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# FORMULATION AND EVALUATION OF ISRADIPINE SUSTAINED RELEASE TABLETS

**Meghana Vemuri*[1], Prathyusha Madireddy[1], Sateesh Kumar Vemula[2], Raj Kumar V[1]**

[1]Chaitanya College of Pharmacy Education and Research, Hanamkonda-506001, Telangana, India.
[2]MAK College of Pharmacy, Moinabad, Rangareddy, Telangana, India-501 504.

*Corresponding Author Email: meghana.729@gmail.com

## ABSTRACT

*The present investigation was aimed to prepare Isradipine sustained release tablet matrix using different concentrations of hydrophilic, hydrophobic, and combination of both the polymers. Different formulations of Isradipine sustained release tablets were prepared by direct compression method using various concentrations of HPMC K4M, K15M, Ethyl cellulose and combination of Ethyl cellulose and HPMC K15M as matrix forming agent. The prepared Isradipine sustained release tablets were characterized for weight variation, hardness, thickness, friability, drug content and swelling studies. Formulations were evaluated for the release of Isradipine over a period of 12 hrs using type-II USP XXIV standard dissolution apparatus in 6.8 pH phosphate buffer at 37 ° C. The in vitro drug release study F14 was the most successful formulation which includes both HPMC K15M and Ethyl cellulose, extended the drug release up to 12 h and exhibited satisfactory drug release in the initial hours. Mechanism of drug release was estimated by using different kinetic models like zero order, first order, Peppas and Higuchi's. The drug release from optimized formulation (F14) followed first-order kinetics via non-fickian (anomalous) diffusion. Therefore, the prepared F14 sustained-release tablets of Isradipine showed better release profiles than other formulations and further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans.*

## KEY WORDS

*Isradipine, Tablets, HPMC K4M, HPMC K15M, Ethyl cellulose, Drug release kinetics.*

## INTRODUCTION

Drugs that are having short half-life are eliminated quickly from the blood circulation, require frequent dosing. To avoid this problem most commonly used approach is formulation of sustained release tablets. Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and release the drug at constant rate for desired time period. In the present work Isradipine (1.5 h half-life) is selected as the model drug to prepare the sustained release tablets.

Isradipine is a dihydropyridine calcium channel blocker. It binds to calcium channels with high affinity and specificity and inhibits calcium flux into cardiac and smooth muscle. It is prescribed widely in diverse cardiovascular diseases, e.g. hypertension, angina pectoris, arrhythmias, and myocardial infarction.

The present work is aimed at preparing and evaluating sustained-release tablets of Isradipine using different polymers. To study the drug release mechanisms and release kinetics from the hydrophilic and hydrophobic

polymers individually and combinedly at different ratios.

## MATERIALS AND METHODS

Isradipine drug obtained as a gift sample was used; HPMC K4M, HPMC K15M & Ethylcellulose were purchased from MSN Laboratories, Hyderabad, India; Avicel PH 102 purchased from Qualikems Fine Chemicals Ltd, Delhi, India; Magnesium stearate and Talc of best grade were used.

**Formulations:** In the formulations prepared, the release retardants included were hydroxypropylmethylcellulose (HPMC K4M, HPMC K15M), ethyl cellulose (EC). Microcrystalline cellulose (Avicel PH 102) was used as diluents. Magnesium stearate 1% and talc 2 % were used as lubricants. Compositions of different formulations were given in the below Table 1.

**Preparation of Isradipine Sustained Release Tablets**

All the sustained tablets of 150mg, each containing 10 mg of Isradipine, were prepared by direct compression method by incorporating the different sustained release polymers.

Accurately weighed amounts of drug, polymer, and diluent were mixed geometrically in a mortar. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 min. The powder blend was then lubricated with magnesium stearate and talc for 2 min and compressed into tablets on a 8-station rotary tabletting machine using 6-mm round, flat-faced punches.

