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Formulation and in-vitro evaluation of Isradipine extended release matrix tablets using dry mixing technique

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ABSTRACT

Isradipine a potent calcium channel blockers belongs to dihydropyridine-DHP used as a most potent calcium channel blocker. Isradipine potentially form bonding with calcium channels inhibiting influx of calcium into smooth muscled of arterial and cardiac region. In the present study, Isradipine ER tablets were prepared by using excipients like HEC, HPMC, and EC (were used as matrix formers) and the formulated by wet granulation method, were subjected to physicochemical and evaluation parameters were compared with marketed product (DynaCirc CR). Formulation development of Isradipine ER Matrix tablets 10 mg by Drug in dry mix. Preparation of all the trials were prLepared by maintaining the effective processing conditions, NMT 50% RH and NMT 60^0c temperature. The release profile of formulation F-07 was showing similar to the innovator product. Analysis of samples was done by HPLC. Stability studies were performed for 1 month at 40^0c, 75% RH according to the guide lines provided by ICH and optimized formulation was developed.

Keywords: Isradipine, HEC, HPMC and ICH.

INTRODUCITON

The ancient mode of drug and dosage administration was through oral route, because of its easy to administer, patience compliance is minimal, having large area of intestinal drug absorption. There is a plethora of oral controlled release products in the market place. Over the past decades the treatment of illness has been accomplished by administering dosage forms, like tablets, capsules, pills, creams, ointments, liquid, aerosols, injectables and suppositories.[2]

These conventional drug delivery systems are still the primary pharmaceutical products commonly seen today in the prescription & OTC drug market place. To reach the minimum therapeutic effect and maintain the drug profile range in therapeutic concentration to act on the target in the body such kind of preparation under extended release drug delivery systems are necessary to formulate.[3]

Isradipine according to its mechanism action it falls under anti-hypertensive a long acting class. Primarily Isradipine exerts its action on vascular tissue, parallel effecting a negative chronotropic action.Mechanism of Isradipine is a voltage gated L-type calcium channel blocker. A gating mechanism is exhibited by the Isradipine by deforming the channel with inhibiting ion-control, parallel influx inhibition of calcium in is observed in membranes of vascular smooth muscles and myocardial muscles, which improves delivery of oxygen to the cardiac smooth muscles and tissues by in-turn inhibition of contractile process in myocardial smooth muscles. [4]

MATERIALS AND METHODS

Isradipine was received from Dr Reddy's labs, Andhra Pradesh. HPMC-15 CPS, HPMC-E-25, PEG-400, and HPC were acquired from Gland Pharma Limited and all other excipients and solvents were purchased from SD fine chemicals Hyderabad

Isradipine extended release tablets formulation and preparation.

In the preparation of extended release tablets of Isradipine wet granulation technique was selected. The effective processing conditions not more than 60% RH and not more than 60^0C temperature were maintained throughout the process.
Dry mix strategy was followed for the preparation.

DRUG IN DRY MIX

Weighing

Weighed the required quantities of Isradipine, diluents (DCP) & other dry mix elements as per given in the table separately.

Sifting

Co sifted the drug, diluents and HPMC E50 from #40 sieve and thoroughly mixed the blend in a poly bag for uniform distribution of API.

Loading and Granulation

Co sifted mixture is loaded into FBP top spray granulation bowl and weighed required amount of water for granulation.

Drying

Tray drier was used for drying granules maintaining a temperature in between 40-45 degrees. Till required percent of moisture is obtained in granules which is measured using LOD Instrument and its values.

Sizing of Granules

The granules obtained are allowed to pass through # 30 seive. Required quantity extra granular material was weighed and sieved from # 30 along with granules.

Lubrication

Required amount of Magnesium stearate was collected and weighed, passed through #40 sieve and blended with blend from step 5 for 1 min.

Compression

The granules obtained were compressed with 8mm STD concave punch using 16 station compression machine.

Table no: 01. Table showing ingredient used for preparation of ER tablets of Isradipine

S.N	Contents Mg/Tab	F1	F2	F3	F4	F5	F6	F7
DRY MIX								
01	Isradipine	10	10	10	10	10	10	10
02	DCP	208	208	208	208	168	213	208
03	HPMC-E-50	60	60	60	30	100	60	--
04	HPMC-E-4	-	-	-	-	-	15	60
BINDER								
05	EC	10	10	-	-	-	-	
06	Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
LUBRICATION								
07	HPMC-E-10	10	15	30	30	-	-	-
08	Mg. Stearate	2	2	2	2	2	2	2
	Weight of Tablet	300	305	310	280	280	290	280

In-vitro evaluation of matrix release tablets

The compressed matrix tablets were evaluated for different official and nonofficial tests .i.e.

