RECENT NOVEL ADVANCEMENTS IN PELLET FORMULATION: A REVIEW

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ABSTRACT: Pelletization can be defined as an agglomeration process that converts fine powders or particles of a bulk drug and excipients into small, free-flowing, more or less spherical units, called pellets. The size of the pellets is 0.5-2mm. Pellets have the free flowing capacity and have low porosity about 10%. Preparation methods include direct pelletizing, powder layering, Suspension or Solution layering, pelletization by extrusion and spheronization, spherical agglomeration, compression/balling, Cryo pelletization, melt spheronization, globulation or droplet formation, fluid bed coating. Pellets have various advantages when compared to normal conventional dosage forms, like they help in giving accurate dosage to the paediatrics and geriatrics and even to the bed ridden persons, reduces peak plasma fluctuation, Minimize potential side effects without lowering bioavailability, avoiding high local concentration, Less susceptible dose dumping. At present usage of pellets has increased largely due to their advantages and there novel approaches, the novel approaches of pellets includes; 1) They help in preparation of modified release multiple dosage form with different release patterns like immediate and sustained release pattern, 2) They help in taste masking of the drugs which are bitter in taste, 3) They are available as mouth melt pellets, 4) Polymer based pellets for control release pattern of drug, 5) As fast dissolving tablets containing micro pellets, 6) As a self-emulsifying pellets, 7) Gastro retentive floating pellets etc. Thus, the usage of pellets provides novel approaches to the patients in providing accurate, and easy in administrating the dosage form.

INTRODUCTION: Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing spherical or semispherical solid units typically from about 0.5-2mm. These are intended usually for oral administration. These are spheres of varying diameter depending on the application and the wish of the producer.

APPLICATIONS are found not only in the pharmaceutical industry but also in agribusiness (e.g. fertilizer, fish food) and the polymer industry 1-3. In the pharmaceutical industry pellets can be defined as a small free flowing spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipient using appropriate processing equipment. The term has been used to describe small rods with spectratio’s of close to unity. Traditionally, the word pellet has been used to describe a variety of systematically produced geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions.
Pellets for pharmaceutical purpose are usually produced in the size range of 0.5 to 2mm.

Pellets are prepared using different technologies such as layering of the drug solution, suspension or powder on the inactive cores, extrusion, spheronization and agglomeration in roto-granulators or rot processors, compression, spray drying and spray congealing.

The recent novel trends of pellets are:

1. They help in preparation of modified release multiple dosage form with different release patterns like immediate and sustained release pattern.
2. They help in taste masking of the drugs which are bitter in taste.
3. They are available as mouth melt pellets.
4. Polymer based pellets for control release pattern of drug.
5. As fast dissolving tablets containing micro pellets.
6. As a self-emulsifying pellets.
7. Gastro retentive floating pellets etc.

This trend of pellets has increased patient acceptance. This novel trends helps in giving the information about the releasing pattern of the drug and its bioavailability of the drug to the systemic circulation of the and how it as increased the patient acceptance of ph sensitive drugs releasing pattern pf drugs, taste mask of the drugs, self-emulsification of pellets, and polymer based control release of the drugs, mouth melt pellets etc.

Advantages of Pellets $^{3-8}$:

- Flexibility in dosage form design and development
- It permits the combination of different release rates of the same drug in a single dosage form
- Controlled release technology
- Disperse freely in the GI& invariably maximize drug absorption
- Reduce peak plasma fluctuation
- Minimize potential side effects without lowering bioavailability
- Avoiding high local concentration
- Less susceptible dose dumping
- Reduce gastric emptying rates so minimize inter and intra subject variability of plasma profile
- Pellets have a low surface area to volume ratio and provide an ideal shape for application of film coatings
- Reproducible fill weights in capsules
- Can be used to mix incompatible drugs.
- Pellets are non-dusting.
- The ingredients that make up a pellet do not separate during transit and storage.
- Pellets also allow the separation of incompatible ingredients with in different layers of the pellet body. Pellets also allow the separation of incompatible ingredients with in different layers of the pellet body.
- Pellets over comes the problems occurred my conventional tablets and crushed tablets.
- The pellets are used to mask the taste of the bitter drugs
- Coated pellets are used to produce the sustain release of drug and also increases the patient acceptance.
- Pellets are easily dispersed in the G.I.T. due to their small size and have a large surface area of absorption and reduce the peak plasma level fluctuations.
- A pellet reduces the gastric emptying rate and intestinal transit time thus reduces the intra and inters subject variability.
Disadvantages of Pellets:\(^\text{13}\):

- Dosing by volume rather than number and splitting into single dose units as required.
- Involves capsule filling which can increase the costs or tab letting which destroy film coatings on the pellets.
- The size of pellets varies from formulation to formulation but usually lies between 1 to 2 mm.
- Preparation of pellets is quite expensive and required qualified persons and specialised equipments.

Desirable properties of Pellets\(^\text{14,15}\):

- Uncoated pellets.
- Uniform spherical shape.
- Uniform size.
- Good flow properties.
- Reproducible packing.
- High strength.
- Low friability, low dust.
- Smooth surface.
- Ease of coating.

Once coated:

- Maintain all of the above properties,
- Have desired drug release characteristics.

The photographic representations of different pellets are given in figure 1.

![Photographs of Pellets](image)

**FIGURE 1:** 1 TYPE OF PELLETS (A) PELLETS, (B) PERFECT PELLET, (C) COATED PELLET

Theory of pellet formation and growth:

A) Nucleation

B) Coalescence

C) Layering

D) Abrasion transfer.
List of Pelletization Techniques 16:

A. Direct Pelletizing:
B. Pelletizing by powder Layering
C. Solution / suspension layering technique
D. Extrusion and Spheronization Technique
E. Spherical agglomeration / balling
F. Cryopellitization
G. Melt spheronization
H. Globulation, or droplet formation

I. Compression
J. Fluid bed coating
i. Top Spray Coating
ii. Bottom Spray Coating (Wurster Coating)
iii. Tangential Spray Coating (Rotor Pellet Coating)

Pelletization techniques 17, 18: The preparation of spherical agglomerates can be approached by several techniques. This can be subdivided into the basic types of systems shown in figure 3.

