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DESIGN AND OPTIMIZATION OF TASTE MASKED PERINDOPRIL ERBUMINE BY HP β –CYCLODEXTRIN

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Abstract

Antihypertensive medication perindopril is used to treat hypertensive urgency. Angiotensin Converting Enzyme (ACE) inhibitors are a class of medications that includes the drug perindopril ter-butyl amine. It tastes bitter. Therefore, the flavor needs to be covered up in order to lessen its harshness, make it more palatable, and boost patient compliance. The preparation of flavorless compounds of perindopril erbumine was the goal of this research project. Traditional taste-masking methods, such as the use of sweeteners, amino acids, and flavoring agents, sometimes fail to cover up the taste of extremely bitter medications. The goal of this study was to develop an inclusion complex creation array employing HP -cyclodextrin to conceal the highly bitter taste of perindopril erbumine. The study convincingly showed that using HP Beta cyclodextrin in a 1:3 kneaded ratio completely masks the harsh taste of perindopril erbumine.

Key-words: Antihypertensive, ACE inhibitors, Taste-Masking, HP Beta Cyclodextrin

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INTRODUCTION

The palatability of an oral dose form and patient compliance are both greatly influenced by taste. Furthermore, it offers a product a unique identification, offering a company an advantage over competitors, especially in the case of over-the-counter products.

A substance in the mouth combines chemically with taste receptor cells on taste buds in the oral cavity, primarily on the tongue, to produce the experience known as flavor as shown in **Figure 1**.[1-3]

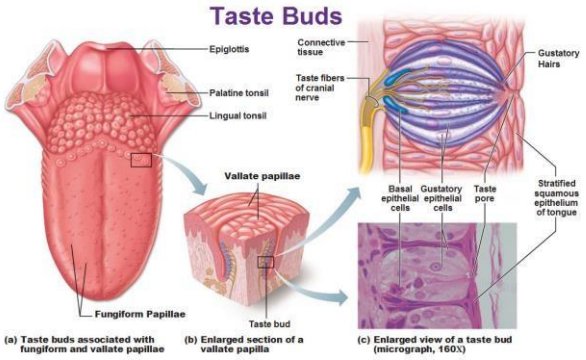

Fig1:Taste buds associated with receptor cells

One of the most importantchallenge is masking the bitter taste of the medicine in order to secure patient compliance. There are numerous ways to mask the taste of medications, either by changing the formulation or by the modification of bitter active medicinal ingredient itself4,5. Different taste masking technologies were shown in **Figure 2.**

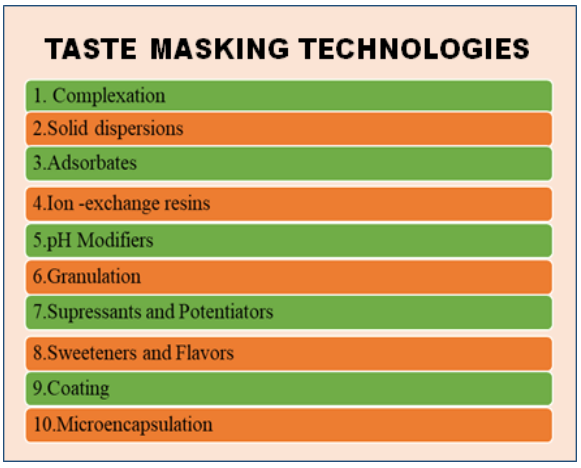

Fig 2: Taste Masking Technologies

Comparing the inclusion of complex array to the addition of sweeteners and flavorings, complex array is a superior strategy. The drug molecule fits into the cavity of a complexing agent in this array, creating a stable complex[6-8]. The most popular complexing agent for inclusion type complexes is HP Beta-cyclodextrin, which works by either lowering oral solubility upon administration or lowering the amount of drug particles exposed to taste receptors, hence lowering the sense of bitterness.

Patients with heart failure or hypertension benefit greatly from the use of perindopril in treatment. The ACE inhibitor class of drugs includes the no sulfhydryl prodrug perindopril erbumine, which works by inhibiting the angiotensin converting enzyme (ACE)[9].

Chemically, perindopril is (2S, 3a, 7aS)-1-[(S)-N-[(S)-1-carboxybutyl] alanyl]Indoline hexahydro-2-carboxylic acid the 1-ethyl estershown in **Figure 3**.

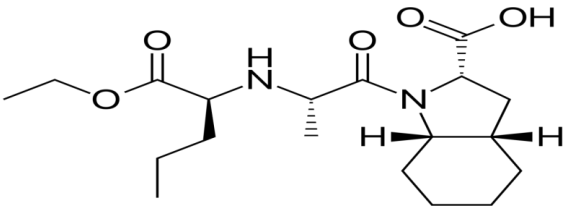

Fig 3: Chemical Structure of Perindopril

Preparation of Inclusion Complexes using Kneaded system[10]:

Wetting agent is prepared with a little amount of water-methanol solution (3:2% v/v).The physical mixture of Perindopril Erbumine and HP -cyclodextrin was triturated using a mortar and pestle. After kneading the thick slurry for 60 minutes, it was thoroughly dried. The dry substance was ground up and put through sieve number 100.The primary purpose of the wetting agent (water: methanol, 3:2%v/v) was to improve the interaction of the medication with the cyclodextrin during the kneading process. With the aid of the drug HP cyclodextrin, three batches of dispersions were prepared in the ratios of 1:1, 1:2, and 1:3.

Determination of drug content in the complexes:

100 mg of complex was weighed and added to a100 ml volumetric flask filled with 0.5% sodium lauryl sulphate solutionand made up the volume with distilled water. After being sonicated for 5 minutes, the solution in the volumetric flask was then filtered using a 0.2 membrane filter. The absorbance at 215 nm was measured using a UV spectrophotometer after 10 ml of the solution was pipetted out of the filtrate and diluted up to 100 ml with distilled water containing 0.5% sodium lauryl sulphate.

