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# Development of Taste Masked Formulation for Bitter Drug

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## ABSTRACT

The objective of this work was to develop a taste masking method for oseltamivir phosphate and formulate the taste masked product into a suitable formulation. A preliminary screening was done using various ion exchange resins, inclusion complexes and solid dispersions. Through this screening, ion exchange method using a polacrilex resin, Tulsion 335 was selected. The process was optimized for drug: resin ratio to get maximum drug loading. A 1:2 ratio of drug: resin was selected. Taste evaluation was carried out by panel method. Drug resin complex (DRC) was evaluated for drug content and formation of complexation by FTIR. The resultant DRC was formulated into dry suspension using xanthan gum, poloxamer 403, sucrose, methyl and propyl paraben and flavor. The dry mixture had satisfactory flow properties and showed negligible sedimentation when reconstituted and allowed to stand for 24hrs.

**Keywords:** Tulsion 335, Drug resin complex (DRC), Panel method, Dry suspension.

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## INTRODUCTION

### Anatomy of tongue

The tongue is a versatile organ with specialized functions like taste and speech. Beneath a cover of taste buds the tongue is almost entirely made up of muscles. The muscles of the tongue are essential for its bodily movement and intrinsic manipulations, required for actions like speech, articulation, and deglutition or swallowing, whistling, licking and even cleaning teeth up to some extent.

The tongue is partly in the oral cavity and partly in the pharynx. The part in the oral cavity is the mobile part of the tongue that is seen in the mouth. The pharyngeal part is situated behind and is fixed. While the fixed position anchors the tongue, it is the free anterior portion in the oral cavity that can change shape and be manipulated for the tongue to execute its various actions.

### Tongue muscles

The muscles of the tongue belong to two groups intrinsic and extrinsic. Intrinsic muscles lie entirely within the tongue; that is their origin and insertions are inside the tongue. There are four groups of them;

- Superior
- Inferior longitudinal
- Transverse or horizontal
- Vertical

The tongue is a highly muscular organ in the mouth. The tongue is covered with moist, pink tissue called mucosa. Tiny bumps called papillae give the tongue its rough texture. Thousands of buds cover the surfaces of the papillae. Taste buds are collections of nerve-like cells that connect nerves running into the brain.

The tongue is anchored in the mouth by webs of tough tissue and mucosa. The tether holding down the front of the tongue is called the frenum. In the back of the mouth, the tongue is anchored into the hyoid bone. The tongue is vital for chewing and swallowing food as well as speech.

The four common tastes are sweet, sour, bitter and salty. A fifth taste called umami results from tasting glutamate (present in monosodium glutamate). The tongue has many nerves that help detect and transmit taste signals to the brain, because of this, all parts of the tongue are able to detect four common tastes; the commonly described taste map of the tongue does not really exist.

**Taste bud anatomy**

Taste buds are composed of groups of about 40 columnar epithelial cells bundled together along their long axes. Taste cells within a bud are arranged such that their tips form a small taste pore, and through this pore extend microvilli from taste buds contain cells bear taste receptors and it appears that most taste buds contain cells that bear receptors for 2-3 of the basic tastes.

Interwoven among the taste cells in a taste bud is a network of dendrites of sensory nerves called taste nerves. When taste cells are stimulated by binding of chemicals to their receptors, they depolarize and this depolarization is transmitted to the taste nerves fibres resulting in an action potential that is ultimately transmitted to the brain. One interesting aspect of this nerve transmission is that it rapidly adapts after initial stimulus, a strong discharge is seen in the taste nerve fibres but within a few seconds, that response diminishes to a steady-state level of much lower amplitude.

Once taste buds are transmitted to the brain, several efferent neural pathways are activated that are important to digestive function. For example, tasting food is followed rapidly by increased salivation and by low level secretary activity in the stomach.

Considerable attention has been devoted to the understanding the benefits to survival and wellbeing that accrue from having a sense a taste. Some have speculated that an ability to taste bitterness may protect animals from ingesting certain natural poisons. There is no doubt that animals, including humans develop taste preferences. That is, they will choose certain types of food in preference to others. Interestingly, taste preference often changes in conjugation with body needs. Similarly animals often develop food aversions, particularly if they become ill soon after eating a certain food, even though that food was not the cause of the illness- surely after you have experienced this yourself. Food preferences and aversions involve the sense of taste, but these phenomena are almost certainly medicated through the central nervous system rather than directly through taste cells.

**Physiology of taste**

The sense of taste is medicated by groups of cells called taste buds which sample oral concentrations of a large number of small molecules and report a sensation of taste to centres in the brainstem. In most of the animals, including humans, taste buds are most prevalent on small pegs of epithelium on the tongue called papillae. The taste buds are themselves too small to see without a microscope, but papillae are readily observed by close inspection of the tongue's surface. To make them easier to see, put a couple of drops of blue food colouring on the tongue of a person. Also you will see a bunch of little light coloured bumps mostly fungi from papiallae stand out on a blue background.

In addition to signal transduction by taste buds, it is also clear that the sense of smell profoundly affects the sensation of taste. The sense of taste is equivalent to excitation of taste receptors for a large number of specific chemicals have been identified that contribute to the reception of taste. These include receptors for such chemicals such as sodium, potassium, chloride, glutamate and adenosine. Perception of taste also appears to be influenced by thermal stimulation of the tongue. In some people, warming the front part the tongue produces a clear sweet sensation, while cooling leads to a salty or sour sensation.

It should be noted that these tastes are based on human sensations and some comparative physiologists caution that each animal probably lives in its own taste world. For animals, it may be more appropriate to discuss tastes as being pleasant, unpleasant or indifferent.

None of the taste is elicited by single chemical. Also, there are thresholds for detection of taste that differ among chemicals that taste the same. For example, sucrose, 1-propyl-2 amino-4-nitrobenzene and lactose all taste sweet to humans, but these at concentrations of roughly 10mM, 2M, 30mM respectively a range of potency of roughly 15,000-fold. Substances sensed as bitter typically have very low thresholds.

**Importance of taste masking**

Taste is an important factor in the development of dosage form. Nevertheless it is that arena of product development that has been overlooked and undermined for its importance taste masking technologies offer a great scope for invention and patents. The bitter and obnoxious taste of drug is a challenge to the pharmacist in present scenario.

Taste, smell, texture, and taste are important factors in the development of dosage forms. These are important factor in product preferences. Good flavour and texture are found significantly affect the sale of the product. There are numerous pharmaceuticals that contain actives, which are bitter in taste. With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patience compliance. The problem of bitter and obnoxious taste of drug in paediatric and geriatric formulation is a challenge to the pharmacist in the present scenario. Molecule interacts with taste receptors on tongue to give bitter, sweet or other taste sensations, when they are dissolved in the saliva. This sensation is the result of the signal transduction from the receptor organs for taste which are commonly known as taste buds. 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 prescription of taste.

Undesirable taste is one of the several important formulation problems that are encountered with certain drugs. The problem of bitter and obnoxious taste of drugs is a challenge to the pharmacist in the present scenario.

