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Evaluation of compatibility of tablet excipients and novel synthesized polymer with lamivudine

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Abstract The present study describes compatibility of anti-HIV drug lamivudine with various selected excipients and a novel synthesized polymer, for the development of its controlled release formulation. Differential scanning calorimetry (DSC), isothermal stability study (ISS) and Fourier transform infrared (FT-IR) spectral analysis were performed to access the compatibility. The compatibility study was performed with various common excipients like spray dried lactose, polyvinyl pyrrolidine K-30, magnesium stearate, talc and a novel synthesized polymer cross-linked sago starch with lamivudine.

Keywords Lamivudine · Excipients · Cross-linked starch · DSC · FT-IR

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 [1–5]. DSC has now become first choice in pharmaceutical industry for compatibility study. Isothermal stability study (ISS) is also an indirect thermal method for study the compatibility, which 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 [6–8]. Fourier transform infrared (FT-IR) spectroscopy is also used to confirm any type of physical interaction with drug and excipient [9–12].

Lamivudine is an analogue of cytidine. It inhibits both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B. 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 [13] (Fig. 1).

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

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 Netherlands. Magnesium stearate (MST), talc and polyvinyl pyrrolidine K-30 (PVP) were purchased from

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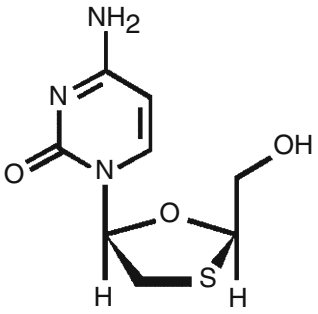


Fig. 1 Chemical structure of Lamivudine

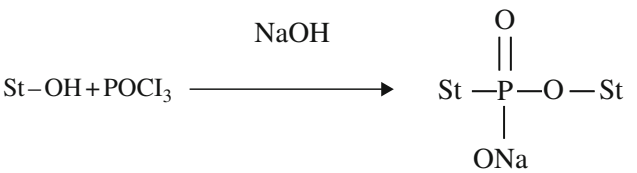
Loba Chemie, Mumbai, India. All other chemicals used were of A.R. grade. Double distilled water is used throughout the study.

Determination of drug purity

The drug purity was determined by DSC, HPLC and UV–Vis spectrophotometry. 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 [14]. 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 200–500 nm to confirm its purity.

Synthesis of novel polymer

Cross-linking of starch was done with $POCl_3$ in alkali containing sodium hydroxide as described by Zheng et al. [15]. The sago starch (50 g, dry basis) was dispersed in distilled water (200 mL), and then starch slurry was adjusted to pH 9.0 with 0.5 N NaOH solutions. The cross-linking reagent $POCl_3$ was added dropwise 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).



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Compatibility study by DSC

A DSC (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) were physically mixed and stored in an aluminium pan. 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 curves were observed for any type of interaction.

FT-IR study

FT-IR spectra were recorded on a Bruker spectrophotometer (Model no. 220, Germany) using KBr discs in the range of 4000–450 cm^{-1}. FT-IR analysis has been performed using sample of lamivudine with various excipients (SDL, PVP K-30, MST, talc and CLSS) at 1:1 mass/mass ratio.

Isothermal stability study [16, 17]

In isothermal stability study (ISS), samples of drug and different excipients (Table 1) were weighed directly in 5 mL glass vials ($n = 3$). After mixing on a cyclomixer for 3 min, 10% (w/w) water was added 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–Vis spectrophotometer (Pharmaspec 1700, Shimadzu, Japan) after 4 weeks of storage at above conditions.

Analysis of samples in ISS

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

Results and discussion

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

Table 1 Results of UV analysis of the samples, under isothermal stability study after 4 weeks of storage

Sample	Ratio Drug/excipient	% Drug remaining[a]		Change in physical appearance
		Control sample[b]	Stressed sample[c]	
Lamivudine/LAM	–	102.12 ± 2.2	101.23 ± 3.1	No
LAM + CLSS	1:2	99.96 ± 1.5	99.12 ± 1.6	No
LAM + SDL	1:2	102.11 ± 1.1	101.34 ± 0.7	No
LAM + PVP	1:1	101.67 ± 2.2	99.87 ± 1.1	No
LAM + Mag. stearate	1:1	102.45 ± 0.5	100.12 ± 2.2	No
LAM + Talc	1:1	99.22 ± 3.1	99.12 ± 2.1	No

