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Design, Fabrication And Evaluation Of Superporous Hydrogel Based Floating Mini Tablets Of Nicardipine

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Abstract: The present work was aimed to formulate Superporous Hydrogels based floating Minitablets of Nicardipine hydrochloride for gastro retentive drug delivery system to improve its bioavailability. Superporous hydrogels were prepared by using Chitosan, Ac-Di-Sol and various other polymers and evaluated for density, porosity and mechanical strength. The dried SPH were compressed into 5mm Minitablet and filled into size '2' capsule. Capsules wereevaluated for dissolution studies states that there is increase in polymeric concentration there isa decline in drug release except for the higher concentration i.e 480 mg. NHT5 selected as the optimized formulation based on 85% drug release. FTIR and DSC proves that there were no critical collaborations between the drug and polymers. There are no significant changes found in the stability studies. The present study shows that polymers like Chitosan, Ac-Di-Sol and others in combination with sodium bicarbonate as a gas generating agent can be used to developsustained release floating tablets of Nicardipine Hydrochloride.

Keywords: Nicardipine Hydrochloride, Chitosan, Ac-Di-Sol, Mini-tablets, DSC, Capsule '2'.

Introduction:

Gastroretentive drug delivery systems are designed to be retained in the stomach for a prolongedtime and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract (1). Local delivery also increases bioavailability of the stomach wall receptor site and increases the efficacy of drugs, to reduce acid secretion (2).

Superporous hydrogels (SPHs) were originally developed as a novel drug delivery system to retain drugs in the gastric medium. These systems should instantly swell in the stomach and maintain their integrity in the harsh stomach environment, while releasing the pharmaceutical active ingredient (3,4). A Superporous hydrogel (SPH) is a three-dimensional network of a hydrophilic polymer that absorbs a large amount of water in a very short period of time due to the presence of interconnected microscopic pores (5,6 & 7).

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyantin the stomach without affecting the gastric emptying rate for a prolonged period of time. Whilethe system is floating on the gastric contents, the drug is released slowly at the desired rate fromthe system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and control of the fluctuation in plasma drug concentration(8,9).

Mini-tablets are very small tablets compared to normal tablets and they have uniform weights (25

mg), shapes and size distribution (circular shape and 3 mm size for all the batches) and it does not vary between formulations. Accurate measured amount of drug can be loaded in each mini-tablet. So, uniformity in drug content, weight and reproducible release profiles can be easilyachieved (10). These mini-tablets also have a smaller size similar to granules and pellets. Theycan also be easily filled in capsules like other multiple unit dosage forms and can be modified in many ways for achieving the desired drug release profile (11,12).

Nicardipine Hydrochloride is dihydropyridine calcium channel blocker is used alone or with an angiotensin-converting enzyme inhibitor to treat hypertension, chronic stable angina pectoris and prinzmetal's variant angina. Nicardipine is similar to other peripheral vasodilators. Nicardipine inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes possible by deforming the channel, inhibiting ion-control gating mechanisms and interfering with the release of calcium from the sarcoplasmic reticulum (13,14).The objective of the present study was to develop and evaluate encapsulated mini-tablet systems, in order to achieve desired target product profile.

MATERIALS AND METHODS:

Materials:

Nicardipine hydrochloride was purchased from Aurobindo Pharma Pvt Ltd, Hyderabad. Chitosanwas obtained as a gift sample from Sunrise Remedies Pvt. Ltd. Acrylamide and Acrylic acid werepurchased from Sigma-Aldrich, Germany. Ac-Di-Sol was obtained as a gift sample from Dr. Reddy's laboratories Pvt. Ltd. Bis-acrylamide (BIS) was purchased from Fluka, Switzerland, Ammonium Persulfate was purchased from Sigma Aldrich Bangalore, India. Sodium bicarbonateand Span were obtained from Sisco Research Laboratories Pvt. Ltd., Mumbai.

Methodology:

Preparation of Standard Curve for Nicardipine hydrochloride:

Standard Solution of Nicardipine Hydrochloride:

The standard stock solutions of Nicardipine Hydrochloride were prepared by dissolving 100 mgof drug in 10mL 0.1N HCL in 100mL volumetric flask, final volume was adjusted with 0.1N HCL and sonicated for about 10 min to get 1000 µg/mL (Stock I). From Stock 1, 1mL was taken and diluted to 100mL to get 100 µg/mL (Stock II) Working standard solutions of 25 µg/mL were scanned in the entire UV range of 400-200 nm to obtain the absorbance spectra. Five working standard solutions for drug having concentration 5, 10, 15, 20 & 25 µg/mL were prepared in 0.1N HCL from stock solution. The absorbance of resulting solutions was measured at respectiveλ max and plotted a calibration curve against concentration to get the linearity and regression equation.

