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A REVIEW ON TASTE MASKING STRATEGIES FOR BITTER DRUGS

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ABSTRACTS

Taste is an important factor in the development of dosage form. Many orally administered drugs elicite bitter taste. Palatability is an extremely important factor in ensuring the likelihood that the recipient will take medicine. Previously the attitude of "Worse the taste of medicine, better the cure" was observed, but now-a-days several approaches of masking the bitter taste have been developed. It includes adding sugars, flavors, sweeteners, use of lipoproteins, numbing taste buds, coating drug, microencapsulation, multiple emulsion, viscosity modifier, vesicles and liposomes, prodrug and salt formation, inclusion and molecular complexes, solid dispersion, application of Ion Exchange Resins (IERs).Taste masking becomes a prerequisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric population. Formulating orodispersible, melt in mouth, buccal tablet and other formulations which comes in contact with taste buds taste is one of critical factor to be consider. Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance which intern decides the commercial success of the product.

Keyword:- Palatability, Orodispersible, Microencapsulation.

1.INTRODUCTION

Flavors of drugs, food or drink is detected by sensation of taste. Palatability and patient compliance is a key parameter to be considered while formulation of oral dosage form [1]. Oral administration is the most accepted routes among multiple drug administration route due to its advantage such as easy, administered by self and painless which increases patient acceptance. The drug of poor palatable should focus mainly on enhancing the palatability [2]. Recent years have seen a rise in the need of acceptable palatability for bitter medications when administered orally, especially for pediatrics and geriatric patients. The combination of taste, smell, and, to a lesser extent, other sensory experiences is known as palatability [3].

There are many medications that contain bitter tasting active ingredients. The harshness of over-the-counter medications, such as cough and syrups, discourages patient adherence. One of the many significant formulation issues that some medications have unpleasant taste. The pharmacist is currently faced with the issue of unpleasant and bitter taste of medications [4]. ODT (Oral Disintegrating tablet) systems were created in the late 1970s to provide pediatric and geriatric patients who had trouble swallowing traditional oral solid dose forms with an alternative to tablets and capsules. The terms orodispersible tablets, mouth dissolving tablets, fast melt tablets, rapid dissolving tablets, and quick dissolving tablets are all used to refer to oral disintegrating tablets [5].

The most popular techniques for taste masking include a variety of chemical and physical techniques that prevent the medication produced by taste receptor interaction. Use of taste enhancer is the simplest technique. Where these approaches fall short, more sophisticated approaches are used. The use of polymer coating, inclusion complex reaction, anesthetic drug complex, ion exchange resins, numersous emulsion, and solubility limiting approaches are only a few of the ways that have been identified for masking tastes [6]. The current review aims to provide a concise overview of both conventional and modern taste masking dosage form technologies, as well as different approaches to measuring the effectiveness of taste masking. To combat the drug's poor taste, two methods are

frequently used. The first involves lowering medication solubility in saliva, where it is important to strike a balance between lowered solubility and bioavailability. Altering the drug's capacity to interact with taste receptors is an alternative strategy [7].

The fact that chemicals with various structural characteristics can produce a single bitter sensation indicates that various mechanisms are involved in the perception and transduction of bitterness. Some of these systems might be used to perceive both sweet and bitter tastes. Compounds that are bitter can become extraordinarily sweet or vice versa with minor modifications in their chemical structure. For instance, D-tryptophan tastes sweet while L-tryptophan is bitter. The interaction between bitter and sweet occurs at the neuronal level and can enhance or decrease one another's flavors in a solution. Individual differences in the ability to detect some bitter tastes are significant [8].

2.PHYSIOLOGY OF TASTE

Taste buds, which are groups of taste receptor cells (50 to 100 cells) grouped together in clusters like bananas, mediate the experience of taste and transmit it to the brainstem's central nervous system (CNS) via sensory neurons. Chemoreceptors that are triggered by oral medications that dissolve in saliva enter the mouth through the taste hole and engage with surface proteins known as taste receptors to cause electrical changes in taste cells that then send signals to the brain [9].

