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Research Article

Formulation and In Vitro Evaluation of Nisoldipine Loaded Hollow Microspheres

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ABSTRACT

The purpose of the study is to create and assess hollow microspheres filled with Nisoldipine. Ethyl cellulose, Polyethleneoxide, Hydroxypropyl cellulose K15M, and Eudragit L 100 were used as polymers, together with dichloromethane and ethanol as solvents, to create Nisoldipine-loaded hollow microspheres. The physicochemical characteristics, in-vitro drug release, and in-vitro buoyancy of the produced hollow microspheres were assessed. The hollow microspheres were studied using Fourier transform infrared spectroscopy and differential scanning calorimetry. The in vitro experiments showed that the largest amount of medication was released from hollow Nisoldipine microspheres made with ethyl cellulose and HPMCK15M in a 2:1 ratio (F2).

INTRODUCTION

The primary drug delivery method has been oral administration. Several oral delivery systems have been created during the last two decades to serve as drug reservoirs from which the active ingredient can be delivered over a certain time period at a planned and controlled pace. Unfortunately, this route has a number of physiological issues, including a quick gastrointestinal transit time and an unpredictable gastric emptying rate that varies from person to person (8- 12 h).

A medication delivery system that can stay in the stomach for a longer and predictable period of time has been developed by researchers as a result of the fact that some pharmaceuticals have a limited absorption window in the upper GIT [1]. By delivering the drug in a controlled and repeatable manner, researchers are working to create a drug delivery system that can maintain therapeutically effective plasma drug concentration for a longer

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period of time, reducing the frequency of dosing and minimising fluctuation in plasma drug concentration at a steady state. Drugs' stomach residence times can be greatly extended by gastro retentive systems since they can stay in the gastric region for several hours. For medications that are less soluble in a high pH environment, prolonged stomach retention increases bioavailability, lowers drug waste, and enhances solubility.

It can be used to administer medications locally to the stomach and nearby small intestines. Hollow microspheres are non-effervescent, gastro-retentive drug delivery systems that are regarded as one of the most beneficial buoyant systems due to their special advantages of multiple unit systems and improved floating characteristics. In the strictest sense, hollow microspheres are empty, spherical particles without a core. These microspheres are often free-flowing powders made of proteins or artificial polymers, and they should preferably be less than 200 micrometres [2]. The type of polymer, plasticizer, and solvents used for preparation have a major impact on the slow release of drug at desired rate and better floating properties of floating microspheres. The release of the drug can be modulated by optimising polymer concentration and the polymer to plasticizer ratio.

Calcium channel blocker Nisoldipine is a dihydropyridine medication. It is used to treat conditions like congestive heart failure, hypertension, and angina pectoris. Due to the substantial pre-systemic metabolism of nisoldipine, it is classified as BCS class-II, meaning that it has low solubility and low bioavailability (3.7 to 8.4%). The development of a gastro retentive dosage form is justified by the Nisoldipine's limited absorption window in the upper gastrointestinal system.

MATERIALS AND METHODS:

Nisoldipine was purchased from Matrix laboratories ltd Hyderabad. Eudragit L 100, HPMC K15M, Polyethylene oxide, Ethylcellulose, Ethanol, Dichloromethane, Tween 80 chemicals of Laboratory-grade from SD Fine chemicals Pvt. Ltd., were used.

METHODS:

Formulation of floating hollow microspheres:

A modified form of the quasi-emulsion diffusion method was used to create floating microspheres with a hollow core. Weighed amounts of the medication, hydroxypropyl methyl cellulose (HPMC K15M), polyethylene oxide, and ethyl cellulose were dissolved in ethanol and dichloromethane (1:1 solvent ratio) at room temperature in a magnetic stirrer at 50 rpm for 50 minutes. This solvent was added drop by drop to 100mL of distilled water that had been kept at a temperature of 50 2°C and contained 2mL of Tween 80. To allow the volatile solvent to evaporate, the resulting solution was agitated with an impeller-type agitator at 1100 rpm for 3 hours. Microspheres were created as a result. **Table 1** provides several polymer ratios that were employed to create the microspheres.

