Research Article

Formulation and Characterization of Asenapine Maleate Nanoparticles

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ABSTRACT

The purpose of present work is to enhance the solubility and dissolution rate of Asnapine Maleate by the preparation of Nanoparticles using Nanoprecipitation technique. Asenapine Maleate is poorly soluble in water. In present work different formulations prepared by using different stabilizers such as Polyvinyal Pyrrolidine K-30, Tween 80 and Poloxamer 188. The Nanoprecpitation technique is simple, less sophisticated technique. The Preformulation studies carried out different techniques such as Fourier Transformed Infrared Spectroscopy and Differential Scanning Calorimetry. Prepared Nanosuspension was evaluated for its Particle Size, Drug Entrapment Efficiency, drug Content and In-Vitro drug release studies. The results showed nanoparticles prepared with stabilizer Poloxamer in Acetone are proved to be better optimized batch. This can be attributed due to increase in surface area of optimized formulation than the pure drug.

Keywords: Asenapine Maleate, Nanoparticles, FTIR, DSC, Saturation Solubility, Particle Size and Zeta Potential.

INTRODUCTION

More than 40% drugs coming from high through output screening are poorly soluble in water. Obviously poorly soluble drugs face so many problems formulating them in conventional dosage forms. One of the critical problems associated with poorly soluble drugs is low bioavailability and erratic absorption. There are number of formulation approaches to resolve the problem of low solubility and low bioavailability include Micronization, Solubilization, Using of Co-Solvents, Surfactant, Dispersion, Salt Formation and Precipitation Techniques. These techniques of solubility enhancement have some limitations and hence have limited utility in solubility enhancement.

Hence, there is need of some different and simple approach to tackle the formulation problem to improve their efficiency. One of such novel technology is Nanosuspension technology.[1]

Nanosuspension is sub-micron colloidal dispersion of nanosized drug particles stabilized by surfactant. Nanosuspension consists of poorly water-soluble drug without any matrix material suspended in dispersion. These can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media.

The drug micro particles/micronized drug powder is transferred to the drug nanoparticles by techniques like Bottom-Up Technology [Precipitation] and Top-Down Technology Or Disintegration method.[2]

MATERIALS AND METHODS

Asenapine Maleate [Yaro Chem, Mumbai], Eudragit L100 [Yaro Chem Products, Mumbai], Eudragit RS 100 [Yaro Chem, Mumbai], Poloxamer 188 [Yaro Chem, Mumbai], Tween 80 [Finar Ltd., Ahemadabad], PVP K-30 [Yaro Chem, Mumbai], Acetone [Finar Ltd., Ahemadabad] and Methanol [Finar Ltd., Ahemadabad].

Methodology

Before formulation of drug substance in to dosage form it is essential that the drug and polymer should be physically and chemically characterized. Preformulation studies give information defines the nature of drug substance and provide a framework for drug combination with pharmaceutical excipients in preparation of dosage form. The Preformulation studies like determination of Organoleptic Properties, determination of Melting Point and determination of λmax was carried out.

Preparation of Asenapine Maleate Nanoparticles

Nanoparticles were prepared by Nanoprecpitation method. Required amount of Polymers [Eudragit L 100/Eudragit RS 100] were dissolved in selected inorganic solvent to form diffusing phase. The specified amount of drug was accurately weighed and added to polymeric solution and allowed to mixing for few minutes and allowed to stand for few minutes to make it air bubble free clear solution.

The aqueous dispersing containing stabilizers constituted non solvent in which polymers are insoluble. Accurately measured 1ml of polymeric solution [diffusing phase] was added to 20ml of dispersing phase with the help of syringe which was positioned such that needle immersed directly into aqueous medium under moderate [500rpm] magnetic stirring [Remi 1 MLH] at room temperature, resulted in combination of nanoparticles.

