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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF MATRIX TABLETS OF NIFEDIPINE BY USING HYDROPHOBIC AND HYDROPHILIC POLYMER.

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Key words:-
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Abstract

Objective: The aim of the present research is to formulate and evaluate matrix tablet of Nifedipine by using hydrophobic and hydrophilic polymer.

Method: The Nifedipine matrix tablets were prepared by wet granulation method. Formulated tablets were characterized by parameters like hardness, friability, content uniformity, weight variation and in- vitro release studies. In vitro drug release studies were carried in dissolution apparatus using 900 ml of 0.1N HCL (pH 1.2 buffer) for first 2 hours and remaining 12 hours in phosphate buffer (pH 6.8) containing 1% w/v sodium lauryl sulfate as dissolution medium. The amount of drug released was determined spectrophotometrically at 235 nm.

Result: The results of the present study based on the in- vitro dissolution studies showed that formulation F5 was shown drug release upto 92.53% at 14 hours was selected as the best formulation from Nifedipine formulations. All the formulated tablets were evaluated for various physical parameters such as hardness, thickness, friability weight variation and drug content was found to be within the limit. In selected formulation, the calculated regression coefficients for drug release kinetics follows the Korsemayer-peppas and drug transport mechanism follow anomalous transport and non- fickian diffusion mechanism release.

Conclusion: The result of the study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of nifedipine.

Introduction:-

Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner by dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials (Loyd, Nicholas and Howard, 2011; Yie, 1992).

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Sustained release dosage form is a modified dosage form that prolongs the therapeutic activity of the drug. Sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect which is followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period of time. sustained release products often times eliminates the need for night dosing, which benefits not only the patients but the care given as well because of the sustained plasma drug levels (Vyas and Khar, 2002; Leon and Andrew, 1999).

The basic rationale of a sustained drug delivery system is to optimize the Pharmacodynamics and Pharmacokinetic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest amount of drug which is administered by the most effective route. Oral route has been the most popular and widely used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design, ease of production and low cost.
Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain fast and complete systemic drug absorption. Such immediate release products results in rapid drug absorption and onset of action. Plasma drug concentration reduces according to the drug's pharmacokinetic profile after absorption of the drug from the dosage form is absolutely complete. Plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in failure of therapeutic efficacy. Before this point is attained, the other dose is usually given if a sustained therapeutic outcome is desired. The other way of administering dose is to utilize a dosage form that will provide sustained release of drug by maintaining the plasma drug concentrations (Afrasim and Shivakua, 2010; Antesh, Bhattacharya and Pankaj, 2009).

Nifedipine is one of a group of compounds thought to act by blocking the transmembrane inward movement of calcium (Lalitha *et al* 2011). Nifedipine being anti- hypertensive agent act by blocking ca+ channel and interfere with the working action of ca+ in blood vessel constriction and heart muscle contraction and nerve conduction in the heart (Gopinath *et al* 2013). Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. Nifedipine is widely used in the treatment of angina pectoris and systemic hypertension. It is a poorly soluble drug and its absorption from gastrointestinal tract is limited by dissolution rate. It has a short biological half-life 2 hrs. Absorption of Nifedipine is poor following administration orally via immediate release dosage forms. It exhibits 45-65% oral bioavailability due to hepatic first pass metabolism. Immediate release formulations of Nifedipine clearly show fluctuation in drug plasma concentration results in specific side effects like increase in heart rate. Sublingual Nifedipine has been used in hypertensive emergencies, however, was found to be unsafe (Barzegar *et al* 2013).

Materials and Method:-

Materials:-

The drug nifedipine was purchased from Yarrow chem. Products (Mumbai, India). Hydroxy propyl methyl cellulose (HPMCK100) was bought from Research lab fine chem. Industries (Mumbai, India). Magnesium stearate was bought from Himedia Laboratories Pvt. Ltd. (Mumbai, India). Poly vinyl pyrrolidone (PVP K30) and Avicel 101(Microcrystalline cellulose) was purchased from Yarrow chem. Products (Mumbai, India). Ethyl cellulose was bought from Balaji Drugs (Gujarat, India). All other chemicals used were of analytical grade.

Methods:-

Preparation of sustained release tablet of Nifedipine:-

Matrix tablets were prepared by wet granulation technique. All the components except lubricants were mixed for 15 minutes in the mortar and pestle. PVP K30 (5%) was dissolved in quantity sufficient of ethanol, and this solution was added into the above drug mixture to form a coherent mass. The wet mass was passed through a ‘’No. 12’’ sieve and it was dried at room temperature, 20-22°C for 8 hrs. Then, the granules were sized by passing through a “No. 16” mesh screen. Then mixed with 2% magnesium stearate and compressed into 8-mm convex tablets using a single-punch tablet machine. The compressed tablets were evaluated for various parameters. The amount of polymers and other ingredients are given in Table 1.

