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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF LIQUISOLID COMPACT TABLET OF BUDESONIDE

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ABSTRACT

The limited solubility of drugs is a challenging issue for industry, during the development of the solid dosage form. Liquisolid technique is a novel and promising approach to overcome this problem. This technique is an efficient method for formulating water insoluble and poorly water soluble drugs. The liquisolid technique is based upon the dissolving the insoluble drug in the nonvolatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptably flowing and compressible powder. The use of non-volatile solvent causes improved wettability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility. Purpose of this study is to develop novel liquisolid technique to enhance the dissolution rate of Budesonide. Liquisolid tablet prepared by using Avicel PH 102, Aerosil 200 and sodium starch glycolate were employed as carrier, coating material and disintegrant respectively. The interaction between drug and excipients in prepared LS compacts were studied by differential scanning calorimetry (DSC) and Powder X- ray diffraction (PXRD).The prepared LS compacts were evaluated for their flow properties such as bulk density, tapped density, angle of repose, Carr's compressibility index and Hausner's ratio. The drug release rates of LS compacts were distinctly higher as compared to directly compressed conventional tablets, which show significant benefit of LS in increasing wetting properties and surface area of drug available for dissolution. LS compact system showed acceptable flowability, Carr's compressibility index and Hausner's ratio. The DSC and XRD studies conforms the no significant interaction between the drug and excipients used in LS compacts. From this study it concludes that the LS technique is a promising alternative for improvement of dissolution property of water-insoluble drugs.

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INTRODUCTION

The low solubility of the many Drugs is one of the challenge in formulating as in suitable dosage form. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The drugs which are poorly water soluble will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is the rate determining step in the drug absorption. The challenge for these drugs is to enhance the rate of dissolution or solubility. This technique improves the solubility, dissolution so that improves absorption and may be improve bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances. The oral route is most preferred route so the formulation scientists formulate and prefer the oral drug delivery. Because of good stability, small bulk, accurate dosage, easy production and economical, solid oral dosage form provide many more advantages over the other oral dosage form. The Biopharmaceutical Classification System (BCS) is an experimental model that measures solubility and permeability. As per the BCS classification the drugs classify under the four classes, they are class-I with high solubility and high permeability. The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class II, compounds which feature poor solubility, high permeability, class-III with high solubility and low permeability and Class IV, compounds which feature poor solubility and poor permeability respectively1.Most of the New drugs come under the BCS Class-II and class-IV. They are poorly aqueous soluble. As there is low solubility, there may be a problem of bioavailability. To overcome the problem, the technique of 'liquisolid compacts' is a new and promising recently developed additional technique towards the new approach of

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dissolution enhancement. Liquisolid compacts possess acceptable flowability and compressibility properties. They are prepared by simple blending with selected powder excipients referred to as the carriers and the coating materials. Many grades of cellulose, starch, lactose, etc. can be used as carriers, whereas silica of very fine particle size can be used as coating materials. In such systems, the drug existed in a molecular state of subdivision and systems were free flowing, on-adherent, dry looking powders. The bioavailability of BCS class II drugs is likely to be dissolution rate limited. But due to their high permeability, the BCS class II drugs have been on focus for solubility enhancement researches in the recent times and several formulation approaches for this class of compounds has been developed. Budesonide is a BCS class II drug. Budesonide is a glucocorticosteroid for the treatment of asthma, noninfectious rhinitis (including hay fever and other allergies), and for treatment and prevention of nasal polyposis. Additionally, it is used for Crohn's disease (inflammatory bowel disease). Budesonide is a locally-acting glucocorticosteroid with an extensive, primarily hepatic, metabolism after oral administration. Budesonide, a pH- and time-dependent oral formulation of Budesonide, was developed to optimise drug delivery. Bioavailability of Budesonide is low which 10-20 % and half-life is 2 to 3.6 hrs. Thus, the aim of present work was to develop a liquisolid compact tablet of Budesonide to overcome the problem associated with poor water soluble drug delivery. The aim of present work is to enhance the solubility and dissolution rate of "Budesonide" using liquisolid compacts. By using this concept liquid medication like solutions of water insoluble solids drugs in non-volatile vehicle formulated into acceptable flowing and compressible powder. Using this new technique, liquid medication may be converted into dry-form, non-adherent free flowing compressible powder by a simple blending with selected powder excipients referred as the carrier material. New mathematical model is applied to calculate the required amount of powder excipients (carrier and coating material) for the formulation of liquisolid tablet. 3^2 full factorial design applied to study the effect of drug: excipient ratio and drug concentration in liquid medication.

MATERIALS AND METHODS

Budesonide was kindly gifted from Wockhardt laboratories, ltd, Aurangabad. Avicel PH 102, Aerosil 200, Sodium starch glycolate, glycol was gift sample from Research-Lab, Fine Chem Industry, Mumbai. Poly ethylene glycol and Propylene glycol was gift sample from LOBA Chemie, Mumbai.

Solubility Studies

Solubility study of Budesonide was carried out in Propylene glycol and PEG 200, 400. Saturated solutions of Budesonide were prepared in vehicles and kept in orbital shaker for 48 hrs at 25°C.

After this period, the solutions were filtered, diluted and analysed by UV spectrophotometer (Jasco v630, Japan) at 243 nm. Three determinations were carried out for each sample to calculate the solubility of Budesonide.

Determination of liquid load factors (Lf)

Appropriate amounts of carrier and coating materials were used to produce acceptable flowing and compactible powders which were be calculated using following equation.

Lf = W/Q

Where, W and Q value weight of liquid medication and carrier material in the system.

The maximum amount of liquid loads on the carrier material, termed ''load factor" (Lf).

