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Elimination of bitter, disgusting taste of Levocetrizine di hydrochloride by HP β –Cyclodextrin

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Abstract: Levocetrizine Di Hydrochloride is second generation piperazine derivative, a potent H_1 selective anti -histaminic or anti- allergic agent. It has bitter taste. So, the taste has to be masked inorder to reduce its bitterness, to increase its palatability and to improve patient compliance. The purpose of this research work to prepare tasteless complexes of levocetrizine di hydrochloride. Conventional taste masking techniques such as use of sweeteners and amino acids and flavoring agents often are unsuccessful in masking the taste of highly bitter drugs. The purpose of this research was to mask the intensely bitter taste of Levocetrizine Di Hydrochloride adopting inclusion complex formation array using HP β -cyclodextrin by Kneading method. The study conclusively demonstrated the complete masking of bitter taste of Levocetrizine Di Hydrochloride with HP Beta cyclodextrin in 1:1 Kneaded ratio.
Key-words: anti –histaminic, Kneading method, HP β –cyclodextrin, palatability.

Introduction:

In order to ensure patient compliance the bitter taste of the drug should be masked[1-3] which is one of the most difficult tasks. Taste masking techniques such as the addition of sweeteners and flavors and coating with some polymers, has their own disadvantages. Addition of sweeteners and flavors is not very successful for extremely bitter drugs where as coating with polymers cause delayed drug release and also requires sophisticated instruments. Inclusion complex array is a qualified technique[4] compared to addition of sweeteners and flavoring agents. Here in this array, the drug molecule fits in to the cavity of a complexing agent forming a stable complex. HP Beta-cyclodextrin is most widely used complexing agent for inclusion type complexes which acts either by decreasing the oral solubility on ingestion or decreasing the amount of drug particles exposed[5-6] to taste buds there by reducing the perception of bitter taste. The cavity of cyclodextrin is occupied by 13–14% w/w water molecules both in crystalline state as well as in aqueous solution. Roughly half of this water is so-called 'crystal water' and the other half is 'inclusion water'. The 'crystal water' is located and bound between the adjacent cyclodextrin molecules, while 'inclusion water' is included into the hydrophobic cavity of cyclodextrin. Hydrophobic drugs form complex by replacing 'inclusion water' while hydrophilic drugs form complex, assuming replacement of 'crystal water'. The objective of the present work was to study the effect of HP Beta-cyclodextrin for its bitterness[7] masking ability for hydrophilic drug, Levocetrizine Di Hydrochloride and to evaluate the bitterness score.

Materials and Methods:

Materials:

Pure drug sample of Levocetrizine Di Hydrochloride was procured as a gift sample from Cadila Pharmaceuticals, Ahmedabad. HP β-cyclodextrin was obtained from Roquette, France and all other ingredients used were of pharmaceutical grade.

Preparation of Inclusion Complexes using Kneaded system:

The physical mixture of and cyclodextrin which were taken in molar ratios was triturated in a mortar with a small volume of water-methanol (3:2% v/v) solution. The thick slurry was kneaded for 60 min and then dried until dryness. The dried mass was pulverized and sieved through sieve no.100.Wetting agent (water: methanol, 3:2%v/v) was used mainly to achieve better interaction of drug with cyclodextrin during kneading process. We have prepared three batches of dispersions using Drug:HP β cyclodextrin in the ratios 1:0.5, 1:0.75 and 1:1. We have taken HP β-cyclodextin in molar ratio.

Determination of drug content in the complexes:

About 100mg complex was weighed and taken in a 100 ml volumetric flask, and the volume was made with distilled water with 0.5% sodium lauryl sulphate. The solution in the volumetric flask was then sonicated for 5min and then filtered using 0.2µ membrane filter. From the filtrate 10 ml of solution was pipetted out and diluted up to 100 ml with distilled water with 0.5% sodium lauryl sulphate and absorbance was measured at 231nm using UV spectrophotometer.

In vitro drug release:

Dissolution rate of Levocetrizine Di Hydrochloride from all complexes (5mg) was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution medium was 900ml of Distilled water with 0.5% Sodium Lauryl Suphate a speed of 50 rpm and a temperature of 37±0.5°C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filler of 0.45µm at different time intervals for 1hr, suitably diluted and assayed for Levocetrizine Di Hydrochloride by measuring absorbance at 231 nm.

