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Research Article

FORMULATION AND EVALUATION OF MATRIX TYPE SUSTAINED RELEASE NIFEDIPINE TABLETS

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ABSTRACT

In the present study, Nifedipine was chosen as a model drug which is a Anti- Hypertensive. Because of its short life (2hr) and its high water solubility it was chosen as a suitable candidate for sustain release matrix tablet formulation. It was formulated in to matrix tablet using hydrophilic polymer such as HPMC, HEC Eudragit RS100, and Ethyl cellulose as releases retardants. All the precompressional parameters (angle of repose, Hausner's ratio and Carr's index) were found to be within the standard limits. Tablets were evaluated for hardness, friability, thickness, drug content, *in-vitro* release, swelling and stability studies. The effect of polymer concentration binary polymer mixture and wet granulation method on drug release profile was studied. It was observed that the type of polymer and its concentration has influence the drug release from matrix tablet. Matrix tablet content a blend of HPMC and ethyl cellulose successfully sustained the release of Nifedipine for a period of 17hr. Precompressional parameter indicated that granules used for preparing tablets with free flowing. Post-copmressional parameters (hardness, friability, thickness and drug content) were within the acceptable limit. The concentration of Nifedipine was kept constant, lactose used as filler. Formulation containing only a single polymer could not control the control the release of Nifedipine as desire. The sustained release from ethyl cellulose and HPMC was due to interaction between ethylcellulose chain ionic polymer and HPMC chain, non-ionic polymer, which resulted in favorable increase in the water uptake capacity and gel viscosity, leading to better control over the release of Nifedipine F4 and G4 showed the sustained release of Nifedipine as desired.The study revealed that the ethyl cellulose and HPMC F4 and G4 can be used for the formulation of sustained release matrix tablet of Nifedipine.

Keywords: Nifedipine, Matrix tablet, HPMC, HEC Ethyl cellulose, Eudragit RS100, Wet granulation.

INTRODUCTION

Sustained- release dosage forms: It is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug".

MATERIALS AND METHOD

Chemicals and Reagents

Nifedipine Hydrochloride was supplied by cipla Ltd, Hydroxypropylmethylcellulose K100M, Hydroxyethylcellulose, HHX Ethylcellulose 10cps, Eudrajit RS100 was supplied by Signet Chemicals. Dicalcium phosphate (Ditab) was supplied by Emcure Pharmaceuticals Ltd. Magnesium Stearate, Aerosil, was supplied by S.D Fine Chemicals

Preparation of tablets

The granules prepared by wet granulation of drug, filler and hydrophilic polymers were compressed into flat faced tablets using by using KBr press. The diameter of the die was 12mm and the batch size prepared for each formulation was of 20 tablets.

Formulation design of Nifedipine hydrochloride tablets by wet granulation method using HPMC

Ingredients(per tablet)	L1	L2
Nifedipine HCl	84.87	84.87
HydroxypropylmethylcelluloseK100M	84.87	169.74
Ethanol (95%)	qs	qs
Lactose	222.6	137.39
Magnesium stearate(%w/w)	4	4
Talc (%w/w)	4	4

Formulation design of Nifedipine hydrochloride tablets by wet granulation method using HPMC

Ingredients(per tablet)	F1	F2	F3	F4	F5	F6
Nifedipine HCl	84.87	84.87	84.87	84.87	84.87	84.87
Hydroxypropylmethyl cellulose100M	84.87	169.74	169.74	169.74	169.74	169.74
Ethylcellulose(2%w/w)	-	-	8	-	-	-
Ethylcellulose(4%w/w)	-	-	-	16		-
EudrajitRS100(4%w/w)	-	-	-	-	16	-
EudrajitRS100(8%w/w)	-	-	-	-	-	32`
Ethanol (95%)	qs	qs	qs	qs	qs	qs
Dicalcium phosphate	222.6	137.39	129.39	121.39	121.39	105.39
Magnesium stearate(%w/w)	4	4	4	4	4	4
Talc (%w/w)	4	4	4	4	4	4

