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Research Article

A STUDY ON SUITABILITY OF NIMESULIDE-BETACYCLODEXTRIN COMPLEX IN ORAL AND TOPICAL DOSAGE FORMS

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ABSTRACT

Some drugs having poor bioavailability are with poor aqueous solubility and or slow dissolution rate in the biologic fluids.Nimesulide is a selective Cox-2 inhibitor used as non-steroidal anti inflammatory analgesic drug having poor aqueous solubility so its solubility has to be enhanced. One of the methods of increasing bioavailability was by using inclusion complex example by using beta cyclodextrin.Nimesulide –BCD solid complex are obtained by co-precipitate method. The complexes are confirmed solubility and DTA analytical methods. Dissolution profile of Nimesulide was improved by complexation with BCD. The prepared complexes are suitable for oral and topical formulation.

Keywords: Nimesulide, Beta-cyclodextrin, Complex and *In Vitro* Dissolution Studies

INTRODUCTION

The therapeutic effectiveness of a drug depends upon the ability of the dosage forms to deliver the medicaments to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. Some drugs having poor bioavailability are with poor aqueous solubility and or slow dissolution rate in the biological fluids. Nimesulide is anti-inflammatory, analgesic and antipyretic. It inhibits cyclooxygenase that may contribute to its anti-inflammatory effects. It inhibits neutrophil activation and exhibits antioxidant properties[1]. It is a selective cox-2 inhibitor used as non-steroidal anti inflammatory analgesic drug having poor aqueous solubility so its solubility has to be enhanced. One of the methods of increasing bioavailability is by using inclusion complex. Example by using Beta-cyclodextrin.

Hydrophilic Cyclodextrins (CD) are known to improve the solubility of insoluble drug by forming inclusion complexes[2] .They are bucket shaped oligosaccharides produced from starch. They act as molecular container by entrapping guest molecules in their internal cavity.Cyclodextrins increase the water solubility of poorly soluble drugs to improve their bioavailability, light, thermal and oxidative stability of actives can be improved through the formation of cyclodextrin complexes. Cyclodextrin have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability[3]. Among α,β,γ,β-CD was used for the study, as it has bigger cavity size of (7.5A) and is the least toxic among the other natural cyclodextrin[4].Cyclodextrins were reported to enhance topical drug delivery in the presence of water[5].The interior environment of a cyclodextrin cavity is hydrophilic ;hence it can entrap unionized form of the molecule which too is hydrophilic[6].

Carbomer used as emulsifying agent in topical formulations.Carbomer grades with a low residual content, such as Carbomer 943p, 974p may additionally used in oral preparations.Carbomer 910,934,934p, 940, 941, 1342 are widely used as copolymers[7].

Various methods have been applied to prepare drug-cyclodextrin complexes such as the

solution method, the co-precipitation method, the neutralization, the kneading method, the slurry method, and the grinding method. Several methods can be used to analyze the solid-dug Betacyclodextrin complex including DSC,TGA,IR,solid nuclear magnetic resonance and x-ray crystallography.[8] Thermal analysis find wide applications in material characterizations, purity of medicinal substances, study of relative heat stabilizers and dynamic properties of new compounds as well as crystallography ,chemical kinetics and generation of phase diagrams[910].

The aim of the present study was to evaluate the influence of β-cyclodextrin (BCD) on the solubility and *in vitro* dissolution characteristics of Nimesulide-betacyclodextrin complex in oral and topical dosage forms.

MATERIALS AND METHODS

Materials: Nimesulide was obtained as gift sample from (Bafna pharmaceutics, Chennai), cyclodextrin was provided by (signet private limited, India)

Preparation

Co-precipitation method

20%w/w solution of β-cyclodextrin(BCD) was prepared at 75°C.An appropriate amount of the drug calculated according to the selected drug:BCD molar ratio (1:0.5,1:1,!;2) was then added to the solution, which was cooled to room temperature while continuously stirring or shaking. During cooling, the solid drug β-cyclodextrin complex precipitated. Complexes of three molar ratio 1:0.5, 1:1, 1:2 (drug: BCD) were prepared by co-precipitation method[8]. These complexes were used for the formulation of capsules and gel.

Preparation of capsules

25 mg drug or drug equivalent complex was weighed and was passed through mesh no.40. It was filled in capsules of appropriate size.

Preparation of gel

Preparation of gel base

100 mg of carbopol was weighed and dispersed in a small quantity of water. Triethanolamine was added and required quantity of water was added with continuous stirring.