Taste evaluation of complexes:

The taste of the complexes was checked following the Rating of Taste evaluation. For this purpose, 10 human volunteers were selected. About 5 mg of drug equivalent complex was placed on tongue and taste evaluated initially and after certain time that is 20seconds. The bitterness level was recorded and over all evaluation by taking an average of evaluation of all the volunteers.

Results and Discussion:

Determination of drug content in the complexes:

Almost all the complexes have shown satisfactory drug content values and the percentage of drug content for all the ratios considered were shown in the **Table 1.**1:1 complex has shown 100% where as 1:0.5 and 1:0.75 have shown above 95% of drug content.

Table 1: Drug content in the complexes.

Drug : HPβ-CD (Inclusion complex)	Drug content in percentage (%)
1:0.5	97
1:0.75	98
1:1	100

In-vitro drug release:

When kneaded system was dispersed in a dissolution medium, a very rapid dissolution was observed. Dissolution studies were based on the observation in order to characterize the inclusion complexation between

the HP beta-cyclodextrin and drug. **Fig 1**shows the dissolution profiles of pure drug and kneaded system of all ratios(1:0.5,1:0.75,1:1) in the official medium of the drug that is distilled water with 0.5% sodium lauryl suphate. The dissolution experiments were conducted in triplicate and the results are shown in the **Table 2.**Among the three ratios 1:1 has shown better release of the drug.

Table 2: Dissolution results of the three ratio complexes and pure drug.

Time (min)	%Drug released			
	Pure drug	1:0.5	1:0.75	1:1
5	33	62	70	77
10	40	69	76	80
15	49	73	81	85
20	52	78	85	93
30	67	81	90	99
45	79	85	94	99
60	87	91	96	99

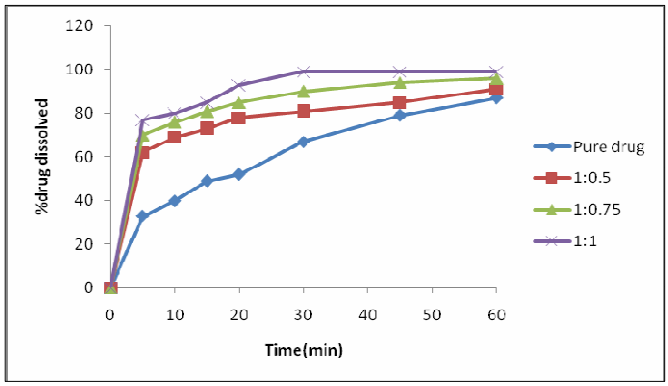

Fig 1: Dissolution profile of pure drug and complexes.

Taste evaluation of complexes:

The tastes of the complexes were evaluated as per the format given in the **Table 3** and the results were shown in the **Table 4** (Initial, final and over all acceptability). 1:1 inclusion complex was confirmed to have better taste masked property by taking in to consideration the average of the opinion of all the volunteers.1:1 complex was found to have less bitter taste.

Table 3: Rating for Taste evaluation.

Point	Initial taste	After taste	Mouth feel	Overall acceptability
	Bitterness	Bitterness		
1	Extremely Bitter	Extremely bitter	Very gritty	Worst
2	Highly bitter	Highly bitter	Gritty	Poor
3	Acceptable/Tolerable	Acceptable/Tolerable	Acceptable	Acceptable
4	Very slightly bitter	Very slightly bitter	Creamy	Good
5	Not at all bitter	Not at all bitter	Very creamy	Very good

Table 4: Taste evaluation of drug complex- Initial , after ,mouth feel and over all acceptability.

Formulation code	Initial taste					After taste					Mouth feel					Over all acceptability				
	Bitterness					Bitterness														
	Extremely bitter-Not at all bitter					Extremely bitter-Not at all 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		√				√						√					√			
(1:0.5) Inclusion complex			√					√					√					√		
(1:0.75) Inclusion complex				√					√				√					√		
(1:1) Inclusion complex					√					√				√					√	

Conclusion:

The study conclusively demonstrated the complete masking of bitter taste of Levocetrizine Di Hydrochloride with HP Beta cyclodextrin in 1:1 Kneaded ratio. Thus complexation of Levocetrizine Di Hydrochloride with HP Beta cyclodextrin increases palatability and acceptability.

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