Formulation design of Nifedipine hydrochloride tablets by wet granulation method using HEC

Ingredients(per tablet)	G1	G2	G3	G4	G5	G6
Nifedipine HCl	84.87	84.87	84.87	84.87	84.87	84.87
Hydroxyethyl cellulose HHX	84.87	169.74	169.74	169.74	169.74	169.74
Ethylcellulose(2%w/w)	-	-	8		-	-
Ethylcellulose (4%w/w)	-	-	-	16	-	-
EudrajitRS100(4%w/w)	-	-	-	-	16	-
Eudrajit RS100(8%w/w)	-	-	-	-	-	32
Ethanol	qs	qs	qs	qs	qs	qs
Dicalcium phosphate	222.6	137.39	129.39	121.39	121.39	105.39
Magnesium stearate(%w/w)	4	4	4	4	4	4
Talc(%w/w)	4	4	4	4	4	4

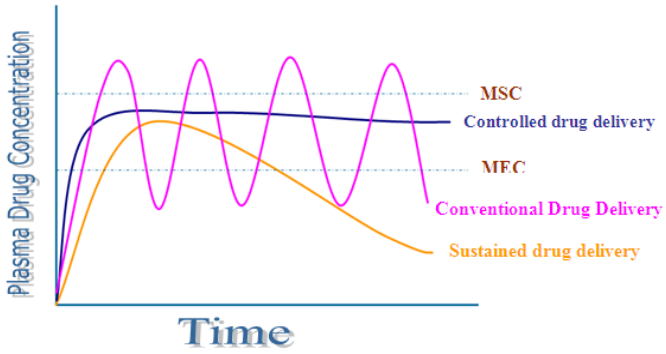


Fig 1: A hypothetical plasma concentration – time profile from conventional multiple and single doses of sustained and controlled delivery formulations[6]

Evaluation of Tablets

1. Thickness and Diameter

Thickness and diameter of tablets was determined using Vernier caliper. Five tablets from each batch were used, and average values were calculated.

2. Weight variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method.

3. Drug content

Five tablets were weighed individually and triturated. Powder equivalent to the average weight of the tablet was weighed and drug was extracted in water for 6 hours. The solution was filtered through 0.45µ membrane. The absorbance was measured at 226.5 nm after suitable dilution.

4. Hardness

For each formulation, the hardness of 6 tablets were determined using the Monsanto hardness tester (Cadmach). The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2. Generally, a minimum of 4 kg/cm^2 hardness is considered acceptable for uncoated tablets.

5. Friability

For each formulation, the friability of 6 tablets were determined using the Roche friabilator (Lab Hosp.). This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed 6 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable[49]. Percent friability (% F) was calculated as follows,

$$\%F = \frac{\text{initial weight} - \text{final weight}}{\text{final weight}} \times 100$$

6. In Vitro Release Studies

In vitro drug release study for the prepared matrix tablets were conducted for period of 8 hours using a six station USP XXVI type II (paddle) apparatus at 37°C ± 0.5°C and 50 rpm speed. The dissolution studies were carried out in triplicate for 8 hours in phosphate buffer of pH 6.8 under sink condition. At first half an hour and then every 1- hour interval samples of 5 ml were withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 226.5 nm for Nifedipine HCl by a UV- spectrophotometer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard.

7. Polymer swelling or water uptake studies

The rate of test medium uptake by the polymer was determined by equilibrium weight gain method. The study was carried out in the USP/NF dissolution apparatus I. The polymer matrices were accurately weighed, placed in dissolution baskets, immersed in 0.05M phosphate buffer (pH 6.8) and maintained at 37±0.5°C in the dissolution vessels. At regular intervals, the pre weighed basket-matrix system was withdrawn from the dissolution vessel, lightly blotted with a tissue paper to remove excess test liquid and re-weighed. The percent water uptake, i.e degree of swelling due to absorbed test liquid, was estimated at each time point using the following equation:

$$\text{\% water uptake or polymer swelling} = \frac{(W_S - W_i) \times 100}{W}$$

Where W_S is the weight of the swollen matrix at time t, W_i the initial weight of the matrix, and W_p is the weight of the polymer in the matrix.

