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Original Article

Microspheres as A Multiparticulate Drug Delivery Systems: A Comprehensive Review

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ABSTRACT

Pediatric treatment of brain-related diseases often requires oral medications, where palatability is crucial for patient adherence and therapeutic success. The unpleasant taste of many drugs, especially those used in neurological or psychiatric conditions, can reduce compliance in children. This review explores various taste-masking strategies, with a particular focus on the use of polymeric coatings for orally disintegrating tablets (ODTs) in the treatment of pediatric disease. The introduction of ODTs has revolutionized pediatric pharmacotherapy by improving drug administration convenience and masking the taste of bitter drugs. This review highlights the importance of taste masking for improved patient compliance, particularly for the drugs with bitter or unpleasant taste , and covers diverse approaches including conventional and novel methods such as microencapsulation, spray drying, and nanotechnology. Emphasis is placed on polymeric coatings, which have demonstrated significant potential in taste masking by forming protective barriers that prevent contact between the drug and taste receptors. Furthermore, the article discusses the types of excipients used in formulation, methods of tablet manufacturing, and evaluation techniques for taste masking. Additionally, challenges such as formulation stability, the risk of altered drug release, and the need for regulatory approvals are addressed. Finally, future directions, including advancements in nanotechnology and patient-centric formulation strategies, are proposed to enhance patient adherence and optimize therapeutic outcomes in pediatric management.

Keywords: Pediatric pharmacotherapy, Taste Masking, Polymeric Coatings, Orally Disintegrating Tablets (ODTs), patient compliance, Brain-related diseases

INTRODUCTION

Importance Of Taste In Pediatric Pharmacotherapy

These are important issues to consider when exploring the effects of taste perception and, in particular, determining at what age children can accurately perceive flavors. This takes into account two different aspects, that having to do with its sensory development or response and also the cognitive maturation which will a child's taste recognition is difficult for identify an age premiere so better appreciate of flavor.[1] The EMEA points out the necessity of age-adapted paediatric formulations to ensure that medicines for use in children are high quality, safe and effective. Correct compliance and concordance are affected by taste of course, as part of all other factors for adherence; this is particularly relevant in children. Formulating tasteful or taste-neutral dosages is crucial in the long game of medication acceptance, particularly for paediatric patients even slight unacceptable flavors may cause rejection eventually leading to better health results and satisfied patients. [2] New born particularly like the sweet flavor of mother, because it is understood to have even analgesic effects. The bitter taste of drug ensures that children turn away from potential toxins or poisons, a protective mechanism we are born with and only gradually learn to override. Moreover, this natural aversion to bitterness helps keep us safe in our early development.[3]

Challenge In Pediatric Medication

Children and adolescents face specific challenges such as family conflict, puberty-associated physiological changes that may be physically and emotionally disruptive, a paucity of psychotropic medications available in child-friendly formulations. The condition's chronic nature and other health determinants also challenge the management of healthcare, resulting in negative impacts upon overall treatment outcomes that necessitate approaches

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designed to overcome barriers for sustaining their well-being as well as adherence. [4] Absence of age adapted pediatric formulations often results in the manipulation of medication not only contributing considerably to concerns about stability and dosing but also incorrect administration due to difficult or inaccurate quantification. This raises the danger of inefficacious treatment or even side effects, thus emphasizing the urgent necessity for more appropriate pharmaceutical formulations targeting children. [5] In pediatric drug studies, "children" are defined as individuals under eighteen (EU) or seventeen (FDA). These studies are essential for drug approval, and their medical justifications are carefully evaluated to ensure that the research is appropriate, ethical, and safe for the pediatric population.[6]

Preterm newborn infants have immature ADME, or absorption, distribution, metabolism, and excretion processes of drugs making them more susceptible to drug related risks. Preterm and term newborns, unlike older children whose medical warning is harmful but unlikely to be deadly, need extra attention. However it seems abundantly clear that age should not to be defined by arbitrary legal criteria or timed with drug administration category cut-offs, but rather some approximation of physiological maturity. This approach to drug therapy allows treatments in this vulnerable population to be safe and more efficacious by tailoring them to the specific developmental trajectories of each child. [6] To ensure that every child receives the appropriate medication, different dose forms, methods of administration, and strengths may be necessary. Many existing formulations are unsuitable for pediatric use, leading to the off-label use of adult medications, often without proper licensing. This practice raises concerns about dosage accuracy, safety, and effectiveness, highlighting the need for pediatric-specific formulations that are tailored to children's unique physiological needs to ensure optimal treatment outcomes.[7] The pediatric population poses unique challenges for pharmaceutical development and clinical research. Pediatric clinical trials involve complex ethical considerations, requiring careful attention to child safety. Ensuring the well-being of young participants is paramount, and any research must prioritize their safety and minimize risks while advancing therapeutic options.[8]

Challenges:

(1) Drug development and trials for children;
(2) Performing comparative effectiveness studies in pediatric populations;
(3) Including parents and children in study teams;
(4) Enhancing parent-child communication; and
(5) Evaluating adverse drug events and child-reported outcomes.[9]

