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Effect of Amphiphilic Graft Co-Polymer Carrier on Solubility and Dissolution Enhancement of Ambrisentan

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Authors' contributions

This work was carried out in collaboration between both authors. Author RR conceptualized, gather the data, carried out the experiment and wrote the manuscript. Author NKJ supervised the project, analysed the data and help in designing the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: Ambrisentan is a endothelin type A selective receptor antagonist used in the management of pulmonary arterial hypertension. Ambrisentan is BCS Class II drug haves very poor solubility in water and shows incomplete absorption after oral administration. The present work was aimed to study the effect of amphiphilic graft co-polymer carrier on enhancement of solubility and dissolution rate of poorly water soluble drug ambrisentan. To improve the aqueous solubility of ambrisentan solid dispersion was formulated by using novel carrier amphiphilic graft co-polymer (Soluplus®).
Materials and Methods: Solid dispersion was prepared by kneading technique by utilizing various ratios of carrier. Obtained solid dispersions ware evaluated for solubility, percentage yield, drug content and in vitro dissolution study. Powder characterization was performed by infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD).
Results: FTIR spectroscopy shows no interaction between drug and polymer. DSC study showed that endothermic peak of drug was completely disappeared in Solid dispersion suggesting

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complete miscibility of drug in Soluplus®. XRD study suggest the conversion of crystalline ambrisentan in to amorphous form. All solid dispersions prepared with Soluplus® as a carrier showed increase in solubility. Solubility of ambrisentan was found to be increased 7.17 fold in optimized SD formulation ASD5. *In vitro* dissolution study showed the faster drug release from SD formulation compare to its pure form. All solid dispersion formulation's release more than 50% of drug in first 10 min.

Conclusion: This study conclude that the preparation of amphiphilic graft co-polymer based solid dispersion prepared by kneading technique is found to be useful in enhancement the solubility and dissolution rate of ambrisentan.

Keywords: Ambrisentan; Soluplus®; Solid dispersion; DSC; XRD; Kneading technique etc.

1. INTRODUCTION

Administartion of medication through oral route is more usual because of its simplicity and ease of ingestion. Swallowing a dose form by oral route is a comfortable and familiar method of taking medication from the patient's standpoint. Apart from its popularity for drug administration, there are number of variables that can limit drug absorption from the gastrointestinal tract. The most common problem among those is poor water solubility of the drug. Drug with low aqueous solubility will show dissolution rate limited absorption and ultimately gives incomplete bioavailability [1]. Aqueous solubility and intestinal permeability is the important parameter to achieved the desired bioavailability of drugs through oral route. In order to achieved intended plasma drug concentration and optimum therapeutic effect, the aqueous solubility of drug is important consideration [2]. Drugs with low solubility is responsible for high dose administration and increased frequency of administration of dosage form. Hence enhancement of solubility and dissolution rate of low aqueous soluble drugs is an challenging task in the drug development and in bioavailability improvement [3]. According to Biopharmaceutical classification system, BCS Class II are class of drugs that have low aqueous solubility and high membrane permeability. Such drugs shows poor or limited absorption from GI tract after oral administration [4]. Hence such drug always demand the solubility enhancement so as to improve its absorption rate.

There are many methods are discussed in literature in the past regarding improvement of solubility and dissolution properties of poor water soluble drug molecule. Solid dispersion is one of the oldest and effective technology successfully utilized by many researcher to increase the drug solubility during formulation and development. Solid dispersion possess several advantages like reduction in particle size, improve wettability of drug, higher particle porosity and amorphous formation of materials [5]. There are various methods are available for the preparation of solid dispersion such as solvent evaporation method, fusion method, hot melt extrusion method and kneading method. Kneading method of SD preparation provide additional advantages of particle size reduction during processing and industrially feasible technique [6].

Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus®) is novel polymer designed by BASF corporation widely useful in increasing solubilizing properties of poorly soluble drugs. Soluplus® is available commercially as white free flowing granular powder [7]. Soluplus® has been widely researched carrier in solubility enhancement using different technique and model drugs like hot melt extrusion, spray drying, high shear dispersions, electrospinning/ electrospraying, microwave radiation and solvent evaporation technique [8].

Ambrisentan is (2S)-2-[(4, 6-dimethylpyrimidin-2-yl) oxy]-3-methoxy- 3, 3-diphenylpropanoic available as white to off-white crystalline powder. Ambrisentan is a BCS class II drug and is practically insoluble in water. Ambrisentan is categorized as endothelin type A (ETA)-selective receptor antagonist used in the management of pulmonary arterial hypertension. Because of its very poor solubility in water, the rate limiting step in the absorption of drug is its solubility in GI fluids. As the solubility of drug increased in water, it eventually fasten the absorption GI membrane which results in improvement of bioavailability of drugs. In this research, it was aimed to study the effect of amphiphilic graft co-polymer carrier (Soluplus®) on improvement of aqueous solubility and dissolution rate of ambrisentan by utilizing solid dispersion technique [9,10].