Method of preparation of liquisolid tablets

Several liquisolid tablets were prepared by direct compression method. Budesonide was dissolved in PEG 400 at different ratio to obtain various drug concentration. Then a binary mixture of carrier-coating material (Avicel PH 102 as the carrier powder and Aerosil 200 as the coating material) was added to the obtained liquid medication under continuous mixing. Depending upon the amount of carrier in formulation, different liquid loading factor were employed in liquisolid preparations. Finally, 5% (w/w) of sodium starch glycolate as the disintegrant, and 1% magnesium stearate were mixed with the mixture. The final mixture was compressed using the rotary tablet punching machine to achieve tablet hardness.

Preparation of conventional tablet

Conventional tablets of Budesonide were prepared by direct compression using manual tablet machine, each containing 9 mg drug with Avicel PH 102, Aerosil 200 and Sodium starch glycolate. Liquisolid compact tablet containing 9 mg of Budesonide were prepared by dispersing in nonvolatile vehicles such as PEG 400.

Flow properties of Liquisolid system

Flow properties of the LS were estimated by tap density, bulk density, angle of repose, Carr's compressibility index and Hausner's ratio. Angle of repose was measured according to the fixed funnel method. The tap density was determined using bulk density apparatus and calculated the Carr's compressibility index and Hausner's ratio.

Fourier Transform Infra Red Spectroscopy

FTIR study was carried out to check compatibility between drug and excipients. IR spectra of budesonide drug, Avicel, Aerosil, PEG, sodium starch glycolate and final liquisolid formulation was determined by Fourier Transform Infrared spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the IR spectrum was taken by FTIR spectrophotometer.

Differential scanning calorimetry (DSC)

DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug (budesonide). The

DSC study was carried out with METTLER DSC, SHIMADZU, Pvt. Ltd., Japan, by using aluminium crucible 40 mL at 10ºC /min heating rate, under nitrogen environment. The temperature range used was 0–300ºC.

Powder X-Ray Diffraction

PXRD analysis was done by irradiating the samples with mono-chromatized Cu Kα radiation (1.506 Å) and analyzed between 3° and 60° (2θ) employing a Bruker AXS D8 Advance Diffractometer with Lynx Eye Detector. The step was at rate of 0.020^0 with step time of 32.8 sec. The diffractogram was produced by using Diffract plus Software.

Optimization by 3^2 Full Factorial Design

The application of mathematical optimization in the pharmaceutical field was first reported by Fonner et al. (1970), using the Lagrangian method as a constrained optimization technique. A factorial design is used to evaluate two or more factors simultaneously. The treatments are the combinations of levels of the factors. The advantages of factorial design over one factor at a time experiment are that they are more efficient and they allow interactions to be detected. Intervention studies with 2 or more categorical explanatory variables leading to a numerical outcome variable are called as" Factorial design ". A factor is simply a categorical variable with 2 or more values referred to as levels. A study in which there are 2 factors with 3 levels is called as 3^2 Factorial designs. For present work 3^2 Factorial designs was selected.In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected .Translation of coded levels and 3^2 full factorial designs are given in table.

Formulation codes assigned to the batches:

Independent Variables:X1= PEG (Solubility enhancer)
X2= Avicel pH-102 (Improve flow)

Dependent variable:Y1= Drug release (%)

Table 1. Translation of the Coded Levels in Actual Units

Coded levels	Actual value in mg	
	X1	**X2**
-1	100	150
0	200	250
+1	300	350

Table 2. Ranges of independent variables used in the 3^2 full factorial design

Batch	Formulation code	PEG 400 conc. level (X_1)		R value level (X_2)	
1	F1	-1	100	-1	150
2	F2	-1	100	0	250
3	F3	-1	100	+1	350
4	F4	0	200	-1	150
5	F5	0	200	0	250
6	F6	0	200	+1	350
7	F7	+1	300	-1	150
8	F8	+1	300	0	250
9	F9	+1	300	+1	350

Evaluation of Liquisolid Compact tablet of Budesonide

Prepared tablets were subjected to evaluation of different properties including content uniformity, weight variation, hardness, friability, tablet dimensions, disintegration time and in-vitro drug release.

Tablet dimensions

Thickness and diameter was measured using Digital vernier calipers (0-150mm) Mack Aurra (Aerospace). Three tablets from each formulation were used and average values were calculated.

Tablet hardness

Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using simple Monsanto hardness tester (Cadmach, Ahmadabad, India).

Friability

Tablet strength was tested by Roche friabilator. Pre weighted tablets were allowed for 100 revolutions in 4 minute and dedusted. The percentage weight loss was calculated by reweighing the tablets. The % friability calculated by: (Indian Pharmacopoeia, 2007).

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight}}$$

Weight variation test

The weight of tablet is measured to ensure that a tablet contain the proper amount of drug. Weight variation test was performed as per Indian Pharmacopoeia. Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. Not more than the two of the individual weights deviate from the average weight by more than 5 % percentage deviation (Indian Pharmacopoeia, 2007).

Drug content uniformity

Drug content uniformity was determined as per Indian Pharmacopoeia using following procedure.

Procedure

20 tablets were weighed and powered. Quantity of powder equivalent to 9.0 mg of drug was weighed and transferred to 100 ml volumetric flask containing 5ml of methanol. The flask was shaken to dissolve the drug and adjusted 100 ml to volume with 0.1 N HCL. From this 1 ml of solution was withdrawn and diluted to 10 ml with methanol and absorbance of resulting solution was measured atλmax of 243 nm.