Role Of Taste In Medical Adherence

Many oral drugs have a bitter taste, which humans naturally find unpleasant. To reduce the intensity of bitterness, masking agents like sucralose can be used, or inhibitors can be employed to minimize the perception of bitterness. Another effective strategy is encapsulating bitter-tasting chemicals to delay their release in the mouth, preventing the immediate detection of the unpleasant taste. This encapsulation method can provide a temporary barrier, allowing the drug to pass through the mouth before releasing its bitter components. In some cases, bitter masking agents may be released earlier, improving the overall taste experience and patient compliance.[10]

ODTs (Orally disintegrating tablets)

The oral route is the preferred method for medication delivery, as it is considered the most convenient, cost-effective, and safe option. It offers the highest levels of patient compliance due to ease of administration, making it the industry standard for delivering medications across various therapeutic areas. [13]

Waterless swallowing is made possible by oral disintegrating tablets (ODTs), which are solid dose forms that dissolve in the mouth in less than 60 seconds. Compared to conventional tablets, this quick dissolve enables a speedier beginning of action since the drug is absorbed more quickly. ODTs are particularly beneficial for patients who have difficulty swallowing pills, including children and the elderly. The fast disintegration in the mouth also enhances patient compliance, offering a convenient, efficient alternative to conventional oral formulations while ensuring faster therapeutic effects.[11] The demand for orally disintegrating tablets (ODTs) has been steadily increasing, driving rapid growth in the pharmaceutical sector. ODTs offer convenience, faster onset of action, and improved patient compliance, especially for those who have difficulty swallowing pills, leading to their growing popularity and development in various therapeutic areas.[12]

Table 1: ODT Formulation By Using Polymeric Coating For Pediatric Use For Different Brain Related Disease

Sr no	Title	Materials /Ingredients	Method	Disease	Ref no
1	Orally Disintegrating Tablet of Lamotrigine	(a) Sodium starch glycolate & crospovidone as super disintegrants (b) Mannitol as excipient (sweetener) (c)PEG 6000 as polymer (d)Colloidal silicon dioxide as glidant (e)Magnesium stearate as lubricant	Direct compression method	Epilepsy	[89]
2	Orally Disintegrating Tablet of Carbamazepine	(a)Talc and Magnesium stearate as lubricant (b)Colloidal silicon dioxide as glidant (c)Perlitol flash as excipient (d)Crospovidone type A & type B as super disintegrants (e) L-HPC LH 11 low substituted hydroxy propyl cellulose as polymer	Direct compression method	Epilepsy	[90]
3	Orally Disintegrating Tablet of Clonazepam	(a)SLS (sodium lauryl sulphate as surfactant (b)Aspartame as sweetener (c)Crospovidone as super disintegrants (d)Talc and Magnesium stearate as lubricant (e)Colloidal silicon dioxide as glidant (f)Maize starch and MCC (Microcrystalline cellulose) as diluents (g)Perlitol flash as excipient	Wet granulation method	Epilepsy	[91]
4	Mouth Dissolving Tablet of Oxcarbazepine	(a) PVPK 30 as polymer (b)Crospovidone as super disintegrants (c)Talc & Magnesium stearate as lubricant (d)Microcrystalline cellulose as diluent (e)Aspartame as sweetener (f)Mannitol as excipient	Direct compression method	Epilepsy	[92]
5	Orally Disintegrating Tablet of Diazepam	(a)Sodium starch glycolate/ Crospovidone/ Croscarmellose as super disintegrants (b)Magnesium stearate as lubricant (c)Lactose M80 as excipient	Direct compression method using Design of experiments approach (DoE)	Epilepsy	[93]
6	Mouth Dissolving Tablet of Acetazolamide	(a) Chitosan as polymer (b)Microcrystalline cellulose as diluent (c)Talc & Magnesium stearate as lubricant (d)Mannitol as excipient (e)Sodium starch glycolate as super disintegrants	Direct compression method	Epilepsy	[94]
7	Orally Disintegrating Combination Tablet of Carbamazepine & Levetiracetam	(a)SLS (sodium lauryl sulphate as surfactant (b)Aspartame as sweetener (c)Crospovidone as super disintegrants (d)Talc and Magnesium stearate as lubricant (e)Colloidal silicon dioxide as glidant (f)Maize starch and MCC (Microcrystalline cellulose) as diluents	Direct compression method & Lyophilization	Epilepsy	[95]
8	Orodispersible Tablet of Phenobarbital	(a) Sodium starch glycolate/ crospovidone as super disintegrants (b) Microcrystalline cellulose as diluent (c) Talc & Magnesium stearate as lubricant	Direct compression method	Epilepsy	[96]

