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Development and *In-Vitro* characterization of risperidone loaded hydroxy propyl beta cyclodextrin nanosponge for enhancing bioavailability

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Abstract

The purpose of the study was to develop and evaluate risperidone loaded nanosponge having prolonged residence time and sustained drug release. Nanosponges were prepared by emulsification solvent evaporation technique using cyclodextrins polymers in varying ratios. The nanosponges were evaluated for its percentage yield, drug entrapment efficiency, particle size and shape and *In vitro* drug release studies. The FTIR studies revealed uniform caging of the drug into the beta cyclodextrin cavity. The cyclodextrin based nanosponge showed particle size, drug entrapment efficiency and yield in the ranges of 148 - 164µm, 68.0 - 85.0% and 67.52 - 87.25% respectively. *In vitro* drug release confirms that formulation F2 was the best formulation as it was discovered that the nanosponge formulation's % release was 98.17±0.31% for 60 mins. This confirms the developed nanosponges are promising and have better bioavailability.

Keywords: Nanosponges; Risperidone; Cyclodextrin; Novel drug delivery system

1. Introduction

Nanosponges are a novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. The fundamental appeal of the nanosponge technology arises from the difficulty experienced with conventional formulations in releasing active ingredients over an extended period of time. Relatively high concentrations and short duration of action are typical features of conventional dermatological and personal care products. This might lead to a cycle of short-term overmedication followed by long-term undermedication. Nanosponges offer controlled release of the actives, which is one of the major advantages of such systems compared to other nanoparticulate delivery systems under development.

Risperidone, sold under the brand name Risperdal among others, is an atypical antipsychotic used to treat schizophrenia and bipolar disorder. It is taken either by mouth or by injection (subcutaneous or intramuscular). The injectable versions are long-acting and last for 2–4 weeks.

This drug is an antagonist of the D1 (D1, and D5) as well as the D2 family (D2, D3 and D4) receptors, with 70-fold selectivity for the D2 family. It has "tight binding" properties, which means it has a long half-life. Like other antipsychotics, risperidone blocks the mesolimbic pathway, the prefrontal cortex limbic pathway, and the tuberoinfundibular pathway in the central nervous system. Its action at Serotonin receptors results in a relatively lesser tendency to cause extrapyramidal side effects, like the reference substance clozapine. At Alpha α1 adrenergic receptors for the orthostatic hypotensive effects and perhaps some of the sedating effects of risperidone. Risperidone is mainly used for the treatment of schizophrenia, bipolar disorder, and irritability associated with autism.

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Being a biodegradable entity, cyclodextrin breaks down gradually in the body. Cyclodextrins are cyclic oligosaccharides made up of a number of dextrose units of (α-1,4)-linked α-D-glucopyranose. These cyclic structures contain a lipophilic central cavity and a hydrophilic outer surface. Cyclodextrins are made up of six, seven or eight dextrose units (α-, β-, and γ-CDs, respectively; the so-called parent cyclodextrins). Cyclodextrins interact with hydrophobic drug molecules to form inclusion complexes and can be used e.g., to improve the aqueous solubility of the drug molecule. For β-CD, which itself has a relatively low aqueous solubility, substitution of any of the hydrogen bond-forming hydroxyl groups, even by lipophilic functions, results in a dramatic improvement in the aqueous solubility of the derivative.

In the pharmaceutical industry, cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of active substances poorly soluble in water, in order to increase their bioavailability and to improve stability. In addition, cyclodextrins can be used to reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions within a formulation (all these properties are based on reduction of the free drug in solution), or to convert oils and liquid drugs into microcrystalline or amorphous powders.

2. Material and methods

2.1. Materials

Risperidone was obtained from Manus aktteva biopharma LLP, Ahmedabad and Ex**c**ipients - Beta cyclodextrin, Methanol and Disodium hydrogen phosphate were obtained from Finar Pvt. Ltd., Ahmedabad, DMF and Sodium chloride from Thomas baker (chemical), Mumbai., Ethanol from Changshu Yangquan Chemical, China., and Potassium dihydrogen phosphate, Molychem, Mumbai.

2.2. Preformulation studies

Pre- formulation is considered as important phase where researcher characterizes the physical and chemical properties of drug substance which helps to develop stable, effective and safe dosage forms and also check possible interaction with various excipients.

