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SOLID STATE COMPATIBILITY STUDIES BETWEEN RANOLZINE WITH SOME EXCIPIENTS BY USING HPLC & FTIR

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ABSTRACT

Compatibility studies are essential for preformulation studies of formulation development. In the present study, the possible interactions between Ranolzine and some excipients (HypermelloseHP55, Ethocol7FP premium, Natrasoltype 250HHX, Klucel HF pharma, Avicel P^H 101) were evaluated by examining the pure drug or drug-excipient powder mixtures which were stored under different conditions (40°C/75%RH after 28 days) using, Fourier Transorform Infrared Spectroscopy(FTIR) and High Performance Liquid Chromatography(HPLC). The results demonstrate the suitability of Ranolazine with HypermelloseHP55, Ethocol7FP premium, Natrasoltype 250 HHX, Klucel HF pharma, Avicel P^H 101.

Key Words; Ranolzine, Compatibility Studies, HPLC, FTIR, Preformulation Studies, method Validation

INTRODUCTION

Ranolazine is used for the treatment of Cardiac ischemia it affects sodium dependent calcium channels during myocardial ischemia [1]. Excipients are included in dosage forms to aid manufacture, administration or absorption. Although considered pharmacologically inert, excipients can initiate, propagate or participate in chemical or physical interactions with drug compounds, which may compromise the effectiveness of a medication. Excipients are not exquisitely pure. Even for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential active pharmaceutical ingredients interactions with trace components. Chemical interactions can lead to degradation of the active ingredient, thereby reducing the amount available for therapeutic effect. Physical interactions can affect rate of dissolution, uniformity of dose or ease of administration [2]. Compatibility studies are usually the last activity done during pre-formulation profiling. All pre-formulation studies, except compatibility studies, are carried out on pure drug substance. Compatibility studies are aimed at studying the interactions of drug substance with other excipients. Selection of excipients is vital for development of a quality drug product. Choice of excipients is guided by the type of proposed dosage form [3]. Compatibility studies aim at identifying potential physical and chemical incompatibility between drug substance and excipients. Excipients may contribute to incompatibility by altering the moisture content, altering the micro-environment pH, and acting as a catalyst for degradation or contributing an impurity that causes degradation [4]. Numerous experimental tools like isothermal stress testing, differential scanning calorimetry (DSC) are used for conducting compatibility studies. Most commonly isothermal stress studies with various stress conditions like thermal, humidity, oxidation and mechanical stress, are employed. Studies can be performed between two or multi-component systems. A typical protocol for isothermal stress studies involves charging the physical mixtures of drug substance and excipients(s), in powder or compacted form, usually at temperature of 50° or 60°C or even higher[5]. Additional stressor like moisture can also be included. The samples are monitored on weekly basis (usually for a period of 4 weeks) for physical observations like color, odor, deliquescence and flow behavior. Samples are also analyzed quantitatively using UV spectroscopy or HPLC. Additional data on solid form changes can also be generated using conventional tools like powder X ray diffraction, FTIR and solid state NMR. Compatibility studies thus allow in systematic selection of excipients, for formulation development. Early detection of incompatibilities also helps in developing strategies to mitigate stability related problems in the dosage forms. The purpose of the present study was to evaluate the physical & chemical stability of Ranolazine when mixed with Excipients using HPLC, FTIR [6].

2. Materials & Methods

2.1 Materials used

The following materials where used in the present investigation Ranolazine, Hypermellose HP 55, Ethocol standards 7 FP premium, Natrasol type 250 HHX, Klucel HF pharma, Avicel p^H 101, Mg sterate.

Methods used

2.2 Preparation of physical powder mixtures

In order to evaluate Ranolzine drug excipient interactions physical powder mixtures of drug and excipients commonly used for extended release tablets were selected for the study. The excipients and drug were taken in different ratios Hypromellose phthalate grade HP-559(1:0.5), Ethocel standard 7FP Premium (1:0.5), Natrosol Type 250HHX (1:0.5), Klucel HF pharm (1:0.5), Avicel pH101 (1:0.5), Magnesium Stearate (1:0.2)and homogeneously mixed

with a mortar and pestle for 10min, then powder mixture was placed in glass vials with a rubber stoppers. These vials were stored at 40°C, 75%RH for a period of 30 days. Samples were analyzed for related substances using HPLC method and the method was validated.

