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REVOLUTIONIZING ORAL DELIVERY: ENTERIC CAPSULES WITH MINI-TABLET TECHNOLOGY

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1. INTRODUCTION TO CAPSULES

Capsules are solid dosage forms that include one or more inert and/or medicinal ingredients encased in a tiny, soluble shell or container, usually composed of hydroxypropyl methylcellulose (HPMC) or gelatine. Because they are adaptable, simple to employ, and can cover up the taste and smell of medications, they are extensively utilized in the pharmaceutical and nutraceutical sectors.

1.1 Definition and Basic Structure

- A capsule is made up of two major components.
  - **Body:** The longer, cylindrical portion that contains the excipients and medication.
  - **Cap:** The shorter, cylindrical portion that covers the body and encloses the contents is called the cap.
- Usually, these two components are made independently and then assembled once the body is filled.[1]

1.2 Advantages of Capsules as a Dosage Form

- **Taste and Odor Masking:** The inert shell effectively conceals \unpleasant organoleptic properties.[2]
- **Ease of Swallowing:** Smooth surface and shape facilitate ingestion.[3]
- **Rapid Drug Release:** Shell dissolution typically leads to quick drug liberation.[4]
- **Versatility in Formulation:** Accommodates various physical forms of drugs and excipients.[5]

1.3 Disadvantages of Capsules as a Dosage Form

- **Incompatible with Highly Hygroscopic Substances (Gela tin):** Can lead to shell degradation.[6]
- **Filling Limitations (Small Doses):** Accurate filling of very low doses can be challenging.[7]

2. TYPES OF CAPSULES

2.1 BY MATERIAL

Type of Capsule	Material Source	Key Benefits	Common Uses
Gelatin Capsules	Gelatin (Bovine or Fish)	Traditional and widely used	Pharmaceutical products
		Excellent low moisture content	Dietary supplements (e.g., fish oil) to protect fatty acids
		Long shelf life	
Vegetarian Capsules	Plant-Based (HPMC or Pullulan)	Suitable for vegetarians/vegans	Herbal products
		Maintains product quality under diverse environmental conditions	Capsules requiring eco-friendly solutions or compatibility with sensitive ingredients
		Extremely low moisture content (pullulan)	
Starch Capsules	Plant-Based (Starch)	Alternative to gelatin	Dietary supplements
		Biodegradable and eco-friendly	Herbal products
PVA Capsules	Plant-Based (Polyvinyl Alcohol)	Offers a robust and stable capsule shell	Pharmaceutical industry
		Avoids the use of animal products	Specialized formulations requiring high stability

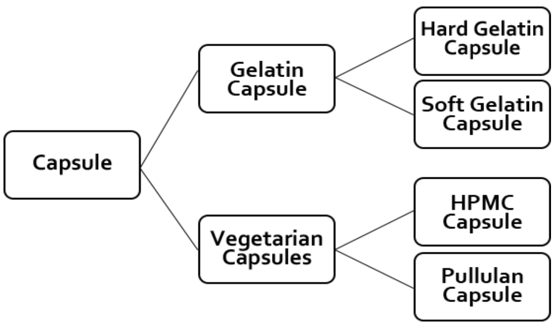

Fig. 1: Types of Capsules.

Gelatin Capsules

One of the earliest types of capsules still in use today is gelatin capsules. Fish or cows are the source of the gelatin used to make them. Because fish gelatin capsules are extremely soluble in fatty acids, they are particularly popular for nutritional supplements like fish oil. Because of their low moisture content, extended shelf life, and ability to effectively protect the active components, gelatin capsules are the recommended form.

Fig. 2: Hard gelatin Capsule.

Vegetarian Capsules

For customers who prefer plant-based capsules, vegetarian options include pullulan and HPMC (hydroxypropyl methylcellulose) capsules. Because HPMC capsules effectively maintain product integrity regardless of external conditions, they are the ideal packaging for herbal goods. Pullulan capsules, on the other hand, are appropriate for items with extremely low moisture content because they are derived from fermented starch.

Fig. 3: Vegetarian Capsules.

Starch and PVA Capsules

PVA and starch capsules are the newest developments in the pharmaceutical sector. Since the shell of these capsules is robust enough to hold a variety of formulations, they can be utilized as an alternative to products derived from animals because they are constructed of plant components.

Fig. 4: Starch Capsule.

