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RESEARCH ARTICLE

Formulation of Dry Suspension Containing Taste Mask Ketoprofen with β-Cyclodextrin by Inclusion Complex Method and its Characterization

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ABSTRACT

The aims of this study are (1) taste masking of highly bitter drug Ketoprofen by β-Cyclodextrin and (2) to prepare dry suspension of drug: β-Cyclodextrin complex. Ketoprofen was complexed with β-Cyclodextrin by Inclusion complex method. A blind test is carried out with the formulation made up of different drug polymer ratios and it was found that Drug: β-Cyclodextrin in the ratio of 1:19 w/w found to be most acceptable for further studies. The Dry suspension contained Ketoprofen: β-Cyclodextrin complex and Sodium benzoate, Disodium EDTA, Sodium saccharine and other excipients. The oral suspension was evaluated for pH, Flowability, Redispersibility, Sedimentation volume, Viscosity and Drug content of formulation. Further stability studies were performed by storing the formulation at 4 ± 1ºC, room temperature, 40ºC temperature for three months. The physical and chemical stability parameters of the dry suspensions showed that pH, flowability was stable at different temperatures, dry suspension can be easily redispersable and there was no change in viscosity and sedimentation volume. The $t_{10\%}$ obtained in case of formulation stored at 40˚C and 25˚C was found lower in comparison with that stored at 4 ± 1ºC, which indicated that the formulation tend to degrade at higher temperature.

KEYWORDS

Ketoprofen, Taste Masking, β-Cyclodextrin, Dry Suspension

INTRODUCTION

Masking the bitter taste of drugs is a potential tool for the improvement of patience compliances, which in turn decides the commercial success of the product.[1] This research is done to achieve pleasant tasting pharmaceuticals in which bitter actives have been successfully masked. The masking of unpleasant taste together with the development of base formulations and flavors complement the active ingredients.[2] Mouth feel is critical and patients should receive a product that feels pleasant.

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The unpleasant gritty feeling can be overcome by keeping the majority of the particles below the detectable size limit.[3] In inclusion complexation, the Ketoprofen molecule (guest molecule) fits into a cavity of a β-cyclodextrin complexing agent (host molecule) forming a stable complex. The complex is capable of masking the bitter taste of the drug by both decreasing the amount of drug particles exposed to the taste buds and/or by decreasing the drug solubility on ingestion, both activities leading to a decrease in the obtained bitterness associated with the drug. There is no covalent bonding between guest and host molecules, the attraction being generally due to Vander Waals force. The β-cyclodextrin is the most widely used

complexing agent for inclusion type complexes. It is sweet and nontoxic cyclic oligosaccharide obtained from starch.[4]

MATERIALS AND METHODS

Materials

Chemicals and Drug

The materials Sodium benzoate, Disodium EDTA, Sodium saccharine, Sorbitol solution, β-cyclodextrin, Glycerin and Ketoprofen were obtained from Sigma Aldrich. All the reagents used were of analytical grade.

Methods

Taste masking is done by the inclusion complex formation with β-cyclodextrin, 24ml of the distil water was weighed into a first beaker fitted with a mixer and steam bath and the beta-cyclodextrin was added and dissolved therein. The solution was heated to 50˚C, while mixing and the ketoprofen was added. Mixing was continued until the solution was clear while maintaining 50˚C. The mixture was then cooled to 25˚C while mixing. In a separate container fitted with a mixer, 20ml of distilled water was added and heated to 70˚C, while mixing. To this hot water was added and dissolved sodium benzoate, sodium saccharine, disodium EDTA, methyl cellulose and sucrose and the solution was then cooled to 25˚C while mixing. There were then added with mixing the ketoprofen/ cyclodextrin solution from the first beaker, the glycerin, sorbitol solution flavor and color solutions. The mixing was continued for an additional ten minutes.[5]

Taste Masking Test

A blind test is carried out with the formulation made up of different drug polymer ratios. Ten volunteers participated in this study. Pure drug was taken as reference control. Formulations were orally given to each volunteer and asked to rate the taste and after taste of the formulations as-

Abbreviations

VB – Very Bitter, B – Bitter, SB – Slightly Bitter, AT – Acceptable taste, TL – Tasteless. [6-9]

The formulation No. 3 of Table 1 (drug: polymer: 1:19) was found to be most acceptable so further preparation and characterization of suspension was done using this ratio.

