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FORMULATION AND *IN- VITRO* EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF ISRADIPINE

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ABSTRACT

Piper betel Linn. Is one of the important plants in the different region belonging to the family piperaceae? The betel plant is an evergreen and perennial creeper with glossy heart shape leaves and white catkin. Piper betel leave extract contains large number of bioactive molecule like polyphenol, alkaloids, steroids, saponin and tannin. Piper betel has light yellow aromatic essential oil with sharp burning taste. The main constituents are Hydroxychavicol (HC)/Hydroxychavicol acetate (HCA), Allylpyrocatechol (APC), Chavibetol (CHV), Piperbetol etc. Other constituents are arecoline, carvacrol, caryophyllene, piperitol, piperbetol, eugenol, isoeugenol, allylpyrocatechol, chavicol, safrole, anethole, chavibetol, cadinene hydroxychavicol, β-sitosterol, β-sitosteryl palmitate, dotriacontanoic acid, tritriacontane, stearic acid, cepharadione, piperine, piperlonguminine, chavibetol acetate, allylpyrocatechol monoacetate , allyldiacetoxy benzene, estragole, methyl eugenol and hydroxycatechol , methylpiperbetol, piperol A and piperol B. cavacrol, eugenol acetate, and allyl pyrocatechol diacetate etc Leaf posses pharmacological activity like antibiotic, antiulcer, and platelets aggregation, anti- fertility, cardio-tonic, antitumor, anti-mutagenic, respiratory depressant and antihelminthetics. Piper betel is subjected to in vitro tests using plate and broth MIC assays bio-film assay, saliva

Key words**:** *Piper betel, C.N.S activity, Carcinogenic, Diuretic activity, Polyphenol, Alkaloids, Steroids, Saponin etc.*

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INTRODUCTION

The oral route of drug administration is the most important method of drugs for systematic affects. It can be said that at least 90% of all drugs used to produce systemic effect by oral route of drugs that are administered orally, solid oral dosage forms represents the preferred loss of product because in this form one usual dose of the drug has been accurately placed.[1]

To achieve and maintain the drug concentration in the body with in the therapeutic range required for a medication, it is often necessary to take controlled drug-delivery system several times a day which results in a see saw pattern drug level.[2] To overcome this a number of technical advancements have been recently made in developing new technologies for the rate of drug ,delivery sustaining the duration of the therapeutic action and /or targeting the delivery of drug to a tissue. These advancements have already led to the development of several novel drug drug delivery systems that could provide controlled administration of a therapeutic dose at a desirable delivery state. These are the simplest and least expensive system for controlled drug delivery.[3]

Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipment's. Secondly, development cost and time associated with the matrix system are viewed as variables, and no additional capital investment is required. Lastly, a matrix system is capable of accomodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.[4] The drug is currently available in market as immediate release tablet and as an extended release capsule. At present the extended release tablets available in the market uses osmotic pressure to deliver the drug at a controlled rate over approximately 24 hours. The present research endeavor was directed towards the development of matrix tablets to be taken once daily reducing the price of drug and make the drug more affordable to the patients.

MATERIALS AND METHODS

Materials

Isradipine was obtained from GlaxoSmithKline Pharmaceuticals Ltd., Nashik, HPMC E4M and HPMCE50 were obtained from Strides Acro Labs, Bangalore., Dicalcium Phosphate, Poly Ethylene Glycol, Isopropyl Alcohol, Aerosil and Magnesium Stearate were obtained from S.D. Fine Chemicals Pvt. Ltd. Mumbai,

Preformulation studies

Evaluation of Granules

Angle of Repose: - It was determined by using the following equation:

$\theta = \text{Tan}^{-1} h / r$, where h and r are the height and radius of the powder cone.

Bulk density:-Bulk density was calculated as
Bulk density = weight of sample in gram /volume occupied by the sample

Tapped density:- Tapped density was determined by using Electro lab density tester,

and calculated using following formula.

Tapped density = Weight of sample in gram / Tapped volume

Compressibility Index and Hausner ratio:- The compressibility index of the granules

was determined by Carr's compressibility index:

Carr's Index (%) = tapped-untapped×100/tapped.

Hausner's Ratio- It is the ratio of tapped density to poured density.

H.R= Tapped density/ Poured density.

Drug excipient compatibility studies

This can be confirmed by carrying out by infrared light absorption scanning spectroscopy (IR) studies. Infra red spectra of pure drug and mixture of formulations were recorded by dispersion of drug and mixture of formulations in suitable solvent (KBr) using Fourier Transform Infrared Spectrophotometer (FTIR). The data are shown in Table.3 and Figs.1 to 3.

