ISSN: 2306-6091

International Journal of Pharmaceuticals and Health care Research (IJPHR)

IJPHR |Vol.12 | Issue 2 | Apr - June -2024

www.ijphr.com

DOI : https://doi.org/10.61096/ijphr.v12.iss2.2024.159-171

Research

Formulation And Evaluation Of Asenapine Maleate Using In Nanoparticles

M.Sowmya[1*], Nampelly Karnakar[2], P Sravanthi[3], Devara Deepthi Sree[4], Basingala Manisha[5], Shurisetti Shalini[6], Syeda Safura[7], Bohini Greeshma[8]

*[*1]Assistant Professor, Department of Pharmaceutics, Bhaskar Pharmacy College, Bhaskar Nagar,Yenkapally,Moinabad,Ranga Reddy, Hyderabad,Telangana-500075.*
[2]Assoc Professor, Department of Pharmaceutics, Bhaskar Pharmacy College, Bhaskar Nagar, Yenkapally, Moinabad, Ranga Reddy, Hyderabad, Telangana -500075.
[3]Asst Professor, Department of Pharmaceutics, Bhaskar Pharmacy College, Bhaskar Nagar, Yenkapally, Moinabad, Ranga Reddy, Hyderabad, Telangana -500075.
[4,5,6,7,8]Research Schloars, Bhaskar Pharmacy College, Bhaskar Nagar, Yenkapally, Moinabad, Ranga Reddy, Hyderabad,Telangana-500075.

*Author for Correspondence: M. Sowmya
Email:soumyamaddukuri8@gmail.com

Published on: 28 May 2024

Published by:
DrSriram Publications

Abstract

Nanoparticles of Asenapine Maleate were prepared with Eudragit RSPO and Poloxomer 188 as polymer. Drug entrapped free flowing nanoparticles of Asenapine Maleate were obtained after optimization using 32 factorial design and characterized for entrapment efficiency, particle size distribution, differential scanning calorimetry (DSC) X-ray diffraction (XRD) scanning electron microscopy (SEM) and *in vitro* studies. The effects of dependent variables drug – polymer ratio and surfactant concentration on particle size encapsulation efficiency were studied. The drug and polymer were not interacting with each other. SEM studies revealed the spherical shape of nanoparticles and in vitro release studies showed sustained drug release. Asenapine Maleate nanoparticles drug delivery system proved to be promising for schizophrenia in adults.

Keywords: Asenapine Maleate , Eudragit RSPO and Poloxomer 188 nanoparticles.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery namely spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed controlled release drug-delivery system can be a major advance towards solving these two problems. It is for this reason that the science and technology responsible for development of controlled-release pharmaceuticals has been, and continues to be the focus of a great deal of attention in both industrial and academic laboratories.

Conventional drug therapy

To gain appreciation for the value of controlled drug therapy, it is useful to review some fundamental aspects of conventional drug delivery. Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug e.g.: A solution, suspension, capsule tablet etc. can produce a drug blood level versus time profile. The term drug blood levels refer to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. Administration of a drug by either intravenous injection or an extra vascular route, e.g., orally, intramuscularly or rectally does not maintain drug blood levels within the therapeutic range for extended periods of time. The short-duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by for e.g., increasing the initial dose of an intravenous injection, toxic levels can be produced at early times. This approach obviously is undesirable and unsuitable. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in multiple dose therapy.

1. If the dosing interval is appropriate for the biological half-life of the drug, large peaks and valleys in the drug blood level may result. For e.g., drugs with short half-lives require frequent designs to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient non-compliance with the multiple-dosing regimens can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multiple dosing can produce the desired drug blood level for extended period of time. Frequently, however these problems are significant enough to make drug therapy with conventional dosage forms less desirable than controlled-release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of controlled-release drug delivery systems.

Terminology

Modified-release delivery systems may be divided conveniently into four categories:

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting.

Delayed-release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated into a single dosage form. Examples of delayed release systems include repeat-action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the systems is successful at maintaining constant drug levels in target tissue or cells, it is considered controlled-release systems.

Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissues, for receptor release, the target

are the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug-delivery systems.

Advantages of controlled release preparations

1. Decreased incidence and/ or intensity of adverse effects and toxicity.
2. Better drug utilization.
3. Controlled rate and site of release.
4. More uniform blood concentrations.
5. Improved patient compliance.
6. Reduced dosing frequency.
7. More consistent and prolonged therapeutic effect.
8. A greater selectivity of pharmacological activity.

Objectives

Control release systems include any drug delivery system that achieves slow release of drug over an extended period of time.

The objectives of oral sustained release formulations are:

1. Frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient.
4. Better control of drug absorption can be attained.

The concept of targeting

The concept of designing specified delivery system to achieve selective drug targeting has been originated from the perception of Paul Elrich, who proposed drug delivery to be as a "Magic Bullet". It was the very first report published on targeting (Paul Elrich, 1902) describing targeted drug delivery as an event where a drug-carrier complex/ conjugate delivers drug(s) exclusively to the preselected target cells in a specific manner. Gregoriadis, 1981 described drug targeting using novel drug delivery system as 'old drugs in new cloths. New drug delivery system represents a means by which drug may be continuously delivered either locally or systemically or a larger site in an effective and repeatable manner. Controlled and targeted drug delivery systems have been receiving more and more attention as new methods of drug delivery. One of the most exciting is the target-organ oriented drug delivery system. Presenting drugs into whole body is not only wasteful but also likely to lead to harmful effects that can be eliminated if the drug is delivered only to specific target organ. Targeted delivery is not restricted to any one route of administration. Oral formulations, parenterals, transdermal and pulmonary route and many other routes are available for effective drug targeting.

