Development and Evaluation of Diltiazem Hcl Polymeric Nanoparticles

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Abstract:

The purpose of the present study was to develop and evaluate the potential use of Polymeric nanoparticles in the delivery of Diltiazem HCl. Nanoparticles were prepared with poly ethylene oxide (PEO) by solvent displacement technique stabilized by polyvinyl alcohol (PVA). The Prepared nanoparticles were characterized for melting point, FTIR, Particle size, Morphology, drug content, entrapment efficiency, In vitro release. Melting point of Diltiazem HCl at 212^0C. FTIR study indicates peaks implies that there was no incompatibility between drug and the excipient. The particle size was determined by Malvern zeta sizer. The average particle size was in the range between 265 nm to 536 nm, particle morphology was found to be spherical or oval shaped. Drug content values from 90.31% to 98.25% suggesting that there was uniform mixing of the drug. The Drug entrapment efficiency was found to be in between72.12 to 90.52% indicated fairly good drug loading in the formulations indicated increased bioavailability of the drug. In order to define perfect model which will represent a better fit for in vitro release data, Korsemeyer-Peppas model was applied indicating diffusion mechanism of drug release from the developed formulations

Key words: Polymeric Nanoparticle, Diltiazem Hcl, Poly ethylene oxide, Poly vinyl alcohol.

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INTRODUCTION:

A solid particle or particulate dispersion with a size between 10 and 1,000 nm is referred to as a nanoparticle. Different biodegradable substances, such as phospholipids, lipids, or polymers, can be found in nanoparticles. Over liposomes, polymeric nanoparticles have some distinct advantages, such as the capacity to improve medication stability and provide beneficial controlled release capabilities. For compounds that are poorly soluble, poorly absorbed, chemically heat- and photo-labile, nanoparticulate systems hold promise as a potential perfect drug delivery strategy. The nanoparticles system has

benefits such as improved bioavailability, site-specific drug administration, sustained drug release over a longer time, and higher patient compliance due to less frequent dosing[1].

The physicochemical properties of the polymer and the drug to be loaded determine the best method for creating nanoparticles. Proteins, polysaccharides, and synthetic polymers are just a few examples of the materials that can be used to create nanoparticles. With the aid of cutting-edge microscopic methods including atomic force microscopy (AFM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM), nanoparticles are characterised based on their size, shape, and surface charge. The physical stability and in vivo distribution of the nanoparticles are influenced by characteristics such the size distribution,,diameter, and charge[2]. In the entire world, cardiovascular disorders are the main cause of death. Some of the most significant cardiovascular problems include coronary artery disease, atrial fibrillation, and hypertensive heart disease. Controlling high blood pressure has become a top concern in order to avoid serious problems because hypertension is a significant risk factor for cardiovascular mortality. Calcium channel blockers are first-line treatments for hypertension, despite the fact that the selection of medications for the condition is still debatable. When used alone or in conjunction with other medications, the calcium channel blocker diltiazem, which is non-dihydropyridine, effectively lowers blood pressure. Diltiazem is an excellent choice for the treatment of stable chronic angina because it lowers myocardial oxygen demand by lowering heart rate, blood pressure, and cardiac contractility. Additionally, diltiazem reduces atrioventricular conduction.

Diltiazem is a calcium channel blocker medication used to treat high blood pressure, angina, and certain heart arrhythmias. It may also be used in hyperthyroidism if beta blockers cannot be used. It is taken by mouth or injection into a vein. When given by injection, effects typically begin within a few minutes and last a few hours. Common side effects include swelling, dizziness, headaches, and low blood pressure. Other severe side effects include an overly slow heartbeat, heart failure, liver problems, and allergic reactions. Use is not recommended during pregnancy. It is unclear if use when breastfeeding is safe. Diltiazem works by relaxing the smooth muscle in the walls of arteries, resulting in them opening and allowing blood to flow more easily. Additionally, it acts on the heart to prolong the period until it can beat again. It does this by blocking the entry of calcium into the cells of the heart and blood vessels. It is a class IV antiarrhythmic

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride is purchased from Yarrow chemicals Ltd, Mumbai, Polyethylene oxide is procured from S.D. Fine chemicals Ltd., India and Poly vinyl alcohol, DMSO is obtained from S.D. Fine chemicals Ltd., India.

