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Pharma Review

Adverse Effects of Uncontrolled Humidity on the Packaging in Pharma Industry....

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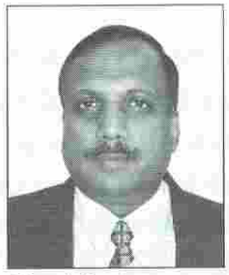

Dinesh Gupta

Manoj Bhatia

The Indian drug and pharmaceutical industry is seeing a rapid advancement in technology, and manufacturing processes with the transition from process research to discovering new products. Today, not only has it achieved global recognition as a "low cost producer of quality bulk drugs and formulations"; leading Indian companies have also established marketing and manufacturing activities in over 60 countries including USA and Western Europe.

However the more modern the pharmaceutical processes, the more stringent is the demand for a higher control of many parameters to ensure a quality final product with long shelf life. In this article, we will be focusing on two of the major parameters:

a) Adverse effects of humidity and the most effective ways to control humidity.

Humidity/moisture is a constant threat to production efficiency and product quality. Moisture causes problems like disintegration of tablets, decomposition of formulations, lumping, caking and agglomeration of chemical compounds, uneven coating on tablets, inability to compress tablets, retarded growth in organic cultures and a shorter shelf life to name just a few.

Pharmaceuticals

Some Typical Problems

- Disintegration
- Chemical reactions leading to decomposition, shorter shelf life
- Non-uniform coating
- Caking/umping and agglomeration

Moisture is your hidden enemy!

b) Need to treat fresh air in processing areas to ensure proper ventilation to maintain IAQ (Indoor Air Quality).

Large quantities of "conditioned" fresh air is needed for ventilation as well as process needs in many areas of pharmaceutical production. Since these areas are very large, conditioning such large volumes of air results in very high-energy cost. The cost effective solution is to use equipment to recover substantial part of energy from exhaust air to keep energy costs down as well as cater to the fresh air needs.

Thus, control of humidity as well as adequate conditioned fresh air becomes imperative for the Pharmaceutical Industry.

Effects of High Humidity

Humidity in processing, manufacturing, testing, packaging and storage areas can be devastating for the pharmaceutical products and can cause

Effects of high humidity

- Increased activity of micro organisms
- Deteriorated characteristics of hygroscopic materials

- Hygroscopic material, which most pharma products are, to deteriorate,
- Moisture regain
- Organic Corrosion
- Biochemical reactions
- Activates injurious activity of micro-organism
- Impairs product accuracy and uniformity in formulations

Deteriorated Characteristics of Hygroscopic Materials

All hygroscopic materials will absorb or desorb moisture from the atmosphere until they reach their equilibrium moisture content. Hygroscopic material will take up or dispel moisture in relation to the relative humidity of the air mixture to which it is exposed. when in equilibrium with air at 100% RH it is hygroscopically saturated. The higher the Relative Humidity in the surrounding air, the higher will be the moisture regain.

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e.g. For gelatine at 10% RH the moisture content by % of dry weight is 0.79% but at 90% RH the moisture content is 11.4% of dry weight.

Certain materials require extremely low or high moisture contents during manufacture and storage.

Injurious Activities of Micro Organisms

An excessive moisture content can indirectly contribute, to the destruction of organic material by increased microbial activity.

Mould, mildew and fungi are all different types of bacteria. Outdoor air is well endowed with this bacteria which are small enough to be carried indoors and which will settle on materials. The spores lie dormant until suitable conditions of temperature and humidity are achieved. In general, the spores will not germinate below 60% RH.

The actual temperature conditions for germination may vary widely between different types of moulds.

Once germinated, the mold prospers and the speed of growth is a function of temperature and humidity. The condensed moisture on materials acts as a medium conducive to the growth of bacteria. Moreover, at high temperature the activity of the microorganism's increases but a certain amount of activity occurs even at very low temperatures. This micro-organism growth is injurious to materials; as it not only results in decomposition but also mechanical weakening of the products. In most cases, bacterial growth can be arrested if RH is maintained below 45%.

Air Humidity and damage caused by too High Humidity

A certain amount of water vapour is always present in the air. The water vapour or moisture is measured in terms of relative humidity.

