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R E S E A R C H A R T I C L E

Characterization of Pure Drug and Drug-Excipient Compatibility Studies of Tadalafil

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A B S T R A C T

Studies of drug-excipient compatibility represent an important phase in the preformulation stage of the development of all dosage forms. Thus any material used in the pharmaceutical drug product will be required to be manufactured under appropriate Good Manufacturing Practices (GMP) and supplied under Good Distribution Practices (GDP). The exact definition of GMP or GDP will depend on the material in question (e.g. excipient, active pharmaceutical ingredient, packaging etc). The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutical properties and stability of the dosage form. Appearance of single DSC endothermic peak and in the FT-IR results, changes observed in the vibrational frequencies associated with amide, acid and chloride groups of the reactants prove to be effective diagnostic features to confirm the formation of molecular complexes. Different Thermal and Non-thermal method of analysis is also discussed. Once the type of interaction is determined we can take further steps to improve the stability of drug and dosage form**.** Drug excipient interaction studies carried out which shows there was no chemical interaction between the drug and the polymers.

Keywords: Excipient, Active Pharmaceutical Ingredient, Excipients, GMP, FT-IR

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Pharmaceutical dosage form is a combination of active pharmaceutical ingredients (API) and excipients [1,2]. Excipients are included in dosage forms to aid manufacture, administration or absorption [3,4]. The ideal excipients must be able to fulfill the important functions i.e. dose, stability and release of API from the formulation. 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 [5,6]. Exicipients are not exquisitely pure [7,8]. In common with virtually all materials of minerals, synthetic, semi-synthetic or natural origin manufacture involves using starting materials, reagents and solvents. Careful selection of the excipients are required for a robust and effective formulation of dosage forms that make administration easier, improve patient compliance, promote release and bioavailability of the drug and increase its shelf life [9,10]. Thus, compatibility screening of an API with excipients or other active ingredients is recognized as one of the mandatory factors and is at the fore front of drug product science and technology research[11]. During preformulation stage solid state properties of Active pharmaceutical ingredient (API) and the conditions under which the candidate drug should be formulated are examined [12]. Key issues include investigation of polymorphism, the ability of a compound to exist in more than one crystalline form, and careful selection of the solid form for further development [13,14]. Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product quality, facilitate the implementation of new technologies, facilitate policy development and regulatory decision making [15]. In the present study, was characterized by thermal (DSC), crystallographic (X-RPD) spectroscopic (FT-IR). Drug excipient interactions studied by spectroscopic (FT-IR) evaluation.

2. Materials and Methods

Characterization of pure drug

The drugs for the research work were obtained from reliable sources. However, the drugs were authenticated by identifying their functional groups/bonds using Fourier Transform Infrared (FTIR) Spectrophotometer, X-ray powder diffraction (XRPD), Differential scanning calorimetry (DSC) and Thermogravimetric Analysis (TGA) [16].

Drug excipient compatibility study

Unfavourable combinations of drug excipient may result in interaction, which leads to physical instability or chemical instability. Physical instability refers to changes in the characteristics of a drug that do not involve chemical bond formation or breakage in the drug structure, which can be identified by changes in the organoleptic parameters such as appearance, form etc. Chemical instability refers to changes in the chemical structure of the drug molecule resulting in drug degradation, reduced drug content and formation of other molecule such as degradation products. Both physical and chemical instability may cause safety concerns. Hence, a thorough drug drug / drug excipient compatibility study is mandatory [17].

Isothermal stress testing (IST) (Liltorp okay *et al*., 2011; Moorthi C *et al*., 2013): IST is commonly used method to assess the compatibility of drug drug/ drug excipient, which involves the storage of samples with or without moisture at an elevated temperature. Subsequently, (a) organoleptic parameters were assessed to determine the physical instability and (b) structural changes using FTIR [18,19,20]

Sample preparation

Pure drugs and excipients were weighed as per table 1. Each mixture was grounded thoroughly using a clean glass mortar to form a blend. Individual drugs, individual excipients and prepared blends were transferred in to an appropriately labelled glass vials. Subsequently, 10µL of ultra pure water (Milli-Q Academic, Milli- Pore) was added to each vial and mixed using a glass capillary, which was left inside the vial after mixing. Each vial was sealed properly and placed in hot air oven (T26/HAO-L, Technico) at 50°C for 4 weeks [21,22]