MATERIALS AND METHODS

Asenapine Maleate from Sura Labs, Dilsukhnagar, Hyderabad, Eudragit RSPO (mg) from Lactel, Durect corporation Birmingham Division, Poloxomer 188 fromEastman company, UK, Dichloro Methane from SRL, Span 80 from Himedia, Methanol (ml) from Himedia.

Preparations of buffer

Preparation of 0.2M Potassium Dihydrogen Orthophosphate Solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed

Preparation of pH 7.4 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 195.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Preparation of Standard Graph: 100mg of Asenapine Maleate pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL(stock solution-2 i.e. 100µg/ml). From this take 0.5, 1, 1.5, 2 and 2.5ml of solution

and make up to 10ml with 7.4 phosphate buffer to obtain 5, 10, 15, 20, and 25µg/ml of Asenapine Maleatesolution. The absorbance of the above dilutions was measured at 254 nm by using UV-Spectrophotometer taking 7.4 phosphate buffer as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2)which determined by least-square linear regression analysis.

Method of preparation of asenapine maleate nanoparticles

Solvent dispersion (Nanoprecipitation)

The nanoparticles are prepared by dissolving the drug in organic phase along with the Eudragit RSPO) polymer and added to the aqueous solution containing Poloxomer 188) which acts as an emulsifier. The solution of organic phase was added in drop wise into aqueous phase under homogenization at 11,000 rpm. The dispersion was kept under magnetic stirring for 4hrs at room temperature. The solution is kept under reduced pressure for about 2-3min. This process forms nanoparticles loaded with drug.

Table 1: Composition of the Nanoparticles

Ingredients	FORMULATION CODE								
	AM1	AM2	AM3	AM4	AM5	AM6	AM7	AM8	AM9
Asenapine Maleate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Eudragit RSPO (mg)	25	50	75	-	-	-	-	-	-
Poloxomer 188(mg)	-	-	-	25	50	75	-	-	-
Dichloro Methane(ml)	20	20	20	20	20	20	20	20	20
Span 80(ml)	10	10	10	10	10	10	10	10	10
Methanol (ml)	10	10	10	10	10	10	10	10	10

RESULTS & DISCUSSIONS

Preparation of Standard Graph

Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 254nm.

Calibration curve

Graphs ofAsenapine Maleate was taken in 7.4 Phosphate buffer

Table 2: Calibration curve data for Asenapine Maleate at 254nm

Concentrations [µg/mL]	Absorbance
0	0
5	0.107
10	0.212
15	0.319
20	0.415
25	0.523

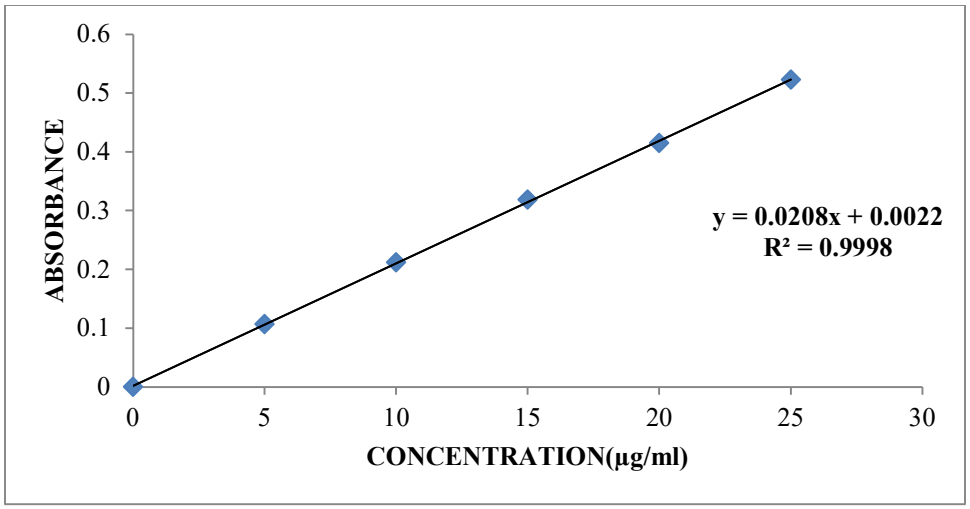

Fig 1: Standard graph of Asenapine Maleatein 7.4 Phosphate buffer

Standard graph of Asenapine Maleatewas plotted as per the procedure in experimental method and its linearity is shown in Table 8.1 and Fig 8.1. The standard graph of Asenapine Maleate showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Evaluation ofrosuvastatin loaded nanoparticles

