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CONSTRAINED RELEASE MATRIX TABLETS WITH FELODIPINE: DESIGN AND IN VITRO ASSESSMENT

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ABSTRACT

Felodipine is commonly used to lower high blood pressure (hypertension). Felodipine relaxes blood vessels so that blood can move through them more easily. This can help lower blood pressure and may reduce your risk for heart attack and stroke. Treatment of hypertension disease with conventional dosage forms is not effective as the drugs do not reach the site of action in appropriate concentration and it is also requiring dosing. Thus, an effective and safe therapy for hypertension disease using specific drug delivery system is a challenging task to the pharmaceutical technologists. Most used method of modulating the drug release is to include it in a matrix system, because of their flexibility, hydrophilic polymer matrix system is widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. The aim of the present study was to develop and evaluate controlled release matrix tablets of Felodipine. The tablets were prepared by direct compression method and by using different concentration of polymers. Six such formulations were made using HPMC and Carbopol as polymer. Compatibility of drug with various excipients was studied by FTIR spectroscopic studies. The preformulation studies showed good flow properties and compressibility index. The compressed tablets were evaluated for various parameters like hardness, weight variation, thickness, friability, uniformity of drug content and *invitro* drug release. *Invitro* release was carried out using USP type-2 at 50rpm in 900ml of phosphate buffer pH 6.8 for 8 hours. Drug release studies indicate that increase in concentration of polymer prolongs the release rate of drug from the results obtained, F4 was selected as best formulation based on physicochemical parameters and *invitro* drug release. The results indicated that the prepared sustain release matrix tablet of Felodipine could perform therapeutically better than conventional tablets with improved efficacy and better patient compliance.

KEYWORDS: Felodipine, Matrix tablets Hypertension and Calcium channel blocker.

INTRODUCTION

Matrix drug delivery systems

The dictionary meaning of matrix is a) Content or framework and b) The rock in which fossils or pebbles are embedded. The active pharmaceutical ingredient is embedded or entrapped in a network formed by polymers called matrix. Within the scope of this general term, there are a variety of controlled-release devices. Included among these are dissolved systems that are prepared from matrix containing a drug at or below its saturation solubility in the polymer and dispersed systems that contain the drug within a matrix at a concentration that greatly exceeds the saturation solubility of the drug in the polymer. Other controlled-release devices include reservoir dispersed matrix systems, which are analogous to the dispersed system except that barrier layer is present at the surface of such device.

Mechanism of drug release from matrix-drug delivery system.

Dissolution of the drug on the surface

Depletion of the drug closer to the surface by diffusion

Elution of the drug present in the next layer by diffusion through the matrix The release of a drug from matrix devices is governed mainly by diffusion of the solute within the matrix phase. The development of appropriate release-rate equation is generated via Fick's first law of diffusion.

Matrix tablets

The medication is uniformly distributed throughout the polymeric matrix in these systems, combined with other excipients, and crushed into tablets. To extend the drug

release, a range of polymers, such as hydrophilic, hydrophobic, waxes, gums, etc., could be added either separately or in combination.

There are three types of matrix tablets i.e.

1. Hydrophilic matrices
2. Fat-wax matrices
3. Plastic matrices

Examples of different types of matrices

Types of matrices	Examples
Hydrophobic matrices (Plastic matrices)	Polyvinylchloride, Ethyl cellulose, Methycrylatemethyl acrylatecopolymer, polyethylene
Lipid matrices	Stearyl alcohol, stearic acid, triglycerides, carnauba waxand polyethylene glycol
Hydrophilic matrices	Methylcellulose, Carboxypolymethylene, hydroxypropyl methylcellulose (HPMC).

Requirements of matrix material

The matrix materials must comply with the following conditions

- They must be non-toxic.
- They must be completely inert and non-reactive with the drug and additives in the tablet.
- They must be able to form stable and strong matrices when compressed either directly or more often granules prepared by the addition of binding agent.[1]

a) Hydrophobic matrices (Plastic matrices)

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining controlled release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Controlled release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compactable polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethylcellulose and acrylate polymers and their copolymers.

