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Drug-Excipient Compatibility Studies In Binary Mixtures of Tadalafil by Using DSC, TGA and FTIR

İkili Tadalafil Karışımlarında DSC, TGA ve FTIR Kullanılarak İlaç-Yardımcı Madde Geçimlilik Çalışmaları

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ABSTRACT

Objective: During drug preformulation studies, thermal analysis and spectroscopic techniques are used to detect physical or chemical incompatibilities between the active compound and the excipients in the formulation, and to demonstrate the safety and/or efficacy of the final product. It has revolutionized erectile dysfunction with the development of a selective cyclic guanosine monophosphate-specific PDE-5 inhibitors. Tadalafil is one of these inhibitors. Excipients are included in dosage forms to assist in manufacture, absorption or application. Although considered to be pharmacologically inert, the drug active compound may impair effectiveness.

Material and Method: DSC, TGA, and FTIR, were used in the work. Ascorbic acid, butylated hydroxyanisole, calcium phosphate dibasic, cellulose, magnesium stearate, mannitol, sodium carboxymethyl cellulose, sucrose, talc, starch, primojel, and citric acid exhibit interaction with Tadalafil. Binary mixtures of drug:excipient have been analyzed.

Results: Based on spectroscopic and thermal results; Tadalafil is incompatible with magnesium stearate, mannitol, sucrose, and ascorbic acid**.**

Conclusion: Studies to investigate drug-excipient compatibility are an important step in drug development studies. Thermal and spectroscopic techniques are widely used in such studies.

Keywords: Tadalafil, Compatibility, Excipient; Fourier Transform Infrared Spectroscopy, *Differential Scanning Calorimetry*

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ÖZ

Amaç: İlaç ön formülasyon çalışmaları sırasında, formülasyondaki aktif bileşik ile yardımcı maddeler arasındaki fiziksel veya kimyasal geçimliliklerini tespit etmek ve nihai ürünün güvenilirliğini ve/veya etkinliğini göstermek için, uygun bir formülasyon eldesinde termal analiz ve spektroskopik teknikler kullanılır. Erektil disfonksiyonda, seçici bir siklik guanozin monofosfata özgü fosfodiesteraz tip 5 inhibitörlerinin geliştirilmesi ile devrim yaratmıştır. Tadalafil de bu inhibitörlerden bir tanesidir. Yardımcı maddeler, üretim, emilim veya uygulamaya yardımcı olmak için dozaj formlarına dahil edilmiştir. Farmakolojik olarak inert olduğu düşünülse de, ilaç aktif bileşiği etkinliği bozabilir.

Gereç ve Yöntem: Çalışmada DSC, TGA ve FTIR sistemleri kullanılmıştır. Askorbik asit, butile hidroksianisol, kalsiyum fosfat dibazik, selüloz, magnezyum stearat, mannitol, sodyum karboksimetil selüloz, sukroz, talk, nişasta, primojel ve sitrik asidin Tadalafil ile etkileşimi incelenmiştir. İkili ilaç karışımları: eksipiyan analiz edilmiştir.

Sonuçlar: Spektroskopik ve termal sonuçlara göre; Tadalafil magnezyum stearat, mannitol, sukroz ve askorbik asit ile geçimsizdir.

Sonuç: İlaç-eksipiyan uyumluluğunu araştıran çalışmalar, ilaç geliştirme çalışmalarında önemli bir adımdır. Bu tür çalışmalarda termal ve spektroskopik teknikler yaygın olarak kullanılmaktadır.

