WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

To Identification and Resolution of Tablet Defect for An Herbal Fixed Dose Combination

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ABSTRACT

Background:

The purpose of this research was to look at the discoloration of commercial fixed-dose herbal tablet formulations. Pharmaceutical incompatibilities are alterations in a dosage form's physical, chemical, and therapeutic qualities brought on by the interaction of the active pharmaceutical ingredient (API) with excipients or other elements of the medicinal product. The kind and degree of pharmacological excipient interactions are influenced by a wide range of variables. The interactions between drugs and excipients can be roughly divided into physical or chemical interactions. Several pharmaceutical products have post-marketing stability issues, which can be expensive for the company and cost doubt on the product's quality. In accordance with the study's FTIR and DSC analysis of the pure medicine and its physical combination with the excipients Also, use the desiccator and hot air oven drying methods to assess the moisture level of tablets.

Results:

It is clear from the examination of the literature that the anti-creaking ingredient calcium carbonate, which is utilized in herbal tablets, is incompatible with Neem, Bhoi Amli, Panchatikta, Haridrakhand, Katho, and Manjistha. Also, since the discolored tablet had a soft feel and a potential for discoloration owing to moisture content, this was also investigated.

Conclusion:

The analytical techniques led to the conclusion that calcium carbonate may be eliminated to provide a stable formulation without color problems. The new efficient formulation created by removing the incompatible excipients from the formulation was used to create the defect-free tablet formulation. Such a study for resolving actual market formulation problems can be highly beneficial to researchers and pharmaceutical formulators.

Keywords: Herbal tablets, Incompatibility, FTIR & DSC study, Discoloration.

Introduction

The aim of this study is to Identification and Resolution of Tablet Defect for An Herbal Fixed Dose Combination. A tablet is a solid dosage form which contains drug substances with or without proper diluents and prepared either by compression or moulding methods. According to the pharmacopoeia, tablets might be round, oval, oblong, cylindrical, triangular, or even discoid in form.

Tablets are a unit dosage form with the best capabilities of all oral dosage forms for the most precise dosing and the least amount of content fluctuation. Packaging and stripping them is simple and inexpensive, Cheap price, Smaller and lighter, Coating techniques can hide offensive odours and harsh tastes [1].

Fixed Dose Combination:

- Fixed-dose combination products (FDCs) are medicines which contain two or more active ingredients in fixed proportions in the same formulation. They are also called as “Fixed Dose Combinations”.
- One product with two or more fixed-dose active ingredients is available on the market [2,3].
- In this project fixed dose combination product are Neem, Bhoi Amli, Panchatikta, Katho, Manjistha, Haridrakhand.

- ✶ Initially, fixed dose combination drug products were used against Anti Allergic.

Drug- Excipient Compatibility Study:

- ✶ Pharmacological incompatibilities are often described as modifications to the physical, chemical, and therapeutic characteristics of a dosage form as a result of the interaction of the active pharmaceutical ingredient (API) with excipients or other elements of the medicinal product.
- ✶ A essential step in the development of a drug product's formulation is the investigation of drug-excipient compatibility.
- ✶ Generally, for excipient compatibility study combination of binary mixture in ratio of 1:1 is assessed.
- ✶ Drug-Excipient incompatibility studies performed by Differential Scanning Calorimetry (DSC) and FTIR.

Actual Product Problem:

- ✶ It is the real time industrial issue.
- ✶ Actual problem of tablet is discoloration after long time storage.
- ✶ Product is Neem, Bhoi Amli, Manjistha, Haridrakhand, Katho, Panchatikta.
- ✶ Main Problem is the Drug-Excipient Interaction in the Product.

Advantages:

- ✓ Tablets are a unit dosage form with the best capabilities of all oral dosage forms for the most precise dosing and the least amount of content fluctuation.
- ✓ Packaging and stripping them is simple and inexpensive.
- ✓ Cheap price.
- ✓ Smaller and lighter.
- ✓ Being the most microbiological and chemically stable of all oral dose formulations.
- ✓ Very suited for industrial manufacturing.
- ✓ Simple to swallow with minimal hang-up potential.
- ✓ Coating techniques can hide offensive odours and harsh tastes.
- ✓ Enteric coating makes sustained release products conceivable.
- ✓ Simple to operate [4].

Method

The aim of this study is to Identification and Resolution of Tablet Defect for An Herbal Fixed Dose Combination for the treatment of used against Anti Allergic. To study discoloration and coating issues of the product. To investigate possible root causes for the discoloration issue. The design of the study included wet granulation method, coating method, drug-excipient incompatibility study. The herbal drug is use in this formulation included Neem, Bhoi Amli, Panchatikta, Katho, Manjistha, Haridrakhand and other excipient use in this dosages form.

Wet Granulation

Wet granulation figure is donated below (Figure 1.)

1. Milling of drugs and excipients
2. Mixing of milled powders
3. Preparation of binder solution
4. Mixing binder solution with powder mixture to form wet mass.
5. Coarse screening of wet mass using 6- to 12- mesh
6. Drying moist granules

7. Screening dry granules with lubricant and disintegrant
8. Mixing screened granules with lubricant and disintegrant
9. Tablet compression [5]

Types of Coating Processes

Three main types of coatings used in the pharmaceutical industry are.