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

b) Lipid matrices

These matrices are prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulations.

c) Hydrophilic matrices

The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. In fact a matrix is defined as well mixed composite of one or more drug with gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.[2]

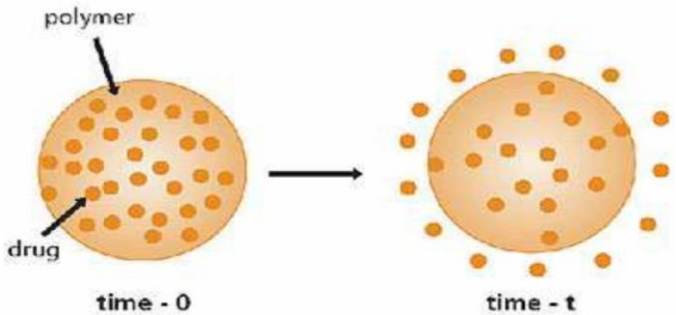

Figure 1: Schematic representation of diffusion sustained drug release matrix system.

MATERIALS AND METHOD

Felodipine was supplied as a gift sample from Astra Zeneca Pharma, HPMC and Magnesium Stearate was obtained from Yarrow chem products Mumbai, Carbopol was obtained from Balaji drugBangalore. Lactoseand Dibasic calcium phosphate anhydrate was obtained from SD Fine chemical limited, Talc was obtained from Central drug house (Pvt) Ltd.

Determination of standard calibration curve of Felodipine using phosphate buffer pH 6.8

A stock solution of 1mg/ml of Felodipine was prepared by dissolving 100mg of drug with phosphate buffer in 100ml volumetric flask. The stock solution was serially diluted to get solutions in the range of 5-25µg/ml.

The absorbance solution was measured in a UV-Visible spectrophotometer at 237.40 nm. A calibration curve was plotted by taking concentration of solution in X axis and absorbance in Y axis and correlation coefficient 'r^2' was calculated.[3]

FT-IR Spectroscopy

This study was carried out to find the compatibility in between the drug and the various excipients, which was used in the formulation of a dosage form.

Procedure

- The sample disc was prepared by triturating approximately 1 or 2 mg of the sample substance with around 10 – 20 mg of Kbr / potassium bromide and the triturate is compressed by a hydraulic press in order to form a thin disc of around 10-15mm diameter, which will be sufficient to give an IR spectrum of a suitable intensity.
- This disc was then placed in a sample holder and it is scanned in the range of 4000-400cm^{-1} in a FTIR spectrophotometer in order to get a spectrum.
- The obtained spectra of drug and the excipients were compared and it was interpreted for the functional group peaks in order to check for any major interactions.[4,5]

Formulation table of felodipine tablets

Table 1: Composition of matrix tablets of felodipine.

Sl. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Felodipine (mg)	5	5	5	5	5	5
2	HPMC K 100M (mg)	80	70	60	_	_	_
3	Carbopol-934 (mg)	_	_	_	80	70	60
4	Lactose (mg)	50	60	70	50	60	70
5	Talc (mg)	5	5	5	5	5	5
6	Magnesium sterate (mg)	5	5	5	5	5	5

Preparation of matrix tablets of felodipine

- The tablet containing 5mg of Felodipine along with various amount of the polymers such as carbopol-934, HPMC K100M, and other excipients lactose, talc and magnesium stearate were used and tablets were prepared by direct compression technique.
- Polymers were passed through mesh no.40
- In the first step, the drug and ingredients with exception of magnesium stearate was mixed for 5minutes.
- Then magnesium stearate was addedand mixture was triturated for an additional 2minutes.
- Tabletswere compressedusing 4mm round flat punches on 10-station rotary tablet compression machine. Matrix tablet with a total weight of 145 mg/tablet.
- Before compression, the surface of the die and punch were lubricated with magnesium stearate
- The compressed tablets were evaluated for various parameters viz. appearance, thickness, diameter, hardness, friability, weight variation, drug content and *in-vitro* drug release studies.

Figure 2: Formulated felodipine matrix tablets.

All the preparations were stored in airtight containers at room temperature for further studies.

Evaluation

Micrometric properties

a) Angle of repose

Theangle ofrepose ofpowderw asdeterminedb ythefixedfunn elmethod. Theaccura telyweighed powderwas takenina funnel. Thepowd erwasallo wedtoflow throughfun nelfreelyont othesurface in such a way that tip of funnel does not touch the heap of powder. Thediame terofthepo wderconew asmeasure dandangle of repose was calculated usingthe following equation.[5]

$\tan \theta = h/r$

b) Bulkdensity

Powderf romeachf ormulation, previousl ylightly shakentob reakanyag glomerat esformedw asintroduc edintoa 100ml measu ringcylinder. After the initialvol umewaso bserved, thecylind erwas allowed tofallunde ritsownwei ghtont oahardsu rfacefromth eheightof 2.5cm at 2second intervals. The tapping was continued until no furtherchangein volume wasnoted and calculated byusingformulas.