When a tastant (such as a drug or food) interacts with taste receptor cells in the taste buds, taste transduction begins. The release of a gustducin is triggered by the tastant's binding to G-Protein Coupled Receptors (GPCRs) in the cells. Gustducin stimulates the effector enzymes phosphodiesterase IA (PDE) or phospholipase C beta2 to start the taste sensation process. The second messengers cyclic adenosine monophosphate (cAMP), inositol 1, 4, 5-triphosphate (IP3), and diacylglycerol (DAG) are affected by the effector enzyme at the intracellular level. The second messengers cause the sodium, potassium, and calcium channels on the extracellular membrane as well as the calcium channel inside the cell to open. This ionisation depolarizes the cell, releasing neurotransmitters that convey nerve impulses to other parts of the body [10]. The resulting sensations are transmitted to the brain by the ninth cranial nerve and tastes are detected. The sensitivity of the tongue to different sensation is affected by the age and is varies widely among individuals [9,10].

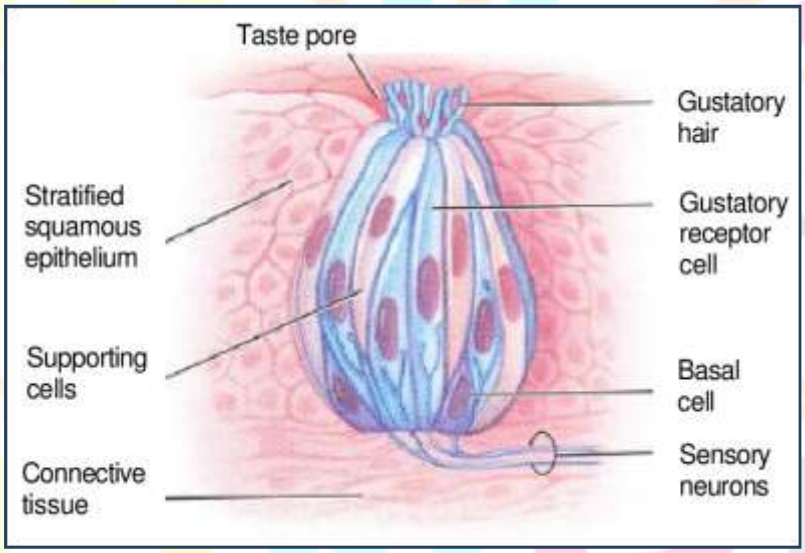


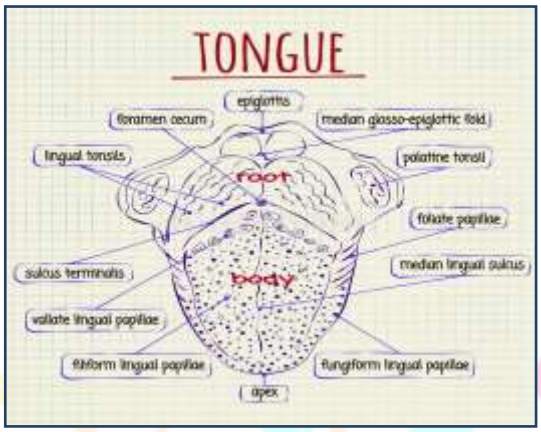
Fig 1. Physiology of taste buds

Table 1. Specific area of tongue and threshold concentration for primary taste sensations

Taste	Area of tongue	Threshold concentration (%)
Sweet(sucrose)	Tip	0.5
Salt (NaCl)	Tip and sides	0.25
Sour (HCl)	Sides	0.007
Bitter (Quinine)	Back	0.00005

The sense of taste

The taste can be defined biologically as the chemical reaction arising from responses of the four main traditional taste perceptions: sweet, salt, bitter and sour and the recently discovered fifth basic taste umami, the taste of certain amino acids (e.g. glutamate, aspartate and related compounds) which is identified by Kikunae Ikeda in 1909[11]. The main function of the taste is to drive the appetite for the body requirements such as sugars and proteins and to protect us from poisons-"gatekeeper to the body".



3.AIMS AND OBJECTIVES

- To prepare taste masked complexes as resinate and polymer carrier system by spray drying.
- To evaluate drug-resin complex and spray drying polymer carrier system.
- To formulate taste masked drug-resin complex into suspension.
- To formulate taste masked polymer carrier system into reconstituable suspension.
- To mask bitter taste of an antibiotic API.
- To check feasibility of incorporating the taste masked complex into a palatable formulation.
- To evaluate the optimized formulation for various quality control parameters.
- To carry out stability studies according for optimized formulation

4.TASTE MASKING AND IT'S TECHNIQUE

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. Taste masking technologies are very important for improving patient compliance and better therapeutic efficacy.

