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Design, Development and Characterzation of Applied Crystal Enginerring on Budesonide Co-Crystal Loaded in Topical Gel.

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KEYWORDS

Cocrystal
Solvent Evaporation,
Solubility
Co-former
4-Hydroxy Benzoic acid

ABSTRACT:

Introduction: The present research work was conducted on poorly aqueous soluble drug Budesonide with 4-Hydroxybenzoic acid co-crystal. Co-crystallization is a viable strategy to improving the solubility of weakly water-soluble medicines. Budesonide (BUD) is a crystalline corticosteroid essential in the management of inflammatory dermatitis, including psoriasis, Budesonide (BUD) cocrystal is a novel formulation that exhibit improved aqueous solubility, the co-former selection is important step in co-crysatallisation it can be selected by different method hydrogen bond theories, pKa-based models, using the solvent evaporation method to produce co-crystals . The combining of Budesonide with a 4 hydroxy benzoic acid to form a new crystalline solid with improved physicochemical properties, including durability, dispersible, absorption and efficacy, while sustaining the therapeutic effect of the Budesonide characterisation peak is determined by Fourier transformed infrared spectroscopy, melting point is determined by Scanning electron microscopy (SEM),Differential scanning calorimetry (DSC) and X- ray diffraction (XRD)obtained particle size of co-crystal. Formulated co-crystal loaded in Topical gel. The formulated Batch of F6 show better permeability , viscosity and PH and Drug release.

Objectives: The Goal of these study is enhance the ability to dissolve substance BCS II along with class IV, of medicament eveloping new drugs, poor water solubility and low oral bioavailability pose significant challenges

Methods: BUD co-crystal established Using the solvent evaporation method. The synthesis of co-crystal different six co-former selected according to GRASS system such as Saccharin, succinic acid, Urea, Para-Amino-benzoic acid (PABA) ,Para- Hydroxy benzoic acid (PHBA), Cinnamic acid etc. Accurately weighed Equimolar weight of Budesonide and 4-Hydroxy benzoic acid 1:1 ratio was soluble in cosolvent of Ethyl alcohol+ Ethyl acetate .(15)The prepared mixture sonicates till 30 min and transferred into petri plate .keep the prepared solution for 24 hr .dry the product collect the crystalline budesonide i.e. co-crystal of budesonide and stored in airtight tight container .

Results: The Formulated Budesonide co-crystal loaded gel were characterised by Spredability, viscosity ,Exturdability ,Ph , In vitro drug release are determined on the basis of it the optomized batch is selected and futher characterisation of co-crystal is determined by XRD,DSC, SEM and FT-IR .

Conclusions: In the present work, cocrystals of BUD and 4 Hydroxy benzoic acid were prepared using the solvent evaporation technique. The Solid state characterization of drug and cocrystals was carried out using DSC, XRD,SEM, and FTIR studies BUD cocrystal formation was confirmed. gel using three-level factorial design.. F5 formulation was found to be optimized batch. From the overall conducted study, we can conclude that the newly developed crystalline form of BUD with 4 Hydroxy benzoic acid showed increased solubility and dissolution rate.

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1. Introduction

Skin disorders like psoriasis are frequent and can have a detrimental impact on both mental and physical well-being. As with other dermatoses.[1]Psoriasis is an inflammatory skin condition that is persistent and recurrent. It is distinguished by an apparent rise in the extent of the epidermis and a specific infiltration of inflammation. Between 0.5% and 3.15% of the US population are thought to have this dermatological condition.[2-4] Around 60% and 70 % of the population have mild psoriasis, which is controlled with topical remedies alone.[5]There are multiple kinds of psoriasis such as guatte psoriasis, inverse psoriasis, pustular psoriasis, and psoriasis arthritis[6]Guttate psoriasis was described by the abrupt formation of small, thickened, rough lesions that spread easily and mostly observed between 3 and 14 mm as a mainly across the upper extremities and located close limbs.[7]

Psoriasis and other inflammatory skin diseases are treated with budesonide . Because of their suppression of immunity, anti-inflammatory, and anti-proliferative properties, corticosteroids are essential. As of right now, we know that certain steroids prevent keratinocytes from generating TNF-α, IL-6, IL-8, and IL-10 in vitro. While (0.1%) betamethasone-17-valerate ointment is more potent, budesonide 0.25% ointment (Preferid®, Brocades Pharma, Leiderdorp, The Netherlands) is still regarded as a moderate to strong corticosteroid[10].