2.2 BY STRUCTURE

Type of Capsule	Key Features	Key Benefits	Common Uses
Hard Capsules	Also known as hard gelatin capsules Pre-manufactured, empty capsules Used for solid oral dosage forms	Versatile, available in a range of sizes Efficient for encapsulating potent drugs	Widely used in pharmaceutical products and dietary supplements
.Soft gel Capsules	Feature soft, seamless shells. Best suited for liquid formulations Easy to swallow	Protects ingredients from stomach acid Enables effective release in the intestinal tract	Popular for fish oil, vitamins, and other supplements dietary supplements
Liquid-Filled Hard Capsules	Hybrid between hard capsules and soft gels Encapsulates liquid formulations while retaining hard-shell properties	Combines the durability of hard capsules with the flexibility of soft gels Ensures extended shelf life	Ideal for both pharmaceutical drugs and herbal products with liquid-based active ingredients
Multi-Chamber Capsules	Designed with separate compartments for different ingredients Prevents interaction between components until ingestion	Ensures the stability of ingredients in varying environmental conditions Supports complex formulations	Used for combination therapies and herbal supplements requiring ingredient separation

Hard Capsules: Hard capsules, commonly referred to as hard gelatin capsules, are typically used to encapsulate solid oral dosage forms. These capsules are ideal for containing highly concentrated active ingredients, and because they come in different sizes, they can be used for vitamins and medications. Usually, their unfilled capsules are readily available in the market and are prepared for filling.

Soft gel Capsule: Soft gel capsules are perfect for liquids like fish oil or any other supplement because of their soft exterior. The non-gel-like structure protects against stomach acid while delivering the substances to the intestine, and the soft texture facilitates swallowing.

Liquid-Filled Hard Capsules (LFHC): A mix of soft and hard capsules make up LFHCs. They combine the advantages of hard capsules, such as shelf life and flexibility, with soft gels for encapsulating liquids and delivering active components in herbal and pharmaceutical preparations.

Multi-Chamber Capsules: Several components can be included in a single capsule by using multi-chamber capsules, but not until the capsule is ingested do they mix. For formulations containing chemicals with varying degrees of stability in various environmental circumstances, this design is beneficial.

2.3 BY FUNCTION

Type of Capsule	Key Features	Key Benefits	Common Uses
Enteric Capsules	Coated with a special layer to resist breakdown in stomach acid	Protects sensitive ingredients Ensures delivery to the small intestine	Medications and supplements targeting the gastrointestinal tract
Sustained-Release Capsules	Gradually releases active ingredients over an extended period	Reduces the need for frequent dosing Improves patient compliance	Long-term treatments where steady levels of the drug are required
Controlled-Release Capsules	Precisely releases ingredients at specific locations in the intestinal tract	Optimizes the effectiveness of active ingredients Targets specific delivery areas	Medications requiring release at a particular point in the digestive system

Enteric Capsules

In order to ensure that the active ingredients reach the small intestine, enteric capsules are designed to withstand the effects of stomach acid. For medications and nutrients meant for the stomach and intestines, these capsules work especially well.

Fig. 5: Enteric Capsule.

Sustained/Controlled Release Capsules

It is possible to incorporate active ingredients into prolonged-release capsules, which reduce the frequency of dosing and increase patient compliance by allowing for gradual dosage administration. In contrast, controlled-release capsules optimize the effective distribution of the contents by enabling the targeting of particular intestinal tract regions at the appropriate dosage.

2.4 BY USE

Type of Capsule	Key Features	Key Benefits	Common Uses
Pharmaceutical Capsules	Focus on protecting and ensuring the controlled release of active ingredients.	Provides accurate dosage Extends the shelf life of medications Protects from environmental conditions	Prescription drugs Over-the-counter medications
Dietary Supplement	Consumer-focused designs with features like	Enhances product quality Promotes overall wellness	Vitamins and minerals Herbal supplements

Capsules	vegetarian capsules and appealing capsule shells	Incorporates fatty acids, vitamins, and herbal products	Omega-3 and other oils

Pharmaceutical Capsules

The main goals of pharmaceutical capsules are to protect and properly dispense active components, enhancing patient health and dose accuracy. The overall goal is to better store medications and protect them from their environment.

Dietary Supplement Capsules

The consumer is the focus of nutritional supplement capsules, which offer features including vegetarian capsules, eye-catching shells, and innovative designs to enhance product quality. For overall health, these capsules may include vitamins, fatty acids, and herbal items.[8]

3. CLASSIFICATION OF NEXT GENERATION CAPSULES

3.1. Advanced Materials for Capsule Shells

- **Enteric Polymers Integrated into the Shell**
  - **Description:** The capsule shell is formed directly from pH-sensitive polymers, which offer intrinsic gastro-resistance, rather than by coating. HPMCAS (Hydroxypropyl Methylcellulose Acetate Succinate) is one example.[9]
- **Pullulan Capsules**
  - **Description:** Oxygen-sensitive medications can benefit from pullulan, which is made from fermented tapioca and has extremely low oxygen permeability. In addition, they have superior film-forming qualities and are vegetarians.[10]
- **Starch-Based Capsules**
  - **Description:** plant-based substitutes with the possibility for customized release and biodegradability. Research on improving their stability and mechanical characteristics is still ongoing.[11]
- **Novel Polysaccharide Blends**
  - **Description:** To make capsules with particular release profiles and mucoadhesive qualities, combinations of polysaccharides such as pectin, chitosan, and alginate are being investigated.[12]

3.2. Innovative Capsule Designs and Functionalities

- **Multi-Compartment Capsules**
  - **Description:** Capsules having distinct chambers that enable pulsatile medication release or the encapsulation of incompatible substances (such as liquid and powder). One such example is the DUOCAP® system.
- **Capsule-in-Capsule Systems**
  - **Description:** Multiple medicines with distinct release characteristics can be delivered, or delayed release can be achieved by enclosing a smaller capsule inside a bigger one.
- **Floating Drug Delivery Systems (FDDS) in Capsules**
  - **Description:** Capsules that are made to stay in the stomach for a long time increase the bioavailability of medications with limited upper gastrointestinal tract absorption windows.[13]
- **Telemetric or "Smart" Capsules**
  - **Description:** Sensors in capsules that can wirelessly send data and track drug release or physiological parameters (pH, temperature, and pressure).

