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Compatibility Studies of Minoxidil with Different Excipients by Using DSC, TGA and FTIR

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Abstract: This study aims to understand the compatibility or incompatibility of minoxidil with these excipients, which are commonly included in drug formulations for various purposes. The study examined the interaction of minoxidil with several excipients including mannitol, calcium phosphate dibasic, butylated hydroxyanisole, magnesium stearate, cellulose, Beta-cyclodextrin, Eudragit S 100, sodium carboxymethyl cellulose, and talc. Morphological and thermal properties were analyzed using techniques such as DSC, TGA, and FTIR. Minoxidil was found to be compatible with Beta-cyclodextrin, calcium phosphate dibasic, cellulose, and sodium carboxymethyl cellulose. This suggests that these excipients can be used in formulations with minoxidil without causing any adverse interactions. However, minoxidil was found to be incompatible with Eudragit S 100, mannitol, magnesium stearate, and talc. This indicates that these excipients may not be suitable for use in formulations with minoxidil due to potential interactions that could affect stability, safety, efficacy, or quality of the drug dosage form. These findings provide valuable insights for formulators and researchers in the pharmaceutical industry to develop stable and effective formulations containing minoxidil. It underscores the importance of understanding the interactions between active pharmaceutical ingredients and excipients to ensure the quality and performance of drug products.
Key words: compatibility, minoxidil, excipients, DSC, TGA, FTIR

1. Introduction

Androgenetic alopecia (AGA) is a common chronic dermatological condition affecting both men and women, with women facing particular challenges [1, 2]. The prevalence of AGA is significant, with 70-80% of men and 30-50% of women experiencing it during their lifetime [3, 4]. While the exact cause remains unclear, it's believed to be influenced by various factors including autoimmune, hereditary, emotional stress, infectious agents, neurological factors, and genetic predisposition [5-7]. Androgenic alopecia, also known as hereditary baldness, is characterized by androgen-induced scalp thinning following a specific pattern. The US Food and Drug Administration (FDA) has approved minoxidil for the treatment of androgenic alopecia [8, 9]. Originally used in the 1970s for severe and persistent hypertension, doctors noticed hair regrowth and generalized hypertrichosis in balding patients [10]. This led to the development of a topical formulation of minoxidil for AGA treatment in both sexes [11].

Minoxidil, a piperidino-pyrimidine derivative ((6-(1-piperidinyl) -2, 4-pyrimidinediamine 3- oxide) ($C_9H_{15}N_5O$)), directly stimulates hair follicles, prompting those in the resting phase to enter the growth phase [12, 13]. This stimulation is believed

to be the mechanism behind minoxidil's effectiveness in promoting hair growth. The hair cycle consists of growth (anagen), regression (catagen), resting (telogen), and shedding (exogen) stages, and minoxidil's action is thought to primarily affect this cycle by prolonging the anagen phase [14, 15]. Overall, minoxidil's topical application has been widely accepted as an effective treatment for AGA in both men and women, providing hope for those affected by hair loss.

Excipients are generally inert additives included in drug formulation to help absorption, manufacture and administration. They also take part in auxiliaries, product differentiation, improving appearance or maintaining quality. If excipients enter into chemical or physical interactions with an active substance, it may cause a decrease in the quality or performance of the drug. Incompatibilities in pharmaceutical products (active substance-excipient) are undesirable physical, chemical or biopharmaceutical processes that occur during preparation, storage or administration that cause the dragee to decompose and not improve the patient's condition. Incompatibilities can occur in the form of drug-drug interactions, drug-additive and additive-additive interactions. Chemical interaction may lead to degradation of the active ingredient, reducing the amount available for therapeutic effect; reaction products can compromise safety or tolerance or may even cause toxicities due to the degradants. The most commonly known modes of degradation pathways include oxidation, hydrolysis, photolysis, isomerization, and polymerization. Physical interactions between active drug compound and excipients do not involve the formation or breaking of chemical bonds in the molecular structure of the drug. Physical interactions may adversely affect dissolution rate, organoleptic properties, dose homogeneity, polymorphic forms, stability profile drug release, crystallization behavior or ease of administration [16, 17, 18].

A wide variety of thermal and non-thermal analytical techniques are used in drug-excipient compatibility studies. These techniques, working principles, sample size, analysis time, type of stress, thermal, mechanical, etc. differs in terms of the complex nature of their interactions, there are no universal standards in the methodology for assessing compatibility between drug and excipients. However, in recent years there has been a significant increase in the number of individual studies reporting the use of one or more techniques to screen for drug-excipient compatibility. Commonly reported techniques include thermo-analytical techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), differential thermal analysis (DTA), and fourier transform infrared spectroscopy (FTIR) [19-35].

The present investigation aims to assess the compatibility of minoxidil with various active pharmaceutical excipients intended for use in formulations. To achieve this, different analytical techniques such as DSC, TGA, and FTIR were employed.

2. Material and Method

2.1. Chemicals and reagents

Minoxidil were purchased from Sigma Aldrich. Mannitol (M, Merck), calcium phosphate dibasic (CP, Sigma), butylated hydroxyanisole (BHA, Sigma Aldrich), magnesium stearate (MS, Sigma Aldrich), cellulose (C, Aldrich), Beta-cyclodextrin (BC, TCI), Eudragit S 100 (ES, Evonik), sodium carboxymethyl cellulose (CMS, Aldrich) and talc (T, Sigma Aldrich) were used for the excipients.

2.2. Methods

Differential scanning calorimetry (Perkin Elmer, DSC 4000) studies were carried out on the drug alone and their physical mixtures (PM) in 1:1 weight ratio. The samples (5-10 mg) were inserted in aluminum pan and heated at the rate of 10°C/min in the temperature range from 25°C up to 400°C. TGA was performed using a thermogravimetric analyzer (SEIKO SII, TG/DTA 7200). The sample (approximately 10 mg) was loaded in the platinum pan of the analyzer and subsequently analyzed at a heating rate of 20°C/min in the temperature range from 30 up to 600°C. Both DSC and TGA analyzes were performed under a nitrogen atmosphere. Fourier transfer infrared spectrophotometry The FTIR (Perkin Elmer, Frontier) studies were carried out on the drug alone and their PM in 1:1 weight ratio. Samples were mixed with IR grade KBr. The prepared disks were scanned over a range of (400-4000 cm^{-1}) [35, 36].

