"PHYSICOCHEMICAL CHARACTERIZATION AND IN-VITRO DISSOLUTION ENHANCEMENT OF RANOLAZINE USING SOLID DISPERSION METHOD"

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Abstract :

The solid dispersions of Ranolazine with PEG, Poloxamer 407& PVP have been prepared in different weight ratios by using methods like solvent evaporation. Phase solubility studies showed a significant solubilizing effect of all polymers on Ranolazine at different temperatures.FTIR, DSC, and X-ray diffraction spectroscopy were used to characterize the samples of solid dispersions and physical mixture. X-ray powder diffraction and thermal analysis indicated that the drug was present in amorphous form at high concentration of both polymers. FTIR study revealed that the characteristic peaks in spectra of pure Ranolazine are also present in spectra of SDs. Drug found compatible with the excipientsThe highest improvements in solubility and *in-vitro* drug release were observed in solid dispersion prepared with Poloxamer 407 by solvent evaporation method. The increased dissolution rate of drug from solid dispersion may be due to surface tension lowering effect of polymer to the medium and increased wettability and dispersibility of Ranolazine. Dissolution Efficiency is calculated form DD solver Software and found maximum in S11 batch.Further the prepared tablets using S11 solid dispersion gives maximum dissolution as compared to as such Ranolazine. Additionally S11 give more and fast drug release than the marketed preparation of Ranolazine. These findings are extremely important from a commercial point of view as the prepared solid dispersion removes drawback of poor dissolution profile of Ranolazine.

IndexTerms: Ranolazine with PEG, Poloxamer 407, FTIR

I. INTRODUCTION

Introduction of Solubility Enhancement

Solvency is a critical physicochemical factor influencing assimilation of medication and its helpful viability. Plan improvement would prompt be disappointment if sedate having poor fluid solvency. The low disintegration rate and low solvency of medication substances in water in watery G.I.T liquid every now and again prompts deficient bioavailability. The dare to enhance the solvency and disintegration of hydrophobic medications stay one of the trickiest undertakings in medication improvement. A few strategies have been acquainted with triumph over this issue. [1]

For upgrade of dissolvability and disintegration rate of inadequately solvent medications, rich industrially reasonable techniques are accessible, for example, liquisolid, in which sedate in arrangement state or broken down medication is adsorbed over insoluble bearers. To enhance wettability and solvency of different lipophilic substances

surfactants can likewise be utilized in plans. Micronization of medication isn't perfect on the grounds that micronized item has the inclination of agglomeration, which prompts decreased successful surface zone for disintegration. Be that as it may, strong scattering is the primarily encouraging technique to formulators on account of its straightforwardness of readiness, simplicity of enhancement, and reproducibility. The term 'strong scattering' has been utilized to depict a group of dose frames whereby the medication is scattered in an organically latent grid, for the most part with a view to upgrading oral bioavailability. [1]

The instrument by which the dissolvability and disintegration rate of the medication is expanded incorporates: the molecule size of the medication is abbreviated to submicron measure or to the atomic size for the situation where strong arrangement is accomplished. The molecule measure decrease more often than not upgrades the rate of disintegration; the changed from crystalline to indistinct shape, the high vivacious state which is exceptionally dissolvable; at long last the wettability of the medication molecule is improved by the disintegration transporter. Despite these promising points of interest, the utilization of strong scattering in pharmaceutical industry has certain limits with the ongoing sunrise of high throughput screening of potential helpful specialists, the quantity of ineffectively. [2]

Dissolvable medication hopefuls has expanded forcefully and the definition of inadequately solvent mixes for oral conveyance right now shows a standout amongst the most regular and most extreme difficulties to detailing researchers in the pharmaceutical business.

Just little measures of strong scattering items are industrially exist. This is because of their poor physical trademark for dose shape plan. The strong scatterings arranged by utilizing water solvent bearer are delicate and crude mass which is difficult to deal with, especially in the container filling and tablet making advancement e.g, pummeling, sieving and blending.

- **CLASSIFICATION OF SOLID DISPERSION:-[8]**

Solid dispersions are characterized by different routes, based on their strong state structure and additionally based on bearer utilized. It is significant to characterize different frameworks of strong scattering according to as their quick discharge systems are concerned. Riegelman and Chiou ordered strong scatterings into the accompanying six delegate types: Simple eutectic blends, undefined precipitations in a crystalline bearer, strong arrangements, glass arrangements and glass suspensions, compound or complex development, and mixes of the past five sorts. Given beneath is grouping of strong scattering based on transporter utilized and strong structure in Figure 1 and 2 individually.