2. MATERIALS AND METHODS

2.1 Materials

Ambrisentan was obtained as a gift sample from Cadila Pharmaceuticals, Mumbai India. Soluplus® was gifted by BASF Corporation India as a free sample. All other chemical and reagents used were of analytical grade.

2.2 Saturation Solubility Study of Drug

Saturation solubility study of pure drug ambrisentan was estimated in distilled water, acetate buffer pH 1.2, phosphate buffer pH 6.8 and phosphate buffer pH 7.4. Extra amount of drug was added to 10 ml study fluid in a glass vial. Samples were then shaken at constant speed on rotary shaker at 25°C±2°C for 48 hr. The resultant saturated solutions were then filtered and analyzed spectrophotometrically after suitable dilution [11].

2.3 Phase Solubility Study

To analyzed the possible solubilizing effect of carrier Soluplus® on solubility of drug, the phase solubility study was carried out. Excess amount of ambrisentan (approx. 100 mg) were added to 10 ml glass vial containing 0.25%, 0.50%, 0.75%, 1% and 2% aqueous solution of carriers. The solution was then shaken for 48 hr on rotary shaker at a controlled temperature of 25^0C±2^0C. The obtained solutions were then filtered through whatman filter paper no 1 and analyzed by UV-spectrophotometer to determine the concentration of the dissolved drug [12,13].

2.4 Gibbs-Free Energy Transfer

Gibbs free energy transfer was most commonly utilized method to judge the possible favorable or unfavorable effect of carrier on solubilisation of drug in aqueous medium. The Gibbs free energy of transfer (ΔG◦tr) values was calculated using the Gibbs–Helmholtz equation. Negative Gibbs-free energy values obtained after calculation indicates improvement in drug dissolution. The $\Delta G\circ$tr values of drug were calculated using the following equation:

$$\Delta G0tr = \{-2.303RTLog\ (S_0/Ss)\}$$

Where S_0/Ss is the ratio of the molar solubility of drug before and after treatment with polymer. R is the value of gas constant 8.31 JK−1 mol−1 and T is temperature in degree kelvin [14].

2.5 Preparation of Ambrisentan - Soluplus® Physical Mixture

A physical mixture of ambrisentan with Soluplus® was prepared by mixing of drug and carrier using mortar and pestle in different ratio (1:1, 1:2, 1:3, 1:4, 1:5). This mixture passed through sieve no 60 and store in desiccators till further use. The composition was shown in Table 1.

2.6 Preparation of Solid Dispersion

Solid dispersion of Ambrisentan with Soluplus® in different weight ratio (1:1, 1:2, 1:3, 1:4, 1:5) ware prepared by kneading method. Mixture of drug and carrier was placed in a mortar and was kneaded thoroughly with water and methanol (1:1) for 20 min. The kneaded mixtures were then dried in oven at 40°C. After drying the mass was then pulverized and screened through 60-mesh and stored in desiccator for further study [15,16]. The composition was shown in Table 1.

3. CHARACTERIZATION OF SOLID DISPERSION

3.1 Determination of Solubility of Solid Dispersion and Physical Mixture

The solubility study of physical mixture and solid dispersion was determined in distilled water and phosphate buffer pH 6.8 in shake flask method. Excess quantities of sample were added in 25 ml of distilled water and phosphate buffer in conical flask and shaken for 24 hours at room temperature on rotary flask shaker. After shaking the samples containing undissolved solid suspended in the test medium were centrifuged at 10,000 rpm for 5 min, the clear supernatants obtained were filtered using whatman filter paper. Further sample ware suitably diluted and analyzed by spectrophotometer at 263.5 nm [17].

3.2 Determination of Percent Yield of Solid Dispersion

The percent yield of ambrisentan solid dispersions was determined by using the following formula:

$$\text{Percent Yield} = \frac{\text{Weight of prepared solid dispersion}}{\text{Weight of drug and carriers}} \text{x } 100$$

3.3 Determination of Drug Content

Ambrisentan solid dispersion equivalent to 10 mg of drug was accurately weighed and dissolved in methanol (100 ml). The solution was filtered after vigorous shaken. The drug content was analyzed at 263.5 nm against blank by UV spectrometer after appropriate dilution [18].