**Table 1 : Composition of Sustained Release Tablets of Isradipine**

| Formulations | Drug (mg) | HPMC K4M (mg) | HPMC K15M (mg) | EC (mg) | Avicel Ph 102 (mg) | Manesium Stearate (mg) | Talc (mg) |
|---|---|---|---|---|---|---|---|
| F1 | 10 | 10 | - | - | 125.5 | 1.5 | 3 |
| F2 | 10 | 20 | - | - | 115.5 | 1.5 | 3 |
| F3 | 10 | 30 | - | - | 105.5 | 1.5 | 3 |
| F4 | 10 | 40 | - | - | 95.5 | 1.5 | 3 |
| F5 | 10 | - | 10 | - | 125.5 | 1.5 | 3 |
| F6 | 10 | - | 20 | - | 115.5 | 1.5 | 3 |
| F7 | 10 | - | 30 | - | 105.5 | 1.5 | 3 |
| F8 | 10 | - | 40 | - | 95.5 | 1.5 | 3 |
| F9 | 10 | - | - | 10 | 125.5 | 1.5 | 3 |
| F10 | 10 | - | - | 20 | 115.5 | 1.5 | 3 |
| F11 | 10 | - | - | 30 | 105.5 | 1.5 | 3 |
| F12 | 10 | - | - | 40 | 95.5 | 1.5 | 3 |
| F13 | 10 | - | 20 | 10 | 105.5 | 1.5 | 3 |
| F14 | 10 | - | 15 | 15 | 105.5 | 1.5 | 3 |
| F15 | 10 | - | 10 | 20 | 105.5 | 1.5 | 3 |

**Evaluation of Matrix Tablets**

**Weight Variation Test:** To study weight variation individual weights ($W_I$) of 20 tablets from each formulation were noted using electronic balance. Their average weight ($W_A$) were calculated. Percent weight variation from average weights of the tablets along with standard deviation values were calculated according to IP 1996.

**Thickness:** Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

**Hardness:** Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

**Friability Test:** The friability was calculated as the percentage weight loss. Percentage friability was calculated according to the standards using Roche friabilator 10 tablets from each batch operated at 25 rpm for 4 minutes upto 100 rotations.

**Drug Content:** The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount.

***In vitro* Drug Release Study:** Drug release was assessed by dissolution test under the following conditions: n=3, USP type II dissolution apparatus (paddle method) at 50 rpm in 900ml phosphate buffer pH 6.8 from 3 to 12 hours, maintained at 37°C ± 0.5°C. Drug content in each sample was analyzed by UV-visible spectrophotometer at 332 nm.

**Kinetic Analysis of Dissolution Data:** in vitro release data was analysed using various kinetic models to describe the release kinetics.

**Mechanism of drug release:** The mechanism of drug release was found by first fitting 60% drug release data in Korsmeyer–Peppas model.

**Swelling and Erosion Studies:** Swelling and eroding behavior was determined by a method similar to that reported by Avachat and Vikram-2007[21]

## RESULTS AND DISCUSSION

**Physical evaluation of sustained release tablets:**

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 2. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 148.1±0.43 and 152.1±0.93 mg. The hardness of the tablets ranged from 5.08 to 6.16 kg/cm$^2$ and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 3.24 to 3.31 mm. All the formulations satisfied the content of the drug as they contained 97.35±0.43 to 100.24±1.25 % of Isradipine and good uniformity in drug content was observed. Thus, all the physical attributes of the prepared tablets were found be practically within control.