Incorporation of drug

The drug content of the medicated gel was 1:1 w/w. The required quantity of drug or complex was incorporated in the base by thorough trituration.

EVALUATION

Preformulation studies

Preformulation studies were performed on free drug and complexes to assess the suitability of the complexes for capsule dosage forms. Bulk density, Tapped density, percentage compressibility, angle of repose of the drug and the complexes were found out.

Thermo grams of the pure drug, BCD and 1:1 complex were recorded by analyzing the samples by differential thermal analysis.

Solubility of the drug and the complex in phosphate buffer pH 7.4 were determined and the values were given in table 1.

In-vitro dissolution studies

Dissolution of drug from capsules

The dissolution profile was studied using USP dissolution rate test apparatus employing paddle stirrer. In 900 ml dissolution medium (2 hrs using 0.1 N HCl and the medium was replaced with phosphate buffer pH 7.4), a sample of 25 mg drug equivalent complex (1:1m, 1:2m) was placed and set rpm at 100 and temperature $\pm 37^0$ C. Aliquots of 5 ml was withdrawn at 10mts intervals of time and replaced with the same medium and analyzed at 394nm by using uv-visible spectrophotometer.

Drug release from gel

A diffusion cell was used to determine the *invitro* drug release from gel. A sample gel

containing 25 mg drug or 25 mg drug equivalent complex (1:1, 1:2) was taken in donor compartment and 25 ml dissolution medium in receptor compartment. Aliquots of 5 ml was withdrawn at half an hour intervals of time and replaced with the same medium. This was analyzed at 394nm. *Invitro* release from gel as given table: 3

Table: 4 Cumulative % release of pure drug, 1:1 complex and 1:2 complexes

RESULTS AND DISCUSSION

The present study involves the influence of inclusion complexes of β-cyclodextrin on solubility of Nimesulide. The drug and complexes are characterized by solubility, Differential Thermal analysis.

Differential thermal analysis (DTA)

The loss weight of drug sample in the pure form occurred at 243.51 c but it has been shifted to 272.65 c suggesting the formation of complex with betacyclodextrin.The shifting of drug peaks in DTA curve from 143.37°C to 142.62°C in complex indicates the interaction between the drug and BCD as shown in the Figure: 1.The peak observed in DTA of BCD and complex in the temperature range 75-77°C may be due to the moisture content of the complexing agent.

