



PREFORMULATION STUDIES OF BUDESONIDE API: AN INTEGRAL PART OF FORMULATION DESIGN

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Abstract: Preformulation is defined as the study of the physical and chemical characteristics of pharmacological compounds both on their own and in combination with excipients. The primary step in the rational development of the dosage forms for the medicinal drug substance is preformulation research. Studying preformulation factors can help create pharmaceutical formulations that are dependable, safe, and effective. The aim of this study is to determine some of the physicochemical properties such as solubility, melting point, lambda max, infra-red spectra, etc. Budesonide is a glucocorticoid used in the treatment of asthma, inflammatory bowel disease, etc. The budesonide was studied for the various properties and the results for the organoleptic characteristics were found to be white crystalline powder. The melting point in average was found to be 228 °C. The solubility of budesonide in water was found to be low and was found to be higher in phosphate buffer pH 1.2.

Index Terms – Preformulation study, Budesonide, Solubility and Analytical methods.

I. INTRODUCTION

Due to a change in the focus of industrial pharmaceutical product development, preformulation emerged in the late 1950s and early 1960s. The earliest programs that may be called "preformulation" were inspired by advancements in analytical techniques^[1]. It is described as a study of the physical and chemical characteristics of pharmacological compounds both on their own and in combination with excipients^[2]. The first stage in the rational development of dosage forms for a medicinal substance is preformulation research^[3]. The study looks at the physical and chemical characteristics of a drug substance both by itself and when coupled with an excipient^[3]. If a deficit is found, a molecular modification is made using salts, prodrugs, solvates, polymorphs, or even new analogues. It comprises preliminary research and molecular optimization by the drug should be tested to evaluate the severity of each suspected issue area^[1]. Preformulation studies are intended to provide essential information, particularly about the physicochemical, physio mechanical, and biological aspects of medicinal compounds^[4]. Preformulation testing's main goal is to generate data that will assist the formulator in creating stable, bioavailable dosage forms that can be mass manufactured^[3]. Preformulation studies are conducted to provide the required information, particularly on the physical, chemical, mechanical, and biological characteristics of drug ingredients, excipients, and packaging components^[3]. The physicochemical characteristics of the novel molecule that may have an impact on therapeutic performance and the development of an effective dosage form should be the focus of these investigations. A thorough comprehension of these characteristics may eventually justify formulation design or demonstrate the necessity of molecular change^[5]. The aim of this study is to determine some of the physicochemical properties such as solubility, melting point, lambda max, infra-red spectra, etc. Budesonide (1S,2S,4R,8S,9S,11S,12S,13R)-11-hydroxy-8-(2-hydroxyacetyl)-9,13-dimethyl-6-propyl-5,7-dioxapentacyclo icosa-14,17-dien-16-one) is a glucocorticoid used in the treatment of asthma. It also has

the role as an anti-inflammatory agent. Therefore, it can be used in various inflammations. It is used to treat Chronic Obstructive Pulmonary Disease (COPD), Crohn's disease, Ulcerative colitis, etc^[6]. 9 milligrams (mg) daily administered orally as a controlled-release capsule is the recommended dosage for treating an acute aggravation of inflammatory bowel disease (Crohn's disease). The daily maintenance dose is 3 mg. Treatment of 6 to 9 patients with active Crohn's disease involved oral administration of a slow release coated version of budesonide, 3 milligrams three times per day for 6 weeks, then 2 milligrams three times per day for 6 weeks.

II. MATERIALS

The drug/API budesonide was purchased from the Vamsi Labs Ltd., A-14/15, MIDC Area, Chincholi, Solapur, Maharashtra, India. Other chemicals such as phosphate buffer pH 1.2 to 7.4, liquid paraffin, potassium bromide, etc. were used of standard grade obtained from the local chemical shops. The instruments used such as Metler Toledo balance, UV-Vis Spectrophotometer V-630 Jasco, FT-IR Spectrophotometer Jasco, Differential Scanning Colorimetry Setline Setaram, etc.

