

Evaluation of Compatibility of Lamivudine with Tablet excipients and a novel synthesized polymer

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Abstract

This study reports compatibility of antiviral drug lamivudine with various selected excipients and a novel synthesized polymer, for the development of its controlled release formulation. Differential scanning calorimetry (DSC), Isothermal stress testing (IST) and Fourier transform infra-red (FT-IR) spectral analysis was performed to access the compatibility. The compatibility study was performed with various common excipients like spray dried lactose, poly vinyl pyrrolidine K-30, magnesium stearate, talc and a novel synthesized polymer cross-linked moth bean starch with lamivudine. The results confirmed that the tablet excipients were compatible with anti HIV drug lamivudine.

Key Words: Compatibility, Lamivudine, Excipients, DSC, FT-IR.

1. Introduction :

In the design of quality drug products, excipients and polymers play an important role. Excipients are the chemical substances which affect the functionality, stability and drug release behaviour. Excipients are selected in formulation development on the basis of its compatibility and functionality with the selected active pharmaceutical ingredient.

In recent years a number of techniques have been introduced for evaluation of drug-excipient compatibility. Differential scanning calorimetry (DSC) is one of the well established techniques in detection of incompatibility in drug/excipient [1&2]. DSC has now become first choice in pharmaceutical industry for compatibility study. (IST) involves storage of drug-excipient combinations with or without moisture at high temperature for a specific period of time to accelerate drug ageing and possible interaction. The samples are then visually observed for any type of change in physical appearance, and the

drug content determined quantitatively [3-5]. Fourier transform infra red (FT-IR) spectroscopy is also used to confirm any type of physical interaction with drug and excipient [6-9].

Lamivudine is an analogue of cytidine. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B (Fig.1). It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated [10].

The purpose of this study was to report the compatibility of lamivudine with common pharmaceutical excipients (spray dried lactose, polyvinyl pyrrolidine K-30, magnesium stearate and talc) and a novel synthesized cross-linked moth bean starch by DSC, IST and FT-IR.

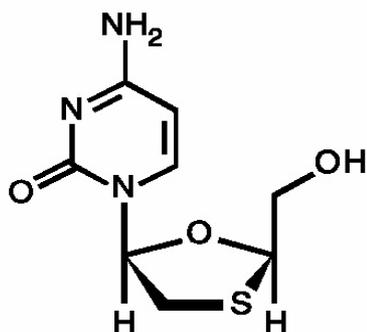


Figure 1: Chemical structure of Lamivudine.

2. Materials and methods

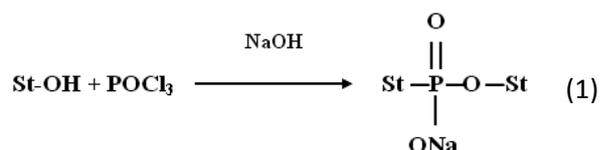
Lamivudine was kindly donated by Ranbaxy Limited, Paonta Sahib, Himachal Pradesh, India. Spray dried lactose (SDL) was kindly gifted from DMV Fonterra excipients, The Netherland. Magnesium stearate (MST), Talc and Polyvinyl pyrrolidone K-30 (PVP) was purchased from Loba Chemie, Mumbai, India. All other chemicals used were of A.R. grade. Double distilled water was used throughout the study.

2.1 Determination of drug purity

The purity of drug was determined by DSC, HPLC and UV-Visible spectrophotometer. The DSC (Perkin Elmer, USA) of drug lamivudine was done to get the endothermic peak (corresponding to its melting point). The HPLC (Waters, USA) of the drug was done as per the method described elsewhere [11]. The UV-Vis analysis (Pharmaspec, Shimadzu, Japan) of the drug was done in buffer solution (pH=6.8). The sample was scanned in the range of 200-400 nm to confirm its purity.

