Identification, Characterization and Drug-Excipient Compatibility of Diltiazem Hydrochloride by Physico-Chemical Techniques

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Abstract

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects. Utilization of cyclodextrins attracted the attention of many researchers for the enhancement of the dissolution rate. The complexation of diltiazem hydrochloride with β-cyclodextrin (CD) was investigated by phase solubility. Phase solubility study was performed to determine stiochiometric proportion of Diltiazem HCl and complexing agent β-cyclodextrin. Solid inclusion complexes of diltiazem hydrochloride-βCD in 1:1 and 1:2 ratios were prepared by different methods, and the results were satisfactorily and complied with compendia. Mouth dissolving tablets were formulated employing Diltiazem hydrochloride alone and their βCD complexes with an objective of evaluating the feasibility of employing drug-βCD complexes in the design of immediate release tablet formulations for obtaining flow and complete drug release in 01 h. All the tablets prepared by optimizing the formula and were evaluated for pre compression, post compression, drug content, and drug release. The overall results indicate that formulation M3 was better and that it satisfies all the criteria as a fast mouth dissolving tablet.

Keywords: Diltiazem hydrochloride, FTIR, DSC, Compatibility

1 Introduction

Preformulation studies have been developed for supporting the dosage form design of a new drug and its quality control. Preformulation studies gained momentum in the 1950s and imposed scientific principles and rationale on formulation development to minimize trial-and-error efforts. Such a study is built on knowledge of physical pharmacy, the study of physical and chemical principles of pharmaceutical science and biopharmaceutics, the study of the influence of formulation on the therapeutic availability of a drug product. Form selection is commonly considered among the primary goals of a preformulation study¹.

Diltiazem hydrochloride is a calcium channel blocker used in the treatment of hypertension, angina pectoris and cardiac arrhythmias. Its biological half life is 3 - 4.5 h, which is relatively short and patients are advised to take DLT in divided daily doses, once in every 6 to 8 h. Such frequent drug administration may lead to fluctuations of blood levels, reduce patient compliance and lower the therapeutic efficacy. The maintenance of a constant plasma level of a cardiovascular drug is important in ensuring the desired therapeutic effect.

The Diltiazem hydrochloride is available in market in various dosage forms. Most preferable dosage form is tablets. Several approaches could be investigated to improve their oral bioavailability, among them; complexation with cyclodextrins is drawing considerable commercial attention these times, because of their low toxicity, low cost, biocompatibility, biodegradability and abundant availability²-⁶. We planned in present study to identify and characterize the Diltiazem hydrochloride; and to check the compatibility of Diltiazem hydrochloride with cyclodextrins.

2 Materials and Methods

2.1 Materials

Diltiazem HCl gifted from Macleods Pharmaceutical Limited Mumbai, India.

2.2 Methods
2.2.1 Identification of Diltiazem HCl

2.2.1.2 Identification of Diltiazem HCl by Melting point

The melting point of Diltiazem HCl was determined by capillary method, using definite quantity of Diltiazem HCl taken and placed in apparatus and determined the melting point and matched with the standards given in USPNF.

2.2.1.3 Identification of Diltiazem HCl by Assay

The solution of Diltiazem HCl containing concentration of 10 µg/ml was prepared in methanol respectively, and UV spectrum was taken using UV spectrophotometer. The sample was scanned in the range of 200-400 nm.

2.2.1.4 Preparation of calibration curve in methanol

An accurately weighed amount of Diltiazem HCl corresponding to 100 mg was dissolved in a small amount of methanol in 100 ml volumetric flask and volume made up to 100 ml with the same methanol. From this stock's solution, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml and 10 ml were withdrawn and diluted up to 10 ml with the pH 6.8 Phosphate Buffer in 10 ml volumetric flask to get concentration of 1µg, 2µg, 3µg, 4µg, 5µg, 6µg, 7µg, 8µg, 9µg and 10µg respectively. The optical density of every solution was calculated by UV-Visible Spectrophotometer at 237 nm for Diltiazem HCl, using methanol as blank.