Methods

Preformulation Study

Preformulation is the first step in rationale development of any pharmaceutical dosage form of a drug. Preformulation study focuses on those physicochemical properties of the compound that can affect drug performance and development of an efficacious dosage form. These preformulation investigations confirm that there are no significant barriers to the compound development [2].

Identification of Drug

Determination of Melting point

Melting point of Diltiazem HCl was determined by open capillary tube method. The method used to determine a solid's melting point is known as a melting-point device. A handful of the compound's crystals are added to a capillary tube with a thin wall that is 10-15 cm long, 1 mm inside diameter, and closed at one end [2].

Fourier Transform Infrared Spectroscopy (FTIR) study

Infrared spectrum of simvastatin, nanoparticle formulation was determined by using Fourier Transform Infrared Spectrophotometer (FTIR-4100, Shimadzu) using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run.

Calibration curve of Diltiazem HCl

An accurately weighed 100mg of Diltiazem hydrochloride was dissolved in water and made up to 100ml in volumetric flask (Stock solution- I 1000µg/ml). From this 10ml of solution was pipette out and made up to 100ml volumetric flask (Stock solution –II 100µg/ml). From this solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0 ml were withdrawn and diluted to 10 ml to give 2, 4, 6, 8, 10, 12, 14,16, 18, 20 µg/ml respectively. Measure the absorbance at 237nm.

Preparation of Diltiazem HCl Loaded Polymeric nanoparticles

Diltiazem HCl polymeric nanoparticles were prepared with poly ethylene oxide (PEO) by solvent displacement technique. Briefly, different concentrations of PEO (0.1, 0.2, 0.3, 0.4gm) and 50 mg Diltiazem HCl were dissolved by heating and sonication in specified volume of acetone and methanol. This organic phase was injected drop wise in to water (aqueous phase) containing 1% PVA as hydrophilic surfactant, added under mechanical[3].

Twelve formulations were prepared by varying the concentration of polymer and drug for the selected polymer. The method was same for all the formulations.

Table 1: Composition of Polymeric Nanoparticles of Diltiazem HCl (F1 to F6)

Formulation Code	COMPOSITION							
	Drug: Polymer	Organic: Water phase ratio	Drug Mg	PEO Mg	PVA Mg	Acetone Mg	Methanol (ml)	Water(ml)
F1	1:2	1:1	50	100	15	15	5	20
F2	1:2	1:2	50	100	15	15	5	40
F3	1:2	1:4	50	100	15	15	5	80
F4	1:4	1:1	50	200	25	15	5	20
F5	1:4	1:2	50	200	25	15	5	40
F6	1:4	1:4	50	200	25	15	5	80

Table 2: Composition of Polymeric Nanoparticles of Diltiazem HCl (F7 to F12)

Formulation Code	COMPOSITION							
	Drug: Polymer	Organic: Water phase ratio	Drug Mg	PEO Mg	PVA Mg	Acetone Mg	Methanol (ml)	Water(ml)
F7	1:6	1:1	50	300	35	15	5	20
F8	1:6	1:2	50	300	35	15	5	40
F9	1:6	1:4	50	300	35	15	5	80

F10	1:8	1:1	50	400	45	15	5	20
F11	1:8	1:2	50	400	45	15	5	40
F12	1:8	1:4	50	400	45	15	5	80

EVALUATION OF NANOPARTICLES

Particle morphology

For SEM, nanoparticle were placed on a stab that was covered in clean glass .The nanoparticle were viewed using a scanning electron microscope at a 20kv accelerating voltage, and photos at an appropriate magnification were taken[4]

Particle size

Particle size was determined using a Zetasizer 300HS. Samples were diluted with distilled water and measured at a temperature of 25°C. The diameter was calculated from the autocorrelation function of intensity of light scattering from Polymeric Nanoparticles[4].

