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Review article

Mechanical microencapsulation: The best technique in taste masking for the manufacturing scale - Effect of polymer encapsulation on drug targeting

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ABSTRACT

Drug taste masking is a crucial process for the preparation of pediatric and geriatric formulations as well as fast dissolving tablets. Taste masking techniques aim to prevent drug release in saliva and at the same time to obtain the desired release profile in gastrointestinal tract. Several taste masking methods are reported, however this review has focused on a group of promising methods; complexation, encapsulation, and hot melting. The effects of each method on the physicochemical properties of the drug are described in details. Furthermore, a scoring system was established to evaluate each process using recent published data of selected factors. These include, input, process, and output factors that are related to each taste masking method. Input factors include the attributes of the materials used for taste masking. Process factors include equipment type and process parameters. Finally, output factors, include taste masking quality and yield. As a result, Mechanical microencapsulation obtained the highest score (5/8) along with complexation with cyclodextrin suggesting that these methods are the most preferable for drug taste masking.

1. Introduction

Taste masking techniques are used to mask the bad taste of drugs and to increase their palatability, especially in pediatric and geriatric patients due to their swallowing difficulties. The importance of taste masking techniques has increased after discovering fast dissolving tablet (FDT) [1–3] as drug must be masked before formulated in FDT. Many techniques are used to mask the drug taste, such as complexation, microencapsulation, hot melt extrusion, coating, granulation, mixing with sweeteners, lyophilization, and printing [4–6].

The bitter taste of drug is sensitized only when drug is dissolved in saliva and come in contact with tongue taste buds. Therefore, taste masking methods focus on making drug completely insoluble in saliva, pH 6.8, by attaching, enveloping, or incorporating it with saliva insoluble compounds as in complexation, microencapsulation, or hotmelt extrusion, respectively.

The main aim for drug taste masking is to hinder drug release in saliva, and simultaneously, to meet the drug release requirements for the dosage form. For example, to allow the drug to release rapidly in stomach, in case of immediate release products such as FDT.

This article is a review of the principle of the most used and currently raising taste masking techniques, namely, complexation, encapsulation and hot melting and it excluded the conventional methods such as coating, granulation, and mixing sweeteners. It also includes an evaluation of these techniques depending on selected factors, including the affordability, and safety of used materials and instruments, process simplicity and cost, and both the quality of drug masking and its yield.

1.1. Complexation techniques

These methods aim to insert the drug into a complex high molecular volume structure either to decrease its solubility in saliva or to prevent drug exposure to taste bud. Taste can be covered in these techniques by complexing drug with ion exchanger or cyclodextrin.

1.1.1. Complexation with ion exchangers

Ion exchangers can be found as resins or fibers. Resins are composed of insoluble cross-linking polymers, e.g. styrene-divinylbenzene copolymer, with charged groups in the form of spherical beads [7]. Whereas, fibers consist of insoluble polymer, e.g. polyethylene, polypropylene, and viscose, with charged groups and have elongated shape [8]. To ensure complexation success, drug must have a charge opposite to the charge of ion exchanger, therefore, ion exchangers are classified into cations or anions according to the charge of guest drug (Table 1) [7,9]. The main differences between resins and fibers are shape and type of drug release. The shape of resin is spherical due to crosslinking process,

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Table 1
Commonly used ion exchange resin for taste masking [7,9].

Type	Functional group	Polymer backbone	Commercial resins
Strong anion	$-N^+R3$	Polystyrene DVB	Amberlite IR 400, Dowex 1, Indion 454, Duolite AP 143
Weak anion	$-N^+R2$	Polystyrene-DVB	Amberlite IR 4B, Dowex 2
Strong cation	−SO3H	Polystyrene DVB	Amberlite IR 120, Dowex 50, Indion 244, Purolite C100 HMR, Kyron-T-154
	−SO3Na	Sodium Polystyrene	Tulsion T-344, Amberlite IRP 69, Indion 254
Weak cation	−COOH	Methacrylic acid-DVB	Amberlite IR 64, Amberlite IRC 50, Indion 204, 234, Tulsion 335, 339, Purolite C102DR, Kyron-T-104, Kyron-T-114, Doshion P544(R),
	−COOK		Tulsion T-339, Amberlite IRP88, Indion 234, Kyron-T-134

consequently, the drug will be released via diffusion and ionic exchange process. While elongated fibers allow the drug to be released by ionic exchange only. Generally, drug complexation with fibers grants faster release compared to resin complexation. However, the later provides better masking of drug taste [10].

1.1.2. Complexation with cyclodextrins

This method uses cyclodextrin as the complexation agent. Cyclodextrins are crystalline, homogeneous, and non-hygroscopic substances built up from 6 to 8 units of glucopyranose units to form a cavity. The outer surface of this cavity is hydrophilic containing hydroxyl groups while the inner surface is hydrophobic [11]. Table 2 shows the drugs masked by complexation techniques in the last two years.

