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Original Article

Development and characterization of Nicorandil loaded maltodextrin based proniosomes

*Sumaiya Fathima Barveen K M, Elango K, Ramesh Kumar K, Ramprabhu R V

Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai, Tamil Nadu, India

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ABSTRACT

The aim of the study was to develop and characterize Nicorandil proniosomes by slurry method using the non-ionic surfactants like Span60, Brij72 and cholesterol as vesicle forming agents and maltodextrin as a carrier. The prepared proniosomes were evaluated for chemical incompatibility by FT-IR, vesicle size analysis, entrapment efficiency, *in vitro* drug release and *in vitro* drug release kinetics. Formulation was optimized based upon the entrapment efficiency and *in vitro* drug release. The optimized proniosomal formulation FP3 containing Span60 exhibited prolonged release profile. Fickian diffusion mechanism was observed with the FP3 which was due to the sustained release property.

Keywords: Nicorandil, Maltodextrin, Proniosomes, Slurry method.

INTRODUCTION

Nicorandil is used therapeutically in the long term treatment of Angina Pectoris. It is primarily absorbed from upper GI tract and has its elimination half-life is 1hr. It is administered orally in 5-20 mg doses twice daily in order to maintain the constant plasma level. [1]

Nicorandil is believed to exert myocardial protection by a process of ischemic preconditioning which appears to reduce myocardial stunning, arrhythmias and infarct size when a coronary artery is suddenly blocked in addition to vasodilatation which is lacked by other vasodilators. Hence, Nicorandil is preferred over than vasodilators. [2]
Proniosomes are dry product which could be hydrated easily, immediately before use this could avoid many of the problems. These dry formulations of surfactant-coated carrier can be measured as needed and rehydrated by brief agitation in hot water to form niosomal dispersion. These are considered superior drug delivery system because of their lower cost, greater stability, non-toxicity, biocompatibility, biodegradability and non-immunogenicity as it is non-ionic in nature. [3, 4] Proniosomes have higher advantages such as additional convenience of dosing, storage, transportation and distribution. It avoids the problems associated with the aqueous noisome dispersion, such as problems of physical stability, aggregation, fusion and leakage. It also avoids the problems associated with liposome like degradation by hydrolysis or oxidation as well as sedimentation. [5]

The objective of the present study is to prepare and characterize for the formulations containing Nicorandil loaded proniosomes with non-ionic surfactants; cholesterol by slurry method in order to reduce the frequency of administration and to improve patient compliance and once daily sustained release formulation of Nicorandil is desirable to provide a safe dosage form with lesser side effects.

MATERIALS AND METHODS

Materials: Nicorandil was obtained as a gift sample from ALCHYMARS ICM SM Pvt. Ltd. Sorbiton monostearate was obtained as gift from SPAK ORGOCHEM India Pvt. Ltd. and Brij72 purchased from Sigma Aldrich. Maltodextrin provided as a gift a sample from Vertex pharma and Cholesterol was purchased from S.D. Fine Chem. Ltd.

Methodology

Compatibility studies by FT-IR: The possibility of drug- excipient (cholesterol, maltodextrin, non-

***Corresponding Author Address:** K.M. Sumaiya Fathima Barveen, Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai -03, India: E-mail: sumaifathi31oct@gmail.com and pharmaceuticsmmcchennai@gmail.com*

ionic surfactants) interactions were investigated by FT-IR spectrum study. The FT-IR spectrum of pure drug and combination of drug with excipient were recorded using Shimadzu FT-IR spectrophotometer. The spectrum was recorded in the wavelength region of 4000 to 400 cm^{-1}. The IR Spectra of the test samples were obtained by Pressed Pellet Technique using Potassium bromide. [6]

Calibration curve for Nicorandil: 100 mg of Nicorandil drug was dissolved in a 100ml standard flask and made up to 100 ml with 0.1N Hydrochloric acid. 2,4,6,8,10 ml of the solution were taken and made up to 100 ml using 0.1N Hydrochloric acid. The same procedure was followed using phosphate buffer pH 6.8 instead of 0.1N hydrochloric acid. The absorbance of the resulting solutions was measured at 262nm using UV spectrophotometer. [7, 8]

Formulation of Nicorandil Proniosomes: Nicorandil proniosomal powders were prepared using slurry method. Formulation table of Proniosomes were represented in Table 1. The non-ionic surfactant, cholesterol and drug were dissolved in a solvent mixture of chloroform: methanol (2:1). The resultant solution was transferred into a 1000 ml of round bottom flask containing 100 mg of maltodextrin to form slurry. The flask was attached to the rotary flash evaporator and the organic solvent was evaporated under reduced pressure (600 mmHg) at a temperature of 45± 2°C. After ensuring the complete removal of solvent, the resultant powders were further dried in a freeze dryer. The obtained dry product of proniosomes was stored in a tightly closed container at 4°C. [9, 10]