Bulkdensity = weight of powder/ bulkvolumeofpowderTappeddensity=weight of powder/tappedvolume of powder

c) Compressibilityindex and Hausner'sratio

Thecomp ressibilityin dexhasbee npropose dasanind irectmea sureofbu lkdensity, sizeandshape, surfacearea, moisture contentan dcohesiven essofmat erialsbeca useallofth esecaninfl uencethe observed ompressi bilityindex. Thecom pressibi lityindex and thehausner'sratioared etermined bymeasuri ngboth thebulk volume and the tapped volumeof apowder.[6]

CompressibilityIndex (%) = (TBD– LBD)× 100 / TBD
Hausner'sratio = TBD / LBD

Physicochemicalparameters

a) Tablethardness

There sistanc eoftable tforshipp ingorbrea kage, underc onditions ofstorage, transport ationandh andling, beforeusage, dependsonit shardness. Thehardn essoftab letofeach formulation wasmeasur edbyusing Pfizerhardness tester.[7]

b) Tablet thickness

Thickness oftablet swasim portant foruniform ityoftab letsize. Thicknes swasm easure dbyusing screwg auge on 3 random lyselected samples.

c) Friability

Friability isthemeas ureoftable tstrength. Rochef riabilato rwasusedfo rtesting thefriability. Tentablet swere weighe daccurately andplacedint heplasticch amber thatrevo lvesat 25rpm for 4mindro ppingthetabl etsthroughadi stanceofsixinc heswitheachr evolution. After 100 revolutions, thetable tswerere-weigh edandthepe rcentagelossi ntabletweight was determined.[8]

%Loss =initialwt. oftablets– finalwt. oftablets / initialwt. of tablets× 100

d) Weightvariation

Twentyta bletswere weighedin dividuallyan dtheaveragewe ightwasde termined. Thenpercen tagedeviati onfromthe averageweigh twascalculated.

e) Uniformity ofdrugcontent

Five tablets from each formulation were powdered individually and a quantity equivalent to 5mg of Felodipine was accurately weighed and extracted with a suitable volume of 6.8 pH buffer. Each extract was suitably diluted and analysed spectrophotometrically at 237.4nm.[9]

f) Drugreleasekineticfromthe sustained releasematrix tabletdosage forms

In vitro release studies were carried out using USP dissolution apparatus (Type 2). The dissolution medium consisted of 900ml phosphate buffer pH 6.8. the rotation of paddle was fixed at 50rpm and the temperature 37 ± 0.5^0C was maintained throughout the experiment. Samples of 5ml were withdrawn at predetermined time intervals and were replaced with same volume of fresh dissolution media after each with drawn. The samples were filtered through Whatman filter paper and analysed after appropriate dilution by UV –Visible spectrophotometer at 237.4nm.

Drugrel easefrom matricesu suallyim plieswater penetration ninthematrix, hydration, swelling, anddiffu sionofth edissolv eddrug. Severalki neticsmo delsrelat ingtothed rugrelea sefromm atrices, selected romthemo stimporta ntmathema ticalmod elswere used.[10]

g) Stability studies

Stability testing fdrugpro ductsbegi nsasapartofdr ugdiscovery andends with the Demise ofthecomp oundorco mmercialpro duct. Thesta bilityst udieswere carriedout ofthemosts atisfactoryfor mulation. Themost Satisfacto ryformu lationsea ledinalum inumpack agingandk eptinhumidi tychamberm aintained at 40±2°C/75±5% RHforth reemonths. Attheend ofstudies, samples wereanalyzed for various parameters.[11]

RESULTS AND DISCUSSION

Standard graph was determined in 0.1N Hcl, λmax offound to be 237.40nm with y=0.0351x+ 0.00048 and R^2 = 0.9992.

Precompression parametersfor formulation F1-F6.

Table 5: Evaluation of pre-compression parameters.

Formulation code	Angle of repose (^{0})	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index %	Hausner's ratio
F1	28.94	0.609	0.66	11.06	1.093
F2	27.61	0.57	0.64	11.41	1.131
F3	24.3	0.612	0.68	10.06	1.112
F4	29.19	0.55	0.616	10.05	1.11
F5	27.8	0.54	0.625	13.12	1.15
F6	25.86	0.58	0.655	10.6	1.118

Precompression data were in the range of angle of repose 24.3-29.19º, bulk density 0.55-0.612g/cm^3, tapped density 0.616 - 0.68g/cm^3, Carr's index10.05-13.12% and Hausner's ratio1.093- 1.131 all the parameter were in limits specified.