3. Results and Discussion

Table 1: Pure drugs and excipients

Sample	Contents	Ratio
1	Tadalafil	NA
2	Tadalafil + Mannitol Spray dried	1:1
3	Tadalafil + Microcrystalline Cellulose spray dried PH 102	1:1
4	Tadalafil + Pregelatinised starch	1:1
5	Tadalafil + Sucralose	1:1
6	Tadalafil + Polacrillin Potassium	1:1
7	Tadalafil + Croscarmellose sodium	1:1
8	Tadalafil + Sodium starch glycolate	1:1
9	Tadalafil + Crospovidone XL10	1:1
10	Tadalafil + Colloidal Anhydrous Silica	1:1
11	Tadalafil + Magnesium stearate	1:1
12	Tadalafil + Cherry flavour	1:1
13	Tadalafil + banana flavour	1:1

Assessment of physical instability

To identify the physical instability, organoleptic parameters such as colour and texture were observed initially and documented for all the samples. The colour and texture of each sample were observed visually at the end of 1st, 2nd, 3rd and 4th week and compared with initial colour and texture.

Assessment of chemical instability

At the end of 4th week, samples were used to record the DSC spectrum and analyzed.

Differential scanning calorimetry (DSC)

Samples of pure Tadalafil and its physical mixtures with different excipients were hermetically sealed in flat bottomed aluminium pans and heated in the DSC instrument (Shimadzu, Japan) in an atmosphere of nitrogen to eliminate the oxidative and pyrolytic effects. The heating rate was 5^0C/min in a temperature range of 25–300^{0}C. The DSC thermo grams were recorded.

Characterization of Pure Drug

The drug Tadalafil for the research work were obtained from reliable sources. However, the drug was scanned using FTIR, XRPD, DSC and TGA as per procedure mentioned. Obtained spectrum is comparable with standard spectrum, so the obtained drug from the commercial sources was genuine.

