Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2014, Volume 2, Issue 12
ISSN: 2321–3647(online)

Solubility Enhancement of Pioglitazone Using Modified Karaya Gum Solid Dispersions

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ABSTRACT

Pioglitazone, a novel anti-diabetic drug of thiazolidone dione group improves insulin sensitivity in insulin resistant patients. It belongs to BCS class-II, having low solubility and high permeability. Its low solubility in biological fluids, results in poor bioavailability after oral administration. To enhance its solubility, solid dispersions using modified karaya gum in different ratios were prepared by three different methods such as physical mixture, solvent evaporation and kneading method. The enhancement of solubility by natural carrier was compared with semi-synthetic carrier (β-cyclo-dextrins). The solid dispersions were evaluated for physico-chemical properties and dissolution studies in distilled water and 0.1N HCL. Among them, the solid dispersion prepared by solvent evaporation method showed maximum solubility (0.355±0.01mg/ml) when compared with β-cyclo-dextrins and pure drug.

Key words: solubility enhancement, solid dispersions, karaya gum, oral disintegrating tablet.

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Received 20 November 2014, Accepted 28 November 2014

Please cite this article as: Prasanthi D *et al.*, Solubility Enhancement of Pioglitazone Using Modified Karaya Gum Solid Dispersions. American Journal of Pharmacy & Health Research 2014.

INTRODUCTION

The oral route is the most preferred route of drug administration because of its convenience, patient compliance and low cost of medicine. For a drug to be absorbed into the systemic circulation by oral administration, the drug has to be dissolved in the gastric fluids. For hydrophobic drugs, dissolution process acts as the rate limiting step, and determines the rate and degree of absorption. Thus, the major challenges for drug development is poor solubility, about 40% of newly developed drugs are poorly soluble or insoluble in water[1]. In addition, up to 50% of orally administered drug compounds face the formulation problems related to their low solubility and high lipophilicity. Bioavailability of poorly water-soluble hydrophobic drugs such as class II drugs in bio pharmaceutics classification system is limited by their solubility and dissolution rate. The rate of dissolution of these drugs can be improvised by decreasing particle size, crystallinity, and increasing the surface area. A number of studies have been carried out to improve the dissolution rate of drugs by minimizing the particle size. Although, the fine drug particles have high tendency to agglomerate due to vander waals attraction or hydrophobicity, which result in a decrease in surface area over time[2, 3, 4]. The technique of solid dispersion has been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting solvent method. The development of solid dispersions as a practically effective method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by co-solvents, and particle size reduction[5]. Studies disclose that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion[6,7]. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug gets released as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves instantly to saturate the gastrointestinal fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. To prepare solid dispersions by different methods in different ratios using modified karaya gum and optimize solid dispersions and compare with synthetic carrier and to find out the best solid dispersion.

MATERIALS AND METHOD

Pioglitazone was gifted by RA chem pharma Ltd. karaya gum, β-cyclo-dextrin, crospovidone

were purchased from yarrow chem products and Kyron T-314 purchased from Corel Pharma Chem Ltd. Sodium lauryl sulphate, spray dried lactose, magnesium stearate, methanol were purchased from SD fine chemicals limited. All the reagents and chemicals used were of analytical grade.

Preparation and evaluation of solid dispersions

Solid dispersions using modified karaya gum (MKG) were prepared by physical mixture, solvent evaporation and kneading method. In all the preparations the weight of drug was taken as 300mg.

Preparation of solid dispersions by physical mixture method (PM)

The physical mixtures of drug with MKG were prepared by blending method by geometric mixing of pioglitazone and MKG in the ratio of 1:1, 1:3, 1:5, 1:7, 1:9 and passing through sieve No 60 and individually designated as PSM-1, PSM-2, PSM-3, PSM-4, and PSM-5 respectively as shown in table 1.