2.3. Melting point

The temperature at which a solid and a liquid are in equilibrium under a combined pressure of one atmosphere is known as a solid's melting point. In experimental settings, the melting point is really defined as the range of temperatures from which the first crystal begins to melt to which the last crystal just vanishes. Melting point equipment was used to determine melting point.

2.4. Solubility

Risperidone's solubility in ethanol, water, DMF, and buffer, among other solvents, was assessed. Excess drug is shaken in a stoppered volumetric flask containing 3 ml of solvent system to conduct solubility studies in triplicate at 25 °C. The flasks were sonicated for 30 minutes and then vortexed for 5 minutes after being sealed. Using a water bath shaker, the mixtures were thereafter allowed to be shaken for 24 hours at 100 rpm. Samples were looked at using UV light after 24 hours (Shimadzu).

2.5. Drug- Excipients compatibility study

To determine whether there was an interaction, the FTIR spectra of the medicine and its improved formulation was examined. With dried KBR used to suitably dilute the samples, IR spectra with a resolution of 4 cm-1 between 400 and 4000 cm-1 were obtained.

2.6. Partition coefficient studies

The partition coefficient (oil/water) is a measure for a drug's lipophilicity and a sign of how evenly it is distributed during equilibrium between the organic and aqueous phases. A way to describe the drug's lipophilic/hydrophilic characteristics is by partition coefficient. At 37±0.5 °C, the partition coefficient of risperidone was calculated using 2.5 ml of octanol and 2.5 ml of water. After shaking, the system was left alone for 30 minutes. In the combination of n-octanol and water, a saturated drug solution was made. And for about 24 hours, the above-formed mixture was not disturbed. Via the use of a separating funnel, two layers were separated, and the amount of risperidone that had been dissolved was assessed by measuring the absorbance at 280 nm in comparison to a reagent blank using a double beam

UV/Vis spectrophotometer. Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in water and the value were reported as log P.

$$\text{Log p} = \frac{concentration\ of\ drug\ in\ non\ aqueous\ phase}{concentration\ of\ drug\ in\ aqueous\ phase}$$

2.7. Quantitation of drug

2.7.1. UV scan of Risperidone

To determine the max for standard curve preparation, a UV scan was conducted of the risperidone solution. An accurately measured amount 10mg of risperidone was transferred into the 100 ml volumetric flask containing methanol. Add methanol, sonicate and make up the volume upto mark. An accurately measured volume 0.2ml of the 100µg/ml solution was transferred into the 10ml of volumetric flask and made up to the volume with methanol up to the mark. drug sample with a concentration of 2µg/ml was created for this purpose using methanol.

2.7.2. Ultra-violet spectra (UV)

Preparation of standard plot of Risperidone in methanol

A standard plot of the drug was generated in methanol at a sufficient concentration range to determine the amount of Risperidone present. Risperidone stock solutions with a concentration of 100µg/ml were created and serially diluted to achieve a concentration range between 1-10µg/ml. They underwent UV spectrophotometer-based spectrophotometric analysis at 280 nm.

2.8. Preparation of Risperidone loaded nanosponge

2.8.1. Preparation of beta cyclodextrin nanosponge

Nanosponges of -cyclodextrin (MW 1,135 g/mol) were made in the manner described. A round bottom flask was filled with 100 mL of anhydrous dimethylformamide (DMF), then anhydrous -cyclodextrin was added to complete the dissolution. Following the addition of Carbonyldiimidazole, the solution was allowed to react at 100 °C for 4 hours. The translucent block of hyper-cross-linked cyclodextrin was roughly crushed after condensation polymerization was finished, and more deionized water was added to get rid of DMF. Lastly, ethanol-based Soxhlet extraction was used to thoroughly eliminate any remaining by-products or unreacted chemicals. The resulting white powder was crushed in a mortar after being dried in an oven overnight at 60 °C. The obtained fine powder was dissolved in water. The colloidal component that was still floating in the water was retrieved and lyophilized. The nanosponges recovered are sub-micron in dimension and with a spherical shape.