In vitro drug release[11]:
LABINDIA DISSO 2000, aneight-stage dissolution rate testing apparatus with paddle, was used to measure perindopril erbumine from all complexes. Each test employed the same dissolution medium, 900 ml of distilled water with 0.5% sodium lauryl sulphate, 50 rpm, and 37 0.5 °C. Samples of the dissolution medium (5ml) were taken out through a filler of 0.45µm at different time intervals for 1hr, appropriately diluted and measured for Perindopril Erbumine by measuring absorbance at 215 nm.

Taste evaluation of complexes:
The complexes flavors were assessed using **Table 3(** Rating of Taste evaluation). Ten human volunteers were chosen for this project. On the tongue, a compound corresponding to around 10 mg of a medication was applied, and the taste was assessed both immediately and 20 seconds later. The degree of bitterness was noted, and an overall evaluation was provided in **Table 4** by averaging the opinions of all the volunteers.

RESULTS AND DISCUSSION:
Determination of drug content in the complexes:
All the prepared complexes have shown satisfactory drug content values and the percentage of drug content.Among all the complexes prepared,1:3 complex has shown 100% whereas 1:1 and 1:2 have shown above 90% of drug content.The results were shown in the **Table 1.**

In-vitro drug release:
A highly quick disintegration was seen when the kneaded system was spread out in a dissolution medium. Dissolution studies were based on the observation in order to characterize the inclusion complexation between the HP - cyclodextrin and drug. **Fig4** shows the dissolution profiles ofpure drug and the prepared complexes of all ratios(1:1,1:2,1:3) in the official medium (0.5% Sodium lauryl sulphate solution). The process of dissolution was conducted in triplicate and the results were shown in the **Table2.**Based on the results, 1:3 complex, has shown improved drug release.

Taste evaluation of complexes:
The tastes of the complexes were evaluatedbased on the rating format given in the **Table 3** and the results obtained were shown in the **Table4 and Figure 5** (based on Initial, final and over all acceptability). The results were noted by taking in to consideration the average of the opinion of all the volunteers. Based on the results obtained, 1:3 inclusion complex was confirmed to have better taste maskingproperty and was found to have less bitter taste.

Table 1: Percent Drug content in the prepared complexes

Ratio of Drug and HP β-CD in Inclusion complex	Drug content (%)
1:1	93
1:2	96
1:3	100

Table 2: Results of Dissolution studies of the prepared complexes and pure drug

Time (min)	%Drug released			
	Pure drug	1:1	1:2	1:3
5	33	67	75	79
10	40	73	78	86
15	49	75	85	93
20	52	79	87	97
30	67	81	90	99
45	79	89	94	99
60	87	93	96	100

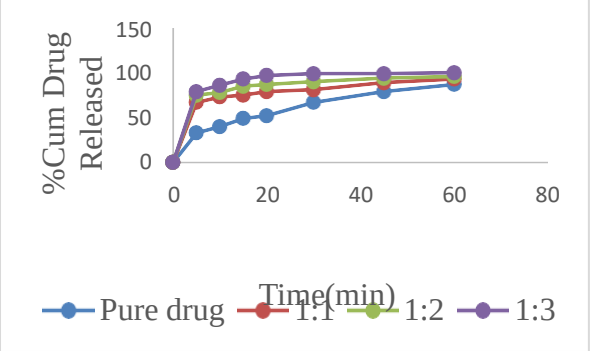

Fig 4: Dissolution profile of pure drug and prepared complexes

Table 3: Rating of Taste evaluation

Point	Initial taste	After taste	Mouth feel	Overall acceptability
	Bitterness	Bitterness		
1	Extreme	Extreme	Very gritty feel	Worst
2	High	High	Gritty feel	unacceptable
3	Acceptable/Tolerable	Acceptable/Tolerable	Acceptable	Acceptable
4	Very slight bitterness	Very slight bitterness	Creamy	Good
5	Not bitter	Not bitter	Very creamy	Very good

Table 4: Taste evaluation of pure drug and drug complexes

Formulation code	Initial taste					After taste					Mouth feel					Over all acceptability				
	Range of Bitterness																			
	Extremebitterness-Not bitter					Extremebitterness-Not bitter					Very gritty -Very creamy					Worst – Very good				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Pure drug		√				√						√					√			
Drug andHP β-CD Inclusion complex1:1			√					√					√					√		
Drug and HP β-CD Inclusion complex 1:2				√					√				√					√		
Drug and HP β-CD Inclusion complex 1:3					√					√				√					√	

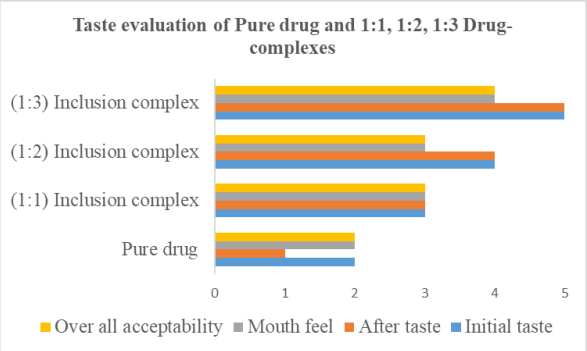

Fig 5: Taste Evaluation of pure drug and prepared complexes

CONCLUSION:

Based on the results obtained the study concluded that 1:3 kneaded ratio of HP Beta cyclodextrin effectively hides the unpleasant taste of perindopril erbumine.Thus, When the bitter drug perindopril erbumine complexed with HP Beta cyclodextrin had improved the palatability and acceptability.

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