Drug Content

The prepared formulations were evaluated for drug content. Weighed, ground to a fine powder, and then dissolved in a solvent in which the drug was entirely soluble was a known quantity of drug-loaded nanoparticles. It was stirred for three hours at a speed of 700 rpm. The UV- spectrophotometric approach was used to estimate the amount of medication in the supernatant[5].

Entrapment Efficiency

For determination of drug entrapment, the amount of drug present in the clear supernatant after centrifugation was determined (w) by UV spectrophotometer at 237 nm. A standard calibration curve of drug was plotted for this purpose. The amount of drug in supernatant was then subtracted from the total amount of drug added during the preparation

(W). Effectively, (W-w) will give the amount of drug entrapped in the particles. Then percentage entrapment of a drug was calculated according to Equation[6]. %Drug Entrapment = (W-w/W) × 100

In Vitro Drug Release

Studies on in vitro release were carried out utilizing a modified Franz diffusion cell. Utilized was a dialysis membrane with a pore size of 2.4 nm and a molecular weight cutoff of 12,000–14,000 (membrane was soaked in double-distilled water for 24 hours prior to mounting in a Franz diffusion cell). The donor compartment received a volume equal to 6 mg of Diltiazam (Practically determined) loaded PNPs formulation, and the receptor compartment received 50 ml of PBS. At 37^0C, a magnetic stirrer was used to agitate the cell's contents. Every hour for up to 24 hours, aliquots were taken out of the receiver compartment using a side tube. Each time, a new PBS media was used to keep the volume consistent. By using UV visible spectroscopy at 237 nm, samples were examined[7].

Kinetics of drug release

The drug release data was subjected various analyses like Zero-order, First- order, Higuchi, Hixson Crowell model and Korsmeyer-Peppas[7].

RESULTS AND DISCUSSION

Determination of Melting point

The melting point of Diltiazem HCl was measured by using open capillary tube method indicate the melting point of Diltiazem HCl at 212^0C .

Fourier Transform Infrared Spectroscopy (FTIR) study

Compatibility study of drug with the excipients was determined by FTIR spectroscopy. The spectra of the drug and other ingredients used in the formulation were compared with the spectra of binary mixture of drug and excipients mixed in the ratio of 1:1. The standard FTIR spectra of the drug matches with the FTIR of the drug sample taken for the study confirms the authenticity of the drug. There was no significant appearance of new peaks or disappearance of characteristic peaks implies that there was no incompatibility between drug and the excipients taken for the study.

