Formulation, Evaluation And Enhancing the Solubility of Orodispersible Tablets of BuclizineHcl.

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Abstract— Drugs have been developed and delivered in patient different delivery system. Among the various dosage forms, tablets taken orally are considered to be the most convenient and stable unit doses forms. But the geriatrics bed ridden, psychotic’s patients travelers and pediatrics find difficulty in swallowing the conventional dosages forms like tablets, capsules etc. Due to dysphagia this problems results in not taking the prescribed medication properly and have the efficacy of treatment being severely affected (Seager et al 1988). Being aware of these problems and to fulfill the medical needs, a segment of formulation better known by the phrase Orodispersible tablets (ODTS) has been developed by (Dobettiet al 2001, Schiermeier et al 2002) Buclizine, 1-(4-tert-butylbenzyl)-4-(4-chlorobenzhydryl) is a piperazine derivative having antiemetic, antihistaminic, antimuscaranic, and selective properties used in motion.

In development of ODT formulation of buclizineHCl the problem faced was with its solubility and there by affecting the release profile. So an attempt has been made to increase the solubility of BuclizineHCl by complexing it with beta-cyclodextrin in 1:1 molar ratio by kneading method formulating this complex of buclizineHCl and beta-cyclodextrin along with optimized polymers and excipients by direct compression method and evaluated. It showed desired characteristics of ODTS and maximum release profile.

INTRODUCTION

Among the various dosage forms, tablets taken orally are considered to be the most convenient and stable unit doses forms. But the geriatrics bed ridden, psychotic’s patients travelers and pediatrics find difficulty in swallowing the conventional dosages forms like tablets, capsules etc. Due to dysphagia this problems results in not taking the prescribed medication properly and have the efficacy of treatment being severely affected (Seager et al 1988). Being aware of these problems and to fulfill the medical needs, a segment of formulation better known by the phrase Orodispersible tablets (ODTS) has been developed by Dobettet al 2001, Schiermeier et al 2002. This is an innovative dosage form that disintegrates in mouth upon contact with saliva in less than 60 second forming a suspension which is easy to swallow without intake of water.

Physical standardization of buclizine hydrochloride:-
Buclizinehcl sample were evaluated for physical appearance, odor solubility in various solvents and melting point.
**SOLUBILITY**

Table 1. Shows solubility of drug sample buclizine hydrochloride.

<table>
<thead>
<tr>
<th>S. no</th>
<th>Solvent</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>Insoluble</td>
</tr>
<tr>
<td>2</td>
<td>Chloroform</td>
<td>Sparingly soluble</td>
</tr>
<tr>
<td>3</td>
<td>Ethanol</td>
<td>Slightly soluble</td>
</tr>
<tr>
<td>4</td>
<td>Methanol</td>
<td>Freely soluble</td>
</tr>
</tbody>
</table>

**FTIR ANALYSIS: FTIR** analysis was done on a FTIR spectrometer; 5mg of the drug substance was weighed. It was thoroughly triturated with 95 mg of potassium bromide. A pellet was made out of the mix and introduced into the instrument in pallet sampling compartment. The spectrum was recorded from 400 to 4000/cm at the ambient temperature.

**PREPARATION OF STANDARD CURVE**

**Preparation of Stock Solution** of Buclizine hydrochloride

Stock solution of BCZ-HCl was prepared by dissolving 10 mgs of drug in 100ml of solvent (100µgm/ml).

**PREPARATION OF STANDARD CURVE OF BUCLIZINE HYDROCHLORIDE IN 0.1N HCL**. A calibration curve was obtained by measuring the absorbance at \( \lambda_{\text{max}} \) of 230 nm against blank. The readings were recorded in triplicate and the experiment was repeated on three consecutive days using freshly prepared standard solution each time. Value of absorbance was plotted against the concentration. Since we are formulating orodispersible tablets so standard curve was plotted in simulated saliva (Gal et al 2001).

**COMPATABILITY STUDIES**

Drug and polymers interactions and compatibilities studies were done by DCS differential scanning colorimeters (Perkin –Elmer DSC-7), FTIR.