3.3. Advanced Manufacturing Technologies

- **Precision Capsule Manufacturing**
  - **Description:** Methods that enable extremely precise control over drug loading, wall thickness, and capsule dimensions, resulting in more reliable performance.[14]
- **3D Printing of Capsules**
  - **Description:** New technology makes it possible to create complicated geometries, unique medication combinations, and bespoke capsules with specific release profiles.[15]

3.4. Enteric Capsules

Oral dose forms called enteric capsules are made to release medication in the small intestine as opposed to the stomach. This is accomplished by covering the capsule shell with a unique enteric coating that dissolves in the greater alkaline pH of the intestine (usually above pH 5.5) but resists the stomach's acidic environment.

a) Based on Shell Material

- **Gelatin Enteric Capsules:** Enteric coating has historically been used for both soft and hard gelatin capsules. However, because gelatin is soluble in water and can cross-link, covering it can be difficult.[16]

- **Non-Gelatin (Vegetarian) Enteric Capsules:** Because of their durability and compatibility with enteric coatings, HPMC (hydroxypropyl methylcellulose) capsules are being utilized more and more for enteric formulations. There are also specialized HPMC pills with built-in enteric qualities.[17]

b) According to the Coating Material

Enteric coatings are made of a variety of polymers, each of which dissolves within a particular pH range.

- **Cellulose Acetate Phthalate (CAP):** Dissolves at pH 6.0 and above. Depending on the grade, hydroxypropyl methylcellulose phthalate (HPMCP) dissolves at pH 5.0 to 5.5 and higher.[18]
- **PVAP (polyvinyl acetate phthalate):** Dissolves at pH 5.0 and above.
- **Eudragit L and S are copolymers of methacrylic acid.** Their grades dissolve at different pH values (e.g., Eudragit L dissolves above pH 6.0, Eudragit S dissolves above pH 7.0).

c) Enteric Capsules' Use and Benefits

- **Safeguarding Acid-Labile Drugs:** Certain medications are unstable and break down in the stomach's acidic environment. These medications are shielded by an enteric coating until they enter the small intestine and are absorbed.[19]
- **Preventing Gastric Irritation:** Some medications can irritate the stomach lining, which can result in ulcers, nausea, and vomiting. By delaying drug release, enteric coating reduces stomach contact.[20]
- **Targeting Drug Release:** Enteric coating guarantees a high concentration of the medication at the site of action for medications meant to act locally in the intestine (such as some antibiotics and anti-inflammatory medications for inflammatory bowel disease).[21]

d) Disadvantages of Enteric Capsules

- **Enhanced production Complexity and Cost:** Adding an enteric coating to the production process adds a step that can make it more complicated and expensive.[22]
- **Potential for Delayed beginning of Action:** In contrast to immediate-release formulations, the beginning of action may be delayed since the drug is not released until it reaches the intestine.[23]

- **Impact of Gastric Emptying:** The release and absorption of the medication may be impacted by variables such as meal consumption, which may alter the amount of time it takes for the capsule to enter the small intestine.[24]

4. MANUFACTURING PROCEDURE FOR CAPSULE

An inventive method that offers insights into formulation considerations and manufacturing techniques for producing enteric capsules directly from enteric polymers is the direct manufacturing of enteric capsules. This approach has the potential to be more economical and efficient than the conventional enteric-coated capsules.

The conventional two-step procedure of filling and coating standard capsules is circumvented by this method. By using a pH-sensitive polymer to build the capsule shell, the enteric properties are directly incorporated into the capsule structure.

4.1 Process

1. Enteric Polymer Formulation: An appropriate solvent or aqueous system is used to dissolve or disperse the selected enteric polymer (such as HPMCAS, HPMCP, Eudragit L/S types, or innovative polysaccharide blends). To provide the capsule shell the appropriate mechanical characteristics and dissolution profile, plasticizers and other required excipients may be included.

2. Capsule Formation (Dipping or other techniques)

- **Pin Dipping:** Similar to the manufacturing of standard gelatin or HPMC capsules, stainless steel mold pins are dipped into the enteric polymer solution. A film of the polymer adheres to the pins.
- **Other techniques:** Research explores alternative methods like hot-melt extrusion to form enteric capsule shells directly.

3. Drying: To eliminate the solvent and create a solid, pH-sensitive capsule shell, the coated pins are dried under carefully regulated temperature and humidity levels.