Table-1: Formula for solid dispersions

Formula code	Ratio of the mixture of drug and carrier(D:C)	Weight of the drug(mg)	Weight of the carrier(mg)	Formula code	Ratio of the mixture of drug and carrier(D:C)	Weight of the drug(mg)	Weight of the carrier(mg)
PSM-1	1:1	300	300	KSM-1	1:1	300	300
PSM-2	1:3	300	900	KSM-2	1:3	300	900
PSM-3	1:5	300	1500	KSM-3	1:5	300	1500
PSM-4	1:7	300	2100	KSM-4	1:7	300	2100
PSM-5	1:9	300	2700	KSM-5	1:9	300	2700
SSM-1	1:1	300	300	SSβ-1	1:01	300	300
SSM-2	1:3	300	900	SSβ-2	1:03	300	900
SSM-3	1:5	300	1500	SSβ-3	1:05	300	1500
SSM-4	1:7	300	2100	SSβ-4	1:07	300	2100
SSM-5	1:9	300	2700	SSβ-5	1:09	300	2700

PSM- Physical mixture method**,** SSM- solvent evaporation method**,** KSM- kneading method**,** SSβ-solvent evaporation with β-cyclodextrin**.**

Preparation of solid dispersions by solvent evaporation method(SM)

The solid dispersions of the drug were prepared by using rotary flash evaporator. Pioglitazone and MKG were dissolved in methanol in 1:1, 1:3, 1:5, 1:7, and 1:9 ratios and kept in rotary flash evaporator at 100 rpm and film was scrapped and pass through sieve No 80 and placed in oven for 3hrs and individually designated as SSM-1, SSM-2, SSM-3, SSM-4, and SSM-5 respectively as shown in table 1.

Preparation of solid dispersions by kneading method (KM).

The solid dispersions of the drug were prepared by kneading method using mortar and pestle. Pioglitazone and MKG were dissolved in methanol in 1:1, 1:3, 1:5, 1:7, 1:9 ratios to make paste, kneaded properly and dried at 45°c for 1 hr and passed through sieve No 80 and individually designated as KSM-1, KSM-2, KSM-3, KSM-4, and KSM-5 respectively as shown in table 1.

Preparation of sold dispersion with β-cyclo dextrin for comparative study.

The solid dispersions of the drug were prepared by solvent evaporation method by taking pioglitazone and β-cyclo dextrin in 1:1, 1:3, 1:5, 1:7, and 1:9 ratios and designated as SSβ-1, SSβ-2, SSβ-3, SSβ-4, and SSβ-5 respectively as shown in table 1.

Evaluation of solid dispersions

Pre-compression parameters of the powder blend [14].

Angle of repose

100 gms of the blend was accurately weighed and carefully poured through the funnel whose tip was secured at a height of 2.5 cm above the graph paper which is placed on a horizontal surface. The blend was poured until the apex of the conical pile just touches the tip of the funnel. Angle of repose is calculated by the following formula, powder flow was determined by comparing with standard values of angle of repose.

$$\theta = \mathrm{Tan}^{-1}(h/r)$$

Where, θ = angle of repose, r=radius of the pile, h=height of the pile.

Bulk density

Apparent bulk density (*b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V*) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

$$*b = M/V*$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time (around 250). The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (*t) was calculated using the formula.

$$*t = M/V_t$$

Carr's index

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index which is

calculated using the formula, powder flow was determined by comparing with standard values of compressibility index.

$$C.I\ (\%) = \frac{\text{Tapped density} - \text{Bulk density} \times 100}{\text{Tapped density}}$$

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the using the formula, powder flow was determined by comparing with standard values of Hausner ratio.

$$\text{Hausner ratio} = *t/*d$$

Where *t=tapped density, *d=bulk density

Assay

Assay of the prepared solid dispersions were determined in distilled water. Accurately weighed amounts of solid dispersions equivalent to 15 mg of drug was taken in a 100 ml volumetric flask, 20 ml methanol was added and shaken for 20 min to dissolve the drug. The volume was made to 100 ml with distilled water containing 0.45%SLS. Dispersions were filtered and 1 ml aliquot of the above solutions were taken and diluted to 10 ml with distilled water containing 0.45%SLS respectively. The absorbances of these solutions were determined at 269nm against the blank. The percentage assay was calculated from the standard curve.