2.2.1.5 Identification of Diltiazem HCl by FTIR

Infrared absorption spectrophotometry (FT-IR) was performed and spectrum was compared with reference spectrum of Diltiazem HCl. A KBr pellet was prepared by grinding the solid sample with solid potassium bromide (KBr) and applying great pressure to the dry mixture. KBr is chosen because it is transparent to infrared Radiation. If the pellet is prepared properly, one can actually see through it, as through a pane of glass. 2 mg of drug sample were taken with dry IR-grade KBr at about 2% sample to KBr ratio in an agate mortar. The grinding was carried out until it was uniformly distributed throughout the KBr. Some amount of the mixture was transferred to the pellet making die and by applying as mall pressure to the die before pulling the vacuum. Then full pressure of 10,000 pounds to 16,000 pounds was applied to the die for 2 min. First vacuum was released then pressure. KBr pellet of the drug sample was prepared. Then a vacuum was pulled for 1 to 2 min. The die set was disassembled by removing the base by twisting it off and releasing the ‘O’ ring seal. The pellet was discharged with the clear cylindrical pellet extractor located above the end of the bore and the plunger located beneath the assembly. Normally background was first scanned by using blank potassium bromide pellet. Then the sample was scanned. The spectra were collected in the 400 cm⁻¹ to 4000 cm⁻¹ region with 8 cm⁻¹ resolution, 60 scans and beam spot size of 10-100 μm.

2.2.1.6 Identification of Diltiazem HCl by thermal analysis

Differential scanning calorimetric (DSC) study was carried out to confirm the thermal behavior of drug and results were compared with melting point of drug. Differential scanning calorimetry (DSC) was performed using DSC-60 calorimeter to study the thermal behaviour of pure drug and the formulations. The instrument comprised of calorimeter (DSC 60), flow controller (FCL 60), thermal analyzer (TA 60) and operating software (TA 60). The samples were heated in sealed aluminum pans under nitrogen flow (40 ml/min) at a scanning rate of 5 °C/min from 0 °C to 350 °C. Same quantity of indium sealed in aluminum pan was used as reference. The heat flow as a function of temperature and enthalpy change was measured for the drug and other formulations.

2.2.2 Assessment of possible Diltiazem HCl - β-Cyclodextrin interaction

2.2.2.1 Interaction studies by FT-IR Spectrophotometry

FTIR Spectroscopic Analysis was carried out for Diltiazem HCl and their physical mixture by similar method stated above in identification by FT-IR and results were compared to know the possible interaction.

2.2.2.2 Interaction studies by DSC

To know the possible interaction between drug and polymer thermal analysis by DSC is an important tool. As we know that mouth dissolving tablets are generally made of β-Cyclodextrin. This β-Cyclodextrin is very variable materials. The operative process needed to produce tablets from the raw material is able to modify the organization of the β-Cyclodextrin in the solid state, leading to some mechanical discrepancies between the various forms, and even to different behaviors during ageing. Such transformations will have immediate consequences for both, the Tg event and the crystallization of the polymer. The use of DSC will then be entirely justified. Thermal analysis is therefore a useful tool in investigating the nature of the dispersion of drugs in microspheres. However, it may also be used to calculate the solubility of the drug in the β-Cyclodextrin and possibility of Diltiazem HCl-β-Cyclodextrin interaction7-10.

3 Results and Discussions

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and combination with excipients.

3.1 Melting point
It is used to determine the purity of the drug. The melting point should be in the range as described. Melting point of Diltiazem HCl was found to be in the range 208-211 °C. It inferred the purity of drug.

3.2 Identification of drug by UV spectroscopy

The Diltiazem HCl was identified by UV spectroscopy method. The Diltiazem HCl exhibited maximum absorption at 237 nm (Fig 1). After scanning, the $\lambda_{\text{max}}$ of the Diltiazem HCl at methanol matches with that of the standard $\lambda_{\text{max}}$ of the Indian Pharmacopeia. This wavelength could be considered as $\lambda_{\text{max}}$ for assay of Diltiazem HCl.

3.3 Standard curves of Diltiazem HCl

The standard curves of Diltiazem HCl were prepared in methanol and results depicted in Table 1.

The calibration curve was drawn for Diltiazem HCl in methanol, and it shows straight line in range of concentration from 1 to 10 μg/ml with $R^2$ value of 0.9992 which follows Beer-Lambert law (Fig 2).

