Orodispersible Tablets

Preparation, Evaluation and Taste Masking Techniques

A project submitted to the department of pharmaceutics as a partial fulfillment for graduation in College of Pharmacy

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Plagiarism Statement

The following work represents a general overview for Orodispersible tablets as a dosage form and the taste masking techniques employed in its formulation. The current investigation was carried out in the College of Pharmacy at Basra University in the period between May 2020 to July 2020 under the supervision of Assistant Lecturer Noor Yousif Fareed. We are Aya Maytham Abdullah and Anwar Thegeal Dafar, certify that we have written all the text in this article with indicating the proper citation from every published work used as a source of information.

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Signature	**Signature**

Acknowledgement

In the present world of extraordinary circumstances, we are immensely obliged to thank the supreme power the Almighty God who is obviously the one who has always guided us, thank you for the protection and for giving us a healthy life. Without his grace this project could not become a reality.

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Foremost, we would like to dedicate this project and express our sincere gratitude to our advisor Dr. Noor Y. Fareed, whose valuable guidance has been the ones that helped us patch this project and make it full proof success, her suggestions and instructions have served as the major contributors towards the completion of the project.

Lastly but not least, we dedicated this work for our loved ones who stood next to us, our friends, families and for all the personnel of the department of pharmaceutics, special thanks for all of them.

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List of Abbreviations

ODT	**Oro -Dispersible tablet**
API	**Active pharmaceutical ingredients**
BCS	**Biopharmaceutical Classification**
DSC	**Differential scanning calorimetric**
FTIR	**Fourier transform infrared spectroscopy**
GIT	**Gastrointestinal tract**
m.p.	**Melting point**
SEM	**Scanning electron microscopy**
Tg	**Glass transition temperature**
XRD	**X- ray diffraction**
λ-max	**WaveLength with Maximum Absorbance**
SD	**Solid Dispersion**
HME	**Hot Melt Extrusion**
CD	**Cyclodextrin**
HPbCD	**Hydroxypropyl beta Cyclodextrin**

IER	**Ion Exchange Resin**
EPO	**Eudragit PO**

Abstract

Over the past three decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. ODTs Orally disintegrating tablets (ODTs) are solid dosage forms that disintegrate in the mouth in less than 30 s, and are thus swallowed without the need for water or chewing. However, the disadvantage that cannot be overlooked is palatability. When releasing the active ingredients, they come in contact with the taste buds, hence the patient senses a bitter taste that affects compliance. To overcome this problem, a wide variety of masking technologies have been developed in order to mask the taste of bitter active substances and achieve patient compliance.

In this review, the unique features and principles of taste-masking approaches used with ODT platforms are discussed, including a literature review of examples on bitter taste drugs have been masked using these techniques. In addition, in this article overview of evaluative tests is presented such as; Pharmacopoeial Tests, evaluative tests specific for ODT and taste masking efficacy evaluation to insure palatability. In vitro testing may not always reflect the real in vivo disintegration of tablets, so volunteers are asked to evaluate the taste of masked ODT to ensure palatability and the results are promising.

Introduction:

The majority of orally administered medications are in the form of tablets. They are cost effective in preparation and patient friendly in term of acceptability and ease of use [(1)]. However, Some groups of patients such as the elderly, children, and mentally retarded uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. For these reasons, there was an urgent need to develop Orally Disintegrating Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take it with water [(2)].

The United States Food and Drug Administration (FDA) defined oral dispersible tablets (ODTs) as a "solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue.[(3)] Products of ODT technologies entered the market in the 1980s, and steadily expanded to accommodate for many drugs of various therapeutic categories as it can be seen in **Table 1.** [(4)]

In comparison to conventional sublingual tablets, buccal tablets, and lozenges, which require more than a minute to dissolve in the oral cavity. The ODTs disintegrate rapidly (within seconds), then the drug is released, dissolved, or dispersed in the saliva, afterward, the active ingredients are absorbed through mucous membranes in the mouth and GIT and enter the bloodstream. [(5)]

Taste is one of the most important parameters that must be considered when developing ODT. Undesirable taste is one of several important formulation problems that leads to patient noncompliance. Therefore, an acceptable degree of palatability must be governed for bitter drugs when formulated as ODT. [(6)]

Table 1: Marketed ODT[4]

Marketed Products: Brand name	Active ingredient	Application	Company
Claritin® RediTabs®	Loratadine	Antihistamine	Scherig corporation
Feldene Melt®	Piroxicam	NSAIDs	
Maxalt® -MLT®	Rizatritpan benzoate	Migrane	Merck
Pepeid® ODT	Femotidene	Anti-ulcer	Merck
Zyperxa®	Olazepine	Psychotropic	Eli Lilly
Zofran® ODT	Olandansetron	Antiemetic	Galaxo Smith kline
Resperdal® M-TabTM	Resperidone	Schizophrenia	Janssen
ZubrinTM (Pet drug)	Tepoxelin	Canine NSAIDs	Scherig corporation
ZelaparTM	Selegiline	Parkinsons disease	Elanl Amarin corporation
Klonopin® wafer	Clonazepam	Sedation	Roche
Childrens Dimetapp® ND	Loratadine	Allergy	Wyeth consumer Healthcare
Imodium Istant Melts	Loperamide HCL	Antidiarrheal	Jannsen
Propulsid® Quicksolv ®	Cisapride Monohydrate	Gastrointestinal prokinetic Agent	Jannsen
Tempra Quicksolv®	Acetaminophen	Analgesic	Bristol-Mters squibb
Remeron® Soltab®	Mirtazapine	Anti-dipression	Organon Inc.
Triaminic® Softchews®	Various combination	Pediatric cold cough,Allergy	Novartis consumer Health
Zomig-ZMT® and Rapimelt®	Zolmitriptan	Anti-migraine AstraZeneca	AstraZeneca Alavert® Loratadine Allergy
DuraSolv® Alavert®	Loratadine	Allergy	Wyeth Consumer Healthcare
NuLev®	Hyoscyamine sulfate	Anti-ulcer	Schwarz Pharma
Kemstro™	Baclofen	Anti-spastic analgesic	Schwarz Pharma
Benadryl® Fastmelt®	Diphenhydramine citrate	sinus pressure relief	Pfizer
Nasea OD	Ramosetoron HCl	Anti-emetic	Yamanouchi
Gaster D	Famotidine	Anti-ulcer	Yamanouchi
Excedrin® QuickTabs	Acetaminophen	Pain reliever	Bristol-Myers Squibb