• Sugar coating

• Compression coating

• Film coating

Sugar Coating

- ✶ It entails coating the tablet core with coating formulations based on sucrose in stages using the appropriate coating equipment.
- ✶ Each pill is covered in a coating of thick sugar when the water from the syrup evaporates.
- ✶ Frequently glossy and strongly coloured, sugar coatings.
- ✶ Typically, tablets are coated in sugar using the panning process, which combines a standard revolving sugar pan with a thermostatically regulated supply of drying air.
- ✶ Tablets are gently poured or sprayed, abused by portion, onto the pan as it rotates, enabling them to come into contact with the coating solutions as warm air is circulated to expedite drying. Only when the earlier coat has dried is the subsequent coat applied.

Steps In Sugar Coating:

1) Seal coating
2) Sub coating
3) Syrup coating/Smoothing
4) Colour coating
5) Polishing

1. Sealing (Waterproofing)

- ✶ To do this, one or more coatings of a water-proofing chemical were applied using an alcoholic spray, such as the conventionally used shellac or synthetic polymers like CAP.
- ✶ WHY?
- ✶ Sugar-coatings are aqueous formulations that allow water to enter the tablet core directly, thus impacting the stability of the product and maybe resulting in an early tablet disintegration.

2. Sub coating

- ✶ The tablet core is frequently covered with thick sugar coatings, which typically increase the pill weight by 50% to 100%.
- ✶ WHY?
- ✶ To smooth down the tablet's edge. This stage involves the bulk of the material build-up, which is carried out by incorporating a bulking agent, such calcium carbonate, into the sucrose solution.
- ✶ Anti-adherents e.g. Talc may be added after partial drying to prevent sticking of the tablets together.

3. Smoothing / syrup coating

- ✶ For covering and fill up imperfections on the surface brought on by sub coating on tablets.
- ✶ To impart desired colour
- ✶ The first syrup coat contains some suspended powders and are call “grossing syrup “
- ✶ Syrup solutions containing the dye are applied until desired size and colour are attained.

- Dilute colourants can be used to create coloured base that helps with consistent coating in following processes.

4. Finishing

- Final syrup coating step
- Few clear coats of syrup may be applied.

5. Polishing

- Desired luster is obtained in this final step.
- Clean standard coating pan, canvas-lined coating pans
- Application of powdered wax or warm solution of waxes in suitable volatile solvent [6].

List of Material

Here listed below (Table 1.)

Results

Evaluation parameter

- The film-coated tablets were evaluated for the quality parameters, namely tablet thickness, uniformity of weight, crushing strength, and friability. A Vernier calliper was used to measure the thickness and diameters of film-coated tablets.
- Evolution parameter result table listed below (Table 2.)
- Batch 1 to batch 7 tablets figures below (Figure 2 to 8)

Drug Excipient Incompatibility

FTIR Study [7-10]

Sample of pure Herbal drug (Neem, Bhoi Amli, Panchatikta, Katho, Manjistha, Haridrakhand) as well as sample of physical mixture (Drug + Excipients) were analysed by Fourier-transform Infrared (FTIR) Study.

FTIR data of physical mixture Beeswax: Calcium Carbonate:

- Characteristic Peaks of Beeswax and Calcium carbonate retained. So, there is incompatibility found between Beeswax and Calcium carbonate.
- FTIR Figure & Table listed below. (Figure 9) (Table 3)

FTIR data of physical mixture Starch: Calcium Carbonate:

- Characteristic Peaks of Starch and Calcium carbonate retained. So, there is incompatibility found between Starch and Calcium carbonate.
- FTIR Figure & Table listed below. (Figure 10) (Table 4)

FTIR data of physical mixture Gelatine: Calcium Carbonate:

- Characteristic Peaks of Gelatine and Calcium carbonate retained. So, there is incompatibility found between Gelatine and Calcium carbonate.
- FTIR Figure & Table listed below. (Figure 11) (Table 5)

FTIR data of physical mixture Iso Propyl Alcohol: Calcium Carbonate:

- Characteristic Peaks of Isopropyl Alcohol and Calcium carbonate retained. So, there is incompatibility found between Isopropyl Alcohol and Calcium carbonate.
- FTIR Figure & Table listed below. (Figure 12) (Table 6)

DSC Study:

Sample of pure Herbal drug (Neem, Bhoi Amli, Panchatikta, Katho, Manjistha, Haridrakhand) as well as sample of physical mixture (Drug + Excipients) were analysed for Differential Scanning Calorimetry (DSC) Study.

DSC Data of Bees wax and Calcium carbonate Physical Mixture:

- Characteristic Peaks of Beeswax and Calcium carbonate retained. So, there is incompatibility found between Beeswax and Calcium carbonate.