2.3 Mobile phase preparation:

Weighed and transferred about 0.5 g of Disodium hydrogen ortho phosphate (Na_2HPO_4) into 1000 ml beaker and 350 ml of Purified water was added and mixed well. pH of the solution was adjusted to 7.0 with diluted orthophosphoric acid. This solution and methanol were mixed in the ratio of 350:650 respectively. Above solution was filtered through 0.45 µ membrane filter and degasify.

2.4 Standard preparation

Accurately weighed and transferred about 50 mg of Ranolazine working standard into a 50mL volumetric flask. Then added about 30 ml of mobile phase and sonicate to dissolve then cooled to room temperature and diluted to volume with mobile phase. 5.0 ml of the solution was transferred into a 50 ml volumetric flask, and made up the volume with mobile phase.

2.5 Sample preparation:

Accurately weighed sample powder equivalent to 500 mg of Ranolazine and transferred to 100 ml volumetric flask. Then added about 50 ml of mobile phase, and sonicate for 20 minutes with occasional shakings. Cooled to room temperature and diluted to volume with mobile phase and mixed well. The solution was filtered though a 0.45 µm membrane filter. 5.0 ml of the solution was transferred into a 25 ml volumetric flask, and made up the volume with mobile phase.

2.6 Procedure:

Separately injected equal volumes (about 20 µL) of mobile phase as blank, and sample preparations into the Agilent Zorbax (150X4.6, 5µ particle size) column and recorded the peak area response at 220nm using EzchromElite software with run time of 10 min .

2.7 Validation procedure of Ranolzine [7]

2.7.1 Linearity

Appropriate aliquots of Ranolzine standard stock solution of 1000µg/ml was transferred to series of 10 ml volumetric flasks and the volume was made up to the mark with mobile phase to get final concentrations of 25 to 175 µg/ml

2.7.2 Accuracy Studies

Accuracy of the proposed method was determined by recovery studies using standard addition method. The percentage recovery studies of Ranolzine was carried out in triplicate 3 different levels 50%,100%,150% by spiking standard drug solution to the placebo.

2.7.3 Method Precision

The method precision of the method are ascertained by injecting 6 replicates of test sample % recovery, %RSD was calculated.

2.7.4 LOD&LOQ [8]

For calculating the LOD and LOQ values, solutions with known decreased concentrations of analytes were injected into the HPLC system. The limit of detection (LOD) and quantification (LOQ) were then measured by calculating the minimum level at which the analytes can be readily detected (signal to noise ratio of 3:1) and quantified (signal to noise ratio of 10:1).

2.8 Drug Excipient Compatibility Studies
Procedure

Separately injected equal volumes (about 20 µL) of mobile phase as blank, and sample preparations into the Agilent Zorbax (150X4.6, 5µ particle size) column and recorded the peak area response at 220nm with run time of 70 min for the analyte peaks and calculated the % of each impurity in the formulation.

Percentage of unknown impurity=

$$\frac{\text{unknown area} * \text{Standard dilution factor} * \text{potency} * \text{Average weight}}{\text{Standard area} * \text{Sample dilution factor} * 100 * \text{Labelled amount}} * 100$$

2.9 Preparation of samples for FTIR

Potassium Bromide pellet method was used in the study. Test samples were prepared by physical mixing of Ranolzine and excipient in different ratios. Initially, potassium bromide was powdered and dried in oven for 45min. 100mg of potassium bromide power was mixed with 2mg of each sample, thoroughly triturated in mortar and pestle. A portion of mixture was compressed using IR pelletizing press. Then the KBr pellet was placed in sample holder of FT-IR spectrophotometer. The spectra were recorded in the wave number region of 4000-500cm^{-1}. In each case the spectra was compared with the pure Ranolzine spectrum to detect the interactions between drug and excipients.

