FORMULATION AND INVITRO CHARACTERIZATION OF BOSENTAN SOLID DISPERSION BY SOLID SOLVENT EVAPORATION TECHNIQUE

G Haris Chandra naik*,M V Sudha rani
Sri Krishnadevaraya university college of pharamaceutical sciences
SK University,Anantapuramu
Harischandra359@gmail.com , mvsudharanireddy@gmail.com

ABSTRACT:
Bosentan is a dual endothelin receptor antagonist used to treat pulmonary arterial hypertension. It is an BCS class-II drug having 5 hours half-life.. Solid dispersions of Bosentan were prepared with different carriers in different ratios of drug and carrier(1:1,1:2and1:3)By using Mannirtol, Cross Povodine, and Sodium Starch Glycolate .Results of prepared solid dispersions of Bosentan by solvent evaporation method were discussed which includes solubility, melting point determination, drug content uniformity,entrapment efficiency and invitro dissolutionstudies.Characterization in solid state was done by various analytical techniques such as FT-IRstudies.Finally by comparing all the formulations, formulation (F3) containing Bosentan+ Crosspovidone(1:3) shows better results by solvent evaporation method at the end of 60 min with maximum drug release of 96.74, hence it was selected as the best formulation. The optimized formulation follows First order release kinetics.

Keywords: Bosentan, Crosspovidone, Manitol, SSG & FTIR.

INTRODUCTION:

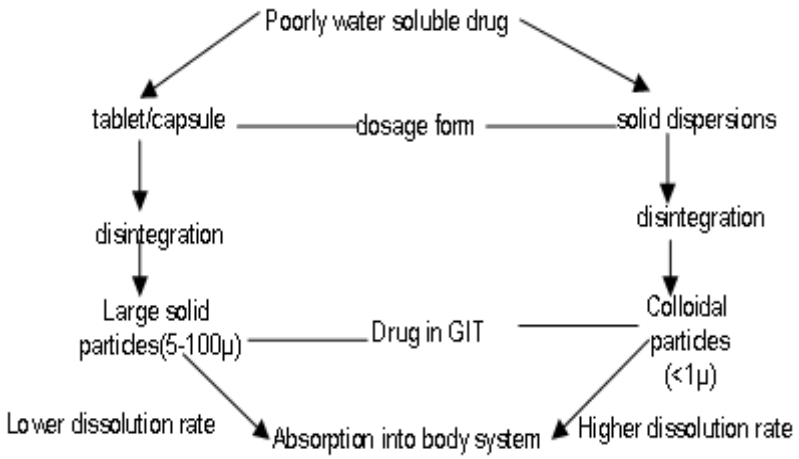
Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.

The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases 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 immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal. The eutectic mixture contained 52 per cent w/w of sulfathiazole and 48 per cent w/w of urea. The possibility of using solid solution approach in which a drug is molecularly dispersed in soluble carrier was subsequently introduced.

A solid dispersion technique has been used by various researchers who have reported encouraging results where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980)[1].

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the offers a variety of processing and excepient options that allow for flexibility when formulating oral delivery systems for poorly water-soluble drugs.



Schematic representation of the bioavailability enhancement of poorly Water soluble drug by solid dispersion technique

Materials and Methodology

Experimental Methods:

Preparation of Buffers

Phosphate buffer solution (pH6.8):

A 200 ml volumetric flask containing 50 ml of 0.2 M potassium dihydrogen ortho phosphate was filled with 22.4 ml of 0.2 M sodium hydroxide, and the remaining volume was filled to the mark with distilled water.

Analytical method development by U.V. Spectroscopy:

UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the U.V-Visible region are called Ultraviolet-Visible spectrophotometers.

In qualitative analysis, organic compounds can be identified by use of spectrophotometer, if any recorded data is available, and quantitative spectrophotometric analysis is used to ascertain the quantity of molecular species absorbing the radiation. Spectrophotometric technique is simple, rapid, moderately specific and applicable to small quantities of compounds. The fundamental law that governs the quantitative spectrophotometric analysis is the Beer -Lambert law.

Beer's law: It states that the intensity of a beam of parallel monochromatic radiation decreases exponentially with the number of absorbing molecules. In other words, absorbance is proportional to the concentration.

Lambert's law: It states that the intensity of a beam of parallel monochromatic radiation decreases exponentially as it passes through a medium of homogeneous thickness. A combination of these two laws yields the Beer-Lambert law.

REGION	**WAVELENGTH**
Far (or vacuum)ultraviolet	10-200 nm
Near ultraviolet	200-400 nm
Visible	400-750 nm
Near infrared	0.75- 2.2 μm
Mid infrared	2.5-50 μm
Far infrared	50-1000 μm

Beer-Lambert law: When beam of light is passed through a transparent cell containing a solution of an absorbing substance, reduction of the intensity of light may occur. Mathematically, Beer Lambert law is expressed

as A=a b c

Where, A=absorbance or optical density

a=absorptivity or extinction coefficient

b=path length of radiation through sample (cm)

c=concentration of solute in solution.

Both b and a are constant so a is directly proportional to the concentration c

When c is in gm/100 ml, then the constant is called A (1%, 1 cm)

$$A = A\frac{1\%}{1cm}bc$$

Quantification of medicinal substance using spectrophotometer may carried out by preparing solution in transparent solvent and measuring it's absorbance at suitable wavelength. The wavelength normally selected is wavelength of maximum absorption (λmax), where small error in setting the wavelength scale has little effect on measured absorbance. Ideally, concentration should be adjusted to give an absorbance of approximately 0.9, around which the accuracy and precision of the measurements are optimal.

The assay of single component sample, which contains other absorbing substances, is then calculated from the measured absorbance by using one of three principal procedures. They are, of standard absorptivity value, calibration graph and single or double point standardization. In standard absorptive value method, the use of standard A (1%, 1 cm) or E values are used in order to determine its absorptivity. It is advantageous in situations where it is difficult or expensive to obtain a sample of the reference substance. In calibration graph method, the absorbances of a number of standard solutions of the reference substance at concentrations encompassing the sample concentrations are measured and a calibration graph is constructed. The concentration of the analyte in the sample solution is read from the graph as the concentration corresponding to the absorbance of the solution. The single point standardization procedure involves the measurement of the absorbance of a sample solution and of a standard solution of the reference substance. The concentration of the substances in the sample is calculated from the proportional relationship that exists between absorbance and concentration

Scanning of λ_{max} of Bosentan:

Making Stock Solution: Bosentan 10 milligrames was taken in a 10 ml volumetric flask. The medication was added and well mixed with 2 cc of ethanol. The solution was adjusted to the proper concentration of 1000 g/ml using buffer with a pH of 6.8. From the above solution, 1 ml is diluted to 10 ml with a 6.8 pH buffer to produce a concentration of 100 g/ml. Take 1 ml of the aforementioned solution, dilute it to 10 ml with a 6.8 pH buffer to get 10 g/ml of concentration. The produced solution, which was a 10 g/ml concentration, was scanned for maximum between 200 and 400 nm using a UV/Visible spectrophotometer.