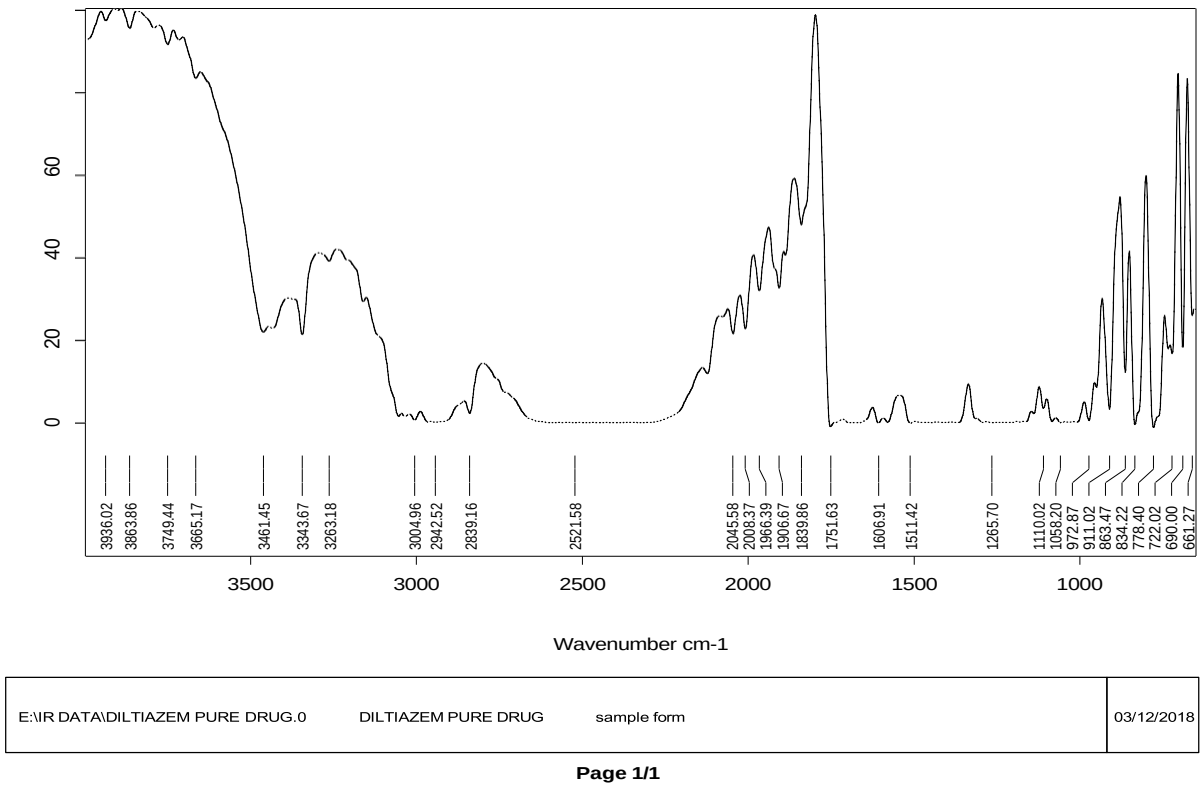

Fig 1: FTIR of Diltiazem HCl drug

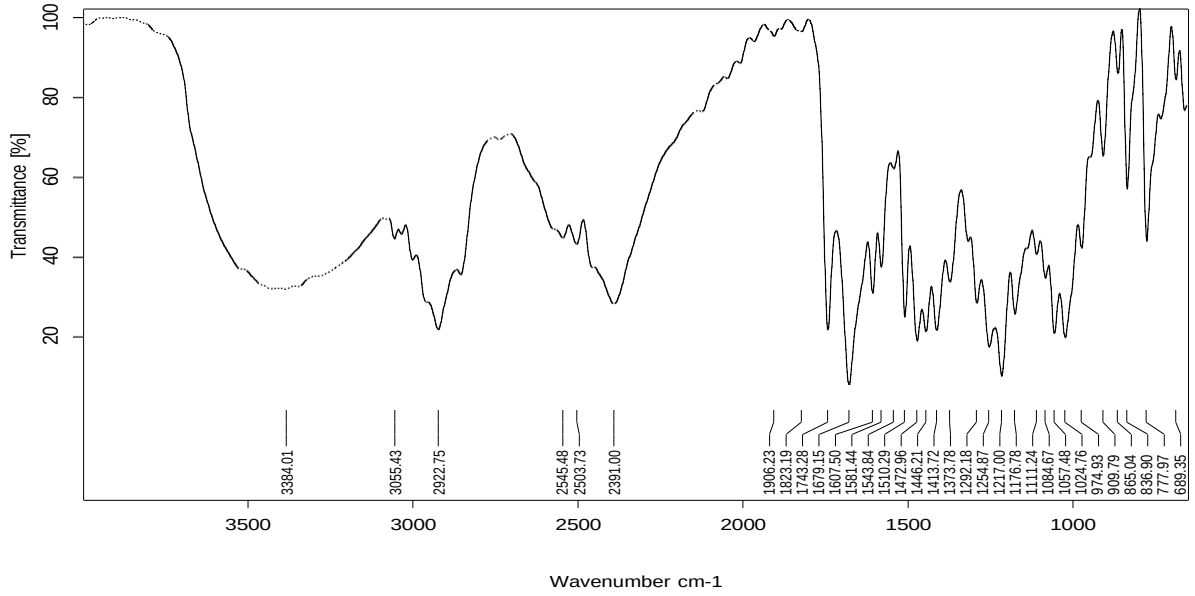

Fig 2: FTIR of Diltiazem HCl+PVA

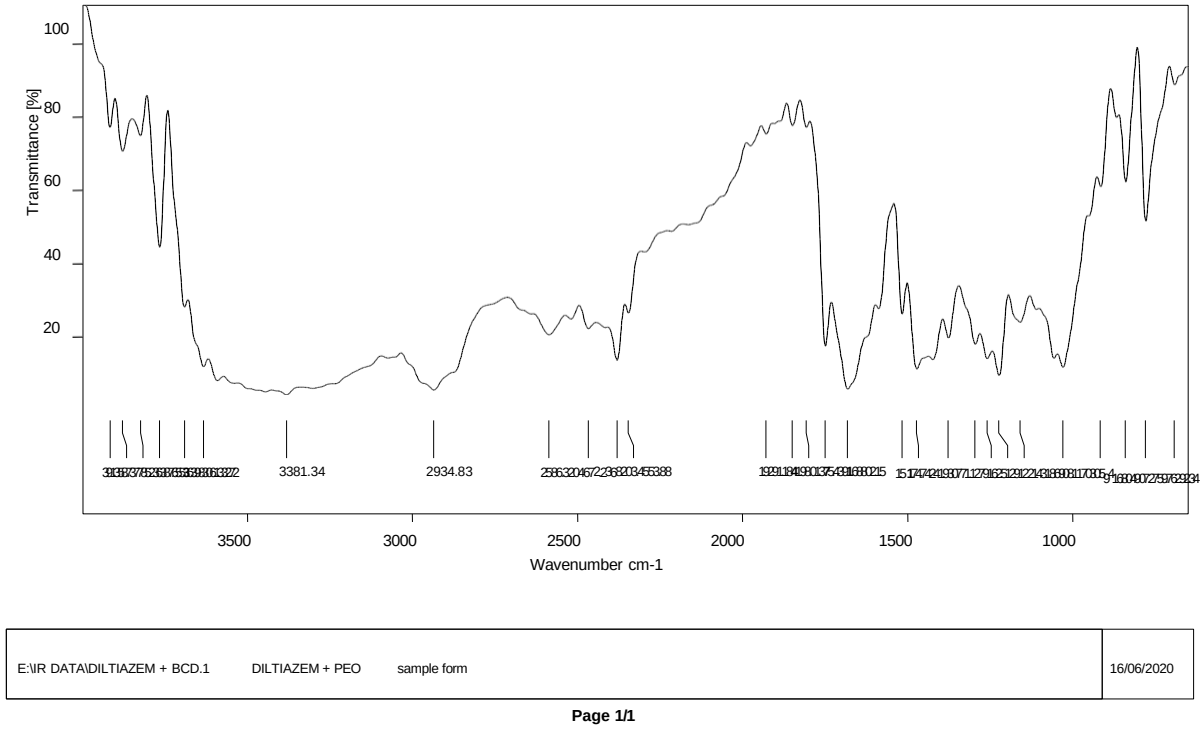

Fig 3: FTIR spectra of Diltiazem HCl + PEO

Table 3: Calibration curve of Diltiazem HCl

Calibration Curve data for Diltiazem HCl at 237 nm

S.No	Conc. µg/ml	Absorbance Nm
1	0	0
2	2	0.091
3	4	0.187
4	6	0.289
5	8	0.378
6	10	0.468
7	12	0.561
8	14	0.661
9	16	0.756
10	18	0.837
11	20	0.931