The following characteristics are necessary for an ideal flavor masking procedure and formulation [12]:-

1. Involve the fewest possible processing equipment.
2. Use readily accessible and reasonably priced excipients to effectively disguise flavor.
3. No negative impact on the drugs bioavailability.
4. Lowest production cost.
5. May be performed in a warm environment.
6. Demand excipients with high margins of safety.
7. Quick and simple to prepare.

Various methods are available to physically mask the undesirable taste of drugs, some of which are described below [13].

1. Taste masking with flavors, sweeteners, and amino acids

2. Polymer coating of drug

3. Formation of inclusion complexes

4. Ion exchange resin complexes

5. Solid dispersion

6. Microencapsulation

7. Mass extrusion

8. Multiple Emulsions

9. Development of Liposome

10. Prodrug concept

11. Taste masking by spraydrying technique

12. Taste masking by adsorption

13. Taste Masking with Lipophilic Vehicles like lipids and lecithins

1.Taste masking with sweeteners and flavors

The easiest method for taste masking is this technique. However, this strategy does not work well with really bitter medications. To increase the effectiveness of taste-masking procedures, artificial sweeteners and flavours are typically utilised alone. The bitter-tasting ingredient eucalyptus oil is a main ingredient in many mouthwash and cough medicine formulations. By using an agent like fenchone, borneol, or isoborneol, its bitter taste can be concealed. Certain flavoring agents cooling effects help to lessen the feeling of bitterness. The only physiological action required is to quickly or gradually numb taste buds, allowing the cooling effect to develop after intake [14].

Table 2: Flavor choice

Taste sensation	Suggested flavour
Salt	Butterscotch and vanilla
Bitter	Walnut and mint
Sweet	Fruit and vanilla
Sour	Citrus flavour

2.Polymer coating of drug

For a variety of pharmaceutical applications, coating is a very helpful approach. The manufacture of sustained release, gastro-resistant dosage forms is its main usage, but it also plays a significant role in flavor masking. Applying a thick layer of coating material alone may not be sufficient to disguise the taste of some medications with unpleasant tests. In addition to making it difficult to achieve the proper drug release profile, thick coating might be troublesome in terms of size and cost. However, the taste of a bitter medicine can be totally covered up by using the proper sort of coating material, without negatively impacting the targeted drug release profile. Any polymer that is non-toxic and soluble at pH 7.4 and soluble at stomach pH considered acceptable for masking of taste [15].

3.Formation of inclusion complexes

A mechanism known as inclusion complexation involves the inclusion of the guest molecule into the hollow interior of a bunch or complexing agent. The complexing agent can mask a medicine's sour taste by either lowering the drug's oral solubility when consumed or reducing the amount of drug particles exposed to taste receptors. The most popular complexing agent for inclusion type complexes is cyclodextrin. It is a sweet, non-toxic, starch-derived cyclic oligosaccharide. The following medications are some examples of those for which creating inclusion complexes can reduce their bitter taste [16].

In order to increase the solubility in various electrolyte solutions, inclusion complex creation has a twofold effect by solubilizing two lipophilic model pharmaceuticals (Indomethacin and furomeside) in the hydrophobic cavity of hydroxypropyl-cyclodextrin. Regarding the solubility characteristics, buffer containing phosphate ions were generally superior to other electrolyte media, and freeze-drying had a positive impact on all the desirable features [17].

4.Ion exchange resin complexes

The creation of sustained release dosage forms using ion exchange resins to conceal the taste of bitter medications. The ability to exchange counter-ions in the aqueous solutions around them is provided by ion exchange resins, which are cross-linked, water insoluble polymers with repeated salt-forming groups. The bitterness of prescription drugs has the oral administration of bitter

medications is frequently complicated by their unpleasant taste, which results in non-compliance and further deterioration of the diseased condition. This plays a crucial role in patient compliance. Based on IER, one of the widely used methods for disguising the bitter taste of medications. Depending on the type of medicine, weak cation exchange or weak anion exchange resins are employed to mask flavor. The drug resin compound has no aftertaste and has no discernible flavor, but its bioavailability is unaffected. To maintain a consistent drug concentration for a predetermined amount of time with a minimum of adverse effects, sustained release dosage forms are created to release a drug at a predetermined rate. The application of IER in the creation of continuous release. Because of their ability to delay the effects of drugs, formulations are important. This review also includes a number of patents on formulations that use IER for prolonged release and flavor masking [18].