3. Results and Discussion

3.1. DSC analysis

DSC is one of the most common thermal techniques used to test for drug-excipient incompatibilities [31]. The most important advantages of the technique are that it can work with a small amount of sample and give fast results. From the results, the melting point of the solids can be easily determined [32].

As a shown in Fig. 5B., Minoxidil had a sharp melting point (T_M) at 282.38°C. About the same melting endotherm peak was observed for the drug and BC, CP, C, and CMS physical mixtures (Table 1). 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 [37-40]. As such there is no interaction between drug–this excipient. The melting points of the mixtures obtained with other excipients are in the range of 270.13-275.19°C. Differences in these values indicate that minoxidil is incompatible with these compounds.

Table 1: Peak temperature values of minoxidil and minoxidil-excipient mixtures

Sample	T_{peak} (°C)	Comments	Result
Minoxidil	282.38		
Minoxidil-ES	270.13	Lowest melting time	Possible interaction
Minoxidil-BC	284.20	Thermally stable	No interaction
Minoxidil-CP	279.28	Thermally stable	No interaction
Minoxidil-M	271.19	Lowest melting time	Possible interaction
Minoxidil-C	284.63	Thermally stable	No interaction
Minoxidil-MS	271.80	Lowest melting time	Possible interaction
Minoxidil-CMS	284.18	Thermally stable	No interaction
Minoxidil-T	275.19	Thermally stable	Possible interaction

3.2. TGA analysis

Another powerful thermal technique is TGA. TGA is an effective way to study changes in physical and chemical properties of drug and drug- excipient mixtures. The thermal stability of the excipients and minoxidil was evaluated (Table 2). Hence, TGA analyses were performed to elucidate the impact of the observed interaction in the stability of the drug combination.

Table 2: Thermal stability of minoxidil and minoxidil-excipient mixture by TG.

Sample	10% mass loss/°C	25% mass loss/°C	50% mass loss/°C	75% mass loss/°C
Minoxidil	273.19	287.82	290.71	437.59
Minoxidil-ES	253.14	273.03	427.31	451.62

Minoxidil-BC	264.75	288.14	334.19	435.91
Minoxidil-CP	282.71	292.69	-	-
Minoxidil-M	265.53	277.31	300.00	318.76
Minoxidil-C	273.12	285.98	347.44	490.65
Minoxidil-MS	262.54	271.73	353.27	475.43
Minoxidil-CMS	269.94	287.48	307.02	-
Minoxidil-T	277.41	285.05	-	-

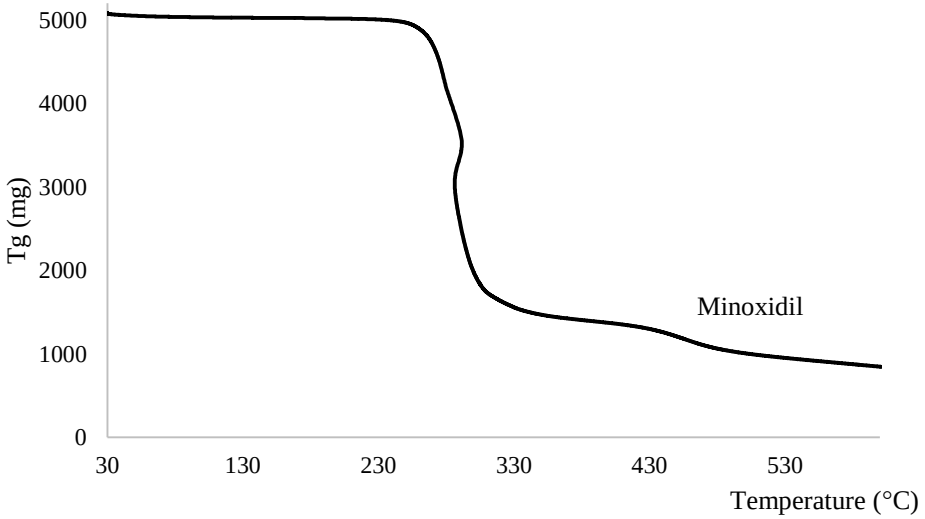

Figure 1. Thermogravimetric analysis profiles of minoxidil

Figure 1 presents the TGA profiles of minoxidil. Minoxidil has a melting and decomposition temperature of approximately 270-295°C [13]. Decomposition began right after the melting and crystallization event at 287.82°C (25% loss). After melting at 282 °C, in the physical mixture, slight anticipation of the decomposition temperature at about 291◦C was observed.

Minoxidil-ES mixture showed three separate weight loss steps at approximately 230°C, 287°C, and 420°C due to glass transition temperature of Eudragit S100 (decomposition of polymer), minoxidil melting point and complete combustion of polymer, respectively (Figure 2). A comparison of the decomposition step of minoxidil alone and that of minoxidil in the complex revealed that minoxidil alone showed a sharp weight loss at 270-295°C, while in the complex, it was gradual over a temperature range of 230–290°C. The TGA result showed that minoxidil-edc was incompatible as in the DSC result.

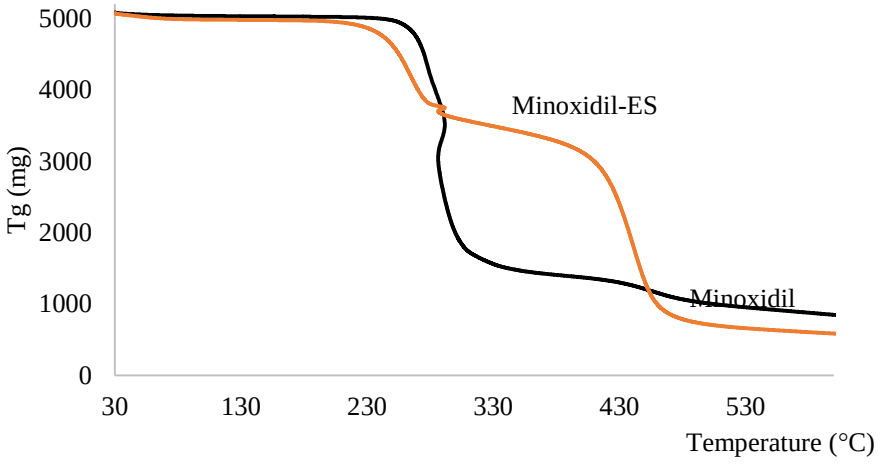

Figure 2. Thermogravimetric analysis profiles of minoxidil-ES

Minoxidil-BC mixture showed three separate weight loss steps at approximately 100°C, 285°C, and 320°C. The first zone under 100°C with a 7.14% mass loss can be attributed to the evaporation of superficial water associated with the cyclodextrin [41]. The TGA/DTG curves of minoxidil-BC appeared to have a peak at 285°C, relating to minoxidil melting point minoxidil. Finally, a third process around 307°C can be related to the degradation of the minoxidil-BC (Figure 3). TGA results, DSC results are supported.