Anahtar Kelimeler: Tadalafil, Geçimlilik, Yardımcı madde, Fourier Dönüşümü Kızılötesi Spektroskopisi, Diferansiyel tarama kalorimetrisi

1.Introduction

Pulmonary arterial hypertension (PAH) is a disease involving a proliferative vasculopathy of various small pulmonary vascular arterioles of different etiologies, but also with a similar clinical presentation and, in most cases, responding to similar medical treatment. Currently, various drugs and prostanoids for symptom relief, endothelin receptor antagonists (ERA), and phosphodiesterase-5 (PDE-5) inhibitors are used as pulmonary arterial standards in the treatment of hypertension and erectile dysfunction [1-11]. Tadalafil is the newest of the three PDE5 inhibitors available. Similar effect to Sildenafil and Vardenafil in terms of mechanism of action, but differing primarily in longer duration of action and half-life [12]. The chemical structures of Tadalafil is given in Figure 1.

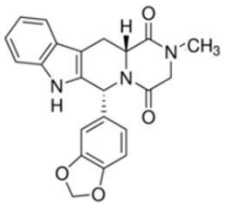

Figure 1: The chemical structure of Tadalafil

The safety, effectiveness, quality and stability of the drug formulation are the main topics of the new drug development process. The stability of a dosage form with these properties is the result of a thorough study of the physico-chemical properties of the active pharmaceutical ingredient (API) as well as all other ingredients (eg excipients, production aids, packaging) [13]. Drug-excipient compatibility studies maximize the stability of a dosage form. In addition, it is important in the discovery and development of new drugs. It helps in formulating the dosage form, determining its stability and maximizing it. Both physical and chemical instability can cause safety concerns on the drug. Negative interactions between drug and excipient result in chemical instability of the drug, change in the chemical structure of the drug molecule, degradation of the drug and decrease in drug content, and formation of other molecules such as degradation products [14].

Spectroscopic and thermal techniques are frequently used for incompatibility studies between drugs and excipients [15-25]. Spectroscopic techniques are sensitive to the structure, functional groups and environment of organic compounds. These techniques are used to determine the solid state behavior and formulations of APIs. In addition, it is also used in scanning potential intermolecular interactions and compatibility between components based on vibrational changes. Thermal analysis techniques are critical in compatibility screening studies. It is widely used for rapid detection and assessment of physicochemical mismatch. XRD is a direct measurement of a material's crystalline form, with the typical output being a plot of intensity versus diffraction angle [26]. Different excipient mixtures are used in drugs containing tadalafil (lactose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, microcrystalline cellulose, sodium lauryl sulfate, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, yellow iron oxide, macrogol/PEG 4000, hypromellose, triacetin, talc, sodium lauryl sulfate, polyvinyl alcohol, lecithin, etc.).

In the present study, the possible interactions between Tadalafil and excipients (ascorbic acid, butylated hydroxyanisole, calcium phosphate dibasic, cellulose, magnesium stearate, mannitol, sodium carboxymethyl cellulose, sucrose, talc, starch, primojel, citric acid) have been evaluated. Ascorbic acid is a powdered compound with preservative properties, which is considered safe for oral administration as an inactivated excipient. Its melting point is 190ºC. Calcium phosphate dibasic is apharmaceutical excipient that contains Calcium ions (Ca^{2+}) together with phosphate anions. It has a white powder structure with a melting point of 109ºC.