III. METHODS

3.1 Organoleptic Characteristics:

The organoleptic characteristics such as color, odor, taste, etc. were visually checked for budesonide API.

3.2 Saturation Solubility:

10 mL of the appropriate pH medium were taken in 50 ml of beaker to determine the saturation solubility of the drug in distilled water and various other buffers ranging from pH 1.2 to 7.4. An excess amount of drug was added in each beaker, and then it was sealed with aluminum foil. The magnetic stirrer was used to stir these glass beakers. The temperature was maintained at roughly $37 \pm 0.5^\circ\text{C}$ while stirring was carried out for 48 hours at a speed of 50 rpm. Then, Whatman filter paper was used to filter the test samples that were the outcome. The filtrate was collected, and the drug's absorbance was measured with a UV Visible Spectrophotometer (UV V-630 Jasco) at 245 nm after suitable dilutions with the same solvent. The drug's standard curve in each relevant solvent was then used to convert the absorbance into concentration^[7].

3.3 Melting Point Determination:

The melting point of the budesonide was determined by using Thiele's tube and capillary method. In this method, the powder sample whose melting point is to be determined is filled into the capillary by sealing one side of the capillary tube. The Thiele's tube containing liquid paraffin is attached to the metal stand. The sealed capillary containing the sample attached to the thermometer is immersed in Thiele's tube. The Thiele's tube was heated with the Bunsen burner and the melting of the sample in the capillary was observed. The temperature at which the sample starts to melt was noted as the melting point.

3.4 Micromeritics:

According to the approach described below, the parameters bulk density, tapped density, Carr's index, angle of repose, and Hausner ratio of the drug budesonide were assessed.

3.4.1 Bulk Density:

10 gm of precisely weighed drug budesonide was added to a 25 ml measuring cylinder. Without moving the cylinder, the budesonide's volume was measured, and the bulk density was determined using the equation below.

$$\text{Bulk Density} = \frac{\text{Weight of drug (g)}}{\text{Volume of drug (ml)}}$$

3.4.2 Tapped Density:

Budesonide, accurately weighed at 10 gm, was added to a 25 ml measuring cylinder. A set number of taps (100) were applied to the cylinder until there was no longer any volume change with further taps. The final volume was recorded, and the tapped density was determined using the equation below:

$$\text{Tapped Density} = \frac{\text{Weight of drug (g)}}{\text{Volume of drug after tapping (ml)}}$$

3.4.3 Carr's Index:

The Carr's compressibility index of the drug can be calculated by using the following formula:

$$\text{Carr's Compressibility Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

3.4.4 Hausner's Ratio:

The Hausner's ratio of the drug can be calculated by using the following formula:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

3.4.5 Angle of Repose:

By using the fixed funnel technique, the Angle of repose (AR) of the drug was calculated. 10 grammes of powder that had been precisely weighed were put through a glass funnel with a capacity of 25 ml and a diameter of 0.5 cm. The funnel has been adjusted such that its stem is 2.5 cm above the horizontal surface. The height of the pile (h) barely reached the funnel's tip because the sample was allowed to trickle out of the funnel. By drawing a border around the pile's perimeter and averaging its three diameters, the diameter of the pile (d) was calculated. The angle of repose was determined using:

$$\theta = \tan^{-1} \frac{2h}{d}$$

3.5 Determination of λ_{max} :

A weighed 10 mg dose of the drug was dissolved in 100 ml of a 50:50 solution of water and methanol in a volumetric flask. One milliliter of this stock solution was pipetted into a 10-milliliter volumetric flask, and the remaining volume was topped off with a 50:50 mixture of water and methanol. A UV/Vis double-beam spectrophotometer was used to scan the resultant solution between 200 and 400 nm^[8].

