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ENTERIC COATING TECHNOLOGIES: ADVANCES IN ORAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Enteric-coated tablets are solid unit dosage forms intended for oral delivery; they are designed to bypass the stomach and release medication in the small intestine instead. The term "enteric" pertains to the small intestine, and enteric coatings prevent medication from releasing before reaching that location. Most enteric coatings work by offering a coated surface that dissolves quickly at a less acidic (slightly more basic) pH while remaining stable in the highly acidic environment of the stomach. Enteric coating materials include fatty acids, waxes, shellac, polymers, plant fibres, CAP, CAT, PVAP, and HPMCP. This study examines enteric coating, including its optimal qualities, advantages, and disadvantages. It also explores the various polymers used, their chemical structures, criteria for drug selection and mechanism, and the processes for production and evaluation of enteric-coated tablets. Given their advantages over traditional drug delivery methods, such as longer dosing intervals and improved patient compliance, these have recently garnered the attention of numerous formulators. The research provides an overview of the latest advancements in this field.

KEYWORDS: Enteric Coated Tablet, Coating Process, Methods of Manufacturing Enteric Coated Tablet, Evaluation, Ideal Properties.

1. INTRODUCTION

The tablet is a pharmaceutical solid dosage form, comprising a mixture of active substances and excipients, commonly in powder form, pressed or compacted right into a stable. Coating is a process by which the coating material is applied to the surface of a dosage form to confer specific benefits to the dosage form. An enteric coating is a barrier that controls the release of oral medication in the stomach and promotes its release in the intestine, where it is absorbed. The word "enteric" indicates the small intestine; therefore, enteric coatings prevent the release of medication before it reaches the small intestine. The enteric coated polymers remain unionized at low pH and, therefore, insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionisation, and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coatings include CAP, CAT, PVAP, HPMCP, fatty acids, waxes, shellac, plastics, and plant fibers.

Ideal Properties of Enteric Coating

- Resistance to gastric fluids.
- Susceptible/permeable to intestinal fluid.
- Compatibility with most coating solution components and the drug substrate.
- Formation of continuous film.
- Nontoxic, cheap and ease of application.
- Ability to be readily printed.

Advantages of Enteric Coating

1. To protect the acid liable drugs from the gastric fluid e. g. enzymes and certain antibiotics.
2. Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow.
3. To forbid gastric distress or nausea due to irritation from a drug, e.g. sodium salicylate
4. To deliver drugs intended for local action in the intestines, e. g. intestinal antiseptics could be delivered to their site of action in a concentrated form.

Disadvantages

1. Process is tedious.
2. Time-consuming.
3. Requires the expertise of highly skilled technician.

Tablet coating

The process of coating involves applying an exterior layer of coating material to a dosage form, which is essentially dry, to provide a range of benefits, from improving product identification to altering the release of medication from the dosage form. Making a decent tablet generally requires coating it. A variety of oral solid dosage forms, such as tablets, capsules, multiparticulates, and drug crystals, can be coated. Applying coating material to a batch of tablets in a coating pan results in a sticky polymeric film covering the tablet surfaces. The applied coating transforms from a sticky liquid to a tacky semisolid and then to a non-sticky dry surface before the tablet surface dries. A sequence of mechanically driven, acorn-shaped coating pans composed of copper, stainless steel, or galvanized iron is employed throughout the coating process. Larger pans are employed for industrial production, whereas smaller pans are utilized for pilot plant, experimental, and developmental operations.

Primary components involved in tablet coating

1. Tablet properties
2. Coating process
3. Coating equipments
4. Parameters of the coating process
5. Facility and ancillary equipment
6. Automation in coating processes

Coating Process Design Control

In most coating techniques, the coating solution is sprayed over the tablets while they are being stirred in a pan, fluid bed, etc. A thin coating forms as the solution is sprayed, adhering directly to each tablet. The coating can be created with a single application or by using several spraying cycles to build it up in layers. Rotating coating pans are a common tool in the pharmaceutical business. The liquid coating solution is added to the pan while the tablets are tumbling after the uncoated tablets have been added to it. The pan is typically tilted at an angle concerning the horizontal. Thereafter, the liquid component of the coating solution evaporates when air is forced across the surface of the falling tablets. A fluid bed coater, on the other hand, works by moving air through a bed of tablets quickly enough to support and divide the tablets into distinct pieces. The tablets are sprayed with the coating mixture once separation has occurred.