Calibration Curve of Isradipine

10mg of Isradipine was accurately weighed and transferred into 100 ml volumetric flask, it was dissolved and diluted to volume with 0.2% Lauryl dimethyl amine oxide in water to give stock solution containing 1000µg/ml. the standard stock solution was then serially diluted with 0.2% Lauryl dimethyl amine oxide in water to get concentration up to 10µg/ml of Isradipine. The absorbance was measured at 239 nm using UV Spectrophotometer. Fig.4.

PREPARATION OF MATRIX TABLETS

300mg tablets were prepared containing 10 mg of Isradipine and different proportions of dibasic calcium phosphate (DCP) and HPMC E4M, HPMC E50. Wet granulation technique was employed, DCP was used as diluents, PEG-400 (5mg) and Isopropyl alcohol (1mg) was used as binders, Magnesium Stearate (2mg) and Aerosil of different proportions were used in different formulations. The drug was blended with the polymers and diluents the granules thereby formed were passed through 30 mesh sieves, after drying the granules were lubricated with Magnesium Stearate and Aerosil and subjected to compression. Table.1

EVALUATION OF MATRIX TABLETS

Matrix tablets were evaluated for shape, size, hardness, thickness, friability, weight variations and drug content. The shape was examined using magnifying lens, tablet dimensions were measured using calibrated dial calipers, hardness was determined by Monsanto hardness tester, thickness was measured by vernier caliper, friability was determined by Roche Friabilator ,weight variations was determined by electronic balance.

Dissolution Studies

The *in-vitro* dissolution study was carried out using type-II dissolution apparatus with 1000 ml 0.2% Lauryl Dimethylamine Oxide (LDAO) in water is used as medium, the wavelength used was 239 nm. Table.5

Kinetic Study

To analyze the mechanism of release and release rate kinetics of the dosage form, the data drug obtained were fitted into Zero order, First order, Higuchi and Koresmeyer-Peppa's model.

Higuchi equation, $Qt = KH \cdot t1/2$, where, Qt= amount of drug released in time t, KH = Higuchi dissolution constant.

Koresmeyer and Peppa's equation, $Mt / M\infty = K \cdot t^n$, Where, $Mt / M\infty$ = the absolute cumulative of drug release at time t and infinite time, K = the release constant, T = the release time, N = the diffusion coefficient for the drug release that is dependent on the shape of the matrix dosage form. Table. 6.

Stability Studies

Stability studies were carried out at 40°C/75%RH for 3 months for the optimum formulation, after specific periods samples were analyzed for its drug release.

RESULTS

Preformulation studies

Angle of repose, bulk density, tapped density, compressibility index were evaluated and the results were found within the limits as shown in Table 2.

Compatibility study

The FTIR study showed characteristic peak as shown in figure 1, 2 and 3 which proved that that the drug, polymer and the excipient used were compatible with each other.

Tablet properties

All the parameters were found within the limits as showed in the Table 4.

***In-vitro* release studies**

All the formulations were subjected to dissolution study and it was observed that F9 showed highest release of 99.08% in 24 hours. Fig no.5

Stability studies

The formulations were stored for 3 months at 40°C/75%RH in stability chamber .after storage the

formulation was subjected to physical evaluation and % drug release. The result shows no significant changes. Table 7.

DISCUSSIONS

The tablets were prepared according to the formula given in table. Physical properties of the granules showed that the granules possess good flow properties, various evaluation of the tablets were carried out and the results were found within the limits. *In-vitro* drug release proved F9 to be the optimum formulation and the drug release and results were fitted into zero order and first order Higuchi and Korsmeyer-peppas which showed non-fickian diffusion, as it occurs by the usual molecular diffusion of the drug due to potential chemical gradient .

This study showed that combination of HPMC and wet granulation could be successfully employed for the preparation of controlled release matrix tablets of Isradipine.

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Tables& Figures

Table-1. Composition of different Formulation (mg/tablet)

MATERIALS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Isradipine	10	10	10	10	10	10	10	10	10
DCP	210	210	210	210	210	200	210	200	200
HPMC E4M	50	60	70	-	-	-	60	60	60
HPMC E50	-	-	-	50	60	70	15	20	30
PEG-400	5	5	5	5	5	5	5	5	5
Isopropyl alcohol	1	1	1	1	1	1	1	1	1
Aerosil	1	1.5	1.5	1.5	1	1	1.5	1	1
Magnesium Stearate	2	2	2	2	2	2	2	2	2

Table-2. Precompression Parameters

Characteristics	Results
Angle of repose	$49^0.56'$
Bulk density	0.39 g/ml
Tapped density	0.221 g/ml
Compressibility index	41.11%
Hausner's ratio	1.698