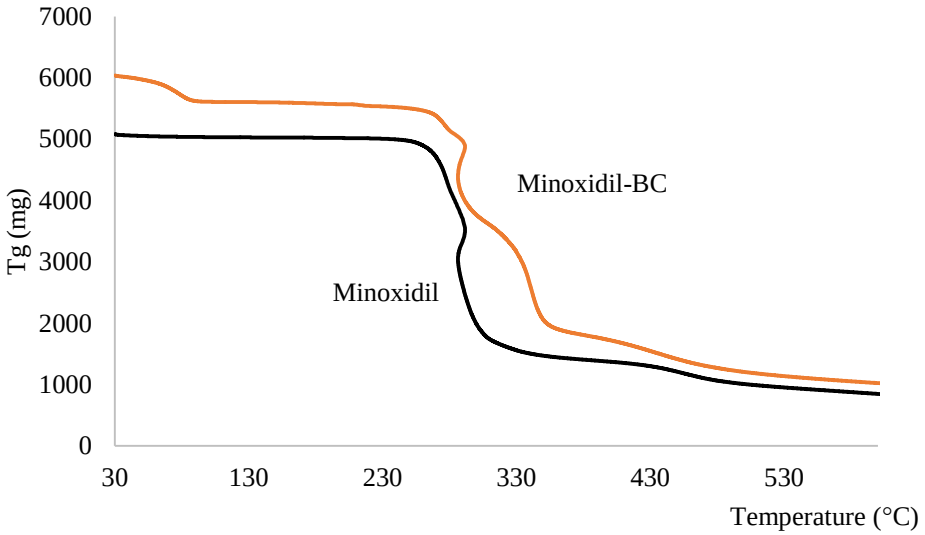

Figure 3. Thermogravimetric analysis profiles of minoxidil-BC

TGA results are located in the thermogram of the minoxidil-CP mixture, the 280-290°C region corresponding to the melting point of minoxidil, as in pure minoxidil. Some degradation temperatures are higher than pure minoxidil. This is an indication of the stability of the structure (Figure 4).

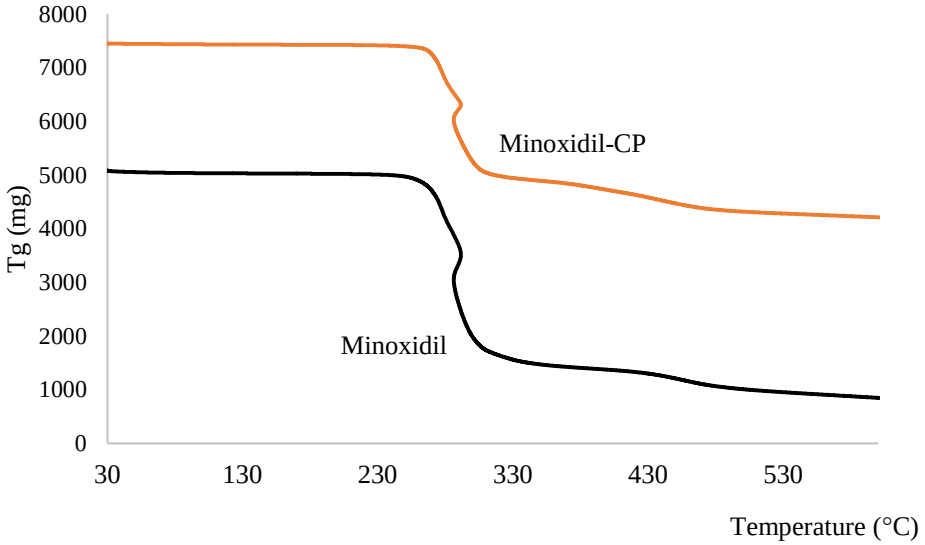

Figure 4. Thermogravimetric analysis profiles of minoxidil-CP

In the Minoxidil-M mixture, the temperature corresponding to the melting point of minoxidil decreased in the range of 10-15°C. This indicates that the stability of the mixture is lower than that of pure minoxidil. DSC results also support this conclusion (Figure 5).

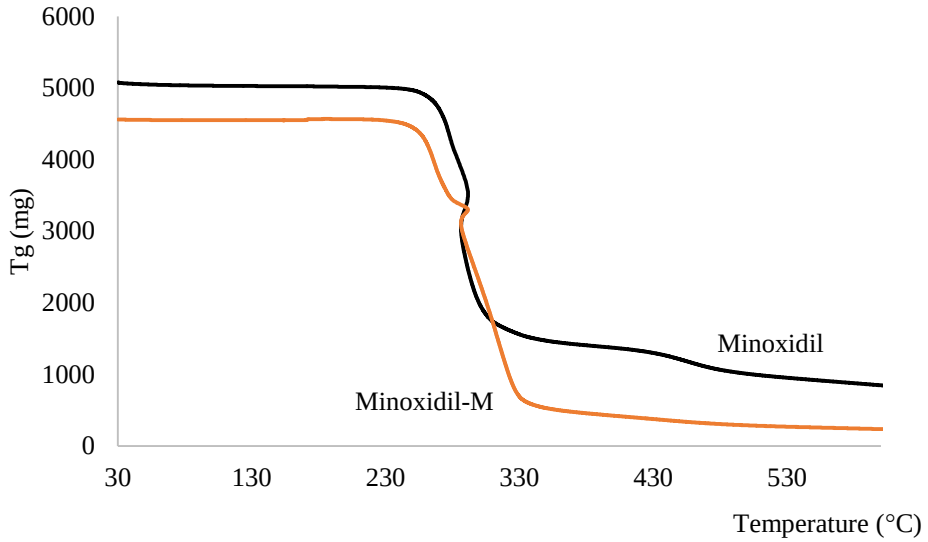

Figure 5. Thermogravimetric analysis profiles of minoxidil-M

The thermogram shows the degradation of Minoxidil in the range of 270–300°C, relative to the percentage weight 50%. Similarly, Minoxidil-C mixture showed a weight loss 50% in temperature range of 270–350°C (Figure 6).