4. Stripping and Trimming: The bodies and caps of the produced capsule shells are taken out of the pins and cut to the proper size.

5. Filling: The medication formulation is put into the capsule bodies.

6. Joining: To seal the capsules, the caps are put on top of the filled bodies.

7. Quality Control: To make sure the final enteric capsules fulfil the requirements, they are examined for drug release in simulated intestinal fluid and acid resistance (dissolution in simulated gastric fluid).

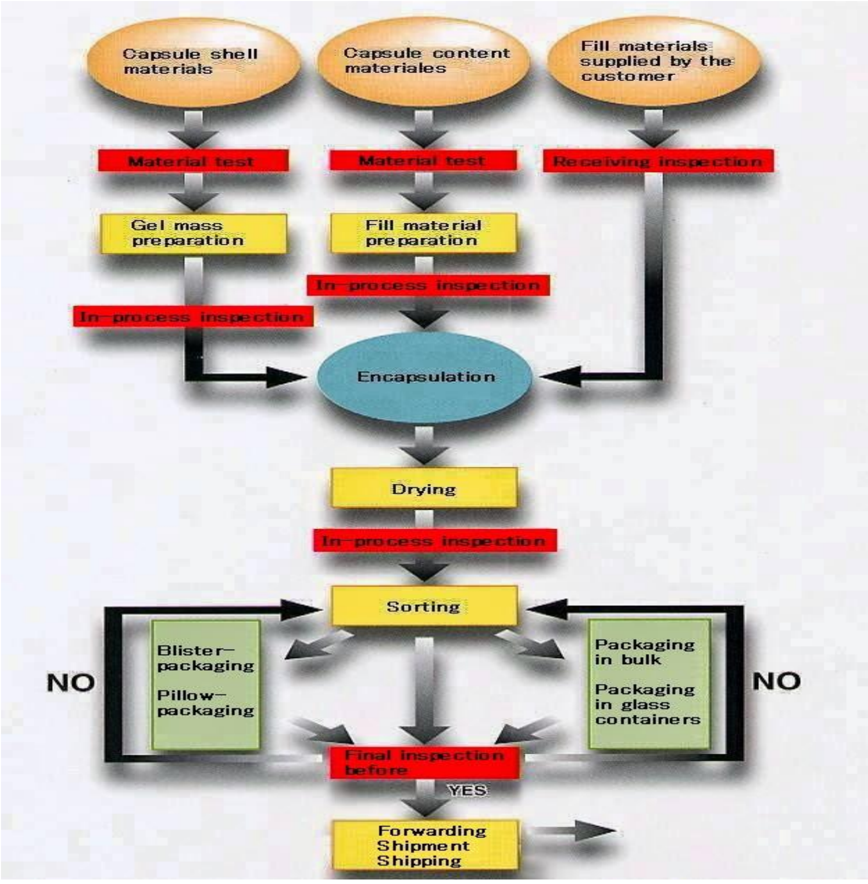

Fig.6: Steps for Manufacturing of Capsule.

4.2. Direct manufacture has the following benefits

- **Simplified Process:** It requires fewer steps in the manufacturing process than coating pre-formed capsules.
- **Possible Cost Savings:** Removes the need for additional coating supplies and machinery.
- **More Uniform Enteric Properties:** Because the enteric polymer is a crucial component of the capsule shell, it may result in more reliable medication release and acid resistance.
- **Adequate for Drugs Sensitive to Moisture:** Since they can be processed without the use of aqueous solvents, certain direct production processes, such as hot-melt extrusion, might be appropriate for moisture-sensitive APIs.
- **Increased Stability:** In certain situations, adding the enteric polymer straight into the shell may provide the medication with superior storage protection.

4.3. Challenges

- **Polymer Formulation and Selection:** It can be difficult to identify enteric polymers with appropriate film-forming qualities for the production of capsules. The formulation must strike a compromise between the capacity to build a strong and useful capsule shell and acid resistance.
- **Process Optimization:** A number of factors, including dipping conditions, drying periods, and polymer concentrations, may need to be significantly optimized in order to develop and scale up the direct manufacturing process.
- **Mechanical Strength:** To endure handling and filling procedures, the resultant capsule shells must have sufficient mechanical strength.
- **Drug Compatibility:** It's critical to make sure the encapsulated medication and the enteric polymer shell are compatible.[25], [26], [27]

5. CONNECTION BETWEEN ENTERIC CAPSULE AND MINI TABLET

Enteric capsules and mini-tablets are related because they work together as a sophisticated oral drug delivery system that shields medications from the stomach's harsh acidic environment and releases them in the small intestine.

