RESEARCH ARTICLE

Formulation and Evaluation of Niosome Containing Haloperidol for the Treatment of Psychosis

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ABSTRACT

Objectives: The goal of the current study was to address the medication's issues, including bioavailability, dose regimen reduction, half-life, and the suitability of niosomal formulation as a drug carrier.

Techniques: Using the Ether injection technique, the niosomal suspension was made by adjusting the concentration of span 60 and the ratios of span 60 to cholesterol. The nine created formulas were assessed based on a number of criteria.

Findings: The validity and purity of the haloperidol were verified by the FTIR and DSC observations. The niosomal dispersion was fluid, odorless, and off-white in hue. It showed no signs of sedimentation and was steady. The pH was discovered to be between 4.6 and 5.4. The drug content was discovered to be between 89.13 and 99.52. The vesicular size of the improved formulation ranged from 2.52 to 3.42 μm. The range of the entrapment efficiency was 79.05 to 98.24. 98.24% was the maximum trapping efficiency. Zeta potential levels were discovered to fall between 20.29 to -30.55 mV. By the conclusion of the 24th hour, the maximal drug release (98.55%) was achieved.

The current investigation comes to the conclusion that the created niosomal solution is an effective and practical delivery system for antipsychotic medications. In addition, it offered regulated medication delivery.

Keywords: Niosomes, Cholesterol, Ether injection method, Vesicular size, Controlled drug delivery.

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INTRODUCTION

After being hydrated in aqueous medium, a combination of cholesterol and a single alkyl chain non-ionic surfactant forms tiny lamellar structures called niosomes. Both hydrophilic and hydrophobic APIs are capable of being handled by niosomes.[1] The surfactant used to make Niosome is inexpensive, precise in its composition, and chemically stable. Niosomes delay the release of the encapsulated API and are more stable than liposomes. Niosomes can be administered intravenously, intramuscularly, subcutaneously, ocularly, orally, or transdermally.[2]

Niosome Structure

The vesicle-forming amphiphile, or non-ionic surfactant, found in niosomesis stabilized by the addition of cholesterol and a little amount of anionic surfactant, which also aids in vesicle stabilization.[3]

Advantages[4]

- Increased patient adherence
- Utilization of several APIs
- The vehicle may be altered to meet needs.
- Increase the bioavailability of APIs; operate as a depot to release the drug gradually, allowing for regulated release; are extremely stable and osmotically active; and don't require any specific storage conditions.
- Increase API penetration;
- Target medication delivery;
- Biodegradable, biocompatible, and non-immunogenic

Drawbacks[4]

- Aggregation, fusion, flow of embedded medicines, and physical instability
- The dispersion's shelf life is shortened by hydrolysis of encapsulated medications.

Composition[5]

1. Cholesterol is one of the two main ingredients required to create niosomes.
2. Surfactants without ions

Production Techniques[6]

Because it affects the number of bilayers, size, size distribution, entrapment efficiency, and permeability, the manufacturing process should be selected based on the niosome's intended function.

1. The procedure of ether injection
2. The thin film hydration approach, or hand shaking method
3. The Sonication Technique
4. The Method of Microfluidization
5. The process of multiple membrane extrusion
6. The technique of reverse phase evaporation (REV)

Use[4]

Drug targeting; cancer treatment; dermal and mucocutaneous infections; delivery of peptide APIs; immunological response research; hemoglobin transport; use in a variety of drug delivery systems, such as transdermal and ophthalmic; and use in SR and cosmetics to improve the safety and effectiveness of API.

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Table 1: Formulations of Haloperidol loaded Niosomes

Sr. No.	Formulation Code	Haloperidol (%)	Span 60 (%)	Cholesterol (%)
1	F1	1	0.5	1
2	F2	1	1	1
3	F3	1	1.5	1
4	F4	1	2	1
5	F5	1	2.5	1
6	F6	1	3	1
7	F7	1	3.5	1
8	F8	1	4	1
9	F9	1	4.5	1

Note: All formulation contains 10 ml diethyl ether

Drug Profile

Haloperidol

Haloperidol is a first-generation typical antipsychotic that is widely used across the world to block the brain's dopamine D2 receptors and produce its antipsychotic effects. The drug is used to treat positive symptoms of schizophrenia, such as delusions and hallucinations.[7]

Mechanism of Action[8]

One common first-generation antipsychotic, haloperidol, works by inhibiting the brain's dopamine D2 receptors. The optimum efficacy of this medication is achieved when 72% of dopamine receptors are inhibited. The D2 receptor is not the only receptor that haloperidol blocks; noradrenergic, cholinergic, and histaminergic receptors are all affected. Numerous negative medication responses are linked to the blockage of these receptors.