The outdoor relative humidity has a direct bearing on the indoor humidity environment. The problem is compounded and distributed as a result of infiltration through ceilings, walls and floors. In addition to the humidity from the outside air, the humidity emitted from people and production processes add to the overall effect as the decisive factors in product spoilage. Having studied the ill effects of high humidity, let us see the effects of moisture in various processes and operations in the Pharmaceutical Industry

One chemical engineer's headache

Hygroscopic nature of Aspirin prevents adhesion, reduces shelf life and potency

Solution: Control of humidity

Processing

Compounding of Tablets

Most pharmaceutical operations use products or chemicals which are hygroscopic by nature and need to be stored, manufactured and packaged in low humidity conditions.

A basic operation of the chemical arid pharmaceutical industries is the bringing together under precise conditions, of the constituents to form compounds. Unwanted moisture may impede desired reactions or cause formation of undesirable end products. The quality of material produced is frequently related directly to efficient control of the atmosphere where compounding takes place.

Many diagonistic products used in medicine today involve radioactive materials that must be mixed or compounded in a humidity controlled environment. Aspirin and many other complex diagnostic compounds are moisture reactive. This leads to poor product quality and shorten shelf life.

Tablet Compression

Many materials used in medicines have a physical affinity for moisture. This results in lumping or caking of powdered material. Some powdered material which are bound into capsule or into tablet form under high pressures will adhere only in the dry state. Humidity may cause falling apart of the tablet and in some extreme cases will even decompose the drug and lesser its medicinal value.

Tablet Coating

In the coating pan for tablets, a heavy sugar solution is added to the tumbling mass. As the water evaporates, sugar crystals cover each piece. Blowing the proper quantity of air (with correct dry and wet bulb temperature) forms smooth, opaque coating. If cooling and drying are not at the desired rate, the coating is rough, translucent and unsatisfactory in appearance; if they are too fast, the coating chips through the interior.

Powder Milling

Atmospheric moisture is the natural enemy of many grinding and pulverizing operations. Water vapour in contact with the product makes the material resilient and therefore difficult to grind. The material clings to the grinding machine and defies pneumatic conveyance from one process to another.

Also Spray / Fluid bed dryers require large quantities of hot air for drying. The quality of the final product is affected by the quality of air entering the dryer. It should be dry, free from contamination, foreign particles and odourless.

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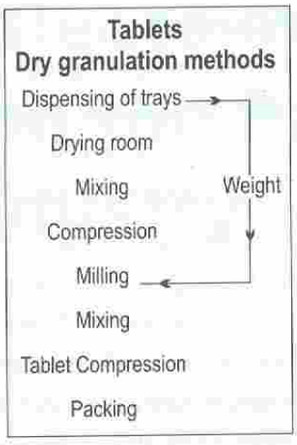


With the growing emphasis on limiting production loses and downtime, which impacts final product quality and thus profits. The importance of using dehumidifiers, in conjunction with Spray Dryer / Fluid Bed Dryer for quality drying, has thus become almost mandatory.

Since, the ambient is changing throughout 24 hrs, 365 days a year, the humidity present in the air, entering the spray/ fluid bed dryer is not constant. This requires close monitoring of the drying temperature and time inside the dryer, as varying level of humidity present in the air entering the dryers, results in different final moisture content in product being dried, thereby degrading the quality of the final product.

It also hinders the free flow of powders/ granules making many downstream operations (e.g. packaging, filtering, handling) difficult and expensive.

The ideal solution is to install a Desiccant Dehumidifier at the inlet (source of air) of the spray/ fluid bed dryer for a constant moisture content supply (dry) air inside the dryer. This helps in reducing the physical monitoring of the drying temperature and time thereby reducing costs and ensuring consistant quality year around.

Glandular Extracts

Glandular and liver extracts requires a low humidity condition after they are dried. Moisture regain in presence of high humidity will cause the product to deteriorate

Manufacturing

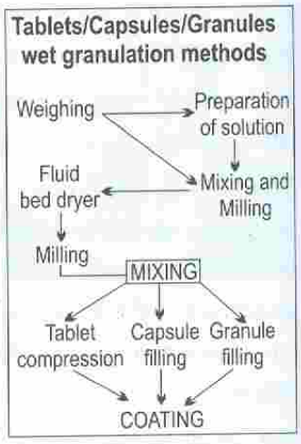
Effervescent Tablet Manufacturing

In the manufacture of effervescent tablets, an excess of atmospheric moisture results in a chemical reaction that makes the tablet stick to the machines and spoils their appearance when finished. Tablets packed in presence of high humidity deteriorate due to carbon dioxide and water formed.

