APPLICATION OF THERMAL AND ISOTHERMAL METHODS FOR COMPATIBILITY STUDIES OF METOPROLOL SUCINNATE WITH CARBOPOL POLYMERS

Preeti Karwa*¹, P V Kasture², Ritu Kimbahune¹
¹Al Ameen College of Pharmacy, Hosur Road, Near Lalbagh Main Gate, Bangalore
²Padm. Dr. D Y Patil College of Pharmacy, Akurdi, Pune.

ABSTRACT
Assessment of compatibility of drug with excipients helps not only in systemic selection of excipients for formulation development but also in developing strategies to mitigate stability related problems in the dosage forms. In the present investigation drug-excipients compatibility study was conducted for Metoprolol Succinate with Carbopol as polymers for development of controlled drug delivery system using non-thermal, thermal and isothermal methods. While the results of Infrared studies (non-thermal) indicated compatibility, the differential scanning calorimeter (thermal) thermograms showed physical incompatibility among drug and polymers. The literature review about physical behaviour of Carbopol at high temperature prompted to undertake isothermal stress testing by HPLC. The results of isothermal stress testing were studied, interpreted carefully and can be concluded that Metoprolol Succinate and Carbopol polymers were found to be compatible.

Please cite this article in press as Preeti Karwa et.al. Application of Thermal and Isothermal methods for Compatibility Studies of Metoprolol Succinate with Carbopol Polymers, Indo American Journal of Pharm Research.2013:3(11).
INTRODUCTION

Study of drug-polymer compatibility is significant process in the development of a stable controlled release dosage form as incompatibility between drug and polymer can alter the stability and bioavailability thereby, affecting their safety and/or efficacy. The compatibility studies are generally carried out by means of Fourier Transform Infrared spectroscopy (FTIR), Differential Thermal Analysis (DTA), Differential scanning calorimeter (DSC) or accelerated stability tests followed by analytical determination (HPLC and other methods) of the drug.[1] The physical mixtures of the drug and the polymers of the formulation are subjected to infrared absorption spectral analysis and thermal analysis. Any changes in chemical composition of the drug after combining it with the polymers were investigated with IR spectra, changes in enthalpy and transition temperature from thermogram. Isothermal stress testing [IST] has specific application in compatibility studies where the interaction between the drug and polymer is visually observed and the drug content is determined quantitatively, however, the disadvantage of this method is that it is time consuming and laborious.[2] The present article discusses the application of non-thermal, thermal and isothermal methods of compatibility study during the development of controlled release matrix tablets of Metoprolol Succinate (MS) using various Carbopol polymers.

Metoprolol Succinate (MS) a selective beta-adrenergic antagonist, (±)(1-Isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol Succinate (2:1) (salt), [3] is used in the treatment of cardiovascular disorders such as hypertension, angina pectoris, cardiac arrhythmias, congestive heart failure and myocardial infarction. [4-6] MS is a suitable candidate for controlled release formulation considering its good absorption in the entire GI tract, rapid elimination and a precise relationship between the beta blocking effect and plasma drug concentration.[7]

Carbopol, a cross linked polymer of acrylic acid, forms a gel in a aqueous solution depending on the degree of hydration of the carboxyl group in Carbopol. [8] Carbopol has been selected for development of controlled release formulation of Metoprolol Succinate, not only considering its controlled release properties like bioadhesion, good binding characteristics, good gel forming ability and mucoadhesivity and also reported compatible with most of the tablet excipients. [9]

MATERIALS AND METHODS:

Metoprolol Succinate was obtained as gift sample from Alembic Ltd., Vadodara (India). Carbopol 934P, 974P, 971P, 71G and Polycarbophil were kindly provided by Noveon Inc., Mumbai (India). IR grade KBr, HPLC grade Acetonitrile, monobasic sodium phosphate, monobasic potassium phosphate, Phosphoric acid, hydrochloric acid were purchased from different commercial sources. Millipore water was used for the HPLC.

INSTRUMENTS:

FTIR Spectrophotometer (Shimadzu 1700) for spectral analysis and DSC-60 (Shimadzu, Japan) comprised of calorimeter (DSC 60), flow controller (FCL 60), Thermal analyser (TA 60) and operating software TA 60 for thermal analysis were used. IST studies had been carried out using Quaternary Gradient HPLC (Agillant 1100 series) system equipped with G1310A Pump, G1314A UV detector and autosampler. The HPLC system was controlled through Chromoleon software. Walk-in-humidity Chamber
Drug – Polymer Compatibility Studies:

Powder blends were prepared using equal proportion of drug and various Carbopol polymers (1:1) and analysed by FTIR, DSC and IST methods.