Fig. 1: Thermogram of Beta-cyclodextrin

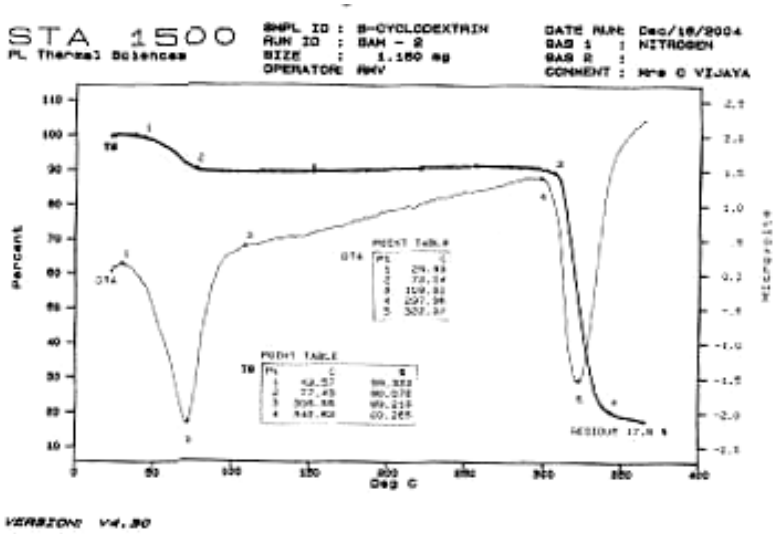


Fig. 2:Thermogram of nimesulide

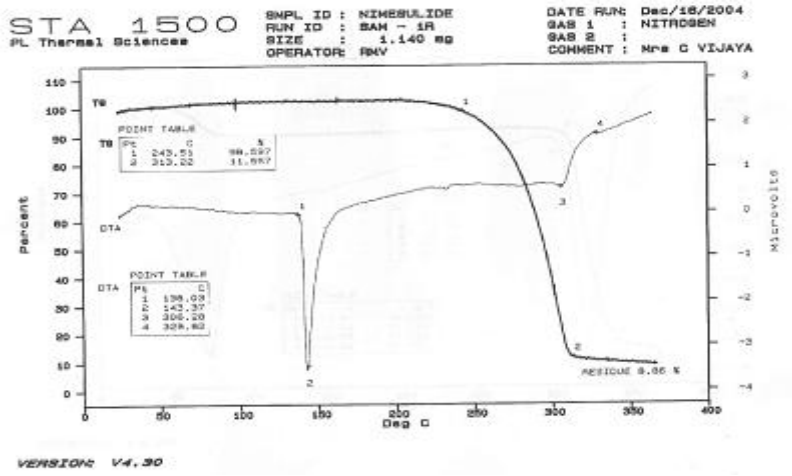
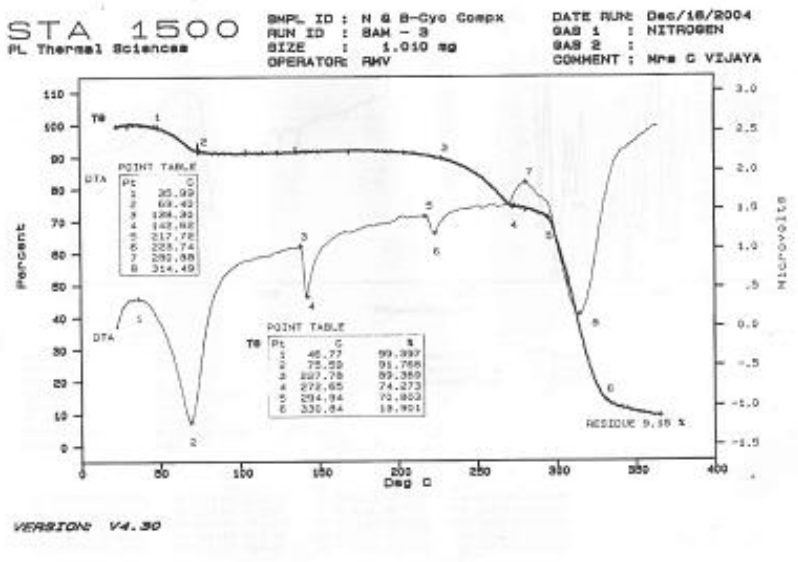


Fig. 3: Thermogram of Nimesulide- Beta-cyclodextrin complex



Solubility analysis

The solubility of the drug was found to be increased considerably by complexation. The results were as shown in table 1.

Table 1: Solubility analysis of pure drug and different ratios of complexes

Samples	Solubility(µg/ml)
Nimesulide	2.25
Drug:BCD(1:0.5)	19.00
Drug:BCD(1:1)	29.75
Drug:BCD(1:2)	30.50

Flow property

The complexation was found to increase the bulk density and tapped bulk density when compared to pure drug, which indicates the suitability of the complex to be formulated into capsules. The reduced percentage compressibility values for complexes shows that the complexes are having improved compressibility behaviour.Complexes are found to have relatively low angle of repose indicating improved flow properties. The results were given in table 2.

Table 2: Flow properties of pure drug and different ratios of complexes.

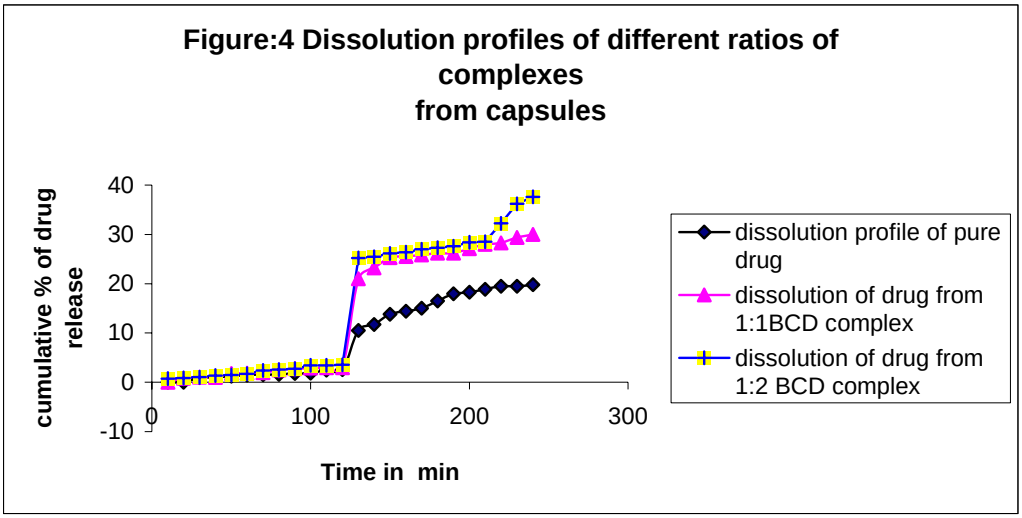
Samples	Bulk Density (g/ml)	Tapped Density (g/ml)	Percentage Compressibility	Angle of Repose(°)
Nimesulide	1.78	2.75	35.27	37 71
Drug:BCD(1:0.5)	1.9	3.45	26.0	29 28
Drug:BCD(1:1)	2	3.8	27.25	28 84