Weight Variation Test [5]

Weigh tablets of total twenty individually of which average weight of was calculated from individual tablets weight using the below formula.

$$\text{Weight variation} = \frac{\text{(Weight of tablet-Average weight)}}{\text{Average weight of tablets}} \times 100$$

Weight variation should not be more than 7.5%.

Hardness [6]

It is performed to check resistance of tablets against abrasion and impact, Monsanto hardness tester was used to determine the hardness of the prepared tablets. The hardness was maintained between six Kg/Cm^2 6 to 8 Kg/Cm^2.

Thickness [7]

Digital verniercaliper was used to determine the thickness of the tablets and thickness was maintained between 2-3mm.

Friability [8]

10 prepared ER tablets of Isradipine was collected and placed in drum of friabilator, then it is allowed to rotate for 5 minutes at 20 RPM, on each rotation tablets were allowed to fall from 2 inch height in the drum.

The percent of friability can be determined by given formula.

Initial weight –final weight/initial weight*100

Content uniformity [9]

Six tablets were taken randomly and allowed to dissolve in zwitter ionic surfactant and after required serial dilutions, the sample were analyzed at 325 nm in UV VISIBLE spectroscopy.

Dissolution [10]

The compressed tablets were evaluated for dissolution release profiles. It is carried out for 24 hrs study using USP-II (paddle type) apparatus.

Dissolution Study [10]

Medium: 0.2% LDAO IN WATER
Type of apparatus: USP - II (paddle type)
RPM: 50 rpm
Volume: 1000ml
Temperature: 37ºC± 0.5
Time: 24 hrs
Time intervals: 2, 4, 6, 8, 10, 12, 16, & 24 hours.

Preparation of Dissolution media (0.2% of 30%)

Transferred 66.0 mL of 30 % Lauryl Dimethyl amine oxide in to 10 Lt of dearerated water and mixed well.

Stability Study[11]

Conditions for Stability According To ICH-Guidelines

The prepared in-house tablets were allowed to expose different environmental temperature and humidity conditions according to guide lines given by ICH which is mentioned in below table.

Table no: 02. One month stability conditions

Study	Storage conditions	One Month
Long term	**25 ± 2°C/ 60 ± 5% RH or 30 ± 2°C / 65 ± 5% RH**	**1 months**
Intermediate	**30 ± 2°C / 65 ± 5% RH**	**1 months**
Accelerated	**40 ± 2°C / 75 ± 5% RH**	**1 months**

Table no: 03. Results blend and tablets of formulations F1 to F3

Parameters	F1	F2	F3
Bulk density	0.37	0.367	0.369
Hardness-kp	5.2	6.4	7.5
Thickness-mm	3-4	3.8-4.2	3.8-4.2

Disintegration-hrs	12	13	12.30
Weight variation	300	305	310
Friability (%)	0.23	0.56	0.87
Assay (%)	98.3	99.89	101.5

Table no: 04. Results blend and tablets of formulations F4 to F7

Parameters	**F4**	**F5**	**F6**	**F7**
Bulk density	0.362	0.35	0.37	0.365
Hardness-kp	7.5	8.4	7.4	7.4
Thickness-mm	3.8-4	5-7	3.8-4	3.8-4
Disintegration-hrs	10	11	13	13.25
Weight variation	280	280	290	280
Friability (%)	0.34	0.12	0.14	0.23
Assay (%)	100.4	99.5	98.16	99.12

RESULTS AND DISCUSSION

An approach **of t**he development of an extended release tablets were obtained by incorporating hydrophilic polymers and coating with the hydrophobic polymers is the method for extending the release of the in soluble drug.

However an attempt has been made to obtain the same objective within polymer based matrix to decrease the dissolution rate of water insoluble drug hydrophilic polymer in these two attempts dissolution is occurred by dissolution mechanism.

In-vitro evaluation parameters

In house prepared trials were conducted for evaluation of physical characterization and in-vitro evaluation parameters. The details of results are given below tables.