3.4 Fourier Transform Infra-Red Spectroscopy (FTIR)

Compatibility studies of ambrisentan and with carrier Soluplus® was performed using FTIR spectroscopy (Shimadzu FTIR-8700). Spectrum of pure drug and solid dispersion was recorded over the frequency range of 400 to 2000 cm-1 at 4cm resolution [19].

3.5 Differential Scanning Calorimetry (DSC)

The thermal analysis was carried out using Shimadzu Thermal analyzer DT 40 (Japan). The samples were placed in sealed aluminum pans and heated at a rate of 10°C per min in the temperature range of 20-300°C under a nitrogen flow rate of 40 ml/min. SDC thermogram was recorded for pure ambrisentan, Soluplus® and solid dispersion formulation [20].

3.6 Powder X-Ray Diffraction (XRD)

X-ray powder diffraction patterns of drug, carrier and solid dispersion was recorded on an X-ray powder diffraction system (Rigaku, Mini Flex 600) The scanning was done over range of 5º to 60º. The position and intensities of diffraction peaks were considered for the comparison of crystallinity [21].

3.7 *In vitro* Dissolution Study

In vitro dissolution study of prepared solid dispersions were determined using USP dissolution test apparatus II (Paddle type) (Esico International, Mumbai). Accurately weighted SD preparation equivalent to 10 mg of ambrisentan ware added to 900 ml of phosphate buffer pH 6.8 as dissolution medium, maintained at 37±0.5°C and stirred at 50 rpm. 5 ml samples were withdrawn at specific time and same volume was replaced with fresh media in order to maintain the sink condition. Collected samples were analyzed at 263.5 nm using UV-visible spectrophotometer against the blank after suitable dilution. Similar procedure was conducted for dissolution study of plain ambrisentan for comparision with SD formulations. The release profile data was analyzed for cumulative percent dissolved at different time intervals [22].

4. RESULTS AND DISCUSSION

4.1 Saturation Solubility Study of Drug

The solubility of ambrisentan in distilled water, acetate buffer pH 1.2, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 is shown in Fig. 1. The solubility of ambrisentan in distilled water was found to be 7.351 µg/ml, suggesting its poor water solubility. Solubility of ambrisentan increases as the pH of aqueous media increases. The solubility of ambrisentan in buffer pH 1.2, 6.8 and 7.4 was found to be 5.16 µg/ml, 28.50 µg/ml and 35.41 µg/ml respectively.

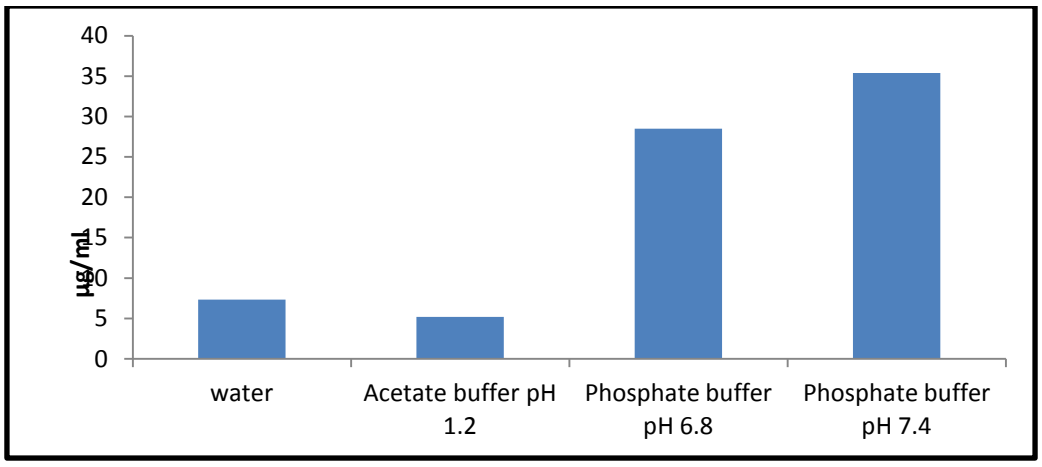

Fig. 1. Solubility profile of ambrisentan in different pH Solvents

4.2 Phase Solubility Study

Phase solubility study of ambrisentan was studied using increasing concentration of hydrophilic polymer. A linear increase of solubility of ambrisentan was seen with an increasing concentration of Soluplus® carriers in water. This increased solubility of drug may be due solubilizing effect of carriers. At 2% w/v concentration of Soluplus® , the aqueous solubility of ambrisentan was increased by 6.2 fold. showed good affinity between drug and polymer. The phase-solubility diagram constructed for Soluplus® in distilled water was linear giving A_L type solubility curve. The apparent stability constant (Kc) calculated from the linear plot of the phase solubility diagram, were found to be 143.98 M^{-1} indicate stronger interactions between the drug and carrier [23]. The solubility of ambrisentan at 0.25, 0.5, 0.75, 1 and 2% aqueous solution of carrier was shown in Fig. 2.

