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Research Article

FORMULATION AND CHARACTERIZATION OF FAST DISSOLVING TABLETS OF ISRADIPINE BY USING DIFFERENT TECHNOLOGIES

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ABSTRACT

Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology. The aim the study was to prepare and characterize fast dissolving tablets(FDT) of Isradipine (a water insoluble drug and belongs to BCS class-II) by employing different technologies like liquidsolid by improving wetting, sublimation by creating porous environment, effervescent and super disintegrant by breaking the tablet fast. The FDT of isradipine were also prepared by adopting direct compression method. Physicochemical properties and *in vitro* release studies were evaluated. The isradipine FDTs of effervescent technology was showing immediate release with T_{90} % within 4 min and hence the effervescent technology was proved to be the promising in comparison with other technology types.By using invitro drug release data, it was found that FDTs of isradipine are following First order kinetics.

KEY WORDS

Isradipine, liquidsolid, sublimation, effervescent, super disintegrant. FDT

INTRODUCTION

Fast dissolving technology is one of the best opportunities to improve bioavailability, immediate relief and patient compliance in comparison to conventional tablets. . Fast dissolving drug delivery can be achieved by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying and sublimation. In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft-moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable or brittle, which are difficult to handle, often requiring specialized peel off blister packaging. Fast dissolving tablets disintegrate or dissolve rapidly in the saliva without the need for water. They contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on the tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach[1, 4]. Isradipine was used as antihypertensive drug which is a

water insoluble drug[2]. By fast releasing and improving the solubility of the drug not only the bioavailability is improved but also immediate relief would be produced[3].

MATERIALS AND METHODS

Isradipine(Matrix Lab, Hyderabad), Ammonium bicarbonate, Aerosil, Citric acid anhydrous, Camphor, Micro crystalline cellulose, Magnesium stearate, Menthol, Mannitol, Poly ethylene glycol 400, Sodium starch glycolate, Sodium bicarbonate, Sodium saccharine, Cetrimide, methanol(S.D. Fine chem Ltd, Mumbai).

METHODS

Preparation of isradipine FDT by liquisolid technology[15, 16]

All the ingredients were sifted through sieve number 80. The required quantity of isradipine was dispersed in the wetting enhancing agent like PEG 400 in the glass mortar. Half of the mannitol was added as a diluent to it and blend was triturated along with SSG, aerosil, menthol, sodium saccharine and magnesium stearate. The remaining mannitol was added and triturated and finally the blend was compressed on 12 station compression machine (CIP Machineries, India) to obtain the tablet weight of 100 mg

Preparation of isradipine FDT by sublimation technology[6, 11, 12]

All the ingredients were sifted through sieve number 80. The required quantities of isradipine, subliming agents, SSG, aerosil, menthol, sodium saccharine magnesium stearate, and mannitol were weighed and the blend was thoroughly mixed in the glass mortar, triturated and finally the blend was compressed on 12 station compression machine (CIP Machineries, India) to obtain the tablet weight of 100 mg. The prepared tablets were heated in the hot air oven (Biotechnics, Mumbai) at 60 °C until constant weight was obtained.

Preparation of isradipine FDT by effervescent technology[13, 14]

All the ingredients were sifted through sieve number 80. The required quantities of sodium bicarbonate and citric acid were accurately weighed, preheated at temperature of 80°C to remove absorbed /residual moisture in the oven (Biotechnics, Mumbai) for about 15 minutes. Weigh the required quantities of isradipine, SSG, aerosil, menthol, sodium saccharine, magnesium stearate, mannitol were added and the blend was then thoroughly mixed in the glass mortar, triturated and finally the blend was compressed on 12 station compression machine (CIP Machineries, India) to obtain the tablet weight of 100 mg.

Preparation of isradipine FDT by using all technology types

All the ingredients were sifted through sieve number 80. The required quantities of isradipine, PEG 400, sodium bicarbonate, citric acid, ammonium bicarbonate, SSG, aerosil, menthol, sodium saccharine, magnesium stearate, mannitol were added and the blend was thoroughly mixed in the glass mortar, triturated and finally the blend was compressed on 12 station compression machine (CIP Machineries, India) to obtain the tablet weight of 100 mg. The prepared tablets were heated in the hot air oven at 60 °C until constant weight was obtained.

