**Research Article**

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# Incompatibility Studies of Tamsulosin HCl using TGA, DSC and IR

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**ABSTRACT**

The Benign Prostatic Hyperplasia is one of the common old age problems and alpha one adrenoreceptor blockers are commonly used for symptomatic relief. Tamsulosin HCl is selective alpha 1A adrenoreceptor blocker with better tolerability profile and once daily dosing advantage. The present study was undertaken to establish the compatibility of Tamsulosin with several commonly used excipients by using thermo analytical technique viz Thermogravimetry and differential scanning calorimetry used in formulation. The Thermogravimetry and differential scanning calorimetry both results demonstrated that ethyl cellulose, Gelatin and lactose found to be incompatible with Tamsulosin and should be avoided for the pharmaceutical preparation.

**Keywords:** Tamsulosin, Differential scanning calorimetry (DSC), Thermogravimetry (TG), Incompatibility study, Fourier transform Infrared (FTIR)

## 1. INTRODUCTION

The condition known as benign prostatic hyperplasia might be characterized as "*a benign enlargement of the prostate gland resulting from a proliferation of both benign epithelial and stromal elements*". It might also be defined clinically as "*a constellation of lower urinary tract symptoms (LUTSs) in aging men*" [1]. Benign prostatic hyperplasia (BPH) is the most well-known age-related proliferative anomaly of the human prostate influencing older men all through the world [2]. Age, hormones and epithelial–mesenchymal connections are for the most part contributing components to the pathogenesis of BPH [3]. Even though BPH is by and large not a dangerous condition, it can markedly affect a patient's QOL. The expense of overseeing BPH is > $4 billion every year [4].

The prostate contains a critical volume of smooth muscle rich in α-adrenergic receptors (ARs). Incitement of these receptors increments prostatic urethral opposition while barricade diminishes obstruction [5].

The smooth muscle of the bladder neck and prostate is heavily influenced by alphaadrenergic nerves. Nonselective alpha blockers convey the most noteworthy danger of orthostatic hypotension, and ought to be begun at a low portion and titrated up over the time of half a month [6].

Tamsulosin (TAM) (Figure 1) is a long-acting specific α1-adrenoceptor antagonist, to oversee lower urinary tract symptoms indications coming about because of BPH. The reports shown that there were 12.4 million prescriptions in 2010 for Tamsulosin in US. Higher affinity for the α1A than for the α1B subtype (12–38-fold) is the reason for better tolerability and safety profile [7]. Internationally, TAM is the most often recommended α1-adrenoceptor enemy for the treatment of LUTS/BPH [8].

Evaluation of possible incompatibility between the medications and diverse excipients by examination of the physical and synthetic property of drug substance alone and in blend with excipients is a significant piece of preformulation studies. Thermoanalytical technique e.g. DSC and thermogravimetry/ differential thermogravimetry (TG/DTG) has been utilized quite a while past by drug specialists for portrayal of the materials before their utilization and/or at some other phase of preformulation [9-11].

The fundamental advantage of DSC is its accessibility to immediately screen potential excipients for inconsistency got from the moving, appearance, vanishing of endothermic/exothermic pinnacle or variety in the relating ΔH (Enthalpy of change) while TG give drug significant information on the evaluation of stability of a formulation [11]. Because of changes in functional group due to interaction with excipients, the IR spectrum of drug may also differ, this forms basis of utilization of FTIR in these types of research [12].

It is invaluable to have information on any physical as well as synthetic associations among drug and excipients before development of suitable formulation [13]. Drug-excipients interaction is a significant exercise in the improvement of a stable formulation [14]. The identification of potential inconsistencies among drug and excipients is one of the essential undertakings to be managed in a pre-formulation research center. In this sense, contriving a fast and precise strategy to test and choose the best possibility for stable dose structures would establish a genuine leap forward in the pre-plan drug store [15].

The aim of this study is to identify interaction of TAM HCl with commonly used excipients of solid dosage forms.

