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Effect of Hygroscopicity on pharmaceutical ingredients, methods to determine and overcome: An Overview

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Abstract

The hygroscopic character of a pharmaceutical material is known to influence the behavior of the material during various stages of pharmaceutical process, manufacturing, packing, storage, and transport. It also influence greatly on the stability, appearance, efficiency of the materials. Hence it is important to classify and overcome the problems of the materials based on their hygroscopic nature. The following review covers the literature reports of classification, determination of hygroscopic materials based on their ability to absorb or adsorb water molecule from the environment. It also discuss about the effect of hygroscopicity due to uncontrolled humid conditions and basic methods to overcome the same.

Keywords: hygroscopicity, stability, water in solids, moisture content, adsorption, desorption.

INTRODUCTION

Hygroscopy is a chance of dragging and bonding with water molecule from the atmospheric air present at surrounding environment at room temperature. Hygroscopicity is done by either absorption or adsorption of moisture from the atmospheric air. Physically changed character of the material is due to the absorption or adsorption of moisture by the substance. This could result in an increase in volume, boiling point, viscosity, or other physical characteristic or property of the substance [30].

The physical and chemical stability of the solid dosage forms, excipients, and polymers for controlled release formulations have been predominantly influenced by Moisture adsorption. The drugs which undergo hydrolysis by absorbing or adsorbing the moisture form the environment. It is necessary to determine moisture adsorption kinetics which includes the rate of moisture uptake, and also the equilibrium moisture content (EMC). Moisture adsorption principles will provide handy data in case of solid dosage forms for selection of excipients, and also informations on humidity control required to be done during production and storage. Influence in the flow, compression, and the hardness of solid dosage forms is depend upon the quantity of moisture adsorbed by pharmaceutical materials at a particular temperature and relative humidity [3].

The percent relative humidity (% RH) quantifies the atmospheric water vapor pressure. The equilibrium moisture content (EMC) is defined as the quantity of moisture at which a solid material forms a water vapor pressure similar to the water vapour present in the surrounding environment's vapour pressure. Moisture adsorbance rate are determined by the following factors:

1) The pressure difference between the water vapor pressure of the material and the vapor pressure of water in the atmosphere
2) A reaction constant related to the solid characteristic
3) The water vapor of the exposed surface area of solid drug
4) The speed of movement of moisture air
5) Temperature

The kinetics relays on the (a) surface adsorption, found to be present at a rate proportional to the gradient between the saturated salt solution and that of the partial pressure of water vapor in the atmosphere, and (b) the at which the diffusion of water into the crystal that dependents on the concentration difference of water and the product of the coefficient of diffusion [1,2].

EFFECT OF UNCONTROLLED HUMIDITY

In Processing

In Powder Milling, Water vapour makes material tough and challenging to reduce into small particles or powder by crushing it. The material holds on tightly to the milling machine and resists during pneumatic conveyance. During tablet compounding, unwanted moisture retard appropriate reactions, forms unwanted end products which results in minimum quality and reduced shelf life. During powder flow, the capacity of the powder materials to flow evenly is reduced due to enhanced moisture content. This is due to the enhancement of thickness of the adsorbed liquid layer. This in turn improves the stability or firmness of liquid bridges formed between particles. Increased surface tension is due to the increased surface moisture, this concludes in attraction between particles [10-14].

In tablet Compression, compression of powdered materials can be done under high pressure only in dry state. Moisture causes clumping and caking, decomposes the drug, minimize the medicinal value and causes deterioration of the tableting process. During tablet Coating, inappropriate cooling and drying of the sugar solution can conclude in rough, translucent and irregular coating [24].

In Manufacturing

For Effervescent Tablets, uncontrolled moisture in manufacturing areas affects surface finish and result in softened tablets. While in cough drop, material adhere to the stamping machine when humidity is high. Since aluminum is moisture sensitive in nature. It can result in penetration of moisture inside the packing during storage [24].

In Packaging

At the time of Dry Powder filling / Vial filling, due to uncontrolled moisture powders get adhere to the conveyor, and influence process of filling.

During strip packaging, increased moisture content in the atmospheric air present in the packaging area will eventually pave the way for the tablets and capsules to absorb moisture from the environment thus decrease the shelf life. This may also reduce efficiency of the final materials [24].

