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Formulation and Evaluation of Propranolol Hydrochloride Solid Dispersions

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ABSTRACT

In the present study, Solid Dispersion of Propranolol Hydrochloride were prepared using solvent evaporation technique using PEG 4000, PVP K-30 and PVA. However absolute bioavailability of Propranololo Hydrochloride is about 30% . To increase the solubility, solid dispersion was prepared. Preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with PVA, PEG 4000, PVP-K30. These solid dispersions were analyzed for the solubility and *In-vitro* dissolution profile, solid dispersion of drug with PEG 4000 had shown enhanced solubility with improved dissolution rate. Further FTIR, DSC, SEM studies were carried out. Solid dispersion prepared with PEG 4000 shows the presence of amorphous form confirmed by the characterization study .The study also shows that dissolution rate of Propranolol Hydrochloride can be enhanced to considerable extent by solid dispersion technique with PEG 4000.

Keywords: Propranolol Hydrochloride, Solid dispersion, PVA, PEG 4000, PVP-K30.

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INTRODUCTION

The solid dispersion method is one effective approach to achieve ideal therapy for drugs with low aqueous solubility by incorporating them into a water soluble polymer matrix The concept of using solid dispersion to improve bioavailability of poorly water soluble drugs was based on the fact that, it provide a means of reducing particle size to the molecular level. Solid dispersion can be defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, melting-solvent method. Dispersion obtained through the fusion processes are often called melts and those obtained by the solvent method are frequently referred to as co-precipitates or co-evaporates. The two basic procedures used to prepare solid dispersion are fusion and co-solvent technique. Modifications of these methods or combination of these methods have also been used.

Propranolol Hydrochloride is a non-selective beta blocker, it blocks the action of epinephrine and norepinephrine on both β1- and β2-adrenergic receptors. It has little intrinsic sympathomimetic activity (ISA) but has strong membrane stabilizing activity (only at high blood concentrations, e.g. over dosage). Research has also shown that Propranolol Hydrochloride inhibitory effects on the norepinephrine transporter and/or stimulates norepinephrine release[1]. Since Propranolol Hydrochloride blocks β-adrenoceptors, the increase in synaptic norepinephrine only results in α-adrenergic activation, with the α1-adrenoceptor being particularly important for effects observed in animal models. Therefore, some have suggested that it be looked upon as an indirect α1 agonist as well as a β antagonist. Probably owing to the effect at the α1-adrenoceptor, the racemic and the individual enantiomers of Propranolol Hydrochloride have been shown to substitute for cocaine in rats, with the most potent enantiomer being S-(–)- Propranolol Hydrochloride. In addition, some evidence suggests that propranolol may function as a partial agonist at one or more serotonin receptors (possibly 5-HT1B).

Both enantiomers of the drug have a local anesthetic (topical) effect, which is normally mediated by blockade of voltage-gated sodium channels. Few studies have demonstrated Propranolol Hydrochloride's ability to block cardiac, neuronal, and skeletal voltage-gated sodium channels, accounting for its known "membrane stabilizing effect" and anti-arrhythmic and other central nervous system effects.[2,3,4]

MATERIALS AND METHOD

Material

Propranolol Hydrochloride was obained as gift sample from IPCA labs Ratlam, MP. All other chemicals like PEG 4000, PVA, PVP K-30 etc and reagents were of analytical grade.

Method of Estimation of Propranolol Hydrochloride[5]

A simple, fast reproducible and precise method of estimation for Propranolol Hydrochloride was carried based on the solubility in methanol. 10µg/ml solution was scanned from 200-400 nm. The absorption maxima was found to be 290 nm. Beers range was found to be 1-10 µg/ml. Solubility measurement of Propranolol Hydrochloride were performed according to a published method (Higuchi and Connors, 1965). An excess amount of Propranolol Hydrochloride was added to 25ml of aqueous solution of water soluble carrier like PVA, PVP K-30 and PEG-4000 in various ratio such as 1:1, 1:3,1:5 & 1:10 in screw capped bottles. Samples were shaken for the 24 hours at room temperature on rotatory shaker. The suspension so obtained was filtered through Whatman filter paper no:1. Filtered solution was diluted properly with methanol and analyzed for atorvastatin in UV at 290 nm.