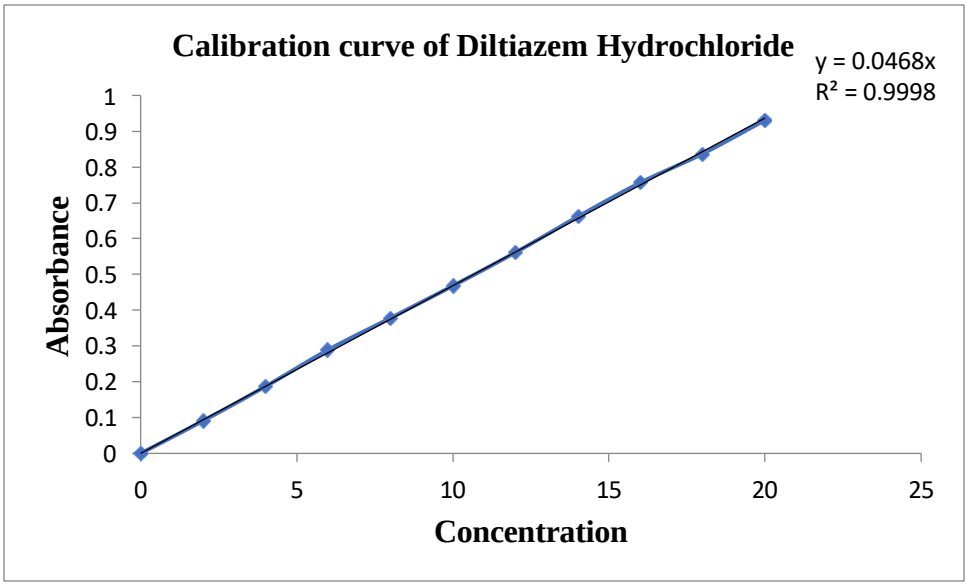

Fig 4: Calibration curve of Diltiazem HCl

Particle morphology

The surface morphology of the nanoparticles was determined by using scanning electron microscopy. All formulations were found to be spherical or oval shaped.

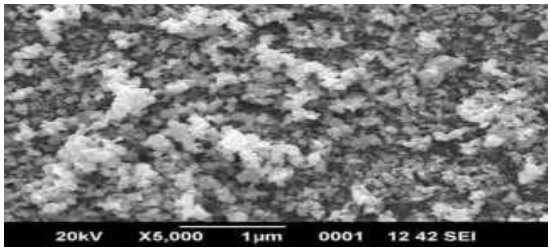

Fig 5: SEM image of Polymeric Nanoparticles

Particle size

Average nanoparticles sizes of the formulations were range from 265 nm to 536 nm (F1-F12) respectively. The nanoparticle size is dependent on PEO concentration. The smallest particle size of were found in batch F1(265 nm) and largest particle of was found in batch F12 (536nm). The data suggested that in an increase in polymer concentration increase the particle size.

Drug content

The results were subjected to statistical analysis to test whether the drug content was uniformly distributed in the nanoparticles or not. Drug content of F1, F2, F3, F4 ,F5,F6,F7,F8,F9,F10,F11andF12formulation s was found to be 91.65%, 91.43%, 90.91%, 90.31%,92.41%,91.15%,94.46%,96.45%,93. 14%,91.16%,98.25%,9416%respectively. Out of the twelve formulations, the highest drug content was observed for F11 formulation.

Entrapment efficiency

The percentage entrapment efficiency varied from 72.12 to 90.52%.. Entrapment efficiency of the formulation increased due to the high concentration of drug.

In vitro drug

The cumulative amount of drug release was calculated. Results revealed that highest cumulative amount of drug release 88.50% up to 24hrs.

