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PREPARATION AND CHARACTERISATION OF TASTE MASKING COMPLEX OF TELMISARTAN BY USING CYCLODEXTRIN

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ABSTRACT

To improve the patient compliance for bitter drugs, Taste masking technique becomes requisite especially in the pediatric, geriatric and non-cooperative patient. Pharmaceutical formulations like Fast dissolving, oro-dispersible, mouth dissolving, and other formulations which come in contact with taste buds, taste is one of crucial factor to be considered. It is important to mask the bitter taste of drugs for the improvement of patient compliance. This study aimed to mask Temlisartan taste by an efficient process of cyclodextrin inclusion complexation. Taste improvement of drug by β-Cyclodextrin was done by simple complexation approach using solvent evaporation method. The present study characterized the possibility of inclusion Complexation of Temisartan with β-Cyclodextrin as an approach for taste masking. Improved capability of β-cyclodextrin in taste masking for Temisartan was evaluated by formulating a complex. The objective of this study was to mask the bitter taste of the Telmisartan and the drug polymer complex (DPC) were prepared in different ratio (1:1, 1:2 1:3 1:4, 1:5 & 1:6) by solvent evaporation method. The evaluation of DPCs were carried out by determining Drug content, In-vitro evaluation of drug complex & Threshold value determination. 200µg/ml is the optimized threshold value for the DPC and 1:3 ratio was selected which masked the taste of drug.

Keywords: Bitter taste, Threshold value, drug polymer complex, Taste bud, Cyclodextrin

INTRODUCTION

Taste masking technique to mask the bitter taste of drugs is an important technique for the improvement of patient compliance. Pharmaceutical formulation with a pleasant taste and better flavor would certainly be favored, transferred into better compliance. This improved compliances leads to effective therapeutic response. Oral administration of bitter drug requires an admissible taste masking of drug. The bitterness of drug is minimized by different physical, chemical and physiological means like use of flavoring agents, sweetening agents, amino acids and by using various techniques such as lipophilic vehicles, coating, inclusion complexation, ion exchange, effervescent agents, solid dispersion system, group alteration and prodrug approach, freeze drying process, wet spherical agglomeration technique and continuous multipurpose melt technology.

Each technique has its own disadvantages. Addition of sweetener and flavoring agents is not very handy for extremely bitter drugs. Cyclodextrins have the ability to mask the bitterness of numerous drugs, first of such observation was done by in 1953 by Freudenberg *et al*. in the very first drug/CD patent. They successfully masked the bad taste of bromoisovaleryl urea by complexing it with Cyclodextrin. Though Cyclodextrin is not considered as a tasteless or only slightly sweet substance, although its taste threshold value is lower than that of sucrose (detection, 0.03 and 0.27%; recognition, 0.11 and 0.52%, respectively). A 0.5% CD solution was as sweet as sucrose and a 2.5% solution as sweet as a 1.71% solution of sucrose.

MATERIAL AND METHOD

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Telmisartan API Cipla Ltd. Goa,β-Cyclodextrin Taste masking polymer (Jay Chem Marketing, Mumbai, India) were received as gift samples.

Method

Preparation of drug-polymer complex (DPC):

Telmisartan is antihypertensive drug have intensive bitter taste. The purpose of forming drug-β-cyclodextrin complex is to mask the bitter taste of Telmisartan. The complex of drug and β-cyclodextrin was prepared in different ratio as described.

Solvent evaporation method was used for preparation of Telmisartan and β-cyclodextrin complex. Aqueous solution of β-cyclodextrin and an alcoholic solution of Telmisartan were added in various ratios 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6. Mixture was stirred for 1 hrs and evaporated at temperature of 45°C until dried. Then dried mass was pulverized in order to obtain a fine powder. A tightly closed container was used to store the powder complexes for further studies. The optimized ratio was

selected on the basis of drug release in phosphate buffer pH 6.8 i.e. *in vitro* taste evaluation.