8. Matrix erosion studies

The standard USP/NF dissolution apparatus I was used for this purpose.

The dry matrices were weighed, placed in dissolution baskets, and subjected to dissolution in 500ml of 0.05M phosphate buffer (pH 6.8) maintained at 37±0.5°C with the baskets rotating at 100 rpm. At regular intervals, basket-matrix assemblies were removed from the dissolution vessels and dried to a constant weight in a hot air oven at 50°C. The percentage matrix erosion at time t, was estimated from the following equation:

$$\text{Matrix erosion (\%)} = \frac{(W_i - W_t) \times 100}{W_i}$$

Where W_i is the initial weight of the matrix, W_t is the weight of the matrix subjected to erosion for time t.

RESULTS AND DISCUSSION

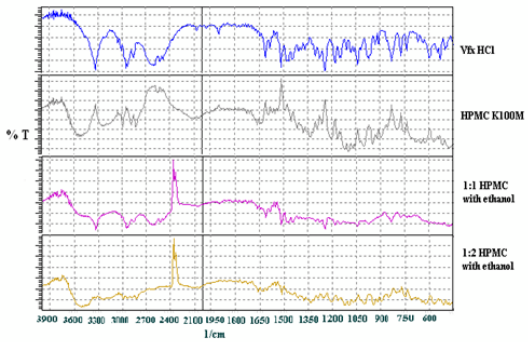
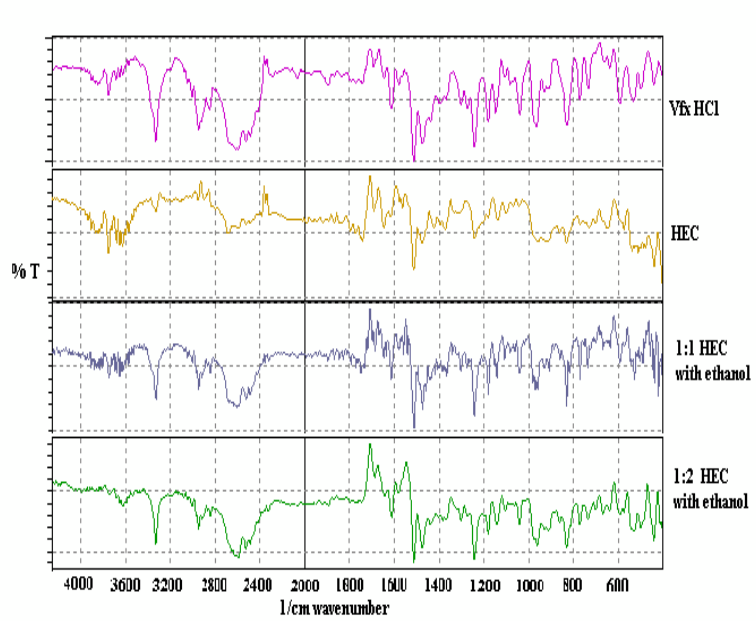


Fig 5 IR spectrum of Nifedipine, HPMC K100M, and granules containing ethanol alone as a granulating agent.

IR interpretation of Nifedipine, HPMC K100M, and granules containing ethanol alone as a granulating agent

Peaks cm^{-1}	Groups	Stretching/Deformation
3320	O-H	Stretching
2980	Aliphatic C-H	Stretching
3151	O-H	Stretching
1630	C=C	Stretching



IR spectrum of Nifedipine, HEC, and granules containing ethanol alone as a granulating agent

IR interpretation of Nifedipine, HEC, and granules containing ethanol alone as a granulating agent

Peaks cm^{-1}	Groups	Stretching/Deformation
3320	O-H	Stretching
3051	Aromatic C-H	Stretching
2821	Aliphatic C-H	Stretching

Specifications for tablets as per Pharmacopoeia of India

Average weight of Tablet	% Deviation
80 mg or less	10
More than 80mg but less than 250 mg	7.5
250 mg or more	5

