A
MINOR PROJECT REPORT

ON

CONTINUOUS MANUFACTURING IN PHARMACEUTICAL INDUSTRY

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Under the guidance of

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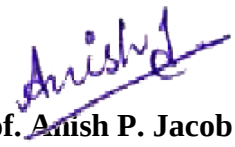
CERTIFICATE

This is to certify that **Aman Narang, Punya Shrivastava, Ritik Jha & Yuvraj Samadhiya,** students of B.Tech 3rd year Chemical Engineering Madhav Institute of Technology and Science, Gwalior (M.P.) have satisfactorily completed **Minor Project (170607)** on "**Continuous Manufacturing In Pharmaceutical Industry**", for the partial fulfilment of degree in Chemical Engineering in the academic year 2021-22.

Under the guidance of



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CANDIDATES DECLARATION

We hereby declare that the project report – "Continuous Manufacturing in Pharmaceutical Industry" which is being submitted for "Minor Project (170607) of 6th semester in "MADHAV INSTITUTE OF TECHNOLOGY & SCIENCE, GWALIOR (MP) is our genuine work done under the guidance of Prof. Anish P. Jacob, Dept. of chemical engineering, "Madhav Institute of Technology & Science ", Gwalior

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Abstract

Innovation in the pharmaceutical manufacturing industry has been limited to the research and development of new active compounds, for a very long time. The structure of the production, dominated by batchwise technologies, has not changed to date. As has already been demonstrated in several other industrial sectors, it has been found that continuous manufacturing (CM) has many advantages over batch processes. It is faster, cheaper, and more flexible way production and can be developed with a significantly higher level of quality assurance. In the recent years the main regulatory agencies not only recognized the need for a change in drug production but also started to promote continuous technologies and encourage pharmaceutical companies to develop and adapt such processes.

Many publications deal with synthetic steps carried out in flow reactors and crystallizations implemented in a continuous manner, and on the formulation side continuous filtration, drying, granulation, and blending have all been studied to a lesser or greater extent. Besides the modification of these traditional processes to continuous operation, intrinsically continuous technologies are being studied as well. In order to take total advantages of CM, the separately developed processes need to be integrated to form end-to-end systems from the raw materials to the final dosage forms. However, even the integration of two technological steps is a challenging task. The aim of this paper is to give an insight into the new directions in integrated continuous pharmaceutical technologies by reviewing the recent literatures in this field.

KEYWORDS: Continuous Manufacturing, End-To-End, Integration, Synthesis, Crystallization, Filtration, Blending, Tableting

CONTENTS

Chapter 1

INTRODUCTION

By the end of the 20th century, most of the largest industrial sectors-built production lines based on assembly line, continuous technologies. In contrast, the pharmaceutical production traditionally relies on batch processes. The facilities are designed for the large-scale batch production of "blockbuster" drugs using large volume centralized batch manufacturing plants. This approach divides the manufacturing process into many separate steps which are clearly isolated in space and time. The two major parts of drug production, i.e., synthesis, isolation, and purification (drug substance manufacturing) and formulation (drug product manufacturing), are often located in different geographical regions, including different countries. This procedure leads to elongation in the supply chains drastically and increases transportation times.

During the batch manufacturing process, samples are taken from each produced batch, which are carried to separate laboratories to conduct in-process-control measurements before moving the material to the next operation. Since the production of a pharmaceutical product can take up to 10−20 steps, this chaotic procedure together with the long supply chains could result in huge expansion of time in the overall production. Pharmaceuticals are manufactured in a "campaign-like" manner, meaning that a given intermediate is prepared in successive batches, collecting a certain amount of material together before moving to the next step. This practice requires substantial storage capacity, which inherently raises the production and thus the product cost.

Also, storing large amounts of hazardous active pharmaceutical intermediates contributes to the safety issues of the manufacturing process. Scale-up is always a great challenge during the development of batch technologies, as the process behaviour can show strong scale-dependence, which is often associated with hydrodynamic effects. Thus, the processes optimized on laboratory scale sometimes require thorough re-optimization, which might be challenging, since ensuring adequate supply for the clinical trials is the priority. Hence, usually the first operating procedure is accepted for industrial-scale operation and submitted to regulatory approval.

