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Research Article

Formulation and Evaluation Of Aripiprazole Nanoparticles

Arif Khan*, Dr. Manoj Goyal

Institute of Professional Studies College of Pharmacy, Gwalior (M.P), India -474001

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Address for Correspondence
Arif khan, Institute of Professional Studies College of Pharmacy, Gwalior (M.P), India

E-mail:
Arkhanpharma@gmail.com

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 and subsequently characterized by particle size distribution, Scanning electron microscope, In vitro drug release studies, zeta potential, Entrapment efficiency.

Keywords: Stearic acid, Aripiprazole, Melt emulsification and low temperature solidification, Nanoparticles

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 [1-3]. Aripiprazole is an antipsychotic drug is used mainly in the management of mental illness and is also used in the treatment of various form of epilepsy [4-7]. 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) [8]. 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 [10-11].

Aripiprazole is a partial agonist at D2 receptors. It may act as an antipsychotic by: lowering dopaminergic neurotransmission in the mesolimbic pathway. Enhancing dopaminergic activity in the mesocortical pathway [12]. In addition to partial agonist activity at the D2 receptor, aripiprazole is also a partial agonist at the 5-HT1A receptors, and like the other atypical antipsychotic, aripiprazole display an antagonist profile at the 5HT2A receptor [13]. Aripiprazole has moderate affinity for histamine and alpha adrenergic receptors, and no appreciable affinity for cholinergic muscarinic receptors. Stearic acid is a saturated fatty acid with an 18-carbon backbone. Stearic acid is found in various animal and plants fat, and is a major component of cocoa butter and shea butter. NCI thesaurus (NCIt) stearic acid is a white solid with a mild odor. The triglyceride derived from three molecules of stearic acid is called stearin. The salts and ester of stearic acid are called stearates [14-17].

MATERIAL AND METHODS

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 [18].

Formulation of Aripiprazole Nanoparticles

Nanoparticles were prepared using melt emulsification and low-temperature Solidification method.100 mg drug (Aripiprazole) was dissolved in 3ml ethanol and mixed with 25ml 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 C temperature. The mixed solution transferred to ice water bath and stirring for four

hours at 3000 rpm [19]. Different formulation of drug loaded nanoparticles were prepared by varying concentration of stearic acid as shown in the blow table (Table 1).

EVALUATION

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 a Malvern zeta sizer (Malvern Instruments, UK). Samples were prepared by diluting with distilled water [20].

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 = Practical mass×100

Theoretical mass

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 [21]. Then percentage entrapment of a drug was calculated according to Equation 2.

% Drug Entrapment = (W-w/W) × 100

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 [22]. 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.

In Vitro Diffusion Studies

In-vitro diffusion studies were performed by dialysis technique. Nanoparticles suspension equivalent to 5mg 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 [23]. The dialysis bag was immersed in beaker containing 250 ml of PH 7.4 phosphate buffer, maintaining at 37 ± 50 c 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 spectrophotometry.

RESULT AND 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 251.72 nm to 371.19nm indicating well within the nanoparticles limits. The particle sizes of formulations were increases as the concentration of tween 80 increases.

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 [24].

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 1. 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 [25].

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) (**Tables 2-6), (Figures 1-8)**.

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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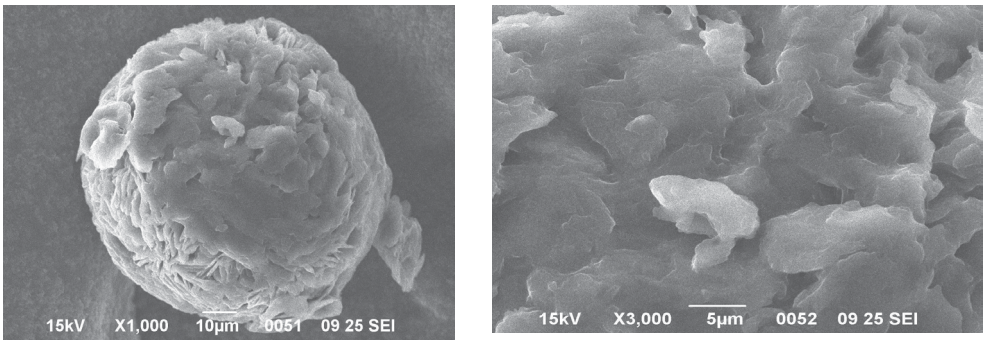

Figure 1. SEM view of Nanoparticles.