Preparation of Nicorandil Niosomes from Proniosmes: Proniosomal powder was transformed to niosomes by hydration with phosphate buffer (pH 6.8) at 80°C using vortex mixer for 2 minutes or subjected to sonication for 3 minutes. [11]

CHARACTERIZATION OF NICORANDIL PRONIOSOMES

Particle size Analysis: Particle size (z- average diameter), Polydispersity index (as a measure of the width of the particle size distribution) of Nicorandil proniosomes was performed by dynamic light scattering also known as photon correlation spectroscopy(PCS) using a Malvern Zetasizer 3000 Nano S (Malvern instruments, UK) at 25°C. Prior to measurements, sample was diluted using ultra-purified water to yield a suitable scattering intensity. The diluted niosomal dispersion was poured into the disposable sizing cuvette which was then placed in the cuvette holder of the instrument and analyzed. Air bubbles were removed from the capillary before measurement. [12, 13]

Scanning Electron Microscopy (SEM): The surface morphology (roundness, smoothness, and formation of aggregates) and the size distribution of proniosomes were studied by Scanning Electron Microscopy (HITACHI S 5 GB). A small amount of sample was mounted on a copper stub using double sided adhesive tape and was made electrically conductive by coating with a thin layer of gold. SEM images were recorded at 5kv accelerating voltage. [14]

Drug content analysis: Proniosomal formulation equivalent to 20 mg of Nicorandil was taken into a standard volumetric flask. Vesicles were lysed with 50 ml of propane-1-ol and 1ml of the mixture was subsequently diluted with phosphate buffer pH 6.8. The absorbance was measured spectroscopically at 262nm and drug content was calculated. [15]

Entrapment efficiency (Indirect method): Proniosomal preparation was transformed into niosomes by hydrating with phosphate buffer pH 6.8 at 80°C using vortex mixer for 2 minutes. Then the Nicorandil containing niosomes were separated from un-entrapped drug by centrifugation with 14000 rpm at 4°C for 30minutes. The supernatant was taken out and diluted with phosphate buffer pH 6.8. The resultant solution was assayed at 262nm using UV spectrophotometer. The entrapment efficiency of vesicles was found using following formula. [15, 16]

$$\% EE = C_T - C_F/C_T \times 100$$

Where,

C_T = Total drug concentration

C_F = Free drug concentration

***In vitro* release study:** *In vitro* dissolution study of proniosomal powders and pure drug was performed using USP type I (basket) apparatus in continuous medium (both acidic and phosphate buffer). [17] The medium was maintained at a temperature of 37°C±0.5°C with 50rpm throughout the experiment. 5 ml of samples were collected at predetermined time intervals up to 12hr and replaced with fresh dissolution medium to maintain constant volume. The samples were analyzed by UV spectrophotometer at 262nm. [19]

Zeta Potential Analysis: Zeta potential analysis (to characterize surface charge of particle) was carried out for determining the colloidal properties of the prepared formulations. The suitably diluted proniosomes derived niosomal dispersion was determined using zeta potential analyzer based

on Electrophoretic Light Scattering and Laser Doppler Velocimetry method. The temperature was set at 25°C. Charge on vesicles and Mean Zeta Potential were obtained. [12]

***In vitro* kinetic release:** The drug release data of Nicorandil loaded proniosomes was fitted to kinetics models i.e., zero order, first order, Higuchi and korsmeyer - peppas kinetic model. The kinetic models with higher values of Coefficient of Correlation (r^2) were considered to be a best fitting model for describing the release.

RESULTS AND DISCUSSION

Compatibility Study: The possible interactions between the drug and the optimized formulation were studied by FT-IR spectroscopy. The results are given in Table 2 and Figure 1, 2. It is confirmed that there is no loss of functional groups in the spectrum of the proniosomal formulation. It is concluded that there is no interaction between the drug and optimized formulation i.e the drug is compatible with all excipients. [20, 6]

Calibration Curve for Nicorandil: The Ultra Violet Spectroscopic method was used to analyze Nicorandil. The absorbance of the drug in various buffers of acidic (pH 1.2) and phosphate (pH 6.8) was measured at a wavelength of 262nm. [7, 8] The data are given in Table 3 and Figure 3, 4. It is found that the solutions of Nicorandil in acidic (pH 1.2) and phosphate buffer (6.8) shows linearity in absorbance at concentrations of 0-10 µg/ml and obeys Beer-Lambert's Law. [6]

Drug Content: Drug content was determined for all Nicorandil proniosomes (FP1-FP6). The drug content was found to be between 82.76% and 96.25% w/w. It was shown in Table 4 and Figure 5.

Entrapment Efficiency: The proniosomes were prepared with various concentrations of each non-ionic surfactant keeping cholesterol and Nicorandil concentrations as constant. The entrapment efficiency of the reconstituted niosomes was determined by centrifugation process. The results are shown in Table 5.