Table 1: Composition of Nisoldipine Loaded hollow microspheres

Formulation code	Ethyl Cellulose (gm)	Polyethylene oxide (gm)	HPMC K15M (gm)	Eudragit L100 (gm)	Drug (mg)
F1	2	2	1.5	1.5	8.5
F2	2	1.5	1	1.5	8.5
F3	1.5	1.5	2	2	8.5
F4	1	1.5	2	1.5	8.5
F5	1	2	1.5	1.5	8.5

F6	1.5	2	2	1.5	8.5
F7	1.5	2	1.5	1	8.5
F8	1	1.5	1	1.5	8.5
F9	1.5	2	1.5	2	8.5
F10	1.5	2	1	1.5	8.5
F11	1.5	1	1.5	2	8.5
F12	2	1.5	1.5	1	8.5
F13	1	1	1.5	1.5	8.5
F14	2	1	1.5	1.5	8.5
F15	1.5	1	1.5	1	8.5
F16	1.5	1	2	1.5	8.5
F17	1	1.5	1.5	2	8.5
F18	1.5	1.5	1	2	8.5
F19	2	1.5	2	1.5	8.5
F20	1.5	1.5	2	1	8.5
F21	1.5	1	1	1.5	8.5
F22	1	1.5	1.5	1	8.5
F23	1.5	1.5	1	1	8.5
F24	2	1.5	1.5	2	8.5

Determination of absorption maxima:

In 0.1N HCl, a drug solution with a concentration of 10g/mL was created. Using a twin beam UV/VIS spectrophotometer, the UV spectrum was captured. Between 200 and 400 nm of the solution was scanned.

Construction of Calibration Curve

Standard graph of Nisoldipine in 0.1N HCl

A precisely weighed quantity of 100 mg of Nisoldipine was put into a 100 ml volumetric flask with 0.1N HCl to dissolve to create the stock solution. The volume was then raised to the appropriate level using 0.1N HCl. The requisite dilutions were prepared from this stock solution to provide concentrations ranging from 0 to 15 g/ml. using a UV/Visible spectrophotometer and 0.1 N HCl as a blank, the absorbance of each test solution was measured at the maximum wavelength, or 258 nm, then graphically plotted to produce the standard graph.

Drug Excipient Compatibility Study:

Differential Scanning Calorimetry:

The physicochemical compatibilities of the drug and the excipients were tested by differential scanning calorimetric (DSC) analysis. DSC thermograms of the drug alone and optimized formulation were derived from DSC (Perkin-Elmer, 4000). The instrument was calibrated with an indium standard. The samples (2-4 mg) were heated (20-300°C) at a constant scanning speed (10 °C / min) in sealed aluminium pans, using nitrogen purged gas.

FTIR Spectroscopy:

Drug-polymer compatibility studies were carried out using the FTIR spectrophotometer (Shimadzu) by KBr pellet technique. Pure drug and optimized formulation were subjected to FTIR study. Compatibility studies were carried out to know the possible interactions between Nisoldipine and excipients used in the formulation. IR spectrum of pure drug and optimized formulation was seen in between 4000-400 cm^{-1}

Evaluation of Nisoldipine hollow microspheres:

Micromeritic Properties:

Hollow microspheres are evaluated by their micromeritic properties such as particle shape and size, bulk density, tapped density, Hausner's ratio, and flow properties, which are determined by carr's index and angle of repose [3, 4, 5]

Yield as a percentage:

Each batch's manufactured hollow microspheres were precisely weighed. The overall percentage yield of floating hollow microspheres was calculated by dividing the weight of the prepared hollow microspheres by the sum of all the excipients and medications employed in the manufacturing of the hollow microspheres [6, 7, 8].