3.0 RESULTS& DISCUSSION

In the present investigation the possible interactions between Ranolzine and Excipients were evaluated using HPLC, FTIR. The HPLC method used in this investigation was Accurate, Precise, and Robust it is validated by using Agilent 1200 series instrument and Agilent Zorbax c18 column (150X4.6, 5µ particle size). Linearity was found to be in the range of 25 to 175 µg/ml regression value was 0.999, % recovery was found to be 99.92 and %RSD of method precision was found to be 0.45 the LOD was found to be 0.0029 µg/ml and LOQ was found to be 0.0090 µg/ml shown in (Table 1). This method was suitable for the estimation of Ranolzine in bulk and Pharmaceutical formulation. The chromatogram of Standard drug subjected to 40°C/75%RH (for 90 days) was shown in (Fig 1).The sample was subjected to same above mentioned conditions chromatogram was shown in (Fig 2) in this chromatogram drug was eluted at a retention time of 10.44min and the unknown impurities were observed at a retention time of 1.558, 2.8349min respectively. The percentage of unknown impurity was calculated. Single unknown impurity were found to be not more than 0.02% and the total impurities were found to be not more than 0.06% shown in Table1 i.e., impurities are within the limit as per ICH guidelines. The selected overlayed FT-IR spectrums of Ranolzine, Excipient and binary mixtures of Drug and excipient subjected to 40°C/75%RH for a period of 90 days were shown in Fig (3 to 9). Furthermore, neither missing in the bands nor appearance of new bands in the IR spectra of powder mixtures was noted. Pure drug Ranolzine or Ranolzine in binary mixtures was stable for 90 days at 40±2ºC/75±5.0%RH since there is no change in peak area or change in Rt and the percentage of impurities was within limits as per ICH guidelines It can be deduced that the drug was stable in pure form or in the presence of excipients tested under these elevated temperature and Humidity conditions. Therefore these excipients were found to be compatible with Ranolzine.

4. CONCLUSION

Many stability problems encountered during development and post-commercialization can be ascribed to inadequate matching of the ingredients in dosage forms, lack of awareness of the complexities of chemical and physical interactions. Hence knowledge of drug–excipient interactions is a necessary prerequisite to the development of dosage forms that are stable and of good quality. The results of HPLC studies showed the method is suitable for the assay of Ranolzine in the given Extended release formulation and that there were no possible interactions between drug and selected excipients HypermelloseHP55, Ethocol7FP premium, Natrasol type 250HHX, Klucel HF pharma, Avicel P^{H} 101 during 90 days under 40°C/75%RH storage conditions. This method was useful for the estimation of drug in the formulation and also for the evaluation of relative substances in drug product.

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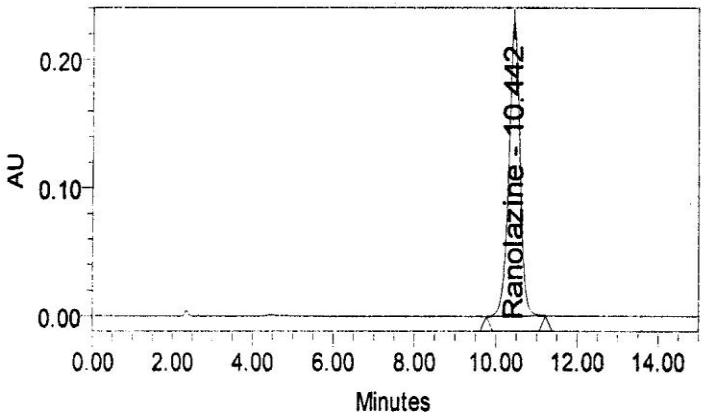

Fig 1 Chromatogram of Pure Ranolzine Stored at 40ºC/75%RH (after 30 days)

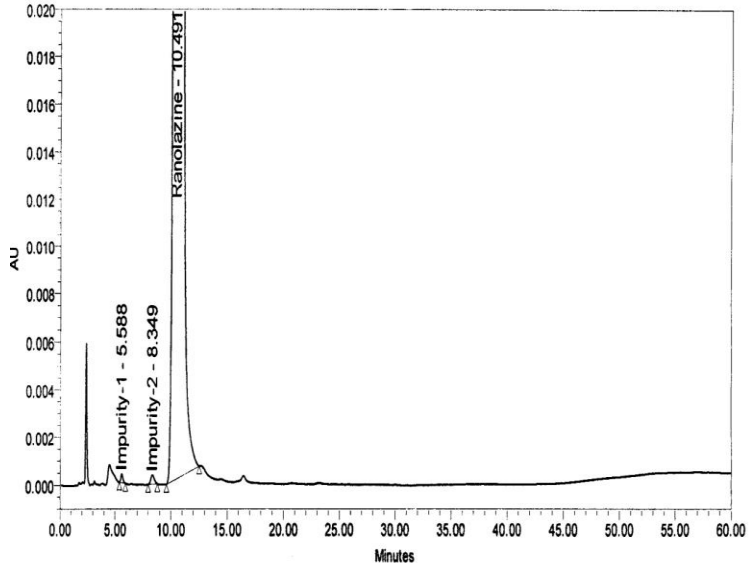

Fig 2 Chromatogram of Ranolzine+All Excepients Stored at 40ºC/75%RH (after 30 days)