Compatibility Studies by FTIR:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtainedon Bruker Alpha II. The potassium bromide pellet method was used for solid samples and for liquids, samples were transferred to Liquid cell followed by recording the spectra over the wavenumber of 4000 to 500cm^{-1}.

DSC Studies:

DSC thermogram of pure drug and mixture were recorded using Diffraction scanning calorimeter(DSC 60, Shimadzu, Japan). The measurement was performed between 30^{o} and 350^{o}C at heating rate

10^{o}C/min.

Formulation of Superporous Hydrogels:

The composition of different Nicardipine Hydrochloride SPH gels formulations are given in the Table 1 & 2. Initially 6% Chitosan solution was prepared in presence of 5% glacial Acetic acid. This chitosan solution was added to the beaker and Ac-Di-Sol, it can be added into mixture as powder.To the above solution Acrylamide and Acrylic acid were added while stirring followed by by BIS,Span 80, APS, TEMED, HPMC and Drug while stirring, later Polymerization was allowed to continue for 10 minutes. Finally, Sodium Bicarbonate was added quickly to the above solution and Stirred for the desired time. SPHs of required size were cut and dried in Oven for 48 Hours (15).

Table 1: Formulation of Superporous Hydrogels using chitosan

S.No	Ingredients	Trials (Quantity of Ingredients)			
		NHH1	NHH2	NHH3	NHH4
1	Nicardipine Hydrochloride (gm)	5	5	5	5
2	Chitosan 6% (mL)	2	4	6	8
3	Acrylamide 50% (mL)	3	3	3	3
4	Acrylic acid 50% (mL)	2	2	2	2
5	BIS 2.5% (mL)	0.7	0.7	0.7	0.7
6	Span 10% (mL)	0.3	0.3	0.3	0.3
7	APS 20% (mL)	0.25	0.25	0.25	0.25
8	TEMED 16.7% (mL)	0.25	0.25	0.25	0.25
9	Sodium Bicarbonate 20% (mL)	2.9	2.9	2.9	2.9
10	Stirring Time (Seconds)	15	15	15	15

Table 2: Formulation of Superporous Hydrogels using Ac-Di-Sol

S.No	Ingredients	Trials (Quantity of Ingredients)			
		NHH5	NHH6	NHH7	NHH8
1	Nicardipine Hydrochloride (gm)	5	5	5	5
2	Ac-Di-Sol (gm)	0.120	0.240	0.360	0.420
3	Acrylamide 50% (mL)	3	3	3	3
4	Acrylic acid 50% (mL)	2	2	2	2
5	BIS 2.5% (mL)	0.7	0.7	0.7	0.7
6	Span 10% (mL)	0.3	0.3	0.3	0.3
7	APS 20% (mL)	0.25	0.25	0.25	0.25
8	TEMED 16.7% (mL)	0.25	0.25	0.25	0.25
9	Sodium Bicarbonate 20% (mL)	2.9	2.9	2.9	2.9
10	Stirring Time (Seconds)	15	15	15	15

Evaluation of Superporous Hydrogels

The prepared hydrogels were evaluated for density, porosity, and mechanical strength/ Ultimate compression pressure.

Mechanical Strength:

A bench comparator was used to test the mechanical properties of the Superporous hydrogels and their composites. A sample swollen in simulated gastric fluid (SGF) was placed longitudinallyunder the lower touch of the bench comparator that was connected to a micrometre gauge. TheSuperporous hydrogel was supported by a lab jack. Weights were applied to the upper touch of the bench comparator in incremental intervals. The swelling height of the Superporous hydrogelunder pressure was read from the gauge. The pressure applied to the Superporous hydrogel was calculated from the weights and the contact area of the lower touch. Two parameters, swelling height under 100 cm water pressure and ultimate compression pressure (UCP), were determined to characterize the mechanical properties of the Superporous hydrogels. The UCP was determined by applying increasing amounts of weights until a point when the Superporoushydrogel started cracking. The pressure at that point was defined as UCP (16).