Table 1 Composition of nanosponge containing different Beta cyclodextrin: cross linker ratio

S. No.	Formulation code	Beta cyclodextrin: cross-linker ratio (millimole)	Amount of beta-cyclodextrin (mg)	Amount of carbonyldiimidazole (mg)
1	N1	01:01	113.5	16.2
2	N2	01:02	113.5	32.4
3	N3	01:03	113.5	48.6
4	N4	01:04	113.5	64.8

2.8.2. Preparation of Risperidone loaded beta cyclodextrin nanosponge

A magnetic stirrer was used to accurately suspend weighed amounts of Nanosponges in 20 mL of Milli Q water. Next, the exact amount of Risperidone was added, and the mixture was then sonicated for 10 min before being left to stand for 24 h while being stirred in the dark. To separate the uncomplexed drug as a residue below the colloidal supernatant, the suspensions were centrifuged at 2,000 rpm for 10 min. At a temperature and operating pressure of 20 °C and 13.33 mbar, the supernatant was lyophilized. Desiccators were used to keep the dried powder dry.

Table 2 Composition of different Risperidone loaded beta cyclodextrin nanosponge

S.No.	Formulation code	Drug: Beta cyclodextrin nanosponge ratio (w/w)	Amount of risperidone (mg)	Amount of Nanosponge (mg)
1	RN1	01:2.5	4	10
2	RN2	01:05	4	20
3	RN3	01:10	4	40
4	RN4	01:15	4	60

2.9. *In vitro* characterization of Risperidone loaded nanosponge

2.9.1. Yield of Nanosponge

Yield of prepared nanosponge was prepared by given below equation:

$$Percentag\ yield = \frac{Practical\ mass\ of\ nanosponge}{Theoritical\ mass\ of\ excipients} \times 100$$

2.9.2. Solubilization efficiency of nanosponge

In order to assess the capacity for solubilization augmentation, the Risperidone solubilization effectiveness of several nanosponge formulations was examined. 10ml water were used to suspend several prepared drug-loaded nanosponges. The volumetric flasks were set up at room temperature on a mechanical shaker. After reaching equilibrium (24 h), the suspension was filtered using a centrifugal filter device, and the filtrate was examined using a calibration curve for the concentration of risperidone in a UV spectrophotometer at 280 nm.

2.9.3. Encapsulation and Loading Efficacy of Risperidone

Accurately weighed amount of each drug-loaded nanosponge were taken and into vails containing 10 ml of methanol. The vails containing dispersion was placed in an orbital shaker and remained there for two hours while being occasionally shaken at a temperature of 37± 0.5 °C. The dispersion was centrifuged at a speed of 15000 rpm for 30 minutes after the allotted time had passed in order to separate the free medication. The resulting supernatant was filtered using Whatman filter paper (No.40). Subsequently, a double beam UV spectrophotometer was used to measure absorbance at 280 nm and determine the amount of drugs present in the filtrate samples.

The percentage drug encapsulation efficiency and percentage drug loaded was determined using the following equation:

$$Percentag\ drug\ encapsulation = \frac{Practical\ amount\ of\ drug}{Theoritical\ amount\ of\ drug} \times 100$$

$$Percentag\ drug\ laoding = \frac{Practical\ amount\ of\ drug}{Amount\ of\ the\ nanosponge\ taken} \times 100$$

2.9.4. Particle Size, Polydispersity and Zeta Potential Determination

Dynamic light scattering was utilised to measure the dimensions of the nanosponges and the polydispersity index using a 90 Plus particle sizer and the MAS Option particle sizing programme at a fixed angle of 90°. Prior to measurements, the samples were properly diluted in water. The same devices were also used to detect zeta potential using an extra electrode. After averaging the three measurements, the mean hydrodynamic diameter (Dh) and polydispersity index (PI) of the particles were estimated in intensity using the cumulant analysis.

2.9.5. In vitro dissolution study

The dissolution test apparatus was used to assess the *in vitro* release of risperidone from nanosponge formulations at 50 rpm and 37 °C. In a nutshell, for the first two hours, at regular intervals (0, 5, 10, 20, 30, 40, and 50 minutes), aliquot samples of a formulation equivalent to 2 mg of risperidone were extracted from 900 ml of simulated stomach juice (pH 1.2) without enzyme. By using a UV-VIS spectrophotometer, the amount of risperidone in the sample was identified.

3. Results and discussion

3.1. Preformulation Study

3.1.1. Melting point

The melting point of risperidone in bulk powder form was discovered to be between 169±1.15 °C -172±0.57 °C.

3.1.2. Partition coefficient determination

The lipophilic nature of the medication in bulk API form was described by the partition coefficient of risperidone in n-octanol-water system, which was determined to be 3.45 ± 0.05.

