Preparation and Development of Aripiprazole Loaded Stearic acid Nanoparticles

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Abstract

Stearic acid nanoparticles loaded with Aripiprazole has been developed as a new therapeutic strategy to achieve its controlled release profile suitable for parenteral administration. Nanoparticles composed of different stearic acid ratio and drug composition were synthesized and loaded with aripiprazole by melt emulsification and low temperature solidification. The melting point of the drug was found to be 176° C. The solution of aripiprazole in PBS (pH 7.4) was scanned in the range of 200-400 nm using SYSTRONICS 2202 UV/visible spectrophotometer. The λmax was found to be 254 nm in PBS (pH 7.4). In order to estimate aripiprazole in experimental protocol, standard curve of drug was prepared in distilled water at 254 nm. Partition Coefficient of drug in n-Octanol/water was found to be 3.66. Subsequently evaluation by Samples with very broad size distribution have polydispersity index values > 0.7, particle size determination 277.22± 20, exhibit size range in between 50-1000 nm,the coated samples were then randomly scanned using a scanning electron microscope (SEM JSM-6510LV). and photomicrographs were taken., Nanoparticles was to be found 25.72± 2.3 to 30.19± 1.6, Data of PDI were found more than 0.7 for all formulation, Percentage yield was obtained in the range of 49.07 to 74.67 determined, In vitro drug release (94.11±1.88) , zeta potential.72± 2.3 to 30.19± 1.6, maximum entrapment efficiency79.45.

Keywords: Stearic acid, Aripiprazole, Melt emulsification and low temperature solidification, Nanoparticles.
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1. Introduction: Aripiprazole is a partial dopamine agonist of the third generation class of atypical antipsychotics with additional antidepressant properties that is primarily used in the treatment of schizophrenia, bipolar disorder, major depressive disorder and

irritability associated with autism. Aripiprazole is an antipsychotic drug is used mainly in the management of mental illness and is also used in the treatmentof various form of epilepsy. Psychosis is a mental disorder which results due to alteration in the monoamine neurotransmitters level in the CNS. The manifestation include elusion, illusion and hallucinogens (Richard E. powers 2008). In recent year, biodegradable nanoparticle for controlled drug delivery become a valuable approach to overcome the potential serious side effect arising from lifelong, systemic administration of therapeutic agent[9]. These nanoparticles are tiny colloidal carried composed of biocompatible or biodegradable lipid matrix that is solid at body temperature, dispersed in aqueous surfactant solution and exhibit size range in between 50-1000 nm.

2. Material and Method

2.1 Material: The sample of drug(Aripiprazole) supplied generously by M/s Cadila Pharmaceutical Ahmedabad, Gujarat was identified by IR spectra and UV absorption maxima. Stearic acid, Acetone solution and methanol solution are available in IPS college of pharmacy Gwalior. The water used was distilled.

2.2 Method: Nanoparticles were prepared using melt emulsification and low-temperature Solidification method. 100 mg drug (Aripiprazole) was dissolved in 3ml ethanol andmixed with 25 ml acetone solution containing different concentration stearic acid . The mixture were sonicated for 15 min., and then added drop wise to Tween 80 solution, stirred at 3000rpm for 0.5 hrs at 70^{o}C temperature. The mixed solution transferred to ice water bath and stirring for four hours at 3000 rpm. Different formulation of drug loaded nanoparticles were prepared by varying concentration of stearic acid as shown in the blowtable.

Table :1 Method Of Preparation Of Aripiprazole Nanoparticles

S. No.	Formulation code	AripiprazoleAmt of drug(mg)	Amount of stearic acid (mg)	Amount of tween 80%
1	F1	100	1000	3.0
2	F2	100	1250	3.0
3	F3	100	1500	3.0
4	F4	100	1000	2.5
5	F5	100	1250	2.5
6	F6	100	1500	2.5
7	F7	100	1000	2.0
8	F8	100	1250	2.0
9	F9	100	1500	2.0

3. Evaluation -

3.1 Determination of average particle size and zeta potential

The particle size and particle size distribution of the formulation was determined by photo correlation spectroscopy with a zeta master (Malvern Instruments, UK) equipped with the Malvern PCS software. Every sample was diluted with distilled water. The surface charge (Zeta potential) was determined by measuring the electrophoretic mobility of the nanoparticles using aMalvern zeta sizer (Malvern Instruments, UK). Samples were prepared by diluting with distilled water.