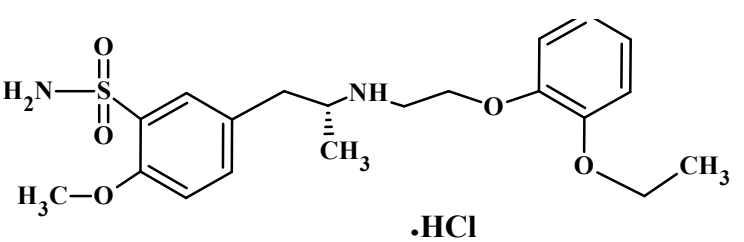


**Fig. 1.** Structural formula of Tamsulosin


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## 2. MATERIAL AND METHODS

### *2.1 Materials*

TAM was kindly gifted by Aurobindo Labs India and structure was confirmed by FTIR spectroscopy. Various excipients viz. Eudragit RS100, Eudragit RL 100, HPMC (5cps), Methyl cellulose, Gelatin, Ethyl cellulose, Eudragit S100, HPMC (15cps), Lactose were purchased from Sigma-Aldrich and Alfa-Aesar (USA).

### *2.2 Identification*

Infrared (IR) spectrums of compounds confirmed the structure. Spectrums were obtained as KBr discs on a Bruker TENSOR-27 FTIR spectrophotometer. The function group like primary Amine, Secondary amine, sulfonamide, ether group, was assigned to vibration specific for those group appeared at 3352 $cm^{-1}$, 3305 $cm^{-1}$ (stretching) and 1585 $cm^{-1}$, 1159 $cm^{-1}$ (symmetric), 1334 $cm^{-1}$ (asymmetric), 1043 $cm^{-1}$ (symmetric) and 1215 $cm^{-1}$ (asymmetric) respectively. Other peak was responsible for vibration corresponding to CH stretching vibration in di-substituted aliphatic and aromatic ring appeared at 2981 $cm^{-1}$ and 3082 $cm^{-1}$ respectively while aliphatic C-H bending appeared at 1460 $cm^{-1}$. The aromatic C=C stretching and OOPB also appeared at 1500 $cm^{-1}$ and 906 $cm^{-1}$ respectively. Particularly at 1261 $cm^{-1}$ appearance of peak was characteristic for C-N stretching vibrations of secondary amine. The N-H OOPB appeared at 819 $cm^{-1}$.

### *2.3 Methods*

#### *2.3.1 TG Study*

The TG/DTG estimation was performed on Pyris 1 TGA (Perkin Elmer TGA Instruments, USA), under nitrogen environment with the stream pace of 40 ml/min. Test was set in platinum container and warmed from ambient temperature to 900°C at a warming pace of 10°C/min. The TG examination has been performed utilizing unadulterated TAM, excipients, and their binary mixtures (1: 1 mass ratio).

#### *2.3.2 DSC Study*

Compatibility studies of TAM with various excipients carried out by Shimadzu DSC- 60 230V. Samples were heated (10°C/min) from ambient temperature to 300°C after weighing and placing on aluminum pan. Analysis performed using pure TAM chlorides, mixtures, and excipients (1:1 mass ratio).

#### *2.3.3 FT-IR Study*

Spectrophotometer (Shimadzu) was used to obtain Diffuse reflectance infrared Fourier transform (DRIFT) spectra, scan range of 400–4000 $cm^{-1}$, average of over 25 scans, spectral resolution of 4$cm^{-1}$ in KBr. For each experimental condition, a background spectrum was obtained**.**

## 3. RESULTS AND DISCUSSION

### *3.1 TG Result*

Thermal stability of TAM and its binary mixtures with different excipients are presented in the Table 1. Figure 2 Show TG of pure TAM. TG/DTG curve showed that TAM was thermally stable up to 151°C and finally decomposed at 797°C with a residual amount of 16.843 % in figure 2. The DSC curve showed an endothermic peak at 235.57°C indicating the melting (Melting Time $M_t$ = 20.30 min).

We have compared TG curve of pure TAM and Eudragit RS100, Eudragit RL 100, HPMC (5cps), Methyl cellulose, Gelatin, Ethyl cellulose, Eudragit S100, HPMC (15cps), Lactose. In binary mixture Initial Decomposition Temperature value may start from a range of 130-162°C. The IDT value is directly proportional to resistibility of drug in mixture form against temperature. The highest IDT value showed by HPMC (5cps) which is quite stable as compared to lactose which has lowest IDT value of 130°C.

The Final Decomposition temperature value of binary mixture may also influence the thermal stability of binary mixture. If the FDT value may raise thermal stability of drug also increase and vice versa. The FDT range of binary mixture should started from 715-799°C. The highest FDT value was found to be 799°C of binary mixture containing HPMC (5cps) hence binary mixture of HPMC (5cps) with drug may increase the thermal resistibility and self-life of formulation against thermal decomposition. The low FDT give thermal instability to formulation when they kept store in temperate region. The lowest FDT value shown by binary mixture containing lactose and gelatin.

