Fabrication and Evaluation of Taste masking Sachats.

Guni Preethi[1]*, A.V Jithan[2]

[1]Department of pharmaceutics, Osmania University, Hydreabad Telangana, India

[2]Department of Technology Consultants, Hyderabad, Telangana, India

Introduction

Children, older persons, and many other persons including disabled or incapacitated patients often have trouble swallowing tablets or capsules. In these situations, it is desirable to provide the drug either in a chewable solid form or a liquid dosage form.1 The undesirable taste is one of several important formulation problems that are encountered with certain drugs [1]. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients.2 Masking of bitter taste of drugs is an important parameter for the improvement of patient compliance. The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario.

Chemoreceptors on the Tongue

Taste is the brain's interpretation of chemicals that trigger receptors on the tongue, which are housed in the taste buds. Molecule interacts with taste receptor on the tongue to give taste sensation, when they dissolve in saliva. This sensation is the result of signal transudation from the receptor organs for taste, commonly known as taste buds [2]. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste (Figure 1).

Four fundamental sensations of taste have been described: Sweet and salty, mainly at the tip. Sour, at the sides. Bitter, at the back. and fifth widely accepted basic taste is Umami1. (Figure 2)

Taste Signaling Pathways

Taste transduction begins with the interaction of a tastant (eg. medicine or food) with taste receptor cells in the taste buds (Fig 3). The tastant binds with G- Protein coupled receptors (GPCRS) in the cells triggering the release the release of G-Protein called Gustducin.3 (Figure 3)

Taste Blocking Mechanism

Taste sensation begins when Gustducin activates the effector enzymes phosphodiesterase IA (PDE) or phospholipase C beta-2(PLC) (Figure 4).

The effector enzyme then changes the intracellular level of second messenger such as cyclic adenosine monophosphate (cAMP), Inositol, 1, 4, 5- triphosphate (IP3) and diacylglycerol (DAG). The second messengers activate calcium ion channel inside the cell and sodium, potassium and calcium channel on extra cellular membrane. Ionization depolarizes the cell causing release of neurotransmitters that send nerve impulses to the brain that carries the signal of bitter taste and taste blockers work by interfering with taste transduction.

Taste masking technologies

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist.[7] Methods commonly used for taste masking involves various physical and chemical method that prevent the interaction of taste bud with drugs, Two approaches are commonly utilized to overcome bad taste of the drug [3].

1. By reducing the solubility of drug in the pH of saliva (5.6 - 6.8).
2. By altering the affinity and nature of drug which will interact with the taste receptor.

An ideal taste masking process and formulation should have the following properties.

1. Involve least number of equipments and processing steps.
2. Effectively mask taste with as few excipients which are economically and easily available.
3. No adverse effect on drug bioavailability.
4. Least manufacturing cost.
5. Can be carried out at room temperature.
6. Require excipients that have high margin of safety.
7. Rapid and easy to prepare

Factors that are taken into consideration during the taste-masking formulation process include: Extent of the bitter taste of the API.

1. Required dose load.
2. Drug particulate shape and size distribution.
3. Drug solubility and ionic characteristics.
4. Required disintegration and dissolution rate of the finished product.

***Correspondence to:** Guni Preethi, Department of pharmaceutics, Osmania University, Hydreabad Telangana, India, E mail: preethiguni123@gmail.com

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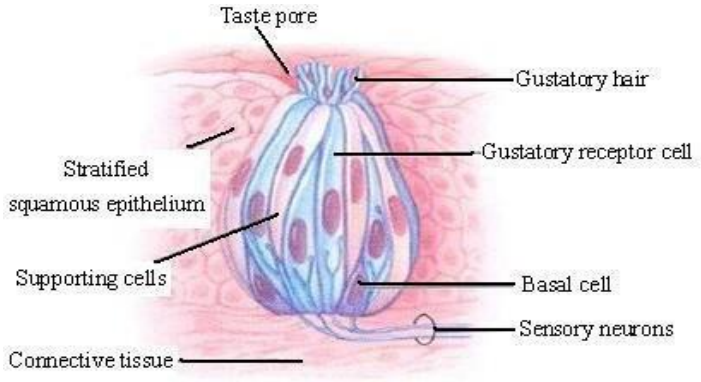

Figure 1: *Physiology of Taste bud.*

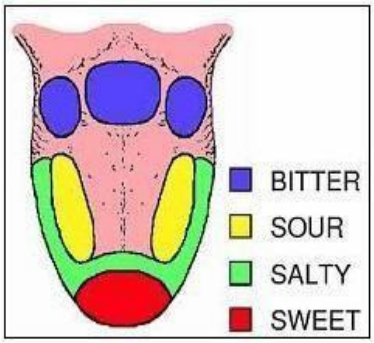

Figure 2: *Taste points in tongue.*

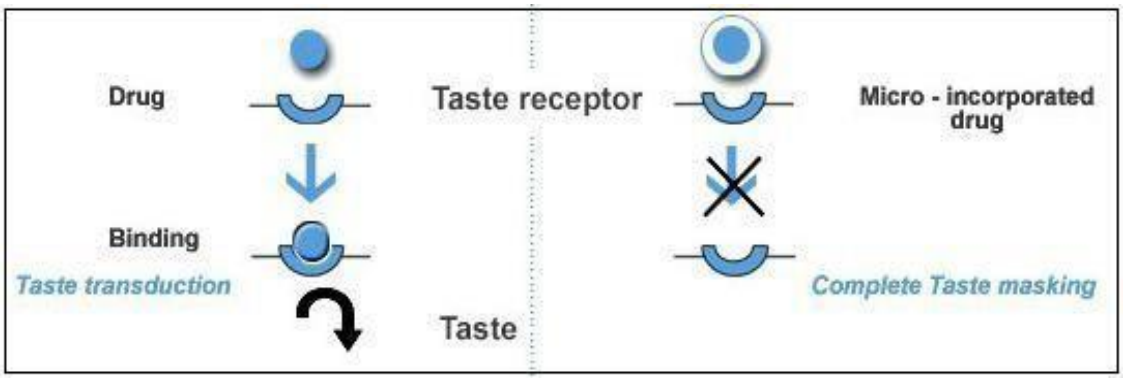

Figure 3: *Taste Signaling Pathways.*

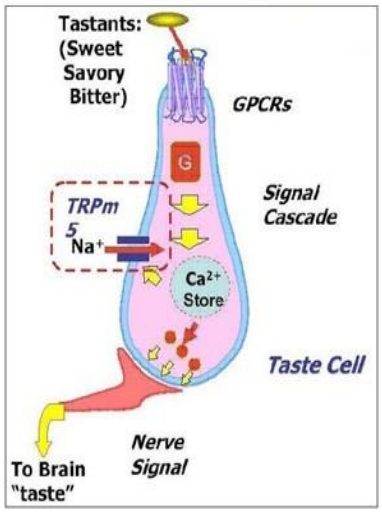

Figure 4: *Taste Blocking Mechanism.*

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5. Desired bioavailability.
6. Desired release profile.
7. Required dosage form.

Factors affecting selection of taste masking technology Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs such as quinine, celecoxib, etoricoxib, antibiotics like levofloxacin, Sweeteners could not achieve taste masking of oral formulation of ibuprofen due to its dominating taste. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique [4]. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions.

Taste Masking Technologies

To achieve the goal of taste abatement of bitter or unpleasant taste of drug. Various techniques reported in the literature are as follows[12]

1. Taste masking with flavors, sweeteners & amino acids
2. Polymer coating of drug
3. Formation of inclusion complexes
4. Ion exchange resin complexes
5. Solid dispersion
6. Microencapsulation
7. Multiple Emulsions
8. Development of Liposome
9. Prodrug approach
10. Taste masking by adsorption
11. Taste Masking with Lipophilic Vehicles like lipids and lecithins
12. Taste Suppressants and Potentiators
13. Taste masking by gelation
14. Formation of salt and derivative
15. Use of Amino Acids and Protein Hydrolysates
16. Miscellaneous.
17. By effervescent agents
18. Rheological modification
19. Continuous multipurpose melt (CMT) technology
20. Wet Spherical Agglomeration (WSA)

Different taste masking patents and patent application filed in the period of year 1997 to 2007. (Figure 5)

About 49.34% of taste masking patents and patent applications are contributed from Asia. North America accounts for about 41.45% of which 62.67% were filed in USA and about 9.30% from Europe (Figure 6).

Taste masking with Flavors, Sweeteners and amino acids

This techniques is simplest approach for taste masking. But this approach is not very successful for highly bitter drugs. Artificial sweeteners and flavors are generally being used alone with other taste-masking techniques to improve the efficiency of these techniques [5]

Flavors Basis of Choosing a Flavor

1. Complementary to existing flavor of the drug
2. Known popularity of particular flavors
3. Age of patients
4. Allergy

Natural Vs Synthetic

1. Cheaper
2. More readily available

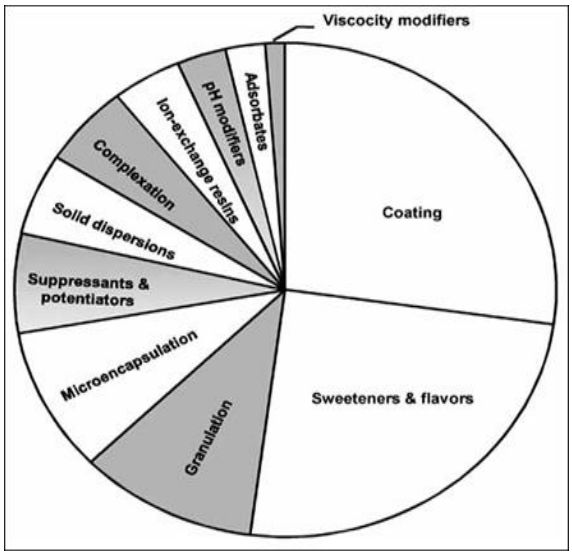

Figure 5: *Taste masking technology filed in the period of year 1997to 2007.*

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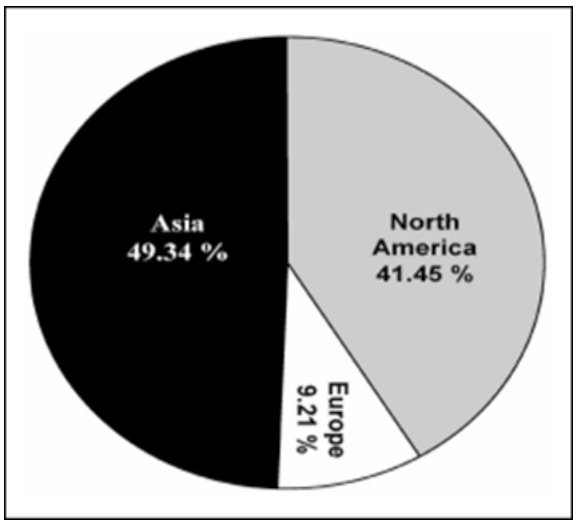

Figure 6: *Geographical distribution of taste masking patents and patent application filed in the period of year 1997 to 2007.*

3. Less variable in chemical composition
4. More stable Flavoring agents for taste masking

Natural Flavors

Raspberry Juices; Liquorices Extract; Lemon & Orange Spirits; Blackcurrant Syrups; Ginger Tinctures; Anise & Cinnamon Aromatic waters; Peppermint & Lemon Aromatic Oils.