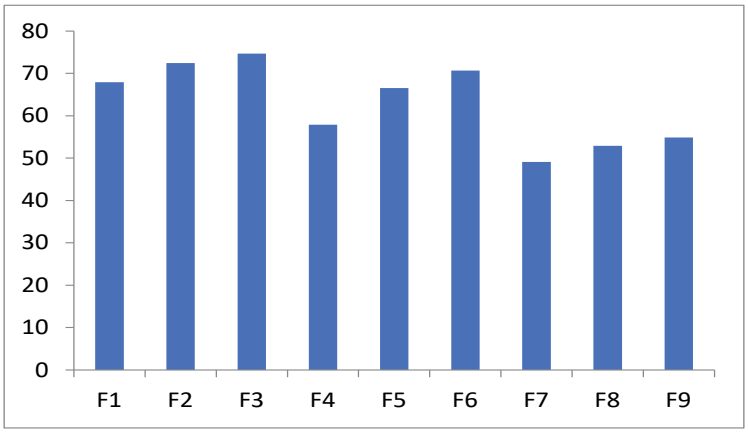

Figure 2. % yield of Nanoparticles.

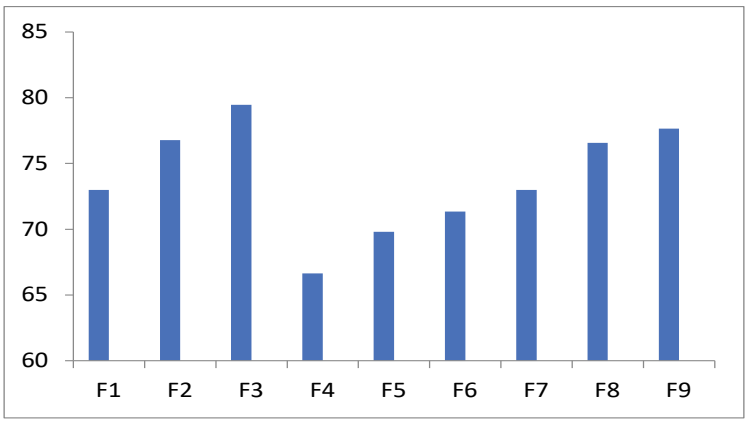

Figure 3. % Entrapment efficiency of Nanoparticles.

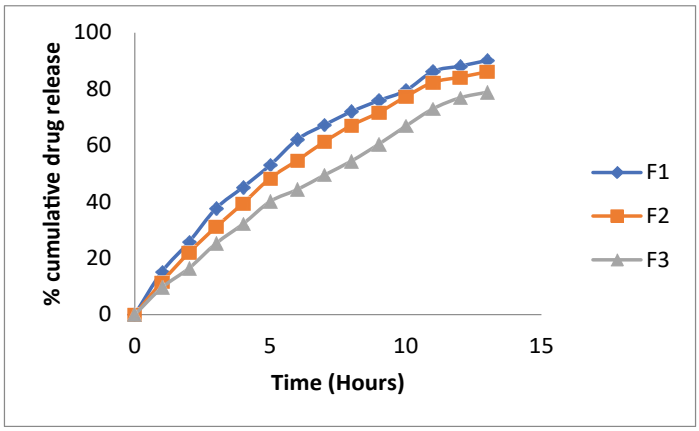

Figure 4. In vitro drug release for F1, F2, and F3.

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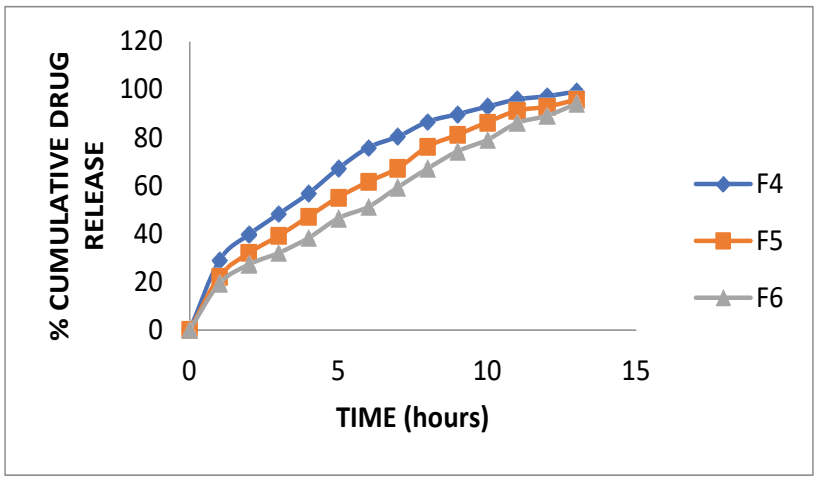

Figure 5. In vitro drug release for F4, F5, and F6.

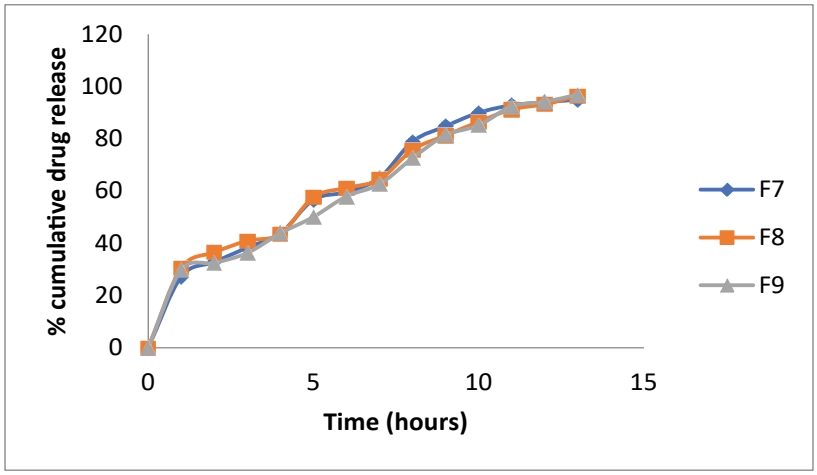

Figure 6. In vitro drug release for F7, F8, and F9.

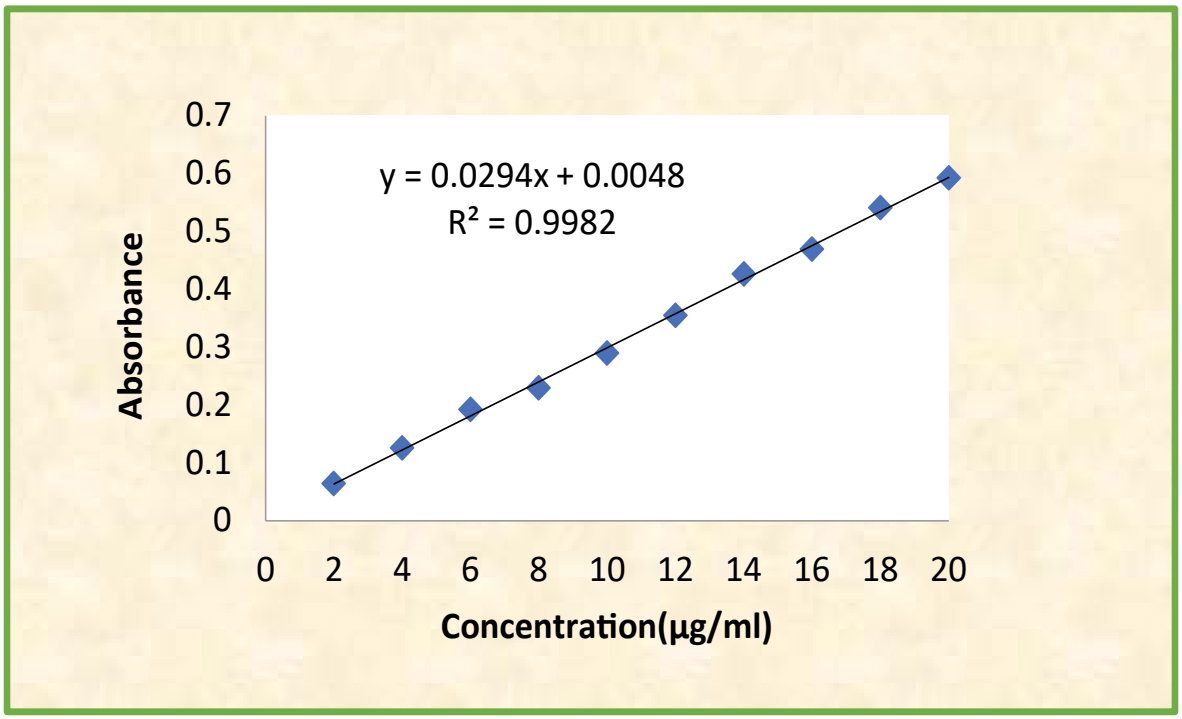

Figure 7. Standard curve of aripiprazole in PBS (pH 7.4).

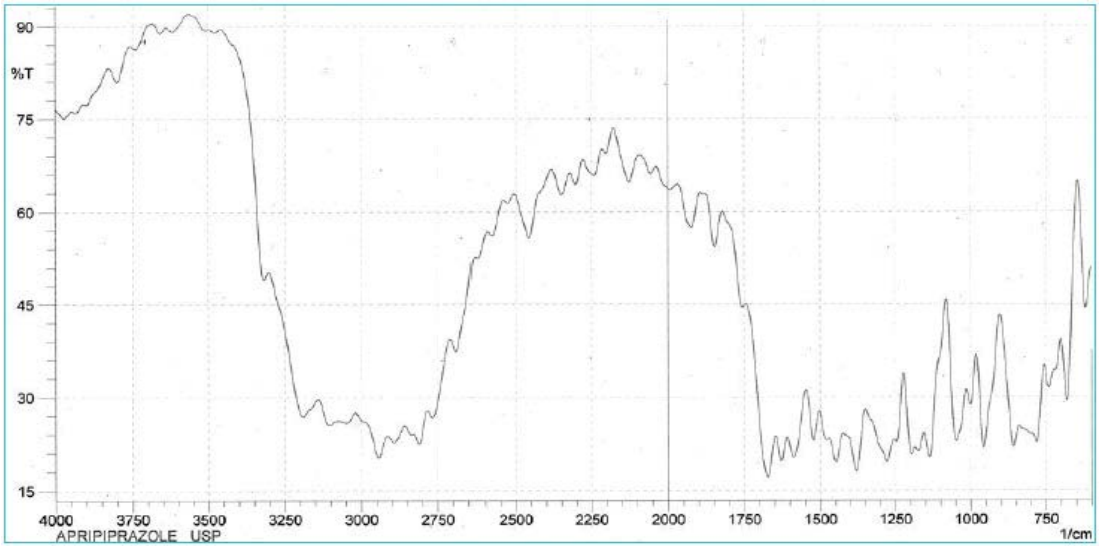

Figure 8. IR spectra of Aripiprazole.

Table 1: Method of Preparation of Aripiprazole Nanoparticles.

S.No.	Formulation code	Aripiprazole Amt 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

Table 2: Determination of particle size.

Sr. No	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.

Sr. No	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.

Sr. No	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

Table 5: Data of % Entrapment efficiency of Nanoparticles.

Sr. No	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

Table 6: In-vitro drug release profile of nanoparticles of various formulations PBS (pH 7.4).

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

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