METHODS OF DETERMINATION

Callahan and co-workers method (regular method

Determinations of equilibrium moisture content is found by depositing exactly weighed sample (0.1-0.2 gram) in bare, weighed dish or bottle and then it is planted into a desiccator accommodating any of the following saturated salt solutions given in following table. A surplus volume of the saturated salt solution (with surplus crystals) (Table-1) is positioned in the pit of the desiccator. Samples were stored in sealed desiccators, each containing a distinct moisture environment. At equilibrium (1 week storage at composed room temperature $25^0C \pm 2^0C$) the samples are detached from the desiccators and the change in

moisture is found for each sample by procuring the resulting weight with the help of a weighing balance. Equilibrium moisture content values were calculated from P (%moisture dry basis) with the help of the equations given below. Initial moisture content (A) of each excipient was accurately determined by a convenient method, such as loss on drying to stable and consistent weight and employed to compute P. Equilibrium moisture content values are computed from P with the aid of the formula given below[4,5]

$$P = \frac{\left\{\left[\left(W * \frac{A}{100}\right) - B\right] * 100\right\}}{\left\{W - \left[W * \frac{A}{100}\right]\right\}}$$

$$EMC = \frac{P}{[P+100]}$$

Where,

P= percentage moisture dry basis
W= initial sample weight in grams
A= Initial % moisture
B= Difference in weight at equilibrium in grams
EMC= Equilibrium moisture content

Table-1: Saturated salt solutions for sustain Constant Relative Humidity conditions in desiccators

Saturated salt solution	% Relative Humidity at Temperature 25°C
Lithium Chloride	11
Potassium Acetate	23
Magnesium Chloride	33
Potassium Carbonate	43
Magnesium Nitrate	52
Sodium Nitrite	64
Sodium Chloride	75
Potassium Bromide	83
Potassium Nitrate	93

European pharmacopoeia method

A surplus amount of saturated salt solution (with surplus crystals) of ammonium chloride was planted in the pit of the desiccators. The humidity and temperature were monitored. Sample material (0.1–0.3 grams) was weighed into bare and weighed plastic petri-plates and then inserted into a desiccator, which was stamped and retained at CRT and 80 ± 2%RH. After 24 hours of storage, the samples are detached from the desiccator, and the end mass of the samples are determined with the aid of weighing balance. The percentage weight gain of the samples is calculated with the aid of the equation given below, and the samples are classified for their hygroscopic nature based on the resulting values as per the EP classification system [4,18].

$$\%\ \text{of increase in mass} = \frac{[(M3 - M2) * 100]}{[M2 - M1]}$$

Where,

M1= weight of empty Petri plate
M2= Initial weight of both Petri plate and sample together
M3= weight of both Petri plate and sample together after 24 hours

Sorption analysis method

This method engages involving the sample to water vapor sorption analysis at controlled temperature of 25°C with the aid of sorption analyzer. Sample vapour is administered to different circumstance of humidity under isothermal conditions, and the feedbacks are determined gravimetrically. Initial drying of the sample inside the sorption analyzer is not executed to bypass the probability of modification in the solid state of the sample. Weigh about 5–15 mg of sample and expose it to expanding environmental humidity ranging from 40%RH to 90%RH. The samples were then exposed to desorption ranging from 90% Relative Humidity to 0% Relative Humidity. The above process is reproduced for another time from 0% Relative Humidity to 90% Relative Humidity again falls back to 0% Relative Humidity. The percentage of weight changed at 25°C and 80% Relative Humidity in the first adsorption cycle is established based on the equation given below. The existence of difference between the desorption and adsorption values is used to determine the characters of the sample. This is in terms of changes in solid state occurred under the varying hygroscopicity determining condition inside the sorption analyzer. Before and after carrying out the sorption analysis, the sample is examined by powder X- ray diffractometry (PXRD) in order to confirm the interpretations drawn from the sorption isotherm,. All diffraction patterns are gathered at a scan speed of 3°/min with a scan step of 0.02° over range of 3–45 °2Θ in continuous mode [4].

$$\%\ \text{weight change} = \left[\frac{W2 + W1}{W1}\right] * 100$$

Where,

W1= sample weight at the initial time of the experiment
W2= sample weight in equilibrium at 25°C and 80% Relative Humidity

Karl Fischer Method

The Karl Fischer Method was constructed to find out the amount of water content present in a substance. The quantitative reaction of water with iodine and sulfur dioxide in the presence of a lower alcohol and an organic base was utilized to find out the amount of water content available in the substance.