Porosity & Density of the Hydrogels:

The porosity of the hydrogel films was measured in a 20 mL beaker, and then the empty beakerweight (W1) was measured. Up to 1 g of hydrogel film was placed into the beaker, and an inert solvent, cyclohexane, was slowly poured in. The weight (W2) of the beaker was then measured. After that, the hydrogel films were removed and weighed (W3). The hydrogel film pores were full of cyclohexane, and the volume of cyclohexane in a hydrogel film pore was taken as the porevolume of the hydrogel films. The porosity of the porous gel (P) was calculated using the following equations

$$Vg = 20 – (W2 − W1 − 1)/ρh \quad (1)$$

$$ρg = 1/Vg \quad (2)$$

$$Vp = W2 − W3 – 1/ρh \quad (3)$$

$$P = Vp/Vp + Vg \quad (4)$$

where ρg is the density of the hydrogel (g/cm^3), ρh is the density of the cyclohexane (g/cm^3), Vgis the volume of the hydrogel (cm^3), and Vp is the volume of cyclohexane in the pore (cm^3) (17)

CAPSULE FORMULATION:

The dried Superporous hydrogels were blended with magnesium stearate and hydrogels were compressed in to 5.0 mm Mini-Tablets using rotary tablet compression machine. Each Mini- Tablet is filled into size ‘2’ capsule shown in the Table 3 & 4.

Table 3: Formulation of Chitosan based Mini Tablets

S.No	Ingredient	NHT1	NHT2	NHT3	NHT4
1	Dried SPH (mg) Eq. to 30 mg of Nicardipine HCl	47.456	51.870	49.010	52.201
2	Magnesium stearate (mg)	0.761	0.729	0.791	0.718
3	Capsule Size ‘2’	1	1	1	1
4	Total weight of Mini-Tablet	48.217	52.599	49.801	52.919
5	Total weight of filled capsule	114.01	112.278	114.568	113.013

Table 4: Formulation of Ac-Di-Sol based Mini Tablets

S.No	Ingredient	NHT5	NHT6	NHT7	NHT8
1	Dried SPH (mg) Eq. to 30 mg of Nicardipine HCl	49.015	49.735	50.455	51.175
2	Magnesium stearate (mg)	0.735	0.746	0.756	0.767
3	Capsule Size '2'	1	1	1	1
4	Total weight of Mini-Tablet	49.750	50.481	51.212	51.943
5	Total weight of filled capsule	112.75	113.481	114.212	114.943

Figure 1: (a) Mini-Tablets using rotary tablet compression machine (b) Mini-Tablet into size 2 capsule

In-Vitro Drug Release studies:

Nicardipine HCl capsules dissolution was performed in 1000ml of 0.1N HCl with paddle RPM of

50. The release of the drug from the Superporous hydrogel tablet after disintegration of tablet could follow steps of initial penetration of surrounding dissolution media into the hydrogel followed by swelling with subsequent dissolution/erosion of matrix followed by transport of thedissolved drug through the hydrated matrix or eroded hydrogel.

Drug Release Kinetics:

Kinetic studies of drug release for selected SPH formulation were carried out concerning different kinetic models viz; Zero-order kinetics, first-order kinetics, Higuchi and Korsmeyer Peppas model. After that regression analysis (R^2) was determined and the diffusion coefficient
(n) was also calculated.

Stability Studies:

The formulations were loaded for stability as per ICH guidelines in to stability chambers which were maintained at 40^{o}C and 75% RH. Stability studies were conducted for 3 months. Samples

were withdrawn at 1 month, 2 months and 3 months. Third month samples were analysed and results are tabulated.

RESULTS and DISCUSSION:

Standard Graph of Nicardipine Hydrochloride:

Standard graph of Nicardipine Hydrochloride was constructed by using concentration 5,10,15,20,25(µg/ml) in 0.1N HCL. It is evident from the figure 2 & 3 and Table 5 that the graph is linear with regression coefficient value of R^2 = 0.9998 and slope = 0.01326 at λ max of 359.0nm.

Table 5: Calibration data for Nicardipine Hydrochloride at 359nm

S.No	Concentration (µg/mL)	Absorbance (nm)
0	0	0
1	5	0.064
2	10	0.136
3	15	0.200
4	20	0.268
5	25	0.329