Table 1:- Formulations of nifedipine

	F1	F2	F3	F4	F5
Nifedipine	15%	15%	15%	15%	15%
HPMC K100	10%	7.5%	15%	15%	10%
Ethyl cellulose	5%	2.5%	7.5%	5%	7.5%
PVP K30	10%	5%	5%	5%	5%
Avicel 101	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2%	2%	2%	2%	2%
Average weight (mg)	200	200	200	200	200

Drug-Excipients Compatibility Study:-

Differential scanning calorimetry (DSC):-

DSC can be used to determine the nature and specification of crystallinity of drug and excipients through measurement of glass transition temperature and melting point temperature and their associated enthalpies. This technique has been used to study the physical and chemical interaction between drug and excipients. Required amount of nifedipine was taken to obtain DSC curve and a physical mixture of drug and polymer was also performed using DSC4000**,** Perkin Elmer. Samples were taken and sealed in aluminium pans and analyzed in an atmosphere of air at flow rate of 25 mL/min. A temperature range of 30°C to 400°C was used where rate of heating was 10°C/min.

Fourier transforms Infrared spectroscopy (FTIR):-

Fourier transform infrared (FTIR) spectra of pure drug nifedipine were performed individually and a physical mixture of drug and polymer were recorded using potassium bromide mixing method on FTIR instrument. The scanning range from 400 $^{-cm}$ to 4000 $^{-cm}$ using FT-IR, Alpha, Bruker, Germany, to evaluate the physical state of the drug.

Evaluation of Granules (Subramanyam, 2003; Lachman and Lieberman, 1991)

Bulk Density:-

The bulk density is used as a measure to describe packing materials or granules. Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

Bulk density = Mass of the blend / Bulk volume

Tapped Density:-

It is achieved by mechanically tapping a measuring cylinder containing a powder sample on tapped density apparatus. The initial volume was noted. The apparatus was set for 100 taps.

The tapped density was determined as the ratio of mass of the blend to the tapped volume.

Tapped density = Mass of the blend / Tapped volume

Carr's Index (CI):-

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

Carr's Index (%) = Tapped density – Bulk density / Tapped density × 100

Hausner's Ratio:-

It indicates the flow properties of the powder and the ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density/ Bulk density

Angle of Repose:-

The internal angle between the surface of the pile of blend and the horizontal surface is known as the angle of repose. The blend is passed through a funnel fixed to a burette stand at a particular height. A graph paper was placed

below the funnel on the table. The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

Angle of repose θ= tan-1 (h / r)
Where, h = height of the pile
r = radius of the pile

Evaluation of tablets (Subramanyam, 2003; Lachman and Lieberman, 1991)

Thickness of Tablets:-
Thickness of tablets was determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness:-
The hardness of the tablet was determined by Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded and the zero reading is deducted from it. Five tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded. It is expressed in kg/cm2.

Friability:-
The Friability of tablets was performed in a Roche Friabilator. It consists of a plastic chamber that revolves at 25 rpm. About twenty tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed. Percentage friability is calculated by using the following formula:
% Friability = W1 – W2/W1 ×100
Where, W1 = weight of the tablets before test
W2 = weight of the tablets after test

Weight Variation:-
Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet from the average weight of tablet was calculated.

Uniformity of drug Content:-
Ten tablets were weighed from each formulation, powdered and equivalent to 30 mg of nifedipine were weighed and dissolved in sufficient quantity of ethanol and make up the volume upto 100 ml with pH 6.8. Further 1ml of the above solution were taken and diluted to 100ml with phosphate buffer pH 6.8. The absorbance of resulting solutions was measured in an UV spectrophotometer (UV 1800, Shimadzu) at 235nm. Drug content was calculated.

In vitro drug release study:-
In vitro drug release rate studies were carried out using the USP XXIII dissolution test apparatus-II (rotating basket) at a rotation speed of 50 rpm using 900 ml of 0.1N HCL (pH 1.2 buffer) for first 2 hours and remaining 12 hours in phosphate buffer (pH 6.8) containing 1% w/v sodium lauryl sulfate as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C. At predetermined time intervals a 5-ml sample was withdrawn and replaced with fresh dissolution media up to 14 hr. The samples were analyzed by the UV spectrophotometric (UV 1800, Shimadzu) method at 235 nm and the results were reported. The absorbances were recorded and percentage drug release was calculated.

Swelling Index (SI) Studies:-
The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in a petridish using dissolution medium as 0.1N HCl (pH 1.2) and pH 6.8 phosphate buffer. After 1, 2, 4, 6 and 8 hours each tablet was withdrawn carefully, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimdzu). The experiment was performed in triplicate for each time interval. Swelling index was calculated by using the following formula.