The amount of residue may also influence the stability of formulation residual content after heating is

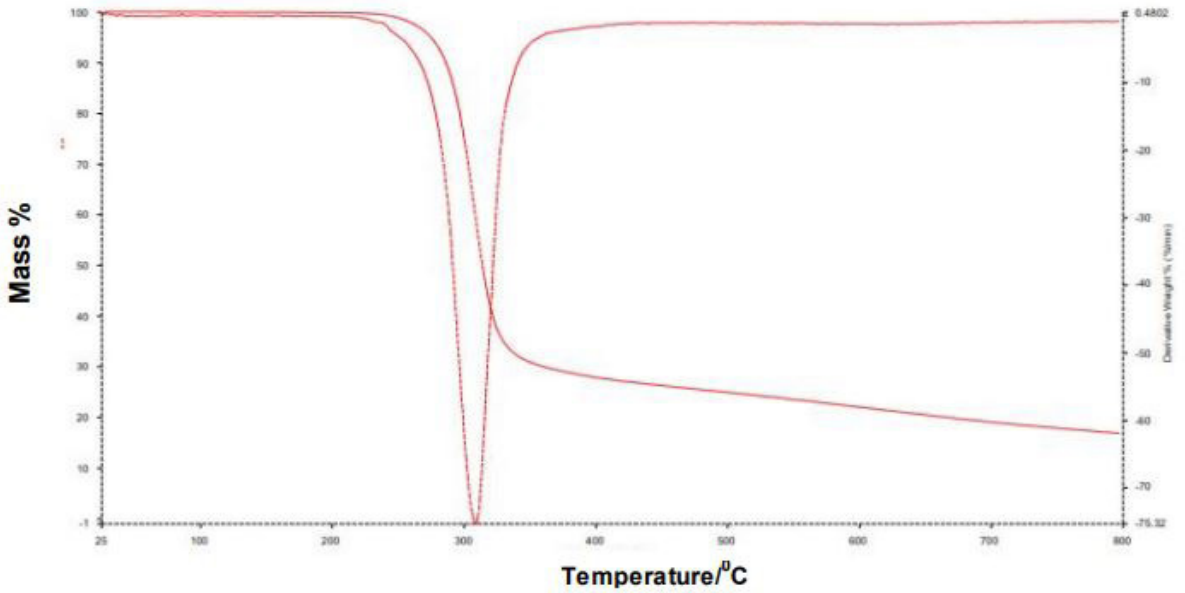


**Fig. 2.** TG curve of Tamsulosin

**Table 1.** Thermal stability of TAM and its binary mixture with excipients by TG.

| S No | Sample | IDT (Initial decomposition temperature) | 10% mass loss /°C | FDT /°C | Residue / % |
|---|---|---|---|---|---|
| 1 | Tamsulosin | 151 | 285 | 797 | 16.843 |
| 2 | Ethyl cellulose | 140 | 273 | 723 | No |
| 3 | HPMC 5cps | 162 | 295 | 799 | No |
| 4 | Eudragit RL-100 | 155 | 288 | 777 | 7.168 |
| 5 | Eudragit S-100 | 156 | 290 | 790 | 0.350 |
| 6 | Eudragit RS-100 | 159 | 290 | 751 | 3.190 |
| 7 | HPMC 15cps | 140 | 283 | 798 | No |
| 8 | Methyl cellulose | 154 | 288 | 740 | No |
| 9 | Gelatin | 148 | 272 | 717 | No |
| 10 | lactose | 130 | 256 | 715 | No |

inversely proportional to the thermal decomposition of drug. The TG curve of all binary mixture show a content of residue range from 0.350-7.168 % of its initial weight. The highest content of residue would be found in case of Eudragit RL 100. This data show than formulation contains Eudragit RL 100 would be thermally stable at high temperature.

## *3.2 DSC Result*

No interaction observed in 1:1% physical mixtures, the $T_{peak}$ value of decomposition event (melting) Substantial modification was seen in gelatin DSC response as compared to pure TAM response, which was enhanced or mediated, by amorphous order of those excipient. DSC graph (1:1%) of TAM with gelatin (Figure 4a) and HPMC 5cps showed endo-


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thermic event at Melting Time 17.87 min and 19.57 min. respectively. (Table 2). The decreased in melting time might be due to hygroscopic nature of excipient. On the other hand, binary mixture containing gelatin may also suspected to interaction due to its second lowest melting at 231.28°C (Melting Time 17.87 min.).