→ ***Classification of solid dispersion on the basis of carrier used:-***

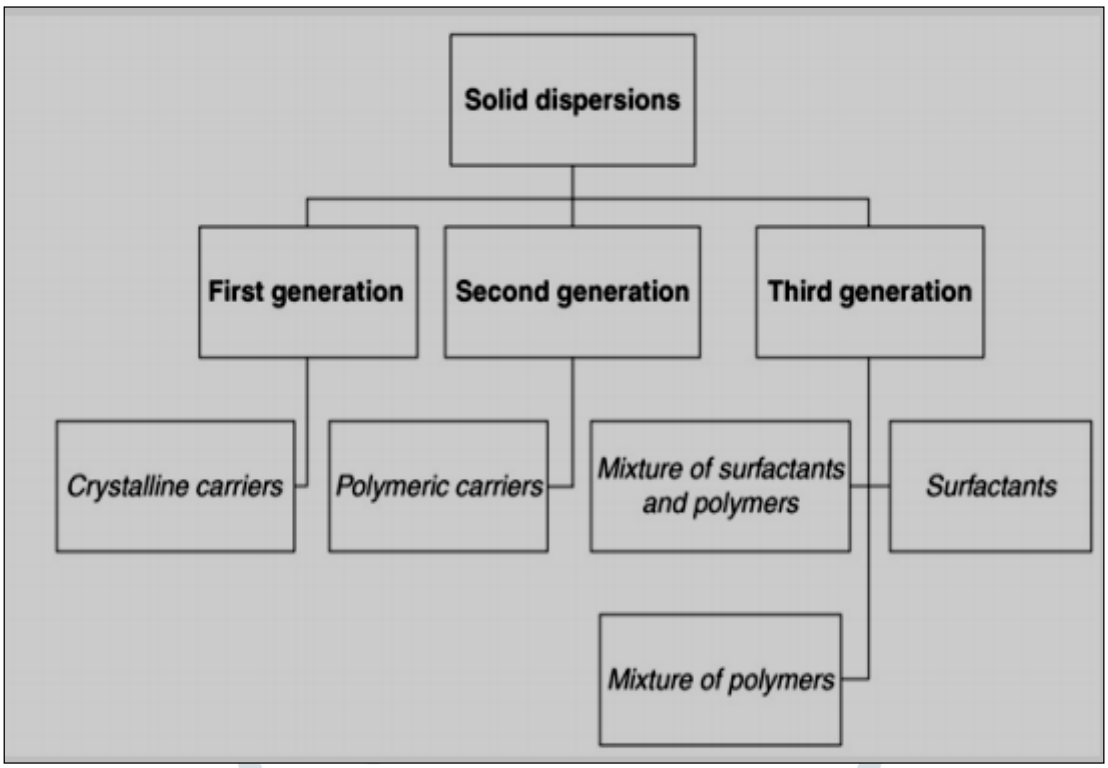


Figure 1: Classification of solid dispersion on the basis of carrier used

→ ***Classification of solid dispersion on the basis of solid structure***

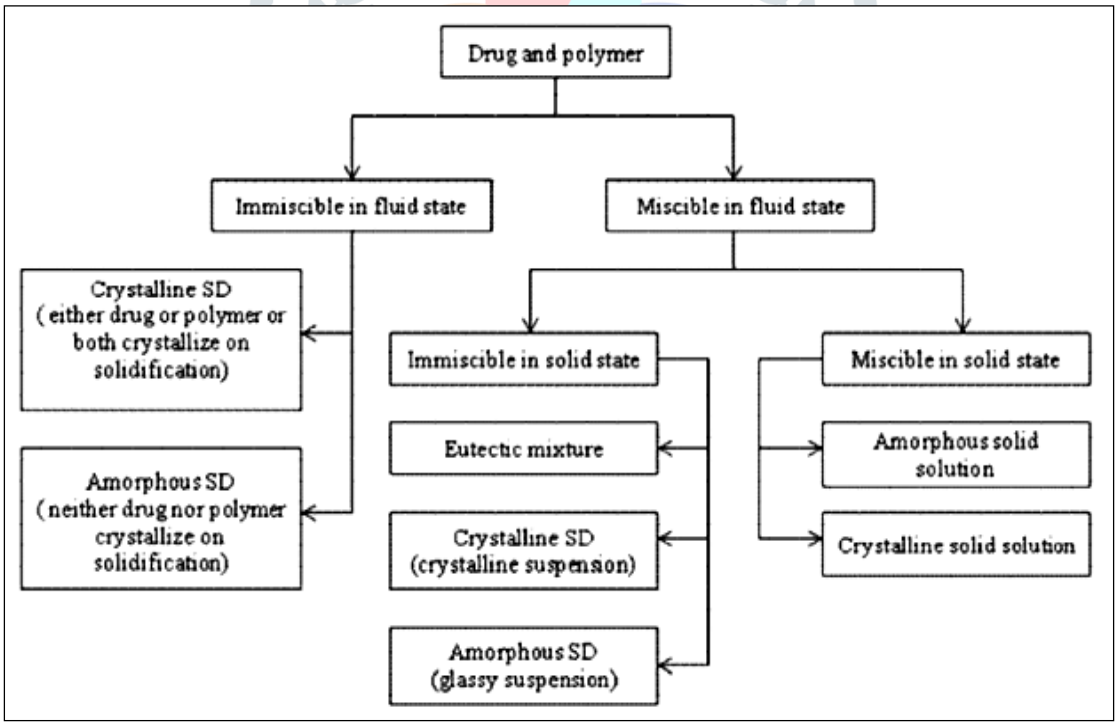


Figure 2: Classification of solid dispersion on the basis of solid structure

A. Drug and polymer exhibiting immiscibility in fluid state

B. Drug and polymer exhibiting miscibility in fluid state

C. Eutectic mixtures

D. Crystalline solid dispersion

E. Amorphous solid dispersion

- **PREPARATION OF SOLID DISPERSIONS:-[9]**

Various methods are used for preparation of solid dispersion system. These methods are;

1. *Fusion / Melting method*
2. *Solvent method*
3. *Melting solvent method (melt evaporation)*
4. *Melt extrusion methods*
5. *Lyophilization techniques*
6. *Melt agglomeration Process*
7. *The use of surfactant*
8. *Electrospinning*
9. *Super Critical Fluid (SCF) technology*

- **CHARACTERIZATION OF SOLID DISPERSION:-[10-12]**

→ **Differential scanning Caloriemetry (DSC)**

Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

→ **X-ray diffraction (XRD)**

→ **Infrared Spectroscopy (IR)**

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material.

→ **Water vapour sorption**

Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

→ **Hot stage and electron microscopy**

→ **Raman Spectroscopy**

→ **Dissolution testing**

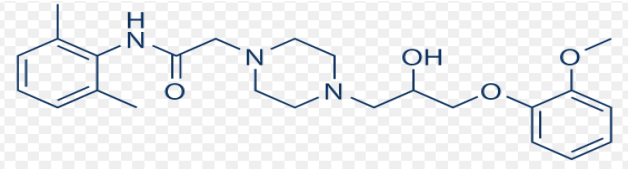
→ **Scanning Electron Microscope (SEM)**

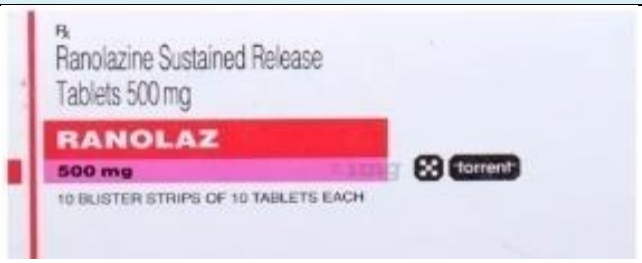
→ **Solubility Studies**

.1 Introduction of Drug

- **Ranolazine:-**[13-18]

Table 1 : Drug Information

General Properties:-	
Name	Ranolazine
Appearance	White or slightly yellow crystalline powder
Structure	
CAS number	95635-55-5
Category	Antianginal
Molecular Weight	427.5365 g/mol
Chemical Formula	$C_{24}H_{33}N_3O_4$
IUPAC Name	N-(2,6-dimethylphenyl)-2-{4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazin-1-yl}acetamide
Solubility	Ranolazine is soluble in dichloromethane, sparingly soluble in methanol, slightly soluble in ethanol or acetonitril
Water Solubility	0.11 mg/ml
Log P	1.6
pKa	13.6
Melting point (°C)	120 °C
Hygroscopic	Non hygroscopic
Identification	FTIR,UV,HPLC
BCS Class	II
Dose	500/1000 mg three to four times in a day
Pharmacokinetic Properties:-	
Absorption	Absorption is very uneven.

Bioavailability	76 %
Protein binding	62 %
Metabolism	Hepatic
Half life	7 hours
Pharmacodynamic Properties:-	
Indication	For the treatment of chronic angina.
Mechanism of action	Unknown
Marketed Preparations:-	
	
Brand Name:-*RANOLAZ* ***Dosage Form:-*** *Tablet* ***Strength:-****500 mg* ***Manufacture by:-*** *Torrent Pharma*	

II. MATERIALS AND EQUIPMENTS

List of Materials

Table 2: List of materials

Sr. No.	Materials proposed to be used	Sources of Material
1.	Ranolazine	Torrent Research Centre, Ahmedabad
2.	Poloxamer 407	BASF India Ltd, Mumbai, India.
3.	PEG 4000 PEG 6000	Unitop Chemicals Pvt. Ltd, Mumbai, India.
4.	PVPK 30	Balaji Chemicals, Ahmedabad.