Table 3: Evaluation of Nanoparticles

Formulation code	Mean Particle size(nm)	%Yield	Drug encapsulation efficiency	PDI	Zeta Potential(mV)
AM1	250±0.95	90.9±0.54	90.9±0.54	0.46±0.94	-38.5±0.83
AM2	224.2±0.36	89.6±0.73	89.6±0.73	0.42±0.76	35.5±0.38
AM3	207.2±0.64	95.1±0.62	95.1±0.62	0.43±0.59	-29.9±0.61
AM4	169.4±0.19	76.8±0.94	76.8±0.94	0.30±0.27	24.7±0.95
AM5	156.5±0.16	80.8±0.92	80.8±0.92	0.15±0.59	28.1±0.67
AM6	146.1±0.35	88.3±0.32	88.3±0.32	0.54±0.48	-22.3±0.71
AM7	135±0.52	65.2±0.64	65.2±0.64	0.19±0.36	-16.7±0.28
AM8	123.4±0.63	72.6±0.34	72.6±0.34	0.22±0.37	17.6±0.58
AM9	101.7±0.23	84.4±0.6	84.4±0.64	1.29±0.25	-18.6±0.59

Percentage yield of formulations AM1 to AM9 by varying drug was determined and is presented in Table. Highest drug content, Highest Entrapment efficiency observed for AM4formulation.
PDI observed in the AM4formulation i.e., 0.168 respectively. The Zeta potential range from -16.7±0.28 mV to -38.5±0.83 mV to all the formulations.

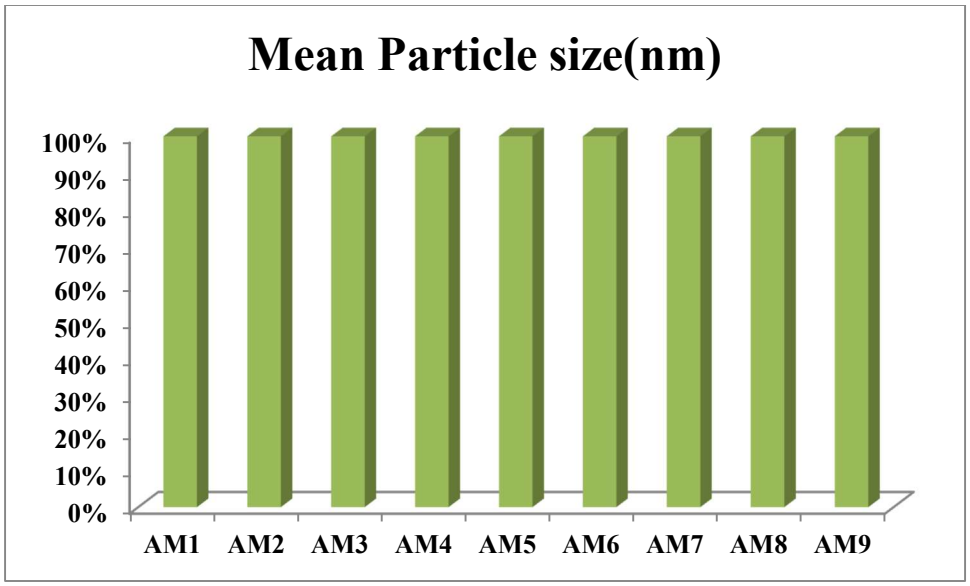

Fig 2: Mean Particle size(nm)