Method of preparation of Solid Dispersion[6]

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability. Solid dispersions were prepared by Solvent evaporation method. In solvent evaporation method, both drug and the carrier were dissolved in a common volatile solvent, and the solvent was evaporated to get solid dispersions. Propranolol Hydrochloride is practically water insoluble molecule. In order to improve its solubility in water solid dispersions were prepared.

Solvent evaporation method[6,7]

In solvent evaporation method, drug and the carrier were dissolved in methanol. Solution was evaporated under low pressure to get the solid dispersion. In this method PVA, PVP K-30, PEG-4000 were used as carrier.

Solubility studies of Propranolol Hydrochloride solid dispersion[8]

Solubility measurements of Propranolol Hydrochloride were performed according to a published method (Higuchi and Connors, 1965). Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution diluted properly with methanol. The diluted solution analyzed for the Propranolol Hydrochloride in UV 290 nm.

Evaluation of solid dispersion

Solid dispersions obtained from the above methods were screened for their solubility. The solid dispersion showing good solubility were further studied for drug content, in vitro release studies, FTIR, DSC study.

Drug content[9]

The amount of drug present in a 10 mg equivalent amount of solid dispersion was determined by, dissolving the powder mixture in 10 ml of methanol and suitably diluted with methanol and UV absorbance was measured at 290 nm. Drug concentration was determined from standard graph.

In vitro release studies[10]

In vitro dissolution studies were performed for selected solid dispersion. The following conditions were maintained for the dissolution process:

Instrument: Electro lab- USP Dissolution test apparatus.

Apparatus: Paddle type.

Temperature: 37±0.10C

RPM: 75

Dissolution medium: Distilled water.

Volume of medium: 900 ml.

Sampling intervals: Every one hour up to 12 hour

Sample volume: 5 ml withdrawn and replaced with 5 ml of distilled water.

IR Studies[11]

Instrument used was Bruker IR spectrophotometer. In this study, potassium bromide disc method was employed. Pure drug, physical mixtures, and solid dispersion studied by IR. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded.

DSC (Differential Scanning calorimetry) studies[12]

Differential scanning calorimetry was conducted using Mettler Toledo Star system, B.R Nahata College of Pharmacy, Mandsore, India. Sample were weighed (2.2 ± 0.3 mg) and placed in sealed alumina pans. The coolant was liquid nitrogen. The samples were scanned at 10^0C/ min from 20^0 C to 300^0 C. DSC thermograms of pure Propranolol Hydrochloride, Pure Carrier, Physical mixtures of drug & carrier and solid dispersions were recorded.

RESULT AND DISCUSSION

Standard Curve

Propranolol Hydrochloride was found to soluble in organic solvents like Methanol. A simple and reproducible method was carried out in methanol ranging from 1-10 µg/ml. solution at 290 nm (Table 1) against the blank the standard curve was obtained was found to be linear with regression coefficient 0.996 (Figure. 1) In case of Solid dispersion initially preliminary solubility

study (Figure. 2 and Table 2) were carried out to the select the appropriate water soluble carriers for the preparation of Solid dispersion in which solubility of pure drug was found to be 0.20mg/ml. From the physical mixtures of PVA, PVP K-30 and PEG 4000 in the ratio 1:1, 1:3, 1:5,1:10 selected for preparation of solid dispersion by solvent method. Solid dispersion produced by solvent method, yield were found to be 84, 88, 96 respectively. Hence yield in case 1:10 ration of drug and carrier was found to highest. So, 1:5 ratio was found to optimum for all formulation.

Table 1: Calibration Curve Data

Concentration (mg/ml)	Absorbance (at 290 nm)
1	0.121
2	0.216
3	0.352
4	0.453
5	0.586
6	0.709
7	0.794
8	0.871
9	0.954
10	0.999
11	1.11

