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Research

PROCESSING TECHNOLOGIES FOR PHARMACEUTICAL TABLETS

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Abstract:
Pharmaceutical oral solid dosage form have been used widely for decades mainly due to their convenience of administration and their suitability for delivery for delivery of drugs for systemic effects. The manufactured using high speed rotary presses where the powder material is comprisesedin die between rigid punches. Compression represents one of the important unit operations because the shape, strength and other important properties of the tablets are determined at this time. The most commonly used pharmaceutical solid dosage from today include granules, pellets, tablets and capsule can be made directly from powders or from granules pellets, or from film coated multiple units.

A mixture of powder is done in order to improve flow Uniformity of contents, better compressibility, improve density and to aid pharmaceutical dosing of the actives. Orally disintegrating tablet (ODTs) has expanded much attention as a preferred alternative to conventional oral dosage form such as tablet and capsules. Conventional preparation technologies like direct compression, lyophilization, spray drying, molding, phase transitions process, melt granulation, sublimation, mass extension, etc., the use of Processing analytical technologies by the pharmaceutical industry is a response to its growing need for improved productivity in order to face the increasing competition in this field.

Key words: Tableting,3D printing, Artificial neural Network,powder blending, Granulation

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Introduction:

A tablet is a compressed solid unit dosage form containing medicament with or without excipients. According to the Indian pharmacopoeia, pharmaceutical tablets are solid flat or biconvex dishes prepared by compressing or mixture of drugs, with or without diluents. Tablets are the most popular dosage form due to their simplicity and economy of manufacture, relative stability and convenience in packaging, shipping and storage[9].

The final properties of the tablets depend on the choice of ingredients used in the powder formulation, the details of the mixing and agglomeration processes and the selection of process parameters applied by the tableting equipment. Tablets are mass produced using high speed rotary presses. The central part of a rotary press is the turret (or die table) which is equipped with a number of tool stations consisting of upper punch–die–lower punch assemblies. A typical die table is presented diagrammatically in As the die table rotates each station passes successively through the following mechanisms[2]

- feed frame, where the powder is introduced into the die
- pre- compression and main compression rollers, where the powder is compress

- ejection Cam, where the tablet is ejected from the die[4]

Finally, the effect of microstructure on tablet behaviour in terms of friability erosion and disintegration is discusses[2].Granulation process has been widely used in the pharmaceutical industry for the preparation of Material for tabletting. Other process which involves the granule formation includes micro Encapsulation, multi-particulate system for modified release mechanism and to prepare Granules to be used by patient directly.

Primarily granules are prepared to improve flow and compression characteristics of the blend but there are many other reasons and some times multiple reasons for granulation such as

- Improving flow properties of the mix and hence the uniformity of the dose; • Increasing the bulk density of product;
- Facilitating metering or volumetric dispensing;
- Controlling the rate of drug release;[3]
- Decrease dust generation and reduce employee exposure to drug product[3].

Implementing process analytical technologies (PAT) in the pharmaceutical industry requires the development of new analytical methodologies that can be readily adapted to existing industrial processes, allows the different steps of the process to be monitored and provides accurate analytical results in a simple, expeditious manner. Near infrared spectroscopy (NIRS) is one of the instrumental analytical techniques most closely meeting these requirements. Its analytical power has been clearly demonstrated in a number of successful qualitative and quantitative applications. The third approach involves preparing laboratory samples by mixing the active principle and excipients in appropriate proportions spanning the desired concentration range for each component in this work, we developed and validated a quantitative method for determining the active principle in commercial tablets with no sample pretreatment. Calibration samples were prepared in the laboratory by pressing a mixture of the active principle and excipients at a pressure that was previously determined by using a compaction[20].

Advantages

- Separation of incompatible material can be achieved In the core and outer shell.
- It will use to develop a modified release product(e.g., delayed release product).
- The Tablet in Tablet of two different drugs can beTargeted in two different areas of the gastrointestinal trac
- The Tablet in Tablet dosage form gives protection To the hygroscopic or thermo-liable drug.
- In single Tablet in Tablet dosage form, immediate Release and sustain release effect of a similar drug or different drug combination can be achived[4].
- They may provide the greatest ease of swallowing with theleast tendency for “hang-up” above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.