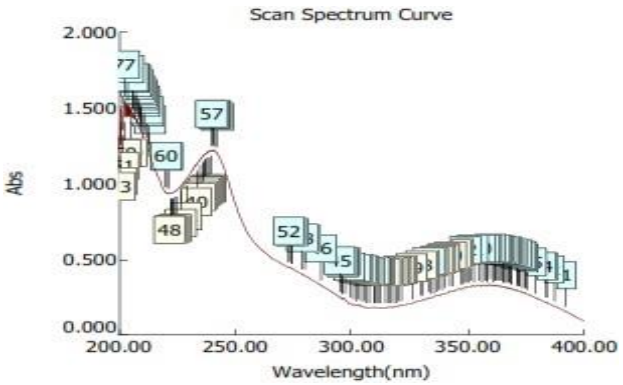

Fig 2: Spectrum of Nicardipine Hydrochloride at 359nm

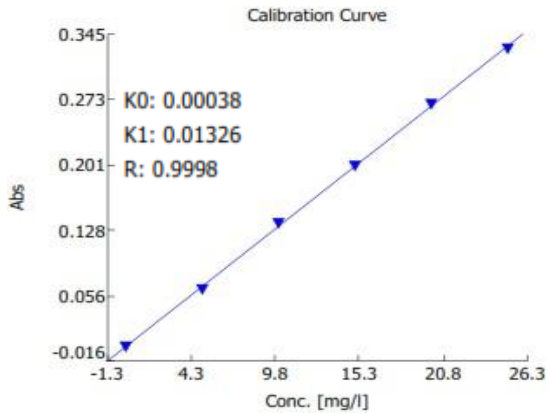

Fig 3: Calibration Curve for Nicardipine Hydrochloride at 359nm

Compatibility Studies by FTIR:

IR spectrum of Nicardipine Hydrochloride showed following Peaks along with wave number depicted in Table 6 and Figure 4 & 5. It is clear that, there is no appreciable change in the positions of the characteristic bands of the drug along with the IR spectrum of the formulation derived during the present investigation. Since there is no change in the nature and position of the bands in the formulation, it can be concluded that the drug maintains its identity without going any chemical interaction with the polymers used.

Table 6: FTIR data of Nicardipine Hydrochloride Pure and Formulation Mixture

S.No	Wave Number (cm^{-1})		Functional Group
	Pure Drug	Mixture	
1	3450.24	3418.17	N-H Free Stretching Vibration
2	3075.60	2956.77	stretching of Ar-H, (-CH)
3	2950.59	2919.31	Methyl group where C-C symmetric
4	1644.62	1637.73	C=O stretching vibration
5	1622.15	1584.10	Pyridine nucleus ring
6	827.19	840.09	C-N stretching