Table 3 Partition coefficient of drug

Partition coefficient of drug	Solvent system	Log p Values	Reference log p value
Risperidone	water: n-octanol	3.45 ± 0.05	3.5

3.1.3. UV Scan of Risperidone

Absorption maxima of Risperidone drug in methanol are 280 nm.

3.2. Preparation of standard curve of Risperidone in methanol

A calibration curve of risperidone was prepared using the absorbance of risperidone at various concentrations. The concentration of unknown samples was determined using the calibration equation for a straight line, which was found to be y = 0.0812x-0.0003 with a correlation coefficient of 0.999.

Table 4 Standard calibration curve of risperidone

Con. (µg/ml)	Absorbance at 280 nm	STD
0	0.00	0.01
1	0.08	0.02
2	0.16	0.04
3	0.25	0.03
4	0.33	0.02
5	0.40	0.04
6	0.48	0.05
7	0.56	0.07
8	0.65	0.01
9	0.73	0.01
10	0.82	0.01

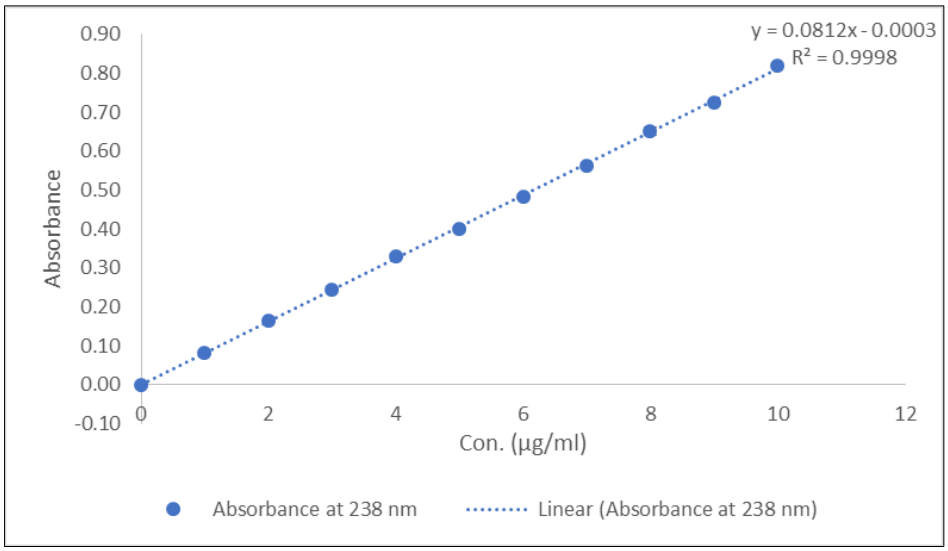

Figure 1 Standard calibration curve of Risperidone in methanol

3.3. Solubility study

Solubility of Risperidone in different solvents i.e., Water, propylene glycol, 0.1NHCl, Buffers, ethanol and methanol is as follows:

Table 5 Solubility of Risperidone in different solvents

S.No.	Name of solvent	Solubility (mg/ml)
1	Water	0.004±0.01
2	Propylene Glycol	0.79±0.09
3	pH 6.8 phosphate buffer	0.69±0.13
4	Methanol	2.46±0.01
5	0.1 N Hcl	1.41±0.06
6	Ethanol	2.13±0.07

Table 5 showed that ethanol and methanol were the two solvents in which risperidone was most readily soluble. But both water and a buffer solution cannot make it soluble.

3.4. FT-IR of Drug and Drug polymer mixture

FTIR spectra of Risperidone showed the characteristic peak at 1615 cm^{-1} (C=O stretching), 1522cm-1 (N-H bending), and 3378 cm^{-1} (N-H stretching). The FTIR spectrum of nanosponge demonstrated the characteristic peak of drug disappears or with reduced intensity indicating uniform caging of the drug into the beta cyclodextrin cavity.