Table no: 05. Drug release of Isradipine from ER Tablets

Time	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**
0	0	0	0	0	0	0
2	13	4	10	5	7	6
4	55	12	31	20	24	23
6	76	54	49	39	48	37
8	91	47	70	56	68	55
10	98	55	88	72	86	68
12	89	74	99	89	99	88
16	90	89	99	99	101	97
24	91	95	99	99	101	97

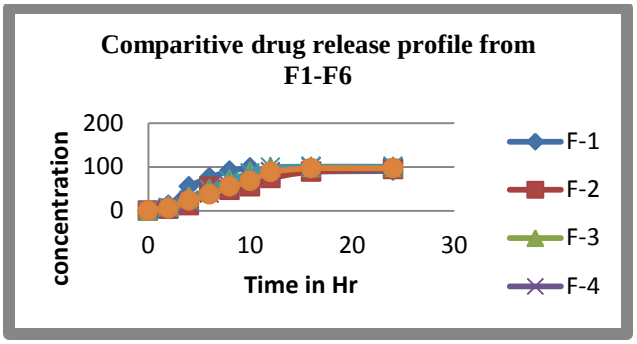

Fig. no: 01. Graphical representation of comparative drug release profile form trial 01 to 06

Optimized formulation in-vitro evaluation

Table no: 06. Physical characterization of optimized formula F-07

Parameters	F-7- OPTIMIZED FORMULA
Bulk density	0.33
Hardness-kp	7.8
Thickness-mm	3.04-3.13
Disintegration	13.24hr
Weight variation	280±2
Friability (%)	0.45
Assay (%)	100.32

Table no: 07. Isradipine release form optimized formula

TIME	F-7-OPTZ
0	0
2	17
4	31
6	49
8	58
10	71
12	89
16	95
24	97

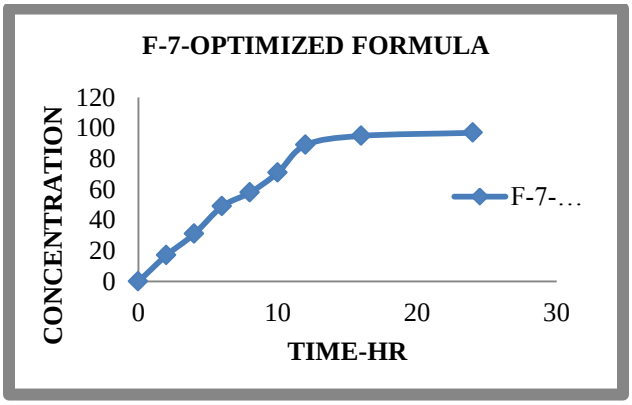

Fig. no: 02. Graphical representation of drug release profile form optimized formula F-07

One month stability studies

In-vitro evaluation parameters were performed after one month. The results are as follows

Table no: 08. Physical characterization of ER tablets after one month stability studies.

Parameters	Long term 25 ± 2°C/ 60 ± 5% RH	Intermediate 30 ± 2°C / 65 ± 5% RH	Accelerated 40 ± 2°C / 75 ± 5% RH
Hardness-kp	7.8	7.4	7.8
Thickness-mm	3.04-3.13	3.12-3.17	3.23-3.45
Disintegration	13.24hr	13.56hr	14.14hr
Weight variation	280±2	280±4	280±6
Friability (%)	0.45	0.12	0.34
Assay (%)	100.32	99.86	99.56

Comparative dissolution studies of Isradipine extended release tablets

Table no: 09. Isradipine release form three different conditions

Time in hours	Long term 25 ± 2°C/ 60 ± 5% RH	Intermediate 30 ± 2°C / 65 ± 5% RH	Accelerated 40 ± 2°C / 75 ± 5% RH
0	0	0	0
2	19	23	28
4	31	39	43
6	42	48	68
8	55	59	82
10	72	79	91
12	97	100	99

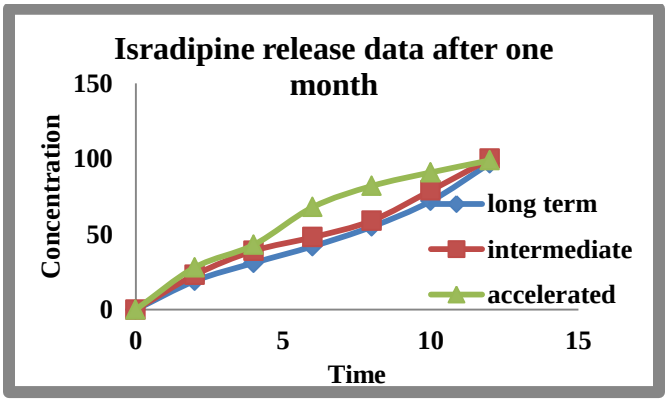

Fig. 03. Graphical representation of 1-month stability studies

Comparative drug release profile of in-house developed ER tablets and innovator tablets [11]

Table no: 10. Drug release of in-house and innovator ER tablets.