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Taste is one of the most important organoleptic aspects determining the favourable acceptance of oral drugs. Because the majority of drugs taste unacceptable due to their functionalities, taste masking is essential to ensure patient compliance [Remington et al 2002].

**COMMON METHODS OF TASTE MASKING**

Various methods are available to mask undesirable taste of drugs. Some of these are given below.

A. Ion exchange resin

Ion exchange resins are solid and suitably insoluble high molecular weight poly-electrolytes that can exchange their mobile ions of equal charge with surrounding medium. The resulting ion exchange is reversible and stoichiometric with the displacement of the one ionic species by another [Borodkin et al 1971].

B. Inclusion complex

Inclusion complexation is a process in which the guest molecule in included in the cavity of a host. The complexing agents masks the bitter taste of the drug either by decreasing the number of drug particles exposed to taste buds, thereby reducing the perception of the bitter taste [Lachman et al 1991].

C. Microencapsulation

It is a process as a mean of applying relatively thin coating to smaller particles of solid, droplets of liquids and dispersion. This process can be used for masking of bitter tasting drugs by microencapsulating drug particle with various coating agent [Bakan et al 1986].

D. Flavouring Agent

Flavouring and sweetening offer the simplest and most convenient way to mask taste. Flavours and sweeteners are chosen based upon their specific taste and release profiles. Sweeteners like sodium saccharin, sucrose and acesulfame potassium, for example give instant sweetness, whereas sweeteners like monoammonium glycyrrhizate give lingering sweetness [Adjei et al 1996].

E. Prodrug

A prodrug is chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent drug. It is useful for bitter tasting drugs which can be chemically modified to get a prodrug which lacks a bitter taste [Desai et al 20003].

F. Polymer coating

It is an extremely useful technique for number of applications in the pharmaceutical field. By co-ordinating the right type of coating material it is possible to completely mask the taste of the bitter drug, while at the same time, not adversely affecting the intended

drug release profile. Any non toxic polymer that is insoluble at pH 7.4 and soluble at acidic pH would be an acceptable alternative for taste masking [Friend DR et al 2000].

G. Melt granulation

It is one of the most widely applied techniques in the array of pharmaceutical manufacturing operations. Melt granulation is currently applied in the pharmaceutical field for the manufacturing of variety of dosage forms and formulation such as intermediate release and sustained release pellets, granules, and tablets. Melt granulation is carried out at higher temperatures (50-80$^{o}$C) using low melting lipids like glyceryl behenate and glyceryl palmitostearate as binders.[http:/www.pharmainfo.net on Dec 2011].

H. Multiple emulsions

Multiple emulsions are complex polydispersed system where both oil in water and water in oil emulsions exist simultaneously which are stabilized by lipophilic and hydrophilic surfactant respectively [Yakoob et al 2006].

**Evaluation of taste masking**

**Sensory Analysis**

Sensory analysis has been used in developed countries for years to characterize flavors, odors and fragrances. In recent times much progress has been made in development of instrumentation methods for characterizing odors and flavors.

These methods are often more useful in aroma and flavor research than in product development where formulation are usually complex and sensory methods can provide equally reliable data on overall flavor character.

Sensor analysis employs objective or analytical methods and subjective or hedonic methods.

**A. Subjective Methods**

1. Preference Test
a. Paired Testing
b. Triangle Testing
2. Hedonic scale

**B. Objective Methods**

1. Difference Test
a. Paired Difference Test
b. Triangle Difference Test
c. Duo-trio Test.
2. Ranking Test
3. Analytical

a. Flavor Profile
b. Time-Intensity Test
c. Single Attribute Test

**A. Subjective Methods:**

Subjective method assesses the performance of a flavored product using a large number of untrained analysts. Field "Pretest" generally falls in this category. Often several preparations are tested against control. Untrained analysts are used and methods are characterized by spontaneity and results are often biased by emotional and personal attitudes.

**1. Preference Tests:**

a. Paired testing

Paired testing compares the taste of two samples, that is, how sweet, bitter, sour or salty they are. Because untrained analysts are employed in such tests, associative effects are not easily quantified. Detection of a difference between samples may be associated with a bias, which would be analogues to the bias attached to things considered different, odd, bad or good. Since analysis of the bias is as important as the magnitude of sample difference, routine testing is not useful in product development. Yet these tests are beneficial in market decision -making because results are based on user preference.

b. Triangle testing:

Like paired tests, triangle test do not provide quantitative data on differences between similar or dissimilar samples. These tests are designed to limit bias and improve confidence in the selection process. They provide quantitative difference between samples. Usually three preparations are tested; two are identical, where as the third is different in one or several respects. Because data generated by triangle testing is largely subjective, criteria for determining accuracy of results and hence validity of prediction from such test are poorly defined and nonexistent. Statistically, the triangle testing is preferred because there is only 33.3% chance of guessing, and only a limited number of test are required compared to a 50% chance of error in paired testing.

**2. Hedonic Scale:**

The term hedonic applies to a scalar measure used to describe the degree of acceptance of a flavor. Hedonics are designed to recognize a fixed point of neutrality (zero point) for a flavor. This allows rating the flavor on the basis of the degree of its negative or positive sensation on a scale. Negative numbers on the degree of unpleasantness, where as the positive numbers reflect the degree of accepting of flavoring agent.

Hedonics in pharmaceutical flavor work provide subjective estimate of the degree of acceptance of a totally flavored product. They are most useful for trained flavor panelists who can apply a continuum of positive numbers to describe the intensity of a specific element f a flavored product. This has the disadvantage that a continuum of positive number ignores the

neutral point and thus compares the relative acceptance to the relative acceptance level for a product based on the performance against a reference.

**B. Objective Method:**

Objective methods in flavor test generally use a small panel of trained analysts with standardization methods of identifying various tastes. The panel members act like an instrument and use their carefully controlled senses to analyze organoleptic quality of a product in such a way that emotional basis is eliminated.

**1. Difference tests:**

A. Paired-difference test:

Paired-difference test are useful in screening formulation studies. This test includes a benchmarked product designated as control sample and a treatment sample. Two groups of samples pair are tested. In one group each pair contains a treatment and a control specimen. In the other group, the pair contains only treatment or only control. Sample The primary question is “Are the sample same or different?” samples are randomly coded in order to eliminate bias.

Finding difference between samples then follows this: “Are there difference between the sample?” after completing this test, the panel director analyzes the data concludes that there are no perceptible differences between samples. However comments from panelist suggest that some perceives slight “after taste” difference, where as other do not. With this information the director decides to perform a confirmatory test using a triangle difference test.

B. Triangle Difference Test

The objective of the panel director is to determine which sample is to differs in “lingering bitter after taste”. In each group two samples are alike and contain either control formulation or the reformulated product. Third sample is different but also contains either control formulation or the reformulated product. The samples are presented in straight line and six possible different sample positions.

C. Duo- Trio Test:

In duo- trio test, the panel director designates one sample usually control, as the reference, In addition, several pairs of samples are given to panelists, each consisting of one control and one treatment sample. All samples are labeled in a randomized fashion. The task of the panelists is to identify the pair that is similar in performance to the reference control sample.