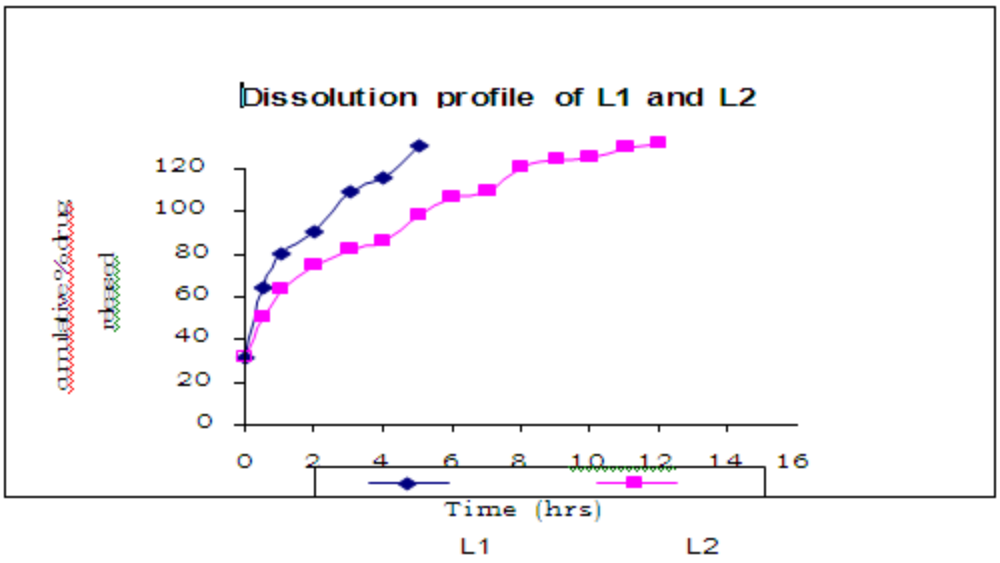
Evaluation of tablets

Formulation code	Hardness	Thickness	% Friability	Deviation in weight variation test (%)	Drug content(%)
F1	4.6±0.24	2.24±015	0.72±0.05	3.895±0.08	95.99±0.09
F2	4.5±0.22	2.26±0.16	0.75±0.02	3.584±0.09	98.56±0.02
F3	4.8±0.16	2.35±0.09	0.68±0.09	2.384±0.07	99.01±0.05
F4	4.9±0.26	2.28±0.13	0.68±0.07	2.604±0.12	99.23±0.1
F5	4.6±0.35	2.32±0.21	0.73±0.12	3.125±0.04	98.9±0.15
F6	4.5±0.12	2.36±0.15	0.75±0.13	2.586±0.05	99.75±0.07
G1	4.1±0.23	2.28±0.21	0.82±0.06	2.753±0.07	97.63±0.11
G2	4.3±0.15	2.27±008	0.81±0.07	3.223±0.05	99.94±0.08
G3	4.5±0.12	2.33±0.25	0.71±0.03	2.943±0.04	98.96±0.05
G4	4.6±0.29	2.37±0.21	0.71±0.14	3.712±0.07	98.83±0.07
G5	4.2±0.22	2.31±0.18	0.81±0.19	2.989±0.06	99.45±0.14
G6	4.1±0.18	2.29±0.11	0.83±0.12	3.604±0.07	99.12±0.11

All the formulations showed uniform thickness. In a weight variation test, the pharmacopoeial limit for percentage deviation for the tablets of more than 250mg is ±5%.The average percentage deviation of all the tablet formulations was found to be within the above limit, and hence all the formulations passed the test for uniformity of weight as per the official requirements. Good uniformity in drug content was found among different batches of tablets, and percentage of drug content was more than 95%. The formulation F4 showed a comparatively high hardness value of 4.9±0.26 kg/cm^2. This could be due to the presence of more ethylcellulose which is generally responsible for more hardness of the tablet. In the present study the percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability. HPC formulations were found to be harder as compared to HEC formulations and corresponding values for friability for HPC formulations were low as compared to HEC formulations. The friability values ranged from 0.54%±0.08 to 0.83%±0.09.