Swelling index (SI) = 100 (W2 - W1)/ W1
Where, W1 = initial weight of the tablet.
W2 = final weight of the tablet.

Drug release kinetic study:-
To analysis the mechanism for the release and release rate kinetics of the formulated dosage form, the data obtained from conducted studies was fitted into zero-order, first-order, Higuchi matrix and Korsemeyer peppas constant. In this by combining the r-values obtained, the best-fit model was selected.

Zero order kinetics:-
Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by following equation:
$$\mathbf{Q_t = Q_o + K_o t}$$
Where, Q_t = amount of drug dissolved in time t,
Q_o = amount of drug in the dissolution,
K_0 = zero order rate constant.
When the data was plotted as cumulative % drug release verses time, if the plot is linear then data obeys zero order kinetics with slope equal to K_o. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First order kinetics:- To study the first order release rate data were fitted to the following equation:
$$\mathbf{Log\ Q_t = Log\ Q_o + K_1\ t / 2.303}$$
Where, Q_t = amount of drug release in time t.
Q_0 = initial amount of drug in solution.
K_1 = first order release rate constant.

When data was plotted as log cumulative % drug remaining verses time yields a straight line indicating that the release follows first order kinetics. The constant K can be obtained multiplying slope values.

Higuchi Model:- Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs in corporate in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media.
$$\mathbf{Q = K_H T^{1/2}}$$

Where, Q = amount of drug at time t,
K_H = Higuchi rate constant.

When data was plotted according to this equation, i.e. cumulative drug released verses square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

Hixson-crowell model:
The release rate data were fitted to the following equation.
$$\mathbf{Q_0^{1/3} - Q_t^{1/} = K_{HC}\ t}$$
Where, Q_t = amount of drug release in time t,
Q_0 = initial amount of drug in tablet,
K_{Hc} = rate constant for Hixson-crowell rate equation.

Korsmeyer- peppas model:
To study this model the release rate data are fitted to the following equation.
$M_t/M\infty = kt^n$
Where, M_t = amount of drug release at time t,
$M\infty$ = amount of drug release after infinite time,
Mt/M∞= factorial drug release % at time t,
K= release constant,
t= release time,
n = Diffusional exponent for the drug release that is dependent on the slope of the matrix dosage forms.

This is used when the release mechanism is not well known or when more than one type of release phenomenon could be involved (Hadjiioannou *et al* 1993; Bourne, 2002; Higuchi, 1963; Hixson and Crowell, 1931; Korsmeyer *et al* 1983).

Results and Discussion:-

Standard graph:-

Preparation of Standard curve of Nifedipine pH 1.2:-

10 mg of Nifedipine was weighed accurately and transferred to a 100 ml volumetric flask and dissolved with little amount of ethanol and then the volume was made up by adding the phosphate buffer solution pH 6.8 in 100 ml volumetric flasks. Then 10 ml from above solution was taken into another 100ml volumetrick flask and volume was made up with stock solution. Volumes of 2ml, 4ml, 6ml, 8ml & 10 ml were taken in 10 ml volumetric flask from the prepared solution and diluted upto the mark with pH 6.8 phosphate buffers.The absorbance of above solution were scanned in UV region and found that nifedipine showed absorbance at 235nm. Calibration curve was prepared by plotting concentration versus absorbance as shown in figure 1.

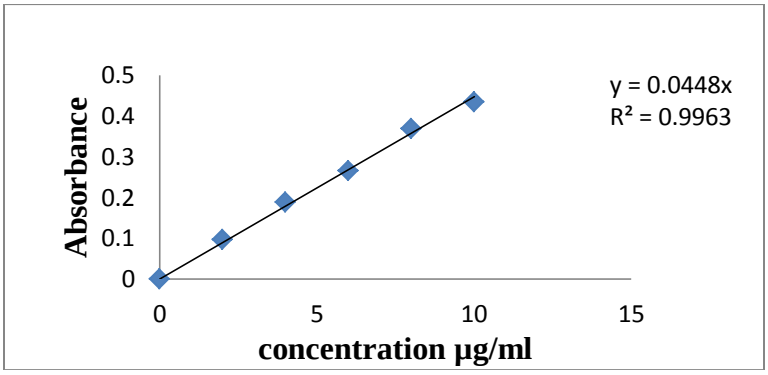

Figure 1:- Standard Graph of Nifedipine at pH 1.2

Preparation of Standard curve of Nifedipine pH 6.8:-

10 mg of Nifedipine was transferred to 100 ml of volumetric flask and dissolved with little quantity of ethanol and then the volume was made up by adding the phosphate buffer pH 6.8 in 100 ml volumetric flasks. Then 10 ml from above solution was taken into another 100ml volumetrick flask and volume was made up with stock solution. Volumes of 2ml, 4ml, 6ml, 8ml & 10 ml were taken in 10 ml volumetric flask from the prepared solution and diluted upto the mark with pH 6.8 phosphate buffers. The absorbance of above solution were scanned in UV region and found that nifedipine showed absorbance at 235nm. Calibration curve was prepared by plotting concentration versus absorbance as shown in figure 2.