Preparation of Dry Suspension

Measure 100ml of the formulation, and kept it for drying for 20-30 minutes in an oven, pass it from sieve of 200 number mesh to form a coarse suspension (75µm). Now mix the suspension in a polybag for 20min. Add sucrose pass through 100 numbers mesh to above suspension and again blend for 10 min. Finally dry the suspension for 5-10min in an oven.

Characterization of Suspension

Dry Suspension was characterized by pH, Flowability, Redispersibility, Sedimentation volume, Viscosity, Drug content and Stability Studies.

Table 1: Taste Panel Evaluation of Drug: Polymer Ratio

S. No.	Ketoprofen : β-cyclodextrin Ratio's	Number of volunteers									
		A	B	C	D	E	F	G	H	I	J
1.	1:1	VB	VB	VB	VB	VB	VB	VB	VB	B	VB
2.	1:9	VB	VB	VB	VB	VB	VB	VB	B	VB	VB
3.	1:19	TL	TL	TL	TL	TL	AT	AT	TL	TL	TL
4.	1:20	TL	TL	TL	AT	AT	AT	TL	TL	TL	TL

pH

Immerse the electrodes in the solution containing 50 ml of the preparation, prepared by using distill water and measure the pH at the same temperature as for the standard solution. At the end of a set of measurements, record the pH of the solution containing the preparation taking reading on the pH meter, under standard conditions of sample preparation, gives the pH of the suspension and determines its physical stability.[10,11]

Flowability

A glass funnel was held in place with a clamp on a ring support over a glass plate. Approximately 20gm of dry suspension was transferred into the funnel keeping the orifice of the funnel blocked by the thumb. The thumb was removed gradually and dry suspension emptied from the funnel and the angle of the heap to the horizontal plane was measured. The height of the pile (h) and radius of the base (r) was measured with a scale and angle of repose was estimated by formula mentioned above [12,13].

$$\tan \theta = h/r$$

An angle of repose < 30 º usually indicates a free flowing material and angle ≥ 40 º suggests a poorly flowing material.

Redispersibility

The sedimented suspension was placed in a 100 ml graduated cylinder and shaken it through 360˚ at 20 rpm on a mechanical stirrer. The end point was taken when the base of the graduated cylinder was free of sediment. The number of revolutions necessary to achieve the end point was recorded. The ultimate test of redispersibility is the uniformity of the suspended drug delivered from the product[14, 15].

Sedimentation Volume

100 ml of suspension was place in a 100ml of graduated cylinder (V_o). Sediment volume (V_u) was measured after 24 hrs and sedimentation volume was calculated by the formula mentioned above.[14, 15]

$$F = V_u / V_o$$

Viscosity

The Helipath attachment used with a Brookfield viscometer is a valuable piece of rheological equipment for measuring the settling behavior and structure of pharmaceutical suspension. The instrument consists of a slowly rotating T- bar spindle, which while descending slowly into 100ml of suspension placed in 250 ml of beaker at 10 rpm encounters new, essentially undistributed material as it rotates. The dial reading of the viscometer measures resistance to flow that the spindle encounters from the structure at various levels in the sediment. Taking rheogram, under standard conditions of sample preparation, gives a description of the suspension and its physical stability.[14, 15]

Drug Content

The drug content of representative dry suspension samples are determined by ultra-violet spectrophotometer (257nm).[10]

RESULTS AND DISCUSSION

The dry suspension bearing β- cyclodextrin was prepared using optimized concentration of β-cyclodextrin (1:19). The dry suspensions were evaluated for:

pH

The measurement of the pH value provides good control over the manufacturing process and shelf life of the product. pH of the formulation was found to be 5.0± 0.06.