5.1. The Function of Enteric Capsules and the Need for Enteric Protection

- Some medications lose their effectiveness in the stomach's low pH because they are acid-labile.
- Enteric coatings are pH-sensitive barriers used on oral dosage forms; others may irritate the gastrointestinal mucosa. The medicine is released at the designated site of absorption when these coatings disintegrate quickly in the small intestine's higher pH (usually >5.5) but remain intact in the stomach's acidic environment (usually pH 1.5–3.5).
- Historically, enteric coatings were applied to single large tablets or capsules. However, this approach can have limitations in terms of drug release uniformity and potential for localized high drug concentrations.[28]

5.2. Mini-Tablets as a System for Delivering Drugs in Multiple Particles

- Mini-tablets are small, usually round, < 3 mm diameter tablets that can be coated or uncoated.
- Compared to single-unit dosage forms, a multi-particulate system, which consists of numerous mini-tablets, has the following advantages.

- **Better medication release and absorption**: They spread out over a greater surface area in the gastrointestinal system, which increases the surface area available for drug breakdown and may result in more reliable and consistent absorption.
- **Lower risk of local irritation**: The smaller units minimize the possibility of gastrointestinal mucosal irritation by preventing high local medication concentrations.
- **More consistent gastric emptying:** Unlike bigger single units, their passage through the stomach is less reliant on the effects of food, resulting in more consistent medication administration.
- **Formulation flexibility**: To achieve complicated release profiles (such as immediate and sustained release), different populations of mini-tablets with different release characteristics can be blended in a single dose form.[29], [30]

5.3. The Connection: Enteric-Coated Mini-Tablets in a Capsule

- Connection is in combining the benefits of enteric protection with the advantages of a multi-particulate system by applying an enteric coating to individual mini-tablets and then encapsulating a defined number of these enteric-coated mini-tablets within a hard gelatin capsule.
- This method provides an advanced oral dose form with the following benefits:
- **Improved medication protection:** The enteric coating offers a strong barrier against the stomach's acidic environment, protecting each mini-tablet separately.
- **Targeted drug release:** Maximizes medication availability at the absorption location by releasing the drug in the small intestine when the enteric coating dissolves at the higher pH.
- **Reduced variability and increased bioavailability**: In the small intestine, the multi-particulate form guarantees a broader distribution and may be more reliable absorption.
- **Lessened local side effects:** The chance of gastrointestinal discomfort is decreased by stopping drug release in the stomach.
- **Accurate dose modification:** By changing the quantity of enteric-coated mini-tablets placed inside the capsule, the dosage can be readily changed.
- **Potential for complicated release profiles:** To create customized medication release patterns, various coated or uncoated mini-tablet forms can be mixed inside a single capsule.

As the last container for the enteric-coated mini-tablets, the enteric capsule essentially serves as a precise and easy method of administering a multi-particulate system that is shielded from the stomach and releases the medication in the small intestine for the best possible therapeutic outcome. When paired with enteric coating and encapsulation, the mini-tablet shape maximizes the benefits of both strategies for better drug delivery.[31], [32], [33]

6. Mini-Tablets

A solid dosage form, mini-tablets usually have a diameter of ≤ 3 mm, while other definitions go as far as 4-5 mm. They are a kind of multi-particulate drug delivery system (MUDS) in which a drug's entire dosage is broken up into a large number of tiny, distinct components. These can be given straight, compacted into larger tablets (as a matrix), or filled into capsules.

Fig. 7: Mini Tablets.

6.1. Important Features of Mini-Tablets

- **Small Size:** The distinguishing feature, which makes swallowing simpler, particularly for elderly and young patients.
- **Multi-Unit System:** This type of dosage form has advantages over single-unit forms since it is divided into multiple subunits.
- **Compression Manufacturing:** Like regular tablets, they are mostly made by compressing powder mixtures on tablet presses with specialized multi-tip punches.
- **Can Be Coated or Uncoated:** To alter medication release, mini-tablets can be coated with functional polymers (such as enteric or sustained-release) or given uncoated for instant release.

- **Uniform size and shape**: Consistent drug release and coating ease depend on uniform size and shape.
- **Good Mechanical Strength:** Strong mechanical properties are essential for withstanding handling and additional processing, such as coating or encapsulating.
- **Precise Dosing:** Allows for accurate dose modifications by adjusting the number of mini-tablets.

6.2. Mini-tablets have the following benefits

- **Increased Bioavailability:** More uniform and predictable medication absorption may result from a wider distribution in the gastrointestinal system.
- **Decreased Risk of Local Discomfort:** By avoiding high local medication concentrations, smaller units reduce the possibility of discomfort.
- **More Uniform Gastric Emptying:** Unlike bigger single-unit dosage forms, this is less impacted by food intake.
- **Formulation Flexibility:** Combining several kinds of mini-tablets into a single dose form allows for the creation of distinct release profiles.
- **Easier Swallowing (Dysphagia):** Much simpler to swallow than traditional big pills, this enhances patient compliance, particularly in older adults and children.
- **Accurate Dosing for Special Populations:** This feature makes it possible to precisely modify dosages according to age or weight, which is essential for paediatric patients.
- **Lower Risk of Dose Dumping:** If the coating on a small number of mini-tablets fails, just a portion of the entire dose will be released, as opposed to single modified-release units.
- **Economical Production:** Usually easier and less expensive to make than other MUDS, such as pellets (which require extrusion and spheronization).
- **Improved Stability:** In comparison to liquid formulations, it may provide improved physical, chemical, and microbiological stability.