3.2 Percentage Yield :

The yield of production of nanoparticles of various batches were calculated using the weight of the final product after drying with respect to the initial total weight of the drug and polymer used for preparation of nanoparticles and percent production yield were calculated as per the formula mentioned below.

$$\%\ yield = \frac{Practical\ mass \times 100}{Theoretical\ mass}$$

3.3 Entrapment Efficiency

For determination of drug entrapment, the amount of drug present in the clear supernatant after centrifugation was determined (w) by UV spectrophotometer at 254 nm. A standard calibration curve of drug was plotted for this purpose. The amount of drug in supernatant was then subtracted from the total amount of drug added during the preparation (W). Effectively, (W-w) will give the amount of drug entrapped in the particles. Then percentage entrapment of a drug was calculated according to Equation 2

% Drug Entrapment = (W-w/W) × 100 …..(2)

3.4 Scanning Electron Microscopy (SEM)

The surface morphology of the nanoparticles was examined by scanning electron microscopy (SEM). One drop of diluted Aripiprazole nanoparticles suspension was placed on a stub covered with a clean glass and subjected to SEM analysis. The samples for SEM were prepared by lightly sprinkling the powder on a double adhesive tape stuck to an aluminum stab. The stubs were then coated with gold to a thickness of about 300 A0 under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned using a scanning electron microscope (SEM JSM-6510LV). and photomicrographs were taken.

3.5 In vitro diffusion studies :

In-vitro diffusion studies were performed by dialysis technique .Nanoparticles suspension equivalent to 5 mg of Aripiprazole was placed in dialysis bag (12,000Da–pore size) which was previously soaked overnight in distilled water and sealed at both the ends. The dialysis bag was immersed in beaker containing 250 ml of PH 7.4 phosphate buffer, maintaining at 37± 50c with speed of 80rpm. 5ml of samples were withdrawn at regulation intervals and replaced with the fresh buffer. The amount of the drug diffused was estimated from the samples at 254 nm using UV spectrophotometer.

4. Result and discussion

4.1 Results :

Table 2 Determination of particle size

SNo.	Formulation no.	Particle Size
1	F1	286.12 ± 18
2	F2	292.22 ± 19
3	F3	305.19 ± 16
4	F4	267.22 ± 20

5	F5	278.56± 18
6	F6	281.72± 23
7	F7	351.72± 23
8	F8	368.32± 42
9	F9	371.52± 32

Table 3 Determination of Zeta potential

SNo.	Formulation no.	Zeta potential
1	F1	26.12 ± 1.8
2	F2	28.22 ± 1.9
3	F3	30.19 ± 1.6
4	F4	27.22 ± 2.0
5	F5	28.56± 1.8
6	F6	29.72± 2.3
7	F7	25.72± 2.3
8	F8	26.32± 2.2
9	F9	27.52± 2.4

Table 4 Percentage Yield of nanoparticles

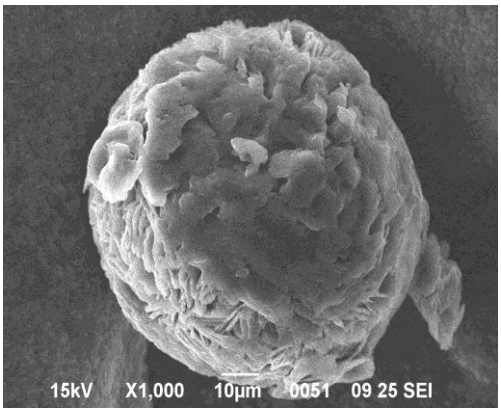
SNo.	Formulation no.	% Yield
1	F1	67.89
2	F2	72.43
3	F3	74.67
4	F4	57.89
5	F5	66.54
6	F6	70.65
7	F7	49.07
8	F8	52.87
9	F9	54.89

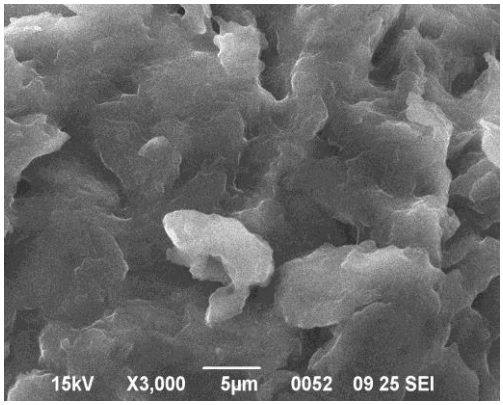
Table5 Data of % Entrapment efficiency of Nanoparticles