EVALUATION OF FORMULATIONS OF ISRADIPINE FDT:

The isradipine formulations were evaluated for the following physicochemical parameters:

General appearance

The general appearance of tablets, its visual identity, and overall elegance is essential for consumer acceptance. The control of general

appearance of tablets involves measurement of number of attributes such as tablet size, color and surface texture and hence the parameters were evaluated.

Weight variation[5]

Ten tablets were selected at randomly from each formulations and average weight was determined (Digital balance, AUX 220, Shimadzu). Then individual tablets were weighed and compared with the average weight.

Thickness[7]

The thickness of diclofenac sodium tablets was measured using a screw gauge (Dwarakamai, Hyderabad). The average values and the standard deviations were calculated.

Hardness [7]

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage, transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto hardness tester (E 30, Dwarakamai, Hyderabad). The average values, and the standard deviations were calculated.

Friability [5]

The friability test was performed using a Roche friabilator (PSM-02, Electro lab, Mumbai). Six pre weighed tablets were rotated at 25 rpm for 4 minutes. The dedusted tablets were then reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula.

% Friability = (Initial weight - Loss in weight) / Initial weight*100

Friability below 1% was considered as acceptable.

Wetting time and water absorption ratio (R) [5]

Five circular tissue papers were placed in a petridish with a 10-cm diameter. Ten ml of water containing methyl red was added to the petridish. The methyl red solution is used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water containing methyl red solution to reach the upper surface and wet the tablets completely was noted as the wetting time. The weight of the tablet prior to placement in the petridish was noted as W_b utilizing (Digital balance, Aux 220, Shimadzu). The wetted tablet was then removed and reweighed as W_a. Water absorption ratio R, was then determined according to the following equation.

$R = 100 (W_a - W_b) / W_b$

Where W_b and W_a are the weight before and after water absorption, respectively.

***In vitro* disintegration test** [5]

Six tablets without the disc were introduced in each tube of the basket of the disintegration test apparatus (TGR56, Electro Lab, Mumbai). The basket was positioned into a beaker containing 900 ml of distilled water and operated at 37 ± 0.5 °C. The stop watch was started and the tablets were observed for disintegration. The stopwatch was stopped when the tablets got disintegrated with no palpable mass remaining in the apparatus and the time was noted as the disintegration time.

Content uniformity of the isradipine tablets in SSF pH 6.75 containing 0.2 % cetrimide[8, 9]

One tablet was taken in 10 ml volumetric flask; 1 ml of water was added to disintegrate the tablet. Then 9 ml of methanol was added and agitated in the cyclomixer (CM 101, Remi Ltd, Mumbai) for 15 min. The volume was made up to mark with methanol. The solutions were filtered, suitably diluted with

SSF pH 6.75 containing 0.2 % cetrimide and analysis was done at 326 nm.

***In vitro* drug release of isradipine in SSF pH 6.75 containing 0.2% cetrimide[8, 9]**

In vitro drug release studies were carried out using Type II apparatus (VDA-D, Veego, India) at 50 rpm. 500 ml of SSF pH 6.75 containing 0.2 % cetrimide was used as the dissolution medium. The temperature of the dissolution medium was maintained at 37 ± 0.5 °C. An aliquot 5 ml of dissolution medium was withdrawn at specific time intervals, filtered and suitably diluted prior to spectrophotometric analysis. The medium was replenished with an equal amount 5 ml of dissolution medium. The absorbance of these solutions was analyzed at 326 nm by UV spectroscopy (UV 1700, Shimadzu).

Kinetic analysis of dissolution data [10]

To study the mechanism of drug release from the matrix tablets, the dissolution data were fitted into Zero order, First order, Higuchi and Hixson's crowell cube root equation.

Table-1 Master formula of isradipine tablets, % (To find effect of technology types)

Ingredients (%)	F_L	F_S	F_E	F_A
Technology type	Liquisolid	Sublimation	Effervescent	All
Isradipine	5	5	5	5
Ammonium bicarbonate	-	25	-	25
PEG 400	1	-	-	1
Sodium bicarbonate	-	-	20	20
Citric acid	-	-	15.25	15.25
SSG	2	2	2	2
Aerosil	0.5	0.5	0.5	0.5
Menthol	0.5	0.5	0.5	0.5
Sodium saccharine	1	1	1	1
Magnesium stearate	1	1	1	1
Mannitol	89	65	54.75	28.75
Total weight of tablet in %	100	100	100	100

