SOLUBILITY ENHANCEMENT OF BIPERIDINE HCL BY COMPLEXATION WITH HYDROXYPROPYL β-CYCLODEXTRIN

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Oral route is the simplest and easiest way of drug administration, because of the greater stability, lesser bulk, and cheap cost of production, accurate dosage and easy process, solid oral dosage forms have several advantages over other dosage forms. All the poor water soluble drugs after oral administrations are not well absorbed and thus leads to decrease in inherent efficiency of drugs. Therefore, for oral drug delivery system the improvement of drug solubility thereby its oral bio-availability is the most important aspect of drug development process. Biperiden HCl is a potent drug (Maximum daily dose is 16mg/day), having extensive first pass metabolism resulting in poor Bioavailability. The pharmacokinetic profile of this drug showed 33±5 % Bioavailability and 18-24 hours elimination half-life ($t_{1/2}$). In the present study attempt has been made to prepare and characterize inclusion complex of Biperiden HCl with Hydroxypropyl β-Cyclodextrin. The inclusion complexes prepared by different methods i.e. Physical mixture, Kneading and Solvent evaporation methods. The prepared complexes were characterized using FT-IR. The inclusion complex prepared by Kneading method exhibited greatest enhancing in solubility and faster dissolution (93.98% drug release in 60 min) of Biperiden HCl.

Keywords: β-Cyclodextrin, Biperiden HCl, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is progressive, neurodegenerative disorder of the central nervous system, it is also known as idiopathic parkinsonism, hypokinetic rigid syndrome/HRS, or paralysis agitans. Death of dopamine-generating cells in the substantianigra (a region of the midbrain) is the main cause for motor symptoms of Parkinson's disease. The poor dissolution of relatively insoluble drugs like Biperiden HCl has a major pharmacokinetic problem in its absorption through oral dosage form and its extensive first pass metabolism resulting in poor Bioavailability.

The three approaches in overcoming the bioavailability problems due to such causes are:

- Pharmaceutical Approach – modification of formulation, manufacturing process or physicochemical properties of drugs without changing the chemical structure
- Pharmacokinetic Approach – pharmacokinetics of drugs is altered by modifying its chemical structure.
- Biological Approach – route of drug administration may be changed such as changing from oral to parenteral route.

In present study, Complexation of Biperiden HCl using Hydroxy propyl β-Cyclodextrin (HPβ-CD) has been used to modify its physicochemical properties.

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MATERIALS AND METHODS

Biperiden HCl was obtained as gift sample from S.K Healthcare Pvt. Ltd, Hyderabad. Hydoxypropyl β-Cyclodextrin was obtained as gift sample from NU Therapeutics Pvt Ltd, Hyderabad. All other chemicals were of Analytical grade and procured from local market.

PREPARATION OF INCLUSION COMPLEXES WITH HYDROXYPROPYL β-CYCLODEXTRIN:[7]

1) Physical mixture: Biperiden HCl with HPβ-CD in different molar ratios (i.e. 1:1M, 1:2M) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in a desiccators over fused calcium chloride.

2) Kneading method: Biperiden HCl with HPβ-CD in different molar ratios (i.e. 1:1M, 1:2M) were taken. First cyclodextrin is added to the mortar, small quantity of 50 % ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried for 24 h, pulverized and passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

3) Solvent evaporation Method: Drug and HPβ-CD in different molar ratio are dissolved in a common solvent to get a clear solution. Mixed the both solutions than the clear solution was kept for stirring on a magnetic stirrer till all the solvent got

evaporated. The mass obtained was dried at 50°C and further sieved No. 80 or 100 sieve. Different variations used for preparation of inclusion complexes are shown in Table 1.

Evaluation of HPβCD – Biperiden HCl Inclusion Complexes

Drug Content Estimation[4]: Inclusion complexes prepared by above methods were assayed for Bi-HCl content by dissolving a specific amount of the complexes (Drug Equivalent to 2mg) in methanol-Water system and analyzing for the Bi-HCl content spectrophotometrically at 258 nm on a spectrophotometer (Table 1).

***In-vitro release profile*:** *In vitro* release studies were carried out by conducting dissolution studies for pure drug and inclusion complexes. 500 ml of 0.1N HCl was used as dissolution medium and the study was carried out using USP II paddle type dissolution apparatus. Speed of rotation of the paddle was set at 50 rpm. Absorbance was measured at 258 nm using UV- Spectrophotometer (Table 2).