Methods

- Tablet in Tablet of cyclophosphamide and Capecitabine:

Cyclophosphamide is a prodrug that is converted into its Active form when it passes through liver; its active form Only is responsible for slowdowns the growth of cancer Cells. The treatments of various cancers like metastatic Breast cancer, ovarian cancer, and leukemia cyclophosPhamide used alone or in combination. Capecitabine is Another drug that is also used for the treatment of metastatic breast cancer. Also, the combination partner of Capecitabine plays an important role in the activation of Thymidine phosphorylase (TP) enzyme, which converts Capecitabine to active 5-FU (fluorouracil)(fig.1).

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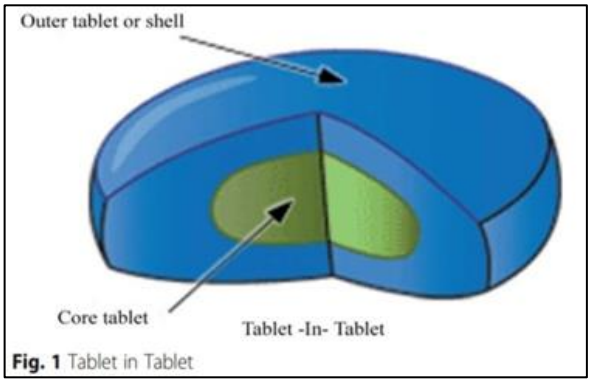

Fig. 1 Tablet in Tablet

- **Tablet in Tablet manufacturing process:**
- The internal core and outer layer are the two parts of The Tablet in Tablet dosage form. The internal core is a Small tablet and prepared by using a somewhat small Size of tooling than tooling used for the preparation of The outer coat..
- **Friability Test:**
- This is the official method to determine the mechanical Strength of the tablet. Weight the randomly selected tablet Samples as per the USP and put into friabilator (Electrolabo; EF-1 W) plastic drum along with twenty polystyrene Beads (Wako Pure Chemical; diameter of 6 mm) [1].
- **Artificial Neural Networks:**
- The development of ANNs was inspired by the information Processing behavior of the human brain, as the calculation Is based on interconnected information processing units, i.e., artifcial neurons (also called nodes or perceptrons), which reDepending on the purpose of the model, arbitrary NN Topologies can be built, e.g., by varying the number of Neurons, their connections to each other, and the applied Transfer functions. In most applications, the nodes with the Same tasks are organized into layers
- **Application Of Anns In Downstream Processes:**
- ANNs could also be applied to process data where the efects of certain factors appear after A time delay. For example, the composition of the blend That leaves the continuous blender could be predicted by aRNN .serving as the digital twin of the blender Based on the mass fow rate of the input material streams And the residenc time distribution of the system . It Was found that a non-linear autoregressive network with Exogenous inputs can yield results comparable to that of Residence time distribution model.
- **Digital Transformation:**
- Following the Pharma 4.0 concept, digitalization is expected To spread signifcantly in the following years, as it can considerably improve the transparency, fexibility, efciency, Productivity, and quality of manufacturing (127). The Authors of (128) from Novartis Global Drug Development—a leader in the digitalization of the pharmaceutical Industry—have expressed that the historical operational Data could be the goldmine to represent the pharmaceutical Company's experience.(fig.2)[2]

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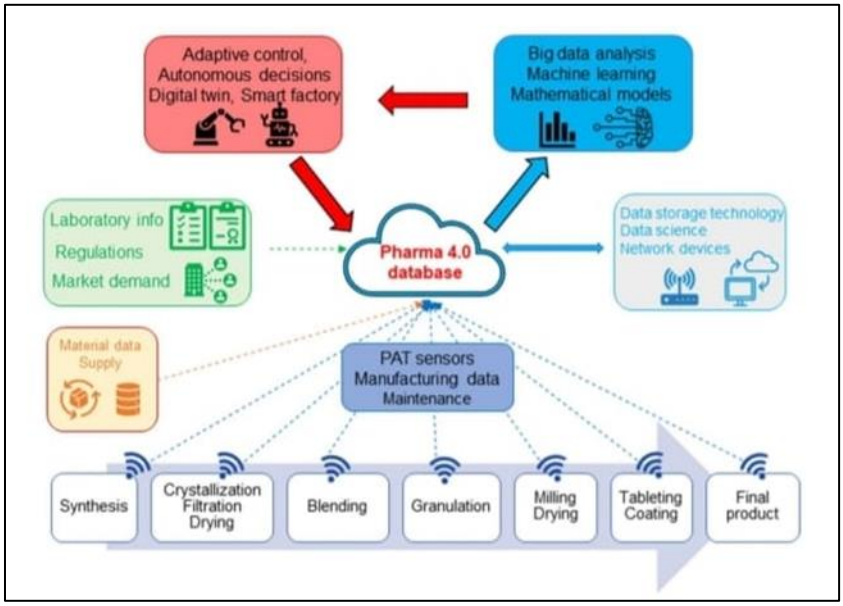


