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# Phospholipid Based Nano Drug Delivery Systems of Phytoconstituents

Mohammad Hossain Shariare and Mohsin Kazi

## Abstract

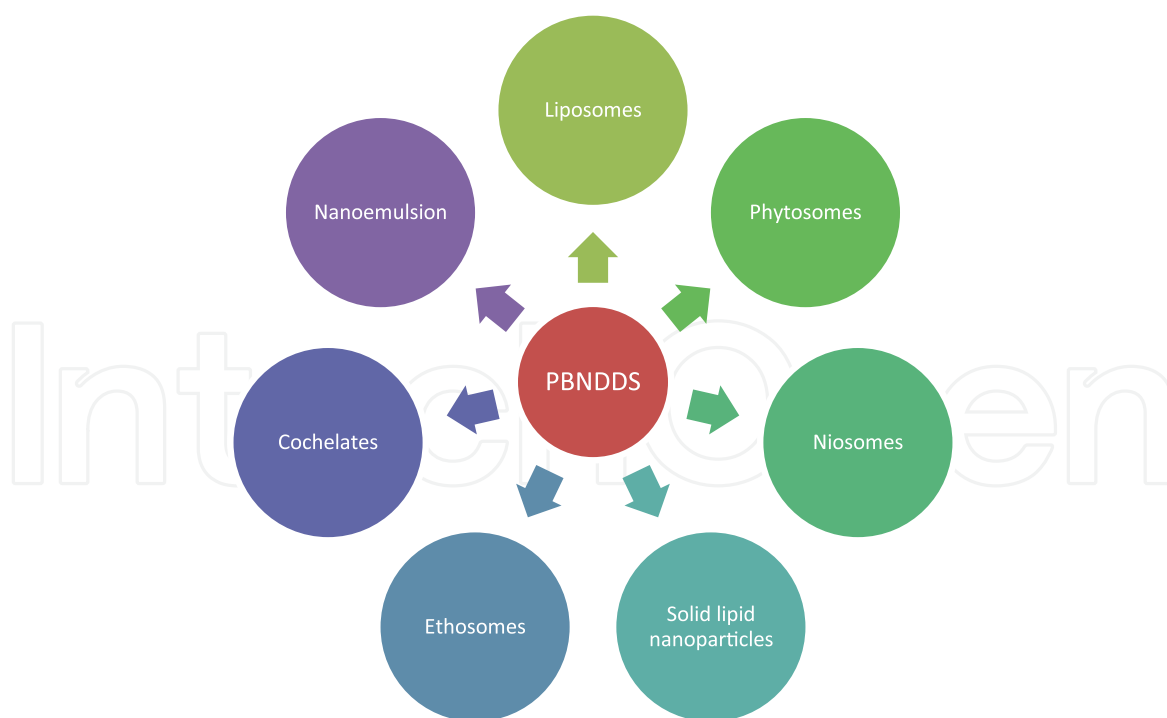
The development of phytochemistry and phyto-pharmacology has enabled elucidation of composition and biological activities of several medicinal plant constituents. However phytoconstituents are poorly absorbed due to their low aqueous solubility, large molecular size and poor membrane permeability when taken orally. Nanotechnology based drug delivery systems can be used to improve the dissolution rate, permeability and stability of these phytoconstituents. The current chapter aims to present the extraction of phytoconstituents, their identifications, and development/utilization of phospholipid based nano drug delivery systems (PBNDDS). The content of the chapter also provides characteristic features, *in-vitro*, *in-vivo* evaluations and stability performance of PBNDDS. The results from the UHPLC and GC-MS showed different phytoconstituents in the extracted samples with quantitative value. Dynamic light scattering (DLS) data showed PBNDDS of different phytoconstituents in the range of 50–250 nm with PDI value of 0.02–0.5, which was also confirmed by the electron microscopic data. Phytoconstituents loading or entrapment for PBNDDS was in the range of 60–95%. PBNDDS exhibited better *in-vitro* and *in-vivo* performance with improved Physico-chemical stability.

**Keywords:** phospholipid, liposome, phytosome, epigallocatechin gallate (EGCG), phytol, *Aphanamixis polystachia*, thymoquinone

## 1. Introduction

Phospholipid based nano drug delivery systems (PBNDDS) are becoming more promising due to its biocompatibility, amphiphilic characteristics, Physico-chemical stability and can be prepared for different diseases with sustain release and targeted delivery of different drugs [1]. PBNDDS can protect the drug from biodegradation, transformation and reduce cell toxicity by altering the bio-distribution. PBNDDS are easy to scale-up, sterilize in product development and cost effective. PBNDDS performance depends on size, morphology of particles and possesses some unique properties like surface area to mass ratio which is larger than other colloidal systems. Controlled release and targeted drug delivery depend on the rate and mechanism of drug release from the carrier based drug delivery systems like PBNDDS, which can vary depending on the formulation, processing and routes of administration [1–6].

Phospholipids are heterolipids which can be extracted from both animal and plant origin, have been shown to generate lipid matrices of low crystallinity.



**Figure 1.**  
Phospholipid based nano drug delivery systems (PBNDs) [1–3].

Different types of phospholipid based nano drug delivery systems (**Figure 1**) are used for both synthetic and natural source of drugs [7, 8].