The greatest drawback of the batch-based structure of pharmaceutical manufacturing is presumably the currently common practice of quality assurance. In the case of drug products, ensuring consistent quality is of utmost importance, which is intended to be achieved by strict regulatory control. The applied practice is the Quality by Testing (QbT) method, which consists of the analysis of samples taken from the raw materials, the intermediates after each step, and

the final products.13,14 If any of the parameters is out of the regulatory approved specifications, the entire batch must be reprocessed or discarded causing significant delays and extra costs. The fluctuations are intended to be minimized by the tightly controlled process parameters. The presented structure of the drug production makes the pharmaceutical industry slow and highly inflexible and thus unable to give quick answers to the changes in demand. It can create a potential public health threat as the root causes of numerous reported drug shortages can be traced back to the problems of the current manufacturing strategy of the industry. Therefore, there is an increasing need for a more agile, robust, and efficient manufacturing structures in order to keep up with changes in market demand, to reduce costs, and to produce pharmaceuticals more reliably with improved quality.

1.1 Advantages of Continuous Manufacturing

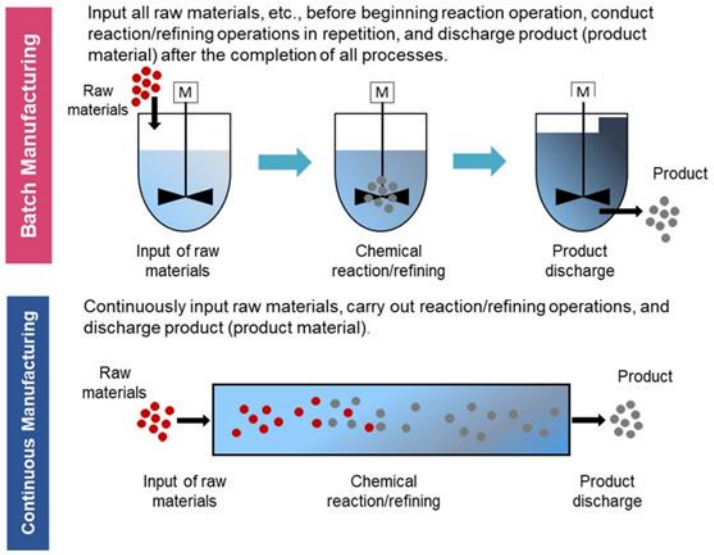
Significant improvements can be accomplished in the production by replacing the batch processes with continuous technologies.

- Unlike batchwise manufacturing, in the case of continuous processes, the raw materials and the product are continuously fed into and discharged from the equipment.
- All the materials are continuously flowing through the system, eliminating the idle time between the different technological steps.
- After a start-up period, continuous processes converge into a steady state, during which the process parameters remain constant in time.
- Monitoring and maintaining these variables on the fixed set point is much easier than handling the dynamic nature of batch operations.
- In the case of an error, the deficient product section can be traced back accurately; hence, discarding the entire amount of material is no longer necessary.
- Continuous technologies are usually developed as a whole, integrating the consecutive steps into one system, this would result in a drastically different and improved production strategy.
- By connecting the currently separated manufacturing sections, the elongated supply chains could be cut down.
- Because of the high-level automation and the lack of termination between the technological steps, human intervention and exposure can be minimized, reducing the toxicityand safety-related issues of traditional batch manufacturing.
- Due to the typically lower material holdup of a continuous system compared to the batch counterpart, the hazards and safety issues of the reagents, solvents, or other involved materials are inherently reduced.
- The productivity can be increased simply by operating the system for a longer time, facilitating provision of a rapid response for sudden changes in demand.
- In the case of continuous technologies, process optimization is usually faster and easier, which means that a more understood and optimized process can be submitted for regulatory approval.

Chapter 2

LITERATURE REVIEW

Recent Progress in Continuous Pharmaceutical Technologies



1. Multistep Flow Synthesis of Pharmaceuticals.

- Principles of Flow Chemistry.