Dosage for Adults[7,8]

Psychosis

Both the oral and instant messaging variants can be utilized for psychosis. It is advised to take 0.5 to 2 mg orally two to three times a day for mild symptomology. Haloperidol doses of up to 30 mg/d may be necessary in some resistant instances.Every four to eight hours, 2 to 5 mg intramuscular injections can be used to quickly reduce acute agitation. 20 mg/d is the highest recommended intramuscular dose.

Schizophrenia

The recommended dosage for mild symptoms associated with schizophrenia is 0.5–2 mg of haloperidol taken orally two to three times per day. The recommended dosage for people with severe symptoms is 3–5 mg of haloperidol taken orally two–three times per day. An oral dose of no more than 100 mg/d is advised.

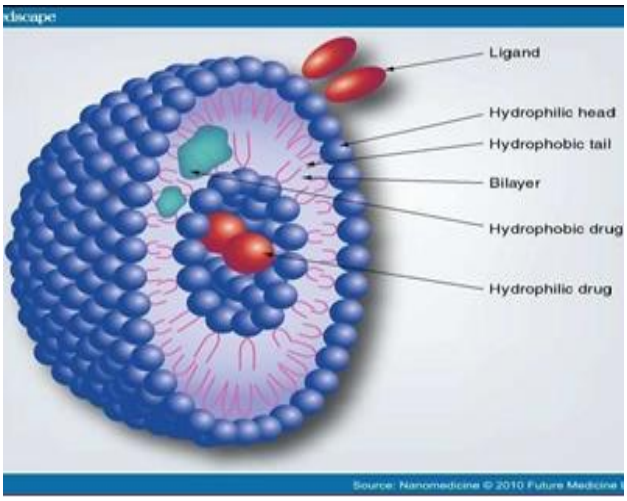

Figure 1: Structure of Niosome[3]

MATERIALS AND PROCEDURES

Drug Preformulation Study

The initial stage in the rational creation of final dosage forms of a pharmacological substance is preformulation testing. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The altogether intension of preformulation study is to gather data beneficial for the formulator in developing stable and bioavailable dosage forms, which can be mass-produced.

Determination of λmax by UV Spectroscopy[9]

Haloperidol is weighed accurately and transferred to a 100 ml volumetric flask; the volume was adjusted to 100 ml with methanol, to get a 1000 µg/ml stock solution, further stock solution was diluted suitably to get 100 µg/ml solution. Further diluted suitably to get concentration of 5µg /ml and 5 µg /ml of Haloperidol.The absorbance of the solution was scanned in the range of 200 to 400 nm in UV-visible double beam spectrophotometer in medium scanning speed against methanol as a blank. Repeat the abovementioned procedure for concentration of 10 µg/ml of Haloperidol.

Melting Point Determination[9]

It was obtained by using capillary tube technique. The perceived value was compared with the reference value.