The entrapment efficiency of the reconstituted niosomes is observed (Figure 6) to be between 22.56% and 68.77%. The entrapment efficiency is found to be **68.77%** and **53.15%** for proniosomes prepared with **SPAN60, BRIJ72** respectively in 200 mg of non-ionic surfactant concentration. From these results, it is concluded that increase in the concentration of surfactant increases the entrapment efficiency of the formulation. [17]

FP3 had higher entrapment efficiency compared to other formulations. This may be due to high Transition temperature and high HLB value of **Span60.** [21] The order of non-ionic surfactants that resulted in better entrapment efficiency is as follows **Span60** > **Brij72.** This result corresponds to earlier reports. [22]

***In Vitro* Drug Release of Nicorandil Proniosomes:** The Nicorandil proniosomes were prepared with various concentrations of different surfactants. The cumulative percentage drug release is found to be in the range from 18.9 to 101.35 for FP1 to FP3 (Table 6, Figure 7), 31.71 to 101.35 for FP4 to F6 (Table 7, Figure 8). From these results, it is concluded that Increase in surfactant concentration increases the drug release of the formulation.

FP3 had higher drug release compared to other formulations. FP3 containing Span 60 has high Transition temperature and high HLB value. This facilitates the stable vesicle formation, so drug leaching from the vesicles may be reduced. [23]
The order of drug release from the formulations with various surfactants

Span60: FP1>FP2>FP3
Brij72: FP4>FP5>FP6

***In Vitro* Release Kinetics:** The values obtained from *in vitro* dissolution of the capsules containing Nicorandil loaded proniosomes were fitted in various kinetic models. The results are given in Table.8

Determination of Release Kinetics of Optimized Formulation: The *in vitro* release of Nicorandil from optimized proniosomal formulation FP3 follows First order kinetics. (Figure 9). Korsmeyer - Peppas plot slope value is found to be 0.397(less than 0.5) which reveals the fact that the drug release follows Fickian diffusion (Figure 10). [23,24]

Scanning Electron Microscopy (SEM): SEM image of optimized proniosomal formulation (FP3) was recorded and shown in Figure 11. The particles are almost spherical and homogeneous. The result shows that the Nicorandil loaded proniosomes have a spherical shape with smooth surface and discrete without any aggregation or agglomeration. [25]

Malvern Particle Size Analysis of FP3: The maximum number of Nicorandil loaded proniosomes is distributed in the range of 355.7 nm. The average particle size of Nicorandil loaded Proniosomes is 433.2 nm and the Polydispersity index (PDI) is found to be 0.449. (Figure 12)

Zeta Potential Analysis of FP3:

The zeta potential of the optimized formulation of Nicorandil proniosomes (FP3) is found (Figure 13) to be -32.2 mV. High charge on dispersed particles, especially negative charge may enhance the particle stability by reducing their tendency to aggregate. [26]

CONCLUSION

Nicorandil was successfully entrapped in the non-ionic surfactant vesicles by slurry method with various concentrations of different surfactants. *In vitro* drug release study revealed that Nicorandil loaded proniosomes were capable of releasing the drug in a slow sustained manner. Taking into considerations, the high efficiency in systemic delivery together with excellent safety profiles and it can be concluded that proniosomes prepared using Span60 and Cholesterol in the ratio 200 mg: 40 mg containing FP3 with better entrapment efficiency and drug release is a promising approach to provide a sustained drug therapy for Angina.

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The authors are thankful to Alchymars ICM SM Pvt. Ltd for providing gift sample of Nicorandil for research work. The authors are highly thankful to College of Pharmacy, Madras Medical College, Chennai for providing all the facilities to carry out the work.

Table 1: Formulation table for Nicorandil loaded Proniosomes by slurry method

Formulation Code	Drug (mg)	Maltodextrin (mg)	Cholesterol (mg)	Span 60 (mg)	Brij 72 (mg)
FP1	20	100	40	100	-
FP2	20	100	40	150	-
FP3	20	100	40	200	-
FP4	20	100	40	-	100
FP5	20	100	40	-	150
FP6	20	100	40	-	200

Table 2: IR Spectral interpretation of Nicorandil

Wave number (cm^{-1})	Type of vibration	Functional group
3247	N-H Stretching	Amino group
3078	=CH Stretching	Aromatic ring
1627	C=O Stretching	Ketone group
1550	C=N Stretching	Heteroaromatic ring
1288	N=O Stretching	Nitrites

Table 3: Data for calibration curve of Nicorandil

S.No.	Concentration (µg/ml)	Absorbance at 262nm	
		pH 1.2	pH 6.8
1	2	0.055±0.0022	0.030±0.0050
2	4	0.113±0.0017	0.067±0.0035
3	6	0.174±0.0025	0.104±0.0063
4	8	0.228±0.0029	0.135±0.0058
5	10	0.281±0.0026	0.163±0.0037
	R^2	0.9998	0.9989