4.3 Gibbs-Free Energy Transfer

Gibbs free energy transfer was studied for ambrisentan in aqueous solutions Soluplus® in order to determine the possible favorable or unfavorable effect of carrier on solubility of drug. The ΔG°tr of drug at different concentration of Soluplus® are shown in 2. Negative values of Gibbs-free energy indicate improved dissolution [24]. In our study, increased in negative ΔG°tr value with increasing concentration of polymer was seen at all concentration levels of polymer, which suggests that treatment of drug and polymer was favorable for improving the solubility of drug [25].

4.4 Solubility Study of Solid Dispersion and Physical Mixture

The solubility of ambrisentan PMs and SDs was determined in distilled water and phosphate buffer pH 6.8. Ambrisentan is poorly soluble in water, having a maximum solubility of 7.351 µg/ml in distilled water. In the present study, a solid dispersion was prepared to increase the solubility and dissolution rate of ambrisentan. All physical mixture of ambrisentan showed improvement in solubility of drug as compare to pure drug. It was found that as the concentration of hydrophilic carrier increases, the solubility also increases. Solubility study of solid dispersion showed multi fold increase in solubility of drug in both the solvent. SD formulation (ASD5) showed maximum increase in solubility of drug in both solvent. Solubility was increased 7.17 fold in distilled water when compare with pure drug and hence considered as optimized formulation. This increased solubility of drug was might be because of conversion of drug in amorphous form or by increased wettability of drug by Soluplus® [26] The solubility of drug from SD formulation was higher in phosphate buffer solution than distilled water. The solubility data for all the PMs and SDs formulations are presented in Table 3.

4.5 Percentage Practical Yield and Drug Content

The percentage practical yields calculated for all SDs formulation was shown in Table 4. Percentage yield for all SDs formulation was found optimum showing effectiveness of kneading technique. Drug content for solid dispersion formulations ASD1 to ASD5 was found to be in the range of 97.99% to 98.70.%. The percentage drug content for all SDs formulation was found within pharmacopoeial limit which indicate uniform distribution of drug in solid dispersion.

4.6 Fourier Transform Infra-Red Spectroscopy

IR spectra of pure ambrisentan, Soluplus® and its SD with Soluplus® are presented in Fig. 3. Sharp characteristic peaks of pure ambrisentan ware also appears in the spectra of optimized SD formulation. The peaks of drug are almost unchanged in the optimized solid dispersion which indicates that the symmetry of drug molecule is not affected significantly [27].

4.7 Differential Scanning Calorimetry

Thermogram of pure drug showed a single sharp endothermic peak at 194.62^0C, corresponding to its melting point indicating the crystalline nature of drug, whereas Soluplus® does not showed any endothermic or exothermic peak representing its amorphous nature. Optimized SD formulation (ASD5) showed complete absence of endothermic peak of drug, which suggests that the drug is miscible in Soluplus® completely. This further proved the crystalline transformation of drug in to amorphous form [28]. Similar observation was reported by Ha et al. [29]. DSC thermogram of pure ambrisentan, Soluplus® and solid dispersion ASD5 are shown in Fig. 4.

Table 1. Composition of ambrisentan physical mixture and solid dispersion

Formulation	Formulation Code	Ambrisentan : Soluplus® Ratio
Physical Mixture	APM1	1:1
	APM2	1:2
	APM3	1:3
	APM4	1:4
	APM5	1:5
Solid Dispersion	ASD1	1:1
	ASD2	1:2
	ASD3	1:3
	ASD4	1:4
	ASD5	1:5

Table 2. Gibbs-Free energy value of Ambrisentan with Soluplus®

Concentrartion of polymer (%)	Concentration of Ambrisentan (µg/ml)*	ΔG° tr (J/Mol)
0	7.351± 0.026	-
0.25	14.694 ± 0.008	-1717.66
0.5	18.367 ± 0.010	-2270.56
0.75	23.510 ± 0.021	-2882.33
1	28.653 ± 0.012	-3372.57
2	45.551 ± 0.004	-4521.38