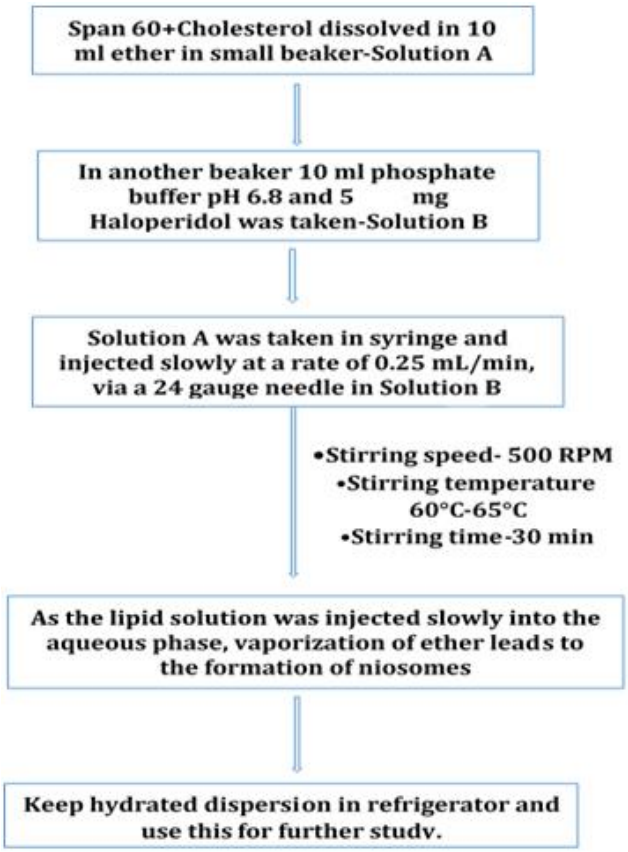

Figure 2: Process flow chart for formulation of Medicated Niosome

Table 2: Results of characterization of pure drugs

Sr. No	Test Parameters		Observation
1	Physical Appearance		A white powder.
2	λmax by UV spectroscopy Methanol		247.5 nm
	67 mM phosphate buffer pH 6.8 with 0.5 % SDS		247.5 nm
3	Melting point		150ºC -152ºC
4	Loss on Drying		0.41 % (NMT 0.5%)
5	Equilibrium solubility study (mg/ml)	Methanol	0.653
		Water	0.160
		0.1 N HCl, pH 1.2	0.081
		Phosphate buffer, pH 6.8	1.321
		Phosphate buffer, pH 7.4	1.384
6	% Purity		99.86 % (98.0 % to 102.0%)
7	Powder characterization		
	Angle of Repose (º)		16.46
	Bulk density (g/ml)		0.4137
	Tapped density (g/ml)		0.5578
	Carr's index		42.361
	Hausner's ratio		1.7328

FTIR Spectroscopy[10]

The IR spectra of Haloperidol was recorded using Fourier transform infrared spectrophotometer with diffuse reflectance principle. Sample preparation involved mixing the sample with potassium bromide (KBr), triturating in glass mortar and finally placing in the sample holder. The spectrum was scanned over a frequency range 4000 – 400 cm-1.

Loss on Drying[10]

A sample of 0.1g of Haloperidol was weighed in a vessel. The sample containing vessel was then placed in a hot air oven at 100oC for 4 h. The sample was cooled in a desiccator and weighed.

DSC Study[11]

The DSC thermogram of Haloperidol was recorded using Differential scanning calorimeter. Approximately 2 to 5 mg of sample was heated in a closed pierced aluminum pan from 30ºC to 180ºC at a heating rate of 5 ºC /min under a stream of nitrogen at a flow rate of 50ml/min.

Saturation Solubility[12]

The shake flask technique was utilized to determine saturation solubility of Haloperidol in