Polymers are macromolecular compounds. They make up a broad and diverse group of substances, including natural polymers, synthetic polymers, semi-synthetic polymers, and fermentation products. These compounds are frequently used in drug formulations due to their excellent binding properties in the dry state. Polymers are macromolecular compounds. They make up a broad and diverse group of substances, including synthetic polymers, semi-synthetic polymers, natural polymers, and fermentation products. These compounds are frequently used in drug formulations due to their excellent binding properties. Polymers are macromolecular compounds. They make up a broad and diverse group of substances, including synthetic polymers, semi-synthetic polymers, natural polymers, and fermentation products. These compounds are frequently used in drug formulations due to their excellent binding properties. Carboxymethylcellulose sodium and cellulose are excipients in the form of white powder. While the melting point of Carboxymethylcellulose sodium is 274ºC, this value is in the range of 260-270ºC for Cellulose. Butylated hydroxytoluene, commonly known as BHT, is an organic compound used as an antioxidant in the pharmaceutical industry. BHT is a substituted derivative of phenol. BHT helps to prevent the formation of free radicals and the oxidation step. It has a powder structure with a melting point in the range of 58-70ºC. Magnesium Stearate ($Mg(C_{18}H_{35}0_2)_2$ or Magnesium Octadecanoate) is a mixture of magnesium salts of fatty acids, mainly palmitic and stearic acid. It is one of the most commonly used excipients. It is a solid and white powder. It is an FDA-approved inactive ingredient commonly used as a lubricant and release agent in pharmaceutical manufacturing. Its melting point is 359.4ºC [27]. Sucrose is a sugar from the monosaccharide group. It is a compound that is used as a preservative especially during the lyophilization of drugs, exists in crystal form and has a melting point of 186ºC [28]. Mannitol, commonly used in pharmaceutical formulations, is a sugar alcohol. It is one of the most common excipients in freeze-dried injectable products and is used as a bulking agent. It is also used as a sweeting agent, diluent and tonicity agent. It has a melting point of 165ºC [29]. Talc is a naturally sourced mineral extracted from the soil, consisting of magnesium, silicon, oxygen and hydrogen. It is an aqueous magnesium silicate with the chemical formula $Mg_3Si_4O_{10}(OH)_2$. It is used to retain moisture, prevent clumping and facilitate the use of the product.

The aim of this paper is to assess the stability of Tadalafil when mixed with several excipients commonly used in the pharmaceutical industry. In the present study, thermal and spectral techniques were used

for drug-excipient interactions. Due to its unique chemical and pharmacokinetic properties, Tadalafil-excipient interaction has been included in our study.

2. Material and Method

Chemicals and reagents

Tadalafil, ascorbic acid (AA), butylated hydroxyanisole (BHA), calcium phosphate dibasic (CP), cellulose (C), magnesium stearate (MS), mannitol (M), sodium carboxymethyl cellulose (SCC), sucrose (S), talc (T), starch (ST), primojel (P), citric acid (CA), potassium bromide (KBr) purchased from Sigma and Merck.

Instrumentation

Fourier transform-infrared spectroscopy (FTIR) spectra were recorded at room temperature using a Frontier Perkin Elmer using KBr compressed discs. Each spectrum was obtained by averaging 32 scans from 4000 down to 450 cm^{-1} [30].

Differential scanning calorimetry (DSC) curves were obtained in Perkin Elmer Calorimeter (DSC 4000). Tadalafil and Tadalafil-excepient mixtures were placed in a pre-weighed stainless steel pan. A pan was containing approximately 10 mg of sample under dry nitrogen atmosphere (flow rate of 20 mL min^{-1}). The sample was equilibrated to 25ºC and then heated from 25ºC to 400ºC at a rate of 10ºC/min. [31, 32].

Thermogravimetric analysis (TG) curves were obtained in a SEIKO SII, model TG/DTA 7200, under dry nitrogen atmosphere (flow rate 30 mL min^{-1}) as the purge gas and heating rate of 10°C min^{-1} in the temperature range between ambient and 800°C. Samples were weighted in platinum pans about 10 mg. α-Al_2O_3 was employed as a reference material in the analysis [33].

3. Results

Recently, thermal and spectroscopic methods have been recommended for such studies. FTIR focuses on the solid state behavior of drug substances. Indicative of no interaction between drug and excipient is the absence of any disappearance of the base group peak of the pure drug. In the dual drug mixture, functional group peaks of the pure drug are included in the spectrum, even if there is a slight decrease in density. For this reason, vibrational changes are considered as an indicator of intermolecular interactions-incompatibility studies between drug-excipients. The spectra are compared (Table 1) (Figure 2).