Time	In House Product	Innovator Product-Dynacirc
0	0	0
2	8	12
4	26	29

6	45	49
8	62	71
10	79	88
12	93	99

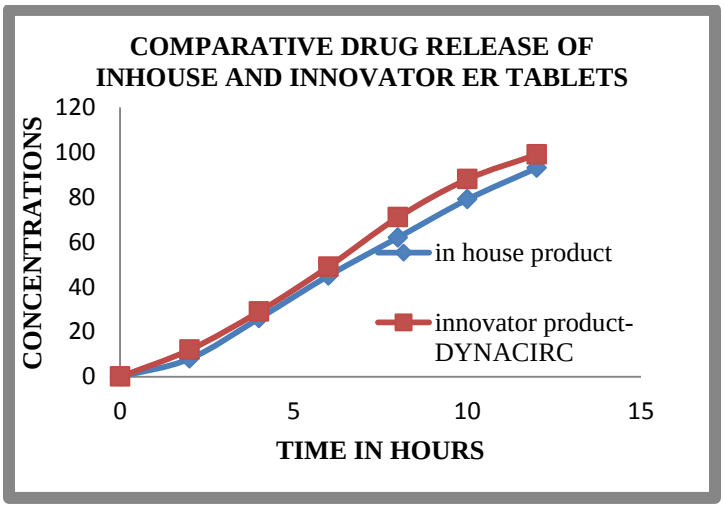

Fig. no: 04. Comparative release profile of In-house and Innovator ER Tablets

Determination of Isradipine release kinetics from after one month stability studies

Release of drug from the prepared extended release tablets was used to determine the kinetics using different models zero order, first order, Higuchis model and KoresmeyerPeppas model

Zero order

Table no: 11. Zero order kinetics time vspercent of drug un-dissolved

Time	% drug un-dissolved
0	100
2	72
4	57
6	32
8	18
10	9
12	1

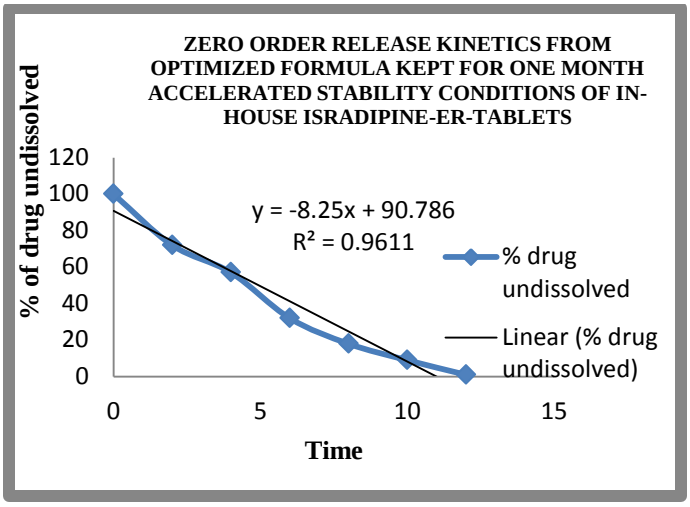

Fig. no: 05. Zero order kinetics- 1- month accelerated stability of In-House ER Tablets

Table no: 12. First order release rate kinetics from I month accelerated stability studies of in house developed ER tablets

Time	log 100-Q
0	2.00
2	1.86
4	1.76
6	1.51
8	1.26
10	0.95
12	0.00

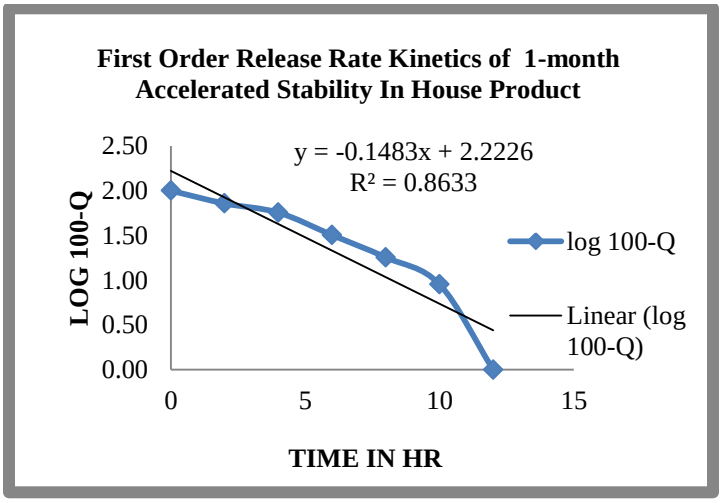

Fig. no: 06. First Order Release Rate Kinetics of 1-month Accelerated Stability In House Product.