The coating process is usually a batch operating task consisting of the following phases:

- Identification of batch and Recipe selection (film or sugar coating)
- Loading/Dispensing (accurate dosing of all required raw materials)
- Warming
- Spraying (Both application and rolling are carried out simultaneously)
- Drying
- Cooling
- Unloading

Within a spinning drum with perforations, tablet coating is done in a regulated environment After the mixture has been placed into the coating pan, preheat the tablets and allow the dust and tablet flash time to depart the pan. Airflow inside the drum and slanted baffles put therein allow for tablet bed mixing. This causes the tablets to be raised and rotated from the sides into the drum's center, covering every tablet surface with an equal layer of coating that has been deposited or sprayed on. Spraying can start as soon as the outlet air temperature reaches 42°C to 46°C, which normally happens in 15 minutes. The coating solution sprayed on the tablet by the spray guns is a thin mist that quickly dries. The liquid spray coating on the tablets was dried by heated air that was drawn through the tablet bed by an intake fan. To give the operator an isolated process atmosphere, the temperature and volume of the airflow are managed to produce controlled drying and extraction rates. At the same time, the drum pressure is kept slightly negative in the room. The particles remain on the tablet in the form of a thin coating while the water evaporates. The secret to coating tablets is to wet the surface just a little bit and let it dry right away. Instead of applying the coating in lengthy, slow exposures, do so in numerous brief exposures. Following the application of the base coating, you can gradually raise the pan speed and the rate of solution addition. Usually, it takes 20 minutes or so to noticeably increase the spray rate and pan speed. Very porous tablets might need an initial spray rate lower than the standard 100 milliliters per minute per gun. Make careful to keep an eye on the spraying process to check whether the pattern changes. If it does, the gun tips probably have a solids buildup on them. Only clean the tips to remedy this, which entails turning off the spray and the pan. Because hot air is constantly entering the drum and entering the tablet bed through the perforations, the enteric coating solution dries on the tablet surface. The film gradually builds up layers upon layers of substances. The pills need to cool once the solution has been applied and dried. The tablets need to stay at a certain temperature, the solution needs to be applied consistently, and the tablets need to move in a

calm but active manner for coatings to cling correctly. If any of these are compromised, a faulty tablet will result.

Enteric Coating Necessary

1. After taking a typical supplement

After being swallowed, the tablet passes down the throat and into the stomach. For 45 minutes to two hours, the pill gets churned and agitated in the stomach's extremely acidic digestive secretions (pH 1-4). Any remaining tablet material will be transported to the small intestine via the duodenum.

2. Fate of Uncoated Tablets

Tablets are broken down by stomach acid, causing the active components (enzyme) to release prematurely.

The stomach's extremely acidic environment destroys the majority of the enzyme's activities. Poor-quality tablets that include fillers and binder may slip through the stomach and intestines without being absorbed.

Primary Component Involved In Enteric Coated Tablets Formulation:-

- Manufacture of Tablet core:
- Coating Composition:

a) Polymers

b) Plasticizer

c) Solvent

d) Colorant

- Coating process

Coating equipment

A modern tablet coating system combines several components

- A coating pan
- A spraying system
- An air handling unit
- A dust collector

Composition of Enteric Coating Between 0.01% and 10% polymer and between 0.01% and 10% resin are found in tablets with an enteric coating. To create an enteric coating on the substrate, the enteric coating composition can be pharmaceutical, nutraceutical, fruit, vegetable, agricultural, or industrial products.

Ideal properties of enteric coating material

1. Resistance to gastric fluids
2. Susceptible/permeable to intestinal fluid
3. Compatibility with most coating solution components and the drug substrate
4. Formation of continuous film
5. Nontoxic, cheap and ease of application
6. Ability to be readily printed

Advantages of tablet coating

- Tablet coatings must adhere to the intricate shapes of embossed characters or logos on tablets, avoid causing the tablets to clump together during the coating process, and be sturdy and stable enough to withstand handling.
- Coatings can also be used to print on tablets if needed. Tablet coatings are required to provide a smoother finish, make big pills simpler to swallow, and cover up an unpleasant flavour.