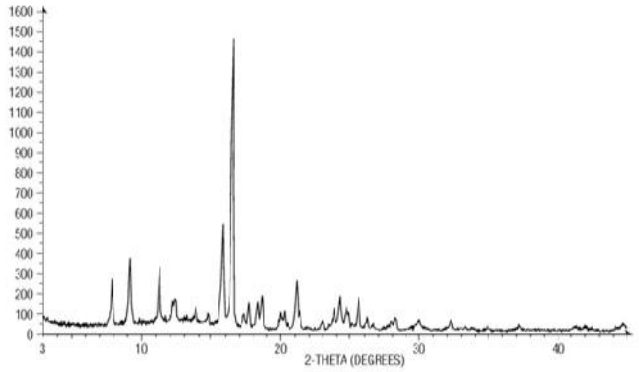

Figure 1: FTIR Spectrum of TadalafilFig.6.2: XRPD Spectrum of Tadalafil

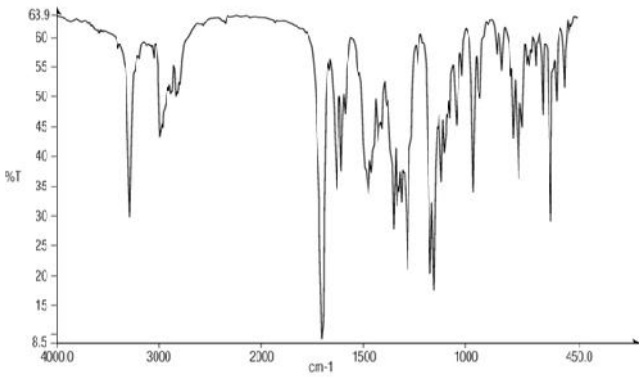

Figure 2: XRPD Spectrum of Tadalafil

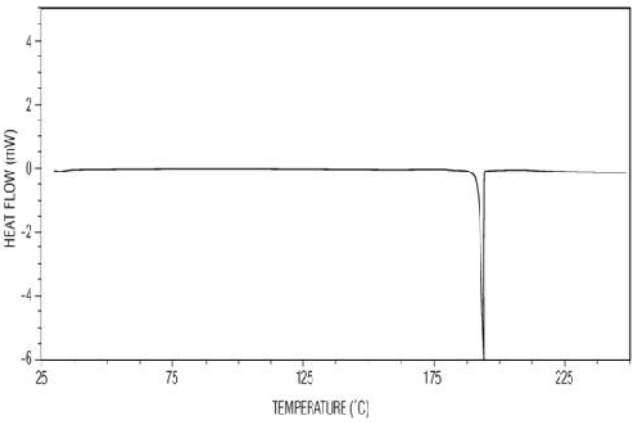

Figure 3: DSC Thermogram of Tadalafil

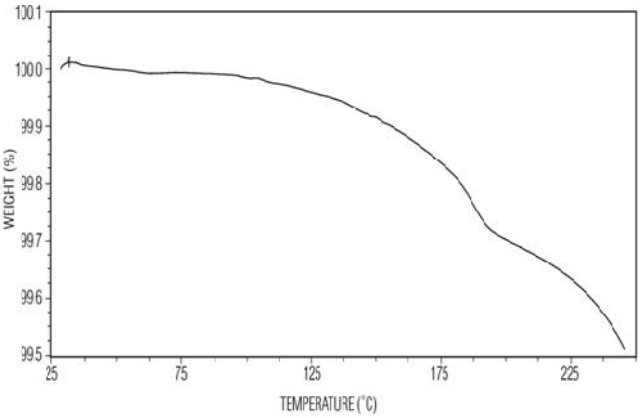

Figure 4: TGA Thermogram of Tadalafil

Drug Excipient Compatibility Study

Un-favorable combinations of drug drug/drug excipients may result in interaction, which leads to physical instability or chemical instability. Both physically and chemical instability may cause safety concerns. Hence, a thorough drug drug/drug excipient compatibility study was performed as per procedure mentioned. Compatibility studies of tadalafil with excipients:

The objective of the study was to determine the compatibility of tadalafil and excipients. Excipient-Drug substance compatibility was assessed through Physical appearance of binary mixtures of excipient and drug substance at different ratio in the solid state. Samples were stored at 25°C/60% RH and 40°C/75%RH in a closed container for one month. Common excipients functioning as Diluent, Binder, Disintegrate, Sweetener, Buffering agent, and Lubricant were evaluated in the excipients compatibility study. The results are summarized in the following table.

6.3 Assessment of chemical instability by Differential Scanning Calorimetry (DSC): The DSC thermograms corresponding to pure drug and drug excipient mixture were performed as per the procedure, shown in Fig.5. The DSC analysis of drug tadalafil alone elicited an endothermic peak at 190°C, which is very close to its reported melting point 192°C, where as mixture of tadalafil with super disintegrate approach additives, Effervescence approach additives and Sublimation approach additives exhibited endothermic peak at 194°C, 189°C, 188°C respectively.

There was no significant changes in terms of peak shifting, appearance or disappearance of peaks were noted with the drugs, excipient and mixtures. Thus, it was thought to indicate the absence of chemical interaction between the selected drugs, and excipients. Absence of incompatibility between the selected drugs and excipients were also confirmed by the DSC pattern matching approach. DSC spectra are given in Fig. 5 respectively.

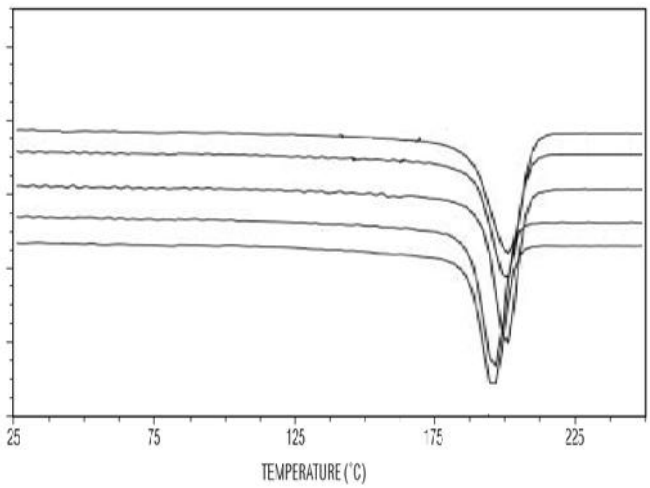

Fig.5: DSC graph of Tadalafil with Mannitol (a), microcrystalline cellulose (b), Pregelatinized starch (c), sucralose (d) and polacrillin potassium (e).