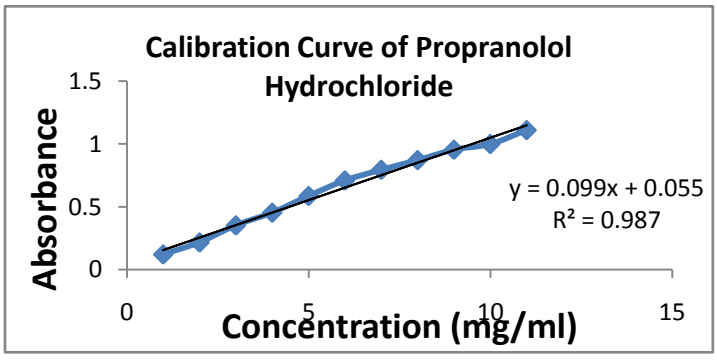

Figure.1: Calibration Curve of Propranlol Hydrochloride

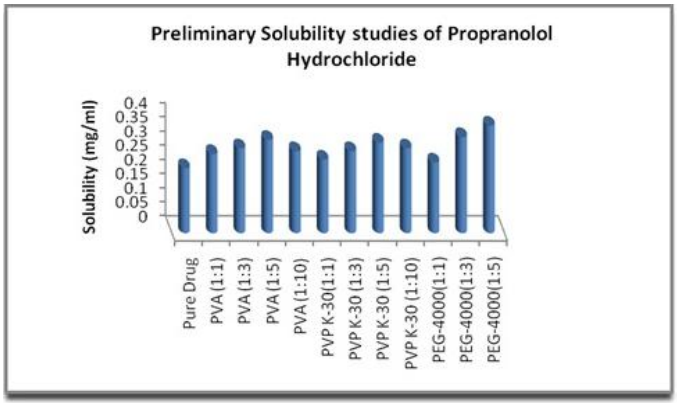

Figure.2: Bar graph of Preliminary Solubility Studies

Table 2 : Preliminary Solubility studies of Propranolol Hydrochloride

S. No	Carrier (Drug: Carrier)	Solubility (in mg/ml)
1.	Pure Drug	0.23
2.	PVA (1:1)	0.28
3.	PVA (1:3)	0.30
4.	PVA (1:5)	0.33
5.	PVP K-30(1:1)	0.26
6.	PVP K-30 (1:3)	0.29
7.	PVP K-30 (1:5)	0.32
8.	PEG-4000(1:1)	0.25
9.	PEG-4000(1:3)	0.34
10.	PEG-4000(1:5)	0.38

Dissolution Study

Dissolution profiles of the Propranolol Hydrochloride and their solid dispersion shown in figure 3.The rate of dissolution was found to be increased in all the solid dispersion as shown by time taken for 50% ($t_{50\%}$) of drug to be released. Solid dispersion prepared with PEG-4000 showed fastest released with $t_{50\%}$ in 7 hours. Thus it was observed that solid dispersions of PEG-4000 in 1:5 ratio had maximum solubility of Propranolol Hydrochloride with enhanced dissolution rate.(Table 3)

Table 3: Dissolution Profile of Pure Drug and Prepared Solid Dispersion

Time	Pure Drug	PVA SD	PVP k-30 SD	PEG 4000 SD
1	4.12	17.02	16.12	18.32
2	8.71	22.14	21.09	25.63
3	13.68	27.92	27.92	29.11
4	15.45	31.02	30.28	33.03
5	19.91	36.08	35.69	39.18
6	22.63	41.03	40.07	45.31
7	25.25	45.09	43.98	50.62
8	29.27	51.01	50.84	56.17
9	32.99	56.19	54.28	60.82
10	37.19	63.87	60.42	66.9
11	39.92	71.96	65.79	73.34
12	42.69	82.44	76.28	86.32
Folds	1	1.93	1.78	2.02

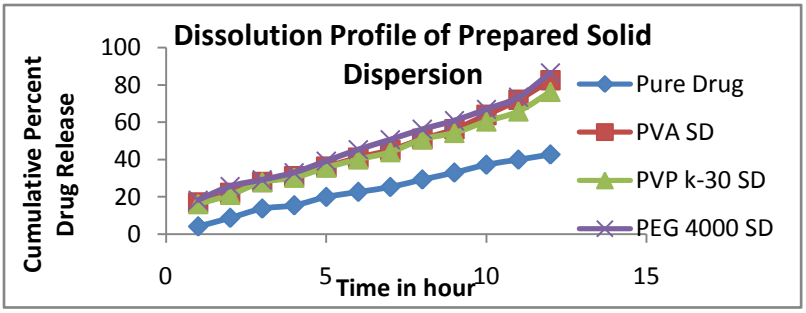

Figure 3 Dissolution Study of Prepared Solid Dispersions

IR Study

IR study of the Pure Drug, Pure Polymer, Drug Polymer Physical Mixture and Solid Dispersion were carried out and compared with standard curve and found to be congruent to that and results were tabulated in Table:4 and Figure. 3