There are two varying methods of determination are available based on iodine-affording principle. One of them is volumetric titration method and another one is coulometric titration method. Iodine needed for reaction with water is formerly dissolved in sample Test Solution in case of the volumetric titration method, and the amount of iodine consumed as a result of reaction with water in a sample is used to measure the water content in the sample. Initially the electrolysis of the reagent containing iodide ion is done in order to produce the required iodine for the reaction in case of the coulometric titration method and then, the amount of electricity essential for production of iodine is measured for determination of the water content in a sample.

While preserving from moisture, the titration of the sample with sample Test Solution and the standardization of the Test Solution should be carried out at the similar temperature. The appliance is constructed with different resistors in a circuit, which is altered slightly to load a definite voltage (mV) between two platinum electrodes dipped into the solution which is to be titrated. The alteration in the current (ΔA) is determined during the falling of sample Test Solution. As the process continues, an immediate and unexpected variation in current in the circuit occurs, but comes back to the initial state within few seconds. At the termination of the titration, the variation in the current continues or prolongs for a particular period of time. At this electric state, the end point of titration is found. In another way, by altering the resistor, a constant current is allowed to pass between the pair of platinum electrodes, and the variation in the potential (mV) is determined during falling of sample Test Solution. As the titration continues, the readings shown by the potentiometer in the circuit falls all of a sudden from a state of polarization of several hundred (mV) to the state of non-polarization, but it returns back to the initial state within few seconds. During termination of the titration, the state of non-polarization continues or prolongs for a particular period of time. When this electric state is attained, the end point of titration can be found.

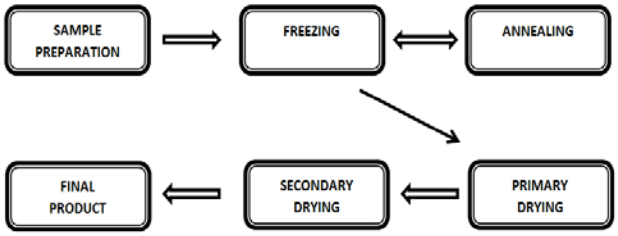
During back titration, an excessive quantity of sample Test Solution remains the needle of micro-ammeter is out of scale, if the amperometric titration method is used at stable voltage. But

when the titration attains the end point, it comes back quickly to the initial position. Likewise, when the potentiometric titration method is used at a stable current, the needle of the millivolt-meter will be at the initial position while a surplus amount of sample Test Solution remains. In the back titration method, the end point of the titration can be found more distinctly when compared to that in the direct titration method [21].

METHODS TO OVERCOME HYGROSCOPICITY

Lyophilization or Freeze-Drying Technique

The moisture sensitive active pharmaceutical ingredient has a general nature of getting detoriate chemically or physically in atmospheric moisture condition and that why it has decreased stability and self-life. Such critical condition can be improved effectively by lyophilization. In the modern era lyophilization is the one of the emerging technology, which is efficiently engaged in several antibiotics preparation. This technique offers quick reconstitution and reduces the expense for storage and shipping. The basic principle involved in freeze drying process is known as sublimation. During the sublimation process water is directly converted from solid phase to the gaseous phase without goes into a liquid phase [7,8,9].



Film Coating

The process of tablet coating involves in spraying of composition of coating materials on to a bed of moving tablets or solid materials using continuous flow of hot air in order to enhance the process of solvent evaporation. Coat has impact on the drug releasing pattern as minimum as reachable and also does significant changes in the resemblance of the formulation. Release of drug may be modified by coating with definite necessity and release mechanism which is adapted to body function prevails in the digestive system. Chemical incompatibilities and sequential drug release is reachable by embodiment of different drug or mixture adjuvant in the composition of coating. Improvement of the pharmaceutical elegance can be done through coating by the use of unique colours and different printings. Major factors which decide tablet coating are properties of tablet, process of coating, equipments used for coating, the coating process parameters, facility and necessary supporting equipments, and automation in the processes of coating, etc. [17,19,20].

In the pharmaceutical industry, spray-atomization technique is used to apply polymeric films to solid dosage forms. In organic solvents, the polymer is dispersed prior to spaying. Proceeding to initiation of the coating process, the tablets in the coating equipment are usually preheated. The solution used for coating is pulverized into tiny droplets with air. These tiny droplets are then sprayed over the surface of the tablets. During contact, the pulverized droplets cover over the surface of the substrate. The polymer materials are thickly packed on the solid surface, as the solvent begins to evaporate. The particles come closely due to the cohesive forces between the materials due to continuation of solvent evaporation. This process is known as coalescence. In order to facilitate solvent evaporation and film formation, heat is usually applied to the equipment. For Further promotion of coalescence and confirm a homogeneous spreading of the plasticizer is done straight away after the termination of the coating process. Coated materials are stored at temperatures higher to the glass transition temperature of the polymer used in this process of coating. By selection of the coating as hydrophobic in nature, it is possible to prevent the entry of moisture into the system from the surrounding environment [15,16,6].