		(d)Aspartame as sweetener (e)Mannitol as excipient			
9	Orodispersible Tablet of Pregablin	(a) Sodium starch glycolate as super disintegrants (b) Microcrystalline cellulose as diluent (c) Talc & Magnesium stearate as lubricant (d)Mannitol as excipient (e)Aspartame as sweetener	Direct compression method	Epilepsy	[97]
10	Orodispersible Tablet of Gabapentin	(a) Sodium starch glycolate/ croscarmellose as super disintegrants (b) Microcrystalline cellulose as diluent (c) Talc & Magnesium stearate as lubricant (d)Mannitol as excipient (e)Sodium saccharin as sweetener	Direct compression method	Epilepsy	[98]
11	Orally disintegrating tablet of levodopa – carbidopa	(a) Mannitol EZ spray as excipient (b)Sorbitol as stabilizing agent (c)Sodium starch glycolate as super disintegrants (d)Avicel PH 102 as binder (e)Crospovidone XL-10 as super disintegrants (f)Sodium stearyl fumarate as lubricant (g)Sodium bicarbonate use to treat heart burn	Direct compression method	Parkinson's disease	[81]
12	Orally disintegrating tablet of pramipexole	(a)Microcrystalline cellulose as diluent (b)Sodium starch glycolate as super disintegrants (c)Colloidal silicon dioxide as glidants (d)Mannitol as excipient (e)Croscarmellose as super disintegrants	Direct compression method	Parkinson's disease	[82]
13	Orodispersible tablets of ropinirole	(a)Eudragit RS100 as polymer (b)HPMC K15M polymer (c)Dichloromethane and acetone as chemicals	Spray drying	Parkinson's disease	[83]
14	Oro-Dispersible Tablets of Entacapone	(a)PEG 4000 as hydrophilic polymer (b)crospovidone as super disintegrant	Inclusion complexation	Parkinson's disease	[84]
15	Fast dissolving tablet of zolpidem	(a)Crospovidone as super disintegrant (b)Croscarmellose as super disintegrants (c)Microcrystalline cellulose as diluent (d)Sodium starch glycolate as super disintegrants (e)Aspartame as sweetener	Direct compression method	Insomnia	[85]
16	Orally disintegrating tablet of Donepezil	(a)Crospovidone XL-10 was used as super disintegrant (b)colloidal silicon dioxide as glidants	wet-granulation method	Alzheimer's disease	[86]
17	Orally disintegrating tablet of Memantine	(a)Methylcellulose as disintegrant or binder (b)D-mannitol as sweetener	layering technique	Alzheimer's disease	[87]

Taste Masking Technologie

Many active pharmaceutical ingredients (APIs) naturally have an unpleasant taste, which can impact patient acceptance, especially among younger patients. As a result, there has been significant interest in developing taste-masked dosage forms. These formulations aim to improve palatability and enhance patient compliance, making medications more acceptable, particularly for pediatric and elderly populations who are more sensitive to bitter or

unpleasant flavors.[14] Taste masking is a primary driver in the formulation of new dosage forms, offering opportunities for innovation and new patents. By improving palatability, especially for pediatric or sensitive patients, it enhances patient compliance and opens avenues for novel pharmaceutical inventions.[15] Various conventional techniques, such as taste masking, coating, and formulation adjustments, can reduce the bitterness of medications, enhancing the palatability of oral drugs and improving patient compliance.[16]

(A)Microencapsulation:

A process introduced by Bakan in 1986, involves encasing small particles or liquid droplets in a thin polymer layer to mask the taste of medications, particularly bitter drugs. In the pharmaceutical industry, this approach is frequently employed to increase patient compliance, particularly for older and pediatric populations. For effective taste masking, the polymer coating must be impermeable to aqueous solvents to prevent drug leaching. If the coating is permeable, the drug can seep out, compromising ultimately decreasing patient acceptance due to the coating's integrity and the taste-masking technique's efficacy [17] Drug particles are coated with various inert agents to mask taste and improve stability. Gelatin, methylcellulose, ethyl cellulose, starch, and povidone, hydroxypropyl methylcellulose, beeswax, carnauba wax, acrylics, and shellac are examples of common coating agents. These materials help enhance patient compliance and protect the active ingredients from degradation. [18] The process of spray drying falls under microencapsulation. It is also one of the most widely used coating methods, using heated air to turn the atomized liquid droplets into dry particles. A pharmacological solution is atomized into tiny droplets and then allowed to evaporate in a stream of heated air, creating dry particles, a process known as spray-drying.[19] Two distinct polymers with varying ratios were tested with taste-masked microspheres made by spray drying for bitter medication used to treat nausea and vomiting. When using Ondansetron hydrochloride (OSH), Eudragit microspheres demonstrated taste masking at a 1:2 drug-polymer ratio, while Chitosan microspheres produced a medication-polymer ratio of 1:1 and were more well-liked by patients.[20]

(B)Inclusion Complex Formation:

Enhances drug solubility and absorption while also masking unpleasant tastes. Cyclodextrins, commonly used in inclusion complexes, consist of a ring-like structure that encapsulates drug molecules in their cavity. This formation creates a stable complex, protecting the drug from degradation and improving its bioavailability. Cyclodextrins also play a crucial role in taste masking by enveloping bitter molecules, preventing them from interacting with taste receptors. Alternatively, they may interact with gatekeeper proteins on the palate, lessening the sense of bitterness. This procedure particularly beneficial to improve the palatability of medications, especially in pediatric and elderly populations, and can increase patient compliance by reducing the unpleasant sensory experience of taking medicine.[21] Six to twelve D-glucopyranose monomers joined at one and four carbon atoms form cyclic oligosaccharides known as cyclodextrins (CDs). The components of industrially manufactured CDs are crystalline, homogenous, non-hygroscopic materials composed of glucopyranose units. There are 6 glucopyranose units in the αCD, 7 in the βCD, and 8 in the γCD. In the carbon conformation where the glucopyranose units are all positioned on the wider ring edge while the major hydroxy groups are all positioned on the narrower edge. It turns out that the ring is actually a conical cylinder with an axial chamber that is hydrophobic and a hydrophilic outside. For inclusion type complexes, β Cyclodextrins is the most often employed complexing agent [22]

C)Extrusion/Spheronization Process:

The invention of the marmorize in 1964 marked the introduction of the extrusion/spheronization process to the pharmaceutical business.[23] Extrusion-spheronization is a multistep process used to create pellets or beads with uniform size and optimal medication loading capacity. The process begins with dry mixing, followed by wet granulation, where a binder is added to form a mass. This mass is then extruded through a die to form cylindrical shapes, which are rounded into spherical particles, or pellets, during spheronization. After spheronization, the beads are dried and screened to ensure uniform size. This method is particularly effective for producing spherical particles, which can be further modified to control drug release and improve patient compliance by minimizing taste or enhancing stability. [24] The

creation of more spherical pellets through extrusion spheronization is a benefit over wet granulation.[25]

(D)Ion Exchange Resins (IER):

This are a traditional and well-known method in the development of taste masking. Polymers known as IER possess the capacity to swap particular ions found in the polymer for ions in a solution that flows past them. IER are high molecular weight poly-electrolytes that are both solid and sufficiently insoluble. They can swap mobile ions with the surrounding medium that have the same charge. Drug-resin complexes, sometimes referred to as drug resinates, can be created by loading pharmaceuticals onto the resins via an exchange reaction. [26]

The resins are Inert because they are high molecular weight water insoluble and cannot be absorbed by the body.[27] An extremely Insoluble material in contact with a liquid undergoes a reversible process known as "on exchange," whereby ions of the same sign are moved from the liquid to the solid.[28]

Since 1950, pharmaceutical companies and doctors have employed synthetic ion exchange resins for regulated drug release or flavor masking.[29]

E)Taste Masking By Prodrug Approach:

Prodrugs are pharmacological agents that remaininactive until metabolized within the body, releasingtheir active parent compounds. By altering the parent molecule's structure, prodrugs can modify the intensity of bitter taste responses or influence taste receptor interactions. This structural modification can also enhance membrane permeability, improving drug absorption, and can help mask bitterness, making the medication more palatable. Additionally, prodrugs can increase lipophilicity, allowing better penetration into cells, or adjust aqueous solubility, ensuring appropriate drug release. These modifications improve the bioavailability and patient compliance of medications, particularly for drugs with undesirable tastes or poor solubility.[30] Tasteless or For better buccal administration, bitter-less opioid analgesic and antagonist prodrugs were created. Enhancing bioavailability while minimizing side effects, making them more acceptable for patient use.[31]

(F)Taste Masking Using Liposome's And Multiple Emulsion:

One way to disguise the unpleasant taste of a medicinal ingredient is to ensnare them in liposomes. Liposomes are carrier molecules that include lipids, usually in the form of spherical structures with several lipid layers. The medicine or biological agent is carried within the lipid molecule. The overall effectiveness of flavor masking is improved by oils, surfactants, poly alcohols, and lipids because they efficiently enhance the viscosity in the mouth, which reduces the amount of bitter medication in touch with taste receptors.[32] Liposomes are a type of microscopic vesicle that mostly consist of phospholipids, either naturally occurring or synthesized, and are completely surrounded by an aqueous volume membrane made of lipid molecules. Phospholipids such soy lecithin, phosphatidic acid, and phosphatidylinositol have been shown to selectively suppress the bitter taste of a variety of medications.[32]

Approaches For Miscellaneous Flavor-Mask

A) Effervescent Agents:

Effervescent substances have been shown to be advantageous when taken orally, and they are also employed as flavor-masking agents. Dose form additives that aren't dissolved in water before administration. Chewing gum containing biting medication was created in order to transport the medication to the mouth cavity for buccal absorption or local administration.. It includes an oral drug, a carbon dioxide taste masking generator, a chewing gum base, and possibly a taste bud desensitizing composition (such as oral anesthetics as spilanthol and benzocaine), in addition to other inert substances including flavorings, fillers, and sweeteners. [59]

Recently, fentanyl and prochlorperazine effervescent tablets were developed to administer these drugs to the oral cavity for absorption through the gingiva, buccal, and sublingual regions.. The arrangements include the medication together with one or more effervescent ingredients to help with oral absorption and to cover up the bitter taste. To further enhance absorption, fentanyl formulation also contained an extra pH-adjusting ingredient. [60]

B) Rheological Modifications:

Gums and carbohydrates are examples of rheological modifiers that can increase viscosity and decrease the passage of bitter substances from taste buds to saliva. It is possible for create acetaminophen suspension with microcrystalline cellulose (0.6–1%) and xanthan gum (0.1–0.2%) to lessen the harsh taste.[61]

Using a polyhydric acid, A syrup composition containing acetaminophen or phenobarbital had a mildly bitter taste. Alcohol such as gum arabic,

gelatin, or polyethylene or polypropylene glycol with polyvinyl pyrrolidone .[62] When gelatin and chocolate flavoring are combined to form a jelly by chilling, the viscosity effects of the tannic acid provide a mask for its bitter taste.[63] Additionally, the bitterness of aqueous solution for Tannic acid (0.1 g) with sodium alginate (0.4 g) was lower than a Tannic acid alone in a water solution.[64] Methionine (a stabilizer) and other ingredients are used to create an aqueous suspension of the antidepressant medication mirtazapine. Maltitol—a thickening substance. In addition to covering up the medicine's bad taste, maltitol also prevents the drug's undesired local anesthetic effect. In the acidic pH range of 2 to 3, it remains stable..[65] Other pharmacological substances that are commercially available that are administered by the current method include ibuprofen, dextromethorphan, and pseudoephedrine HCl.[66]

C) Freeze Drying Process:

Fast-dissolved oral methods like Lyoc & Zydis are developed using this technique. Zydis is a dose form that resembles a tablet and spontaneously dissolves quickly in the mouth. This is because the process of freeze drying results in a high porosity. The active component of the Zydis method must be suspended or dissolved in a water-soluble structure former aqueous solution. After that, this mixture frozen-dried and placed into the laminate film's premade blister pockets. While other appropriate excipients, such as starches, gums, etc., can be employed, gelatin and mannitol are the two most often utilized structural excipients. Since low-solubility pharmaceuticals can be freeze-dried more easily, this method is perfect for them. For this kind of food, taste is crucial.[67]

Zydis technology can hide the taste of a variety of medications. These include ondansetron (Glaxo Wellcome), rizatriptan (Merck), loperamide (Janssen), piroxicam (Pfizer), lorazepam (Wyeth), and loratadine (Schering Plough). Scopolamine/chlorpheniramine (Taisho), selegiline (Elan), olanzapine (Eli Lilly), etc. [67]

D) Group Alteration and Prodrug Approach:

When taken orally, the clarithromycin 2' position's alkyloxyalkyl carbonates had significantly reduced bitterness and increased bioavailability.[68] Opioid analgesic and antagonist prodrugs that are tasteless or bitter less were developed for better buccal administration. To increase absorption in comparison to oral dosage without the typical bitter taste,& the tasteless prodrugs of levallorphan, butorphanonol, oxymorphone HCl, nalbuphine HCl, naltrexone, and naloxone were developed for buccal administration. The prodrugs had a 90% bioavailability rate in rats. Conclusion: When prodrugs were given, bioavailability increased without causing any obvious side effects. [69]

E) Systems of Solid Dispersion:

A solid dispersion is one or more active ingredients spread across an inert solid container. Solid medication distribution aided by Taste masking works great with polymers, sugar, or other appropriate substances. By producing the drug's solid dispersion with polyvinyl acetate phthalate, the harsh taste of dimenhydrinate can be mitigated. [70]

(F) Salt Preparation Method:

Adding alkaline metal bicarbonate, like sodium bicarbonate, helps mask the taste of water-soluble ibuprofen salts in aqueous solution [71] The bitter taste of caffeine can be reduced by adding sodium bicarbonate, ascorbic acid, citric acid, and tartaric acid to make a carbonated oral solid formulation [72]

Magnesium aspirin pills lose their flavor when they are made into salts. Two flavorless penicillin preparations are N,N'-dibenzylethylene-diamine diacetate salts and N,N'-bis (deyhdroabiety) ethylenediamine salts. [73] Magnesium salts, starch, and cellulose are used to sweeten tablets of dihydrocodeine phosphate, DL-methylephedrine HCl, and D-chlorpheniramine maleate with less bitterness. [74]

Table 2: Taste Masking By Polymer Coating For Other Class Drugs

Sr no	Drug / Active ingredient	Method	Polymer used for taste masking	Ref no
1	Sparfloxacin	Using Coating method for taste masking	(a)Low substituted hydroxy propyl cellulose (L-HPC) (b)Ethyl cellulose (EC) (c)Hydroxy propyl methyl cellulose (HPMC) (d)Titanium dioxide and	[39],[40]