SNo.	Formulation no.	% EE
1	F1	72.98
2	F2	76.78
3	F3	79.45

4	F4	66.65
5	F5	69.80
6	F6	71.34
7	F7	72.98
8	F8	76.56
9	F9	77.65

4.1.1 SEM view of Nanoparticles





(A) **(B)**

Table 6 In vitro % Cumulative drug release

Time (h)	% Cumulative drug release*								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15.16 ±4.03	11.59 ±3.01	9.58 ±2.78	28.98 ±1.37	22.32 ±1.68	19.34 ±1.34	27.24 ±4.07	30.54 ±1.68	29.86 ±1.68
2	25.75 ±4.39	21.97 ±4.37	16.44 ±3.41	39.76 ±1.70	32.12 ±1.95	27.32 ±2.20	32.81 ±5.07	36.49 ±2.69	32.45 ±2.69
3	37.65 ±4.69	31.13 ±5.79	25.25 ±3.75	48.34 ±2.57	39.23 ±2.30	32.12 ±2.38	38.33 ±5.79	40.94 ±2.74	36.29 ±3.39

4	45.22 ±4.76	39.51 ±6.16	32.21 ±4.14	56.89 ±2.07	47.27 ±2.05	38.34 ±2.07	43.77 ±5.78	43.52 ±3.75	43.82 ±4.11
5	53.07 ±6.15	48.41 ±2.24	40.15 ±5.16	67.23 ±1.42	55.23 ±2.41	46.54 ±2.43	56.66 ±2.29	57.63 ±4.15	50.08 ±3.81
6	62.16 ±4.27	54.72 ±1.57	44.36 ±5.22	75.88 ±1.78	61.65 ±2.91	51.23 ±2.14	59.58 ±2.14	61.16 ±2.93	57.96 ±3.93
7	67.28 ±3.32	61.33 ±1.69	49.51 ±5.30	80.48 ±1.45	67.36 ±2.46	59.45 ±2.80	65.02 ±1.60	64.43 ±2.54	62.59 ±3.35
8	72.01 ±2.68	67.11 ±1.77	54.49 ±6.36	86.66 ±2.17	76.34 ±2.17	67.23 ±2.20	78.90 ±1.94	75.74 ±1.10	72.62 ±2.92
9	75.89 ±3.39	71.65 ±3.29	60.42 ±5.46	89.79 ±1.57	81.23 ±1.50	74.34 ±2.19	84.79 ±1.57	81.23 ±1.50	81.34 ±2.19
10	79.47 ±4.29	77.30 ±4.07	66.85 ±5.88	92.95 ±1.17	86.45 ±0.94	79.12 ±1.88	89.95 ±1.17	86.45 ±0.94	85.12 ±1.88
11	86.21 ±3.87	82.34 ±2.61	72.98 ±5.62	95.91 ±1.18	91.23 ±1.44	86.11 ±1.89	92.79 ±1.57	91.23 ±1.50	92.34 ±2.19
12	88.12 ±2.46	84.19 ±3.56	76.87 ±4.43	97.26 ±1.14	92.89 ±1.26	89.12 ±1.92	93.95 ±1.17	93.15 ±0.94	94.11 ±1.88
18	90.12 ±2.46	86.09 ±3.56	78.87 ±4.42	99.26 ±1.14	95.89 ±1.94	94.12 ±1.45	94.95 ±1.12	96.45 ±0.94	96.92 ±1.88

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All readings are mean of three ± S.D. * Average of 3 readings