**2. Ranking Tests**

Ranking tests are used when more than two samples are to be evaluated. If six samples are to evaluate of a formulation for sweetness difference, the task panel is to rank the series in order from the least to most sweet. A typical rank test score sheet is shown in Table. 4

**3. Analytical Test:**

a. Flavor profile:

The flavor profile is widely used descriptive analytical test. It is based on a natural process, often performed instinctively, for evaluating and comparing flavor. A flavor profile measure s objectively, qualitatively the perceptible factors of a product that is aroma flavor by mouth, feeling factor and after use sensations.

b. Time intensity study:

The Arther D. Little flavor Laboratories, 1954, developed this method of flavor analysis. It is useful in time dependent product quality assessment.

Panelist record after taste impression as a function of time and several sessions are allowed until a consensus is arrived at. Data from the test sessions are compiled and graphically summarized with intensity on Y-axis and time on X-axis.

**C. Single-Attribute Tests:**

Single attribute test are valuable in quality control and routine release testing of products by manufacturer. The technique is similar to the flavor profile method, except that the panel concentrates on one attribute only. For example a product during a mixing step at manufacture relative to time and temperature can be investigated by single attribute.

**Oseltamivir phosphate**

Oseltamivir phosphate is an anti-viral agent. It is a neuraminidase inhibitor in Influenza virus. It acts against the virus hence administered in case of flu. The trade name of the same is being Tamiflu. The drug acts a competitive inhibitor towards sialic acid, found on the surface proteins of normal host cells. By blocking the activity of the viral neuraminidase (NA) enzyme, oseltamivir prevents new viral particles from being released by infected cells.

In situations like H1N1 infection which is commonly termed as swine flu, treatment becomes very crucial especially for pediatric patients. Oseltsamivir (Tamiflu) is the drug of choice which should be administered to the patient within first 48 hours without which many deaths have been reported. Because of very bitter taste, administration of oseltamivir to kids is difficult. Many times vomiting is observed immediately after administration. Injectable form of oseltamivir is not currently available. Thus taste masking of oseltamivir is of great importance; hence it was selected for studies.

## MATERIALS AND METHODS

**Oseltamivir Phosphate**[www.rxlist.com accessed November 2011.]

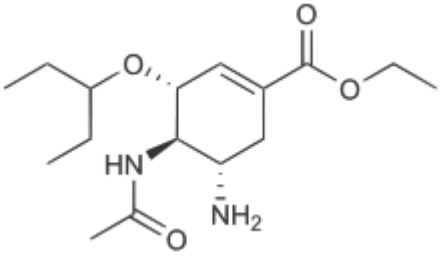
It is an antiviral drug, slows the spread of influenza (flu) virus between cells in the body by stopping the virus from chemically cutting ties with its host cell; median time to symptom alleviation is reduced by 0.5–1 day. The drug is sold under the trade name Tamiflu, and is taken

orally in capsules or as a suspension. It has been used to treat and prevent influenza A virus and influenza B virus infection in over 50 million people since 1999.

Oseltamivir is a prodrug, a (relatively) inactive chemical which is converted into its active form by metabolic process after it is taken into the body. It was the first orally active neuraminidase inhibitor commercially developed. It was developed by C.U. Kim, W. Lew, and X. Chen of US-based Gilead Sciences, and is currently marketed by Hoffmann–La Roche (Roche). In Japan, it is marketed by Chugai Pharmaceutical Co., which is more than 50% owned by Roche.

As of December 2010, the World Health Organization (WHO) reported 314 samples of the prevalent 2009 pandemic H1N1 flu tested worldwide have shown resistance to oseltamivir.

**Oseltamivir**




**Uses**

Oseltamivir is used to treat symptoms caused by the flu virus (influenza). It helps make the symptoms (such as stuffy nose, cough, sore throat, fever/chills, aches, and tiredness) less severe and shortens the recovery time by 1-2 days. This medication is also used to prevent the flu if you have been exposed to someone who already has the flu (such as a sick household member) or if there is a flu outbreak in the community. This medication works by stopping the flu virus from growing. It is not a substitute for the flu vaccine.

**Precautions**

Before taking oseltamivir, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details. Before using this medication, tell your doctor or pharmacist your medical history, especially of: kidney disease. Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).During pregnancy, this medication should be used only when clearly needed. Discuss the risks and benefits with your doctor. This medication passes into breast milk. Consult your doctor before breast-feeding.

**Drug Interactions**

Drug interactions may change how your medications work or increase your risk for serious side effects. This document does not contain all possible drug interactions. Keep a list of all the products you use (including prescription/nonprescription drugs and herbal products) and share it with your doctor and pharmacist. Do not start, stop, or change the dosage of any medicines without your doctor's approval. Tell your doctor if you have received flu vaccine in the nose within 2 weeks before treatment with this medication. This medication may lower your

protection from flu vaccine given in the nose. Wait at least 2 days after ending treatment with this medication before receiving flu vaccine given in the nose.

**Overdose**

If overdose is suspected, contact a poison control center or emergency room immediately. US residents can call the US National Poison Hotline at 1-800-222-1222. Canada residents can call a provincial poison control center.

**Notes**

Do not share this medication with others. This medication is not a substitute for the flu vaccine. Consult your doctor about the risks and important benefits of receiving a yearly flu shot to lower your chances of getting the flu.

**Missed Dose**

If you miss a dose, use it as soon as you remember. If it is within 2 hours of your next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

**Storage**

Store at room temperature away from light and moisture. Do not store in the bathroom. Keep all medications away from children and pets. Do not flush medications down the toilet or pour them into a drain unless instructed to do so. Properly discard this product when it is expired or no longer needed.

**2. XANTHAN GUM**[http:/www.wikipedia.org Accessed Dec 2011]

**1. Nonproprietary Names**

BP: Xanthan gum

PhEur: Xanthani gummi

USPNF: Xanthan gum

**2. Synonyms**

Corn sugar gum; E415, polysaccharide B-1459.

**3. Chemical Name and CAS Registry Number**

Xanthan gum [11138-66-2]

**4. Empirical Formula and Molecular Weight**

$(C_{35}H_{49}O_{29})_n$ Approximately $2 \times 10^6$

The USPNF 23 describes xanthan gum as a high molecular weight polysaccharide gum. It contains d-glucose and d-mannose as the dominant hexose units, along with d-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

**5. Structural Formula**

Each xanthan gum repeat unit contains five sugar residues: two glucose, two mannose, and one glucuronic acid. The polymer backbone consists of four β-d-glucose units linked at the 1 and 4 positions, and is therefore identical in structure to cellulose. Trisaccharide side chains on alternating anhydroglucose units distinguish xanthan from cellulose. Each side chain comprises a glucuronic acid residue between two mannose units. At most of the terminal mannose units is a pyruvate moiety; the mannose nearest the main chain carries a single group at C-6. The resulting stiff polymer chain may exist in solution as a single, double, or triple helix that interacts with other xanthan gum molecules to form complex, loosely bound networks.

**6. Functional Category**

Stabilizing agent; suspending agent; viscosity-increasing agent.

**7. Applications in Pharmaceutical Formulation or Technology**

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range

**8. Description**

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

**9. Stability and Storage Conditions**

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids, and bases.The bulk material should be stored in a well-closed container in a cool, dry place.