3.6 Calibration Curve:

In a volumetric flask (10 ml), 10 mg of budesonide was precisely weighed, dissolved in 5 ml of phosphate buffer (pH 7.4), and the volume was adjusted to 10 ml using the phosphate buffer (pH 1.2, 6.8, 7.4). To obtain a stock solution of 100 µg/ml, a 1 ml aliquot of the solution was collected, transferred to a volumetric flask (10 ml), and weakened to 10 ml using phosphate buffer solution. Aliquots of 1 ml, 2 ml, 3 ml, 4 ml, and 5 ml from this stock arrangement were transferred to volumetric flasks (10 ml) and volume was built up to 10 ml buffer of phosphate. Utilizing Whatman filter paper, the liquids were purified. Then the solution was compared to a blank phosphate buffer to screen for absorbances at 245 nm. The calibration curve was established by graphing the drug absorbance versus budesonide concentration. With the use of a regression linear analysis program, a straight line of best fit was obtained^[8].

3.7 Fourier Transform Infra-Red (FT-IR) Spectroscopy:

The infrared spectrum is crucial proof that provides sufficient information on a compound's structure. The FTIR method provides a range that includes a sizeable amount of the band of absorption from which a wealth of information about the structure of an organic chemical can be deduced. The FTIR spectra was obtained by triturating the sample in the ratio of drug: potassium bromide (1:10). The sample budesonide was taken around 10 mg and potassium bromide was accurately weighed 100mg and both were triturated in the mortar and pestle to fine powder. Using this sample, the IR spectra were obtained against the blank as potassium bromide. The IR spectra was obtained in the range of 400 to 4000 cm⁻¹ ^[9].

3.8 Differential Scanning Calorimetry (DSC):

One of the most crucial factors for determining the purity of a drug is DSC. The melting point is sharp and constant in pure substances. The spectrum of melting points that may be used to describe the medicine is limited because it contains a variety of substances. The DSC determined the melting point. In a non-hermetically crimped aluminum pan, 2- 4 mg of the sample were heated at a rate of 5°C/min from 0 to 300°C. The melting point of Budesonide was determined using the DSC thermogram that was acquired^[10].

3.9 Loss on Drying (LOD):

Although occasionally it may relate to the volatile matter loss from the sample, this approach is primarily used to determine the moisture of a sample. The IR moisture balance determination measures LOD. First, the instrument's knob was used to calibrate it. Next, 5.00 g of powder was heated to between 100°C and 105°C for 15 minutes. After that, the knob was used to set a steady reading and calculate the percentage of moisture^[10].

IV. RESULTS AND DISCUSSIONS:

4.1 Organoleptic Characteristics:

The organoleptic characteristics such as color, appearance, and nature of the drug budesonide were checked. The results are given in the below table.

Table 1: Organoleptic characteristics of Budesonide.

Drug Name	Organoleptic Characteristics	Results
Budesonide	Color	White or almost white
	Appearance	Crystalline
	Nature	Solid

4.2 Saturation Solubility:

The saturation solubility of the drug budesonide was studied in distilled water and the phosphate buffer solutions of pH 1.2, 6.8, and 7.4. The data compiled after 48 hrs. is given in the below table. As the result obtained the budesonide was found to have limited solubility in distilled water. The highest solubility was found in the buffer with pH 1.2.

Table 2: Saturation solubility of Budesonide in different Solvents.

Sr No.	Drug	Solvent	Saturation Solubility
1.	Budesonide	Water	26.076 µg/ml
2.		Phosphate buffer pH 1.2	98.145 µg/ml
3.		Phosphate buffer pH 6.8	70.983 µg/ml
4.		Phosphate buffer pH 7.4	30.928 µg/ml

4.3 Melting Point:

The melting point of the budesonide was determined by using the capillary method. The melting of the budesonide was found to be 228°C in an average with three replicates which was compared to that found in the literature in the range of 224 to 232°C. The obtained melting point is in the range of standards obtained from literature. This confirms the purity of the obtained budesonide sample.

Table 3: Melting point of Budesonide.