2.2 Synthesis of novel polymer

Cross-linking of starch was done with POCl_3 in alkali containing sodium hydroxide as described by Zheng *et al* [12]. The moth bean starch (50 g, dry basis) was dispersed in distilled water (200ml), and then starch slurry was adjusted to pH 9.0 with 0.5 N NaOH solutions. The cross-linking reagent POCl_3 was added drop wise in different concentrations (0.5-2.5% w/v). The starch dispersion was stirred for 1 h and stored for 12 h at room temperature for completion of the reaction. The starch suspension was adjusted to pH 6.5, by adding 1 N HCl which leads to termination of the reaction. Extensive washing was done to ensure the removal of un-reacted salt. After drying overnight at 40°C in a vacuum oven, the cross-linked starch was grounded and sieved (60 meshes).



Scheme 1: Cross-linking of starch with POCl_3

2.3 Compatibility study by Differential scanning calorimetry

A differential scanning calorimetry (JADE DSC, Perkin Elmer, USA) was used to study the thermal analysis of drug-excipient compatibility. Firstly, binary mixtures of lamivudine and excipients (in 1:1 mass/mass ratio). The drug-excipient mixture was scanned in the temperature range of 50-220°C under an atmosphere of nitrogen. The heating rate was 20°C/min and the obtained thermograms were observed for any type of interaction.

2.4 Isothermal stress testing [13&14]

In isothermal stress testing (IST), samples of drug and different excipients (Table-2) were weighed directly in 5 ml glass vials (n=3). Mixing was done on a cyclomixer for 3 min, with 10% (w/w) water in each of the vial. The glass vials, after teflon sealing, were stored at 50°C in hot air oven. Drug-excipient blends without added water and stored in refrigerator served as controls. The drug-excipient blends were periodically examined for any change in physical appearance. Samples were quantitatively analyzed using UV-Visible spectrophotometer (Pharmaspec 1700, Shimadzu, Japan) after 4 weeks of storage at above conditions.

2.5 Analysis of samples in Isothermal stress testing

The stored samples were quantitatively analyzed using UV-Visible spectrophotometer. The drug-excipients samples were diluted in phosphate buffer solution (pH =6.8). The samples were centrifuged, filtered and analysed at 270 nm in UV-Visible spectral analysis.

3. Results and discussion

The purity of drug was assessed by HPLC and the purity was confirmed by getting chromatogram with same retention time (shown in Fig-2). The UV-Visible spectrophotometer analysis of drug lamivudine showed maximum absorption at (λ_{max}) 270 nm which confirms its purity (Fig-3).

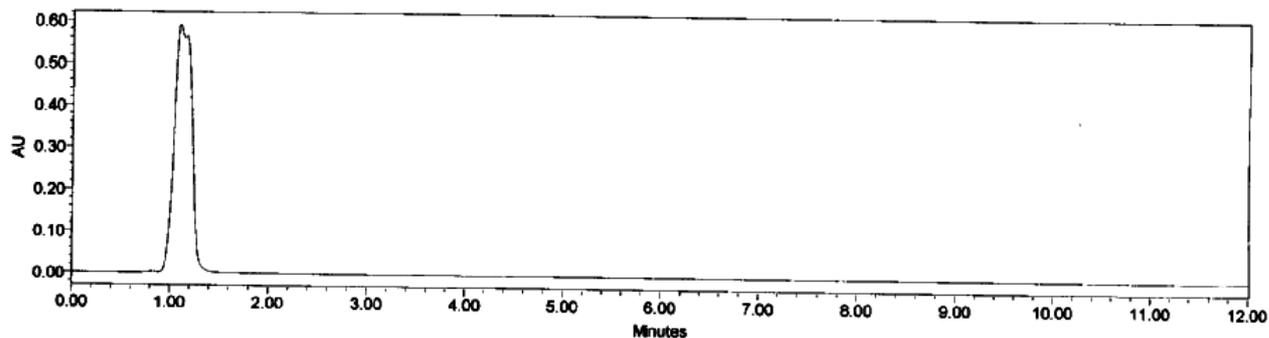


Figure 2 : HPLC chromatogram of pure lamivudine drug.