It is calculated by using the following formula,

Percentage yield = Actual yield of product / Total weight of excipients and drug

Entrapment Efficiency:

Based on the overall drug content and the amount of unentrapped drug in the floating Hollow microspheres, the amount of drug that was entrapped in the Hollow microspheres was computed. By using one dose equivalent of floating Hollow microspheres and washing them with 0.1N HCl to eliminate any free drug on the surface, the unentrapped drug was identified. By dispersing 8.5 mg of the formulation (which was precisely weighed) in 10 ml of 0.1 N HCl and then stirring it with a magnetic stirrer for 12 hours to dissolve the polymer and extract the drug, the drug content of Hollow microspheres was ascertained. A Whatman filter was used to filter both the whole and unentrapped drug solutions. The drug concentration was then measured spectrophotometrically at 258 nm after the required dilution with 0.1N HCl. [9, 10].

Percentage entrapment efficiency was calculated as follows.

% Entrapment efficiency = Total drug content - unentrapped drug 100 / Total drug content

***In-vitro* Buoyancy:** On top of 900ml of 0.1 N HCl in a USP dissolution equipment type II, hollow microspheres were dispersed. A paddle rotating at 50 rpm stirred the medium for 12 hours. Hollow microspheres' floating and settling parts were individually retrieved. Drying and weighing of the hollow microspheres was done.

The mass of the hollow microspheres that remained afloat was divided by the overall mass of the hollow microspheres to determine buoyancy percentage.

Percentage buoyancy = Qf 100 / Qf + Qs

Where, Qf and Qs are the weight of the floating and the settled Hollow microspheres, respectively.

Drug Content:

Using spectrophotometry, the amount of medication in each formulation that is comparable to a unit dose (8.5 mg) was found. Each formulation was taken, ground to a fine powder in a glass mortar, and then dissolved in 0.1 N HCl solution for six hours. After filtering the solution, absorbance at 258 nm was measured. [11]

***In-vitro* Drug Release Study:**

The USP dissolving apparatus type 2 apparatus was used for the drug release investigation, and 900 ml of 0.1 N HCl (pH 1.2) was used as the dissolution medium. At predetermined intervals up to 12 hours, 5 ml of the sample solution was taken

out. The samples were then filtered using Whatman filter paper, appropriately diluted, and subjected to spectrophotometric analysis with a UV-Visible spectrophotometer at a maximum absorbance wavelength of 258 nm. Immediately following the removal of the test sample, an equal volume of new dissolving medium was replaced [12, 13, 14, and 15]. The average percentage of medication release was estimated once the dissolution studies were completed.

RESULTS AND DISCUSSION:

Construction of Standard Graph of Nisoldipine in Acidic Buffer (0.1N Hcl) P^H 1.2