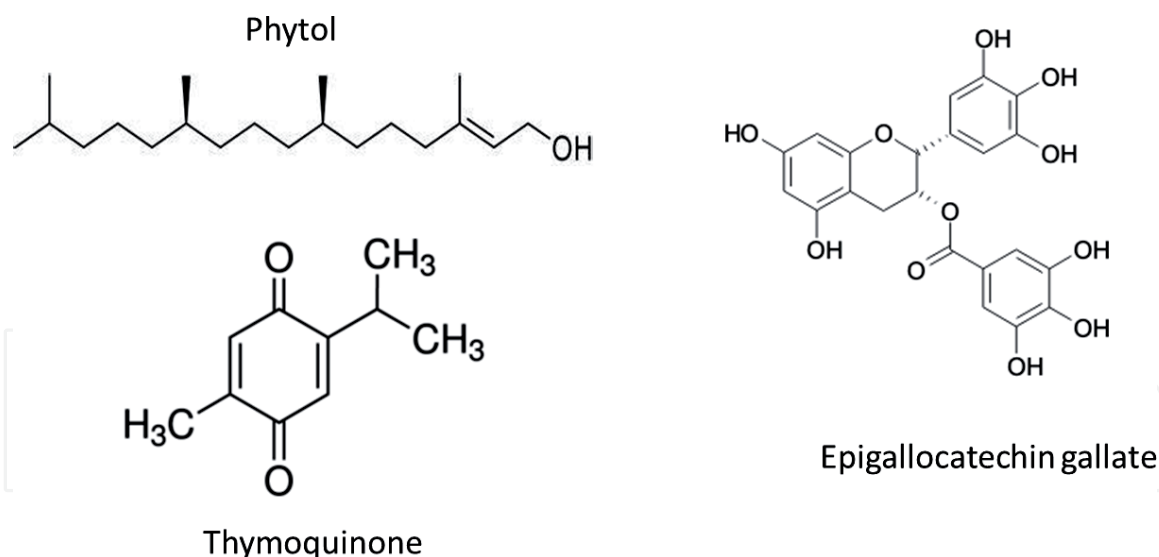
Natural source of medicines have been used from ancient time [9]. Phytoconstituents present in plants having different pharmacological properties are useful substitutes to synthetic drugs. There are over 100 active ingredients derived from natural plants for use as drugs and medicines. Chronic inflammatory (stroke, chronic respiratory diseases and heart disorders), and central nervous system (CNS) diseases are major cause of global mortality. Different synthetic drugs used to treat these diseases results in severe adverse effects. Research is going on for the development of new drugs from natural medicinal plants [10].

Phytoconstituents showed strong anti-inflammatory activities due to their strong free radical scavenging action [11] and have shown beneficial effects on cancers, diabetes, cardiovascular diseases, stroke and obesity etc. Phytoconstituents also exhibit activity against neurodegenerative diseases (Alzheimer's disease, and Parkinson's disease) through different pathways [12–21].

## 2. Natural plant extract and phytoconstituents

In this chapter four different plant extracts and its phytoconstituents (Black seed oil containing thymoquinone, Jute leaf extract containing phytol, *Aphanamixis polystachia* leaf extract, green tea extract containing EGCG) are discussed (**Figure 2**), which were formulated as phospholipid based nano drug delivery systems (PBNDs).

Thymoquinone a natural component of Black seed oil, which can be obtained from the seeds of *Nigella sativa*, found to have different pharmacological activity for the treatment of various diseases [22–26]. However, despite the various pharmacological properties of thymoquinone, its administration *in-vivo* remains crucial due to its poor water solubility and stability issues. Therefore an advanced drug



**Figure 2.**  
 Chemical structure of phytol, thymoquinone and epigallocatechin gallate.

delivery system is required to improve the therapeutic outcome of thymoquinone by enhancing the solubility and stability in water [27].

Jute leaf obtained from *Corchorus olitorius* L. [28, 29] has been used as traditional medicine. Jute leaf extract contains different phytoconstituents which are medicinally active and exhibits pharmacological effects against different diseases [30–33]. Phytol is one of the main phytoconstituents found in jute leaf extract demonstrates pharmacological activity against different diseases and in different *in-vitro* cell line studies [29, 34]. Phytol due to its multiple ring structure shows poor water solubility and absorption through the intestinal wall.

*Aphanamixis polystachya* a natural plant which contains phytoconstituents found to have different medicinal activities [35–38]. Leaf extract of *A. polystachya* plant showed CNS activities [39], therefore in this chapter *A. polystachya* leaf extracts and its phospholipid based nano drug delivery system (PBNDDS) activity against animal model of dementia is discussed.

Epigallocatechin-3-gallate (EGCG) is a main potent constituent of green tea extract (*Camellia sinensis*), which is one of the major catechins [40]. EGCG exhibit pharmacological activity against different diseases [41, 42] and also showed activity against carcinogenic effects in different animal models with different cancers [43–46]. EGCG has high water solubility however it exhibits low permeability across the gastrointestinal tract (GIT) leading to poor bioavailability [47, 48].

### 3. Issues with natural phytoconstituents

Phytoconstituents showed a range of pharmacological activity and less side effects compared to synthetic drugs; however phytoconstituents exhibit low water solubility, poor permeability through gastrointestinal tract and impede fast systemic clearance [49]. Physical and chemical stability of phytochemicals is another issue [50–54]. Treatment of CNS and cancer diseases require targeted drug delivery for better therapeutic outcome. Nano drug delivery systems may be a promising platform for the improvement of aforementioned issues of natural plant extracts and their phytoconstituents. Therefore phospholipid based nano drug delivery systems of natural phytoconstituents could be the potential delivery system with better performance and stability [55].

#### 4. Nanoparticle based drug delivery of phytoconstituents

Novel nano drug delivery systems can improve the solubility, permeability, physicochemical stability and reduce toxicity of drugs [52]. Previous studies showed that the phospholipid based nano drug delivery systems can improve the oral delivery of thymoquinone [56, 57], and effective against breast cancer cell line. Mesoporous silica and chitosan nanoparticles are developed for delivery of thymoquinone to the brain [58]. In other study self nanoemulsifying and alginate beads delivery system were developed to improve the bioavailability, stability and targeted delivery of black seed oil [59].