Table 4: *In-vitro* diffusion data for formulation F1 to F6

S.No	Time (hr)	% Cumulative drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	10.70	10.93	12.90	11.92	11.02	10.12
3	2	19.31	18.73	21.37	18.96	18.32	17.10
4	3	25.42	24.85	26.26	25.80	25.83	24.29
5	4	34.05	30.55	34.97	31.79	31.06	31.91
6	5	41.64	36.90	40.50	37.36	40.05	37.01
7	6	47.14	45.98	47.53	45.28	48.21	44.65
8	7	52.86	50.45	54.35	50.86	55.34	51.87
9	8	57.32	55.77	63.30	58.16	62.26	59.10
10	12	69.14	67.18	76.69	73.13	74.82	70.77
11	24	83.27	79.46	90.32	88.12	89.68	83.72

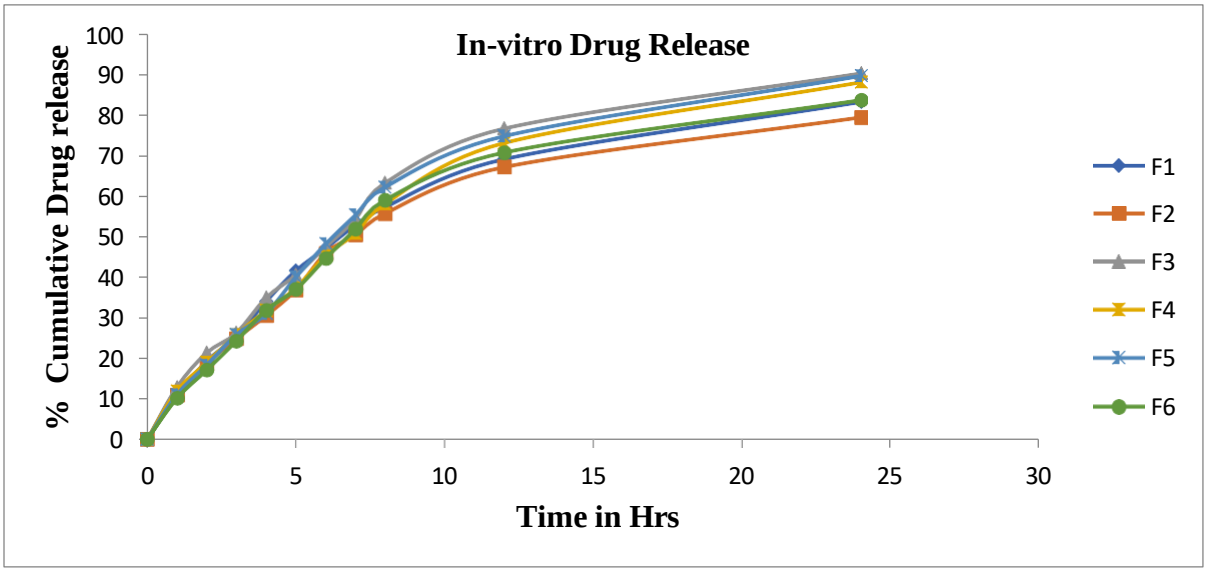

Fig 6: *In-vitro* release profile for formulations F1 to F6

In-vitro diffusion data for F7 to F12

S.No	Time (hr)	% Cumulative drug release					
		F7	F8	F9	F10	F11	F12
1	0	0	0	0	0	0	0
2	1	9.975	10.56	9.497	10.33	10.17	10.77
3	2	16.09	18.55	16.32	18.78	18.60	17.28
4	3	22.83	26.94	23.56	26.19	25.86	24.62
5	4	30.38	33.75	29.16	32.12	30.98	28.30
6	5	36.32	38.97	36.01	38.70	37.08	34.43
7	6	40.64	44.80	42.24	45.91	43.98	38.94
8	7	49.64	51.83	49.10	51.24	49.50	43.46
9	8	55.40	60.66	55.35	58.04	54.84	50.82
10	12	66.45	73.09	66.56	68.02	65.87	60.23
11	24	79.55	87.13	78.40	80.76	78.27	74.72