** Values are mean ± SD, n = 3*

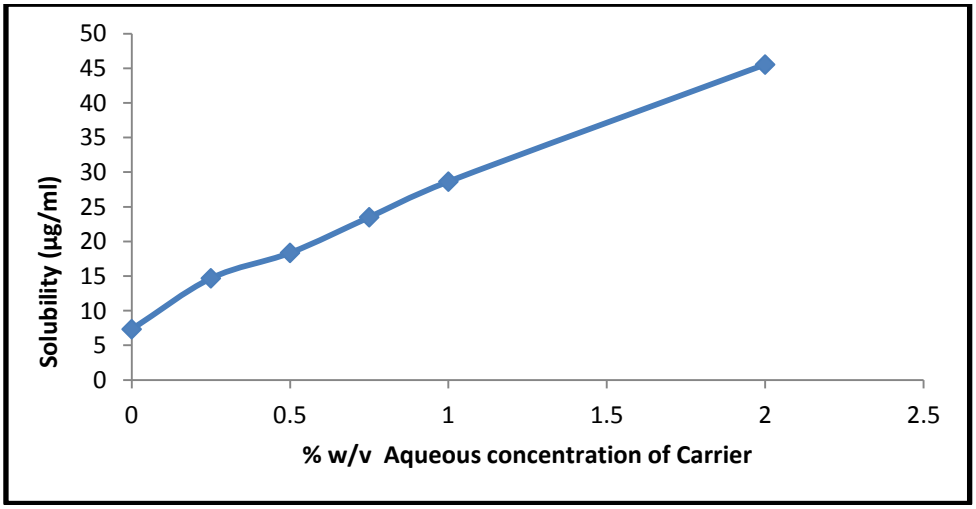

Fig. 2. Phase solubility study of ambrisentan in Soluplus®

Table 3. Solubility of physical mixtures and solid dispersions of Ambrisentan

Formulation code	Distilled Water (µg/ml)	Phosphate Buffer pH 6.8 (µg/ml)	Formulation code	Distilled Water (µg/ml)	Phosphate Buffer pH 6.8 (µg/ml)
APM1	17.61 ± 0.54	78.45 ± 0.15	ASD1	30.36 ± 1.69	114.31 ± 0.81
APM2	19.26 ± 1.43	83.64 ± 0.36	ASD2	36.61 ± 0.66	136.83 ± 0.56
APM3	22.87 ± 0.87	92.87 ± 0.87	ASD3	41.32 ± 1.63	153.20 ± 1.24
APM4	26.14 ± 0.52	102.5 ± 0.14	ASD4	46.81 ± 0.81	176.74 ± 0.69
APM5	29.58 ± 1.13	113.31 ± 0.22	ASD5	52.67 ± 1.24	213.8 ± 1.63

Values are mean ± SD, n=3

Table 4. % Drug Content and Practical Yield of SD Formulations (ASD1 to ASD5)

Sr. No	Formulation Code	% Practical Yield	% Drug Content*
1	ASD1	90.61	97.99 ± 0.30
2	ASD2	91.56	98.21 ± 0.41
3	ASD3	92.34	98.46± 0.34
4	ASD4	92.46	98.15 ± 0.16
5	ASD5	92.52	98.70 ± 0.72