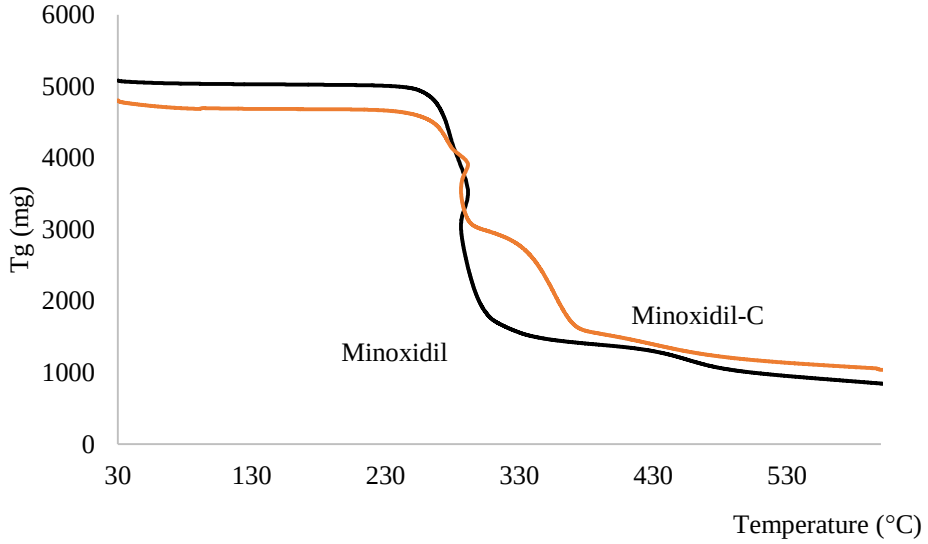

Figure 6. Thermogravimetric analysis profiles of minoxidil-C

As can be seen from the TGA curve, while 10% of minoxidil decomposes at approximately 273°C, this temperature decreased to 263°C in the Minoxidil-MS mixture. This result, like the DSC result, shows that Minoxidil and MS are incompatible (Figure 7).

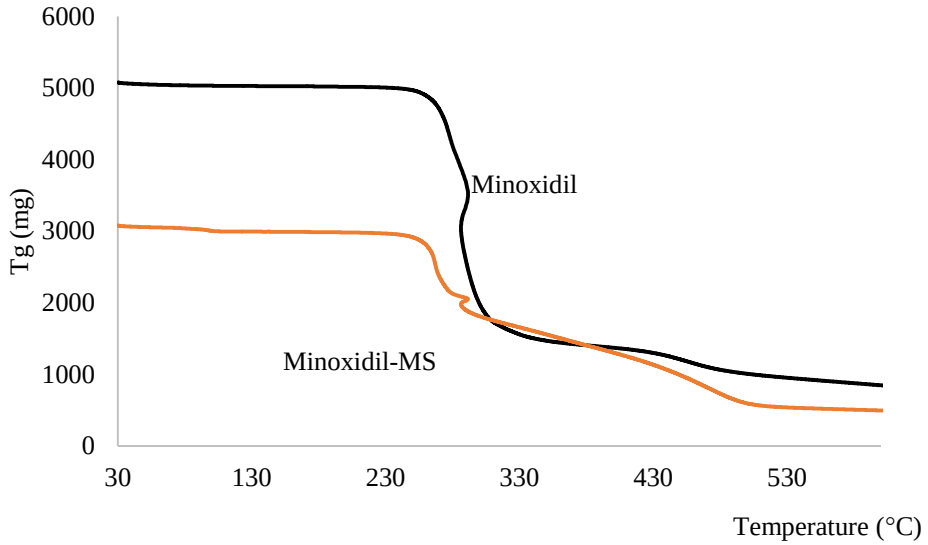

Figure 7. Thermogravimetric analysis profiles of minoxidil-MS

According to DSC data, the melting temperature of Minoxidil-CMS mixture is 284°C. In addition, when we look at the data obtained from TGA, 10% of the minoxidil-CMS mixture decomposed at 270°C and 25% at 287°C (Figure 8). Data obtained from both thermal systems show the compatibility of minoxidil and CMS.

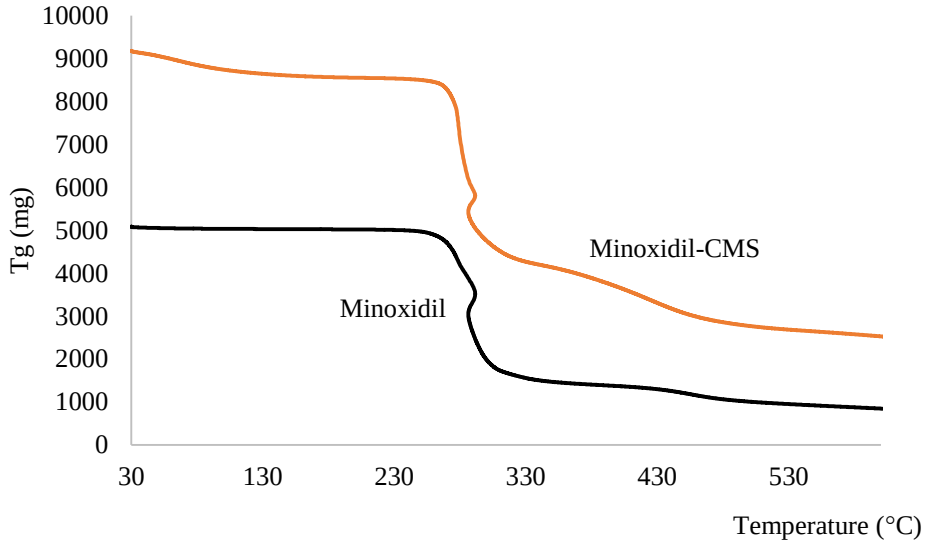

Figure 8. Thermogravimetric analysis profiles of minoxidil-CMS

From the TGA analysis of the mixture between T and minoxidil, the temperature required for 10% degradation was 277°C, while at 25% this value was calculated as 285°C. From DSC analysis, the melting temperature of minoxidil-T mixture was calculated as approximately 275°C. The results show the compatibility between minoxidil-T (Figure 9).