In vitro Dissolution Study

In vitro drug release studies of the prepared Liquisolid tablets were conducted for a period of 2 hours by using an USP Type

II (Paddle) Dissolution apparatus (Electrolab TDT 08L, India) at 37± 0.5° C. The agitation speed was 50 rpm. The dissolution study was carried out in 900 ml 0.1 N hydrochloric acid at 37±0.5 ºC for up to 2 hours 10 ml of the sample was withdrawn at regular intervals and the same volume of fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a whatman filter no.1 and the drug content in each sample was analyzed with UV spectrophotometer. The amount of drug present in the samples were calculated with the help of calibration curve constructed from reference standard.

RESULTS AND DISCUSSION

Solubility Studies

Saturated solubility study of drug was carried out in three different nonvolatile solvents, i.e. PEG 200, PEG 400 and PG by preparing saturated solutions of the drug in these solvents and analyzing their drug content spectrophotometrically.

Table 1. Solubility Budesonide in non volatile solvents

S.No	Solvent	Solubility (mg/ml)
1	PEG 200	3.24
2	PEG 400	4.12
3	PG	2.41

Characterization of Budesonide by FT-IR spectroscopy

Infra- red spectrum of Budesonide shown in Fig.1 The major peaks observed and corresponding functional groups are given Table.8.7 Infra-red spectrum shows peak characteristic of structure of Budesonide.The IR spectra of Budesonide was recorded and analysed for the functional groups and the observed peaks comply with reported literature (Indian Pharmacopoeia, 2007).

Table 2. Interpretation of FT-IR Spectra of Budesonide

S. No	Functional Group	Standard frequency (cm-1)	Observed IR frequency (cm-1)
1	O-H Stretch	3500-3490	3493
2	C=O Stretch	1730-1710	1720
3	C=C Stretch	1670-1660	1664

Characterization of drug and polymer (FT-IR)

FTIR spectra of the samples were obtained in the range of 400 to 4000 cm^{-1} using FT-IR spectrophotometer by the KBr disc method. The FT-IR spectrum of polymer is shown in Fig. 2.

Table 3. Interpretation of FT-IR Spectra of (drug and polymers)

S. No.	Functional Group	Standard frequency (cm-1)	Observed IR frequency (cm-1)
1	O-H Stretch	3480-3470	3477
2	C=O Stretch	1730-1710	1720
3	C=C Stretch	1670-1660	1664

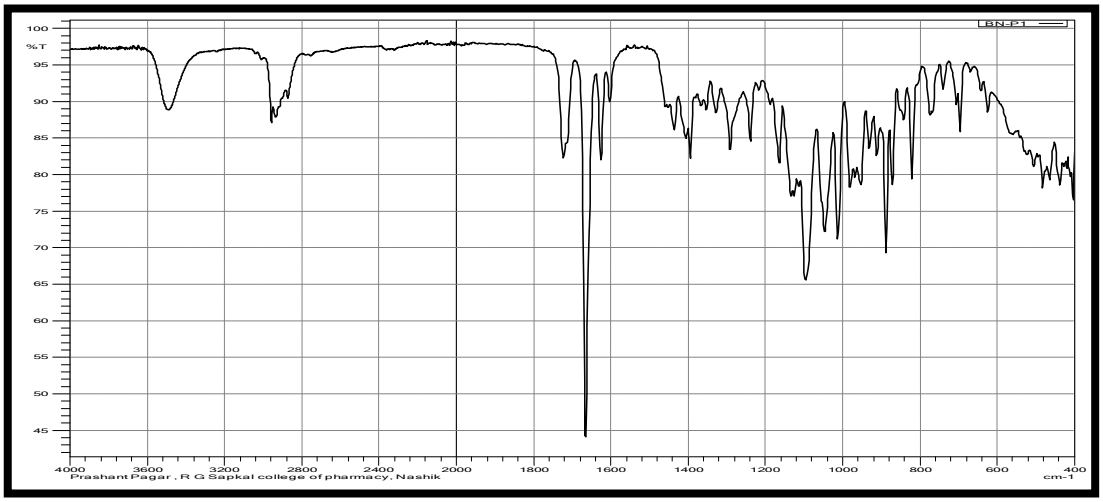

Fig.1. FT-IR spectra of Budesonide

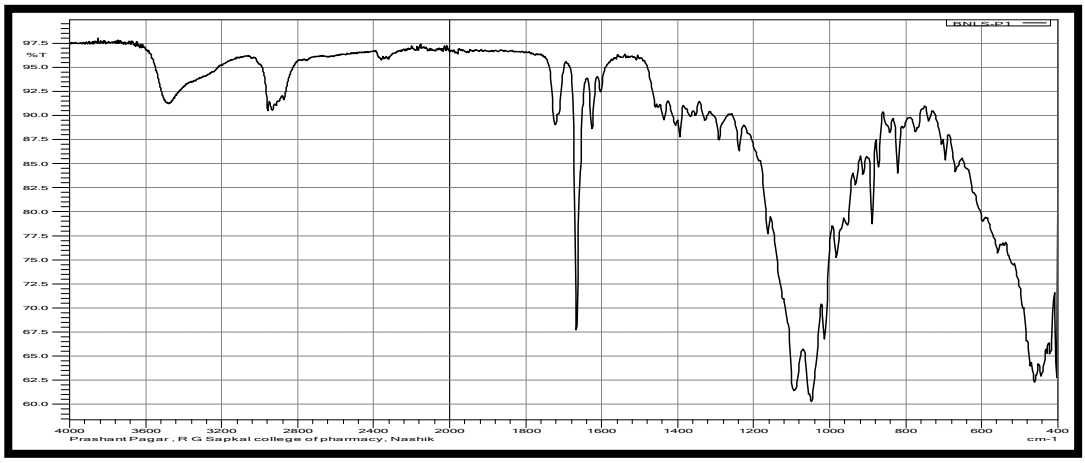

Fig.2. FT-IR spectra of mixture (drug and polymers)