Table 4: Drug content of proniosomes FP1 to FP6

Non-ionic surfactant	Formulation code	Drug content (% w/w)
Span 60	FP1	82.76
	FP2	87.11
	FP3	88.62
Brij 72	FP4	87.25
	FP5	91.17
	FP6	96.25

Table 5: Entrapment efficiency of proniosomal formulation FP1 to FP6

Non-ionic surfactant	Formulation code	Entrapment efficiency(% w/w)
Span 60	FP1	24.45
	FP2	63.97
	FP3	**68.77**
Brij 72	FP4	22.56
	FP5	38.45
	FP6	**53.15**

Table 6: *in vitro* release of proniosomes containing span60 in different ratios

Time(hr.)	Cumulative percentage drug release (%)			
	Control	**FP1**	**FP2**	**FP3**
0.5	63.92	21.95	18.9	31.28
1	88.26	40.31	22.64	37.71
1.5	101.54	48.62	31.68	44.29
2	-	60.55	38.16	47.37
3	-	83.39	50.36	50.85
4	-	98.33	64.09	64.58
5	-	-	76.31	75.96
6	-	-	83.64	78.28
7	-	-	93.52	83.12
8	-	-	100.06	88.23
9	-	-	-	92.92
10	-	-	-	94.54
11	-	-	-	95.92
12	-	-	-	101.82

Table 7: *in vitro* release of proniosomes containing Brij72 in different ratios

Time(hr.)	Cumulative percentage drug release (%)			
	Control	**FP4**	**FP5**	**FP6**
0.5	63.92	33.03	31.71	33.48
1	88.26	43.50	39.53	35.58
1.5	101.54	55.41	46.09	38.59
2	-	62.11	53.59	42.50
3	-	82.27	69.29	50.38
4	-	98.82	81.21	57.59
5	-	-	95.63	64.14
6	-	-	101.35	71.51
7	-	-	-	78.46
8	-	-	-	84.94
9	-	-	-	93.24
10	-	-	-	100.12

Table 8: Drug Release Kinetics for FP3

Formulation code	Zero order	First order	Higuchi model	Korsmeyer peppas		Hixon crowell
	r^2	r^2	r^2	r^2	N	r^2
FP3	0.883	0.972	0.984	0.983	0.397	0.987