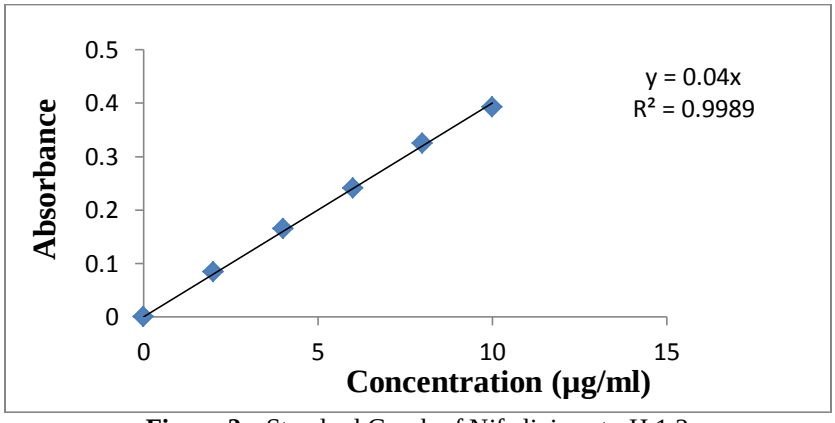

Figure 2:- Standard Graph of Nifedipine at pH 1.2

Drug-Excipients Compatibility Study:-

Differential scanning calorimetry (DSC):-

The thermograms (DSC) of drug and drug-polymer were presented in figure 3 and figure 4 respectively. The DSC curve of pure nifedipine showed a melting endothermic peak at 174.99^{0}c, while the physical mixture of drug and polymer exhibited an endothermic peak at 145.23^{0}c. Thus, by comparing the thermograms of drug and drug-polymer it was found that it has a suitable compatibility for further formulation.