Table I: FTIR description of Tadalafil

Peak wavenumber (cm^{-1})	**Description [34, 35]**
3330	Absorption bands characteristic of amine (N-H)
3073	=C-H stretching in an aromatic ring
2907	–C-H stretchings in the alkanes
1677	lactam (N-H)
1678 and 1650	C=O
1600–1585 and 1500–1400	Carbon–carbon stretching vibrations in the aromatic rings
1300–1000	C-N stretching
1200–1000	C-H deformation

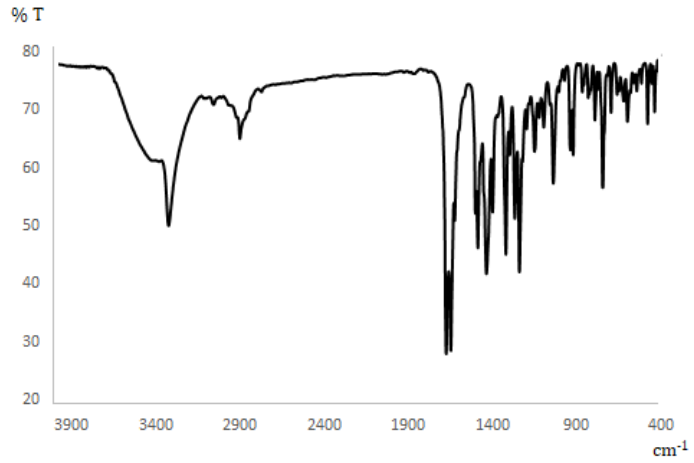

Figure 2: FTIR specturum of Tadalafil

The FTIR spectrum of Tadalafil-BHA mixture showed sharp band at 3404 cm^{-1}, 3392 cm^{-1}, 2979 cm^{-1}, 2951 cm^{-1}, 1506 cm^{-1}, 1200 cm^{-1}, and 1033 cm^{-1}. These peaks are either not included in the spectrum of Tadalafil or their peak intensities are very low (Figure 3).

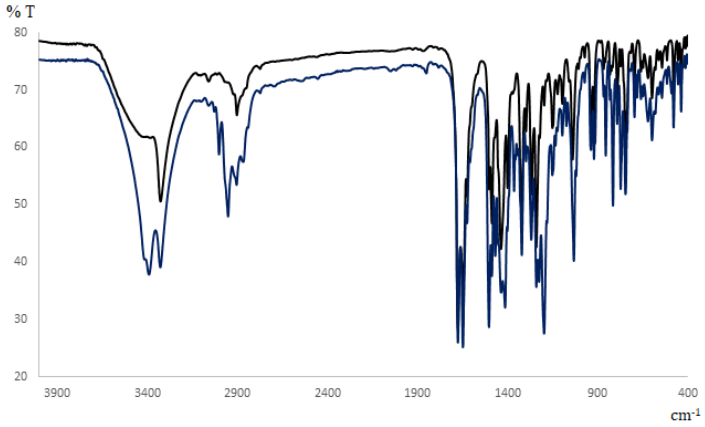

Figure 3: FTIR specturum of Tadalafil-BHA mixture

Apart from the peaks in Tadalafil, there are also sharp peaks in 3400 cm^{-1}, 3287 cm^{-1}, 2971 cm^{-1}, 2947 cm^{-1}, 1082 cm^{-1}, and 1021 cm^{-1} for Tadalafil-M mixture (Figure 4).

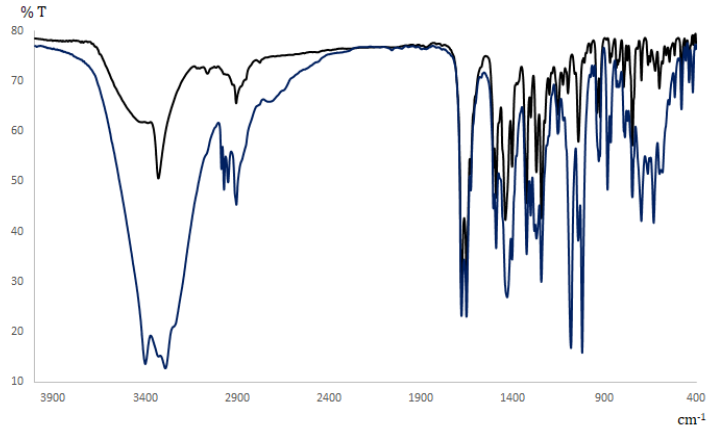

Figure 4: FTIR specturum of Tadalafil-M mixture

In addition to the characteristic peaks of Tadalafil, there are 3564 cm^{-1}, 3389 cm^{-1}, and 1068 cm^{-1} peaks of different intensities in the Tadalafil-S mixture (Figure 5).