Nanoparticulate based drug delivery system of phytol was used for Alzheimer's disease [60]. Previous research also showed strong cytotoxic, anti-phytopathogenic and hepatoprotective effect of phytol loaded nano drug delivery systems [61, 62]. Phospholipid based nano formulation of EGCG are developed to enhance the release characteristics, bioavailability, and stability [63–66]. Previous study data suggest that nanoparticulate based delivery of EGCG showed better cytotoxic and *in-vivo* performance compared to pure EGCG [67–69].

#### 5. Phospholipid based nano drug delivery systems (PBNDDS) of plant extracts and phytoconstituents

Two types of phospholipid based nano drug delivery systems (PBNDDS) have been discussed in this chapter for four different natural extracts and its phytoconstituents, which are liposomes and phytosomes.

Liposome is a phospholipid based lipid bilayer vesicles where both hydrophilic and lipophilic drugs can be entrapped. Liposomal drug delivery system has become a budding technology for delivering drugs to improve the bioavailability, efficacy, safety and stability of both synthetic and natural source of medicines [70, 71]. Liposomal drug delivery system can be used to deliver drugs for neurodegenerative diseases through blood brain barrier (BBB) [72–74].

Phytosomes are structures prepared using natural plant extract with phospholipid matrix. Phytosomal delivery system can improve the absorption and bioavailability of phytoconstituents. In phytosome drug form complex with phospholipid like matrix formation while in liposomes, drug is entrapped in the core or lipid bilayer of phospholipids. Phytoconstituents of plant extracts showed better biological activity when delivered through phytosomes [75–79].

This chapter is mainly focused on the development, preparation and solid state characterization of liposomal drug delivery systems of black seed oil, *A. polystachya* leaf extracts and *Corchorus olitorius* leaf extracts and their main phytoconstituents. Phytosomal delivery system development of green tea extract and EGCG is also discussed with different solid state characterizations. Finally stability, *in-vitro* and *in-vivo* studies were discussed for phospholipids based nano preparations of all extracts and their phytoconstituents.

Phospholipid can be extracted from both plant and animal source of origin. Phospholipid used in these studies was extracted from egg yolk, which is known as lecithin or egg lecithin. Results (UHPLC data) showed the presence of phosphatidylcholine (PC) peak (the main phospholipid component for liposome) and suggest that per gram of egg lecithin contain 100–200 mg of PC, where filtrate of egg phospholipid contain the most of the PC content compared to solid residue (Table 1) [80]. Phosphatidylcholine (PC) content was also quantified for peanut using UHPLC analysis and results demonstrate that less amount of PC is present in per gram of peanut (Table 1).



Sample no/name	Mass (mg/g)	%
Egg sample 1 (filtrate)	212.80 ± 3.22	21.38
Egg sample 2 (solid residue)	9.71 ± 1.19	0.97
Peanut	5.56 ± 0.27	0.56

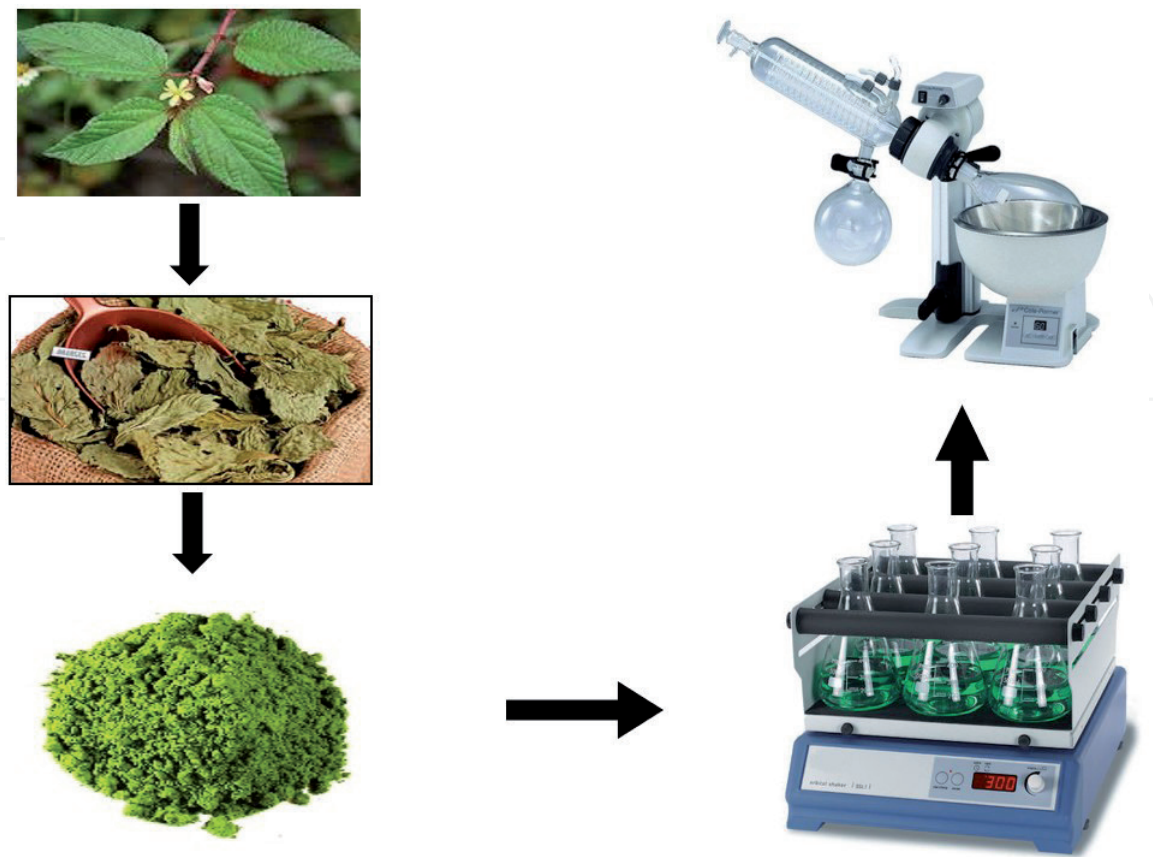
**Table 1.**  
Amount of PC present in egg yolk. Sample 1 represents extracted PC as filtrate and sample 2 represents PC as solid residue. Data are mean ± SD (N = 3).