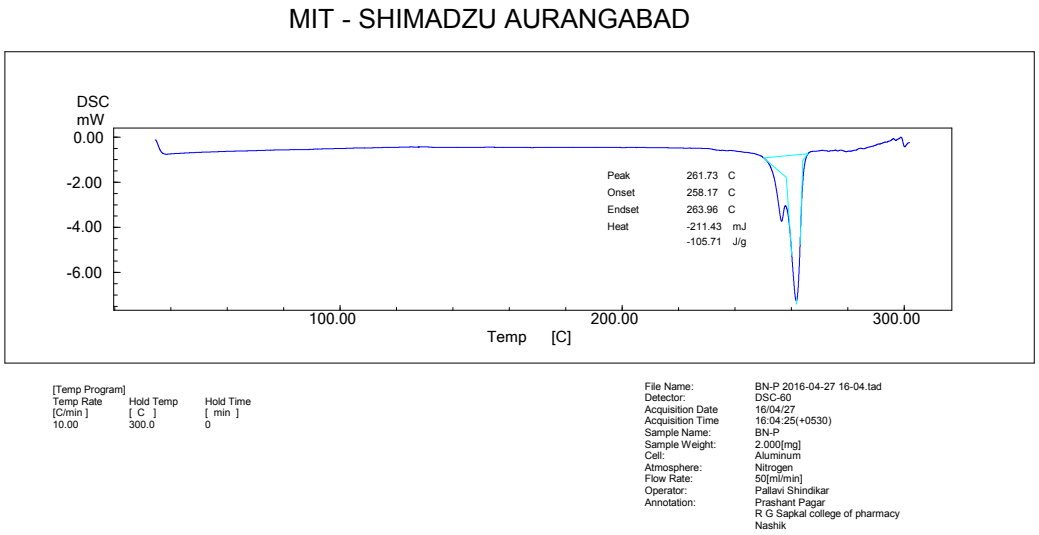

Fig. 3. DSCthermogram of Budesonide

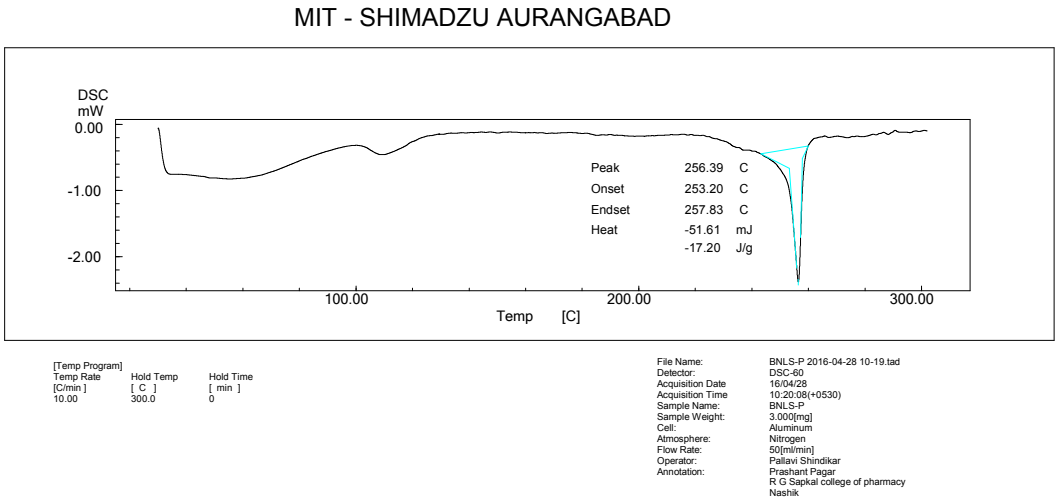

Fig.4. Differential scanning calorimetry (DSC) of physical mixture

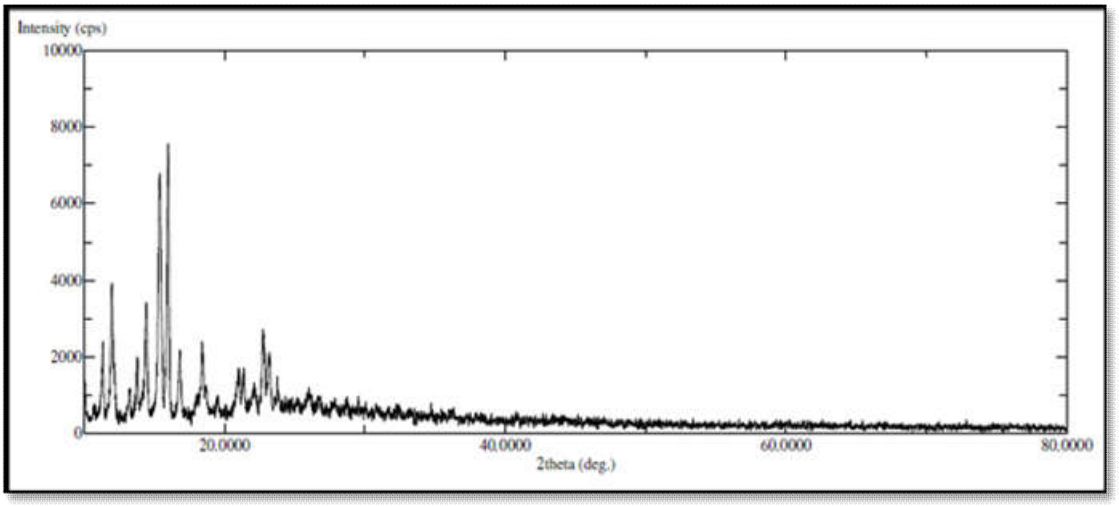

Fig. 5. PXR-Diffractogram of Budesonide

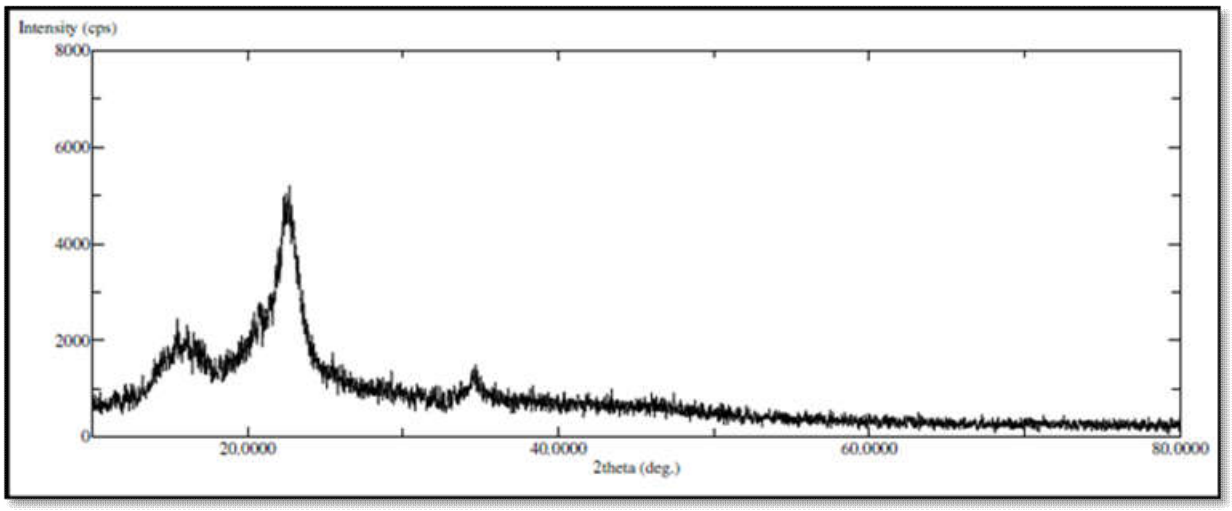

Fig. 6. PXR-Diffractogram of physical mixture (Liquisolid compact)

Interpretation

The FT-IR spectra of mixture containing Budesonide, avicel, aerosol, PEG 400 and crospovidone was recorded and analyzed for the observed peaks and the functional groups assigned to them.

Differential scanning calorimetry (DSC)

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation. Fig.3 illustrates DSC profiles of Budesonide.

The DSC thermogram of the drug depicts a sharp exothermic peak followed by an endothermic peak at 258.17°C corresponding to the melting transition temperature of and decomposition Budesonide. Such sharp endothermic peak signified that Budesonide used was in pure amorphous state.

Differential scanning calorimetry (DSC) of physical mixture

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation. Figure.4 illustrates DSC profiles of physical mixture (Budesonide and excipients)

Powder X-Ray Diffraction

The X-ray Diffractogram of pure Budesonide (Fig.5) clearly show the peak indicating that drug is in crystalline form. The peak intensity of drug in liquisolid compact (Fig.6) was reduced indicating that the drug was converted in to amorphous nature. In the X-ray Diffractogram of Budesonide at a diffraction angle of50, 100, 110, 120, 150, 160, and 220 indicates the crystallinity of the drug. The liquisolid compact show sharp peaks at 11.70, 160, and 16.50 revealed that some of the crystalline peaks of the drug were still detectable but with reduced intensity and less number in the Diffractogram.

