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# STUDIES OF DRUG-POLYMER INTERACTIONS OF SIMVASTATIN WITH VARIOUS POLYMERS

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## ABSTRACT

The purpose of the present study is to prepare different combinations of drug Simvastatin (SV) with different polymers like Sodium alginate (SA), Hydroxypropylmethylcellulose (HPMC), Pectin (P), Dillenia (D) and Hydroxy propyl β- cyclodextrin. (HPC), thereby determine and report any possible interactions between the drug Simvastatin (SV) and various polymers both from natural and synthetic sources. The natural plant fruit seed mucilage Dillenia(D) was extracted from the plant *Dillenia indica* ,Family Dilleniaceae and was dried. Individual polymers and their combinations with drug SV were tested analytically and comparison of the results was done to find out any interactions. The analytical techniques used for the purpose are Fourier Transform Infrared Spectroscopy (FTIR) and Thermogravimetric analysis (TGA). The techniques of FTIR and TGA serves as a good means for determination of any interactions as the change in characteristics of the drug peak and its melting point can be detected by the two techniques respectively. From the study it was Simvastatin when complexed with Hydroxy propyl beta cyclodextrin (HP) showed some changes but these changes were not because of the other polymers used in the combination process.

**INTRODUCTION:** Simvastatin is a cholesterol lowering agent that is derived synthetically from a fermentation product of *Aspergills terreus* [1] and is widely used to treat hypercholesterolemia. The drug is an inactive lactone and is converted to corresponding β, δ-dihydroxy acid in liver by cytochrome P450 (CYP) 3A after oral administration [2, 3]. The drug (SV) is practically insoluble in water and poorly absorbed from the gastro intestinal (GI) tract [4, 5].

Before formulation of the drug in any delivery systems, several methods like use of solid dispersion [6, 7], use of complexing agents [8] are tried to increase the solubility of the drug (SV) in water. Previously it was reported that SV forms inclusion complexes with HydroxylPropyl β- Cyclodextrin (HP) [8] thereby increasing the solubility of SV in water and this is confirmed here in the present study by use of phase solubility studies.

In the present study, physical mixtures of the drug (SV) in solid form along with a series of polymers of both natural and synthetic origin were prepared and they were analyzed by using Fourier Transform Infrared (FTIR) spectroscopy and Thermogravimetric analysis (TGA), to characterize any polymer-polymer, drug-polymer interactions. The natural substance was obtained from the seeds of the fruit of *Dillenia indica* Linn. (Family-Dilleniaceae) named as “Dillenia”. This study is done so that future formulations can be prepared based on these results.

**MATERIALS AND METHODS:** Simvastatin (SV) as a model drug was generously gifted by Glenmark Pharmaceuticals Ltd. (India), HydroxyPropyl β-cyclo dextrin (HPC) was a gift from Gangwel Chemicals Ltd. Mumbai, Pectin (P) was purchased from Loba chemicals, Hydroxypropylmethylcellulose E15- LV (HPMC) was a generously gifted by Colorcon, Sodium Alginate (SA) was obtained from Loba chemicals, India.

**Preparation of the SV-polymer physical mixture:** Physical mixtures (PM) of SV with various polymers were prepared using physical mixing in a glass mortar pestle for a period of 15 min until homogenous mixture was obtained. The various polymers used are enlisted in **Table 1**.

**TABLE 1: DRUG (SV)-POLYMER COMBINATIONS**

| Combinations of Drug and Excipients | Description of combinations |
|---|---|
| SVHPSAD | Simvastatin(SV) + Hydroxy Propyl Beta Cyclodextrin(HP) + Sodium Alginate (SA) + Dillenia (D) |
| SVHPSAHPM | Simvastatin (SV)+ Hydroxy Propyl Beta Cyclodextrin (HPC)+ Sodium Alginate(SA)+ Hydroxy Propyl Methyl Cellulose (HPMC) |
| SVHPSAP | Simvastatin (SV) + HydroxyPropyl Beta Cyclodextrin (HPC) + Sodium Alginate (SA)+Pectin (P) |

**Study of the Physical Mixtures (PM) by use of analytical techniques:** The prepared physical mixtures as well as the individual polymers were studied for any drug-polymer, polymer-polymer incompatibility by using Fourier Transform Infrared (FTIR) spectroscopy (SHIMADZU, IR PRESTIGE -21) [9], Thermogravimetric analysis (TGA) [10] by using Perkin Elmer, Sll, Pyris Diamond, TG/DTA Instrument (with sample weighing about 14mg and a programmed heating of samples were done at a rate of 20°C/Min with temperatures staring from 10°C to 500°C ) various plots were recorded.