Solubility studies[17]

An excess of pure pioglitazone and prepared solid dispersions were added to screw capped bottles containing distilled water. Bottles are shaken mechanically at 26°C for 24 hours and aliquots are withdrawn filtered and assayed for drug content at 269 nm spectrophotometrically.

Dissolution study of solid dispersions

Dissolution studies were performed with solid dispersions prepared by three different methods and also with pure drug using USP dissolution apparatus II (Paddle type) (Electrolab TDT-0.8L).The dissolution test was performed using 900ml of distilled water at 37˚c ± 0.5˚c .The speed of rotation of paddle was set at 75 rpm. 5 ml samples were withdrawn at time intervals of 10 minutes and the same volume was replaced with fresh distilled water. Absorbance of solution was checked by UV spectrophotometer (ELICO–164 double beam spectrophotometer, Hyderabad, India) at a wavelength of 269 nm and drug release was determined from standard curve.

RESULTS AND DISCUSSION

Interaction studies by FTIR

FTIR studies were done to verify if there was any interaction between the pure drug and various excipients employed. The various FTIR graphs both of pure drug and various excipients were mixed and the blend was formulated into IR pellet and scanned. The different plots are shown in figure 1 and figure 2.

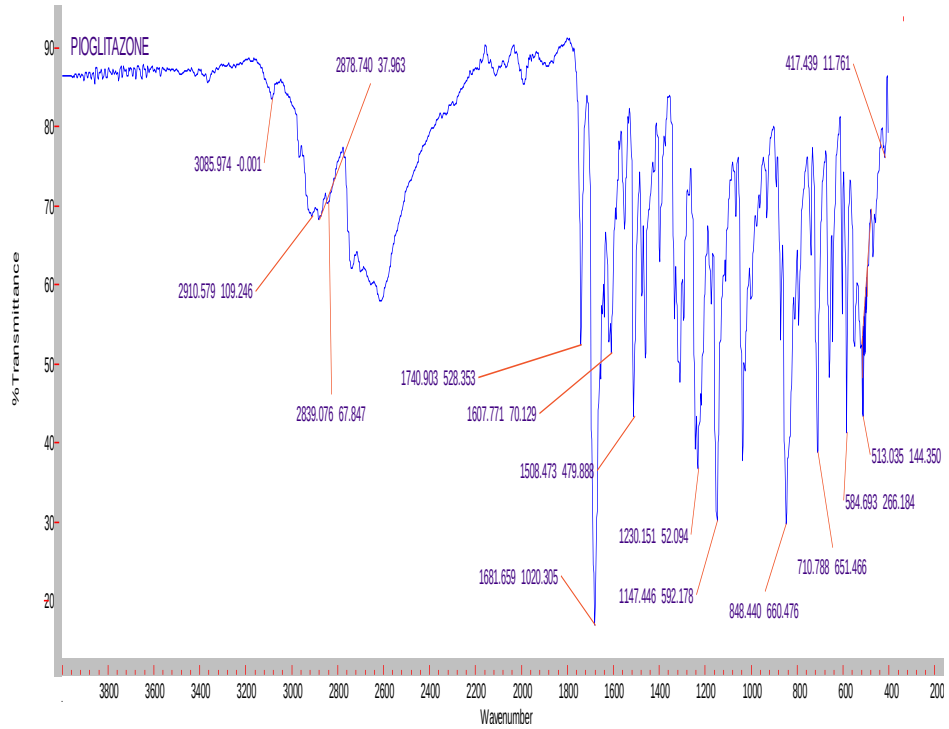

Figure 1: FTIR graph of pioglitazone.