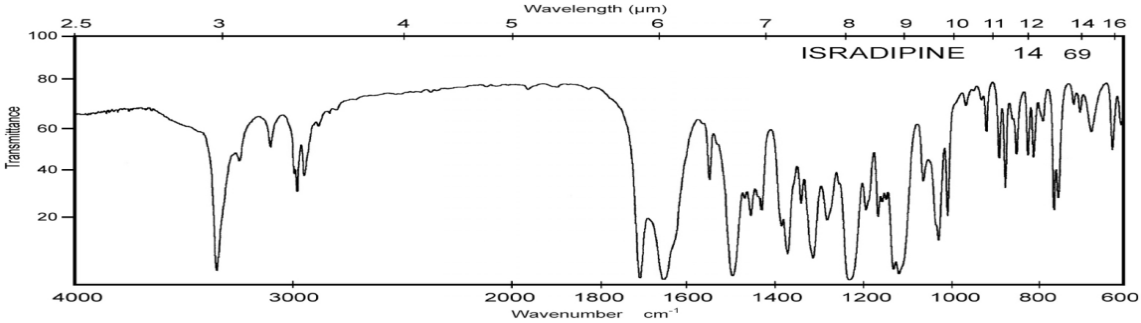

Fig.1 FTIR Spectra of Isradipine

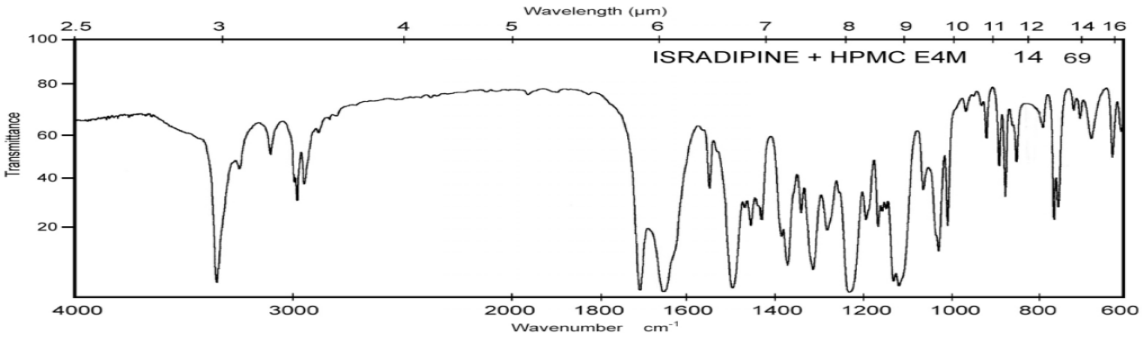

Fig.2 FTIR Spectra of Isradipine and HPMC E4M

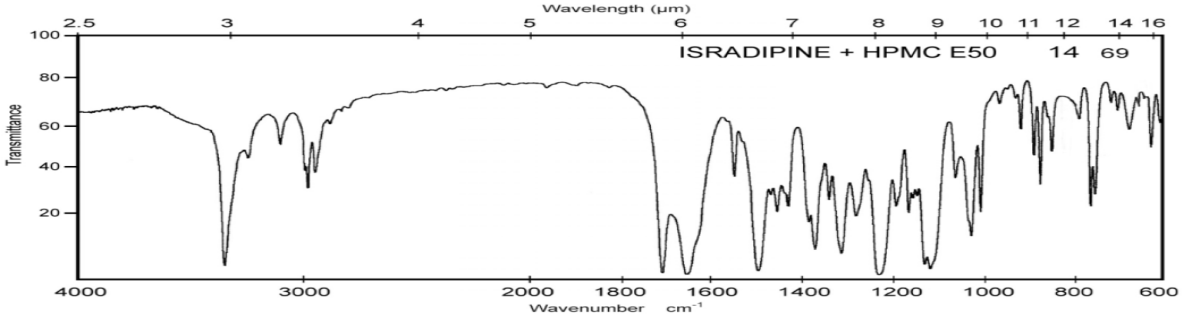

Fig.3 FTIR Spectra of Isradipine and HPMC E50

Table-3. FTIR Peak of Various Components

Wave number in cm^{-1}	Characteristic bands	Observed peak
900-670	C-H stretching	780 cm^{-1}
1720-1700	C=O	1710 cm^{-1}
1615-1510	$CH\text{-}CH_2CH_2$	1540 cm^{-1}
2850-2815	$O\text{-}CH_3$	2827 cm^{-1}
1680-1620	C=C	1670 cm^{-1}
1690-1590	C=N bending	1630 cm^{-1}