The multistep synthesis of complex organic molecules from simple precursors represents a significant achievement but is also one of the greatest challenges of the synthetic organic chemistry. The traditional batchwise synthetic route consists of a series of batch reactions with workup procedures, purification, and isolation after each step. Although this approach is the basis of all modern syntheses, such a procedure is usually time-consuming and wasteful compared to the single-cell multistep biosynthetic pathways. Continuous flow chemistry offers several options for the implementation of organic syntheses. In flow systems the materials are flowing in tubes with small diameter (usually between 50 and 1000 μm), and the reactions take place in these so-called microreactors. The starting materials are fed by pumps, and mixer elements provide the sufficient mixing of the liquid. Backpressure regulators (BPRs) can be applied at the end of the tubes to pressurize the system, allowing increase of the boiling point. Directly connectable devices are available for the purification of the reaction mixtures.

These systems have a number of advantages over traditional batchwise reactors. The small cross-section of the tubes means that the heat transfer area to reactor volume ratio is about 50−60 times bigger. In the pressurized system significantly, elevated temperatures can be applied, thus accelerating the reactions and making new pathways possible that are otherwise not

accessible. Reduced reaction time, excellent yield and selectivity, enhanced safety, and good reproducibility were reported in the literature numerous times. Naturally, new challenges have arisen with the new technology, for example dealing with solid materials and the issue of clogging, the integration with in-line purification techniques, or the cost of flow equipment, which all must be handled during the development of a flow chemistry process.

- Flow Synthesis of Pharmaceuticals.

  By connecting several flow reactors, multistep syntheses can be carried out in an uninterrupted system.56,83 The great benefit of this approach is that the isolation of intermediates can be eliminated, simplifying and accelerating this process (Figure 1b). Without transportation and off-line quality testing after each step, the footprint of the production facility can be reduced, improving flexibility at the same time. This is especially true for the synthesis of APIs, as these complex compounds often require 6−10 synthetic steps from the starting materials.78 Usually some compromises are inevitable and the synthetic route is split up to shorter sequences for intermediate purification of the reaction mixtures or for solvent switch.84 Integrating the operation steps, including in-line purification, workup, and real-time analysis requires holistic optimization and deep process understanding.

  Nevertheless, the telescoped synthesis of APIs under flow conditions has a growing body of literature70,72,80,83,85,86 and due to the challenge of the integration of in-line purification into a flow system, this topic is also gaining more and more attention.59,87,88 In Table 1 APIs with reported continuous flow total synthesis are summarized. Regarding the industrial application of flow chemistry, in 2018 Hughes collected seven examples from the patent literature for API synthesis, during which at least one reaction step is carried out under flow conditions.89 However, in these cases it was not public whether these routes are used for commercial manufacturing or not.

- API Flow Syntheses Integrated with Downstream Processes.

  In order to build end-to-end systems, the developed multistep flow synthesis of the APIs must be connectable to the subsequent technological steps. The final reaction is usually followed by the purification of the synthesized API, which can be carried out by numerous methods, including liquid−liquid extraction, chromatography, etc., but the compound must be brought to solid form with a continuous crystallization step. This is usually carried out in mixed suspension mixed product removal (MSMPR) crystallizers of plug flow reactors (PFRs).

2. Continuous Crystallization and Filtration.

Crystallization is a key purification and separation technique in the pharmaceutical industry, and it is a critical step in connecting synthesis and formulation. More than 90% of the currently marketed APIs are going through at least one crystallization step during their production. The crystal size and shape have a strong impact not only on the downstream operations through bulk density or flowability but also on the dissolution rate and bioavailability of the final drug product. The importance of the process drew attention to continuous crystallization in the recent years. In the technological line crystallization is followed by filtration for the isolation of the solid product. This technique is usually assessed by the filterability of the crystals, the moisture content of the filter cake, and the recovered mass. Also, the process might affect the crystal size through agglomeration. Continuous filtration is a relatively new area of study in the pharmaceutical industry, and only a handful of papers were published.

- Continuous Crystallization.

Currently, the vast majority of crystallizations in the pharmaceutical industry is carried out in stirred batch reactors. These systems have been used for decades, and the processes are thoroughly optimized and reasonably well-understood. However, there are still significant issues with batch-to-batch variability, which can lead to substantial difficulties in the downstream processing of the crystal product. The root cause of batch-to-batch variability is the highly nonlinear crystallization kinetics, as well as the high sensitivity of secondary on the process parameters and seed quality, which, in practice, cannot be fully eliminated. The continuous systems offer improved control and reproducibility over the physical characteristics of the product. By setting the appropriate operating conditions, the key parameters such as particle size and shape can be accurately controlled.