- DSC data figure listed below (Figure13)

DSC Data of Pure Neem and Calcium carbonate Physical Mixture:

- Characteristic Peaks of Neem and Calcium carbonate retained. So, there is incompatibility found between Neem and Calcium carbonate.
- DSC data figure listed below (Figure 14)

DSC Data of Pure Gelatine and Calcium carbonate Physical Mixture:

- Characteristic Peaks of Gelatine and Calcium carbonate retained. So, there is incompatibility found between Gelatine and Calcium carbonate.
- DSC data figure listed below (Figure 15)

DSC Data of Pure Starch and Calcium carbonate Physical Mixture:

- Characteristic Peaks of Starch and Calcium carbonate retained. So, there is incompatibility found between Starch and Calcium carbonate.
- DSC data figure listed below (Figure 16)

Discussion

In this study is to Identification and Resolution of Tablet Defect for An Herbal Fixed Dose Combination. In this project fixed dose combination product are Neem, Bhoi Amli, Panchatikta, Katho, Manjistha, Haridrakhand. Initially, fixed dose combination drug products were used against Anti Allergic. An essential step in the development of a drug product's formulation is the investigation of drug-excipient compatibility. It is the real time industrial issue. Actual problem of tablet is discoloration after long time storage. We have performing Identification of incompatible excipients. Exploration of possibility for replacing incompatible excipients. Preparing final stable formulation without discolorations issue. Benefits to this project we will get the more stable dosage form compared to previous dosage form. Benefits from this project we will get better coated tablets compared to previous uncoated tablets to overcome problems of hygroscopicity and uneven shape. Calcium carbonates are incompatible with Iso propyl alcohol, active ingredient, bees wax, starch, gelatin. So, calcium carbonate removed in this formulation and find a new formulation without discolorations issue.

Conclusion

In this project investigate discoloration issue of marketed fixed dose herbal tablet formulation Neem, Bhoi Amli, Panchatikta, Katho, Manjistha, Haridrakhand. As per the study performing FTIR and DSC study of Drug and Excipients physical mixture and pure drug. As per literature survey, it was evident that both herbal AIP, bees wax, starch, isopropyl alcohol, gelatine is incompatible with calcium carbonate. From the analytical methods, it was concluded that calcium carbonate can be removed to obtain final stable formulation without discoloration issues. Benefits to this project we will get the more stable dosage form compared to previous dosage form. Benefits from this project we will get the better coated tablet compared to previous uncoated tablets to overcome problems of hygroscopicity and uneven shape.

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List of Tables

Table 1. Formulation table

Sr no.	Drug & Excipient	Defective formulation (Each tablet)	New formulation (Each tablet)
1.	Neem	50mg	50mg
2.	Panchatikta	40 mg	40 mg
3.	Katho	40 mg	40 mg
4.	Haridrakhand	30 mg	30 mg
5.	Manjistha	40 mg	40 mg
6.	Bhoi Amli	50 mg	50 mg
7.	Gelatine	100 mg	100 mg
8.	Sugar	180 mg	180 mg
9.	Starch	100 mg	100 mg
10.	Shellac	7.5 mg	7.5 mg
11.	Iso Propyl Alcohol	20 ml	20 ml
12.	Talc	60 mg	60 mg
13.	Calcium Carbonate	100 mg	-
14.	Brilliant Blue	0.35 mg	0.35 mg
15.	Bees Wax	0.3 mg	0.6 mg
16.	Carnauba Wax	0.3 mg	-
17.	Benzene	9 ml	-
18.	Iso Propyl Alcohol	-	9 ml

Table 2. Evaluation Parameter Result

Parameter	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7
Colour	Brownish	Light blue	Light blue	Dark blue	Greenish	Brilliante blue	Brilliante blue
Hardness (kg/cm^2)	9	8	8	6	7	4	3
Thickness (mm)	10	9	11	11	9	7	7
Friability (%)	0.399	0.365	3.955	3.857	0.372	0.324	0.302
Dissolution (%)	85.52	89.74	85.31	95.00	97.76	98.26	98.93
Disintegration (min)	16	17	19	15	14	14	14
Weight variation	Pass	Pass	Pass	Pass	Pass	Fail	Fail

TABLE 3. Physical mixture Beeswax: Calcium Carbonate

Functional group	Reference bands (cm^{-1})	Observed bands (cm^{-1})
For Beeswax identification [20]		
Stretching vibrations of C-H groups	2894	2849
Stretching vibration of C-O-C groups	1733	1794
Stretching vibration of C-O-C groups	1170	1377
Bending of C-H groups	956	874
Nonplanar skeletal deformation vibration of long chain hydro	780	730
For Calcium carbonate identification [21]		
Out plane bending & Asymmetrical stretching vibration peaks O-C-O	713, 865,1419	730, 874, 1463

TABLE 4. Physical mixture Starch: Calcium Carbonate

Functional group	Reference bands (cm^{-1})	Observed bands (cm^{-1})
For Starch identification [22]		
Stretching mode of O-H	3393	3304
Intermolecular H-bond involving Carboxyl group	1648	1638
C-O	1155	1151
C-H	2931	2918
For Calcium carbonate identification [21]		
Out plane bending & Asymmetrical stretching vibration peaks O-C-O	713, 865,1419	762, 874, 1397