FTIR:
The IR spectrum was recorded in the region of 4000 to 400 cm$^{-1}$ using KBr pellet of pure drug, pure polymer and powder blend.

Differential Scanning Calorimetry (DSC)

DSC was calibrated by using indium as a standard with melting point $T_{\text{fus}}$ at 156.03°C and calibration energy $H_{\text{fus}}$ of 28.89 J/g. Accurately weighed sample (5 mg) was placed in a sealed aluminium pans and cramped lids with holes in order to allow dehydration of samples. Then it is heated under nitrogen flow (30 mL/min) at a scanning rate of 5°C/min from 30 - 300°C. Empty aluminium pan was used as a reference. Differential scanning calorimetry performed for pure drug, pure polymers and drug-polymers blends. The DSC thermograms obtained were compared for possible drug-polymer interactions.

Isothermal Stress Testing (IST)

In the IST studies, drug and polymers were weighed directly into 4 mL glass vials (n=3) and mixed on a vortex mixer for 2 min. Each vial was sealed using a Teflon-lined screw cap and stored at stressed conditions as 25°C/65% RH, 40°C/75% RH and 60°C in hot air oven. The samples were periodically examined for any unusual colour change. After 3 weeks of storage under the above conditions, samples were quantitatively analyzed using the HPLC method in accordance with USP monograph. The assay was performed using thermo BDS Hypersil C$_{18}$ Column (150 × 4.6mm, 5µm) and mixture of pH 3.0 Phosphate Buffer and Acetonitrile (375:125) as a mobile phase maintained at flow rate of 1.0 mL/min. Accurately 40 µL of analyte was injected through auto sampler. The detection was carried at 280 nm while column temperature was maintained at about 25°C.

RESULTS AND DISCUSSION:

Metoprolol Succinate and polymers like Carbopol 934P, 971P, 974P, 71G and Polycarbophil were mixed, subjected to spectral and thermal analysis and finally compatibility of drug and polymers were confirmed by Isothermal Stress Testing studies. There were no major shifts have been observed in MS vibrational frequencies in FTIR spectra of mixture of drug and polymers. The functional groups like OH, secondary NH and ether frequencies of drug and carbonyl group of Carbopol remain unchanged in the mixture, indicating no chemical interaction (Figure 3).

Figure 3: Overlain IR spectra of Metoprolol Succinate and Carbopol polymers (934P, 971P, 974P, 71G) and Polycarbophil
The DSC thermogram of MS showed one sharp endothermic peak at about 138°C which may be associated with the melting of MS while the DSC study showed Carbopol had melted and decomposed at approximately 280°C sequentially. The broad endothermic peak near 100°C was attributed to the evaporation of physically bound or absorbed water from the polymers during heating. [19,20]

In some cases, the shape of the DSC curve of the pure Carbopol polymers differed from that of the mixture. This may be due to variations in the quantities of polymer used and sample geometry during mixing for the analysis. The peak shape and enthalpy depend on quantity of material used whilst the peak transition temperature associated with complete fusion is independent. Since the amount of polymer present in the corresponding mixture is less than that in the pure substance. The difference in peak shape was apparent. Therefore, peak transition temperatures were taken into account for interpretation of DSC curves.

It has been reported that due to heating chain relaxation of Carbopol polymer may take place resulting in entrapment of drug molecule in the relaxed polymer network which in turn drug might disperse in the gel structure of Carbopol (as it is well known fact that Carbopol is a material of choice for the preparation of gels). [21] Hence the shift in endothermic peak of MS in mixture may due to the increased protective effect of Carbopol on MS in a drug polymer blend.

The disappearance or suppression of the MS peak in the DSC thermograms (Figure 4 to 6) of the MS-Carbopol polymer mixtures may be because of some physical incompatibility between MS and Carbopol polymers. [22] DSC is unquestionably a valuable technique, but the sample is exposed to high temperatures (upto 300°C or more), which in reality is not experienced by the dosage form. Hence no definite conclusion could be drawn based on the DSC results alone. Therefore, the MS-Carbopol mixtures were subjected to IST studies at different stressed conditions.
Figure 6: DSC thermograms of Drug with Carbopol 971P

Isothermal stress testing was carried out by storing pure drug and mixture of drug and polymer at 25°C±60%RH, 40°C±75%RH and 60°C for three weeks. The analyses of samples were carried by HPLC method and results are show in Table 1. The degradation of the drug was found to be less than 10% in the mixture and is within the set limits while there was no change found in the retention time (3.229 min) and the shape of the MS peak. The analysis was run more than 12 min and no extra peak has been found as shown in figure7-11.

