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A BRIEF REVIEW ON NITROSAMINE FOOTPRINTS IN PHARMACEUTICAL INDUSTRIAL LAYOUT

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Abstract:

Nitrosamines impurities are highly mutagenic which are generally produced from the chemical reactions between amino groups like secondary amines and tertiary amines and nitro sating agents prominently. Nitrosamines production depends on the environment, storage factors like pH, temperature etc.., these may get developed while preproduction, intermediate processing and post production also, mostly from the excipients, raw materials used in the production process. In this review, an industrial layout was explained briefly from the initial step of procurement of required materials from the market to the end sale of the product into the market. Industrial layout includes the warehousing areas, manufacturing areas, packaging areas and storage areas. Quality checking documentation for the nitrosamine's traces are recommended for the approval from regulatory authorities, explaining the details of cross contamination, quality testings, factors affecting during production and finally the new methods and basic steps should follow to manage the cross contamination and risk management approaches to ensure the quality. Manufacturing steps like mixing, grinding, compression/ punching, filling, packaging etc... are involved in nitrosamine contamination risks, packaging materials are also responsible for the nitrosamine's contamination. Waste water containing nitrosamine is treated over for the environmental quality management. Minimizing the risk of contamination ensuring the safety, quality, of the product by adapting the mitigation strategies.

Key Words : Nitrosamine impurities, Excipients, Quality risk management, Industrial layout, Cross contamination.

1. Introduction

In pharmaceutical manufacturing process involves the management of production of a dosage form with quality and safety along the better therapeutic efficacy. Quality might affect the safety which sometimes indulges with therapeutic activity. Nitrosamines impurities in the production due to cross contamination/ synthesis of these compounds because of variation of environmental factors/ processing conditions like pH, acidity, concentration of amines etc. Industrial layout in this review explain the basic processing steps involve in manufacturing of dosage form from the initial step of stocking of raw materials from the marketing agent to the distributors who sale out the product. Which involves in different steps (Flow Chart:1)

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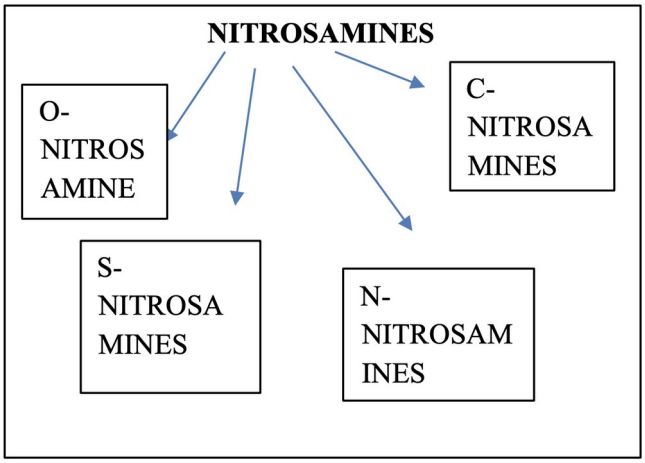