Binary mixture containing lactose (Figure 4 b) showed endothermic event at 229.28°C, (Melting Time 19.64 min.) which found to be interaction of excipients with drug. On the other hand, binary mixture containing ethyl cellulose may also suspected to interaction due to its second lowest melting at 229.38°C, (Melting Time 19.59 min.) (Figure 4 c).

**Table 2.** Thermal stability of TAM and its binary mixture with excipients by DSC.

| S No | Excipients | $T_m$/° C | Time (Min) | Comments | Result |
|---|---|---|---|---|---|
| 1 | Tamsulosin | 235.57 | 20.30 | - | - |
| 2 | Ethyl cellulose | 229.38 | 19.59 | Second Lowest Melting temperature | Possible interaction |
| 3 | HPMC 5cps | 230.57 | 19.57 | Thermally less stable | Possible interaction |
| 4 | Eudragit RL-100 | 232.20 | 20.65 | Thermally stable | No interaction |
| 5 | Eudragit S-100 | 234.49 | 20.18 | Thermally stable | No interaction |
| 6 | Eudragit RS-100 | 234.77 | 20.18 | Thermally stable | No interaction |
| 7 | HPMC 15cps | 230.46 | 19.65 | Thermally less stable | Possible interaction |
| 8 | Methyl cellulose | 232.95 | 19.91 | Thermally stable | No interaction |
| 9 | Gelatin | 231.28 | 17.87 | Lowest Melting time | Possible interaction |
| 10 | Lactose | 229.28 | 19.64 | Lowest Melting temperature | Possible interaction |