"Homogenous (single phase) crystalline structures composed of two or more components in a specific stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts) and the components of a cocrystal may nevertheless be neutral as well as ionized," according to the way the European Medicines Agency (EMA) describes cocrystals.
[12] Cocrystals are distinct from hydrates, solvates, polymorphs, and salts. [13]The coformer's chemical and physical attributes are modified by the API's hydrogen-bonding interactions with it, resulting in improved pharmacological qualities. [14].co-crystal loaded in gel to treat Guatte psoriasis

2. Objectives

The Goal of these study is enhance the ability to dissolve substance BCS II along with class IV, of medicament eveloping new drugs, poor water solubility and low oral bioavailability pose significant challenges. Incorporation of co-crystal in gel improve the solubility in topical prepration.

Methods

Materials:

Budesonide (Gift sample from Avik pharmaceuticals Vapi,Gujarat. pvt. Lmt.) , Due to the medicament is water-insoluble, it has been chosen as the primary treatment. 4 hydroxy benzoic acid, was used as a Co-former Analytical grade cosolvent used throughout research work .

Method:

BUD co-crystal established Using the solvent evaporation method. The synthesis of co-crystal different six co-former selected according to GRASS system such as Saccharin, succinic acid, Urea, Para-Amino-benzoic acid (PABA) ,Para- Hydroxy benzoic acid (PHBA), Cinnamic acid etc. Accurately weighed Equimolar weight of Budesonide and 4-Hydroxy benzoic acid 1:1 ratio was soluble in cosolvent of Ethyl alcohol+ Ethyl acetate .(15)The prepared mixture sonicates till 30 min and transferred into petri plate .keep the prepared solution for 24 hr .dry the product collect the crystalline budesonide i.e. co-crystal of budesonide and stored in airtight tight container

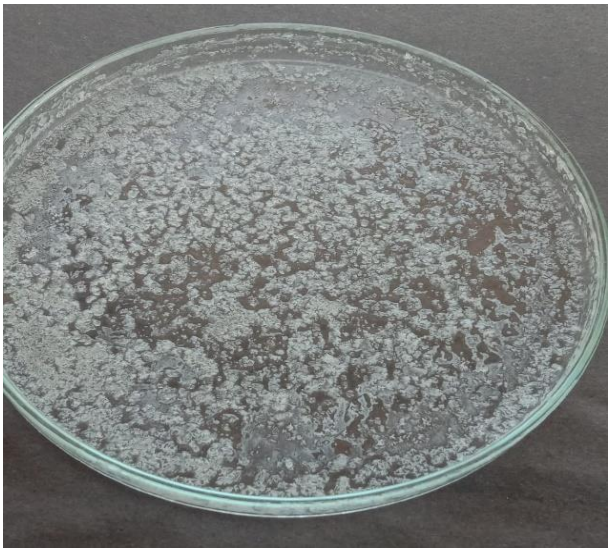

Fig 1: Co-crystal of BUD + 4 Hydroxy benzoic acid

Preformulation of co-crystal :[16,17]

Repose Angle (Θ)
The powder's angle of repose was measured by applying the funnel technique.10 grammes of powder were carefully weighed and placed in a funnel. Following the adjustment of the height, the powder was let to pass

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through the funnel and onto the surface. The diameter of the powder funnel and the angle of repose were calculated using the following formula.

Tan = r /h,

θ = angle of repose
h = funnel height
r = funnel radius

Bulk density:
Equivalent to 10 grams of powder from each formulation, which has been gently shaken prior to break up any agglomerates that may have formed

was added to a measuring cylinder holding 50 ml. The powder's mass and bulk volume were calculated. The following formula was utilized to get the bulk density.

$$\text{Bulk density} = \frac{\text{Wt of co-crystal granules}}{\text{Volume of co-crystal granules}}$$

Tapped density:
A predetermined amount of time was put into the measuring cylinder which held a known blend mass. The smallest amount of space used in the cylinder, and the mass of the blend was ascertained.. The following formula was used to get the tapped density.

$$\text{Tapped density} = \frac{\text{Wt of granules of co-crystal}}{\text{Volumes of co-crystal granules after 100 tapping}}$$

Carr's Index :
The most convenient technique to obtained the Compressibility is the unimpeded passage of particles., which is a measure of how easily a Carr's index, which becomes established in the following way, indicates the amount of material that can be converted to flow.

$$\text{Carr's index (\%)} = \frac{\text{TBD-LBD}}{\text{TBD}} \quad \text{X } 100$$

Hausner's ratio :
Less than 1.25 for Hausner's ratio suggests an orderly flow, and more than 1.5 for poor flow properties. This was computed by applying the formula that follows.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Characterisation of Co-crystals :

Physical characteristics: The color, texture, and odor of prepared BUD cocrystals were examined visually
Differential scanning calorimetry (DSC) :