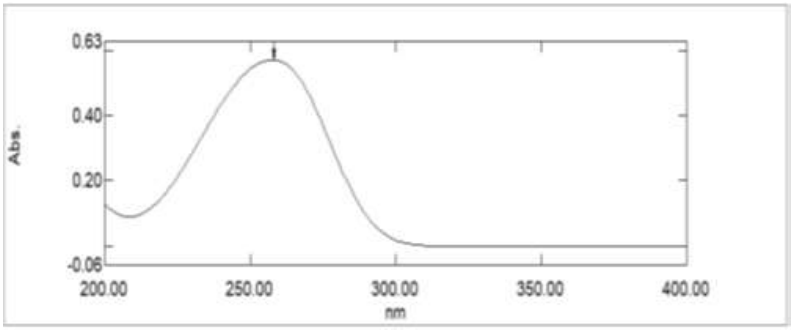

Figure 1: UV-Spectrum of Nisoldipine

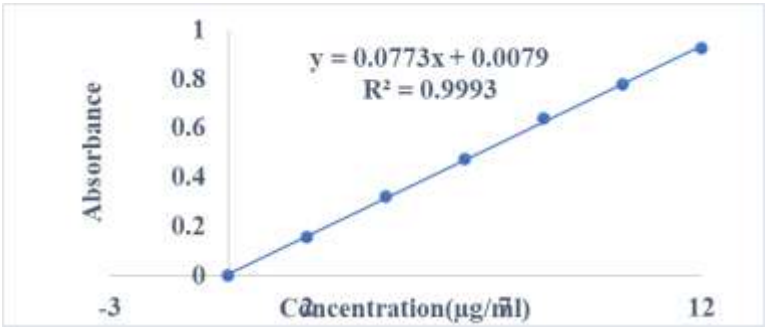

Figure 2: Standard curve of Nisoldipine in acidic buffer P^H 1.2

Drug Excipient Compatibility Study

Differential Scanning Calorimetry

DSC thermogram of the pure drug is shown in Fig. 3 endothermic peak was observed at 155.71°C indicates the drug melting point for the pure drug. In formulation mixer the peak was found at 69.35 ^{0}C indicating that the formulation was stable up to 69^{0}C shown in **Figure 4**

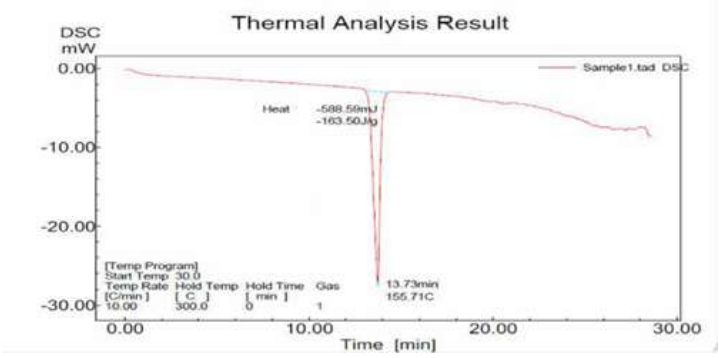

Figure 3: DSC thermogram of pure Nisoldipine

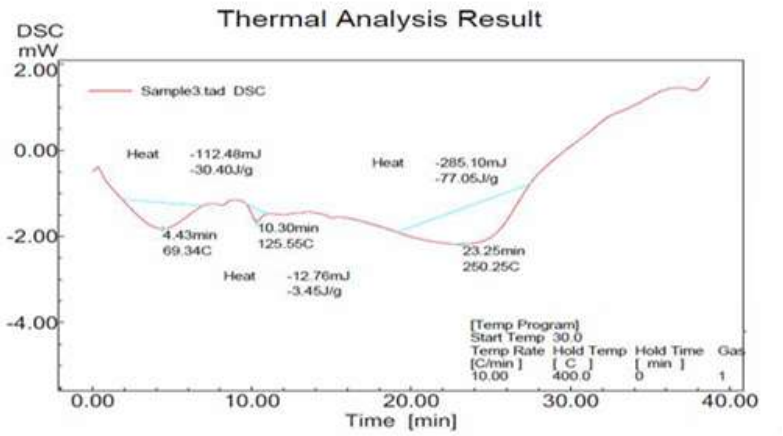

Figure 4: DSC thermogram of optimized formulation

FTIR Spectroscopy: Fourier transform infrared spectroscopy was used to conduct the drug-excipient compatibility research. Nisoldipine's FTIR spectra revealed peaks at 3410, 2941, 1629, 1530, 1400, and 1060 cm-1, respectively, due to stretching of the -OH molecule, the C-H molecule, the C-O molecule, the N-H molecule, the C-H bending in plane, and the C-C molecule. Peaks of 2929, 1462, 1163, 1022, 947, and 850 cm-1 were visible in the FTIR spectra of HPMC K 1500 PH PRM, corresponding to C-H stretching, O-H stretching, and C-C stretching. In **Figures 5, 6, and 7**, the FTIR spectra of the improved formulation revealed both peaks associated with the drug and the polymer, showing no drug-polymer interaction.