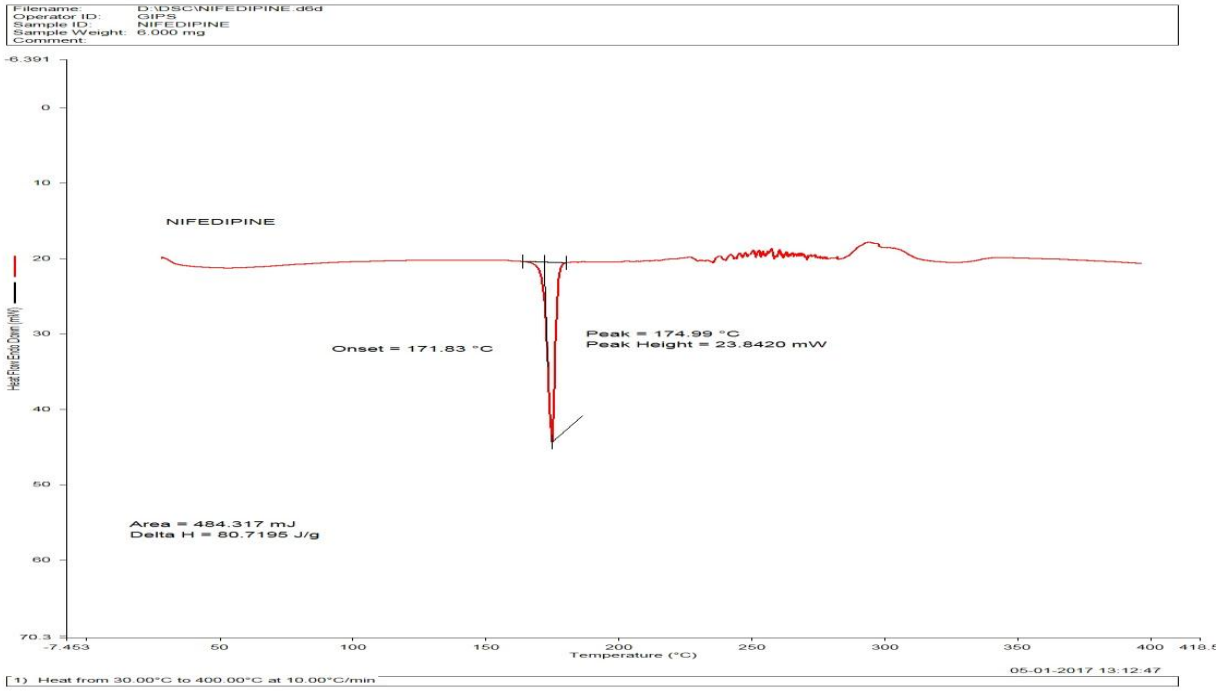

Figure 3:- DSC of nifedipine

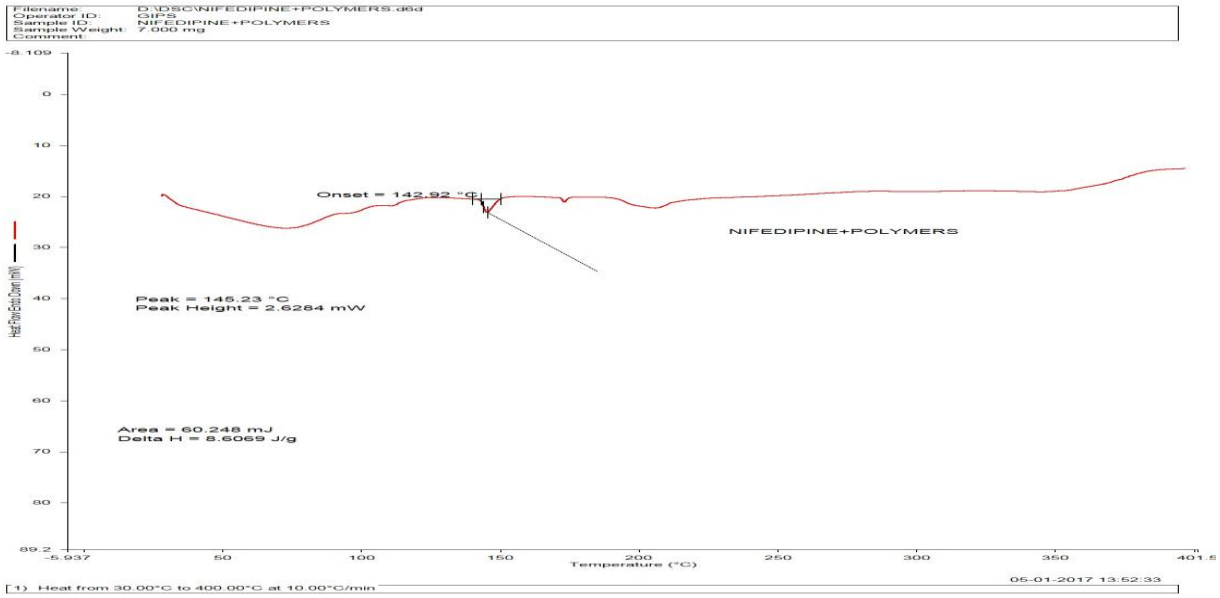

Figure 4:- DSC of drug-polymer

Fourier transforms Infrared spectroscopy (FTIR):-

FTIR spectroscopy was performed to identify the supplied pure drug. The FTIR study is carried out to find out the possible interaction between drug and the polymer. FTIR study of Nifedipine showed the peak at 3250.26, 1677.21, 1224.14, 1119.06, 1018.86 and 711.14 cm^{-1} due to the functional group like C-H, C=C, O-H, C-C, C-O and N-H respectively. The physical mixture of drug and polymer also retaining the same peak, which reveals that, there is no interaction between the selected drug and the polymers. The FTIR spectra of nifedipine and polymer mixture are shown in figure 5 and figure 6.

FTIR interpretation of nifedipine and Drug polymer Mixtures.

SL.NO	Functional group	IR absorption bands (cm-1)	
		Nifedipine	Drug polymer mixture
1	C-H	3250.26	3331.09
2	C=C	1677.21	1644.58
3	O-H	1224.14	1228.04
4	C-C	1119.06	1097.22
5	C-O	1018.86	1030.14
6	N-H	711.14	714.43