**Table 2: Physical Evaluation of Sustained Release Tablets**

| Formulation | Weight (mg) | Hardness (kg/cm$^2$) | Thickness (mm) | Friability (%) | Drug content* (%) |
|---|---|---|---|---|---|
| F1 | 149.8±1.48 | 5.50±0.44 | 3.24±0.17 | 0.36 | 98.25±1.37 |
| F2 | 150.4±0.54 | 5.50±0.31 | 3.27±0.25 | 0.39 | 97.28±0.80 |
| F3 | 148.6±0.41 | 5.58±0.40 | 3.24±0.80 | 0.43 | 99.12±2.47 |
| F4 | 149.8±1.64 | 5.66±0.55 | 3.20±0.20 | 0.12 | 100.22±0.88 |
| F5 | 150.6±1.14 | 4.25±0.57 | 3.28±0.66 | 0.54 | 100.24±1.25 |
| F6 | 148.2±0.83 | 4.08±0.30 | 3.31±0.25 | 0.58 | 99.53±1.87 |
| F7 | 149.9±0.67 | 4.25±0.57 | 3.24±0.71 | 0.64 | 99.28±1.99 |
| F8 | 148.1±0.43 | 4.41±0.60 | 3.31±0.89 | 0.37 | 95.35±1.14 |
| F9 | 150.5±0.80 | 5.00±0.44 | 3.30±0.73 | 0.77 | 96.34±2.18 |
| F10 | 151.2±0.83 | 5.00±0.31 | 3.30±0.68 | 0.42 | 99.29±0.98 |
| F11 | 152.1±0.93 | 5.08±0.37 | 3.26±0.88 | 0.48 | 97.35±0.43 |
| F12 | 151.2±0.97 | 5.41±0.70 | 3.29±0.36 | 0.15 | 98.88±0.88 |
| F13 | 149.2±0.83 | 4.33±0.50 | 3.26±0.46 | 0.27 | 98.57±1.22 |
| F14 | 151.2±0.92 | 4.58±0.57 | 3.28±0.38 | 0.29 | 99.35±2.09 |
| F15 | 150.0±1.22 | 4.75±0.77 | 3.28±0.37 | 0.53 | 99.54±2.15 |

**All values represent mean ± Standard Deviation (SD) * n=3; n=6; n=20**

**Table 3: *In vitro* Release Data of Isradipine from HPMC K4M Matrices (n=3)**

| Time | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| **0.5** | 22.64±1.12 | 19.22±0.86 | 16.98±0.41 | 14.57±0.78 |
| **1** | 41.94±0.87 | 39.96±0.93 | 37.12±1.22 | 36.78±1.53 |
| **2** | 53.88±0.44 | 50.99±0.68 | 50.20±0.37 | 48.13±1.12 |
| **3** | 74.58±1.10 | 67.43±0.49 | 63.09±0.96 | 62.99±0.84 |
| **4** | 82.35±1.35 | 80.50±1.77 | 77.61±0.42 | 75.35±0.59 |
| **6** | 94.28±1.79 | 89.47±1.35 | 86.23±1.49 | 83.30±0.97 |
| **8** | - | 97.55±0.21 | 93.83±0.74 | 91.15±0.68 |
| **10** | - | - | - | 98.47±0.81 |
| **12** | - | - | - | - |

**Table 4: *In vitro* Release Data from HPMC K15M Matrices (n=3)**

| Time (h) | F5 | F6 | F7 | F8 |
|---|---|---|---|---|
| **0.5** | 19.54±1.34 | 17.15±1.23 | 16.14±0.32 | 13.91±0.63 |
| **1** | 37.23±0.97 | 35.38±1.47 | 35.16±1.32 | 34.93±0.58 |
| **2** | 51.72±1.68 | 50.46±0.83 | 50.08±1.27 | 49.86±0.94 |
| **3** | 71.58±0.87 | 69.17±0.65 | 67.58±0.94 | 66.97±0.75 |
| **4** | 80.71±0.54 | 78.32±0.87 | 77.73±1.57 | 76.82±0.38 |
| **6** | 89.43±1.63 | 86.87±0.42 | 83.83±0.59 | 81.87±0.96 |
| **8** | 97.29±0.53 | 94.55±0.74 | 90.87±1.79 | 89.89±0.72 |
| **10** | - | 98.25±1.62 | 96.14±1.05 | 93.97±0.27 |
| **12** | - | - | - | 98.77±0.12 |