Diagram 1:Classification based on hetero atoms bound in nitrosamine molecule

1.1 Basic layout of pharmaceutical manufacturing unit:(flow chart :1)

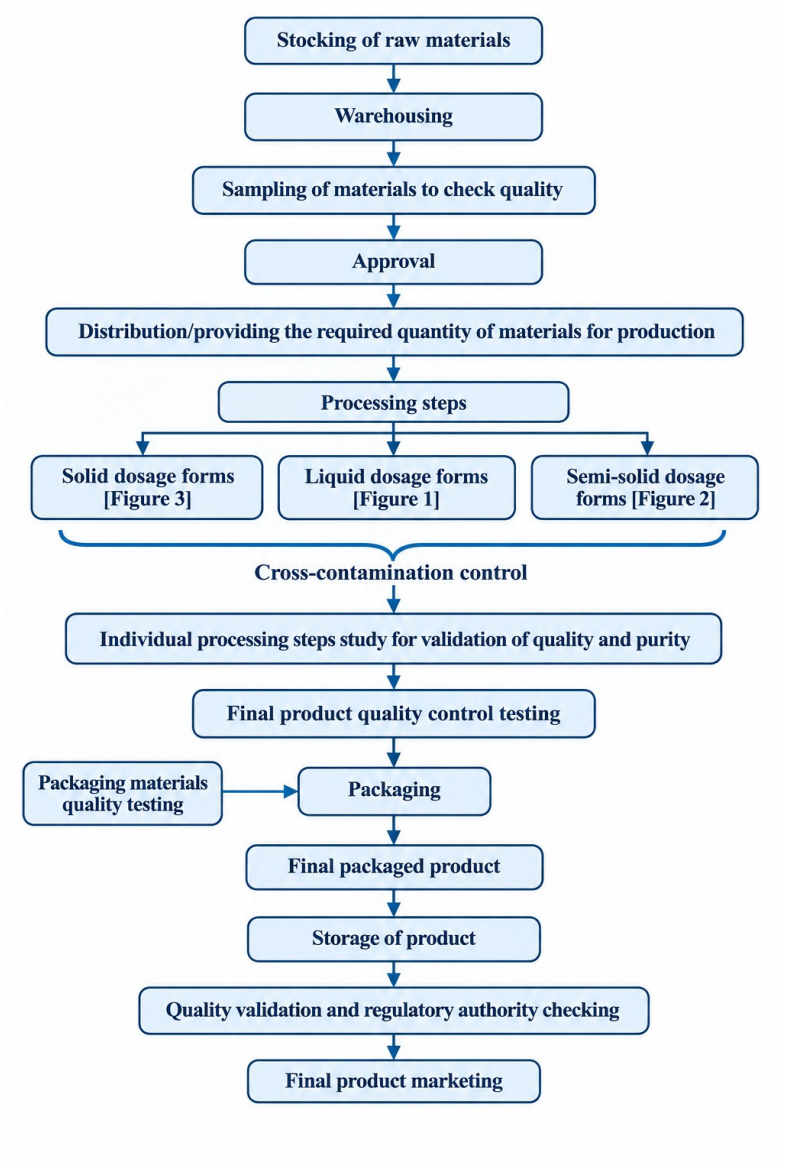
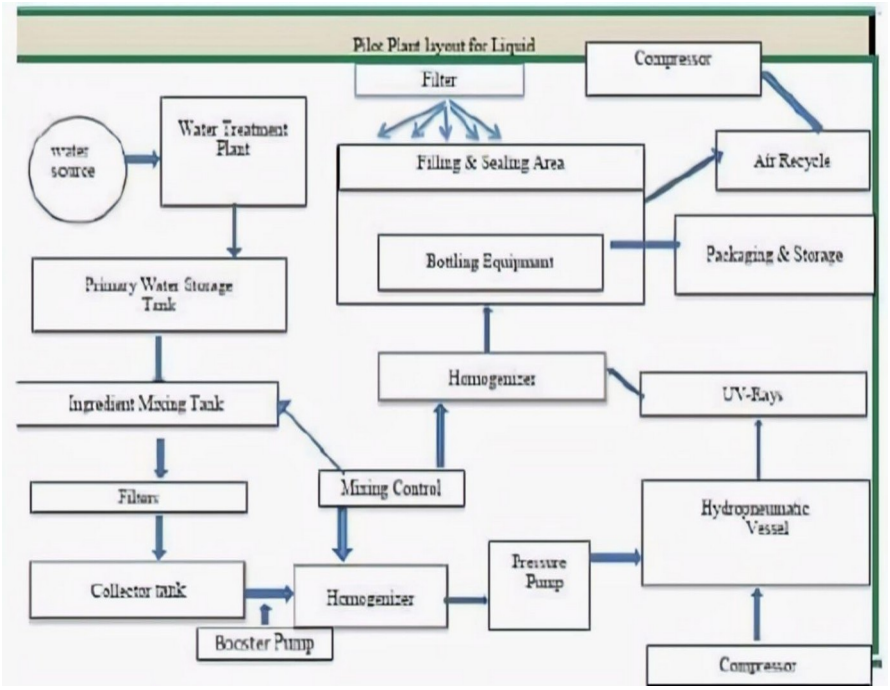