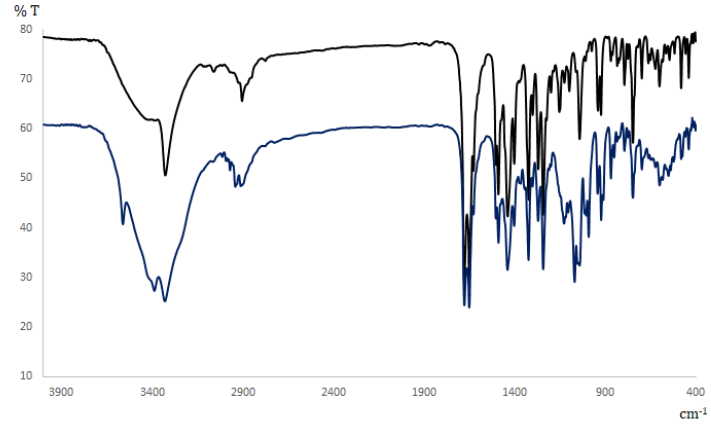

Figure 5: FTIR specturum of Tadalafil-S mixture

In the spectrum of Tadalafile-AA, there are peaks of different intensities at 3525 cm^{-1}, 3408 cm^{-1}, 3213 cm^{-1}, and 1578 cm^{-1}. In addition, due to the differentiation in the structure, the twin peak at 1678 and 1650 cm^{-1} of C=O shifted to 1700 cm^{-1} and the shape of the peak changed. It is seen from the spectrum that the peak intensities differ in the range of 1400 cm^{-1} -900 cm^{-1} (Figure 6).

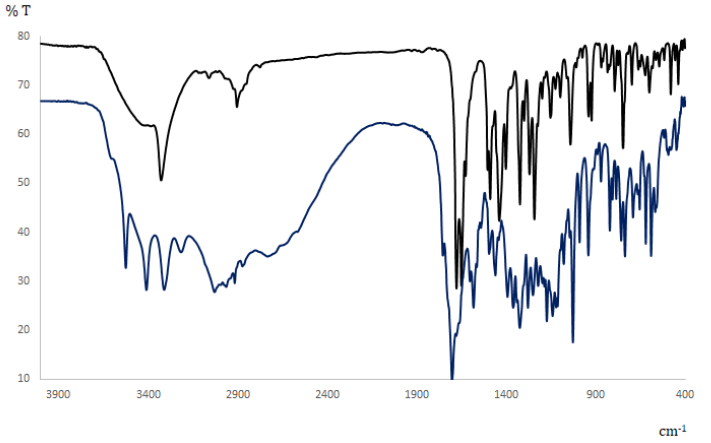

Figure 6: FTIR specturum of Tadalafil-AA mixture

In the spectrum of the Tadalafile-CA mixture, there are peaks of different intensities, especially at 3496 cm^{-1}, 3446 cm^{-1}, 3294 cm^{-1}, 1361 cm^{-1}, and 1176 cm^{-1} In addition, there are two peaks at 1755 cm^{-1} and 1683 cm^{-1} next to the twin peaks at 1678 and 1650 cm^{-1} belonging to two C=O in the structure (Figure 7).