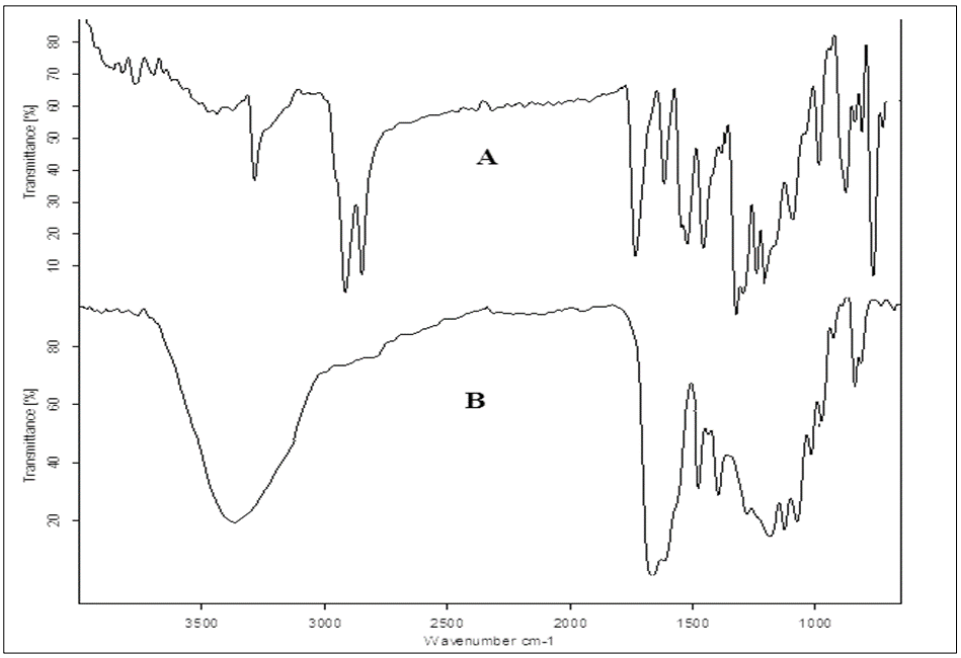

Figure 2 FT-IR of A) Risperidone and B) optimized formulation

3.5. Preparation of Beta cyclodextrin nanosponge

In this study, novel risperidone formulations were developed using beta-CD-based nanosponges produced by the interaction of b-cyclodextrin with carbonyldiimidazole. NS are solid, colloidal-sized, hyper-cross-linked cyclodextrin polymers having nanosized cavities. After being dispersed in water while being stirred, these nanostructured materials created a nanosuspension of fairly homogeneous, spherical-shaped nanoparticles. Drug molecules could fit inside the nanocavities of -CD, according to NS structural characterization, and because of the cross-linking, it may be possible for the guest molecules to interact with additional -CD units. Moreover, the cross-linked network may create nanochannels in the NS structure for the polymer mesh.

3.6. *In vitro* characterization β-cyclodextrin nanosponge

3.6.1. Effect of β-cyclodextrin: cross linker ratio

Percentage yield

Table 6 displays the prepared formulation's percent yield.

Table 6 Percentage yield of all prepared nanosponge formulation

S.No.	Formulation code	Percentage yield (%)
1	N1	92.77±0.57
2	N 2	98.69±1.73
3	N 3	98.70±1.01
4	N 4	99.08±1.52

Table 6 showed that the range of the total prepared formulation's percentage yield was found to be between 92.77±0.57% to 99.08±1.52%. The highest percentage yield, 99.08±1.52%, was discovered, but the finished product was not free flowing and had clumps in it. Hence, N3 formulation was chosen for additional assessment.

3.6.2. Effect of Beta cyclodextrin: cross linker ratio

Percentage yield

Table 7 displays the prepared formulation's percent yield.

Table 7 Percentage yield of all prepared nanosponge formulation

S.No.	Formulation code	Percentage yield (%)
1	RN1	81.33±0.57
2	RN2	97.23±0.50
3	RN3	96.21±1.52
4	RN 4	96.35±0.47

Table 7 showed that the whole prepared formulation's percentage yield ranged from 81.33±0.57% to 97.23±0.50%. The maximum percentage yield for RN2 was determined to be 96.96±1.154%, hence it was chosen for further analysis.

3.6.3. Aqueous solubility of Risperidone loaded nanosponge formulation

Solubilization capacity of all prepared drug loaded nanosponge formulation was as follows