[a] Values expressed as average ± standard deviation

[b] Drug 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

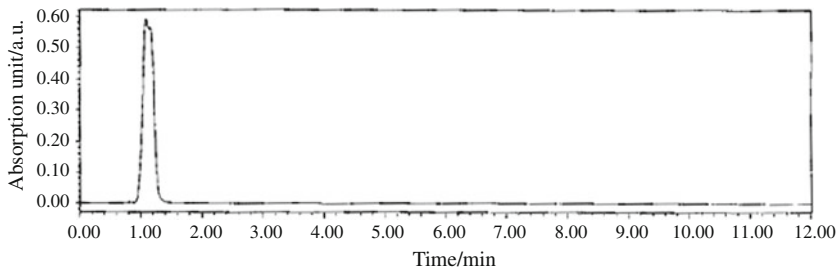

Fig. 2 HPLC chromatogram of pure lamivudine drug

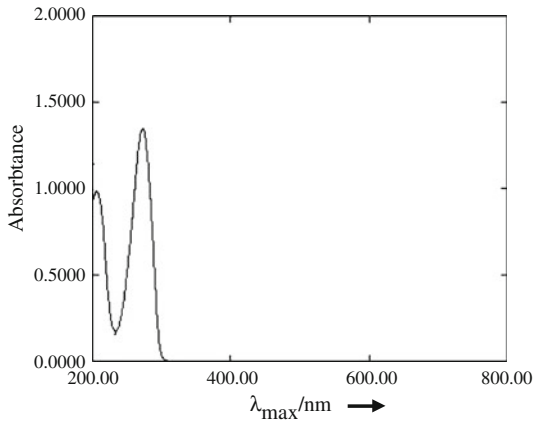

Fig. 3 UV–Vis spectra of pure lamivudine drug

The DSC curve of drug lamivudine showed a sharp endothermic peak at 182.73 °C (ΔH = 74.54 J/g) with a melting temperature (T_{onset} = 177.39 °C) (Fig. 4). In the DSC curves of binary mixtures (Fig. 5), they exhibited neither the shifting nor the disappearance of peaks. The retention of original peak suggested that the drug was physically stable in combinations with all the selected excipients. The novel synthesized cross-linked sago starch also shows no type of interaction with the drug (Fig. 6).

In the isothermal stability studies, 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 1 showed % drug remaining at the end of the study at 50 °C.

Pure lamivudine showed the characteristic band peaks at 1651.12 cm^{-1} which corresponds to cystedine nucleus. A characteristic bands peak at 3407.58 and 3198.77 cm^{-1} owing to amino and hydroxy group present in lamivudine. Peaks present at 1287.37 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. 7) showed none type of physical interaction except with magnesium stearate. In the FT-IR spectral diagram of drug–magnesium stearate, there is introduction of absorption bands at 2955.18 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.

Conclusions

Compatibility study in pre-formulation 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