TABLE 5. Physical mixture Gelatin: Calcium Carbonate

Functional group	Reference bands (cm^{-1})	Observed bands (cm^{-1})
For Gelatin identification [23]		
Amide-I	1630	1649
Amide-II	1565	1561
Amide-III	1240	1397
Symmetric Methyl group	1460	1459
Asymmetric Methyl group	1380	1397
For Calcium carbonate identification [21]		
Out plane bending & Asymmetrical stretching vibration peaks O-C-O	713, 865,1419	734, 874, 1459

TABLE 6. Physical mixture Iso Propyl Alcohol: Calcium Carbonate

Functional group	Reference bands (cm^{-1})	Observed bands (cm^{-1})
For Isopropyl Alcohol identification [24]		
C-H Stretch	2930	2929
C=O Stretch	1710	1703
C-H	1457	1610
For Calcium carbonate identification [21]		
Out plane bending & Asymmetrical stretching vibration peaks O-C-O	713, 865,1419	711, 872, 1379

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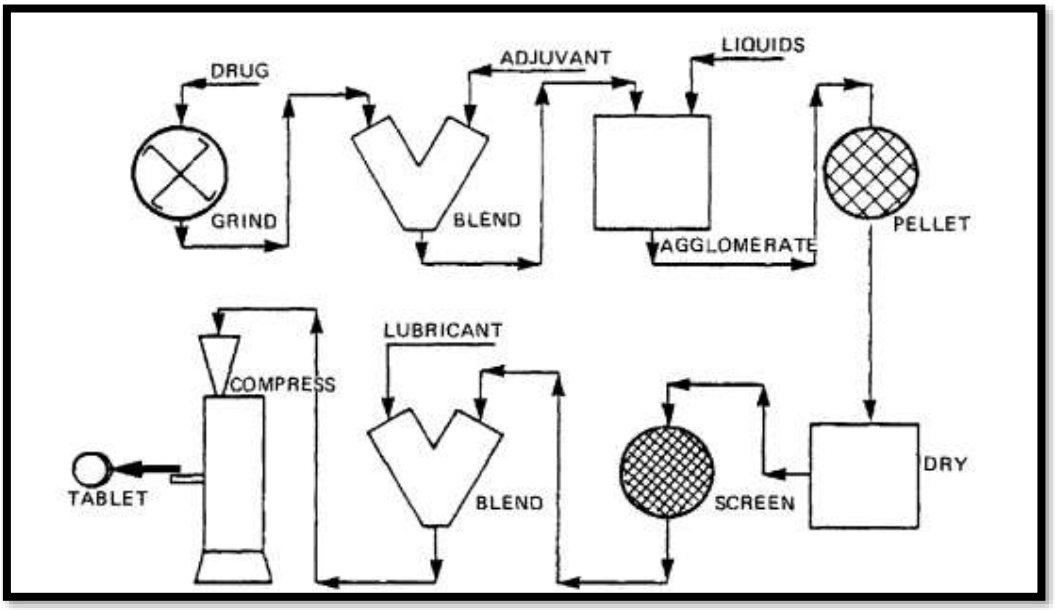

Figure 1. Wet Granulation Method [18]