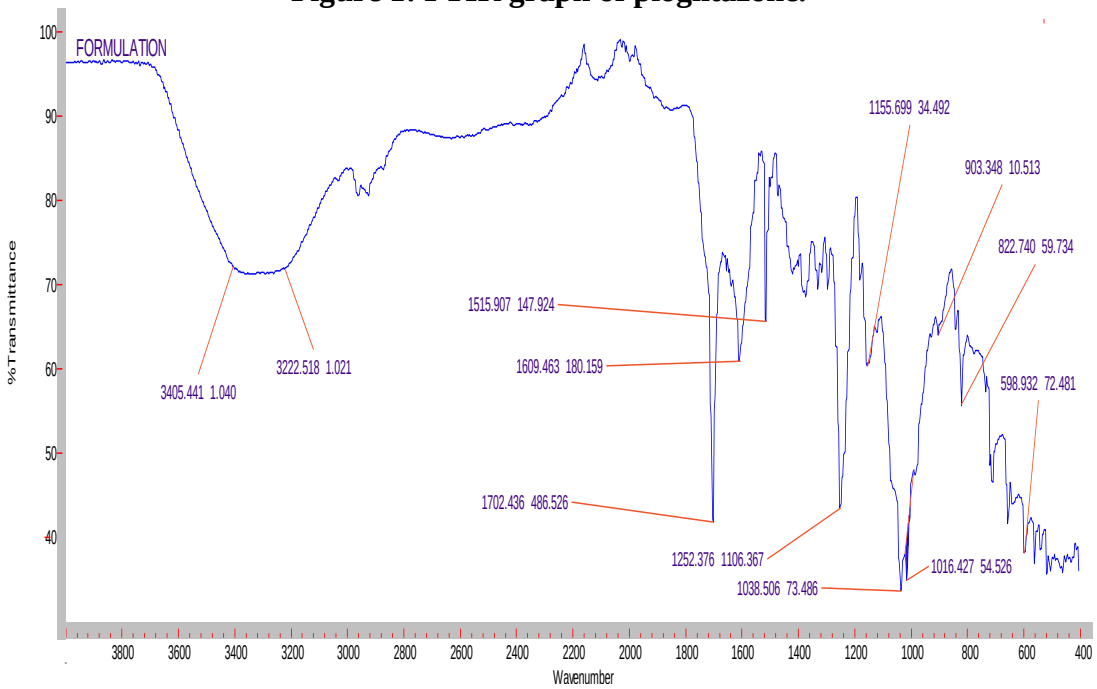

Figure 2: FTIR graph of drug + karaya gum

From the above IR graphs the peaks representing the pure drug were similar in formulation graph suggesting that there is no interaction and the pure drug is not altered functionally.

Evaluation of solid dispersions

Solid dispersions were prepared by three different methods physical mixture, solvent evaporation and kneading method. These were evaluated for assay, solubility, pre-compression parameters and dissolution studies.

Assay

The prepared solid dispersions complied with the requirements of assay. The result for assay was 98.65%. These percentage drug values indicated that the drug content is uniform in all the batches.

Solubility studies

With physical mixture method PSM-5 showed maximum solubility of 0.278±0.008mg/ml. With solvent evaporation method SSM-5 formulation showed solubility of 0.355±0.010mg/ml and with kneading method KSM-5 showed 0.298±0.009 mg/ml solubility. It has been observed as the concentration of carrier (MKG) increased, the solubility was enhanced. Among the three different methods solvent evaporation method showed maximum solubility of 0.355±0.010 mg/ml when compared with pure drug as shown in table 2.

Table 2: Pre-compression parameters and solubility profile of prepared formulations