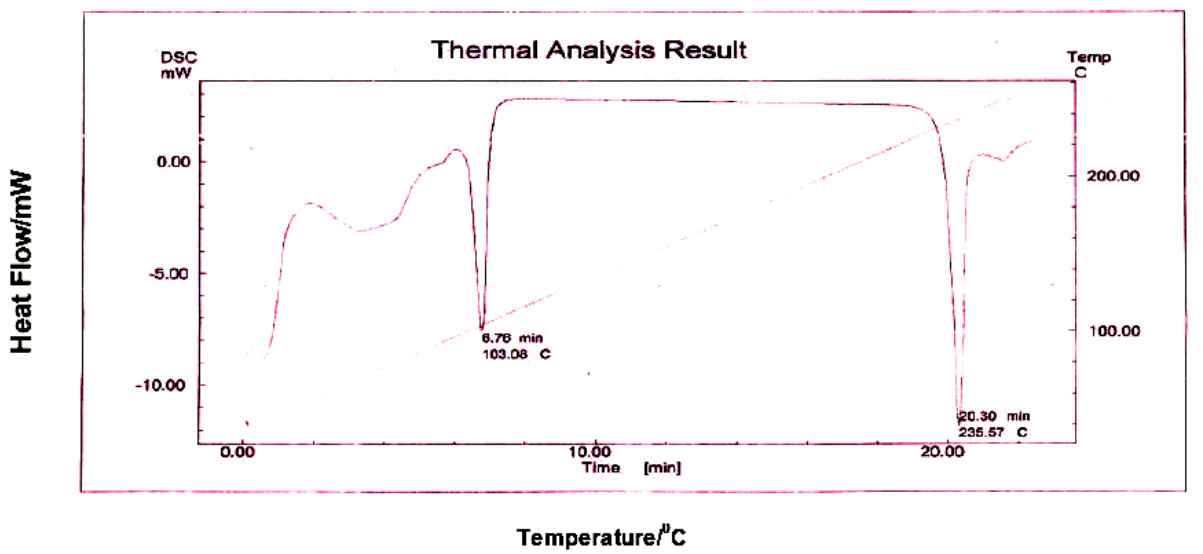


**Fig. 3.** DSC curve of pure Tamsulosin

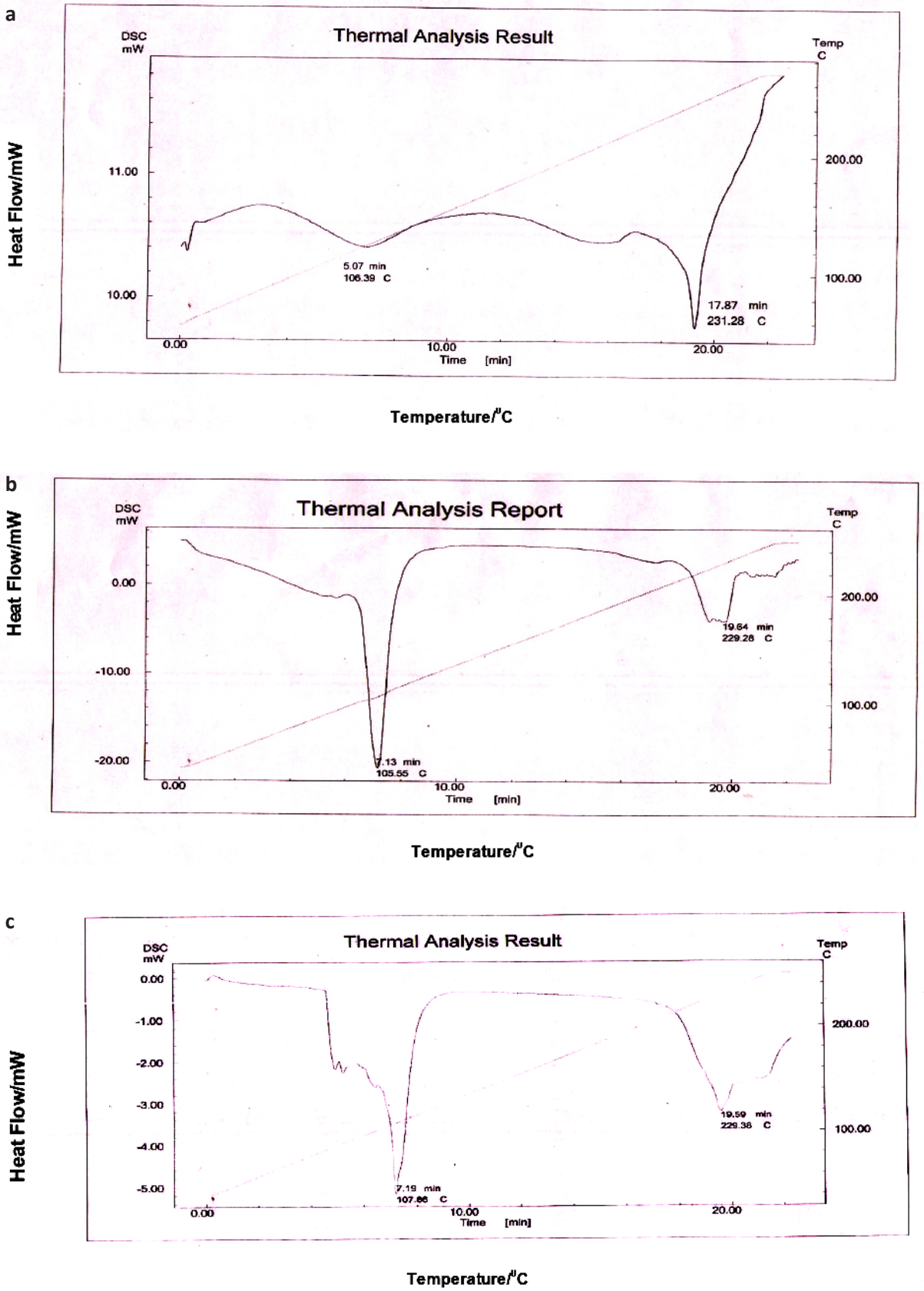


**Fig. 4.** DSC overlay of Tamsulosin and its binary mixture with (a) Gelatin (b) Lactose (c) Ethyl cellulose


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### *3.3 IR Results*

In binary mixture of drug and binary mixture of all combination show respective functional group peak at respective position with slight decrease in intensity. The similar thermal behavior was seen in IR spectra of (1:1 %) binary mixture of drug and excipient. there is not any disappearance of basic group peak of pure drug which favor that there is no interaction between the drug and excipient. The IR spectra of binary mixture of HPMC 5cps, ethyl cellulose and lactose show alteration of vibration frequency of C-H bending, C-H (aromatic) stretching and N-H bending respectively did showed evidence on chemical interaction in the solid state. However, the spectra of binary mixture didn't show any absence or shift of vibration band of TAM.