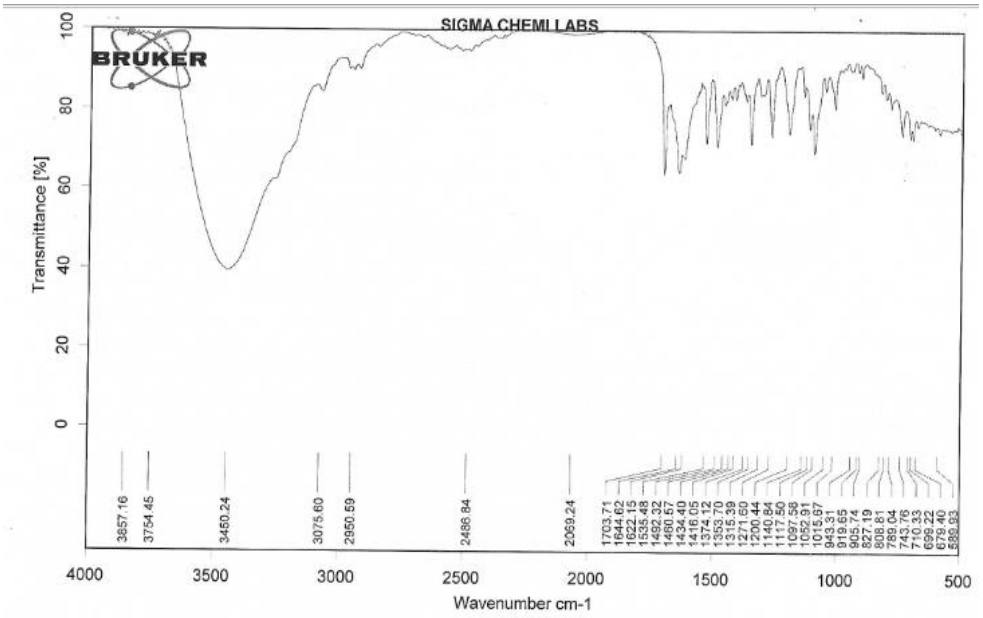

Figure 4: FTIR Spectra of Pure Drug Nicardipine Hydrochlorid

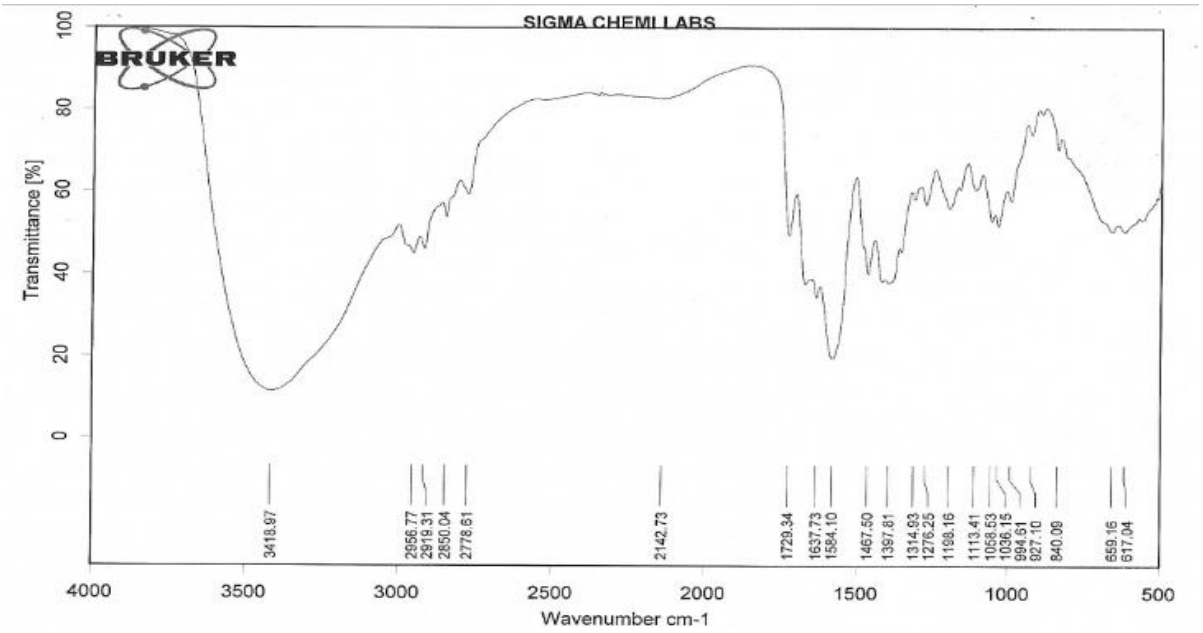

Figure 5: FTIR Spectra of Formulation Mixture

Evaluation of Superporous Hydrogels:

The hydrogels were prepared and evaluated for density, porosity and mechanical strength. Density, % Porosity and UCP increased as amount of Polymer Chitosan & (Sodium CMC) increased. As sodium CMC is a water swellable polymer and as the amount of polymer increasedthe swelling nature of SPH increased due to this there is increase in porosity. The mechanical strength of SPH's increased as the amount of polymer increased. As there is increase in polymernetwork at higher amount the strength of hydrogel increased. At higher amount of polymer thereisn't proportional increase in UCP, this might be due to the higher water absorption capacity which will weaken the SPH structure. Based on the above results depicted in Table 7 indicates that Density, % Porosity, Mechanical Strength are found satisfactory for formulations prepared with Ac-Di-Sol in comparison with Chitosan.

Table 7: Density & Porosity of Formulations

Trial		Density	%Porosity	Ultimate compression Pressure (cm water pressure)
NHH1		1.106	57.05	195.38
		0.740	87.29	185.00
		1.379	41.31	205.38
	Average	**1.075**	**61.88**	**195.25**
NHH2		1.496	50.94	265.38
		1.038	66.55	215.38
		1.649	76.03	235.35
	Average	**1.393**	**64.51**	**238.70**
		1.339	45.80	315.38
		1.736	24.53	379.79

NHH3		1.014	29.02	329.79
	Average	**1.363**	**33.12**	**341.66**
NHH4		0.980	29.53	390.61
		1.370	17.15	432.54
		1.479	41.76	379.79
	Average	**1.276**	**29.48**	**400.98**
NHH5		1.890	80.693	517
		1.529	76.097	506
		1.646	74.365	526
	Average	**1.688**	**77.052**	**516.33**
NHH6		1.608	82.161	635
		2.272	82.292	626
		1.708	82.382	642
	Average	**1.863**	**82.279**	**634.33**
NHH7		2.715	88.384	641
		2.342	80.987	633
		1.712	83.435	646
	Average	**2.256**	**84.269**	**640.00**
NHH8		2.655	87.004	645
		3.136	85.481	651
		2.397	80.782	638
	Average	**2.729**	**84.422**	**644.67**

The release of the drug from the Superporous hydrogel tablet after disintegration of tablet couldfollow steps of initial penetration of surrounding dissolution media into the hydrogel followed by swelling with subsequent dissolution/erosion of matrix followed by transport of the dissolved drug through the hydrated matrix or eroded hydrogel.