Table 4: IR values of Pure drug

Functional Groups	Wave number in cm-1	
	Range	Pure Drug
O-H Straching		3602.6
C-H Straching	2962-2853	2927.7
N-H Straching	3500	3405.2
C-O Straching	1750-1735	1727.8
C-C Aliphatic Straching	1485-1445	1489.2
Benzene	750	789.5
	840-885	771.5
	700	669.3
	700	617.2

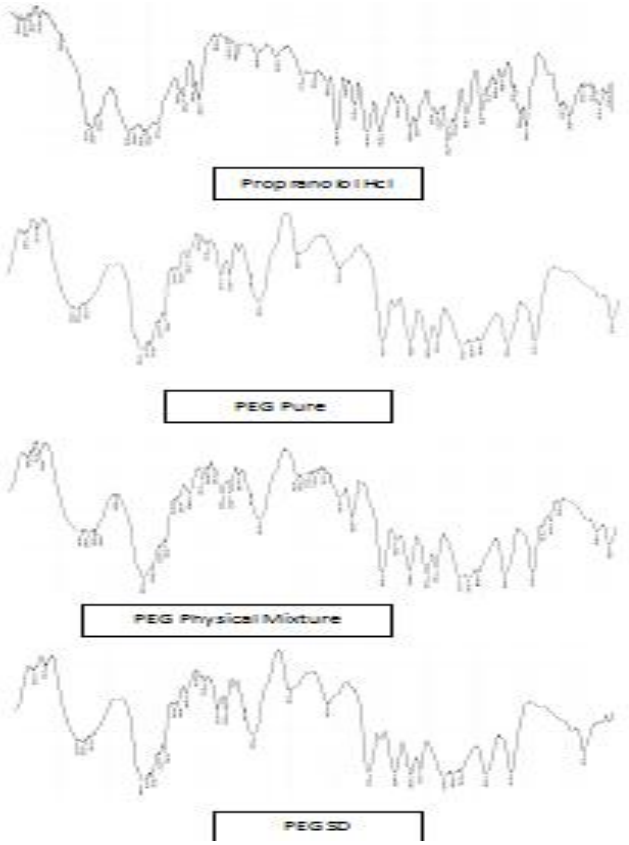

Figure. 4: IR Spectra

DSC studies

DSC thermo gram of Propranolol Hydrochloride showing (Figure. 5) one endothermic peaks one of which at165 ˚C corresponding to the melting point of Propranolol Hydrochloride. In case

of physical mixture (Figure. 7) of Propranolol Hydrochloride and PEG 4000 systems it has seen that the persistence of the endothermic peak of Propranolol Hydrochloride as well as PEG 4000. However the drug peak has shifted toward slightly higher temperature with lower intensity. Similarly PEG 4000 (Figure. 5) shows a broad endothermic effect from 60.06˚C having a peak at 63.90˚C. Solid dispersion of Propranolol Hydrochloride with PEG 4000 shows (Figure.8) no peaks related to Propranolol Hydrochloride, was seen. This indicates that Propranolol Hydrochloride no longer present in the crystalline form, may have got converted into the amorphous form. It also suggests that Propranolol Hydrochloride appears to be soluble in the liquid phase of PEG 4000.

In case of physical mixture (Figure. 10) of Propranolol Hydrochloride and PEG 4000 systems it has seen that the persistence of the endothermic peak of Propranolol Hydrochloride as well as PVP K-30. However the drug peak has shifted toward slightly higher temperature with lower intensity. Similarly PVP K-30 (Figure.10) shows a broad endothermic effect from 148.22˚C having a peak at 150.98˚C. Solid dispersion of Propranolol Hydrochloride with PVP K-30 (Figure.8) no peaks related to Propranolol Hydrochloride, was seen. This indicates that Propranolol Hydrochloride no longer present in the crystalline form, may have got converted into the amorphous form. It also suggests that Propranolol Hydrochloride appears to be soluble in the liquid phase of PVP K-30.