Characterization of DPC:

Threshold value determination:

Weigh accurately 20 mg of Telmisartan. Transferred it in to volumetric flask. 4ml of methanol was added and using simulated salivary fluid, made volume up to 20ml . Filter the solution and dilutions were prepared at different concentration as standard solutions 50, 100, 200, 400 µg/ml respectively. Then one drop of each dilution was tasted by human volunteer after each 10 min. interval. The threshold value was correspondingly selected from the different concentrations as the lowest concentration that had a bitter taste. The human volunteers were informed instruction regarding the oral toxicity of drug if any and obtained their consent form.

RESULT AND DISCUSSION

Drug content

By solvent evaporation method Drug-polymer complexes (DPC) were prepared in ratio of 1:1, 1:2, 1:3, 1:4, 1:5 & 1:6 were subjected to content uniformity. The percent of drug present in1:3 ratios were found 99.93. This indicated that, the drug contents are within limit of official compendia **(Table 1)**.

Threshold value determination

As per the study of threshold value, the numerical values for the inferences obtained by human volunteers are depicted in **Table 2**. The concentrations used for the threshold value are shown in **Table 2**. From the study by panel of volunteers, three volunteers found drug bitter in taste with concentration of 200 mcg/ml. DPC of 1:3 ratio in same concentrations were administered to same volunteers and found drug very slightly bitter by four volunteers. Here we confirmed that the drug taste is masked. This might be happened due to imbibing effect of beta-cyclodextrin.

Infrared spectrum analysis:

From the spectra of Telmisartan-β-cyclodextrin complex was observed that all characteristic peaks of Telmisartan were present in the combination spectrum, thus indicating compatibility of the Telmisartan & polymer. IR spectra shown in **Figure 1**.

FT-IR spectroscopy shows various vibrations between the functional groups at different bond. All the corresponding tables **(Table 4-6)** shows clear stretching vibration due to varying functional groups and indicating no overlapping found over the peaks. Hence, all the excipients and drug are compatible with each other.

Differential scanning colorimetry:

Differential scanning colorimetry indicates the quantitative detection of all processes in which energy is required or produced i.e. endothermic or exothermic. The thermograms of Drug Polymer Complex are presented in **Figure 3, 4.** Telmisartan

showed melting endotherm at 122.02˚C with enthalpy of fusion 6.24 J/gm were as pure β- cyclodextrin showed melting endotherm at 109.04˚C. The spectrum of DPC indicated that the intensive peak of Telmisartan was absent; it might be due to solubilzed the drug in betacyclodextrin. This indicated that the drug was completely dispersed in structure of betacyclodextrin.

***In-vitro* taste evaluation of drug complexes:**

In-vitro taste evaluation study of drug complexes was done in simulated salivary fluid for approximate estimation of drug release in same fluid (pH 6.8). Optimized drug-polymer ratio for DPC was selected by this method. % drug released in vitro in pH 6.8 was studied.

Drug-polymer complex in the ratio showed 62.53% drug released, which is less than the threshold concentration (91.23) that gives bitter taste with concentration of drug 200 µg/ml,

This study showed that the drug polymer ratio 1:3 was capable of producing a tasteless complex. Hence, the ratio 1:3 was selected as optimized drug polymer ratio for the preparation of drug polymer complex. The % of drug released from each ratio was shown in **Table 5**.

Table 1: Evaluation of drug content

Sr. No.	Complex ratio	Drug content (%)
1	1:1	96.57
2	1:2	97.45
3	1:3	99.93
4	1:4	98.20
5	1:5	96.87
6	1:6	96.98

Table 2: Numerical scale representing taste

Rating	Taste Inference	Concentration µg/ml
0	Tasteless	----
1	Very slightly bitter	50
2	Slightly bitter	100
3	Bitter	200
4	Strong bitter	400

Table 3: Evaluation of bitterness score by panel of volunteers

	Volunteers rating				
Formulation	0	1	2	3	4
Pure Drug	---	---	1	3	1
1:3 complex	---	4	1	---	---

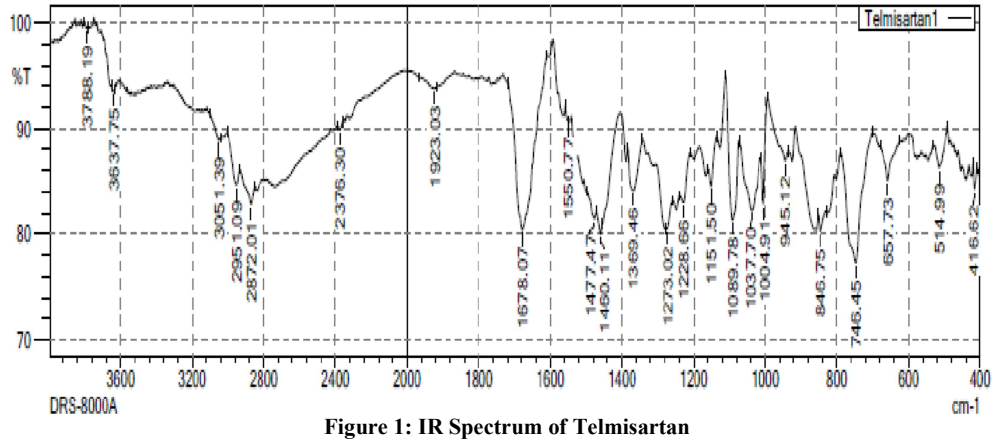

Figure 1: IR Spectrum of Telmisartan

Table 4: FTIR Spectral data of Telmisartan

Sr. No.	Functional group	Peaks cm^{-1}
1	O-H stretch	3637.75
2	C-H Aromatic stretch	2951.09
3	C-H Aliphatic stretch	2872.01
4	C=O stretching in carboxylic acid	1678.07
5	C-H bend	1460.11
6	C-N stretch	1089.78
7	O-H bend	945.12

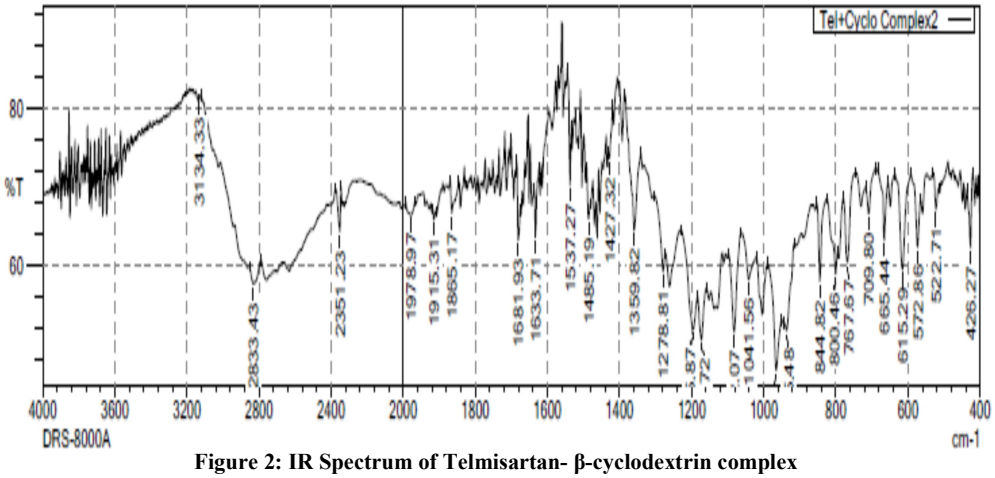

Figure 2: IR Spectrum of Telmisartan- β-cyclodextrin complex

Table 5: FTIR Spectral data of Telmisartan- β-cyclodextrin complex

Sr. No.	Functional group	Peaks cm^{-1}
1	C-H Aromatic stretch	3134.33
2	C-H aliphatic stretch	2833.43
3	C=O stretch	1681.93
4	O-H bending	1195.87
5	C-N stretch	1082.07