In vitro dissolution studies for sustained release Nifedipine HCl tablets

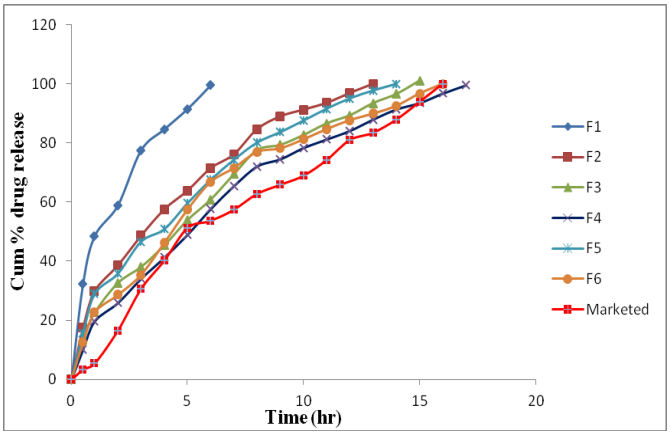
Time(hrs)	L1	L2
0.5	32.45±0.99	19.21±085
1	48.58±1.02	31.66±1.74
2	58.9±1.85	42.99±1.36
3	77.58±2.05	50.552.78
4	84.67±1.56	54.56±0.85
5	99.56±1.77	66.5±0.67
6		75.1±2.05
7		77.36±1.78
8		89.4±1.15
9		92.66±1.53
10		93.45±0.83
11		98.23±1.28
12		99.98±1.88



Dissolution profile of formulation containing HPMC K100M and lactose as a diluent and ethanol alone as a granulating agent

Dissolution data of formulation containing HPMC K100M

Time (hr)	F1	F2	F3	F4	F5	F6	Marketed
0.5	32.45	17.54	13.50	10.11	15.66	12.57	3.42
1	48.58	29.95	22.62	19.71	28.99	22.79	5.51
2	58.95	38.61	32.66	25.91	35.84	28.64	16.54
3	77.58	48.63	38.11	34.11	46.64	35.44	30.66
4	84.67	57.56	45.36	41.23	50.85	46.23	40.22
5	91.55	63.87	53.94	48.99	59.64	57.46	51.24
6	99.56	71.45	60.86	57.70	67.55	66.81	53.67
7		76.15	69.41	65.47	74.31	71.52	57.45
8		84.63	77.54	72.11	80.11	76.98	62.79
9		88.96	79.31	74.53	83.63	78.17	65.86
10		91.26	82.64	78.36	87.54	81.22	68.91
11		93.54	86.59	81.25	91.55	84.68	74.23
12		96.87	89.31	84.15	95.04	87.71	80.99
13		99.97	93.44	87.99	97.67	89.91	83.44
14			96.51	91.41	99.91	92.54	87.88
15			101.01	93.54		96.70	93.85
16				96.77		99.99	100.01
17				99.55			