Calibration curve of Bosentan in 6.8pH buffer:

Preparation of stock solution:

10mg of Bosentan was taken in a10ml volumetric flask.To The solution was made up to the mark with 6.8pH buffer to give 1000 µg /ml concentration. From this solution1mlisdilutedto10mlwith,6.8pH buffer to give 100 µg /ml concentration. From the above stock solution subsequent dilutions containing 2 to 12 µg/ml solutions were prepared.

The absorbance of each test solution was measured at λ_{max} i.e 270 nm of Bosentan in UV/Visible spectroscopy against blank.

PREPARATION OF SOLID DISPERSIONS OF BOSENTAN:[29-32]

There are several carriers,which have been reported for the preparation of solid dispersions by using Mannitol, Cross povidone and SSG various methods of preparation.

a. Solvent evaporation

The drug and carriers were combined in 1:1, 1:2, and 1:3 ratios in ethanol for the solvent evaporation technique. Solvent was eliminated through evaporation at a low pressure. The bulk was ground up and sent through sieve #60. The finished object was now assembled.

Formulation code	Drug : Polymer ratio (Bosentan:Cross povidone)
F1	1:1
F2	1:2
F3	**1:3**

Formulation code	Drug : polymer ratio (Bosentan:Mannitol)
F4	1:1
F5	1:2
F6	1:3

Formulation code	Drug : Polymer ratio (Bosentan:SSG)
F7	1:1
F8	1:2
F9	1:3

Evaluation of Solid Dispersions:[25-31]

Prepared polymer drug conjugates were evaluated by

- Estimation of drug content
- Entrapment efficacy
- *In- vitro* dissolution studies
- In vitro Release kinetics

1.Estimation of Drug Content:

A quantity that was precisely measured and transferred to a 100 ml volumetric flask was equal to 5 mg of the medication. After adding a 6.8 pH buffer and shaking the volume for 10 minutes, the drug's total solubility was checked. After that, the remedy was filtered. By dissolving 5 mg of the standard medication in a 6.8 pH buffer, the same concentration of the standard solution was created. Bose's in UV-Visible spectrophotometer was used to detect absorbance at 270 nm

for both the sample and standard solutions.

2)Entrapment efficacy:

Entrapment efficiency of the solid dispersions was an important characteristic to assess the quantity of material entrapped inside solid dispersions before the study of behaviour of this entrapped drug in physical and biological systems, since the effects observed experimentally are usually dose related. Solid dispersions formulation of a drug can only be developed if the encapsulation efficiency of therapeutic doses can be delivered with a reasonable amount of drug, since the lipids in higher doses may be toxic and also result in non-linear (saturable) pharmacokinetics of formulation. An optimized loading procedure would achieve trapping efficiencies of 90% and more. This obviates the need for removal of non entrapped material because loading doses of 10% or less of free drug can usually be tolerated. Procedures such as dialysis and passage through exclusion column, for removal of non entrapped material are often time consuming, tedious, costly and recovery of non entrapped material is usually difficult.

Entrapment efficiency was calculated by following formula:

%Entrapment efficiency= Drug content *100/Drug added in each formulation

***3)In vitro* dissolution study**:

The generated solid dispersions were put in a capsule with 5 mg of bosentan weight equivalent and were then subjected to in vitro disintegration. USP type 2 paddle methods were used in the dissolution test (apparatus II). 6.8 pH buffer was employed as the dissolution media, and the dissolution medium was maintained at 37 0.5 o C. The stirring speed was 50 rpm. 5 ml samples were taken out at regular intervals, filtered, and replaced with 5 ml of fresh dissolution medium. Dilutions were made as needed, and the samples were then tested for the presence of bosentan at 270 nm using a UV-visible spectrophotometer.

4)KINETICS OF DRUG RELEASE:

The mechanism of drugrelease for the Bosentan solid dispersions was determined using zero order and first order.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

- **Zero Order Kinetic**

It describes the system in which the drug release rate is independent of its concentration.

$$Qt = Qo + Ko\ t$$

Where,

Qt= Amount of drug dissolved in time t

Qo = Initial amount of drug in the solution, which is often zero and

Ko = zero order release constant.

If the zero order drug release kinetic is obeyed, then a plot of Qt versus twill give a straight line with a slope of Ko and an intercept at zero.

- **First Order Kinetic**

It describes the drug release from the systems in which the release rate is concentration dependent.

$$\text{Log } Qt = \log Qo + kt/ 2.303$$

Where,

Qt = amount of drug released in time t.

Qo = initial amount of drug in the solution k = first order release constant If the first order drug release kinetic is obeyed, then a plot of log (Qo- Qt)versus twill be straight line with a slope of kt/ 2.303and an intercept at t=0 of log Qo.

RESULTS & DISCUSSION.

PRCORMULATION STUDIES

Solubility: Solubility of was carried out at 25^0C using 0.1 N HCL, 6.8 phosphate buffer, 7.4 pH buffer , methanol and ethanol.

Table:Solubility studies data of Bosentan

MEDIUM	SOLUBILITY (mg/ml)
0.1 N HCL	0.628
6.8 pH buffer	0.972
7.4 pH buffer	0.706
Methanol	1.014
Ethanol	1.258