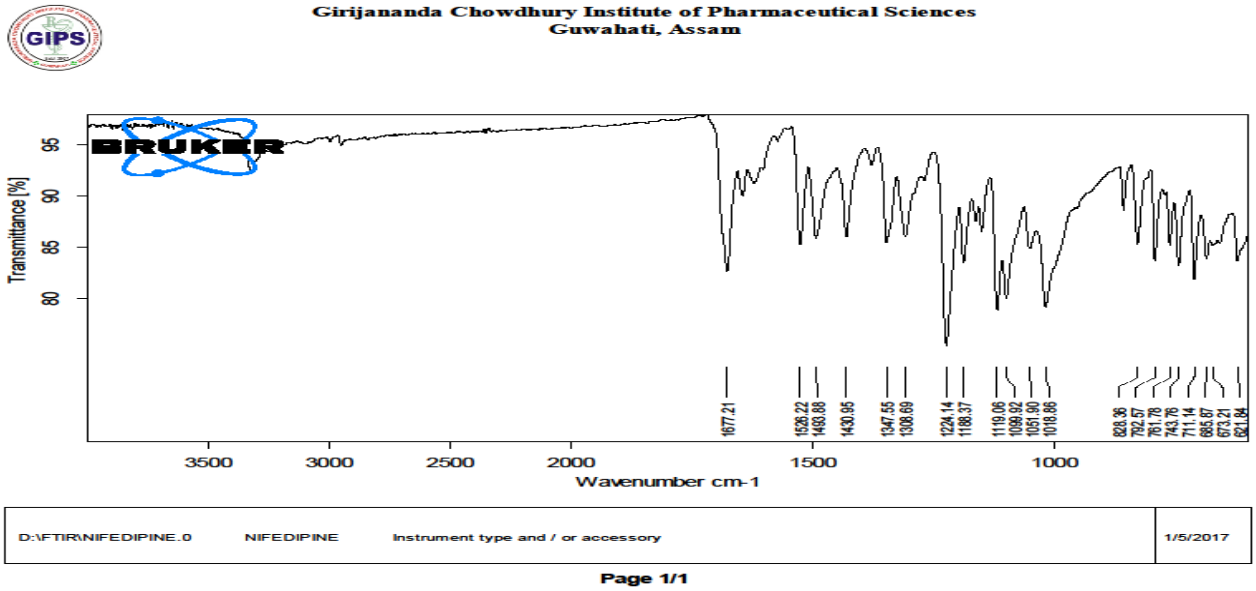

Figure 5:- FTIR of nifedipine.

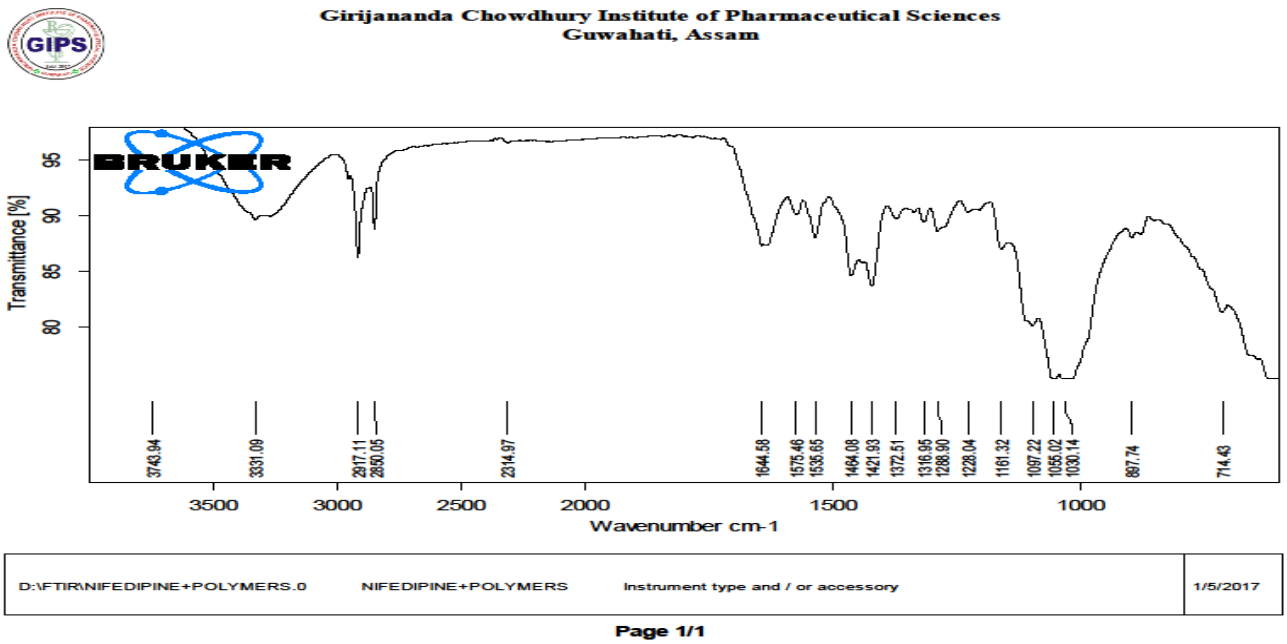

Figure 6:- FTIR of drug- polymer

Evaluation of nifedipine granules:-

The prepared granules of formulation of nifedipine were evaluated for the flow properties are shown in Table 2. Results of characterization of prepared granules showed Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. These values indicate that the prepared granules exhibited good flow properties and it was found that all the parameters measured are within limits.