Figure 2. batch 1

Figure 3. batch 2

Figure 4. batch 3

Figure 5. batch 4

Figure 6. batch 5

Figure 7. batch 6

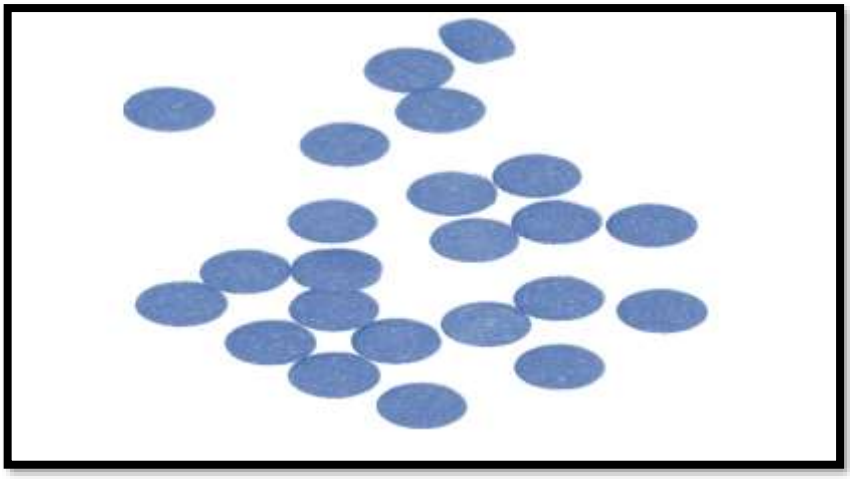

Figure 8. batch 7

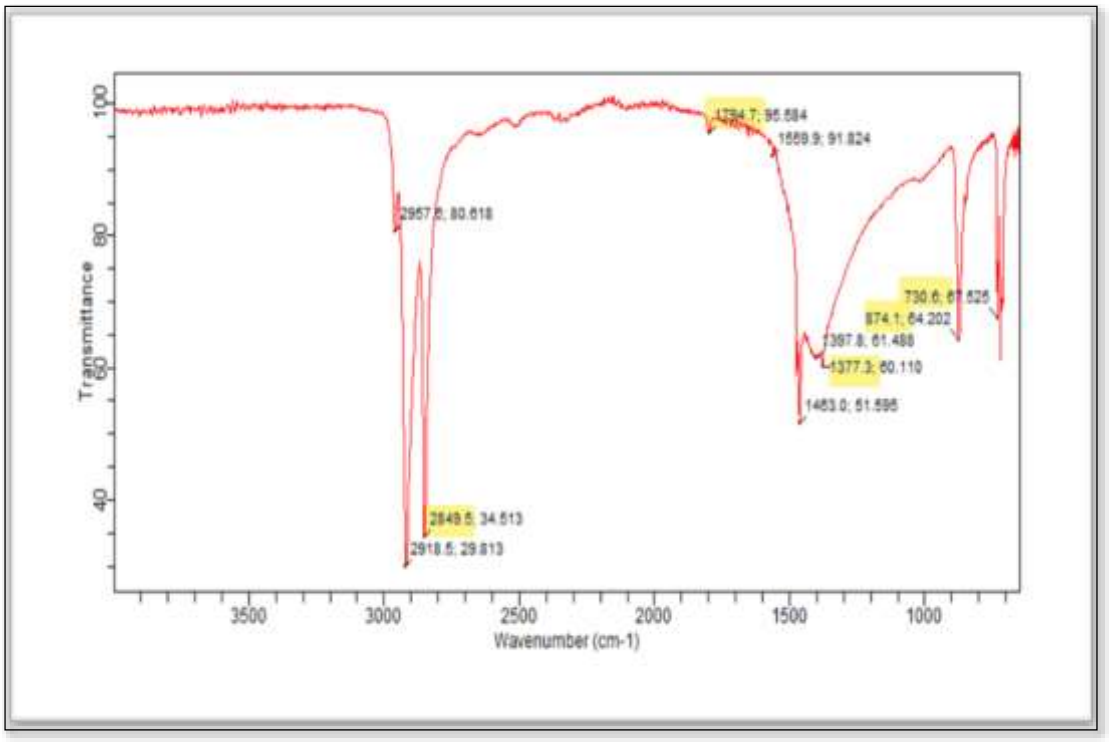

Figure 9. FTIR data of physical mixture Beeswax: Calcium Carbonate

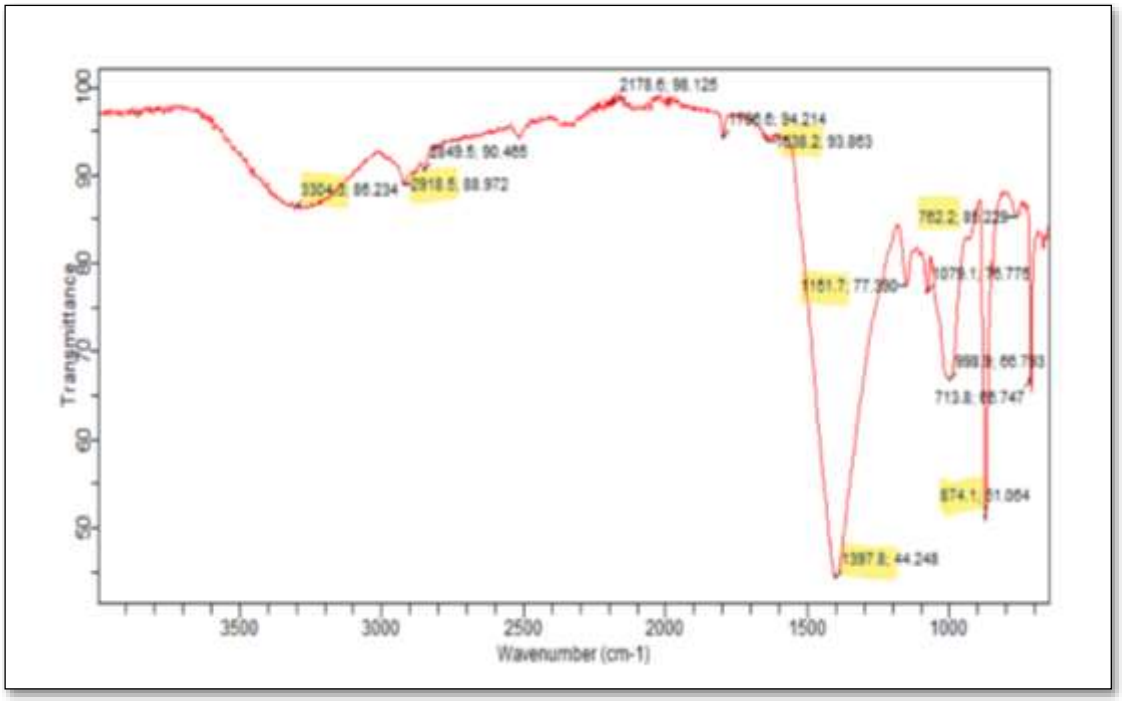