Formu-lation	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)	Solubility (mg/ml)
PSM-1	31.5±0.98	0.409±0.01	0.5±0.01	1.22±0.01	18.2±0.23	0.236±0.01
PSM-2	31.8±0.80	0.440±0.01	0.510±0.01	1.15±0.02	13.72±1.53	0.252±0.01
PSM-3	30.0±0.81	0.542±0.01	0.608±0.01	1.12±0.02	10.8±0.56	0.262±0.01
PSM-4	27.5±0.92	0.605±0.01	0.662±0.01	1.09±0.09	8.6±0.33	0.271±0.01
PSM-5	29.0±0.86	0.590±0.01	0.670±0.01	1.11±0.01	11.9±0.78	0.278±0.01
SSM-1	32.0±0.90	0.360±0.01	0.450±0.01	1.25±0.01	20.00±0.09	0.289±0.01
SSM-2	31.0±0.72	0.565±0.01	0.664±0.01	1.17±0.01	14.90±0.81	0.305±0.01
SSM-3	29.5±0.82	0.773±0.01	0.890±0.01	1.15±0.01	13.48±0.78	0.321±0.01
SSM-4	28.0±0.81	0.661±0.01	0.725±0.01	1.09±0.02	8.82±0.33	0.336±0.01
SSM-5	26.5±0.87	0.595±0.01	0.508±0.01	1.01±0.01	1.57±0.56	0.355±0.01
KSM-1	32.0±0.90	0.366±0.01	0.450±0.01	1.25±0.01	18.66±0.94	0.258±0.01
KSM-2	30.8±0.72	0.592±0.01	0.750±0.01	1.23±0.01	21.0±0.81	0.276±0.01
KSM-3	29.5±0.82	0.808±0.01	0.936±0.01	1.15±0.01	13.67±0.78	0.283±0.01
KSM-4	27.6±0.81	0.707±0.01	0.785±0.01	1.11±0.01	9.93±0.33	0.290±0.01
KSM-5	26.5±0.87	0.580±0.01	0.604±0.01	1.04±0.01	3.97±0.12	0.298±0.01
SSβ-1	25.26±1.03	0.642±0.01	0.735±0.01	1.14±0.01	12.58±1.52	0.269±0.01
SSβ-2	23.52±0.98	0.646±0.01	0.735±0.01	1.13±0.01	12.09±0.23	0.284±0.01
SSβ-3	24.78±0.82	0.617±0.01	0.722±0.01	1.17±0.01	14.53±0.92	0.302±0.01
SSβ-4	24.89±0.80	0.634±0.01	0.720±0.01	1.13±0.02	11.99±1.73	0.317±0.01
SSβ-5	24.21±0.72	0.645±0.01	0.742±0.01	1.15±0.01	13.24±0.16	0.330±0.01

*PSM-physical mixture method, SSM-solvent evaporation method, KSM-kneading method, SSβ- solvent evaporation solid dispersion of β-cyclodextrin.

Pre-compression parameters

Solid dispersions prepared by three methods (physical mixture, solvent evaporation and kneading method) were evaluated for pre-compression parameters, mainly flow properties. The angle of repose of all the formulations ranged between 26.5±0.87 to 32.0±0.90 inferring excellent flow or good flow property. Carr's index calculated from bulk density and tapped density ranged from1.57±0.562 to 11.9±0.782 for ratios 1:7 and 1:9 inferring excellent flow and other ratios ranged from 13.48±0.782 to 21.0±0.813 inferring good or fair flow property and Hausner's ratio ranged from 1.01±0.007 to 1.25±0.012 inferring excellent or good flow property as shown in table 2.

Dissolution studies

In vitro release profiles of solid dispersions by physical mixture method

Dissolution studies of solid dispersions by physical mixture method showed 39.88±1.47% to 54.02±1.21% release in 60 minutes. Formulation containing Drug: carrier ratio of 1:9, PSM-5 showed maximum release of 54.02±1.21% in 60 minutes as shown in figure 3.