Synthetic Flavors- Alcoholic solutions; Aqueous solutions; powders.

Sweeteners

- Complement flavors associated with sweetness
- Soothing effect on the membranes of the throat

Natural Sweetener- Sucrose, Glucose, Fructose, Sorbitol, Mannitol, Honey, Glycerol, Liquorice.

Artificial Sweetener- Saccharin, Saccharin Sodium, Aspartame.

Nutritive Sweeteners- Sucrose, Fructose, Glucose.

Non-Nutritive Sweeteners- Aspartame, Sucralose, Neotame, Saccharine.

Polyols- Mannitol, Sorbitol, Xylitol, Erythritol, Maltitol.

Novel Sweeteners- Trehalose, Tagatose (Table 1).

Aminoacids

Amino acids and their salts (alanine, taurine, glutamic acid, glycine) in combination with bitter drugs reduces the bitterness of the drugs for example, taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets.

Polymer coating of drug

This is the simplest and most feasible option to achieve taste masking. The coating acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of chewable tablets provides excellent taste masking while still providing acceptable bioavailability [6]. In this approach, powders as fine as 50 mm are fluidized in an expansion chamber by means of heated, high-velocity air, and the drug particles are coated with a coating solution introduced usually from the top as a spray through a nozzle. Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH, would be an acceptable alternative for taste masking. Taste masking of ibuprofen has been successfully achieved by using the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid copolymer coating that provides chewable taste masked characteristics [7].

Agents used for coating

- Carbohydrates (Cellulose)
- Synthetic polymers (Eudragits etc)
- Proteins, Gelatine, and Prolamines (Zein)
- Zeolites

It is classified based on the type of coating material, coating solvent system, and the number of coating layers. Hydrophobic polymers, lipids, sweeteners and hydrophilic polymers can be used as coating materials, either alone or in combination.

Multilayer coating has been used to overcome the challenges of coating imperfections, which otherwise lead to a decline in the taste masking performance, especially for the aggressively bitter drugs [8]. The core materials were coated with a first smooth and uniform spacing layer, which can minimize the coating imperfections during the second layer coating and can also act as an instant barrier between the taste receptors and the bitter core material (Figure 7)

Formation of inclusion complexes

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent, i.e. the host molecule, forming a stable complex, a low stability constant would lead to a rapid release of free drug in the oral cavity, resulting in inefficient taste masking. Bitterness elimination is depend upon the

Table 1: *List of FDA approved Non-Nutritive Sweeteners.*

Sweeteners	Sweetness factor, sucrose = 1
Aspartame	180-200
Sucralose	600
Acesulfame	K 200
Neotame	7,000-13,000
Saccharin	300

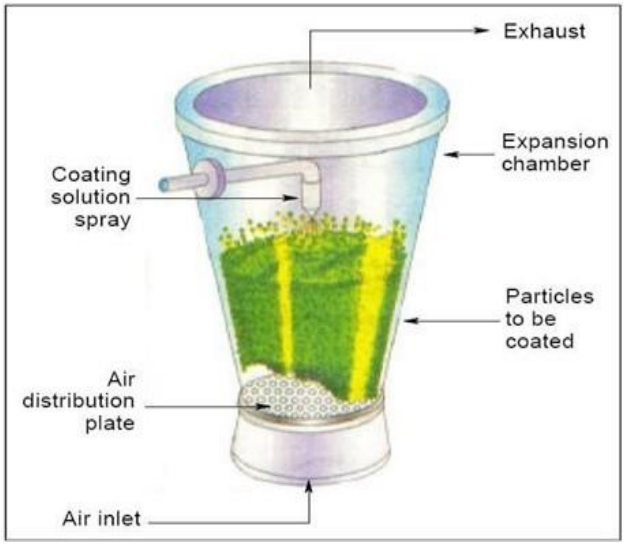

Figure 7: *Schematic representation of fluidized bed coating technique.*

extent of Complexation of guest molecule with host, value of complex association constant, temperature and the host /guest ratio.[1] Vander Walls forces are mainly involved in inclusion complexes. The complexing agent mask the bitter taste of drug by either decreasing its oral solubility or decreasing the amount of drug particles exposed to taste buds, thereby reducing the perception of bitter taste. This method is most suitable only for low dose drugs. ,-CD is the most widely used complexing agent for inclusion type complexes [9, 10]. It is a sweet, non-toxic, cyclic oligosaccharide obtained from starch.

Hydrophobic drugs form complex by replacing inclusion water while easily migrating (hydrophilic, well soluble) drugs form complex, assuming replacement of crystal water.

Physical Mixture (PM), Kneading Method (KM), Solid dispersion/co-evaporated dispersion method, Precipitation method (Figure 8)

Ion exchange resin complexes

Ion-exchange resins (IERs) are high molecular weight polymers with cationic and anionic functional groups attached to water insoluble polymer backbone. These groups have an ability to exchange for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to weak ionic bonding so that dissociation of the drug- resin complex does not occur under the salivary pH conditions, thus resulting in taste masking [11]. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug.

Classification

Strong cation exchanger- sulphuric acid sites Weak cation exchanger- carboxylic acid moieties**.**

Strong anion exchanger- quaternary amine ionic sites Weak anion exchanger- predominantly tertiary amine substituents. (Table 2)

Solid dispersion

Solid dispersion has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Solid dispersion of drug with the help of polymers, sugar, or other suitable agents, is very useful for taste masking [12].

Carriers used in solid dispersion systems include povidone, polyethylene glycols, hydroxypropyl methylcellulose, urea, mannitol and ethylcellulose. Various approaches for preparation of solid dispersion are described below.

Melting method

In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled & solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed & pulverized.

Solvent method

In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion

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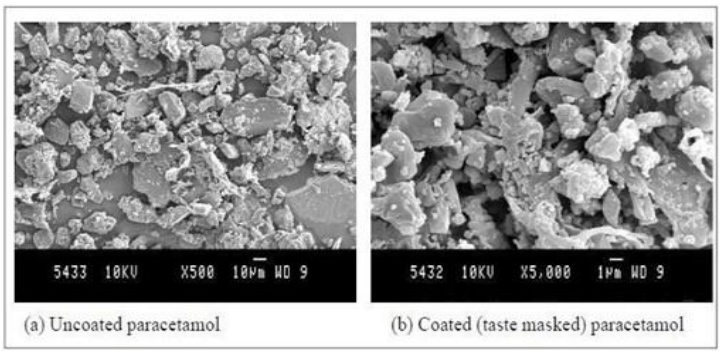

Figure 8: *Scanning electron micrograph of uncoated (bitter) and coated (taste masked) paracetamol particles.*

Table 2: *Commonly used ion exchange resins.*

Type	Functional group	Commercial resin	Taste masked drug
Weak cation	-COOH	Indion 204, Tulsion T-335, Amberlite IRC 50	Norfloxacin, Ofloxacin, Roxithromycin
	-COO-K+	Tulsion T- 339,Indion 234, Amberlite IRP 88	Ciprofloxacin, chloroquinine
Strong cation	-SO3H	Indion 244,Dowex 50,Amberlite IR 120	Chlorpheneram-ine maleate, Ephedrine Hydrochloride
	-SO3Na	Tulsion T-344, Amberlite IRP 69 Indion 254	Dicyclomin, Rantidine, Dextromethorp-hen, Pseudoephedri-ne, Buflomedil.
Weak anion	N-R2	Amberlite IR4B, Dowex 2	NTM
Strong anion	N-R3	Amberlite IR400, Dowex 1, Indion 454, Duolite AP143	NTM

Melting solvent method

In this method drug in solutions is incorporated into molten mass of polyethylene glycol at a temperature 70˚C without removing the solvent.

The bitter taste of dimenhydrinate can be masked by preparing the solid dispersion of the drug with polyvinyl acetate phthalate.

Microencapsulation

Microencapsulation is a process of applying relatively thin coating to small particles of solids, droplets of liquids and dispersions, using various coating agents, such as gelatin, povidone, hydroxyethyl cellulose, ethyl cellulose, bees wax, carnauba wax acrylics and shellac [13]. It is important to understand that only soluble portion of the drug can generate the sensation of taste. Coating the active drug with a properly selected polymer film can reduce its solubility in saliva and thus taste could be masked. Coating the drug particles created a physical barrier between the drug and the taste buds and taste of active could be masked. Polymers have been exclusively used as coating materials, either alone or in combination, as a single or multi-layer coat, in the taste masking of bitter medicaments. Combinations of pH independent water insoluble polymers such as cellulose ethers, cellulose ester, polyvinyl acetate and water soluble polymers such as cellulose acetate butyrate, Polyvinylpyrrolidone, hydroxyethyl cellulose have been used to attain a balance between the taste masking and in vitro release [14].

The unpleasant taste of clarithromycin was masked when the drug was encapsulated in combination of gelatine and acrylic resins such as Eudragit L-100, Eudragit S-100 & E-100. (Table 3)

Multiple Emulsions

The w/o/w or o/w/o type multiple emulsion are vesicular systems in which active ingredients can be entrapped in internal phase. The entrapped substances can be transferred from internal phase to external phase through the membrane phase. This phase controls the release of drug from system. If the system is stable enough for a reasonable shelf life, the formulation could also mask the taste of drug. Both w/o/w or o/w/o multiple emulsion of chloroquine phosphate have been prepared and reported to be partially effective in masking the bitter taste of drug [15].