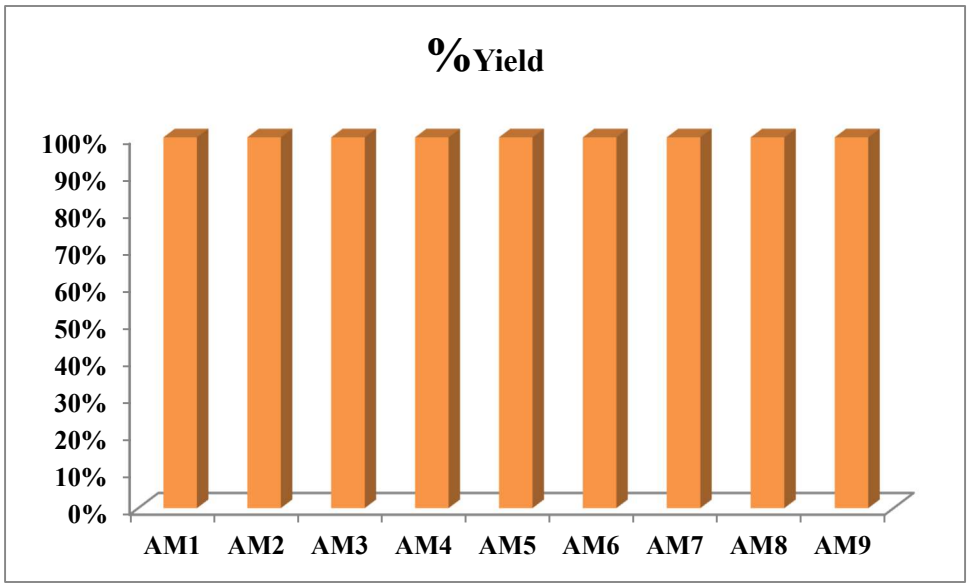

Fig 3: %Yield

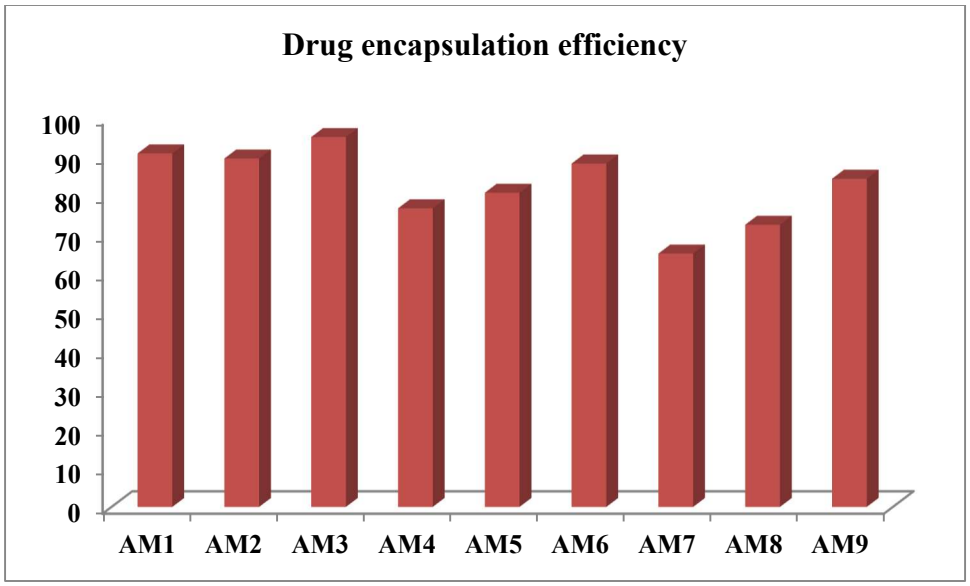

Fig 4: Drug encapsulation efficiency

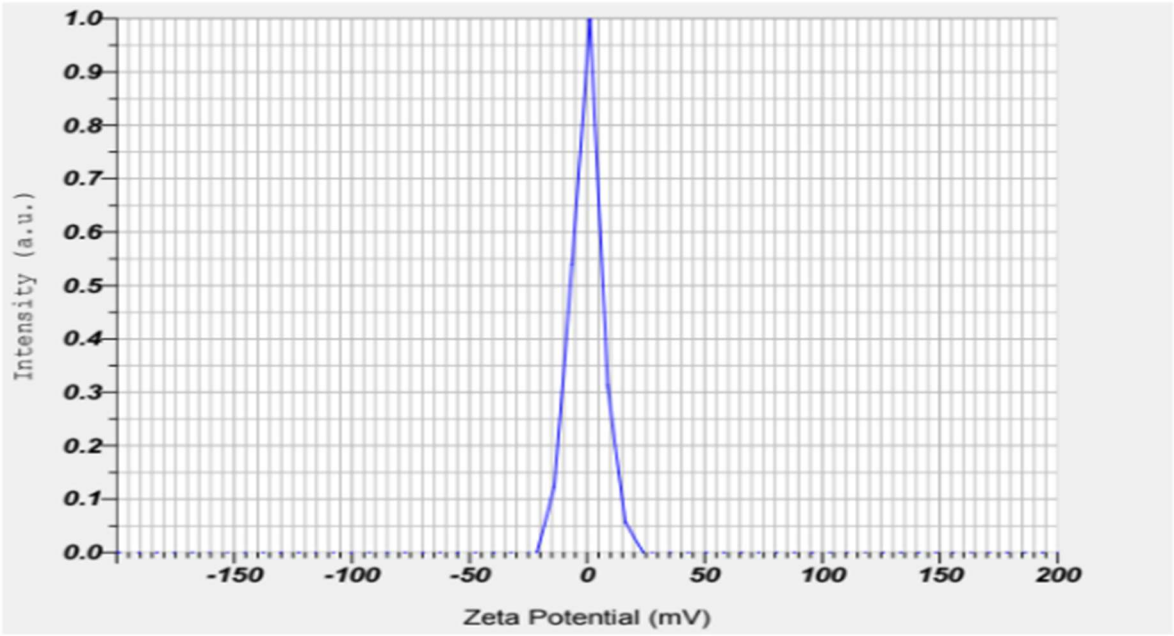

Fig 5: Zeta Potential of F4 Formulation

***In vitro* Drug release studies**

Table 4: *In vitro* Drug release studies of Asenapine Maleate AM1, AM2, AM3

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED		
	AM1	AM2	AM3
0	0	0	0
1	16.49	15.69	19.99

2	20.26	20.18	28.14
3	24.68	25.39	38.62
4	32.53	31.68	40.89
5	38.54	38.89	45.81
6	44.08	42.18	52.48
7	48.52	49.88	58.84
8	55.42	53.99	65.63
9	59.38	58.36	80.49
10	62.43	62.81	83.34
11	68.25	86.10	86.22
12	83.48	81.98	90.31

