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Solubility and Dissolution Enhancement of Budesonide by Solid Dispersion Using Rotary Evaporation Method

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ABSTRACT

The aim of the present study was to formulate and evaluate budesonide solid dispersion using PVP K-35 and HPMC K-15 polymers with the help of solvent evaporation method followed by rotary evaporation method to improve solubility and dissolution of budesonide. Solid dispersion of budesonide was prepared with different drug: carrier ratios using solvent evaporation method followed by rotary evaporation method. F1 to F9 batches were prepared. The solubility study of F1 to F9 batches were carried out. Batch F6 has shown highest solubility, and was F6 batch was selected as optimized batch. FT-IR and DSC were performed to identify the physicochemical interactions between drug and optimized formulation. The dissolution test was carried out to check the percentage drug release of solid dispersion. The drug release of solid dispersion is after 60 min was 9.92% for optimized batch.

Keywords : Budesonide, PVP K-35, HPMC K-15

I. INTRODUCTION

The challenging in formulation development is to enhance the solubility and dissolution of drug that have low solubility. BCS class II drug have low solubility and high permeability. Solid dispersion technique involves at least two different components i.e., hydrophilic matrix and a hydrophobic drug which are combined together by different methods like solvent evaporation, gel entrapment method, fusion, lyophilization technique, spray drying, extruding method. Solid dispersion of lumefantrine was prepared by using Soluplus which improved the solubility[1]. One of the glucocorticoids with an effect on a wide range of human organs is budesonide. Budesonide is a highly hydrophobic drug. Solid dispersion systems which contain molecular dispersion of the active pharmaceutical ingredient (API) within an inert amorphous or crystalline carrier have been increasingly implemented[2]. Budesonide has a high topical anti-inflammatory activity and low systemic effects, as a result of its strong affinity for corticosteroid receptors and rapid pass metabolism in the liver. Budesonide is currently marketed as a nasal

spray, a dry powder inhaler, a ileal release capsule, and a ointment for the treatment of asthma, allergic rhinitis, inflammatory bowel disease, Crohn's disease and inflammatory dermatoses, respectively[3]. Solid dispersion is a viable and economic method to enhance bioavailability of poorly water-soluble drugs and also overs=comes the limitations of the previous approaches. The improvement of the dissolution of drugs from solid dispersions is based mainly on three different mechanisms like the wettability of the drug (which is improved by direct contact with the hydrophilic matrix), the reduction in the particle size and increased surface area, and the conversion of the crystalline state to the more soluble amorphous state[4].

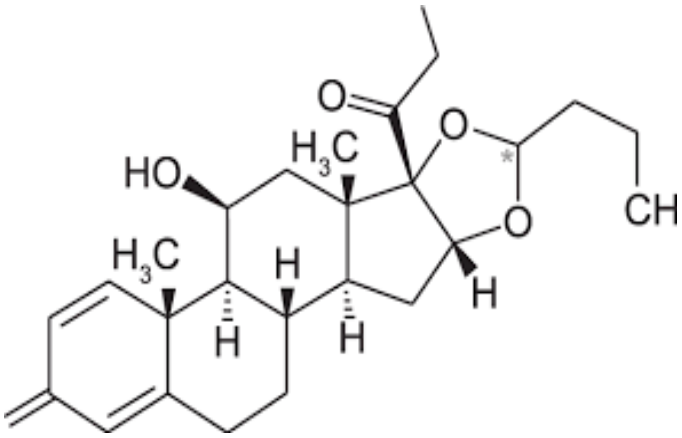

Fig.1: Structure of Budesonide

II. MATERIALS AND METHODS

Materials:

Budesonide was obtained as a sample from Vamsi Labs Ltd. A- 14 and 15, MIDC Area, Chincholi, Solapur-413255. Maharashtra India. Polymers Polyvinylpyrrolidone K-35 and Hydroxy Propyl Methylcellulose K-15 were obtained from Sai Chemicals Solapur. All chemicals and reagents of analytical grades.

METHODS:

Saturated Solubility Study:

The study was carried out by adding excess of drug solution in different solvents, for examole, water and phosphate buffer pH 6.8,1.2,7.4 and methanol. The saturated solutions werw kwpt on magnetic stirrer for 48 hours at room temperature. After 48 hrs, supernatant liquid was taken filtered through Whatman filter paper (0.45 µ). The amount of Budesonide disslved was quantified by taking supernatant and by making dilution (if required) using UV 2201 (Systronics) spectrophotometer at 244.8 nm[5].