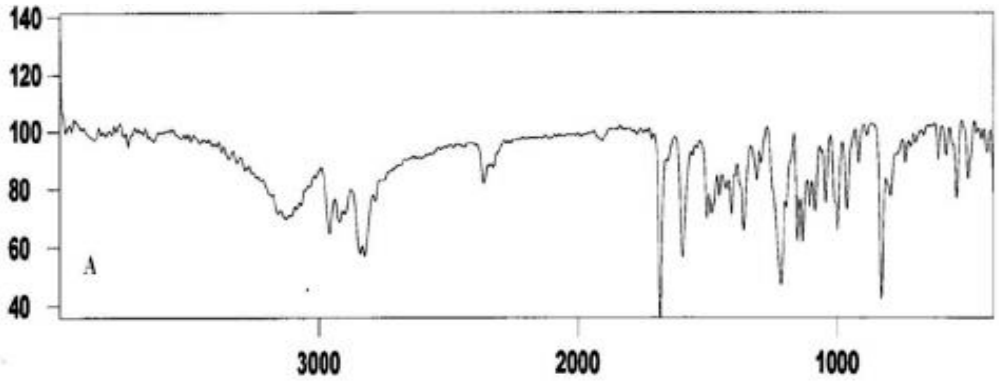

Figure 2: FTIR Spectrum of Haloperidol pure drug

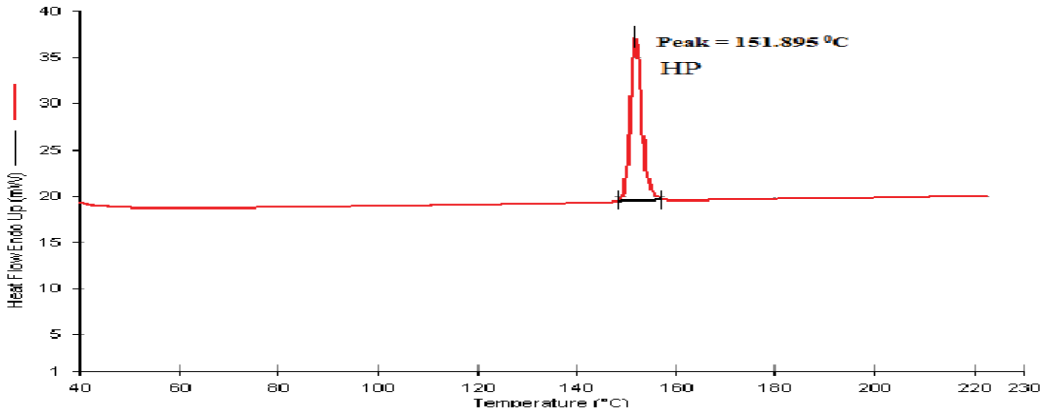

Figure 3: DSC thermogram of Haloperidol pure drug

Table 3: Standard calibration curve data of Haloperidol in phosphate buffer (pH 6.8) at λmax 247.5 nm

Sr. No.	Concentration (ug/ml)	Absorbance			Absorbance (Mean*± SD)
1	5	0.103	0.102	0.104	0.103 ± 0.001
2	10	0.215	0.219	0.219	0.217 ± 0.0023
3	15	0.319	0.318	0.321	0.319 ± 0.0015
4	20	0.454	0.456	0.453	0.454 ± 0.0015
5	25	0.592	0.59	0.592	0.592 ± 0.0012
6	30	0.763	0.762	0.76	0.761 ± 0.0015
7	35	0.92	0.92	0.921	0.920 ± 0.0005
8	40	1.234	1.233	1.235	1.234 ± 0.001

Table 4: Organoleptic properties of medicated niosome

Sr. No.	Batch No	Appearance/Colour	Odour
1	F1	Milky white	Odourless
2	F2	Milky white	Odourless
3	F3	Milky white	Odourless
4	F4	Milky white	Odourless
5	F5	Milky white	Odourless
6	F6	Milky white	Odourless
7	F7	Milky white	Odourless
8	F8	Milky white	Odourless
9	F9	Milky white	Odourless

Table 5: pH of medicated niosome

Sr. No.	Batch No	pH (Mean*± SD)
1	F1	4.7±0.057
2	F2	4.6±0.051
3	F3	5.1±0.049
4	F4	4.9±0.035
5	F5	4.7±0.053
6	F6	5.2±0.041
7	F7	5.4±0.038
8	F8	5.1±0.045
9	F9	4.8±0.056

SD:Standard deviation,*:Mean of each 3 readings

differentsolvent(i.e.Methanol,0.1NHClpH1.2,Phosphate buffer pH 6.8 and Phosphate buffer pH 7.2). Excess quantity of Haloperidol was added separately in 10 ml of different solvent which were then mixed in vortex mixture at 37°C and at 100 rpm for 24 h.Solutions were filtered using whatman filter paper. The filtrates were diluted suitably and solutions wer eanalyzed using UV-visible spectrophotometer against methanol, 0.1N HCl pH 1.2, Acetate buffer pH 4.5, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.2 as a blank.

% Purity[12]

For % purity,100mg of Haloperidol was weighed and transferred to a 100ml of volume tric flask. Then the volume was made upto100 ml mark with methanol. The flask was kept on a sonicator individually for 5 min. Solution was then filtered using a whatmann filter paper.Then a liquot 10ml from the filtered solution and dilute it up to 100 ml using methanol. Then absorbance of the resulting solution was measured at the λ max 247.5 nm usingUV-Visible double beam spectrophotometer against methanol as blank. The linearity equation obtained from calibration curve was used for estimation of purity of Haloperidol.

Powder Characterization (Physical Properties)[13]

Angle of Repose

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the Powder was determined by the funnel method.