## 6. Plant extraction, identification and quantification by UHPLC and GC-MS

All four plants described in this chapter was extracted using maceration method (Figure 3). Plant extraction, its phytoconstituents identification and quantification were performed using UHPLC and GC-MS analytical methods [80–83]. Results from UHPLC data showed that the concentration of thymoquinone was  $2.28 \pm 0.68$  mg/g of black seed oil [80].

Table 2 shows main phytoconstituents determined for *Aphanamixis polystachya* leaf extracts using GC-MS including Octadec-9-enoic acid, hexadecanoic acid, 2-Pentanone, 2-hydrazino-2-imidazoline and beta-elemene etc. [81]. Previous researches in this area suggest that these phytoconstituents exhibit strong antioxidant, anticancer and anti-inflammatory property [84–88], which found to have impact in neurodegenerative disorders including stroke [89–92]. However few of these phytoconstituents have poor solubility in water.

Major phytoconstituents present in the methanolic extract of *Corchorus olitorius* leaf are mentioned in Table 3, which are oleic acid, hexadecanoic acid, and



**Figure 3.**  
Plant extraction process using maceration method.

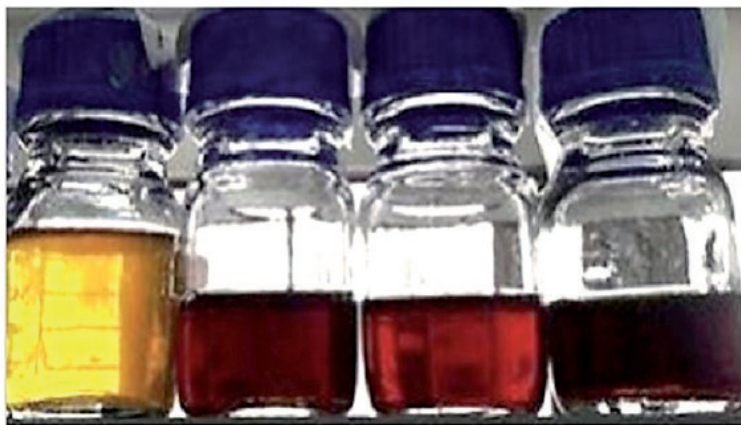
No.	Name	RT	Area %	N area %
1	4-hexen-2-one	4.68	1.72	6
2	Acetic acid, butyl ester	5.06	2.36	8.24
3	3-acetoxydodecane	5.68	1.83	6.39
4	2-pentanone	5.88	14.62	51.08
5	4,4-dimethyl-1-hydroxy-2-cyclo	8.94	2.55	8.92
6	Acetic acid, hexyl ester	10.78	4.73	16.53
7	1,2-cyclohexanediol	13.76	4.12	14.39
8	Acetic acid	15.4	4.05	14.14
9	2-hydrazino-2-imidazoline	17.6	3.41	11.91
10	Beta-elemene	22.4	0.4	1.39
11	5-hydroxypipelicolic acid	29	1.88	6.56
12	2-hexadecen-1-ol, 3,7,11,15-TE	33.36	0.63	2.19
13	Octadecanal	33.48	0.67	2.36
14	9-hexadecenoic acid	35.88	5.66	19.77
15	Hexadecanoic acid	36.32	8.83	30.84
16	4-hydroxytetradec-2-ynal	38.96	1.69	5.89
17	Octadec-9-enoic acid	39.72	28.63	100
18	1.beta.-allylperhydro-2.alpha.	44.32	1.32	4.6
19	Cyclopentadecanone	44.86	4.02	14.02
20	1-tetradecene	45.82	3.18	11.09
21	Tridec-4-en-2-ynal	50.06	3.71	12.96

**Table 2.**  
*List of major components present in the ethanolic leaf extract of *Aphanamixis polystachya* (adapted from [81]).*

No.	Name	RT	Area %	N area %
1	2,3-dihydro-3,5-dihydroxy-6-me	15.1	4.58	8.08
2	D-neoisomenthol	15.9	1.21	2.14
3	Neophytadiene	33.36	1.15	2.02
4	Tetradecanoic acid	35.3	3.25	5.72
5	14-pentadecenoic acid	35.9	4.31	7.6
6	Hexadecanoic acid	36.36	16.16	28.48
7	Hexadecanoic acid	37.28	1.54	2.72
8	Caryophyllene diepoxide	38.7	1.76	3.1
9	2-hexadecen-1-ol	38.96	6.48	11.41
10	Oleic acid	39.76	56.75	100
11	9-tricosene	41.84	2.81	4.94

**Table 3.**  
*List of major components present in the methanolic leaf extract of *Corchorus olitorius* (adapted from [82]).*

2-hexadecan-1-ol (phytol) etc [82]. Chromatographic results also suggest that 500 µg EGCG was present in one milliliter of green tea leaf, which was extracted using water as solvent at different temperatures [83]. Results also suggest that