**Table 5: *In vitro* Release Data from Ethyl Cellulose Matrices (n=3)**

| Time (h) | F9 | F10 | F11 | F12 |
|---|---|---|---|---|
| **0.5** | 20.56±0.24 | 18.25±1.21 | 16.12±0.28 | 12.36±0.12 |
| **1** | 42.27±0.57 | 38.7±0.82 | 28.64±1.42 | 22.31±0.54 |
| **2** | 52.47±0.67 | 47.28±0.69 | 35.62±0.71 | 32.42±0.62 |
| **3** | 64.86±0.73 | 59.73±0.87 | 42.34±0.54 | 42.83±0.81 |
| **4** | 77.27±0.84 | 74.95±0.31 | 56.84±0.37 | 54.86±0.42 |
| **6** | 86.63±0.79 | 82.62±0.64 | 64.92±0.84 | 68.03±1.57 |
| **8** | 98.31±0.52 | 91.59±0.63 | 75.72±0.53 | 72.26±0.46 |
| **10** | - | 99.34±0.87 | 83.56±0.83 | 80.92±0.75 |
| **12** | - | - | 97.28±0.27 | 89.56±0.71 |

**Table 6: *In vitro* Release Data from HPMC K15M and EC Matrices (n=3)**

| Time (h) | F13 | F14 | F15 |
|---|---|---|---|
| **0.5** | 19.42±0.24 | 14.25±0.64 | 11.62±0.57 |
| **1** | 27.06±0.85 | 25.38±1.54 | 19.56±0.42 |
| **2** | 40.68±0.93 | 37.09±1.65 | 31.86±1.36 |
| **3** | 54.27±1.29 | 51.93±1.69 | 44.35±1.54 |
| **4** | 66.82±1.48 | 62.15±1.99 | 51.84±0.79 |
| **6** | 80.72±1.79 | 73.88±2.01 | 59.43±1.46 |
| **8** | 88.25±1.88 | 81.09±2.92 | 68.24±0.27 |
| **10** | 95.17±2.38 | 88.04±2.48 | 76.82±1.04 |
| **12** | - | 99.21±2.59 | 87.43±1.96 |

**Table 7: Drug Release Kinetics of Optimized (F14) Matrix Tablets**

| Zero order | | First order | | Higuchi | | Hixson-Crowell | | Korsmeyer-Peppas | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $r^2$ | $K_0(h^{-1})$ | $r^2$ | $K_1(h^-)$ | $r^2$ | $K_H(h^{-1/2})$ | $r^2$ | $K_{HC}(h^{-1/3})$ | $r^2$ | N | $K_{KP}(h^{-n})$ |
| 0 .898 | 5.881 | 0.995 | 0.201 | 0.966 | 27.839 | 0.980 | 0.1997 | 0.974 | 0.66 | 0.3238 |

$r^2$ = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

**Table 8: Swelling and Erosion Study of Optimized Formulation (F14)**

| Time (hours) | % Swelling | % Erosion |
|---|---|---|
| 1 | 76.43 | 18.72 |
| 2 | 128.35 | 24.37 |
| 3 | 84.57 | 28.73 |
| 4 | 71.94 | 42.62 |
| 6 | 60.64 | 56.83 |
| 8 | 49.53 | 64.52 |
| 10 | 36.72 | 72.41 |
| 12 | 24.83 | 93.29 |

***In vitro* Drug Release Studies**

**Drug Release from HPMC K4M and K15M Matrices:**

Results for the drug release from HPMC matrices showed in Table 3 & 4 and Figure 1 & 2. Formulations containing HPMC (F1 to F8) have shown initial burst release and extended the release for 8 to 12h. Among these formulations F8 showed good dissolution profile (98.77% at 12h).

