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Hybrid Nanoparticles: Synthesis, Characterization and Biomedical Application

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ABSTRACT

Polymeric lipid hybrid nanoparticle of Rivastigmine hydrogen tartrate were prepared for specific brain delivery incorporating herbal extract of Shankhpushpi having memory enhancing ability. Using different concentrations of lipid soya lecithin, polymer poly (lactic-c-glycolic acid) i.e., PLGA, various formulations of polymeric lipid hybrid nanoparticles (PLHN) of drug Rivastigmine hydrogen tartrate (RHT) and Shankhpushpi extract were prepared by using film hydration method, containing drug RHT alone (from NF1 to NF 7) and those containing both drug RHT and Shankhpushpi herbal extract (NF 8 to NF 14). The optimization was done using particle size, zeta potential, turbidity measurements, drug loading and entrapment efficiency. Characterization of optimized formulations was done by DSC, FTIR and XRD.

1. Introduction

Drug Rivastigmine, used in Alzheimer's disease, is both hydrophilic and has got good permeability as, it belongs to (Biopharmaceutics Classification system) BCS class I, but still its use is limited because of low bioavailability, its poor penetration through blood brain barrier (BBB) and short half-life of only 1.5 hrs when administered orally [1]. So, to overcome these issues polymeric lipid hybrid nanoparticles of the drug by incorporating Shankhpushpi were prepared. Traditionally, Shankhpushpi (*Convolvulus pluricaulis*) has been used as a nervine tonic, sedative, anthelmintic, antiepileptic, and against leukoderma. Extract of Shankhpushpi has shown to have memory boosting properties and used in Alzheimer's disease [2].

Nanocarriers having the size range of 1-500 nm have advantage of carrying the drug through BBB, which otherwise cannot travel in their free form. The polymeric lipid hybrid nanoparticles of drug and extract consist of three distinct functional components: (i) a biodegradable hydrophobic polymeric core made up of polymers like PLA, PLGA etc., that can carry drug and release them over time; (ii) a stealth material soya lecithin forming a hydrophilic shell that can help the particles evade immune system components by generally making them PEGylated and lengthen their half-lives in the body making the sustained drug action and (iii) a lipid monolayer at the interface of the hydrophobic core and the hydrophilic shell controlling the escape of drug in the environment. The surface of these nanoparticles can be functionalized with targeting molecules for targeted delivery applications [3]. These nanoparticles have the advantage of improved stability, sustained drug action, enhanced drug loading capacity, improved bioavailability and hence improved therapeutic efficacy. With its high drug encapsulation yield, adjustable and prolonged drug release profile, superior serum stability, and potential for selective targeting of cells or diseases, hybrid nanoparticles can be a reliable drug delivery platform [4].

Recently polymeric lipid hybrid nanoparticles (PLHN) have been utilised to achieve targeted drug delivery by using targeting ligands. In one study, these nanoparticles were used for site targeting where experimental designs were used to obtain optimized formulation of Norfloxacin for topical delivery [5]. Enhanced oral absorption of poorly water-soluble drugs was explored using PLHN like Paclitaxel [6] using chitosan, first line therapy for delivering an antiepileptic drug carbamazepine [7]. In different studies targeted delivery of drugs was achieved by

specifically designed nanoparticles for controlled and sustained delivery of docetaxel in breast cancer [8], doxorubicin delivery to glioblastoma multiforme using terpolymer hybrid lipid nanoparticles [9], enhanced oral delivery of enoxaparin[10], using chitosan as polymer, curcumin loaded nanoparticles were prepared by encapsulating hydrophobic model drug curcumin into biotinylated chitosan polymer with high drug loading [11].

Recently these polymeric hybrid nanoparticles were particularly used for brain targeting. Use of surfactants crossing BBB helps in achieving brain delivery. The surfactant Tween 80 (polyethylene glycol sorbitan monooleate), which was considered the gold standard for effectively crossing rutin to BBB by using stealth lipid polymer hybrid nanoparticle [12], brain targeting of hybrid nanoparticle loaded hydrophilic drug was done by bioinspired lipid-polysaccharide dextran–cholic acid (DxC) which increase its targeting to BBB [13].

Rivastigmine hydrogen tartrate (RHT) loaded PLHN were formulated to enhance the drug loading capacity and increase the effectiveness of drug in treating Alzheimer's disease by polymer and lipid core material so that controlled release formulation was obtained which provides the desired action to drug. In addition, synergistic effect of Shankhpushpi extract was studied. The desired characteristic of brain targeting and site specificity was achieved by choosing surfactant Tween 80 with brain targeting action. Optimized of formulation was achieved by particle size, zeta potential, entrapment efficiency and drug loading studies. Co-administration of Shankhpushpi (a memory enhancing) with drug has demonstrated reduced first pass metabolism with a significant increase in drug availability and its activity in Alzheimer's disease by Morris maze water test in mice model. These elements convincingly show the effectiveness and adaptability of PLHNs as a drug delivery technology. The research article provides an optimized formulation development, factors that influence the optimized formulation and their related characterization, and future in development of the effective delivery of PLHN as an emerging tool for the herbal hybrid drug delivery system.

2. Materials and methods

2.1 Material

Rivastigmine Hydrogen Tartrate (RHT), PLGA (Poly-L- lactide-co-glycolide) PURASORB PLDG Shankhpushpi plant was collected from nearby areas of Yamuna Nagar, Haryana. Pluronic F-68, oleic acid, tween 80 and soya lecithin, methanol, chloroform and ethanol All of the solvents used in the experiments were of analytical grade.

2.2. Methods

2.2.1. Collection and preparation of Shankhpushpi extract

The plant *Convolvulus pluricaulis* commonly named as Shankhpushpi belonging to family Convolvulaceae, was collected from nearby area of Bilaspur District Yamuna Nagar, Haryana in the months of January-February. The leaves of the plant were air dried at room temperature, powdered and allowed to pass through sieve no. 20. Approximately 100g of sieve dried material was extracted with 400 ml of methanol for 48 h for three times at room temperature. Filtered extracts were collected and dried under reduced pressure. Finally, the extract was air dried to remove last traces of solvent and used. [14]

2.2.2. Preparation of Rivastigmine Hydrogen Tartrate (RHT) Hybrid nanoparticles

Hybrid nanoparticles were prepared by film hydration method, with slight modification [10], which allowed the incorporation of hydrophilic drug. Briefly, oleic acid, soya lecithin (1:1) tween 80 (surfactant) and polymer PLGA (as shown in Table 1) in different concentrations, were dissolved in methanol: chloroform (3:2) in a round bottom flask followed by evaporation of solvent under vacuum using a rotary evaporator to remove even the last traces of organic solvent. The film was dried in rotary evaporator for approximately 1hr at the temperature of 40-50 ^{0}C under 250 mbar, and was left over night for the removal of any possible traces of methanol and also to prevent the formation of emulsion due to the residual organic solvent. The dried film formed was then hydrated at ambient temperature for 1 h with aqueous phase (7% Ethanol) having Shankhpushpi, drug and Pluronic F-68. The prepared formulation was sonicated (5-8 min) to form the uniform size dispersion and stored in tightly closed glass vials at room

temperature. By evaporation technique the organic solvents were removed at 40 ^{0}C under normal pressure, and the nanoparticles were separated by using cooling centrifuge for 15 min at 10000 rpm. Supernatant liquid was removed and nanoparticles were washed with distilled water and freeze. Optimization of drug amount was performed by varying the concentration of lipid: polymer concentration and evaluating its effect on entrapment efficiency.

Table 1: Formulation of different RHT loaded PLHN

Formulation Code	Tween 80 (%)	Shankhpushpi (mg)	RHT (mg)	Lipid Phase: PLGA (%)	Pluronic F-68 (%)
NF1	1		10	5:10	2
NF2	1		10	10:10	2
NF3	1		10	15:10	2
NF4	1		10	20:10	2
NF5	1		10	25:10	2
NF6	1		10	30:10	2
NF7	1		10	35:10	2
NF8	1	50	10	5:10	2
NF9	1	50	10	10:10	2
NF10	1	50	10	15:10	2
NF11	1	50	10	20:10	2
NF12	1	50	10	25:10	2
NF13	1	50	10	30:10	2
NF14	1	50	10	35:10	2

Methanol: Chloroform (3:2) =10ml

3. Result and Discussion

3.1. Preparation and Optimization of PLHN

The PLHN was successfully prepared using the film hydration method. For PLHN the, lipid and polymer both have their significant effect on the entrapment efficiency, particle size. To obtain the desired nanoparticle size and surface charge and hence pharmacokinetic properties, the lipid/polymer weight ratio and PLGA molecular weight need to be optimized. As depicted by Zhang et al., 2008, the lipid/polymer weight ratio of 10-20% results in nanoparticles with desired particle size range of 200nm, and zeta potential value of (+30 to -35 mV) for drug delivery application [15]. One possible reason can be that, at this particular ratio, the amount of lipids is completely sufficient to cover the surface of the PLGA hydrophobic core. But when the ratio of lipid to polymer is too high, the extra lipid is above the critical micellar concentration (CMC) of lipid, resulting in the assembly of lecithin liposomes with size more than 100nm and these would increase the size of hybrid nanoparticles and decrease the zeta potential. On the other hand, if the ratio is too low, deficiency of lipids to cover the surface of PLGA core would result in high zeta potential value. Lipid polymer hybrid nanoparticles were formulated (1 mg/mL) using different lipid/polymer weight ratios and used oleic acid with soya lecithin as lipid phase in 1:1 concentration, as oleic acid was used for brain targeting. Pluronic F-68 helps in film making. Tween 80 (1%) also help in crossing BBB by acting as brain targeting agent.

3.2. Particle size, polydispersity index and zeta potential

The lifespan of nanoparticles in systemic circulation and their ability to passively aggregate in tissues are two of the most important aspects that are determined by particle size. All the formulations containing RHT (NF 1 to NF 7) have mean particle diameter sizes between 195 ± 8 nm to 235 ± 12 nm with PDI ranged between 0.01 ± 0.36 to 0.20 ± 0.66. Change in lipid: polymer ratio resulted in change in size of nanoparticles during PLHNs formulation. Increasing the concentration resulted in a rapid drop in particle size. Further increasing the ratio has essentially no impact on particle size. Higher lipid: polymer amounts have been linked to smaller particle sizes and improved stability for small lipid droplets by preventing coalescence. No major change in size was observed when ration was increased above 15:10 %w/w. Table 2 show the result of Particle size, PDI, Zeta potential, % EE, %DL and turbidity values of different

formulations. Similarly, formulations containing both drug and herbal extract (NF 8 to NF 14) have mean particle diameter size between 280 ± 8 nm to 317± 10 nm with PDI ranged between 0.20 to 0.43. This can be attributed to presence of Shankhpushpi extract along with drug.

A zeta potential value other than −30 mV to +30 mV is generally considered to have sufficient repulsive force to attain better physical colloidal stability. On the other hand, a small zeta potential value can result in particle aggregation and flocculation due to the van der Waals attractive forces act upon them. These may result in physical instability. The zeta potential of formulations with drug RHT (NF 1 -NF 7) has values between -34.5 ± 0.5 to -23.0 ± 0.3 and similarly zeta potential for formulations (NF 8-NF 14) having both drug and extract have values ranged between -25.7 ± 0.5 to -38.5 ± 0.4.

3.3. Entrapment efficiency, drug loading and turbidity measurements

Surfactants oleic acid, tween 80 were used to create the appropriate particle size and acceptable PDI during the optimization phase of PLHNs. Out of all the formulations of PLHNs, formulation NF4 have average particle size of 198.6 ± 7 nm with 56.7 ± 4.1 % EE and 7.33 ± 0.45 % DL. This formulation has PDI of 0.12 and zeta potential value of -27.9 ± 2.2. The produced PLHNs would be stable in nature, according to the acceptable values of PDI and zeta potential with maximum EE and DL. So, this was selected as optimized formulation. Similarly, the formulation NF 11 with mean particle size of 295 ± 16 nm with PDI value of 0.16 and zeta potential -35 ± 0.3 have maximum % EE value (54.7 ± 4.3) and % DL (7.29 ± 0.57) visibly better then rest of formulations containing drug and herbal extract. Hence was accepted as optimized formulation.

The results of the turbidity measurement studies support the fact of micelles formation at higher concentration of lipid as turbidity increases with increasing the concentration because at low concentration of lipid, partition coefficient favors the lipid phase and causes expansion of lipid bilayers resulting in increased turbidity of vesicle dispersion. Based on observations of results for zeta potential, particle size, PDI and morphological appearance of formulations, batches NF-4, NF-11 were selected for further studies.

Table 2: Particle size, PDI, Zeta potential, % EE, %DL and turbidity values of different formulations

Sr. No.	Formulation Code	Particle Size (nm)	PDI	Zeta Potential	%EE	% Drug Loading	Turbidity
1	NF1	235 ± 12	0.08	-23.0 ± 0.3	51.4 ± 6.2	6.645 ±0.68	+
2	NF2	232 ± 10	0.01	-24.5 ± 0.4	48.1 ± 3.4	6.218 ±0.37	+
3	NF3	230 ± 9	0.08	-28.5 ± 0.6	46.5 ± 8.6	6.011 ±0.94	++
4	NF4	198 ± 7	0.12	-27.9 ± 2.2	56.7 ± 4.1	7.33 ± 0.45	++++
5	NF5	197 ± 15	0.15	-27.9 ± 1.1	41.2 ± 7.2	6.360 ±0.79	+++
6	NF6	195 ± 8	0.20	-23.8 ± 1.3	42.4 ± 2.1	6.774 ±0.23	+++
7	NF7	195 ± 8	0.05	-34.5 ± 0.5	40.5 ± 6.4	5.235 ±0.70	+++
8	NF8	317± 10	0.43	-36.8 ± 0.4	48.5 ± 4.5	6.464 ±0.59	+
9	NF9	312 ± 13	0.27	-35.9 ± 0.3	35.4 ± 7.5	4.718 ±0.99	+
10	NF10	309 ± 12	0.36	-38.5 ± 0.4	36.7 ± 5.4	4.891 ±0.72	++
11	NF11	295 ± 16	0.16	-35 ± 0.3	54.7 ± 4.3	7.29 ± 0.57	++++
12	NF12	287 ± 15	0.5	-25.7 ± 0.5	50.4 ± 4.8	6.717 ±0.64	+++
13	NF13	285 ± 18	0.2	30.0 ± 1.5	49.7 ± 8.8	6.623 ±1.17	+++
14	NF14	280 ± 8	0.25	-30.0 ± 0.3	38.2 ± 8.6	5.091 ±1.45	+++

Morphological Appearance of Formulations +: Clear to colloidal ++: Less turbid and colloidal

+++: Turbid and colloidal ++++: Dense and colloidal

3.4. TEM

Surface morphology of the optimized formulation with drug RHT (NF 4) and with drug and Shankhpushpi extract (NF 11) was confirmed by TEM images (Fig 1). As shown the PLHN were observed as dark spherical nanoparticles against light background. Fig 1 (A) show the image of spherical shape of optimized formulation NF 4, with no visible cracks and pinholes, and spherical morphology. The images confirmed the round, smooth and drug crystals free nanoparticles. The same was observed for the NF11 formulation, whereas for plain drug image 1 (C) the particles are more crystalline without any smooth surface.

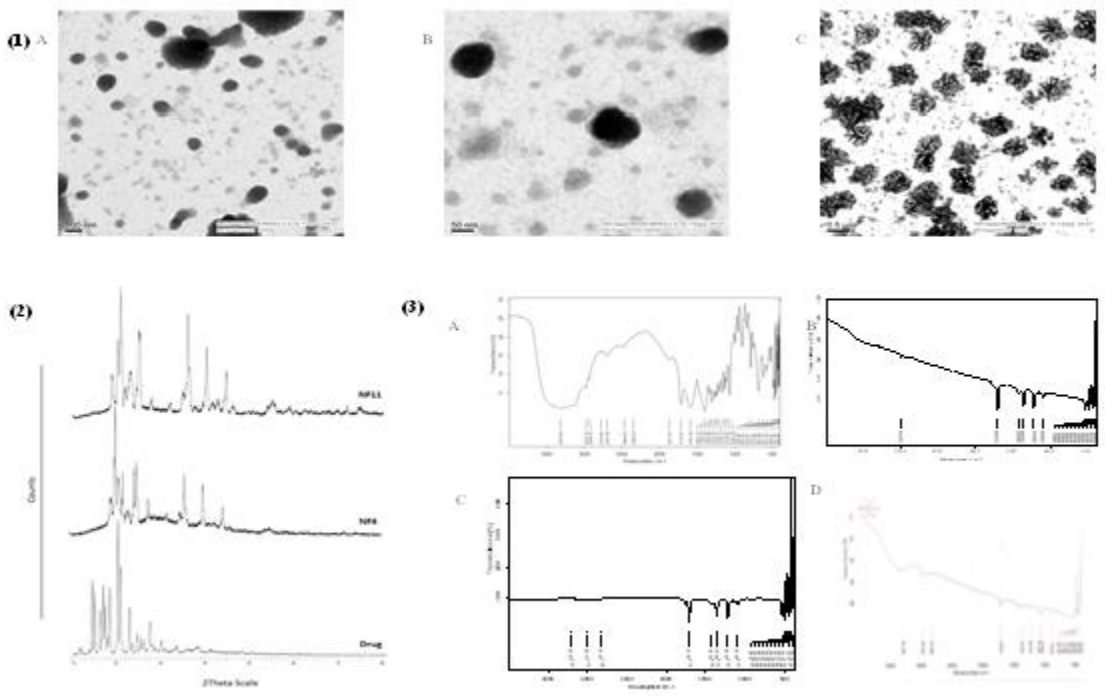

Figure 1: (1) TEM photomicrographs of (A) optimized formulation NF4, (B) NF 11 and (C) Plain drug, (2) XRD of Pure drug RHT, optimized formulation NF 4 and NF 11, (3) FTIR representation of (A) RHT pure drug sample, (B) PLGA, (C) Drug RHT loaded optimized PLHN (NF 4) (D) FTIR of Drug RHT and Shankhpushpi containing optimized formulation (NF 11)

3.5. XRD Analysis

The crystalline structure of the different nanoparticle formulations was analyzed by XRD Figure 1 (2). Determination of the crystalline structure of lipid containing nanoparticles became a

relevant tool since the release properties and the stability of encapsulated drug was significantly influenced by specific polymorphisms. In the study, XRD (X-ray diffraction) spectra were obtained for optimized formulations of RHT loaded PLHN (NF 4). They showed no evidence of infarction in any of the formulations, indicating that there were no detectable changes in the crystalline structure of the drug or the excipients. Infarction refers to the formation of crystalline aggregates in a drug formulation, which can lead to reduced drug efficacy, stability, and bioavailability. Absence of infarction in the PLHN formulations was a positive sign, indicating the drug was well dispersed in the nanoparticles and that the formulations were stable. The same was observed in optimized formulations with Shankhpushpi extract (NF 11) also. The XRD spectra also showed the characteristic peaks of drug, indicating that the drug was present in the nanoparticles in its crystalline form.

3.6. FTIR Analysis

FTIR results of pure drug RHT, polymer PLGA, optimized formulation with drug (NF 4) and optimized formulation containing Shankhpushpi extract (NF 11) are shown in Figure 1(3). FTIR spectra of pure drug RHT showed 3 (a) a specific N-H stretching peak at 3318.58 cm^{-1} wavelength, N-H bending peak at 1591.56 cm^{-1}, C-H stretching peak at 2936.25 cm^{-1} and specific C-O stretching peak at 1169.72 cm^{-1}. All the characteristic peaks of RHT along with minor shifts were shown by the spectra. FTIR spectra of PLGA polymer showed 3(b) specific N-H stretching at 3003.38 cm^{-1}, C=O stretching at 1707.99 $cm^{-1}$and C-O stretching at 1220.75 cm^{-1}. Optimized formulation (NF 4) showed specific N-H stretching at 3003.92 cm^{-1}, C=O stretching at 1709.71 cm^{-1} and C-O stretching at 1219.94 cm^{-1}. Optimized formulation NF-11 showed specific O-H stretching at 3291.56 cm-^{1}, C-H stretching at 2974.93 cm^{-1}, C=O stretching at 1705.67 cm^{-1}, C-O stretching at 1087.50 cm^{-1}. The result revealed that there is no considerable change in the IR peaks of drug and optimized formulations even after including Shankhpushpi extract indicating the absence of any interaction between the drug, polymer and Shankhpushpi.

3.7. In vitro drug release studies

In vitro drug release studies were carried out for all formulations of PLHN with drug (NF 1 to NF 7) with varying lipid: polymer ratios, and those containing drug as well as Shankhpushpi (NF 8 to NF 14) for 24 hours and the results obtained were presented in Table 3. All of the nano

formulations (NF 1-NF7) were shown to have good in vitro drug release profile. They showed early drug release as a burst, but afterwards it was seen as a steady drug release, as illustrated in Figure 2. Lower concentration of lipid retarded the drug release whereas higher concentration showed faster drug release nearly 50% at end of 5th hour. This shown unequivocally that cumulative percent drug release reduced when drug pay-load rose, and vice versa. Hence, it may be said that a higher drug payload led to a longer drug release time. The results of the study showed that NF-4 exhibited the best drug release, with a release rate of 76.46% in 24 hours. This is an important finding because the release rate of a drug from a nanoparticle formulation may affect its pharmacokinetic and pharmacodynamic properties. The lipid: polymer ratio is an important parameter that can impact the physicochemical properties of PLHNs and their drug release behavior. In the study, the lipid: polymer ratio of NF-4 was 20:10, which may have contributed to its superior drug release performance. The lipid component of PLHNs can provide a hydrophobic environment for the encapsulated drug, while the polymer component can impart stability to the nanoparticles and control their drug release behavior. The optimal ratio of lipid to polymer can vary depending on the specific drug and the desired drug release profile. Formulation NF-11 showed maximum release up to 79.19%, at the end of 24 hours.

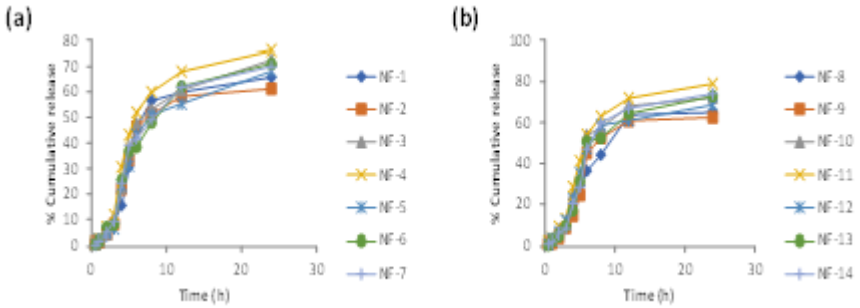

Figure 2: %Cumulative drug release profile of Polymeric lipid hybrid formulation of drug RHT (NF 1- NF 7) and (b) %cumulative drug release profile of PLHN containing both drug RHT and Shankhpushpi (NF 8-NF 14)

Table 3: Shows the % cumulative drug release from different formulations for 24hrs

Time (h)	% Cumulative Drug Release from different formulations													
	NF-1	NF-2	NF-3	NF-4	NF-5	NF-6	NF-7	NF-8	NF-9	NF-10	NF-11	NF-12	NF-13	NF-14
0.5	0.65	0.96	1.00	1.02	0.86	0.78	0.46	1.62	0.98	1.35	1.84	1.22	0.56	1.05
1	1.33	1.56	2.21	2.36	2.14	1.73	1.87	2.14	1.55	2.88	3.26	3.1	2.36	1.96
2	4.23	4.69	4.97	6.93	5.21	6.82	4.98	6.56	4.23	7.53	8.93	6.25	5.00	5.78
3	9.35	8.13	10.24	11.68	6.25	8.00	9.16	9.48	8.21	10.00	12.68	11.98	9.23	7.88
4	15.43	21.82	22.45	30.52	23.26	25.51	24.26	18.66	14.28	24.57	28.52	22.39	16.87	20.12
5	30.78	33.36	36.88	43.12	31.00	36.72	39.11	29.00	24.35	32.05	41.12	35.14	31.14	28.36
6	46.17	46.29	47.72	52.00	43.21	38.36	41.63	36.28	45.03	53.86	54.00	47.23	50.72	46.98
8	56.58	51.37	53.23	60.00	51.00	47.87	49.13	44.13	52.39	57.27	63.00	58.69	52.36	59.78
12	60.00	58.23	60.71	68.00	55.36	62.14	61.9	63.79	60.88	68.16	72.00	61	64.37	67
24	65.74	61.28	72.52	76.46	68.12	71.02	70.00	65.00	62.51	72.23	79.19	68.64	72.98	74.08

4. Summary and Conclusion

PLHN were well prepared by using film hydration method. One set containing drug Rivastigmine (NF 1 to NF 7) alone and second set contains drug Rivastigmine and Shankhpushpi (NF 8 to NF 14). Two optimized formulations were selected from fourteen sets of hybrid nanoparticles with various concentrations of lipid, herbal extract, and polymer PLGA. Optimization was done using mean particle size, zeta potential, PDI, turbidity measurements, drug loading and entrapment efficiency. Zeta potential of selected formulations NF4 and NF 11 was found -27.9 ± 2.2 and -35 ± 0.3 mV, particle size 198.6 ± 7 and 295 ± 16 nm respectively. Both NF4 and NF11 were further characterized using TEM, FTIR, XRD and DSC. Further, formulation NF-4 showed maximum release of 76.46% the drug at the end of 24 h and NF-11 showed the release up to 79.19%, in 24th hours. Anti-Alzheimer's activity was further confirmed by *in vivo* studies. All formulations were found stable with respect to particle size and drug loading for 4-week period under 5±3ºC/ 75± 5%RH and 40±2ºC/ 75± 5%RH. Results confirm the effectiveness of these nanocarriers as potential alternative for treatment of Alzheimer's disease.

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