Fig.1 % yield of Nanoparticles

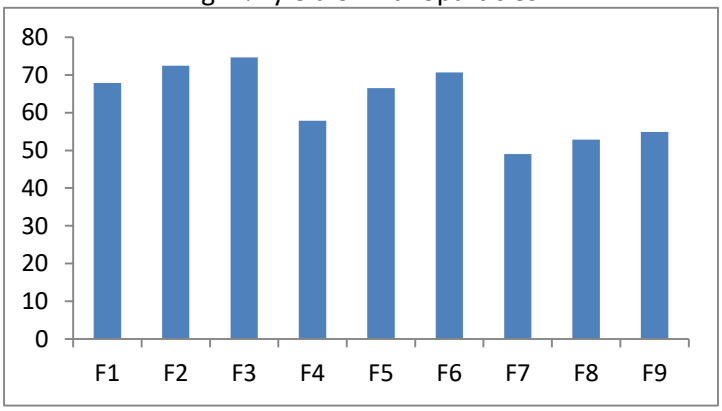


Fig. 2 % Entrapment efficiency of Nanoparticles

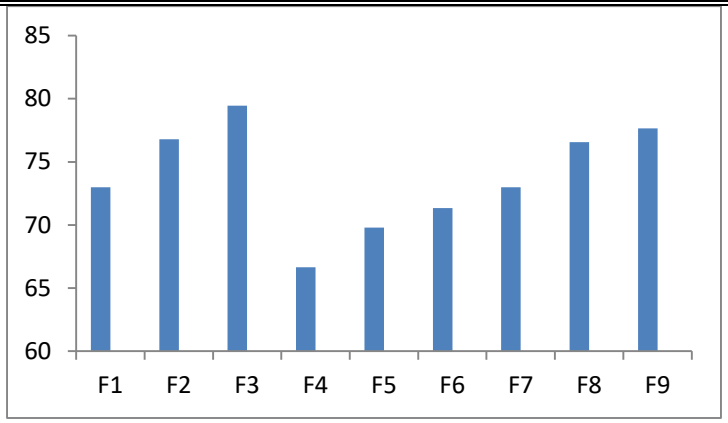


Fig. 3 In vitro drug release for F1, F2, and F3

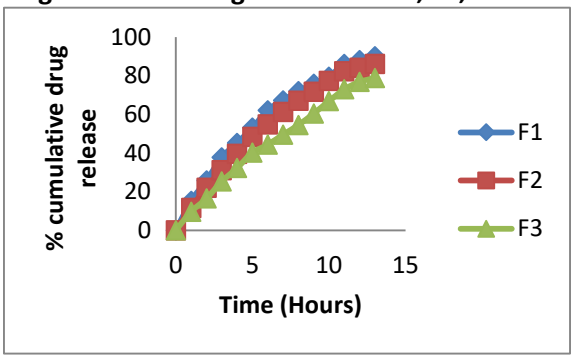


Fig. 4 In vitro drug release for F4, F5, and F6

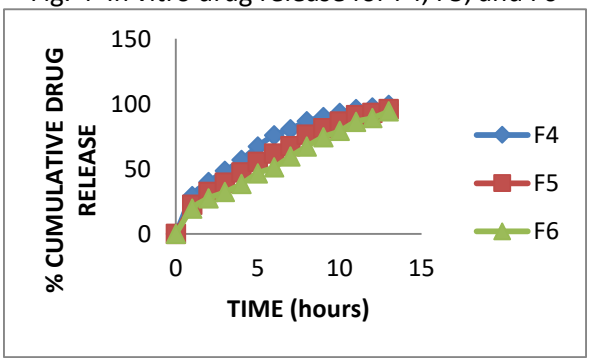


Fig.5 In vitro drug release for F7, F8, and F9

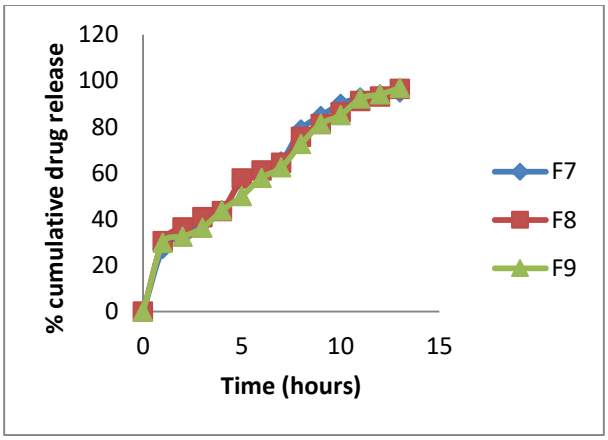


Fig.6 Standard curve of aripiprazole in PBS (pH 7.4)