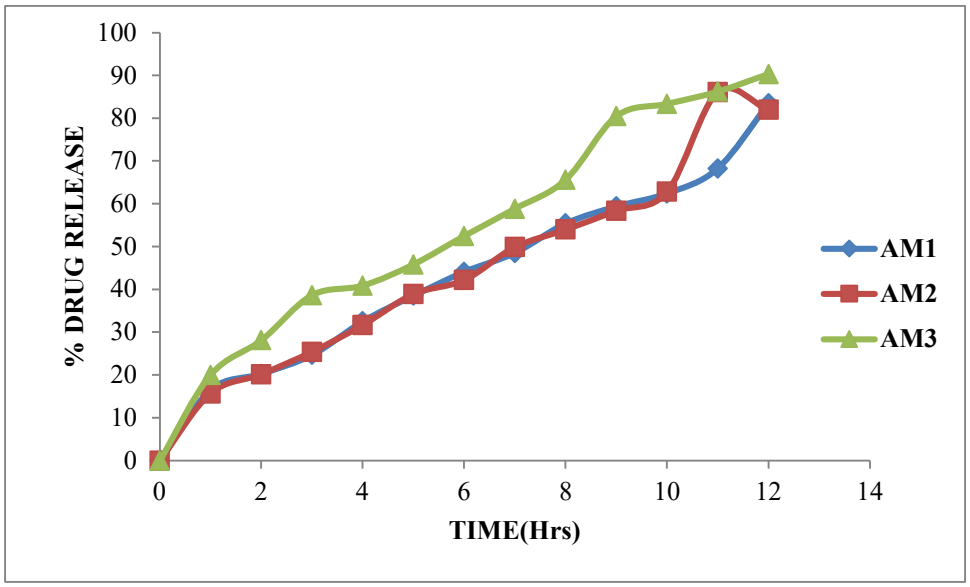

Fig 6: Dissolution study of Asenapine MaleateNanoparticles

Table 5: *In vitro* Drug release studies of Asenapine Maleate AM4, AM5, AM6

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED		
	AM4	**AM5**	**AM6**
0	0	0	0
1	22.91	19.95	22.91
2	29.49	28.64	29.49
3	38.97	38.42	38.95
4	48.63	40.99	48.63
5	52.56	45.61	52.65
6	60.19	52.88	61.91
7	69.51	58.28	68.15
8	86.85	65.83	85.58
9	80.92	80.57	80.89
10	88.61	83.14	86.16
11	91.85	86.45	90.25
12	99.32	92.43	96.37

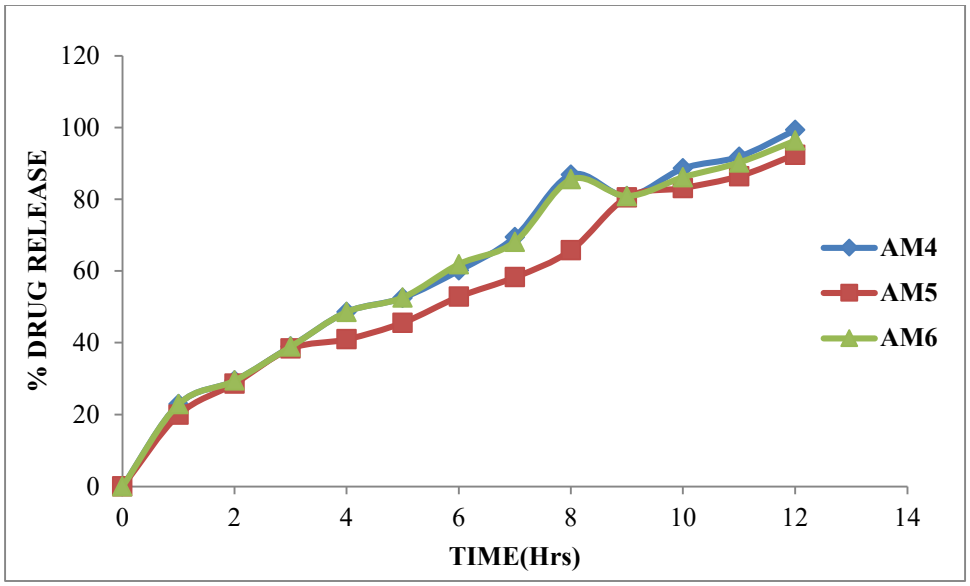

Fig 7: Dissolution study of AsenapineMaleate Nanoparticles

Table 6: *In vitro* Drug release studies of Asenapine Maleate AM7, AM8, AM9

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED		
	AM7	AM8	AM9
0	0	0	0
1	26.89	19.93	20.59
2	35.84	23.24	26.93
3	49.92	30.85	31.83
4	56.41	34.51	38.51
5	62.82	38.10	42.32
6	68.28	41.16	46.89
7	83.48	55.82	65.24
8	80.68	60.88	68.10
9	86.12	68.14	82.85
10	91.85	83.48	86.98
11	95.28	89.95	81.18
12	98.16	89.62	86.42