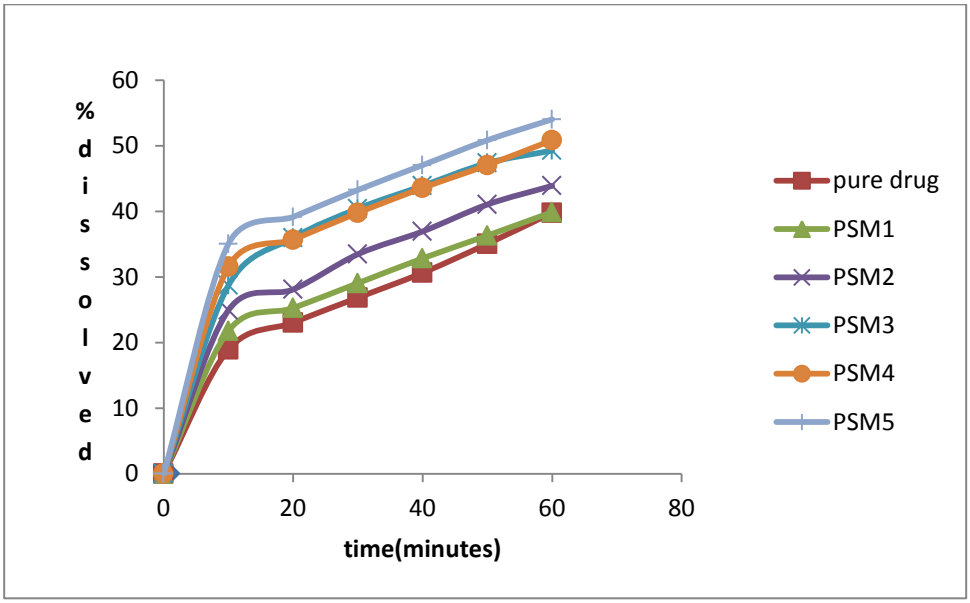

Figure 3: In vitro release profiles of solid dispersions by physical mixture method

***In vitro* release profiles of solid dispersions by solvent evaporation method**

Solid dispersions by solvent evaporation method showed 83.05±0.32% to 99.15±0.32% release in 60 minutes. Formulation containing Drug: carrier ratio of 1:9, SSM-5 showed maximum release of 99.15±0.32% in 60 minutes as shown in figure 4.

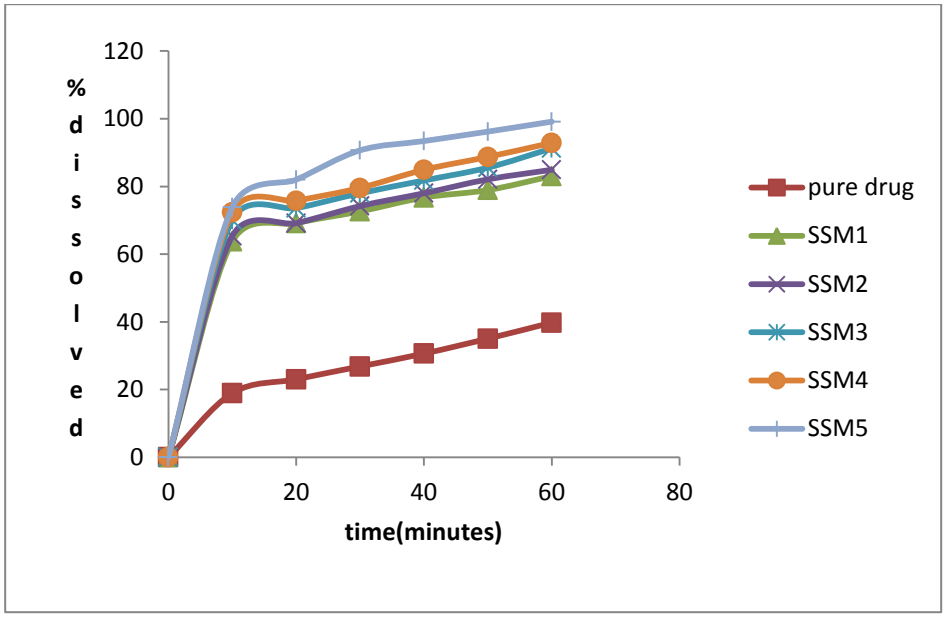

Figure 4: *In vitro* release profiles of solid dispersions by solvent evaporation method

Drug release study of solid dispersions prepared by kneading method.

Solid dispersions by kneading method showed 74.20±1.9% to 85.89±1.42% release in 60 minutes. Formulation containing Drug: carrier ratio of 1:9, KSM-5 showed maximum release of 85.89±1.42% release in 60 minutes as shown in figure 5.