			(e)Sucrose fatty acid ester mixture is used	
2	Ibuprofen	Using Coating Method for taste masking	(a)Hydroxy ethyl cellulose (HEC)(b)Hydroxy propyl methyl cellulose (HPMC)	[41]
3	Aspirin	-	(a)Cellulose acetate latex and (b)Triacetin is used	[42]
4	Famotidine	Using Coating method for taste masking	(a)Hydroxy propyl cellulose (HPC) (b)Hydroxy propyl methyl cellulose (HPMC) (c)Cellulose acetate is used	[43]
5	Amoxycillin trihydrate	Granulation method is used for taste masking	(a)Microcrystalline cellulose (MCC) (b)Low substituted hydroxy propyl cellulose (L-HPC)	[44]
6	Acetaminophen	Use of Coating method for taste masking	(a)Cellulose acetate (b)Cellulose acetate butyrate (c)Hydroxy propyl cellulose (HPC) /cellulose acetate (d)Eudragit E 100 (e)Polyvinylpyrrolidone (PVP)	[45],[46]
7	Morphine Hydrochloride	Using Coating Method for masking taste	(a)Cellulose and (b)Eudragit NE 30D	[47]
8	Amiprilose Hydrochloride	Use of Coating method for taste masking	(a)Calcium gluconate and (b)sodium alginate	[48]
9	Terfenadine	Mixing method is used for taste masking	(a)Sodium alginate (b)Carrageenan and (c)Macrogol-400	[49]
10	Beclamide	Microencapsulation method is utilized for taste masking	(a)Gelatin	[50]
11	Pinaverium bromide	Coating method is used	(a)Shellac (b)Cellulose	[33]
12	Propantheline bromide	Coating method is used	(a)Low substituted hydroxypropyl cellulose (L-HPC) (b)Ethyl cellulose (EC)	[33]
13	Ibuprofen	Air-suspension coating method	(a)Methacrylic acid (b) Eudragit used as copolymer	[34]
14	Triprolidine Hydro chloride	Dispersion coating method is utilized	(a)Hydroxy propyl methyl cellulose (HPMC)	[35]
15	Dimenhydrinate	-	(a)Carboxy methyl cellulose(CMC) (b)starch (c) Eudragit	[36]
16	Cefeanel daloxate Hydro chloride	Coating method is used	(a)Polyvinylpyrrolidone (PVP) (b) Ethyl cellulose (EC) (c)Hydroxy propyl methyl cellulose (HPMC) (d)trisodium citrate	[37]
17	Enoxacin	coating method is used	(a)Hydroxy propyl cellulose (HPC), (b)Hydroxy propyl methyl cellulose (HPMC), (c)Ethyl cellulose (EC)	[38]
18	Clarithromycin	Roto granulation method is applied	(a)Carbopol (b) Polyvinylpyrrolidone (PVP)	[51]
19	Roxithromycin	Coating method is used	(a)Polyethylene glycol (PEG) (b)Eudragit L 100–55	[52]

20	Nizatidine	Spray drying method utilized	(a)Eudragit E 100	[53]

5) Methods Used For Manufacturing Of Polymeric Coated Tablets

a)Direct Compression

Since it offers the quickest, most efficient, and least complicated method of producing tablets, direct compression is the most widely used option. When several substances may be blended together, this method is typically employed. This works better in damp and hot conditions. APIs that are sensitive because it does away with the need for wetting and drying stages and increases the stability of the active ingredient by minimizing negative (bad) effects. In this procedure, the API is combined with the lubricant and excipients, and then the product is compressed to make processing it easier. [54]

b)Dry Granulation

This innovative process produces granules in a semi-automated manner. Any solid dose pharmaceutical product can be made using this procedure. The current technologies for developing and producing solid dosage forms are replaced by the dry granulation process. Enabling improved quality and faster development. This method compresses the powder mixture without the use of heat or solvent. For dry granulation, there are two approaches. Slugging is a method that is more frequently utilized, in which the powder is recompressed and the resulting tablet is ground to produce the granules. [54]

C) Wet Granulation

The most popular type of granulation is wet granulation. This procedure entails wet sizing, drying, and massing of the powder blend using a granulating liquid. The solvent included in the granulating liquid needs to be volatile in order to be eliminated by drying and ought to be naturally non-toxic. Water, ethanol, and isopropyl alcohol are examples of common liquids. To create wet granules, which are then dried, the wet material is pushed through a screen in the conventional wet granulation process. [54]

Table 3: General Excipients Used In The Formulation Of Tablets [54]

Sr no	Agent	Source/Description	Sweetness Level	Key Characteristics	Application
1	Dextrose	Sugar obtained from starch hydrolysis	~70% of sucrose	Hygroscopic, available in anhydrous and monohydrate forms	Used in formulations requiring mild sweetness.
2	Lactose	Monosaccharide from whey (cheese byproduct)	~15% of sucrose	Low sweetness, requires artificial sweeteners for chewable	Used in tablet formulations, needs sweetness enhancers.
3	Mannitol	Crystalline polyol, sweetener with cooling sensation	~50% of sucrose	Freely soluble, imparts mild cooling effect when dissolved	Common in chewable tablets, smooth consistency.
4	Sorbitol	Isomer of mannitol, more hygroscopic	Slightly sweeter than mannitol	More hygroscopic, available in various tablet types	Used in direct compression chewable.
5	Flavoring agents	Various forms (solutions, oils, powders, emulsions, etc.)	Variable, depends on formulation	Enhances taste perception and mouth-feel	Essential for chewable tablet taste masking.

6	Flavor Selection & Formulation	Process of choosing and optimizing flavors in combination with drug properties	-	Involves evaluating drug taste, formulation components, and optimizing organoleptic characteristics	Critical for balancing taste and pharmaceutical properties.

