide these stability studies cannot be performed at one place as the temperature and other factors vary from country to country and place to place. Due, to this purpose the world has been divided into four zones depending on their climatic conditions so that the degradation of the product and the shelf life could be predicted

accurately. Based on this data the real-time stability testing and accelerated stability testing have been derived. The standard climatic zones for the use of pharmaceutical products stability studies has enumerated and break-up of the environmental conditions derived from long term storage condition has given by WHO are also been presented in Table 4.

Table 4: Climatic Zones and Long term stability conditions.

Climatic Zones	Climate	Countries	MAT*	Long-Term Testing Conditions
I	Temperate	United Kingdom, Russia, USA	<15C/<11hPa	21°C/45%RH
II	Subtropical and Mediterranean	Japan, Southern Europe	>15-22°C />11-18hPa	25°C/60%RH
III	Hot and Dry	Iraq, India	>22°C/<15hPa	30°C/35%RH
IV a	Hot and Humid	Iran, Egypt	>22°C/>15-17hPa	30°C/65%RH
IV b	Hot and very humid	Brazil, Singapore	>22°C/>27hPa	30vC/75%RH

*MAT - Mean annual temperature measured in open air.[3, 13, 14, 15]

7. STABILITY STUDY PROTOCOL

The stability testing is one of the processes for drug development. Stability data for the stability studies are used to determine the storage conditions and packaging materials for a bulk of the prepared formulated products. The stability studies are used to determine the expiry date of the substance. These stability protocols are pre-requisite for the stability studies and necessary a written document that has a key of instructions for the regulation and well-controlled stability studies. Each formulation has different types of containers to be packed hence the protocol can also depend on the type of the drug substance. The protocols can also depend on the drugs already in the market and the newly prepared drugs. The protocols should reflect the regions that are proposed by the ICH. A well designed stability study protocol should include the following information:

1. Number of batches
2. Containers and Closures
3. Orientation of storage of containers
4. Sampling time points
5. Test storage conditions
6. Test parameters.

1. Number of batches

Stability testing is carried out in batches as performing the stability studies in a single step is difficult hence they are divided into batches. For a product that is stable without any reactions the stability studies are performed on a single batch. When the substances are unstable or not when the drug is newly registered the stability studies are performed on three batches. When any one of the batch shows unstable activity then the stability is performed for six respective batches if the unstable repeats then the whole product formulated has to be discarded as they cannot be administered. The initial data is not a full scale production batch, the first three batches should be post approval which are long term studies using the same protocol as in approved drug applications. The data collected from the laboratory are not accepted for the primary stability data. The selections of batches contribute to the random sample from the population of pilot or production batches.

2. Containers and Closures

The selection of containers and closures is very important and stability studies on containers and closures as when the products are to be packed in the suitable medium. The packaging materials include the aluminium strip packs, blister packs, Alu-Alu packs, HDFE bottles etc. this may also include the secondary packaging but not the shippers. The products packed in all closures are to be tested for the stability studies as the unsuitable container can degrade the drug physically. For, the bulk containers the prototype containers are allowed. While packaging is done the prepared drug is placed in the suitable containers as the containers can contaminate the product and shelf life of the drug can be reduced than the actual time period.

3. Orientation of storage of containers

The samples of solutions, semi-solid drug products for stability studies must be placed upright in such a way that the drug comes in contact with the containers. This helps to know that when the drug comes in contact with the containers is undergoing any chemical changing which leads to the degradation of the drug. This degradation may be due to the absorption or loss of water.

4. Sampling time points

The testing is important at particular time intervals to establish the stability profile of the new drug substance. The products with a shelf life of months in the first year, then 6 months for the second year and then yearly thereafter throughout the prediction of shelf-life. In the case of accelerated stability studies, a minimum of three time points like 0, 3, and 6 months. In

case, when the same product of different strength, size etc to be tested. Retained stability testing can be used which involves less number of points. The reduced testing plans are based on the bracketing and matrixing statistical designs. Bracketing is the design only when the samples on the certain design factors such as strength and package size are tested at all the three time points as in full design. The factors that can be matrixes can include the strength, batches, container sizes, and intermediate time points. The environment, sampling time and there selective climatic zones[3,16] were shown in Table 5.

Table 5: Test Schedule for stability testing of new products

Environment	Sampling Time Points (Months)	Method & Climatic zone
25°C/60% RH	3, 6, 9, 12, 18, 24,36	Long term for zones I and IV
30°C/35% RH	3, 6, 9, 12, 18, 24,36	Long term for zones III
30°C/65% RH	3, 6, 9, 12, 18, 24,36	Long term for zone IVa, or intermediate condition for zones I and II
30°C/75% RH	3, 6, 9, 12, 18, 24,36	Long term for zone IVa, or intermediate condition for zones I and II
40°C/75% RH	3, 6, 9, 12, 18, 24,36	Accelerated condition for all zones

5. Test storage conditions

The storage conditions to be selected on the basis of the climatic zones in which the product has to be marketed. General recommendation on the storage conditions has been given by ICH, CPMP, and WHO. The ICH and WHO Stability studies storage conditions for drug products[7, 13, 16] was shown in Table 6.

Table 6: Stability studies storage conditions for drug products.

Intended Storage Condition	Type of Stability Studies	Storage Conditions for					
		ICH			WHO		
		Temperature (°C)	RH* (%)	Time (Months)	Temperature (°C)	RH (%)	Time (Months)
Room Temperature	Long term	25 ± 2°C	60 ± 5%	12	25 ± 2°C	60 ± 5%	**12**
		30 ± 2°C	65 ± 5%				
	Intermediate	30 ± 2°C	65 ± 5%	6	--	--	--
	Accelerated	40 ± 2°C	75 ± 5%	6	--	--	--
Refrigerator	Long term	5 ±3°C	--	12	5 ±3°C	--	
	Accelerated	25 ± 2°C	60 ± 5%	6			
Freezer	Long term	-20 ± 5°C	--	12	-20 ± 5°C		

*Relative Humidity (RH)

6. Test parameters

The test parameters used in the stability studies must be evaluated of the stability samples. The test of sample mainly includes the quality, purity, efficacy, and identity which can be depending upon the climatic conditions. Therefore appearance, assay, degradation products, microbiological tests include sterility, preservative measures etc. The stability testing batches should also reach the testing parameters including the heavy metals, residue of ignition, residual solvents, etc. These tests are also been discussed in the ICH guidelines (QA6).

8. STABILITY STUDIES EQUIPMENT

The equipment used for stability testing is called stability chamber. These are specialized environmental chambers that can simulate the storage condition and enable evaluation of product stability based on real-time, accelerated and long-term protocols. They are available in both walk-in and reach-in styles. Smaller chambers are preferred for accelerated testing, as the retention time of products is much less in these cabinets, while the walk-in chambers are preferred for long-term testing. Such chambers or rooms are engineered and qualified to ensure uniform exposure of the set conditions to all the samples in the chamber. These chambers are expected to be dependable and rugged because of the requirement of uninterrupted use for upto years. They are fitted with appropriate recording, safety and alarm devices. In addition, photo stability chambers are also available and utilized both with and without temperature and humidity control. Two types of light sources are usually employed in photo stability chambers, one is the combination of cool white & near UV fluorescent tubes and second one is artificial daylight lamps e.g: xenon or metal halide. It is required to obtain a total exposure of 1.2 million lux hour. The visible light intensity is estimated using a lux meter. The calculation is made on how many hours of exposure are needed.[3,9]

Estimation of shelf life

The shelf life is determined from the data obtained from the long term storage studies. The data is first linearized and test for goodness of fit is applied. The linearized data is then analyzed to see that the slope and the intercepts are matching. The different possibilities in the pattern of the concentration-time data of the three batches were shown in Table 7. The data is pooled accordingly and used for estimation of the common slope.[3] For determination of significance of difference in case of slope or intercept, statistical tests like t-test should be applied.

Table 7: Pattern of concentration-Time data and Pooling decision.

Slope	Intercept	Variation Factor	Pooling
Identical	Identical	Nil	Yes
Identical	Different	Batch e.g. unequal initial drug concentrations	No
Different	Identical	Storage e.g. difference in the rate of drug loss	No
Different	Different	Interactive Forces-Both batch and storage factor	No

Evaluation of stability studies

A systematic approach must be done in evaluating the stability studies which may include results from the physical, chemical, biological, and microbiological tests, even including the dosage forms of the substances. These evaluations help to know the degradation of the product with the analysis of the data obtained during testing. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine all the data into one to estimate. When the substance starts showing the degradation and with the data analyzed the shell life is apparently predicted.