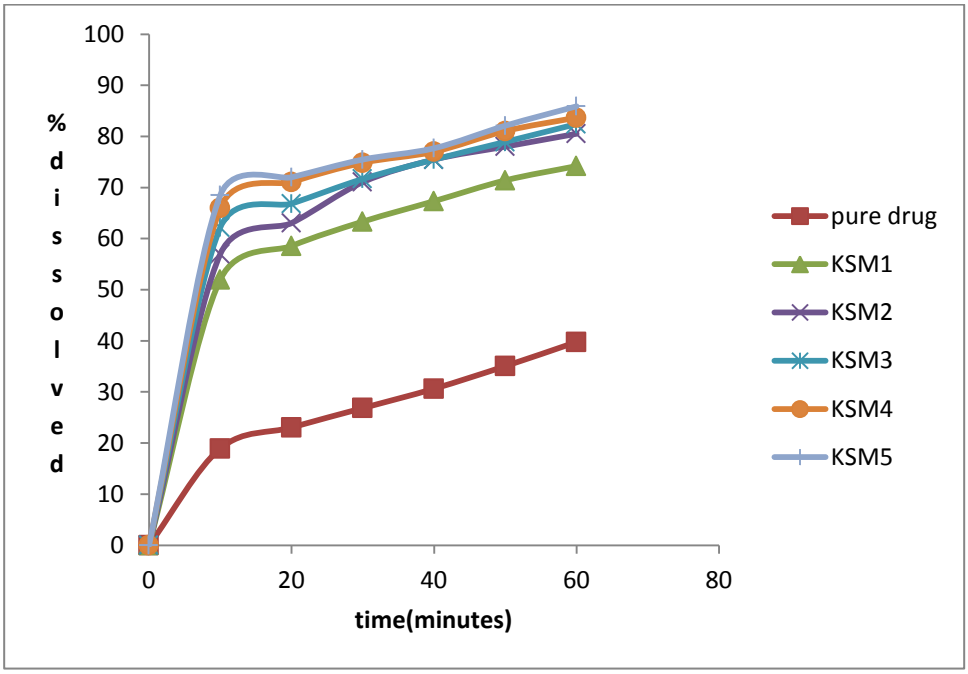

Figure 5: *In vitro* release profiles of solid dispersions by kneading method

Comparison with β-cyclo-dextrins

Solid dispersions of synthetic carrier (β- cyclo-dextrins) were prepared by solvent evaporation method. Dissolution studies were performed and compared with solid dispersions of modified

karaya gum (MKG). It was observed that percentage drug released from (solvent evaporation solid dispersion with β-cyclo-dextrins**)** SSβs of pioglitazone showed increased release when compared to pure drug. The β-cyclo-dextrins SSβs showed greater dissolution than the other ratios which may be due to the greater hydrophilic and swelling properties of it. SSβ-5 showed maximum release of 90.28±1.85% in 60 minutes and pure drug (39.78±0.50%) in 60 minutes as shown in figure 6.