Capsule Formulation:

The dried Superporous hydrogels were blended and compressed into mini tablets and filled insize 2 capsule and evaluated for in-vitro dissolution studies.

Evaluation of Mini-Tablets Filled Capsules:

In Vitro Drug Release Profile: Nicardipine HCl capsules dissolution was performed in 1000mlof 0.1N HCl with paddle RPM of 50.

Table 8: In Vitro Drug Release Profile for Formulations NHT1-NHT8

Time (in hours)	**% Cumulative drug release**							
	NHT1	**NHT2**	**NHT3**	**NHT4**	**NHT5**	**NHT6**	**NHT7**	**NHT8**
0	0.00	0.00	0.00	0	0	0	0	0

0.5	23.04	25.69	17.15	45.44	36.13	36.67	37.21	44.82
1	35.71	45.95	30.84	57.37	46.18	45.93	45.67	56.48
2	55.85	63.40	43.59	64.6	55.10	53.63	52.16	63.48
3	65.90	72.03	52.66	75.36	60.73	59.05	57.36	68.58
4	74.98	77.40	61.52	83.54	64.66	62.61	60.56	71.16
5	81.75	81.72	68.61	90.67	68.05	65.56	63.06	73.20
6	84.90	85.68	73.39	94.67	71.02	68.09	65.31	75.16
7	89.56	90.50	77.11	96.67	73.28	70.39	67.28	76.86
8	90.54	91.86	82.12	97.57	75.52	72.56	69.01	78.34
10	-	-	-	-	80.43	77.45	72.56	80.94
12	-	-	-	-	84.52	81.61	75.34	83.34

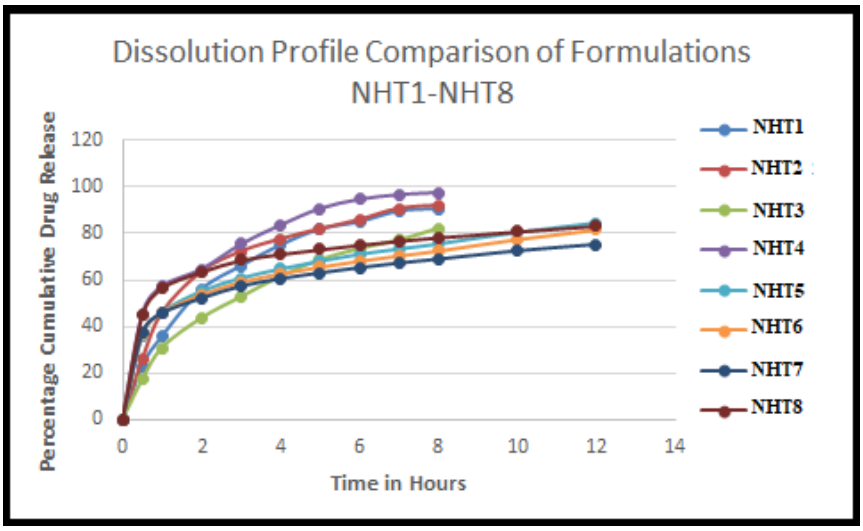

Figure 6: Dissolution Profile Comparison of Formulations NHT1-NHT8

The drug release profile suggests that, as there is increase in polymeric concentration there is a decline in drug release except for the higher concentration i.e 480 mg. This shows the release retarding effect of polymer i.e Chitosan & Sodium carboxy methyl cellulose (Sodium CMC). In trial NHT4 & NHT8 which is containing higher amount of polymer, initially higher drug release has been observed but after the initial few points i.e after 2 hours drug release is slower in case of formulation containing Ac-Di-Sol.

This might be due to the swelling characteristics of SodiumCMC due to which initial burst release has been observed but retarding drug release after that due to the polymeric retarding characteristic.From the above results depicted in Table 8 concludes that Superporous hydrogel formulation containing Ac-Di-Sol has good release retarding properties in comparison to Chitosan preparedSuperporous Hydrogels.