Drug Name	Melting point results		
	Practical	Average	Standard
Budesonide	227°C	228.3°C	224-232°C
	230°C		
	228°C		

4.4 Micromeritics:

The bulk characteristics of the budesonide were examined by using the procedures explained. The obtained results are given in the table. As per the results, Carr's index of the budesonide was found to be 15.29 which indicates the flow property of budesonide is good. Similarly, Hausner's ratio and the Angle of repose of budesonide were found to be 1.18 and 34.12 respectively which similarly indicate the flow property of budesonide as good.

Table 4: Bulk characterization of Budesonide.

Sr. No.	Bulk Characterization parameter	Results	Flow property
1.	Bulk density	0.72 g/ml	-
2.	Tapped density	0.85 g/ml	-
3.	Carr's index	15.29	Good
4.	Hausner's ratio	1.18	Good
5.	Angle of repose	34.12	Good

4.5 λ_{max} of Budesonide:

The λ_{max} of budesonide was determined by UV-Vis spectrophotometer via a spectra measurement option. The solvents used for the determination of the calibration curve of budesonide were methanol and water in a 1:1 ratio and phosphate buffer pH 6.8. The λ_{max} in both the solvents was found to be 245 nm (Figure 8) which is closer to that of the standard λ_{max} which is 246.

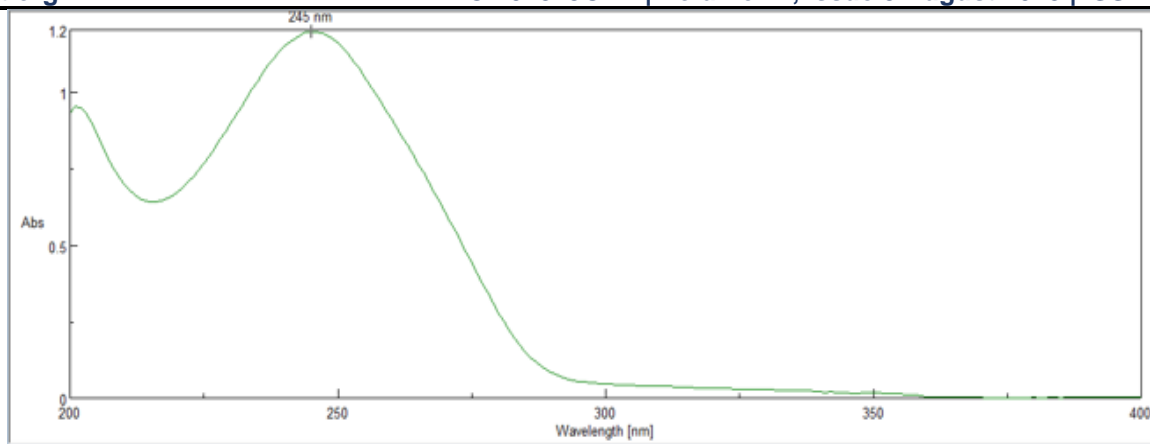


Figure 1: λ_{\max} of Budesonide.

4.6 Calibration curve of Budesonide:

The calibration curve of the budesonide was determined by using UV-Vis spectrophotometer via a fixed wavelength measurement option. The solvents used for the determination of the calibration curve include water, phosphate buffer pH 1.2, phosphate buffer pH 6.8, and phosphate buffer pH 7.4. The calibration curve obtained were all following Beer's Lambert's law. The calibration curve obtained from using water has an R2 value of 0.995. Similarly, other solvents such as PBS 1.2, PBS 6.8, and PBS 7.4 were found to have the R2 value of 0.9992, 0.9882, and 0.975 respectively.