Drug release studies - by dissolution studies and sample were analysed by using double beam UV spectrophotometer. Formulation of ODT BUCLIZINE HYDROCHLORIDE (BCZ HCl) which is Biopharmaceutical classification system BCS11 is poorly soluble drug. Initially the required dose was directly prepared by compressing the ingredients containing the microcrystalline (avicol 102) aerosol and other ingredients fillers; lubricants flavouring agents. sweetening agents. However, **in-vitro** dissolution studies showed that orodispersible tablets did not release the drug completely. The problem was overcome later by forming 1:1 BCZ HCl, BCD complex.

**Preliminary Studies**

**Characterisation of complexes**

Thermal behavior of BCZ HCl were examined X-ray diffraction studies (XRD) were performed to study the physical mixture by using X-ray Model no. DY2020 X’PERRT pan analytical Netherland.

**FTIR AND SEM (Scanning electron microscope)**

Photomicrograph of pure drug and the complex in molar ratio 1:1 were taken at 10.00 kx magnifications using SEM ZEISS EVO-50 Germany.

Dissolution studies were carried out for the complex also and compared with the marketed product LONGEFENE UCB Pvt. Limited. And stability studies carried out as per ICH guideline.

Table 2: - showing formulation of Orodispersible tablets of BCZ HCl.

Average weights of each tablet of all formulation are kept at 200 mg.

<table>
<thead>
<tr>
<th>Code</th>
<th>Drug</th>
<th>HPMC</th>
<th>MCC</th>
<th>Asp</th>
<th>fla</th>
<th>Mgst</th>
<th>ccs</th>
<th>lac</th>
<th>Aero</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0</td>
<td>25</td>
<td>10</td>
<td>50</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>A1</td>
<td>25</td>
<td>10</td>
<td>50</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>A2</td>
<td>25</td>
<td>10</td>
<td>50</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>A3</td>
<td>25</td>
<td>10</td>
<td>50</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>98</td>
<td>4</td>
</tr>
<tr>
<td>A4</td>
<td>25</td>
<td>10</td>
<td>50</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>A5</td>
<td>25</td>
<td>10</td>
<td>50</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>94</td>
<td>4</td>
</tr>
<tr>
<td>A6</td>
<td>25</td>
<td>10</td>
<td>50</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>14</td>
<td>92</td>
<td>4</td>
</tr>
</tbody>
</table>

**Drug - Buclizine HCl**

HPMC-Hydroxy propyl methyl cellulose
MCC - Microcrystalline cellulose
Asp - Aspartame sweetening agent
Fla - Flavouring agent
Mgst- Magnesium stearate
Ccs - Croscarmellose sodium
Lac- lactose
Aero – Aerosil

Table 3 shows the composition of tablets formed by complexation with beta cyclodextrin.

<table>
<thead>
<tr>
<th>Drug</th>
<th>HPMC</th>
<th>MCC</th>
<th>Mgst</th>
<th>Asp</th>
<th>fla</th>
<th>ccs</th>
<th>lac</th>
<th>Aero</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>81.25</td>
<td>10</td>
<td>50</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>43.75</td>
<td>4</td>
<td>200</td>
</tr>
</tbody>
</table>

All the above given values are in milligrams showing formulation for one tablet.

Drug complex: -BuclizineHCl and betacyclodextrin 1:1 molar ratio.

**Physical evaluation of ODTs of BCZ & BCD complex**

In physical parameter, all the batches were evaluated for weight variations, hardness, disintegrating time appearance, friability and wetting time.

**Phase Solubility Study**

Solubility studies were performed according to the method described by Higuchi & Connors. An excess amount of buclizineHCl was placed in different concentrations of betacyclodextrin.

The contents of the flask were equilibrated by shaking for 72 hrs in thermostatically controlled water bath at 25°C. After attainment of equilibrium the content of each flask was then filtered. The filtrate was then assayed spectrophotometrically for BuclizineHCl at 222nm using UV spectrophotometer (Shimadzu, KOITO, Japan)

**DISSOLUTION STUDIES OF COMPLEX**

Dissolution test were performed in triplicate with USP apparatus-2 (VEEGO- VDA 80 India) at temperature 37°C and paddle method at 50 rpm.