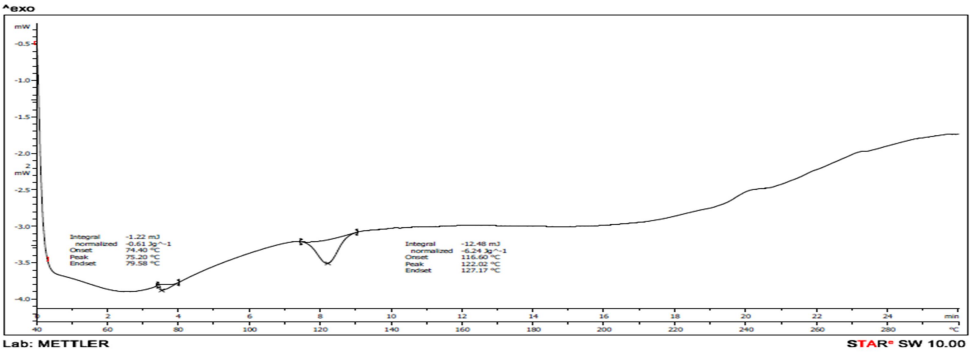

Figure 3: DSC Thermogram of Telmisartan

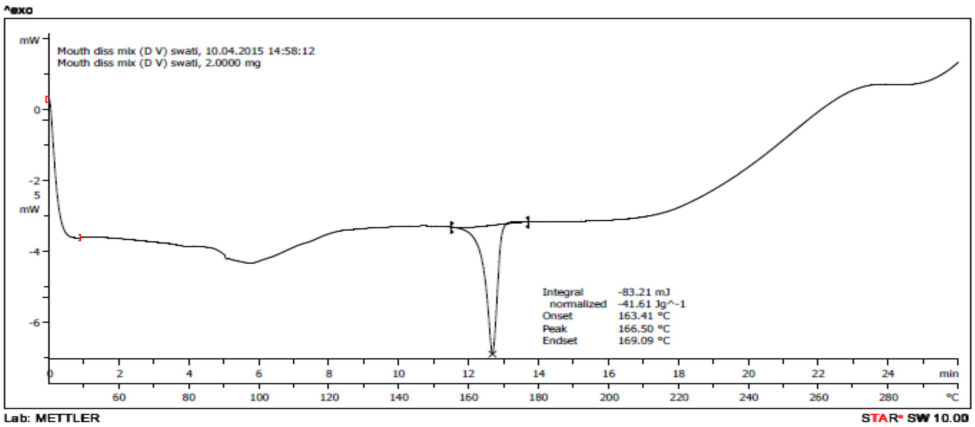

Figure 4: DSC Thermogram of the DPC

Table 6: In-vitro taste evaluation of drug complex

Sr. no.	Ratio	% Drug released	Threshold concentration for 200 µg/ml
1	1:1	82.24	91.23 %
2	1:2	73.86	
3	1:3	62.53	
4	1:4	62.61	
5	1:5	61.94	
6	1:6	61.87	

CONCLUSION

The aim of this study is to improve patient acceptance for bitter drug by masking the taste. The drug-polymer complex (DPC) were prepared by solvent evaporation method to mask the bitter taste of the drug in various ratio (1:1, 1:2, 1:3, 1:4, 1:5 & 1:6). The evaluation of DPCs were carried out by determining Drug content, *in-vitro* evaluation of drug polymer complex & Threshold value determination. 200 µg/ml is the optimized threshold value for the DPC and 1:3 ratio was selected which masked the taste of drug. Bitter taste of drug was completely masked by betacylcodexrtrin. It played dual role of taste masking and solubility enhancement. This study also concludes that, betacyclodextrin is acts as a hydrophilic drug carrier.

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