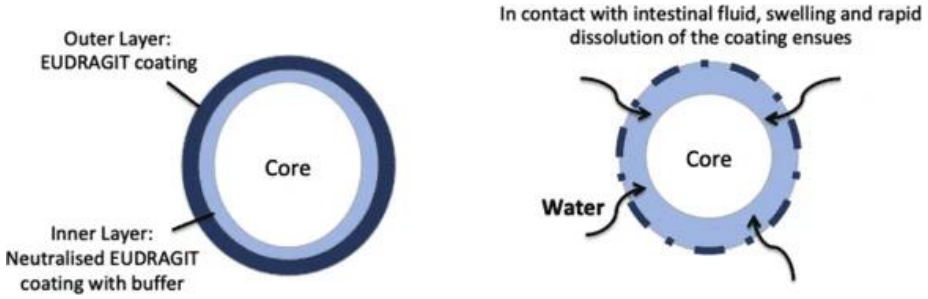
Disadvantages of tablet coating

- Other coating materials are being used as a result of sugar coating's drawbacks, which include its comparatively expensive cost, lengthy coating time, and large bulk.
- However, coating is a laborious and time-consuming operation that calls for the knowledge of a highly qualified professional.

1.1 Enteric Coating

Delayed release or Enteric coatings are coating in which the tables remain intact in the stomach a gastric or acidic environment but will dissolve and release the contents once they reach the small intestine at basic environment. Due to enteric coating, the active content which is degraded by the acidic environment of the stomach may cause nausea or any other gastric irritation. Cracking or damage of the film during application or storage will result in a loss of enteric properties or its desired action. So, consideration must be given to the physical nature of the outer film. Cracking problems might be effectively overcome with the help of

proper plasticization. Plasticizers can be used to reduce the permeability of the polymer films. The choice of suitable Plasticizer is restricted to non-water soluble materials or hydrophobic materials because these are likely to be most effective.



ADVANTAGES OF ENTERIC COATING

- To protect the drug from the stomach
- To protect the acid liable drugs from the gastric fluid e. g. enzymes and certain antibiotics
- Coatings can also facilitate printing on tablets if required. Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow.
- To forbid gastric distress or nausea due to irritation from a drug, e.g. sodium salicylate.
- To deliver drugs intended for local action in the intestines, e. g. intestinal antiseptics could be delivered to their site of action in a concentrated form.

DISADVANTAGE

This process is tedious and time-consuming and it requires the expertise of highly skilled technicians.

COMPOSITION OF ENTERIC COATING

An enteric coating composition includes about 0.01% - 10% resin and about 0.01% - 10% polymer. The enteric coating composition may be applied to a substrate, such as pharmaceutical, neutraceutical, fruit, vegetable, agriculture, or industrial product to form an enteric coating on the substrate A resin- e.g.- shellac, A polymer-e.g – alginate, A plasticizer- e.g.-tri ethyl citrate, A preservative- e.g.- sorbates, A detoxifying agent- e.g.- monostearate, A lubricant- e. g.-palmitic acid, A colorant- e.g.- FD & C lake yellow no 5, A flavor- e. g.- blueberry, butterscotch, A sweetener- e.g.- sucrose, honey, A taste maskant- e.g.- carboxy methyl cellulose, An opacifier- e.g.- titanium dioxide, A buffering agent- e.g.- sodium citrate, An antioxidant- e.g.- tocopherol, A solvent- e.g.- ethanol, water, and combinants therefore.

Limitations

The existence of a broad variety of pH values and distinct enzymes in the GI tract that the medications must interact with before reaching the intended spot casts doubt on the dependability and effectiveness of the administration.

2. MATERIAL AND METHODS

Doxycycline Hyclate provided by Athena Drug Delivery Solution Pvt. Ltd., HPMC K100M, Ethyl cellulose, HPMC phthalate, Microcrystalline Cellulose, Magnesium stearate, PVP K 30M, Aerosil.