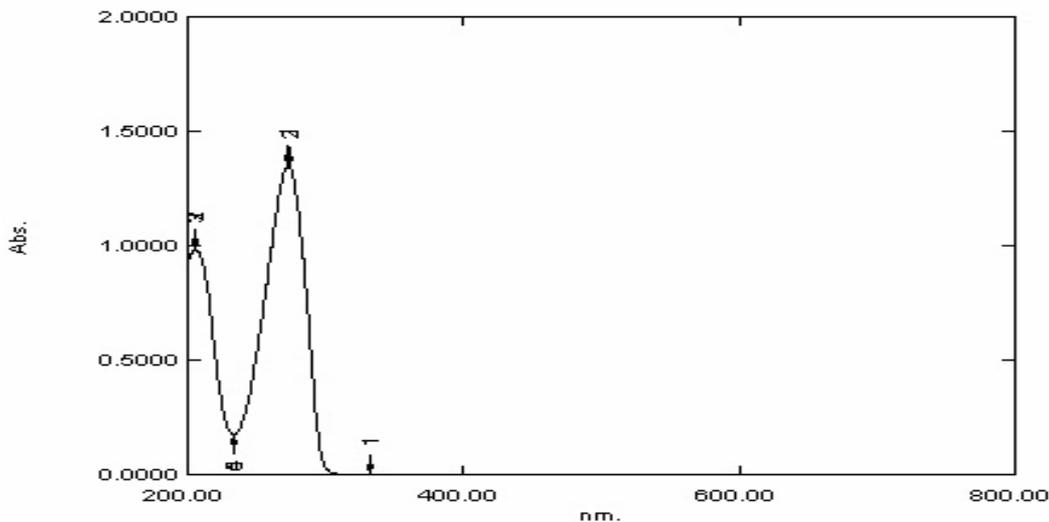


Figure 3: UV-Visible spectra of pure Lamivudine drug.

DSC thermograms of drug and drug-excipient mixtures are shown in Fig 4-9, and corresponding peak temperatures and enthalpy values (ΔH) of LAM with various excipient mixtures are summarized in Table-1. DSC curve of LAM showed a sharp endothermic peak at 182.73^oC corresponding to its melting point (Fig.4). The

endothermic peak of the drug was well retained in majority of cases. However, in some combinations there were slight changes in peak temperature and peak shape, which might be due to mixing of excipients with the drug as this reduces the purity of component in mixtures.

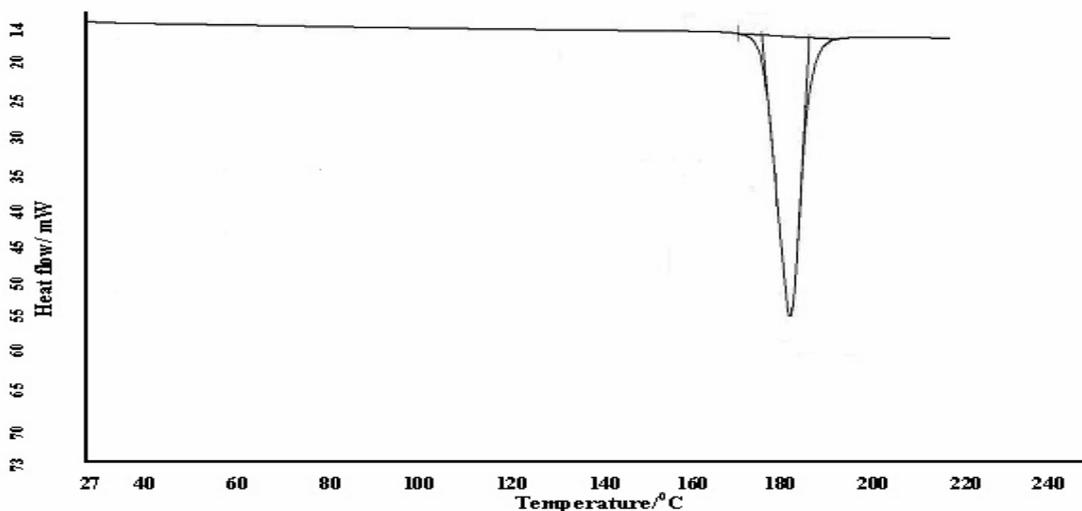


Figure 4 : DSC thermogram of pure Lamivudine drug.