Preparation of Solid Dispersion:

Solid dispersion of BUD was prepared by rotary evaporation method. The ratio of BUD to polymer (3:2). methanol was used as the solvent as both drug and polymer are freely soluble in it. The process was done by taking drug - polymer ratio of various concentrations as mentioned above. The solvent was evaporated using rotary evaporator at a temperature of 40°C to obtain a solid dispersion. The dry mas was pulverized and passed through 60 mesh sieve and stored in desiccator for further studies[6].

Characterization of Solid Dispersion:

Fourier Transform Infrared (FTIR) Spectroscopy:

Fourier transform infrared (METTLER TOLEDO DSC 823e) spectra of powdered samples of budesonide, polyvinylpyrrolidone K-35 and hydroxy propyl methylcellulose K-15 solid dispersions (SD) of different ratios were obtained using a FTIR spectrophotometer by potassium bromide (KBr) mixture method (4 mg sample in 250 mg KBr). The scanning range was 400-4000 cm^{-1} [7].

Differential Scanning Calorimetry (DSC):

The thermograms were recorded for budesonide solid dispersion (SD) using METTLER TOLEDO DSC823e differential scanning calorimeter. A heating rate 10°/ min was employed in the 30-300°C temperature range. Standards aluminium sample pans were used. An empty pan was used as a reference standard. The analysis was performed on 5 mg samples under nitrogen purge (40 ml / min)[8].

In - *Vitro* Dissolution Studies:

The in - *vitro* drug release studies were performed for solid dispersion of same ratio using USP type 2 dissolution apparatus (Electrolab) using phosphate buffer pH 6.8 (900 ml) and the temperature was maintained at 37 ˚C and the stirring speed was 50 rpm. The sample aliquots were withdrawn at a time intervals of 5, 10, 15, 30, 45, 60, 90, 120 min and the same quantity was replaced by fresh medium to maintain the sink conditions. The samples were analyzed by using UV-Visible spectrophotometer (Systronics 2201) at 244.8 nm. The cumulative percentage drug release was calculated[9].

III. RESULTS AND DISCUSSION

Preparation of Solid Dispersion:

Various methods are used to prepare solid dispersions depending on the nature of drug and polymer. These include solvent evaporation, melt method, hot melt extrusion and gel entrapment method. Melt method and melt extrusion method involve heating to melt the carriers and this may cause unwanted changes in the physicochemical profile of the drug such as degradation, crystallographic changes, etc. hence in present study rotary evaporation method was used to prepare solid dispersions of budesonide with polyvinylpyrrolidone K-35 and hydroxy propyl methylcellulose K-15 with methanol as the solvent. In this method the drug is also in molecular form and carrier such as 3:2 was used. All the solid dispersions were found to be fine free flowing powders. F1 to F9 batches were prepared.

Saturation Solubility Studies:

The solubility of pure budesonide solid dispersion in distilled water and phosphate buffer pH 6.8 ,7.4, 1.2 and 0.1 M HCL was found to be 20.81 µg/ml, 27.28 µg/ml, 28.72 µg/ml, -4.5µg/ ml, 21.55 µg/ml respectively. It indicates that the drug is practically soluble. Therefore, using rotary evaporation method solid dispersion was employed for solubility and dissolution enhancement of budesonide. The results for solubility study in different are reported in table 2.

Table 2. solubility studies:

Sr. No	Solvent	Absorbance	Amount of drug soluble (µg/ml)
1	Distilled water	0.921	20.81
2	Phosphate buffer pH 6.8	1.209	27.28
3	Phosphate buffer pH 7.4	1.273	28.72
4	Phosphate buffer pH 1.2	-0.209	-4.5
5	0.1 M HCL	0.954	21.55

FTIR Studies of Solid Dispersions:

The prominent peaks of budesonide and solid dispersion were observed “Fig. 2, 3”, in the region of 3490.24 cm^{-1} and 3442.18 cm^{-1} due to the alcoholic and phenolic -OH stretching, a peak at 2596.90 cm^{-1} and 2924.53 cm^{-1} due to C-H stretching and a peak at 1665.82 cm^{-1} and 1712.27 cm^{-1} due to C=C stretching, a peak at 1405.79 cm^{-1} and 1039.19cm^{-1} aliphatic C-H stretching and a peak at 930.9 cm^{-1} and 449.53 cm^{-1} due to aromatic stretching. The spectra of solid dispersion indicates that budesonide was molecularly dispersed in the polymer matrix.