**3. POLOXAMER 407[www.pharmagateway.net/ArticlePage. Accessed on Dec 2011]**

It is a hydrophilic non-ionic surfactant of the more general class of copolymers known as poloxamers. Poloxamer 407 is a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol. The approximate lengths of the two PEG blocks is 101 repeat units while the approximate length of the propylene gycol block is 56 repeat units.[1] This particular compound is also known by the BASF trade name Pluronic F127.

Uses of poloxamer 407

Most of the common uses of poloxamer 407 are related to its surfactant properties. For example, it is widely used in cosmetics for dissolving oily ingredients in water. It can also be found in multi-purpose contact lens cleaning solutions, where its purpose there is to help remove lipid films from the lens. It can also be found in some mouthwashes. There is a research ongoing for using poloxamer 407 for aligning severed blood vessels before gluing them surgically.

Reports of adverse effects

It was reported in The Australian newspaper 18 November 2006 that this common ingredient in toothpaste and mouthwash can cause high cholesterol. A team from the Centre for Ageing and the ANZAC Research Institute in Sydney found that when P407 was given to mice, it coated cells in the liver that control cholesterol levels, leading to a 10-fold increase in levels. The dose administered was 1g/kg by inter-peritoneal injection.

**SUCROSE** [Rowe R, Sheskey P and Owen S Eds. Handbook of Pharmaceutical excipients]

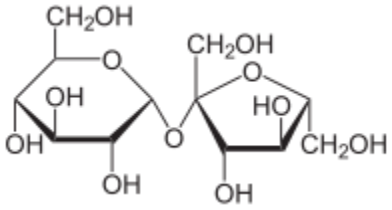
It is the organic compound commonly known as table sugar and sometimes called saccharose. A white, odorless, crystalline powder with a sweet taste, it is best known for its role in human

nutrition. The molecule is a disaccharide composed of glucose and fructose with the molecular formula $C_{12}H_{22}O_{11}$.

**Synonyms**

Sugar; Saccharose; α-D-glucopyranosyl-(1→2)-β-D-fructofuranoside; β-D-fructofuranosyl-(2→1)-α-D-glucopyranoside; β-(2S,3S,4S,5R)-fructofuranosyl-α-(1R,2R,3S,4S,5R)-glucopyranoside; α-(1R,2R,3S,4S,5R)-glucopyranosyl-β-(2S,3S,4S,5R)-fructofuranoside

Sucrose



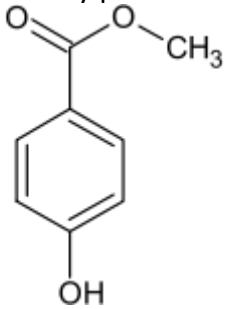

**METHYLPARABEN**[Rowe R, Sheskey P and Owen S Eds. Handbook of Pharmaceutical excipients] Methylparaben, also methyl paraben, one of the parabens, is a preservative with the chemical formula $CH_3(C_6H_4(OH)COO)$. It is the methyl ester of p-hydroxybenzoic acid.

**IUPAC name**

Methyl 4-hydroxybenzoate

Methylparaben is found in several fruits, in particular blueberries, [1][2][3] where it acts as an antimicrobial agent.

Methylparaben




**Uses**

Methylparaben is an anti-fungal agent often used in a variety of cosmetics and personal-care products. It is also used as a food preservative and has the E number E218.

Methylparaben is commonly used as a fungicide in Drosophila food media. Usage of methylparaben is known to slow Drosophila growth rate in the larval and pupal stages.

**PROPYLPARABEN** [Rowe R, Sheskey P and Owen S Eds. Handbook of Pharmaceutical excipients]

Propylparaben the propyl ester of p-hydroxybenzoic acid, occurs as a natural substance found in many plants and some insects, although it is manufactured synthetically for use in cosmetics, pharmaceuticals and foods. It is a preservative typically found in many water-based cosmetics, such as creams, lotions, shampoos and bath products. As a food additive, it has the E number E216.

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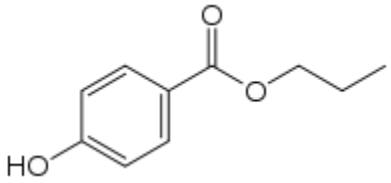
Sodium propyl p-hydroxybenzoate, the sodium salt of propylparaben, a compound with formula $Na(C_3H_7(C_6H_4COO)O)$, is also used similarly as a food additive and as an anti-fungal preservation agent. Its E number is E217.

Propylparaben




**METHODS**

**UV Spectroscopy**

**Determination of λ max**

Oseltamivir phosphate was accurately weighed and dissolved in distilled water to make concentration1 mg/ml. This solution was then suitably diluted to 100ml using distilled water to get a final solution of concentration 100µg/ml. A solution of the same concentration was prepared in 0.1 N HCl. UV spectrum was recorded over the wavelength range 200- 400 nm.

**Evaluation of taste of oseltamivir phosphate[ Sharma et al 2007].**

A panel of 10 healthy human volunteers was selected for study. A written consent was obtained from all volunteers. They were asked to rinse the oral cavity with demineralized water and to keep 30mg of oseltamivir on tongue and rate the bitterness on following scale: 0- non bitter, 1- slightly bitter, 2- bitter and 3- very bitter.

**Selection of method for taste masking of oseltamivir phosphate**

In order to achieve more pleasant dosage forms, various masking techniques have been described in the literature [Madgulkar et al 2007]. The simplest method is to add flavours or sweeteners. However, in most cases, these are rather limited and may not be effective enough to mask the unpleasant taste of some drugs. A number of more useful approaches have been tried, including capsule formulations, coating with water-insoluble polymers or pH-dependent water-soluble polymer, absorption to ion-exchange resin, microencapsulation with various polymers, and inclusion complexes with cyclodextrins.

Coatings of the active ingredient may often rupture during compressing and chewing of the tablet, as well as contribute to a gritty feel [Derle D.V. et al 2003].Microspheres or microencapsulated material may also face the same problem.

In recent days, taste masking by complexing the drug with ion exchange resins or cyclodextrins is becoming more popular. Release of drug from ion exchange complex is pH dependent. Cyclodextrins form inclusion complexes with the drug and may improve the solubility of the drug. Both of these methods do not increase the particle size of the drug and they are stable to compression process. So, selection of taste masking method was primarily focused on cyclodextrins, ion exchange resins and solid dispersions.

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**Taste masking by formation of inclusion complexes with β-cyclodextrin (BCD)** [Derle et al 2003, Peeters et al 2001]

Inclusion complex of oseltamivir phosphate and BCD were prepared by kneading method. Kneading method was selected as it is simpler and less time consuming than the solvent evaporation method. Oseltamivir phosphate and BCD were weighed separately in 1:1 and 1:2 molar ratios. Thick slurry of BCD in water was prepared. Oseltamivir phosphate was added to it in small quantities while continuous kneading. Kneading was continued for 2 h and the complexes were evaluated for taste masking.