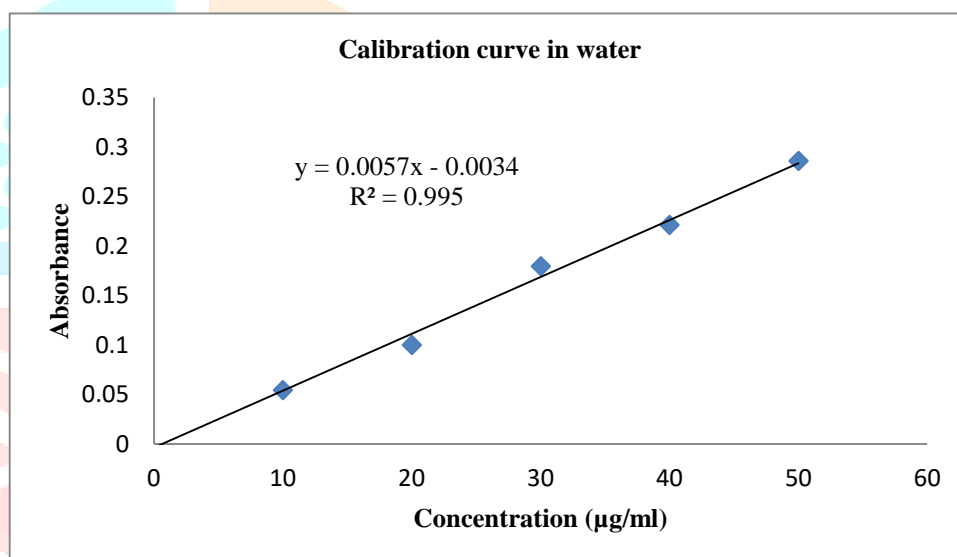


Figure 2: Calibration curve of Budesonide in water.

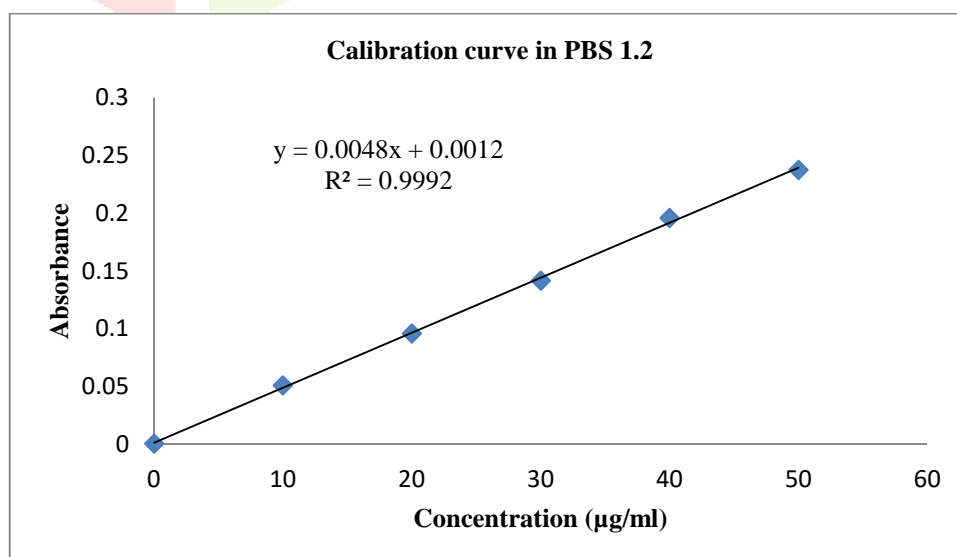


Figure 3: Calibration curve of Budesonide in PBS 1.2.