Hence, control of humidity becomes absolutely essential in the manufacture of effervescent tablets.

Soft Gelatine Capsule Manufacturing

In soft gelatine manufacturing, the capsulating process works in the following way, warm liquid gelatine is spread over a slowly revolving stainless steel drum. A supply of chill dry air congeals the gelatine as the drum rotates so that a tacky, elastic band rolls off the -other end. This thin band is then automatically formed into capsules, filled with medicine, food or other product, sealed and dropped into a tray.



If air blowing against the drum has too low a temperature, gelatine will set too rapidly. Then it becomes brittle and the ribbon breaks stalling the manufacturing process.

Too high an air velocity will disturb the constant thickness of the gelatine ribbon being formed. If air temperatures and humidity are too high, gelatine will start softening and prevents solidification into a ribbon.

The control of temperature and humidity are the two most important factors in the manufacturing process of soft gelatine capsules.

Cough Drops Manufacture

In pharmaceutical operations, during cough drops manufacture, the material is in plastic state during the process. It must flow and it must be shaped by stamping machines. The presence of excess moisture causes the material to become sticky, it will not flow freely and will stick to the stamping machine.

Dry air is also critical in hardening surface coatings. Oven drying using elevated temperatures, will impair the quality of the products. In order to eliminate this serious production problem the equipment and material can be surrounded by dry air.

Penicillin Manufacture

The penicillin incubation process requires temperatures and humidity rigidly controlled within ± 0.25 ^{O}C and ± 3% RH. The manufacture and packaging also require stringent temperature and humidity conditions. When packed in the presence of high humidity, the deteriorate due to carbon-di-oxide and water formed.

Drying

Vitamin Capsule Drying

From the capsulating machines the soft, moist capsules are transferred to drying drums or chambers for rapid drying. The extent of moisture to be removed during drying depends on the size of the capsule, the number of capsules and the period over

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which the moisture is to be removed. The moisture has to be removed gradually from the gelatine shell to prevent superficial surface hardening.

Drying at elevated temperatures will impair the quality of the product hence it becomes necessary to lower the dewpoint of surrounding air so that the capsules will give up the moisture to attain an equilibrium moisture content.

Hence control of humidity becomes important in the drying process.

Packaging

Dry Powder/Vial Filling

The filling operations always require conveying of powdered substances to packaging areas in a high velocity air-stream and filling of the powder in minute quantities in the vials and capsules.

The powder must be free flowing and dry. The hygroscopic nature of the powder in presence of high humidity may cause it to slick and cluster together to the conveyors, thus preventing airveying and lilting operation.

The obvious answer to the problem lies in surrounding the processing and manufacturing Area with dry air. In the pharmaceutical industry dehumidified airveying is critical in the transport of hygroscopic chemicals from storage to processing areas. Also critical is the prevention of moisture regain when airveying moisture sensitive particulars to filling and packaging operations.

Strip Packaging

Dehumidified airveying, becomes critical in the Pharmaceutical Industry, or hygroscopic chemicals from storage to processing areas. Also, critical is the prevention to moisture regain when airveying moisture sensitive products to filling and packaging operations. The final packaged material must maintain its viability during the expected shelf life. The product package must maintain the "as manufactured" moisture level considering that air is packed with the product in the final step. Hence, the necessity to surround the packaging area with dry air.

Basic Drug Packaging Area

Basic drugs like Cloxa Cilline Sodium, Sephaxine, Norfaxasin, etc. are extremely hygroscopic. They tend to absorb moisture from the surrounding air during packaging resulting in deterioration of quality and product spoilage. Dehumidifying the packaging air prevents damages and preserves quality of the processed drugs.