As soon as the polymers containing solvent diffused into the dispersing medium, the polymers precipitated resulting in immediate drug entrapment. The rapid nanoparticles formulation was governed by so called

Marangoni effect, which is due to interfacial turbulence that takes place at interface of solvent and nonsolvent.

Table 1: List of Ingredients Taken For Formulations

Ingredients	F1	F2	F3	F4	F5
Asenapine Maleate [mg]	10	10	10	10	10
Eudragit L 100 [mg]	1	-	1	-	1
Eudragit RS 100 [mg]	-	1	-	1	-
Poloxamer 188 [mg]	20	20	-	-	-
Tween 80 [mg]	-	-	20	20	-
PVP K 30 [mg]	-	-	-	-	20
Acetone [ml]	5	5	5	5	5

Evaluation of Asenapine Maleate Nanoparticles

Fourier Transformed Infrared Spectroscopy[3]

FTIR spectroscopic studies were conducted to determine possible interaction between Active Pharmaceutical Ingredient and excipients. Spectra analysis of Asenapine Maleate with excipients was carried out to investigate changes in chemical composition of drug after comparing with excipients. The compatibility study on FTIR was carried out by [IR Affinity-1, Shimadzu, Japan] in frequency range 4000-400cm^{-1}.

Differential Scanning Colurimetry[4]

Thermo gram of Pure drug Asenapine Maleate and selected Nanoparticles formulations were obtained using DSC-4000 [Perkin Elmer, Singapore]. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The sample was separately weighed and hermitically sealed in Aluminum pans. The system was heated from ambient temperature 250°C at pre-programmed heating rate of 10°C/min.

Particle Size[5]

The particle size and size distribution of the Asenapine Maleate Nanoparticles were determined by Photon Correlation Spectrometry using Zeta Sizer 2000 [Malveren Instrument L.td, U.K]. Nanoparticles were diluted with filtered [0.22µm] ultra pure water and analyzed using Zeta sizer, yielding the mean particle diameter of Nanoparticles [Z-Average measuring range: 20-100] and Polydispersity Index.

Zeta Potential

Zeta potential of Nanoparticles was measured by zeta sizer [Malveren Instrument L.td, UK]. The zeta sizer mainly consists of laser which is used to provide light source to illuminate the particles within the sample. Zeta sizer software produce a frequency spectrum from which the electrophoretic mobility hence zeta potential is calculated.

Saturation Solubility Study[6]

Solubility studies were carried out by preparing saturated solution of drug in different solvents [1.2 buffer, 7.2 buffer, 6.8 buffer and 1.2 buffer]. Excess quantity drugs with approximately 2ml of solvent taken in glass vial with rubber stopper. Then the vial was shaking with mechanical stirrer [Remi, Mumbai, India] for 24hours at room temperature. After 24 hours sample was centrifuged at 3000rpm for 20mins. The supernant liquid was pipette out from each sample followed by dilution with suitable solvent and solubility was determined in the UV-Visible Spectrophotometer [Elico Double Beam Spectrophotometer] at 200-400nm. Similarly the solubility was determined for different formulations.

Drug Entrapment Efficiency[7]

The encapsulation efficiency of Nanoparticles was determined by separation of Drug-loaded nanoparticles from the aqueous medium containing non-associated Asenapine Maletae. The entrapped drug was determined by taking 2ml of Nanoparticles suspension and centrifuged [Remi R 8C] at 5000rpm for 30mins. The amount of Asenapine Maleate loaded in to Nanoparticles was calculated as the difference between the total amount used to prepare the Nanoparticles and the amount that was found in supernant. The amount of free Asenapine Maleate in supernant was measured at 270nm using UV-Visible Spectrophotometer [Elico Double Beam Spectrophotometer] after suitable dilution with 7.2 Phosphate buffer. The Asenapine Maleate encapsulation efficiency of Nanoparticles was determined in triplicate and calculated as follows:

$$Percentage\ drug\ entrapment\ efficiency = \frac{W\ Initial\ drug - W\ Free\ drug}{W\ Initial\ drug} \times 100$$