Because of the close contact of the API with at least one excipient in a dosage forms, there exists a risk of chemical and/or physical interactions between them. Any such interactions might bring about an adverse consequence on the performance, stability, or physical properties of the medication item.[16] The analytical methodologies frequently used for evaluation of any such interaction are TG, DSC and FTIR.[17] The purpose of this work is to demonstrate the compatibility of TAM with common excipients using DSC and TG/DTG technologies. TG results clearly demonstrate that HPMC is quite stable with drug at elevated temperature. On the other hand, lactose was proved to impart least stability with drug in same conditions. The chemical interaction between lactose and secondary amine (Maillard reaction) is well reported in literature.[18] For example, fluoxetine forms formyl fluoxetine (major product) by interaction with lactose.[19] The TAM also contains secondary amine, thus potential interaction using lactose cannot be neglected. The presented study also indicated the same result, and thus avoiding presence of lactose in formulation of TAM is suggested. Gelatin is commonly used ingredient in many pharmaceutical formulations.[20] However, the reports suggested interacting in surfactant-like manner with nortriptyline HCl,[21] or may be due to hygroscopic nature of gelatin.[22]. With the lowest final decomposition temperature, lactose and gelatin may also not good choice. Hence two excipients lactose and gelatin were found to be incompatible as far as thermal stability of Tamsulosin formulations is concern. DSC curve demonstrated suspected interaction with gelatin may be due to its hygroscopic nature.

Endothermic shift in melting point was also demonstrated in the case of lactose and ethyl cellulose proved suspected interaction with drug. The IR spectra of binary mixture of HPMC 5cps, ethyl cellulose and lactose show alteration of vibration frequency