F_L -Formulation of liquisolid technology
F_S -Formulation of Sublimation technology
F_E -Formulation of Effervescent technology

RESULTS AND DISCUSSION

Analytical method of isradipine and its formulations

Isradipine was estimated by UV spectrophotometer (UV 1700, Shimadzu). The dissolution medium for isradipine tablets official in British Pharmacopoeia was employing 0.1 % w/v solution of N, N-dimethyldodecyl amine N- oxide in water**.** This may due to improve the wetting of drug. Where as, for isradipine capsules as per USFDA official information, 0.2 w/v % of

lauryl dimethyl amine oxide in water was used as the dissolution medium. As cetrimide was similar to lauryl dimethyl amine oxide and easily available, 0.2 % w/v solution of cetrimide in SSF pH 6.75 was used as dissolution medium. The λ_{max} of isradipine in SSF pH 6.75 containing 0.2 % cetrimide was studied by scanning over the range of 200 - 400 nm and found to be 326 nm as shown in *Figure-1*. This was matching with the literature value of 326 nm. The absorbance of isradipine in SSF pH 6.75 containing 0.2 % was found to be linear over range from 5 - 40 µg/ml with R^2 value of 0.9986 Figure-2. The bench top stability studies of isradipine in SSF pH 6.75 containing 0.2 % cetrimide were studied and the results showed that the solution was stable on bench top (25 - 30 ºC) for two days, with the decrease in absorbance of less than 1 % of the initial absorbance value. Even though, it was indicated that isradipine was stable under the experimental conditions, but all the samples were analyzed immediately without storing them.