Post compression parametersfor formulation F1-F6

Table 6: Evaluation of post compression parameters.

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	5	5.3	0.28	145±0.23	97.9%
F2	5.2	5.1	0.28	142±0.33	99.33%
F3	5	4.6	0.26	142±0.43	83.9%
F4	5.1	5.7	0.24	143±0.45	99.3%
F5	5.1	5.4	0.30	142±0.66	94.30%
F6	5	5.1	0.27	145±0.76	95.44%

Post compression data were in the range of Thickness 5-5.2 mm, Hardness 4.6-5.7kg/cm^2, Friability 0.24-0.28%, Weight variation 145-142mg and Drug content 83.9-99.3%.

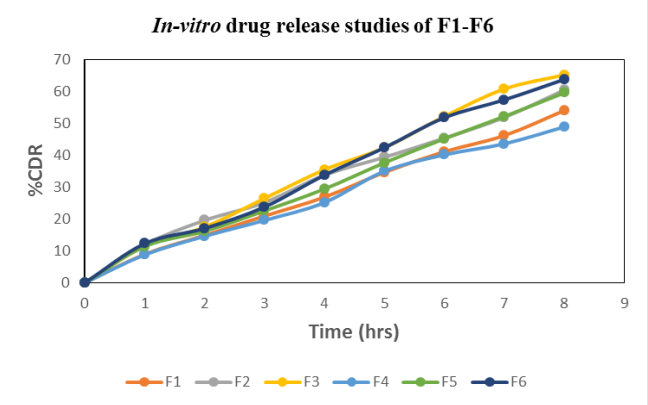

Figure 7: *Invitro* drug release studies of F1-F6.

Invitro dissolution study are carried out by using phosphate buffer pH 6.8 as dissolution medium and samples were withdrawn at every 1hr time intervals and the same was quantity of sample was replaced up to 8hrs. All the formulations released above 48% and F4 was releasing the drug in sustained manner. Hence based on all parameters obtained F4 was selected as best formulation and further kinetic models were fitted for F4 formulation.

Table 8: Kinetics modeling data.

Formulation	Zero order		First order		Higuchi model		Korsmeyer Peppas	
	R^2	Slope 'n' value	R^2	Slope 'n'value	R^2	Slope 'n' value	R^2	Slope 'n' value
F4	5.4244	5.424	0.9311	0.1025	0.9912	6.106	0.9311	0.1025

Kinetic data indicates that F4 follows first order reaction as R^2 values are greater in first order kinetics. Higuchi model indicated that the drug was diffused through the matrix. Korsmeyer Peppas mechanism of release was non Fickian transport.

Table 9: Accelerated study data for F4 formulation.

F4	Initial day	30 days
Weight variation(mg)	145	145
Hardness(kg/cm^2)	5.7	5.3
Drug content	99.3	98.6

Table 10: *Invitro* release data for F4 during Accelerated stability studies.

Time (hrs)	Initial day	30days
1	8.8	7.6
2	14.66	12.8

3	19.67	18.7
4	25.25	24.7
5	35.02	33.8
6	40.16	39.8
7	43.6	45
8	48.9	51.8

Accelerated stability studieswas carried for one month and the results indicated that the formulation was stable for 1 month of study.

CONCULSION

The basic goal of research was to design sustain release matrix delivery system using Felodipine as model drug to reduce the dosing frequency , reduce dose , so as to maintain the therapeutic blood levels uniform for extended period of time, increase effectiveness and efficacy with minimum side effects of the drug. FTIR spectrum obtained for drug with excipients showed characteristics peaks of drug at their respective wavelength with no major shifts indicating drug and excipients were compatible. The sustain release matrix tablets were prepared by direct compression method and formulated using different polymer ratio, totally 6 formulations were prepared.

Formulations were subjected for pre compression and post compression parameters. Pre compression parameters were determined to analyse the flow properties which includes angle of repose, bulk density, tapped density, Hauser'sratio and compress ability index. The result of pre compression parameters showed good flow properties and compress ability.

Post compression parameters such as physical appearance, thickness, weight variation, hardness, friability, and *invitro* drug release kinetics study, were all in limits specified. F4 sustained the drug release for a longer period. Hence F4 was considered as the best formulation.

The short term stability studies at 40 ± 2^{0}C/75±5% relative humidity for 1 month was carried on best formulation and there were no significant changes were observed. Hence the prepared sustain release tablets of Felodipine may be good choice for preventing hypertension.

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