Fig 3. Ion Exchange Resins [19]

5.Microencapsulation

The technique of encasing or wrapping solids, liquids, or even gases in another material with a continuous coating of polymeric components to produce microscopic particles is known as microencapsulation (ranging from less than 1 micron to several hundred microns in size). In this procedure, thin coating is used to encapsulate and surround small discrete solid particles or small liquid droplets and dispersions in order to preserve the environment and regulate the release characteristics or availability of coated active components. The microencapsulation procedure is frequently used to alter and postpone the release of drugs from various pharmaceutical dosage forms. The contents encapsulated or wrapped within the microcapsules are known as the covering materials or wall materials, and the pay-load materials or nucleus are known as the core materials [20]. The most popular polymer for taste-masking microencapsulation is Eudragit E. A cationic polymer called Eudragit E is composed of methyl methacrylate, butyl methacrylate, and dimethylaminoethyl methacrylate. Up to a pH of 5, it is soluble in both stomach juice and slightly acidic buffer solutions. Eudragit E has a glass transition temperature of 48^0 C. It dissolves quickly by generating salts at acidic pH levels lower than 5, but forms swellable, permeable, and insoluble films when used as a covering polymer in microencapsulation at pH 5 or higher. Contrary to saliva, which has a pH between 6.8 and 7.4, this polymer dissolves right away in gastric juice, which has a pH between 1.0 and 1.5 [21].

6.Prodrug concept

A prodrug is an inert drug precursor that has undergone chemical modification; when it is biotransformed, it releases the pharmacologically active parent substance. The degree of a bitter taste reaction or the taste receptor-substrate adsorption constant may be altered by altering the chemical configuration of the parent molecule. Prodrugs can be used to change the parent molecule's membrane permeability, hide bitterness, boost lipophilicity, enhance absorption, and raise or reduce the parent molecule's water solubility. In table.no.3, examples of prodrugs are presented.

Table.No.3 Examples of Prodrugs with improved taste [22]

Parent drug	Prodrug
Erythromycin	Erythromycin Propionate
Clindamycin	Clindamycin Palmitate ester
Chloramphenicol	Chloramphenicol Palmitate ester
Morphine	N-oxide derivatives of all Morphine
Triamcinolone	Triamcinolone diacetate ester
Gabapentin	Gabapentin XP_{13512}
Norfloxacin	Norfloxacin alkyl carbamates

7.Taste masking technique by adsorption

In order to adsorb a substance, one must first prepare a solution of the substance, combine it with an insoluble powder that will adsorb the substance, drain the solvent from the resulting powder, and then dry the resulting powder. The dried adsorbates are then used to create the final dosage form. Several substrates favour. For the creation of an adsorbate of bitter drugs3, veegum, bentonite, silica gel, and silicates can be utilised. Adsorbates are frequently employed in conjunction with other taste-mapping techniques. The medication may be adsorbed or retained in the porous component's matrix, delaying the release of the bitter active during passage through the oral cavity and accomplishing taste muffling in this way [23]. Adsorbate of a medicine with a bitter taste is comparable to a less saliva-soluble form of that drug. In this method, bitter drug adsorbates are created by the adsorption process. In this procedure, insoluble substances like silica gel, bentonite, veegum, etc. are used to adsorb the medication solution. The resulting powder, known as the adsorbate, is dried and employed in the creation of final dosage forms [24].

8.Taste masking with lipophilic vehicles

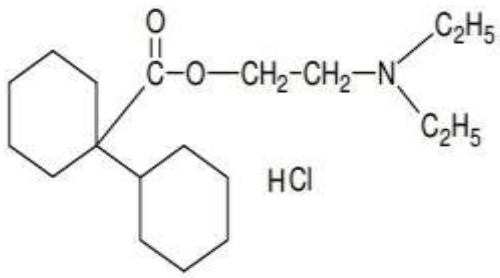
Oils, surfactants, polyalcohols, and lipids all work to coat taste buds and increase oral viscosity, making them potential taste-masking substances. Acetaminophen granules are combined with acceptable tablet excipients and sprayed with molten stearyl stearate. A component of a chewable tablet composition that masks the taste. Pharmaceutical manufacturers assert that formulations with a significant excess of lecithin or compounds similar to it can reduce bitterness [25] .

