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Research Paper

Formulation and Evaluation of Taste Masked Cachets of Tenofovir Disoproxil Fumarate A Prodrug of Tenofovir

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Tenofovir disoproxil fumarate (a prodrug of tenofovir) In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase. Tenofovir is water soluble drug. Thus the Purpose of this study is to formulate and evaluate taste masked cachets of Tenofovir. Cachets of Tenofovir were prepared by using β- cyclodextrin as taste masking agent. Sodiumcarboxy methyl cellulose as suspending agent, citric acid monohydrate used as Ph modifiers. The prepared cachets bitter taste intensity was evaluated using volunteers by comparison of test samples with standard solution containing quinine at various concentrations.

Key words: Tenofovir disoproxil fumarate, Taste masking.

INTRODUCTION

There are numerous pharmaceutical formulations that contain active 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 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. In order to ensure patient compliance bitterness masking becomes essential. Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. This sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulse via the seventh, ninth and tenth cranial nerve to these areas of the brain, which are devoted to the perception of taste[1]

The term “prodrugs” or “proagent” was first introduced by Albert in 1950 to signify pharmacologically inactive chemical derivatives that could be used to alter the physicochemical properties of drugs, in a temporary manner, to increase their usefulness or to decrease their toxicity. Prodrugs can be considered in different aspects and divided into several categories[2].

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According to the International Union of Pure and Applied chemistry (IUPAC), the term Prodrug is defined as "any compound that undergoes biotransformation before exhibiting its pharmacological effects. Prodrugs can thus be viewed as drugs containing specialized non toxic protective groups used in transient manner to alter or to eliminate undesirable properties in the parent molecule"[3].

Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor. An ideal taste masking process and formulation should have the following properties[4].

1) Involve least number of equipments and processing steps.
2) Require minimum number of excipients for an optimum formulation.
3) No adverse effect on drug bioavailability.
4) Require excipients that are economical and easily available.
5) Least manufacturing cost.
6) Can be carried out at room temperature.
7) Require excipients that have high margin of safety.
8) Rapid and easy to prepare.

Methods of Taste Masking

Various methods are available to mask undesirable taste of the drugs. From those method we have chosen

Taste masking by 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. The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Vander waals forces are mainly involved in inclusion complexes[5].

Beta-cyclodextrin is mostly used complexing agent for inclusion type complexes. It is sweet, cyclic oligosaccharide obtained from starch. Strong bitter taste of carbapentane citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with cyclodextrin. The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma, beta cyclodextrin[6].

MATERIAL AND METHODS

Tenofovir was obtained as gift sample from Ranbaxy Rsearch Labarotory Ltd, Guargon, india.βcyclodxtrin purchasd

from sigma Aldrich, Bangalore, india. Quinine sulphate was purchased from S.D.fine chemicals Mumbai, india. All other chemicals used were of analytical grade.

Preparation of Physical Mixture

The following system of Tenofovir and β-CD were prepared in 1:25 molar ratio

Physical mixture (PM): The physical mixture of Tenofovir and CD was obtained by mixing individual components geometrically, that had previously been sieved through sieve no. 44, together with a spatula.

Fourier Transform Infra-red Spectroscopy (FTIR) FTIR transmission spectra were obtained by using KBr discs by means of hydrostatic press. The scanning range was 400 to 4000cm The characteristics peaks were recorded.

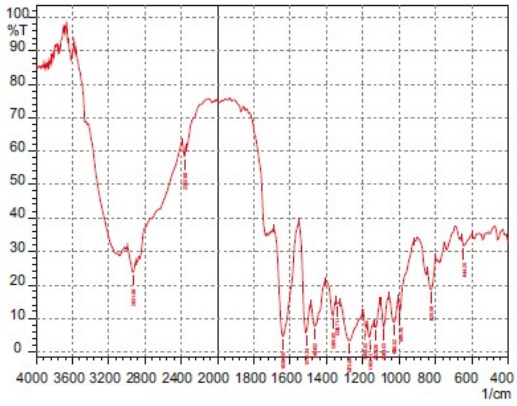

Fig. 1: IR Spectrum for Tenofovir with β- Cyclodextrin

Differential Scanning calorimeter (DSC) was performed using Differential Scanning Calorimeter (Mettler Toledo, DSC 822).