Figure 10. FTIR data of physical mixture Starch: Calcium Carbonate

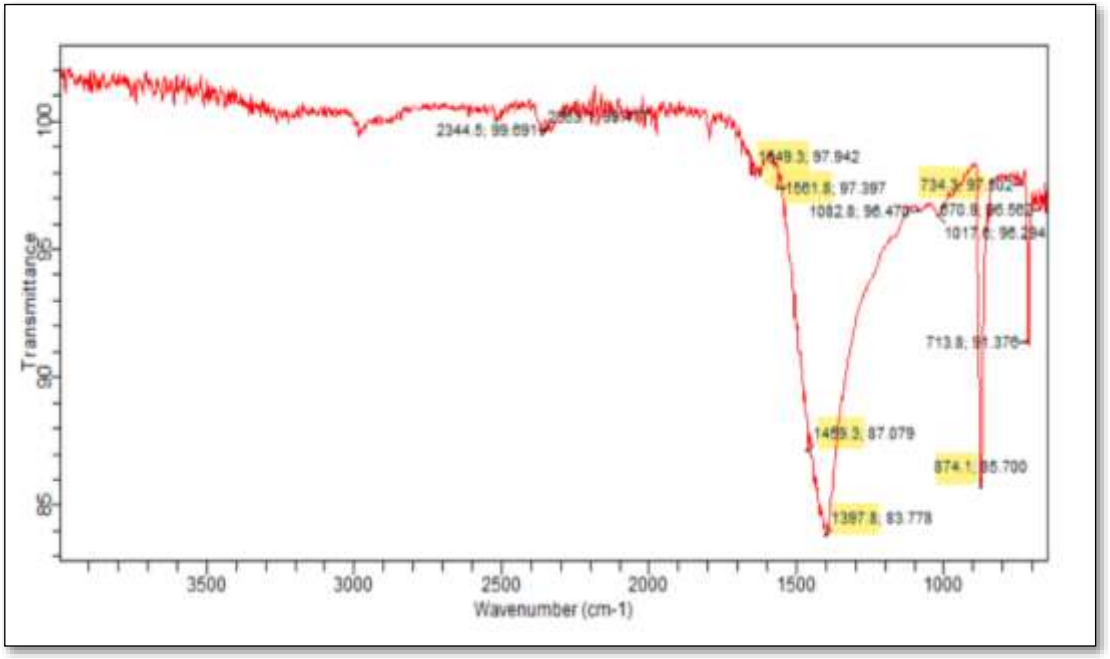

Figure 11. FTIR data of physical mixture Gelatine: Calcium Carbonate

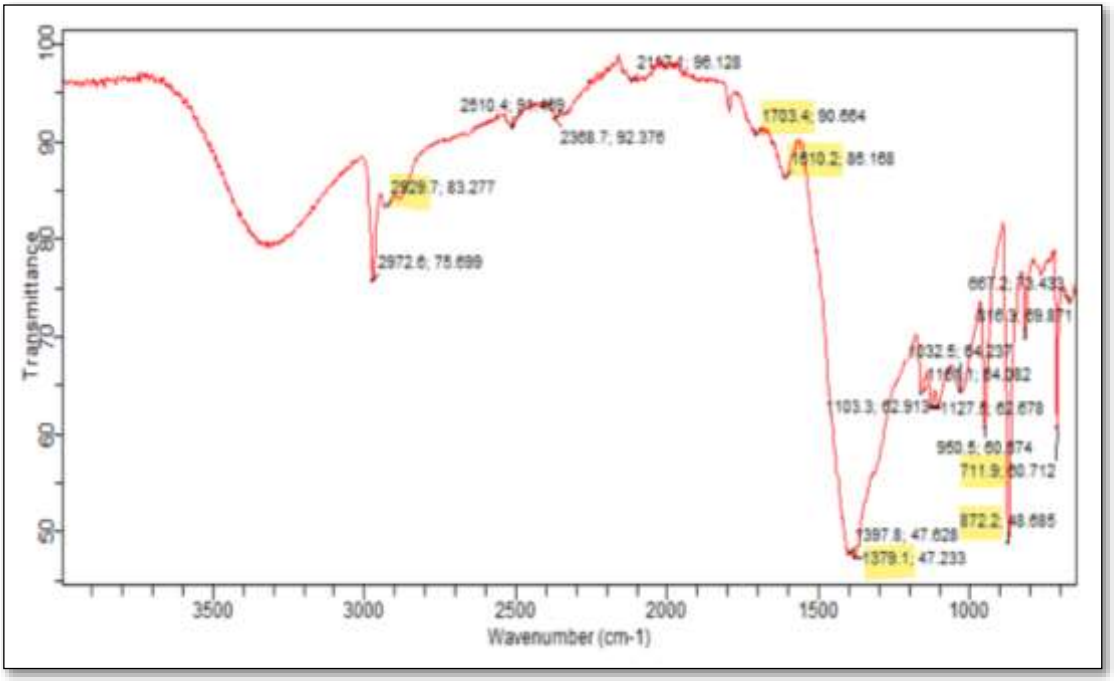

Figure 12. FTIR data of physical mixture Iso Propyl Alcohol: Calcium Carbonate