Angle of repose was then calculated with the use of the following vformula:

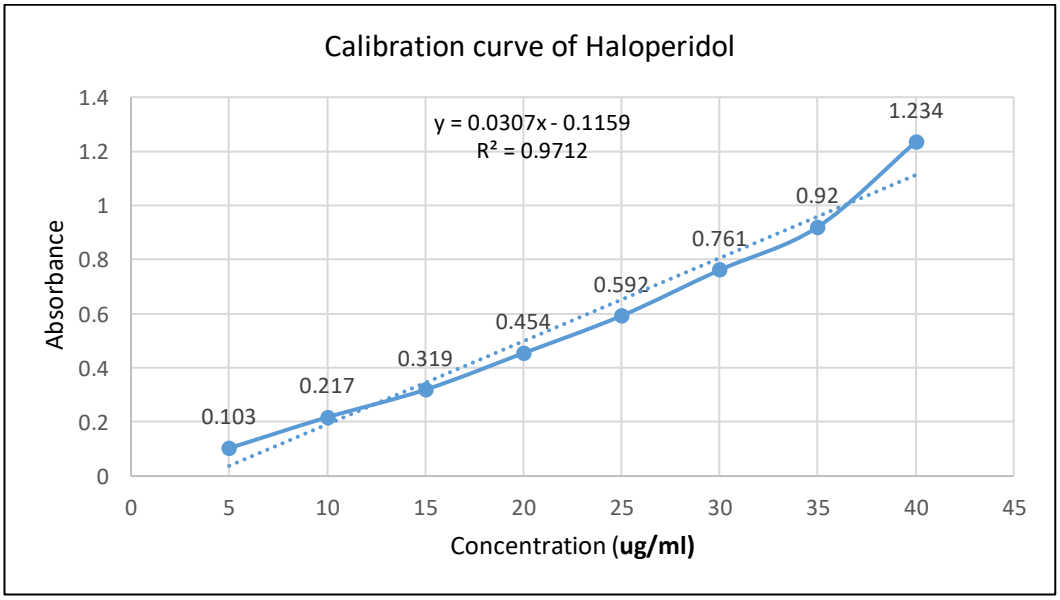

Figure 4: Standard calibration curve of Haloperidol in phosphate buffer (pH 6.8)

Table 6: Total drug content of medicated niosome

Sr. No.	Batch No	Drug content (%)(Mean*± SD)
1	F1	89.23 ± 1.75
2	F2	90.20 ± 0.61
3	F3	89.13 ± 0.79
4	F4	95.41 ± 0.90
5	F5	97.76 ± 1.50
6	F6	97.29 ± 0.59
7	F7	99.52 ± 0.97
8	F8	97.93 ± 1.25
9	F9	98.45 ± 1.19

SD:Standard deviation,*:Mean o feach 3 readings

Table 7: Entrapment efficiency of medicated niosome

Sr. No.	Batch No	Entrapment efficiency (%)(Mean*± SD)
1	F1	85.52 ± 1.13
2	F2	83.60 ± 1.39
3	F3	79.05 ± 1.14
4	F4	89.60 ± 2.26
5	F5	88.09 ± 1.94
6	F6	84.84 ± 1.60
7	F7	98.24 ± 1.50
8	F8	93.24 ± 2.25
9	F9	90.16 ± 1.03

$$\tan\theta = \frac{h}{r}$$

Where,
θ= angle of repose
h=heightofthepile
r=averageradiusofthepowdercone

Bulk Density

Bulk density of the powder was determined by pouring gently 10gms of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated as follows:

$$Bulk\ density\ (g/ml) = \frac{Weight\ of\ sample\ in\ g}{Volume\ occupied\ by\ the\ sample}$$

Tapped Density[13]

10 grams of sample was poured gently through a glass funnel into a 50ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping was recorded and tapped density was calculated as follows:

$$Tappeddensity\left(\frac{g}{ml}\right) = \frac{Weight\ of\ sampleing}{Volume\ occupied\ by\ the\ sample(after\ tapping)}$$

Carr'sindex[13]