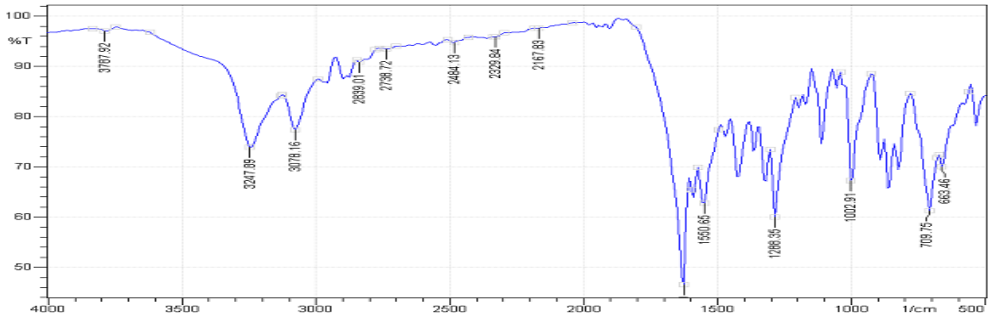

Figure1: FT-IR Spectrum of Nicorandil Pure drug

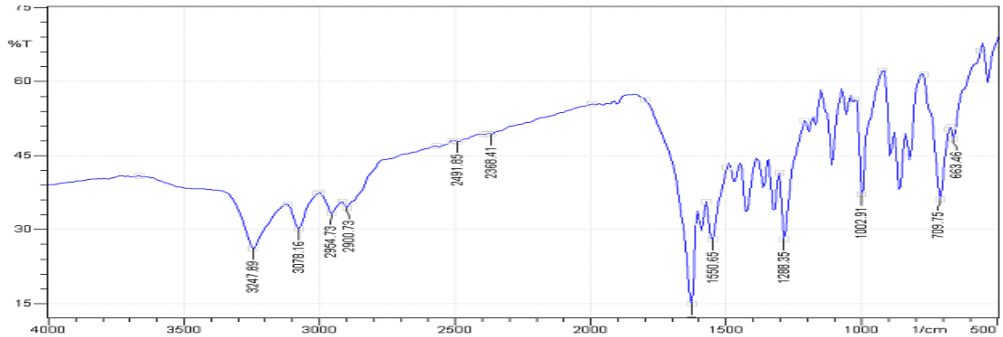

Figure 2: FT-IR Spectrum of optimized formulation

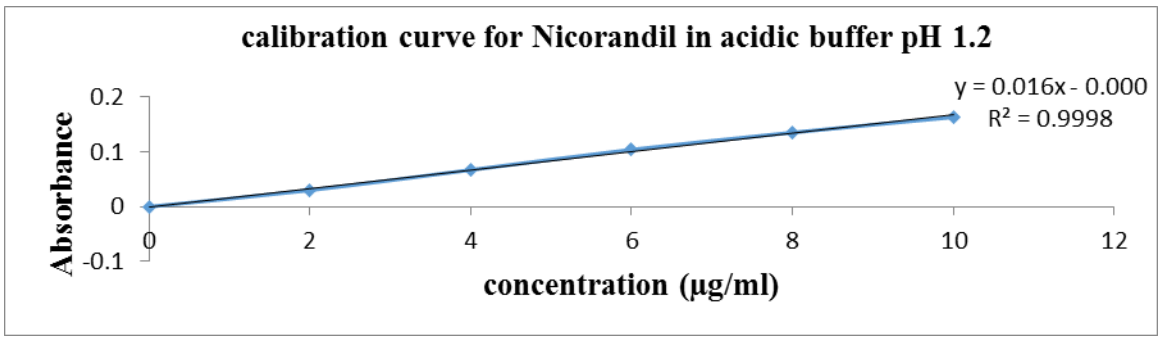

Figure 3: Calibration curve of Nicorandil in acidic buffer pH 1.2

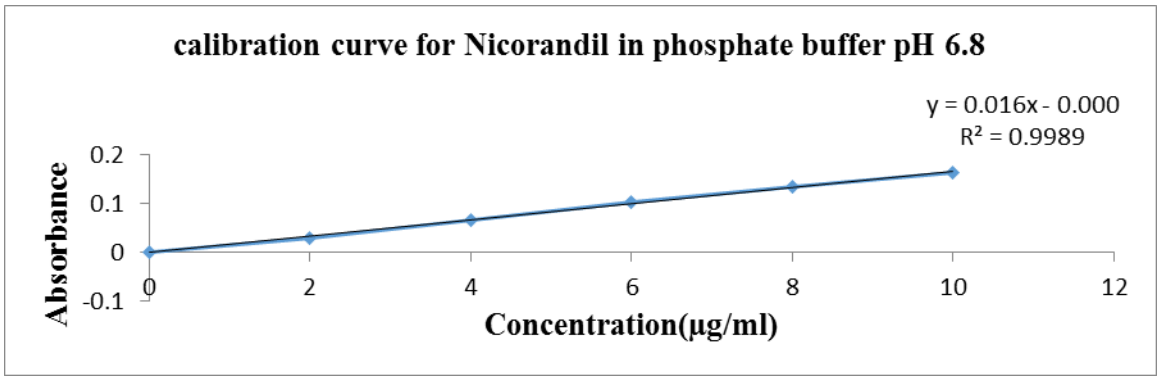