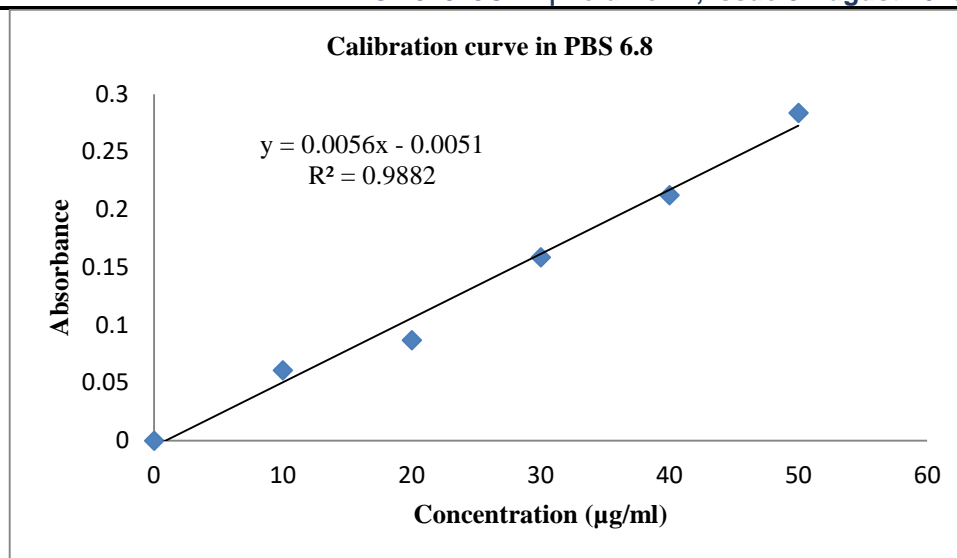


Figure 4: Calibration curve of Budesonide in PBS 6.8.

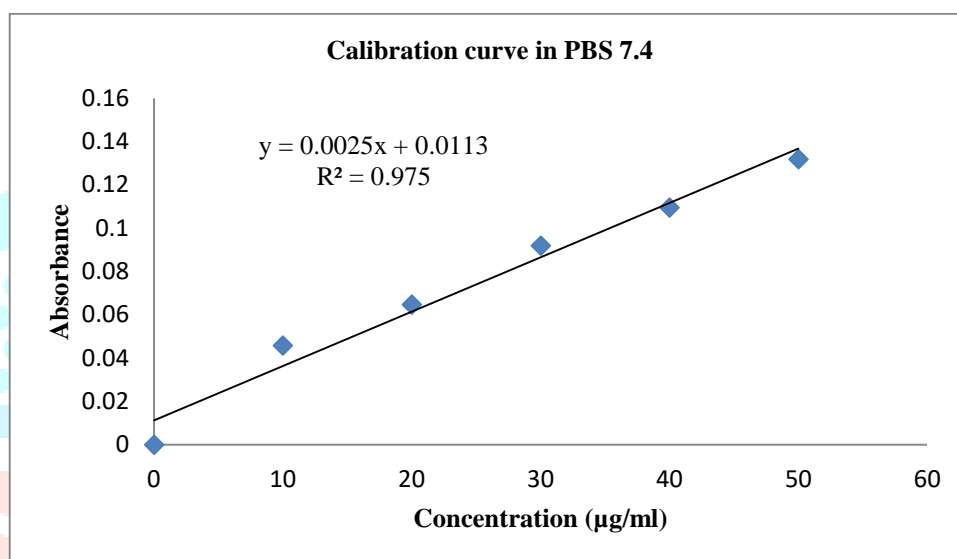


Figure 5: Calibration curve of Budesonide in PBS 7.4.

4.7 Fourier-Transform Infra-Red (FT-IR) Spectroscopy:

The FTIR spectroscopy of the budesonide API was done by using FT-IR- Alpha T, Bruker, Germany instrument. The graph was obtained with wavenumber cm^{-1} versus transmittance (%). The various functional groups were determined using the peaks obtained and comparing those to that of the standard reference table. The graph of the FTIR obtained is shown in Figure 13. The functional groups detected are given in the table below. The graph represents the aromatic C-H stretching group, along with -OH stretching, and the C=O group with aromatic C - H bending and C=C group. This confirms the structure and groups present in the budesonide API. The FTIR spectrum and its peak interpretations of budesonide are given in Figure 6 and Table 5.