Hence, from the results of IST studies, it can be concluded that MS and the Carbopol polymers are found to be compatible and can be used for controlled release formulations.

Table 1: Summary of HPLC assay of isothermally stressed samples of MS with various Carbopol polymers

<table>
<thead>
<tr>
<th>SAMPLE NAME</th>
<th>TEMP/RH</th>
<th>RT (MIN.)</th>
<th>PEAK AREA (µA*sec)</th>
<th>% RECOVERED</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS (STD.)</td>
<td></td>
<td>3.229</td>
<td>432269</td>
<td>99.99</td>
</tr>
<tr>
<td>MS + C 934P</td>
<td>25°C/60% RH</td>
<td>3.243</td>
<td>401846</td>
<td>92.96</td>
</tr>
<tr>
<td></td>
<td>40°C/75% RH</td>
<td>3.247</td>
<td>419326</td>
<td>97.01</td>
</tr>
<tr>
<td></td>
<td>60°C</td>
<td>3.248</td>
<td>436178</td>
<td>100.90</td>
</tr>
<tr>
<td>MS + C 974P</td>
<td>25°C/60% RH</td>
<td>3.236</td>
<td>413065</td>
<td>95.56</td>
</tr>
<tr>
<td></td>
<td>40°C/75% RH</td>
<td>3.243</td>
<td>410098</td>
<td>94.87</td>
</tr>
<tr>
<td></td>
<td>60°C</td>
<td>3.250</td>
<td>384859</td>
<td>89.03</td>
</tr>
<tr>
<td>MS + C 971P</td>
<td>25°C/60% RH</td>
<td>3.237</td>
<td>405715</td>
<td>93.86</td>
</tr>
<tr>
<td></td>
<td>40°C/75% RH</td>
<td>3.247</td>
<td>400294</td>
<td>92.60</td>
</tr>
<tr>
<td></td>
<td>60°C</td>
<td>3.248</td>
<td>397939</td>
<td>92.06</td>
</tr>
<tr>
<td>MS + C 71G</td>
<td>25°C/60% RH</td>
<td>3.251</td>
<td>407187</td>
<td>94.20</td>
</tr>
<tr>
<td></td>
<td>40°C/75% RH</td>
<td>3.245</td>
<td>406418</td>
<td>94.02</td>
</tr>
<tr>
<td></td>
<td>60°C</td>
<td>3.250</td>
<td>419610</td>
<td>97.07</td>
</tr>
<tr>
<td>MS + Polycarbophil</td>
<td>25°C/60% RH</td>
<td>3.248</td>
<td>428978</td>
<td>99.23</td>
</tr>
<tr>
<td></td>
<td>40°C/75% RH</td>
<td>3.248</td>
<td>426882</td>
<td>98.75</td>
</tr>
<tr>
<td></td>
<td>60°C</td>
<td>3.252</td>
<td>426251</td>
<td>98.61</td>
</tr>
</tbody>
</table>
Figure 7: Chromatograms of isothermally stressed samples of MS with Carbopol 934P by HPLC

Figure 8: Chromatograms of isothermally stressed samples of MS with Carbopol 974P by HPLC

Figure 9: Chromatograms of isothermally stressed samples of MS with Carbopol 971P by HPLC
CONCLUSION:
Metoprolol Succinate and polymers like Carbopol 934P, 971P, 974P, 71G and Polycarbophil were studied for compatibility during development of controlled release matrix tablets of Metoprolol Succinate. Differential Scanning Calorimeter thermograms showed changes in temperature and shape of endothermic peak of Metoprolol Succinate in the mixture. But this may be due to gelling property of Carbopol. From the results of IR and IST studies, it can be concluded that Metoprolol Succinate and Carbopol polymers are compatible to each other and Carbopol polymers are found to be suitable for controlled release formulation of Metoprolol Succinate.

ACKNOWLEDGEMENT:
The authors are thankful to Alembic Ltd., Vadodara (India) and Noveon Inc., Mumbai (India) for providing gift samples of Metoprolol Succinate and Carbopol 934P, 974P, 971P, 71G, Polycarbophil respectively. The authors are also thankful to Micro Labs for providing differential scanning calorimeter for thermal analysis and Principal and management of Nargund College of pharmacy and Al Ameen College of pharmacy for providing necessary research facility for the work.
REFERENCES: