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Enhancement of solubility of Rosiglitazone through solid dispersion technique: *in-vitro* and *in-vivo* permeation study analysis

***K. Punitha[a], Daisy Chella Kumari [b], V.Venkatesh Kumar[c] , S. Suresh Kumar[a]**

[a]*Vels university, Dept. of Pharmaceutics, Pallavaram, Chennai, Tamilnadu*
[b]*Madras Medicals College, Dept. of Pharmaceutics, Park town, Chennai, Tamilnadu*
[c]*KMCH College of Pharmacy, Dept. of Pharmaceutics, Coimbatore, Tamilnadu*

ABSTRACT

The purpose of the study was to prepare solid dispersions of sparingly soluble drug Rosiglitazone by dispersion method with PGS and SSG as polymers to enhance the aqueous solubility of the drug and thereby bio availability. 12 batches of solid dispersions with two polymers (PGS, SSG) with varying drug: carrier ratios (1:1, 1:2, 1:4, 1:6, and 1:8 and 1:10) were prepared for optimization. All the formulation batches were subjected to phase solubility, IR diffraction, XRD, wettabilty, saturation solubility, assay, and in-vitro dissolution. Among the formulations batches that showed highest dissolutions R-PGS (1:1, 1:4) and R-SSG (1:1, 1:2) were selected and the in-vivo Permeation study in goat intestine was performed. FT-IR spectra indicated no interaction between the drug and the carriers in the dispersions. Reduced crystallinity of the drug was evident in the x-ray diffraction patterns. The decreased crystallinity of the dispersion along with decreased particle size, disaggregation of the particles, and increased wetability all accounts for the enhanced dissolution of the drug from solid dispersions.

Key words: - Solid dispersion, Rosiglitazone, PGS, SSG and *in-vivo* Permeation.

INTRODUCTION

Drug research can be categorized as drug discovery and drug development. Drug discovery is identification and characterization of new targets, synthesis and screening of new lead molecules for *in-vitro* and *in-vivo* biological studies. Drug development focuses on evaluation of safety, efficacy and toxicity of new drug either alone or in formulation development. There was a significant amount of molecules failure in drug development which is due to poor bio-pharmaceutical factors. A close observation of the findings for molecules failure accounts as

40% is due to poor bio pharmaceutical factors. The pharmaceutical factors effecting absorption of drugs are solubility, pka, particle size, surface area, shape, plasma protein binding, polymorphism, first pass effect etc.

Solubility is the amount of drug that must be available at the site of absorption as aqueous solution which is important for drug absorption. Two main proposed approaches to enhance the solubility of solute are

By chemical modification or solid state manipulation.
Modification in the formulation process.

Modification in formulation process involves Co-solvency, Solubilisation, conversion to its salt form, Solid dispersion, Complexation, Inclusion of buffer, Solid solutions and Lyophilization.

Solid Dispersions

Solid dispersion is the dispersion of one or more active ingredients in an inert carrier or matrix at solid state melting, solvent or melting solvent method. Mechanism of increased dissolution rate of active ingredients from solid dispersions may be due to particle size reduction, reduced agglomeration of the particles, solubilization effect by the carrier, increased wetabillity due to the nature of the carrier, decrease in crystalinity of the drug and phase transition of the drug from crystalline to amorphous form.

This novel research is aimed to overcome the poor aqueous solubility of model drug Rosiglitazone by formulating as solid dispersions using dispersion technique.

The formulation showing higher release rate was taken and *in-vivo* studies were performed in comparison with pure drug.

MATERIALS AND METHODS

Rosighitazone was gifted from M\s. Aristo pharmaceuticals, Mumbai and all other chemicals used were of laboratory grade.

Linearity range of Rosiglitazone

Linearity range of rosiglitazone in 0.1N Hcl at 288 nm was found to be 1-5 µg/ml.

Phase solubility study

Drugs and carriers as per the drug carrier ratios were weighed and added to caped bottle with 25ml of water. The container was allowed to rotate/shake in orbital incubator shaker maintained at 25°c for 24 hrs. After filtration the filtrates absorption was measured at 288nm.

Dispersion technique

Drug and carriers were weighed according to drug carrier ratio. Drugs were dissolved in chloroform separately and triturated with the carrier till a porous mass was formed. The mass was then dried in vaccum at 1 kg/cm² at room temperature and was pulverized by passing through sieve No. 80.

IR spectroscopy
Minimum quality of solid dispersions were mixed with IR grade KBr and made to form a thin film in pelleting machine. The sample was analyzed in IR spectrometer using KBr as negative control.

X-ray diffraction
All the selected solid dispersion and pure drug was subjected to X-Ray diffraction at CECRI, karaikudi

Wetability study
100mg of pure drug and solid dispersions were punched to form individual pellets using single punch peletting machine. To each pellet 10µl of water is added on the surface using micro syringe and the contact angle was noted from the photograph.

Saturation solubility study
Weighed amount of pure drug and solid dispersions equivalent to 40 mg of pure drugs were shaken in a rotary shaker with 10ml of distilled water at 27°C for 24 hrs. The equilibrated solutions were filtered and their solubility was studied.

Assay of solid dispersions
Solid dispersions equivalent to 50 mg of drug was taken and dissolved in 50ml standard flask with 0.1N HCl. Further graded dilutions were made and the absorbance was noted at specified wavelength.

In-vitro release study
Weight equivalent to 50mg of all formulated solid dispersion batches were weighed and the release after 15mins, 30, 45, 60, 75, 90, 105, and120mins were observed in Phosphate buffer PH-7.4, Type-II Dissolution flask apparatus at ±35ºC.

Best Formulations
From the release rate of all the 12 formulations, 4 formulations with higher release rates were taken as the best formulations and characterization was done for those formulations.

***In-vivo* permeation study**
Permeation study was performed for the selected batchesO-PGS1,O-PGS4,O-SSG1,O-SSG4, R-PGS1, R-PGS4, R-SSG1 and R-SSG2.

Composition for 1000ml of transport buffer
Calcium chloride-0.132g
Magnesium chloride-0.2438g
Disodium hydrogen phosphate-0.3406g
Sodium di hydrogen phosphate-0.0624g
Sodium bi carbonate-2.1002g
Potassium chloride-0.3726g
Sodium chloride-6.6716g
Glucose-0.8970g
Distilled water- Req to produce 900ml.

Permeation study was carried out using goat small intestine by everted sac technique. For which freshly sacrificed goat intestine preserved in transport buffer was cut and sticked to one end of the open ended cylinder to form a pouch. The level of the buffer inside the cell and in the beaker was maintained the same level and the tissue was made alive with the help of aerator and the buffer solution maintained at 37± 0.5ºC.The samples at predetermined time intervals were withdrawn and the same volume of fresh buffer was replaced and the study was carried out for three hours.

RESULTS AND DISCUSSION

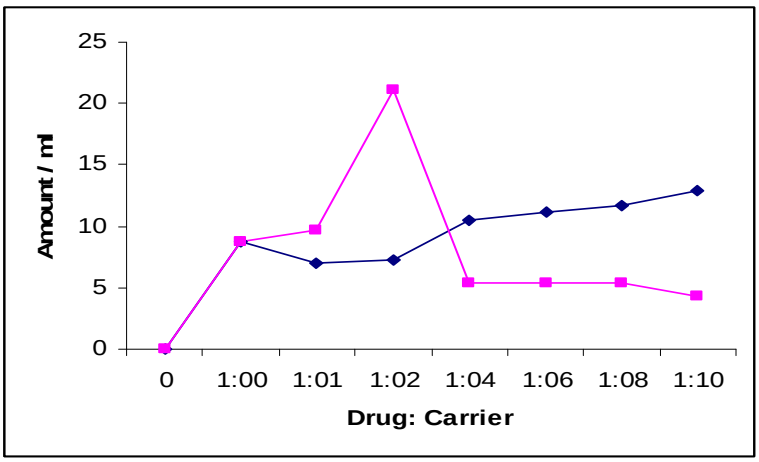
Phase Solubility Study

The phase solubility of solid dispersions of rosiglitazone-PGS was found to increase gradually and in rosiglitazone-PGS there was increase in solubility up to 1:2 and it decreased gradually. (Table.1 and Fig.1)

Table: 1 Phase Solubility Data of Rosiglitazone Solid Dispersions

Drug:Carrier	Rosiglitazone Amount in 1ml	
	PGS	SSG
Pure drug	8.737	8.737
1:1	6.957	9.735
1:2	7.242	21.130
1:4	10.447	5.320
1:6	11.160	5.390
1:8	11.657	5.375
1:10	12.940	4.322

FIG: 1 Phase Solubility Profile of Rosiglitazone -PGS and SSG



♦ *-R-PGS;* ■*-R-SSG*

IR studies

IR spectra of solid dispersions and pure drug were carefully studies for the peaks position and their characteristic peak. The different peaks and their position observed in pure drug were also found in solid dispersions. (Table.2)

Table: 2. IR Spectroscopy of Rosiglitazone

Drug	Position	Group identity	Nature of peak
Rosiglitazone	1244.83	Aromatic para di substituted	Sharp peak
	1079.94	Aromatic ether	Medium banned
	1697.05	Secondary amine	Sharp peak
	1510.95	Lactam ring	Sharp peak
	1364	N- methyl group	Sharp peak
	1611.23	Conjugated amide	Sharp peak

XRD analysis

XRD pellets of pure drugs and solid dispersion samples showed the same number of peaks and the relative intensity percentage values were less in formulated solid dispersions than pure drug. This property is attributed to the phase change of the drug from crystalline to amorphous state where the crystallinity of the samples was decreased. (Fig 2).

NIRT

The absorbance values of the observed peaks in solid dispersions were found to decrease when compared to that of pure drug absorbance which confirms the reduction in particle size. The NIRA spectra of pure drugs and their formulation were analyzed for peak height, peak area and FWHM values which shows reduction in crystalline nature of the sample and occurrence of phase transition.

Wettability

The contact angle data of pure drug pellet was around 60 degrees. But the contact angles of solid dispersion pellets were negligible as the samples showed instant absorption. This behavior may be attributed to the increased wettability of the hydrophilic carriers being used.

FIG.2 XRD analysis of pure drug and its formulations

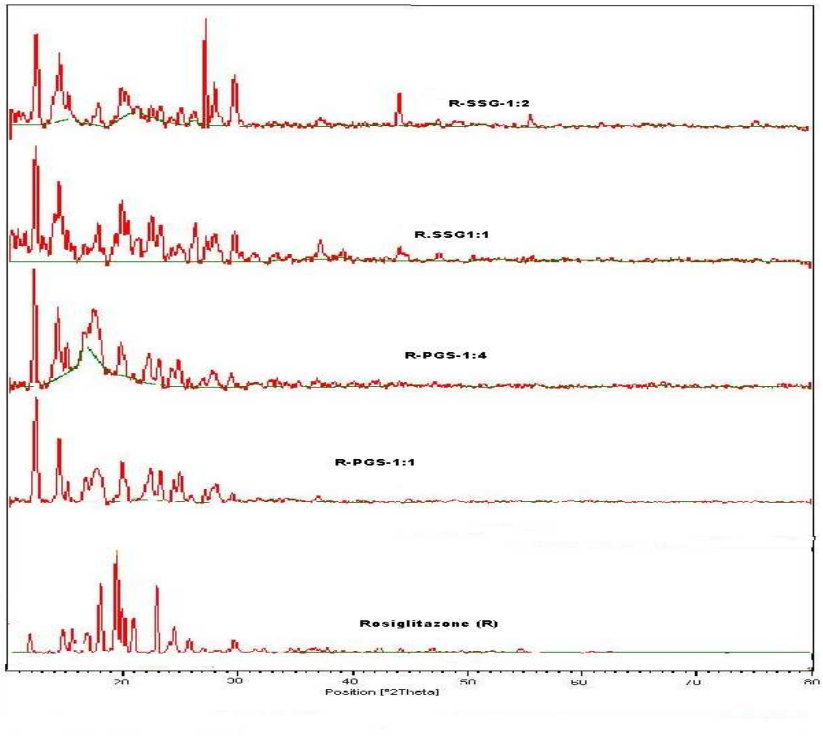


TABLE: 3 *In-Vitro* release data of Rosiglitazone – PGS Solid Dispersions compared with pure drug in phosphate buffer pH 7.4

Time (mins)	% Cumulative Release*						
	Control	Drug: Carrier					
		1:1	1:2	1:4	1:6	1:8	1:10
15	8.3±0.02	0.9±0.03	11.0±0.21	3.6±0.14	10.4±0.03	12.5±0.05	8.7±0.05
30	9.2±0.21	32.4±0.26	17.1±0.03	26.3±0.01	16.3±0.05	18.0±0.02	10.9±0.04
45	9.7±0.11	35.1±0.12	30.4±0.06	43.0±0.03	27.0±0.31	18.6±0.05	18.7±0.02
60	9.9±0.22	37.2±0.10	35.4±0.09	42.8±0.01	32.8±0.08	21.6±0.21	20.3±0.06
75	10.6±0.12	57.7±0.05	42.5±0.12	66.8±0.03	42.3±0.02	36.9±0.22	21.6±0.15
90	11.2±0.03	67.0±0.05	52.2±0.03	78.4±0.00	55.0±0.03	42.4±0.05	27.2±0.08
105	13.5±0.21	73.2±0.02	68.7±0.05	83.9±0.01	73.1±0.01	45.5±0.03	36.9±0.11
120	14.6±0.01	**83.9±0.03**	75.7±0.21	**91.2±0.21**	78.5±0.04	50.7±0.04	42.4±0.13

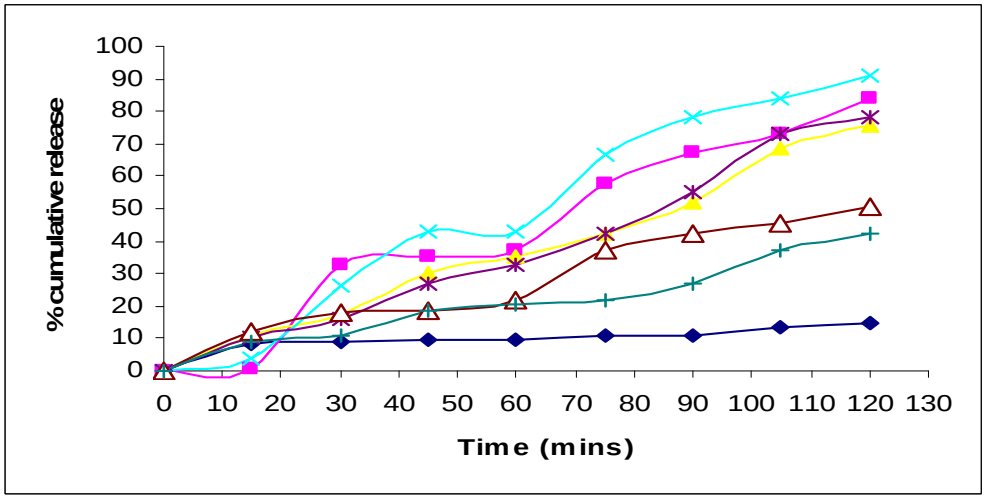
** SEM ± n = 3*

Saturation Solubility
Saturation solubility of Rosiglitazone solid dispersions were higher than pure drug 1.133mg/ml thus there was an increase the drug solubility.

Assay
The assayed drug content in formulated solid dispersions were found to be with in the range of +or – 5% of theoretical amount.

***In-Vitro* release**
A close observation of the release rate of the solid dispersions was found to be higher than pure drug release rate. Rosiglitazone-PGS solid dispersions release rate was 92% for 1:4 in two hours. (Table.3 and Fig.3).The release rate of Rosiglitazone-PGS was found to decrease on increase the concentration of carrier.

FIG: 3 *In- Vitro* release profile of Rosiglitazone-PGS Solid Dispersions compared with pure drug ♦-PURE DRUG; ■-R-PGS $_1$; ▲- R-PGS $_2$; ×- R-PGS $_4$; *- R-PGS $_6$; Δ- R-PGS $_8$; +- R-PGS $_{10}$.



Release of Roglitazone- PGS was maximum of 66% in R-PGS 1:1(Table.4 and Fig.4) there was a decrease in release rate on increase in concentration of carrier to the formulation.

Permeation Study
Permeation study data of Rosiglitazone solid dispersions were compared with pure drugs. The amount permeated through the isolated intestine was found to be higher in selected batches than pure drug indicating enhanced absorption from samples. It was also shown that amount permeated also increases when the concentration of the carrier added is increased further in the samples. The permeation data and profile was shown in table5, 6, and Fig 5 and 6.

TABLE: 4 *In-Vitro* release data of Rosiglitazone – SSG Solid Dispersions compared with pure drug in phosphate buffer pH 7.4

Time (mins)	% Cumulative Release*						
	Control	Drug: Carrier					
		1:1	1:2	1:4	1:6	1:8	1:10
15	8.3±0.02	11.7±0.32	6.3±0.21	6.3±0.05	7.7±0.02	6.3±0.05	3.6±0.05
30	9.2±0.21	29.7±0.21	6.9±0.05	11.7±0.21	9.7±0.08	6.5±0.05	17.1±0.06
45	9.7±0.11	32.7±0.02	18.9±0.05	17.1±0.06	17.1±0.03	17.1±0.12	19.2±0.21
60	9.9±0.22	42.3±0.06	35.5±0.11	27.3±0.08	22.0±0.21	18.9±0.15	21.6±0.22
75	10.6±0.12	43.6±0.11	42.5±0.13	29.3±0.06	35.2±0.22	24.3±0.16	27.3±0.06
90	11.2±0.03	45.0±0.22	52.2±0.12	32.6±0.09	42.6±0.12	24.5±0.05	32.6±0.08
105	13.5±0.21	52.4±0.15	55.0±0.01	39.7±0.15	52.4±0.11	27.1±0.17	42.4±0.09
120	14.6±0.01	**65.9±0.20**	**57.9±0.06**	52.7±0.12	55.1±0.08	32.5±0.21	50.5±0.05

* SEM ± n =3

FIG: 4 *In -Vitro* release profile of Rosiglitazone- SSG Solid Dispersions compared with pure drug ♦-PURE DRUG; ■-R-SSG $_1$; ▲- R-SSG $_2$; ×- R-SSG $_4$; *- R-SSG $_6$; Δ- R-SSG $_8$; +- R-SSG $_{10}$

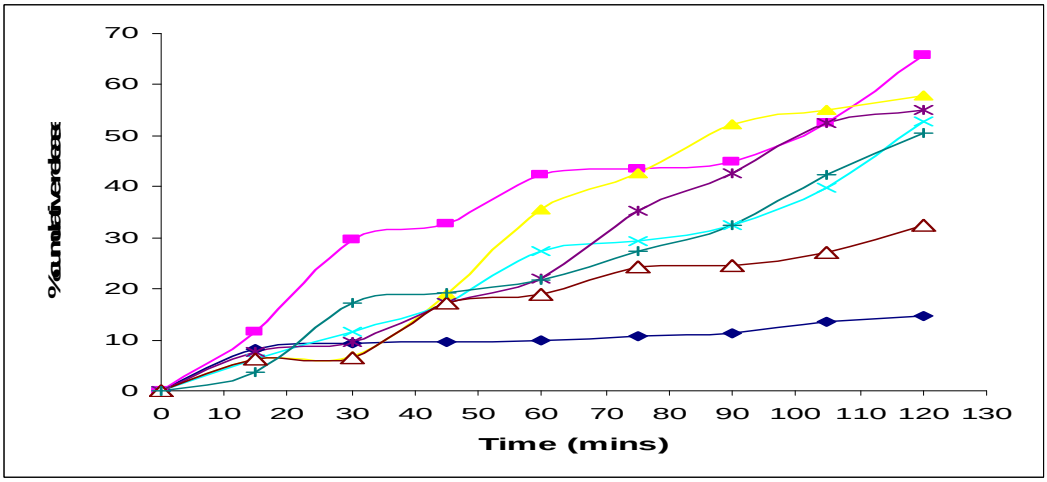


TABLE: 5 Permeation data of batches R-PGS$_1$ and R-PGS$_4$ compared with pure drug

Time (mins)	Amount permeated / ml		
	Pure drug	1:1	1:4
15	0.004	0.039	0.024
30	0.014	0.041	0.034
45	0.014	0.049	0.044
60	0.016	0.050	0.061
90	0.017	0.043	0.065
120	0.009	0.078	0.073
150	0.008	0.059	0.081
180	0.010	0.062	0.082

TABLE: 6 Permeation data of batches R-SSG$_1$ and R-SSG$_2$ compared with pure drug

Time (mins)	Amount permeated / ml		
	Pure drug	1:1	1:2
15	0.004	0.042	0.014
30	0.014	0.051	0.023
45	0.014	0.055	0.024
60	0.016	0.058	0.014
90	0.017	0.061	0.023
120	0.009	0.073	0.011
150	0.008	0.071	0.008
180	0.010	0.056	0.015

FIG: 5 Permeation profiles of batches R-PGS$_1$ and R-PGS$_4$ compared with pure drug. ♦- PURE DRUG; ■- R-PGS$_1$; ▲- R-PGS$_4$.

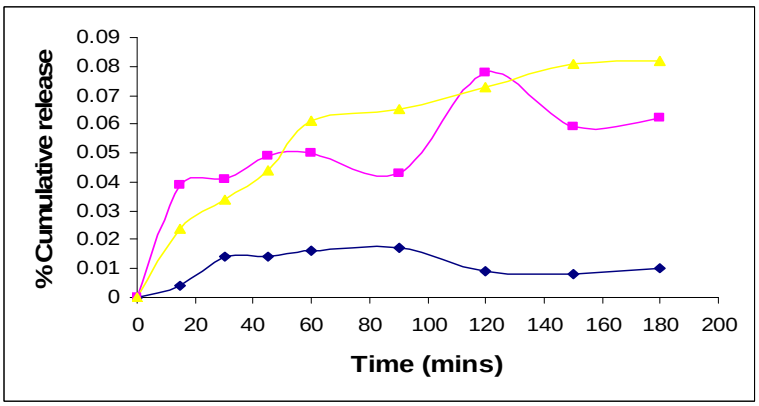
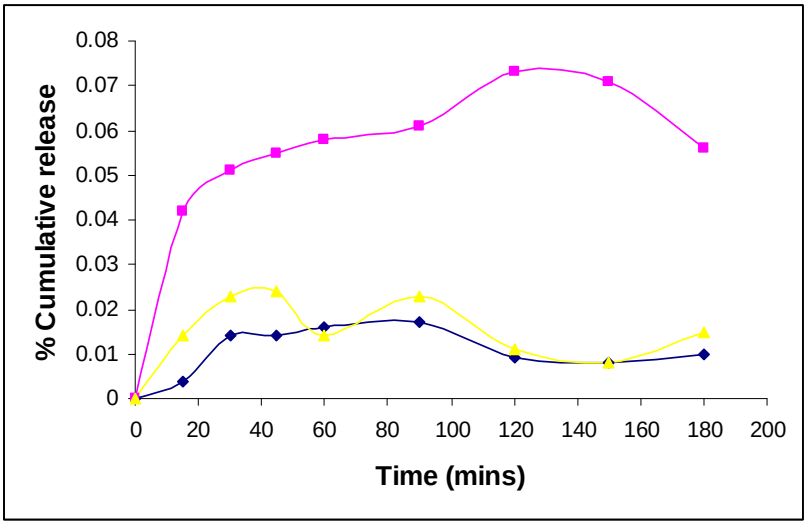


FIG: 6 Permeation profiles of batches R-SSG$_1$ and R-SSG$_2$ compared with pure drug ♦- PURE DRUG; ■- R-SSG$_1$; ▲- R-SSG$_2$.



CONCLUSION

Earlier studies reveals that researchers adopted solid dispersion approach by employing physiologically inert carriers in order to improve dissolution of poorly soluble drugs. In the present study a novel drug-polymer solid dispersion approach was attempted and investigated for dissolution characteristics of Rosiglitazone. Rosiglitazone a diabetic drug was chosen as a model for investigating the possibility of the novel drug-polyme solid dispersion approach. Rosiglitazone being poorly soluble may impose dissolution rate limited problem and hence it is formulated using solid dispersion technique with hydrophilic polymer PGS and SSG in six different ratios for each polymers.
Phase solubility of Rosiglitazone solid dispersions of both the polymers were found to increase by increasing the concentration of the carrier up to specific limit after that the solubility remained constant.

The dissolution studies showed an enhanced rate of dissolution of Rosiglitazone from solid dispersions as compared to that of pure drug. The R-PGS$_1$ showed 84% and R-PGS$_4$ showed 92% release in 2 hours. R-SSG$_1$ and R-SSG$_2$ showed 66% and 58% cumulative release in 2 hours. Based on release rate the four best releasing formulations (above mentioned) were selected and characterization was done for the selected formulations. The saturation solubility and the wetability of the solid dispersions were found to be enhanced when the drug is dispersed in carriers like SSG and PGS. Additionally, NIRA spectra showed decrease in peak area and peak width of the formulations when compared with pure drug peaks confirming the particle size reduction in formulations. A transition from crystalline to amorphous form of drug was confirmed from XRD.As a result of transition and particle size reduction there is an increase in the surface area which may be the reason for increased rate of dissolution.Infra-red spectral analysis indicated the absence of chemical interaction between drug and polymers.

The amount permeated through goat intestine was high in selected batches than pure drug indicating enhanced drug absorption due to increased solubility of drug. It was also shown that amount permeated through the intestine was found to be increased on increasing the carrier concentration.

The present novel drug – polymer solid dispersion approach proposes the view that wherever a poorly soluble drug is combined with hydrophilic polymers, the polymers play a vital role for enhanced dissolution and absorption of poorly soluble drugs. This gives a signal to extending this approach to similar combinations of drugs used in clinical practice so as to improve bioavailability of poorly soluble drugs through improved dissolution.

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