List of Equipments

Table 3: List of equipments

Sr. No.	Equipments	Manufacturers
1.	Digital weighing balance	Reptech weighing balance ltd., Ahmadabad
2.	Dissolution apparatus	Electro lab ltd, Mumbai
3.	U. V. Visible spectrophotometer	Shimadzu-1601, Kroyoto, Japan.
4.	FTIR	FTIR8400S, Shimadzu, Kroyoto, Japan.
5.	DSC	Mettler, DSC 823, Germany

III. RESULT AND DISCUSSION

6.1PREFORMULATION STUDIES

6.1.1: Physical properties of API

Table 4: Physical properties of API-Ranolazine

Sr. No.	Parameters	Results
1	***Organoleptic evaluation***	White to off-white solid crystalline powder
2	***Bulk density (gm/ml)***	0.535 g/ml
3	***Tapped density (gm/ml)***	0.850 g/ml
4	***Compressibility index (%)***	37.06 %
5	***Hausner ratio***	1.580
6	***Angle of repose (degree)***	58^0

Based on results tabulated in above table 6, Ranolazine shows very poor flow property. Hausner ratio is 1.580 and CI index is 37.06%.

6.2 CALIBRATION CURVE OF RANOLAZINE

Table 5: Calibration curve of Ranolazine in 0.1N HCl

Sr. No.	Concentration (µg/ml)	Absorbance± SD (n=3)
1	0	0
2	4	0.144±0.004
3	8	0.283±0.005
4	12	0.433±0.007
5	16	0.566±0.005
6	20	0.626±0.004
7	24	0.778±0.003

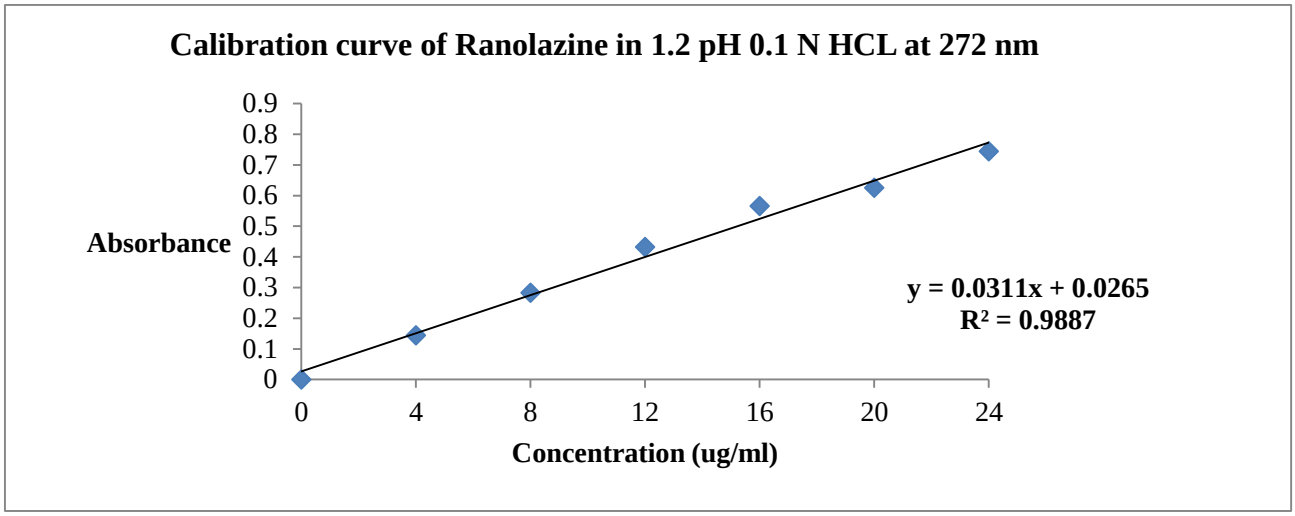


Figure 3 : Calibration curve of Ranolazine in 0.1 N HCL at 272 nm

6.3 PHASE SOLUBILITY STUDIES

The effect of different polymers concentration at different temperature on the solubility of Drug (Ranolazine) checked by using all four polymers Poloxamer 407, PEG 4000, PEG 6000and PVPK 30 at 25 ºC and 37 ºC.

The plots of drug solubility against the polymer concentrations at the investigated temperatures indicated a linear relationship between drug solution & polymer concentrations. The results show that in all cases, the solubility of Ranolazine increased with increasing temperature and carrier concentration.

Solubility of Ranolazine in pure water at 25°C was very low. At the highest polymer concentration (10% w/w), the solubility increased approximately 10-foldin all polymers at 25°C. The same tendency was observed for the other temperatures.

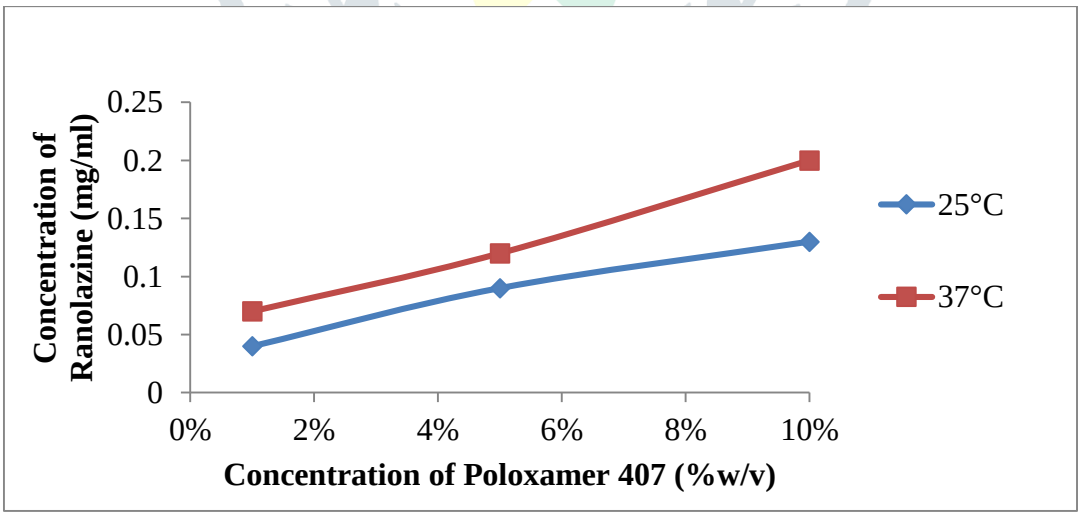


Figure 4: Solubility of Ranolazine in aqueous solutions of Poloxamer 407 in water at 25°& 37°C