**Taste masking by preparing solid dispersions [**Kaloiselvan et al 2006]

Solid dispersions of oseltamivir phosphate were prepared in PEG 4000 in 1:1, 1:1.5 and 1:2 drug: carrier ratios by weight. Melt solidification method was used for solid dispersions with PEG. The solid dispersions so prepared were evaluated for taste.

**Taste masking by formation of complexes with ion exchange resins** [Padalkar et al 2009, Avari et al 2004, Vimala devi et al 2004]

Various resins supplied by Thermax India Ltd. and Ion Exchange India Ltd. were used to select the resin that showed excellent taste masking ability and optimum drug loading. Tulsion 335, 339; Indion 234 were used in 1:1 drug: resin ratios. 100 mg of each resin was allowed to swell separately in 50 ml of deionized water for 90 min. 100 mg of oseltamivir phosphate was added to each of them and stirred for 5 hrs. Each slurry was filtered and the residue i.e. resinate or drug resin complex (DRC) was washed again with 25 ml of deionized water. The combined filtrate was evaluated for drug content. The difference between amount of drug used initially and that remaining in the filtrate is the amount of drug loaded on the resin. The resin that showed optimum loading was subjected to optimization of drug loading process.

**Optimization of drug resin ratio for maximum drug loading [**Chaudhari 2007, Pisal et al 2004]**.**

Drug loading process was optimized for maximum at various drug: resin ratios like 1:1, 1:1.5 and 1:2. Drug loading was carried as described above.

**Characterization of DRC.**

**Taste evaluation by panel method**

Taste evaluation was carried out by the panel method as described earlier.

**Confirmation of complexation [**Khan et al 2007, Chaudhari et al 2007].

**FTIR studies**

Oseltamivir phosphate, Tulsion 335 and DRC were subjected for FTIR studies. Samples were prepared using KBr disc method and spectra were recorded over the range 400 cm-1 to 4000 cm-1. Spectra were analyzed for drug- resin interactions and functional groups involved in the complexation process.

**Estimation of drug content**

100 mg of DRC was stirred with 100 ml of 0.1 N HCl for 60 min so as to release the entire drug from DRC. The mixture was filtered and 1 ml of the filtrate was diluted to 100 ml using 0.1N HCl. The absorbance of this solution was measured at 216 nm using 0.1 N HCl as blank and the content of oseltamivir was estimated.

**FORMULATION DEVELOPMENT OF DRY SUSPENSION**

Based on literature and market studies, it was decided to prepare a dry suspension that would have a concentration of 12mg/ml of oselatamivir. The formula was prepared for 30 ml of reconstituted suspension.
Xanthan gum was selected as viscosity imparting agent and poloxamer 407 as suspending agent. Sucrose was added as sweetener, encapsulated strawberry flavor and preservative combination of methyl and propyl paraben were other additives.
The composition of dry suspension was as follows:

**Evaluation of dry suspension**

**Micromeritic properties**
Bulk density and tapped density were determined using a bulk density apparatus.

**Flow properties**
Angle of repose, compressibility index and Hausner ratio were evaluated as per methods described in USP 30-NF25.

**Angle of repose**
For determining angle of repose a funnel was mounted on a stand at a fixed height and a fix weighed quantity of each blend was poured through the funnel. The height and the base diameter of the pile was noted and angle of repose was calculated as
Angle of repose = $\tan^{-1}$ (height/ 0.5 base)

**Compressibility index and Hausner ratio**
In the recent years compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The basic procedure to calculate the compressibility index and Hausner ratio involves measuring the bulk volume (V0) and final tapped volume (Vf). A 250 ml volumetric cylinder with 100 gm of the material is used for this purpose. The calculations are done as:
Compressibility index = 100 (V0 - Vf )/ V0 Hausner ratio = (V0 )/ Vf

**Sedimentation rate:**
The dry suspension was reconstituted with demineralized water upto 30ml in a measuring cylinder and allowed to stand for 24 hrs. Volume of sediment was observed and reported.

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## RESULTS AND DISCUSSION

The objective of the present study was to mask the bitter taste of oseltamivir phosphate and formulate into dry suspension.

### UV Spectroscopy

**1. Determination of $\lambda_{max}$ of oseltamivir phosphate**

$\lambda_{max}$ of Oseltamivir phosphate in 0.1 N HCl was found to be 216 nm.

**2. Calibration curve of oseltamivir phosphate in o.1 N HCl**

Calibration curves were constructed in 0.1 N HCl. Beer's law was obeyed in the concentration range of 2-20 µg/ml. The high values of regression coefficient estimated the linearity of relationship between concentration and absorbance (Fig.6).

**Evaluation of taste of oseltamivir phosphate**

When oseltamivir phosphate was subjected to taste evaluation by a panel of 10 healthy human volunteers, the outcomes were as follows

**Selection of methods for taste masking of oseltamivir phosphate**

The taste masked form of the drug should release the drug quickly in gastric juice but not in saliva. For suspensions, mouth feel is as important factor as the taste masking. The suspension should not have large particles that cause gritty feel. Considering these criteria, granulation and coating of the drug as well as microspheres were not selected as approaches for taste masking. So approaches i.e. inclusion complexes, ion exchange complexes and solid dispersions were investigated.

**1. Taste masking by formation of inclusion complexes with BCD**

Inclusion complexes of Oseltamivir phosphate with BCD were prepared in 1:1 and 1:2 molar ratios by kneading for 3 h. Kneading method was selected as it is simpler and less time consuming than the solvent evaporation method. It was observed that the inclusion complexes were not able to mask the bitter taste of Oseltamivir phosphate. Probably complex was not formed which resulted in poor taste masking.

**2. Taste masking by preparing solid dispersions**

Solid dispersions of Oseltamivir phosphate in PEG 4000 were prepared by melt solidification method. PEG was not able to mask the bitter taste. Solubility of this polymer in water results in the release of drug which causes bitterness. The drug was not properly enclosed in the polymer matrix and caused bitter sensation as it was exposed to the taste buds.

**3. Taste masking by formation of complexes with ion exchange resins**

Batch process was used to load Oseltamivir phosphate on the ion exchange resins (1:1 drug: resin ratio) in the preliminary trials. Indion 234 showed very small loading of the drug (< 15%) and poor taste masking. Tulsion339 showed improved taste masking but low values of drug loading (<30%). Tulsion335 showed excellent taste masking and high drug loading (94%). The process was repeated to check reproducibility of the results and showed a small variation (standard deviation ± 0.94). Based on these studies, Tulsion335 was selected for masking the bitter taste of Oseltamivir phosphate

**4. Optimization of drug resin ratio**

Loading of Oseltamivir phosphate on Tulsion 335 was carried out by batch process. Batch process is the preferred method for loading a drug into finely divided ion exchangeprocesses commonly used with ion exchange resins. Due to its fine particle size, Tulsion335 does not lend itself to conventional columnar operations commonly used with ion exchange resins. Higher swelling efficiency in the batch process makes more surface area available for ion exchange. So batch process was selected.

Drug loading in different drug: resin ratio were found to be 54% for 1:1, 71% for 1:1 and 94% for 1:2 ratio. Therefore oseltamivir and Tulsion 335 were selected in ration of 1:2 respectively for preparation of drug resin complex (DRC).