Advantages of ODT

The advantages of Orodispersible tablets can be summarized in the following points[7]:

1. Easy to administer to the patient who cannot swallow such as pediatric, geriatric, bedridden, stroke victim and institutionalized patient (specially for mentally retarded and psychiatric patients).
2. Improved compliance/added convenience due to it will be easier for patients who are unwilling to swallow solid preparation due to fear of choking. Also for a middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her drug.

3. The ODTs will bypass the hepatic metabolism due to pregastric absorption leading to increased bioavailability/ rapid absorption of drugs from mouth, pharynx and esophagus as saliva passes down to the stomach.
4. No chewing needed, can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth.
5. Excellent mouths feel property produced by use of flavours and sweeteners help to change the perception of "medication as bitter pill" especially in the pediatric population.
6. Rapid onset of action due to the fast disintegration of tablets leads to quick dissolution and rapid absorption of the active ingredient.
7. This new proprietary method allows the incorporation of microencapsulated drugs for enhanced bioavailability, flexibility of dosing & immediate and/or controlled release.

Disadvantages of ODT

The disadvantages of Orodispersable tablets are illustrated by the following points [8]:

1. ODT is hygroscopic in nature so must be kept in a dry place, it cannot maintain physical integrity under normal conditions of temperature and humidity.
2. It also shows the fragile, effervescent granules property.
3. ODT requires special packaging for proper stabilization & safety of stable products.
4. Palatability is a problem, As the drug disintegrates or dissolves in a patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.
5. The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose.

APPROACHES FOR PREPARATION OF ODTs

Some of the basic pharmaceutical processes to manufacture ODTs are explained as follows:

Spray drying:

The formulations are compounded by hydrolyzed and unhydrolyzed gelatins as supporting agents, mannitol as bulking agent, croscarmellose sodium or sodium starch glycolate as disintegrating agent. An acidic material (e.g., citric acid) or alkali material (e.g., sodium bicarbonate) is used to improve disintegration and dissolution behavior. Tablets prepared by the compression of spray dried powder, when immersed in an aqueous medium, showed a disintegration time of 20 s. [68]

Freeze drying

Lyophilization process involves removal of solvents from a frozen drug solution or a suspension containing structure-forming excipients. The tablets formed by this process are usually very light and have highly porous structures that allow rapid dissolution or disintegration. Lyophilization is done at very low temperature to eliminate the adverse thermal effects that may alter drug stability during processing. The freeze dried dosage form have relatively few stability concerns during its shelf life. The drying process may give rise to the glassy amorphous structure of excipients and drug substance. [69][70]

Mass extrusion

The mass extrusion technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol and methanol. Expulsion of softened mass through the extruder or syringe is carried out, to get a cylinder of the product which is then cut into even segments using a heated blade to form tablets. [71][72]

Direct compression

Direct compression is the easiest and cost-effective tablet manufacturing process. This method can be applied to manufacture ODT by selecting appropriate combinations of excipients, which can provide fast disintegration and optimum physical resistance. [73] [74]

Zydis technology

Zydis is the first mouth dissolving dosage tablet within the market. Tablets are prepared by distinctive freeze drying technology. The active drug is incorporated into an exceedingly soluble matrix, that is then reworked into blister pockets and freeze dried to get rid of water by sublimation. Zydis matrix is created from a variety of ingredients so as to get completely different objectives. Polymers like albumin, dextran or alginates are used to impart strength throughout handling. [75]

Durasolv

As a second generation technology, the DuraSolv technology produces stronger tablets that can be packed in blisters or bottles. The key ingredients in these formulations are non-direct compression fillers and lubricants. The particle size of the non- direct compression filler is preferably between 20-65 μm, while for direct compressible fillers at least 85 % of the particles are over 100 μm in size. These non-direct compression fillers, such as mannitol, dextrose, sorbitol, sucrose and lactose have the advantage of quick dissolution and avoid some of the sandy or gritty texture usually present in direct compressible versions of the sugar. [76]

Evaluation of ODT

Being a tablet, ODT shares the same compendial test specified for Oral tablets by the pharmacopeial authorities. However, some tests are being specific for ODT. Furthermore, Taste masking efficiency should be evaluated When taste masking is performed for a bitter taste drug to ensure palatability.

A. Pharmacopoeial Tests

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness was recorded using Vernier Calliper (9) .

Weight variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 10% for 100 mg tablets and none by more than double that percentage. [10]

$$\%\ weight\ variation = \frac{Average\ weight - weight\ of\ eact\ tablet}{Average\ weight} * 100$$

Friability

Friability attempts for decreasing the disintegration time increase the friability of ODTs than the conventional tablets. Dosage forms like zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. [11]

Pre-weighed tablets are placed in the friabilator. Friabilator consists of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test, tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as[12] :

$$\%\ Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} * 100$$

Hardness (crushing strength)

Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of ODTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. [13]

B. Evaluations Specific for ODT

Wetting time

Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting is measured. [14]

Disintegration Test

The time for disintegration of ODTs is generally less than one minute and actual disintegration time that a patient can experience ranges from 5-30 seconds. The standard procedure of performing disintegration tests for these dosage forms has several limitations and they are not suitable for the measurement of very short disintegration times. The method needs to be modified for ODTs as disintegration is required without water; thus the test should mimic disintegration in salivary contents. A modified dissolution apparatus is applied to an ODT with a disintegration time that is too fast to distinguish differences between tablets when the compendial method is used. A basket sinker containing the tablets is placed just below the water surface in a container with 900 mL of water at 37 0C, and a paddle rotating at 100

rpm is used. The disintegration time is determined when the tablet has completely disintegrated and passed through the screen of the sinker. [15]