Figure:1 liquid dosage form manufacturing process



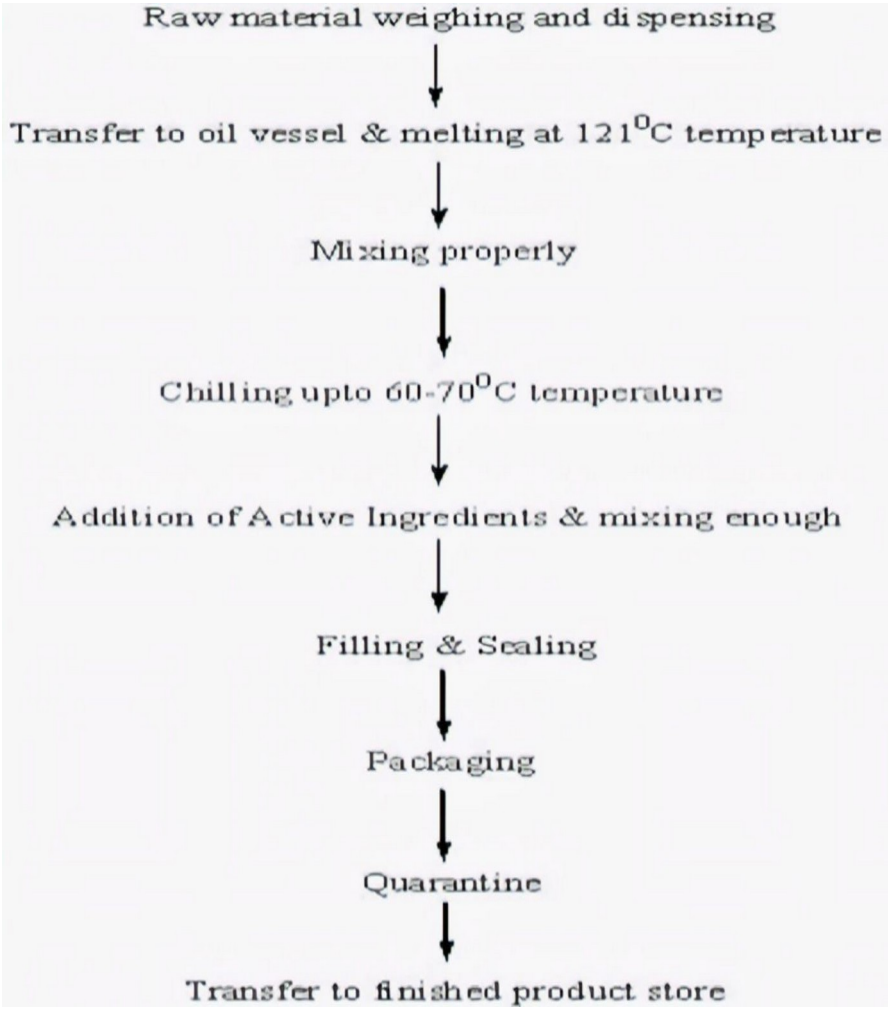


Figure:2 semisolid dosage form manufacturing process

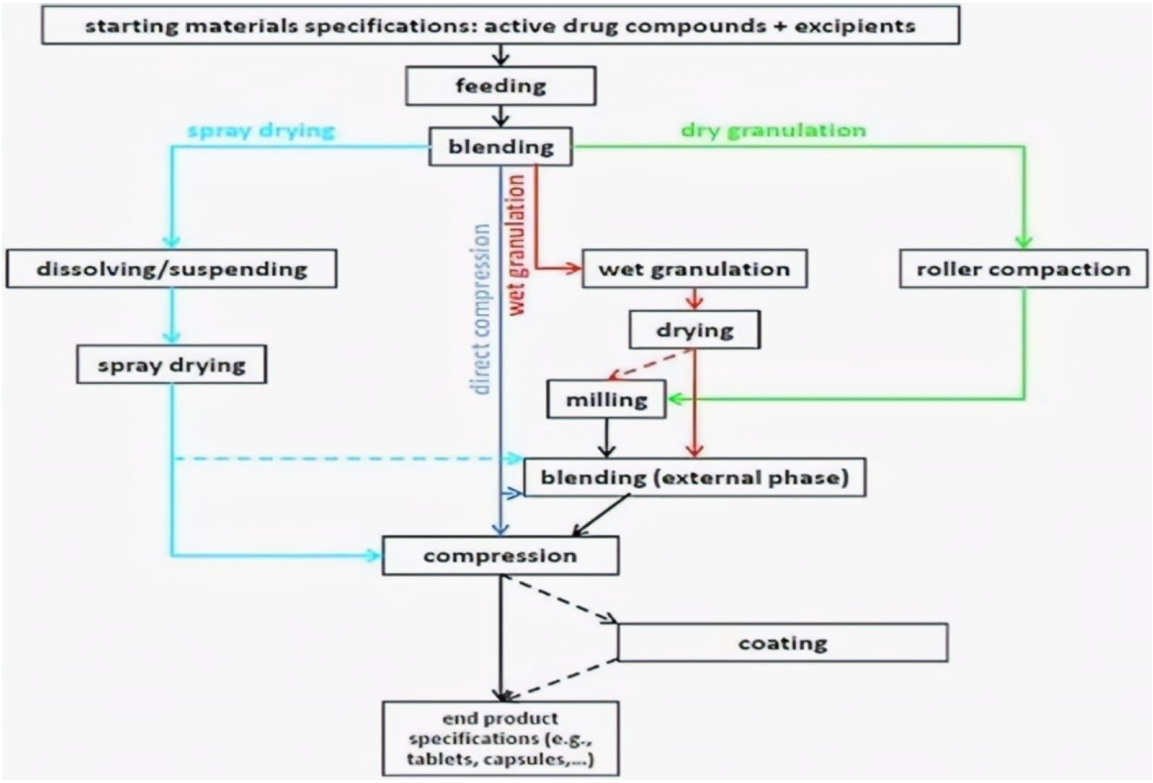


Figure:3 solid dosage forms manufacturing process

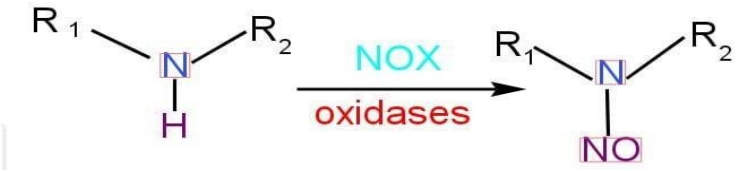
Nitrosamines impurities are found in water, food, tobacco, pesticides, plastics and as well as medicinal products, excipients. They may introduce while the synthesis steps or cross contamination. Nitrosamines contamination may occur during the processing steps like milling, blending, grinding, sieving, drying, granulation, compression, filling, packaging. Nitrosamines are genotoxic where produced for interaction of secondary amines/tertiary amines with nitro sating agents. Nitrosamines contains N-N=O functional groups. Most commonly observed in nitrosamines in pharmaceutical products like NDMA(N-nitroso dimethylamine), NDEA(Nitroso di ethylamine), NDIPA(N-nitroso sodium isopropyl amine), NEIPA(N-nitroso ethyl iso propylamine), NDBA(N-nitroso-di-n-butylamine), NEMA(N-nitroso methyl ethylamine), NDPA(N-nitroso-di-n-propylamine), NMBA(N-nitraso-n-methyl-4-aminobutyric acid), NMPA(N-nitroso-isopropyl ethylamine), NDELA(N-Nitrosodiethanolamine), NMOR(N-Nitroso morpholine), NPIP(N-Nitrosopiperidine), (N-Nitrosodiisopropanolamin),NNATL(N-Nitrosoanatalline),NFLX(N-Nitroso-Fluoxetine), COX-NDSRI(e.g. N-Nitroso-Celecoxib / N-Nitroso-Etoricoxib), NRLE(N-Nitroso-Ramelteon), NBMTEM(N-Nitroso bumetanide), NO-MCTZ(N-Nitroso-Methyclothiazide). In those, NDMA