Oneoftheimportantmeasuresthatcanbeobtainedfrombulk andtappeddensitydeterminations is the percent compressibility or the Carr's index (I), which isdeterminedbythefollowingequation:

$$Carr's\ compressibility\ index = \frac{Tapped\ density - Bulk\ density}{Bulk\ density} \times 100$$

Hausner's Ratio

Table 8: Mean particle size and Polydispersibility index of medicated niosome

Sr. No.	Batch No.	Polydispersibility index	Particle size(μm) (Mean*± SD)
1	F1	0.411	2.76 ± 0.84
2	F2	0.389	2.99 ± 0.97
3	F3	0.42	3.24 ± 0.86
4	F4	0.385	3.08 ± 0.55
5	F5	0.325	3.20 ± 0.90
6	F6	0.37	3.42 ± 0.77
7	F7	0.387	2.52 ± 1.50
8	F8	0.404	2.90 ± 0.60
9	F9	0.395	3.32 ± 0.61

SD: Standard deviation, *: Mean of each 3 readings

Table 9: Zeta (ζ) Potential of medicated niosome

Sr. No.	Batch No.	Zeta potential (Mv) (Mean*± SD)
1	F1	-27.77 ± 1.55
2	F2	-24.84 ± 0.79
3	F3	-20.29 ± 1.03
4	F4	-25.44±0.92
5	F5	-21.07±1.75
6	F6	-24.57±0.16
7	F7	-25.69 ± 1.87
8	F8	-28.27±0.28
9	F9	-30.55±0.28

SD: Standard deviation, *: Mean of each 3 readings

Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is measures of relative importance of inter particulate interactions.

Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula,

$$Hausner's\ ratio = Tapped\ density\ /Bulk\ density$$

Preparation of Standard Curve of Haloperidol[14]

Preparation of Standard Curve of Haloperidol in Phosphate Buffer (Ph 6.8)At247.5 Nm

Preparation of Standard Stock Solution (1000μg/Ml)

Accurately weighed 100 mg of Haloperidolwas dissolved in 100 ml of phosphate buffer (pH 6.8) to get a concentration 1000 μg/ml. This course of action was then used for arranging working standard plan.

Preparation of Working Standard Solution (100μg/ml)

10 ml standard stock solution of Haloperidolwas transferred to a 100 ml volumetric flask and volume was adjusted to 100 ml with phosphate buffer (pH 6.8) to get a concentration of 100 μg/ml.

Preparation of Dilutions for Calibration Curve

Aliquots of 5,10,15,20,25,30,35 and 40 ml of working standard solution were pipetted out into 50 ml volumetric flasks. The volume was made up to the mark with phosphate buffer (pH 6.8). These dilutions gave 5,10,15,20,25,30,35 and 40μg/ml concentration of Haloperidol respectively. The absorbance of prepared solutions of Haloperidol in phosphate buffer (pH 6.8) was measured at wavelength maximum 247.5 nm using Shimadzu UV-1800 spectrophotometer against phosphate buffer (pH 6.8) as blank. The experiment was performed in triplicate and based on average absorbance the equation for the best line was generated.

Table 10: *In-Vitro* drug release data of medicated niosome

Sr. No.	Time (Hr)	% Cumulative drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	2	4.45	5.02	4.22	5.25	4.45	5.24	6.45	3.45	3.56
3	3	8.34	9.56	7.23	8.64	7.54	8.02	9.56	7.55	6.28
4	4	10.11	12.11	10.25	11.43	10.96	12.89	15.23	9.95	9.25
5	5	14.43	16.34	14.43	14.56	12.53	15.04	18.25	13.56	12.43
6	6	24.21	24.5	22.58	23.41	19.96	20.48	26.95	21.11	19.55
7	7	32.23	34.16	30.23	30.54	29.78	32.11	34.11	28.24	26.65
8	8	39.55	40.11	36.55	37.78	38.57	40.67	42.56	42.05	33.43
9	12	62.45	64.78	60.44	62.65	63.98	65.43	68.45	63.45	60.23
10	18	82.61	83.49	82.54	86.56	85.46	88.9	92.36	78.59	75.43
11	24	90.26	87.67	88.21	91.55	90.23	92.45	98.55	85.65	82.25

Preparation of Drug Loaded Niosomal Dispersions

Medicated Niosomeswas prepared by using following process flow chart.