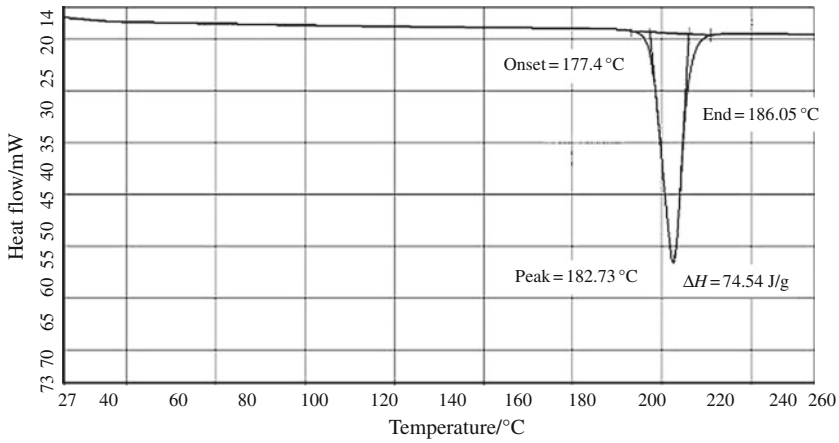

Fig. 4 DSC curve of pure lamivudine drug

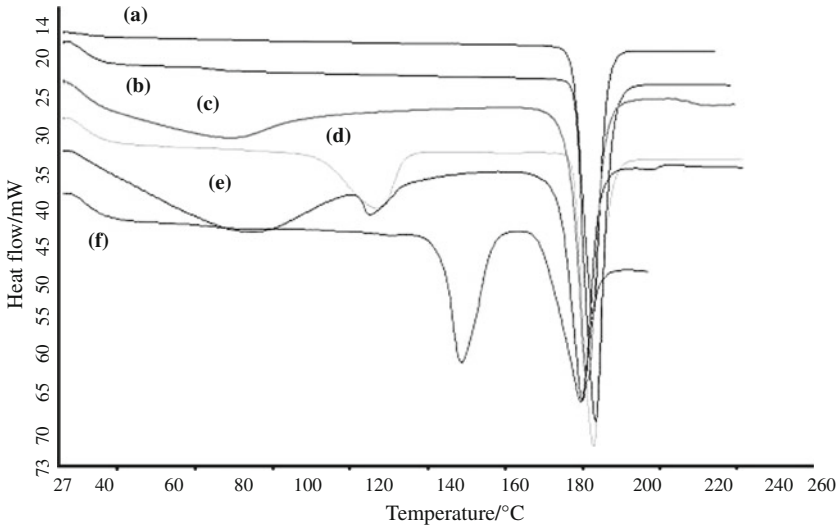

Fig. 5 Comparative DSC curves of pure drug lamivudine (*a*), lamivudine + talc (*b*), lamivudine + cross-linked sago starch (*c*), lamivudine + magnesium stearate (*d*), lamivudine + polyvinyl pyrrolidine (*e*) and lamivudine + spray dried lactose (*f*)

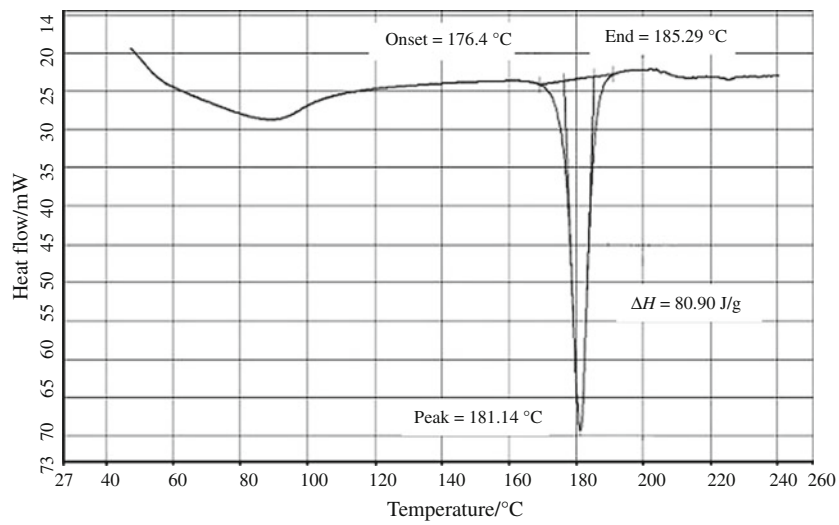

Fig. 6 DSC curve of pure drug lamivudine with cross-linked sago starch

with various excipients like spray dried lactose, PVP K-30, magnesium stearate, talc and novel synthesized cross-linked sago starch. The DSC and ISS showed none type of interaction in all drug–excipient combinations, while FT-IR showed only one interaction with magnesium stearate. But this interaction was not reconfirmed with DSC

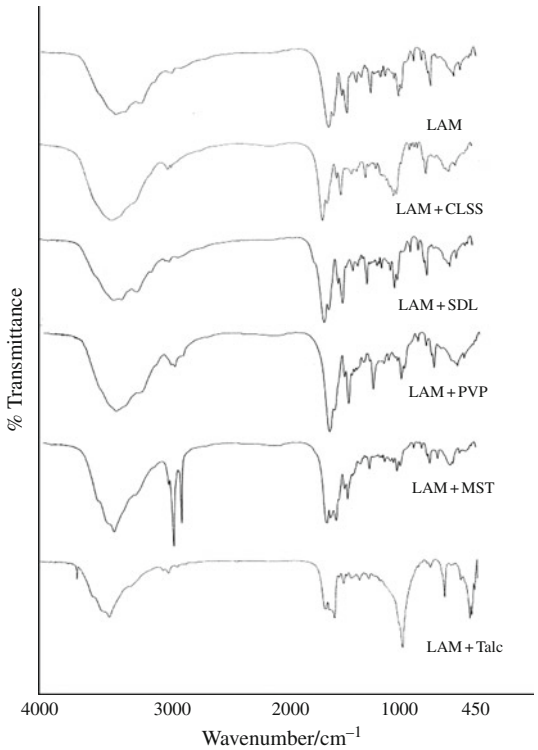

Fig. 7 Comparative FT-IR spectra of pure drug lamivudine (LAM), lamivudine + spray dried lactose (LAM + SDL), lamivudine + polyvinyl pyrrolidine (LAM + PVP), lamivudine + magnesium stearate (LAM + MST), lamivudine + talc (LAM + Talc) and lamivudine + cross-linked sago starch (LAM + CLSS)

and ISS, so we concluded that magnesium stearate is compatible with lamivudine.

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