0.1N HCl is used as a dissolution media. Volume of media is 1000ml.

Sampling done at time interval 2, 5, 10, 15, 20, 25, 30 mins and filtered and dilution done appropriately. The samples
were studied spectrophotometry at 222nm and percent of cumulative release was calculated.

COMPARISON WITH MARKETED BRAND
The dissolution of complex drug was compared with marketed brand of buclizine hydrochloride (Longifene) UCB Pvt Ltd. INDIA

STABILITY STUDIES
The stability studies of optimized batch were subjected to stability studies as prescribed in ICH (International Conference on Harmonization) guide lines. Article QIA (R2) which mentions the guideline of stability testing of new drug substances and products, modules selected was intermediate and accelerated stability studies of as per ICH guideline.

Tablets from the optimized batch were kept at intermediate stability conditions of 30°C ±2°C 65%RH ±5 RH and accelerated stability condition of 40°C ±2°C,75% ± 5%RH for six months. The humidity was attained by keeping a supersaturated solution of sodium chloride and sodium nitrite respectively for 75% and 65 %RH respectively in the desiccators. The tablets were packed by first wrapping in thin plastic sheet and then in aluminium foil, kept in the desiccators. The desiccators were placed in control temperature incubators. The stability samples were subjected to in-vitro analysis, FTIR and DSC after 0,3,6 month variations observed. If no significant changes then the product formulated is stable.

Result and Discussion

FIG 1 SHOWS THE FTIR PEAK
Peaks were compared with standard BuclizineHCl|Clark’s analysis of drug and poisons
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Principle peak at wavelength 1002cm⁻¹, 1131cm⁻¹,754cm⁻¹,800cm⁻¹, 1075cm⁻¹.

DRUG POLYMER INTERACTION STUDIES

FIG 3 SHOWS THE DSC OF DRUG WITH CROSPOVIDONE AND OTHER EXCIPIENTS

Standard curve was prepared by plotting absorbance against different concentrations of drug solution in simulated saliva PH 6.8. The equation obtained was linear with a regression coefficient of 1.

Standard curve of buclizine Hydrochloride have shown the linear relation between concentrations and Absorbance (follows Beer Lambert “s law), these equations can be used to calculate unknown Concentration of drug when absorbance is known in respective media.
DSC shows that endothermic peak of drug in physical mixture of drug with crospovidone and other excipients was found to be 237.21

DSC analysis of drug with excipients shows that endothermic peak of drug remains within limits. No significant shifts in endothermic peak were found in physical mixture of drug and excipients as compared with the pure drug which was found to be at 238.25.°

Therefore the drug and excipients are compatible in formulation.

EVALUATIONS OF FORMULATIONS

- Physical parameters of formulation

All the batches of the formulation were evaluated for weight variation, hardness, Disintegration time, thickness, wetting time, friability.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Weight Variations</th>
<th>Hardness</th>
<th>Disintegration</th>
<th>Thickness</th>
<th>Wetting Time</th>
<th>Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0</td>
<td>201.5 ± 0.22</td>
<td>34.2 ± 0.10</td>
<td>24.40 ± 0.02</td>
<td>2.5 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>200.8 ± 0.06</td>
<td>34.2 ± 0.10</td>
<td>14.40 ± 0.02</td>
<td>2.5 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>200.5 ± 0.12</td>
<td>34.2 ± 0.10</td>
<td>14.40 ± 0.02</td>
<td>2.5 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>200.3 ± 0.08</td>
<td>34.2 ± 0.10</td>
<td>14.40 ± 0.02</td>
<td>2.5 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A4</td>
<td>200.6 ± 0.06</td>
<td>34.2 ± 0.10</td>
<td>14.40 ± 0.02</td>
<td>2.5 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5</td>
<td>201.9 ± 0.15</td>
<td>34.2 ± 0.10</td>
<td>14.40 ± 0.02</td>
<td>2.5 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A6</td>
<td>201.9 ± 0.15</td>
<td>34.2 ± 0.10</td>
<td>14.40 ± 0.02</td>
<td>2.5 ± 0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disintegration time of A0 is more than 3 mins and hence it does not fulfill the requirement characteristics of ODTs. A3, A4, A5, A6 shows a good disintegration time but they cannot withstand the rigors of manufacturing process and handling due to insufficient strength. In addition, tablet should be able to withstand reasonable abuse when in hands of consumer such as bouncing about in woman’s purse. Adequate tablet hardness and resistance to powdering and friability are necessary for consumer acceptance. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable.