Drug Content[8]

The actual quantity of Asenapine Maleate Nanoparticles formulation was measured using UV Spectrometric method after dilution with Methanol of 10mg equivalent weight of formulation. The absorbance of sample was measured at maximum wavelength 270nm. Theoretical10 quantities of drug in nanoparticles were compared with actual quantity of drug. Drug content was calculated by using actual and theoretical value as shown in equation.

$$Drug\ Content = \frac{ADC}{TDC} \times 100$$

Where

ADC - Actual Drug Content

TDC - Theoretical Drug Content

In-Vitro Drug Release Studies[9]

The *In-Vitro* drug release studies were performed using thee dialysis membrane diffusion technique. The membrane was soaked before use in distilled water for 4 hours then rinsed with distilled water. 10mg of Asenapine Maleate Nanoparticles dispersion, was transferred in to dialysis bag, tied and placed in backer containing 100ml of Dissolution Medium. The entire system was kept at 37±5°C continuous magnetic stirring [50rpm] and the

study was carried out in dissolution media 7.2 phosphate buffer. At appropriate time interval 5ml of release medium was removed and 5ml of fresh medium was added into system to maintain sink condition. The amount of Asenapine Maleate in the release medium was evaluated by UV Spectrophotometer at 270nm.

RESULTS AND DISCUSSION

Asenapine Maleate is a poorly soluble drug belongs to class IV. Thus, it was challenging to enhance the solubility of Asenapine Maleate in aqueous solution. Precipitation method has been employed to produce nanoparticles of Asenapine Maleate.

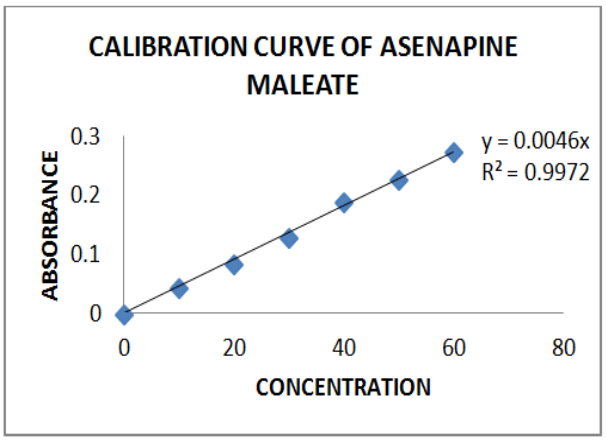


Figure 1: Calibration Curve of Asenapine Maleate

Organoleptic Properties

Asenapine Maleate was found to be White to Off-White powder and odorless.

Drug - Excipients Compatibility Studies

FTIR Studies

FTIR Studies were conducted to determine possible interaction between pure drug and excipients. FTIR spectra of pure drug Asenpine Maleate and drug with polymers and excipients were obtained and are super impossible to each other which show no chemical interactions between drug and excipients. The results of FTIR Spectra were shown in Figure 2.

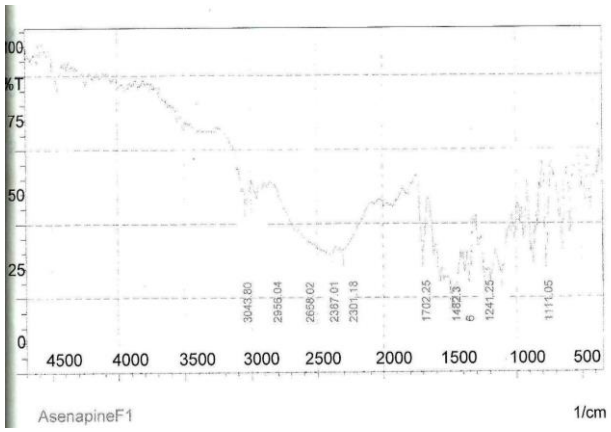


Figure 2: FTIR Spectra of Pure Drug Asenapine Maleate

DSC Studies

DSC Studies were characterizing the physical state of drug in various formulations.