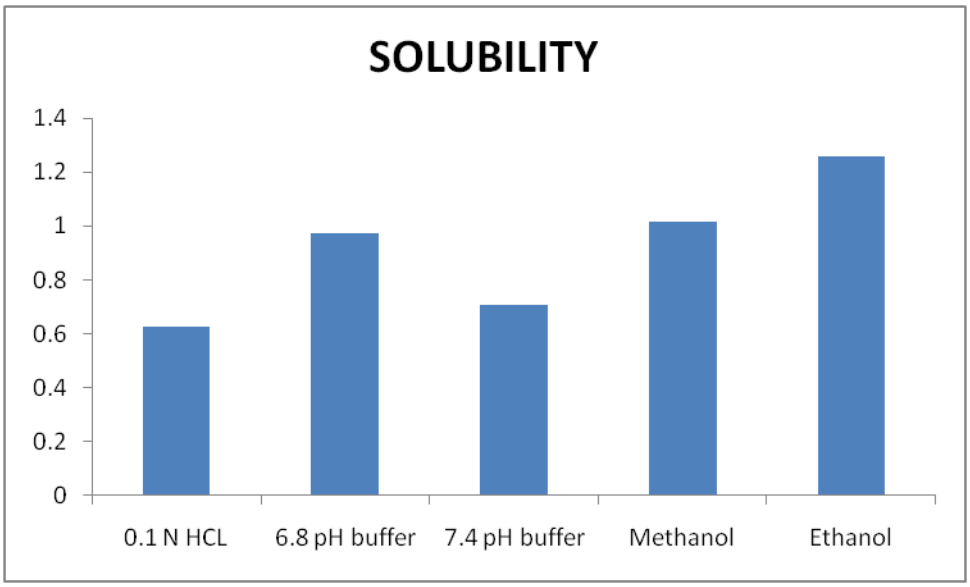


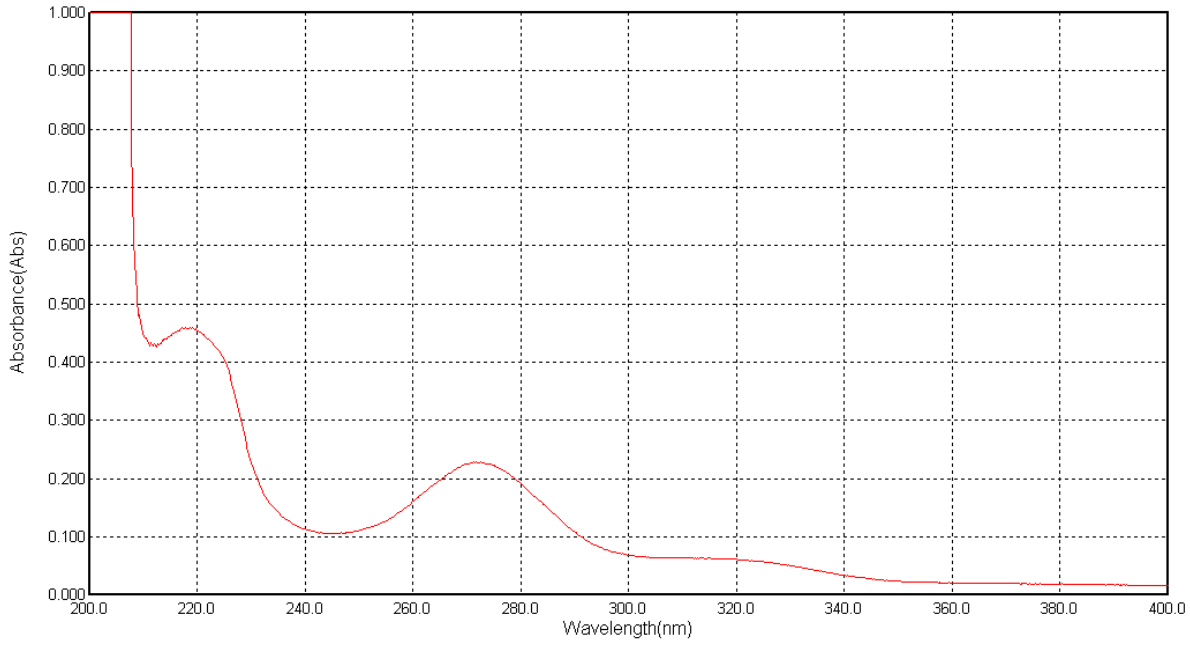
Fig: Graphical representation of BosentanSolubility studies

Discussion:

From the above conducted solubility studies in various buffers we can say that 6.8 pH buffer solution has more solubility when compared to other buffer solutions.

Analyticalmethod development by U.V. Spectroscopy:

Uv Scan Spectrum of Bosentan:



Discussion: Bosentan at 10µg/ml was found to be 270nm.

Calibration curve of Bosentan in 6.8pH buffer:

Concentration (µg/ml)	Absorbance
0	0
2	0.161
4	0.32
6	0.475
8	0.635
10	0.796
12	0.946