Evaluation Parameters for Medicated Niosomes[15-17]

Organoleptic Properties

The drug loaded dispersion was evaluated for colour, odour and appearance.

pH

The pH of niosome dispersion was checked by digital pH meter.

Total Drug Content

Assay of drug loaded niosomal dispersions were carried out by U.V. method.

2 ml of niosomal dispersion was dissolved into 50 ml Phosphate buffer solution having pH 6.8. The sample was stirred at 100 rpm to break the niosomes. Drug content was determined using UV spectrophotometer at respective absorption maxima.

Mean Particle Size and Polydispersibility Index

The particle size analysis of the formulation (F7) was determined using Beckman particle size determination technique..

Entrapment Efficiency[15]

Unentrapped drug from niosomal dispersion was separated by centrifugation method. Niosomeswere centrifuged at 20,000 rpm at controlled temperature of 40°C for 60min. By using UV spectroscopy unentrapped drug was quantified at respective absorption maxima. The results of Haloperidol loaded niosomewere shown in Table

Zeta Potential (ζ)[16]

Zeta potential of the dispersion was determined by Malvern zetameter. Time duration for zeta potential determination was 60 seconds and charge was find out.

***In-Vitro* Drug Release Studies[17]**

The release of Haloperidol from niosomes was determined by using membrane diffusion technique. The niosomal formulation equivalent to 51.14 mg of Haloperidol was placed in a glass tube of diameter 2.5 cm with an effective length of 8 cm which was tied with previously soaked cellulose membrane (12,000-14,000 Da Molecular weight cut off), which acts as a donor compartment. The glass tube was placed in a beaker containing 100 ml of phosphate buffer (pH 6.8), acting as a receptor compartment. The whole assembly was fixed in such a way that the lower end of tube containing suspension was just touching (1-2 mm depth) the surface of diffusion medium. The temperature of

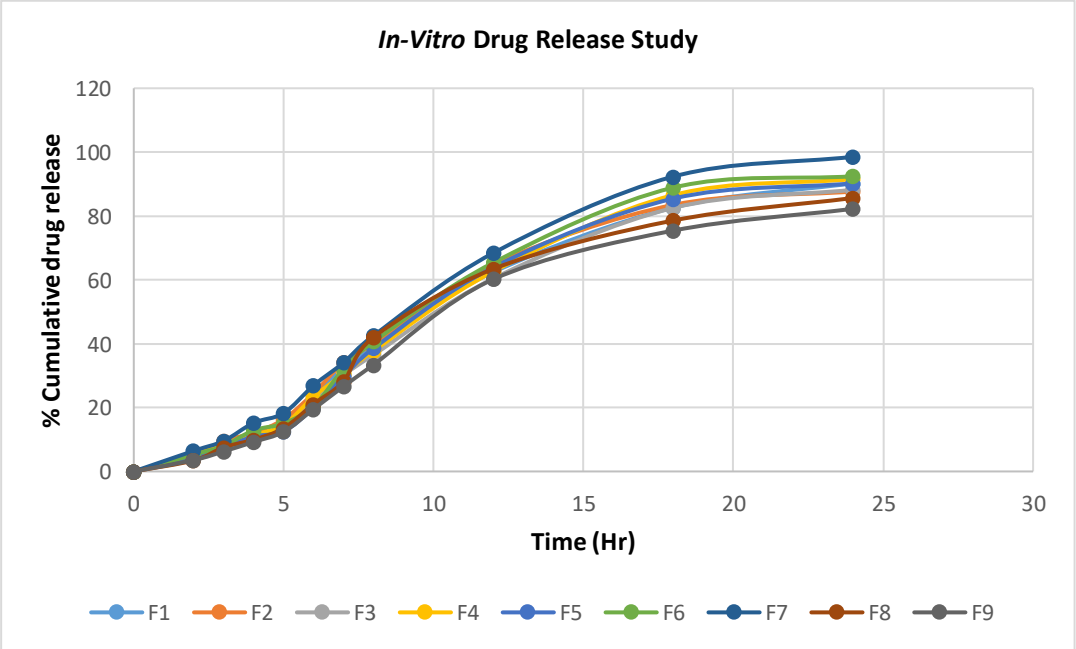

Figure 5: *In-Vitro* drug release data of niosome formulations

receptor medium was maintained at 37 ± 5° C and was agitated at the speed of 100 rpm using magnetic stirrer. Aliquots of 5ml sample were withdrawn periodically and after each withdrawal same volume of medium was replaced. The collected samples were analyzed at 247.5 nm in double beam UV-VIS spectrophotometer using Phosphate Buffer (pH 6.8) as blank.