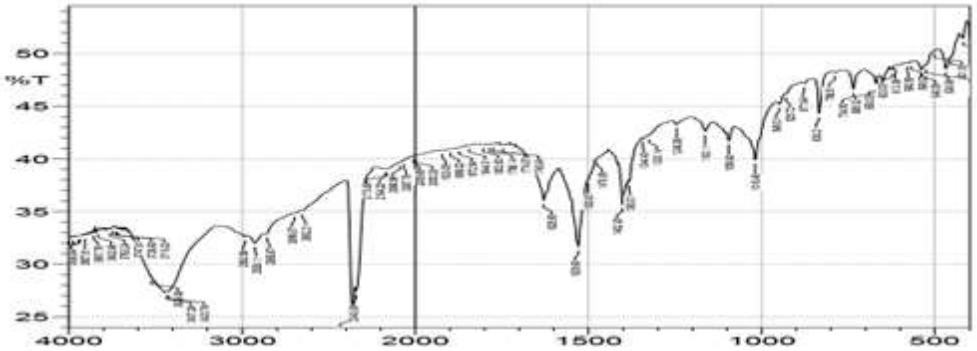

Figure 5: FTIR spectrum Nisoldipine pure drug

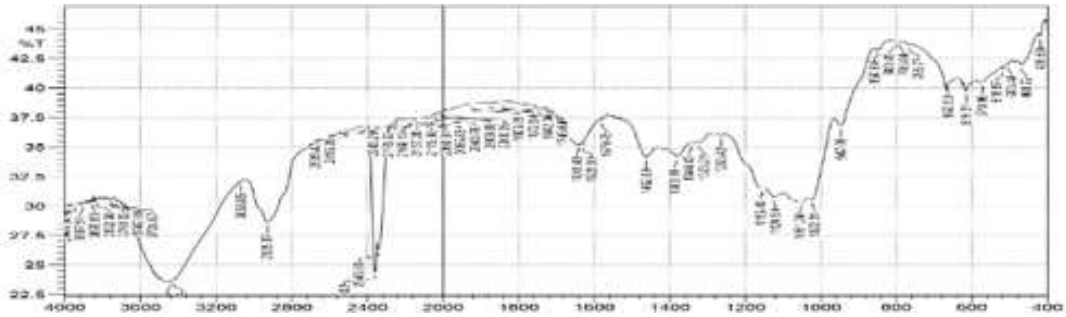

Figure 6: FTIR spectrum of Drug and Polymers

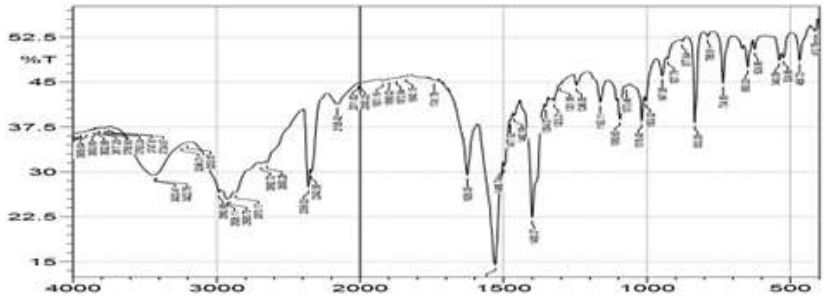

Figure 7: FTIR spectrum of Nisoldipine optimized formulation

Scanning Electron Microscopy

As shown in the figure, developed floating microspheres (F6) were discovered to be smooth, spherical, and porous. The perforated microsphere was formed at a high stirring rate of 1100, which may be related to the quick solvent evaporation that occurs and causes void creation. The porous structure of the microspheres, which makes them light weight and less thick, may have contributed to the formulation (F6high)'s floating time of 12 hours, as seen in **Figure 8.**

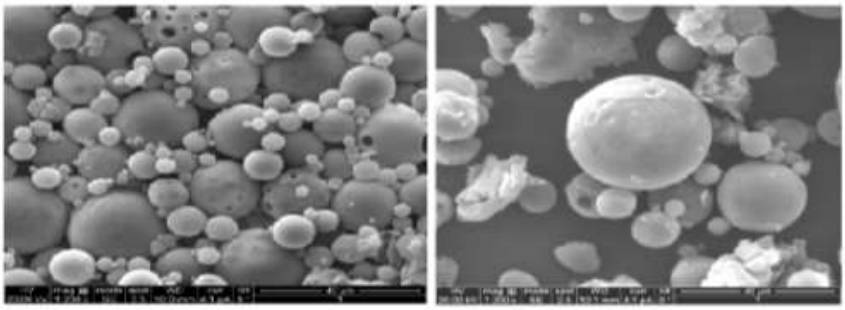

Figure 8: Scanning Electron microscopy image of optimized formulation F6

Micromeritic Properties:

The Bulk Density, Tapped Density and Hausner's ratio of formulation (F1 to F10) was in range of 0.1000 to 0.1424. The Carr's index was in range of 8.3% to 15.8% and angle of repose was between 10.34 to 25.26.