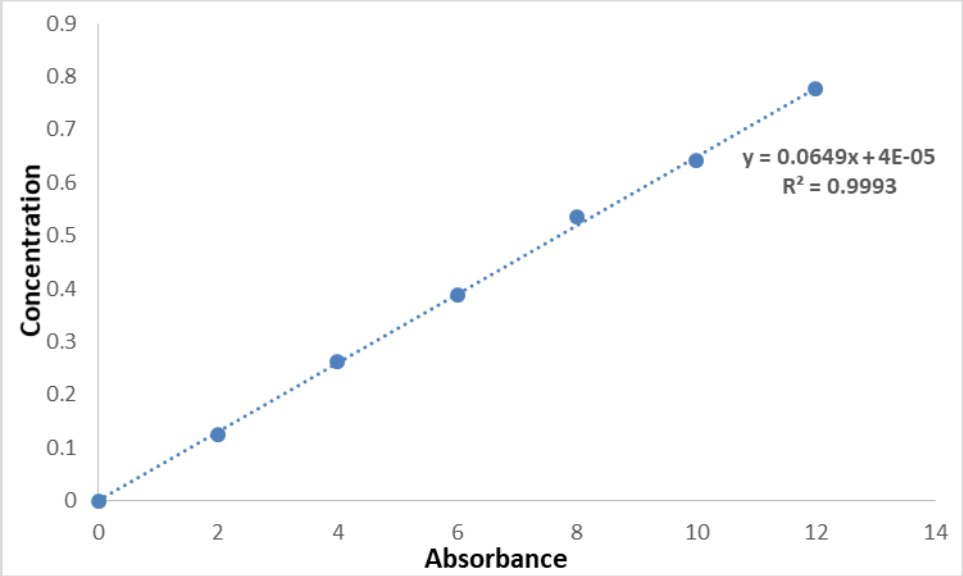


Fig: Calibration curve of Bosentan in 6.8pH buffer

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

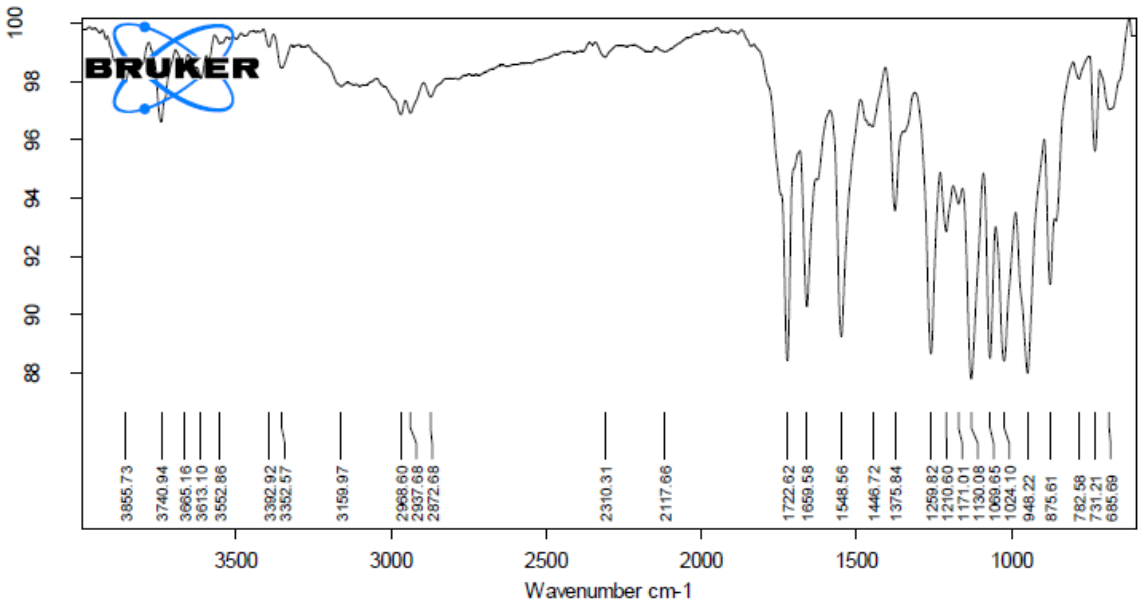


Fig: IR spectrum of pure Bosentan

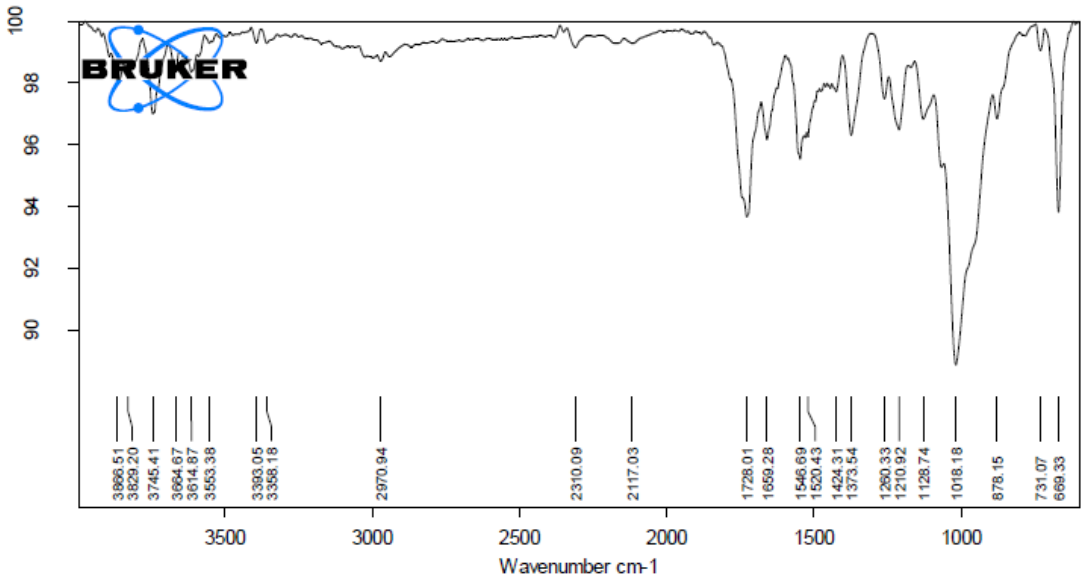


Fig: IR spectrum of BosentanOptimised Formulation

Discussion: From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Bosentan) and optimized formulation (Bosentan: excipients) which indicates there are no physical changes.

Percentage yield of solid dispersions

Table: Percentage yield of solid dispersions

Formulation code	Percentage yield
F1	90.64
F2	94.43
F3	**96.12**
F4	94.12
F5	92.25
F6	94.36
F7	96.64
F8	92.67
F9	95.43

Discussion: The Percentage yieldof theformulatedsolid dispersions wasfoundto beinthe rangeof90.54- 96.64% respectively.

Entrapment efficacy: -

Entrapment efficiency of solid dispersions by solvent evaporation method

Form.code	Entrapment efficiency
F1	92.25±0.067
F2	92.64±0.071
F3	93.10±0.001
F4	94.46±0.039
F5	94.82±0.042
F6	95.68±0.050
F7	95.53±0.063
F8	95.81±0.077
F9	96.62±0.018

Discussion: The entrapment efficacy of the formulated solid dispersions by solvent evaporation method was found to be in the range of 92.25±0.067-98.86±0.067 respectively.

INVITRO DRUG RELEASE STUDIES OF SOLID DISPERSIONS:

Table:*Invitro* drug release studies for formulations (F1-F9)

Time (Min)	Percentage drug release								
	Bosentan : Crosspovidone			Bosentan :Mannitol			Bosentan : SSG		
	1:1 (F1)	1:2(F2)	1:3 (F3)	1:1 (F4)	1:2 (F5)	1:3(F6)	1:1(F7)	1:2(F8)	1:3(F9)
0	0	0	**0**	0	0	0	0	0	0
5	38.24	45.75	**57.78**	31.35	41.24	28.71	44.35	35.26	42.66
10	54.75	53.12	**64.35**	44.74	55.75	34.92	50.69	47.53	57.67
15	60.35	67.65	**75.75**	50.95	62.98	46.61	59.78	56.71	64.97
30	68.69	72.78	**78.95**	67.32	78.62	59.22	67.25	65.52	75.53
45	76.78	88.34	**86.35**	78.75	85.35	68.46	74.35	73.78	86.82
60	88.78	95.86	**96.74**	89.86	94.78	79.22	89.78	89.48	94.94

Discussion:*In-vitro* drug release of Bosentan solid dispersions with Crosspovidonein various ratios were observed which shows at the end of 60 mins, the formulation F1 releases 88.78%, formulation F2 releases 95.86%, F3 releases96.74%, while Mannitol used as carrier showsformulation F4 releases 89.86%, formulation F5 releases 94.78%, and formulationF6 releases 79.22%, while SSG used as carrier showsformulation F7 releases 89.78%, formulation F8 releases 89.24%, and formulation F9 releases 94.94%.Among all formulation F3 formulation shows maximum drug release at the end of 60minutes so it was chosen as optimized formulation.