Fig: Pharma database2

- **Process parameters during die fill:**
  The majority of full scale production presses are equipped with a Powder feed mechanism which consists of a mass flow hopper Attached to a feed frame. The feed frame usually contains a number of Paddle wheels which transfer the powder from the hopper outlet over To the die opening. Powders flow under the applied forces. The flow behaviour is Dependent on the particle characteristics (i.e. size, shape, morphology,Etc.), applied loads (i.e. dilute flow, high shear mixing, etc.),Environmental conditions (i.e. humidity, temperature, etc.) and the Current state of the powder (i.e. aerated, tapped, etc.). In a typical experiment the shoe velocity is prescribed. As the shoe travels across the die opening, the material is deposited in the die. At low shoe velocities the die is completely filled. If the velocity is increased then incomplete fill is observed.
- **Tablet formulation:**

In addition to the active pharmaceutical ingredient (API), tablets Also contain functional ingredients called excipients. Excipients are Needed both to bulk out the actives, to facilitate compression or to Modify the biopharmaceutical properties of the tablet. For example,Fillers are used to add bulk. Binders assist granule and compact Formation. Disintegrants are used to assist the tablet break-down in Contact with fluids in the body. Wetting agents are employed to assist With the dissolution particularly for hydrophobic API. Lubricants are Used to reduce the friction between powder and die.[3]

Molded tablets

While most commercially available tablets are primarily Prepared by compression, tablets can also be prepared by Molding. Molded tablets are prepared by tablet machinery or Manually by forcing dampened tablet material into a mold of Any shape.

Compressed tablets

They are the most widely used solid dosage form so they Must satisfy a number of physical requirements in terms of Hardness, thickness, friability and weight.

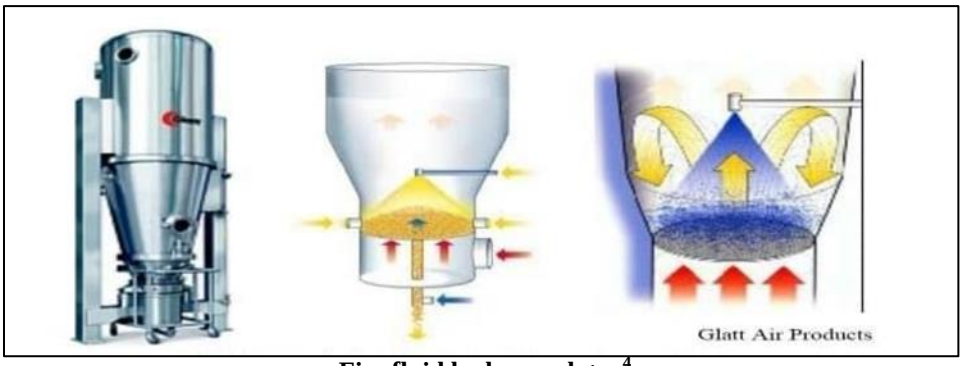
Direct compression tablet

Direct compression consists of compressing tablets directly From powdered materials without modifying physical nature Of materials. This method is applicable for crystalline Chemicals having good compressible characteristic and flow Properties such

as: Potassium salt (chlorate, chloride,Bromide), Sodium chloride, Ammonium chloride,Methenamine etc. .

Fluid bed granulation :

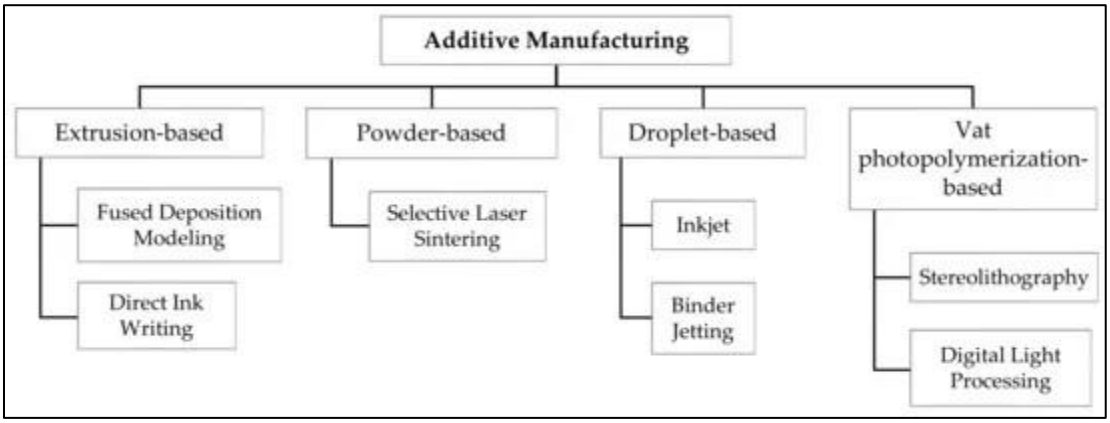
Fluid bed granulation is a process by which granules are produced in single equipment by Spraying a binder solution onto a fluidized powder bed. The material processed by fluid bed Granulation are finer, free flowing and homogeneous. The system involves the heating of air And then directing it through the material to be processed. Later, the same air exit through the viods of the product.(fig.3)