FIG 4 SHOWS THE RELEASE OF BATCH A1

Result: The maximum release was 62.32% in 5 mins. in batch A1

As the concentration of disintegrant goes increasing the hardness decreases and it cannot withstand the rigors of manufacture and shipment. Hence batch A4, A5, A6 were not considered. Considering the release profile of A2 the release of the drug was maximum in five mins in all the batches hence it can be inferred that we can formulate the orodispersible tablet with these polymers and excipients but its release is less than 80% hence its absorption and bioavailability will be erratic. We can bring a good release by enhancing the solubility of the drug buclizine hydrochloride by complexing with the beta cyclodextrin. Complexation is done in molar ratio 1:1 by kneading method. And following are the results of characterization performed; the complexes were stable. Formulated ODTs by using this complex, crospovidone 3% (optimized conc of disintegrant) and other polymers and release profile of the formulated ODT were studied as given below and is compared with marketed product (longifene).

EVALUATIONS OF FORMULATIONS

- Physical parameters of formulation

There is a shift in the endothermic peak of the drug and that of complexing agent betacyclodextrin indicating reduction in drug crystallinity due to complexation. The peak for drug before complexing was 238.25°C and it has come down to 212°C and the endothermic peak of beta cyclodextrin disappeared and a new peak with different shape appeared at 89.63°C which can be attributed to the formation of an inclusion complex.

These shifts in peak shows that there is complex formation...
The marketed product shows a release of 77.6% in 45 minutes. Hence it is to be taken 30 mins before traveling. And release profile is studied.

**CONCLUSION**

BuclizineHCl as orodispersible tablet and optimized formula was subjected to physico-chemical and pharmacokinetic evaluations.

Technique of direct compression of drug with compressible excipients like MCC, aerosol and superdisintegrant crospovidone, crosscarmellose in different ratio were added to formulate the ODTs and give taste palatable and disintegrates in less than 30 seconds. It is being found that drug BCZ HCl is compatible with HPMC, crospovidone, MCC, Lactose, crosscarmellose in the formulation. It was shown by DSC & FTIR studies. Hardness, wetting time, disintegrating time of tablet containing crospovidone show promising result and hence it is selected for preparation of the ODTs (orodispersible tablets). Since the drug BCZHCl is practically insoluble in water hence its dissolution profile was poor. Hence the drug is complexed with beta-cyclodextrin in molar ratio 1:1 by kneading method. Complexation was characterized by DSC, FTIR, & SEM. Results reveal that complexation result in increase of solubility and dissolution rate for the drug suggesting a possible enhancement of its oral bioavailability. Dissolution profile of the orodispersible tablet (formed by complexation) shows a fast release nearly 86.5% in gastric PH (1.2) in first five minutes in *in-vitro* conditions. Comparison of dissolution profile of the optimized tablets (3% crospovidone) and marketed product (Longifene). The optimized formulation shows the burst release at 5 mins whereas the marketed product shows its maximum release of 77.6% at 45 minutes. Hence it is to be taken 30 mins before traveling.

Stability studies DSC thermograms of the optimized table has confirmed the stability of the drug molecule in the tablet form after intermediate and accelerated storage condition. On the basis of above conclusion BCZ HCl at dose 25 mg can be formulated as orodispersible tablets (ODTs) by direct compression method solubility is enhanced by complexing with beta cyclodextrin and this method is simple, reliable and cost effective without any liquid intake. Finally it can be concluded that ODTs of BCZ HCl was ideal for geriatric pediatric and travelers consuming tablet in supine position intake of liquid. This formulation is highly patient compliant and should be tried with other drug candidates.

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Sir R.K. Nando
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