Development of Liposome

Liposomes are simple microscopic vesicles in which an aqueous volume (drug or biological agent) is entirely closed by a membrane composed of lipid molecules, lipid bilayers mainly composed of natural or synthetic phospholipids. Bitter substances are commonly hydrophobic in nature. Selective inhibition of bitter taste of various drugs by phospholipids such as phosphatidic acid, phosphatidylinositol, soy lecithin, has been reported. The bitter taste of Chloroquine phosphate in HEPES (N-2- hydroxyetylpiperzine-Ní- 2- ethane sulfonic acid) buffer was masked at pH 7.2. by incorporating into a liposomal formulation prepared with egg phosphatidyl choline [16, 17]. Bitter taste of polymyxin B sulfate and trimethoprim sulfamethoxazole have been masked by BMI 60 obtained by fractionating soy lecithin.

Prodrug approach

A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmacologically active parent compound. By changing the molecular configuration of the parent molecule, the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified. Prodrugs can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effects, and alter membrane permeability of the parent molecule. (Table 4)

Table 3: *Marketed taste masked drugs by drug particle coating technique.*

Technique	Polymer	Taste masked drugs
Air Suspension Coating	Methacrylic acid copolymer	Ibuprofen
Phase separation Coacervation	Eudragit E- 100, Chitosan	Clarithromycin, Paracetamol
Fluidized Bed/Sprayn Coating	Hydrogenated Oil and Surfactant	Indeloxazine
Solvent Evaporation Method	Eudrgit E, PEG, Ethyl Cellulose	Pseudoephedrine, Ranitidine
Extrusion Coating	Eudragit E- 100	Oxybutinin, ofloxacin, pirezepin.

Table 4: *Examples of Prodrugs with improved taste.1.*

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 XP13512
Norfloxacin	Norfloxacin alkyl carbamates

Tasteless prodrug of nalbuphine HCL, naltrexone, naloxone, oxymorphone HCL, butorphanonol, and levallorphan were synthesized for buccal administration to improve bioavailability relative to that of oral dosing without the characteristic bitter taste [18].

Taste masking by adsorption

Adsorbate of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will adsorb the drug, removing the solvent, drying the resultant powder, and then using this dried adsorbates in the preparation of the final dosage form.Many substrates like veegum, bentonite, silica gel and silicates can be used for the preparation of adsorbate of bitter drugs. Loperamide and phenyl propanolamine have been adsorbed on magnesium aluminium silicates also known as Veegum F to prepare bitter taste masked suspension of these drugs.

Taste Masking with Lipophilic Vehicles like lipids and lecithins

Oils, surfactants, polyalcohols, and lipids effectively increase the viscosity in the mouth and coat the taste buds, and therefore they are potential taste masking agents. Acetaminophen granules are sprayed with molten stearyl stearate, mixed with suitable tablet excipients, and incorporated into a taste masked, chewable tablet formulation. Formulations with a large excess of lecithin or lecithin-like substances are claimed to control bitter taste in pharmaceuticals. Magnesium aluminum silicate with soybean lecithin is used to mask the unpleasant taste of talampicillin HCl.

Taste Suppressants and Potentiators

Most of the Linguagenís bitter blockers(e.g. adenosine monophosphate) compete with bitter substances to bind with the G-protein coupled(GPCR) receptor sites. In general, the hydrophobic nature of these bitter substances contributes greatly to their binding and inter-action with the receptor sites. Lipoproteins are universal bitter taste blockers. Study on animal model showed that lipoproteins composed of phosphatidic acid and lactoglobulin inhibit the taste nerve responses to the bitter substances without affecting those due to the sugars, amino acids, salts or acids. Venkatesh and Palepu(2002) described the application of taste suppressants like phospholipid(BMI- 60) in taste making of bitter medicaments. Neohesperidine phospholipids have bitter taste suppression characteristics by interacting chemically with the taste receptors. Cooling and warming agents suppress unpleasant taste of medicament by subjecting taste receptors to extreme sensations to overpower the bitter taste and confuse the brain. Mixture of cooling(e.g. eucalyptol) and warming agents(e.g. methyl salicylate) was used for taste masking of thymol. Potentiators increase the perception of the taste of sweeteners and mask the unpleasant after taste. Potentiators such as thaumatine, neohesperidine dihydrochalcone (NHDC) and glycyrrhizin can increase the perception of sodium or calcium saccharinates, saccharin, aspartyl-pheny- lalanine, acesulfame, cyclamates, and stevioside. Thaumatine was used with sugar alcohols to achieve the taste masking of bromhexine. Bitter taste blockers such as hydroxyl flavanones, adenosine monophosphate and ,,-aminobutanoic acid were found to be effective to achieve the taste masking of bitter drugs [19].

Desensitizing agents

Desensitizing agents like phenols, sodium phenolates desensitize the taste buds by interfering with taste transduction (Fig. 4), the process by which taste message from the mouth to the brain and thus mask the taste of drug.

Taste masking by gelation

Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking. Sodium alginate has the ability to cause water insoluble gelation in presence of bivalentmetal ions. Tablet of amiprolose hydrochloride have been taste masked by applying an undercoat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate react with bivalent calcium and form water insoluble gel and thus taste masking achieved.

Formation of salt and derivative

Decreasing the solubility of drug by its salt formation makes the drug as tasteless as become less soluble in saliva

so less sensitive to taste buds. Modified as N, N- di benzyl ethylenediamine diacetate salts or N, N bis (deyhdroabiety) ethylene diamine salts is tasteless. Adding alkaline metal bicarbonate such as sodium bicarbonate masks the unpleasant taste of water - soluble ibuprofen salts in aqueous solution. [20] Aspirin tablets can be rendered tasteless by making magnesium salt of aspirin. D- chlorpheniramine maleate is taste-masked salt of chlorpheniramine. Sodium salts such as sodium chloride, sodium acetate, sodium gluconate have been shown to be potent inhibitors of some bitter compound. The mechanism is not known, however, research shows that sodium act at peripheral taste level rather than a cognitive effect.

Use of Amino Acids and Protein Hydrolysates

By combining amino acids or their salts with bitter drugs, it is possible to substantially reduce the bitterness. Some of the preferred amino acids include sarcosine, alanine, taurine, glutamic acid, and glycine. The taste of ampicillin improved markedly by preparing its granules with glycine and mixing them with additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets.

Miscellaneous

By effervescent agents

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have also been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament was formulated to supply the medicament to the oral cavity for local application or for buccal absorption. It comprises a chewing gum base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition (e.g. oral anesthetics such as benzocaine and spilanthol) and other non active material, such as sweeteners, flavouring components, and fillers.

Recently, effervescent tablets of fentanyl and prochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulation contains the drug in combination with effervescent agent to promote their absorption in the oral cavity and to mask their bitter taste [21]. An additional pH adjusting substance was also included in fentanyl formulation for further promotion for absorption.

Rheological modification

Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. This provides a taste masked liquid preparation for administration of a relatively large amount of unpleasant tasting medicines. The composition of such a formulation comprises a taste masking liquid base with a high viscosity induced by thickening agents such as polyethylene glycol and sodium carboxy methylcellulose. Acetaminophen suspension can be formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6- 1%) to reduce bitter taste. The antidepressant drug mirtazapine is formulated as an aqueous suspension using methonine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides masking the unpleasant taste of the drug, it also inhibit its undesirable local anesthetic effect. cough syrups, terbutaline given in doses of 4mg/5ml can be effectively administered by increasing the viscosity of the formulation.

Continuous multipurpose melt (CMT) technology

The CMT method was developed for the continuous granulation and coating of pharmacologically active substances. It was concluded that this method could be successfully applied for taste masking of bitter drugs.

Wet Spherical Agglomeration (WSA)

A novel Microencapsulation process combined with the wet spherical agglomeration (WSA) technique was used to mask the bitter taste of enoxacin.

Evaluation

Sensory evaluation

Taste, to think of, is a very subjective perception.n Depending on individuals, the perceived taste may vary to different degrees. To quantitatively evaluate taste sensation, following methods have been reported in literature.

1. Panel testing (human subjects)
2. Measurement of frog taste nerve responses.
3. Multichannel taste sensor/ magic tongue
4. Spectrophotometric evaluation/ D30ísvalue

In vivo Evaluation

Panel testing (human subjects)

The panel testing is a psychophysical rating of the gustatory stimuli. In vivo taste evaluation carried out on a trained taste panel of 5-10 healthy volunteers with organoleptic sense, with their prior consent. On placing the dosage form in mouth for 60 seconds, bitterness recorded against pure drug using a numerical scale. The numerical scale may bears values as 0 = pleasant, 1 = Tasteless, 2 = No bitter but after taste give bitterness, 3= immediately gives bitterness, 4 = slightly bitter, 5 = extremely bitter. In vivo assessment usually demands large panels and elaborate analysis, raises safety and scheduling issues and can be time consuming and expensive [22].

Measurement of Frog Taste Nerve Responses In this method, adult bull frogs are anaesthetized intraperitoneally and the glossopharyngeal nerve is then located and dissected from the surrounding tissue and cut proximally. An ac-amplifier and an electronic integrator are used to respectively amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response.

In vitro Evaluation

Multichannel Taste Sensor / Magic tongue

Invention of ìE-Tongueî electronic sensor array technology overcomes this problem, which is a device for recognition,

quantitative multicomponent analysis and artificial assessment of taste and flavor. It recognizes three levels of biological taste including receptorlevel (Taste budsin humans, probe membranes inE-Tongue), circuit level (neural transmission in humans, transducer in E-Tongue), and perceptual level (cognition in the thalamus humans, computer and statistical analysis in the E- Tongue).The probes consist of a silicon transistor with proprietary organic coatings, which govern the probeís sensitivity and selectivity, and measurement done potentiometrically. Each probe is cross selective to allow coverage of full taste profile and statistical software interprets the sensor data into taste patterns. Liquid samples directly analyzed without any preparation, whereas solids require a preliminary dissolution before measurement. Reference electrode and sensors are dipped in a beaker containing a test solution for 120 seconds (Figure 8). A potentiometric difference between each sensor and a reference electrode measured and analyzed by the E-Tongue software. Quinine hydrochloride was taken as thestandard for bitterness. Basic drug with amino groups in the molecule such as quinine; show a comparatively good correlation between the relative response electric potential (mV) of channels 1 or 2 of the taste sensor, which contain negatively charged membranes, and the bitterness as determined by human gustatory sensations tests (Figure 9).