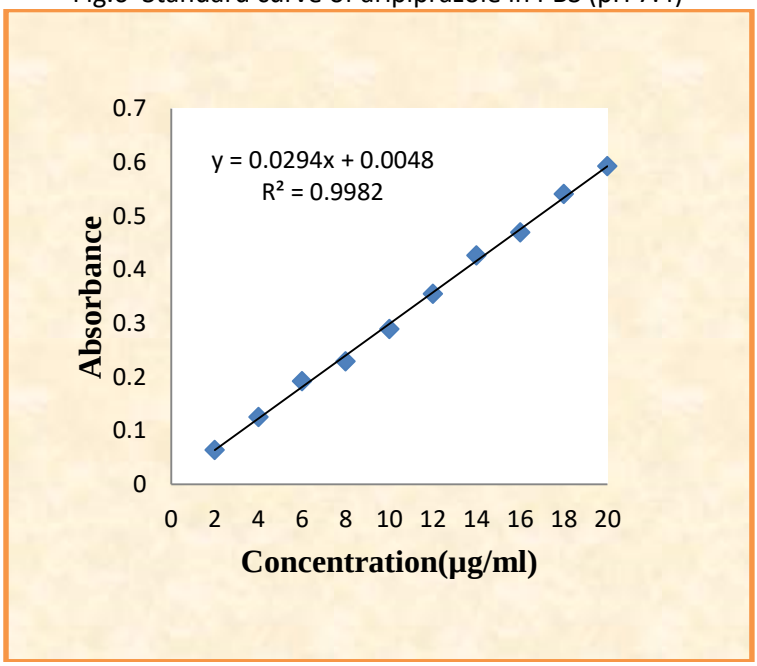
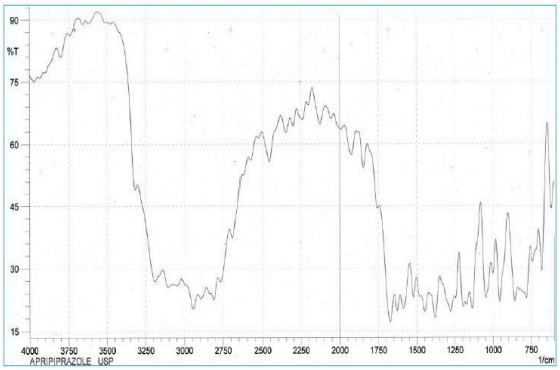


Fig.7 IR spectra of Aripiprazole



4.2 Discussion

nanoparticles (Aripiprazole) were prepared using melt emulsification and low-temperature Solidification method. The particle size distribution of Aripiprazole nanoparticle formulation was estimated using particle size analyser range. The Particle size range of nanoparticles formulations F1 & F9 were ranged between 251.72nm to 371.19nm indicating well within the nanoparticles limits. The particle sizes of formulations were increases as the concentration of tween 80 increases as shown in table 5.2.

The zeta potential of the SLN dispersion is given in the table 5.3. Zeta potential of nanoparticles Nanoparticles was to be found 25.72± 2.3 to 30.19± 1.6. The presence of drug causes a diminution of surface charge of all the investigated samples because probably a share of drug is situated on the lipid nanoparticles surface. Data of PDI were found more than 0.7 for all formulation.

Percentage yield was determined for all 9 formulations (F1 to F9). The result for all different formulated was obtained in the range of 49.07 to 74.67. Entrapment efficiency was determined for all 9 formulations (F1 to F9). The result for all different formulated was obtained in the range of 66.65 to 79.45. The maximum entrapment 79.45 was found for the Formulation 3 of nanoparticles, because it was higher concentration polymer.

It was observed that the reason may be concentration of polymer. As concentration of polymer was increased, the % entrapment was increased.

SEM images of the nanoparticles loaded with Aripiprazole were shown in Figure . The particles had spherical in shape and smooth surface.

The releases of drug from formulation were studies in PBS (pH 7.4). Results revealed that the release rate depends upon the polymer concentration, amount of adsorbed polymer as well as the composition ratio of the stearic acid in the polymer solution.

The cumulative release of Aripiprazole significantly decreased with increasing strearic acid concentration due to lipophilicity property of stearic acid polymer. There was no burst effect from any of these formulations. The increased density of the polymer matrix at higher concentrations results in an increased diffusion path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller nanoparticles f4 are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to maximum drug release (94.11±1.88).

5.Conclusion

Aripiprazole loaded stearic acid nanoparticles were produced by Hot emulsification and low temperature solidification method and tested for their in-vitro release behavior. The three most important properties affecting the release behavior were identified as: particle size and zeta potential. The mechanism of drug release was confirmed to be diffusion controlled by the application of mathematical models and the corresponding drug diffusivities were established to be a function of both polymer hydrophobicity and particle size. Hence the release profile from Aripiprazole loaded stearic acid nanoparticles can be tailored to achieve desired objectives by selective manipulation of particle properties.

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