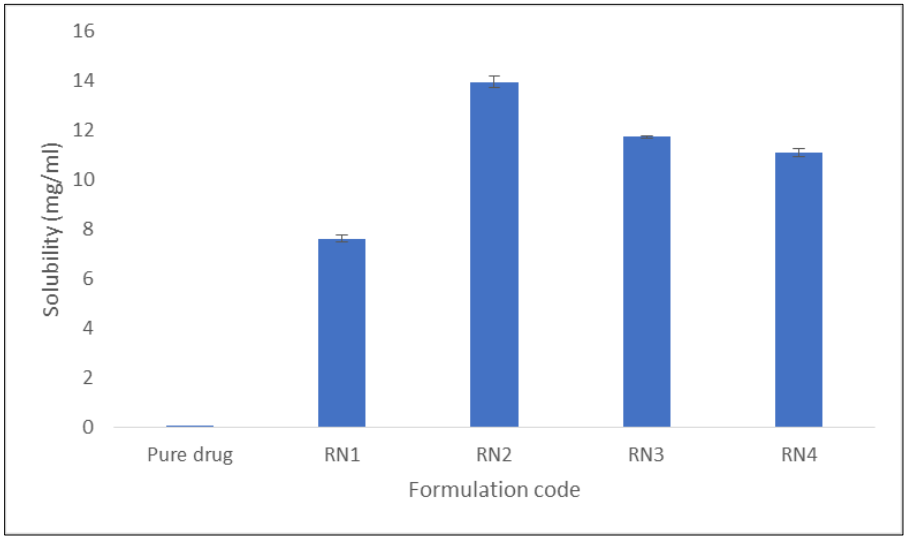

Figure 3 Aqueous solubility of all prepared nanosponge formulation

Figure 3 illustrates the range of aqueous solubility of all produced formulations, which ranged from 0.004±0.001mg/ml to 13.965±0.217mg/ml. The produced formulations showed noticeably improved solubility than the medication Risperidone in its pure form. The formulation RN2 was shown to have the highest solubility at 13.965±0.217mg/ml, followed by pure risperidone at 0.004±0.001mg/ml. The extent of the NS form inclusion complexation with the medication may be influenced by the degree of cross-linking. The overall solubility effect of NS may result through inclusion complex formation with the drug as well as trapping in the matrix.

3.6.4. Percentage Encapsulation and Loading Efficacy of Risperidone loaded nanosponge

Encapsulation and loading percentages. The effectiveness of each manufactured nanosponge formulation for risperidone is shown in table 8 below.

Table 8 Percentage Encapsulation Efficacy of all prepared nanosponge formulation

Formulation Code	%Entrapment efficiency
RN1	51.35±0.65
RN 2	99.07±0.21
RN 3	97.22±0.61
RN 4	91.07±0.55

Table 9 Percentage drug loading of all prepared nanosponge formulation

Formulation Code	% Drug loading
RN1	20.54±0.261
RN 2	39.63±0.087
RN 3	38.39±0.261
RN 4	36.42±0.170

All produced formulations were found to have percentage drug loading and percentage encapsulation efficacy ranging from 51.35±0.65% to 99.07±0.21%, 20.54±0.261% to 39.63±0.087% respectively. The formulation RN2 was determined to have maximum percentage drug encapsulation efficiency and percentage drug loading at 99.07±0.21% and 20.54±0.261%, respectively. The percentage of drug encapsulation rises as the ratio of drug to nanosponge is increased, but only until a certain point after which it falls. The overall solubility effect of NS may result through inclusion complex formation with the medication as well as trapping in the matrix.

The *in vitro* characterization parameters led to the selection of the RN2 formulation for further analysis.

3.6.5. Particle Size, Polydispersity and Zeta Potential Determination

According to table 10, the particle size study of RN2 showed that the typical particle size as determined by the laser light scattering method is between 100 and 150 nm.

Table 10 Particle Size, Polydispersity and Zeta Potential Determination of optimized formulation RN2

S. No	Formulation code	Particle size (nm)	PDI	Zeta Potential(mv)
1	RN2	104.56	0.187	-19.84

3.6.6. In vitro dissolution

In-vitro drug release study of RN2 nanosponge formulation and pure drug was as given below