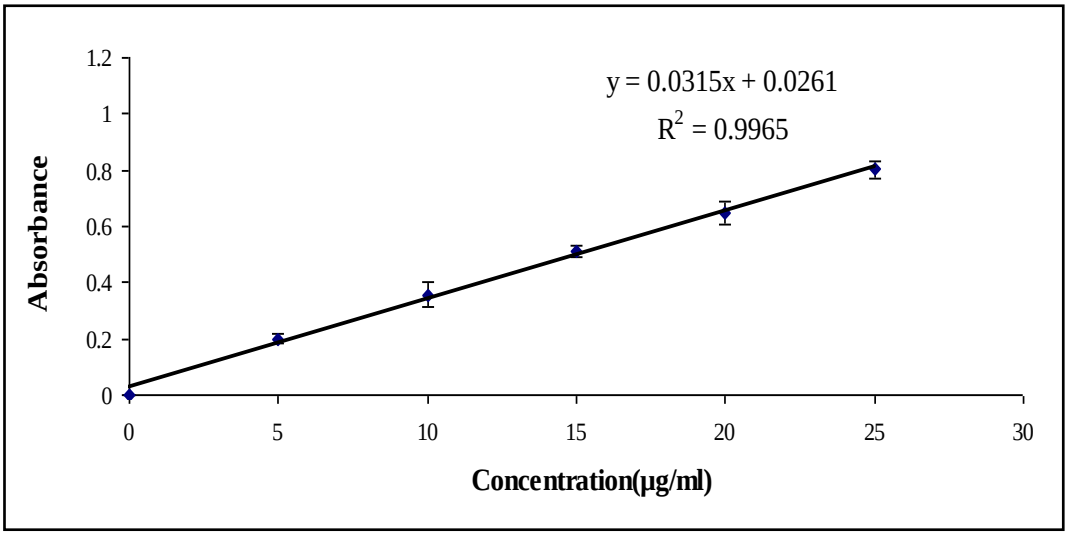

Figure-1 Standard plot of diclofenac sodium in SSF pH 6.75, λ_{max} = 276 nm

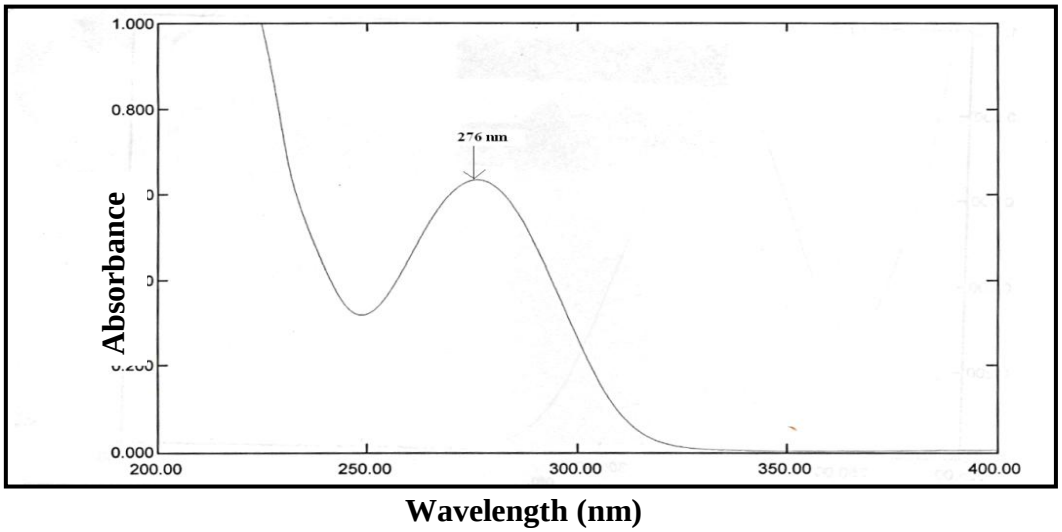

Figure-2 UV Scan of diclofenac sodium in SSF pH 6.75, 25 µg/ml, λ_{max} = 276 nm.

Study of interference of excipients on isradipine analysis

The UV scans of excipients used in isradipine formulations in SSF pH 6.75 containing 0.2 % cetrimide indicated that the excipient did not show absorbance at λ_{max} 326 nm. The drug excipient blend was not showing shift in λ_{max} in comparison to pure drug as shown in *Figure-3.* As the excipients used were non UV absorbing at 326 nm and the λ_{max} of isradipine was not changed showing that the excipients were not interfering with the drug.