5.DRUG PROFILE[26]

DICYCLOMINE HCl

Description: Dicyclomine is mainly antispasmodic and antiulcer drug. This is mainly anticholinergic. The drug is used in sever spasm of stomach.

Molecular Structure:



Dicyclomine HCl

Molecular weight : 385.8

Storage : Store at 20° to 25°C (68° to 77°F); excursions Permitted to 15°to 30°C(59° to86°F) Maximum Dose : 750 mg

Molecular formula : C19H26ClNO2

Dissociation Constant: 6.09

Chemical name : N , N -diethylaminoethyldicyclohexanoate

Category : Anticholinergic.

Dose : Antispamodic 100 mg.

Description : Faintly White to yellowish crystalline powder. Slightly hygroscopic in nature.

Solubility : Freely soluble in methanol, soluble in ethanol (95%) and practically insoluble in chloroform.

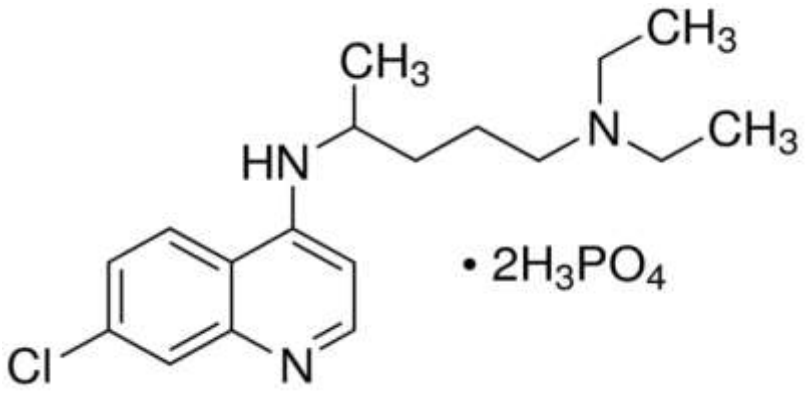
Melting point : 134-135 °C.

Therapeutic Use : Antibiotics.

CHLOROQUINE PHOSPHATE

Chloroquine phosphate is one of vast arrangement of 4 aminoquinolines examined regarding far reaching agreeable project of antimalarial research in united states amid world war second. The goal was find and less harmful suppressive executor the Quincrine.

Molecular structure:



Chloroquine Phosphate

Molecular weight : 515.9

Molecular formula : $C_{16}H_{28}ClN_3PO_4$

Chemical name : N^4-(7-Chloroquinolin-4-yl)-N^1, N^1 – diethylpentane-1,4- diamine phosphate or 7-Chloro 4-[{4-(Diethylamino)-1-meth butyl}amino] quinoline Phosphate

Category : Antimalarial.

Dose : 200 mg, 400 mg daily in divided doses

Description : A white or almost crystalline powder; odourless or almostodourless, very bitter in taste.

Solubility : Soluble in 4 part of water; very slightly soluble in ethanol (750g/h), slightly soluble to soluble in methylene chloride,slightly soluble in methanol.

Storage : Chloroquine phosphate should kept a well closed container.

6.CONCLUSION

For bitter medications in particular, taste masking is a realistic way to increase patient compliance. Various methodologies may be used to offer a palatable formulation. Innovative pharmaceutical technologies have led to the development of taste-masked medications, which not only increase the commercial gains, but they help build a company's brand. While using sweeteners to mask bitterness is a tried-and-true tactic, the current trend is exploring powerful sweeteners with natural origins that can hasten commercialization and pro drugs are discovered to be a more effective approach. One can greatly increase product liking by using these strategies and correctly evaluating the flavour masking impact. Additionally, the creation of taste masking techniques necessitates high levels of technical expertise and the need for massive experimentation.

7.REFERENCES

1.Khar R.K, Sohi H, Sultana Y. Taste masking technologies in oral pharmaceuticals; recent developments and approaches. Drug development and approaches. 2004; 30(5): 429-448.

2.Elmeshad A.N, Fares A.R, Hussein Nasr N.E. Nanocarrier in taste masking. Scientia Pharmaceutica. 2022; 90(20): 1-14.

3.Kar S, Momin M, Rathod S. Taste masking techniques for bitter drugs-an overview. International Journal Of Pharmacy and Technology. 2012; 4(2): 2100-2118.

4.Datrange P, Kulkarni S, Padalkar R.R. Development of taste masked formulation for bitter drug. Research Journal Of Pharmaceutical, Biological and Chemical Sciences. 2012; 3(3): 727-753.