**Mean ± SD, n=3*

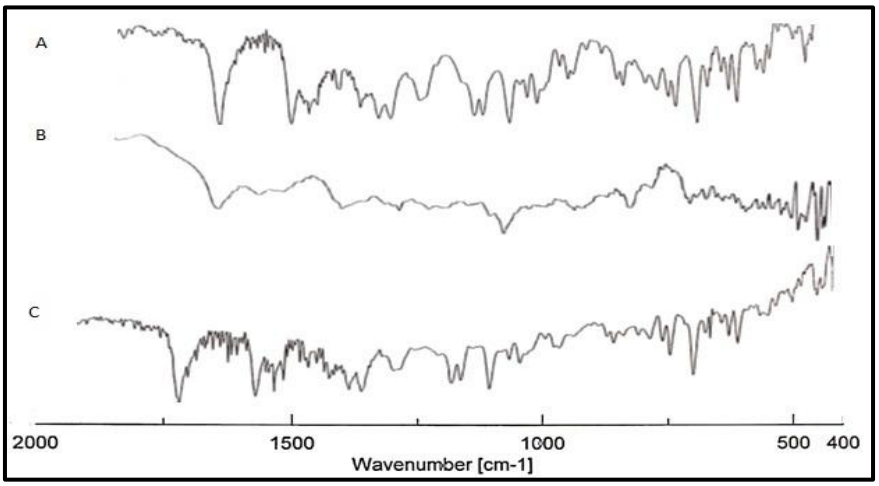

Fig. 3. FTIR Spectra (A) Ambrisentan (B) Soluplus® (C) Ambrientan Soluplus® SD

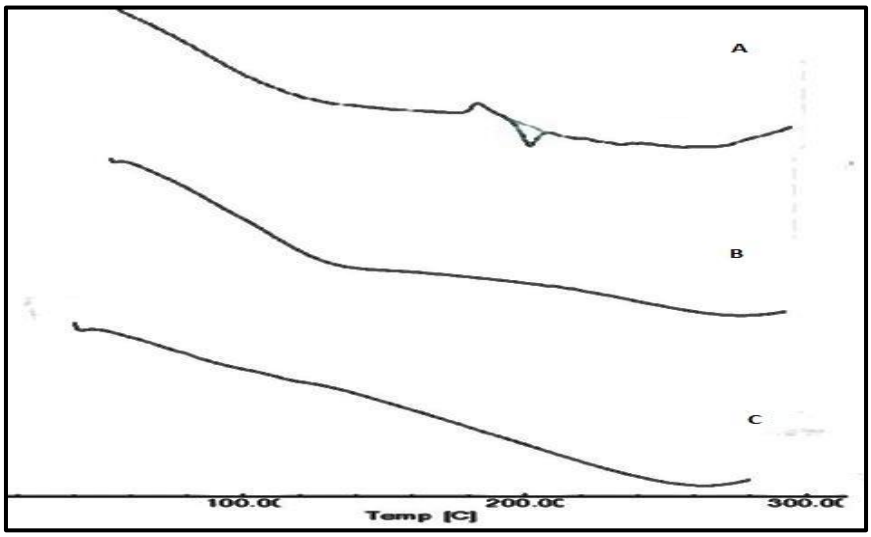

Fig. 4. DSC thermogram of A)Pure ambrisentan, B) Soluplus® and C) Ambrisenatn:Soluplus® SD (ASD5)

4.8 Powder X-Ray Diffraction

XRD patterns of ambrisentan, Soluplus® and solid dispersion of ambrisentan (ASD5) are shown in Fig. 5. The x-ray diffractograms of pure ambrisentan showed characteristic sharp high-intensity diffraction peaks at 2θ values of 12.26°, 14.09°, 14.78°, 15.48°, 17.75°, 18.39°, 18.79°, 19.43°, 20.48°, 22.77°, 24.16° and 26.77°, which indicates the highly crystalline nature of ambrisentan. XRD pattern of Soluplus® does not showed any characteristic high-intensity diffraction peaks at 2θ values, which reflected the amorphous nature of Soluplus® [30]. Solid

dispersion (ASD5) showed less and low-intense peaks compare to pure drug, indicating conversion of highly crystalline ambrisentan to less crystalline or amorphous form, which results in increased solubility and dissolution rate of drug [31].

4.9 *In vitro* Dissolution Study

In vitro dissolution study was carried out for all solid dispersion formulations and the pure ambrisentan. The study was conducted using phosphate buffers pH 6.8 as the dissolution media. The pure ambrisentan has shown very low drug release of 40.25% at the end of 60 min, indicating poor solubility. Dissolution study showed that, all SD formulation gives faster drug release as compare with pure form and it was found that as concentration of polymer increased the drug dissolution also increased. SD formulations ASD1 to ASD5 showed the drug release of 90.44%, 91.69%, 93.62%, 96.26% and 98.87% respectively at the end of 60 min. All SD formulations showed more than 50% drug release in 10 min showing its significant improvement in drug dissolution. Optimized SD formulation (ASD5) containing drug and Soluplus® in 1:5 ratio showed highest drug release. The drug release profile of all SD formulation and pure ambrisentan are shown in Fig. 6.

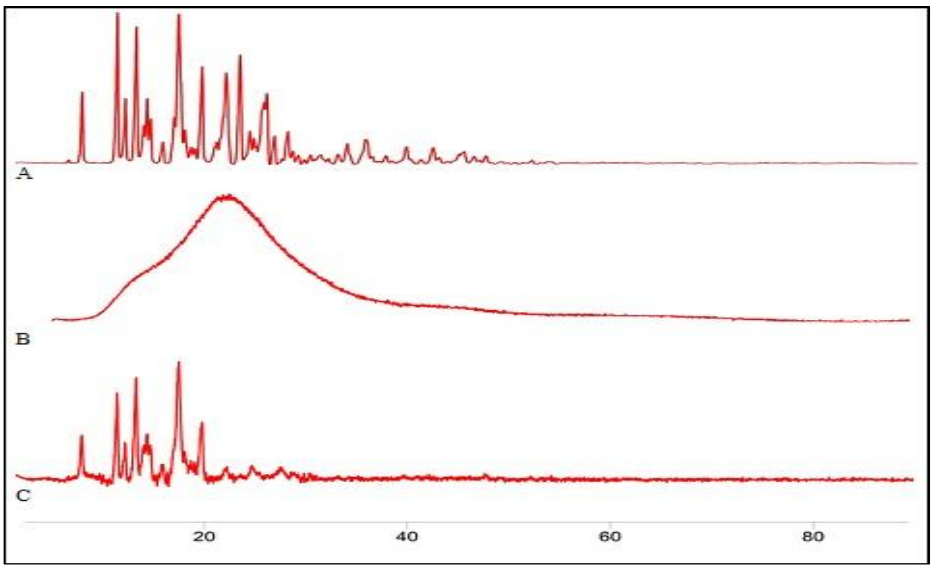

Fig. 5. XRD spectra A) Ambrisentan B) Soluplus® C) Ambrisentan Soluplus® SD (ASD5)