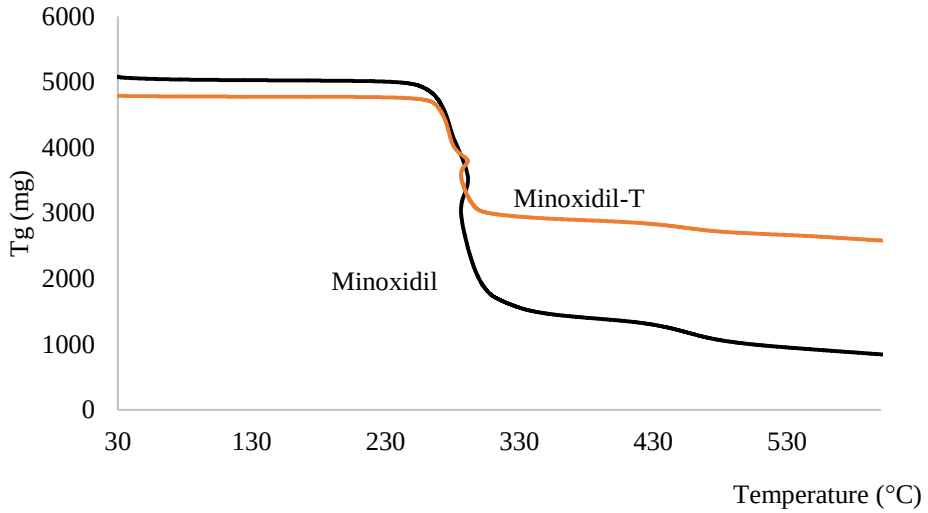

Figure 9. Thermogravimetric analysis profiles of minoxidil-T

3.3. FTIR analysis

Before any formulation development, it is necessary to check possible drug-excipient incompatibility. This is performed on FTIR studies were conducted to ascertain the interaction between the drug and selected excipient. FTIR wavelength values of pure minoxidil, and their physical mixture with minoxidil-excipient were presented in Table 3.

Table 3: FTIR description of minoxidil and minoxidil-excipient mixture [13, 42-43]

Sample	NH (Stretching) (cm^{-1})	Hydrogen bonded N-H (cm^{-1})	CH (Stretching Aromatic & Aliphatic) (cm^{-1})	C=N (Stretching Aromatic) (cm^{-1})	Aromatic C=C (Stretching N-H Bending) (cm^{-1})	N-O (Stretching Aromatic C-N) (cm^{-1})	N-H wag (cm^{-1})
Minoxidil	3452, 3412, 3370, 3314	3271, 3025	2976, 2951, 2940	1644, 1611	1556, 1462, 1450, 1431	1251, 1234, 1211	758
Minoxidil-ES	3452, 3410, 3371, 3314	3269, 3015	2978, 2953, 2941	1641, 1633	1554, 1463, 1446, 1435	1247, 1234, 1119	758
Minoxidil-BC	3454, 3412, 3370, 3317	3265, 3018	2962, 2954, 2941	1645, 1612	1550, 1471, 1446, 1438	1253, 1232, 1209	758
Minoxidil-CP	3440, 3410, 3396, 3361	3232, 3030	2980, 2951, 2933	1641, 1613	1556, 1483, 1450, 1423	1259, 1230, 1119	754
Minoxidil-M	3440, 3418, 3387, 3310	3273, 3028	2978, 2954, 2935	1640, 1610	1550, 1470, 1442, 1430	1263, 1238, 1210	754
Minoxidil-C	3431, 3399, 3350, 3220	3265, 3030	2980, 2953, 2949	1643, 1606	1558, 1483, 1448, 1431	1259, 1244, 1217	752
Minoxidil-MS	-	-	2943, 2918, 2848	-	1573, 1539	-	-

Minoxidil-CMS	3431, 3398, 3365, 3310	3257, 2997	2953, 2933, 2914	1641, 1606	1558, 1480	1261, 1217, 1211	754
Minoxidil-T	3373	3226	-	1608		1010	-

The spectra of pure drug shown the major peaks at 3452 cm^{-1} (N-H stretching, primary amine), 1644 cm^{-1} (N-H bending, primary amine), 1450 cm^{-1} (C=C aromatic stretching), 1251 cm^{-1} and 1211 cm^{-1} (C-N stretching), 758 cm^{-1} (N-H wag). There was no significant shift in major peaks observed from the spectra of drug and excipient physical mixtures, which indicates there were no major interaction between drug and selected excipients (Figure 10) [13, 42-43].

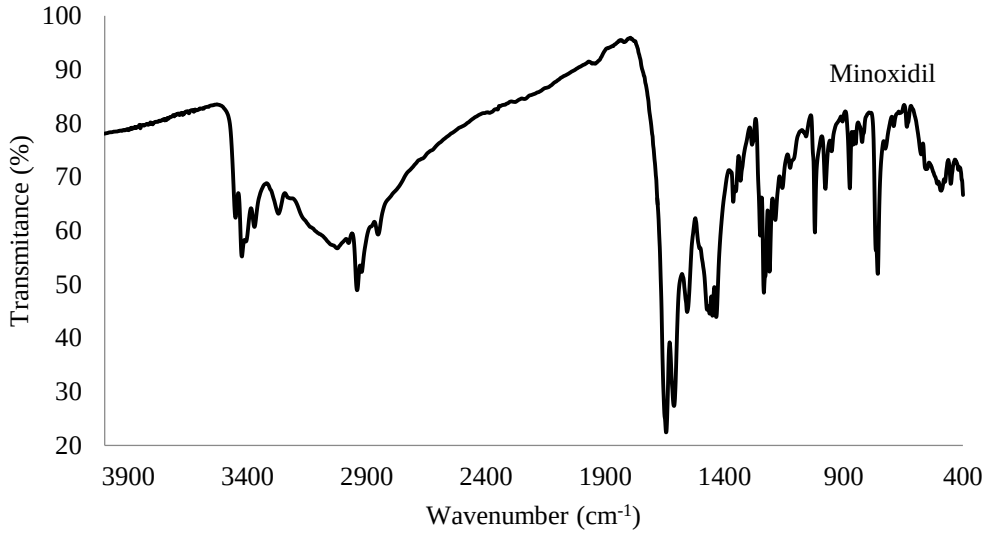

Figure 10. FTIR spectrum of minoxidil

It can be seen that the main peaks of minoxidil in Table 3 are the same in BC, CP, C, and CMS. These results support TGA and DSC (Figure 11, Figure 12, Figure 13, and Figure 14).