These data represent the input for mathematical treatment that will deliver results. The E-Tongue enables us to test taste accurately without the need for human volunteers at earlier stages of drug development. Furthermore, the E-Tongue cannot be poisoned and it wonít fatigue or lose its sense of taste after long periods of testing. The bitterness of drugs and their compatibility with taste masking agents that does not affect the bioavailability of drug.

Spectrophotometric Method

A known quantity of the taste-masked formulation is mixed with 10 ml of distilled water in 10 ml syringe by revolving the syringe, end to end, five times in 30 seconds. The test medium is then filtered through a membrane filter, followed by spectrophotometric determination of the concentration of the drug in the filtrate. If this concentration is below the threshold concentration, it may be concluded that the bitter taste would be masked in vivo. This technique has been applied to evaluate the taste masked granules of sparfloxacin, with threshold concentration being 100µg/ml. Generally the taste evaluation involves the objective or analytical method and subjective or hedonic method.

Aim and objectives

Vilazodone is a novel compound with combined high affinity and selectivity for the 5- hydroxytryptamine (5-HT) transporter and 5-HT(1A) receptors.Vilazodone may also be associated with less sexual dysfunction and weight gain. This leads to lower bioavailability of Vilazodone, and also having bitter taste. So to improve its bioavailability and to mask the taste solid dispersion technique was used using different carriers like Poloxamer&PEG-6000.

Objectives

1. Selection of suitable carriers for preparing of taste masking sachets by solid dispersion technique.
2. To perform preformulation studies forVilazodone.
3. To perform Drug-Excipient Compatibility Studies.
4. To formulate and develop taste masking sachets by solid dispersion technique for Mirtazapine with various proportions by various methods.
5. To determine the drug content uniformity of all the prepared formulations.
6. To establish In–vitro drug release compliance with the established criteria.

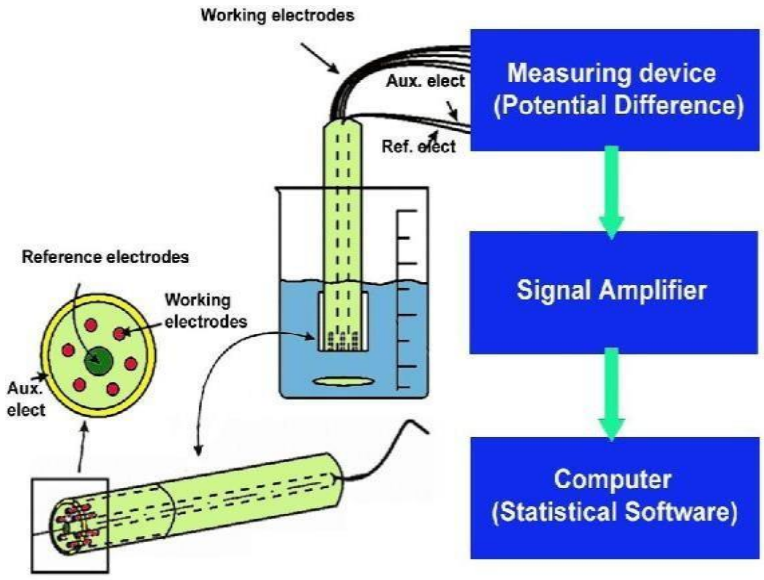

Figure 9: *Evaluation of taste using e-tongue.*

Citation: *Preethi G. Fabrication and Evaluation of Taste masking Sachats. Asian J Biomed Pharm Sci. 2024;14(103):212*

Planofwork

Preformulation studies

- Solubility
- Spectrophotometric studies
- Compatibility studies

Formulation of Tate masking sachets by solid dispersion techniques

Preparation of Tate masking sachets of Vilazodone by solvent evaporation & kneading method using Poloxamer&PEG-6000as carriers.

Evaluation studies

- Druginteraction study(FTIR) Drugcontent uniformity
- In vitro dissolution studies
- Kinetics of dugrelease.

Literature Review

Perumala Harish Kumar etal,The main aim of present work is to formulate solid dispersions of poorly water soluble BCS class 2 drug Vilazodone, which give the application of solid dispersions results in increasing the solubility of many poorly soluble drugs the objective of the present study, investigated to improve the solubility of and Vilazodone by using HP β Cyclodextrin and β Cyclodextrin to improve patient compliance. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs the first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co- dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980). Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water-soluble drugs.

The purpose of the present study was to formulate solid dispersion incorporated fast dissolving tablet of vilazodone to improve the aqueous solubility, dissolution rate and to facilitate faster onset of action. Solid dispersion of vilazodone was prepared with various carrier in different drug:carrier ratio using solvent dispersion technique. The objective of the study was to formulate and evaluate fast dissolving tablet of Viladazone. Direct compression method was used to formulate orally disintegrating tablet of Viladazone by employing solid dispersion, magnesium stearate (lubricant), Talc (glidant). These prepared formulations were then evaluated. In vitro Dissolution tests were performed using USP apparatus II and ultraviolet spectrophotometry, respectively. All formulations showed compliance with pharmacopeia standards. The effect of carrier concentration and direct compression method on drug release profile was studied. Release profile of F2 were found to be satisfactory comparing to other formulations. F2 Formulation as processed excipient was found to be the best carrier for the preparation of Viladazone fast dissolving tablets formulations. Due to it has exhibited faster disintegration time and best dissolution profile when compared to other formulations.

Vilazodone is approved for treatment of acute episodes of major depression (Major Depressive Disorder (MDD). It is a BCS Class – II drug, offer challenges in developing a drug product with adequate bioavailability. The aim of present investigation was to formulate and evaluate vilazodone sublingual tablets using poloxamer 407 as a carrier by lyophilized solid dispersion technique.The lyophilized solid dispersion of vilazodone prepared by poloxamer 407 (1:5) showed more than 85% drug release within 5 min, so it was used for the development of sublingual tablets by direct compression technique. The physicochemical, solid-state properties, dissolution behaviour of lyophilized solid dispersion as well as sublingual tablets were evaluated. Finally, the bioavailability studies of the prepared tablets were performed by sublingual administration to rabbits. The sublingual tablets showed a higher in vitrodis solution rate and bioavailability compared with the commercial tablets. It is evident from the results herein that the developed sublingual tablets provide a promising drug delivery system in drug development, owing to their excellent performance of a rapid onset of action and improved bioavailability.

Quetiapine fumarate is a tetracyclic piperazino-azepine antidepressant agent. It is given with a dose of 15-45mg orally once a day. The absorption of this drug is rapid and complete. Due to first pass metabolism in the liver and metabolism in the gut wall, absolute bioavailability is about 50%. Peak blood concentrations are attained within about 2 hours after an oral dose. This leads to lower bioavailability of Quetiapine fumarate also having bitter taste. So to improve its bioavailability and to mask the taste solid dispersion technique was used using different carriers like PEG 6000, & Poloxamer. Results of prepared taste masking sachets by solid dispersion technique of Quetiapine fumarate by Fusion method & kneading method were discussed which includes solubility, drug content uniformity, and in vitro dissolution studies. Characterization in solid state was done by FT-IR studies. Finally by comparing all the formulations i.e., F1-F12 containing Quetiapine fumarate, Poloxamer and PEG 6000 in different ratios, Invitro drug release of Quetiapine fumarate with PEG 6000 in 1:3 by Fusion method shows 98.62% drug release at the end of 60mins. By comparing the release kinetics studies of best formulation of Quetiapine fumarate with zero order and first order we can say that the best formulation follows Zero order release kinetics studies.

Citation: *Preethi G. Fabrication and Evaluation of Taste masking Sachats. Asian J Biomed Pharm Sci. 2024;14(103):212*

Aim of this research work was to develop mouth dissolving tablet that disintegrates rapidly in mouth by using tasteless complex of Levocetirizine and Tulsion-335. Effect of different parameters such as swelling time, resin activation, drug resin ratio as well as stirring time was optimized by taste and percentage drug loading. Formulated DRC (Drug Resin Complex) was characterized by infrared spectroscopy, thermal analysis and X-ray diffraction pattern. Tablets were formulated by wet granulation with PVP as binder, Sodium Starch Glycolate (SSG) and Crospovidone as super disintegrants. In these batches optimum hardness was achieved but disintegration time was found to be very high as ≥ 70 second, so further trials were planned by using different superdisintegrants such as Croscarmellose sodium, Sodium Starch Glycolate (SSG) as well as Crospovidone by wet granulation method. Tablets formulated with 7.5% crospovidone showed comparatively low disintegration time (25 sec), wetting time (20 sec) and friability (0.60 %) than the other batches. In present study we optimized the conditions required for maximum drug loading of Levocetirizine with Tulsion-335. Among different superdisintergants, crospovidone was found suitable with drug-resin complex to get the low disintegration time, wetting time and friability of tablets.

Develop rapidly dissolving formulations of curcumin that could photoinactivate both Gram-positive and Gram-negative bacteria.Curcumin solid dispersions with methyl-β-cyclodextrin and hyaluronic acid (HA), hydroxypropyl methylcellulose (HPMC) or both HA and HPMC were prepared through lyophilization. The lyophilizates were characterized by curcumin drugload [%(w/w)],differential scanning calorimetry, photostability, thermal, stability, theirability to form super saturated solutio nsandby invitro photoinactivationof Enterococcus faecalis and Escherichia coli.The lyophilizates were amorphous solid dispersions with a curcumin drug load in the range of 1.4–5.5% (w/w) depending on the included polymer and the ratio between curcumin and the cyclodextrin. The lyophilizates were photolabile, but thermally stable and dissolved rapidly in contact with water to form supersaturated solutions. Selected lyophilizates demonstrated >log 6 reduction of colony forming units/ml of both E.faecalis and E. coli after exposure to low curcumin concentrations (0.5–10 μM) and blue light dose (1116 J/cm2). The high drug load of the lyophilizates, rapid dissolution, ability to form relatively stable supersaturated solutions and the very high phototoxicity towards both E. faecalis and E. coli make these lyophilizates suitable for in vivo aPDT.This treatment with optimized curcumin formulations should be explored as an alternative to topical antibiotics in the treatment of wound infections.