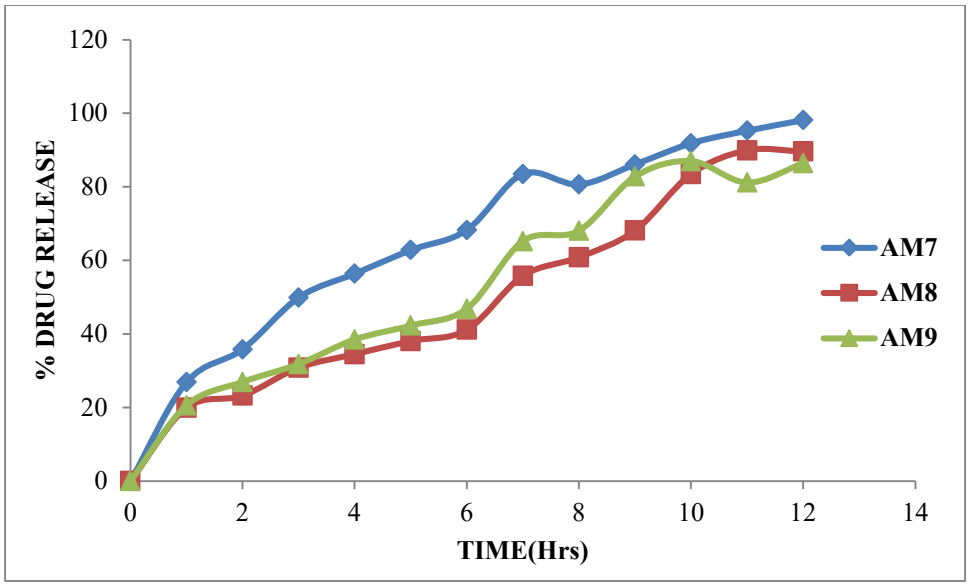

Fig 8: Dissolution study of Asenapine Maleate Nanoparticles

Hence based on dissolution data of 9 formulations, AM4 Poloxomer 188**(**25mg**)**formulation showed better release (99.32%) up to 12 hours. SoAM 4 formulation is optimised formulation.

Application of Release Rate Kinetics to Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of drug release from Nanoparticles. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table it follows the zero order kinetics

Table 7: Release kinetics data for optimized formulation (AM4)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
22.91	0.5	0.707	1.360	-0.301	1.887	45.820	0.0436	-0.640	77.09	4.642	4.256	0.386
29.49	1	1.000	1.470	0.000	1.848	29.490	0.0339	-0.530	70.51	4.642	4.131	0.510
38.97	2	1.414	1.591	0.301	1.786	19.485	0.0257	-0.409	61.03	4.642	3.937	0.704
48.63	3	1.732	1.687	0.477	1.711	16.210	0.0206	-0.313	51.37	4.642	3.717	0.924
52.56	4	2.000	1.721	0.602	1.676	13.140	0.0190	-0.279	47.44	4.642	3.620	1.022
60.19	5	2.236	1.780	0.699	1.600	12.038	0.0166	-0.220	39.81	4.642	3.415	1.227
69.51	6	2.449	1.842	0.778	1.484	11.585	0.0144	-0.158	30.49	4.642	3.124	1.518
86.85	7	2.646	1.939	0.845	1.119	12.407	0.0115	-0.061	13.15	4.642	2.360	2.281
80.92	8	2.828	1.908	0.903	1.281	10.115	0.0124	-0.092	19.08	4.642	2.672	1.969
88.61	9	3.000	1.947	0.954	1.057	9.846	0.0113	-0.053	11.39	4.642	2.250	2.392
91.85	10	3.162	1.963	1.000	0.911	9.185	0.0109	-0.037	8.15	4.642	2.012	2.629
99.32	11	3.317	1.997	1.041	-0.167	9.029	0.0101	-0.003	0.68	4.642	0.879	3.762
99.23	12	3.464	1.997	1.079	-0.114	8.269	0.0101	-0.003	0.77	4.642	0.917	3.725