Table 2:- Evaluation of granules of nifedipine formulations.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	22.2±0.1	0.554±0.1	0.621±0.3	13.62	1.09
F2	23.4±0.2	0.432±0.2	0.523±0.2	12.50	1.12
F3	26.5±0.5	0.620±0.1	0.718±0.1	14.53	1.24
F4	28.1±0.6	0.589±0.3	0.498±0.3	13.64	1.05
F5	24.2±0.3	0.525±0.4	0.836±0.1	15.21	1.08

Evaluation studies of nifedipine tablets:-

All the formulations were prepared according to the formula given in Table 1. All the batches were produced under similar conditions to avoid processing variables. The prepared matrix tablets were evaluated for various physical properties and evaluation tests such as thickness, uniformity of weight, drug content, hardness, friability and *in vitro* dissolution. And the results are given in Table 3 which shows that prepared formulation fall within the limits.

Table 3:- Evaluation of tablets

Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Deviation in Weight variation (mg)	Drug Content (%)
F1	5.6±0.4	3.1±0.02	0.29±0.02	203.8±1.12	93.4±0.07
F2	4.3±0.1	3.4±0.04	0.23±0.05	201.8±1.02	91.4±0.02
F3	5.1±0.3	3.3±0.07	0.35±0.01	199.1±1.21	94.1±0.05
F4	4.8±0.2	3.2±0.05	0.22±0.03	200.4±1.18	97.86±0.03
F5	4.9±0.3	3.3±0,02	0.24±0.07	202.4±1.13	98.44±0.04

Drug release profile:-
Among the developed formulations of nifedipine, F5 showed good dissolution profile and drug release over a period of 14 hours.

Table 4:- In-vitro release of nifedipine from different formulations

TIME	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	13.8825	15.49	10.9425	13.0875	10.4875
1	19.9675	18.4675	13.015	15.9875	18.46
2	23.57	21.02	18.7675	27.075	24.6925
4	30. 965	26.7825	30.9725	37.895	42.7225
6	41.1325	35.84	45.2925	44.62	50.0375
8	48.835	41.175	55.53	56.0275	58.5425
10	56.075	48.45	60.93	65.6325	71.225
12	64.5325	58.6025	71.535	75.1825	80.5872
14	74.5625	67.83	84.195	87.15	92.5325

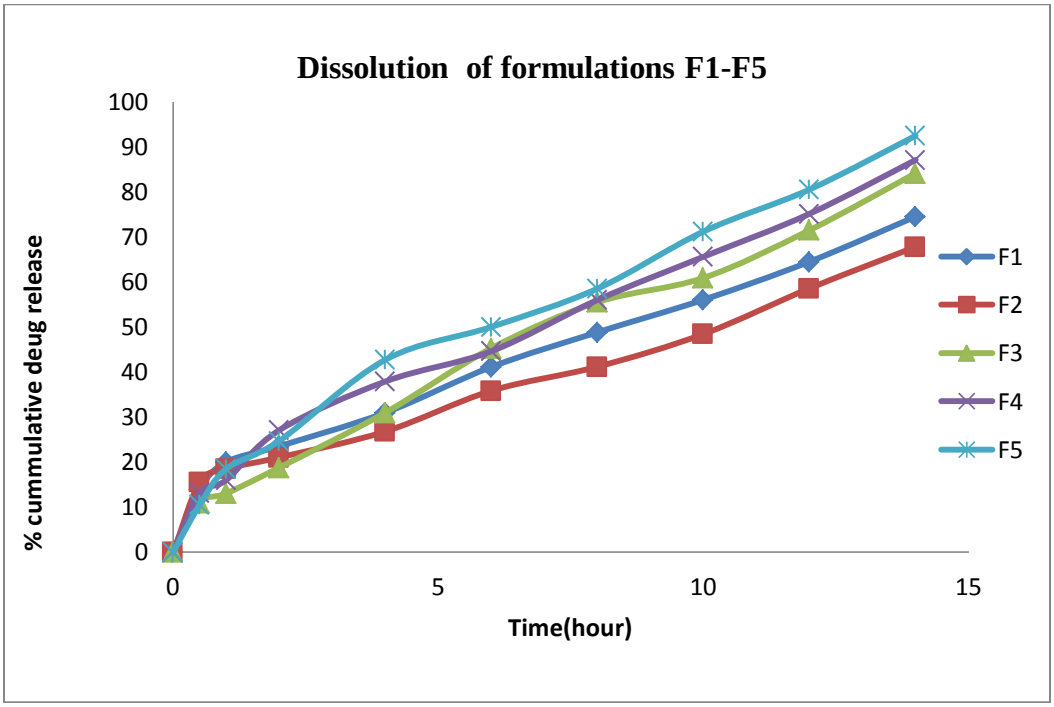

Fig.7:- Dissolution of formulations F1-F9

Swelling index (SI) studies:-
Swelling index for all the formulations were satisfactory and found to be within the limits as shown in Table 5.