Dissolution test

The development of dissolution methods for ODTs is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for ODT much in the same way as their ordinary tablet counterparts.It has been suggested that USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used. [16]

Moisture uptake studies

Moisture uptake studies for ODT should be conducted to have an insight into the stability of the formulation, as several excipients used are hygroscopic. Ten tablets from each formulation are kept in a desiccator over calcium chloride at 370C for 24 h. The tablets are then weighed and exposed to 75% RH at room temperature for two weeks. The required humidity (75% RH) is achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for three days. One tablet as control (without superdisintegrant) is kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight is recorded. [17]

Clinical Studies

In vivo studies have been performed on oral fast-disintegrating dosage forms to investigate their behavior in the oral–esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. The fast-disintegrating forms examined showed improved pharmacokinetic characteristics when compared with reference oral solid formulations. For example, the absorption rate of the acetaminophen Flashtab was higher than that of the brand leader, while having the same bioavailability.[18] Increased bioavailability and improved patient compliance were observed in Lyoc

formulations for different drugs such as phloroglucinol[19], glafenine, and propyphenazone[20]. Increased bioavailability using Zydis for all the drugs that can be absorbed through the buccal and esophageal mucosa exhibited. This is helpful particularly in drugs with marked first-pass hepatic metabolism[21] . Finally, the suitability of ODT s for long-term therapy was also assessed. Lyoc formulations containing aluminum were positively tested in patients with gastrointestinal symptoms[22]

Evaluating the Efficiency of Taste Masked ODT

1-Invitro Methods

The in vitro methods used to evaluate the success of the taste masking procedures are :

- Spectrophotometry involves mixing of formulation to 10ml distilled water and then analyzing API concentration. If API concentration is below the threshold, sufficient taste masking is considered to be achieved.The spectrophotometry method is not an absolute taste evaluation test[23].
- The use of an electronic (e) tongue which emulates the three levels of biological taste recognition: The receptor level (taste buds in humans, probe membranes in the e-tongue), the circuit level (neural transmission in humans, transducer in the e-tongue), and the perceptual level (cognition in the thalamus in humans, computer and statistical analysis in the e-tongue). In e-tongue, the formulation or API is evaluated against standard (e.g., quinine hydrochloride) and the software generates taste patterns that form the basis of evaluation[24][25]. Figure 1 represents an illustration for the electronic tongue.

2-In Vivo Tests

Human panel testing and frog taste nerve responses can be used to evaluate taste of formulations. In human panel testing, large groups of healthy volunteers are asked to take bitter drugs and then the taste-masked formulation. They are then asked to comparatively rate the formulation on various organoleptic properties. In frog taste nerve responses, the

glossopharyngeal nerve of bullfrogs is connected to AC amplifiers and responses to bitter drug and formulation are taken. The peak height obtained is used to assess taste masking[26][27].

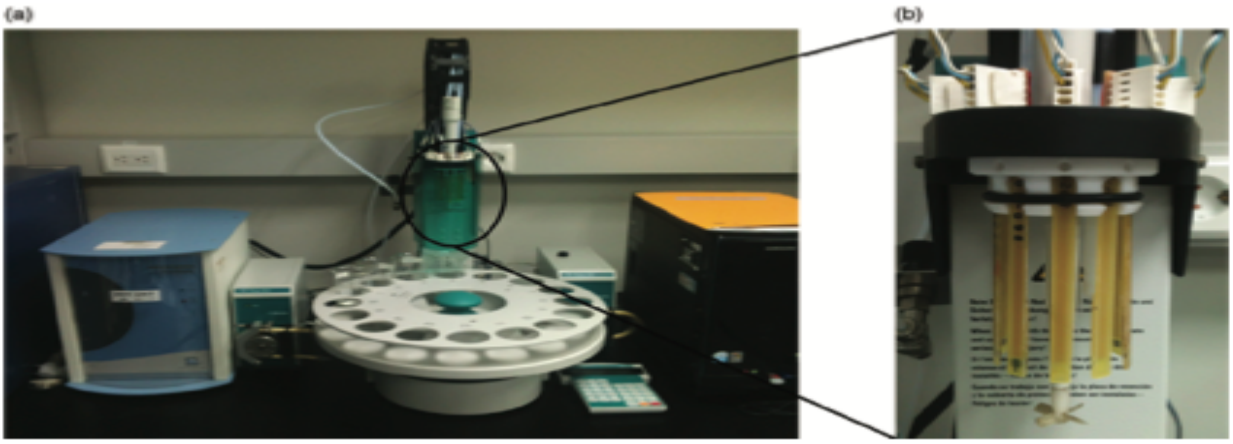

Figure 1. An Alpha Astree II electronic tongue system connected with LS16 auto sampler unit (a) and the seven-sensor set with a stirrer of the electronic tongue (b).

Taste Masking Techniques

The Addition of Sweetener, Flavorant, and Other Excipient

It is considered as the simplest technique employed for taste masking of orally administered drugs[28]. Sweeteners, being highly water soluble, dissolve in saliva and coat the taste buds, thereby retarding the interaction of bitter API with taste buds. Flavorants enhance the formulation and give it a distinct taste[29]. They are to be added in addition to primary taste masking agents. Certain cooling flavorings such as menthol numb the taste buds and retard bitter taste perception. The choice of flavorant is mainly dependent on the taste sensation required to be masked as shown in Table 2 .Some examples of sweeteners i.e., aspartame, acesulfame potassium, cyclamate, glycyrrhizin, lactose, mannitol, saccharin, sucrose, and sucralose . In addition, other excipients such as bitterness inhibitors can also be added[30].