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy

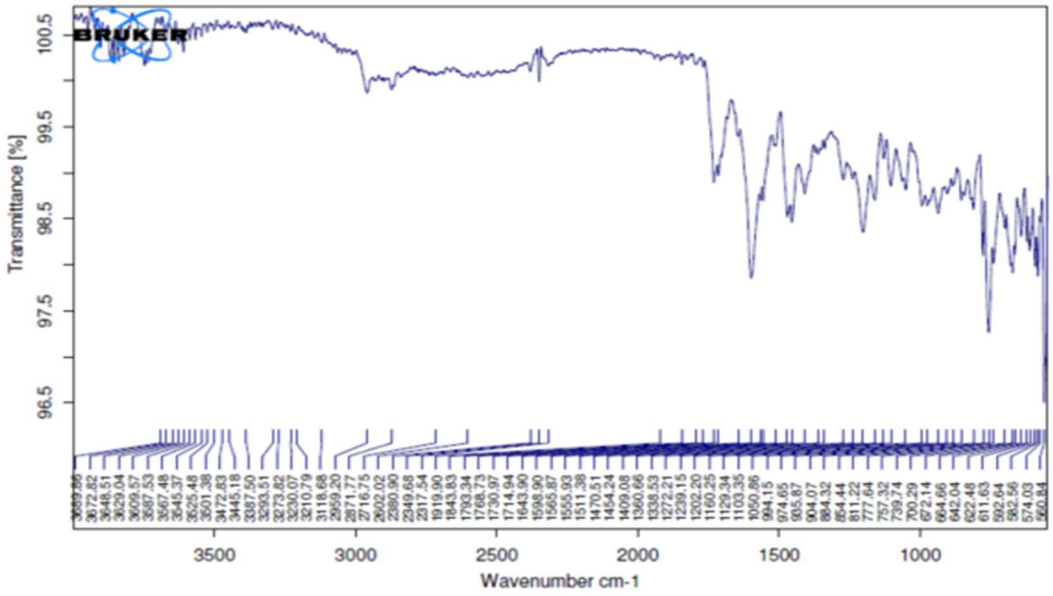

Fig 9: FT-TR Spectrum of Asenapine Maleate pure drug

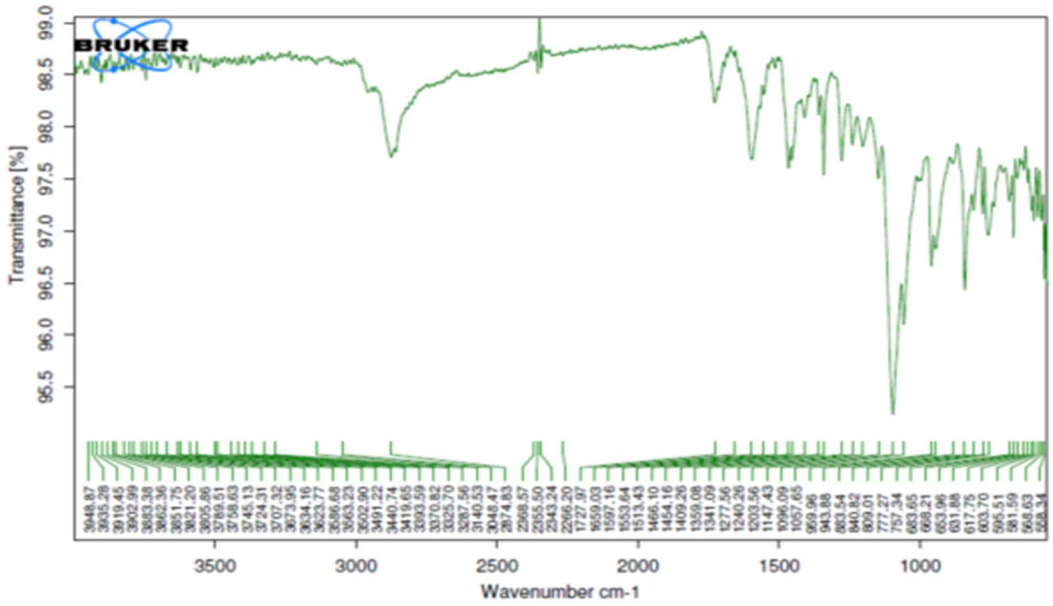

Fig 10: FT-IR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearance of peaks of pure drug and in optimised formulation.

SEM

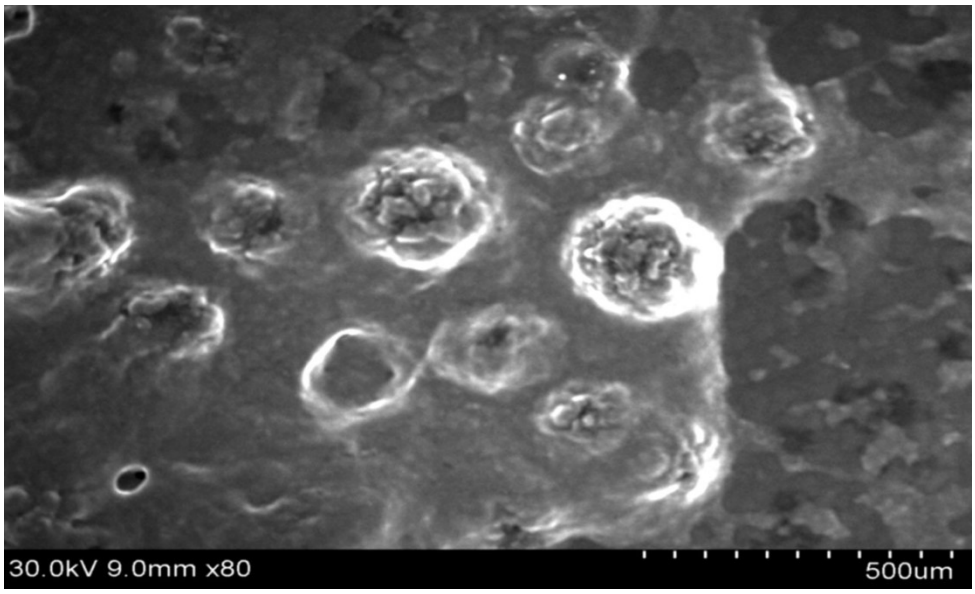

Fig 11: SEM graph of optimized formulation

SEM studies showed that the Asenapine Maleate - loaded nanoparticles had a spherical shape with a smooth surface as shown in Figure.