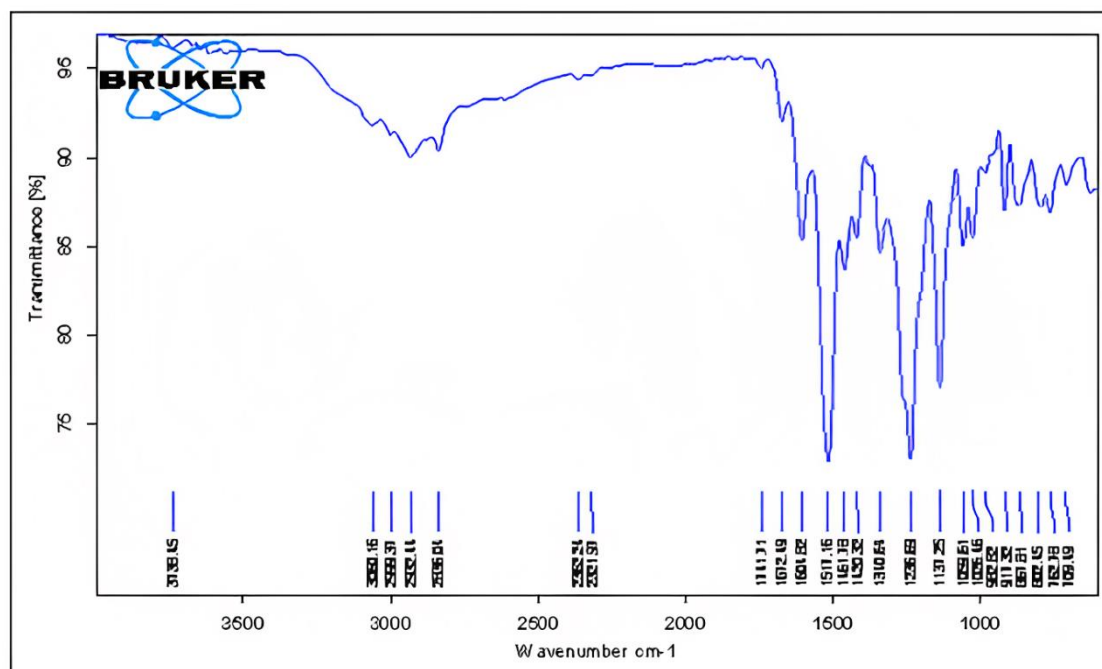


Figure 6: FTIR Spectrum of Budesonide.

Table 5: FTIR interpretation of Budesonide.

Sr No.	Peak	Interpretation
1.	3735	-OH stretching
2.	2836	-C-H stretching
3.	1672	-C=O stretching
4.	1511	-C=C stretching

4.8 Differential Scanning Colorimetry (DSC):

The DSC graph of the budesonide API was obtained to know the melting point. The DSC graph showing the peak of the melting point is given in Figure 7. The DSC graph has a peak at 228°C indicating the melting point of the budesonide API. The thermogram does not show any other peak other than that of melting point at 228°C. This indicates that the drug is in pure form and is not a mixture.

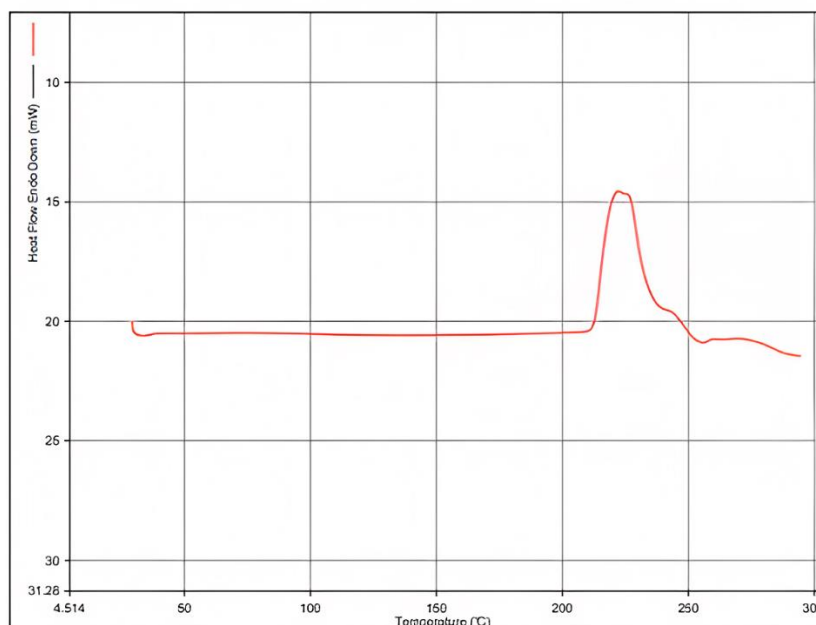


Figure 7: DSC thermogram of Budesonide.