1.2. Encapsulation techniques

Microencapsulation is described as a process of enclosing micron-sized particles of solids, droplets of liquids, or gasses in an inert polymeric shell, which in turn isolates and protects them from the external environment. Microcapsules are generally produced within the size ranging from 1 to 1000 μm [19] whereas nanocapsules are 1 to 1000 nm [20].

Microencapsulation technique is intended for wide range of applications, depending on the chosen encapsulating polymer, including, drug protection, taste masking, controlling/targeting drug release, avoiding gastric irritation and safe handling [21]. Nanoencapsulation technique is employed for all mentioned microencapsulation applications in addition to improving drug permeability across biological barriers [22].

Regarding taste masking microencapsulation, the most used polymer is Eudragit E (Table 3). Eudragit E is a cationic polymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It is soluble in gastric fluid as well as in weakly acidic buffer solutions, up to pH ~ 5. The glass transition temperature of eudragit E is ~48° C. If used as covering polymer in microencapsulation, it forms swellable, permeable, and insoluble films at pH 5 or higher, yet dissolves rapidly by forming salts at acidic pH, lower than 5. This polymer can prevent the drug release in saliva, pH 6.8–7.4, on the other hand, dissolves immediately in gastric fluid, pH 1.0 – 1.5 [23].

Table 2
List the drugs masked by complexation technique.

Drug	Complexation material	Ref
Propranolol hydrochloride	Ion-exchange fiber ZB-1	[10]
Clarithromycin	Tulsion-335	[12]
Ciprofloxacin	Indion 234	[13]
Clindamycin	Amberlite IRP69	[14]
Famotidine	Amberlite IRP-69	[15]
Primaquine Phosphate	Cyclodextrin	[16]
Levocetrizine dihydrochloride	Cyclodextrin	[17]
Promethazine Hydrochloride	Cyclodextrin	[2]
Meloxicam	Cyclodextrin	[18]

Table 3
List the drugs masked by microencapsulation technique.

Drug	Microencapsulation	Taste masking material	Ref
Ciprofloxacin	Interfacial polymerization	Methacrylic acid divinyl benzene copolymer	[32]
Chlorpheniramine maleate	Ionotropic gelation	Alginate/chitosan	[33]
Prednisolone	Spray drying	Eudragit E	[34]
Sildenafil citrate	Spray drying	Eudragit E	[35]
Lafutidine	Fluidized-bed	Ethylcellulose & hypromellose	[36]
Berberine hydrochloride	Fluidized-bed	Eudragit E	[37]
Atomoxetine HCl	Fluidized-bed	Methacrylate copolymer	[38]
Naproxen sodium	Fluidized-bed	Eudragit E	[39]
Diclofenac	Fluidized-bed	Eudragit E	[40]
Propiverine hydrochloride	Fluidized-bed	Eudragit E	[41]
Famotidine and amlodipine	Spray drying	Ethyl cellulose	[42]
Acetaminophen	Spray congealing	Eudragit E	[43]
Drotaverine hydrochloride	Solvent evaporation	Polyvinyl pyrrolidone	[44]
Ondansetron hydrochloride	Solvent evaporation	Eudragit E	[45]
Ayurvedic medicines	Granules (coating in pan)	Eudragit E	[46]

1.2.1. Microencapsulation methods

There are three approaches for drug microencapsulation [19]; Chemical polymerization, physicochemical microencapsulation, and mechanical microencapsulation.

1.2.1.1. Chemical Microencapsulation. Chemical Polymerization is the most common among chemical methods. A chosen monomer is dissolved in a liquid core material then dispersed in aqueous phase containing dispersing agent. Furthermore, polymerization reaction can be set by co-reactant in interfacial polymerization method or free radical in free radical polymerization method. This results in rapid polymerization at interface where capsule shell generation takes place [24,25].

1.2.1.2. Physicochemical process. This approach can be achieved by two methods; coacervation (phase separation), or ionotropic gelation method.

In coacervation method, drug is dispersed in polymer solution then the solubility of polymer is partially decreased by addition of acid or salt to change pH value, addition of non-solvent to the dispersion medium, or change emulsion temperature, which result in precipitation and continuous coating of wall polymer around the core droplets [26,27].

Ionotropic gelation involves the dropwise addition of drug loaded anionic polymer to an aqueous solution of polyvalent cations. The diffusion of cations into the polymeric drops leads to a three dimensional lattice of ionically crosslinked moiety [26–28].

1.2.1.3. Mechanical Microencapsulation. Mechanical process can be