and PDEA are the popular cancerous nitrosamines which are classified by IARC (International agency for research for cancer) They act by alkylating the DNA bases which leads to cancer. Industries should follow mitigation techniques to avoid these nitrosamines impurities. Which should give an authorized quality and safe product which are under regulations. Even nitrosamines are harmful, unintentional allow into body have given for acceptable ranges for nitrosamine impurities. Some of the nitrosamines are here:

Nitrosamine	Acceptable ranges (ng/day)	Examples of drugs
NDMA	96	Sartan, ranitidine, metformin, chloroquine
NDEA	26.5	Sartan, food, water
NDIPA	26.5	Sartans, metformin, water
NMPA	26.5	Solvents
NMBA	1500	Sartan drugs
NEIPA	400	Water, food, sartan, metformin
NDBA	26.5	Elastomer, packaging overwrap

Table :1- acceptable ranges of some of the nitrosamines

1.2. Synthesis of Nitrosamines:

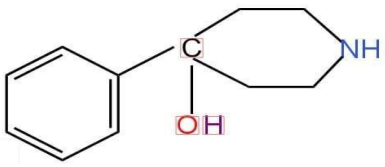
Nitrosamines synthesis should need primarily the presence of nitrogen compounds like amines (1°,2°,3°) in presence of nitro sating agents at typically favourable conditions like pH, acidity, temperature.



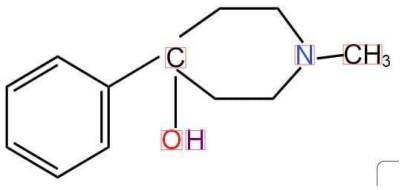
These combinations mostly observed in food, pharmaceuticals drugs, excipients, soil, etc.

1.2.1 Amines

In comparison 3° amines are less affective in synthesis of nitrosamines as compared with 2° amines because of interaction of multiple compounds (bulkiness) of the groups. Whereas the 2° amines comparatively more prone for synthesis of nitrosamines.