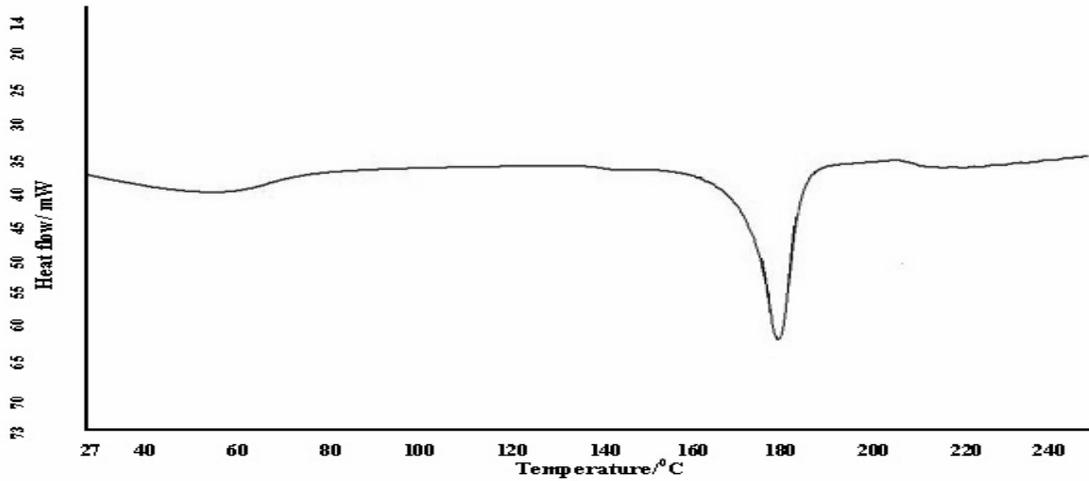


Figure 5: DSC thermogram of Lamivudine and Cross-linked moth bean starch (1:1).