Storage

Powder Storage

Most pharmaceutical powders are hygroscopic and moisture reactive. Maintaining low humidity in storage prior to manufacture, after manufacture and in packaging areas is of prime importance

Capsule Storage

Finished capsule need to be stored in a dry environment prior to packaging to prevent moisture regain and spoilage of products

Typical climatic requirement standards

1. Effervescent tablets 90°F and 15% RH
2. Tablet coating 80OF and 5% - 30% RH
3. Tablet Compressing 70°-80°F and 10% - 40% RH
4. Penicillin packaging 80°F and 5% - 15% RH
5. Capsule storage 75°F and 35% - 40% RH
6. Powder milling 80°F and 35% RH

Aluminum Foil Storage

Aluminum, extensively used in the packaging of tablets and capsules, is moisture sensitive in nature and needs to be stored in humidity-controlled environment prior to being used for packaging

These are some of the areas where high humidity plays havoc with the product and processes in the pharmaceutical industry.

Desiccant Dehumidification – A specialisation in it's own right

To Dehumidify or Dehumidification – literally means "pulling out or removing" the moisture/humidity from the air.

It is often assumed that airconditioning will lower the relative humidity in a space. And it surprises people when the exactly opposite happens.

It is quite possible that the relative humidity actually increases when the temperature in the room is lowered, as cold air cannot retain the same amount of moisture as warm air can.

Thus, dehumidification, which has been recognized as an essential parameter of pharma manufacturing process and as a specialisation and a science in it's own right.

Desiccant Dehumidifiers in combination with air-conditioning provides the required humidity and temperature parameters for various areas of Pharmaceutical Industry.

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Using Desiccants to Dry Air

The most simple, straightforward way to obtain dry air is to use desiccants-that is, adsorbants or materials that have a natural affinity for water. A desiccant is able to take up the additional moisture given up by the air without changing its size or shape. So an air stream can pass through a desiccant bed and become significantly drier without elaborate cooling, compression, cooling water, or other complex systems or controls. After the drying task is complete, the desiccant is regenerated via heat. Then the desiccant is ready to dry more air.

Comparing Desiccants to Convention Cooling

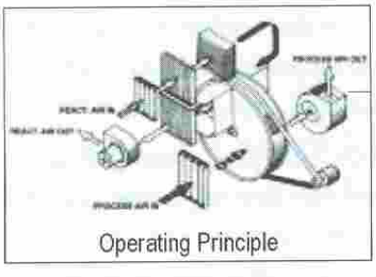
(Desiccant Dehumidification Vs. Mechanical Refrigeration)

Both desiccant dehumidifiers and mechanical refrigeration systems can remove moisture from the air, so the question is - which type is best suited for a given application? There really are no simple answers to this question but there are several generally accepted guidelines which most dehumidifier manufacturers follow:

Both desiccant-based and refrigeration-based dehumidification systems work most efficiently when used together. The advantages of each compensate for the limitations of the other.

Refrigeration-based dehumidification systems are sometimes more economical than desiccant based dehumidifiers when higher temperatures and humidity in the conditioned space is acceptable. In general, mechanical refrigeration systems are seldom used for applications below 50% RH at about 22°C or for a dewpoint lower than 11°C.

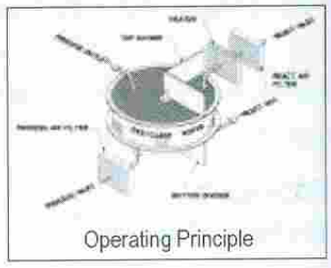
Desiccant-based systems are more economical than refrigeration systems at lower temperatures and lower moisture levels. Typically, a desiccant dehumidification systems is utilized for applications below 45% RH down to less than 1% RH. Thus, in many applications, a DX or chilled water pre-cooling coil is mounted directly at the dehumidifier inlet. This design allows for removal of much of the initial heat and moisture prior to entering the dehumidifier where the moisture is reduced even further.



Operating Principle

The simplest and most cost effective way to control humidity is to use the desiccant based fluted dehumidifiers.

Fluted Media Based Desiccant Dehumidifiers



Operating Principle

The dehumidifier design uses a rotating fluted wheel/ rotor to present the desiccant to the process and reactivation airstreams. This is sometimes called a fluted media/ honeycomb type dehumidifier. The desiccant is impregnated/ synthesized on "honeycomb" like corrugated rotor. The principle of operation is the same as the solid desiccant (granular) based system.