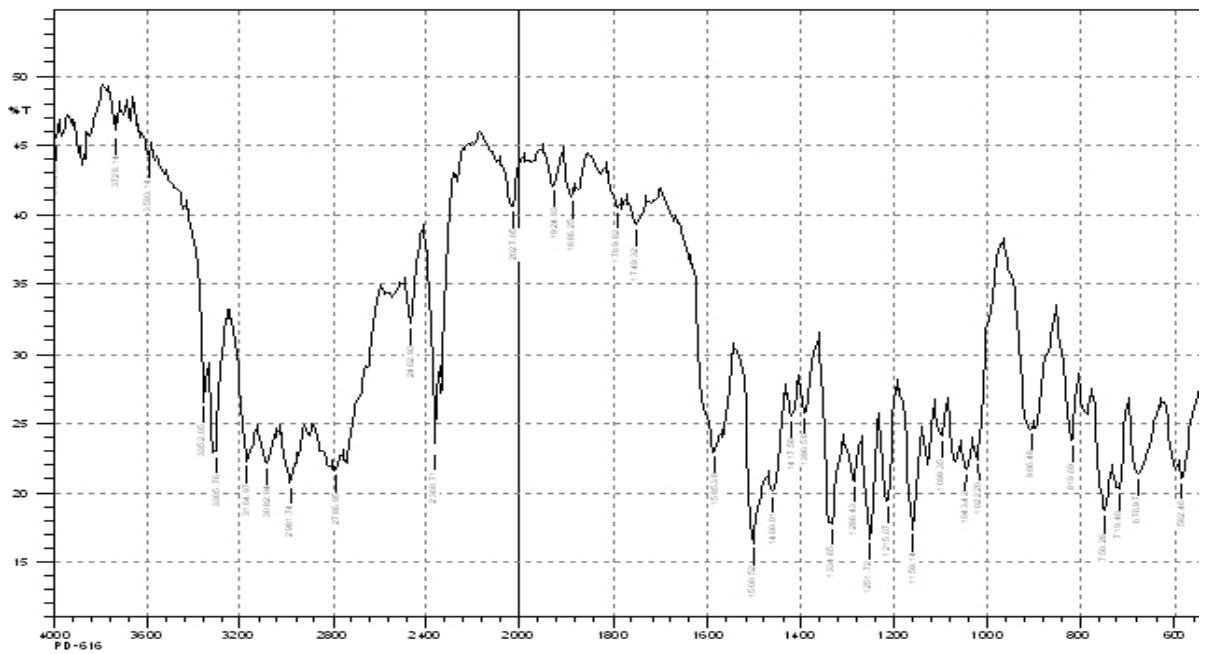


**Fig. 5.** IR Spectra of pure Tamsulosin

**Table 3.** Thermal stability of Tamsulosin and its binary mixture with excipients by IR.

| Functional groups | IR frequency of Drug & its binary mixtures with excipients ($cm^{-1}$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Tamsulosin** | **Ethyl cellulose** | **HPMC 15cps** | **Lactose** | **Eudragit S-100** | **Methyl cellulose** | **HPMC 5cps** | **Eudragit RL-100** | **Eudragit RS-100** | **Gelatin** |
| N-H stretching (Pry. amine) | 3352, 3305 | 3307.69 | 3353.98 | 3307.69 | 3305.76 | 3352, 3305 | 3352.05, 3307 | 3352, 3305.76 | 3352.05,3305.76 | 3352.05,3305.76 |
| C-H stretching (aromatic) | 3082.04 | 2977.89 | 3082.04 | 3082.04 | 3082.04 | 3082.04 | 3082.04 | 3083.96 | 3085.89 | 3082.04 |
| C-H stretching (aliphatic) | 2981.74 | 2977.89 | 2981.74 | 2981.74 | 2991.39 | 2985.60 | 2981.74 | 2985.60 | 2952.81 | 2979.82 |
| N-H bending ((Pry. amine)) | 1585.38 | 1585.38 | 1585.38 | 1577.66 | 1589.23 | 1585.38 | 1585.38 | 1585.38 | 1585.38 | 1583.21 |
| C=C stretching (aromatic) | 1500.58 | 1500.52 | 1500.52 | 1500.52 | 1496.66 | 1500.58 | 1502.44 | 1500.52 | 1498.59 | 1500.52 |
| C-H bending (aliphatic) | 1460 | 1386.72 | 1460.01 | 1460.65 | 1456.16 | 1460 | 1417.58 | 1456.32 | 1450.37 | 1460.01 |
| S=O (Asym) | 1334.65 | 1334.65 | 1334.65 | 1334.65 | 1334.65 | 1334.65 | 1334.65 | 1336.58 | 1334.65 | 1334.65 |
| C-N stretching (amino) | 1261.72 | 1251.72 | 1251.72 | 1251.72 | 1261.72 | 1261.72 | 1286.43 | 1251.72 | 1251.72 | 1251.72 |
| C-O-C stretching (Sym) | 1215.07 | 1215.07 | 1215.07 | 1215.07 | 1215.01 | 1215.07 | 1215.07 | 1215.07 | 1215.07 | 1215.07 |
| S=O(Sym) | 1159.14 | 1157.21 | 1157.21 | 1157.21 | 1157.21 | 1159.14 | 1159.14 | 1159.14 | 1159.14 | 1159.14 |
| C-OC stretching (Asym) | 1043.42 | 1043.42 | 1043.42 | 1041.49 | 1068.49 | 1043.42 | 1043.42 | 1043.42 | 1018.34 | 1043.42 |
| C-H OOPB (aromatic) | 906.48 | 908.41 | 906.48 | 892.98 | 914.20 | 906.48 | 906.48 | 914.20 | 908.41 | 906.48 |
| C-N OOPB (amino) | 819.48 | 819.69 | 819.69 | 817.76 | 819.69 | 819.69 | 817.76 | 821.62 | 825.48 | 817.76 |


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of C-H bending. The result of IR study of drug and their binary mixtures with excipient were constant and showed as supportive result of TG and DSC. However, further analysis is required using more sophisticated analytical methods e.g. NMR is required to confirm the interaction.

## 4. CONCLUSION

TG and DSC thermo-gram of TAM and its parallel combinations, with various excipients were recorded and their outcome were analyzed based on thermal stability pattern or mass percentage in TG while change or moving of endothermic peak and presence of new peak concerning temperature in DSC. TG and DSC join result showed that there is cooperation between to TAM with the ordinarily utilized excipients like ethyl cellulose, lactose and gelatin in different definitions while utilizing TG and DSC. However, while confirming suitability of these excipients through DSC decrease in melting point was found in the case ethyl cellulose, lactose and gelatin which is supposed to be an interaction. This interaction was slight confirmed by IR and therefore the study concludes that ethyl cellulose, lactose and gelatin were found to be incompatible with TAM and to be avoided for the preparation of thermally stable pharmaceutical formulations. More deep studies is required to confirm the interaction.

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## Conflict of Interest

The authors declare that the contents in this article have no conflict of interest.

## Statement of Contribution of Researchers

Both the authors have equal contribution.

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