Drug Release Kinetics:

The drug release kinetics suggest lower Zero order regression (R^2) value and higher first order regression (R^2) values for all the trials suggesting that rate of drug release is dependent on the drug concentration in the hydrogel. The higher Higuchi regression (R^2) values suggest that drugrelease is by diffusion. To check the type of diffusion the release data was fitted in to Krosmeyer's – Peppas equation and based on the 'n' values depicted in Table 9. The drug release was found to be fickian diffusion since

'n' values are lesser than 0.45 in case of formulations prepared withAc-Di-Sol and Anomalous transport (non-Fickian transport mechanism) in case of formulations prepared with Chitosan as n-values are greater than 0.45 but less than 0.89.

Table 9: Release Kinetics of Formulations NHT1 – NHT8

		NHT1	NHT2	NHT3	NHT4	NHT5	NHT6	NHT7	NHT8
Zero order	R^2	0.698	0.685	0.634	0.548	0.755	0.792	0.854	0.905
First order	R^2	0.987	0.977	0.989	0.991	0.915	0.895	0.828	0.794
Higuichi	R^2	0.278	0.367	0.414	0.456	0.905	0.893	0.859	0.792
Peppas	R^2	0.936	0.955	0.980	0.994	0.994	0.995	0.995	0.971
	n	0.771	0.879	0.929	0.947	0.255	0.239	0.214	0.181

Based on the observed values, NHT5 is selected as the optimized formulation as it sustained drug release and approximately 85% of drug in 12 hours at a lower concentration of polymer. Even NHT8 also released more than 80% of drug in 12 but it is due to the higher initial release but at later time points it released lesser amount of drug compared to other formulations. All Chitosan prepared hydrogels are retarded for 8 hours.

Stability data of Nicardipine HCl:

DSC Studies: DSC is conducted for Formulation mixture before and after stability as shown in the Figure 7 & 8, and they exhibited both exothermic and endothermic peaks and there is no muchsignificant changes observed.