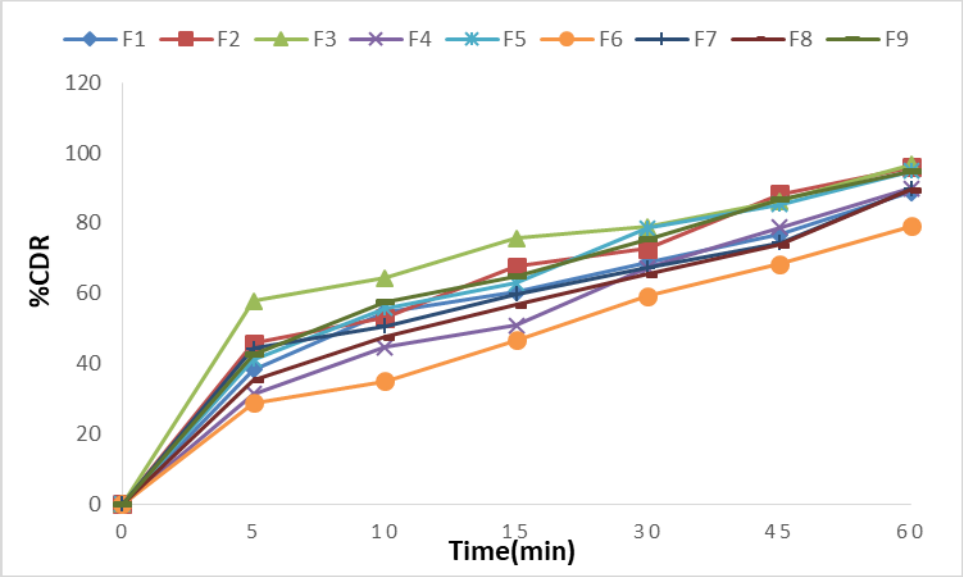


Fig: *Invitro* drug release profile for (F1-F9)

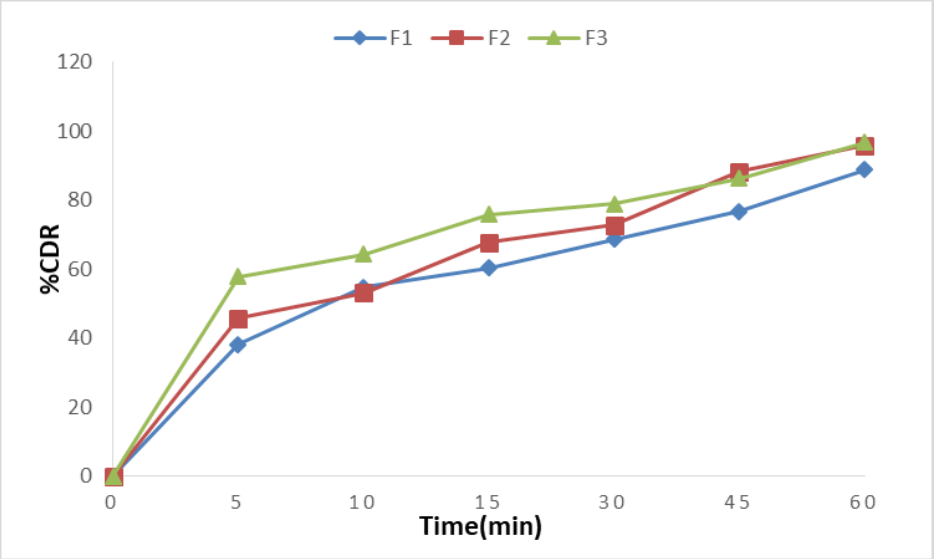


Fig: *Invitro* drug release profile for (F1-F3)

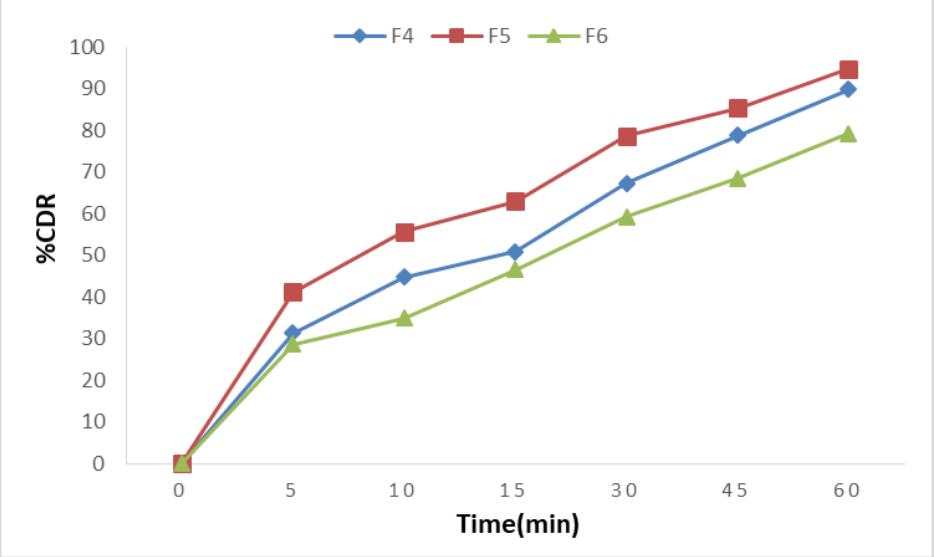


Fig: *Invitro* drug release profile for (F4-F6)

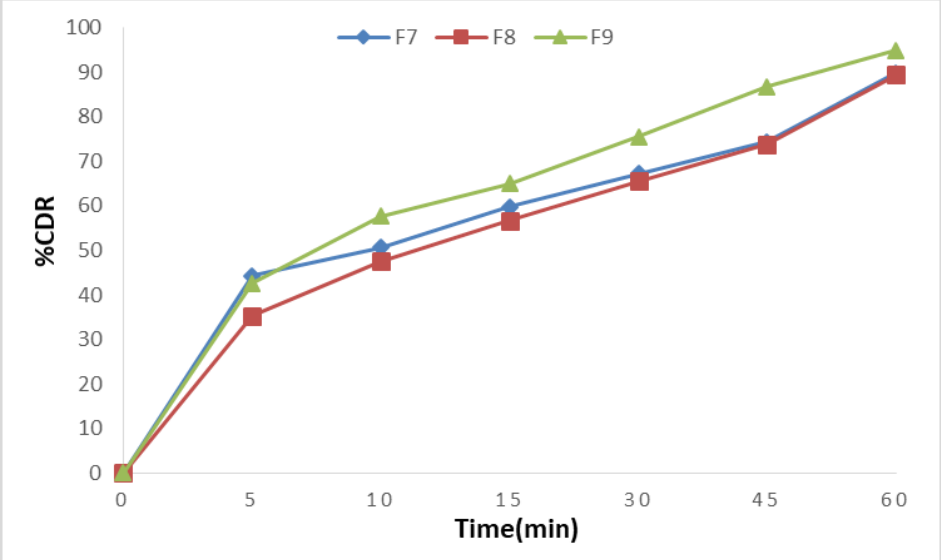


Fig: *Invitro* drug release profile for (F7-F9)