6.3. Procedures for Producing Mini-Tablets

Direct compression is the main technique used to make mini-tablets; it works similarly to traditional tablets but makes use of multi-tip punches. Other methods include.

- **Wet Granulation:** Before compression, a powder mixture is granulated using a liquid binder.

- **Dry granulation:** Also known as slugging or roller compaction, involves compressing powder into big masses that are subsequently broken down and crushed again into tiny tablets.
- **Melt extrusion:** It involves melting and extruding the drug and excipients, after which they are chopped into tiny pieces.
- **3D printing:** A cutting-edge technique for creating intricate mini-tablet compositions with customized release characteristics.[34], [35], [36], [37], [38], [39], [40], [41], [42], [43]

7. NSAIDS MINI-TABLETS THAT CAN BE ADDED TO ENTERIC CAPSULES

The broad principles of enteric coating for NSAIDs and the benefits of mini-tablets as a multi-particulate system give a platform for understanding suitable candidates, even though particular research directly comparing the suitability of various NSAID mini-tablets for enteric capsules may be limited.

7.1. Common NSAIDs with an enteric coating (which makes them potentially appropriate as mini-tablets in enteric capsules)

1. Aspirin: A well-known product designed to lessen stomach irritation is enteric-coated aspirin. By dividing the dosage into smaller portions, creating mini-tablets inside a capsule could increase this advantage even more.[44]

2. Naproxen: Enteric-coated naproxen is provided to decrease stomach distress. Mini-tablet formulation in a capsule could offer similar advantages to aspirin.[45]

3. Diclofenac: To lessen gastrointestinal side effects, enteric-coated diclofenac is used. This approach would be compatible with enteric capsules containing diclofenac mini-tablets.[46]

4. Ibuprofen: Enteric-coated ibuprofen formulations exist to assist in reducing stomach irritation. For this NSAID in an enteric capsule, mini-tablets might be a good alternative.[47]

5. Ketoprofen: The availability of enteric-coated ketoprofen indicates that it is appropriate for this kind of formulation.

7.2. Benefits of Including NSAID Mini-Tablets in Enteric Capsule Formulations

- **Improved Gastric Protection:** Unlike a single large enteric-coated tablet, each mini-tablet is separately coated, offering a stronger barrier against stomach acid.
- **Increased Bioavailability:** Once the coating dissolves, the multi-particulate nature of mini-tablets may result in a greater dispersion and possibly higher absorption in the small intestine.

- **Less Local Irritation:** Even if there are some coating flaws, dividing the dosage into several smaller units can help reduce high local NSAID concentrations in the stomach.
- **Accurate Dosing:** By changing the quantity of enteric-coated mini-tablets in the capsule, the dosage can be changed.
- **Flexibility in Release:** It may be possible to combine many populations of mini-tablets with various release properties (such as varied coating thicknesses or polymers) in a single capsule for customized

7.3. 8 Important factors to take into account include

- **Mini-Tablet Formulation:** The selected NSAID needs to be able to be made into sturdy mini-tablets that can resist the coating process.
- **Enteric Coating Process:** Optimal coating methods and parameters are needed to apply a consistent and efficient enteric coating to a large number of tiny mini-tablets. For this, common enteric polymers such as methacrylic acid copolymers (Eudragit), cellulose acetate phthalate (CAP), and hydroxypropyl methylcellulose phthalate (HPMCP) are utilized.

Several NSAIDs commonly found in enteric-coated tablets are suitable candidates for incorporation into enteric capsules as mini-tablets. This approach combines the benefits of gastric protection with the advantages of a multi-particulate dosage form for potentially improved therapeutic outcomes and reduced side effects. However, formulation and coating processes need careful optimization to ensure product quality and performance.[48]

8. What makes NSAIDs small enough to fit into enteric capsules?

NSAIDs are designed as mini-tablets to be taken in enteric capsules for several important reasons, chief among them being to increase patient compliance, safety, and effectiveness. The following is a summary with citations.

1. Enhanced Gastric Protection

- NSAIDs are known to decrease the production of prostaglandins in the stomach lining, which can result in gastrointestinal (GI) adverse effects such as bleeding, ulcers, and discomfort.
- Enteric coating is used to stop the NSAID from releasing in the stomach's acidic environment. The medicine is released distally when the coating dissolves in the small intestine's higher pH, but stays intact in the stomach's low pH.