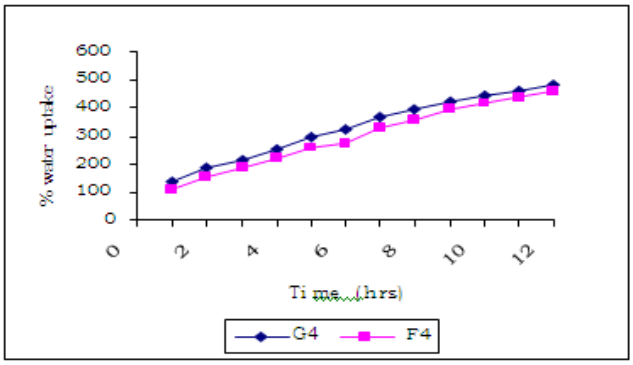


Dissolution profile of formulation containing HPMC K100M

Release kinetics

Formulations	Zero order	First order	Higuchi	Korsemeyer- peppas	Hixon-crowell
F1	0.8036	0.9219	0.9890	0.9898 n=0.3948	0.9716
F2	0.8350	0.9662	0.9943	0.9928 n=0.5222	0.9922
F3	0.9109	0.9313	0.9942	0.9946 n=0.5762	0.9908
F4	0.9212	0.9011	0.9915	0.9955 n=0.6011	0.9321
F5	0.8874	0.9297	0.9969	0.9942 n=0.5488	0.9919
F6	0.889	-	0.9918	0.9921 n=0.5653	0.9453
G1	0.8142	0.9781	0.9936	0.9995 n=0.4142	0.9827
G2	0.8242	0.9904	0.9921	0.9906 n=5247	0.9906
G3	0.9248	0.9458	0.9946	0.9975 n=0.5478	0.9912
G4	0.9183	0.8945	0.9936	0.9983 n=0.6989	0.9349
G5	0.9913	0.8914	0.9951	0.9951 n=0.5104	0.9798
G6	0.9175	0.9222	0.9966	0.9984 n=0.5994	0.9885

Swelling Study



Plot of percent swelling or water uptake by HPMC and HEC matrices as a function of time

Plot of log percent swelling or water uptake by HPMC and HEC matrices as a function of log time according to Vergnaud model

Formulation	Kinetic constant (k)	Swelling exponent (n)	Correlation Coefficient(r^2)
G4	14.47	0.5323	0.9921
F4	8.93	0.5959	0.989

DISCUSSION

The current investigation deals with the optimization of Sustained release matrix tablets of Nifedipine Hcl using hydrophilic Polymers. Polymers used were HPMC K100M, HEC, Ethyl cellulose and Eudragit RS100. The hydrophilic matrices for Nifedipine Hcl (water soluble drug) containing a blend of one or more gel forming polymers. The melting point was found to be in the range of 215°C – 217°C which was in good agreement with the reported values. The formulation F1 with HPMC 2 %, releases drug 99.56 % in 6hrs and the formulation F2 with HPMC 4 %, releases drug 99.97 % in 13 hrs. The formulation F3 with HPMC /EC 2 %, releases drug in 15 hrs &the formulation F4 with HPMC /EC 4 %, releases drug in 17 hrs. The quick release from EC containing system is due to high solubility of EC at pH 6.8.The Formulation F5 with 4%,release drug 99.91% in 14 hrs & the formulation F6 with 8% in 99.99% in 16 hrs. This polymer characteristic gives to the matrix a quick gel erosion rate and a high erosion degree of the overall system. Means matrices with only EC as release rate retardant were not able to control the release rate for very soluble drug Nifedipine Hcl for 17 hrs.

CONCLUSION

The ultimate aim of the present study was to prepare sustained release matrix tablet of Nifedipine HCL using hydrophilic polymers like HEC, EC and Eudragit by wet granulation technique. The hydrophilic matrix tablet prepared were containing a blend of one more gel forming polymer. The conc. of Nifedipine HCL was kept constant. Lactose was used as filler. Following conclusions were made.

a) The FT-IR study indicates that there is no interaction of the drug with polymer used for the study.
b) Precompression parameter indicated that granules prepared with dry binders were free flowing.
c) Postcompression parameter (hardness, friability, thickness and drug content) was within the

acceptable limit.

d) Formulation containing only a single polymer could not control the release of Nifedipine HCL as desired.
e) Matrix tablet of Nifedipine HCL that contained a blend of HPMC& Ethylcellulose successfully sustained the release of Nifedipine HCL for a period of 17 hrs.
f) The swelling behavior of F4 and G4 showed that matrices containing a HPMC achieve higher swelling index, HPMC&EC combination of ionic and non-ionic polymer, swelling was higher and more control over the release of Nifedipine HCL was observed.
g) The control release from HPMC and EC combination was due to interaction between EC chain, ionic polymer and HPMC chain, non-ionic polymer, which resulted in favourable increase in the water uptake capacity and gel.
h) The drug release mechanisms for formulations were best described by Higuchi's equation. The formulations followed anomalous behavior.

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