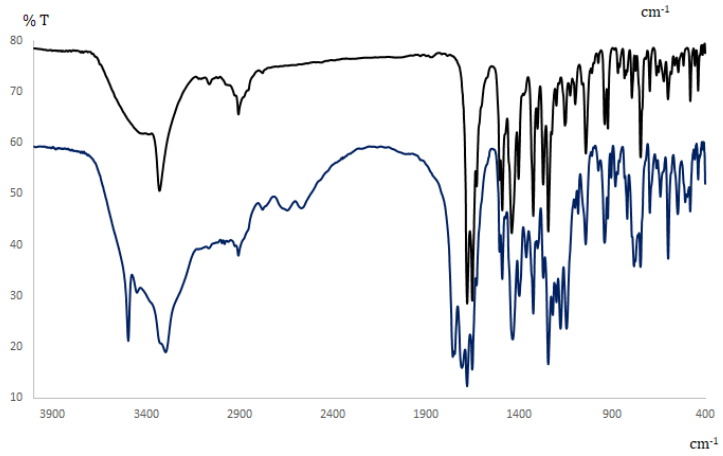

Figure 7: FTIR specturum of Tadalafil-CA mixture

According to FTIR results, BHA, M, S, AA and CA excipients were found to be incompatible with Tadalafil. If the main peaks of the drug are also included in the spectrum of the drug-excipient physical mixtures, it is an indication of the absence of possible interactions between the active drug and excipients [36, 37]. The characteristic peaks of Tadalafil were unchanged or preserved in mixtures of Tadalafil-CP, Tadalafil-C, Tadalafil-SCC, Tadalafil-T, Tadalafil-ST, and Tadalafil-P (Figure 8).

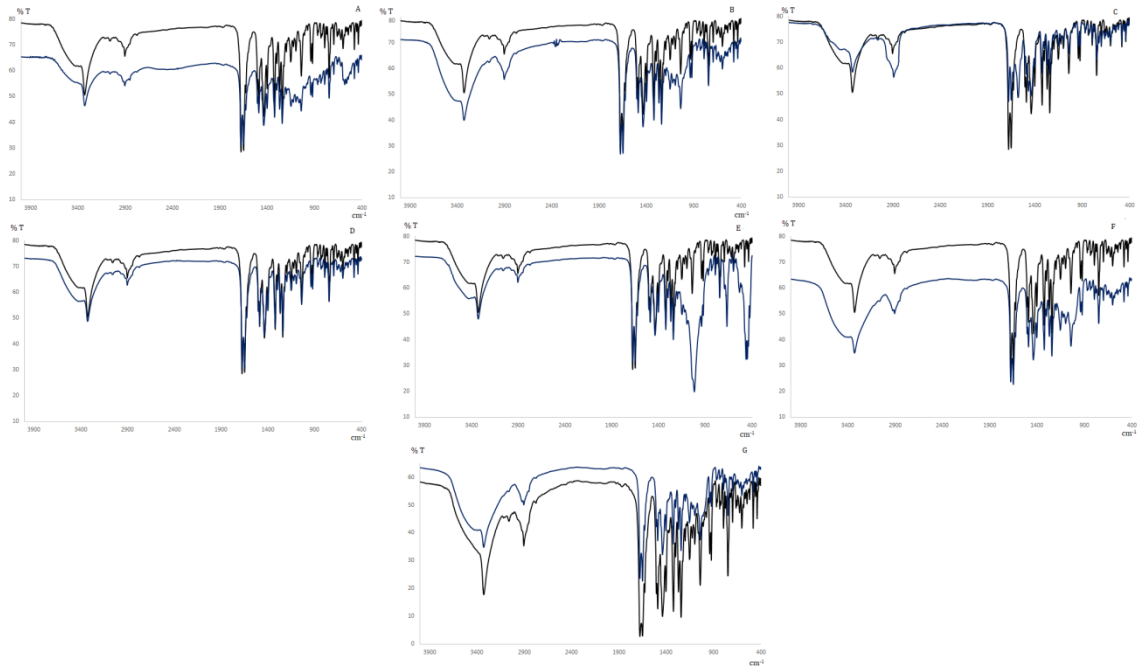

Figure 8: FTIR specturums of a) Tadalafil-CP mixture, b) Tadalafil-C mixture, c) Tadalafil-MS mixture, d) Tadalafil-SCC mixture, e) Tadalafil–T mixture, f) Tadalafil–ST mixture, and g) Tadalafil-P mixture

The TGA curve of Tadalafil is illustrated in Figure 9.