***In-vitro* drug release kinetics studies for best formulation F3:**

Zero order release kinetics studies:

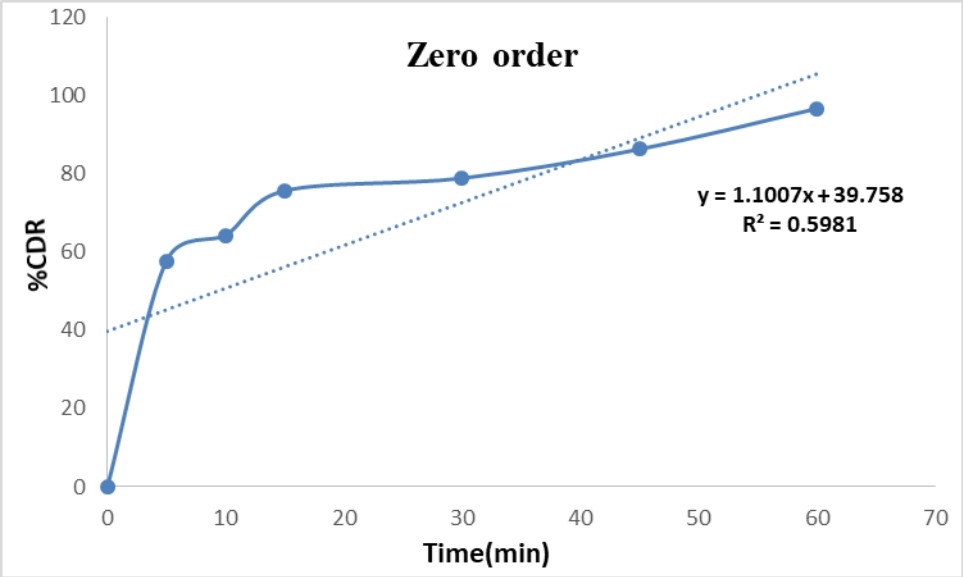


Fig: Zero order release profile for best formulation (F3)

First order release kinetics studies:

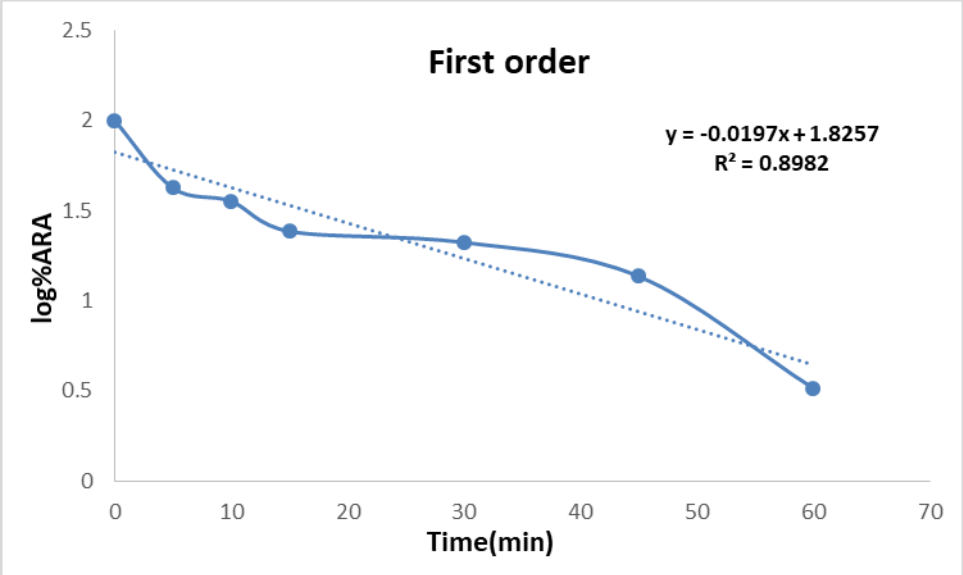


Fig: First order release profile for best formulation (F3)

DISCUSSION:

By comparing the release kinetics studies of best formulation with zero order and first order we can say that the best formulation follows first order release kinetics studies having R^2 value 0.898 were as zero order release kinetics studies having R^2 value 0.598, hence we can say that the best formulation follows first order release kinetics.

Table 7.8 : order of kinetic values of FormulationF9:

Order of kinetics	Zero Order	First Order
Regression values	0.598	0.898

Discussion:

The drug release from the tablets was explained by using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation F9 follows First order kinetics.

8. SUMMARY AND CONCLUSSION

SUMMARY:

The ability of a pharmaceutical treatment intended for oral administration to treat a condition depends on how well it is absorbed by the digestive system. It is generally known that the rate-limiting stage in the gastro intestinal absorption of a medicine from a solid dose form is frequently disintegration. Pharmaceuticals that are poorly soluble have been shown to be unpredictable and slow to be absorbed when compared to drugs that are more soluble. As a result, these medications pose significant obstacles to the creation of bioavailable dosage method can considerably improve the bosentan's capacity to dissolve.Bosentan is a dual endothelin receptor antagonistand used to treat pulmonary hypertension by blocking the action of endothelin molecules that would otherwise promote narrowing of the blood vessels and lead to high blood pressure..

Therefore, an effective formulation that can increase the solubility and dissolution rate of this model medicine may be useful. In order to increase the solubility and, consequently, the dissolving rate, efficiency, and bioavailability of the weakly soluble medication Bosentan, investigations were conducted using the solid-dispersion technique using mannitol, Crosspovidone, and SSG.

The introduction section provided a succinct explanation of solid dispersions. In addition, in the chapter's introduction, numerous methods for improving solubility, particularly solid dispersion technology, were covered. The aim and objective was also discussed.

Bosentan's entire pharmacological profile and excipient profiles included information on their use, contraindications, and side effects.

literature review of prior preparation and research on solid dispersions using a variety of medications and techniques.

In-depth explanations of the methodology, materials used, and experimental techniques used in this study were provided. assessment parameters work. Bosentan solid dispersions were created using several carriers in varying drug and carrier ratios (1:1, 1:2 and1:3).

Results of Bosentan solid dispersions made using the solvent evaporation method, including solubility, melting point estimation, drug content homogeneity, entrapment efficiency, and in

vitro dissolution experiments, were discussed. Numerous analytical methods, including FT-IR studies, were used for solid-state characterization.