Fig; fluid bed granulator[4]

- **Spray drying:**
  Spray Drying as a process has been used to produce microcapsules, food ingredients, flavours, And variou biotechnological preparations. This process differs from the methods discussed Above in that it is a continuous process in which a dry granular product made from a solution or a suspension rather than initially dried the primary powder particles.[4]
- **AM Technologies:**
  In this review, the AM technologies used for oral tablet printing are classified under four main groups: extrusion-based, vat photopolymerization-based, droplet-based, and power base printing.
- **Materials for 3D Printing Oral Tablets:**

Polymers:



Polymers are the most versatile category of biomaterials and have a wide range of Utilizations in tablet development. Polymers are mainly used as excipients to improve the Function and delivery of the APIs, yet polymers can also be designed as APIs (or drugs). In this review, we will focus on the former case where the polymer has no therapeutic effect

Tablet Printing Using AM Technologies

AM technologies have become an attractive option for the fabrication of oral tablets and drug delivery systems. AM technologies, including FDM, DIW, SLS, SLA, DLP, inkjet, And BJ, were successfully used to fabricate tablets with custom-designed shapes and release profile.

- FDM-Printed Tablets
- In tablet printing applications, drug-loaded filaments are commonly utilized with printing technology. APIs containing filaments can be fabricated either by directly Incorporating the API into filaments during the HME process (Figure 2a) or by immersing. The prefabricated filament in an API solution/suspension to allow diffusion of the API into the filament[5]
- Tablet Moulding
- Compression Moulding process: This manufacturing process involves moistening the powder blend with a hydroalcoholic Solvent followed by pressing into mould plates to form a wetted mass (compression Moulding).[15]

- Cotton candy Process
- The FLASHDOSE® is a MDDDS manufactured using Shear form™ technology in Association with Ceform TI™ technology to eliminate the bitter taste of the medicament. The Shear form technology is employed in the preparation of a matrix known as ‘floss’, made from a combination of excipients, either alone or with drugs.
- Micrometrics of the granules the granules obtained after melt extrusion process were evaluated for physicochemical properties.[16]
- Granules practice size distribution
- The extruded granules particle size distributions were measured by sieve analysis.30gm of samples Placed on the top sieve of the stacked sieves and subjected for agitation for 20min.The weight of Granules retained on each stacked sieves were calculated as a percentage of the weight and used to Determine the granule particle size distribution.
- Scanning electron microscopy
- The scanning electron microscopic study revealed the surface morphology and shape of the API, Lipidic material and extruded formulation. The pure aceclofenac shown 50-100µm size with rod and spherical shape, the extruded batches with Compritol 888 ATO ® exhibited agglomerated Particles with voids between them as described in figure.[17.]
- Continouse 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 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
- Continuous Crystallization
- Currently, the vast majority of crystallizations in the pharmaceutical industry is carried out in stirred batch reactors. These systems have been used decades, and the processes are thoroughly optimized and reasonably well-understood.
- The implementation of novel continuous processes can provide a number of advantages in the area of crystallization. Continuous technologies naturally require smaller and thus cheaper equipment, reducing the production footprint.
- 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.[15]

Conclusion

Tablet compression is a complex engineering problem. During Compaction, the material is transformed from loose powder form into A dense compact. The strength of tablets is dependent on the com-Position of powders or granules and the parameters of the compression process. For a given formulation, the strength of the material Is primarily

dependent on the compression state of the powder which Is determined by the applied pressure.Film and sugar coatings are an important part of the formulation of the tablet to achieve superior appealing Quality like color, texture, mouth feel, and taste masking.Film and sugar coatings have several disadvantages; the Most important one is the utilization of aqueous or organic solvent leads to toxicity.

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