Solid dispersion (SD) was prepared by melting, solvent evaporation and kneading method using different ratios of drug and polymers (PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L- 100). Phase solubility study revealed highest solubility in PVP K-30 at 1:2 ratios. The solid state characterizations of selected solid dispersion formulation (SD-15) were performed by infrared spectroscopy, differential scanning calorimeter, X-ray diffraction study and scanning electron microscopy. In vitro dissolution was carried out in phosphate buffer (pH 7.4) at 50 rpm in 900 ml of volume. The in vivo pharmacokinetic study of selected formulation (SD-15) was carried out in male Wistar rats using non-compartment analysis by linear trapezoidal method after a single oral dose of 10 mg/kg of EM. Results: The solid state characterization revealed no such drug-polymer interactions and rapid transformation of crystalline drug in an amorphous state, which amplifies the aqueous solubility and hence the dissolution rate. The in vitro dissolution study of the dispersions prepared by PVP K-30 (1:2) was found to be 95.5% after 1 hr. In vivo pharmacokinetic study in Wistar rats showed significant improvement in oral bioavailability of EM in SD-15 with the 2.4 fold increments than the pure drug.

Vernoniaamygdalina solid dispersions SDs containing varying concentrations0:1, 1:0 1:1, 1:3 and 3:1, of Vernonia amygdalina: PEG 4000 were prepared using the fusion -solvent evaporation method. Wound contraction ability in excision wound model was measured at different time intervals and study was continued until wound is completely healed. The effects of the preparation on the activities of liver were similarly assessed. Tensile strength was measured in 9th – dayold incision wound. Preparation (d) containing 1:3 of PEG: V.amygdalina showed statistically significant response, in terms of wound contracting ability, wound closure time, period of epithelization, tensile strength of the wound, when compared with the individual components and the control group (negative control), the results were comparable to those ofa commercial neomycin formulation (positive control). The liver parameters and hematological studies did not show much variation to that of the control. It is believe that SDs of this extracted could be formulate into pharmaceutical dosage form and used as an alternative in wound healing.

Solid dispersions of poorly soluble drugs like Cefixime, Valsartan and Ibuprofen were prepared and evaluated. Suitable carriers such as PVP K30 and HMPC etc. in different ratios were chosen. They were prepared by physical mixing and kneading method. The standard curves were prepared for cefixime, ibuprofen and valsartan in methanol. The release studies were carried out and compared. The results showed a marked increase in release of the drug from solid dispersions compared to the drug in its pure form. The percentage of the drug released for Ibuprofen increased from 12.78 to 52.4% (1:1 ratio), 70.2% (1:2 ratio) and 68.2% (1:3 ratio). The use of cefixime with hydroxypropylmethylcellulose (HPMC) greatly improved the solubility of the drug and enhanced its dissolution rate. The percentage of the drug released increased from 13.2 to 31.4% (1:1 ratio), 34.9% (1:2 ratio) and 43.9% (1:3 ratio). The ratios which showed the best release were considered as the optimized formulations.

The development of meaning fuldissolution procedure for drug produc ts with limited water solubility have beena challenge to the pharmaceutical industry. In the present study, parameters such as solubility, medium PH, surfactant type, dissolution behavior of formulations, influence of sink conditions, stability and discriminatory effect of dissolution testing were studied for the selection pf proper dissolution

Citation: *Preethi G. Fabrication and Evaluation of Taste masking Sachats. Asian J Biomed Pharm Sci. 2024;14(103):212*

medium. The discriminating dissolution method foraceclof enacformulationispaddleat50rpm;900ml pH 6.8-phosphate buffer, greater than 80% of the label amount is released over 60 minutes.

The present investigation aims at studying the effectof mixed surfactants system of sodium laurylsulphate(SLS) and alkyl polyglucosides(C10APG,C12APGandC12/14A PG)on dissolutionrate enhancement of poorly water-soluble drug. Aceclofenac—a non-steroidal anti- inflammatory agent used as a model drug as with limited water solubility. The influence of the surfactant concentration in various blends on the dissolution rate of Solid Dispersion (SD), prepared using solution method with ethanol as the solvent, The observed results in the dissolution rate enhancement could be attributed to the drug—surfactant interactions as evident from FT-IR, SEM and XRD results. They aimed to enhance the bioavailability of process included fast dissolving esomeprazole cogranulated with PEG 4000 by usingsolventmethod. itwasfoundthattheabsorptionrateofSDEZentericcapsule is lower than that Nexiuminoral administration, whichcorresponds with in-vitro dissolution.

Studied what are the unexpected differences observ edind is solution behaviour of poorly water soluble drug, tablets prepared from solid dispersion with a surfactant sodium lauly lsulphate, physically mixed or incorporated. Studied the physical stability of ternary solid dispersions of itraconazole PEG-6000/HPMC 2910 E5 blends, finallythe dissolution data showed that an increase in the crystallinity of itraconazole was directly related to a decrease in the extent of dissolution. Thesearerevealedthatthedissolutionbehaviourofglipizide-cyclodextrin polymer systems in highly dependent on polymer type and concentration. incorporation of 5% PEG 4000 inglipizide-HP-B-CD complex improves significantly the dissolution behaviour of drug. Studied the modulation of micro-environmentalPh and crystallinity of ionizable telmisartan using alkalizers in solid dispersion for controlled release. Studied to enhance dissolution properties of carbamazepine with solid dispersion, solvent evaporation technique by using different types of carriers- PVP-K30, PEG-6000 and PEG-4000, finally it concluded that this solid dispersion technique had been shown a successful approach toimprovedissolution. Studied the enhancement of dissolution rate of piroxicam with cross carmellose sodium, pregelatinized starch, primojel, cross povidone, MCC, PVP and PEG., finally concluded that solid dispersions in super disintegrates an effective and efficient technique for enhancing the dissolution rate of piroxicama poorly soluble drug.

Methodology

List of materials (Table 5)

List of equipments (Table 6)

Pre formulation studies

Pre formulation testing is the first step in the rational development of dosage forms of a drug substance.

Definition

It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Objective

Overall objective of pre formulation testing is to generate information useful to the formulator in developing stable and bio-available dosage forms.

The following pre formulation studies were carried out for Vilazodone

a) Solubility studies

b) Drug– excipient compatibility studies

Solubility studies

Solubility of Vilazodone was carried out in different buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Vilazodone was determined spectrophotometrically at 257 nm.

Drug–polymer compatibility studies

In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility

Table 5: *List of materials.*

S. No.	Material	Manufacturer
1	Vilazodone	BMR Chemicals, Hyderabad
2	Poloxamer	S.D FINE CHEMICALS
4	PEG-6000	S.D FINE CHEMICALS
5	Methanol	S.D FINE CHEMICALS

Table 6: *List of equipments.*

Instrument used	Manufacturer
Electronic weighing balance	Shimadzu 2000
UV-Visible Spectrophotometer	Shimadzu-1700, Mumbai
Dissolution test apparatus USP23 (LABINDIA DISSO 2000)	Tab machines, Mumbai
Hot air oven	Tapman, Mumbai
Dessicator	Hindustan Apparatus Mfg. Company

Citation: *Preethi G. Fabrication and Evaluation of Taste masking Sachats. Asian J Biomed Pharm Sci. 2024;14(103):212*

between Vilazodone, and the selected polymers. The pure drug and drug with excipient were scanned separately.

FT-IR studies

Sample/KBr ratio

The concentration of the sample in KBr should be in the range of 0.2% to 1%. The pellet is much thicker than a liquid film, hence a lower concentration in the sample is required (Beer's Law). Too high a concentration usually causes difficulties obtaining clear pellets. The IR beam is absorbed completely, or scattered from the sample which results in very noisy spectra.

Sample preparation

Completely dried potassium bromide was transferred into a mortar. About 2 % of drug sample was weighed in digital balance, mixed and grind to a fine powder. Two stainless steel disks were taken out of the desiccator. A piece of the precut cardboard (in the tin can next to the oven) on top of one disk was placed and cutout hole was filled with the finely ground mixture. The second stainless steel disk was kept on top and transfers the sandwich onto the pistil in the hydraulic press. With a pumping movement, hydraulic pump handle moved downward. The pistil will start to move upward until it reaches the top of the pump chamber. Then, the pump handle moved upwards and continued pumping until the pressure reaches 20,000 prf. Rest for a few seconds and with the small lever on the left side, the pressure was released. Removing of the disks and pulling apart. Obtained film was homogenous and transparent in appearance. Than inserted into the IR sample holder and attach with scotch tape and run the spectrum.

The physical mixtures of drugs were prepared in 1:1 ratio and then passed through sieve # 30. Samples of drug and excipients were placed in vial, closed and labelled. Then the vials were stored under two different conditions at 4˚C and at 40˚C±75% RH. Observations of all the mixtures were done on 0th day, 7th day, 15th day and 30th day. The compatibility of drugs with excipients was studied by FT-IR. X-Ray Diffractometry The solid state of the drugs was investigated.

Experimental Methods

Determination of UV spectrum

10mg of Vilazodone was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8pH phosphate buffer to give stock solution containing 1000µg/ml.

From the stock solution 1ml was pipette out and transferred into 10ml volumetric flask and make up to the mark with 6.8pH phosphate buffer for making 100µg/ml concentration. From the stock solution 1ml was pipette out and transferred into 10ml volumetric flask and make up to the mark with 6.8pH phosphate buffer for making 10µg/ml concentration. This solution was analyzed in UV spectrum against blank.

Preparation of Standard Calibration Curve of Vilazodone in 6.8pH phosphate buffer

10mg of Vilazodone was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8pH phosphate buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 6.8pH phosphate buffer to get 2 to 12µg/ml of Vilazodone. The absorbance of the solution was measured against 6.8pH phosphate buffer as blank at 238 nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Formulation of vilazodone taste masking sachets by

Solvent evaporation method

In this method, accurately weighed quantities of carriers in the stated proportions were carefully transferred into boiling test tubes, and dissolved in Methanol. To these solutions, accurately weighed quantities of drug were added, and allowed to dissolve. The solution was transferred to a petridish, the solvent was allowed to evaporate at room temperature, and the dispersions were dried at room temperature for 1 h, and then dried at 65^{o}c for 6h in a hot air oven. The mass obtained in each case was crushed, pulverized, and sifted through 100 mesh.