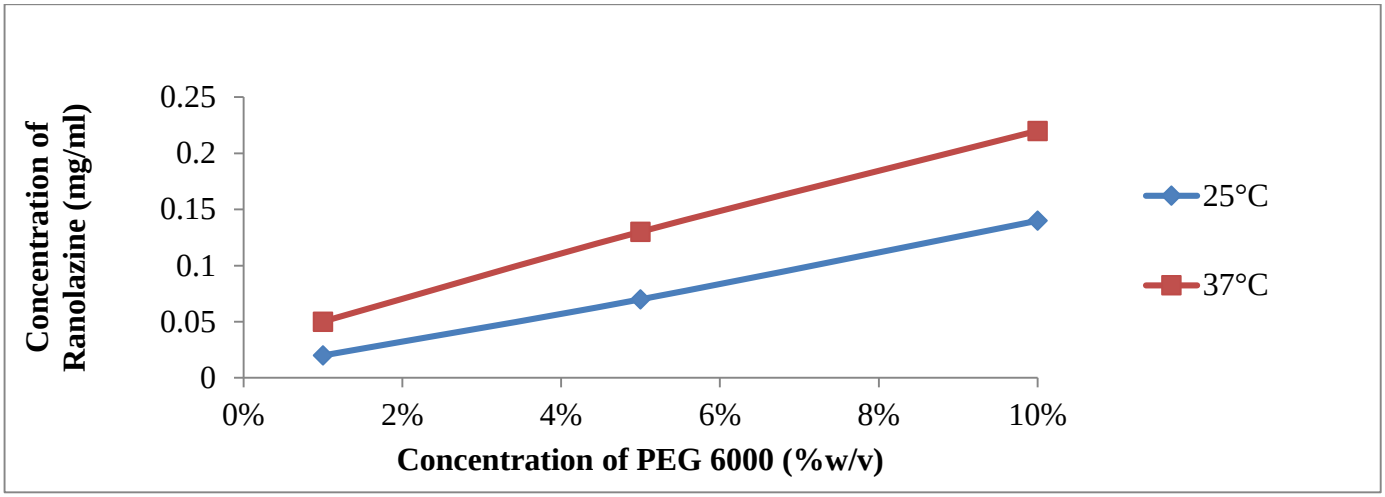


Figure 5: Solubility of Ranolazine in aqueous solutions of PEG 6000 in water at 25°& 37°C

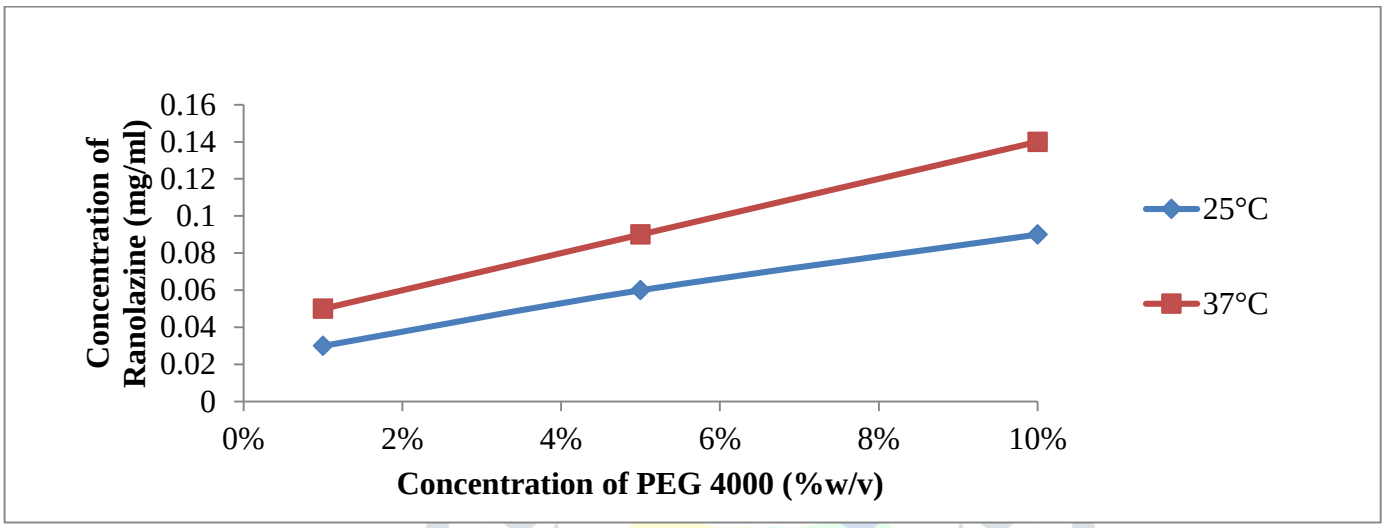


Figure 6: Solubility of Ranolazine in aqueous solutions of PEG 4000 in water at 25° & 37°C

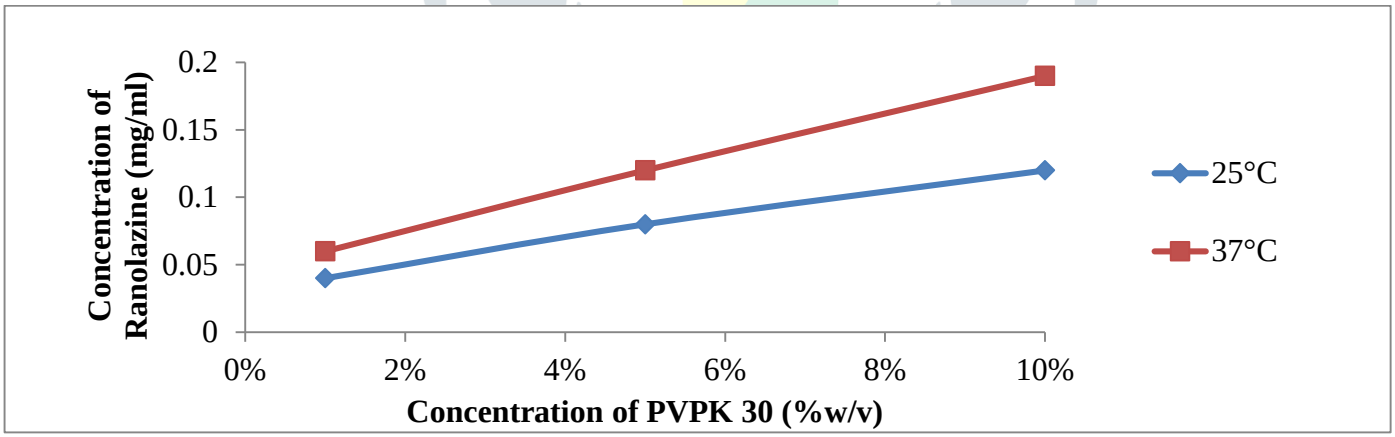
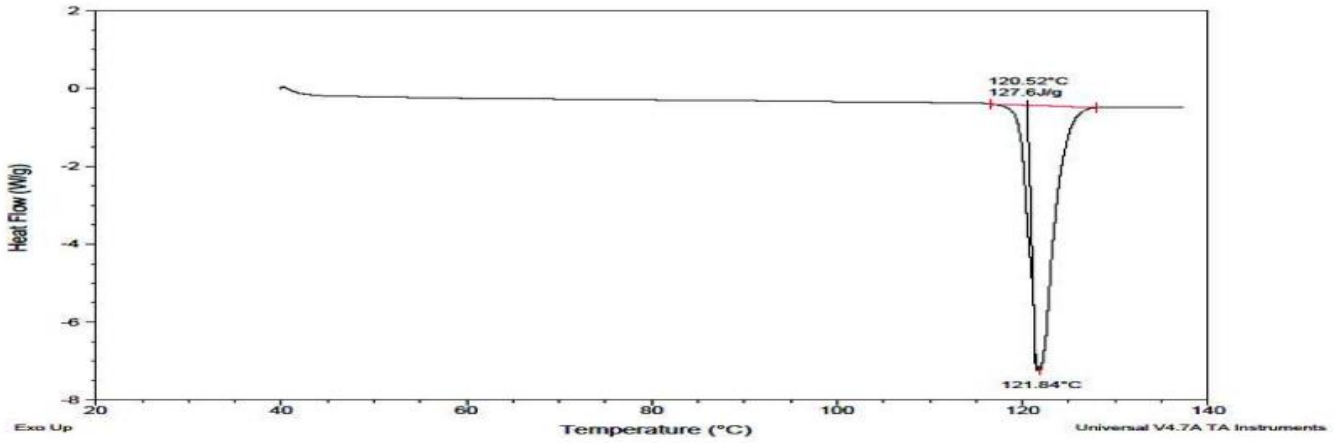