The heat capacity (Cp) of a material can be determined using Differential Scanning Calorimetry (DSC), an analytical method, across various temperatures. In this study, a DSC-60A calorimeter from Shimadzu was employed to both create cocrystals and analyze the thermal behavior of the drug on its own. The samples were subjected in hermetically closed aluminium pans and heated at a rate of 100°C per minute, ranging from 100°C to 500°C, with a nitrogen purge at a flow rate of 20 ml/min to maintain an inert atmosphere.[18]

X-ray Diffraction technique (XRD) :

XRD diffraction data recorded for Pure Budesonide and BUD co-crystal were recorded on (Szimandzu 7000) . The data collection carried out at 275.15K/min and voltage 40kv by using Savitzky - Golayi method. The Co-crystal were exposed to Cu-K radiation at an angular speed 10°C/min[19]

Fourier infrared spectroscopy(FT-IR) :

The infrared spectrum for the BUD and BUD cocrystals has been obtained by the FTIR spectrophotometer. After the samples were crushed into a disk. and mixed with the potassium bromide in a 1:1 molar ratio, they were scanned at a dimension of 4 cm−1 between 4000 and 400 cm−1. The drug-conformer interface has been verified using IR spectroscopy.[20]

Scanning electron microscopy:

Using SEM, the morphology of surface of BUD Co-crystals was examined. SEM (Analytical Labs) were employed to determine the formulation's shape. Scanner microscopy was used to measure the Co-crystals' diameters.

Drug Content :

100 millilitres of methanol were used to dissolve 10 milligrammes of produced BUD cocrystals. To obtain a uniform solution, the solution was then ultrasonically agitated for 15 minutes. The corresponding solution's absorbance was then measured at 247 nm by an ultraviolet light (UV)-visible spectrophotometer.[21]

Saturated solubility study :

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The dried BUD cocrystal was accurately measured and the equivalent of one gram of BUD was formed by 50 millilitres of water that has been double-distilled in a cotton-inserted conical flask. Using an orbital shaker . it was shaken for two days. Validated UV-visible spectrophotometry was used to calculate the amount of dissolved BUD. For both pure BUD and a physical mixing of BUD, the same steps were repeated 4-Hydroxybenzoic acid .[22]

In vitro dissolution study of cocrystal:

By Using United States Pharmacopoeia (USP) type 2 dissolving test equipment. dissolution tests (%) were carried out in 900 ml of pH 7.4 phosphate buffer solution for one hour at 37 ± 0.5 and 50 rpm. The investigation used 10-milligrams of the medication BUD as well as BUD cocrystals. Within the allotted time, five millilitres of sample were taken out and exchange with an identical volume of brand-new dissolving medium right away. The Whatman filtering paper has been employed for filtering the sample. Afterwards, the sample was diluted appropriately and examined at 247 nm by a UV-visible spectrophotometer.[23]

Formulation of BUD co-crystal loaded topical gel

The topical administration gel loaded with BUD co-crystal was designed and optimized using the software Design Expert (version 13) by two variables & two distinct stages using a three-level factorial design. The Carbapol-934 and HPMC concentration were the two independent variables (Table 1). Spreadability (X2) and in vitro drug release (X1) were examined for each formulation as dependent variables.

Method of Preparation of BUD co-crystal loaded in Topical gel :

Weigh accurately Carbopol 934 and HPMC was slowly transferred into a different beaker holding an adequate amount of distilled water and letting it soak for 5-6 hrs.Soaked HPMC, Carbopol- 934 and was stirred separately for about 30min at 600 rpm. In another Beaker B Propyl p-hydroxy benzoate and methyl p- hydroxy benzoate were taken as a conservative in a propylene glycol. Stirrer the above solution at 30°C for 30 min .addition of glycerine and polyethylene glycol 400, co-crystal of Budesonide was mixed with previously prepared polymeric solution by vigorous stirring at 1100 rpm for 10min with the help of a mechanical stirrer. To achieve a viscous, uniform gel, triethanolamine was added dropwise to the final mixture and vigorously agitated. Triethanolamine was used as a pH adjuster.

Fig 2: BUD co-crystal loaded gel

Characterization of Co-crystal of gel loaded in gel :

Physical appearance

The gel combination were evaluated visually for physical attributes, a uniformity and color.

Homogeneity

The gels were added to the proper container. and the homogeneity was assessed visually. The appearance and existence of any form of particle material in the gels was observed.

pH determination

The digital pH meter used to measured pH of the prepared gels and the observed readings were recorded.