2°amines



3° amines

But in comparison furtherly with 2° amines the salt forms of 2° amines are more prone for the reaction than the 2° amines free bases.

1.2.2 Nitro sating agents:

Nitro sating agents acts as catalysers the agents which promotes the reaction nitrous acid (HNO_2), nitrite (NO_2), Dinitrogen trioxide(N_2O_3), Dinitrogen tetra oxides(N_2O_4), Nitrosyl chloride(NSCL), Nitrosonium tetrafluoroborate ($NOBF_4$),and Nitrothiocynate (CN_2O3), Nitric acid ,Nitroso alkyl, Nitro allyls, Inorganic nitrite in excipients, Nitrites in in water helps in nitrosamine synthesis.

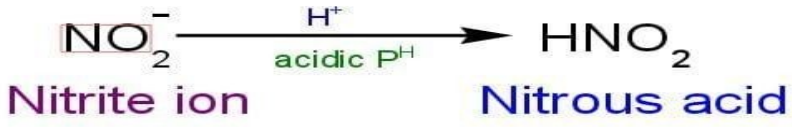
Even the microbes are involving in the synthesis of nitrosamines. (figure:1)

1.3 Mechanism of nitrosamine production

N-nitrosamines formed by the nitrosation reactions between amines and HNO_2 derived from Nitrites in presence of heat and acidic conditions.

1.3.1 Steps involved in synthesis of nitrosamines:

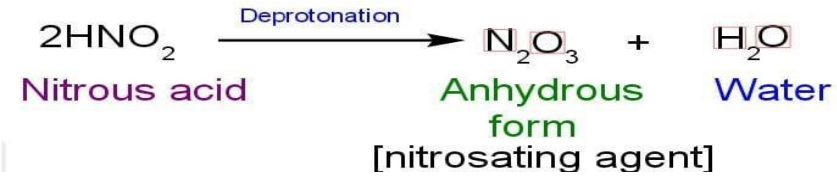
- Step 1:



This step helps in existing the compounds in equilibrium state and also acting as nitro sating agent.

Higher the acidity -Faster the reaction.

- Step 2:

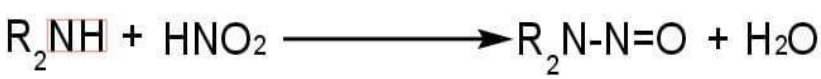


- Step 3:
  -Nitrosation of 2° amines-

  When the N_2O_3 reacts with 2° amines forms nitrosamines.



  - It can simply be represented as

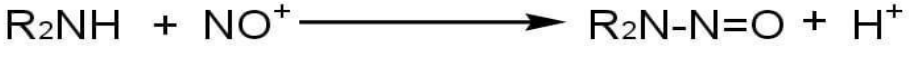


  -HNO_2 contributes for formation of nitro sating agents for sample.





-NO^+ acts as nitro sating agent



Nitrogen oxide (NOx) as nitro sating agent

Step 1: hydrolysis



Step 2: deprotonation



Step 3: Protonation





N_2O_3 can be consider as nitro sating agent in nitrosamine production.