Figure 4: Calibration curve of Nicorandil in phosphate buffer pH 6.8

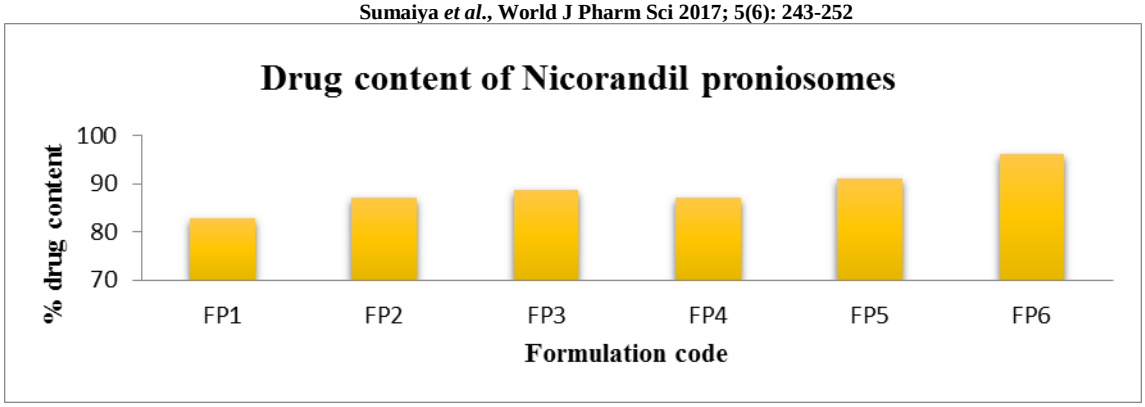

Figure 5: Drug content of proniosomes FP1 to FP6

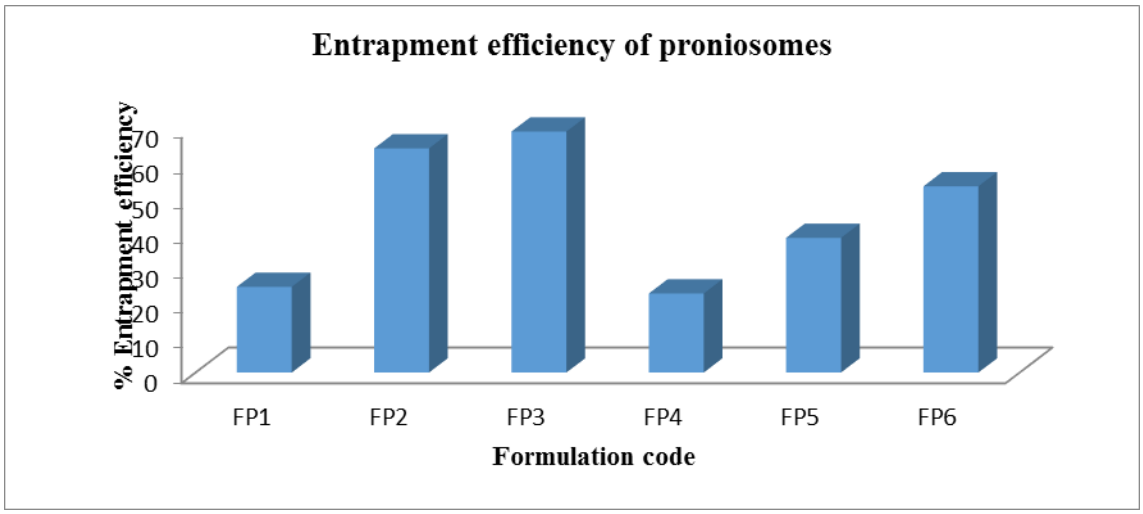

Figure 6: Percentage entrapment efficiency of Proniosomes FP1 to FP6

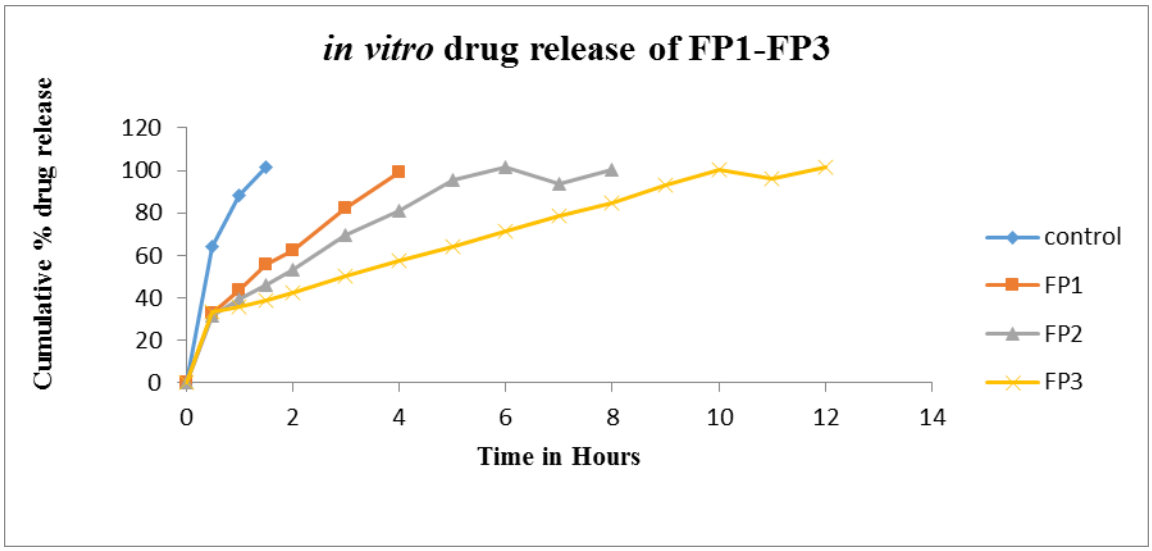