In the case of continuous crystallization, the API solution is continuously fed into the equipment, while the product slurry is continuously withdrawn. Numerous different systems have been published for the implementation of such a process. The two most widespread technologies are the MSMPR crystallizers and the PFRs. The MSMPR crystallizers are conventional jacketed stirred tank reactors, with continuous input of starting material and continuous product removal. The practical advantage of these systems is that the existing stirred tank equipment can be further utilized and can help to convert the existing batch crystallization processes to continuous operation. By connecting several MSMPR reactors into a multistage cascade system, flexible temperature profiles can be used resulting in better control over crystallization mechanisms, and the final stage concentration can be adjusted close to equilibrium for yield considerations.

On the challenges side, the continuous tank systems have broad residence time distributions, and the scale-up difficulties of the original batch processes cannot be overcome easily. MSMPR crystallization of APIs is a frequently studied topic in the literature. In tubular crystallizers the API solution is continuously flowing through a tube with constant flow rate. The great benefit of these systems is the excellent process control due to the relatively small tube diameter being often on the order of centimetres, easy scale-up, and the narrow residence time distribution, which can provide improved product uniformity. An important variant of PFRs is the continuous oscillatory baffled crystallizer (COBC), where a piston provides an oscillatory flow which, in combination with and the internal orifices (baffles), can greatly reduce the sedimentation and clogging even at low net flow rates, i.e. long residence times.

- Continuous Filtration.

  The produced crystals are separated from the mother liquor in the filtration step. This is a technique often developed by practical and empirical understanding due to the complex nature of cake growth and properties and to the interacting process parameters. Therefore, it is necessary to carry out experiments with the actual slurry on the required scale since predicting filtration performance is cumbersome. In the pharmaceutical industry filtration is generally carried out in batch mode, but there are already a few examples for continuous filtration devices. The low number of publications dealing with pharmaceutical related continuous filtration is probably due to the fact that it is a complex technical challenge and involves the use of less established technologies. Cross flow filtration is a well-known continuous filtration technique, mainly utilized during the processing of biological products to concentrate slurries.

- Integrated Continuous Crystallization and Filtration.

  In 2012, Wong et al. presented a study about a single-stage MSMPR crystallizer with a recycle system. In this system standard batch filtration was directly connected after crystallization using a coarse glass filter disk with a filter paper having 1 μm thickness. After the filtration of crystals, the mother liquor was subjected to an organic solvent nanofiltration method in order to eliminate the impurities and increase the concentration of the remaining dissolved API, deferasirox. A buffer tank was applied between the two steps, and after the optimization of filtration parameters, stable operation was achieved with this two-step system. By applying scraped wall crystallization, improvements were accomplished in terms of better kinetics and reduced aggregation, and the semi batch application of the hybrid device saved a considerable amount of time and material, while appropriate performance was achieved with each step. A unique impeller was applied to enhance the processability of needle-like crystals of ciprofloxacin hydrochloride, and this way they successfully reduced the amount of lumps in the material following filtration and drying.

3. Continuous Powder Blending and Tableting.

Blending of powders is an essential step in many industrial sectors such as the manufacture of chemicals, construction materials, foods, and drugs. Ensuring the homogeneity of the produced powder blend is pivotal, and it is especially true for drug products. The appropriate distribution of the API in the excipients is the key to produce final dosage forms, i.e. tablets with acceptable drug content uniformity. Continuous blending has long been known in the mentioned industries; however, in the pharmaceutical industry, batch mixers are applied in the vast majority of cases to date. Steady state operation can be reached within a few minutes, in which process control is much more accurate, improving quality. The equipment used for process development can be used for production, eliminating the difficulty of scale-up and reducing the footprint. The continuous operation makes the integration possible with the following continuous tableting step. Thus, the overall efficiency and final product quality can be increased. These advantages can significantly reduce costs during development and manufacturing of pharmaceuticals.