2.1 Method of manufacturing enteric-coated

- ***Dry mix method***

Co-Sift Ingredient Doxycycline hydrochloride, Microcrystalline Cellulose (PH 102), Pregelatinized Maize Starch (Starch 1500), Colloidal Anhydrous Silica through 40. Mix the above-sifted material in a blender (25 liters) at twenty-four RPM for five minutes. Further, sift World Journal of Pharmaceutical Research magnesium stearate through 40 and mix the sifted magnesium stearate with the above blend in a blender (25 liters) for five minutes at twenty-four RPM.

- **Compression**

Dry Mix was made according to the process mentioned earlier, and the formulation and compression were performed on a 10-station tablet press. (Make: Cadmach, INDIA).

Punch size: 8.73 mm

Shape: Round and biconvex.

2.2 PREFORMULATION STUDIES

2.1.1 Identification of drug

- **Angle of repose**

The angle of repose has been used as an indirect method of quantifying powder flow ability because of its relationship with inter-particle cohesion. A static heap will slide when the angle of inclination is large enough to overcome frictional forces and stop when gravitational forces balance the forces. The sides of the heap will make an angle horizontal, which is called the angle of repose.

Angle of repose=tan-1h/r

[: *Where h is the height of the pile and r is the radius of the pile.]*

- **Bulk density**

Bulk density is given by the mass "m" of the powder occupying a known volume 'v' according to the relationship.

Pb =(M/V)g/cc

It depends on particle size, shape, and tendency of the particle to adhere.

- **Tapped density**

The weighed powder sample was transferred to a graduated cylinder and placed on a tapped density apparatus, which was operated for a fixed number of taps (100). It is the ratio of the weight of the sample to the tapped volume.

Tapped density=mass/tapped

- **volume Carr's Index**

The percentage compressibility of the bulk drug was determined using the following formula, based on the apparent bulk density and the tapped density.

%Compressibility= tapped density-bulk density/tapped density X100

- **Hasner's Ratio**

The ratio of tapped density to bulk density of the powders is called Hasner's ratio.

- **Absorption maxima determination**:

A solution of Doxycycline hyclate at a concentration of 10mg/ml was prepared using water. It was scanned over the wavelength range of 200-400 nm using a double-beam UV spectrophotometer with water as a blank.

- **Melting point determination**

The melting point was determined by the open capillary method.

- **Preparation of calibration curve of standard plot Doxycycline Hyclate**

Doxycycline hyclate was accurately weighed (10mg) and dissolved in 10 ml of phosphate buffer 6.8 and 1.2 to produce a primary stock solution of 1mg/ml (1000ug/ml). The 1ml of primary stock solution was suitably diluted with 100ml of distilled water to produce a working stock solution in a concentration of 10ug/ml. From the above solution withdraw 1ml, 2ml, 3ml, 4ml, and 5ml solution in a volumetric flask with continuous dilution to make a final volume of 10 ml for each withdrawing WSS solution, to the final concentration

achieved was 1ug/ml to 5. The absorbance of the solution was recorded at 268 nm using a double-beam UV spectrophotometer with water as a blank.

- **Formulation of delay-release tablets for trial batches**

The tablets were formulated by using a direct compression technique. All ingredients were mixed in geometrical order as mentioned in the formula tablet by passing through sieve 24 except only magnesium stearate passed through sieve 60 sieve. After trituration mixture was blended and then directly compressed using capsule-shaped punches.

2.3 Evaluation of preliminary (trial) batches

- **Thickness**

Thickness and diameter were measured using a Vernier caliper.

- **Hardness**

The hardness of the tablet of each formulation was measured by a Monsanto hardness tester. The hardness was measured in terms of kg/cm2.

- **Weight variation**

Randomly 20 tablets were selected after compression and the average weight was determined. None of the tablets deviated from the average weight by more than + 7.5%. The weight values were expressed in milligrams. This is an important parameter in process quality control tests to be checked frequently. Corrections were made during the compression of tablets. Any variation in the weight of tablets (for any reason) leads to either medication in overdose. So every tablet in each batch should have a uniform weight.

- **Disintegration test**

Dosage forms were kept in the apparatus and placed in a one-liter beaker and the time taken to disintegrate the tablets was evaluated.

3. Preparation of enteric-coated tablets

The compressed tablets of the doxycycline were coated with different delayed releases of enteric coating polymers like hypromellose phthalate, Eudragit L30D55, acryl EZE, and cellulose acetate phthalate. The composition of Doxycycline hydrochloride gastro-resistance tablets is given in mentioned table below.