Figure 7: *in vitro* release of Span60 containing Nicorandil proniosomes

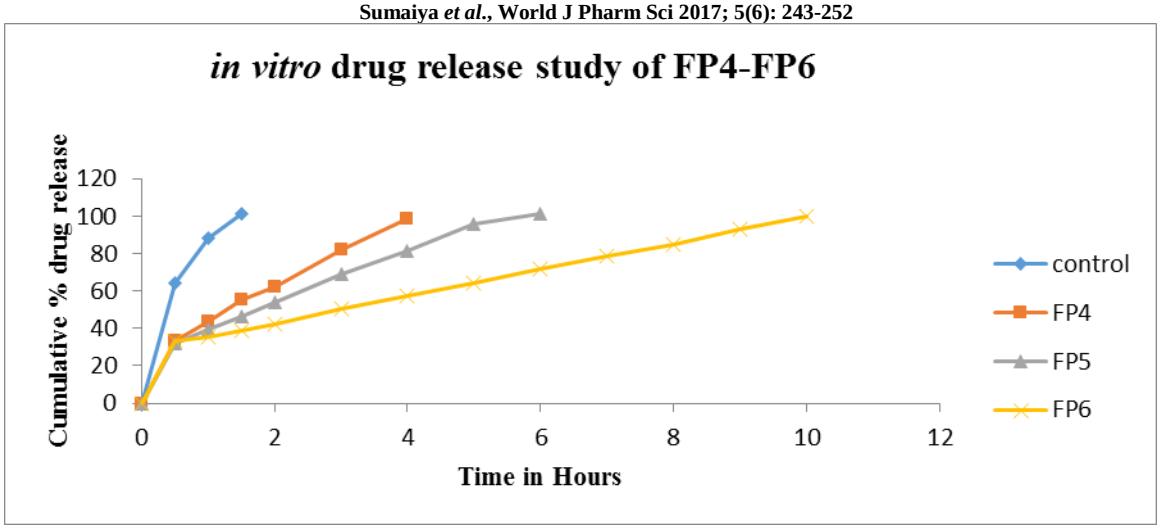

Figure 8: *in vitro* release of Brij72 containing Nicorandil proniosomes

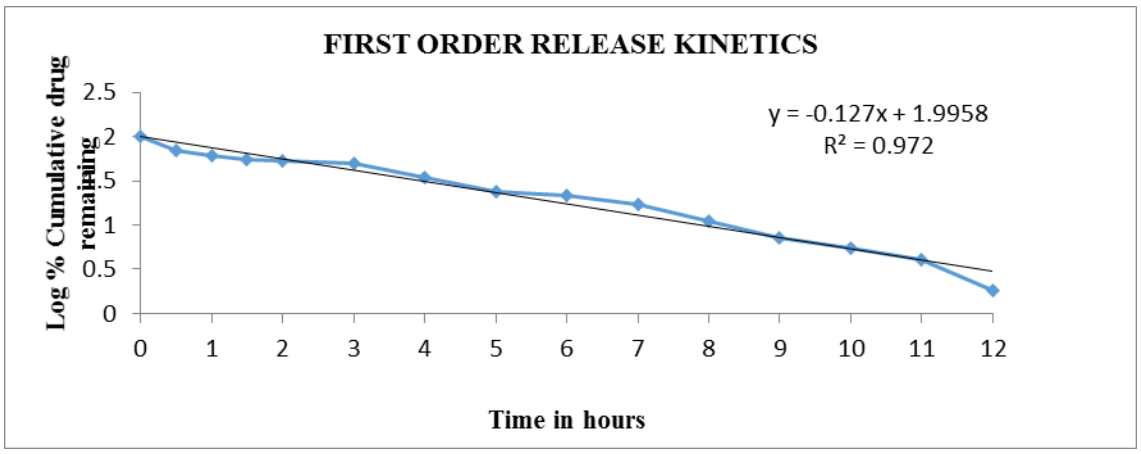

Figure 9: First order release kinetics

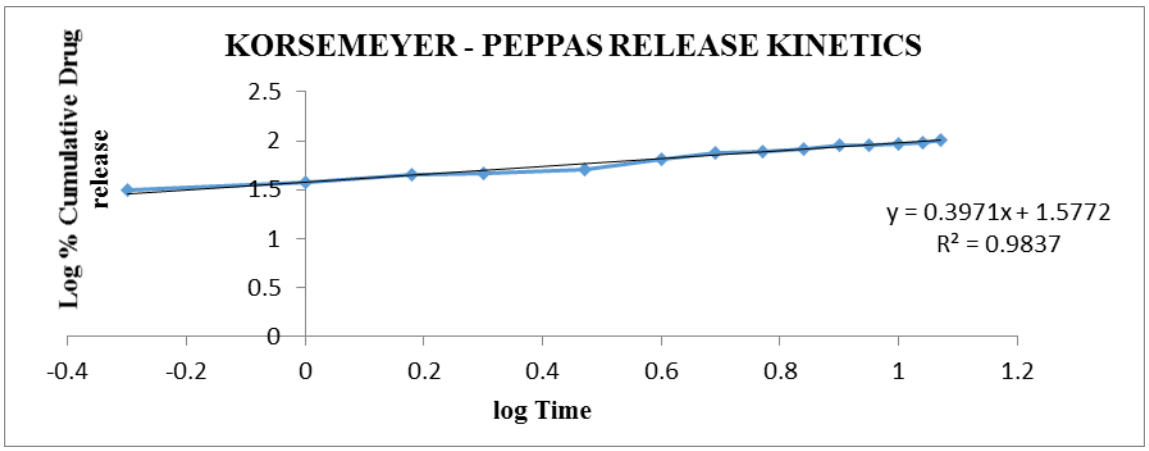

Figure 10: Korsmeyer-peppas release kinetics