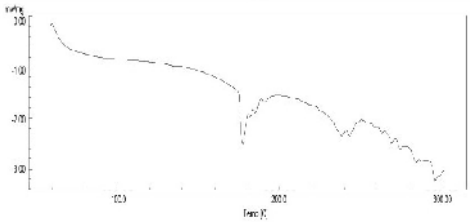

Fig. 2: DSC Thermograph of Tenofovir with β- Cyclodextrin

Samples were heated in an open aluminium pans at a rate of 5 °C per min under a nitrogen flow of 40 ml/min

Formulation of Suspension Powder:

Dry suspension powder containing equivalent of 10 mg of Tenofovir and Physical mixture. Sodium carboxy methyl cellulose (HVP) was used as suspending agents. Citric acid monohydrate was used as Ph modifier. The following procedure was applied to prepare a suspension powder. The smallest amount of physical mixture was mixed with the same amount of another excepient, following the principle of geometric dilution. To prepare the reconstituted suspension, an appropriate 10 ml of water was added to the suspension powder and stirred with glass rod until homogeneous product was obtained[7] (Table 1&2).

Evaluation of suspension Powder:

To study the sedimentation in suspension, the sedimentation volume was determined as function of time. The sedimentation Volume, F is defined as the ratio of the final, equilibrium volume of the sediment, Vu to the total volume Vo before settling, as expressed in the following equation: F= (Vu/Vo) In this study, the sedimentation

Table 1: Formulation of Suspension Powder

Drug/Excipients 0 .250gm Per cachet	
Tenofovir	0.010
β - Cyclodextrin	0.175
Xanthine Gum(g)	0.002
MCC(g)	0.054s
Citric acid(g)	0.006
Methyl Paraben(g)	0.002
Sunset Yellow (FCF)(g)	0.001
Total Weight	0.250

volume was determined as function of time. 10 ml suspension (height = 12cm) was decanted in a cylinder of 10 ml with diameter of 1.5 cm. After 1h, the sedimentation volume F was determined.

Table: 2 F-value and PH of Suspension Powder

Parameters	Tenofovir
F value after Reconstitution±SD	3±o.53
PH after Reconstitution	6-6.5

Gustatory sensation test of Tenofovir

Test was carried out according to the method described by Mou-young et al., Twenty healthy male human volunteers in the age group of 23-27 years were selected based on quinine sensitivity test. The non-taster and super taster were rejected. 0.250 g of Tenofovir suspension cachet each respectively dispersed in 10 ml water for 15 sec. For comparison of pure Tenofovir was subjected to taste evaluation by the panel. Immediately after the preparation, each volunteer held about 1 ml of the dispersion in the mouth for 30s. After expectoration, bitterness level was recorded. A numerical scale was used with following values:

0 = tasteless, or Sweet taste.

0.5 = very slightly bitter,

1 = slightly bitter,

1.5 = slight to moderate bitter,

2 = moderately bitter,

2.5 = moderate to strong bitter,

3 = strongly bitter,

3+= very strong.

This numerical scale was validated by testing samples randomly. The oral cavity was rinsed with distilled water three times to avoid bias. Wash out period between testing different samples was 15 min (Table 3).

CONCLUSION:

The study conclusively demonstrated the complete masking of bitter taste of Tenofovir disoproxil fumarate with β – cyclodextrin in suspension. The FTIR and DSC studies indicated inclusion

Table:3 Bitterness Score Evaluation

Number of volunteers rating the Preparation as								
Formulation	0	0.5	1	1.5	2.0	2.5	3.0	3+
Tenofovir							17	3
Tenofovir Phycial Mixture	20							

complexes in physical mixture. The taste masking is due to β – cyclodextrin enwraps bitter tasting drugs, impeding its interaction with the taste buds. Further the sweet taste of β – cyclodextrin imparted additive effect.

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