Table-4. Post compression Parameters

Batch code	Hardness (Kg/cm^2)	Thickness (mm)	Weight variation	Friability (%)
F1	6-7	3.8-4.2	1.44	0.72
F2	5-6	3.94	1.23	0.79
F3	6-.7	4.00	1.48	0.81
F4	7-8	2-2.5	1.63	0.86
F5	7-9	3.8-4.1	1.38	0.91
F6	7-9	4.8-5.0	1.24	0.75
F7	7-9	3-4	1.28	0.67
F8	7-9	3-4	1.20	0.61
F9	7-9	3.3-3.5	1.20	0.46

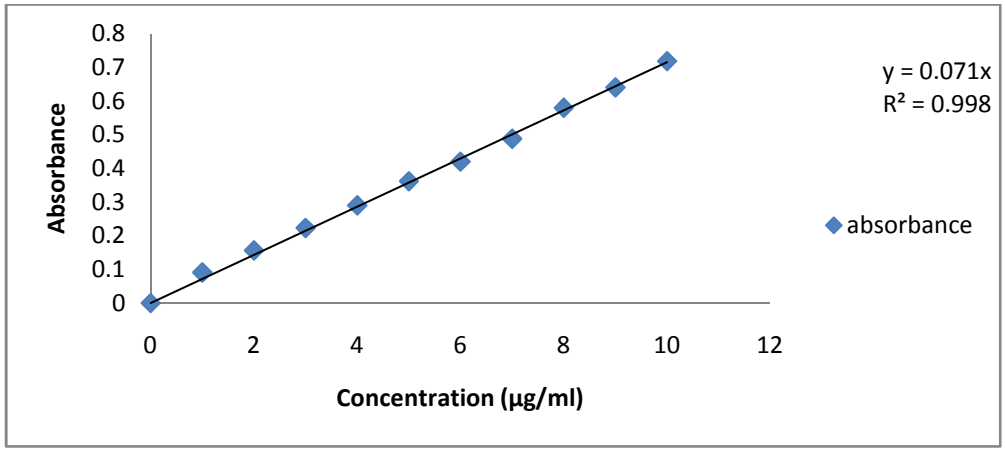

Fig.4 Standard Curve of Isradipine

Table-5. *In-vitro* release profile of different batches

Time (hours)	Cumulative percentage drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	13.0	12.16	12.0	24.29	24.7	22.17	13.01	15.01	17.00
4	24.30	22.65	20.25	37.43	36.42	33.72	23.0	25.26	30.16
6	36.42	35.14	32.61	52.13	52.0	51.14	36.30	39.84	43.80
8	52.34	49.31	45.36	65.82	64.79	61.32	55.0	57.06	60.04
10	67.71	64.45	61.72	76.55	75.41	72.63	68.40	69.29	74.39
12	77.67	75.67	71.88	88.38	82.62	84.27	82.01	84.17	89.00
16	88.62	81.65	80.36	98.68	97..0	93.05	89.08	91.10	94.11
24	92.87	91.12	90.73	_	_	_	94.15	96.30	99.08

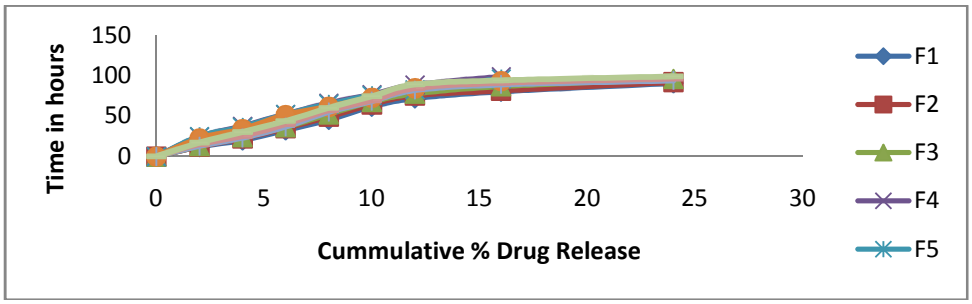

Fig.5 In-vitro release profile of Isradipine F1-F9.

Table 6.Kinetic studies of optimum formulation F9.

Formulation	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-peppas R^2	n	Mechanism of drug release
F9	0.974	0.826	0.972	0.6574	0.758	Zero order non fickian diffusion

Table 7. Stability studies of optimum formulation F9.

Time in hours	Cumulative % drug release		
	1st month	2nd month	3rd month
0	0	0	0
2	17	16.99	16.93
4	30.1	30.07	30.02
6	43.73	43.69	43.61
8	65.89	65.82	65.79
10	74.27	74.21	74.19
12	88.95	89.9	88.87
16	94.08	94.08	94
24	99.02	99.02	98.99

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