This data confirms that the sharp peak of drug are absent in the defractogram of liquisolid compact. This indicates that crystallinity of drug is reduced in the liquisolid compact, which leads to enhancement of dissolution of the drug.

Preformulation Studies of Formulation

Powder flow is a complicated matter and was influenced by so many interrelated factors; the factors list is long and includes physical, mechanical as well as environmental factors. Therefore, determination of angle of repose, Carr's index, Hausner's ratio is important before formulation because it influenced compressibility, tablet porosity and dissolution.

As formulation F1 contains minimum amount of Avicel PH 102 and low L_F value so it had the poor flowability parameter as compared to next formulation.

The batch F6 contain the good flowability parameter.

Table 4. Flowability Parameters of Tablet

Formulation No.	Angle of repose ± SD	Compressibility index ± SD	Hausner's ratio ± SD
F1	27.98±0.97	8.38±1.09	1.09±0.05
F2	27.26±0.62	5.78±1.98	1.05±0.02
F3	26.75±0.70	5.54±1.23	1.05±0.07
F4	29.94±0.65	9.63±1.15	1.10±0.01
F5	28.71±0.58	8.85±1.88	1.07±0.02
F6	27.64±0.34	12.63±3.42	1.14±0.04
F7	30.19±0.53	10.90±5.33	1.12±0.05
F8	29.59±0.75	9.50±3.03	1.09±0.08
F9	28.93±0.36	9.73±2.43	1.08±0.02

(All values are expressed as mean ± SD (n=3)

Evaluation of Liquisolid Compacts of Budesonide

Tablet dimensions

Thickness of liquisolid compacts ranged from 4.39±0.006 to 5.76±0.004 mm and diameter of all the liquisolid compacts was found to be 8.64 ± 0.016 to 9.82 ± 0.014 mm.