The process air flows through the flutes formed by the corrugations, and the desiccant in the structure adsorbs the moisture from the air. The rotating desiccant bed picks up moisture, and well before "saturation" the rotor/wheel rotates into the reactivation segment where it is heated to drive off the moisture.

Fresh Air Needs in the Pharmaceutical Industry

Let us look a little more closely at needs of Indoor Air Quality which dictate the choice of a system for Treating Fresh Air.

In recent years, the attention of environmental researchers has been focused on indoor air pollution, as a result of reports of symptoms or specific diseases that occur mainly in airconditioned and mechanically ventilated buildings. Studies have proved that level of contaminants in the indoor air can be often several times higher than outdoor air.

Airconditioning is a major factor affecting Indoor Air Quality (IAQ). Majority of airconditioning systems are designed with very little or almost no provision for fresh air, as fresh air means, more kilowatts of conditioning and thus, higher energy cost.

The Solution to Pollution is Dilution

Environment researchers have found that increasing ventilation helps in diluting the pollutants. In fact, concentration of pollution is inversely proportional to ventilation rate; doubling the ventilation, halves the concentration. Thus, increasing ventilation is the most effective method for improving IAQ.

Improper ventilation in capsulation, formulation, tablet coating, tablet compression, granulation and bio lab areas result in

- Ineffective humidity and temperature control
- Poor IAQ (Indoor Air Quality)

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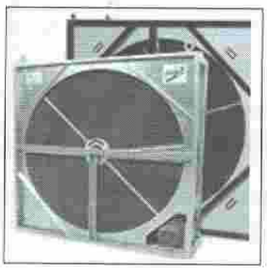
- Mixing of contaminant in exhaust air-stream with incoming fresh air
- High utility bills

These areas need large quantities of "conditioned" fresh air to brought in for ventilation as well as process needs. The fresh air needs to be conditioned to maintain the comfort level temperature and humidity in the area. Conditioning such large volumes of air entails a very high energy cost.

The ideal way to ensure that ventilation needs are catered to while keeping energy costs low is to use Treated Fresh Air (TFAs) Units incorporating the energy recovering heat wheels which preconditions the fresh air.....

- By using energy from the exhaust air, thus bringing the energy needs down considerably
- For acceptable IAQ, humidity and temperature control, energy conservation/ efficiency and in the process reducing the space envelope.
- And has two separate airflow which ensures that the exhaust and supply air stream is totally separate and there is no cross contamination or leakage.



TFAs are typically used for treating/ preconditioning ventilation air i.e. fresh air as well as far achieving acceptable IAQ, Humidity control, Energy conservation/ efficiency, and in the process reducing the building envelope.

TFAs incorporating Energy Recovery differ in many ways from the conventional system. Some major areas of difference are listed below :

Two tier system handling exhaust and supply air stream

- Exhaust air section
- Supply air section
- Inlet damper section
- Filter section both for exhaust and supply
- Rotary Heat Exchanger section
- Cooling section (optional)
- Supply air blower and motor section

The TFA incorporating Energy Recovery device exchanges the energy from the exhaust air to incoming fresh air.

The exhaust air drawn through the exhaust section is passed through half section of the rotary heat exchanger, where it give up its energy to the exchanger.

The filtered supply air passes over the other half of the rotating heat exchanger, in the supply section and exchanges the energy. This, pretreated air passes over a cooling (optional) coil, for further, before it is supplied into the area.

These TFAs incorporates the 'Eco-fresh' Rotary heat recovery wheels which gives it an overwhelming advantage over conventional systems. Some benefits of using the Ecofresh wheels are :

- Typical recovery: 80%.
- No cross contamination between exhaust and fresh air.
- Selective adsorption: special grade molecular sieve desiccant allows mainly water molecules to pass through it rejecting all other pollutants.
- Two tier system handling exhaust and supply air stream.
- Inlet damper section
- Filter section both for exhaust and supply, bag filters for dusty application.
- Incorporates Ecofresh Heat Wheel along with filtration, damper control, other airtreatment devices/options.
- Supply and exhaust air blower and motor.
- Double skinned, eco-friendly insulation.
- Eliminates need for complicated ducting.
- Available in range 0.3m3/s to 6.0m3/s.

To conclude, equipment for moisture/humidity control and treating fresh air is today a must to ensure quality of the final pharma product.