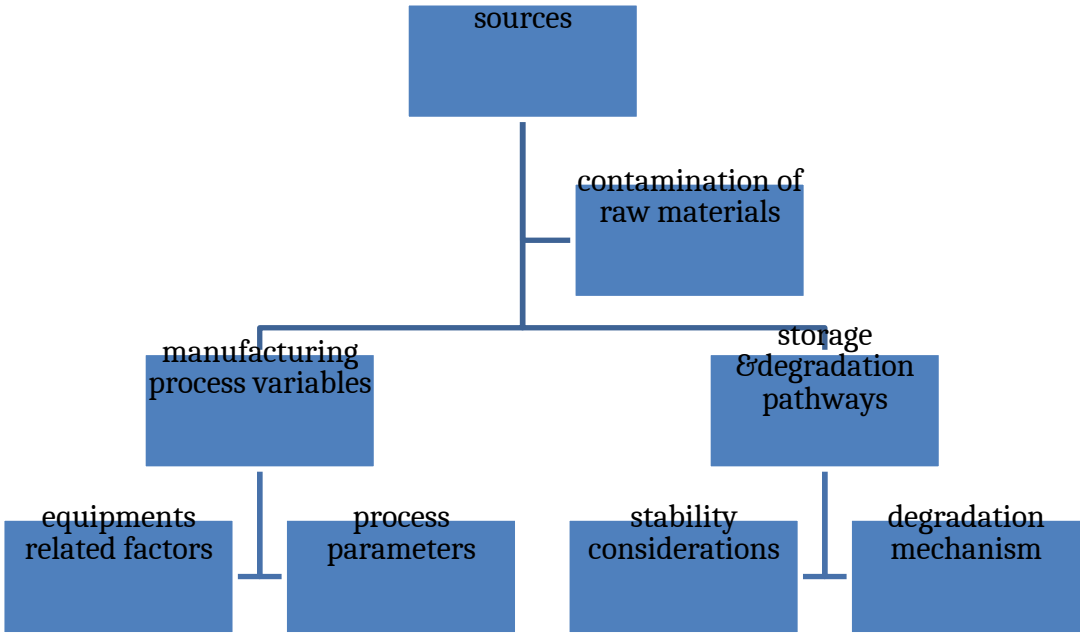
Can be simply written as



1.4 Sources of Nitrosamines (Table :2)

Sources	Category	Examples
Food	Vegetables, fruits, fish, curd etc…	Spinach, orange, Broccoli, Carrot, Tomato, Mustard greens, Banana etc…
Excipients	Diluents, Anti adherents, Disintegrants, Lubricants, Preservatives	microcrystalline cellulose, cellulose, lactose, starch, povidone, cross povidone stearate, stearic acid, hydroxy propyl cellulose, formaldehyde, polyethylene glycol, polyvinyl pyrrolidone, lactose monohydrate, polysorbate etc…
Packaging materials	Primary and secondary packaging materials	Rubbers, polypropylene infusion bags, aluminium foil seals, infusion bag tubing, printing ink, lidding foil, rubber stoppers etc…
Pharmaceuticals	classification	Metformin, Satrans, ranitidine, rifampicin, bumetanide, at orvastatin, Nifatidine, linsopril, enalapril, cilostazol, propranolol, pioglitazone, sunitinib malate etc…
Solvents	Organic and inorganic solvents, water	Water (ground water, sea water, recycled water)

Diagram :2- sources for production of nitrosamines



1.5 Factors affecting nitrosamine products:

Nitrosamines production is influenced by the pH, temperature, light, concentration, Nitrosation catalysts, water presence, kinetic energy etc...

- pH – Nitrosamine production is fastened/improved only in the presence acidic pH in b/w 3.0 to 6.0 reaction rate is maximum at pH 3.0-3.4.
- Temperature and time- Between 25 ℃ to 80 ℃ , nitrosamine production is well observed at drying/storage.
- Humidity and light- As these parameters are favourably available, they induce the chemical reaction for synthesis higher humidity mobilizes the concentration.
- Concentration- nitrites and amines helps in getting more reactive and involves in much more production increases concentration-increases production.
- Nitrosation catalysts/Nitro sating agents- Promotes the forward reaction fluids causes contamination of products metal ions/salts acts as catalysts.
- Kinetic energy- As temp, concentration, nitro sating catalysts imparts and effecting reaction the movement of the molecules increases-causes increases kinetic energy leads to increased production of nitrosamines.

2. Risk of nitrosamine impurities in manufacturing processes:

2.1. Procurement & storage of raw materials:

Raw materials containing amino groups are sensitive for reaction due to increased kinetics in the molecules. raw materials in ware housing area are stored in the racks should be perfect &evidenced. In case of long-term storage of raw materials, without considering the first in first out (FIFO), first expiry and first out (FEFO) concept, the materials reach the shelf life & furtherly may involves in the production of impurities due to kinetics.

Warehouse is the high-risk area for contamination.

2.2. Sampling of materials:

During sampling of materials there may be a risk of contamination. sampling involves the weighing of materials for quality testings. During weighing of materials, cross contamination may happen due to lack of proper cleaning of balances, scoops /spatulas improper cleaning after sampling. During supply of materials to the production area using trollies which causes contamination when proper cleaning is not done.

2.3. Contamination during production:

In production process there is a risk of nitrosamine impurities either by contamination or by chemical synthesis due to favourable conditions & kinetics in the components.

Cross contamination may due to improper cleaning validation processes after the batch completion, there is a risk of chemical reaction due to dust& contaminants of chemical samples which are remained in the large container, lids &edges. Improper sterilization also leads nitrogenous reactions due to microorganisms.

2.3.1 Solid dosage forms:

Solid dosage forms include tablets &capsules. Manufacturing includes wet granulation, dry granulation and direct compression methods, which includes different steps as following using different equipment.