Different Pelletization Techniques

A) Direct pelleting: Means of manufacturing of pellets directly from powder.

Effective process: Pellets are manufactured directly from powder with a binder or solvent, fast process, low usage of auxiliary materials.

Product advantages: Compact, round pellets are ideal for automatic dosing and even coating and pellet diameter also obtained between 0.2 mm and 1.2 mm.

Comparison: Pellets have a higher density than spray granulates and agglomerates.

Process principles: Powder is mixed and moistened. A solvent or binder can also be added. The powder bed is set into a centrifugal motion. (Fluid Bed Pelletizing in the rotor). The impact and acceleration forces that occur in this process result in the formation of agglomerates, which become rounded out into uniform and dense pellets. The speed of rotation has a direct influence on the density and size of the pellets. The moist pellets are subsequently dried in the fluid bed. If required, the systems can be made inert for applications with organic solvents.
Another alternative for direct pelletizing is Spray Granulation. With suitable additives, pellets can be made into tablets or used to fill capsules.

The round shape is ideal for uniform coating. Pellets are good for automatic dosing. The various steps of process principle are given in figure 4.

**FIGURE 4: PROCESS PRINCIPLES OF DIRECT PELLETIZING**

**Pelletization by Drug Layering:** Pelletization by layering is nothing but pellet build-up, layer by layer, around a given starting core. Pellet diameter may be between 0.6mm and 2.5mm (figure 5).

**B) Powder layering:** Powder layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids.

As powder layering involves simultaneous application of binding agents and dry powders, hence it requires specialized equipments like spheronizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked off by the wet mass of pellets that is being layered.

**FIGURE 5: PRINCIPLE OF THE POWDER LAYERING PROCESS**

**C) Suspension or Solution layering:** Solution or suspension layering involves the deposition of successive layers of solution and/or suspensions of drug substances and binder over the starter non-peril seeds, which is an inert material or crystals or granules of the same drug. In fact the coating process involved in general is applicable to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, Wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used (figure 6).

**FIGURE 6: PRINCIPLES OF THE SUSPENSION AND SOLUTION LAYERING PROCESS**
With suitable additives pellets can be made into tablets or used to fill capsules. The round shape is ideal for uniform coating. Pellets are good for automatic dosing.

D) **Pelletization by Extrusion and Spheronization:** The process involves first making extrudes from the powder material and then converting extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, Ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc). Beads as fine as 0.6mm. The capsule filling method has to be gentle enough on the pellets to retain the integrity of the coating. As with powder filling, the filling of pellets into capsules can be dependent or independent. A dependent method often performed uses a modified augur type machine, in which the pellets are simply poured by gravity into the capsule shells. The critical formulation aspect of this approach is ensuring that the required dosage of active substance is present in the volume of pellets taken to fill the capsule body. An independent method uses a volumetric fill by a modified dosator method. The piston inside the dosator is narrower than those used for powder filling, and this allows air to flow between the piston and the dosator wall. The dosator is lowered into the pellet bed, but in this case, there is no compression applied. A vacuum source is applied from above the piston to retain the pellets as the dosator is moved above the capsule body. Once over the capsule body, the vacuum is removed, and the ejection of the pellets is aided by an air jet (figure 7).

![Figure 7: Principle of the extruded product spheronizing process filling capsules with pellets](image)

E) **Spherical agglomeration / balling:** This is a pelletization process in which powders, on addition of an appropriate quantity of liquid or when subjected to high temperatures, they are converted to spherical particle by a continuous rolling or tumbling action. Spherical agglomeration can be divided into two different categories, liquid induced and melt induced agglomeration. Over the years, spherical agglomeration has been carried out in horizontal drum palletizes, inclined dish palletizes, and tumbling blenders. More recent technologies use rotary fluid bed granulators and high shear mixers.

F) **Cryopelletization:** This is the process whereby droplets of liquid formulations are converted into solid spherical particles or pellets by using liquid nitrogen as fixing medium. The technology which was initially developed for lyophilization of viscous bacterial suspension can be used to produce drug-loaded pellets in liquid nitrogen at 160°C. The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and thus the large surface area facilitate the drying process. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solids content and temperature of the solution or suspension being processed. It is usually between 3 and 5 kg per kilogram of finished pellets.

G) **Melt spheronization:** It is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The drug is blended with the excipients, polymers, and waxes and extruded at predetermined temp.
The extrusion temp must be high enough to melt at least one of the components. The extrudates is cut into uniform cylindrical segments with a cutter. Then they are spheronized. Resulting pellets are dried.

H) **Globulation or droplet formation:** Consists of two related processes, spray drying and spray congealing. Spray drying is the process in which drugs in the suspension or solution without excipients are sprayed into a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates, hence bioavailability of poorly soluble drugs.

I) **Compression:** Compression is one type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing.

i. **Fluid bed coating:**

1) **Top spray coating:** This process is used for general coatings right up to enteric coating. With top spray Coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The coating liquid is sprayed into the fluid bed from above against the air flow (countercurrent) by means of a nozzle. Drying takes place as the particles continue to move upwards in the air flow. Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform.

Coating in the continuous fluid bed is particularly suitable for protective coatings/color coatings where the product throughput rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Depending on the application, the System is sub-divided into pre-heating zones, spray zones and drying zones. The dry coated particles are continuously extracted.

2) **Bottom spray coating (Wurster coating):** This process is particularly suitable for a controlled release of active ingredients. In the Wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed. By using a Wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the Wurster tube and fed through the spray cone concurrently. As the particles continue traveling upwards, they dry and fall outside the Wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube where they are once again accelerated by the spray. This produces an extremely even film. Particles of different sizes are evenly coated.