Spreadability

It was estimated using the gel's "slip" and "drag" characteristics. Distributing precisely measured 100 (mg) of gel on two glass plates and applying 500 g of weight over the plate for 60 seconds allowed researchers to calculate the spreadability (cm) of the gel compositions. Afterwards, the diameter of the gel spread

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across the plate in 60 seconds was measured to ascertain the spreadability. [24]
Spreadability was then calculated by using the formula:

$$S = M.L / T$$

Where,

S = Spreadability
M = Weight of upper slide
L = Length of upper glass slide
T = Time

Extrudability :

The BUD gel is extruded. from the aluminum collapsible container is a significant factor in its application to the skin and patient compliance. This investigation is helpful in determining whether or not the gel loaded with BUD crystals easily separate from the aluminum folding tube during application. Highly viscous gels might not squeeze out of the tube, even though barely viscous gels do, hence a proper viscosity is required to extrude the gel from the collapsible tube. Collapsible aluminum tubes were filled with gel. The extrudability of the formulations was measured when the tubes were compressed to extrude the gel in a band of approximately 0.5 cm in 10 seconds.

Viscosity

Readings were taken after the substance had settled at 25°C for 30 minutes. used the Brookfield Viscometer to measure the viscosity of gel in various speeds of change at a fixed temperature. Ten revolutions per minute were used to rotate the spindle.[25]

In vitro drug release study

The drug release has been studied in vitro using the vertically positioned Franz diffusion cell set up (%). A cellophane membrane was used for this experiment. The cellophane membrane that separated the donor and receiver compartments of the Franz diffusion cell was filled with the proper quantity (0.5 g) of gel. A receptor compartment containing 20 millilitres of pH 7.4 phosphate buffer, which served like a diffusion media, came into contact with the membrane's whole surface. The entire assembly was placed in a magnetic stirrer for ninety minutes[26].

Stability studies :

The Prepared formulations loaded with co-crystal that were developed were kept in appropriate containers and underwent stability testing in accordance with ICH recommendations. The formulations were maintained at 40°C, 25°C, and room temperature for two months. Samples were taken at intervals of one, two, and three months to evaluate their physical properties, spreadability, and drug release..[27,28]

Sr.no.	Carbopol Concentration 934 %w/v	HPMC Concentration %w/v
1	0.0946699	0.625
2	1	1
3	0.625	0.0946699
4	1.15533	0.625
5	0.625	0.625
6	0.25	0.25
7	1	0.25
8	0.625	1.15533
9	0.25	1

Table 1: Central composite design for formulation of BUD co-crystal load in gel**.**

Result and Discussion:

Pre-formulation study :

Drug appearance of formed BUD co-crystal were discovered to be white in colour.

Sr No	Micrometrics Properties	API (Budesonide)	BUD+4HBA
1	Bulk density	0.603±0.030	0.625±0.034
2	Tapped density	0.565±0.071	0.714±0.069
3	Angle of repose	39.48	35.16
4	Carr's index	24.11±0.010	24.14±0.014
5	Hausner's ratio	1.24±0.34	1.14±0.32

Table 2: Preformulation study of BUD co-crystal

Determination of drug content:

The BUD co-crystals drug content was found to be 88.4%. This level of drug content was adequate for formulating the cocrystals into a suitable dosage form

Fourier infrared spectroscopy (FTIR) :

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An essential instrument for determining the conformation of cocrystals, FTIR demonstrated the hydrogen bonds formation between pure drugs and conformers. The FTIR spectrum of BUD with Cinnamic acid, Succinic acid , 4-Amino benzoic acid , saccharin and Urea (1:1) co-crystal does not show any new peak, indicating that the hydrogen bond was not formed. between API and co-former. BUD with 4 Hydroxy benzoic acid (1: 1) co-crystal showed a new peak that determined the hydrogen bond was formed between API and co-formers . FTIR spectra ,BUD and BUD cocrystals were recorded and are displayed in Figures 3 and 4. Significant changes in the peaks were identified, and the essential bands were determined. The IR spectrum of pure BUD exhibited distinctive peaks, which were documented. Changes in peak intensities, broadening, and shapes were observed, indicating the development and characterisation of a novel crystalline phase in the BUD cocrystal.

Functional group	Wavenumber
-OH (Hydroxyl)	3506
-CH (Aldehyde)	2871.41
-C=OOH(carboxylic acid ,ketone)	1720.50
-C=C (Aromatic)	1475
-C-H (Bending)	1381.03
-C-O Stretching (Aromatic)	1168.86

Table 3: Fourier infrared spectroscopy :

Compatibility study of FTIR of BUD with six different co-former;