- A multi-particulate system is provided by NSAIDs formulated as mini-tablets inside an enteric capsule. This may lessen excessive local concentrations of the medication that can still irritate the small intestine by distributing it more evenly after release.[49]

2. Better Bioavailability and Absorption

- A multi-particulate system can also offer more predictable gastric emptying and transit through the intestines compared to a single large enteric-coated tablet, potentially leading to more consistent drug absorption.
- Mini-tablets' small size increases the surface area for drug dissolution and absorption in the small intestine once the enteric coating dissolves.[50]

3. Improved Patient Compliance

- Compared to traditional large tablets, mini-tablets are simpler to swallow, which can be especially helpful for patients with dysphagia (difficulty swallowing), including youngsters and the elderly. Administration is made easier by encapsulating them.[51]

4. Flexibility in Formulation and Dosing

- By adjusting the number of mini-tablets in a capsule, the formulation of NSAIDs as mini-tablets enables precise dose adjustments; • For customized drug delivery, different types of mini-tablets with different release profiles (such as enteric-coated and immediate-release) may be combined in a single capsule.[52]

5. Lower Risk of Dose Dumping

- The full dosage of the NSAID may be discharged in the stomach if the enteric coating of a single big tablet fails. The risk of localized high concentrations and subsequent discomfort may be decreased with several enteric-coated mini-tablets since the failure of a few units would only release a portion of the entire dose.[53]

8.1. Why is diclofenac sodium better than other medications for treating?

It is incorrect and oversimplified to say that diclofenac sodium is "more beneficial" than all other medications for every condition, even though it is a commonly used and efficient NSAID. The particular condition being treated, the patient's unique characteristics, and the risk-benefit ratio of alternative options all play a significant role in determining whether a drug is appropriate.

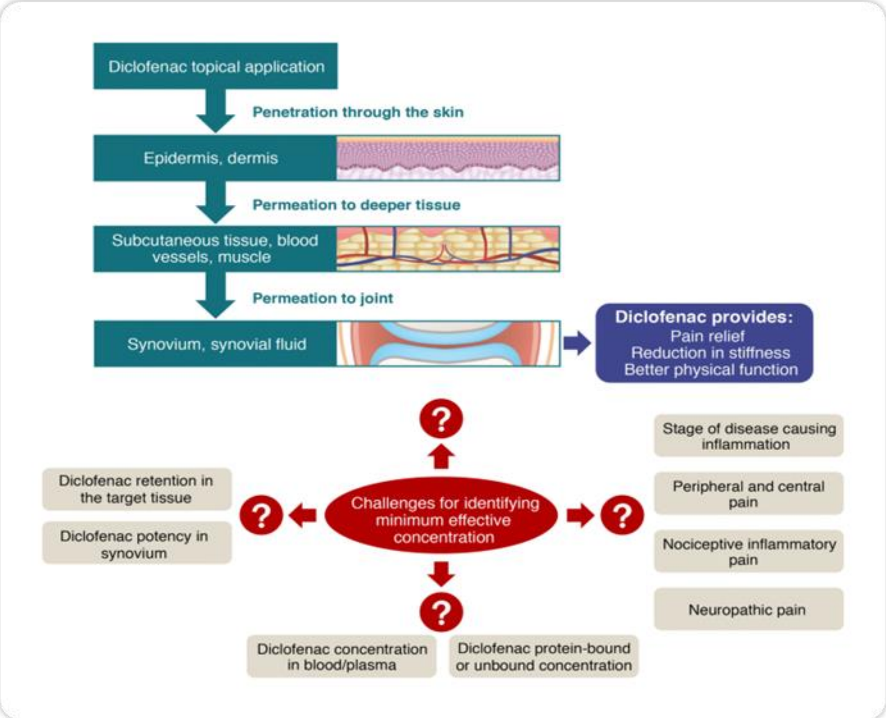

Fig. 8: Flow of diclofenac from topical application to the joint capsule showing known steps (green arrows) and potential influencers of minimum effective concentration (red question marks).

8.2. Possible Advantages of Sodium Diclofenac

1. Effectiveness in Pain and Inflammation: Diclofenac is a strong nonsteroidal anti-inflammatory drug (NSAID) that is well-known for its ability to effectively reduce pain, swelling, and inflammation brought on by a variety of illnesses. For some types of pain, especially arthritis, studies have found it to be on par with or even more effective than some other NSAIDs.

2. Potency: According to some data, diclofenac may be more effective than some other NSAIDs, such as ibuprofen, which means a lower dosage may be required to produce the same level of pain relief.[54]

3. Diverse Formulations: Diclofenac comes in several forms, including injectable forms, topical gels, patches, oral tablets with immediate and delayed release, and even ophthalmic solutions. This enables customized care according to the kind and location of inflammation or pain. For example, topical formulations may have fewer systemic adverse effects while offering localized relief.[55], [56]

4. Particular Indications: The FDA has approved the oral solution of diclofenac for the treatment of acute migraine attacks and ankylosing spondylitis.[57]

8.3. Crucial Factors and the Reasons It's Not Always "Better"

- **Cardiovascular Risk:** Compared to some other conventional NSAIDs, diclofenac has been linked to an increased risk of cardiovascular events (heart attack, stroke), especially when taken in people who already have heart problems and at larger dosages.[58], [59]
- **Risk to the Stomach:** Diclofenac, like all non-selective NSAIDs, raises the possibility of stomach ulcers, bleeding, and perforation. Enteric-coated formulations are designed to lessen this danger, but it is not completely removed.[60]

9. THE NSAID CLASSIFICATION SYSTEM

NSAIDs (non-steroidal anti-inflammatory drugs) can be categorized mainly according to two standard criteria.