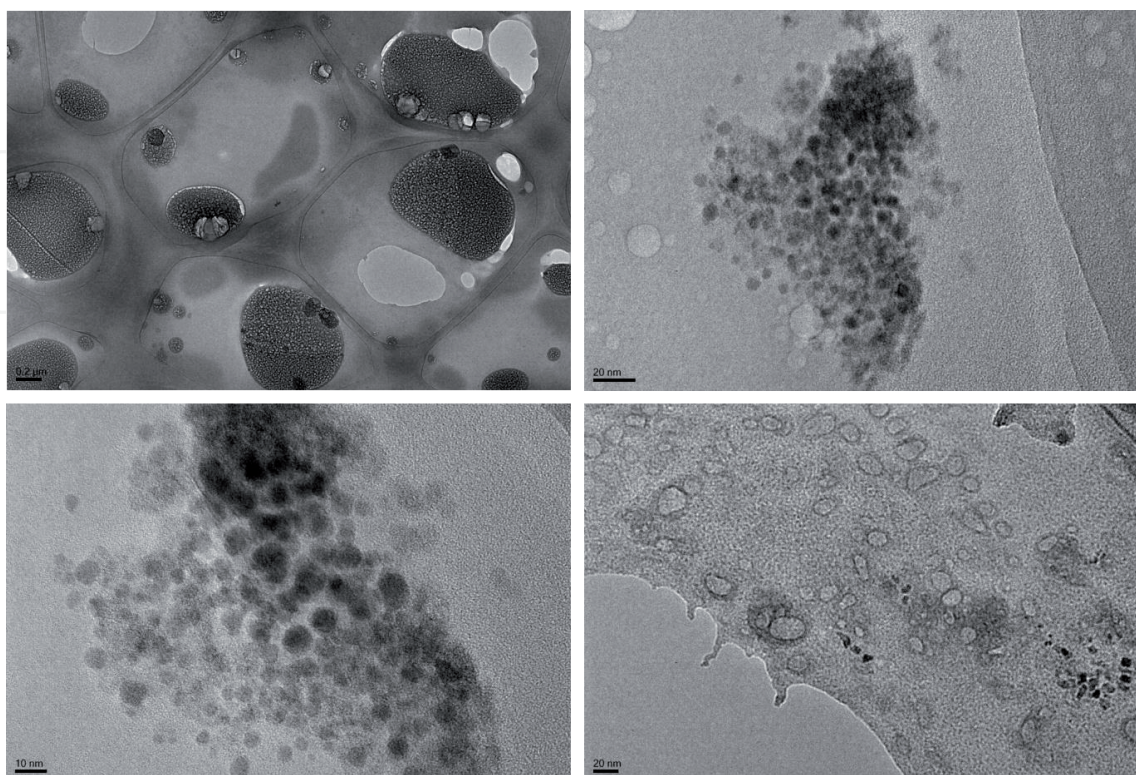


**Figure 4.**  
*Green tea leaf extracted at different temperature using water as solvent.*

extraction process performed at high temperature (80°C) exhibited high content of EGCG, which was also observed by other research study (**Figure 4**) [83].

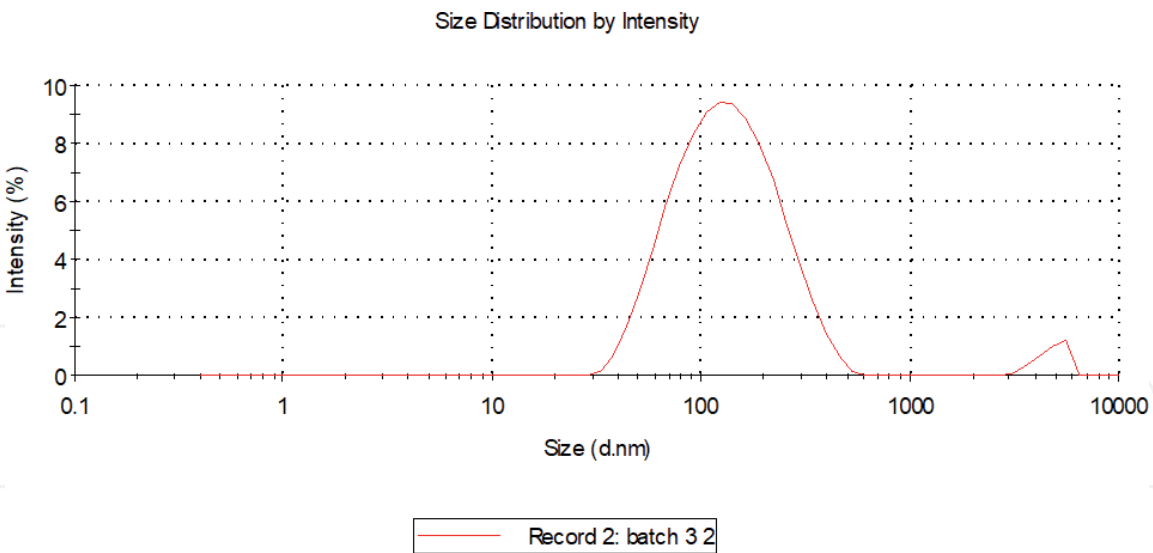
## 7. Preparation of PBNDDS of plant extracts and its phytoconstituents

Phospholipid based nano drug delivery systems using liposomes & phytosomes were prepared for plant extracts and phytoconstituents. Phospholipid based nano drug delivery systems (PBNDDS) batches of plant extracts and its phytoconstituents showed average particle size of 50–250 nm, PDI value of 0.02–0.5 and entrapment efficiency up to 90% (**Figures 5 and 6**). It was observed that the average size, polydispersity and entrapment efficiency of PBNDDS were markedly affected by the process and formulation factors used in different studies.