The formulation **(F3)** combining bosentan+crospovidone (1:3) showed better results by solvent evaporation method at the end of 60 min with drug release of 96.74%, hence it was chosen as the best formulation after comparing all the formulations (F1-F9).

CONCLUSION:

By using the solvent evaporation method, solid dispersions were prepared using crosspovidone and mannitol. By examining the Bosentan with Crosspovidone dissolution studies (1:3). indicates improved medication release. Additionally, all of the created solid dispersions underwent evaluation, with the results detailed in the preceding information.

The following conclusions were drawn from the present investigations.

- From the Solubility studies in various buffers we can say that 6.8 pH buffer has more solubility when compared to other buffer solutions for Bosentan.
- Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes.
- All the formulations of Bosentan were prepared solvent evaporation method
- All the prepared solid dispersions were evaluated for drug content and entrapment efficiency.
- The invitro dissolution studies of Bosentan was performed.

8. REFERENCES

- Noyes, A.A., and Whitney W.R., (1897). The rate of solution of solid substances in their own solutions, *J. Am. Chem. Soc*., 19: 930-934.
- Van Drooge, D.J. et al. (2006). Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. *Int. J. Pharm,*. 310: 220–229.
- Galia, E., Nicolaides, E., HoÈrter, D., LoÈbenberg, R., Reppas, C., and Dressman, J.B., (1998). Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. *Pharm. Res*., 15: 698-705.
- Sengodan guruswamy, V., and Mishra, D.N., 2006. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. *The Pharmaceutic.Soc. Jap.,* 126(2): 93-97.
- Hancock, B.C., and Zogra, G., (1997). Characteristics and significance of the amorphous state in pharmaceutical systems (review). *J. Pharm.Sci.*, 86: 1-12.
- Hoerter, D., and Dressman, J.B., (1997). Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract (review). *Adv.Drug Delivery Rev.*, 25-14.
- Loftsson, T., and Brewster, M.E., (1996). Pharmaceutical application of cyclodextrins. 1. Drug solubilisation and stabilization (review). *J.Pharm. Sci.*, 85: 1010-1025.
- Sekiguchi, K., and Obi, N., (1961). Studies on absorption of eutectic mixtures. I. A

comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem.Pharm. Bull.,* 9: 866-872.

- Taylor, L.S., and Zogra, G., (1997). Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.,* 14: 1691-1698.
- Goldberg, A.H., Gibaldi, M., and Kanig, J.L., (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II ± experimental evaluation of a eutectic mixture: urea±acetaminophen system. *J. Pharm. Sci*., 55: 482-487.
- Chiou, W.L., and Rielman, S., (1971). Pharmaceutical application of solid dispersion system. *J.Pharm.Sci.,* 60: 1281-1302.
- Goldberg, A.H., Gibaldi, M., and Kanig, J.L., (1965). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures I theoretical considerations and discussion of the literature. *J.Pharm. Sci.,* 54: 1145-1148.
- Kreuter, J., Kreuter, J., and Herzfeldt, C.D., (1999). Grundlagen der Arznei-formenlehre Galenik, 2, Springer, Frankfurt am Main. 262-274.
- Chiou, W.L., and Riegelman, S., (1969). Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.*, 58: 1505-1510.
- Vasconcelos, T.F., Sarmento, B., and Costa, P., (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug discovery today*., 12: 1069-1070.
- 6. Sekiguchi, K., and Obi, N., (1964). Studies on Absorption of Eutectic Mixture. II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. *Chem. Pharm. Bull.,* 12: 134–144
- Sekiguchi, K. and Obi, N., (1961) Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem.Pharm. Bull.,* 9: 866–872.
- Levy, G., (1963). Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. *Am. J. Pharm. Sci.,* 135: 78–92.
- Kaning, J.L., (1964). Properties of Fused Mannitol in Compressed Tablets. *J. Pharm. Sci.*, 53: 188– 192.
- Goldberg, A.H., et al. (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. IV. Chloramphenicol–urea system. *J. Pharm. Sci.,* 55: 581–583.
- Simonelli, A.P., et al. (1969). Dissolution rates of high energy polyvinylpyrrolidone (PVP)- sulfathiazole coprecipitates. *J. Pharm. Sci.*, 58:
- 538–549.
- Chiou, W.L., and Riegelman, S., (1969). Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.*, 58: 1505–1510.
- Urbanetz, N.A., (2006). Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000. *Eur. J. Pharm. Sci.*, 28: 67–76.
- Vilhelmsen, T., et al. (2005). Effect of a melt agglomeration process on agglomerates

containing solid dispersions. *Int. J. Pharm.*, 303: 132–142.

- Goldberg, A., Gibaldi, M., and Kanig, L., 1996. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II experimental evaluation of a eutectic mixture: urea-acetaminophen system, *J. Pharmaceut.Sci.,* 55: 482-487.
- Serajuddin, A., 1999. Solid dispersion technique. *J. Pharmaceut. Sci.,* 88 (10): 891-900.
- Narang, A., and Shrivastava, A., 2002. Melt extrusion solid dispersion technique. *Drug Dev. Ind. Pharm.,* 26(8): 111-115.
- Breitenbach, J., 2002. Melt extrusion: from process to drug delivery technology. *Europ. J. Pharmaceut.Biopharmaceut.,* 54: 107-117.
- Chokshi, R., and Hossein, Z., 2004. Hot Melt Extrusion Technique: A Review. *Int. J. Pharmaceut*. Res., 3: 3-16.
- Perissutti, B., Newton, J.M., Podezeck, F., and Rubessa, F., 2002. Preparation of extruded Carbamazepine and PEG 4000 as a potential rapidrelease dosage form. *Europ. J. Pharmaceut.Biopharmaceut.,* 53: 125-132.
- Vilhelmsen, T., Eliasenm, H., and Schaefer, T., 2005. Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int. J.Pharmaceut.,* 303 (1- 2): 132-142.
- Tsinontides, S.C., Rajniak, P., Hunke, W.A., and Placek, J., 2004. Freeze drying-principles and practice for successful scale-up to manufacturing. *Int.J. Pharmaceut.,* 280 (1): 1-16.
- Seo, A., and Schaefer, T., 2001. Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer. *Europ. J. Pharmaceut.Biopharmaceut.,* 52(3): 315-325.
- Ansel C. Howard, Allen V. Loyd, Popovich A. Nicholas, Pharmaceutical dosage forms and drug delivery systems, 7th edition, 2000, 248-252.
- Modi A and Pralhad T. Enhancement of dissolution profile by solid dispersion (kneading) technique. *AAPS, Pharm Sci Tech*, 2006, 129-132.
- Khadilkar M, Avari J and Gudsookar VR. Solid dispersions of Ketoprofen. *The Eastern pharmacist*, 1997, 40, 129-131.
- Kuchekar BS and Yadav AV. Studies on solid dispersion of Paracetamol. *The Eastern Pharmacist*, 1995, 38, 149.
- Patel DM, Shah RR. Studies on release profile of Piroxicam solid dispersion. *Indian Journal of Pharmaceutical Sciences*, 65, 2003, 264-266.
- Gopalrao M, Suneetha R. Improvement in dissolution of poorly soluble Naproxen. *Indian Journal of Pharmaceutical Sciences,* 67(1), 2005, 26-29.
- Soniwala MM, Patel PR. Studies on dissolution profile of Rofecoxib by formulating solid dispersions. *Indian Journal of Pharmaceutical Sciences*, 67(1), 2005, 61-65.
- Habib MJ. Pharmaceutical Solid Dispersion Technology, Washington. CRC, 2000, pp. 35-78.
- Craig DQM. The mechanisms of drug release from solid dispersions in water soluble polymers. *Int. J. Pharm*., 231(2), 2002, 131-144.