By Kneading method

Drug and carriers were weighed accurately in various ratios and transferred to china dish sufficient quantity of methanol: water (1:1) was added and the thick slurry was needed for 1hr and then dried at 45^{0} C until dryness. The dried mass was pulverized and sieved through sieve number #120. The resulting solid dispersions were stored for 24 hrs in desiccators to congeal. The mass obtained was crushed, pulverized. Finally, dispersions were stored in air tight containers till further use. (Table 7-10)

Evaluation Studies

Prepared polymer drug conjugates were evaluated by

1. Estimation of drug content
2. Practical yield estimation
3. *In- vitro* dissolution studies
4. Evaluation of taste of complexes

Table 7: *Formulation of Vilazodone with Poloxamer by Kneading method.*

Formulation code	Drug: polymer	Drug : polymer ratio
F1	Vilazodone: Poloxamer	01:00.5
F2		1:01
F3		01:01.5

Citation: *Preethi G. Fabrication and Evaluation of Taste masking Sachats. Asian J Biomed Pharm Sci. 2024;14(103):212*

Table 8: *Formulation of Vilazodone with Poloxamer by Solvent evaporation method.*

Formulation code	Drug: polymer	Drug : polymer ratio
F4	Vilazodone: Poloxamer	01:00.5
F5		1:01
F6		01:01.5

Table 9: *Formulation of Vilazodone with PEG-6000 by kneading method.*

Formulation code	Drug: polymer	Drug : polymer ratio
F7	Vilazodone: PEG-6000	01:00.5
F8		1:01
F9		01:01.5

Table 10: *Formulation of Vilazodone with PEG-6000 by Solvent evaporation method.*

Formulation code	Drug: polymer	Drug : polymer ratio
F10	Vilazodone: PEG-6000	01:00.5
F11		1:01
F12		01:01.5

Drug Content

A quantity, which was equivalent to 15 mg of drug, was accurately weighed and transferred to 100 ml volumetric flask. Then the volume was made up with, 6.8pH phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 15 mg of standard drug in 6.8pH phosphate buffer. For both the sample and standard solutions absorbance was measured at 238 nm for Vilazodone in UV-Visible spectrophotometer.

Practical yield

percent yield = actual yield / theoretical yield x 100%

In Vitro Dissolution Studies

The quantity of solid dispersion equivalent to 15 mg of Vilazodone was filled in a capsule and kept in dissolution medium. The dissolution study of solid dispersions were conducted using dissolution testing USP apparatus I (basket method) in 900 ml of 6.8pH phosphate buffer at 37±0.5ºC and at a speed of 50 RPM. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 238 nm against suitable blank using UV-visible spectrophotometer (T60 PG Instruments).

Evaluation of taste of complexes

The sample of drug β-CD complex underwent sensory evaluation by a panel of five members with respect to the bitter taste; the evaluation was performed by classifying the bitter taste into the following five classes.

Class 5: Very strong bitter taste

Class 4: Strong bitter taste

Class 3: Moderately bitter taste

Class 2: Slightly bitter taste

Class 1: No bitter taste

The pure drug was used as a standard control, with a mean bitter taste of 5.0. Written consent was obtained from the members of the panel and it was explained that the procedure involved testing the taste of complexes. Each of the members was given the control, *i.e.*, the pure drug. They were asked to compare the bitterness of each of the ratios of the complex with that of the control, indicating the level of bitterness perceived by them. The members of the panel were asked to gargle and wait for 20 minutes before another sample was given to them for tasting. The mean bitterness value of each of the ratios was calculated based upon the level of bitterness sensed by each individual member of the panel [23].

Kinetics of drug release

The mechanism of drug release for the Vilazodone solid dispersions was determined using zero order and first order.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

Zero Order Kinetic

It describes the system in which the drug release rate is independent of its concentration.

$Qt = Qo + Ko\ t$

Where,

Qt= Amount of drug dissolved in time t

Qo = Initial amount of drug in the solution, which is often zero
Ko = zero order release constant.

If the zero order drug release kinetic is obeyed, then a plot of Qt versus t will give a straight line with a slope of Ko and an intercept at zero.

First order kinetic

It describes the drug release from the systems in which the release rate is concentration dependent.

Log Qt = log Qo + kt/ 2.303

Where,

Qt = amount of drug released in time t. Qo = initial amount of drug in the solution k = first order release constant

If the first order drug release kinetic is obeyed, then a plot of log (Qo- Qt) versus t will be straight line with a slope of kt/ 2.303 and an intercept at t=0 of log Qo.

Results and discussion

Preformulation studies

Solubility

Solubility of Vilazodone was carried out at 250C using 0.1 N HCL, 6.8 phosphate buffer, 7.4pH buffer, methanol and ethanol. (Table 11, Figure-10)

From the above conducted solubility studies in various buffers we can say that 6.8pH phosphate buffer has more solubility when compared to other buffer solutions & methanol as greater solubility when comparted to organic solvents.

Analytical method development by UV Spectroscopy

UV Scan Spectrum of Vilazodone (Figure 11)

Calibration curve data of Vilazodone In 6.8pH phosphate buffer (Table -12, Figure-12)

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation. (Figure 13, 14)

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Vilazodone) and optimized formulation (Vilazodone: excipients) which indicates there are no physical changes.

Evaluation Studies

The entrapment efficiency of formulations F1-F12 were found to be in the range of 94.63-99.12%.

The percentage yield of formulations F1-F12 were found to be in the range of 96.53- 99.25%.

Invitro Drug Release Studies of Vilazodone Taste Masking Sachets (Figure 15, Table -13, Figure -16)

Invitro drug release of Vilazodone taste masking sachets with mannitol in various ratios by kneading method were observed which shows at the end of 60 mins, the formulation F1 releases 85.64, formulation F2 releases 89.15, F3 releases 96.48%. (Table -14, Figure -17)

Invitro drug release of Vilazodone taste masking sachets with mannitol in various ratios by solvent evaporation method were observed which shows at the end of 60 mins the formulation F4 releases 86.74, formulation F5 releases 92.94, formulation F6 releases 97.24% (Table 15, Figure 18).

Table 11: *Solubility studies of Vilazodone.*

Medium	Solubility (mg/ml)
Methanol	1.684
Ethanol	1.029
0.1N HCL	0.686
6.8pH buffer	1.535
7.4pH buffer	0.526

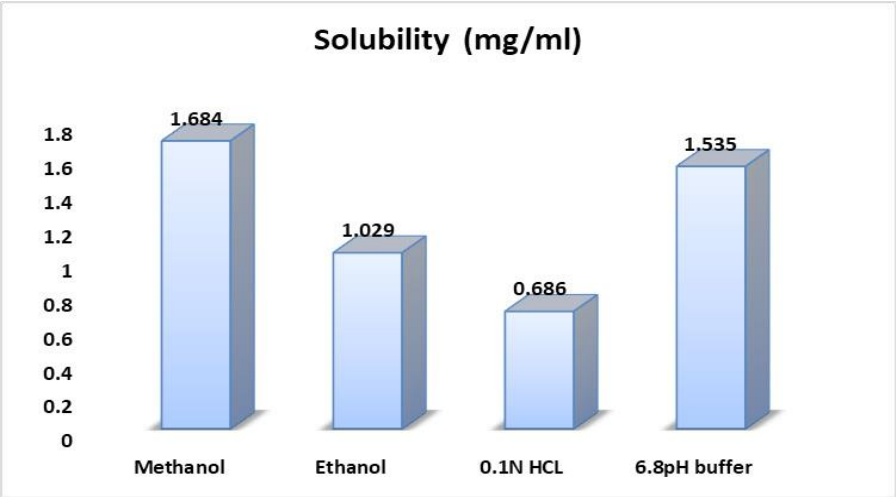

Figure 10: *Solubility studies of Vilazodone.*

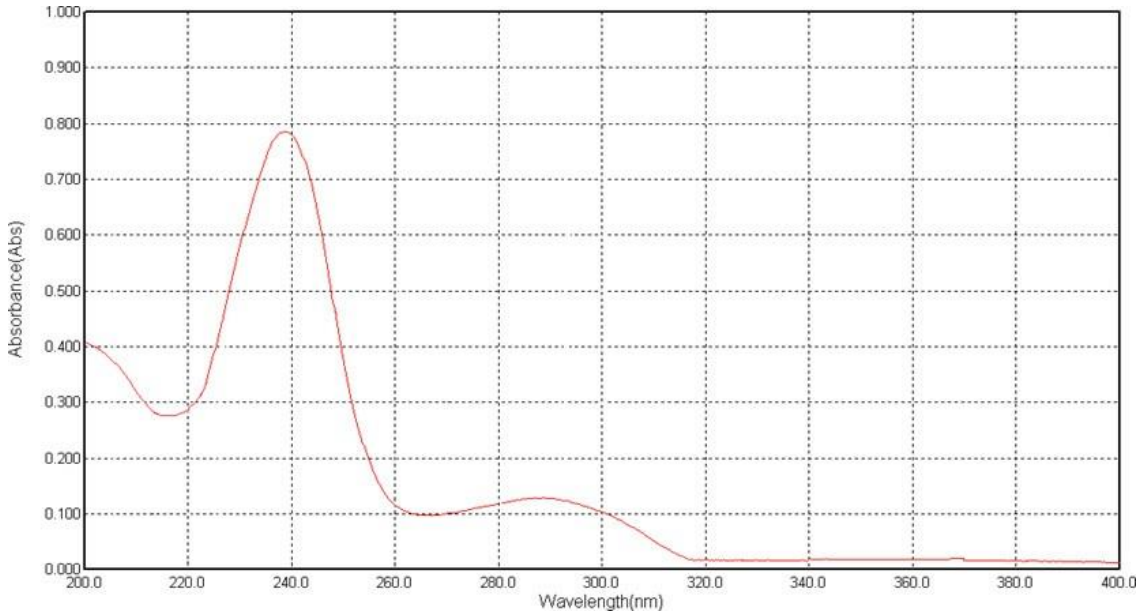

Figure 11: *UV Scan Spectrum of Vilazodone.*

Table 12: *Calibration curve data of Vilazodone In 6.8pH phosphate buffer.*

Concentration (µg/ml)	Absorbance
0	0
2	0.165
4	0.328
6	0.456
8	0.615
10	0.786
12	0.921