9.91. According to Chemical Structure, NSAIDs are a broad class of substances with various chemical constructions. Their pharmacological characteristics and possible adverse effects can be better understood thanks to this classification, even though their modes of action may overlap. The main categories of chemicals are as follows.

- **Salicylates:** Examples: Diflunisal, aspirin (acetylsalicylic acid) and salsalate.[61]
- **Derivatives of Propionic Acid (Profens):** Examples: Ketoprofen, Naproxen, and Ibuprofen.[62]
- **Derivatives of Acetic Acid**: Examples: Diclofenac, Indomethacin, and Ketorolac.[63]
- **Derivatives of Enolic Acid (Oxicam):** Examples: Meloxicam, Tenoxicam, and Piroxicam.[64]
- **Derivatives of Anthranilic Acid (Fenamates):** Examples: Mefenamic acid, Meclofenamate are two examples.[65]
- **Selective COX-2 Inhibitors (Coxibs):** Examples: Celecoxib, Etoricoxib (not available in the US), and Rofecoxib (withdrawn from the market in several places).[66]
- **Sulfonanilide:** Examples: Nimesulide (its use is prohibited in certain countries because of its hepatotoxicity).[67]

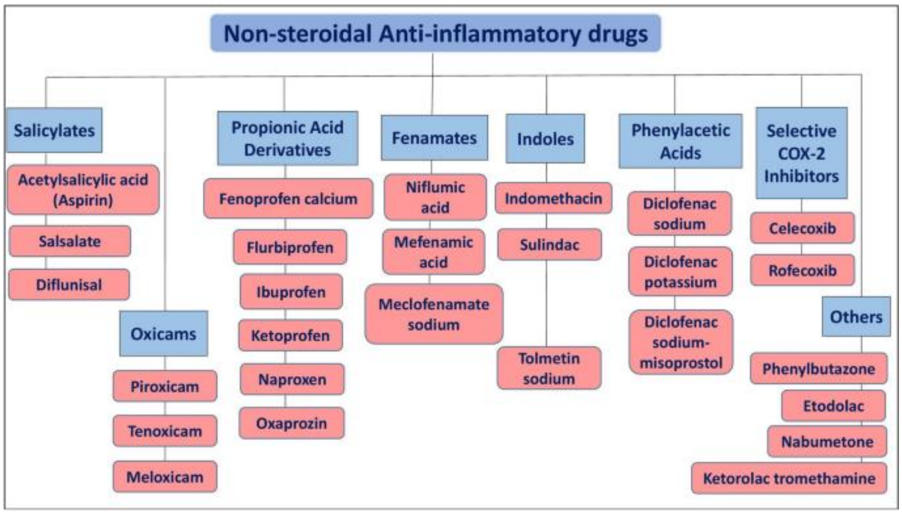

Fig. 9: Classification of NSAID.

9.2. Based on Cyclooxygenase (COX) Selectivity

The fundamental mechanism of action of NSAIDs includes the inhibition of cyclooxygenase (COX) enzymes, which are responsible for the manufacture of prostaglandins, essential mediators of pain, inflammation, and fever. The two primary COX isoforms that NSAIDs are selective for determine their classification.

- **Conventional NSAIDs, or non-specific COX inhibitors:** To differing degrees, these inhibit the COX-1 and COX-2 enzymes. While COX-2 inhibition promotes the analgesic and anti-inflammatory benefits, COX-1 inhibition is linked to gastrointestinal adverse effects. Aspirin (at lower doses, more COX-1 selective), Ibuprofen, Naproxen, Diclofenac, Indomethacin, Ketoprofen, and Piroxicam are a few examples.[68], [69]
- **Preferential COX-2 Inhibitors:** These medications aim to lessen gastrointestinal adverse effects while preserving their anti-inflammatory and analgesic properties. They exhibit some selectivity for COX-2 over COX-1. Some still block COX-1 at greater dosages, though. Etodolac, Nimesulide, and Meloxicam are a few examples (selectivity varies and can be dose-dependent).[70]
- **Selective COX-2 Inhibitors (Coxibs):** Unlike non-selective NSAIDs, these medications are developed to selectively inhibit COX-2 to reduce inflammation and pain while lowering the risk of gastrointestinal ulcers. Nonetheless, in certain people, they have been linked to an elevated risk of cardiovascular events. Celecoxib and Etoricoxib are two examples.[71]

CONCLUSION

The development of diclofenac sodium mini-enteric capsules has shown promising results in terms of enteric coating protection, rapid dissolution in the intestinal environment, and potential for improved patient compliance. While further in vivo studies and long-term stability assessments are necessary to confirm these findings, the mini-enteric capsule formulation presents a viable strategy for optimizing diclofenac sodium therapy, potentially reducing gastric side effects and enhancing bioavailability. This research paves the way for future investigations into the clinical applications of mini-enteric capsules for improved drug delivery.

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