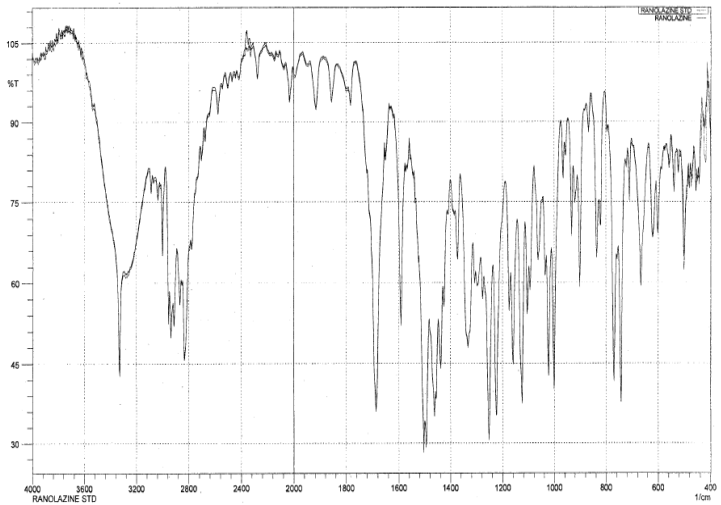

Fig 3 FTIR Spectrum of pure Ranolzine 40°C/75%RH (after 30 days)

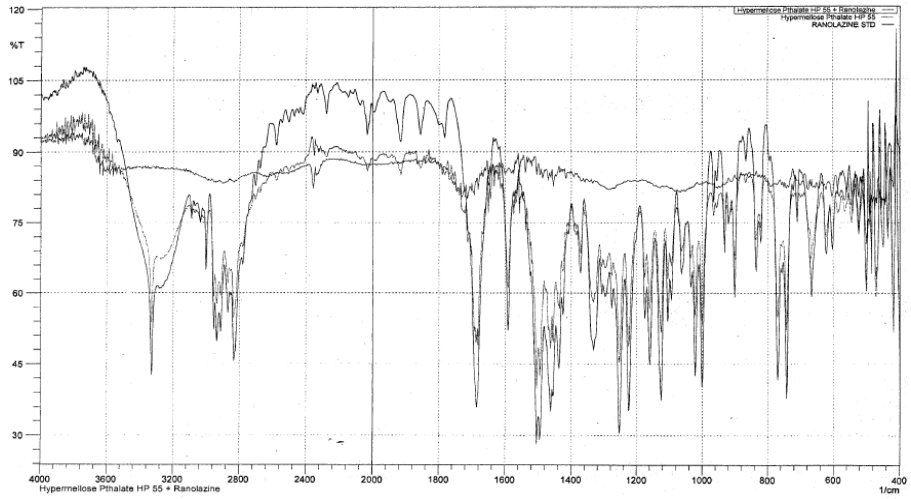

Fig 4 Overlay IR spectrum of Ranolazine, Hypromellose Phthalate grade HP55 and Binary mixture of Ranolazine and Hypromellose Phthalate grade HP55 at 40°C/75%RH (after 30 days)