Flowability

The flowability is measured by determining angle of repose. The flowability of formulation was found to be 21.25± 1.02.

Redispersibility

Redispersibility of reconstituted suspension was found to be 5.0 ± 0.57.

Sedimentation Volume

The sedimentation volume of formulation was found to be 0.45 ± 0.05.

Viscosity

The viscosity of formulation was found to be 2000 cps.

Drug Content

The formulation was assayed by analyzing the drug content. The drug content of formulation was found to be 99.3%.

From the above evaluated results it is clearly indicated that there is no significant change in pH, Flowability, Redispersibility, Sedimentation volume, Viscosity and Drug Content of formulation. Therefore, a further stability studies was performed by storing the formulation at different temperature for three months, for determining the formulation with acceptable shelf life.

Storage Stability

Prepared formulations were stored in screw capped small glass bottles at 4±1˚C, room temperature, and 40˚C. Samples were analyzed for residual drug contain after a period of 1, 2 and 3 months. Initial drug content was taken as 100 % for each formulation.

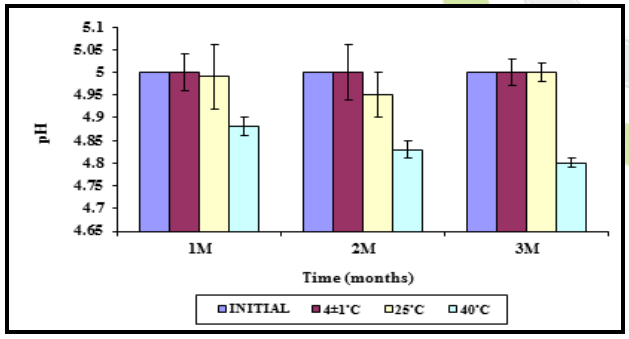

Figure 1: pH of formulation at different storage Condition

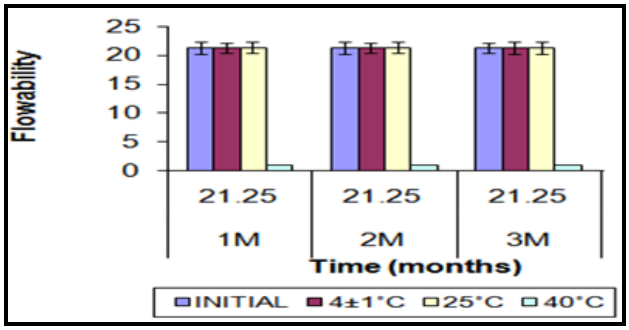

Figure 2: Flowability of formulation at different storage conditions

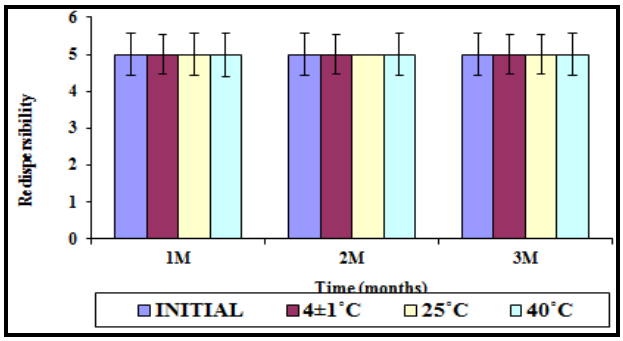

Figure 3: Redispersibility of formulation at different storage conditions

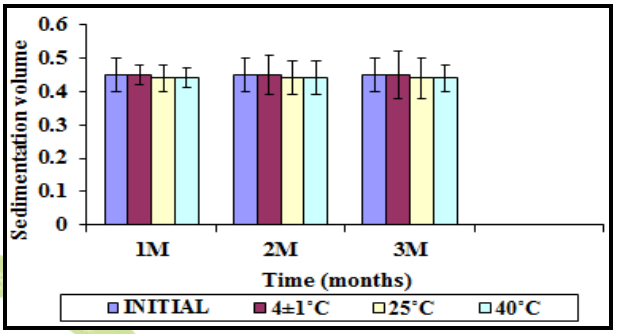