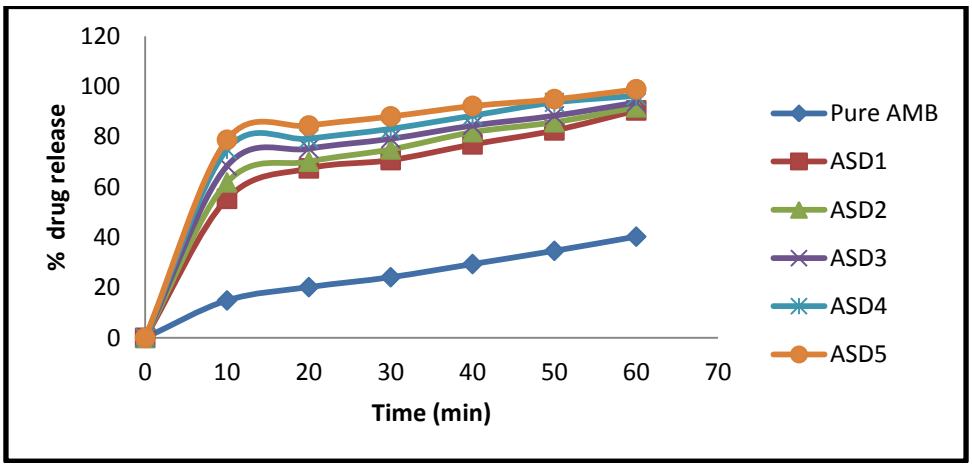

Fig. 6. In-vitro drug dissolution of pure ambrisentan and its SDs in 6.8 pH phosphate buffer

5. CONCLUSION

In this investigation, an attempt was made to improve the aqueous solubility and dissolution rate of drug using novel amphiphilic graft co-polymer (Soluplus®) carrier. Results of prepared SD formulation suggest that solubility of ambrisentan was improved manyfold. DSC and XRD study demonstrate the that crystallinity of drug was reduce and amorphous state of drug was formed. From this study, it was concluded that the solid dispersion prepared using Soluplus® is an effective way of enhancement of solubility, dissolution and bioavailability of poorly water soluble drugs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONCENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Naseem A, Olliff CJ, Martini LG, Lloyd AW, Effects of plasma irradiation on the wettability and dissolution of compacts of griseofluvin, Int J Pharm, 269(2):443-50.
2. Singh G, Kaur I, Gupta D, Sharma S, Enhancement of the Solubility of Poorly Water Soluble Drugs through Solid Dispersion: A Comprehensive Review, Indian J Pharm Sci. 2017;79(5);674-687.
3. Aulton ME, Pharmaceutics: The science of dosage form design, 1st ed, London: Churchill Livingstone; 1996.
4. Vo CL, Park C, Lee B. “Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs”, European Journal of Pharmaceutics and Biopharmaceutics. 2013;8(3)(Parte B):799-813.
5. Sareen S, Mathew G, Joseph L. “Improvement in solubility of poor water-soluble drugs by solid dispersion”, International Journal of Pharmaceutical Investigation. 2012;2(1):12-17.
6. Ghareeb MM, Abdulrasool AA, Hussein AA, Noordin MI, Kneading Technique for Preparation of Binary Solid Dispersion of Meloxicam with Poloxamer 188, AAPS PharmSciTech. 2009;10(4):1206-12015.
7. Raymond C. Rowe, Paul J. Sheskey, Marian E. Quinn. Handbook of Pharmaceutical Excipients. 6th edition, Pharmaceutical Press; 557-560
8. Tsinman O, Tsinman K, Ali S, Soluplus®: An Understanding of Supersaturation From Amorphous Solid Dispersions, Drug Development & Delivery January. 2015;15 (1):20-26.
9. European medicine agency; Evaluation of medicines for human use, Assesment reportfor volibris Doc. Ref.: EMEA/ 123999/2008. P.N.1-44.
10. Barst RJ. A review of pulmonary arterial hypertension: role of ambrisentan. Vasc Health Risk Manag. 2007;3(1):11.
11. Higuchi T, Connors KA. Phase-solubility techniques. Adv Anal Chem Instr. 1965;4: 117–212.
12. Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res Pharm Sci. 2010;5(1):49–56.
13. Maulvi FA, Dalwadi SJ, Thakkar VT. Improvement of dissolution rate of aceclofenac by solid dispersion technique, Powder Technol. 2010;207:47–54.
14. Modi A, Tayade P, Enhancement of Dissolution Profile by solid dispersion (Kneading) Technique. AAPS Pharm Sci Tech. 2006;7(3):68.
15. Iqbal A, Hossain MS, Shamim MA, Islam M, Siddique MAT. Formulation, in vitro