Table 4: Nanocarrier Or Nanotechnology Used In Taste Masking [88]

Sr no	Nano carrier system	Characteristics
1	Polymeric Micelles	In aquatic media, synthetic amphiphilic copolymers create micelles with a lipophilic core distributed.
2	Polymeric Nanoparticles	sphere-shaped polymer particles that can be either nanospheres or nanocapsules
3	Liposomes	sphere-shaped vesicles made of bilayer amphiphilic lipids
4	SLNs	Solid lipids stabilized by surfactant at normal temperature make up particles
5	NLCs	Particles are a mixture of liquid and solid lipids that have been stabilized by a surfactant.
6	Reverse Micelles	Micelles distributed in an organic medium with a surfactant's assistance
7	Submicron Lipid Emulsion	distributed nanoparticles in the nearly transparent liquid with the help of co- and surfactants
8	Nanogel	Polymer particles that have undergone physical or chemical crosslinking in an appropriate solution

6)Evaluation Of Taste Masking Efficiency

(a)Panel Testing

Using reference materials, a group of approximately 5–10 human participants are trained to evaluate flavor. Tastes ranging from extremely harsh to insipid. These levels of bitterness are then given numerical numbers (zero–five, for example). To assess its bitterness, the test response is then tasted and graded using the same scale. The literature consistently documents panel testing for every taste-masked capsule under evaluation. [55]

(b)Measurement Of Frog Taste Nerve Reactions

Located, separated, and reduced proximally from the surrounding tissue. A digital integrator and an ac-amplifier are utilized to the nerve impulses, respectively, to lengthen and unite. The response's importance is then determined by measuring the height of the integrated reaction. [56]

(c)Versatile Taste Sensor/Magic Tongue

This automatic taste sensor measures the degree of bitterness in a pharmacological ingredient. The apparatus features a transducer, which is composed of many lipid/polymer membrane types with distinct characteristics that may perceive taste in a way akin to human gustatory perception. The flavor reaction is transferred into a sample made up of the receptor element's membrane potential electric indicators. Certain substances provide various flavor characteristics that require the acquisition of specific reaction electric ability patterns. [57]

(d)Method Of Spectrophotometry

Resolving a known amount of the taste-masked components in 10 mL of pure water in a 10 mL syringe five times in thirty seconds, from the syringe's end to its tip. After the check medium is filtered using a membrane filter, the drug's attention inside the filtrate is measured using spectrophotometry. It is possible to conclude that the sour taste would be muted in vivo if this knowledge is below the brink concentration. The sparfloxacin taste-masked granules have been evaluated using this method, with a 100 µg/mL threshold. [58]

Structural Evaluation

To verify that the final masked product is a solid dispersion of API in masking agent, this evaluation can be conducted using a variety of analytical techniques, including FT-IR, DSC, and PXRD. While DSC and PXRD guarantee that API has distributed uniformly within the network of masking agents, FT-IR guarantees that there has been no chemical contact between the masking agent and API.[75]

(f)In Vitro Evaluation

To verify that an Active Pharmaceutical Ingredient (API) is soluble in the location of maximum

absorption rather than in saliva, an in vitro dissolution test is performed in multiple media simulating different parts of the digestive system. This helps to assess how the API dissolves under various conditions. Additionally, an e-Tongue, a sensory electronic device, is employed to evaluate the masked formulation for its ability to effectively conceal any undesirable taste. The e-Tongue simulates human taste perception, providing a quantitative analysis to ensure the final formulation is both effective and palatable.[75]

(g)In Vivo Evaluation

While e-Tongues can confirm that an unpleasant taste has been masked, in vivo evaluation is essential for definitive proof of taste concealment. To determine the bitter taste threshold in vivo, healthy volunteers are recruited to participate in sensory testing. These volunteers are exposed to various concentrations of the formulation, and the lowest concentration at which the bitter taste is perceived is identified as the threshold. This method ensures that the formulation effectively masks the unpleasant taste, providing direct human sensory feedback and confirming the success of the taste-masking process.[75]

7)Challenges

(A) API Properties:

- Solubility: APIs with high solubility in saliva (pH 6.2–7.0) are harder to taste-mask than those with low solubility.
- Particle Size and Shape: Small particle sizes and irregular shapes are more challenging to coat than larger, spherical particles.
- Dose: Higher doses of the API limit the amount of sweeteners or excipients that can be used for masking.

(B) Polymer Selection Criteria:

- Solubility Type: Consider whether the polymer is water-soluble, insoluble, or pH-dependent for optimal interaction with the API.
- Hydration Mechanism: Choose between polymers that swell (delaying API diffusion) or gel (increasing viscosity to minimize contact with taste receptors).
- Coating Film Thickness: The thickness of the polymer coating impacts the effectiveness of taste masking.