3) **Bottom spray coating (Continuous fluid bed):** Particularly suitable for protective coatings/color coatings where the products throughout rates are high. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. Dependent on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones where by spraying can take place from below in the form of a bottom spray. The dry, coated particles are continuously extracted.

4) **Tangential spray coating (Rotor pellet coating):** Ideal for coatings with high solid content. The product is set into a spiral motion by means of a rotating base plate, which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays concurrently into the powder bed. Very thick film layers can be applied by means of the rotor method. The graphical representation of top spray coating, bottom spray coating and tangential coating are displayed in figure 8.
Recent advancement of Pellets:

Pellets have the novel approaches, they are:

1. Multiple unit dosage form by the combination of:
   a. immediate release
   b. sustained release

2. As taste masking dosage form of pellets.

3. As a self-emulsifying pellets

4. Pectin film coated based pellets for site specific target delivery.
   a. Gastro retentive floating pellets.

5. Fast melting pellets in mouth.


Commonly used excipients for pellets preparation: (table 1).

TABLE 1: COMMONLY USED EXCIPIENTS FOR PELLETS PREPARATION

<table>
<thead>
<tr>
<th>Filler</th>
<th>MCC, Starch, sucrose, lactose, mannitol.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binder</td>
<td>Sucrose, Starch, HPMC, HPC, Gelatin, MC, PVP</td>
</tr>
<tr>
<td>Lubricant</td>
<td>Glycerin, PEG, Magnesium stearate, Calcium stearate</td>
</tr>
<tr>
<td>Separating agent</td>
<td>Kaolin, Talc, silicon dioxide</td>
</tr>
<tr>
<td>Disintegrate</td>
<td>Alginate, cross carmellose sodium.</td>
</tr>
<tr>
<td>PH adjuster</td>
<td>Citrate, Phosphate, Meglumine</td>
</tr>
<tr>
<td>Surfactant</td>
<td>SLS, Polysorbate</td>
</tr>
<tr>
<td>Spheronization enhancer</td>
<td>MCC, Sod. CMC</td>
</tr>
<tr>
<td>Glidant</td>
<td>Talc, starch, Magnesium stearate</td>
</tr>
<tr>
<td>Release modifier</td>
<td>Ethyl cellulose, Shellac, Carnauba wax</td>
</tr>
</tbody>
</table>

Preparation of Sugar Spheres: Sugar spheres should contain no more than 92% of sugar calculated on dry bases, the remaining consist of maize starch according to European pharmacopoeia.

Multiple unit dosage form: Pellets are useful for the preparation of multiple unit dosage form, the technique used for the preparation of multiple unit dosage form is solution layering technique, in the multiple unit dosage form we can prepare the combination of two drugs which may be immediate release or sustained release e.g.: combination of desloratadine (immediate release) pseudoephedrine hydrochloride (sustained release).

MATERIALS AND METHODS: Active ingredient (Drug), non-perils seeds, excipients and reagents.

Methods:

1. Preparation of immediate release pellets formulation
2. Sustained release pellet formulation

Preparation of immediate release pellet formulation:

Seal coating on base materials: Polymer seal coating was given on non-peril seeds (sugar sphere 18-20#) using insta coat R&D coater. Polymer used for seal coating was HPMC.
Here, seal coating was done because of uniform surface available for drug loading. Solution of HPMC in isopropyl alcohol: methylene chloride as a solvent with talc as a glidant

**Drug coating on seal coated pellets:** Drug coating was performed on seal coated pellets along with binder HPMC and PVP. Here, binder was used because drug particles can stick to the seal coated pellets and make a uniform drug coating on seal coated pellets.

**Film coating on drug-coated pellets:** Polymer used for film coating was instacoat universal. Talc was added for reducing the static charge into pellets. By adding talc into spraying solution, evaporate during spraying and stick to the pellets and remove the static charge of pellets during spraying and drying.

**Preparation of sustained release pellet formulation:**

**Seal coating on base materials:** Polymer used for seal coating was HPMC. Seal coating was done on non-peril seeds as a core material, using Insta R&D coater. Solution of HPMC in Isopropyl alcohol: methylene chloride as a solvent with talc as a glidant.

**Drug coating on seal coated pellets:** Drug coating was performed on seal coated pellets along with binder HPMC and PVP K-30.

Solution of pseudoephedrine hydrochloride in solvent with binder is processed in Insta R&D coater. Pellets are used as novel technique to mask the taste of the drug:

**TABLE 2: LIST OF THRESHOLD CONCENTRATIONS FOR PRIMARY TASTE SENSATIONS ON SPECIFIC AREAS OF TONGUE**

<table>
<thead>
<tr>
<th>Taste</th>
<th>Threshold concentration</th>
<th>Area of tongue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet</td>
<td>0.5%</td>
<td>Tip of tongue</td>
</tr>
<tr>
<td>Salt</td>
<td>0.25%</td>
<td>Tip and sides of tongue</td>
</tr>
<tr>
<td>Sour</td>
<td>0.007%</td>
<td>Sides of tongue</td>
</tr>
<tr>
<td>Bitter</td>
<td>0.00005%</td>
<td>Back of tongue</td>
</tr>
</tbody>
</table>

**Taste Masking Techniques:** Various techniques reported in the literature are as follows

1. Addition of flavors and sweeteners
2. Coating
3. Microencapsulation
4. Ion exchange resin
5. Inclusion complexes
6. Granulation
7. Adsorption
8. Prodrug approach
9. Bitterness inhibitors
10. Multiple emulsion, Gel formation

**Factors to be considered during taste masking of the pellets are as follows**

1. Extent of the bitter taste of the API
2. Required dose load
3. Drug particulate shape and size distribution
4. Drug solubility and ionic characteristics
5. Required disintegration and dissolution rate of the finished product
6. Desired bioavailability
7. Desired release profile