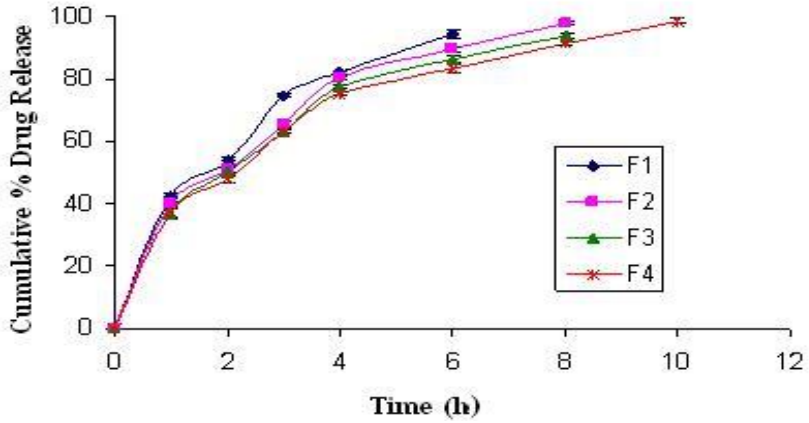


**Figure 1: Release Profiles of Isradipine from HPMC K4M Matrices**

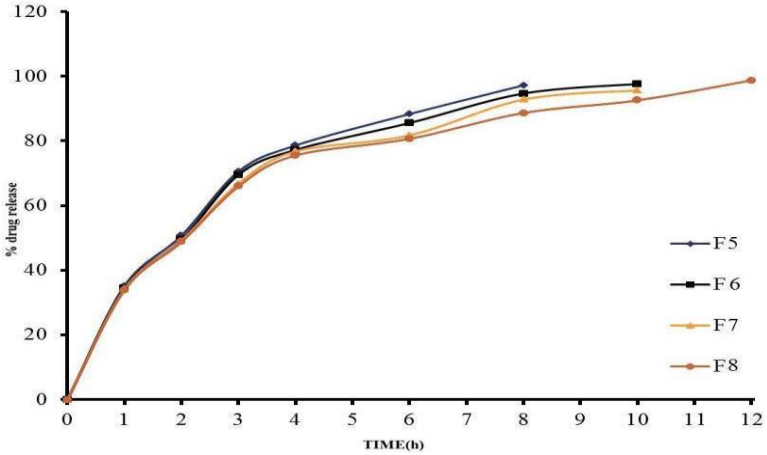


**Figure 2: Release Profiles of Isradipine from HPMC K15M Matrices**

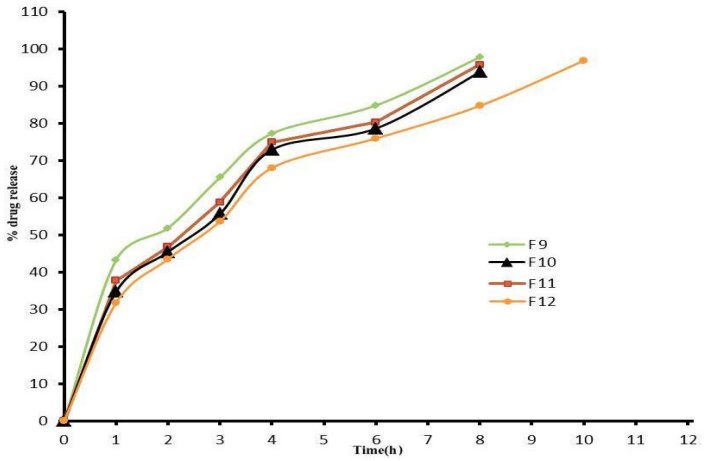


**Figure 3 : Release Profiles of Isradipine from Ethyl Cellulose Matrices**

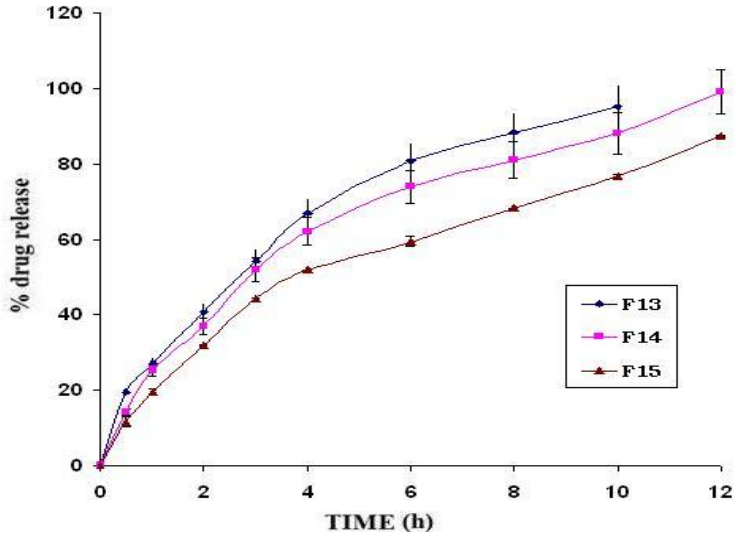


**Figure 4: Release Profiles of Isradipine from HPMC K15M and EC Matrices**

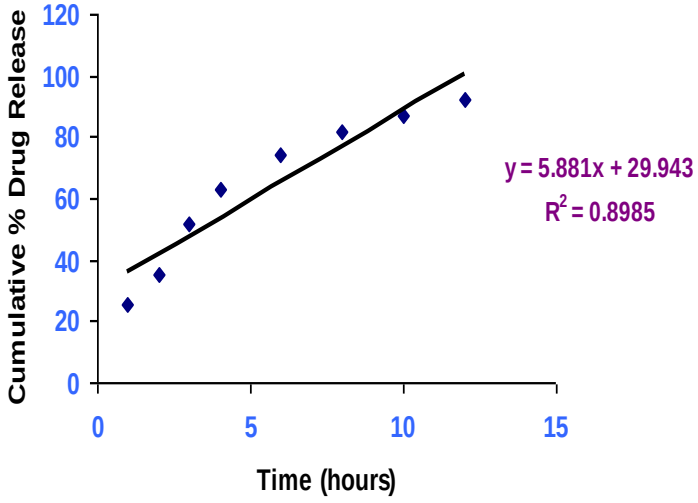


**Figure 5: Zero Order Graph of Optimized Formulation (F14)**

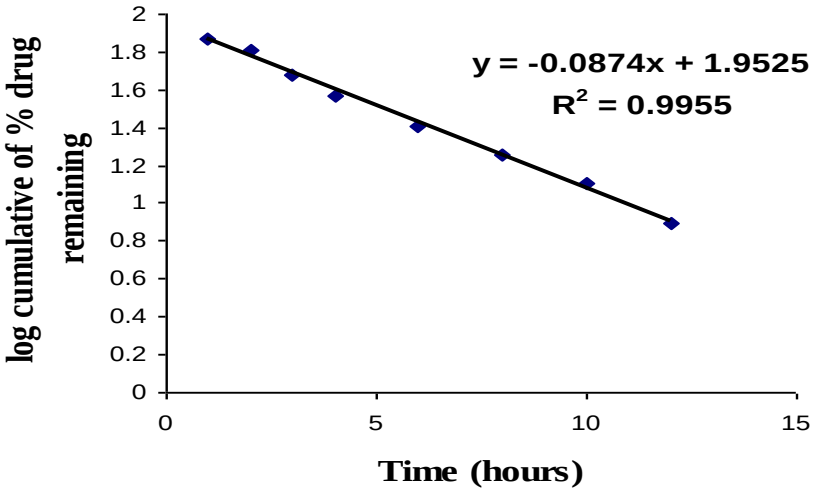


**Figure 6: First Order Graph of Optimized Formulation (F14)**

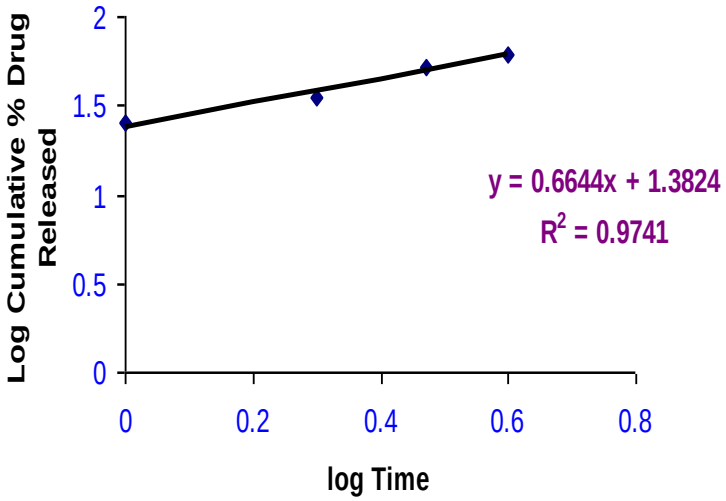