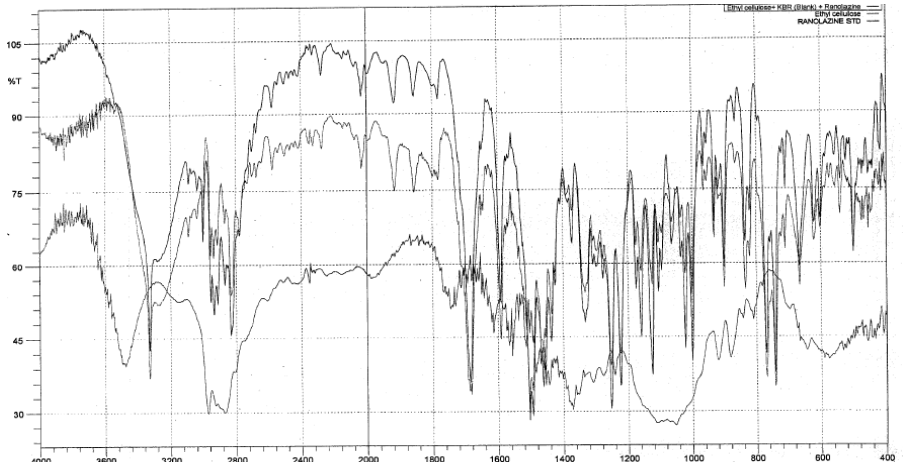

Fig 5 Overlay IR spectrum of Ranolazine , Ethocel standard 7FP Premium and Binary mixture of Ranolazine and Ethocel standard 7FP Premium at 40°C/75%RH (after 30days)

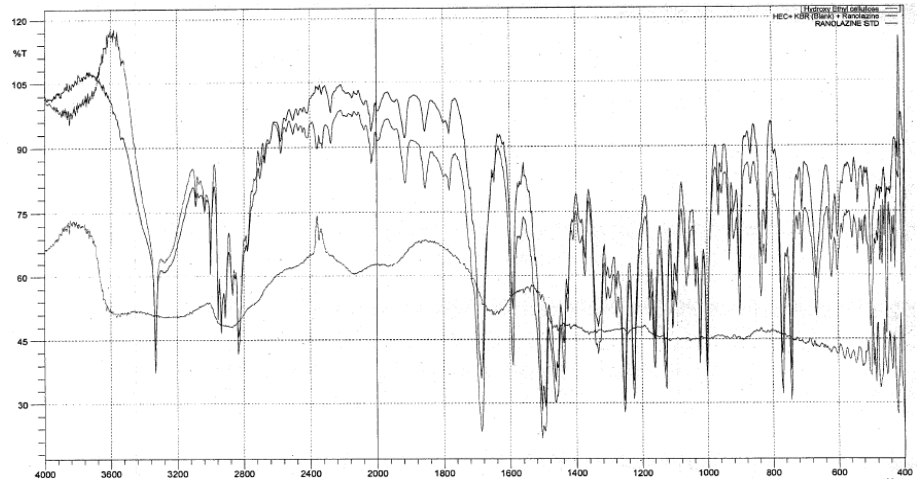

Fig 6 Overlay IR Spectrum of Ranolazine, Natrosol Type 250HHX and Binary mixture of Ranolazine and Natrosol Type 250HHX at 40°C/75%RH (after 30days)

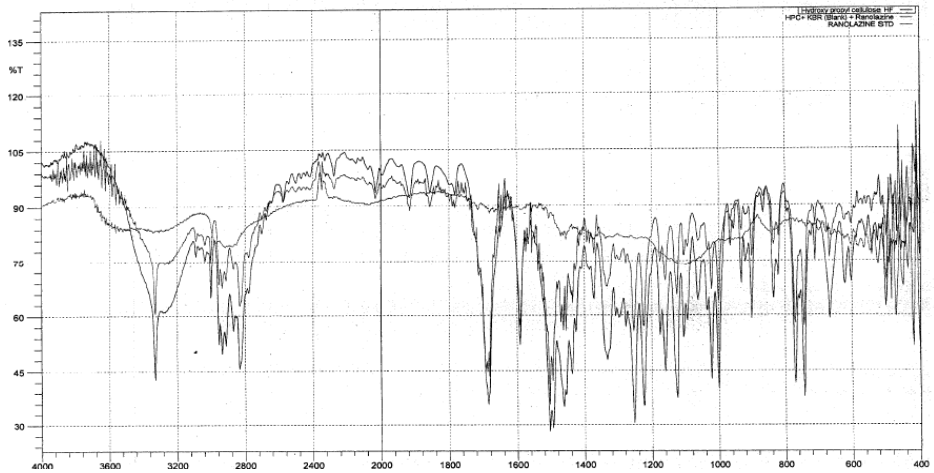

Fig 7 Overlay IR Spectrum of Ranolazine, Klucel HF pharm and Binary mixture of Ranolazine and Klucel HF pharm at 40°C/75%RH (after 30 days)