**Figure 5.**  
*TEM images for PBNDDS of phytoconstituents.*



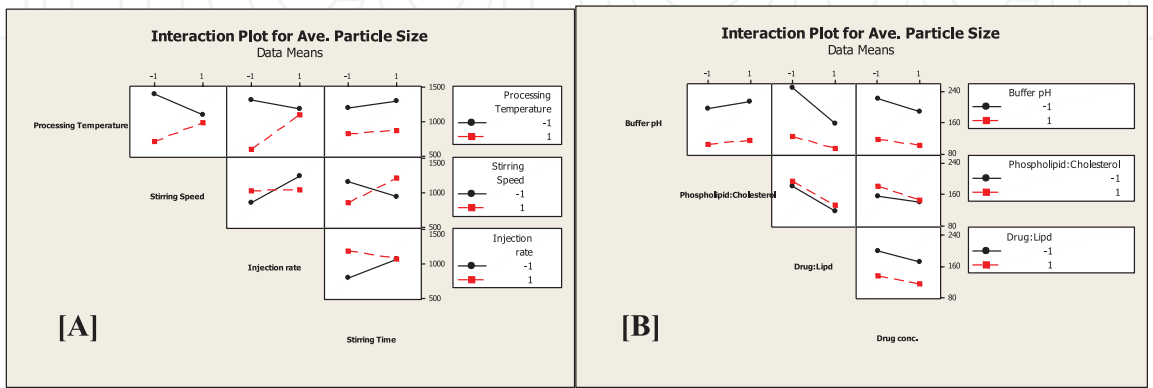


**Figure 6.**  
*DLS data of PBNDDS of phytoconstituents.*

Entrapment efficiency of black seed oil loaded liposomes was increased markedly while cryoprotectant (sugar) and cholesterol were used in the preparation of liposomes. It was also observed that entrapment efficiency of liposomes was high for larger sized liposomes compared to small average size of liposomes.

**8. Effect of process parameters and formulation attributes on development of PBNDDS of plant extracts and its phytoconstituents**

Process parameters perspective injection rate, stirring speed, stirring time and processing temperature (solvent-antisolvent mixing) found to have marked impact on the average particle size, polydispersity and entrapment efficiency of PBNDDS [80–83, 93, 94]. It was observed that high injection rate and processing temperature found to have major impact leading to low average size of phospholipid based nano drug delivery systems (PBNDDS). Low stirring speed (<1000 rpm) and stirring time exhibit low average size of PBNDDS. Interactions between process parameter also have marked impact on average size of PBNDDS, where batches prepared using high injection rate and slow stirring speed demonstrate low average size (**Figure 7a and b**).



**Figure 7.**  
*Two way interaction plots of [A] process parameters and [B] formulation attributes for average particle size of PBNDDS.*

Processing temperature found to be the most important process parameters which have significant impact on entrapment efficiency or loading of phytoconstituents on PBNDDS [83]. PBNDDS prepared using high temperature and injection rate leading to low entrapment efficiency. This phenomenon also probably related to low average size of PBNDDS developed at these conditions, while PBNDDS with high average particle size having high entrapment or loading efficiency. Polydispersity of PBNDDS was markedly affected by processing temperature and stirring speed and suggesting that batches processed at low temperature and high stirring speed found to be less polydispersed [81, 82].

Formulation attributes - ratio of drug: phospholipid and phospholipid: cholesterol, solvent system and its properties (phytoconstituents solubility, pH of the solvent), drug concentration found to have major impact on average particle size, polydispersity and entrapment efficiency of PBNDDS of phytoconstituents [80–83].

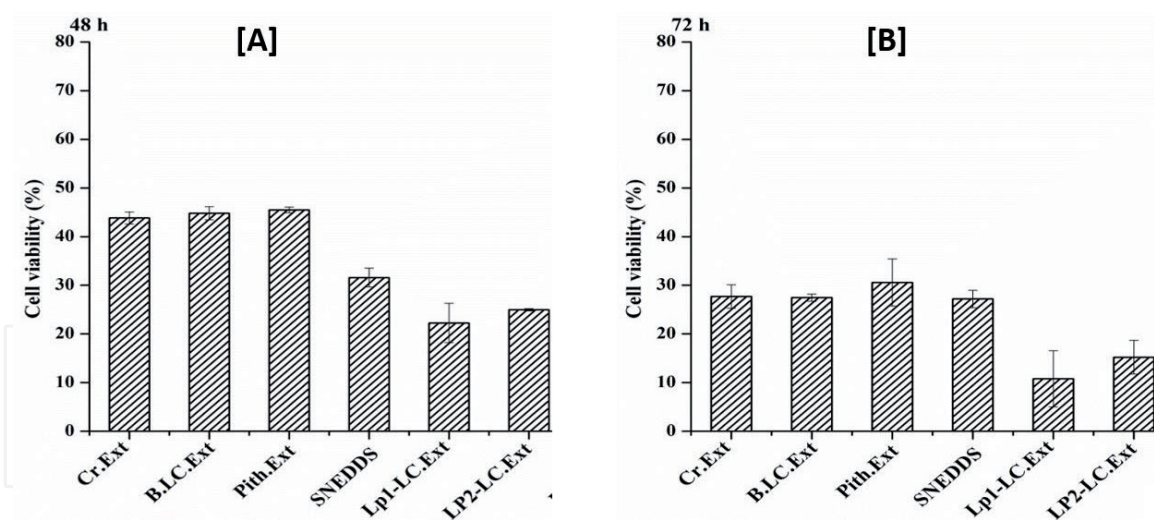
It is very imperative to find out the optimum level and amount of each of these process parameters and formulation attributes to achieve low average size with high entrapment or loading of phytoconstituents for PBNDDS. It was evident that not only the impact of individual parameters but its interactions also exhibited marked impact on the average size and loading of phytoconstituents for PBNDDS (Figure 7) [81–83].