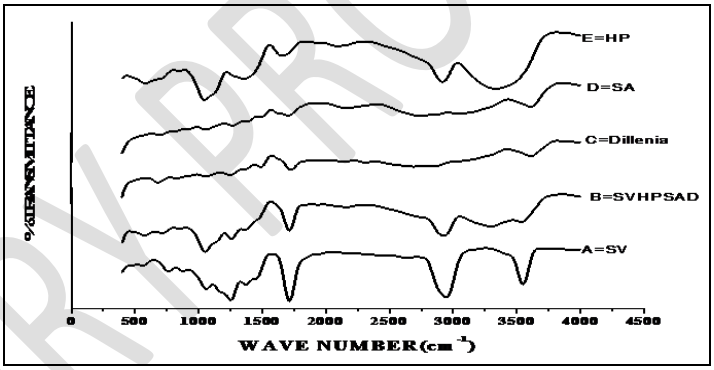


**FIG. 1: OVERLAY SPECTRA OF SIMVASTATIN WITH DILLENIA, SODIUM ALGINATE AND HYDROXYPROPYL β- CYCLODEXTRIN**

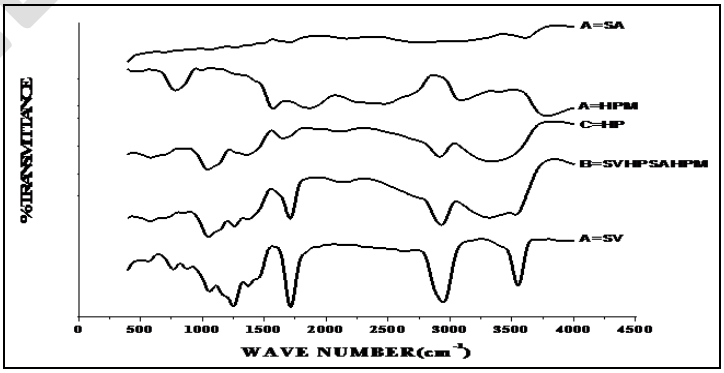


**FIG. 2: OVERLAY SPECTRA OF SIMVASTATIN WITH HYDROXY PROPYLMETHYLCELLULOSE, SODIUM ALGINATE AND HYDROXYPROPYL β- CYCLODEXTRIN**

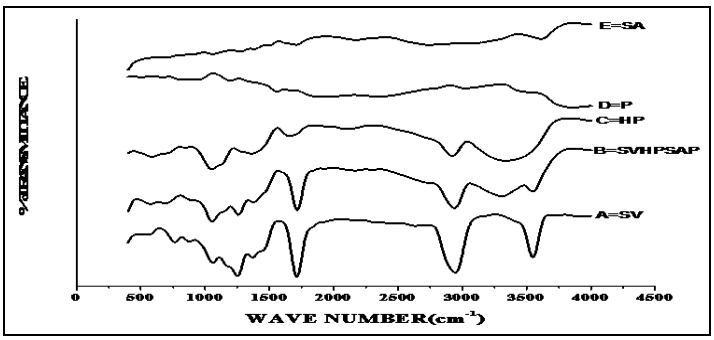


**FIG. 3: OVERLAY SPECTRA OF SIMVASTATIN WITH PECTIN, SODIUM ALGINATE AND HYDROXYPROPYL β- CYCLODEXTRIN**

**RESULTS AND DISCUSSIONS:**

**Analytical studies of Drug-Polymer physical mixture:**

**FTIR analysis:** As observed in **Fig. 1**, the FTIR spectrum of **SV** shows that the drug has wave number of 3549.02cm$^{-1}$ showing the presence of O-H bond, also the wave number of 2960.73 cm$^{-1}$ shows the presence of C-H bond, the presence of 1700 cm$^{-1}$ wave number shows the presence of C=O bond, also the wave number of 1381.03 cm$^{-1}$ corresponds to the C-H bond. The physical mixture of SVHPSAD, SVHPSAHPM and SVHPSAP as seen in **Fig. 1, 2, 3** respectively, shows almost similar wave number as that of pure drug, but the intensities of the peaks were less than in comparison to pure drug SV and were more broader. Thus this proves that there is weak interaction between SV and other polymers. This interaction may be because of the complex formation between SV and HP as already proved by Seoung Wook Jun *et al.*, [8].