Higuchis model

Table no: 13. Mean percent of drug dissolved

Sq. time	Mean % drug dissolved
0	0
1.41	28
2	43
2.45	68
2.83	82
3.16	91
3.46	99

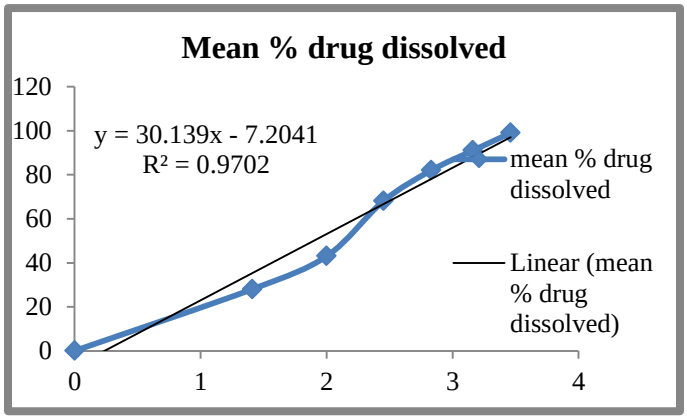

Fig. no: 07. Graphical representation of HIGUCHIS kinetic model

Koresmeyerpeppas plot

Table no: 14. Log cumulative % of drug release vs. log time

log time	log cumulative percent of drug release
0	0
0.30	1.23
0.60	1.68
0.78	1.99
0.90	2.19
1.00	2.35
1.08	2.50
1.20	2.61
1.38	2.71

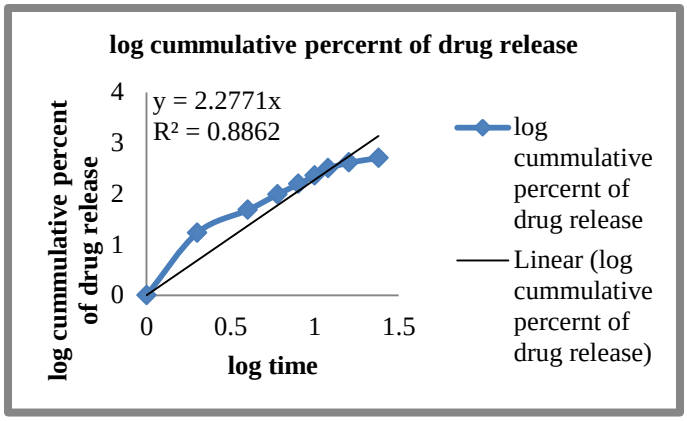

Fig. no: 11. KoresmeyerPeppas plot

Based on the "n" value of 0.87 obtained for F-07 formulation, the drug release was found to follow Anomalous (non-Fickian) diffusion. This value indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process.

Also, the drug release mechanism was best explained by HIGUCHI MODEL with order of equation, as the plots showed the highest linearity (r^2 = 0.970), followed by Zero order equation (r^2= 0.961). As the drug release was best fitted in HIGUCHIS order kinetics, it indicated that the rate of drug release is concentration independent.

The "r^2" value for Higuchi plot was found to be 0.961 indicating that drug release included diffusion as one of the release mechanisms.

CONCLUSION

Formulation-F07 Containing ISRADIPINE 10 mg per tablet and developed employing Lactose Monohydrate and Hydroxy ethyl Cellulose in dry mix is similar and equal to the innovator product in respect of all tablets properties and dissolution profile.

No significant change was observed in the drug content, physical properties and dissolution rate of these tablets after the storage period of 2 months at 40^o c and 75%RH. Hence the study resulted in the development of Isradipine Matrix Release Extended tablets comparable to the innovator product for Isradipine fulfilling the objective of the study.

The identified formula shall be utilized for the formulation development and other studies for successful launching of the product as it was proved to be stable and robust, cost effective compared to osmotic device.

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