## 9. Stability study of PBNDDS of phytoconstituents

Stability study data suggest that PBNDDS of phytoconstituents prepared using egg phospholipid were stable at 25°C and 65% RH for three months compared to accelerated conditions (10°C/45% RH and 40°C/75% RH) [80]. However previous research study suggested that PBNDDS developed using DPPC was more stable at 10°C/45% RH compared to other storage conditions [95]. This phenomenon probably related to egg phospholipid composition which is different from DPPC. DPPC is only one type of phosphatidylcholine, while egg phospholipid (lecithin) contains multiple types of phosphatidylcholine and phospholipids. PBNDDS blank and phytoconstituents loaded PBNDDS were studied using gastric media (pH 1.2) to evaluate the physical stability of PBNDDS. It was observed that PBNDDS batches of phytoconstituents were stable in gastric medium after 4 hours (maximum transit time in the stomach) and also suggests that no physical changes (precipitation or degradation) were observed for PBNDDS prepared using egg phospholipid even after 24 hrs [81].

## 10. *In-vitro* and *in-vivo* study of PBNDDS of phytoconstituents

Sustain release of phytoconstituents was observed when delivered through PBNDDS, which can be utilized for better therapeutic outcome against certain diseases. PBNDDS of phytoconstituents demonstrate better performance during *in-vitro* cancer cell line study performed on different cell lines. *In-vitro* cell line study data suggest that PBNDDS of phytoconstituents showed better activity in terms of % cell viability against AML and leukemia cell line compared to pure



**Figure 8.**

*In-vitro* cell line study of plant extracts and PBNDDS of different plant extracts after [A] 48 h and [B] 72 h.

phytoconstituents only. It was also observed that PBNDDS of phytoconstituents showed better activity against specific AML and leukemia cell lines compared to all cell lines used in the study. This is possibly due to more permeability of PBNDDS occurred through those specific cell lines, which suggest that PBNDDS may be selective for specific cancer cell lines which may be related to the phospholipid composition, type and drug delivered through PBNDDS [82]. PBNDDS of different phytoconstituents also exhibited better activity against breast cancer cell line (MCF7) study compared to phytoconstituents in isolation (**Figure 8**).

Significant improvement was observed for *in-vivo* analgesic activity for the PBNDDS of black seed oil containing thymoquinone compared to black seed oil only and control groups. This phenomenon probably related to the improve bioavailability of thymoquinone when delivered through PBNDDS. Previous research study also showed analgesic and anti-inflammatory activity for black seed oil containing thymoquinone [80, 96].

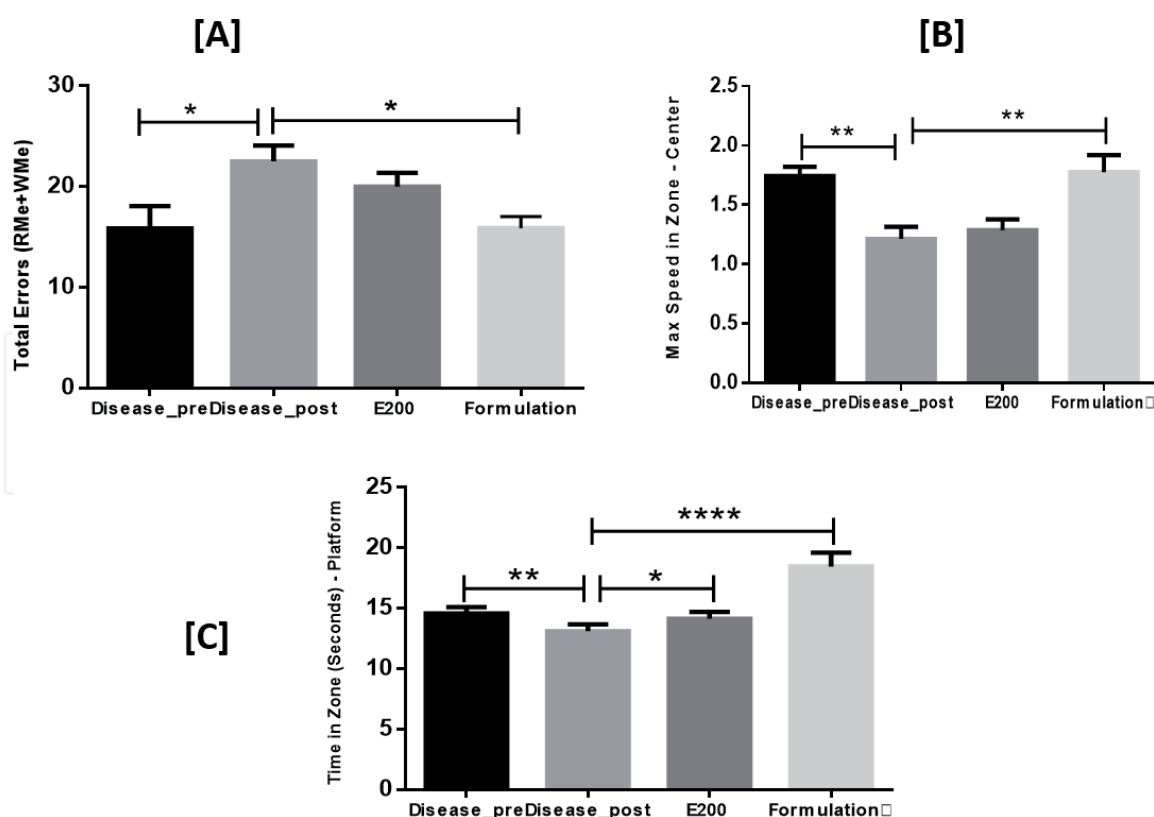
Strong anti-inflammatory activity was observed for different plant extracts and its phytoconstituents against carrageenan induced paw edema (**Table 4**). It was also observed that plant extract and phytoconstituents delivered through PBNDDS exhibit better anti-inflammatory activity, which is possibly due to enhancement of dissolution, bioavailability and stability of phytoconstituents when delivered through PBNDDS [81–83].