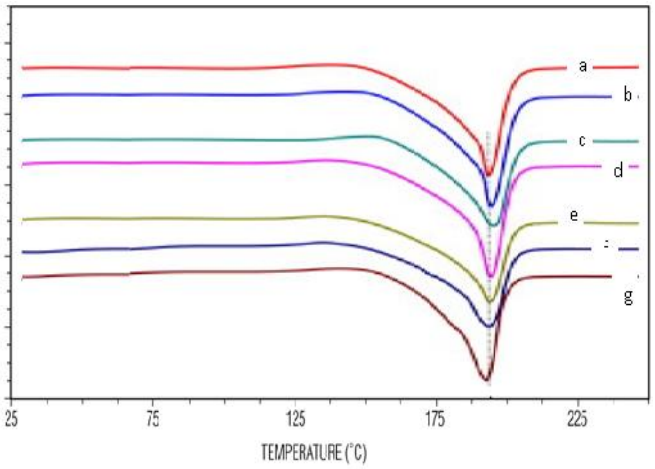

Fig. 6: DSC graph of Tadalafil with croscarmellose sodium (a), sodium starch glycolate (b), Crospovidone XL10 (c), Colloidal anhydrous silica (d), Magnesium stearate (e), cherry flavor (f) and banana flavor (g).

4. Conclusion

Drug-excipient interactions/incompatibilities are major concerns in formulation development. Selection of the proper excipient during preformulation studies is of prime importance. 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, or the unheralded presence of a residue in one of the excipients. Many such issues concern low levels of novel entities formed by drug– excipient interactions that pose questions concerning safety or tolerance. Drug-excipient interactions may take a long time to be manifested in conventional stability testing programmes, and are not always predicted by stress and pre-formulation studies. On the basis of the results obtained from DSC, FTIR, TGA and XRPD studies, all the excipients used were found to be compatible with the drug and can be used for the development of formulation.

Table 2: Tadalafil + Excipients compatibility study (binary mixture)

S.NO.	MIXTURE	Ratio	TESTS	INITIAL	40°C/75%RH	25°C/60%RH
					1 M	1 M
1	Tadalafil	NA	Appearance	White - off white powder	White - off white powder	White - off white powder
2	Tadalafil + Mannitol Spray dried	1:1	Appearance	White- off white powder	White - off white powder	White - off white powder
3	Tadalafil + Microcrystalline Cellulose spray dried PH 102	1:1	Appearance	White- off white powder	White - off white powder	White - off white powder
4	Tadalafil + Pregelatinised starch	1:1	Appearance	White- off white powder	White - off white powder	White - off white powder
5	Tadalafil + Sucralose	1:1	Appearance	White - off white powder	White - off white powder	White - off white powder
6	Tadalafil + Polacrillin Potassium	1:1	Appearance	White - off white powder	White - off white powder	White- off white powder
7	Tadalafil + Croscarmellose sodium	1:1	Appearance	White - off white powder	White - off white powder	White- off white powder
8	Tadalafil + Sodium starch glycolate	1:1	Appearance	White - off white powder	White - off white powder	White- off white powder
9	Tadalafil + Crospovidone XL10	1:1	Appearance	White - off white powder	White - off white powder	White- off white powder
10	Tadalafil + Colloidal Anhydrous Silica	1:1	Appearance	White - off white powder	White - off white powder	White- off white powder
11	Tadalafil + Magnesium stearate	1:1	Appearance	White - off white powder	White - off white powder	White- off white powder

12	Tadalafil + cherry flavour	1:1	Appearance	White - off white powder	White - off white powder	White- off white powder
13	Tadalafil + banana flavor	1:1	Appearance	White - off white powder	White - off white powder	White- off white powder

Based on the above data, it was concluded that the excipients used in the study are compatible with tadalafil as there was no change in appearance and no loss in assay in any of the mixtures at 40°C/75% RH and 25°C/60 % RH in one month period.

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