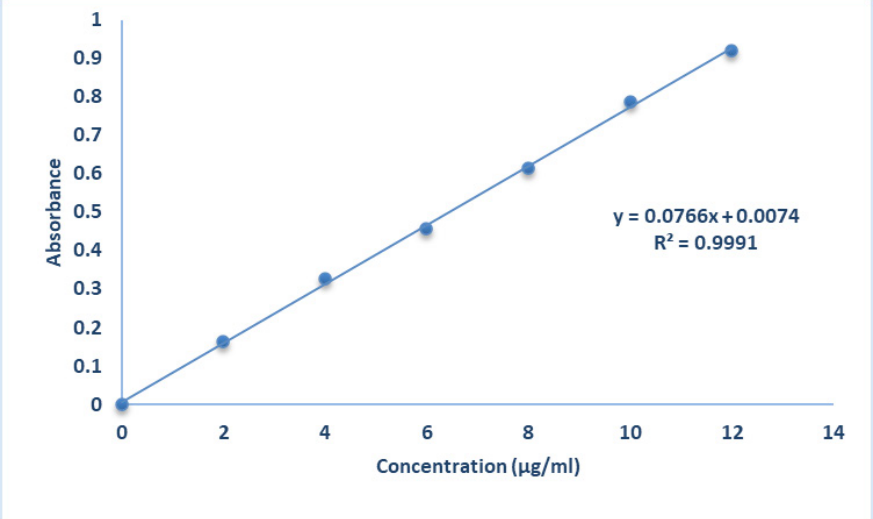

Figure 12: *Calibration curve of Vilazodone in 6.8pH phosphate buffer.*

Invitro drug release of Vilazodone with β cyclodextrin in various ratios by kneading method were observed which shows at the end of 60 mins the formulation F7 releases 88.59, formulation F8 releases 93.08, formulation F9 releases97.62% (Table 16, 17, Figure 19)

Invitro drug release of Vilazodone with β cyclodextrin in various ratios by Solvent Evaporation method were observed which shows at the end of 60 mins the formulation F10 releases 86.42, formulation F11 releases 90.56, formulation F12 releases 98.62%.

Finally, by comparing all the formulations F1-F12 formulation F12 containing Vilazodone: PEG-6000 (1:1.5) by solvent

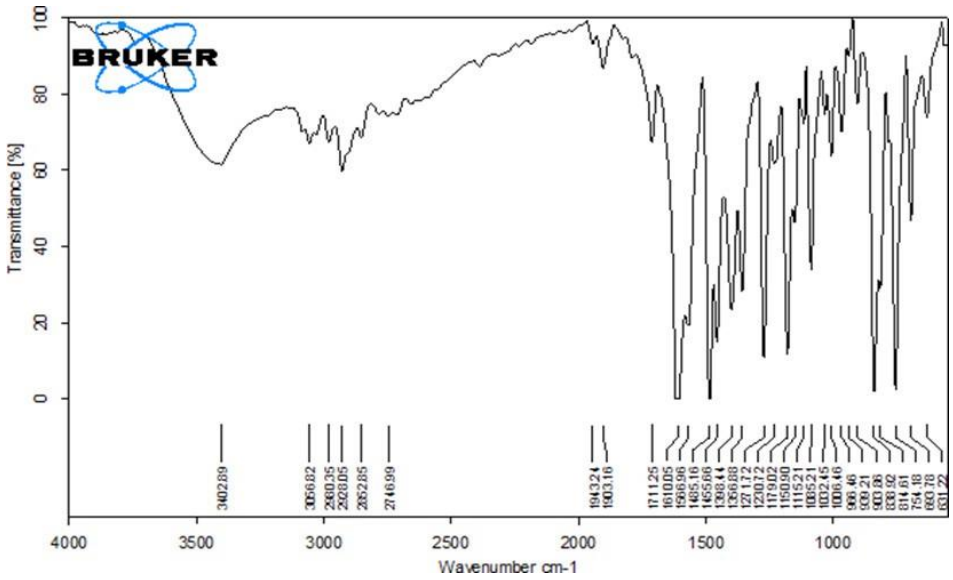

Figure 13: *IR spectrum of pure Vilazodone.*

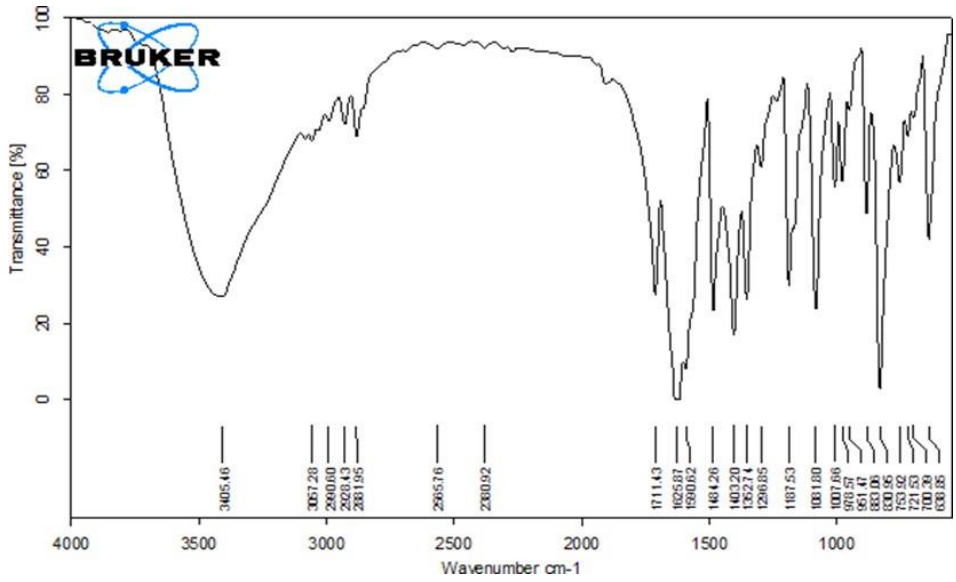

Figure 14: *IR spectrum of Vilazodone Optimised Formulation.*

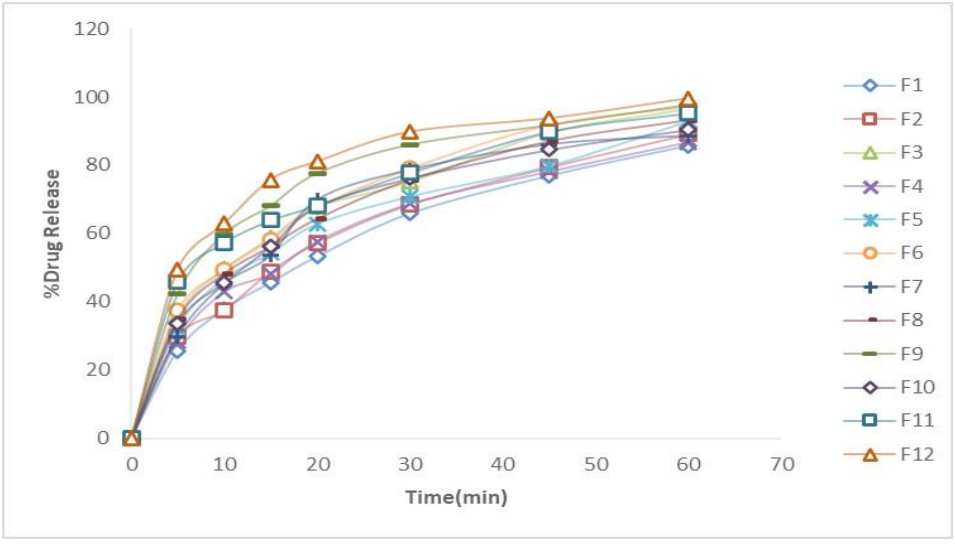

Figure 15: *Invitro drug release studies for formulations (F1-F12).*

Citation: *Preethi G. Fabrication and Evaluation of Taste masking Sachats. Asian J Biomed Pharm Sci. 2024;14(103):212*

Table 13: *Evaluation Studies of Vilazodone Taste masking sachets.*

Formulation Code	Drug content	Practical Yield (%)
F1	94.63	97.27
F2	96.65	98.53
F3	95.43	96.61
F4	97.42	97.38
F5	98.63	96.41
F6	96.32	97.1
F7	95.05	96.53
F8	97.04	96.2
F9	95.56	96.6
F10	94.63	95.85
F11	96.06	97.1
F12	99.12	99.25

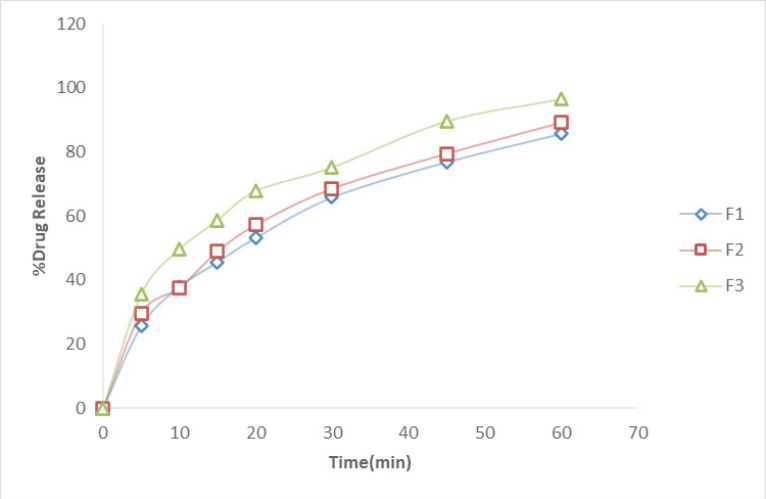

Figure 16: *Invitro drug release profile for F1-F3.*

Table 14: *Invitro drug release studies for formulations (F1-F3).*

Time (Min)	Percentage drug release		
	F1	F2	F3
0	0	0	0
5	25.68	29.64	35.65
10	37.81	37.58	49.61
15	45.61	48.92	58.71
20	53.17	57.21	67.81
30	65.78	68.54	75.18
45	76.81	79.45	89.57
60	85.64	89.15	96.48

evaporation method shows better results at the end of 60 min with drug release of 99.57%, hence it was selected as the best formulation among all the formulations.

Drug release kinetics studies for best formulation F12

Zero order release kinetics studies (Figure 20) ***First order release kinetics studies*** (Figure -21)

By comparing the release kinetics studies of best formulation with zero order and first order we can say that the best formulation follows first order release kinetics studies having R2 value 0.935 were as zero order release kinetics studies having R2 value 0.638, hence we can say that the best formulation follows first order release kinetics.