**Figure 7: Higuchi Plot of Optimized Formulation (F14)**

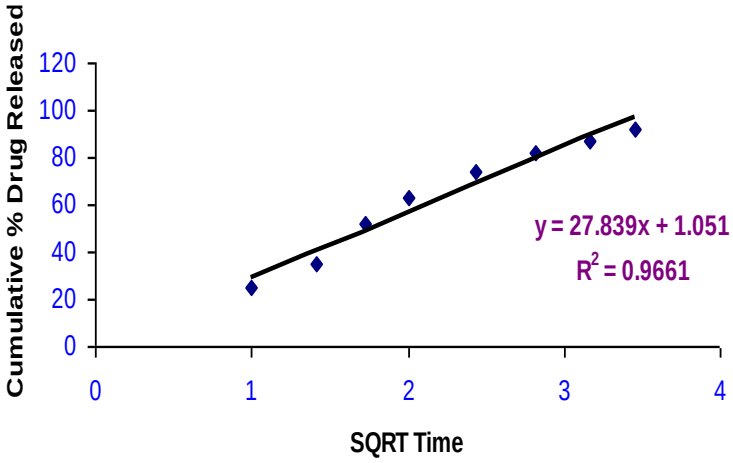


**Figure 8: Korsmeyer-Peppas Graph of Optimized Formulation (F14)**

**Drug Release from Ethyl Cellulose Matrices:** Batches containing ethyl cellulose (F9 to F12) as release retardant extended the release up to 12 h with initial burst release. As drug polymer ratio increased, the release rate was decreased. During dissolution the erosion was observed. The results were shown in Table 5 and Figure 3.

**Drug Release from Combination of HPMC K100M and Ethyl Cellulose Matrices:**

Formulations containing combination of HPMC K15M and ethyl cellulose (F13 to F15) have shown better release profiles as represented in Table 6 and Figure 4. There was no burst release observed with these formulations and release was extended up to 12 h. Formulation F14 was found to be optimum, as it shown desired drug release profile due to combination of both hydrophilic and hydrophobic polymers in the optimum ratio.

**Kinetic analysis of dissolution data**

The release rate kinetic data for the F14 is shown in Table 7. As shown in Figures 5-9, drug release data was best explained by first order equation, as the plots showed the highest linearity ($r^2$ = 0.9955), followed by Hixson-Crowell ($r^2$ = 0.9800) and Higuchi's equation ($r^2$ = 0.9661). As the drug release was best fitted in first order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. The applicability of the formulation to the Hixson-Crowell cube root law indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