XRD

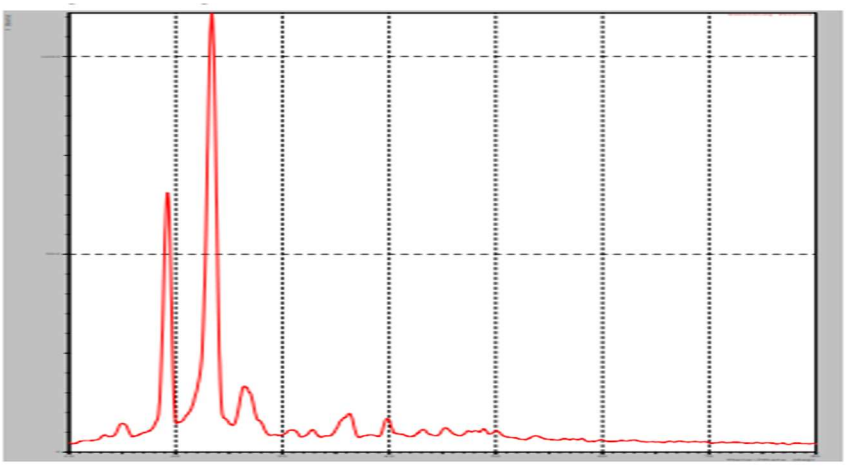

Fig 12: Asenapine MaleateAM4optimised formulation

CONCLUSION

The present work objectives was to assess the various formulation and process parameters to enchance the incorportation of water soluble drug in to nanoparticles prepared by central composite design and to study the influence of choosen independent variables on the responses selected. The Poloxomer 188 had been successfully incorporated in to nanoparticles has been achieved. Results show that on span 80 from 10% w/v a decrease in particle size was observed. The major outcome of this work was the successful entraoment of a Poloxamer 188 and drug with in a liquid core. Despite of the zeta potential the prepared nanoparticles were stable. It can be concluded that using span80 concentrations in optimum concentration i.e 1ml and sonication for more time during the process of formulation better

narrow size is achieved and by this nanoparticles approach and preparation by solvent injection method the drug release can be sustained and may lead to the avoidance of frequent drug administration.

REFERENCES

1. Remington: The Science and Practice of Pharmacy, 20 th Edition, Vol. 1 Edited byAlfonso R Gennaro Published by Lippincot Williams and Wilkins, Philadelphia, 2000; Page No. 903.
2. Controlled Drug Delivery Fundamentals and Applications, 2 nd Edition edited by Robonson JR, Lee VHL, New York: Dekker, 1987; Page No. 3.
3. Controlled and Novel Drug Delivery", 1 st Edition, Edited by Jain NK, Published by CBS Publishers & Distributors, New Delhi, 1997; Page No. 1.
4. The Theory & Practice of Industrial Pharmacy, 3 rd Edition Edited by Leon Lachman, Herbert A. Liberman, Joseph L.Kanig Published by, Varghese Publishing House, Bombay, 1991; Page No. 430-439.
5. Targeted and Controlled Drug Delivery Novel Carrier Systems. 1 st Edition, Edited by SP Vyas and Khar RK, CBS Publishers & Distributors, New Delhi, 2002; Page No. 39.
6. Subal C Basak, Novel Drug Delivery Systems. The Indian Pharmacist, April 2005: 7-10.
7. Pharmaceutical Biotechnology, 1 st Edition Edited by Vyas SP and Dixit VK, Published by CBS Publishers & Distributors, New Delhi, Page No. 395; 1998.
8. Encyclopedia of Pharmaceutical Technology, 2 nd Edition edited by Elias Fattal, Christine Vauhier. Published by, Marcel Dekker, Inc. New York, 2002; pg (1864).
9. L.S. Nair, C.T. Laurencin. Prog. Polym. Sci. 32 (2007) 762–798.
10. VJ Mohanraj and Y Chen, Nanoparticles – A Review, Tropical Journal of Pharmaceutical Research, June 2006; 5 (1): 561-573.
11. R. Singh, J.W. Lillard Jr. / Experimental and Molecular Pathology 86 (2009) 215–223.
12. Peltonen L, Aitta J, Hyvönen S, Karjalainen M, Hirvonen J. Improved Entrapment Efficiency of Hydrophilic Drug Substance During Nanoprecipitation of Poly(l)lactide Nanoparticles. AAPS Pharm Sci Tech. 2004; 5(1): article 16
13. T. Musumeci, C.A. Ventura, I. Giannone, B. Ruozi, L. Montenegro, R. Pignatello and G. Puglisi. PLA/PLGA nanoparticles for sustained release of Docetaxel. International Journal of Pharmaceutics Volume 325, Issues 1-2, 15 November 2006, Pages 172-179.
14. Lim Liancy, Feng Si-Shen and Seow Pei Hsing. Nanoparticles of Biodegradable polymers Applied for clinical Administration of Anti cancer Drugs. www3.ntu.edu. UROP Report
15. L.Mu and S.S.Feng worked on A novel controlled release formulation for the anticancer drug Paclitaxel(taxol);PLGA nanoparticles containing Vit E TPGS. Journal of controlled Release 86(2003) 33-48.