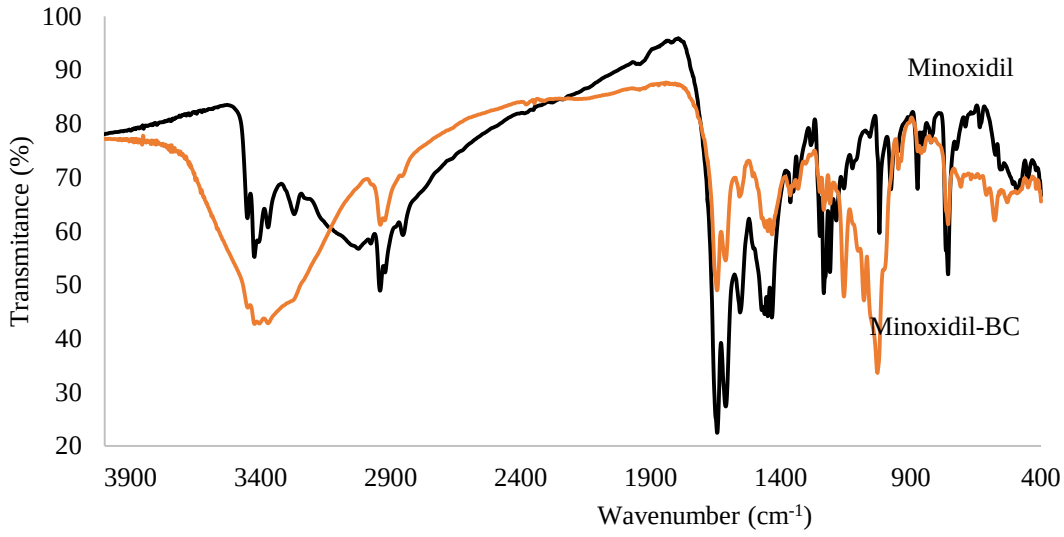

Figure 11. FTIR spectrum of minoxidil-BC

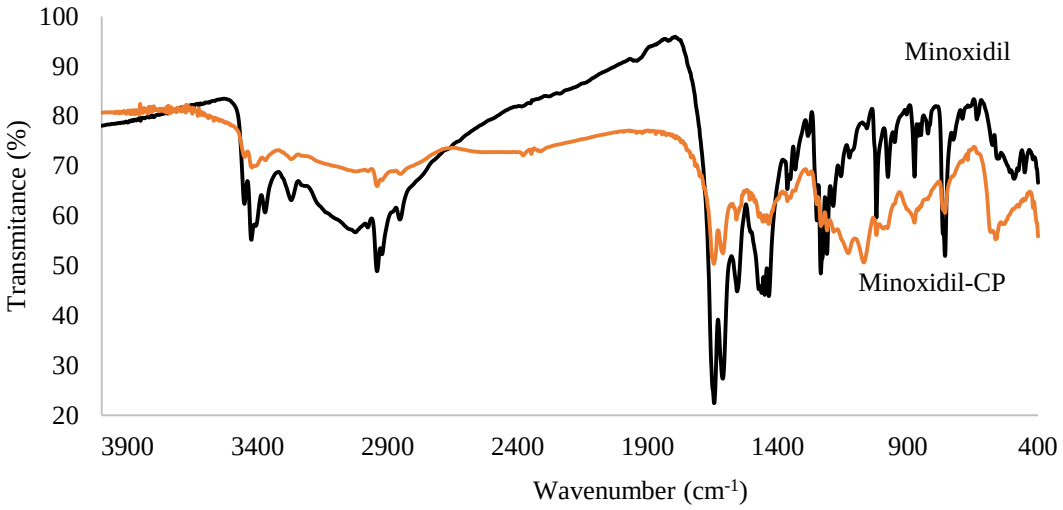

Figure 12. FTIR spectrum of minoxidil-CP

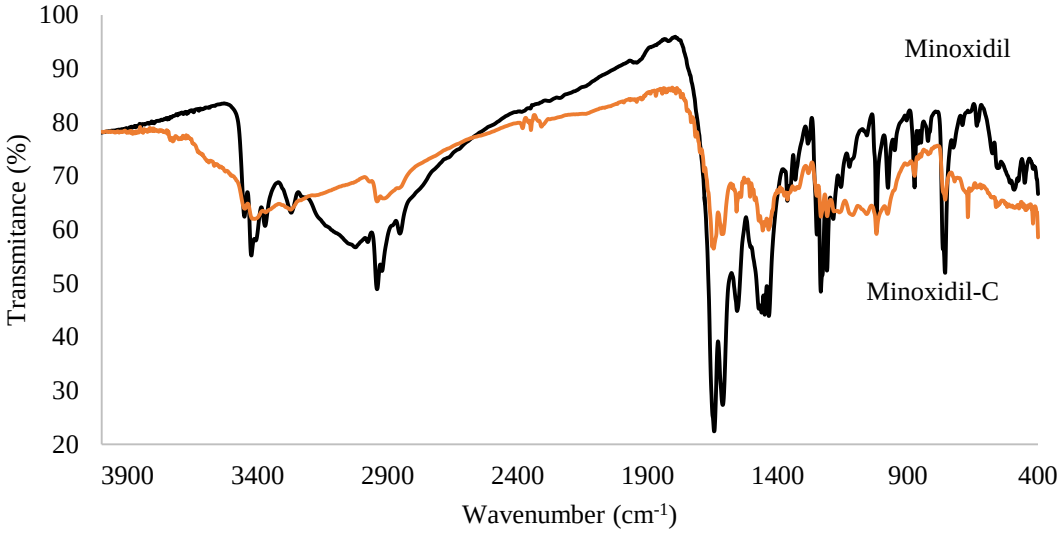

Figure 13. FTIR spectrum of minoxidil-C

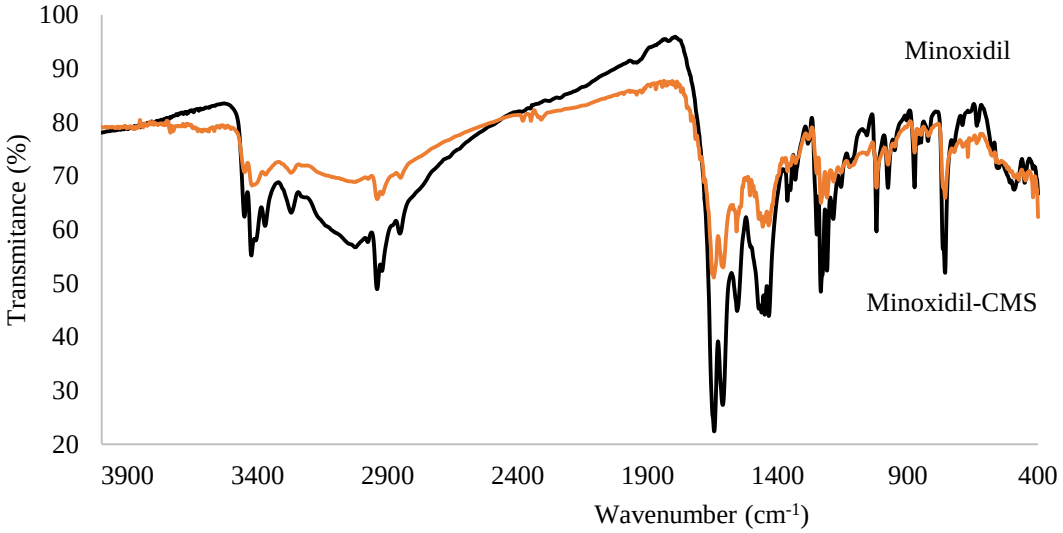

Figure 14. FTIR spectrum of minoxidil-CMS

Although the main peaks of minodil are in the minoxidil-ES mixture, different peaks at 1730 cm^{-1}, 1234 cm^{-1}, 1168 cm^{-1}, and 1135 cm^{-1} indicate degradation in the structure. This shows that there is incompatibility between minoxidil and ES (Figure 15).