Hardness

Hardness was found to be in the range of 3.14±0.20 kg/cm^2 to 3.76±0.24 kg/cm^2

Friability

All the liquisolid compacts had acceptable friability as none of the tested formulae had percentage loss in tablet's weights that exceed 1%. Friability below 1% is an indication of good mechanical resistance of the tablets. This ensures that tablets could withstand to the pressure, shocks during handling, transportation and manufacturing processes.

Drug content

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets. Uniform drug content was observed for all the formulations (95.42±0.65% to 99.50±0.41%), which is as per the IP specification (85%-110%).

Weight variation test

Weight variation test revealed that the tablets were within the range of Pharmacopoeial specifications. All the formulations passes weight variation test.

Table 5. Evaluation of liquisolid compacts

Formulation No.	Thickness (mm)	Hardness (kg/cm^2)	Weight Variation (mg)	Friability (%)	% Drug Content
F1	4.39±0.006	3.14±0.20	178.44±5.48	0.49±0.12	97.63±0.61
F2	5.47±0.004	3.42±0.50	278.18±5.78	0.34±0.08	95.42±0.65
F3	5.75±0.002	4.16±0.20	379.02±6.60	0.37±0.10	98.44±0.81
F4	4.32±0.008	3.22±0.63	178.96±4.25	0.46±0.01	99.12±0.24
F5	5.43±0.006	3.12±0.16	278.23±4.71	0.43±0.01	96.12±0.85
F6	5.71±0.004	3.62±0.55	379.05±6.72	0.42±0.15	99.50±0.41
F7	4.40±0.003	3.24±0.74	179.05±4.10	0.33±0.05	98.52±0.87
F8	5.46±0.002	3.40±0.46	279.10±5.48	0.32±0.13	96.12±1.05
F9	5.76±0.004	3.76±0.24	379.14±5.48	0.39±0.32	97.63±0.61

All value expressed as mean ± SD (n=3)

Table 6. *IN VITRO* Drug Release for all batches (F1-F9)

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	12.91 ±3.11	11.37 ±0.39	11.27 ±0.39	12.43 ±2.79	10.93±0.36	14.68 ±1.70	12.85 ±1.70	13.99 ±1.09	12.43 ±2.79
20	19.33 ±2.06	15.28 ±0.08	14.44 ±0.08	17.62 ±2.23	19.14±0.48	18.70±2.06	17.08±1.67	17.00 ±0.20	17.62 ±2.23
30	23.92±2.85	19.86 ±1.42	17.92 ±1.42	23.86±5.10	23.72±0.82	22.91±2.23	21.86±3.86	21.76 ±0.49	23.86±5.10
40	27.38±2.13	23.95 ±0.22	21.05 ±0.22	29.35±02.4	27.22±0.43	26.2 ±2.46	25.56±0.86	23.15 ±1.57	28.35±02.4
50	31.62±1.27	29.99 ±0.44	24.63 ±0.44	33.25±0.72	33.79±2.11	33.52±1.66	30.72±2.01	27.25 ±0.92	35.25±0.72
60	36.69±0.29	37.99 ±0.77	33.65 ±0.77	38.35±1.13	37.25±0.48	42.35±0.42	37.05±0.61	30.11 ±0.58	42.35±1.13
70	39.02±2.11	45.74 ±0.34	41.06 ±0.36	42.65±0.64	42.55±0.52	51.24±0.43	45.7 ±0.43	38.03 ±0.84	48.65±0.64
80	43.26±0.63	52.03 ±0.21	50.42 ±0.12	47.55±0.36	47.34 ±0.35	61.41±0.34	53.61 ±0.34	46.08 ±0.81	57.55±0.36
90	48.71±0.25	61.21 ±0.12	56.67 ±0.62	52.27±0.69	52.63±0.27	69.68±0.62	60.72 ±0.21	58.34 ±1.51	65.27±0.69
100	54.88±0.24	69.04 ±0.34	62.84 ±0.29	57.48±0.12	57.19±0.52	79.92±0.34	69.93±0.34	64.65 ±0.70	74.48±0.12
110	62.12±1.65	76.02 ±0.31	70.69 ±0.18	61.66±0.13	62.06±0.52	87.42±0.31	77.17±0.12	70.09 ±0.30	82.66±0.13
120	67.48±0.32	80.98 ±0.23	76.17 ±0.27	65.85±0.26	68.01±0.47	95.83±0.42	65.92±0.63	78.09 ±0.42	90.14±0.41

All values are expressed as mean ± SD (n=3)