Figure 7: Solubility of Ranolazine in aqueous solutions of PVPK 30 in water at 25°& 37°C

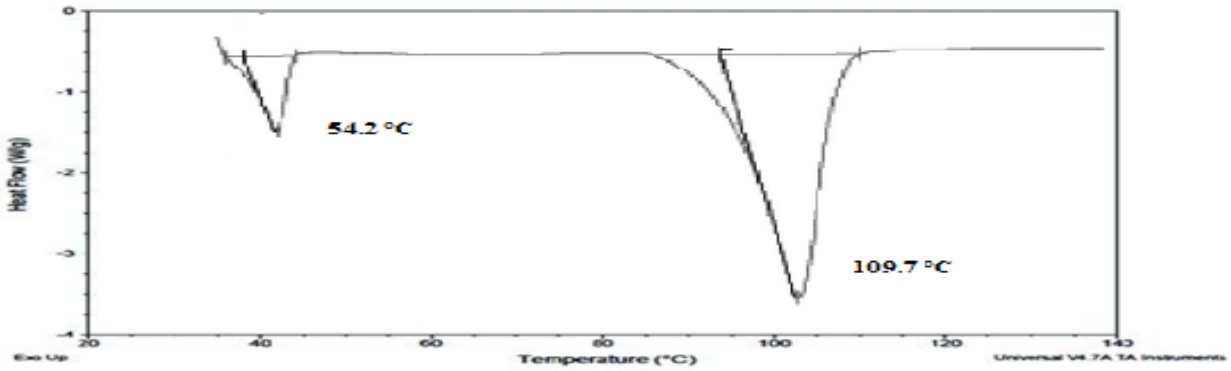
6.4 CHARECTERIZATION OF SOLID DISPERSIONS:-

6.4.1 Differential Scanning Caloriemetry (DSC) Analysis:-

DSC spectra of Pure Ranolazine shows in figure 9 which indicated melting of Ranolazine around 121.84^0 C. where SD of Ranolazine also shows the melting peak at near 109.7 °.



A.



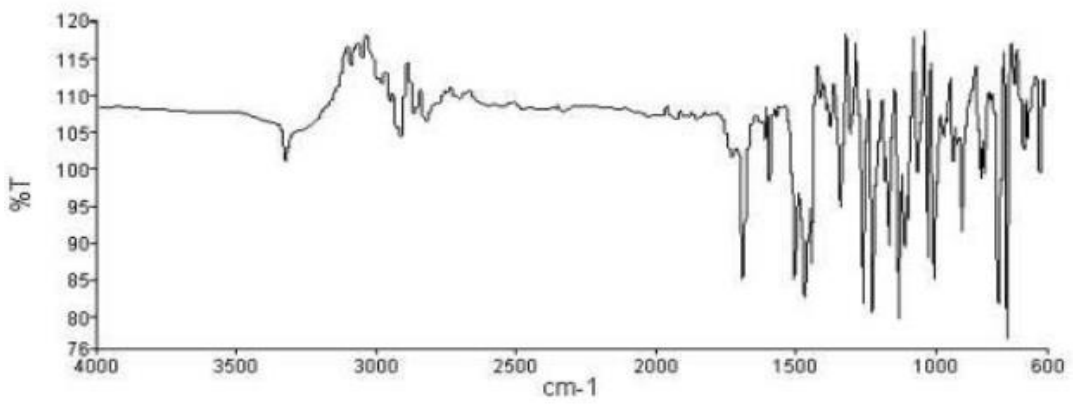
B.

Figure 8: DSC Spectra of A) Pure Drug Ranolazine B) SD of Ranolazine

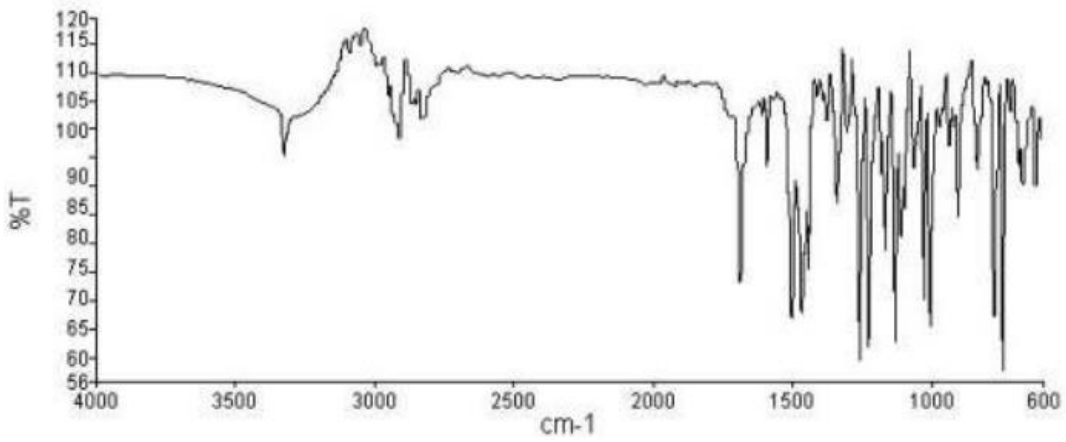
From the DSC spectra of SD with drug. It was indicated that reduction in peak intensity on boarding of peak due to conversion of crystalline state to amorphous structure. Drug was also stable because peak of drug (109.7°C) was not change to its position in both spectra.