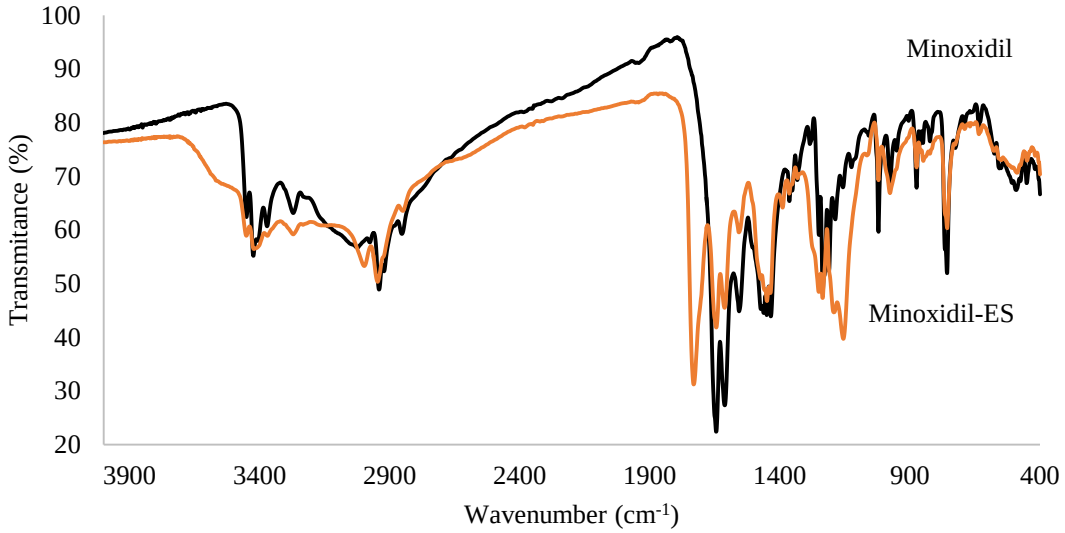

Figure 15. FTIR spectrum of minoxidil-ES

Main peaks of minoxidil are present in the mannitol mixture. However, different peaks are seen as intense in the 1320-970 cm^{-1} region. This shows the incompatibility between minoxidil and mannitol, as in the results in thermal systems.

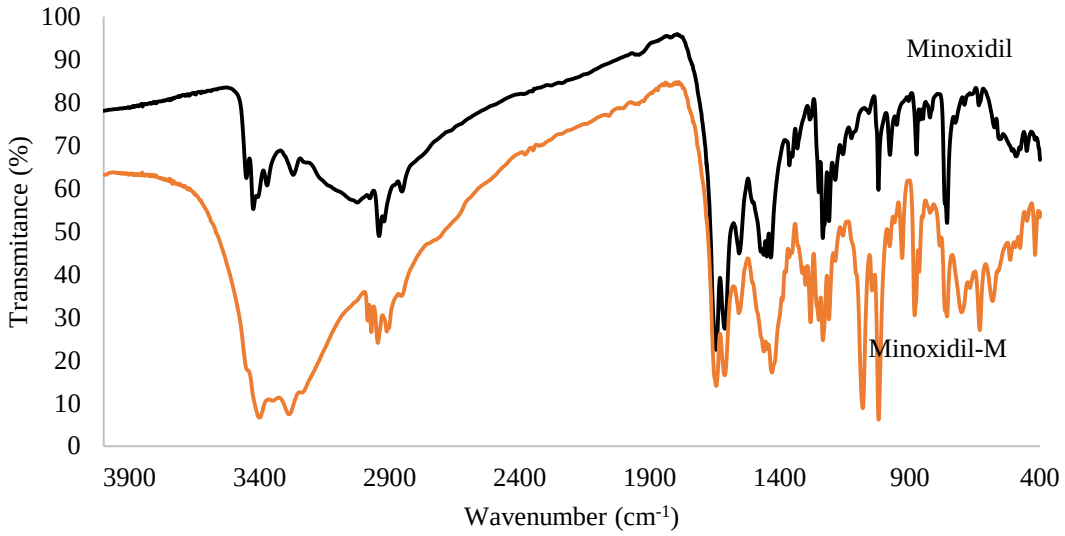

Figure 16. FTIR spectrum of minoxidil-M

In the mannitol-MS mixture, N-H ((Stretching)), N-H (Hydrogen bonded), C=N (Stretching Aromatic), N-O (Stretching Aromatic C-N), N-H wag peaks belonging to minoxidil disappeared. This shows the incompatibility between Mannitol and MS.