**Coating:** Coating is a most common and efficient way to mask the taste of the pellets are used generally coating material is classified into lipids, polymers and sugars can be used single or in combination to mask the taste **(table 3).**
TABLE 3: COATING POLYMERS USED

<table>
<thead>
<tr>
<th>Type of Polymers</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water soluble polymers</td>
<td>Cellulose acetate butyrate, PVP, hydroxyl cellulose</td>
</tr>
<tr>
<td>Water insoluble polymers</td>
<td>Ethyl cellulose, PVA, Cross povidone</td>
</tr>
<tr>
<td>Reverse enteric polymers</td>
<td>Eudragit E100, Eudragit EPO, vinyl pyridine</td>
</tr>
<tr>
<td>Enteric polymers</td>
<td>Phthalate, hydroxyl phthalate, acrylic acid esters</td>
</tr>
</tbody>
</table>

Acidic compounds like citric acid and malic acid used for releasing of drug in the upper intestine from drug particles coated with reverse enteric polymers by creating acidic micro environment\(^{24}\).

**Ion exchange resins:** Ion exchange resins are synthetic organic polymers inert in nature, consists of a hydrocarbon chain to insoluble groups are attached and they have ability to exchange their labile ions for ions present in the solution with which they are in contact.

**Types**\(^{25}\): Based on the charge of the functional groups ion exchange resins are classified into:

- Cation exchange resins
- Anion exchange resins, each class based upon the affinity for counter ions there are further classified into strong and weak

Cation exchange resins are exchangers of Sodium, Potassium or Aluminium salts and anionic resins are for chloride ions. The drugs are loaded on to the resins by column method and batch method (\textbf{table 4}).

Reactions involved in complexation of drug with resins:

**Acidic drug:**
\[
\text{Re-N(CH}_3\text{)} + 3 \text{ Cl}^- + \text{Drug}^- \rightarrow \text{Re-N(CH}_3\text{)} + 3\text{Drug}^- + 3\text{Cl}^-
\]

**Basic drug:**
\[
\text{Re-COO-H}^+ + \text{Drug}^+ \rightarrow \text{Re-COO}^- \text{Drug}^+ + \text{H}^+
\]

Typical reactions involved in gastrointestinal fluids

**Acidic drug:**

In stomach:
\[
\text{Re-N(CH}_3\text{)} + 3\text{ Drug}^- + \text{HCl} \rightarrow \text{Re-N(CH}_3\text{)} + 3\text{ Cl}^- + \text{Drug} \quad \text{(Free form)}
\]

In intestine
\[
\text{Re-N(CH}_3\text{)} + 3\text{ Drug}^- + \text{NaCl} \rightarrow \text{Re-N(CH}_3\text{)} + 3\text{ Cl}^- + \text{Drug} \quad \text{(Sodium salt)}
\]

**Basic drug:**

In stomach
\[
\text{Re-COO}^- \text{Drug}^+ + \text{HCl} \rightarrow \text{Re-COOH}^- + \text{Drug}^- + \text{HCl}
\]

In intestine: \[
\text{Re-COO}^- \text{Drug}^+ + \text{NaCl} \rightarrow \text{Re-COONa}^- + \text{Drug}^- + \text{HCl}
\]
TABLE 4: IS A LITERATURE REPORT OF VARIOUS ION EXCHANGE RESINS EMPLOYED IN TASTE MASKING OF DRUGS

<table>
<thead>
<tr>
<th>Type of Resin</th>
<th>Functional group</th>
<th>Functional backbone</th>
<th>Commercial resins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong anion</td>
<td>-N+R₁</td>
<td>Polystyrene-DVB</td>
<td>Amberlite IR 400, Dowex 1, Indion 454, Duolite AP 143</td>
</tr>
<tr>
<td>Weak anion</td>
<td>-N+R₂</td>
<td>Polystyrene-DVB</td>
<td>Amberlite IR 4B, Dowex 2</td>
</tr>
<tr>
<td>Strong cation</td>
<td>-SO₃H</td>
<td>Polystyrene-DVB</td>
<td>Amberlite IR 120, Dowex 50, Indion 244, Purolite C 100 HMR, Kyron –T-154</td>
</tr>
<tr>
<td>Weak cation</td>
<td>-COOH</td>
<td>Methacrylic acid-DVB</td>
<td>Amberlite IRC 50, Indion 204-234, Tulsion 335, 339, Purolite C 102DR, Kyron-T-104, Tulsion T 335, Doshion P544 (R)</td>
</tr>
<tr>
<td>Weak cation</td>
<td>-COOK</td>
<td>Methacrylic acid-DVB</td>
<td>Amberlite IRP 88, Indion 234, Tulsion T 339, Kyron-T-134</td>
</tr>
</tbody>
</table>

**Flavors and Sweeteners:** Sweeteners are mixed with the bitter drugs and masks the taste of them. Sweeteners based upon origin there are classified into natural and synthetic. Synthetic sweeteners such as sucralose, aspartame, and saccharin are showing their prominence in taste masking than the natural ones. These sweeteners are used in combination with sugar alcohols like lactitol, maltitol and sorbitol to decrease their after taste (table 5).

**Perception:** Sucralose can be used with acids (citric acid) to increase the taste masking efficiency of the sweetener 24, 26.