6.4.2 FTIR Study:-

FTIR spectra of solid dispersion of Ranolazine and Pure Ranolazine are shown in figure 10. The spectra of pure Ranolazine presented characteristic peaks at 1663 cm^{-1} (C═O stretching of acid), 3363 cm^{-1} (N–H stretching), 3486 cm^{-1} (O–H stretching) and 1295 cm^{-1} (C–N stretching) respectively. The characteristic peaks of SD at 1713 cm^{-1} (C═O stretching of acid), 3400 cm^{-1} (N–H stretching), 3440 cm^{-1} (O–H stretching) and 1288 cm^{-1} (C–N stretching) are also present in spectra of SDs.



A.



B.

Figure 9: FTIR Spectra of A. Pure Drug Ranolazine and B. Solid Dispersion of Ranolazine

6.4.3 Powder X-ray Diffraction (PXRD) Analysis

Powder XRD of pure Ranolazine and its solid dispersion are shown in Figure 11. The presence of numerous distinct peaks in the X-ray diffraction spectrum indicates that Ranolazine is present as a crystalline material with characteristic diffraction peaks appearing at a diffraction angle of 2θ at 10.1°, 10.40°, 12.26°, 14.36°, 15.00°, 16.5°, 19.34°, 21.41°, 23.44°, 24.65°, 25.45°, 27.26°, 30.21°, 31.26° and 43.72° etc. Spectroscopy of SD was characterized by reduction in peak intensity while comparing with pure drug X-ray pattern. It was indicated that drug was converted into amorphous form during SD preparation.

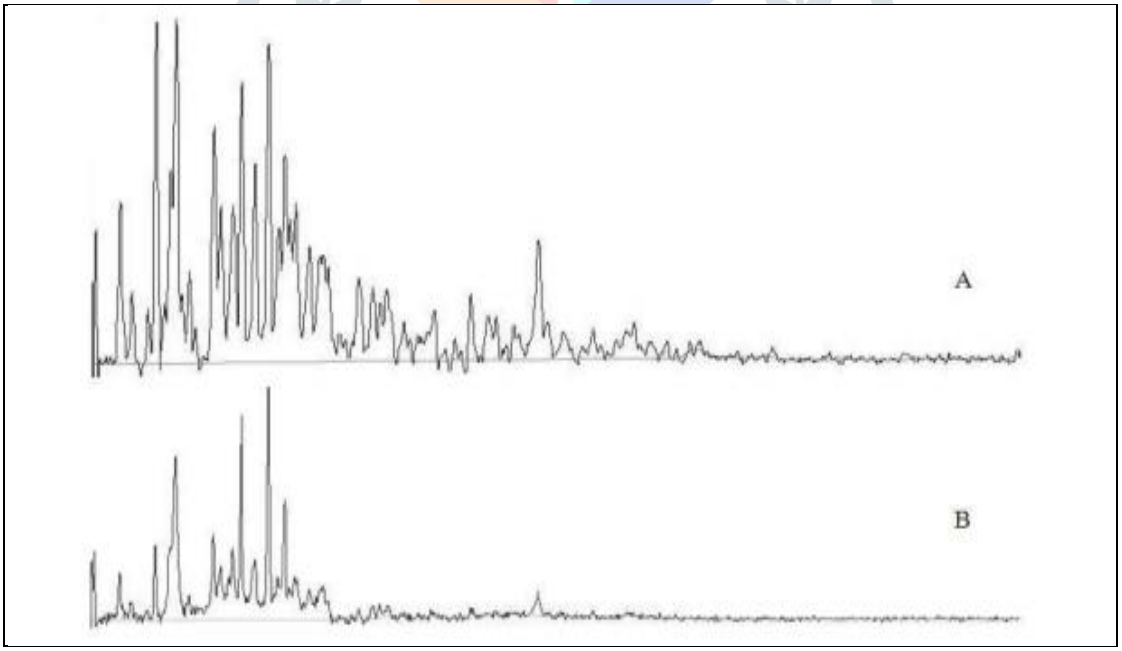


Figure 10: XRD Spectra of A) Pure Drug Ranolazine and B) SD of Ranolazine

6.4.4 Dissolution Study:-

Dissolution studies of pure Ranolazine and all other prepared Solid Dispersions were carried out in 0.1 N HCl (pH 1.2).

Table 6: In vitro % cumulative release of drug from solid dispersion prepared by solvent evaporation method

Sr. No	Formulations	Ratio	Code	Time (min) (n=3)					
				5	10	15	30	45	60
				% Cumulative drug release					
1	***Drug: PEG 4000***	1:0.3	S_1	23.51±1.25	26.54±0.39	29.54±1.25	32.54±2.71	36.66±3.54	38.95±0.21
2		1:0.5	S_2	26.66±0.45	29.33±1.98	33.54±3.25	39.54±0.36	42.22±1.54	45.95±0.32
3		1:0.7	S_3	30.22±1.12	34.44±1.65	37.21±1.21	42.22±1.45	45.94±2.12	47.77±1.02
4	***Drug: PVPK30***	1:0.3	S_4	29.88±0.32	31.11±1.85	34.41±3.24	37.78±0.65	39.93±1.52	40.53±0.23
5		1:0.5	S_5	33.14±1.02	36.65±1.65	39.92±3.01	42.23±0.34	45.56±3.32	47.71±1.02
6		1:0.7	S_6	36.63±1.35	39.54±0.32	42.21±2.32	45.59±0.42	48.81±0.84	50.54±2.32
7	***Drug: PEG 6000***	1:0.3	S_7	39.95±1.01	43.51±0.10	46.63±1.97	49.92±0.48	51.24±0.21	53.55±1.32
8		1:0.5	S_8	42.25±0.98	45.52±0.32	48.86±4.54	52.24±1.85	55.39±0.96	58.81±2.01
9		1:0.7	S_9	46.68±1.99	51.14±3.12	54.41±3.21	59.92±2.52	63.65±1.32	69.92±1.02
10	***Drug: Poloxamer 407***	1:0.3	S_{10}	47.75±1.36	50.02±2.12	54.42±1.32	57.75±1.65	59.95±2.32	61.54±3.21
11		**1:0.5**	**S_{11}**	**59.65±0.52**	**66.54±0.96**	**69.71±0.85**	**74.65±3.65**	**81.64±1.32**	**87.9±2.32**
12		1:0.7	S_{12}	51.18±1.48	54.48±0.65	57.74±5.32	63.51±2.65	67.74±2.65	70.59±1.32
13	***Drug***	_	API	11.42±0.36	14.62±1.32	19.42±2.32	26.73±2.65	31.62±2.35	33.42±3.21

From above release study as in Table 8, drug release from S6 (i.e. drug: PVPK30 (1:0.7)), S9(i.e. drug: PEG6000 (1:0.7)) and S12 (i.e. drug: Poloxamer 407 (1:0.5)) was higher than from S3 (i.e. drug: PEG 4000). It might indicate that PEG has more ability to give hydrophilicity and drug release rate than that of PVP-K30. The highest drug release was obtained by S_{11} (i.e. drug: Poloxamer 407 (1:0.7)).