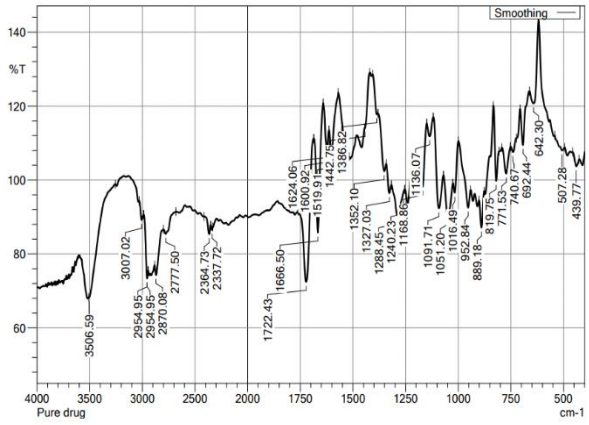

Fig 3:FTIR Spectrum of Pure Budesonide

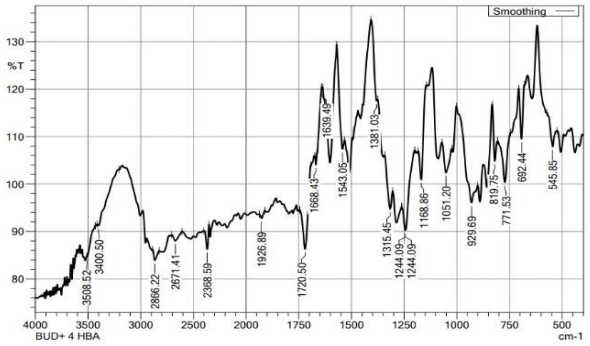

Fig 4 :FTIR Spectrum of BUD:4 HBA

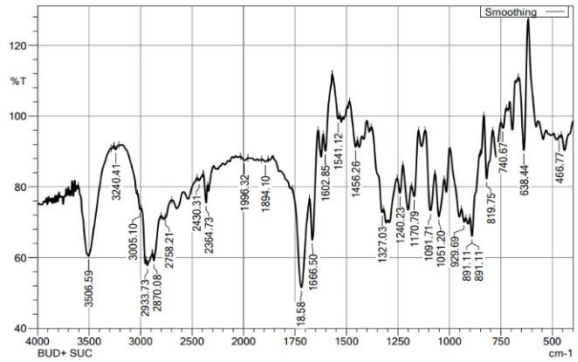

Fig 5: FTIR Spectrum of BUD: Succinic acid

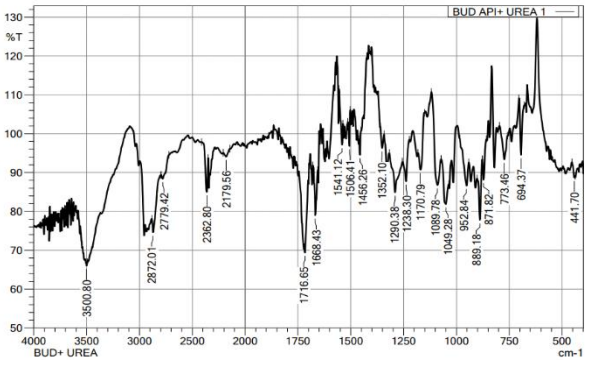

Fig 6 : FTIR Spectrum of BUD: Urea

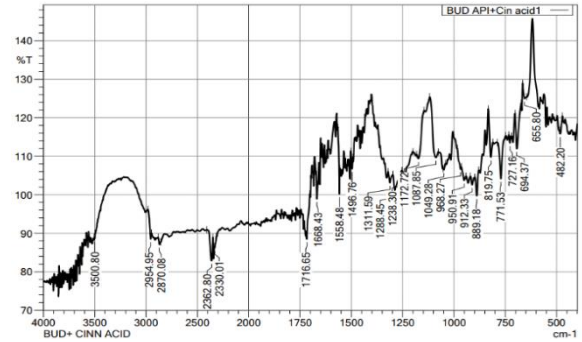

Fig 7: FTIR Spectrum of BUD: Cinnamic acid

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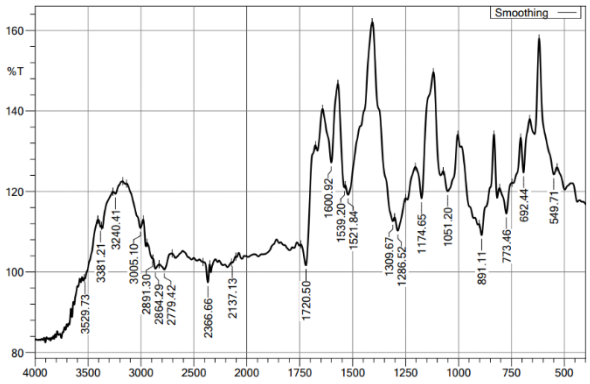