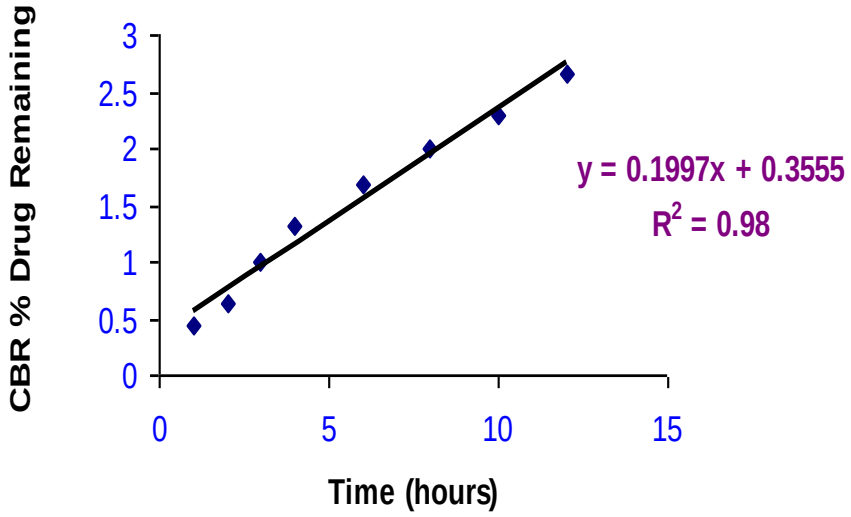


**Figure 9: Hixson-Crowell Plot of Optimized Formulation (F14)**

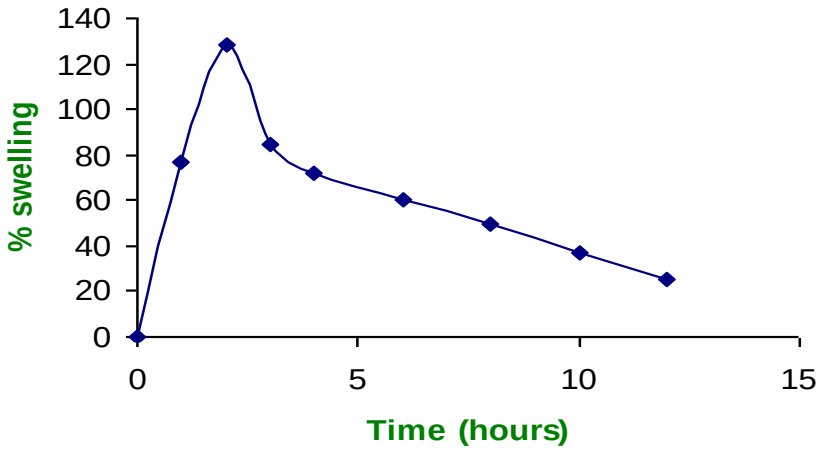


**Figure10: Swelling Study of Optimized Formulation (F14)**

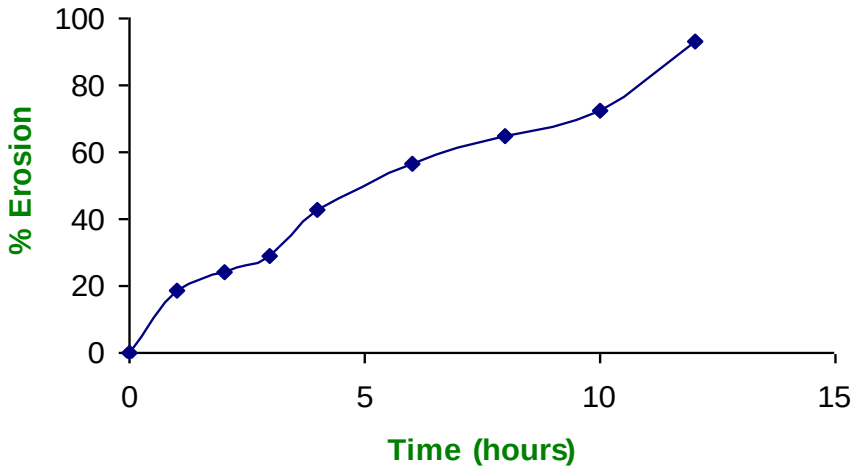


**Figure 11: Erosion Study of Optimized Formulation (F14)**

**Mechanism of drug release:**

As shown in Figure 9, the corresponding plot (log cumulative percent drug release vs time) for the Korsmeyer-Peppas equation indicated a good linearity ($r^2$ = 0.9741). The diffusion exponent n was 0.66, which appears to indicate a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and may indicate that the drug release was controlled by more than one process.

**Determination of swelling and eroding behaviour**

Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets were determined. Simultaneously with the swelling study, the percentage erosion of polymer was determined. The percentage swelling and erosion of optimized tablet was shown in Figures 10 & 11, and data was given in Table 8. Maximum swelling was observed in first 2 h and gradually it was decreased with simultaneous erosion of polymer.

## CONCLUSION

The present study was investigated to formulate Isradipine sustained release with addition of release retarding polymer HPMC, Ethyl cellulose and combination. Due to its short half-life of Isradipine, this drug will be a suitable candidate to formulate into sustained release dosage forms. From the *in vitro* drug release studies, F14 was found to be the best formulation and sustained the drug release for 12 h. The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the n value of 0.66 in Korsmeyer's plot. There was an alteration in the surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time, as indicated in Hixson-Crowell plot. Sustained release dosage form of Isradipine can provide better patient compliance and prolonged drug release. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans.

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***Corresponding Author:**
***Meghana Vemuri****
*Email:* **meghana.729@gmail.com**