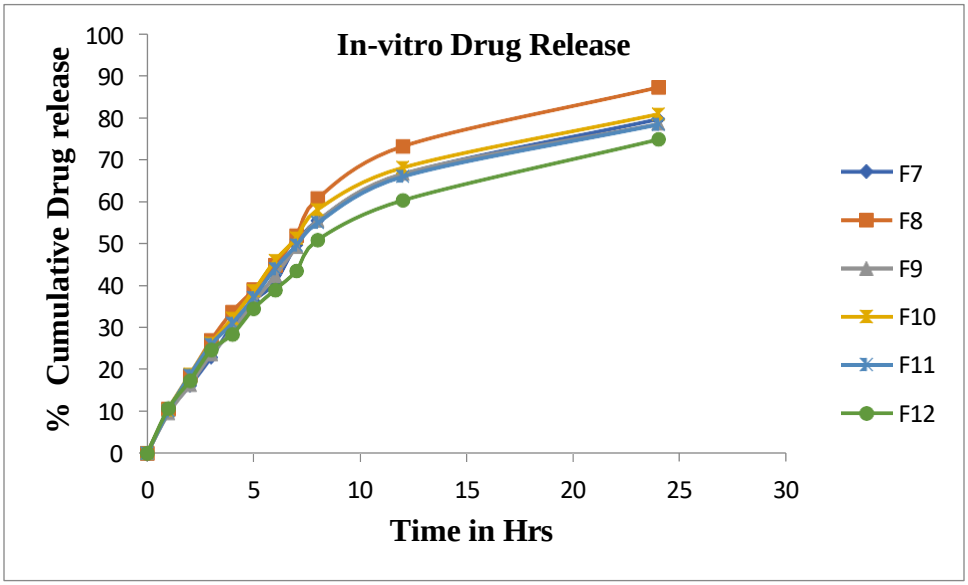

Fig 7: _In-vitro_ release profile for formulations F1 to F6

Kinetics of drug release

The in vitro release data was subjected to zero order, first order, Higuchi's and Korsemeyers-Peppas model in order to establish the drug release mechanism and kinetics of the drug release from the Polymeric Nanoparticles

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Release Kinetics Data of the Formulations F1 to F12

Formulation code	Zero order R^2	First order R^2	Higuchi's R^2	Korsemeyer Peppa's	
				N	R^2
F1	0.8047	0.9619	0.9601	0.6804	0.9575
F2	0.8045	0.9426	0.9559	0.6675	0.9625
F3	0.8228	0.9816	0.9591	0.6597	0.9700
F4	0.8467	0.9853	0.9659	0.6770	0.9764
F5	0.8213	0.9821	0.9527	0.7150	0.9629
F6	0.8150	0.9578	0.9517	0.7176	0.9619
F7	0.8203	0.9503	0.9549	0.708	0.9623
F8	0.8258	0.9753	0.9601	0.7023	0.9601
F9	0.8109	0.9393	0.9516	0.7141	0.9570
F10	0.7986	0.9446	0.9551	0.6861	0.9606
F11	0.8062	0.9424	0.9600	0.6726	0.9760
F12	0.8388	0.9561	0.9735	0.6426	0.973

CONCLUSION

Using PEO AND PVA as polymer, Diltiazem HCl polymeric nanoparticles were prepared by solvent displacement technique. Twelve formulations were prepared,Out of the twelve formulations, F11 formulation was found to be the best formulation with drug content of 98.25%, entrapment efficiency varies from 72.12 to 90.52%, nanoparticles sizes of the formulations were range from 265nm to536 nm (F1-F12). FTIR spectrum revealed no drug-polymer interaction, in-vitro drug release data showed 88.50% of drug release sustained up to 24 hrs. Furthermore, drug release from the NPs was controlled indicating its potentials in controlled drug delivery. The release was found to follow zero order, first order release kinetics, Higuchi, korsmeyer with franz diffusion mechanism for all batches. So, it concludes that Diltiazem Hcl Loaded polymeric nanoparticles could be effective in prolonged drug release.

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