It might be due to Poloxamer 407 increased drug entrapment efficiency in its polymer matrix and its hydrophilicity which led to increased solubility and subsequently drug release rate.

From the above release study as in Table 8, the formulation S_{12}(i.e. drug: Poloxamer 407 (1:0.7)) was giving highest drug release as compared to S_{10}(i.e. drug: Poloxamer 407 (1:0.3)) and S_{11} (i.e. drug: Poloxamer 407 (1:0.5)) at the end of 60 min.

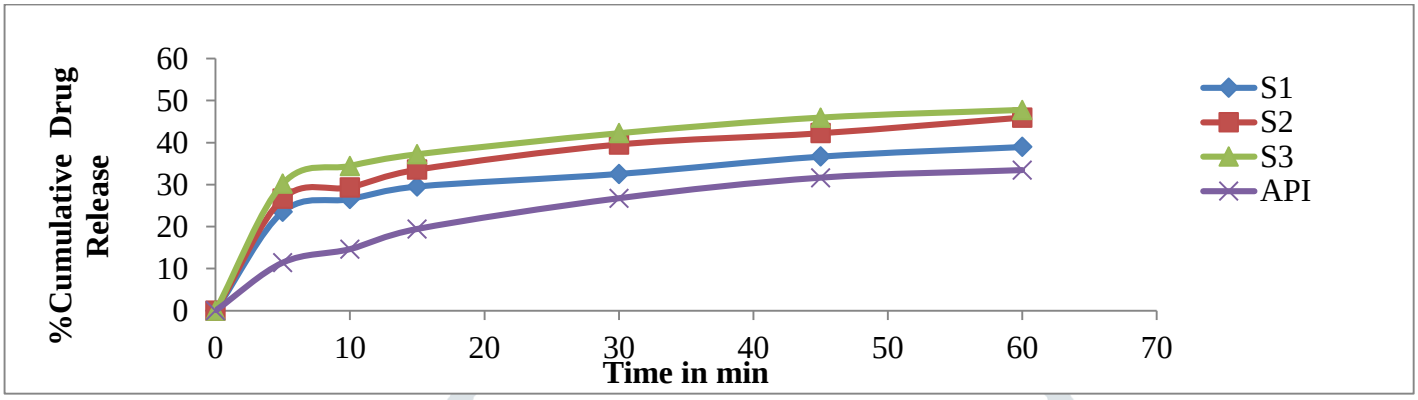


Figure 11: In vitro release of drug from solid dispersion prepared by using PEG 4000

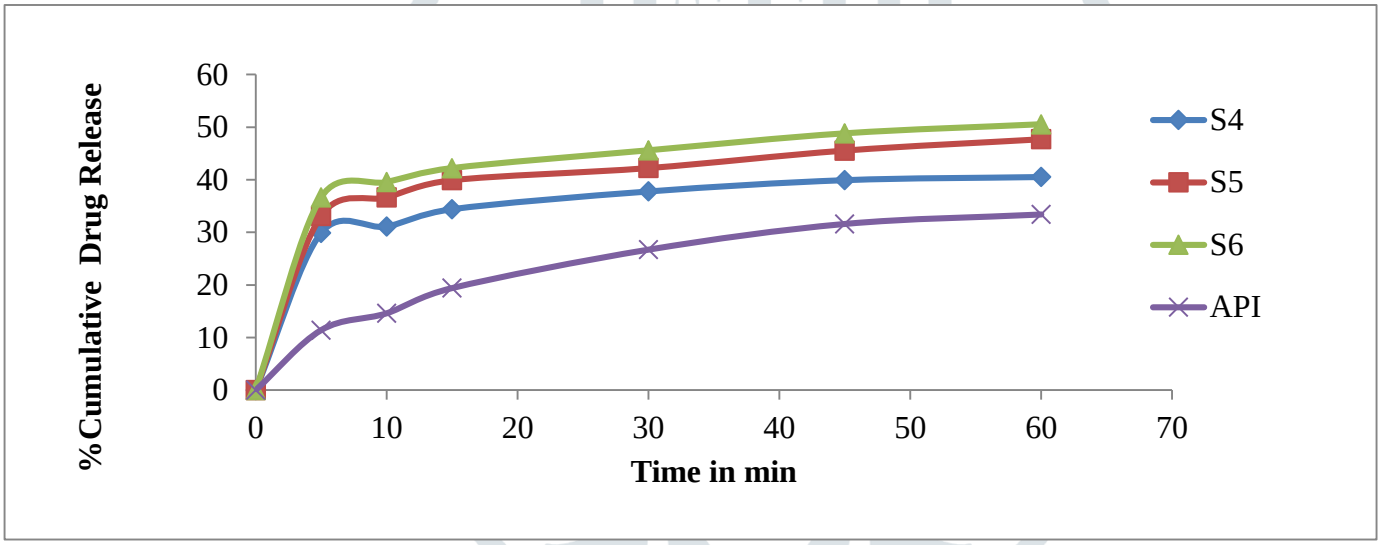


Figure 12: In vitro release of drug from solid dispersion prepared by using PVPK30

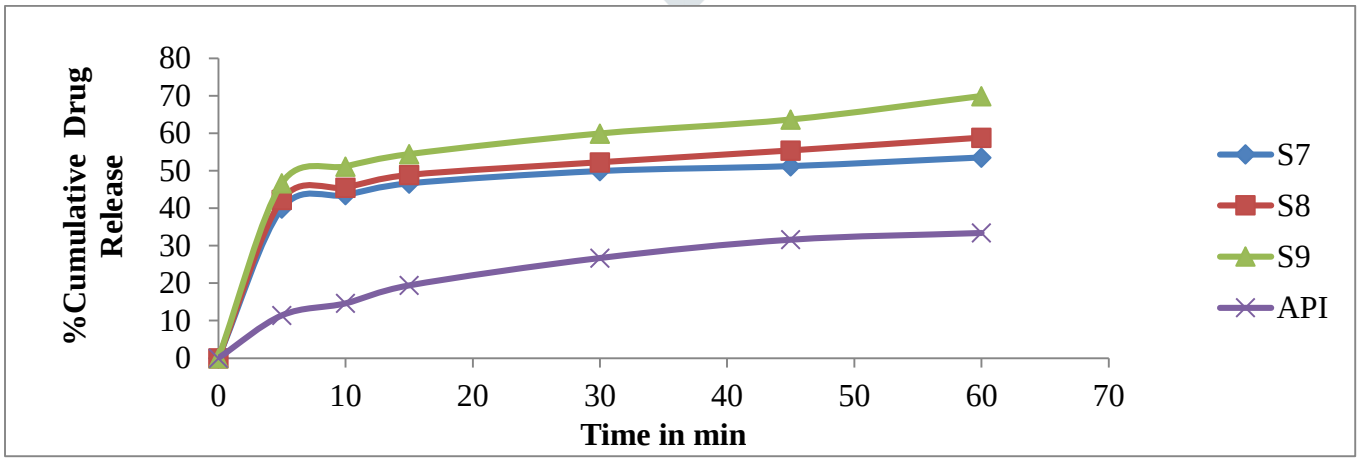


Figure 13: In vitro release of drug from solid dispersion prepared by using PEG 6000