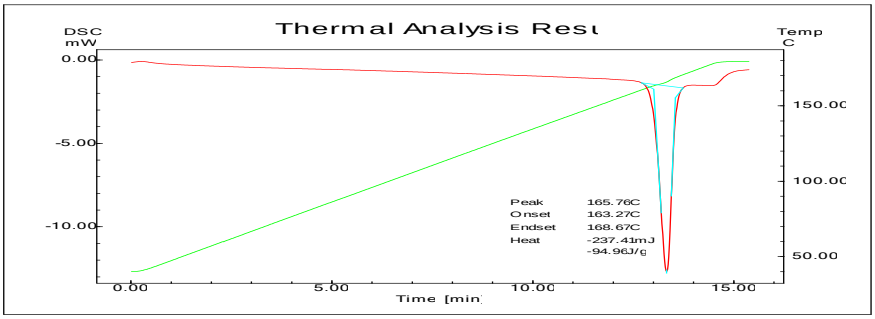

Figure. 5: DSC Thermogram of Pure Drug Propranolol Hydrochloride

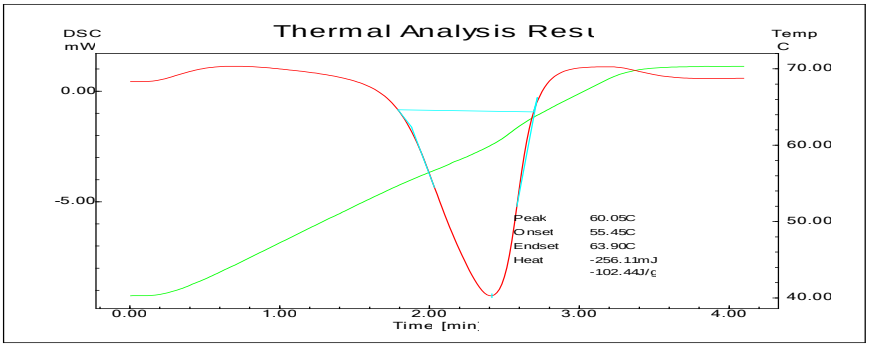

Figure.6: DSC Thermogram of PEG-4000

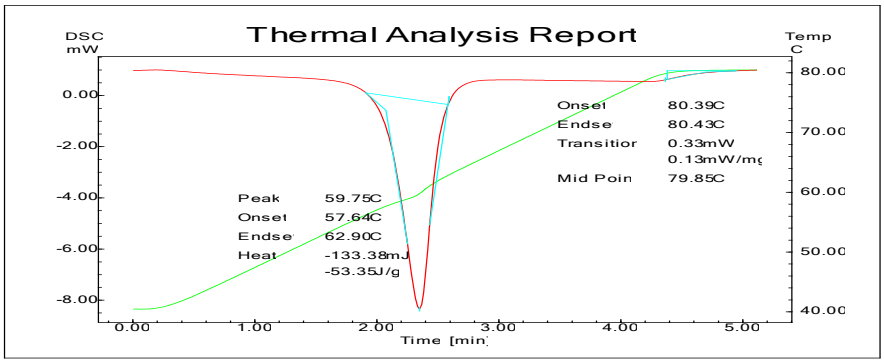

Figure. 7: DSC Thermogram of Drug and PEG-4000 Physical mixture

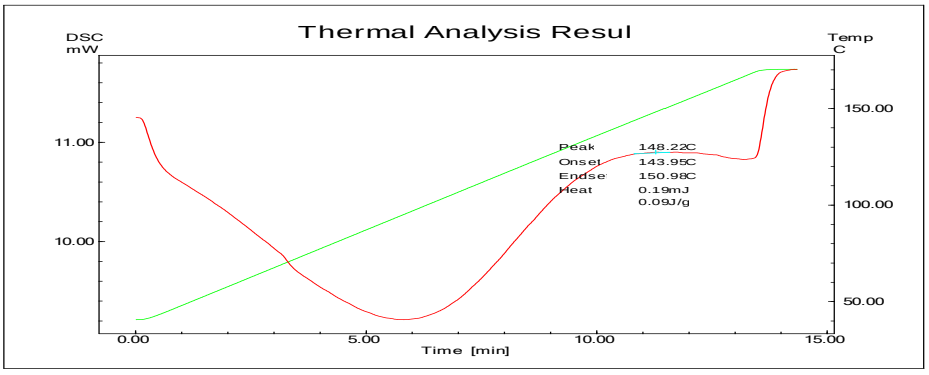

Figure. 8: Thermogram of PEG-4000 Solid Dispersion

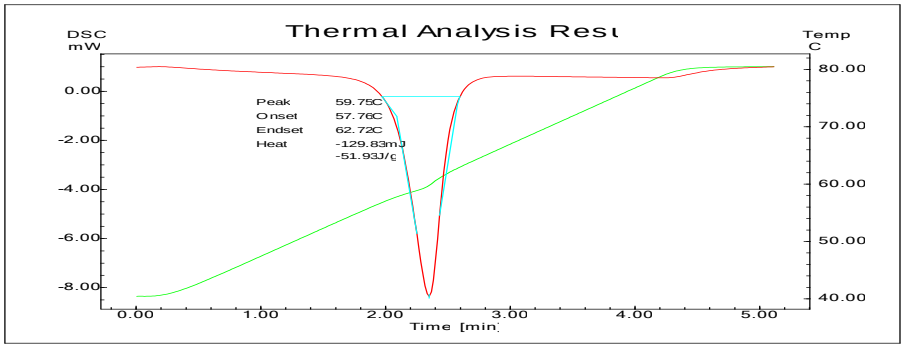

Figure. 9: DSC Thermogram of PVP K-30 Pure

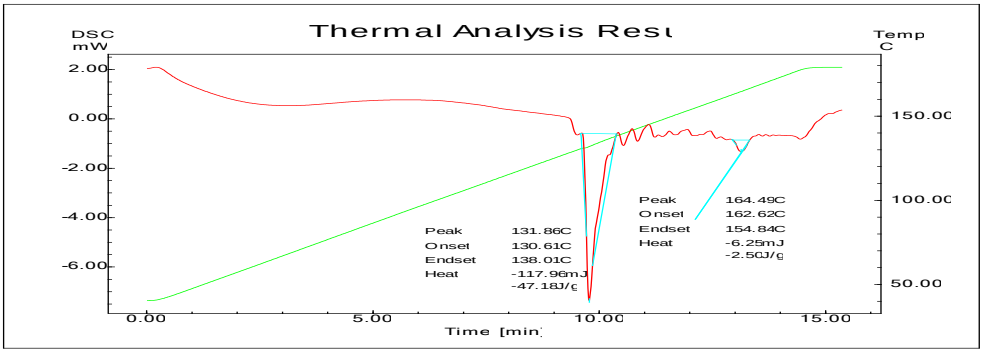

Figure. 10: DSC Thermogram of Drug and PVP K-30 Physical Mixture

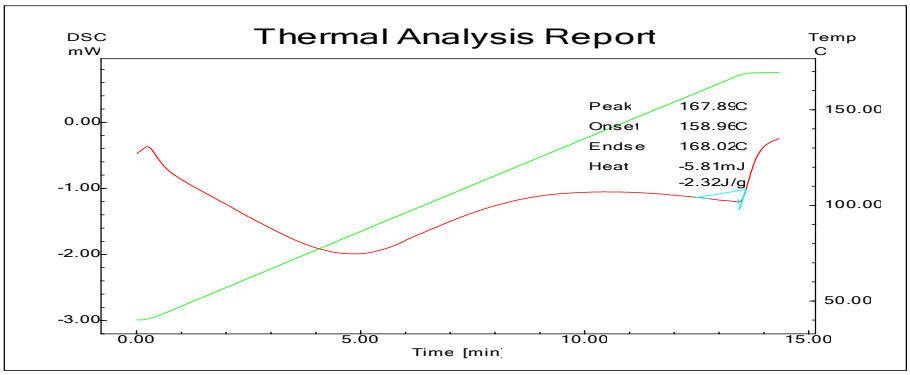

Figure.11: DSC Thermogram of PVP K-30 Solid Dispersion

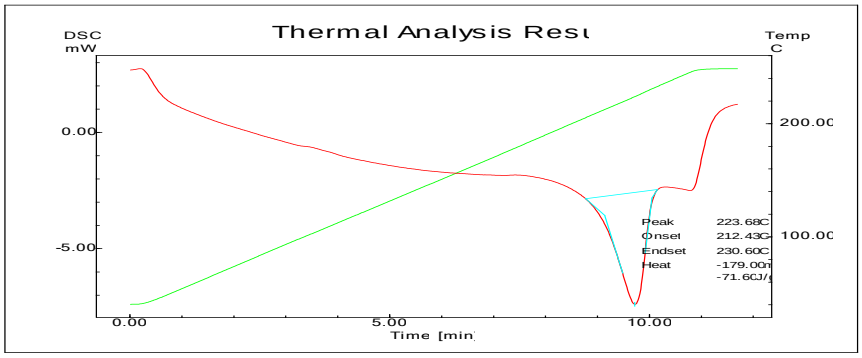

Figure.12: DSC Thermogram of PVA

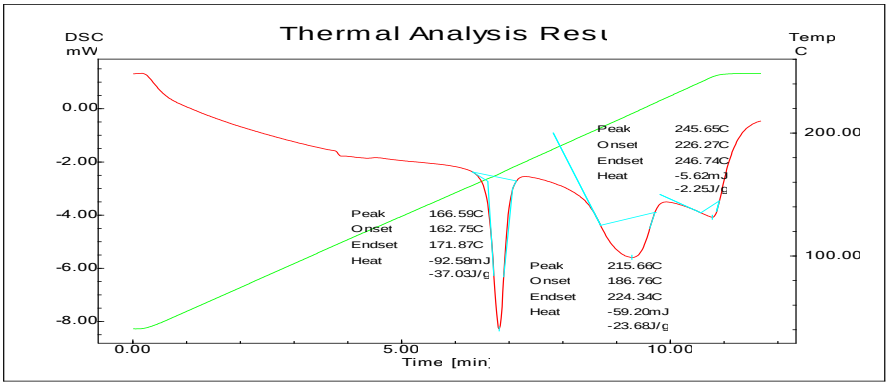

Figure.13: DSC Thermogram of Drug and PVA Physical mixture

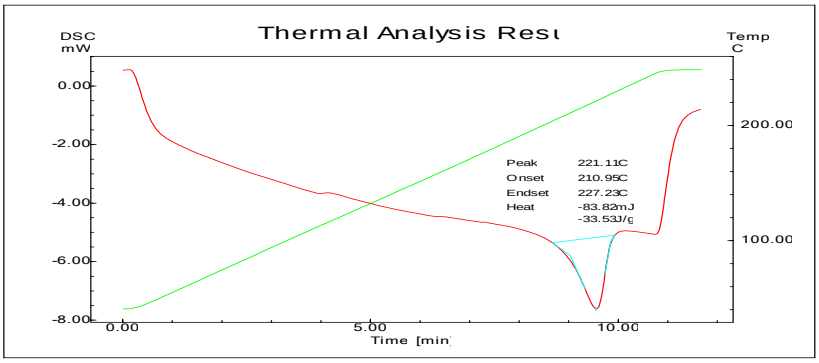