**TABLE 5: LIST OF COMMONLY USED SWEETENERS AND THEIR RELATIVE SWEETNESS**

<table>
<thead>
<tr>
<th>Sweetening agent</th>
<th>Relative sweetness</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartame</td>
<td>200</td>
<td>Less stable in solution</td>
</tr>
<tr>
<td>Acesulfame potassium</td>
<td>137-200</td>
<td>Bitter in higher concentration</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>40</td>
<td>Banned</td>
</tr>
<tr>
<td>Glycerrhizin</td>
<td>50</td>
<td>Moderately expensive</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.16</td>
<td>High amount is required</td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.60</td>
<td>Negative heat of solution</td>
</tr>
<tr>
<td>Saccharin</td>
<td>450</td>
<td>Unpleasant after taste</td>
</tr>
<tr>
<td>Sucralose</td>
<td>600</td>
<td>Synergistic sweetening effect</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1 ( Standard )</td>
<td>Most commonly used</td>
</tr>
</tbody>
</table>

**TABLE 6: CLASSIFICATION OF FLAVORING AGENTS**

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural</td>
<td>Peppermint</td>
<td>Less stable</td>
</tr>
<tr>
<td>Artificial</td>
<td>Vanilla</td>
<td>Highly stable</td>
</tr>
<tr>
<td>Natural and artificial</td>
<td>Strawberry</td>
<td>Effective at low concentrations</td>
</tr>
</tbody>
</table>

**TABLE 7: SELECTION OF FLAVORS BASED ON SENSATION OF TASTE**

<table>
<thead>
<tr>
<th>Sensation</th>
<th>Flavor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt</td>
<td>Butterscotch, apple, apricot, peach, vanilla</td>
</tr>
<tr>
<td>Bitter</td>
<td>Wild cherry, walnut, chocolate, mint, passion fruit</td>
</tr>
<tr>
<td>Sweet</td>
<td>Fruit and berry, vanilla</td>
</tr>
<tr>
<td>Sour</td>
<td>Citrus flavors, liquorice, root bear, raspberry</td>
</tr>
</tbody>
</table>

Selection of suitable flavoring agent to be added depends on the original sensation of drug substance (table 7).

**TABLE 8: LITERATURE REPORT ON TASTE MASKING BY ADDITION OF FLAVORS AND SWEETENERS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Dosage form</th>
<th>Taste</th>
<th>Taste masking agent used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eucalyptus oil</td>
<td>Freshener</td>
<td>Mouth wash</td>
<td>Bitter</td>
<td>Fenchone, Borneol</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>NSAID</td>
<td>Syrup, Suspension</td>
<td>Bitter</td>
<td>Saccharin sodium, sucrose, sorbitol</td>
</tr>
<tr>
<td>Thymol, triclosan</td>
<td>Dental caries</td>
<td>Oral rinses</td>
<td>Bitter</td>
<td>Citrus flavor, limonene</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>Fluoroquinolone, antibiotic</td>
<td></td>
<td>Aspartame, Sucralose, Saccharin sodium</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aspirin/NSAID, Menthol, Aspartame and or Sucralose</td>
<td></td>
</tr>
</tbody>
</table>
Formation of inclusion complexes: Inclusion complex is a ‘host-guest’ relationship in which the host is complexing agent and guest is the Active moiety. The complexing agent is capable of masking bitter taste either by decreasing its oral Solubility or decreasing the availability of drug to taste buds. Vanderwaals forces are mainly involved in inclusion complexes e.g. β- cyclodextrin is widely used complexing for taste masking of drugs due to its sweet taste and is nontoxic in nature (table 9).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Dosage form</th>
<th>Complexing agent used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>Recover zinc deficiency</td>
<td>Oral liquid</td>
<td>Anethol -β- cyclodextrin complex and saccharin</td>
</tr>
<tr>
<td>Gymnema sylvestre</td>
<td>Local anaesthetic</td>
<td>Oral liquid</td>
<td>Cyclodextrins</td>
</tr>
<tr>
<td>Chloroquine phosphate</td>
<td>Anti-diabetic</td>
<td>Oral liquid</td>
<td>Hydroxypropyl β- cyclodextrin</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Anti-emetic</td>
<td>Syrup</td>
<td>β- cyclodextrin, Chitosan</td>
</tr>
</tbody>
</table>

Prodrug approach: Prodrugs are therapeutic agents that are initially inactive but on biotransformation liberate active metabolite by which the therapeutic efficacy is obtained. Molecular geometry of the substrate is important the taste receptor adsorption reaction i.e., mechanism of taste. Hence if any alteration is done in molecular geometry, it lowers the adsorption rate constant. Thus taste masking can be achieved.

Microencapsulation: Microencapsulation is a process in which the active moiety (solid or liquid droplets) is coated with a Polymeric material or film (table 10).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Dosage form</th>
<th>Coating material used</th>
<th>Technique used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Anti-pyretic</td>
<td>Dispersible tablet</td>
<td>Cross carmellose</td>
<td>Wurster fluid bed coating</td>
</tr>
<tr>
<td>Caffeine / Cimetidine</td>
<td>Diure anti-histamine</td>
<td>Chewable tablet</td>
<td>Eudragit RL 30D, RS 30D</td>
<td>Wurster fluid bed coating</td>
</tr>
<tr>
<td>Chloroquine di phosphate</td>
<td>Anti-malarial</td>
<td>Powders</td>
<td>Eudragit RS 100</td>
<td>Coacervation phase separation</td>
</tr>
<tr>
<td>Metronidazole Ibuprofen, ketoprofen</td>
<td>Anti-amoebic</td>
<td>Dry suspension</td>
<td>Eudragit E, Fatty base</td>
<td>Solvent evaporation</td>
</tr>
<tr>
<td>Aspirin and Fenamic acid</td>
<td>NSAIDs</td>
<td></td>
<td>Sodium alginate and calcium salt</td>
<td>Solvent evaporation</td>
</tr>
</tbody>
</table>

Granulation: Granulation process is used to mask the bitter taste of the drugs. This granulation is the major step in the tablet formation. In this approach, saliva insoluble polymers are used as binding agents in the tablet preparation. As these polymers are insoluble in saliva, thus the bitter taste of the drug can be masked 31, 32, 33. The taste masked granules can also be formulated as chewable tablet and rapidly disintegrating tablets (table 11).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Granulating agent used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium compounds</td>
<td>Mineral supplement</td>
<td>Sugar alcohol</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Macrolide</td>
<td>Alginic acid</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Anti tussive</td>
<td>Cyclodextrin</td>
</tr>
<tr>
<td>Vitamins</td>
<td>Diet supplement</td>
<td>Polyglycerol ester of poly valent fatty acids</td>
</tr>
<tr>
<td>Penicillins,</td>
<td>Macrolides Antibiotics</td>
<td>Hydrogel or Wax</td>
</tr>
</tbody>
</table>

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Adsorption: Adsorbate of bitter tasting drug can be considered as less saliva soluble version of that drug. In this technique, adsorbates of the bitter drugs are prepared by adsorption process. This process involves the adsorption of the drug solution using insoluble materials like silica gel, bentonite, veegum etc. The adsorbate (resultant powder) is dried and used for the formulation of final dosage forms.