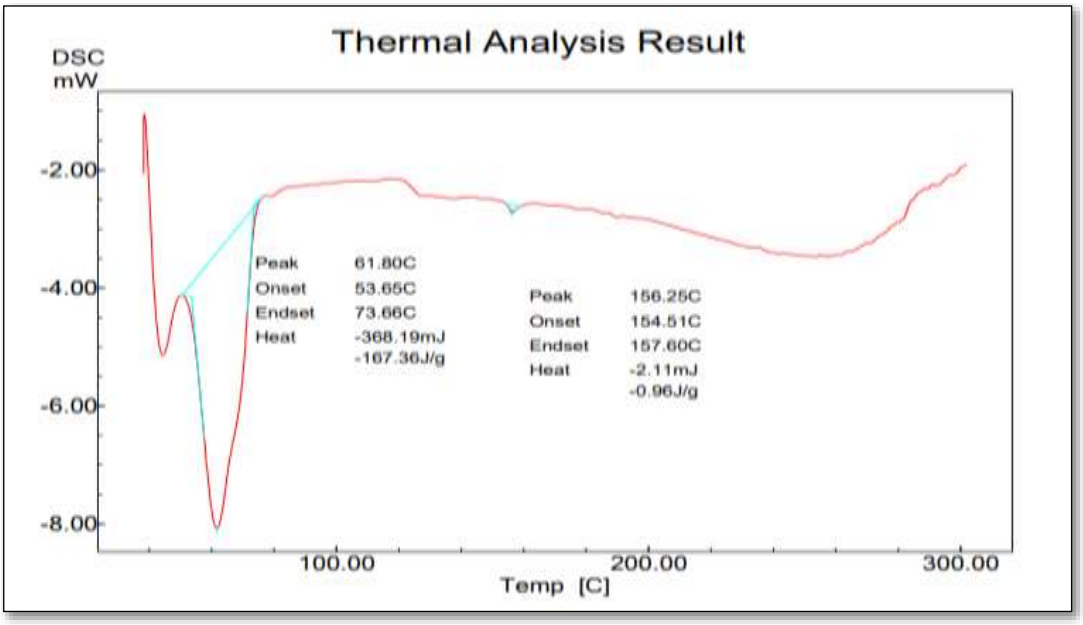

Figure 13. DSC Data of Pure Beeswax and Calcium carbonate Physical Mixture

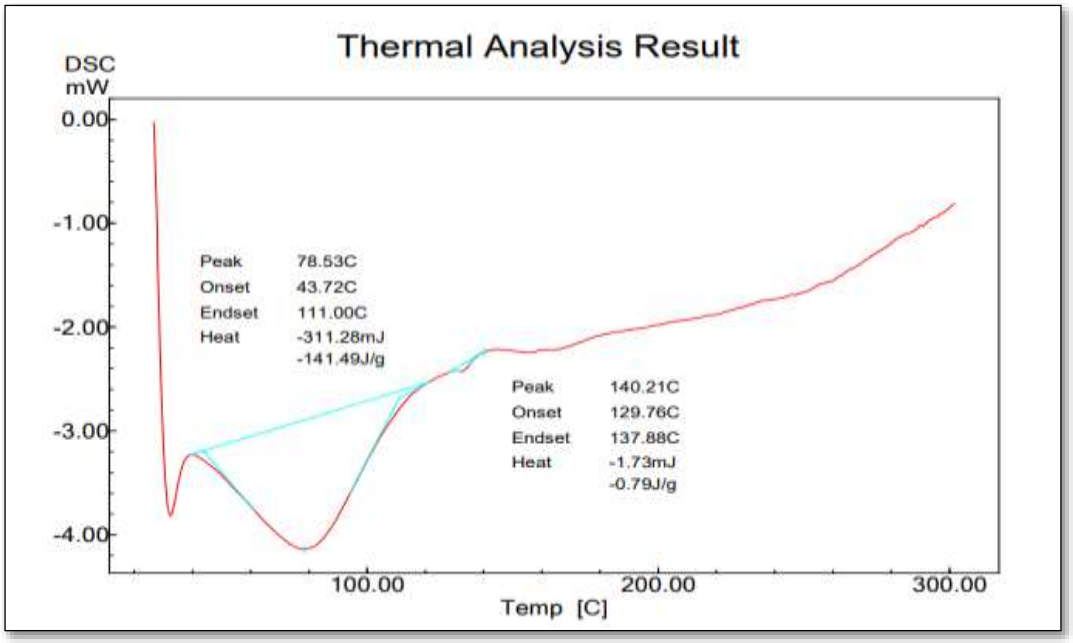

Figure 14. DSC Data of Pure Neem and Calcium carbonate Physical Mixture

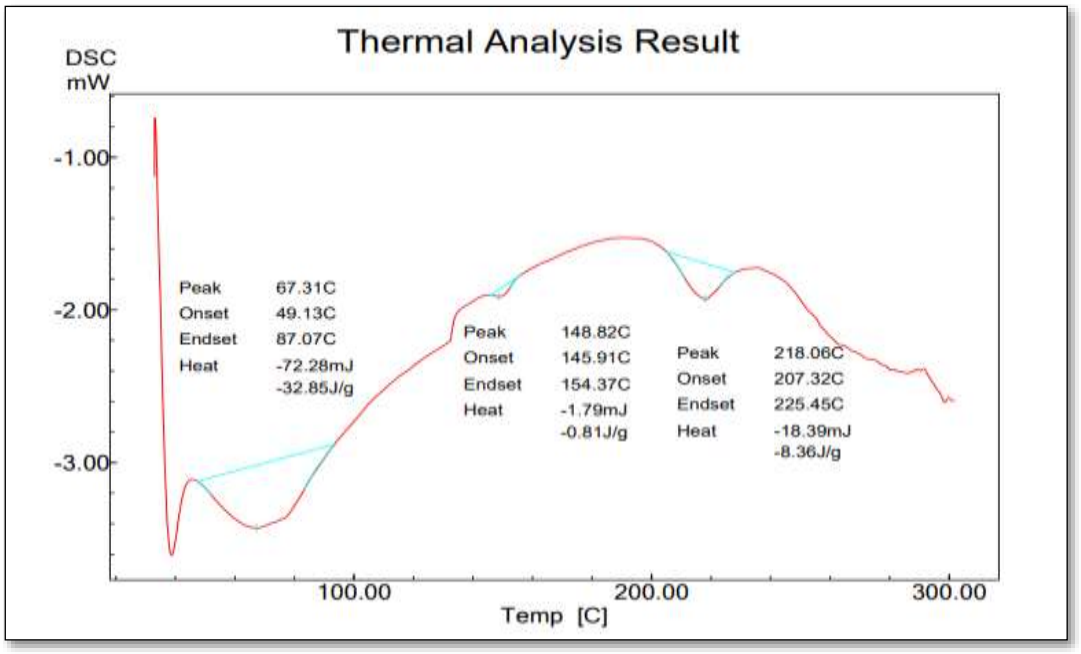