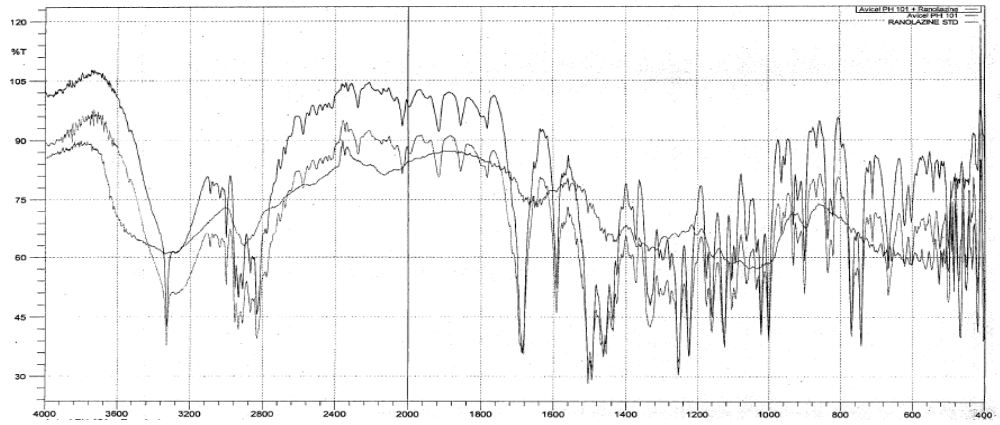

Fig 8Overlay IR Spectrum of Ranolazine, Avicel pH101 and Binary mixture of Ranolazine and Avicel pH101 at 40°C/75%RH (after 30 days)

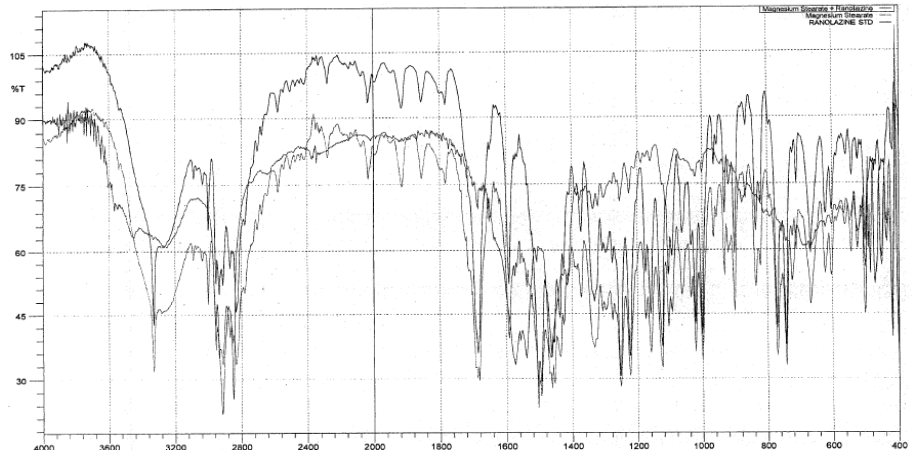

Fig 9 Overlay IR Spectrum of Ranolazine, Magnesium Stearate and Binary mixture of Ranolazine and Magnesium Stearate at 40°C/75%RH (after 30 days)

PARAMETER	VALUE
Linearity	25 to 175 µg/ml
Slope	17601
Y intercept	84675
Accuracy	99.92%Recovery
Method Precision	0.45%RSD
Limit of detection	0.0029µg/ml
Limit of Quantification	0.0090µg/ml

Table 1 Validation Results of Ranolzine

S.No	Ingredients	API : Excipient Ratio	Impurities Percentage	
			Initial	At 40°C/75%RH for 30 days
1	Donepezil		0.124	0.131
2	Donepezil l+Mannitol	1:6.4	0.121	0.139
3	Donepezil +MCC	1:6.4	0.132	0.141
4	Donepezil +SSG	1:0.8	0.129	0.232
5	Donepezil +Mg state	1:0.2	0.124	0.265
6	Donepezil +Talc	1:0.2	0.121	0.286
7	Donepezil +All Excipients		0.221	0.399

Table: 2 Results of Ranolzine +Excipient Compatibility Studies