Adsorbents

The relative humidity (RH) inside a system is maintained with the aid of adsorbents as low as possible. They are used in the process of drying of compressed air system in the industries. This is done by passing the compressor discharge air to flows through a bed of adsorbents and adsorbents adsorb moisture in the compressor discharge air, and thus preventing the destruction due to moisture air at the point of use of the compressed air [26,29].

Desiccant

Hygroscopic substance that implies or preserves a dryness state (desiccation) is known as desiccant. Solids that absorb water are commonly used pre-packaged desiccants. For some specialized purposes, desiccants can be used in forms other than solid, and they works based on different principles, like chemical bonding of water molecules. In addition to moisture protection, desiccants are also effective at absorbing odors and other elements from the air [26,28].

Desiccators

Desiccators are enclosures with capable of sealing, containing desiccants used for maintaining moisture-sensitive materials in its original state. A desiccator is used to preserve hygroscopic substance or the materials which react with water from atmospheric air. When a desiccator is opened, the materials stored inside it are freely exposed to atmospheric air, when the desiccator is again closed it requires certain amount of time to reduce the humidity to lower level than that of atmospheric level. Hence they are not advisable for storing materials such as the alkali metals, which react vigorously or violently with moisture moisture present in atmospheric air. The desiccators are made using heavy glass and in circular shape. The materials to be stored away from atmospheric moisture content are stored over a platform which can be removed. Beneath the platform the desiccant consists of inert solids such as silica gel are placed in order to absorb or adsorb the excess moisture present inside the chamber. In some cases in order to denote the necessity of change of desiccants, silica which changes its Colour over a period of time due to absorption of moisture content is used. When the materials absorb moisture, the desiccants packed with silica gels generally convert into pink from blue colour. In order to evacuate the desiccator a stopcock may be included. These are also known as vacuum desiccators in which vacuum is applied to maintain a tight seal [25,27].

Controlled Humidity condition

During production and final packaging presence of high humidity can make the products to absorb moisture. If moisture is absorbed, then they are degraded, and their effectiveness will be reduced to an extent. Packing of moisture sensitive materials under the wrong conditions results in degrade over time when the product is long-term exposed. Therefore, the control of the production environment is becoming more crucial and critical as product development moves forward. Conditions are created by dehumidifying the entire production premises or adding the dry air directly into the process. With the aid of dehumidification system, low humidity of 20% RH for tableting, compressing, are easily obtained [22,23].

Table 2: Effect of hygroscopicity at different stages of formulations

Areas	Problems	Consequence	Measures
Processing	Adherence to milling machine and conveyor	Improper size reduction, improper flow.	Maintenance of controlled RH, Use of adsorbents.
Compression	Adherence to punches	Clumps and cakes, Capping, lamination.	Use of Adsorbents, sufficient lubricants.
Coating	Uncontrolled Cooling and drying	Improper coating	Maintenance of controlled RH
Effervescence tablets	Improper surface finishing	Softening of dosage	Proper coating
Filling	Adherence to hopper or conveyor	Improper filling,	Maintenance of Controlled RH, Use of Adsorbents, Glidants

Table 3: Matrials used for blister and striping process

Materials of Construction / Type	Critical Properties	Area of use
PVC 200/250/350	Low barrier / Simple unit pack / Aesthetic	Stable products like Paracetamol, Co-trimoxazole, certain softgel capsules etc.,
PVC / PVdC (250/40)	Low barrier better than PVC	Products not very sensitive to moisture, gases and with moderate self life- Multivitamin tablets and capsules
PVC / PVdC (250/60)/ (250/90)/ (250/120)	Good barrier	Moderate to high sensitive range of products, certain FDC/ Enzyme products
PVC / PE / PVdC (200/25/60) (250/25/90)(300/30/90)	Good barrier	Quite high sensitive range of products – 4 FDC(RHZE)
Ultrasafe Duplex	High barrier/economical	Quite high sensitive range of products
Ultrasafe Triplex	High barrier/economical	Quite high sensitive range of products
PVC/Aclar (10µ to 100µ) PVC/COC, PE/COC	Excellent barrier	Extremely moisture sensitive range of products
OPA/Al foil/PVC, Alu/Alu	Excellent barrier	Extremely sensitive range of products – Cefuroxime Axetil tablets, Levocetirizine Tablets,
OPA/Al foil/PVC, Alu/Alu with desiccant	Excellent barrier	Extremely moisture sensitive range of products
Aluminium foil with HSL (Hard tempered) 0.02 / 0.025	Excellent barrier	Lidding foil for blister packing
Aluminium foil (Hard tempered with special coating)	Excellent barrier	Lidding foil for COC
Aluminium foil / poly (30 –40 microns (soft tempered)	Excellent barrier	For strip packing use of very sensitive range of products – Omeprazole Capsules, Ranitidine Tablets etc.,
Aluminium foil / VMCH (30 – 40 microns (soft tempered)	Excellent barrier	For strip packing use of dark colored sugar coated tablets.
Paper /Poly	Very low barrier / Simple unit pack / Aesthetic look	Very economical pack for very stable products.
Paper/al/HSC	Excellent barrier	For Child resistance blisters pack

Packaging

Packaging is a technique, which regulates and protects pharmaceutical product from the time of production until it is used. Providing protection from external influences is the major role of pharmaceutical packaging. Packaging of pharmaceuticals typically provides regulation, safety, identity, comfort of handling and ease delivery [31,33].The external factors that may reduce the quality or potency of pharmaceutical products are light, moisture, oxygen, contaminations, mechanical damage, etc. Primary Packaging is an envelope which will be in direct contact with the dosage form. The primary package should be inert, that is there should be no interaction with the drug. E.g. Blister packages, Strip packages, etc.

For primary packaging, it is crucial to know the undesirable interactions between the container and the dosage form. During the primary research and development stage product stability and compatibility are confirmed. The packaging itself should not interact with the dosage form to produce a new undesirable or objectionable changes, while reducing or removing the effect of external factors on the dosage form,.

Packaging must safeguard the physical properties and secure against damage or breakage. It should protect the identity of the product and safeguard the characteristic properties. It must conserve the product against unsatisfactory or adulterating chemical, biological or physical particles [32].

2. Secondary Packaging: This is a successive covering which stores pharmaceuticals packages in it for their alignment. E.g. Cartons, boxes, etc.

3. Tertiary packaging: This is to helps bulk handling and shipping of dosage from one place to another. E.g. Containers, barrels, etc [31].

CONCLUSION

The hygroscopicity of the pharmaceutical materials will differ largely at different environments, based on the local sources available and atmospheric moisture content. Considering the vital importance that hygroscopicity has the direct and indirect effects on stability, appearance, and efficiency, the work has been done based on the literature survey to give a basic idea on classification, determination of hygroscopic materials, impact of moisture content on the materials and methods to overcome the effect. Hence these in formations are very helpful in case of analyzing the materials during any instability issues occurring in commercial formulations or problems associated with hygroscopicity of materials during the new formulation development. In a pharmaceutical system, once problems associated with the effect of hygroscopic nature of materials are understood, the required solutions can be done in order to avoid the unwanted reactivity and enhance the stability and improve the efficiency for the desired outcome products.

REFERENCE

[1] Ali Nokhodchi. An Overview of the Effect of Moisture on Compaction and Compression. Pharm. Technol., January 2005.

[2] S. Mikuliniskii and R.I. Rubinshtein, "Velocity of Moisture Absorption by MgSO4" *J. Phys. Chem.* 9 (431), (1937).

[3] Kaisiri Umprayn, R.W.Mendes. Hygroscopicity and moisture adsorption kinetics of pharmaceutical solids: a review. Drug Dev. Ind. Pharm., 13(4&5), 653-693 (1987).

[4] Vasudha Murikipudi, Piyush Gupta, and Vaibhav Sihorkar. Efficient throughput method for hygroscopicity classification of active and inactive pharmaceutical ingredients by water vapor sorption analysis. Pharm. Dev. Technol., 2013; 18(2): 348–358.

[5] J. C. Callahan, G. W. Cleary, M. Elefant, G. Kaplan, T. Kensler & R. A. Nash. Equilibrium Moisture Content of Pharmaceutical Excipients. Drug Dev. Ind. Pharm., 8:3, 355-369.

[6] WassimAbdelwahed, GhaniaDegobert, SergeStainmesse, HatemFessi. Freeze-drying of nanoparticles: Formulation, process and storage considerations. Adv. Drug Deliv. Rev., Volume 58, Issue 15, 30 December 2006, Pages 1688-1713.

[7] Shivanand A, Mukhopadhayaya S; A Review on Lyophilization: A Technique to Improve Stability of Hygroscopic, Thermolabile Substances; PharmaTutor; 2017; 5(11); 28-39.

[8] Sandip K., Rajesh K.and Mallinath H; A review on freeze drying process of pharmaceuticals; Int J Res Pharm Sci;2013; 4(1); 76-94
[9] Nireesha GR., Divya L and Sowmya C; Lyophilization freeze drying: A review;IJNTPS; 2013; 3(4);87-98
[10] Erica Emery, Jasmine Oliver, Todd Pugsley, Jitendra Sharma, Joe Zhou. Flowability of moist pharmaceutical powders. Powder Technol., 30 June 2008.
[11] M.E. Plinke, D. Leitch, F. Loffler, Cohesion in granular materials, Bulk Solids Handling 14 (1994) 101–106.
[12] T.A. Bell, Industrial needs in solids flow for the 21st century, Powder Handling and Processing 11 (1999) 9–12.
[13] J. Fitzpatrick, L. Ahrné. Food powder handling and processing: Industry problems, knowledge barriers and research opportunities, Chemical Engineering and Processing. 44 (2005) 209-214.
[14] J. Prescott, R. Barnum. On powder flowability, Pharm.Technol. 24 (2000) 60-84
[15] Parmar Krutin D, Bhatt Nayana M, Pathak Nimish L, Patel Laxmanbhai D, Kela Amit N, Nathani Hitesh S and Chauhan Vijay V. An Overview: Aqueous Film Coating Technology on Tablets. Int. j. pharm. chem. biol. sci., vol. 1 (3) jul-sep 2012 994-1001.
[16] Soham Shukla. Freeze Drying Process: a review. Int.j.pharm.sci.res., 2011; Vol. 2(12): 3061-3068.
[17] Lachman L, Liberman H, and Kanig J. The Theory and Practice of Industrial Pharmacy. 3rd edition. 1992; 293-345, 346-373
[18] Anonymous. Characters section in monographs. European Pharmacopoeia 6, version 6.8, Section 5.11 ed2010
[19] Mahmodul Haque Tusher. Pharma Mirror. Cutting Edge Peer Reviewed Contents over The Pharma Arena. NSTU. 2010; 9
[20] Aulton M. Pharmaceutics: The Science of Dosage Form Design. International Student Edition, 304-321, 347-668.
[21] <921> Water Determination USP40 https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c921.pdf
[22] Pharmaceutical Application guide. Increased quality, productivity, and hygienics: air treatment for today's pharmaceutical production. https://webdh.munters.com/webdh/.../Application%20Guide-20Pharmaceutical.pdf
[23] Humidification in pharmaceutical manufacturing. https://www.condair.co.in/knowledge-hub/humidification-in-pharmaceutical-manufacturing
[24] Effect of Uncontrolled Humidity. https://www.bryair.com/industries-applications/applications-of-dehumidifiers-anddryers/production-and-processing/pharmaceutical-industry/general-pharmaceutical
[25] Richard Watson. Personally portable vacuum desiccator. US 6648862 B2. https://www.google.com/patents/US6648862
[26] Desiccants & Adsorbents. Texas Technology, Inc. 512-267-0100. https://www.texastechnologies.com/moisture-corrosion-control/desiccants-and-adsorbents.html
[27] Desiccator-Wikipedia https://en.wikipedia.org/wiki/Desiccator
[28] Desiccant-Wikipedia https://en.wikipedia.org/wiki/Desiccant
[29] Adsorption-Wikipedia https://en.wikipedia.org/wiki/Adsorption#Adsorbents
[30] Hygroscopy-Wikipedia https://en.wikipedia.org/wiki/Hygroscopy
[31] Vikas Pareek*, Dr. Alok Khunteta, Pharmaceutical Packaging: Current Trends And Future, International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491 Vol 6, Issue 6, 2014
[32] Annex 9, Guidelines on packaging for pharmaceutical Products, World Health Organization, WHO Technical Report Series, No. 902, 2002
[33] Nityanand Zadbuke, Sadhana Shahi, Bhushan Gulecha, Abhay Padalkar, Mahesh Thube, Recent trends and future of pharmaceutical packaging technology, Journal of Pharmacy and Bioallied Sciences April-June 2013 Vol 5 Issue 2.
[34] Jnanadeva Bhat M., Role of packaging material on Pharmaceutical product stability www.agc.world.com