4.9 Loss on Drying (LOD):

The LOD was determined using the mentioned procedure in methods. The LOD was determined to identify the purity of the compound and the moisture content present in the compound. The LOD of budesonide API was found to be 0.18 which is less than the standard specifications mentioned in Indian Pharmacopoeia (IP). The LOD mentioned in IP is not more than 0.5%. Therefore, as per the results obtained, 0.18, which is not more than 0.5% indicates the purity of the budesonide sample.

V. CONCLUSION

The preformulation stage is crucial for determining the characteristics of the medicine that will allow for an accurate risk assessment during development. It often starts in the lead optimization stage, lasts through predominance, and then enters the early stages of development. Therefore, it is essential that preformulation be carried out as carefully as possible to enable making logical conclusions. The goal of the Budesonide API preformulation project is to produce data that will be helpful in creating stable and bioavailable dosage forms.

VI. ACKNOWLEDGEMENT

I am thankful to Vamsi Labs Pvt. Ltd. for helping me with the drug sample. I am also thankful to Mr. Rajat Sayyed for his help for performing the experiment. I am thankful to MCE Society's Allana College of Pharmacy, Pune for providing the chemicals and instruments required for the experiment.

VII. REFERENCES

- [1] Chaurasia G, A review on pharmaceutical preformulation studies in formulation and development on new drug molecules, *International Journal of Pharmaceutical Sciences and Research*, 2016, Vol. 7, Issue 6, Page no. 2313-2320.
- [2] Vilegave K, Gali V, and Chandankar P, *Preformulation Studies of Pharmaceutical New Drug Molecule & Products: An Overview*, *American Journal of Pharmacy and Health Research*, 2013.
- [3] Kumar D, Kumar A, and Malik J, *Preformulation Studies of Drotaverine HCL: An Integral Part of Formulation Design*, *European Journal of Biomedical and Pharmaceutical Sciences*, 2019, Page no. 304-307.
- [4] Desu P K, G Vaishnavi, K Divya, and U Lakshmi, *An Overview on Preformulation Studies*, *Indo American Journal of Pharmaceutical Sciences*, 2015;2 (10) Page no. 1399-1407.
- [5] Mehta R.M. *Processing of tablets*, *Pharmaceutics-1*. Delhi: Vallabh prakashan, 2002; 238-267.
- [6] Ellul-Micallef R, Hansson E, Johansson SA. Budesonide: a new corticosteroid in bronchial asthma. *Eur J Respir Dis* 1980;61:167-73.
- [7] Colombo M, Minussi C, Orthmann S, Staufenbiel S, Bodmeier R. Preparation of amorphous indomethacin nanoparticles by aqueous wet bead milling and in situ measurement of their increased saturation solubility. *European Journal of Pharmaceutics and Biopharmaceutics* 2018;125:159-168.
- [8] Gouda MM, Shyale SS, Rajesh kumar P, Shabaraya A R, Shabaraya RA. Development and validation of selective UV spectro-photometric analytical method for budesonide pure sample. *J Appl Pharm Sci* 2011;1:158-61.
- [9] Berthomieu C, Hienerwadel R. Fourier transform infrared (FTIR) spectroscopy. *Photosynth Res* 2009;101:157-70. <https://doi.org/10.1007/s11120-009-9439-x>.
- [10] Schubnell M, De Caro C, Kunz R. Moisture content, water content, loss on drying, Part 1: What exactly is meant and how are these quantities determined? n.d