***In-vitro* dissolution studies**

As the amount of betacyclodextrin in the complex was increased, the dissolution was also found to be increased. Dissolution profile of different ratios of complexes from capsule as given in figure 4

Table 3: Cumulative % release of pure drug, 1:1 complex and 1:2 complexes after 240 minutes in pH 7.4 phosphate buffer.

Different Drug Complex Ratios	Cumulative % Release From Capsules
Pure drug	19.8%
1:1 Nimesulide-BCD Complex	30.0%
1:2 Nimesulide-BCD Complex	37.6%

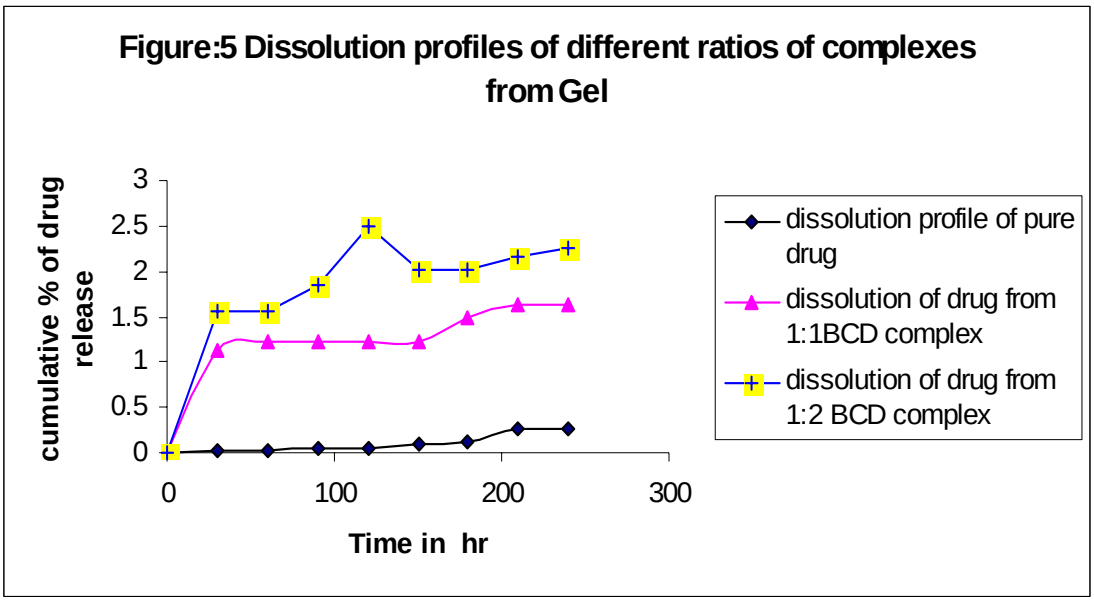


***In-vitro* release of Nimesulide from gel**

The release of lipophilic Nimesulide from a topical gel was found to be increased by the complexation with hydrophilic BCD. Dissolution profile of different ratios of complexes from Gel as shown in figure 5 Cumulative % release from pure drug and Different drug complex ratios are given in table 4.

Table 4: Cumulative % releases from pure drug and different drug complex ratios

Different Drug Complex Ratios	Cumulative % Release From Gel
Pure drug	0.275
1:1 Nimesulide-BCD Complex	1.635
1:2 Nimesulide-BCD Complex	2.25



CONCLUSION

Dissolution profile of Nimesulide was improved by complexation with BCD by co-precipitation method. This complex with the ratio of 1:2 (drug: complex) may contribute for better drug release profile .The physicochemical of properties of complex was amenable for capsule formation. *In vitro* release of Nimesulide from gel was enhanced for inclusion complex. The prepared complexes are suitable for oral and topical formulation.

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