- Sethia S. Solid dispersions-revival with greater possibilities and applications in oral drug delivery. *Crit. Rev. Ther. Drug Carrier Syst*., 20(2-3), 2003, 215-247.
- 44.Tapan Panda etal, Formulation Development of Solid Dispersions of Bosentan using Gelucire 50/13 and Poloxamer 188 ,6(9):027-033,2016
- 45. Ranga Harish, Formulation and Evaluation of Bosentan Solid Dispersion,11 (1) | 75,2017.
- 46 . Ravindra Bhanudas Saudagar etal,Solubility And Dissolution Enhancement Of Bosentan
- Monohydrate By Solid Dispersion Technique,3 Issue 8, July 2016
- 47.Rahul Radke etal,Solubility and Dissolution Enhancement Bosentan by Third Generation Solid Dispersion,24,2,1333 – 1343,2020.
- 48.Koji Takeda et.al.,Surfactant-Free Solid Dispersions of Hydrophobic Drugs in an Amorphous Sugar Matrix Dried from an Organic Solvent,*Mol. Pharmaceutics*, 2017, *14* (3), pp 791–798
- 49.Kristine Opsvik Wikene et.al.,Formulation and characterization of lyophilized curcumin solid dispersions for antimicrobial photodynamic therapy (aPDT): studies on curcumin and curcuminoids LII, Drug Development and Industrial Pharmacy Volume 41, 2015 - Issue 6.
- **50.Pankaj Vijay Dangr**e et.al.,Improved Dissolution and Bioavailability of Eprosartan Mesylate Formulated as Solid Dispersions using Conventional Methods,Indian Journal of Pharmaceutical Education and Research, 2016; 50(3s):S209-S217,
- 51.Momoh et.al., Formulation And In Vitro Evaluation Of Solid Dispersions Of Methanolic Extract Of *Vernonia Amygdalina*- Peg-4000: A Wound Healing Study,World Journal of Pharmaceutical Research Volume 4, Issue 12, 468-479. Research Article ISSN 2277– 7105.
- 52.Alka Ahuja et.al., Preparation of Solid Dispersions of Poorly Soluble Drugs, The Pharmaceutical and Chemical Journal, 2016, 3(4):98-109.
- 53.Tejal Soni, Chirag Nagda, Tejal Gandhi and N.P.chotai., Development Of Discriminating Method For Dissolution Of Aceclofenac Marketed Formulations., *Dissolution Technologies*., may 2008: 31-35.
- 54. Ashok R. Patel and Vishal Y. Joshi, Evaluation of SLS: APG Mixed Surfactant Systems as Carrier for Solid Dispersion, *AAPS PharmSciTech*, 2008, 9 (2); 583-590.
- 55. Sandrien Janssens, Hestor Novoa de Armas, ward D Autry , Ann Van Schepdael , Guy Van den Mooter, Characterization Of Ternary Solid Dispersions Of Itraconazole In PEG-6000/PVPVA64 Blends., *European Journal Of Pharmaceutics And Bio-Pharmaceutics,*2008 (Article In Press).
- 56. Yongmei Xie, Ping Xie, Xin Song ,Xiaohai Tang, Hang SOng, Preparation Of Esomeprazole Zinc Solid Dispersion And Its Pharmacokinetics, *Int.J. Pharmaceutics*, 2008 (Article In Press).
- 57. H. de waard, W.L.J.Hinrichs, M.R.Vissev, C.Bologna, H.W.Frijlink., Unexpected Differences Observed In Dissolution Behaviour Of Poorly Water Soluble Drugs, tablets prepared from solid dispersions with a surfactant sodium

laulyl sulphate, physically mixed or incorporated, *Int. J. Pharmaceutics*, 2008, 349;66-73.

- 58. Sandrien Janssens, Clive Roberts, Emily F.Smith, Guy van den Mooter., Physical Stability Of Ternary Solid Dispersions Of Itraconazole Peg- 6000/Hpmc 2910 E5 Blends, *Int. J. Pharmaceutics*, 2008, 355; 100-107.
- 59. Patel V.P., Patel N.M. and Chaudhari B.G., effect of water soluble polymers on dissolution profile of glipizide cyclodextrin complex, *Indian Drugs*, 2008,45(1); 31-36.
- 60. Phuong HA Lien Trana, Huyen Thi Thanh Trana and Beom Jin Lee, modulation of micro-environmental Ph and crystallinity of ionizable telmisartan using alkalizers in solid dispersion for controlled release., *Int. J. controlled release*, 2008, 129(1);59-65.
- 61. S.T. Prajapati, M.C.Gohel, L.D.Patel, studies to enhance dissolution properties of carbamazepine., Indian, J. Pharm.Sci., 2007, 69(3);427-430.
- 62. P.Srinivasa Babu., A.Ramu, R.Sasidhar, S.Vidyadhara, Enhancement Of Dissolution Rate Of Piroxicam By Solid Dispersions Using New Carriers, *The Pharma Review*, Aug 2007, 163-166.
- 63. Asyaries., Rachmawati H., In vivo and In vitro evaluation of a solid dispersion system of gliclazide : PEG 6000. *J. Pharm. Sci. Technol.*, 2007, 61 (5), 400- 410.
- 64..KH Janardhana etal ,Development of sustained release tablets containing solid dispersions of baclofen,5(2),1112-9867, (2013).
- 65.ArunButreddy etal,Quality-by-design in hot melt extrusion based amorphous solid dispersions: An industrial perspective on product development, 158,105655,2021