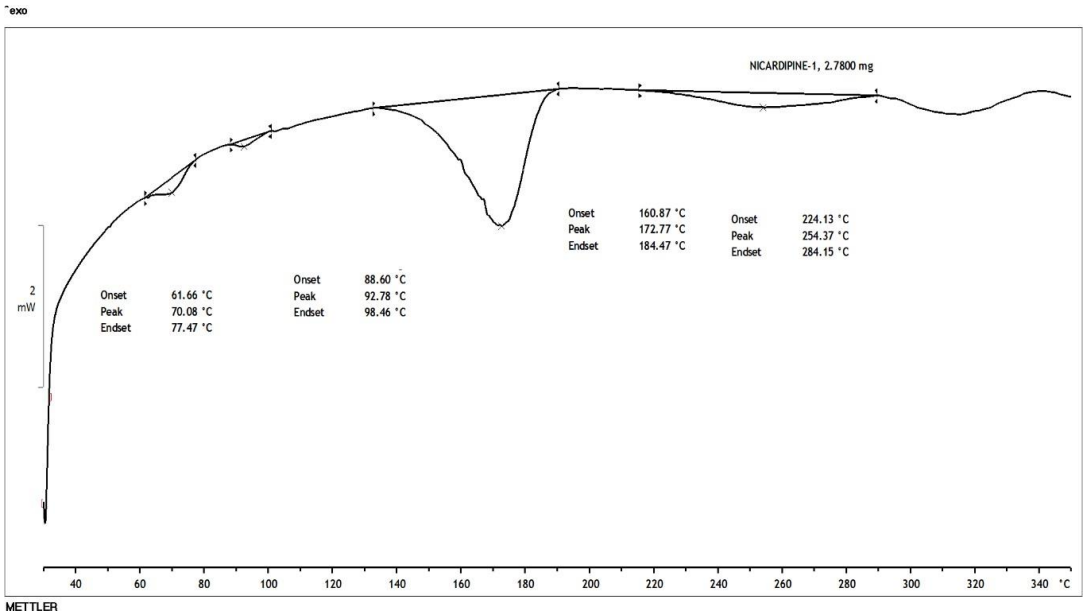

Figure 7: DSC Spectra of Formulation mixture before stability

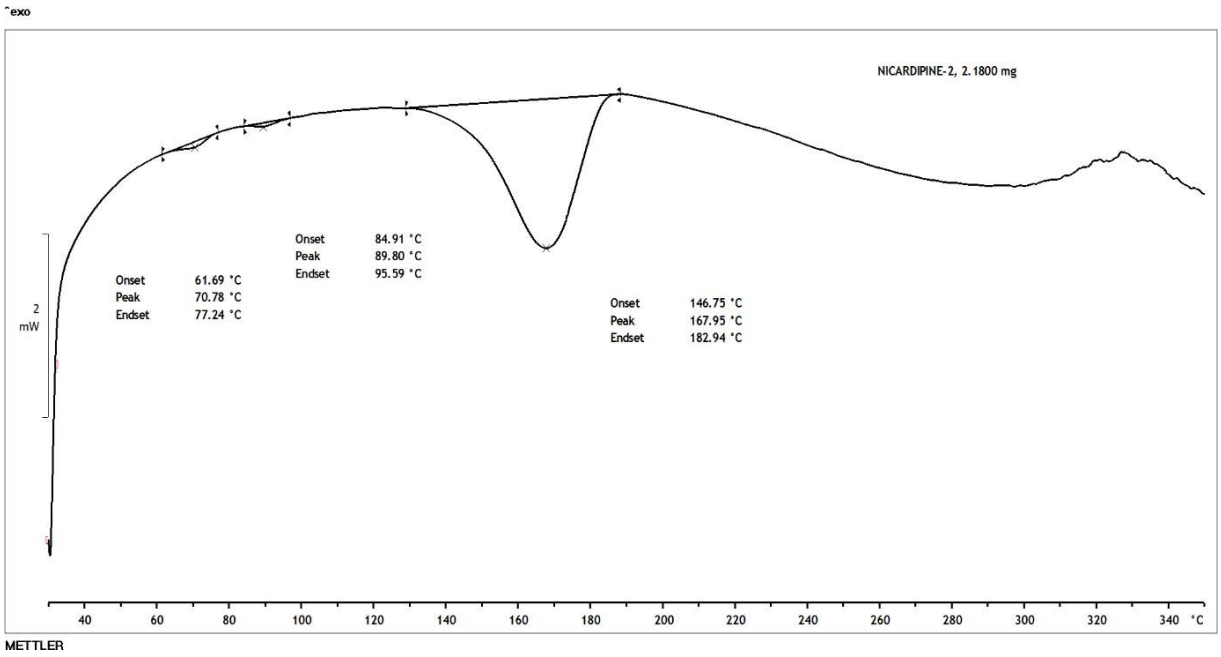

Figure 8: DSC Spectra of Formulation mixture after stability

The optimized formulation was subjected to stability studies at 40 ^{o}C ± 2 ^{o}C/ 75%±5 RH for 3 months, NHT5 as the optimized formulation evaluated for Density, Porosity, Ultimatecompression pressure and invitro dissolution studies. There were no much significant changes in Density, Porosity, Ultimate compression pressure and invitro dissolution studies and results were depicted in the Table 10.

Table 10: Stability data of Nicardipine

Stability data of Nicardipine at 40 deg.C and 75% RH					
	Initial	**After 3 months**		**In-Vitro studies**	
Formulation	**NHH_5**			**Formulation**	**NHT_5**
Density	1.89	1.726		**Initial**	**After 3 months**
	1.529	1.954	**Time**		
	1.646	1.639	0	0	0
Avg.	**1.688**	**1.773**	0.5	36.13	34.26
			1	46.18	43.54
%Porosity	80.693	78.358	2	55.1	51.86
	76.097	82.647	3	60.73	56.64
	74.365	75.592	4	64.66	61.27
Avg.	**77.052**	**78.866**	5	68.05	66.84
			6	71.02	72.34
Ultimate compression Pressure (g/sq.cm)	517	528	7	73.28	75.42
	506	534	8	75.52	77.68
	526	513	10	80.43	83.25
Avg.	**516.33**	**525**	12	84.52	88.46

Conclusion:

Nicardipine HCl formulations were successfully developed by filling mini-tablets in a capsule body. Initially Nicardipine HCl Superporous hydrogels were prepared using Chitosan and Ac-Di-Sol and

evaluated for density, porosity and mechanical strength. As the amount of polymer increased the swelling nature of SPH increased due to this there is increase in porosity. The mechanical strength of SPH's increased as the amount of polymer increased. The drug release profile suggests that, as there is increase in polymeric concentration there is a decline in drug release except for the higher concentration i.e 480 mg. This shows the release retarding effect ofpolymer. Based on the observed values, NHT5 is selected as the optimized formulation as it sustained drug release and approximately 85% of drug in 12 hours at a lower concentration of polymer. Hence the mini-tablet formulation of Nicardipine HCl can be suitable for optimum floating drug delivery.

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