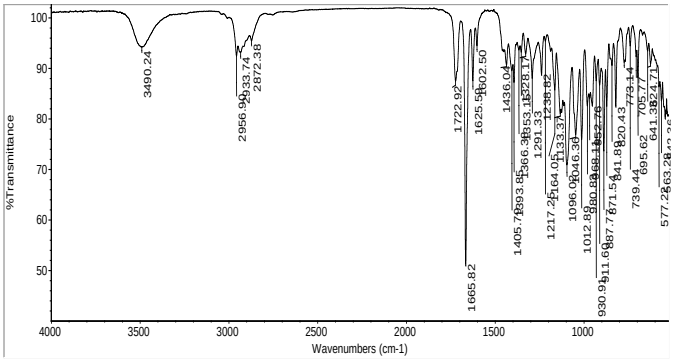

Fig.2 FTIR studies of Budesonide

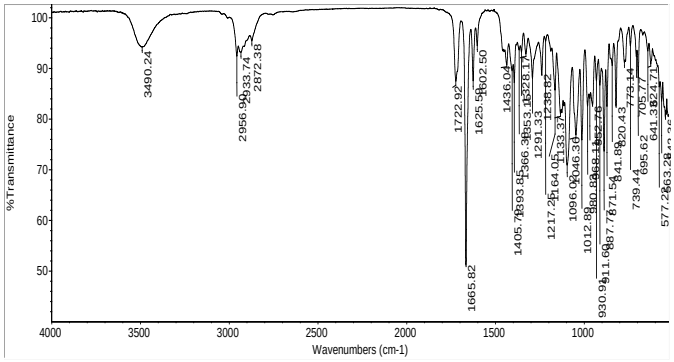

Fig.3 FTIR studies of solid Dispersion

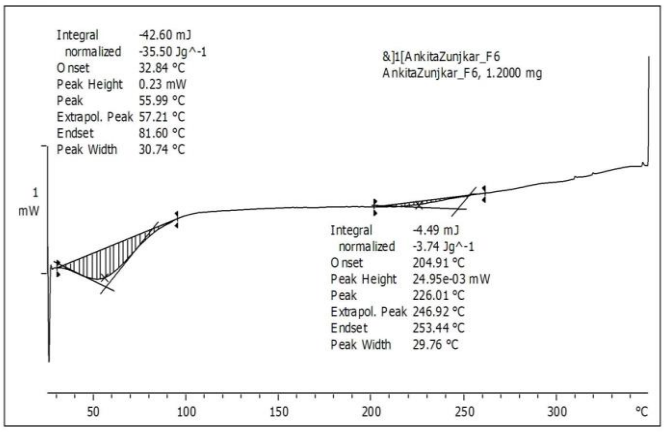

Fig.5 DSC studies of solid Dispersion

Differential Scanning Calorimetry:

The DSC thermogram of budesonide showed in "Fig.4", shows a sharp endothermic peak at melting point 260.23 ℃, indicating that the drug is highly crystalline. This sharp peak confirmed the purity of drug with no noticeable impurities present. Budesonide was found to be stable to heat up to 250℃ without any signs of moisture and phase transition. In "Fig. 5", solid dispersion shoes a broad endothermic peak correspond to budesonide at 55.99℃. the short endothermic peak was found to be 226.01℃. it shows a gradual decrease pattern emphasizing the fact that physical interaction should be present in the solid dispersion. the presence of broader peak, or the complete absence of melting peak, is a clear indication that a drug is partially or completely dispersed in polymeric carriers.

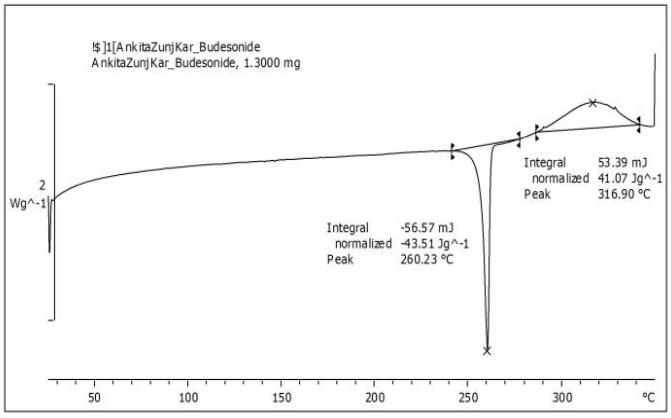

Fig.4 DSC studies of Budesonide

In-*Vitro* Dissolution of Solid Dispersion:

The in-*vitro* dissolution revealed that dissolution rate of solid dispersion was higher as compared to that of drug alone "Fig.6". from the study it was found that solid dispersion showed nearly 90% release in after 60 min. the slower release in presence of higher polymer concentration could be attributed to the ability of polyvinylpyrrolidone K-35 and hydroxy propyl methylcellulose K-15 to form matrix type solid dispersion which results in slower drug diffusion through the tortuous channels formed in the matrix. The improvement in the dissolution of the drug may be due to its entrapment within the molten carrier during the process, or due to the molecularly dispersed state of the drug in the solid dispersion. also, the drug is converted into amorphous state and its wetting property is improved. Thus, the cumulative effect is improvement in solubility and dissolution rate. The optimized batch was F6 it shows highest solubility.