Roller compaction is another way to modify the particle size. Moreover, the powder mixture can directly be filled into capsules. As interest in CM is growing in the pharmaceutical industry, more and more research is performed on integrated powder-to tablet manufacturing lines. Direct compression is the easiest way to develop such an integrated system, as controlling the flowability and compressibility of the components is paramount to obtain tablets of good quality. The importance of good flowability was also underlined, as the best results were obtained with the good-flowing samples with large particle size.

4. Novel Continuous Formulation Techniques.

Many technologies exist which are inherently continuous, and the spread of CM in the pharmaceutical industry can bring the breakthrough for these processes. Such techniques are for example electrospinning (ES) and hot-melt extrusion (HME), allowing the preparation of amorphous solid dispersions (ASDs).

- Hot-Melt Extrusion and Dropwise Additive Manufacturing.

Among the formulation methods of ASDs, HME is probably the most popular technique. HME was originally adapted from the plastic industry. During the process, a drug-polymer mixture is fed into the heated equipment, where usually corotating screws transport the melted material toward the end of the extruder. After cooling, the product is forwarded to cutting or grinding. This technique is intrinsically continuous, having as the main advantage over ES the solvent-free operation. As a limitation, HME is suitable exclusively for thermostable APIs. HME has been applied several times for the continuous formulation of pharmaceutical products.

Dropwise techniques like injection molding and 3D printing have been coupled to HME as well, allowing the production of either sustained- or immediate-release matrix tablets. Zhang et al. investigated the differences between tablets produced by HME and 3D printing and direct compression of milled extrudates and tablets prepared from physical mixtures of the ingredients. In another publication, carvedilol-loaded 3D-printed floating tablets were produced. It was found that the integration of HME and printing techniques is advantageous for both bioavailability improvement and production efficiency. This is a promising approach for personized medicine; albeit, its throughput is significantly lower than e.g. in tableting.

- Electrospinning.

ES is a well-known technique for the production of ASDs by applying high voltage on a solution containing an API and a polymer excipient. The pharmaceutical utilization of the technique is reported in a vast amount of literature, since the versatility of the available polymers allows the formation of ASDs with sustained, controlled, and ultrafast release. The applicability of electrospinning for the continuous production of orally dissolving web (ODW) formulations containing a poorly soluble API was presented in 2019. As regards the industrial applicability of ES, scaling the laboratory-size ES process up to industrially relevant volumes has recently been presented. The downstream processing of the electro spun material, enabling the direct integration of ES into the CM line, has also been published. Despite the promising studies, the high potential shown in laboratory systems, and its intrinsically continuous manner, ES has not become a widely applied industrial technique yet.

5. End-to-End Continuous Production of Final Dosage Forms.

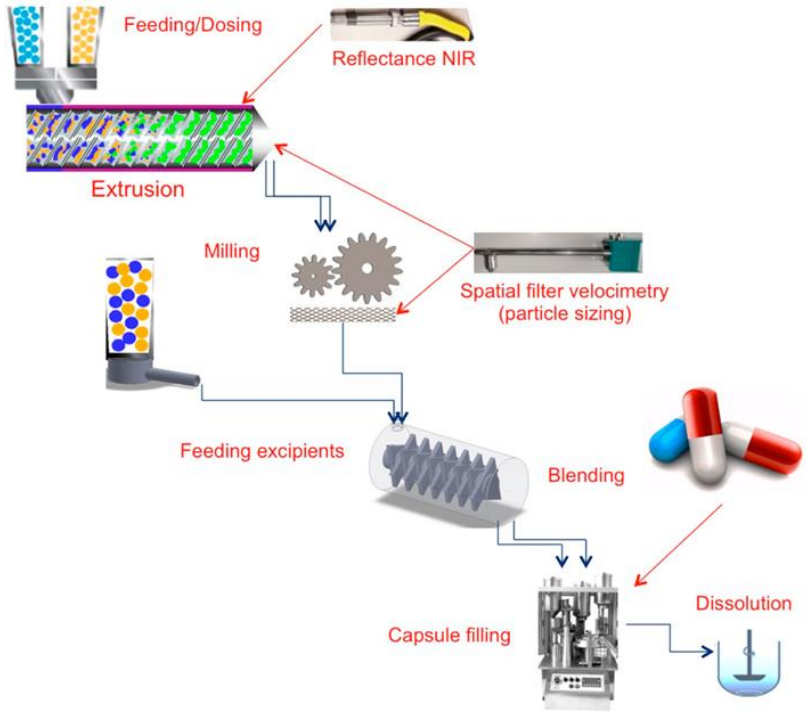
The first fully automated end-to-end commercial ready CM pilot plant was developed by Continues Pharmaceuticals, a spinoff company of the Novartis MIT collaboration, and presented by Hu et al. in 2019. This system consisted of a dissolution unit for the raw materials, a five-stage reactive MSMPR crystallization cascade, a continuous filter followed by resuspension, a novel continuous drum dryer, and hot melt extrusion for the preparation of the final heat-mold tablets. PAT probes were applied for real-time analysis, e.g. in the reactive crystallization and for the monitoring of particle size after filtration. The E-factor analysis of the system in another publication revealed substantial improvements compared to batch manufacturing. The same group published the design and commercialization of a pilot scale end-to-end CM system, where the significantly lower capital and operating costs were highlighted.