Taste evaluation of the complexes (Table 18)

Summary and conclusion Summary

Vilazodone is an antidepressant agent used for the treatment of major depressive disorder that targets the 5-HT transporter and 5-HT1A receptors. It is given with a dose of not more than 20 mg orally once a day. The absorption of this drug is rapid and complete. Due to first pass metabolism in the liver and metabolism in the gut wall, absolute bioavailability is about 50%. Peak blood concentrations are attained within about 2 hours after an oral dose. This leads to lower bioavailability of Vilazodone hydrochloride, and also having bitter taste.

Table 14: *Invitro drug release studies for formulations (F1-F3).*

Time (Min)	Percentage drug release		
	F1	F2	F3
0	0	0	0
5	25.68	29.64	35.65
10	37.81	37.58	49.61
15	45.61	48.92	58.71
20	53.17	57.21	67.81
30	65.78	68.54	75.18
45	76.81	79.45	89.57
60	85.64	89.15	96.48

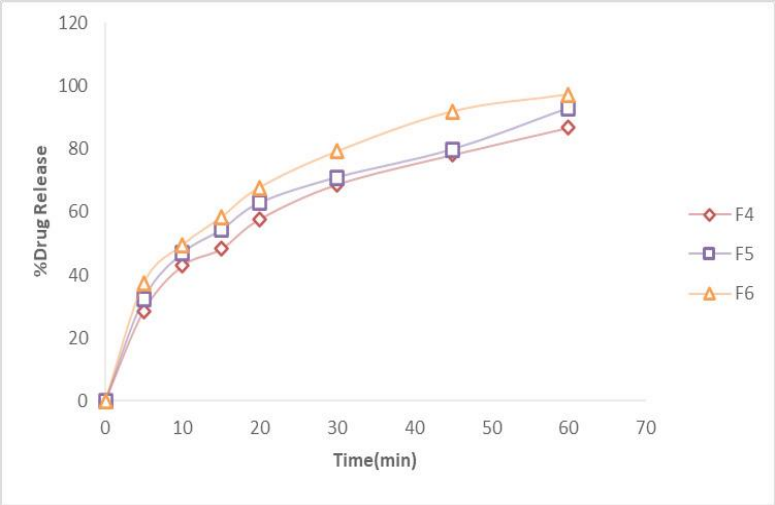

Figure 17: *Invitro drug release profile for F4-F6.*

Table 15: *Invitro drug release studies for formulations (F4-F6).*

Time (Min)	Percentage drug release		
	F4	F5	F6
0	0	0	0
5	28.59	32.47	37.48
10	42.86	46.84	49.47
15	48.18	54.24	58.24
20	57.68	62.84	67.75
30	68.68	70.89	79.15
45	78.15	79.84	91.89
60	86.74	92.94	97.24

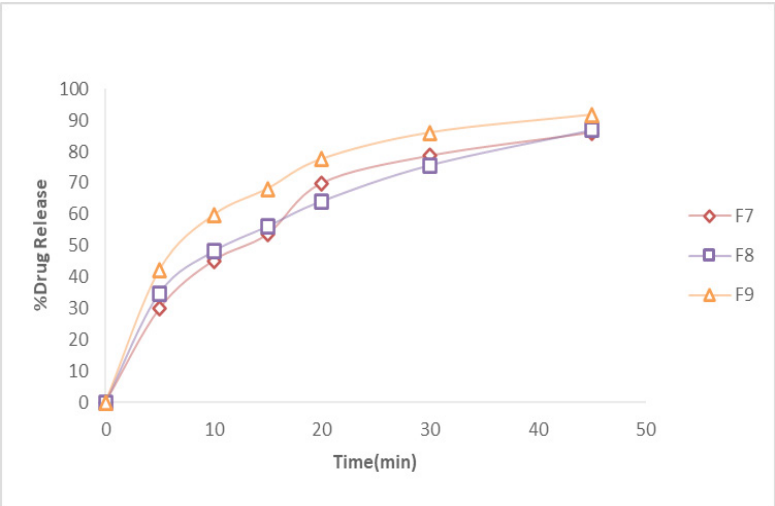

Figure 18: *Invitro drug release profile of F7-F9.*

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Table 16: *Invitro drug release studies formulations for F7-F9.*

Time (Min)	Percentage drug release		
	F7	F8	F9
0	0	0	0
5	29.89	34.86	42.18
10	45.22	48.17	59.68
15	53.62	56.14	68.07
20	69.86	64.18	77.53
30	78.64	75.68	85.94
45	86.05	86.91	91.65
60	88.59	93.08	97.62

Table 17: *Invitro drug release studies formulations for F10-F12.*

Time (Min)	Percentage drug release		
	F10	F11	F12
0	0	0	0
5	33.65	45.86	49.47
10	45.65	57.32	62.85
15	56.18	63.86	75.72
20	67.85	68.24	81.09
30	76.19	77.74	89.75
45	84.56	89.84	93.72
60	90.42	95.27	99.57

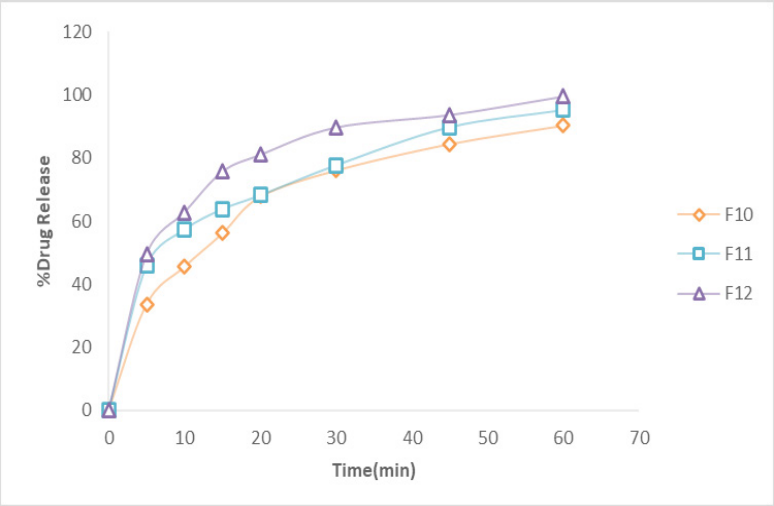

Figure 19: *Invitro drug release profile of F10-F12.*

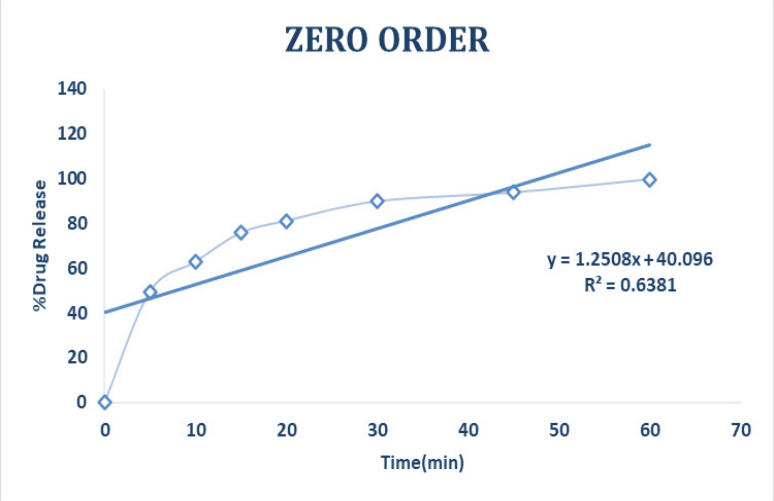

Figure 20: *Zero order release profile for best formulation (F12).*

Figure 21: *First order release profile for best formulation (F12).*

Table 18: *Taste evaluation of the complexes.*

Formulations	Mean bitterness value		
	Pure drug	Poloxamer	PEG-6000
01:00.5	5	4	3
1:01		3	2
01:01.5		2	1

So to improve its bioavailability and to mask the taste solid dispersion technique was used using different carriers like Poloxamer & PEG-6000.

The brief introduction about taste masking technologies solid dispersions were explained in the introduction part. Furthermore, in this chapter introduction on dissolution rate and various approaches to improve the solubility; particularly on solid dispersion technology was elaborated. The aim and objective were also discussed. Drug profile and excipient profiles were included with complete drug description of Vilazodone and out lined their usage, contraindication and side effects. Literature survey related to preparation and past research work on solid dispersions with various drugs and also by different methods.

Methodology as well as materials used and experimental methods employed in the present investigation were explained in detail. Later introduction regarding all the evaluation parameters and method of preparation of solid dispersions of Vilazodone by solvent evaporation method & kneading method was explained. Solid dispersions of Vilazodone were prepared with polymers in different ratios of drug and carrier (1:0.5, 1:1, and 1:1.5) by solvent evaporation method& kneading method. Results of prepared solid dispersions of Vilazodone were discussed which includes solubility, drug content uniformity, and in vitro dissolution studies. Characterization in solid state was done by various analytical techniques such as FT- IR studies.

Finally by comparing all the formulations i.e., F1-F12 containing Vilazodone, Poloxamer and PEG-6000 in different ratios. The formulation F12 containing PEG- 6000 (1:1.5) shows better results by solvent evaporation method at the end of 60 min with drug release of 99.57%, hence it was selected as the best formulation. By comparing the release kinetics studies of best formulation of Vilazodone with zero order and first order we can say that the best formulation follows first order release kinetics studies having R2 value 0.935 were as zero order release kinetics studies having R2 value 0.638.

Conclusions

Poloxamer, PEG-6000 was used in the preparation of solid dispersions for taste masking by solvent evaporation & kneading method. By observing the dissolution studies Vilazodone with PEG-6000 (1:1.5) by solvent evaporation method shows better drug release than the other formulations.

The following conclusions were drawn from the present investigations.

- From the Solubility studies in various buffers, we can say that 6.8pH buffer solution has more solubility when compared to other buffer solutions for Vilazodone.
- Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes.
- All the formulations of Vilazodone were prepared by using Kneading & solvent evaporation method.
- All the prepared solid dispersions were evaluated for practical yield, drug content.
- The *invitro* dissolution studies of Vilazodone was performed including the release kinetics studies.
- Among the all 12 formulations, formulation with PEG-6000 (1:1.5) shows better drug release than the other formulations.
- Taste evaluation of the complexes also revealed that the PEG-6000 (1:1.5) along with Vilazodone was found to

be taste masked successfully by using solid dispersion technique.

- So it was concluded that the PEG-6000 was used as a carrier for enhancing the taste of Vilazodone.

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