Table 3. In-*Vitro* Release of F1-F9 Formulations of Budesonide Solid Dispersion

Time (min)	**Percentage drug released**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	3.38	1.42	3.96	1.76	1.29	8.65	1.80	1.57	6.93
10	6.63	1.47	1.52	2.88	2.29	8.35	4.14	2.53	1.80
15	3.06	1.41	2.10	2.93	2.41	9.57	7.15	1.52	7.35
30	1.80	4.14	5.05	5.08	3.62	8.46	5.08	1.41	6.63
45	6.72	5.70	4.53	5.95	4.88	8.91	3.06	2.05	5.70
60	7.02	6.08	6.77	6.12	5.76	9.92	7.35	2.39	1.52
90	7.12	6.65	7.15	7.46	5.07	9.07	2.10	1.76	2.93
120	7.38	6.93	7.35	7.35	5.47	9.36	6.02	2.50	7.38

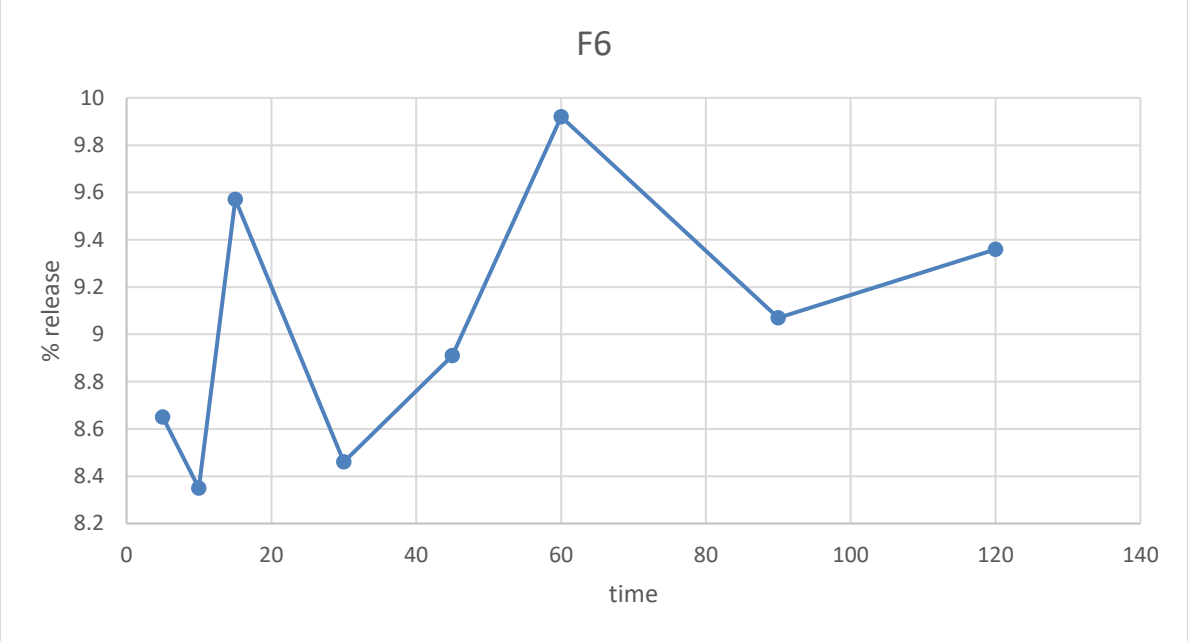

Fig. 6 In - *Vitro* Drug Release of Budesonide

IV. CONCLUSION

From the above studies, it can be concluded that solubility and dissolution enhancement is a major aspect in drug development. The solubility and dissolution rate of budesonide was enhanced by solid dispersion prepared by rotary evaporation method using polyvinylpyrrolidone K-35 and hydroxy propyl methylcellulose K-15. (3:2 carrier ratio) showed improved solubility and dissolution rate. FTIR and DSC studies confirmed amorphization of the drug.

Results of FTIR concluded that there was interaction between budesonide and polyvinylpyrrolidone K-35 and hydroxy propyl methylcellulose K-15. In-*vitro* release studies shows better solubility and dissolution. we may hence conclude that solid dispersions of budesonide using polyvinylpyrrolidone K-35 and hydroxy propyl methylcellulose K-15 showed improved aqueous and dissolution rate.

V. ACKNOWLEDGEMENTS

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