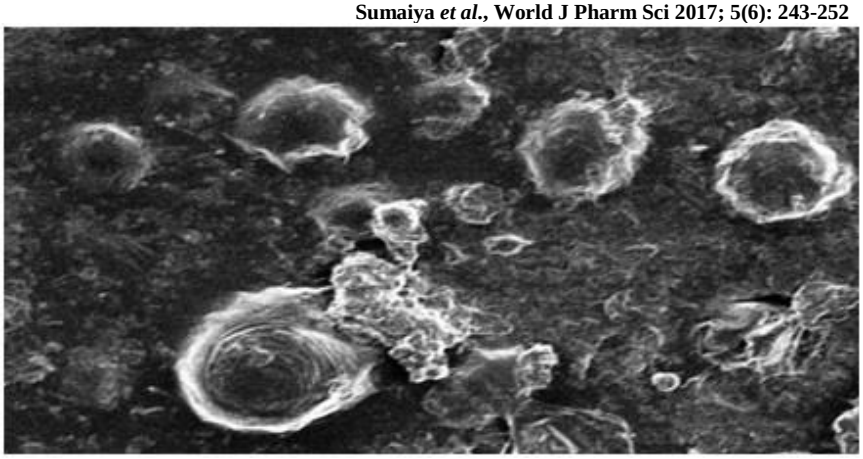

Figure 11:SEM Photograph of Proniosomes

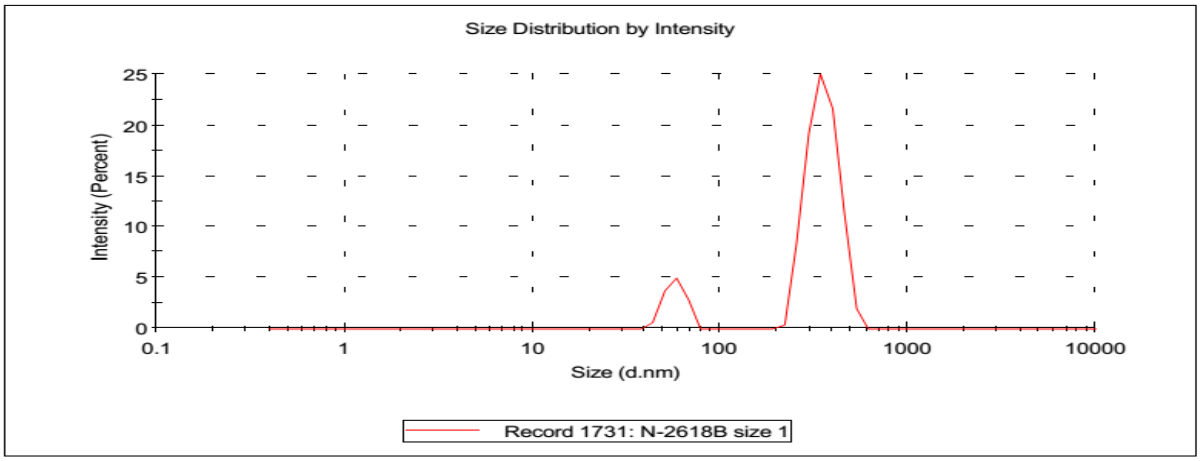

Figure 12: Particle size analysis of FP3 by Malvern zetasizer

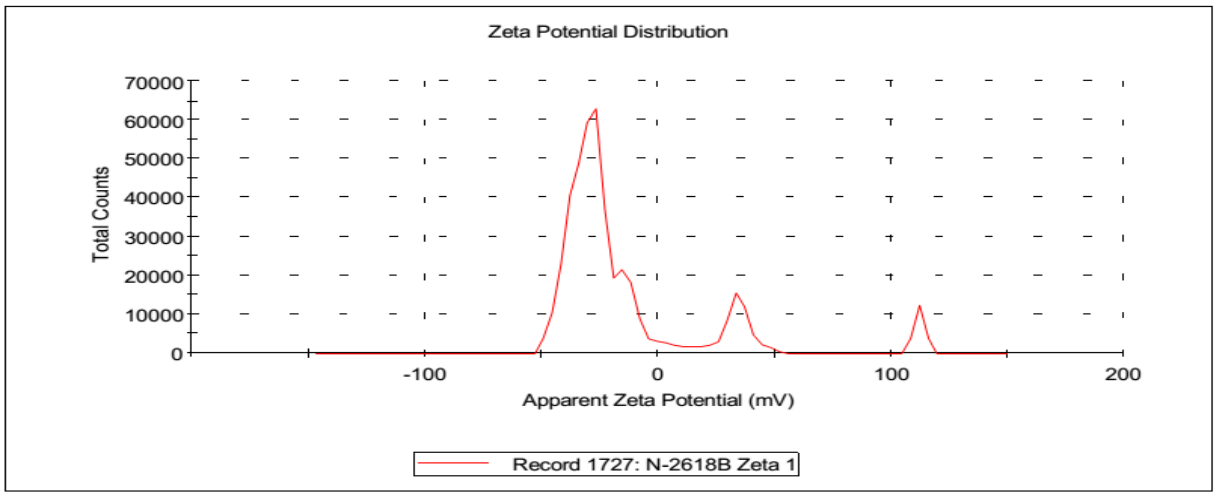

Figure 13: Zeta Potential analysis of FP3

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