Table 2: Selection of flavors based on sensation of taste

Sensation	Flavor
Salt	Butterscotch, apple, apricot, peach, vanilla
Bitter	Wild cherry, walnut, chocolate, mint, passion fruit
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, liquorice, root bear, raspberry

Prodrug formation

Prodrugs are molecules that are initially inactive but, upon biotransformation, are converted to active forms[31]. The basic aim of prodrug design is to mask undesirable drug properties including the unpleasant taste by physicochemical modification of bitter taste and thereby inhibits/retards their interaction with taste receptors[32]. An example is the alkoxy alkyl carbonates of the clarithromycin 2' position have remarkably alleviated bitterness and improved bioavailability when administered orally[33].

Salt Preparation:

Adding a group to the drug to form salt masks the unpleasant taste of the drugs, for example, Magnesium aspirin tablets are rendered tasteless by preparing magnesium salts of aspirin[34].

Coating Technique:

Taste masking using coating techniques is widely employed in the field of dosage form design. The aim of this technique is to apply a polymeric film that prevents the release of the drug in the salivary environment but allows its release in the gastrointestinal fluid due to the difference in pH between the oral cavity and the stomach[35]. Examples on these polymers include; Eudragit RL 30 D, Kollicoat Smartseal 30 D and Eudragit 100[36], Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups[37].

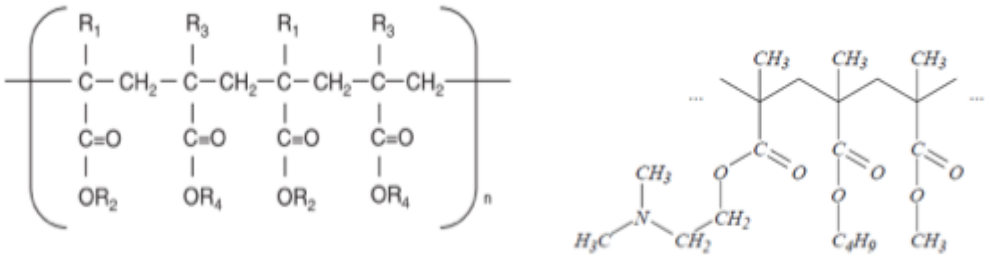

Figure 2: The chemical structure of Eudragit polymers

Literature Reviews

The development of taste masked prednisolone microspheres as an ODT . Microspheres containing prednisolone were prepared by the solvent evaporation method using acetone as solvent for pH-sensitive polymer and light liquid paraffin as the encapsulating medium. Prepared microspheres were characterized with regard to the yield, drug content, particle size and size distribution, surface features, *in vitro* drug release and taste. Tablets, prepared by direct compression containing microspheres, were evaluated with regard to crushing strength, friability, disintegration time, drug content and *in vitro* drug release and taste. The results obtained showed that the average size of microspheres is influenced greatly by the speed of stirring. Microspheres prepared by the solvent evaporation method in acetone were of a regular spherical shape with satisfactory results in terms of the size and size distribution. The comparison of the dissolution profiles of microspheres in different media shows that microspheres produce a retarding effect in pH 6.8 buffer. Taste evaluation studies confirmed that microspheres of PDL having a drug to polymer ratio of 1: 10 are tasteless and these were further used for formulation into ODTs. Compression of microspheres resulted in breaking of a fraction of the microspheres but this did not adversely affect the taste. Effective taste-masking was achieved for PDL using the technique of microencapsulation and ODTs of acceptable characteristics were obtained by disintegrant addition and direct compression[38].

Another example of coating procedure for taste masking is the coating berberine hydrochloride with Eudragit E100 using a fluidized bed. It was found that microcapsules with a drug–polymer ratio of 1:0.8 masked the bitter taste obviously. The microcapsules were formulated to orally disintegrating tablets and the optimized tablets containing 6% (w/w) crospovidone XL and

15% (w/w) microcrystalline cellulose showed the fastest disintegration, within 25.5 s, and had a pleasant taste. The dissolution profiles revealed that the taste-masked orally disintegrating tablets released the drug faster than commercial tablets in the first 10 min. However, their dissolution profiles were very similar after 10 min. The prepared taste-masked tablets remained stable after 6 months of storage. The pharmacokinetics of the taste-masked and commercial tablets was evaluated in rabbits. The Cmax, Tmax, and AUC0−24 values were not significantly different from each other, suggesting that the taste-masked orally disintegrating tablets are bioequivalent to commercial tablets in rabbits[39].

Promethazine Hydrochloride taste masking for ODT preparation was also performed by coating . Eudragit E100 and solvent evaporation techniques were employed as coating polymer and a coating technique , respectively . Sublimation method was used to prepare the ODT by using camphor as a subliming agent, sodium starch glycolate and crospovidone as a superdisintegrant . Tablets were evaluated with regard to a variety of pharmacopoeial tests, drug release, and disintegration time in the oral cavity and taste masking effeciency . In vitro dissolution studies at pH 6.8 showed that no significant amount of drug is released while tablet is in mouth and approximately 92.3% of the release takes place in 15 min at gastric pH of 0.1N HCl indicating that taste masking the drug with the pH-sensitive polymer does not affect the release of the drug in the stomach. Sensory evaluation for taste by a time intensity method on 6 healthy volunteers confirms the successful formulation of the oral palatable fast disintegrating tablets which disintegrates in the oral cavity in 15±0.4 s[40].

Cyclodextrins Complexation:

Cyclodextrins are ‘bucket-like’ molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type[41]. As a result, cyclodextrins possess the ability to include guest molecules inside their cavities, forming inclusion complexes. These inclusion complexes can enhance drug solubility, mask bitter taste of the active pharmaceutical ingredient (API) and prevent degradation of drug molecules[42].