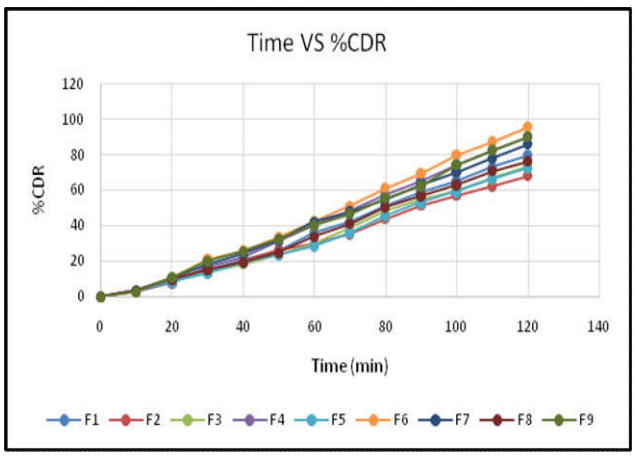

Fig.7. % CDR Vs Time

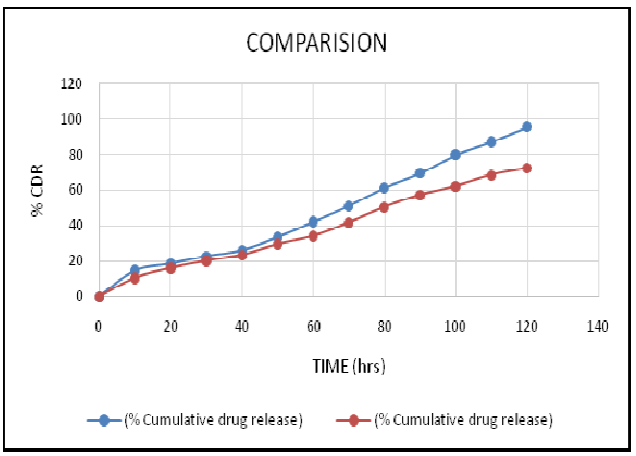

Fig. 8. Model assessment for the dependent variables

In-vitro drug release

The results of in-vitro percentage amount of drug released at different time intervals plotted against time to obtain the release profiles. All the liquisolid compacts showed higher drug release than the conventional tablet. The result shows that there was significant difference (P< 0.0001) between the release profile of the conventional tablet and all the liquisolid compacts. The enhanced dissolution rates of liquisolid compacts compared to conventional tablet may be attributed to the fact that, the drug is already in solution in PEG, while at the same time, it was carried by the powder particles (microcrystalline cellulose and silica).

Table 7. The In-vitro Dissolution Data of Tablets of formulations F6 and conventional tablet

Time (Min)	(% Cumulative drug release)	
	F6	conventional tablet
0	0	0
10	14.68	10.56
20	18.70	16.13
30	22.91	20.26
40	26.20	23.54
50	33.52	29.51
60	42.35	34.18
70	51.24	41.85
80	61.41	50.52
90	69.68	57.28
100	79.92	62.26
110	87.42	68.56
120	95.83	72.45

All values are expressed as mean ± SD (n=3)

Thus, its release was accelerated due to its increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. PEG facilitated wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface.

From the figure it shows that when Liquisolid formulation compared with conventional tablet formulation, the conventional tablet formulation shows 79.45 % release in 2 Hrs, in 0.1 N HCL, when compared with liquisolid formulation i.e. F6 formulation shows 95.83% drug release in 2 Hrs in 0.1N HCL. For formulation F6 it shows about 95% of drug release up to 2 Hrs. So, it is concluded that increase in the concentration of polymer and addition of PEG 400 , the release increases, hence it can be optimum batch for formulation.

Statistical analysis

3^2 Full Factorial Designs

The purpose of using 3^2 full factorial designs was to conduct comprehensive study of effect of process parameters like carrier: PEG 400 concentration (X_1) and coating material ratio i.e. R value (X_2) and their interactions using a suitable statistical tool (Design expert software version 7.1.5) by applying one way ANOVA at 0.05 levels. Mathematical modelling was carried out. Polynomial equation was obtained depending on significant influences among 2 factors on their experimental design. The influence of the main effects on responses was further elucidated by response surface methodology. It is widely used tool in the development and design of the dosage form. The three dimensional response surface plot and corresponding two dimensional contour plots were generated by the software. The response surface plot is very useful for determination of the main and interaction effects of the independent variables whereas two dimensional plots give visual representation of values of responses. This reveals that mathematical model obtained by factorial design to produce optimized responses was well fitted shown in Fig. 9-10.Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings.

Tables 8 shows ANOVA for the dependent variable % drug release after 2 hrs. The values of X_1 and X_2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. Increasing the concentration of the R value i.e. carrier and coating ratio resulted in the increase in the release of Budesonide Variable caused significant change in the responses.

Table 8. ANOVA for 2hrs response

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	612.75	5	122.49	12.84	0.0307	significant
A-PEG 400 conc	213.25	1	213.25	22.36	0.0179	
B-R value	55.58	1	55.58	5.83	0.0947	
Residual	28.61	3	9.54			
Cor Total	641.06	8				

The Model F-value of 12.84 implies the model is significant. There is only a 3.07% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. The relationship between the response and independent variables can be directly visualized from the response surface plots. The response surface plots were generated using Design Expert 7.1.5 software presented in fig.9 to observe the effects of independent variables on the response studied % drug release after 2hr. From response surface 3 level factorial design was chosen using quadratic design mode. The 9 run was performed for the response % drug releases and models were found to be linear.

Stability Study

Short term accelerated stability study was performed at 40^0C and 75 % RH for 90 day. After the period of 30, 60 and 90 days the Liquisolid formulation was tested for drug content. Results are shown in following Table 9.Results of stability studies showed that there is no significant change in content uniformity and drug release for optimized formulation after elevated temperature and humidity conditions during stability studies. Thus it can be proved from the stability studies that the prepared formulation is stable and not affected by humidity and temperature conditions.