3.1 Drug content

Weight and powder ten tablets. The above powder weight powder equivalent to 100 mg of doxycycline hydrochloride and the same was dissolved in pH 6.8 phosphate buffer. Different concentrations of the drug were prepared and analyzed spectrophotometrically.

3.2 In-Vitro Dissolution Test

The release of active content from the pharmaceutical dosage form was done in a dissolution test apparatus.

- Apparatus: Paddle
- RPM: 100
- Time points: two hours in acidic media i.e. 0.1 N HCl Followed by phosphate buffer pH 6.8 for 45 minutes. Dissolution performed as per US Pharmacopoeia.

4. MECHANISM OF ENTERIC-COATED TIME-RELEASE PRESS COATED (ETP) TABLETS

ETP tablets are composed of three layers, a drug-containing core tablet (rapid release function), the press-coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time-release function), and an enteric coating layer (acid resistance function). The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. The enteric coating layer rapidly dissolves after gastric emptying and the intestinal fluid begins to slowly erode the press-coated polymer (HPC) layer. Rapid drug release occurs when the erosion front reaches the core tablet since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying.

5. METHOD OF MANUFACTURING ENTERIC COATED TABLET BY SPRAY COATING TECHNIQUE

5.1 Preparation of core tablets

Granules were prepared using the wet granulation method. Drug and other excipients were passed through 80no. Sieve and add sufficient quantity of binding agent slowly to get dough mass. The mass was sieved through # 8 and dried at 45ºC for about 1 hr. and then these granules were passed through # 20 and lubricated with magnesium stearate. The mixed blend was compressed into tablets on a single punch tablet compression machine to a weight of 250 mg each with a thickness of 4.46 ± 0.21 mm and diameter of 7.9 mm using shallow concave plain/plain punch.

5.1.1 Coating of core tablets: Preparation of enteric coating solution

A weighed amount of pectin was dissolved in 50 ml of water and ethyl cellulose was dissolved in 50 ml of isopropyl alcohol. The two solutions were then mixed well to form a homogeneous solution and PEG-6000 was added as a plasticizer.

5.1.2 Coating of core tablets

Enteric coating of the compressed tablets is achieved by the standard coating pan technique. Tablets were taken and coated in a pan coater at 50 rpm at a temperature of 50ºC and 10 ml/min flow rate. The coating was carried out with the spraying method and dried. These solutions are applied over tablets using a spray gun at appropriate pressure. The coated tablets are primarily dried using a heat blower and secondarily dried in a tray drier.

5.1.3 Coating methodology

Tablet coating was performed in a conventional coating pan with one spray gun. The coating pan was previously cleaned using alcohol 95%. A batch size of 3.5 kg core tablets was selected for coating. The core tablets were loaded into the coating pan. Tablet cores were pre-heated to about 40°C utilizing a dryer and air compressor. Warm air was introduced into the coating pan (up to 50–55°C) during the entire coating process. The spray gun was filled with enteric coating solution and operated at a proper flow rate. The pan was set into motion and seal coating dispersion was sprayed on to the falling cores under suitable air pressure (87.0-116.0 psi) 6-8 bar. The air heater was switched off and tablets were blow-dried for 20-25 minutes in the coating pan. The core tablets gained 10 ± 2% weight after coating with enteric coating.

CONCLUSION

The enteric coating was done using four different enteric coating materials (Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate, and Acryl-EZE) to achieve 5% weight gain. Evaluation of these tablets indicated that the coated tablets failed the dissolution test in 0.1 N HCl. However, formulations that were enteric coated to 9% weight gain could pass the dissolution test carried out at pH 1.2. By looking here at the dissolution profile of the same tablets in pH 6.8 phosphate buffer, the formulation with Batch No. D5 and D8 coating layers dissolve faster than the formulation with Batch No. D6 and D7. The formulation with Batch No. D5 and D8 containing Eudragit L 30 D 55 show better results compared to the formulation containing hypromellose phthalate and cellulose acetate

phthalate. Formulation with Batch No. D5 and D8 remain intact in 0.1 N HCl and dissolve fast in pH 6.8 phosphate buffer.

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