9. CURRENT TRENDS IN STABILITY STUDIES

The Current trends in stability studies are the multinational pharmaceutical companies, is to define conditions for stability testing for global marketing. For this the companies are orienting their protocols to single set of conditions that covers extreme environmental conditions. The specific changes for global testing include increase in duration of accelerated testing period from 6 to 12 months and conduct of additional tests at 50°C/75% RH for 3 months. The concept behind this change is to avoid repetition of stability testing for other regions and efficient and optimum use of resources as all tests are done in one laboratory. Moreover testing under combination of three environmental factors, viz., temperature, humidity and light, has been reported to result in stronger deleterious effect on drug substances and products, than under temperature and humidity conditions only.[3, 16, 17, 18, 19]

10. CONCLUSION

The stability studies of pharmaceutical products the key procedural contribution in the development program for new drugs as well as new formulations and these tests has become easy to predict the shelf life including the effect of environmental factors for the degradation of the product. Any deviation from the established stability profile could affect its quality, safety and efficacy. Stability tests are carried out so that recommended storage conditions and shelf life can be included on the label to ensure that the medicine is safe and effective throughout its shelf life. Therefore, the stability tests should be carried out following proper

scientific principles and after understanding of the current regulatory requirements and as per the climatic zones.

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12. REFERENCES

1. Saranjit Singh and Monika B. Guidance on Conduct of Stress Tests to Determine Inherent Stability of Drugs, Pharmaceutical Technology online, 2000; 24-36.
2. Matthews RB. Regulatory Aspects of Stability Testing in Europe, Drug Development and Industrial Pharmacy, 1999; 25(7): 831-856.
3. Saranjit Singh. Stability testing during product development in Jain NK Pharmaceutical product development, CBS publisher and distributors, India, 2006; 272-293.
4. Thorat Punam, Warad Shubhangi, Solunke Rahul, Ashok Sargar, Anagha Bhujbal, and Asha Shinde. Stability Study of Dosage Form: An Innovative Step. World Journal of Pharmacy and Pharmaceutical Sciences. 2014; 3(2): 1031-1050.
5. Panda A, Kulkarni S and Tiwari R. Stability Studies: An Integral Part of Drug Development Process. International Journal of Pharmaceutical Research and Bio-Science, 2013; 2: 69-80.
6. Kommanaboyina B and Rhodes CT. Trends in stability testing, with Emphasis on Stability during Distribution and Storage, Drug Development and Industrial Pharmacy, 1999; 25(7): 857-868.
7. WHO. Stability studies in a global environment. Geneva meeting working document QAS/05.146 with comments, 13-14 December 2004.
8. Geoffrey Anderson and Milda Scott. Determination of product shelf life and activation energy for five drugs of abuse. Clinical Chemistry. 1991; 37(3): 398-402.
9. Kenneth A. Connors, Gordon L. Amidon, and Valentino J. Stella. Chemical stability of pharmaceuticals: A handbook for pharmacists, 2nd Edition., New York; John Wiley and Sons; 1986; 8-119.
10. Carstensen JT and Rhodes CT. Clinical Research Drug Regulatory Affairs, 1993; 10 (3): 177-185.
11. Carstensen JT. Drug Stability: Principles and Practices, 3rd Edition., New York; Marcel Dekker; 2000.

12. CPMP. Guideline on stability testing: Stability testing of existing active substances and related finished products, CPMP/QWP/122/02; 2003.
13. ICH Q1A (R2). Stability testing guidelines: Stability testing of new drug substances and products, ICH Steering Committee, 6th February 2003.
14. Grimm Wolfgang. Extension of the international conference on harmonization tripartite guideline for stability testing of new drug substances and products to countries of climatic zones-III and IV, Drug Development and Industrial Pharmacy, 1998; 24(4): 313-325.
15. Mundhe Akshay Vitthalrao, Fuloria Neeraj Kumar, and Biyani Kailash Radheshyam Cocrystalization: An alternative approach for solid modification. Journal of Drug Delivery and Therapeutics, 2013; 3(4): 166-172.
16. Sanjay Bajaj, Dinesh Singla and Neha Sakhuja, Stability Testing of Pharmaceutical Products, Journal of Applied Pharmaceutical Science. 2012; 02(03): 129-138.
17. Singh S, Bhutani H, Mariappan TT, Kaur H, Bajaj M and Pakhale SP. Behaviour of Uptake of Moisture by Drugs and Excipients under Accelerated Conditions of Temperature and Humidity in the Absence and the Presence of light. 1. Pure Anti-Tuberculosis Drugs and their Combinations. International Journal of Pharmaceutics. 2002; 245(1-2): 37-44.
18. Saranjit Singh, Hemant Bhutani and Mariappan T.T, Behavior of Uptake of Moisture by Drugs and Excipients under Accelerated Conditions of Temperature and Humidity in the Absence and the Presence of light. Part II. Packaged and Unpackaged anti-Tuberculosis drug products. Pharmaceutical Technology. 2003; 27: 44-52.
19. Dhiren P. Shah, Bhavesh patel and Chainesh Shah, Nanosuspension technology: A innovative slant for drug delivery system and permeability enhancer for poorly water soluble drugs. Journal of Drug Delivery and Therapeutics, 2015; 5(1): 10-23.