Neurobehavioral study of PBNDDS of phytoconstituents was performed using open field, arm maze and water maze studies (**Figure 9**). Marked improvement in locomotor activity, ambulatory performance and memory function of dementia induced mice model was observed for PBNDDS of phytoconstituents compare to disease and plant extract groups [81]. This phenomenon probably related to strong anti-inflammatory along with antioxidant activities observed for the plant extract in different research studies. CNS inflammation is one of the pathway for developing neurodegenerative disorders, therefore by reducing inflammation significantly through PBNDDS of plant phytoconstituents in dementia induced mice model might be an option to treat neurodegenerative disease. Natural phytoconstituents may contain some ingredients which also can be effective against neurodegenerative disease through another mechanism of action which need to be confirmed in future study.

Time	Positive control	<i>Corchorus olitorius</i> leaf extract		Extract PBNDDS		Standard	
	Paw volume (ml)	Paw volume (ml)	(%) Reduction	Paw volume (ml)	(%) Reduction	Paw volume (ml)	(%) Reduction
5 h (1 day)	1.95 ± 0.15	1.31 ± 0.24	30.98	1.31 ± 0.35	33.5	0.75 ± 0.08	59.32
2 days	1.74 ± 0.32	1.20 ± 0.30	29.6	0.88 ± 0.34	50	0.20 ± 0.04	88.04
4 days	1.08 ± 0.20	0.45 ± 0.22	55.57	0.30 ± 0.27	79.06	0.14 ± 0.05	89.1
Time	Positive control	Green tea leaf extract		Extract PBNDDS		Standard	
	Paw volume (ml)	Paw volume (ml)	(%) Reduction	Paw volume (ml)	(%) Reduction	Paw volume (ml)	(%) Reduction
5 h (1 day)	1.92 ± 0.14	1.40 ± 0.12	25.8	1.80 ± 0.11	7.5	0.78 ± 0.08	59.02
2 days	1.70 ± 0.30	1.05 ± 0.10	37.52	1.35 ± 0.12	21.93	0.34 ± 0.09	80.67
4 days	1.05 ± 0.20	0.48 ± 0.13	52.53	0.51 ± 0.15	67.64	0.12 ± 0.05	88.78
Time	Positive control	<i>A. polystachya</i> leaf extract		Extract PBNDDS		Standard	
	Paw volume (ml)	Paw volume (ml)	(%) Reduction	Paw volume (ml)	(%) Reduction	Paw volume (ml)	(%) Reduction
5 h (1 day)	1.90 ± 0.15	1.12 ± 0.18	39.8	0.62 ± 0.17	68.54	0.76 ± 0.08	61.02
2 days	1.71 ± 0.32	0.90 ± 0.07	46.56	0.34 ± 0.13	80.68	0.37 ± 0.09	79.05
4 days	1.06 ± 0.20	0.63 ± 0.06	40.21	0.08 ± 0.05	92.73	0.12 ± 0.05	88.79

**Table 4.**  
*Anti-inflammatory studies of plant extracts, and its PBNDDS (adapted from [81–83]).*





**Figure 9.**

[A] Number of total errors for different mouse groups in arm maze study [B] maximum speed into central zone for different mouse groups in open field study [C] time spent on platform for different mice groups in water maze study (where \*\*\*\* means  $p \leq 0.0001$ , \*\* means  $p \leq 0.01$  and \* mean  $p \leq 0.05$ ) [four different groups—1. Pre disease group 2. Post disease group 3. E 200 - extract group and 4. Formulation—PBNDDS of extracts] (adapted from [81]).

## 11. Conclusion

Plant extract found to have a range of major phytoconstituents which were identified and quantified by UHPLC and GC-MS. Major phytoconstituents demonstrate marked pharmacological activities which were evident by different *in-vitro* and *in-vivo* studies. Phytoconstituents delivered through PBNDDS exhibit better performance compared to phytoconstituents in isolation. It was observed that process parameters and formulation attributes showed significant impact on average size, polydispersity and entrapment or loading of phytoconstituents for PBNDDS. Processing temperature, injection rate, solvent system properties (pH, solubility level), phospholipid concentration related to drug and cholesterol are major factors affecting the quality output of PBNDDS. PBNDDS prepared using egg phospholipid was physico-chemically stable even at ambient conditions (25°C, 60% RH). This phenomenon might be a great advantage for developing PBNDDS of different phytoconstituents for improving the bioavailability, stability and targeted drug delivery. PBNDDS also exhibit better selective activity against cancer cell lines which is an indication for treating different types of cancer by developing PBNDDS using different formulation attributes. PBNDDS also showed better analgesic, anti-inflammatory and neurobehavioral activities compared to phytoconstituents only. Therefore PBNDDS can be a promising platform for delivering phytoconstituents with better therapeutic outcome. PBNDDS having average size of <150 nm with  $\geq 85\%$  entrapment or loading might exhibit desirable performance to treat chronic inflammatory disease, cancer, and CNS diseases.

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## Conflict of interest

The authors declare no conflict of interest.

## Author details


Mohammad Hossain Shariare<sup>1\*</sup> and Mohsin Kazi<sup>2</sup>

1 Department of Pharmaceutical Sciences, North South University, Dhaka, Bangladesh

2 Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia

\*Address all correspondence to: [mohammad.shariare@northsouth.edu](mailto:mohammad.shariare@northsouth.edu)

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