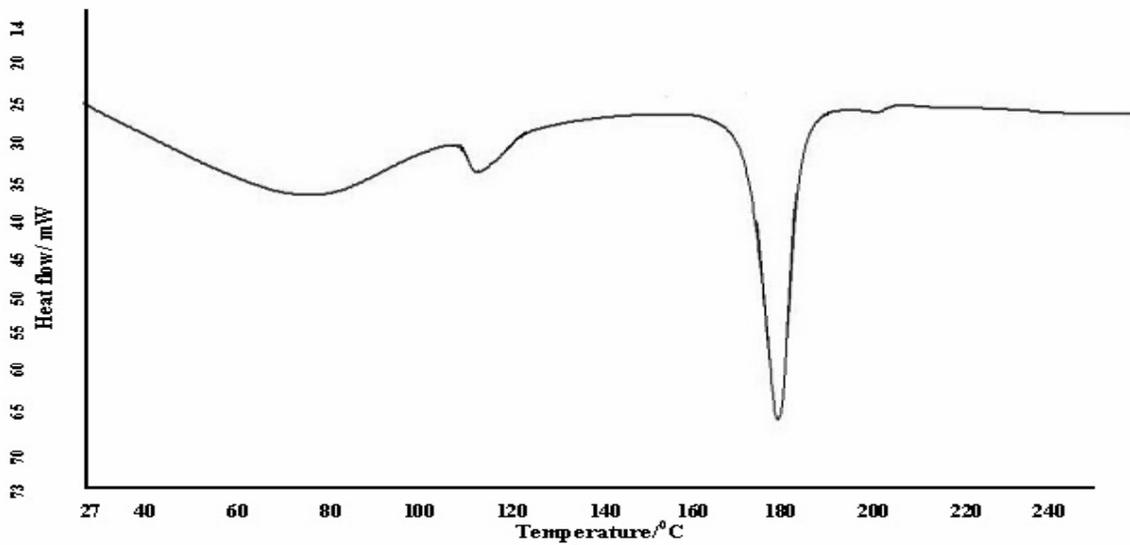


Figure 6: DSC thermogram of Lamivudine and PVP K-30 (1:1).

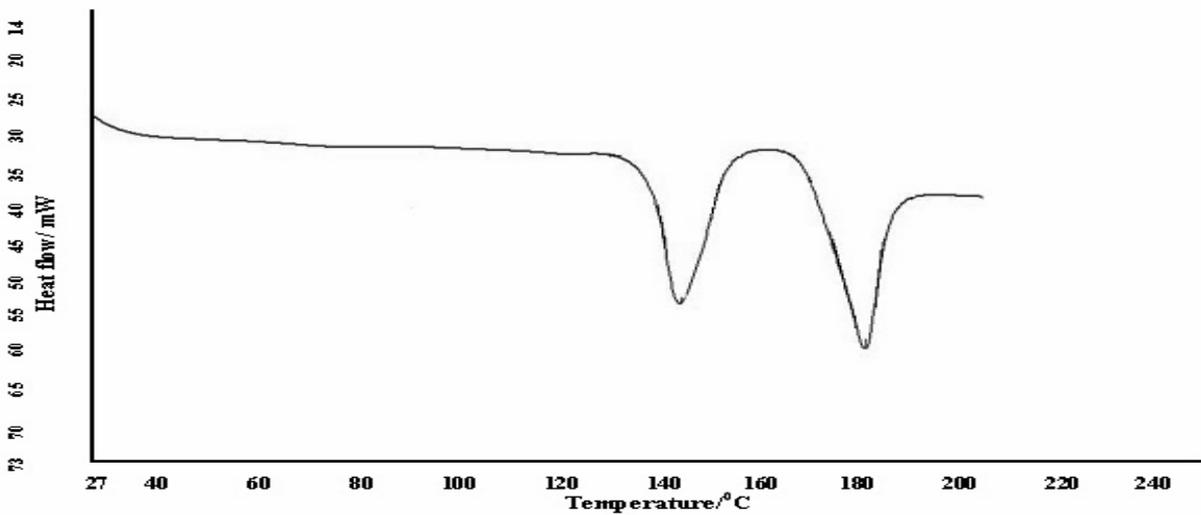


Figure 7: DSC thermogram of Lamivudine and Spray dried lactose (1:1).