Liposomes and Multiple Emulsions: Liposomes are carrier molecules comprising several layers of lipids, in which the entrapment of bitter drug is within the lipid molecule occurs. Oils, surfactants, polyalcohol’s and lipids effectively increase the viscosity in the mouth due to which the time of contact between the bitter drug and taste receptors is decreases, thus improving the overall taste masking efficiency.

Inhibition of bitterness of drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, that can be administered as a suspension or sprinkle on easy to swallow foods. This is developed with a wide variety of flavors and is compatible with customized release profiles.

Recent Trends: AdvaTab ODT Technology: AdvaTab ODT Technology is developed by APTALIS Pharmaceutical technologies.

Advantages offered by this technology include high physical stability, stability during package and transport, pleasant taste (with Microcap Technology) and good patient compliance.

Micro caps ODT Technology: Microcap ODT technology is developed by APTALIS Pharmaceutical technologies. This technology uses coating method for taste masking. The polymeric membrane eliminates the unpleasant taste and / or odor, offers advantages like precise taste masking, good release profiles and patient compliance.

Liquitard ODT Technology: This sophisticated Liquitard technology is developed by APTALIS Pharmaceutical technologies with an aim to provide an effective, convenient, ready-to-use, taste-masked powder formulation in single dose sachets that can be administered as a suspension or sprinkle on easy to swallow foods. This is developed with a wide variety of flavors and is compatible with customized release profiles.

KLEPTOSE® Linecaps: Roquette offers a new taste-masking technology: KLEPTOSE® Linecaps, uses a peamaltodextrin for masking the bitter taste of drugs by decreasing the overall amount of drug particles exposed to the taste buds.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Taste masking agent used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoprothiolane</td>
<td>Plant growth regulator</td>
<td>Hydrogenated oil and HPMC</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>NSAIDs</td>
<td>Molten stearyl stearate</td>
</tr>
<tr>
<td>Talampicillin HCl</td>
<td>Penicillin antibiotic</td>
<td>Magnesium Aluminium silicate</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Macrolide antibiotic</td>
<td>Glyceryl monostearate and AMCE</td>
</tr>
<tr>
<td>Indeloxazine HCl</td>
<td>Cerebral activator</td>
<td>Hydrogenated oil and surfactants, soya lecitlin</td>
</tr>
</tbody>
</table>

TABLE 12: LITERATURE REPORT ON TASTE MASKING BY LIPOSOMES AND MULTIPLE EMULSIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Taste suppressant and / potentiator used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromhexine</td>
<td>Mucolytic</td>
<td>Thaumatin and sugar alcohol</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Diuretic</td>
<td>Hydroxylflavones</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Diuretic</td>
<td>Gamma-amino butyric acid</td>
</tr>
</tbody>
</table>

TABLE 13: LITERATURE REPORT ON TASTE MASKING BY ADDITION TASTE SUPPRESSANTS AND OR POTENTIATORS
Self-emulsification Pellets: Because of the inherent physical instability, the large volume of the two phase emulsion, and the poor precision of dose, the use of conventional emulsions becomes problematic. Micro emulsions or self-emulsifying drug delivery systems over the problems that are occurred by the conventional emulsions (SEDDS). The most famous example of a micro emulsion based system is the Neoral formulation of Cyclosporine, which replaced Sandimmune. SEDDS have shown a success in improving oral bioavailability of poorly water soluble and lipophilic drugs.

SEDDS are composed of a mixture of oil and a surfactant results in the formation O/W emulsion upon gentle agitation condition provided by gastrointestinal motion. In such system, the lipophilic drug is presented in solution, in small droplets of oil, leading to the elimination of the dissolution step which can be the rate-limiting step in absorption of poorly water soluble drugs. The pellets prepared by self-emulsion based as increased the absorption of the drugs.

Materials used are Avicel PH 101 (Microcrystalline cellulose (MCC)) was used as the pellet forming material. Solutol HS 15 (Macrogol-15-Hydroxy stearate), Cithrol GMS_ (C18 mono- and diglycerides). Tempolbenzoate (4-hydroxy- 2, 2, 6, 6-tetramethylpiperidine-1-oxyl-benzoate, TB) and Tempol (2, 2, 6, 6-tetramethyl-4-hydroxy-piperidin-1-oxyl, TL),Sudan._red 7B dye.

Methods of preparation of pellets of the self-emulsification method is carried out as follows

Preparation of self-emulsification pellets is similar to that of normal pellets;

The preparation of the self-emulsifying mixture involved the following steps:

1. Melting of GMS and Solutol at 70°C
2. Dissolving the model drug, the dye or the spin probe in the molten blend
3. Addition of water to the molten lipid blend until a creamy mass is produced
4. Cooling to room temperature
5. Addition of the dry MCC and mixing in a kneader for 15 min

Further addition of water until a mass suitable for extrusion is obtained.

Extrusion/spheronization: The wet mass was extruded at 40 rpm in a radial screen twin-screw extruder equipped with a die of 1mm diameter circular openings and 1mm thickness. The extrudate was then spheronized for 5 min in a 250mm radial plate spheronizer using a cross-hatch frictional plate of 3.3 mm² pitch and 1.2mm depth. The resulting pellets were dried in an oven at 50°C until a constant weight had been reached.