5.Bin L.K. Investigational of taste masking techniques and development of Dapoxentine HCl orally disintegrating tablet. 2017; 1-24.

6.Agrawal Y.S, Barhate S.D, Luhade T.S, Pagar H.B, Sonawane R.O. Taste masking; a review. Research Journal Of Pharmacy and Technology. 2012; 5(2): 152-157.

7.Sawan M.S. Review on taste masking approaches in oral pharmaceutical dosage form. Lebda Medical Journal. 2015; 1: 33-43.

8.Guo Z. Insights of taste masking from molecular interactions and microstructures of microspheres. University of Bradford. 1-151.

9.Bakhale S.S, Dhakate C.S, Dixit G.R, Umate R.M, Upadhye K.P. Taste masking by co-crystallization: a review. World Journal Of Pharmaceutical Research. 2017; 6(7): 1531-1548.

10.Kumar D, Rathore M.S, Sharma D, Singh G, Singh M. Taste masking technologies: a novel approach for the improvement of organoleptic property of pharmaceutical active substance. International Research Journal Of Pharmacy. 2012; 3(4); 108-116.

11.Kurihara K. Glutamate: from discovery as a food flavors to role as a basic taste(umami). The American Journal Of Clinical Nutrition. 2019; 719S-722S.

12.Biswal P.K, Kesharwani A, Keshawani A, Maqbool A, Mishra M.K, Pathak S. Various approaches toward taste masking: an overview. International Journal Of Pharmaceutical Research and application. 2017; 2(4): 01-09.

13.Ahire S.B, Bankar V.H, Gayakwad P.D, Pawar S.P. A review: taste masking techniques in pharmaceuticals. An International Journal Of Pharmaceutical Science. 2012; 3(3): 68-82.

14.Hawaldar A.H, Saiffee M, Shinde N.Y, Sonawane V.M, Pawar N.A. An update of taste masking methods and evaluation techniques. Der Pharmacia Lettre. 2010; 2(6): 1-15.

15.Garg S, Kandarapu R, Nanda A. An update on taste masking technologies for oral pharmaceuticals. Indian Journal Of Pharmaceutical Science. 2002; 64(1): 10-17.

16.Chauhan R. Taste masking: a unique approach for bitter drugs. Journal Of Stem Cell Biology and Transplantation. 2017; 1(2): 1-6.

17.Alopaeus J.F, Breit K.J, Gobel A, Shande S.A, Tho I. Investigation of hydroxypropyl-beta-cyclodextrin inclusion complexation of two poorly soluble model drugs and their taste sensation effect of electrolytes, freeze-drying and incorporation into oral film formulation. Journal Of Drug Delivery Science and Technology. 2020; 1-9.

18.Bilandi A, Mishra A.K. Ion-exchange resin; an approach towards taste masking of bitter drugs and sustained release formulations with their patents. International Research Journal Of Pharmacy. 2013; 4(8): 65-74.

19.Waters HPLC Separation Modes. https://www.waters.com/nextgen/us/en/education/primers/beginers-s-guide-to-liquid-chromatography/hplc-separation-modes.html

20.Nayak A.K. Microencapsulation: seemanta institute of pharmaceutical sciences. 1-25.

21.Al-kasmi B, Alsirawan B, Bashimam M, El-zein H. Mechanical microencapsulation: the best technique in taste masking for the manufacturing scale-effect of polymer encapsulation on drug targeting. Journal Of Controlled Release. 2017.

22.Kiran A.S, Kumar R.S. Taste masking technologies: a boon for oral administration of drugs. Journal Of Drug Delivery and Therapeutics. 2019; 9(4-A): 785-789.

23.Formulation Development and Evaluation Of Taste Masked Cefuroxime Axetil Oral Suspension. Department Of Pharmaceutics KMCH College Of Pharmacy.

24.Nagpal D, Vumaneni V. Taste masking technologies: an overview and recent updates. International Journal Of Research in Pharmaceutical And Biomedical Sciences. 2012; 3(2): 510-524.

25.Minde D.S, Saudagar R.B. A review on taste masking a novel approach of new trends for the abnoxious drugs.World Journal Of Pharmaceuticals Research. 2016; 5(9): 410-428.

26.Indian pharmacoepia eighth edition. 2018; 2: 1587,1815.