Diltiazem HCl showed good linearity in all the solution systems at a concentration range of 1-10 μg/ml.

The outcomes inferred that Diltiazem HCl produces higher $R^2$ value in methanol; it indicates better solubility in methanol.

3.4 Identification of drug by FTIR

Infrared spectrum of any compound given information about the functional group present in particular compound. An Infrared spectrum of drug was taken using KBr pellet method. Various peaks in IR spectrum were interpreted for presence of different group in the structure of drug (Table 2). The spectra of FTIR (Fig. 3) indicate that the sample used was Diltiazem HCl.

3.5 Identification of drug by DSC

The thermal behavior of drug was studied using Differential scanning calorimetry in order to confirm the purity and identity. The samples were heated from 0 to 350 °C at a heating rate of 5 °C/min under a nitrogen flow, flowing at a rate of 30 mL/min through the DSC cell. The thermogram exhibited melting of drug at 186.23 °C (Fig 4). This value indicates the purity of drug.

<table>
<thead>
<tr>
<th>Concentration in µg/ml</th>
<th>Absorbance at 237 nm</th>
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<tbody>
<tr>
<td>1</td>
<td>0.116</td>
</tr>
<tr>
<td>2</td>
<td>0.213</td>
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<tr>
<td>3</td>
<td>0.312</td>
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<tr>
<td>7</td>
<td>0.699</td>
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<tr>
<td>8</td>
<td>0.810</td>
</tr>
<tr>
<td>9</td>
<td>0.901</td>
</tr>
<tr>
<td>10</td>
<td>0.989</td>
</tr>
</tbody>
</table>

3.6 Drug β-Cyclodextrin compatibility studies by FTIR

After performing FTIR of the Diltiazem HCl and physical mixtures Diltiazem HCl and β-Cyclodextrin it was found that the peaks obtained in formulation were in between the range of main principle peaks and were found to be very near to previously performed FTIR of pure drug Diltiazem HCl. No major deviation in peaks were
obtained in IR spectra, hence this indicates that drug was compatible with other ingredients (Fig 5).

The results of IR spectra suggest that selection of excipient for complexes were suitable. Hence it cannot alter the therapeutics efficacy of Diltiazem HCl.

Table 2 Interpretation of FTIR spectra

<table>
<thead>
<tr>
<th>IR frequency (cm⁻¹)</th>
<th>Assignment</th>
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<tbody>
<tr>
<td>3035</td>
<td>Aromatic C-H stretch</td>
</tr>
<tr>
<td>2966</td>
<td>Aromatic C-H stretch</td>
</tr>
<tr>
<td>2837</td>
<td>O-CH₃ C-H stretch</td>
</tr>
<tr>
<td>2393</td>
<td>Amine HCl N-H stretch</td>
</tr>
<tr>
<td>1743</td>
<td>Acetate C=O</td>
</tr>
<tr>
<td>1679</td>
<td>Lactam C=O</td>
</tr>
<tr>
<td>839</td>
<td>O-substituted aromatic C-H out-of-plane deformation</td>
</tr>
<tr>
<td>781</td>
<td>p-substituted aromatic C-H out-of-plane deformation</td>
</tr>
</tbody>
</table>

3.7 Drug β-Cyclodextrin compatibility studies by DSC

Compatibility of the drug with excipients was determined by DSC analysis. This study was carried out to detect any change on chemical constitution of the drug after combination with the β-Cyclodextrin in the ratio (1:1). The thermogram of mixture is depicted in figure 6.

4 Conclusions

The results of melting point, UV assay, FTIR and thermal analysis indicates that the gift sample provided was Diltiazem hydrochloride. The FTIR and DSC study were performed to determine the drug-excipient compatibility of Diltiazem hydrochloride. The findings of Diltiazem HCl - β-Cyclodextrin interaction inferred that there was no physical and chemical interaction between drug and β-Cyclodextrin.

5 References


2. Yaku K, Keiichi A, Noriyuki N, Tadashi S, Fujio M. Chiral resolution of four optical isomers of diltiazem hydrochloride on Chiralcel columns by packed-column supercritical fluid