(A) Self-emulsifying pellet formulation.
(B) Reference pellets, containing Sudan red dye, after 30 min of dissolution in distilled water at a temperature of 37°C and Microscopic picture of the release media of
(C) Self-emulsifying pellets.
(D) Reference pellets.

Pectin film coated based pellets for site specific (colon) target: These systems are able to pass unaffected through the upper part of the gastrointestinal tract (GIT), showing biodegrade-ability only in the colonic environment, due to the anaerobic microflora resident in this region. Among these polysaccharides; pectin has been widely evaluated as a colon specific drug delivery entity.
It can be broken down by pectinase enzymes produced by anaerobic bacteria of the colon and can control drug release by this principle. Drug, Ethyl cellulose was used in the form of Surelease (E-7-19040, 25% solids), Eudragit RS30D and Eudragit NE30D, Pectin, microcrystalline cellulose, Hydroxypropyl methylcellulose, lactose monohydrate 200, talc and triethyl citrate, citric acid, Trinitro benzene sulfonic acid

Preparation of site-specific release drug pellets:

Preparation of Drug Core Pellets: Pellet cores containing drug (1.5% w/w), Avicel PH 101 (6% w/w), Avicel RC581 (24% w/w) and lactose (68.5% w/w) were prepared by extrusion-spheronization (extruder model 20 and spheronizer. Distilled water was used as granulating liquid. They were dried at room temperature for 24 hrs. Pellets with the size range of 840-1000 µm were used for subsequent coating.

Preparation of Coated Pellets:

Pectin (2% w/w) was first dispersed in purified water.

Add it to the aqueous dispersions of polymers with the ratio’s of 1:2, 1:3, 1:4 (w/w) stirred for 2 h prior to coating.

Talc was used as anti-adherent for Eudragit aqueous dispersions (50% talc based on dry polymer weight).

The Eudragit RS30D aqueous dispersion also had triethyl citrate (TEC) as plasticizer (25% based on dry polymer weight).

The pellet cores were coated in a FL-Mini coater, top spray fluidized bed coater until a weight gain of 15, 20, 25, 30 and 35% (w/w) was achieved.

Then sub coat of HPMC was applied to the pellets that consisted of HPMC (5.71%, w/w), citric acid (0.2%, w/w), TEC (1.71%, w/w), talc (2.65%, w/w) and water (89.73%, w/w).

Gastroretentive Floating Pellets: The main principle OF Gastro retentive floating pellets is to increases the residence time and releases the drug in a controlled manner. Due to low bulk density of the floating pellets they float on the gastric environment for a longer period and increase the bioavailability of the drug.

Preparation of Floating Pellets: Steps involved in preparation of floating pellets

All the polymers, drug and all the excipients were weighed and the pellets are prepared with the help of extruder technique.

The floating pellets are prepared by soaking the sodium alginate (1%w/w) overnight in the demineralized water which was homogenized by using electronic stirring rotating at 4000rpm for half an hour.

The HPMC polymer was also stirred for half an hour, to form suspension

Drug was added and continued stirring for 45 min

This homogenized solution was sprayed on to the cationic solution (i.e. CaCl₂ 0.1%)

Leave it for 15min to form pellets

Thus formed pellets were collected and washed four times with distilled water and dried for 12hrs at room temperature.
Mouth Melt Pellets: The usage of mouth melt pellets has increased at present due to their increased bioavailability of the drug by melting of the pellets in the mouth even without taking of water, they melt in the saliva and drug is dispersed or dissolved in the saliva and makes the drug available to the systemic circulation for its therapeutic activity.

Materials used are crosspovidone (Polyplasdone® XL-10) an extrusion spherization aid, Indion® 234s (cross-linked acrylic polymer with COO⁻ K⁺ functional group), Indion® 204 (o) (cross-linked acrylic polymer with COO⁻ H⁺ functional group), Indion® 414 (cross-linked acrylic polymer with COO⁻ K⁺ functional group), Indion® 254 F (polystyrene cross-linked with divinyl benzene with SO₃⁻ Na⁺ as functional group) as taste masking agent.

Extrusion–spheronization aids like Avicel® PH-101 and Avicel® RC-591 (mixture of MCC and sodium carboxymethylcellulose); xylitol (Xylisorb® 300; bulking agent) Pineapple flavor (Instacoat® IC-F-105, Citric acid, mannitol and dextrose and aspartame. Purified water was used as wet massing liquid.

Taste Masking Using Polyplasdone® XL-10: Triturating drug with Crosspovidone (Polyplasdone® XL-10) causes physical interaction between them. Drug was triturated with Crosspovidone (Polyplasdone® XL-10) for 30 min using mortar and pestle.

Taste Masking Using Ion Exchange Resin: As the drug is a salt of weak base and strong acid, there are groups which can interact with cation exchange resins. Resin was stirred with water for 15 min to obtain a uniform dispersion using overhead stirrer. Drug was slowly added to the dispersion with continuous stirring. The stirring was continued for 4 h.

Resinate was poured in the stainless steel trays and dried in the hot air oven at 40°C and sieved through 40# sieve. Differential scanning calorimetric (DSC) studies were carried out by heating separately drug, resin and resinate from 32°C to 300°C at the heating rate of 10°C/min in nitrogen environment.

Fast Dissolving Tablets containing Micro Pellets: The uncoated micro pellet improves the drug bioavailability by increasing the dissolution and disintegration time and micrometric properties of a drug which are necessary for the development of the fast dissolving tablets. These tablets disintegrate quickly after placing on the tongue and the released drug may be either dispersed or dissolved with the saliva. This type of formulations commonly used in the preparation of NSAIDS. The uncoated pellets are prepared by spherical agglomeration technique for the formulation of fast dissolving tablets.

Materials used are drug, Crosscarmellose, sodium, sodium starch glycolate, and mannitol, Avicel-PH101 (Microcrystalline cellulose), Crosspovidone and magnesium stearate.