Table 1: Biperiden HCl, Hydroxypropyl β-Cyclodextrin Complexes and its drug content

Method	Drug to Carrier	Drug : Carrier	Batch Code	% Drug content
Physical Mixture	Bi-HCL : HP β-CD	1:1	BPM1	99.05
	Bi-HCL : HP β-CD	1:2	BPM2	99.95
Kneading Method	Bi-HCL : HP β-CD	1:1	BKN1	105.35
	Bi-HCL : HP β-CD	1:2	BKN2	100.25
Solvent evaporation method	Bi-HCL : HP β-CD	1:1	BSE1	100.05
	Bi-HCL : HP β-CD	1:2	BSE2	100.5

Table 2: Comparison of *In-vitro* dissolution data of all formulations

Time (min)	% Cumulative Drug Release						
	PURE DRUG	**BPM1**	**BPM2**	**BKM1**	**BKM2**	**BSE1**	**BSE2**
0	0	0	0	0	0	0	0
5	6.532	36.787	39.75164	42.16765	53.7648	39.14328	48.00836
10	20.546	55.702	58.58979	58.89765	74.67490	56.76489	55.98548
15	25.670	60.891	63.71974	76.65487	82.56387	72.87487	77.64870
30	26.0274	62.262	78.86750	82.8764	85.98465	76.77498	79.60935
45	27.79	74.460	81.54981	83.6954	90.88674	80.69804	82.92465
60	28.634	79.650	83.66899	86.48768	93.98354	82.37658	87.89275

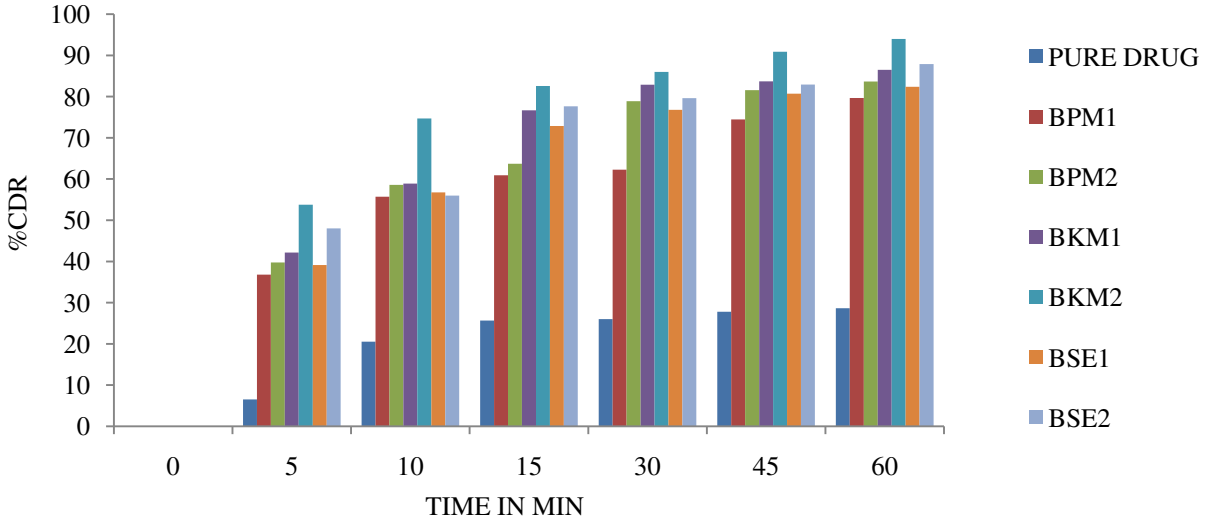
The results of dissolution data fitted to Zero order and First order equation. The kinetic values obtained for different formulations are tabulated in Table. The linearity indicates that the release of drug from the complex is followed First order.

CONCLUSION

In the present work, studies were carried out on design, formulation development and evaluation of Biperiden HCl inclusion complex with a view to improve its aqueous solubility, dissolution rate and oral bioavailability. *In-vitro* dissolution studies for pure drug and inclusion complexes were carried out in 500 ml of 0.1N HCl using USP II paddle type dissolution apparatus. It is evident that the complex prepared was exhibited a faster dissolution when compared to pure drug dissolution data. A marked improvement in the dissolution rates observed with BKM2 prepared by Kneading method. The higher dissolution rates observed with inclusion complexes prepared by Kneading may be due to better interaction of drug Hydroxypropyl β- cyclodextrin.

The inclusion complex of Biperiden HCl i.e.BKM2 complex was subjected to short-term stability studies by storing them at room temperature and at 40^0C and relative Humidity of 75%RH. The samples were analysed at an interval of one week, three weeks and six weeks for their physical appearance, drug content values and dissolution profiles. No appreciable changes observed with the above parameters.

Figure 1: Dissolution Rate Data Profile graph of Biperiden HCl and its complexes



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