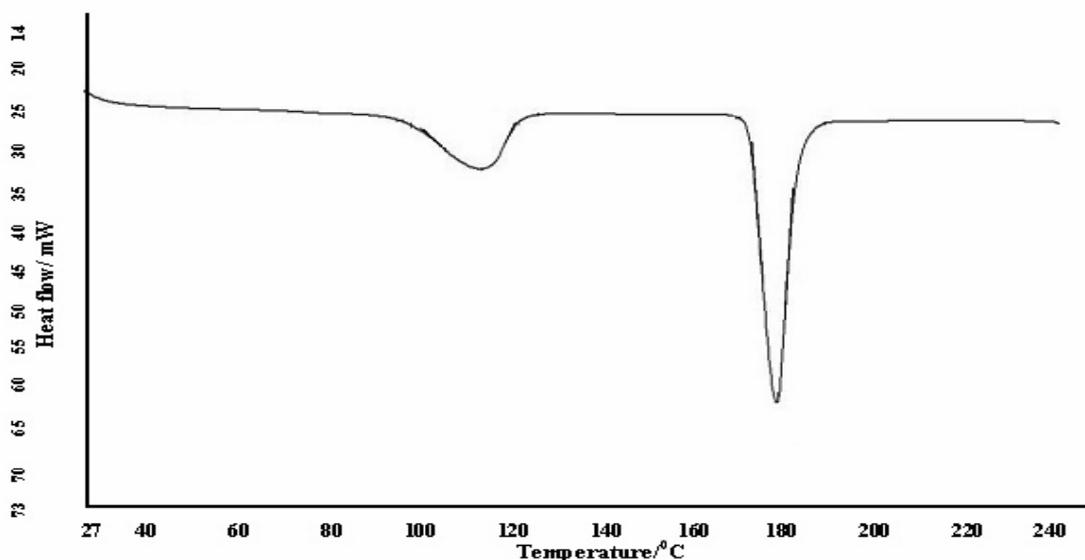


Figure 8: DSC thermogram of Lamivudine and Magnesium stearate (1:1).

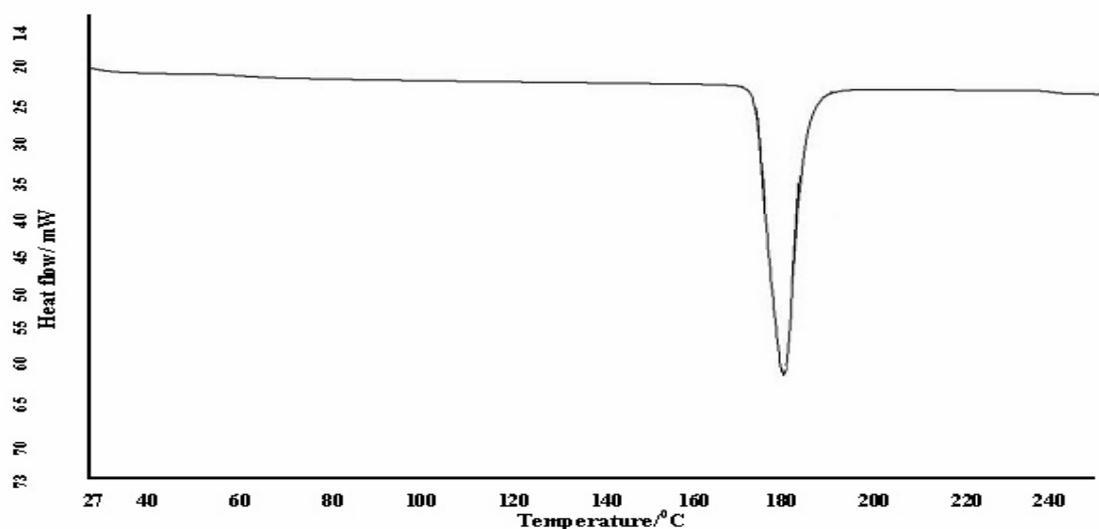


Figure 9: DSC thermogram of Lamivudine and Talc (1:1).

In the DSC thermogram of LAM+CLMBS, the endothermic peak of LAM was well retained in the mixture (Fig.5), with a slight change in the enthalpy value. The thermogram of spray dried lactose and drug combination showed an early peak at 148.18°C that is observed due to the bound water present in lactose. The endothermic peak of drug was well retained in the DSC curve of LAM+SDL mixture (Fig.6), from this it can be concluded that SDL is compatible with the drug lamivudine. The DSC curve of PVP K-30 shows that the melting endotherm of LAM was well preserved in the mixture and heat of enthalpy is nearly same to the parent drug, concluding its

suitability with LAM. One extra peak was observed at 82°C (Fig.7), which is of the adsorbed water present on PVP K-30. In the DSC thermogram of drug and magnesium stearate mixture (Fig.8), one peak at 116°C was observed that might be due to bound water present in magnesium stearate, while the peak of parent drug was well retained in the mixture, which confirming its suitability with the drug. In the DSC curve of Lam+ Talc mixture (Fig.9), no shifting was observed in the endothermic peak of the drug, while there is slight increase in the enthalpy value of the mixture that might be a solid-solid interaction rather than incompatibility.