Fig 8: FTIR spectrum of BUD : PABA

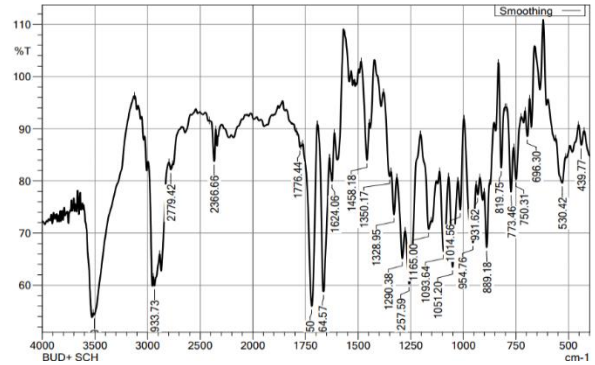

Fig 9: FTIR Spectrum of BUD:Saccharin

X-ray Diffraction (XRD):

The XRD configuration of the BUD and BUD Cocrystal showed in following figure(10,11) the XRD spectrum of formulated co-crystals showed intense endothermic peaks as compared to XRD of pure BUD . Co-crystal showed crystallinity at 6.220°, 10.080°, 12.220°, 16.160°, 18.580°, 21.040°, 23.100°, 26.880°, 38.220°, 39.720°, 41.560°, 43.600° (2θ) with peak intensities of 599, 611,705,934,966,1275,1488,3600,26439, and 37480 in height (counts) indicating its crystalline nature.

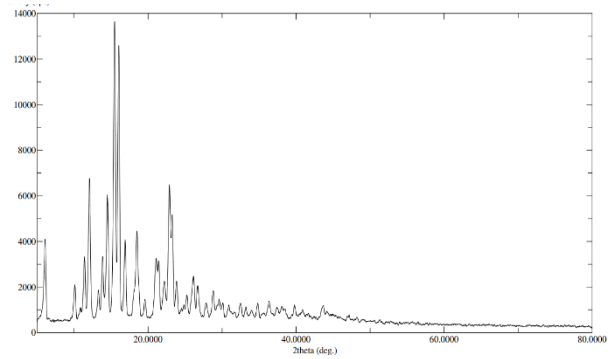

Fig 10 :XRD of Pure Budesonide Drug

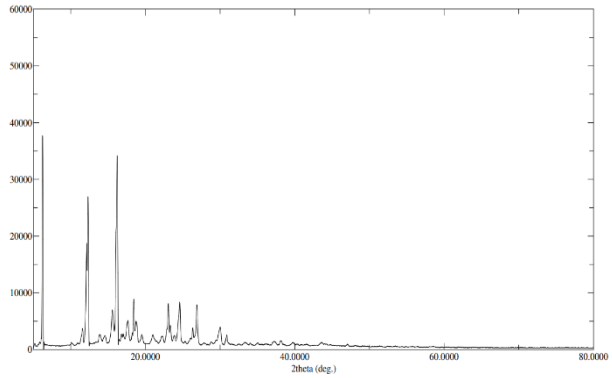

Fig 11 : XRD of Budesonide Co-crystal

Differntial Scanning calorimetry (DSC) :

DSC was employed in the investigation to determine the molecular dispersion. of BUD in the optimal co-former.4-Hydroxy benzoic acid. The DSC thermogram of BUD and formulated co-crystal of BUD were compared. The pure BUD exhibited an endothermic peak at 236.4°C. The pure 4-hydroxy benzoic acid exhibited an endothermic peak at 102.87°C, while the formed co-crystal exhibited an endothermic peak at 160.07°C, which was lower than the endothermic peak of pure BUD and co-crystal.

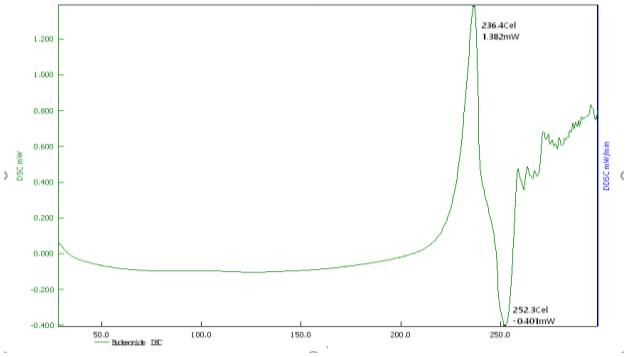

Fig 12 : Differntial scanning calorimetry of pure Budesonide

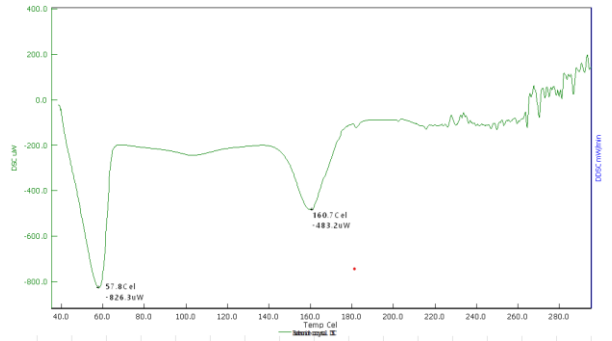

Fig 13: Differntial scanning calorimetry of BUD Co-crystal

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Scanning electron microscopy :