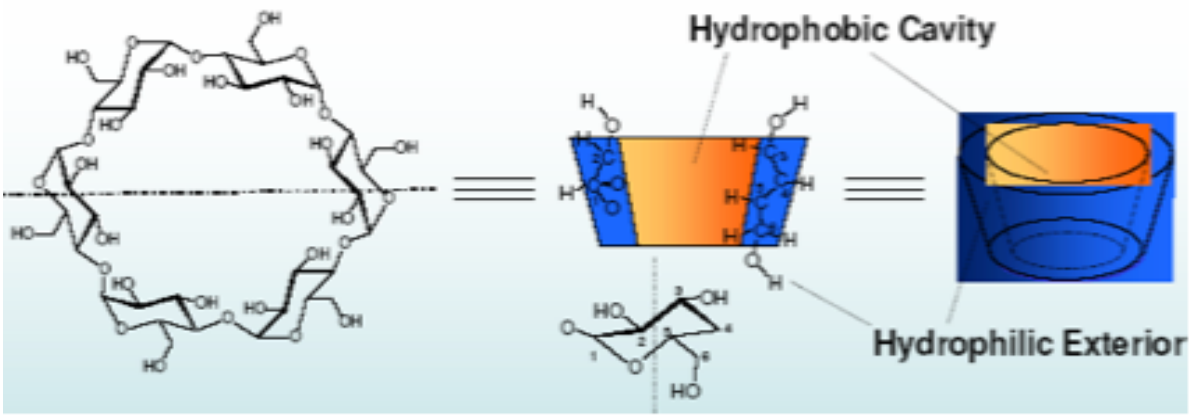

Fig. 2. Cyclodextrins structure and inclusion complex formation

The a-, b- and g-CyDs are the most common natural CyDs, consisting of six, seven and eight glucose units, respectively. Recently, various kinds of CyD derivatives, such as hydrophilic, hydro- phobic and ionic derivatives, have been devel- oped to extend physicochemical properties and inclusion capacity of natural CyDs[43].

Table 3 :Chemical structures of cyclodextrins derivatives[44].

Derivative	R_1	R_2	R_3
Hydrophilic derivatives			
Methylated cyclodextrins:			
▪ 2,6-di-O-methyl-cyclodextrins	CH_3	H	CH_3
▪ 2,3,6-tri-O-methyl-cyclodextrins	CH_3	CH_3	CH_3
▪ Randomly methylated cyclodextrins	H or CH_3	H or CH_3	H or CH_3
Hydroxylalkylated cyclodextrins:			
▪ 2-hydroxyethyl-cyclodextrins	H or CH_2CH_2OH	H or CH_2CH_2OH	H or CH_2CH_2OH
▪ 2-hydroxypropyl-cyclodextrins	H or $CH_2CH(OH)CH_3$	H or $CH_2CH(OH)CH_3$	H or $CH_2CH(OH)CH_3$
Branched cyclodextrins:			
▪ 6-O-glucosyl-cyclodextrins	H	H	H or glucose
▪ 6-O-maltosyl-cyclodextrins	H	H	H or maltose
Hydrophobic derivatives			
Alkylated cyclodextrins:			
▪ 2,6-di-O-ethyl-cyclodextrins	C_2H_5	H	C_2H_5
▪ 2,3,6-tri-O-ethyl-cyclodextrins	C_2H_5	C_2H_5	C_2H_5
Acylated cyclodextrins:			
▪ 2,3,6-tri-O-acetyl-cyclodextrins	$COCH_3$	$COCH_3$	$COCH_3$
▪ 2,3,6-tri-O-propanoyl-cyclodextrins	COC_2H_5	COC_2H_5	COC_2H_5
▪ 2,3,6-tri-O-butanoyl-cyclodextrins	COC_3H_7	COC_3H_7	COC_3H_7
▪ 2,3,6-tri-O-valeryl-cyclodextrins	COC_4H_9	COC_4H_9	COC_4H_9
▪ 2,3,6-tri-O-hexanoyl-cyclodextrins	COC_5H_{11}	COC_5H_{11}	COC_5H_{11}
▪ 2,3,6-tri-O-octanoyl-cyclodextrins	COC_7H_{15}	COC_7H_{15}	COC_7H_{15}
Ionizable derivatives			
▪ 6-O-(carboxymethyl)-cyclodextrins	H	H	H or CH_2COONa
▪ 6-O-(carboxymethyl)-O-ethyl-cyclodextrins	C_2H_5	C_2H_5	H, C_2H_5 or CH_2COONa
▪ Cyclodextrin sulfates	H or SO_3Na	H or SO_3Na	H or SO_3Na
▪ Sulfobutyl-cyclodextrins	H or $(CH_2)_4SO_3Na$	H or $(CH_2)_4SO_3Na$	H or $(CH_2)_4SO_3Na$

.

Literature Review

The Technique of complexation with CD was applied to mask the intensely bitter taste of Aceclofenac (ACF) prior to its formulation as ODT. Hydroxypropyl-b-Cyclodextrin (HPbCD) complex with the drug was prepared by kneading and Neutralization methods in a molar ratio of 1:1 .

The kneading method (KM) involves the trituration of specific quantities of HPbCD according to molar ratio with the drug in a pestle for 2 h. The complex prepared was placed in a desiccator for 48 h to ensure proper drying. While the neutralization method involves the dissolving the drug and HPbCD in 10 mL of 0.1 N sodium hydroxide solutions with mixing Hydrochloric acid was added drop wise till the pH 7.50–7.55 at which the complex is precipitated. The precipitate formed was filtered through Whatman filter paper of 0.45 lm washed with water until it was free from chloride ions. The residue was air dried at room temperature. The complex prepared was placed in a desiccator for 48 h to ensure proper drying.

DSC analysis of the prepared complexes showed considerable diminution of the diffraction peaks, suggesting that it is less crystalline than the pure drug and The endothermic peak of aceclofenac at 152.9 °C disappeared but showed only peak corresponding to HPbCD with reduced intensity as a consequence of interaction between the components. This phenomenon is an indicative of complex formation/ drug amorphization and/or stronger interaction in the solid state between aceclofenac and HPbCD.