**Characterization of drug resin complex (DRC)**

**Taste evaluation by panel method**

The volunteers did not report any bitterness for DRC throughout the study. Thus it was concluded that the taste masking of Oseltamivir phosphate by making an ion exchange complex with Tulsion 335 was complete and satisfactory.

**Confirmation of complexation**

Formation of an ion exchange complex between Oseltamivir phosphate and Tulsion 335 was confirmed by FTIR studies. Objective was to study the interaction between drug and resin.

**FTIR studies**

The IR spectrum of Oseltamivir phosphate showed amine stretch at 3351 $cm^{-1}$, C-H stretch at 2873 $cm^{-1}$, C-C stretch at 875 $cm^{-1}$, C=O stretch at 1720 $cm^{-1}$and peak corresponding to ether, ester groups at 1261,1133 $cm^{-1}$ ; also for alkene groups at 1658 $cm^{-1}$.

The spectrum of Tulsion 335 [fig. (B)] showed distinct C=O stretch of the –COOH functional group of the resin polymer matrix which was not seen in the spectrum of DRC. The absence of other peaks of Oseltamivir phosphate in the spectrum of DRC indicated that the drug was completely embedded in the resin polymer matrix and thus the complexation was confirmed [Fig. (C)]. The peaks corresponding to C-N stretch and C-H stretch disappeared in the spectrum of DRC.

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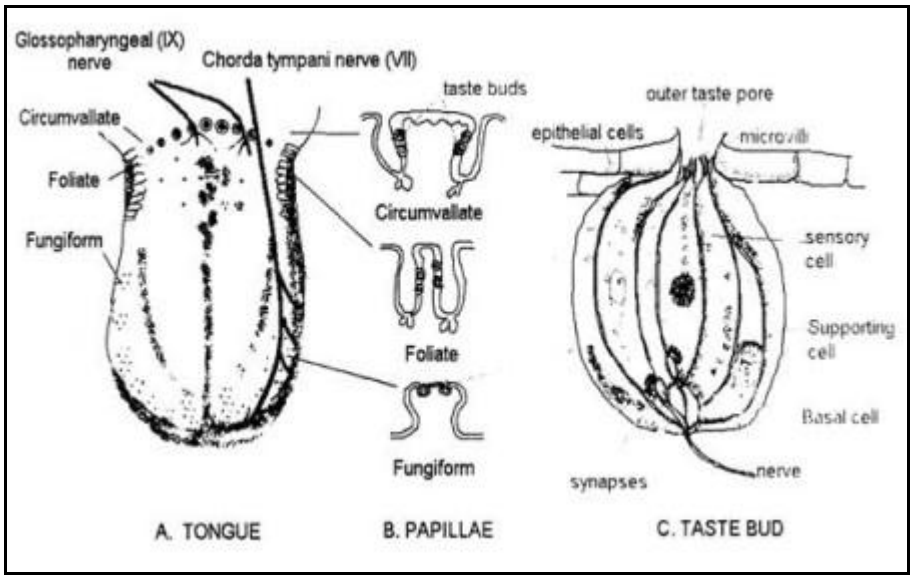


Figure 1

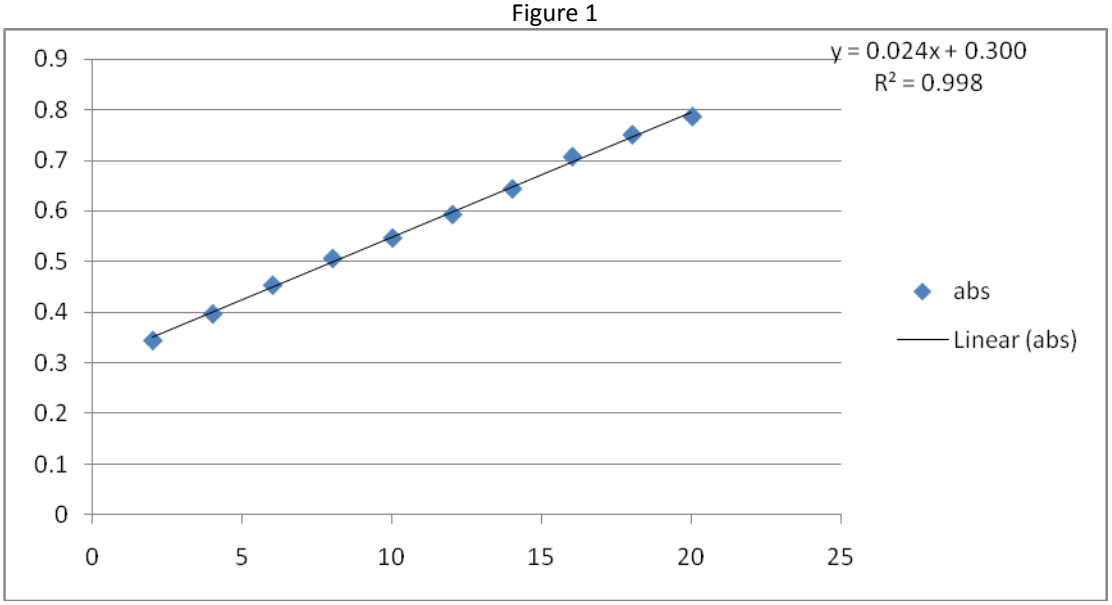


**Fig.2 Calibration curve of oseltamivir phosphate in 0.1N HCl.**

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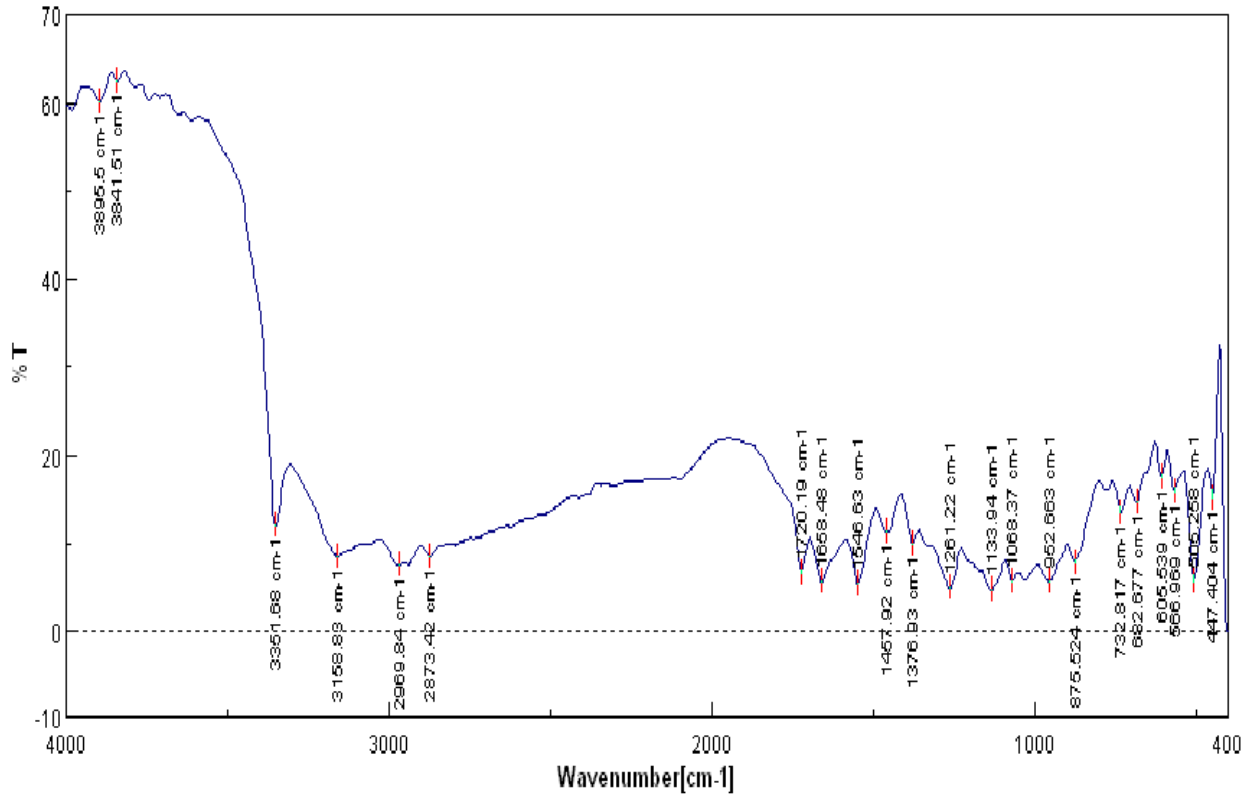