The SEM analysis was carried out at nanoscale to detect the shape and structure of co-crystals. The shape and structure of BUD co-crystal exhibited smooth, homogeneous, uneven in shape

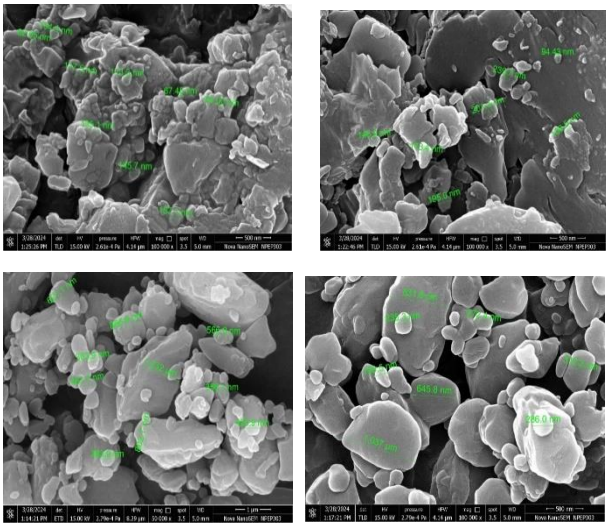

Fig 14 : Scanning electron microscopy images of Co-crystals

In vitro dissolution study :

The in vitro dissolution (%) analysis of both pure BUD and BUD cocrystals was conducted appropriately. Figure 15 presents the dissolution curves for pure BUD and BUD cocrystals in a 7.4 pH phosphate buffer. The results demonstrate that BUD cocrystals with 4-Hydroxy Benzoic acid significantly improve the rate of dissolution compared with pure drug..

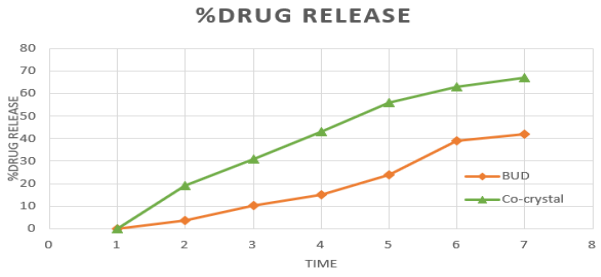

Fig 15 : In vitro dissolution of BUD and BUD Co crystal

Saturated solubility study:

The dissolution of BUD and associated cocrystals in water (µg/ml) was successfully determined. It was found that pure BUD had a solubility of 7.48 µg/ml (139.92 µg/ml) in distilled water. The cocrystal structure of the drug significantly increased its solubility. This increase in solubility was due to the chemical interaction between BUD and the coformer 4-hydroxy benzoic acid, which formed hydrogen bonds and non-covalent bonds.

Evaluation of BUD co-crystal loaded in topical gel :

Physical appearance:

A visual inspection was conducted on the prepared BUD cocrystal-loaded gels. The gel was discovered to be white with a smooth texture

Extrudability and pH:

The Extrudability, pH and Viscosity of formulation was found to be effective. The acquired information was provided in Table 4

Formulation Code	Extrudability cm	pH	Viscosity
F1	0.6	6.4	200.13
F2	0.3	6.7	460.24
F3	3.3	6.4	128.67
F4	2.9	7.0	550.78
F5	1.2	7.1	101.12
F6	0.9	6.4	229.11
F7	1.6	6.8	339.98
F8	2.0	6.8	550.28
F9	2.1	7.0	438.78

Table 4 : Result of Extrudability , pH and Viscosity of all formulation

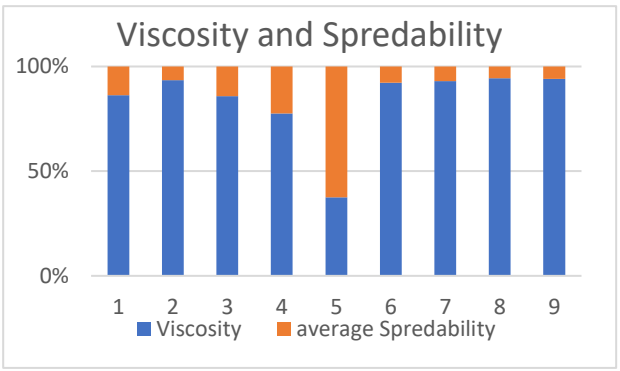

Fig 16: Measurement of Viscosity and Spredability

Spredability :

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For spreadability the quadratic model was found to be significant, the F value is 16.56 and a p-value less than 0.0500. The quadratic equation generated by the software is shown below:

Spreadability = Conc.of carbolpol =17.33,32.41,21.37,31.38,22.43: Conc of HPMC spredability : 19.22,25.37,32.44,27.48 etc

According to the equation, each of the parameters (X1 & X2) have a considerable effect on gel spreadability. A 3D graph revealed that as the Carbopol concentration increased, so did its spreadability. As the concentration of HPMC grows, it also increases its spreading ability. It was found that the the spreading ability for each formulation ranged between 5.8 and 6.2.
(fig. 17 and 18).