- **Size reduction- Milling, Cutting, Attrition, Impact, Sieving** (Cutter mill, Roller mill, Hammer mill, Ball mill, Fluid energy mill, Edge runner mill, Colloidal mill, Pin mill).
- **Size separation[sieving]- Elutriation, Classification (**Perforated screenings, Sieve shaker, Alpine air jet sieve, Cyclone separator, Air separator, Bag filter, Double cone classifier, Static tanks).
- **Drying**- (Tray dryer, Freeze dryer, Drum dryer, Fluidised bed dryer, Spray dryer, Vacuum dryer, Infrared dryer, Microwave dryer).
- **Mixing /blending**: Mortar and pestle, Double cone blender, V-cone blender, Cube blender, Ribbon blender, Sigma blender, Planetary-P-needle, Fluidised mixer, Barrel type, Continuous mixer, Zigzag type continuous mixer.

These are basic steps involved in production but also includes minor processing like compression, coating etc... not all equipment involved in the process involves for nitrosamines production. But the chances of contamination vary like in wet granulation technique, moisture effects cause the contamination where as in dry granulation techniques temperature/heat effects the production.

2.3.2Liquid and Semi-solid dosage forms:

- **Centrifugation- (**Perforated& nonperforated centrifuge, Basket centrifuge, semi continuous centrifuge, Horizontal continuous centrifuge, Super centrifuge, Conical disc centrifuge**).**
- **Filtration:**(Filter papers, Sintered glass filters, Seitz filters, Membrane filter, Plate &frame filter press, Chamber press, Filter leaf, Meta filter, Cartridge filters, Streamline filter, Pressure sand filter.
- **Mixing of liquids**: Propellers, Turbines, Paddles, Emulsifiers, Homogenisers
- **Mixing of semisolids:** Anchor agitator, scraped surfaces agitator, Counter rotation agitator, Triple roller mill.

- **Distillation:** Simple distillation, Fractional distillation, Molecular distillation, Flash distillation, Steam distillation, Destructive distillation, Compression distillation {falling film molecular still, centrifugal molecular still}
- **Evaporator**: Multiple effect evaporator, forced circulation evaporator, falling film evaporator, Climbing film evaporator, Vertical tube evaporator, Horizontal tube evaporator, Evaporation pan
- **Separation/ elutriation:** Static tank, Multiple fraction separation
- **Crystallization, Distillation, Evaporation, Drying, Sterilization:** Heat exchangers and heat interchanger {tubular heater, multi pass heater, two pass floating head heater, scraped surface heat exchanger} Finned tubes, Steam traps.

Equipment contamination for liquid and semisolids is as similar to the other equipment in solids but liquids and semisolid dosage majorly effected with the, moisture and microbial levels.

2.3.3 Chances for contamination risk during production:

1.Equipment used in the processing are complex and critical. They are larger and heavier where the cleaning and sterilization of the equipment tumblers are critical, sophisticated equipment are typical to handle which may cause difficulty in cleaning. There may be a chance of cross contamination risks at higher levels, remaining of drugs and components in the edges of the equipment leads to contaminants risks.

2. Chemical reactions: During processing, drugs components may interact with the containers involving in oxidation, hydrolysis like reactions which effects the chemical nature of the API& excipients allows the formation of nitrosamine impurities

3. Temperature factor: During process the equipment may affected with overheating due to over loads or else due to heavy speeds & movements heat may generated which accelerates the chemical reaction with drug & materials also causes drug degradation which intern allows the nitrosamine formation.

4. Moisture and pH: When the cleaning process& sterilization methods are not under regulates leads to remains of cleaning agents causes change in pH, if the moisture after cleaning causes corrosion of the metals / hydrolytic reaction/ microbial growth which further allows the risk of nitrosamine contaminations.

2.4 Packaging process:

Even after the completion of production interaction of drug with primary packaging materials lack of regulated conditions on storage while packaging or may be risk of printing inks as source of impurities & residuals of chemicals improper sterilization causes the nitrosamine s synthesis. For example, nitrocellulose present in the printing inks used as packaging materials for packing of drugs like tetrazoles may cause cross reactions forms nitrosamines.

3. Wastewater purification & reuse:

Water plays a major role in production process which has been useful for cleaning procedures, process as solvent, in coolers &boilers.