(C) Additional Factors:

- Polymer's Drug Release Pattern: The desired drug release profile should align with the polymer's characteristics (e.g., controlled, delayed, or immediate release).
- Sweeteners and Other Excipients: High-dose APIs limit the amount of sweeteners and excipient solid content that can be used for masking.[76]

8)Recent Advances / New Technologies For Odt Formulation

(a)ODT Technology AdvaTab :

The company APTALIS Pharmaceutical Technologies develops the Advatab ODT Technology. Diverse Benefits of this technology include excellent patient compliance, high physical stability, stability during packaging and transportation, and a pleasing flavor (thanks to Microcaps technology).[77]

(b)ODT Microcaps Technology:

APTALIS Pharmaceutical Technologies is the company behind Microcaps ODT technology. As this Technology masks tastes via the coating approach. The offensive flavor and/or odor are eliminated by the polymeric barrier. Provides benefits like patient compliance, appropriate release profiles, and accurate taste masking.[77]

(c)ODT Liquated Technology:

APTALIS Pharmaceutical is the company behind this advanced Liquitard technology development. Using single dose sachets of an efficient, practical, ready-to-use, taste-masked powder formulation that may be sprinkled over foods that are simple to swallow or used as a suspension. This is made using a large range of flavors and works with personalized release profiles.[77]

1)The Formula coat and Formullex:

Pierre Fabre created novel taste-masking methods that involve coating nano- or micro-sized particles with nonorganic solvent at room temperature.[77]

2) A Novel Method Of Flavor Masking Is Provided By KLEPTOSE® Linecaps Roquette:

By reducing the total quantity of drug particles exposed to the taste buds, KLEPTOSE® Linecaps use pea maltodextrin to disguise the bitter taste of medications.[77]

9)Regulatory Aspects

The needs and preferences of neonates and infants differ significantly from those of adults, which must be considered while creating pediatric formulation. When compared to an adult, they differ in how they digest and eliminate certain ingredients. Guidelines

about their use have been established by a number of regulatory agencies, including the European Medicines Agency (EmeA). Documents released by the US Food and Drug Administration (US FDA) and European Commission contain more information.

Every artificial flavor that is used needs to be listed under "Generally Recognized as Safe" (GRAS). Like lemon, orange, peppermint, cardamon, wild cherry, Anise oil. The FDA Is in charge of establishing the guidelines for the manufacture and preparation of foods and beverages that allow the use of safe food additives. The Code of Federal Regulation (CFR), Title 21, Part 173 (secondary direct food additives permissible in food for human consumption), lays out these requirements. This section specifically addresses the application of ion exchange resins.

Regulations restrict the use of cyclodextrins, particularly in pediatric formulations.[78]

10)Patient Compliance

In the field of pharmaceuticals, patient compliance is crucial. A pharmaceutical corporation will do all within its power to guarantee that people take their prescriptions on a regular basis. [80]

Medication acceptability and patient compliance are strongly linked. The pharmaceutical business has realized that it needs to look closely at ways to improve and concentrate on the underlying causes of non-acceptance. Researchers looked into cutting the size of tablets to improve the physical properties of oral solid dose forms.[79]

11)Future Perspective for Taste Masking

a) Personalized Medicine :

Customized fruit-chew designs for children were created using 3D printing, which effectively concealed taste and improved palatability. The recipe, which included sweeteners and strawberry flavor in predetermined quantities, was used to mimic candies. The extruded filaments' good taste masking of the drug's harsh taste was observed by trained panellists evaluating the taste.[99]

b) Biotechnological Taste Masking:

Many different proteins that make things taste sweet have been identified. These include lysosyme, thaumatin, mabinlin, monellin, pentadin, brazzein, miraculin, curculin, and lysozyme. All of these proteins are found in tropical plants, except for lysozyme, which is found in egg whites. Researchers have been studying these proteins for many years, looking into some of their most important properties. This proteins are use to reduce bitter taste of drug in pediatric formulations.[100]

c)Taste Masking By Using Artificial Intelligence (AI) And Machine Learning (ML) :

In taste-masking pediatric medication formulations, it covers the function of artificial neural networks (ANNs) and human taste panels. Therefore, the problem of predicting the level of bitterness in pediatric formulations may be addressed using machine learning classifiers. While there have been improvements, more research is still required to determine the most efficient taste-masking strategies for certain medication compounds. Paediatric formulation development can be improved and taste-masking issues can be solved with the help of human panellist acceptability scores and ongoing machine learning algorithm refining.[101]

CONCLUSION

In conclusion, the palatability of oral medications is crucial for ensuring patient adherence, particularly in pediatric brain-related diseases where non-compliance can hinder therapeutic success. Orally disintegrating tablets (ODTs) have revolutionized pediatric pharmacotherapy by improving administration convenience and masking unpleasant drug tastes. This review emphasizes the importance of taste-masking technologies, especially for bitter drugs, to enhance patient compliance. A variety of strategies, including microencapsulation, spray drying, and nanotechnology, have been explored, with polymeric coatings proving highly effective in creating protective barriers that prevent drug-taste receptor interaction. However, challenges such as formulation stability, drug release alteration, and regulatory concerns remain. Recent advances in nanotechnology and patient-focused formulations show promise in addressing these challenges and improving compliance. Continued innovation in these areas will be essential to meet the needs of pediatric patients and optimize the management of brain-related diseases

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