RESULT AND DISCUSSION

Characterization of Pure API

From the above results it was concluded that all the practical results were complied with theoretical values.The melting point of Haloperidol was found to be 150°C - 152°C ,which complies with theoretical valuesthus indicating purity of obtained drug sample.The solubility test indicates that Haloperidolhas poor solubility in 0.1N HCl but its permeability was found to be more towards acidicside. Hence further emphasis was given to evaluate the drug dissolution at this particular media along with pH 6.8 buffer as its solubility was found to be comparatively more at this particular media. From thesolubility study data Haloperidol also shows lower solubility in water. Powder characteristics indicate that both the drug has good flowability.

FTIR Spectroscopy

The FTIR spectrum disclosed characteristic peaks of haloperidol ν(C=O), ν(C-F) and ν(C-Cl) bands appeared at 1658, 1226 and 740 cm-1, respectively.

Differential Scanning Calorimetry (DSC) Study

DSC thermogram of Haloperidol was recorded in the range of 20-180°C. The DSCthermogram of Haloperidol showed sharp endothermic peak at its melting point of 151.89ºC.This observation confirmed the purity and authenticity of the Haloperidol.

Standard Calibration Curve

Evaluation Parameters for Medicated Niosomes

Organoleptic Properties

The results of Organoleptic properties i.e. Appearance, Colour and Odour for all the nine formulations are summarize in below table.

The Haloperidol niosomal dispersion was off-white in color, odourless and fluid in nature. It was stable and did not show sedimentation.

pH

The results of pH value for all the nine formulations are summarize in below table

The pH was found in the range of 4.6-5.4.

Total Drug Content

The results of drug content for all the nine formulations are summarize in below table

The drug content was found in the range of 89.13 to 99.52

Entrapment Efficiency

The results of Entrapment efficiency for all the nine formulations are summarize in below table

The Entrapment efficiency was found in range of 79.05 to 98.24.

Mean Particle Size and Polydispersibility Index

The results of Mean particle size and Polydispersibility index for all the nine formulations are shown in table

The mean vesicle size of drug loaded niosomes of the different batches ranged between 2.52 - 3.42 μm. The polydispersibility index (PdI) was in the range of 0.325 – 0.420 for drug loaded niosomes which indicates a narrow vesicle size distribution.

Zeta (ζ) Potential Determination

The results of Zeta potential for all the nine formulations are shown in table

The values of ζ potential of the drug loaded niosomal formulation were in the range of-20.29 to -30.55mV. Values of zeta potential showed that the drug loadedniosome had sufficient charge and mobility to inhibit aggregation of vesicles.

In-Vitro Drug Release Studies

The results of *In-Vitro* drug release studies for all the nine formulations are shown in table

For all the nine formulations there was no initial burst release but the release was constant in a controlled manner for a period of time upto 24 hrs. The results of in- vitro drug release revealed that the drug was released in a controlled manner from all the formulations and F7 showed maximum drug release (98.55 %) at the end of 24th hour.

CONCLUSION

The present study concludes that the prepared niosomal suspension is a convenient and efficiency carrier for the delivery of antipsychotic drug to conquer the troubles associated with it, like the poor solubility, low bioavailability, and half-life of the drug, thereby increasing the duration of action and thereby increasing the half-life. The pre- formulation studies were carried out; from the study, it was clear that it satisfy the entire characteristic for oral drug delivery. The niosomal dispersion was off-white in color, odourless and fluid in nature. It was stable and did not show sedimentation. The pH was found in the range of 4.6-5.4. The drug content was found in the range of 89.13 to 99.52. The optimized formulation had a vesicular size of 2.52 - 3.42 μm. The Entrapment efficiency was found in range of 79.05 to 98.24. The highest entrapment efficiency was 98.24%. The values of zeta potential were found in a range 20.29 to -30.55mV. The maximum drug release (98.55 %) at the end of 24th hour. On the basis of result it was concluded that F7 was found the best formulation among all the nine formulations.

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