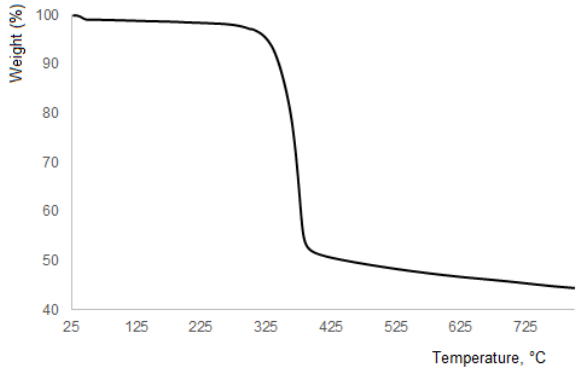

Figure 9: TGA curve of Tadalafil

From TGA curve, little weight loss from 25 to 300°C was detected for Tadalafil because chemical degradation with 3% of impurities. As shown in Fig. 9, Tadalafil had a sharp melting point (T_M) at 303°C [38, 39]. Thermal stability of Tadalafil and its binary mixtures with different excipients are presented in the Table 2. TG/DTG curve showed that Tadalafil was thermally stable up to 300°C and finally decomposed at 400°C with a residual amount of 48.27%. The DSC curve showed a sharp endothermic peak at 303.64°C indicating the indicating the (T_M) [38-40]. We have compared TG curve of pure Tadalafil and BHA, CP, C, MS, M, SCC, S, T, AA, ST, P, and CA. In binary mixture %10 decomposition temperatures were start from a range of 128-355°C. In drug-excepient binary mixture %10 decomposition temperatures were start from a range of 138-599°C. The decomposition temperature value is directly proportional to resistibility of drug in mixture form against temperature.Table 2 shows seven compounds close to the decomposition temperature of Tadalafil. These are CP, C, MS, SCC, T, ST and P.

Based on the 10% and 15% decomposition temperatures, the temperature values of the T and ST mixtures are higher than the other mixtures. This shows that these binary mixtures (Tadalafil-T and Tadalafil-ST) are more stable than others Tadalafil-CP, Tadalafil-C, Tadalafil-MS, Tadalafil-SCC, and Tadalafil-P).

Table 2: Thermal stability of Tadalafil and Tadalafil-excipient mixture with excipients by TG.

Sample	10% mass loss/°C	15% mass loss/°C	Total weight loss (600°C/%)
Tadalafil	344.91	355.12	52.85
Tadalafil-BHA	128.79	138.13	86.18
Tadalafil-CP	343.75	354.84	45.39
Tadalafil-C	323.23	332.38	79.79
Tadalafil-MS	317.77	326.52	70.74
Tadalafil-M	295.48	305.02	72.93
Tadalafil-SCC	311.68	341.14	21.39
Tadalafil-S	234.36	249.62	72.44
Tadalafil-T	352.59	366.48	24.07
Tadalafil-AA	238.13	278.15	32.82
Tadalafil-ST	355.89	599.67	15.28
Tadalafil-P	331.70	357.95	18.69
Tadalafil-CA	199.87	216.17	29.36

The amount of residue may also influence the stability of formulation residual content after heating is inversely proportional to the thermal decomposition of drug. The TG curve of all binary mixture show a content of residue range from 13.82-84.72% of its initial weight. The highest content of residue would be found in case of ST.