FTIR analysis of ACF–HPbCD obtained by and inclusion complexes prepared by KM and NM, shows no sharp peak in 3,400 cm-1, suggested that the hydroxyl group of aceclofenac was entrapped into the host cavities, during inclusion complexation as shown in

Properties like hardness, friability, and drug content of tablets of all the batches were found to be within acceptable limits as shown in Remarkable improvement in the in vitro drug release profiles in pH 6.8 phosphate buffer was observed with all complexes, especially the neutralization. The complexes of ACF–HPbCD (1:1) was compressed into tablet and properties of tablets such as tensile strength, wetting time, in vitro disintegration time of tablets containing complex of aceclofenac–HPbCD (NM) shows lesser DT

and wetting time compared to tablets containing complex of aceclofenac–HPbCD (kneading method) and aceclofe- nac–HPbCD (PM).

Between the two used disintegration test methods, a newer developed method was found to provide more comparable results with the in vivo test. Taste evaluation of ODT in human volunteers revealed considerable taste masking with the degree of bitterness below threshold value. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity [45].

In another study, Cetirizine hydrochloride (HCl) was taste masked by complexation with different cyclodextrins (Beta-cyclodextrin and HP-beta (HP-b)-cyclodextrin) using Zydis process . It is distinguished from lyophilization by the rapid freezing of using liquid nitrogen tunnels, with a separate subsequent freeze-dryer stage. The separate freezing and freeze-drying steps are critical to producing the rapid disintegrating properties of the table methods .

The oral lyophilisates were produced by firstly dissolving the active ingredients and a carrier material composed of gelatin and mannitol in an aqueous solution, using a conventional pharmaceutical mixer, then additional excipients such as cyclodextrins, pH modifiers, flavors and sweeteners are also added and allowed to dissolve. The mixture is then dosed by weight into the pockets of preformed blister packs. Then, the water in the suspension is frozen at <60 C in the blister pockets by passing through a liquid nitrogen tunnel to rapidly freeze the formulation and provide ice crystals of a size that ultimately promotes the rapid disintegration of the freeze-dried tablet. The frozen units are loaded into low temperature freezer for short-term storage (<2 days), then loaded onto the shelves (pre-cooled <10 C) of a specially designed freeze-drier, where a vacuum is then applied to the frozen product within the freeze dryer chamber and the shelf temperature is increased to above 0 C until lyophilisation is complete. Once dried, the units in the blister packs are sealed.

Disintegration testing showed rapid dispersion time. The dissolution testing results for the CD formulations complied with USP criteria, with the release profile of cetirizine HCl demonstrating over 85% release in 30 min. Accelerated stability testing was performed and the dissolution profile of both cyclodextrin formulations (b- and HP-b-CD) remained unchanged after six months' storage at 40 C/85% RH. The physical appearance and

microbiological purity of the tablets remained the same throughout the stability study. Taste masking was evaluated using the electronic taste sensing system and human volunteers .Taste-masking was achieved b-CD, followed by HP-b-CD, and that higher levels of the CD provided a greater taste-masking effect. The human taste trial (30 volunteers aged 18 -63) confirms the acceptability of the selected formulations [46].

Ion Exchange Resin Approach

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups. The most frequently employed polymeric network is a copolymer of styrene and divinylbenzene [47].

The various ion exchange materials available can be classified as shown in Fig. 1 on the basis of nature of structural and functional components and ion exchange Process. Ion exchange resins contain positively or negatively charged sites and are accordingly classified as either cation or anion exchanger as shown in table 3 below [48].

Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions[49]. This suitably masks the unpleasant taste and odor of drugs. Drug release from the resin depends on the properties of the resin and the ionic environment within the gastrointestinal tract (GIT). Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecules out of the resins[50].

Table 4: Common ion exchange resins

Type of resin	Functional group	Functional backbone	Commercial resins
Strong anion	$-N^+R_3$	Polystyrene-DVB	Amberlite IR 400, Dowex 1, Indion 454, Duolite AP 143
Weak anion	$-N^+R_2$	Polystyrene-DVB	Amberlite IR 4B, Dowex 2
Strong cation	$-SO_3H$	Polystyrene-DVB	Amberlite IR 120, Dowex 50, Indion 244, Purolite C 100 HMR, Kyron -T-154
Strong cation	$-SO_3Na$	Polystyrene-DVB	Amberlite IRP 69, Indion 254, Tulsion-T-344
Weak cation	-COOH	Methacrylic acid-DVB	Amberlite IRC 50, Indion 204-234, Tulsion 335, 339, Purolite C 102DR, Kyron-T-104, Tulsion T 335, Doshion P544 (R)
Weak cation	-COOK	Methacrylic acid-DVB	Amberlite IRP 88, Indion 234, Tulsion T 339, Kyron-T-134

Literature Reviews

The utilization of the ion exchange resins (Indion 294 and Indion 204) as a taste masking agent for Tinidazole , a broad spectrum antiprotozoal agent having a bitter taste. Drug-resin complexes were prepared by wet granulation method with different concentration ratios of drugs and the resins .Lactose was used as diluent and polyvinylpyrrolidone k-30 as binder. The granules were evaluated for their flow properties . The ODT were formulated by direct compression of tinidazole:Indion 204 granules after incorporating different superdisintegrants croscarmellose sodium and crospovidone. Orange flavour is used as a flavouring agent. Magnesium stearate was added as lubricant. The pre and post compression parameters were evaluated for the prepared ODT. Results showed that the granules were free flowing and met the test for weight variation, hardness, thickness and diameter. Rapid disintegration time (21 sec.) was achieved in tablets containing crospovidone as super disintegrating agents with Indion 204. From dissolution study, it is concluded that complete drug release was obtained within 15 minutes in all batches. Relatively acceptable taste was achieved in tablets containing drug: resin ratio 1: 1.5. FTIR study shows compatibility between drug and excipients[51].