Figure 4: Sedimentation volume of formulation at different storage conditions

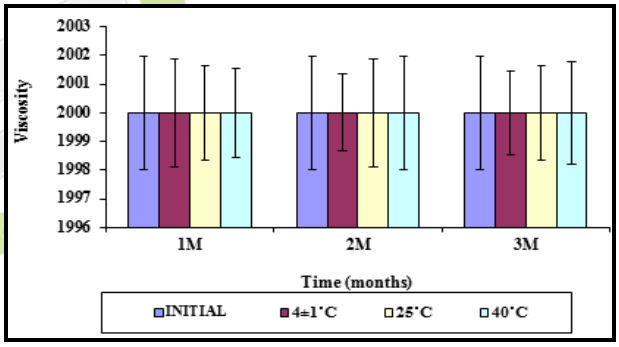

Figure 5: Viscosity of formulation at different storage conditions

Residual Drug Content

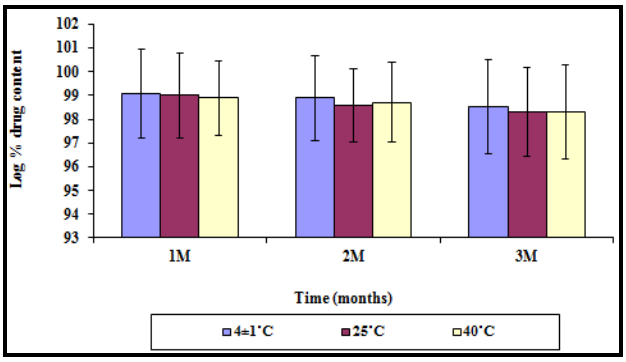

Figure 6: log % drug content at different storage conditions

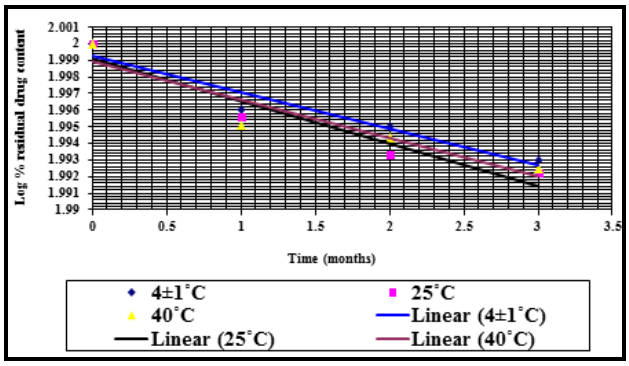

Figure 7: Calculation of K value from the plot for formulation at different storage temperature

DISCUSSION

From the above evaluated results it is clearly indicated that there is no significant change in pH, Flowability, Redispersibility, Sedimentation volume, Viscosity and Drug content of formulation. Therefore, a further stability studies was performed by storing the formulation at different temperature for three months, for determining the formulation with acceptable shelf life.

The results of stability studies suggest that the formulation is stable and for adequate shelf life of dry suspension the ideal storage temperature is 4 ± 1ºC.

CONCLUSION

Conclusion drawn from the present study is that the β- Cyclodextrin dry suspension is a suitable dosage form for taste masking. The optimization techniques were applied to optimize the drug/ polymer and solvent/ solvent ratio. β-Cyclodextrin was found to be a better taste-masking agent. The dry suspension was found to be more stable even after three months. Thus a dry suspension powder has been developed from which a stable suspension can be prepared after reconstitution.

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