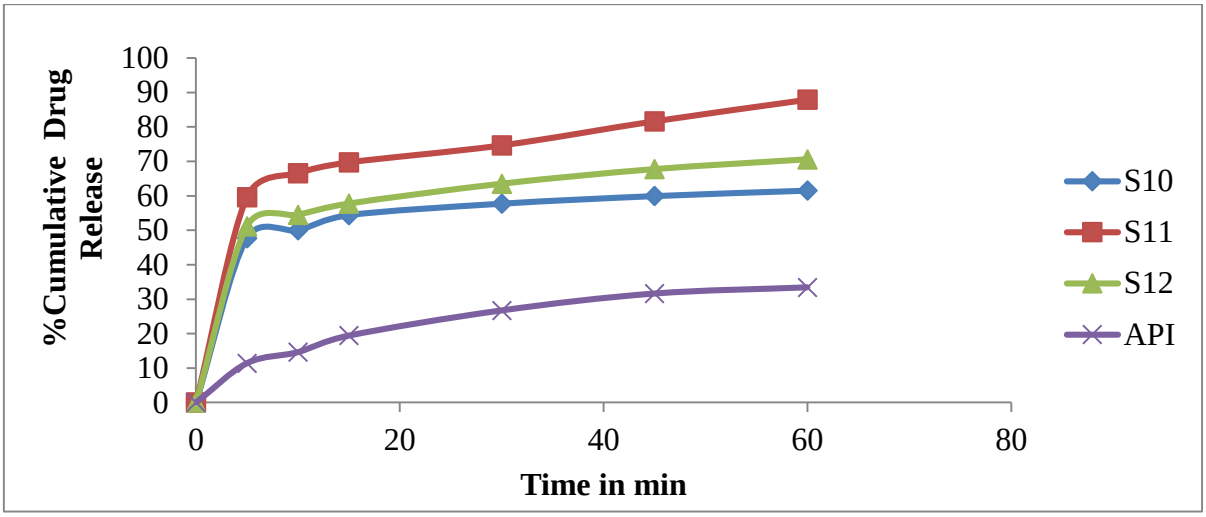


Figure 14: In vitro release of drug from solid dispersion prepared by using Poloxamer 407

From the dissolution study of all the formulations, the highest drug release was obtained by Solid dispersion using Poloxamer 407.

6.4.5 % Drug Content of Solid Dispersion

Table 7: Drug Content of S1-S12

Batch	S1	S2	S3	S4	S5	S6
Drug Content (%) (n=3)	96.3 ± 0.6	97.5 ± 0.7	97.7 ± 0.9	97.3 ± 0.7	97.8 ± 0.6	96.1 ± 0.6
Batch	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**
Drug Content (%) (n=3)	97.3 ± 0.7	97.4 ± 0.9	96.6 ± 0.7	95.8 ± 0.9	**97.7 ± 0.2**	96.6 ± 0.8

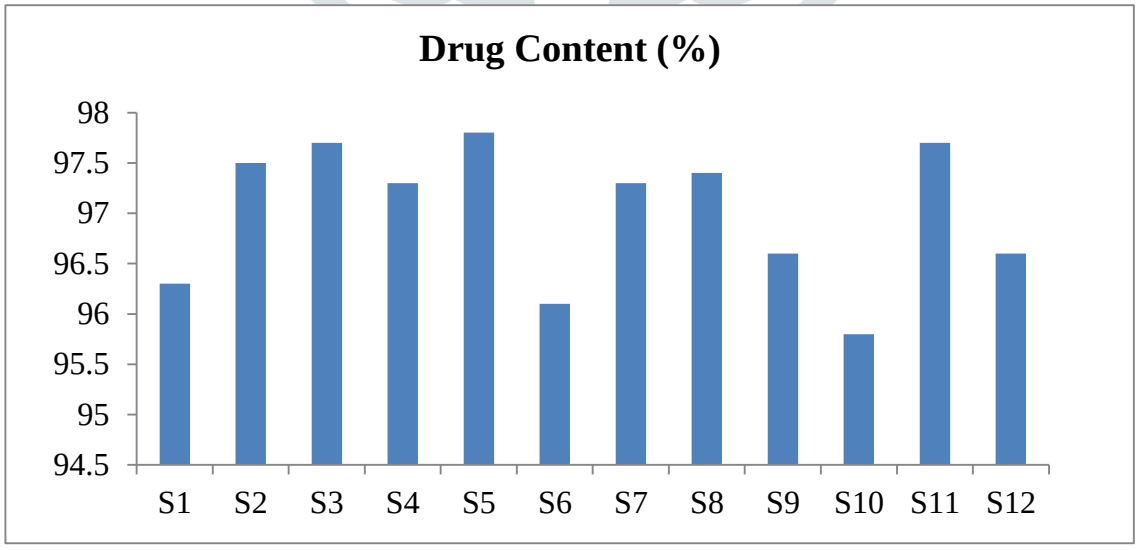


Figure 35: Drug Content of S1-S12

All batches show the drug content well within in acceptable range. No further loss of API was observed.

IV. CONCLUSION

The solid dispersions of Ranolazine with PEG, Poloxamer 407& PVP have been prepared in different weight ratios by using methods like solvent evaporation. Phase solubility studies showed a significant solubilizing effect of all polymers on Ranolazine at different temperatures.FTIR, DSC, and X-ray diffraction spectroscopy were used to characterize the samples of solid dispersions and physical mixture. X-ray powder diffraction and thermal analysis indicated that the drug was present in amorphous form at high concentration of both polymers. FTIR study revealed that the characteristic peaks in spectra of pure Ranolazine are also present in spectra of SDs. Drug found compatible with the excipientsThe highest improvements in solubility and *in-vitro* drug release were observed in solid dispersion prepared with Poloxamer 407 by solvent evaporation method. The increased dissolution rate of drug from solid dispersion may be due to surface tension lowering effect of polymer to the medium and increased wettability and dispersibility of Ranolazine. Dissolution Efficiency is calculated form DD solver Software and found maximum in S11 batch.Further the prepared tablets using S11 solid dispersion gives maximum dissolution as compared to as such Ranolazine. Additionally S11 give more and fast drug release than the marketed preparation of Ranolazine. These findings are extremely important from a commercial point of view as the prepared solid dispersion removes drawback of poor dissolution profile of Ranolazine.

V. AKNOWLEDGEMENT

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VI. REFERENCES

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