The end-to-end production of an ODW final dosage form containing ASA was published by Balogh et al. in 2018, presenting the development and optimization of the two-step flow

synthesis of the API. High voltage was applied on the reaction mixture leaving the second microreactor; thus, the synthesized API was processed directly by ES to form a nanofibrous product. The ASA-loaded nanofibers produced from the flow reaction mixture were collected on the surface of a continuously moving carrier film, and the formed double-layered strip was cut it into smaller pieces ready for patient administration.

CHAPTER 3

Methodology



Schematic diagram of CM processing by using a twin-screw extruder, PAT tools, and downstream equipment for the formation of pharmaceutical cocrystals

- Raw Materials for Capsules:

The raw materials used in the manufacture of both hard and soft gelatin capsules are similar. Both contain gelatin, water, colorants and optional materials such as process aids and preservatives.

A) Gelatin - gelatin is the major component of the capsules and has been the material from which they have traditionally been made. Gelatin has been the raw material of choice

because of the ability of a solution to gel to form a solid at a temperature just above ambient temperate conditions, which enables a homogeneous film to be formed rapidly on a mould pin. The reason for this is that gelatin possesses the following basic properties:

- It is non-toxic, widely used in foodstuffs and acceptable for use worldwide.
- It is readily soluble in biological fluids at body temperature.
- It is good film-forming material, producing a strong flexible film
- The gelatin films are homogeneous in structure, which gives them strength.

Some of the disadvantages with using gelatin for hard capsules include: it has a high moisture content, which is essential because this is the plasticizer for the film and, under International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) conditions for accelerated storage testing, gelatin undergoes a cross linking reaction that reduces its solubility.

Gelatin is a translucent brittle solid substance, colourless or slightly yellow, nearly tasteless and odourless, which is created by prolonged boiling of animal skin connective tissue or bones. Type A gelatin is derived from an acid-treated precursor and exhibits an isoelectric point in the region of pH 9, whereas type B gelatin is from an alkali-treated precursor and has its isoelectric zone in the region of pH 4.7. Capsules may be made from either type of gelatin, but mostly a mixture of both types is used considering availability and cost. Difference in the physical properties of finished capsules as a function of the type of gelatin used is slight.

Blends of bone and pork skin gelatins of relatively high strength are normally used for hard capsule production. The bone gelatin produces a tough, firm film, but tends to be hazy and brittle. The pork skin gelatin contributes plasticity and clarity to the blend, thereby reducing haze or cloudiness in the finished capsule.

B) Colorants

The colour of pharmaceutical product plays an important role in their use. Colour is used principally to identify a product in all stages of its manufacture and use. In the manufacturing company it assists in complying with GMP norms by helping the operators differentiate between products. The colorants that can be used in capsules are of two types: water soluble dyes or insoluble pigments. To make a range of colours dyes and pigments are mixed together as solutions or suspensions. Three most commonly used dyes are erythrosine. indigo carmine and quinolone yellow. The two types of pigments used are iron oxides- black. red and yellow and titanium dioxide which are white and used to make the capsule opaque. Capsules are coloured by the addition of colorants to the gelatin solution during the manufacturing stage.