The bitter taste of Phencynonate HCl should be masket prior to its development as an ODTs . For this purpose , Amberlite IRP-88 which is a weakly acidic resin was employed in nature. The cationic drugs with special moiety such as amino functional group are adsorbed on to the carboxylic functional group of the resin to form a complex which does not dissociate under salivary pH conditions.The drug– resin complexes (DRCs) were prepared by adsorbing the drug onto ion exchange resin using a batch method. Firstly, phencynonate HCl was dissolved in deionized water and Amberlite IRP-88 was slowly added under constant mixing at room temperature until the adsorption equilibrium was reached. Secondly, the drug–resin complex was separated from the supernatant by filtration, washed with sufficient water to remove any unattached drugs, and then dried. The resultant complex was characterized by SEM , XRD and DSC . The ODTs were prepared by direct compression method for the powder blend consisting of the proper amounts of complex equivalent to the dose of the drug , D-mannitol and mannitol–starch mixture (filler) and crospovidone, sodium starch glycolate or croscarmellose sodium (superdisintegrants) for 10min and then magnesium stearate (lubricant) . In vitro properties (dissolution, wetting time and disintegration time) and in vivo behavior (disintegration time and taste-masking effect) in healthy volunteers of the prepared ODTs were also investigated.The SEM, XRD and DSC revealed that the drug was changed from the crystal structure to the amorphous form in the DRC. The wetting time, disintegration time and dissolution of the ODTs were remarkably improved compared to the conventional tablets. In vivo taste-masking efficiency and dissolution patterns of ODTs were also improved.Hardness and friability results ensured the mechanically stable of the tablets .The in vitro disintegration time for each formulation of ODTs was from 9 to 96 s and decreased with the content of superdisintegrants increasing from 10% to 20%. The in vivo disintegration time of all ODTs was delayed as compared with in vitro results [(52)].

Another example is the taste masking of donepezil bitterness by ion exchange resin drug complex prepared at three different ratios (1:2, 1:1, 2:1) . The complexation was carried out by using a spray- drying method. The resultant complex was prepared into ODT containing superdisintegrants (crospovidone, croscarmellose sodium, and sodium starch glycolate) were prepared by the direct compression method. The physical properties and morphologies of the drug -resin complex were characterized by scanning

electron microscopy (SEM), X-ray powder diffraction (PXRD) and electrophoretic laser scattering (ELS), respectively. The in vitro taste masking efficiency was measured with an electronic tongue (e-Tongue). In vivo bitterness scale was also evaluated by human volunteers and then we defined a new term, (bitterness index)to link in vitro e-Tongue. There was a good correlation between in vitro e-Tongue values and in vivo bitterness index , in vitro/in vivo disintegration time. The optimal IRDC-loaded ODTs displayed similar drug release profiles to the reference tablet (Aricept® ODT) in release media of pH 1.2, pH 4.0, pH 6.8 and distilled water but had significantly better palatability in vivo taste masking evaluation[53].

Miscellaneous taste masking methods:

By Effervescent Agent:

Effervescent agent is a useful technique for dosage forms that are not dissolved in water prior to administration. The disintegration of ODT in the mouth is caused by the action of an effervescent agent, activated by saliva[54].

Literature Review

A Novel approach was employed to tablets with enhance palatability of levocetirizine HCl by preparing taste-masked blends of using HPβ-CD by IC technique or MN by SD technique .The chosen blends from each technique were incorporated into different formulations of effervescent tablets containing different percentages of effervescent mixtures.

Accurately weighed amounts of the Levocet and HPβ-CD or MN at different molar and weight ratios, respectively, were thoroughly mixed . A suitable amount of solvent (ethanol:water 1:2) was added portion-wise while mixing until complete solubility or dispersion was achieved. The different blends were dried at 40 C in a thermostatically controlled oven. The dried powder was ground, sieved through 80#, and stored in well-closed amber-glass containers. Z use of HPβ-CD at a molar ratio of 1:10 showed a considerable positive effect on the taste masking of the drug through the complete inclusion of the drug within the crystal lattice of the used CD. This mechanism was confirmed through FT-IR and DSC studies. On the other hand, the SD of levocetirizine HCl:MN prepared at a weight ratio of 1:20 showed an obvious increase in the acceptability of the taste of the drug, devoid of any possible drug–carrier.

The effervescent tablet blends prepared were subjected to several in vitro pre- and post compression evaluation tests, inc. Results revealed that all prepared effervescent blends possessed acceptable flowability and compressibility properties. Prepared compressed tablets showed an immediate high in vitro drug release within 5 minutes. All prepared tablets disintegrated within 14–60 seconds in saliva with pleasant taste and smooth mouth feel[55].

Granulation

Granulation is major and a common process in tablet production. It can be used for taste masking of a bitter taste drug[56]. In this approach, saliva-insoluble polymers are used as binding agents in the tablet preparation. As these polymers are insoluble in saliva, thus the bitter taste of the drug can be masked[57]. The taste masked granules can also be formulated as chewable tablets and rapidly disintegrating tablets[58].

Literature Review

Granulation of Ranitidine was used as an attempt to mask its better taste and sulfur like odor when an ODT preparation is to be applied. The granules were prepared by adding ranitidine to the hydrated NaCMC gel with a viscosity of about 70 cps. The mixture was dried in a vacuum oven at 50 °C for two hours. The dried gel was triturated and passed through a 30 mesh sieve. Different ratios of polymer to drug were prepared, also containing saccharin and xylitol as sweeteners. The selected granular formulation was developed into an ODT containing avicel as the filler, sodium starch glycolate as the super-disintegrant and sodium benzoate as the water soluble lubricant. The direct compression method was applied for tablet preparation and four series of taste masked formulations were prepared .

The results obtained for flowability, based on the Carr's index and Hausner's ratio, showed poor powder flow which needs the addition of appropriate lubricants for modification.Flowability of all formulations was improved in comparison with the ranitidine powder, due to the addition of property modifying excipients such as sodium benzoate. Furthermore this formulation complied well with all the physicochemical tests conducted, particularly disintegrating within 5 second and providing a desirable taste and aftertaste within the buccal cavity[59].