As a shown in Fig. 10, Tadalafil had a sharp (T_M) at 303.64°C as reported [38]. About the same melting endotherm peak was observed for the drug and CP, C, and T physical mixtures (Table 3). The endotherm peak for Tadalafil-MS at 279.33°C, Tadalafil-SCC at 296.33°C, Tadalafil-ST at 297.14°C, Tadalafil-P at 298.48°C. According to papers, very little temperature change in enthalpy peaks in DSC thermograms is due to their low impurity in the compounds used for analysis [38-41]. As such there is no interaction between drug–this excipient.

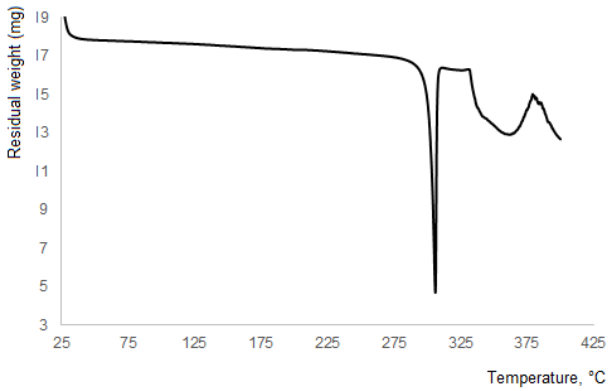

Figure 10: DSC curve of Tadalafil

Table 3: Peak temperature and enthalpy values of Tadalafil and Tadalafil-excipient mixtures

Sample	T_{peak} (°C)	Comments	Result
Tadalafil	303.64		
Tadalafil-BHA	169.28	Lowest melting time	Possible interaction
Tadalafil-CP	304.41	Thermally stable	No interaction
Tadalafil-C	304.46	Thermally stable	No interaction
Tadalafil-MS	279.33	Thermally less stable	Low impurity
Tadalafil-M	169.21	Lowest melting time	Possible interaction
Tadalafil-SCC	296.78	Thermally less stable	Low impurity
Tadalafil-S	182.40	Lowest melting time	Possible interaction
Tadalafil-T	304.44	Thermally stable	No interaction
Tadalafil-AA	193.95	Lowest melting time	Possible interaction
Tadalafil-ST	297.14	Thermally less stable	Low impurity
Tadalafil-P	298.48	Thermally less stable	Low impurity
Tadalafil-CA	156.97	Lowest melting time	Possible interaction

The endotherm peak for Tadalafil-BHA at 169.28°C, Tadalafil-M at 169.21°C, Tadalafil-S at 182.40°C, Tadalafil-AA 193.95°C, and Tadalafil-CA 156.97°C, thus suggesting a probable interaction.

4. Discussion and Conclusion

The FTIR, TGA and DSC results of the drug and its binary mixtures containing excipients are important in terms of determining the interaction between the drug and excipient. Studies to investigate drug-excipient compatibility are an important step in drug development studies. Thermal and spectroscopic techniques are widely used in such studies. Tadalafil is the new and the most versatile PDE5 inhibitor in the treatment of hypertension. Parallel combinations of Tadalafil and Tadalafil-excipient mixtures with TG and DSC thermogram and various excipients were recorded. When evaluating the results, the focus was on the thermal stability model, or mass percent in the TG, during the change or movement of the endothermic peak and the presence of the new temperature-related peak in the DSC. In this study,

DSC, TGA, and FTIR systems were used to determine the possible interactions between Tadalafil and some excipients like BHA, M, S, AA, and CA. TG results clearly demonstrate that CP, C, MS, SCC, ST, T and P are stable with drug at elevated temperature. While the 10% and 15% mass loss temperatures of Tadalafil-T and Tadalafil-ST are higher than pure Tadalafil, the values of the others are slightly lower. DSC curve demonstrated suspected interaction with BHA, M, S, AA and CA. In the FTIR spectra of the binary mixtures of BHA, M, S, AA and CA, there have been shifts in the places of some of the main peaks of Tadalafil or different peaks. The result of FTIR study of drug and there binary mixtures with excipient were constant and showed as supportive result of TG and DSC.

Declaration of Ethical Code

In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out.

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