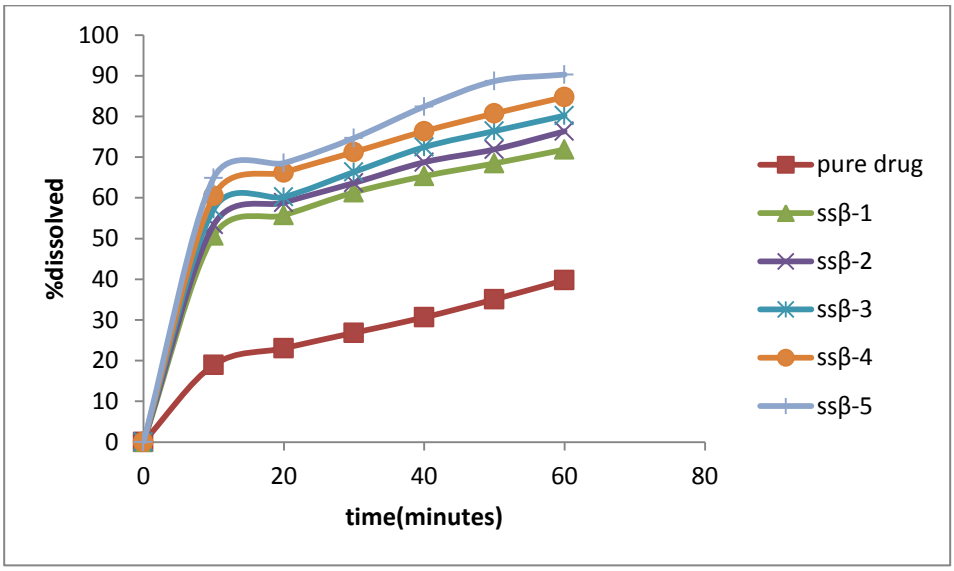

Figure 6: In vitro release profiles of solid dispersions by solvent evaporation with β-cyclo-dextrins

Comparison of optimized formula with pure drug in distilled water

Dissolution studies of MKG formulation SSM-5 by solvent evaporation method was compared with synthetic carrier (β-cyclo-dextrins) formulation SSβ-5 and pure drug as shown in figure 7.

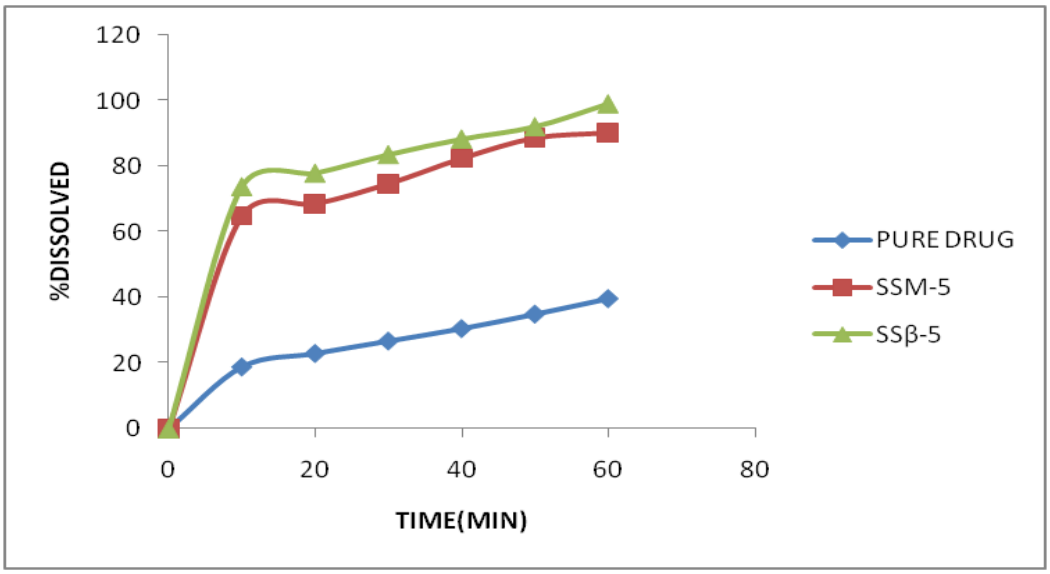

Figure 7: Percentage release profiles of pioglitazone pure drug, SSM-5 and SSβ-5

CONCLUSION

To enhance solubility of pioglitazone, solid dispersions with modified karaya gum were prepared by physical mixture, solvent evaporation and kneading method. Drug-excipient compatibility studies by FTIR have shown there was no interaction between the drug and carrier. Modified gum karaya proved to be a potential carrier in the dissolution rate enhancement of pioglitazone and overcomes the processing problems of higher viscosity of karaya gum. Solid dispersions by solvent evaporation method showed enhanced water solubility when compare to pure drug, the formulation containing drug: carrier ratio of 1:9, PSM-5 showed maximum release of 99.15±0.32% in 60 minutes.

ACKNOWLEDGEMENT

The authors are thankful to Principal Dr.B.Madhava Reddy, Dr.P.K Lakshmi and Staff of Department of Pharmaceutics, the Management of G. Pulla Reddy College of Pharmacy, Hyderabad, Andhra Pradesh, India for their assistance, kind suggestions and providing infrastructure and facilities during the study.

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