The melting point of Asenapine Maleate was determined by DSC Studies and it was crystalline drug with melting point 154°C with narrow melting point range of 141-162°C.

Particle Size and Zeta Potential

In nanoscale normally seen going from 100-1000nm range, is suitable for Nanoparticles preparation.

In order to obtain the Nanoparticles exhibit good stability, for electro statically stabilized system a minimum zeta potential of ±30V required.

The particle sizes were determined. It was found that the optimized formulation particle size was in the range 105nm.

All the formulation have particle size in nanorange and showed ideal surface morphology and zeta potential value was found to be -9.65 which was consider as stable formulation.

Table 2: Results of Particle size and Zeta Potential

Formulations	Particle Size	Zeta Potential
F1	105.5	-9.65
F2	275.5	-17.75
F3	395.2	-8.66
F4	396.4	-11.13
F5	303.1	-12.16

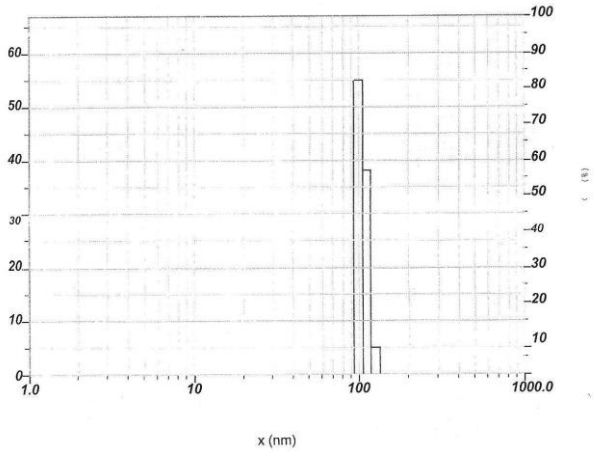


Figure 3: Particle Size of Formulation F1

Solubility Study

Saturation solubility study showing nanoparticles formulation showing increased solubility compared to unprocessed drug. It has been shown that the solubility of Nanoparticles formulation was showing 80-90% increase in solubility.

This may be due to nanoparticulate system having increased in surface area.

Drug Entrapment Efficiency

The drug entrapment efficiency of formulations was shown in Table 3.

The optimized formulation has entrapment efficiency 92.20%.

Drug Content

The direct relationship between drugs incorporated in formulation and lipophilicity of the drugs. Drugs with higher lipophilicity can be encapsulated more than the other drugs. The optimized formulation had drug content 98.4%.

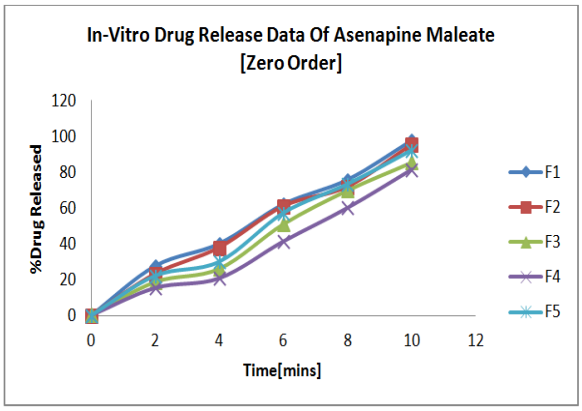
Table 3: Results of Solubility, Drug Entrapment Efficiency and Drug Content

Formulations	Solubility [mg/ml]	Drug Entrapment Efficiency [%]	Drug Content [%]
F1	24.49	92.20	98.4
F2	22.1	90.20	96.21
F3	21.76	89.2	98.38
F4	17.17	88	89.5
F5	20.61	88.29	92.42