Solid Dispersion Technique

This technique is very useful for taste masking; it is done by dispersion of one or more active ingredients in an inert solid carrier[60]. For example, The HME has multiple inherent advantages such as elimination of organic solvents and fewer processing steps compared to the other pharmaceutical technologies, it has been used to form solid dispersions in order to increase the bioavailability of many drugs by increasing their solubility[61]. In this technique a conversion of the crystalline lattice to the amorphous phase occurs and then disperses the drug molecules in a suitable carrier in order to enhance the solubility of the drug and mask the taste[62].

An example of using Solid dispersion techbique for taste masking was employed for Mefenamic acid. It has an unpleasant taste, which could lead to patient compliance issues. HME technology not only masked the taste but also improved the solubility with maximized drug load. Eudragit® EPO was chosen as the primary matrix-forming polymer due to its cationic nature that could facilitate drug–polymer interactions. In addition, EPO's solubility in gastric media up to pH 5 renders it an excellent carrier in order to provide immediate release of the active substance. Also It withstands the HME process because it is extremely thermally stable[63][64].

Literature Review

The first research example related to the application of solid dispersion technique for taste masking of Mefenamic acid . The SD was prepared by blending the drug with Eudragit® E PO at different drug loadings using a V-shell blender. The binary mixtures of drug and polymer were extruded using a co-rotating twin-screw extruder at 110°C with a screw speed of 100 rpm. The extrudates were further processed using a comminuting mill, which was sieved by USP mesh (#35). DSC studies of the extrudates showed complete miscibility between the drug and Eudragit® EPO at all of the drug loadings.FT-IR analysis was performed on the extruded samples to study the drug-polymer interactions and corroborate the miscibility results obtained by DSC.

The selected extrudes were determined based on content uniformity and dissolution study and the used inthe ODT preparation after mixing with the

appropriate excipients. The ODT were prepared by direct compression. The ODTs were successfully prepared with excellent friability and rapid disintegration time in addition to having the desired taste-masking effect. All of the extruded formulations and the ODTs were found to be physically and chemically stable[65].

Another example is to mask the bitter taste of the well known NSAID Ibuprofen. Hot-melt extrusion was employed using the Eudragit EPO as a polymer matrix. The drug- excipients composition consisted of IBU/EPO/talc was prepared and compared at two different ratios of 25/25/50 and 50/40/10 (% w/w). The extrudates were collected as strands with diameter of approximately 1.5mm and milled under cryogenic milling conditions (6000 rpm, 10min) to obtain the final taste-masked granules. The particle size distribution of the produced IBU granules was measured by dry sieving. The IBU/EPO extrudates were studied by XRD analysis and no peaks were apparent in the diffractogram indicating amorphous IBU . DSC analysis showed that the presence of a single Tg confirms the complete miscibility of IBU/EPO and the creation of a glassy solution where IBU is molecularly dispersed within EPO.

The extruded granules were incorporated in ODT formulations with various superdisintegrants in different forms such as sodium croscarmellose and cross-linked polyvinylpyrrolidone grades. Precompression analysis showed excellent batch flowability and compressibility properties. The ODT were prepared by a direct compression.

The ODTs developed showed disintegration times and crushing resistance similar to commercial Nurofen® tablets but improved tablet friability. Also the increased IBU release rates of the developed ODTs were faster to the commercial Nurofen® tablets.Estimation of taste masking efficiency was performed on 10 healthy human volunteers; the equivalent of 10 mg of pure IBU (200mg for Ibuprofen) was held in the mouth for 10 s and then spat out, and 1 ODT (containing equal amounts of IBU) was held in the mouth until complete disintegration (three tablets per trained volunteer). Bitterness was recorded immediately and at several intervals for 15min according to the bitterness intensity scale from 0 to 3 where 0, 0.5, 1, 2, and 3 indicate no, threshold, slight, moderate, and strong bitterness[66].

Another example of this technique is the preparation of Tizanidine HCl granules . Solid dispersion of the drug with eudragit E100 was prepared to mask its bitter taste. Solid dispersion of Tizanidine HCl with Eudragit E100 was prepared in a ratio of 1:3 by solvent evaporation method. Accurately weighed quantity of Eudragit E100 was dissolved in methanol, weighed quantity of tizanidine HCl was further dissolved in the above solution by stirring. The solution was transferred to a Petri dish, where the solvent was allowed to evaporate overnight at room temperature. The mass obtained in each case was crushed, pulverized, and sifted through 80 mesh.The ODT was prepared using spray dried coprocessed excipients such as microcrystalline cellulose with SSL-hydroxypropyl cellulose grade Before compression flowability of powders were determined, the static angle of repose , lower angle of repose indicates good flow property which is due to increased sphericity so the granules obtained by spray drying technique . The chemical stability of the prepared formula was confirmed by FTIR and there was no significant shift in characteristic absorption bands of the drug during co-processing and in formulation confirming compatibility and stability of the drug. DSC analysis showed shifting in the pure drug peak from 291.81° to lower range 251° in the selected formula with broadening and reduction in the height of the peaks .These changes indicate that change in the particle size gave a more amorphous type of product, which attributes to improved drug release from formulations. It was also observed a strong correlation between wetting time and disintegration time of the tablet[(67)].

Conclusions

Taste masking is an essential requirement for mouth dissolving tablets for commercial success. Mouth dissolving tablets, which disintegrate or dissolve in the saliva produce a positive or negative taste sensation. Most of the drugs have an unpalatable taste in which taste masking plays a critical role in formulating ODT. The negative taste sensation of drugs can be reduced or eliminated by various approaches like Addition of Sweeteners and Flavors, prodrug formation, Coating of Unpleasant drugs, Cyclodextrins Complexation,ion exchange resin and miscellaneous taste masking methods. Conventional disintegration tests for ordinary tablets may not allow precise measurement of the disintegration time of ODTs because of their fast disintegration, so a modified dissolution apparatus is applied to an ODT. When developing ODT formulations, it is important to evaluate the effect of different excipients on the disintegration time, such as some coatings of the tablets. In vitro testing may not always reflect the real in vivo disintegration of tablets, so the use of an electronic (e) tongue has been reinforced with vivo studies on volunteers to insure the efficacy of taste masking methods.

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