C) Process aids

Preservatives and surfactants are added to the gelatin solution during capsule manufacture to aid in processing. Gelatin solutions are an ideal medium for bacterial growth at temperatures below 55 C. preservatives are added to the gelatin and colorant solutions to reduce the growth of microorganisms until the moisture content of the gelatin film is below 16% w/v. at moisture content below that value, the bacterial population will decline in numbers with time. The materials used as preservatives include: sulphur dioxide which is added as the sodium salts bisulfited or metabisulfite, sorbic acid or the methyl propyl esters of para- hydroxy-benzoic acid, and the organic acids, benzoic and propanoic acids.

- Manufacture of hard gelatin capsules :-

Steps involved in making hard gelatin capsules…

- Dipping
- Spinning
- Drying
- Stripping
- Trimming and Joining
- Polishing

a) Dipping -

Pairs of the stainless-steel pins are dipped into the dipping solution to simultaneously form the caps and bodies. The dipping solution is maintained at a temperature of about 500C in a heated, jacketed dipping pan.

b) Spinning –

The pins are rotated to distribute the gelatin over the pins uniformly and to avoid the formation of a bead at the capsule ends.

c) Drying –

The gelatin is dried by a blast of cool air to form a hard shell. The pins are moved through a series of air-drying kilns to remove water.

d) Stripping –

A series of bronze jaws strip the cap and body portions of the capsules from the pins.

e) Trimming and joining –

The stripped cap and body portions are trimmed to the required length by stationary knives. After trimming to the right length, the cap and body portion are joined and ejected from the machine.

f) Polishing –

- Pan Polishing: Acela-Cota pan is used to dust and polish.
- Cloth Dusting: Capsule are rubbed with cloth.
- Brushing: Capsule are feed under soft rotating brush.

Types of materials for filling into hard gelatin capsules:

- Dry solids – powders, pellets, granules or tablets
- Semisolids – suspensions or pastes
- Liquids – non - aqueous liquids

➢ Capsule shell filling :-

Hand operated hard gelatin capsule filling machines – hand operated and electrically operated machines are in practice for filling the capsules but for small and quick dispensing hand operated machines are quite economical.

- A bed with 200-300 holes.
- A capsule loading trays
- A powder trays
- A pin plate having 200 or 300 pins corresponding to the number of holes in the bed and capsule loading tray.
- A lever
- A handle
- A plate fitted with rubber top.

All parts of the machine are made up of stainless steel. The machines are generally supplied with additional loading trays, beds, and pin plates with various diameters of holes so as to fill the desired size of the capsules. These machines are very simple to operate, can be easily dismantled and reassembled.

➢ Capsule filling devices :-

A number of different manually operated capsule filling devices are commercially available for filling up to 50 or 100 capsules at a time. The method of using these machines requires a careful determination of the capsule formulation. The powder is blended as previously discussed. Empty gelatin capsules are placed into the device and, oriented so that the cap is on

top. The machine is worked to separate the base from the cap and the portion of the machine holding the caps is removed and set aside.

The capsule bases are allowed to “drop” into place so that the tops are flush with the working surface. The powder mix is spread over the working surface. A plastic spatula can beused carefully to spread the powder uniformly and evenly into the capsule bases or the machine can be“tapped” to spread the powder and drop it down into the capsule bases. A small device consisting of several “pegs” on a handle can be used to tamp the powder into the capsule bases gently and evenly. Any remaining powder then is spread evenly over and into the capsule bases and tamped. These procedures are repeated until all of the powder is in the capsules. The capsule caps are then fitted over the machine, fixed in place, and the filled capsules removed, dusted using a clean cloth, and packaged.