Preparation of Mouth Melt Pellets:

All the ingredients including drug were mixed in a planetary mixer for 15–20 min

Purified water was added to the above mix along with stirring until the appropriate mass was formed

The wet mass extruded using single screw extruder.

Immediately after extrusion, the extrudates were rounded in the spheronizer with cross-hatched plate of diameter 150 mm in a batch size of 50 g each time.

The spheronization of MCC and Crosspovidone extrudates were carried out at 750 rpm for 1-2 min and 500 rpm for 30 s, respectively.

Thus obtained pellets were dried in fluid bed drier at 40°C for 30 min.
**Preparation of Drug Micro Pellets:** Drug uncoated micro pellets were prepared using spherical agglomeration technique.

The drug solution was prepared by dissolving 1.5g of drug in 20ml acetone

This drug solution was poured drop by drop into 100ml of demineralized water at room temperature under continuous stirring at 400-500 rpm by using a magnetic stirrer.

After 20 min of continuous stirring 6ml of bridging liquid isopropyl acetate (10%v/v) was introduced in drop wise manner into the crystallization medium to produce spherical micro pellets having mean diameter of 100-200 µm.

The stirring continued for 2 hrs to get stable and spherical micro pellets

The spherical micro pellets formed were separated by filtration and dried at 45°C for 24hrs in a hot air oven.

**Preparation of Fast Dissolving Tablets (FDTs):**

All ingredients and uncoated drug pellets were passed through a # 100 sieve, weighed, and blended.

Ethanol was used as granulating fluid and it was added slowly to the power blend, and kneading was performed for few minutes until wet mass is formed.

The dried granules were re-sieved through a # 20 sieve

Then mix all the lubricant, the lubricated granules were compressed by a single station tablet punching machine, using flat faced Punches

The pellets retained on #10 were rejected. The pellets retained on each sieve were weighed and the percent fraction of the total weight of these fractions was calculated.

**Yield and water requirement:** Pellet yield was determined from the particle size distribution data. It was calculated on the basis of pellet fraction between 850-1400 µm and was presented as the percent of the total pellet weight. Depending upon the type of spheronizing agent used for the preparation of pellets, amount of water required for extrusion-spheronization was determined.

**Friability studies of pellets**

Resistance to abrasion was determined using USP method for measurement of pellet friability. A sample of accurately weighed uncoated pellets (10 g) was placed in the (Roche TAR 10) friabilator. Drum was rotated 100 times and pellets were removed. After dedusting, weight loss from the pellets was measured by sieving the pellets through #20 sieve. The percent of weight lost was calculated and...
Friability was determined three times for every batch and reported as average ± standard deviation.

**Gustatory Sensation Test** 56: In this test, quinine hydrochloride solution 1 mM was considered as standard for bitterness with a bitterness score of 5 and purified water as 0. The human volunteer study was done according to ethical guidelines for biomedical research on human subjects by Indian Council of Medical Research. The protocol for the test was approved by institutional ethical committee.

The test was performed with ten well-trained volunteers. The developed pellets were rated between 0 and 5 depending upon intensity of bitterness, 0 being tasteless and 5 very bitter. After tasting each sample, volunteers gargled well with water and waited for at least 20 min before tasting the next sample. Also, the volunteers rated the pellets for mouth feel and dispersion in mouth (how fast polymeric material disperses the saliva) on the scale of 1 to 5.

**Assessment of Self-Emulsification:** The self-emulsifying formulation was able to introduce Sudan Red into water and gentle agitation is done. While the reference pellets, composed of MCC and GMS, were not able to deliver the lipophilic dye into the media. Microscopic examination of the release media of the self-emulsifying pellets showed lipid droplets, incorporating the dye. On the other, microscopic examination of the release media of the reference pellets did not show any droplets.

**Pellet Disintegration:** The pellet disintegration in water was evaluated by a tablet disintegration tester DT 2 (ROLEX Tablet disintegration rate test apparatus IP). Special transparent tubes of 10-mm diameter and 15-mm length were used. Sieves of 710-mm mesh size were at the top and the bottom of this tube. After filling 100-mg pellets in each tube, they were inserted in the standard tablet disintegration tester. The disintegration time of six dried samples at 37°C was determined at a speed of 30 dips per minute. Pellet formulations which were passing the evaluation tests (Friability, flow properties, disintegration and dissolution tests) were chosen for further improvement in their disintegration properties.

**In-vitro dissolution studies:** The prepared pellets by different approaches taken for conducting in vitro dissolution studies, dissolution studies of pellets were carried out in a suitable dissolution medium. The dissolution studies for all the pellet batches were carried out according to the USP (XXIV) paddle method as per the USP general drug release standard, with a paddle speed of 100 rpm at 37±0.5°C in 900 ml of dissolution medium.

Pellets equivalent to 7.5 mg were subjected to the dissolution studies in 900-ml dissolution medium. The sample of 5 ml was withdrawn from dissolution vessel at 10-min time interval and was assessed spectrophotometrically at a wavelength in nm with a UV spectrophotometer (UV2401PC, SHIMADZU, Kyoto, Japan). Sample amount used for analysis was replaced by fresh dissolution medium to maintain the sink conditions.

**CONCLUSION:** Taste masking of bitter drugs, polymers used in the preparation of pellets in control release of drugs, self-emulsification of pellets, mouth melt pellets etc. is a big challenge to scientist. However we have made an attempt to describe various methods, techniques to solve the problem. These, techniques mentioned in this review can be used for bench scale and pilot scale also. With application of these techniques one can improve product preference to a large extent. In addition to oral drug delivery, the recent novel trends of pellets research is gaining importance for the quality of the treatment provided to patients, especially children and old. As evidenced by number of patients and technology developments, an attempt of this novel trend of pellets is widely accepted in the development of palatable dosage forms having good patient compliance without interfering with the drug release.

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