Percentage Yield:

The concentration of polymer affected the percentage yield of the floating microspheres. The percentage yield of floating microspheres declines as polymer concentration rises.

Particle Size:

The microsphere formulations (F1 to F24) were found to have a mean particle size that ranged from 43.481.06 to 56.671.76. The outcome showed that as polymer concentration increases, so does particle size. As the concentration of polymers rises, the solution's viscosity rises as well, increasing the interfacial tension. Higher viscosities also result in decreased shearing effectiveness, which causes the particle size to grow.

***In- vitro* Buoyancy:**

To examine the buoyancy of produced microspheres, an in-vitro buoyancy test was conducted. The table below displays the floating ability for the formulations (F1 to F24). The results also indicated that a microsphere's ability to float increased with size.

***In vitro* drug release**

The cumulative percentage drug releases of F1–F24 at the end of 12h were 68.35±1.76, 58.46±1.25, 45.25±1.33, 52.54±1.36, 43.35±1.78, 69.25±2.56, 60.36±4.67, 48.35±1.34, 50.45±1.46, 43.35±2.67.

Table 2: UV Spectrophotometric data for the estimation of Nisoldipine in acidic buffer

Sr. No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.159±0.0015
3	4	0.323±0.0016
4	6	0.477±0.0016
5	8	0.64±0.0014
6	10	0.779±0.0015
7	12	0.924±0.0015

All the values are represented as Mean ± SD (n=3)

Table 3: Various Flow Properties of Formulations

Formulation Code	Parameters				
	Angle of Repose (θ)	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Hausner's Ratio (HR)	Carr's Index (%)
F1	12.73	0.1000	0.1176	1.189	15.8
F2	10.34	0.1123	0.1435	1.142	10.3
F3	14.54	0.1334	0.1564	1.153	18.5
F4	13.32	0.1345	0.1342	1.165	14.3
F5	21.32	0.1422	0.1325	1.143	8.3
F6	12.45	0.1424	0.1245	1.147	13.4
F7	15.65	0.1244	0.1432	1.135	12.5
F8	17.54	0.1310	0.1431	1.134	14.7
F9	13.45	0.1231	0.1423	1.146	13.4
F10	25.26	0.1311	0.1253	1.132	12.3
F11	26.52	0.1542	0.1245	1.165	14.3
F12	15.24	0.1541	0.1432	1.143	8.3
F13	15.26	0.1354	0.1431	1.147	13.4
F14	13.24	0.1365	0.1245	1.135	12.5
F15	14.26	0.1245	0.1432	1.135	14.7
F16	13.24	0.1365	0.1435	1.134	13.4
F17	16.14	0.1245	0.1564	1.146	12.3
F18	15.24	0.1254	0.1342	1.165	14.7
F19	11.23	0.3254	0.1325	1.143	13.4
F20	12.45	0.2458	0.1435	1.147	12.3
F21	14.78	0.2458	0.1456	1.135	14.3
F22	18.96	0.1457	0.1564	1.135	8.3
F23	16.34	0.1487	0.1342	1.134	13.4
F24	13.57	0.1254	0.1325	1.146	12.5

Mean ± SD, n=3, SD: Standard Deviation

Table 4: Various Evaluation Parameters of Formulations

Formulation Code	% Yield	Mean Particle Size (µm)	Drug Entrapment Efficiency (%)	Drug Loading (%)	Buoyancy percentage (%)
F1	83.52±0.2	47±0.1	78.9	42.32± 1.34	63.76±2.35
F2	87.12±0.4	43±0.32	76.5	43.32± 1.24	67.54±1.43
F3	74.25±0.5	55±0.14	82.5	34.43±1.36	63.42±2.35
F4	77.14±0.6	52±0.45	78.6	23.54± 1.56	61.43±2.64