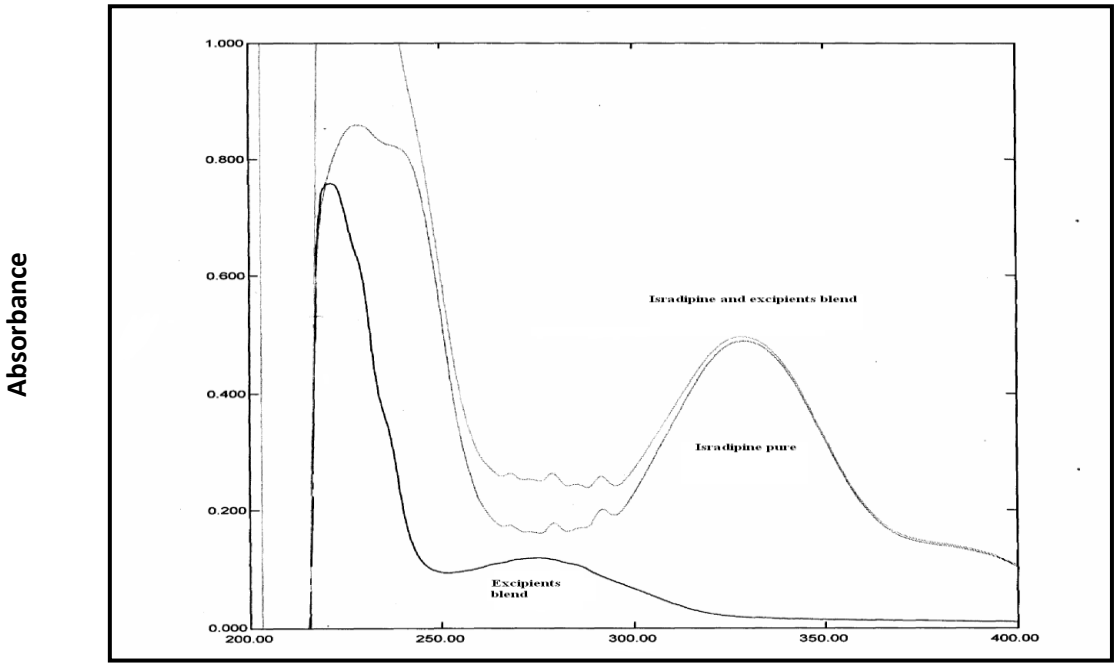

Figure-3 Study of interference of excipients with isradipine

Table-2 Evaluation data of powder blend of isradipine tablets

Powder characteristics	F_L	F_S	F_E	F_A
Bulk density (gm/ml) [a]	0.562± 0.02	0.566 ± 0.06	0.540 ± 0.06	0.549 ± 0.05
Tapped density (gm/ml) [a]	0.636± 0.02	0.647 ± 0.03	0.642 ± 0.06	0.623 ± 0.05
Compressibility index [a]	11.62 (Good)	15.91 (Good)	15.85 (Good)	11.85 (Good)
Hausner's ratio [a]	1.131 (Good)	1.189 (Good)	1.189 (Good)	1.134 (Good)
Angle of repose(θ)[a]	19.03 ± 0.11	19.03 ± 0.11	17.17 ± 0.11	20.55 ± 0.51

[a] Each value is an average of three determinations ± SD

Table-3 Evaluation data of isradipine tablets by different technologies

Evaluation parameters	F_L	F_S	F_E	F_A
Weight variation (mg)[a]	99.96 ±0.88	102.62 ± 0.88	100.15 ± 0.42	100.75±1.26
Thickness (mm) [b]	2.29 ± 0.08	2.38 ± 0.10	2.42 ± 0.03	2.39 ± 0.03
Hardness (kg/cm^2) [b]	1.56 ± 0.20	1.93 ± 0.15	1.13 ± 0.60	2.13 ± 0.25
Friability (%) [b]	0.70 ± 0.10	0.86 ± 0.55	0.93 ± 0.75	0.83 ± 0.65
Wetting time (sec) [b]	21 ± 1.52	15 ± 0.57	41 ± 0.57	24 ± 1.15
Water absorption ratio(%)[b]	28 ±0.30	63 ± 0.28	30 ±0.66	32 ±0.38
In vitro D.T (sec) [c]	12 ± 0.57	5 ± 1.15	22 ± 0.57	43 ±1.52
Content uniformity (%) [b]	98.9 ± 0.60	100.7 ± 1.17	99 ± 0.66	99.2 ± 0.41

[a] Each value is an average of twenty determinations ± SD

[b] Each value is an average of three determinations ± S

[c] Each value is an average of six determinations ± SD

Table- 4 Cumulative % drug release data of isradipine tablets in SSF pH 6.75 containing 0.2 % cetrimide (To find the effect of technology types)

Batch no	F_L	F_S	F_E	F_A	5 mg pure drug
Time(min)	**Cumulative % drug release**				
2	52 ± 5.81	55 ± 1.70	54 ± 0.94	34 ± 3.02	35 ± 3.90
4	60 ± 3.08	60 ± 6.31	90 ± 1.90	50 ± 4.03	44 ± 5.86
6	66 ± 5.90	64 ± 5.47	96 ± 0.47	57 ± 1.60	59 ± 6.55
8	69 ± 3.97	70 ± 4.70	100± 2.30	60 ± 2.12	71 ± 4.21
10	73 ± 2.99	75 ± 5.93	-	63 ± 3.45	76 ± 5.50
15	77 ± 3.21	80 ± 3.55	-	69 ± 2.12	80 ± 4.02
20	82 ± 3.99	88 ± 4.33	-	74 ± 4.84	86 ± 3.54
25	88 ± 4.32	94 ± 5.91	-	82 ± 2.53	91 ± 4.35
30	96 ± 4.38	100 ± 5.79	-	93 ± 1.86	94 ± 4.04