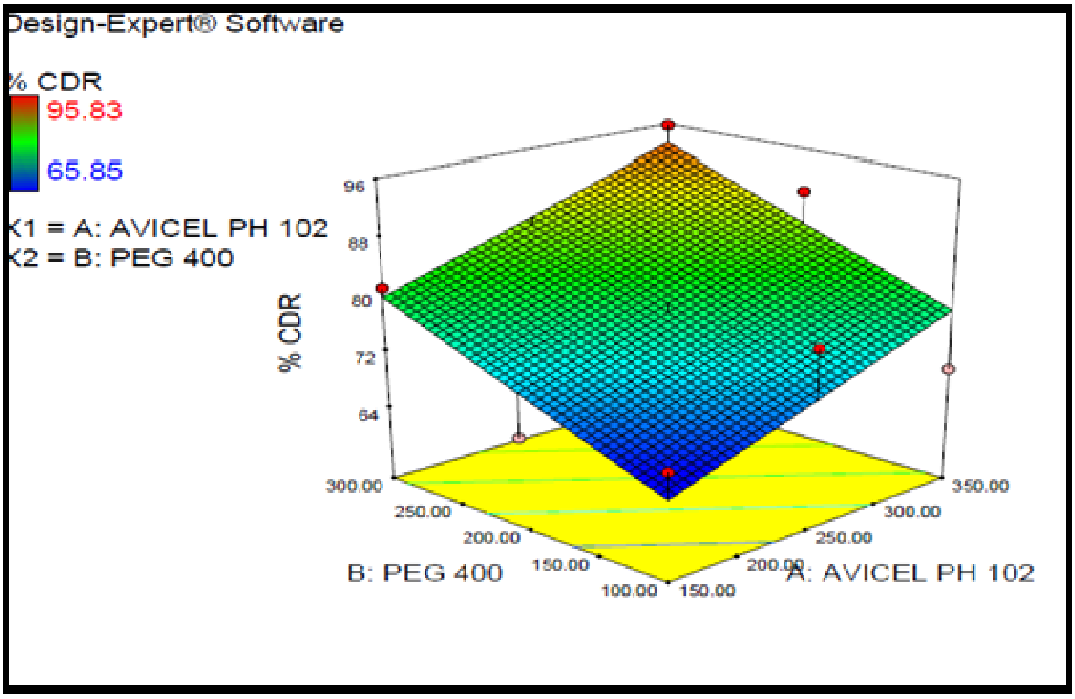

Fig. 9. Surface response plot showing effect of Carrier material and PEG400 conc. on % CDR after 2hrs

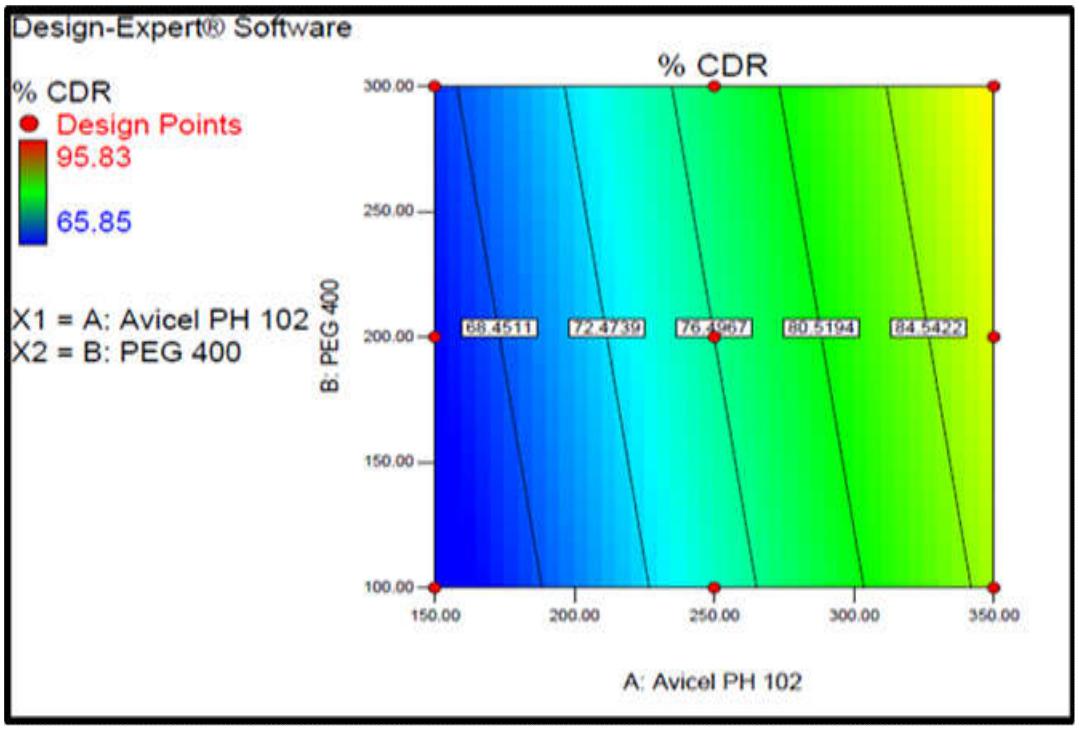

Fig. 10. Counter plot showing effect of Carrier material :PEG 400 conc. on % CDR after 2hrs

Table 9. Stability study of optimized Liquisolid formulation

Evaluated Parameters	Initial	After 1 month	After 2 month	After 3 month
Appearance	White, acceptable	White, acceptable	White, acceptable	White, acceptable
Hardness± S.D.	3.62±0.55	3.61	3.59	3.58
Drug content (%) ± S.D.	96.12±0.85	96.10	96.9	96.6
Friability± S.D.	0.42±0.15	0.41	0.40	0.39
Weight variation	379.05±6.72	379.04	378.09	377.02
%Cumulative drug released	95.83±0.42	95.67	95.32	95.29

Summary and Conclusion

The potential of liquisolid systems to improve the dissolution properties of a water-insoluble agent was investigated using Budesonideas the model drug. Liquisolid compacts of Budesonidedisplayed significantly enhanced in-vitrodrug release properties. The results showed that technique of liquisolid compacts could be a promising alternative for formulation of water-insoluble drugs. The enhanced rate of Budesonided is solution from liquisolid tablets was probably due to an increase in ratio of carrier and coating material (R-value) and surface area of drug particles available for dissolution. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. The FTIR analysis confirmed that the excipients are compatible with the drug. There was no any interaction occurred during the process of formulation.

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