F5	81.25±0.6	51±0.78	87.7	41.43± 1.53	64.43±2.54
F6	74.89±0.7	56±0.11	72.5	32.24± 1.35	69.76±2.34
F7	77±0.2	51±0.02	73.5	45.45± 1.25	62.54±2.15
F8	81±0.1	52±0.25	74.4	23.46± 1.78	61.24±2.65
F9	78.25±0.3	52±0.23	75.5	34.25± 1.46	61.76±1.43
F10	79.58±0.3	53±0.11	76.8	34.43± 1.54	58.47±2.52
F11	78.25±0.1	52±0.56	77.24	34.76±1.99	62.43±2.64
F12	81.41±0.2	48±0.89	75.69	23.98± 1.43	64.43±2.96
F13	77.85±0.3	51±0.12	74.85	41.32± 1.36	68.76±2.25
F14	80.11±0.2	49±0.36	73.65	35.43±1.98	63.54±2.32
F15	79.85±0.3	50±0.87	85.24	23.54± 1.27	62.24±2.87
F16	79.87±.25	48.5±0.25	88.41	42.43± 1.95	63.43±2.75
F17	77.25±0.2	55±0.11	83.45	32.24± 1.43	65.43±2.24
F18	79.25±0.1	52±0.32	84.34	46.45± 1.25	70.76±2.21
F19	77±0.01	53±0.25	75.16	23.46± 1.94	62.54±2.43
F20	75.14±0.1	52±0.22	76.34	35.25± 1.32	67.24±2.86
F21	79.25±0.2	49±0.36	75.48	34.43±1.36	61.43±2.32
F22	75.48±0.3	55±0.25	73.24	23.54± 1.56	64.43±2.37
F23	77.25±0.1	54±0.85	74.29	41.43± 1.53	69.76±2.98
F24	73.12±0.2	56±0.14	81.35	32.24± 1.35	62.54±2.66