**Fig.3 FTIR spectra of Oseltamivir phosphate (A)**

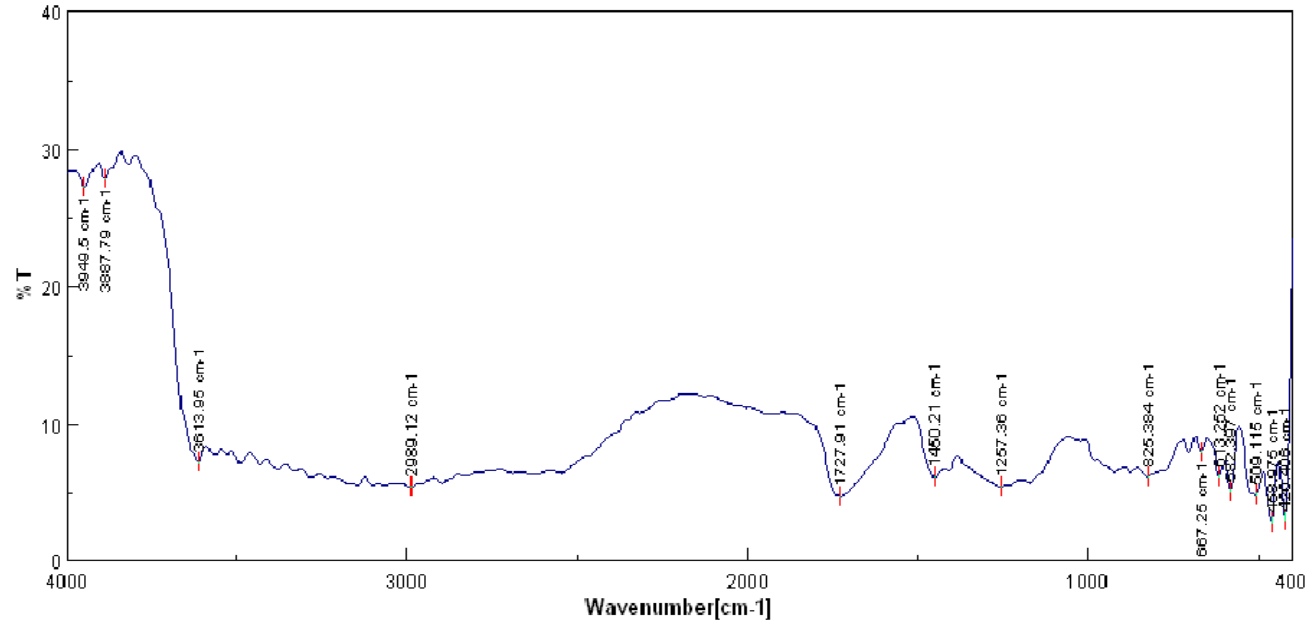


**Fig.3 FTIR spectra of Tulsion 335(B)**

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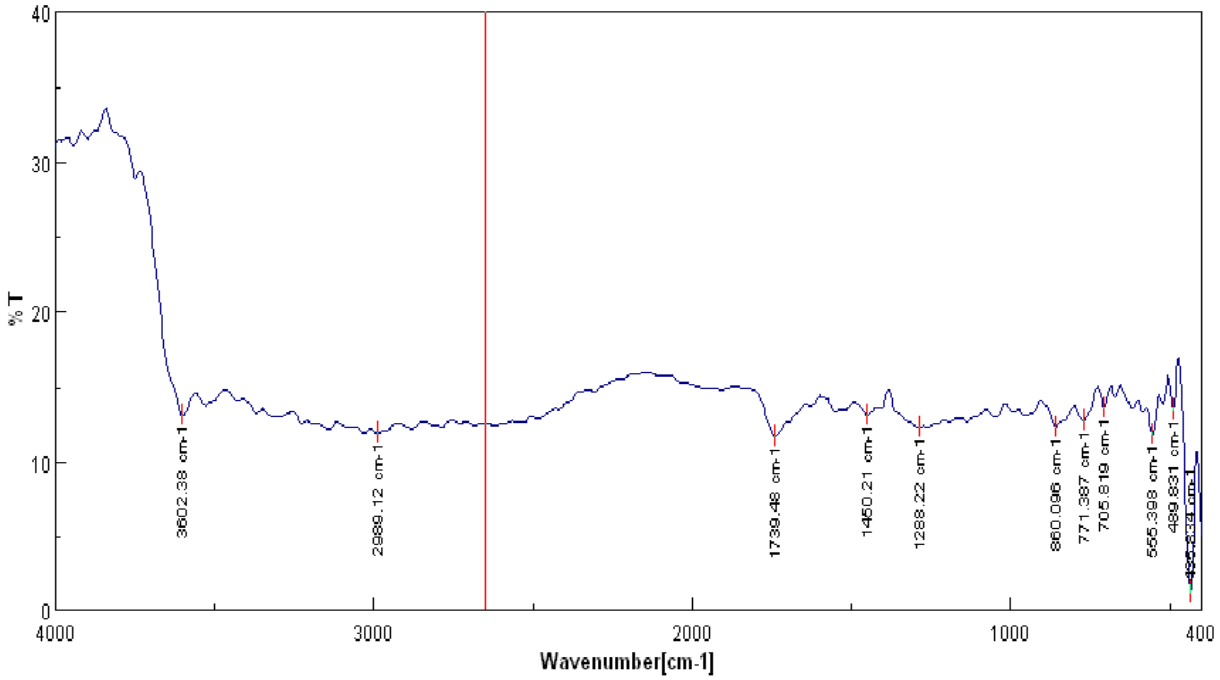


**Fig.3 FTIR spectra of DRC(C)**

**Table 1: Example of some human threshold**

| Taste | Substance | Threshold for tasting |
|---|---|---|
| Salty | NaCl | 0.01M |
| Sour | HCL | 0.0009M |
| Sweet | Sucrose | 0.01M |
| Bitter | Quinine | 0.000008M |
| Umami | Glutamate | 0.0007M |

Table 2

| Group I | Group II |
|---|---|
| OX | XO |
| XO | OX |
| XX | XO |
| OX | OO |

O = control sample. X = treatment sample.