Each value is an average of three determinations ± SD

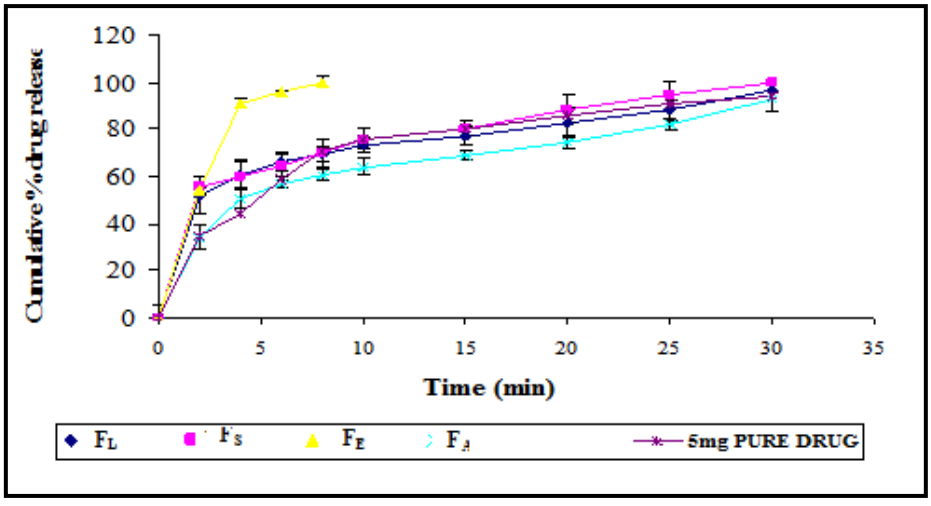

Figure-4 Cumulative % drug release plot of isradipine tablets in SSF pH 6.75 containing 0.2% cetrimide (To find the effect of technology types)

Table-5 T_{90} % and T_{100} % data of isradipine tablets

Batch no	T_{90} %	T_{100} %
F_L	30 min	-
F_S	25 min	30 min
F_E	4 min	8 min
F_A	30 min	-
5 mg pure drug	25 min	-

- Not achieved in 30 min

Table-6 Drug release kinetics data of isradipine tablets prepared by using by different technologies.

Batch no	Parameters	Zero order	First order	Higuchi	Hixson's crowell cube root
F_L	R^2	0.7952	**0.9506**	0.9283	0.5700
	K	2.0870	-0.0355	5.7353	-0.0753
F_S	R^2	0.8219	**0.9514**	0.9434	0.5846
	K	2.2817	-0.0524	5.7353	-0.0783
F_E	R^2	0.9074	**0.9956**	0.9829	0.8031
	K	12.1	-0.25303	2.73741	-0.5041
F_A	R^2	0.8699	**0.9559**	0.9694	0.6289
		2.2483	-0.0299	5.7353	-0.0810
5 mg pure drug	R^2	0.8513	**0.9828**	0.4747	0.6364
	K	2.4849	-0.0375	5.7353	-0.0851

R^2 - correlation coefficient, K - release rate constant

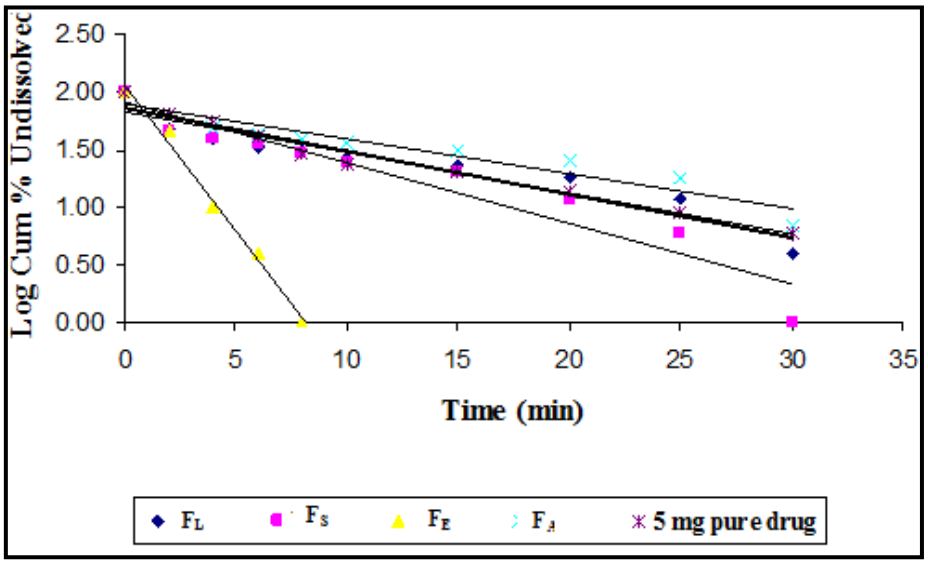

Figure -5 First order release kinetics plot of isradipine tablets by different technologies

CONCLUSION

Fast dissolving tablets of Isradipine were prepared by 3 different technologies (Liquisolid, effervescent, sublimation) and compressed by direct compression method by using superdisintegrants. The effervescent technology was showing T90% within 4minutes. Hence it is concluded that the batch prepared by effervescent technology was optimized batch. All the formulations of Isradipine are following First order kinetics.

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