**TGA analysis:** The thermogravimetric curve of SV in $N_2$ environment as seen in Fig. 4, presents mass loss event of 93.095% starting from 35.15°C ending at 500°C [10]. Whereas in the physical mixture SVHPSAD, SVHP SAHPM and SVHPSAP, as observed in **Fig. 4, 5 and 6**, there are two mass loss events starting from temperature 30°C to 100°C with mass loss event of 8.293% and 215°C to 500°C with mass loss event of 54.549%. The results show that there is weak interaction of the drug with other excipients. This interaction may be mainly due to complex formation of the drug SV with Hydroxylpropyl β-cyclodextrin (HP).

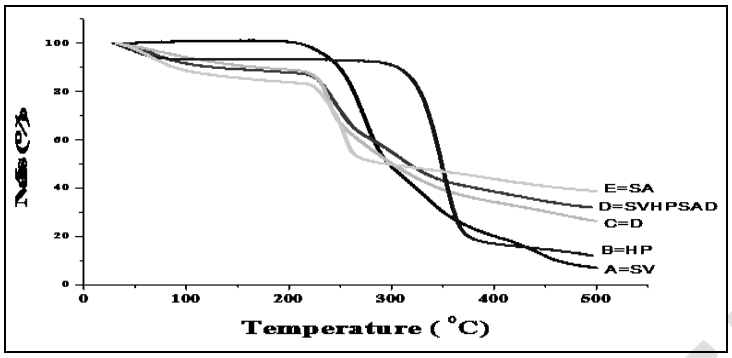


**FIG. 4: THERMOGRAMS OF SIMVASTATIN (SV), SVHPSAD, DILLENIA, HPC, SA**

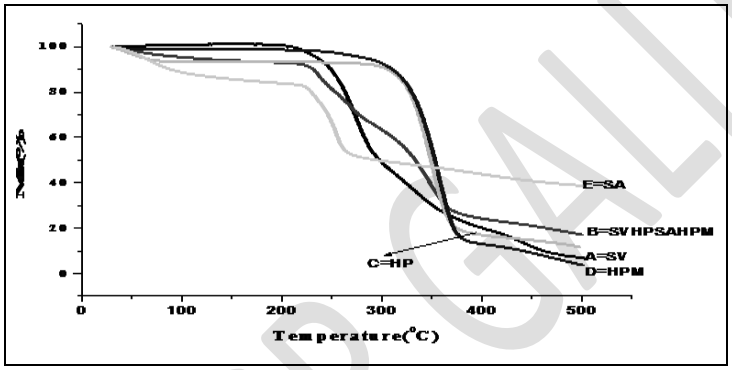


**FIG. 5: THERMOGRAMS OF SIMVASTATIN (SV), SVHPSAHPM, HPMC, HPC, SA**

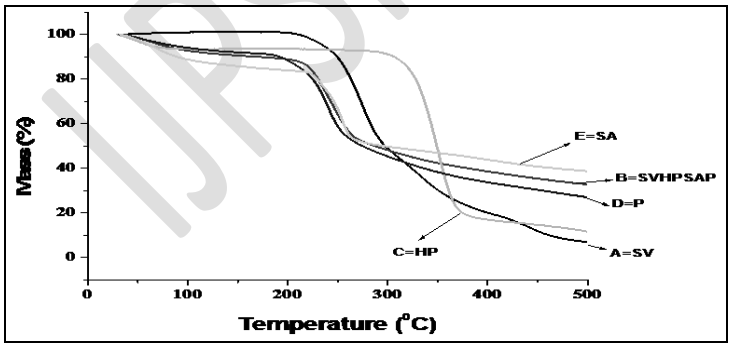


**FIG. 6: THERMOGRAMS OF SIMVASTATIN (SV), SVHPSAP, HPC, P, SA**

**CONCLUSION:** Thus it is confirmed from the above studies, that the drug Simvastatin (SV), shows weak interactions with HydroxyPropyl β-Cyclodextrin (HPC) but other polymers like Pectin, HPMC LV E-15, Dillenia, and Sodium Alginate has no role in any interactions with the pure drug SV. Thus, it is concluded that the drug Simvastatin (SV) can be formulated with all the above mentioned polymers in various drug delivery systems.

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