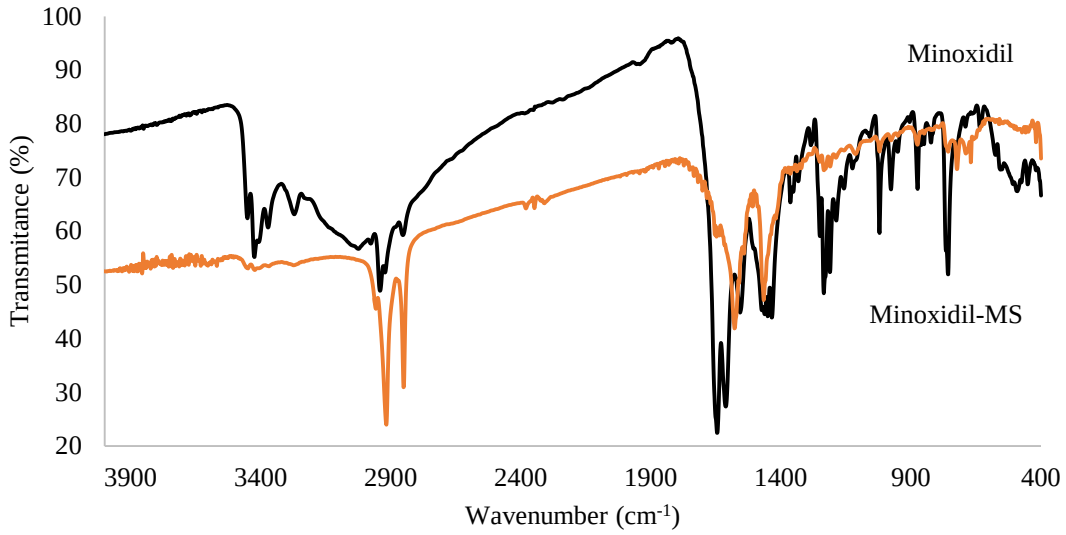

Figure 17. FTIR spectrum of minoxidil-MS

In the mannitol-T mixture, the CH (Stretching Aromatic & Aliphatic), aromatic C=C (Stretching N-H Bending) and N-H wag peaks of minoxidil disappeared. In addition, there are strong peaks at 1016 cm^{-1}, 669 cm^{-1} and 449 cm^{-1}. This shows the incompatibility between it and Mannitol-T.

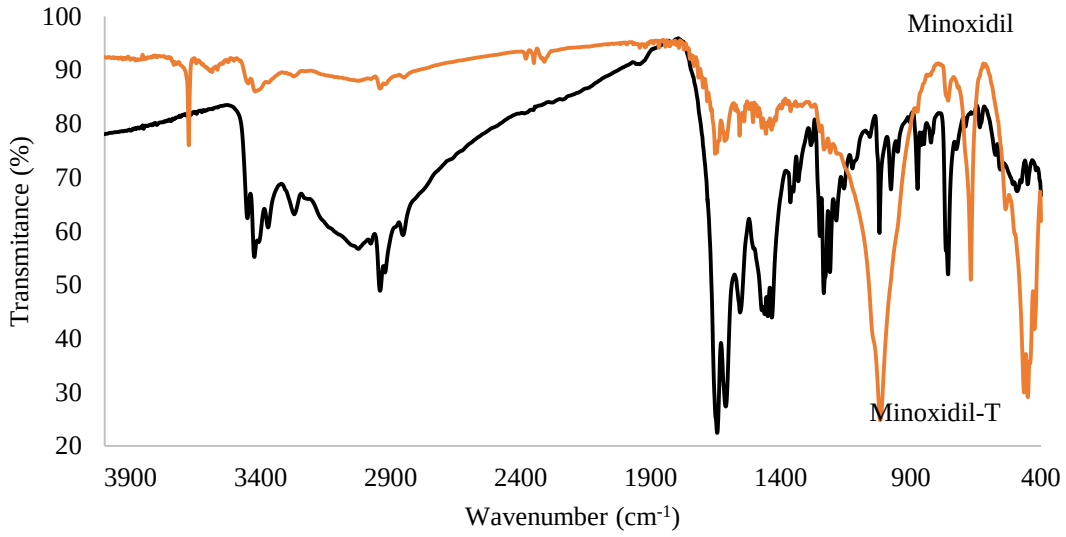

Figure 18. FTIR spectrum of minoxidil-T

4. Conclusion

Understanding the chemical and physical structure of excipients, their associated impurities or residues, and how they may interact with other materials or each other helps prevent future pharmaceutical developments. Incompatibilities between drug excipients may be directly visible to the eye or may sometimes occur in a hidden manner. Visible incompatibilities are usually caused by insufficient resolution, color or odor change, viscosity changes, turbidity, etc. Hidden incompatibilities that are not visible to the naked eye can be difficult to detect. For this purpose, thermal, spectroscopic or chromatographic systems are used. The results of the studies confirmed that DSC, TGA and FTIR could be used as rapid methods to evaluate the compatibility between minoxidil and excipients.

The results obtained from drug-excipients mixed in a 1:1 ratio showed the compatibility of BC, CP, C, and CMS with minodil, but the incompatibility with ES, M, MS, and T.

Authorship contribution statement

H Seçilmiş: Research, Methodology, Validation, Data processing.

R Altınkaya: Research, Methodology, Data processing.

M Doğantürk: Research, Methodology, Data processing.

Declaration of competing interest

As the authors of this study, we declare that we do not have any conflict of interest statement.

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