Table 4: Comparative Cumulative % Drug Release of Formulations

Time [mins]	% Drug Released				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	27.62	26.28	23.00	28.00	26.87
4	40.12	38	32.14	52.62	58.12
6	62.12	65.12	62.13	66.5	73.00
8	75.82	78	81.00	86.37	86.67
10	97.75	95.55	93.87	92.2	94.25

In-Vitro Drug Release Studies



In-Vitro release studies of Asenapine Maleate performed by diffusion method. The results were shown in Table 4. From the results the cumulative percent best has shown by formulation with Eudragit L 100 and Eurdagit RS 100 as polymers and Poloxamer 188 as stabilizer.

The data from *In-Vitro* release fitted to various models to determine the kinetics of drug release. The main models were zero-order and first-order to determine the drug release from Nanoparticles. The 'r' values found to be in the range of 0.91-0.98. The corresponding plot [%Drug remained vs time] first order shows good linearity. The prepared formulation follows first order.

CONCLUSION

A Nanoprecpitation method was developed to prepare Asenapine Maleate Nanoparticles using different stabilizers and polymers. The Nanoprecpitation technique has many advantages, such as simple method of preparation, less requirement of excipients, increase in dissolution rate and solubility.

In this process, the particle size of Asenapine maleate obtained in Nanosize ranges by selecting proper stabilizers. It has been found that Nanoparticles obtained by using Poloxamer 188 as stabilizers, Eudragit L 100 and Euragit RS 100 as polymers in Acetone at moderate stirring speed 500rpm for 1hour, shown comparatively good results than others. Among the stabilizers Poloxamer 188 in concentration 1% gave best results.

In conclusion, the Nanoprecpitation method offers a direct process to obtain the drug particles of desired size, amenable for continuous and consistent production. That the experimental work performed to enhance the solubility and bioavailability of drug Asenapine Maleate [belongs to Class-IV] was successful. Asnapine Maleate is

Antischezophenic drug. Nanoparticles formulation can overcome the limitations of low solubility, dissolution and bioavailability.

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REFERENCES

1. H.A. Liberman, M.M. Riger and G.S. Banker. Pharmaceutical dosage forms: Dispersion system. 2nd ed. Vol 3, 97-99.
2. V.P. Torchilin, Nanoparticulates as drug carriers. 29, 307-329, 58-61.
3. Maindares R.M and Evangelista R.C. "PLGA nanoparticles containing Praziquntel: effect of formulation variables on size distribution". Int J Pharma, 290[1-2], 2005, 197-144.
4. Molpeceres J, Guzman M, Chacon M and Berges L. "Application of central composite design to the preparation of Polycaprolactone Nanoparticles by solvent displacement". J Pharma Sci., 85[2], 1996, 206-213.
5. Rajalakshmi R and Thanda Venkataramudu. Design and characterization of Valsartan Nanosuspension. Int J Pharamacotherapy, ISSN, 2001, 2249-7765.
6. Fessi H, Puiseieux F, Devissaguest J.P, Ammoury N and Benita S. "Nanocapsule formulation by interfacial polymer deposition following solvent displacement". Int J Pharma, 55[1], 1989, R1-R4.
7. Zhang Y, Tang L, Sun L, Bao J, Song C, Huang L and Liu K. A novel Paclitaxel-loaded Poly [e-caprolactone]/Polaxamer 188 blend nanoparticles overcoming multidrug resistance for cancer treatment. Acta Biomaterialia, 2010, 2045-2052.
8. Avagoutakis K. "Pegylated poly [lactide] and Poly [lactidcoglycolide] Nanoparticles: preparation, properties and possible supplications in drug delivery". Curr Drug Delivery, 1[4], 2004, 321-333.
9. Mahmoud M, Randa Tag and Salwa Salah. Preparation and characterization of Oflaxacin loaded biodegradable poly D, L-Lactide Nanoparticles. A factorial design study. 2, 2012, 121-128.

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