evaluation and characterization of atorvastatin solid dispersion. Tropical Journal of Pharmaceutical Research. 2020;19 (6):1131-1138.
16. Sathali AAH, Jayalakshmi J. Enhancement of solubility and dissolution rate of olmesartan medoxomil by solid dispersion technique. J. Curr. Chem. Pharm. Sc. 2013;3(2):123-134.
17. Shamma RN, Basha M. Soluplus®: A novel polymeric solubilizer for optimization of Carvedilol solid dispersions: Formulation design and effect of method of preparation. Powder Technology. 2013;237:406–414.
18. Yunoos M, Lavanya NSL, Sravani G, Madhuri Rao P, Krishna CH. Development of a Validated UV Spectrophotometric Method for the Estimation of Ambrisentan in Pure and Marketed Formulations. Sch. Acad. J. Pharm. 2014;3(6):427-431.
19. Yang M, Wang P, Huang CY, Ku MS, Liu H, Gogos C. Solid dispersion of acetaminophen and poly (ethylene oxide) prepared by hot-melt mixing. Int J Pharm. 2010;395(1-2):53-61.
20. Jain P, Yalkowsky S H; Solubilization of poorly soluble compounds using 2 pyrrolidone, Int J of Pharmaceutics. 2007;35:223-227.
21. Varma MM, Razia Begum SK. Formulation, Physicochemical Evaluation and Dissolution Studies of Carbamazepine solid dispersions. International Journal of Pharmaceutical Sciences. 2012;5(3):1790-1807.
22. Avachat A, Raut V. Solubility and dissolution enhancement of Nebivolol hydrochloride using hydrophilic carriers. Asian Journal of Pharmaceutical Sciences. 2012;7(5):337-345.
23. Maulvi FA, Dalwadi SJ, Thakkar VT, Soni TG, Gohel MC, Gandhi TR. Improvement of dissolution rate of aceclofenac by solid dispersion technique. Powder Technol. 2014;207:47–54.
24. Yadav PS, Kumar V, Singh UP, Bhat HR, Mazumder B. Physicochemical characterization and in vitro dissolution studies of solid dispersions of ketoprofen with PVP K30 and D-mannitol. Saudi Pharm J. 2013;21(1):77–84.
25. S. Biswal S, Sahoo J, Murthy PN, Giradkar RP, Avari JG. Enhancement of Dissolution Rate of Gliclazide Using Solid Dispersions with Polyethylene Glycol 6000. AAPS PharmSciTech. 2008;9(2):563–570.
26. Daravath B., Tadikonda RR, Vemula SK. Formulation and pharmacokinetics of gelucire solid dispersions of flurbiprofen. Drug Dev Ind Pharm, Early Online: 1-9.
27. Kumar BS, Saraswathi R, Dhanaraj SA. Solid-state characterization studies and effect of PEG 20000 and P90G on particle size reduction and stability of complexed glimepiride nanocrystals. J Young Pharm. 2013;5(3):83-89.
28. Mehanna MM, Motawaa AM, Samaha MW. In sight into tadalafil-block copolymerbinary solid dispersion: Mechanistic investigation of dissolution enhancement. International Journal of Pharmaceutics. 2010;402(1-2):78-88.
29. Ha ES, Baek I, Cho W, Hwang SJ, Kim MS, Preparation and Evaluation of Solid Dispersion of Atorvastatin Calcium with Soluplus® by Spray Drying Technique, Chem. Pharm. Bull. 2014;62(6):545–551.
30. Zhang Y, Liu Y, Luo Y, Yao Q, Zhong Y, Tian B, Tang X. Extruded Soluplus® /SIM as an oral delivery system: characterization, interactions, in vitro and in vivo evaluations. Drug Delivery. 1902-1911;23:6,
31. Babu GVMM, Prasad CDS, Murthy KVR. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water soluble drug nimodipine. Int. J. Pharm. 2002;234:1-17.

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