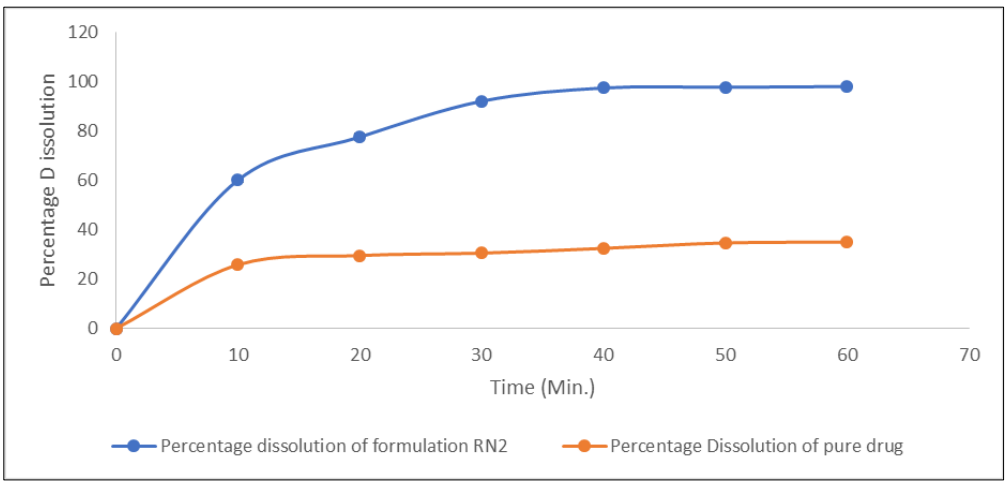

Figure 4 *In-vitro* dissolution study of RN2 nanosponge formulation and pure drug

Figure 4 revealed that the rate of release was significantly improved by the nanosponge RN2 formulation. This might be a result of complex creation and processes' higher solubility and wettability. For 60 minutes, it was discovered that the nanosponge formulation's % release was 98.17±0.31%.

4. Conclusion

The melting point of risperidone in bulk powder form was discovered to be between 169±1.15 °C -172±0.57 °C. The lipophilic nature of the medication in bulk API form was described by the partition coefficient of risperidone in n-octanol-water system, which was determined to be 3.45 ± 0.05. A calibration curve of risperidone was prepared using the absorbance of risperidone at various concentrations. The concentration of unknown samples was determined using the calibration equation for a straight line, which was found to be y = 0.0812x-0.0003 with a correlation coefficient of 0.999. In solubility study, that ethanol and methanol were the two solvents in which risperidone was most readily soluble. But both water and a buffer solution cannot make it soluble. FTIR spectra of Risperidone showed the characteristic peak at 1615 cm^{-1} (C=O stretching), 1522cm-1 (N-H bending), and 3378 cm^{-1} (N-H stretching). The FTIR spectrum of nanosponge demonstrated the characteristic peak of drug disappears or with reduced intensity indicating uniform caging of the drug into the beta cyclodextrin cavity. Range of the total prepared formulation's percentage yield was found to be between 92.77±0.57% to 99.08±1.52%. The highest percentage yield, 99.08±1.52%, was discovered, but the finished product was not free flowing and had clumps in it. Hence, N3 formulation was chosen for additional assessment. Further the whole prepared drug loaded formulation's percentage yield ranged from 81.33±0.57% to 97.23±0.50%. The maximum percentage yield for RN2 was determined to be 96.96±1.154%, hence it was chosen for further analysis. The aqueous solubility risperidone in all produced formulations, which ranged from 0.004±0.001mg/ml to 13.965±0.217mg/ml. The produced formulations showed noticeably improved solubility than the medication Risperidone in its pure form. The formulation RN2 was shown to have the highest solubility at 13.965±0.217mg/ml, followed by pure risperidone at 0.004±0.001mg/ml. The extent of the NS form inclusion complexation with the medication may be influenced by the degree of cross-linking. The overall solubility effect of NS may result through inclusion complex formation with the drug as well as trapping in the matrix. All produced formulations were found to have percentage drug loading and percentage encapsulation efficacy ranging from 51.35±0.65% to 99.07±0.21%, 20.54±0.261% to 39.63±0.087% respectively. The formulation RN2 was determined to have maximum percentage drug encapsulation efficiency and percentage drug loading at 99.07±0.21% and 20.54±0.261%, respectively. The percentage of drug encapsulation rises as the ratio of drug to nanosponge is increased, but only until a certain point after which it falls. The overall solubility effect of NS may result through inclusion complex formation with the medication as well as trapping in the matrix. The *in vitro* characterization parameters led to the selection of the RN2 formulation for further analysis. The particle size study of RN2 showed that the typical particle size as determined by the laser light scattering method is between 100 and 150 nm. The rate of release was significantly improved by the nanosponge RN2 formulation. This might be a result of complex creation and processes' higher solubility and wettability. For 60 minutes, it was discovered that the nanosponge formulation's % release was 98.17±0.31%. Regression coefficients that were calculated for higuchi, first order, and zero order models. First order model was determined to have the highest R2 value and to best describe the *in vitro* drug release of formulation RN^2 since the plot displayed the highest linearity.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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