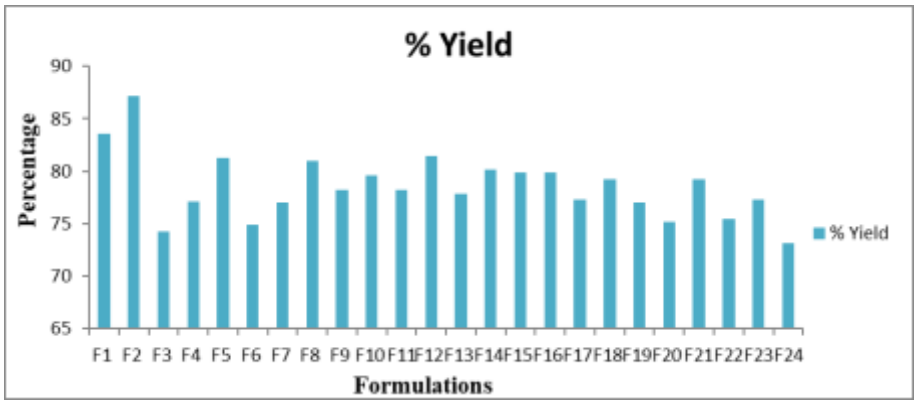

Figure: % yield of formulations F1-F24

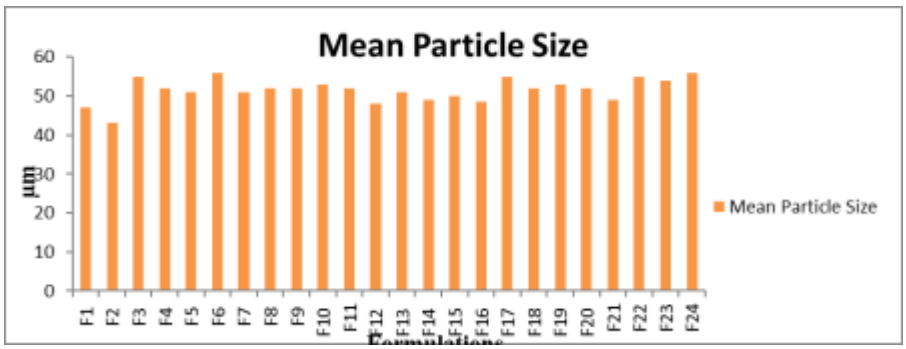

Figure: Mean Particle size of formulations F1-F24

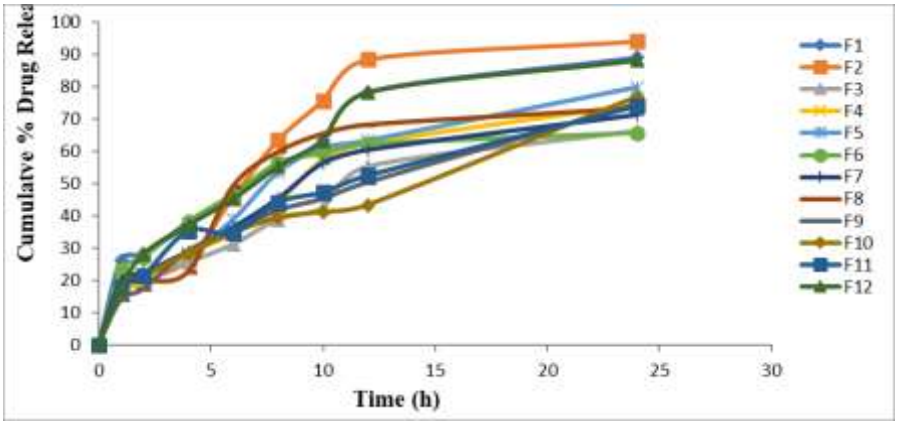

Figure 9: : *In-Vitro* drug release of Nisoldipine loaded hollow microspheresF1- F12

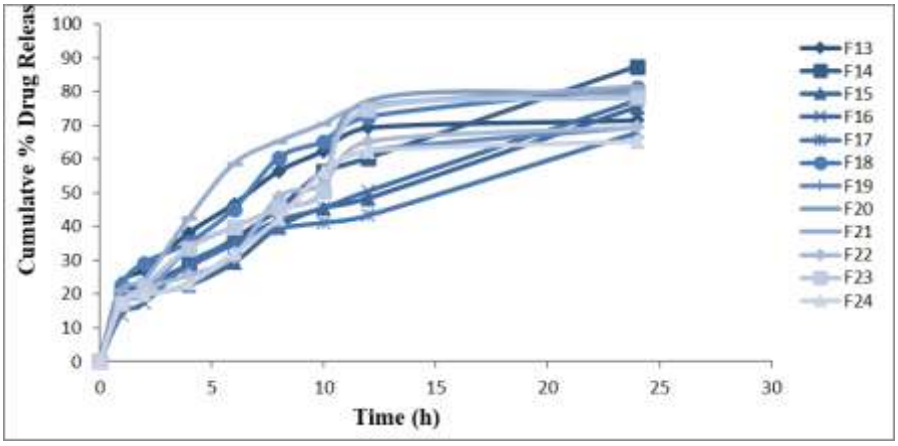

Figure 10: *In-Vitro* drug release of Nisoldipine loaded hollow microspheres F6- F10

CONCLUSION:

In the current work, Eudragit L 100, HPMC K15M, Polyethylene Oxide, and ethyl cellulose polymers were used to create Nisoldipine-loaded hollow microspheres. According to the study's findings, Nisoldipine hollow microspheres can be successfully prepared using the quasi-emulsion diffusion approach. The drug was determined to be compatible with all of the excipients utilised in the study after a drug-excipient compatibility analysis was conducted using DSC & FTIR. The *in vitro* experiments showed that the largest amount of medication was released from hollow Nisoldipine microspheres made with ethyl cellulose and HPMCK15M in a 2:1 ratio (F2).

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