Figure 15. DSC Data of Pure Gelatin and Calcium carbonate Physical Mixture

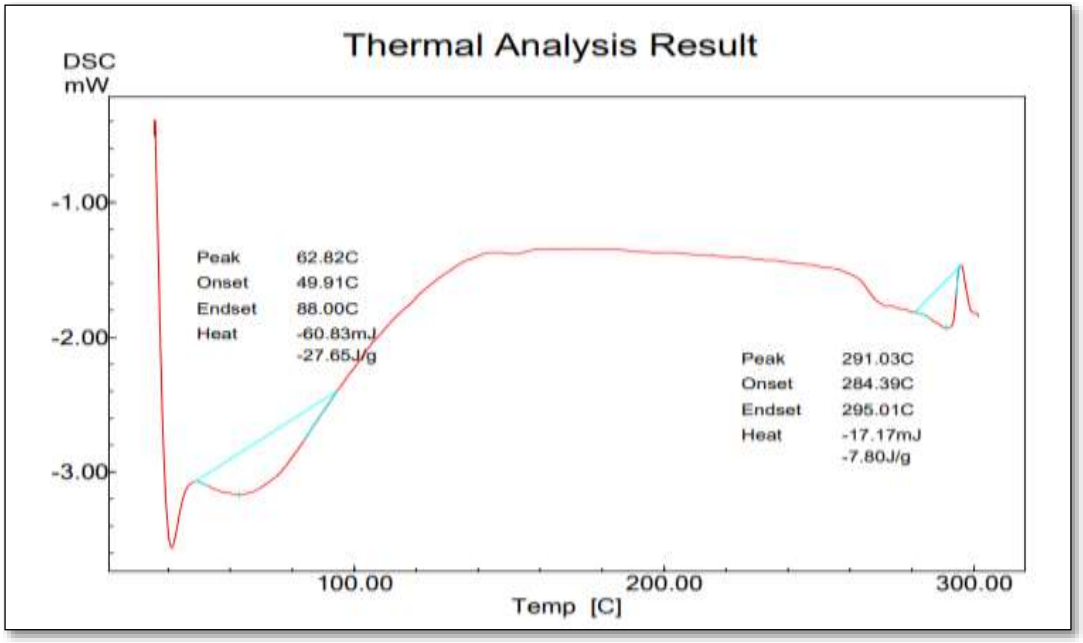

Figure 16. DSC Data of Pure Starch and Calcium carbonate Physical Mixture

Abbreviations

FTIR	Fourier-transform Infrared
DSC	Differential Scanning Calorimetry
API	Active Pharmaceutical Ingredient
FDC	Fixed dose combination