As a water from cleaning are polluted with many impurities. Some pollutants in water from the pharmaceutical industries are poly cyclic aromatic hydrocarbons, arsenic trioxide chlorambucil, epinephrine, cyclophosphamide, nicotine, daunomycin, nitro-glycerine melphalan, physostigmine, mitomycin, physostigmine salicylate, streptozotocin, warfarin over 0.3%, uracil mustard, halogenated & non halogenated

solvents, organic chemicals, sludges &tars, heavy metals, test animal remains. inorganic solvents include amines & ammonia where NO_2 & water produces ammonia & its components. These ammonical nitrogens are purified by many techniques & methods like adsorption, chemical precipitation, membrane filtration, reverse osmosis, ion exchange, air stripping, break point chlorination, biological nitrification & denitrification, electrodialysis, distillation. Generally, waste purified by different techniques are reused for agriculture, chemicals as ammonia sources& industrially for the source of some cleaning procedures, boilers and coolers but under the USFDA &EMA regulations, it is prohibited strictly for the use of recycled water even after purification.

4. Risk assessment and testing methods for qualification:

As there are risk of nitrosamines at different levels, there must be a qualified testing procedures to be done at every level as per the USFDA, EMA regulations. Cleaning validations should be done under ICH Q9 guidelines (Quality risk management) where the risk factors determined, validated, and controlled. Testing procedures includes chromatographic and non-chromatographic techniques, spectroscopic techniques (mass spectroscopy). nitrite excipients data base has been created by an organization called Lhasa. This Lhasa nitrites consortium and data base was established after the nitrosamine crisis in sartan drugs. Acceptable limits for the impurities can be measured for risk assess

Majorly used testing techniques are 6:

1. Ion chromatography with conductivity /UV detection (IC-CD/IC-UV):
   In this method direct detection of nitrites is observed, where anion exchange is measured by conductivity. In UV method at 190-230nm but it is not much preferred due to chloride interference.
2. Griess derivatisation with HPLC- UV:
   It is an indirect method for detection of nitrites, here the nitrites react with sulphanilamide in acidic pH which forms diazonium salts. later produces N-(1-napthyl) ethylene diamine, while using Bratton Marshall reagent forms red -pink azo dye which was observed at absorbance 525nm.
3. DAN(2,3-diaminonapthalene) derivatisation with HPLC-FL/UV/MS**:**
   When nitrites are added to DAN at acidic pH leads to formation of 2,3-napthatriazole (NAT)which gives strong fluorescence.
   For fluorescence it gives 0.5ng/mL LOD .it is highly sensitive equipment detected under UV at 380nm.
4. Cyclamate derivatisation with head space GC-FID/GC-MS(HS-GC):

In this method, when water soluble cyclamate is in contact with nitrite with acidic pH produce volatile non polar cyclo hexane & nitrogen gas. it is highly sensitive.

5. IC with post column derivatisation (IC-PCD-UV):
   Here ion exchange by anions &Griess derivatisation together works. Auxiliary pump adds Griess reagent via T-piece, detection made at 480 nm in UV. It is widely used method, highly specific and sensitive.
6. HPLC-MS/MS after Griess derivatisation with stable isotope dilution assay (SIDA):
   It is most accurate and advanced method for testing nitrite impurities .15N -labelled nitrite is used as internal standard. it is highly specific and corrects matrix effects.

5. MITIGATION STRATEGIES FOR NITROSAMINE CONTAMINATION:

- Primarily the nitrosamine risk should be detected.
- Care should be taken to avoid the cross contamination.
- Cleaning validation should be done properly

- Maintaining the environment factors to avoid drug detoriation.
- Nitrosamine drug substance related impurities (NDSRI) should be detected earlier in the drugs and their and assessment to control the impurities, nitrite scavengers can be used like
  Ascorbic acid, $\propto$- tocopherol, maltol, resveratrol, propyl gallate, BHA, BHT, caffeic acid, ferulic acid , $\propto$- amino acids (glycine, lysine, histidine), L-cysteine, para-amino benzoic acid, urea, sodium sulphate, ammonium chloride, sodium carbonate by different mechanism like redox reaction, diazotisation reaction, pH modulation.

6. CONCLUSION:

Focussing on the nitrosamine impurities in the different pharmaceutical manufacturing processes which is helpful to prevent the major side effects, carcinogenic and mutagenic problems in the consumers. Industries must follow the quality check for these impurities at every processing steps. Pre determination techniques for identification of chances of nitrosamine production, helpful for following earlier mitigation strategies. it is helpful for avoiding the callback of drugs and for the economic growth in the markets because of their quality standards. accelerated stability studies for the formulation improves the standards for exporting of drugs to other countries continuous risk assessment and quality management minimizes the contamination risk by understanding the complete concept of cross contamination. Nitrosamines consumption due to contamination having ranges &acceptable limits. As per the ICH M7, safety limit is 1.5μg/day for most mutagenic impurities but the nitrosamines at even the 1.5μg/day causes severe risks. so, these impurities need much more advanced analytical techniques.

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