Figure. 14: DSC Thermogram of PVA Solid Dispersion

In case of physical mixture (Figure. 13) of Propranolol Hydrochloride and PVA systems it has seen that the persistence of the endothermic peak of Propranolol Hydrochloride as well as PVA. However the drug peak has shifted toward slightly higher temperature with lower intensity. Similarly PVA (Figure.12) shows a broad endothermic effect from 223.68˚C having a peak at 230.60˚C. Solid dispersion of Propranolol Hydrochloride with PVA (Figure. 14) no peaks related to Propranolol Hydrochloride, was seen. This indicates that Propranolol Hydrochloride no longer present in the crystalline form, may have got converted into the amorphous form. It also suggests that Propranolol Hydrochloride appears to be soluble in the liquid phase of PVA.

Table 5: Yield obtained in the solid dispersions

S. No	Carrier (Drug: Carrier)	Theoretical Yield (gm)	Practical Yield(gm)	Percentage Yield (%)
1.	PVA (1:5)	2.5	2.1	84
2.	PVP K_{30} (1:5)	2.5	2.2	88
3.	PEG-4000 (1:5)	2.5	2.4	96

Table 6: Drug Content of prepared Solid Dispersion

S. No	Carrier (Drug:Carrier)	Amount of drug present in 10 mg equivalent power (mg)	Percentage Yield (%)
1.	PVA (1:5)	8.627	86.27
2.	PVP K_{30} (1:5)	8.887	88.87
3.	PEG-4000 (1:5)	9.346	93.46

CONCLUSION

Solid dispersion preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with PVA , PEG 4000 and PVP-K30. These solid dispersions were analysed for the solubility and Invitro dissolution profile, solid dispersion of drug with PEG 4000 had shown enhanced solubility with improved dissolution rate. In present study solid dispersion prepared with PVA, PVP K-30 and PEG 4000 shows the presence of amorphous form confirmed by the characterization study.

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