To check its suitability the combination was further checked in isothermal stress testing.

Table 1: Corresponding peak temperatures and enthalpy values of lamivudine in various Drug-excipient mixtures-

Sample	Ratio (drug: excipient)	T _{onset} (°C)	T _{peak} (°C)	ΔH (Jg ⁻¹)
LAM	-----	177.40	182.73	74.54
LAM+CLMBS	(1:1)	174.14	180.39	58.56
LAM+ PVP K-30	(1:1)	174.32	180.09	72.43
LAM+ SDL	(1:1)	171.56	179.44	48.78
LAM+ Mag. Stearate	(1:1)	177.63	182.91	80.66
LAM+ Talc	(1:1)	178.64	183.32	98.38

Table 2: Results of UV Analysis of the samples, under Isothermal stress testing after 4 weeks of storage.

Sample	Ratio (Drug-excipient)	% Drug remaining ^a		Change in physical appearance
		control ^b sample	stressed ^c sample	
Lamivudine (LAM)	-----	101.12±3.2	99.97±3.1	No
LAM+ CLMBS	1:2	101.96±2.5	99.12±1.6	No
LAM+ SDL	1:2	102.51±2.1	102.34±0.7	No
LAM+PVP	1:1	103.67±2.2	101.87±1.1	No
LAM+ Mag. Stearate	1:1	101.45±1.5	100.12±2.2	No
LAM+ Talc	1:1	101.22±4.1	100.02±1.1	No

^aValues expressed as average ± standard deviation (n=3).

^bDrug excipient blends without added water and stored in refrigerator.

^c Drug excipient blends with 10% added water and stored at 50°C for 4 weeks.

In the isothermal stress testing, drug-excipient binary mixtures showed no change in physical appearance at ambient temperature. The blends remain physically stable and no discoloration, liquefaction or gas formation was observed during

storage. There is also no significant drug degradation was observed with any type of excipients. Table-2 showed % drug remaining at the end of the study at 50°C.