**The experimental protocol is shown below in Table 3**

| Sample Identity | Material Designation | Test Score |
|---|---|---|
| 1 | OOX | |
| 2 | OXO | |
| 3 | XXO | |
| 4 | XOX | |
| 5 | XOO | |
| 6 | OXX | |

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In this method the director as supportive information to determine consistency of the panelists in identifying different samples uses comments from panelists. Reyes Vega et al applied triangle difference test to detect lot-to-lot variation in organoleptic properties in aluminum and magnesium hydroxide antacid suspension from 22 lots prepared in different dates.

**Table 4 Typical Rank Test Score Sheet**

| Sample | Intensity |
|---|---|
| A | 2 |
| B | 1 |
| C | 2 |
| D | 0 |
| E | 3 |

Intensity Score:

0 = absent, 1 = threshold, 2 = moderate, 3= moderate ranking test are useful to formulation scientist because they provide information about a specific characteristic of flavor or aroma. Ranking test is also used to determine which formulation is most or least bitter.

**Table 5 Materials and their suppliers**

| Sr. No. | Chemical and reagents | Suppliers |
|---|---|---|
| 1 | Oseltamivir phospahte | Stride Labs |
| 2 | Tulsion 335 | Thermax India Ltd, Pune |
| 3 | Xanthan gum | Research Lab, Pune |
| 4 | Sucrose | Research Lab, Pune |
| 5 | Methyl Paraben | Research Lab, Pune |
| 6 | Propyl Paraben | Research Lab, Pune |
| 7 | Poloxamer 407 | Analab Fine Chemicals |
| 8. | Encapsulated strawberry flavour | Keva flavours, Mumbai |
| 9 | Hydrochloric acid | Vijay Chemicals |

**Table 6Instruments and their manufacturers**

| Sr. No. | Instrument/machine | Model | Make |
|---|---|---|---|
| 01 | Uv-Vis Spectrophotometer | V 530 | Jasco |
| 02 | Mechanical Stirrer | E2D | Remi |
| 03 | Bulk Density Apparatus | - | Lab. Hosp. |
| 04 | FTIR | 460 Plus | Jasco |

**Table 7: Composition of dry suspension for 30 ml of reconstituted volume**

| Name of the ingredient | Quantity (gm | category |
|---|---|---|
| DRC equivalent to 360 mg of oseltamivir | 1.149 | Drug resin complex |
| Xanthan gum | 0.2 | Viscosity imparting agent |
| Poloxamer 407 | 0.2 | Suspending agent |
| Sucrose | 2.5 | Sweetener |
| Methyl paraben | 0.1 | Preservative |
| Propyl paraben | 0.04 | Preservative |
| Encapsulated strawberry flavour | 0.1 | Flavouring agent |

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**Table 8: Flow properties corresponding to angle of repose as per USP30-NF25.**

| Flow character | Angle of repose (degrees) |
|---|---|
| **Excellent** | 25-30 |
| **Good** | 31-35 |
| **Fair-aid not needed** | 36-40 |
| **Passable-may hang up** | 41-45 |
| **Poor** | 46-55 |
| **Very poor** | 56-65 |
| **Very, very poor** | >66 |

**Table 9: Flow properties corresponding to compressibility index and Hausner ratio as per USP30-NF25**

| Flow character | Compressibility index (%) | Hausner ratio |
|---|---|---|
| **Excellent** | <10 | 1.00-1.11 |
| **Good** | 11-15 | 1.12-1.18 |
| **Fair** | 16-20 | 1.19-1.25 |
| **Passable** | 21-25 | 1.26-1.34 |
| **Poor** | 26-31 | 1.35-1.45 |
| **Very poor** | 32-37 | 1.46-1.59 |
| **Very, very poor** | >38 | >1.60 |

**Table 10:Evaluation of taste of oseltamivir phosphate**

| Volunteer no. | Taste rating | | | |
|---|---|---|---|---|
| | 0 (non bitter) | 1 (slightly bitter) | 2 (bitter) | 3(very bitter) |
| 1 | | | | √ |
| 2 | | | | √ |
| 3 | | | | √ |
| 4 | | | | √ |
| 5 | | | | √ |
| 6 | | | | √ |
| 7 | | | | √ |
| 8 | | | | √ |
| 9 | | | | √ |
| 10 | | | | √ |

**Table 11: Evaluation of taste drug resin complex (DRC)**

| Volunteer no. | Taste rating | | | |
|---|---|---|---|---|
| | 0 (non bitter) | 1 (slightly bitter) | 2 (bitter) | 3(very bitter) |
| 1 | √ | | | |
| 2 | √ | | | |
| 3 | √ | | | |
| 4 | √ | | | |
| 5 | √ | | | |
| 6 | √ | | | |
| 7 | | √ | | |
| 8 | √ | | | |
| 9 | √ | | | |
| 10 | | √ | | |

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**Table 12: Evaluation of physical properties of dry suspension**

| Evaluation parameter | Observation | Inference |
|---|---|---|
| **Bulk density (gm/ml)** | 0.766 | --- |
| **Tapped density (gm/ml)** | 0.851 | --- |
| **Hausner ratio** | 1.10 | Excellent |
| **Compressibility index** | 10.0 | Excellent |
| **Angle of repose (degrees)** | 27.3 | Excellent |

### Determination of drug content

When DRC was prepared with 1:2 drug:resin ratio the dsdrug content was found to be 47% w/w.

### Evaluation of dry suspension

Prepared dry suspension was analyzed for various micromeritic and flow properties. Values of compressibility index were less than 15. Hausner ratio was between 1 and 1.17. Angle of repose was less than 30°. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The outcomes of these parameters indicated excellent flow properties and the blends were suitable for direct compression.

### Sedimentation rate

No sedimentation was observed in the reconstituted suspension at the end of 24 hrs. The reasons may include the fine particle size, viscosity built by xanthan gum and poloxamer 407.

## SUMMARY AND CONCLUSION

The objective of this work was to develop a method of masking the bitter the taste of oseltamivir and formulate into a suitable formulation.

From preliminary screening, ion exchange resin complexation method was selected. Tulsion 335 was found to show good taste masking characteristics and maximum drug loading. The drug content in the drug resin complex (DRC) was found to be 31.33%. Panel method revealed no bitterness for DRC. FTIR studies revealed formation of complex between oseltamivir and Tulsion 335. DRC was formulated into dry suspension using xantan gum, poloxamer 403, sucrose, flavour, methyl and propyl paraben. Dry suspension showed satisfactory flow properties. Reconstituted suspension showed negligible sedimentation after standing for 24 hrs.

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