Table 5:- Data for Swelling

Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	60	56	69	71	74
2	137	128	140	145	147
4	187	174	195	200	205
6	172	165	185	189	192
8	162	159	169	174	185

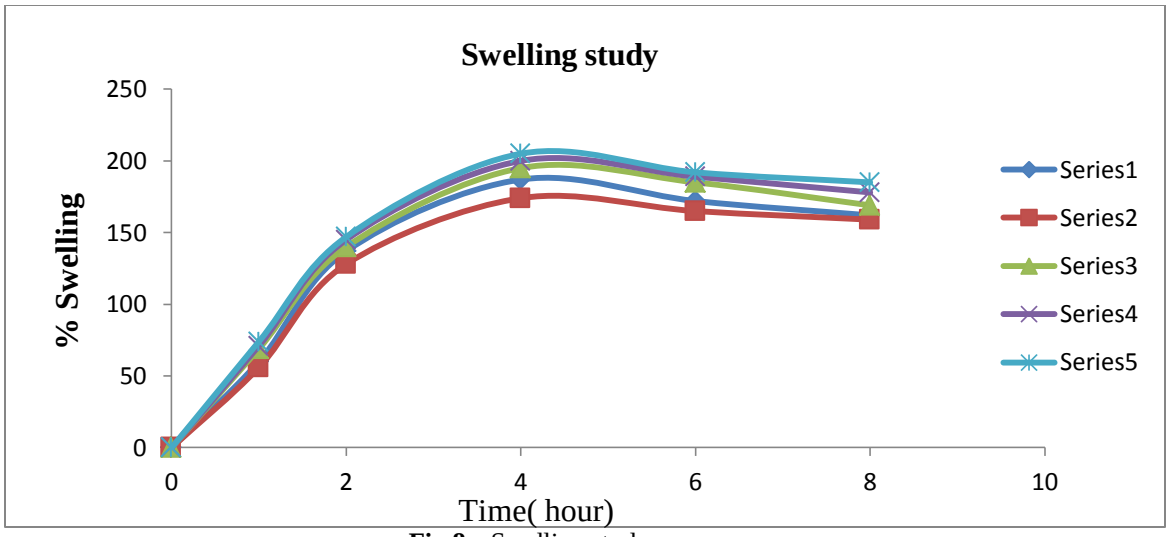

Fig 8:- Swelling study

Drug release kinetic study:-

The drug release mechanism and kinetics of the formulation is determined by the application of kinetics models such as zero order, First order, Higuchi's model, Korsmeyer - peppas model, and Hixon - Crowel kinetics as shown in Table 5. From the kinetic models of dissolution study, all the formulation batches (F1- F5) follows the korsmeyer - peppas model as their r^2 values in the range between 0.9606 –0.9947 and which n value not less than 0.5 and not more than 1 ($0.5 < n < 1.0$). The n values are between in 0.572 to 0.725. This confirmed that drug release kinetics follows the Korsemayer-peppas and drug transport mechanism follow anomalous transport and non- fickian diffusion mechanism release.

Table 6:- kinetics of drug release from nifedipine matrix tablets.

Formulation code	Zero order (R2)	First order (R2)	Higuchi (R2)	Hixon crowell (R2)	Korsmeyer peppas	
					R2	N
F1	0.8745	0.9419	0.9797	0.9291	0.9836	0.572
F2	0.8596	0.9094	0,9601	0.8990	0.9606	0.568
F3	0.9597	0.9828	0.9539	0.9856	0.9939	0.725
F4	0.9208	0.9692	0.9745	0.9657	0.9913	0.636
F5	0.9293	0.9772	0.9739	0.9767	0.9947	0.649

Conclusion:-

The result of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of nifedipine.

Nifedipine matrix tablet were prepared by wet granulation method were found to be good and free from shipping and capping. Total Five formulation of matrix tablet of Nifedipine were prepared. All the formulated tablets were evaluated for various physical parameters such as hardness, thickness, friability weight variation and drug content was found to be within the limit. And flow properties of granules it was found that all the parameters measured are within limits. The dissolution was carried out in two different media to mimic the conditions of gastro intestinal tract first 2 hours in 1.2 pH buffer and the rest 12 hours in pH 6.8 phosphate buffer. From among all the developed formulations (F1-F5) respectively, F5 formulation was shown drug release upto 92.53% was selected as the best formulation.

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