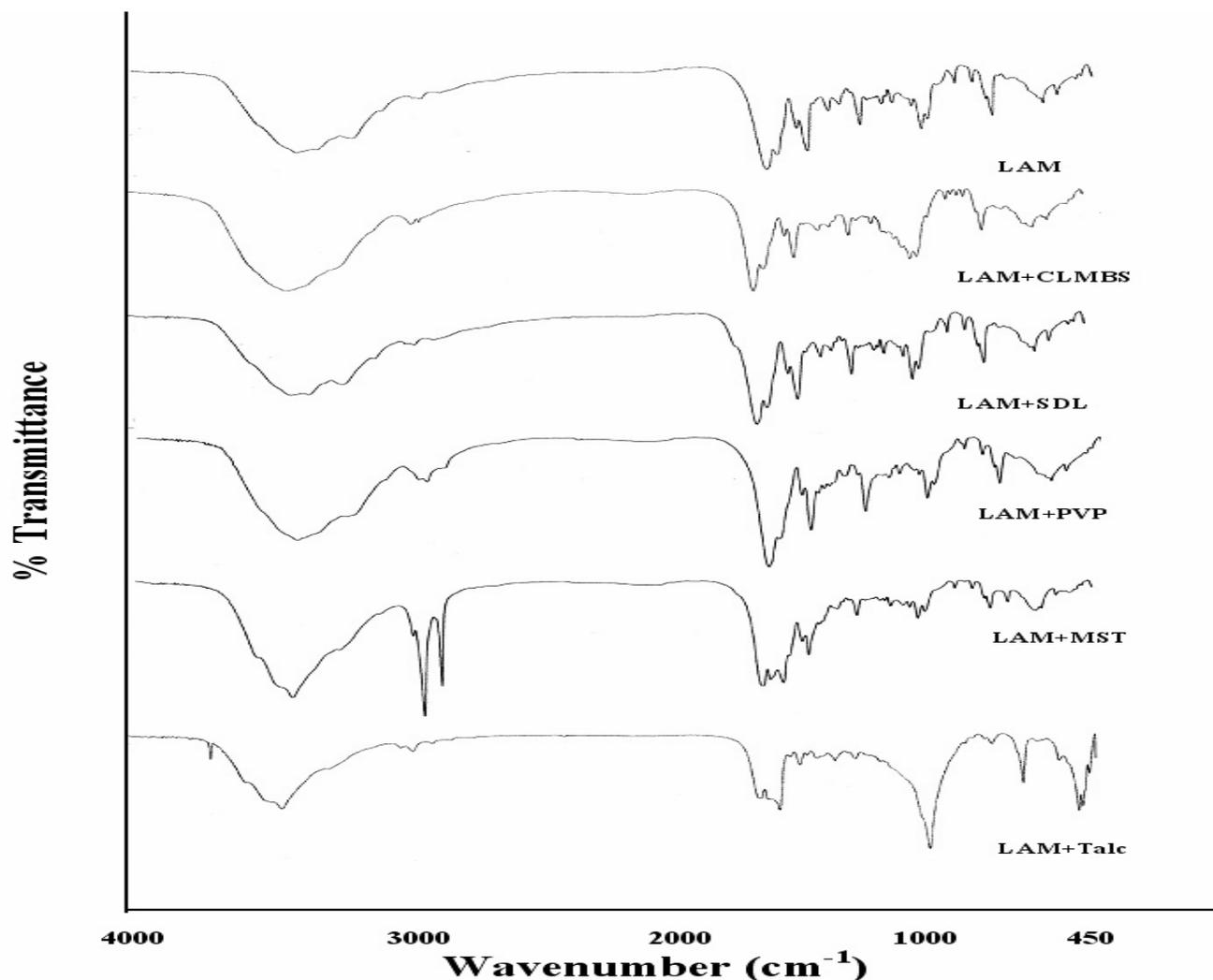


Figure 10 : Comparative FT-IR spectra of pure drug Lamivudine (LAM), Lamivudine + spray dried lactose (LAM+SDL), Lamivudine + polyvinyl pyrrolidone (LAM+PVP), Lamivudine+ magnesium stearate (LAM+MST), Lamivudine+Talc (LAM+Talc) and Lamivudine+ cross-linked moth bean starch (LAM+CLMBS).

Pure lamivudine showed the characteristic band peaks at 1651.12 cm^{-1} which corresponds to cysteine nucleus. A characteristic bands peak at 3407.58 cm^{-1} and 3198.77 cm^{-1} owing to amino and hydroxy group present in lamivudine. Peaks present at 1287.37 cm^{-1} and 1160.32 cm^{-1} owing to asymmetrical and symmetrical stretching of C-O-C group present in oxathiolane ring of lamivudine. All the binary mixture of drug and excipient (Fig.10) showed none type of physical interaction except with magnesium stearate. In FT-IR spectral diagram of drug-magnesium stearate there is introduction of absorption bands at 2955.18 cm^{-1} and 2850.32 cm^{-1} , which might be a type of physical interaction, but in thermal analysis (DSC and IST) there is no confirmation for the same.

4. Conclusion

Compatibility study in preformulation stage of formulation development is now become an essential step. The thermoanalysis provides information about the thermal stability and decomposition of drug and used excipients. The results demonstrated the suitability of drug lamivudine with various excipients like spray dried lactose, PVP K-30, magnesium stearate, talc and novel synthesized cross-linked moth bean starch. The DSC and IST showed none type of interaction in all drug-excipient combinations, while FT-IR showed slight physical interaction with magnesium stearate. But this interaction was not reconfirmed with DSC and IST, so magnesium stearate is compatible with lamivudine.

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