- Cleaning and Packaging:

It is imperative that every precaution to minimize traces of moisture or body oils on capsules be taken to reduce powders sticking to the surface, which would create disagreeable appearance and taste. Cleaning capsules is difficult if they have become moist or sticky. The capsules should be handled so that they retain their dryness and shiny appearance. Use of gloves provides a more hygienic environment and helps preserve the dry, shiny capsule appearance. An old method, where gloves are unavailable, is:

(1) Wash and dry hands thoroughly,

(2) Keep the fingers dry by the friction of a towel that is stripped through the tightly clenched fingers until a clearly perceptible heat is generated,

(3) Four or five capsules may be prepared before there will be a need to repeat the process. If the capsules have been kept dry, clinging surface powder can be removed by rolling between folds of a cloth or by shaking in a cloth formed into a bag or hammock. Another method of cleaning capsules is to place them in a container that is filled with sodium bicarbonate, sugar or salt then gently to roll the container. The contents then can be poured into a 10-mesh sieve and the “cleaning salt” allowed to pass through the screen, which collects the capsules. It must be emphasized that these cleaning methods are only effective if the capsules have been kept clean and dry. Once capsules become soiled and dull, they cannot be cleaned effectively.

- Quality control of capsules:

Whether capsules are produced on a small scale or large scale all of them are required to pass not only the disintegration test, weight variation test and percentage of medicament test but a visual inspection must be made as they roll off the capsule machine onto a conveyor belt

regarding uniformity in shape, size, colour and filling. As the capsules moves in front of the inspectors the visibly defective or suspected of being less than the perfect are picked out.

The hard and soft gelatin capsules should be subjected to following tests for their standardization.

- Shape and size
- Colour
- Thickness of capsule shell
- Leaking test for semi-solid and liquid ingredients from soft capsules
- Disintegration tests
- Weight variation test
- Percentage of medicament test

➢ Packaging and storage of capsules:

Capsules should be packed in a well-closed glass or plastic containers and stored in a cool place. These types of containers have advantage over cardboard boxes that they are more convenient to handle and transport and protect the capsules from moisture and dust. To prevent the capsules from rattling a tuft of cotton is placed over and under the capsules in the vials. In vials containing very hygroscopic capsules a packet-containing desiccant like silica gel or anhydrous calcium chloride may be placed to prevent the absorption of excessive moisture by the capsules. Now a days capsules are strip packaged which provide sanitary handling of medicines, ease in counting and identification.

Empty gelatin capsules should be stored at room temperature at constant humidity. High humidity may cause softening of the capsules and low humidity may cause drying and cracking of the capsules. Storage of capsules in glass containers will provide protection not only from extreme humidity but also from dust.

Storage of filled capsules is dependent on the characteristics of the drugs they contain. Semisolid filled hard gelatin capsules should be stored away from excessive heat, which may cause a softening or melting of the contents.

CHAPTER 4

Result and Discussion

To realize continuous manufacturing, it is essential to develop new catalysts and processes to replace batch reactions with continuous ones, and to develop sensor technologies that help achieve advanced continual monitoring. Among sensors, drawing attention is the development of virtual measurement technologies, called soft sensors, which fully leverage simulation technology to estimate data that is difficult to obtain through actual measurements.

CONCLUSIONS

Reviewing the recent literature of the continuous pharmaceutical technologies revealed that significant progress has been made to achieve CM in pharmaceutical manufacturing. In the case of flow synthesis, it is clear that although the total synthesis of a few dozen APIs has already been published, more research is necessary to build continuous end-to-end systems. The multistep synthesis of pharmaceuticals must be developed in a way to be connectable with the following technological steps for the workup of the reaction mixture. Although numerous examples exist for integrated continuous blending−tableting systems, connection with the upstream manufacturing was made only in a handful of studies. The majority of continuous technologies are developed separately by examining the individual steps alone. The true integration of the processes is often full of challenges, related to the throughput at which the individual operations are being developed, the effect of impurities, and the propagation of disturbances through the continuous system.

The development of true end-to-end CM systems for the production of any type of final dosage form is an important scientific topic. Therefore, it would be of great interest and high techno-economic impact to develop further end-to-end systems to produce either novel drug delivery systems or conventional tablets. The integration of separate technological steps and unit operations allow leveraging the advantages of CM from every perspective, starting from process safety improvements, through the economic and ecological advantages, to the realization of shorter supply chains and production times. Clearly, developing true end-to-end integrated CM technologies requires wide interdisciplinary efforts, ranging from fundamental chemistry aspects to advanced process monitoring and plant-wide control, and recently, machine learning and artificial intelligence are also involved.

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