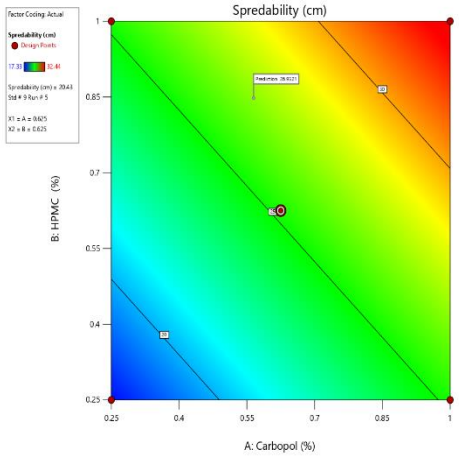

Fig17 : Counter plot of Spredability

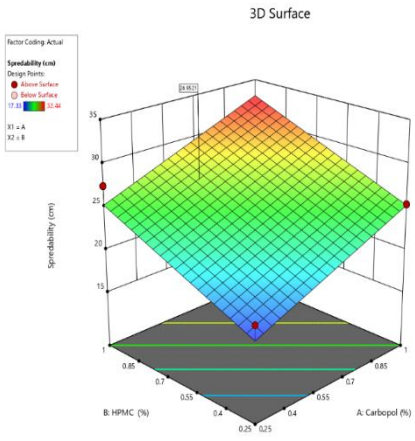

Fig 18 : 3D Plot of Spredability

In vitro drug release (%) : For in vitro drug diffusion , the quadratic model f value is 51.98 and p value less than 0.0500 was determined to be significant based on the p value.

The software generates a quadratic equation that is as follows:

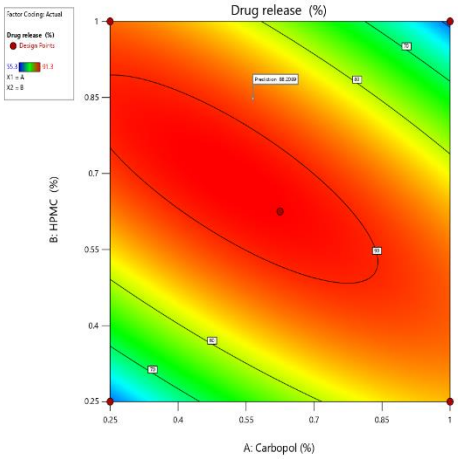

Fig 19 : Counter plot of % Drug release

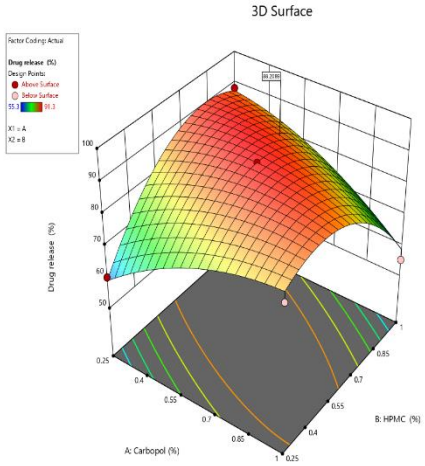

Fig 20 : 3D Plot of % Drug release

Month	Temperature condition	Spredability (cm)	Drug release
1	25°C ± 2°C	5.82±0.002	98.23±4.213
	40°C ± 2°C	5.91±0.102	99.01±3.124
2	25°C ± 2°C	5.61±0.001	99.15±1.758
	40°C ± 2°C	5.91±0.213	99.01±1.346

Table 5: Stability studies of BUD cocrystal loaded in topical gel

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Optimization of study

After evaluating all of the formulated formulations (F1 to F9), the F5 batch was selected as optimal batch, with spreadability and drug release of 5.81 cm and 99.24%, respectively.

Stability study :

Storing gel loaded with BUD cocrystals may lead to changes in its physicochemical properties, such as drug release and spreadability. In order assess stability, the produced formulations were then keep in a 2-month stability testing at room temperature and under accelerated conditions. The BUD-loaded gel had been found to be stable in both the conditions.

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