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# DESIGN AND *IN-VITRO* EVALUATION OF INDAPAMIDE SUSTAINED RELEASE TABLET USING METHOCEL K15 MCR AND METHOCEL K100M LVCR

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## ABSTRACT

Indapamide, a low-dose thiazide-type diuretic, is used for the treatment of essential hypertension. In this study, we developed an indapamide sustained release formulation using Methocel K15M CR and Methocel K100M LVCR, starch 1500, talc and magnesium stearate considering technical feasibility and performed a comparative study with the release pattern. The tablets showed sustained release curves at pH 6.8 phosphate buffer for up to 12 h. The granules showed satisfactory flow properties, compressibility index and drug content etc. All the tablets complied with pharmacopoeial specifications. The results of dissolution studies indicated that the formulations F-6 and F-8 could extend the drug release up to 12 h. The data obtained from the dissolution profiles were compared in the light of different kinetics models and the regression coefficients were also compared. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport, which was only dependent on the type and amount of polymer used. The drug release followed both diffusion and erosion mechanism in all cases. This study explored the optimum concentration and effect of polymer(s) on Indapamide release pattern from the tablet matrix for 12 h period.

**INTRODUCTION:** Indapamide, a thiazide-type diuretic, is a widely used antihypertensive agent. Numerous randomized controlled studies have shown its antihypertensive efficacy in the immediate-release (IR) formulation at the dosage of 2.5 mg/day.

In accordance with the current recommendations, a sustained- release (SR), low- dose formulation (Indapamide SR 1.5 mg) was developed with the objective of achieving an optimal efficacy/ acceptability ratio [1-7]. Indapamide free base is practically insoluble in water (0. 75 mg/L) and thus poorly absorbed from the gastro-intestinal tract. It exhibits poor absolute bioavailability of 30-40% [5].

Half life of Indapamide is 14-18 h [6]. It's very poor aqueous solubility indicates that its absorption is dissolution rate-limited which might result in irregular and delayed absorption. During the past 30 years, as expenses and complications involved in marketing new drug molecules have increased with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on the development of controlled release drug delivery systems (CRDDS). The goal in designing CRDDS is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action reducing the dose required or providing uniform drug delivery [13].

The use of controlled release (CR) formulations offers many potential advantages, such as sustained blood levels, attenuation of adverse effects and improved patient compliance. It is important especially in the case of antihypertensive agents to maintain constant blood levels, as otherwise dose dumping may cause hypertension.

The primary benefit of an SR preparation of indapamide is that a lower dosage is needed to maintain a uniform blood plasma concentration and therefore uniform clinical effect. This drug is challenging to formulate due to its low dose and the fact that this is practically insoluble in water. Indapamide SR 2.5 mg/day was well tolerated and demonstrated reduced blood pressure as effectively as therapeutic dosages of amlodipine, candesartan, enalapril, hydrochlorothiazide or indapamide.

In the present investigation, an attempt has been made to formulate Indapamide as sustained release tablet matrix with the addition of release retarding polymers and to evaluate the effect to sustain the release of Indapamide from tablet matrix. Methocel derivatives have been widely used in the design of complex controlled release systems because of their low toxicity and pH-independent swelling and drug embedding ability.[8] These polymers are hydrophilic in nature and can hold active ingredients firmly that depend on the concentration or ratio of polymers used [9].

Methocel K15M CR and K100 LVCR are two typically used Methocel polymers for the formulation of hydrophilic matrix systems, providing a robust mechanism for the slow release of drugs from oral solid dosage forms. They are suitable for preparing formulations with soluble or insoluble drugs and at high or low dosage levels. Hydration of polymers results in the formation of a gel layer that controls the release rate of drug from the core of matrix tablets [15].

The permeability of drug through Methocel K15M CR and/or K100 LVCR is independent of the pH of the digestive tract. Soluble drugs are released by the combination of diffusion and erosion mechanisms whereas erosion is the predominant mechanism for insoluble drugs.

As Methocel derivatives are highly hydrophilic in nature, the involvement of water or moist granulation can make the process highly problematic; therefore, a dry process that produces acceptable powder characteristics and does not intervene with drug release characteristics would be desirable.

**MATERIALS AND METHODS:** Methocel K15 MCR Methocel K100M LVCR, the modified HPMC, was purchased from Colorcon Ltd, India. Starch was procured from Colorcon Ltd. Magnesium stearate was obtained from Wilfrid Smith Ltd. UK. Indapamide was a generous gift from Incepta pharmaceuticals Ltd., Bangladesh. The solvents and reagents were of analytical grade.

**Preparation of Indapamide matrix tablets.** The formulations evaluated in this study have been listed (**Table 1**). Indapamide tablets were prepared by direct compression method. Indapamide and starch for each batch was pre-blended for 5 minutes. The Methocel K15 MCR Methocel, K100M LVCR, talc and magnesium stearate are measured and mixed together.

**TABLE 1: FORMULATION OF INDAPAMIDE**

| Formula | Indapamide (in mg) | HPMC K15M (in mg) | HPMC K100M (in mg) | Talc ( in mg) | Mg stearate (in mg) | Starch (in mg) |
|---|---|---|---|---|---|---|
| F1 | 1.5 | 50 | 40 | 3 | 3 | 99.5 |
| F2 | 1.5 | 50 | 30 | 3 | 3 | 112.5 |
| F3 | 1.5 | 50 | 20 | 3 | 3 | 122.5 |
| F4 | 1.5 | 40 | 40 | 3 | 3 | 112.5 |
| F5 | 1.5 | 40 | 30 | 3 | 3 | 122.5 |
| F6 | 1.5 | 40 | 20 | 3 | 3 | 132.5 |
| F7 | 1.5 | 30 | 40 | 3 | 3 | 122.5 |
| F8 | 1.5 | 30 | 30 | 3 | 3 | 132.5 |
| F9 | 1.5 | 30 | 20 | 3 | 3 | 143.5 |
| **Total = 200mg** | | | | | | |

* Percent ratios of Methocel K15M CR and K100 LVCR used were: i. 25%: 20%, ii. 25%: 15%, iii. 25%: 10%, iv. 20%: 20% v. 20%: 15% vi. 20%: 10%, vii. 15%: 20% viii. 15%: 15% ix. 15%: 10% of the total weight of the formulation

**Evaluation of Tablets:** The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a hardness tester (Monsanto tester, England). Friability of the tablets was determined by a friabilator (Roche Friability tester, Germany). The thickness of the tablets was measured with a Vernier Calliper. Weight variation test was performed according to an official method. Drug content for indapamide was carried out by measuring the peak area of standard and samples at 240 nm using HPLC method.

***In vitro* Dissolution Studies:** Dissolution testing was performed in a '' EUROLAB Model Dissolution Tester, Germany'' using USP Apparatus 2 (paddle method) at 100rpm. The dissolution medium was 900ml of 0.05M pH 6.8 phosphate buffers at 37.0 ± 0.5$^{o}$C. The amount of drug present was determined according to the USP monograph for Indapamide tablets using

**Physical Evaluation of Powders:** The powders were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity, and drug content etc (**table 2**).

**Bulk Density:** LBD (Loose Bulk Density) and *TBD* (Tapped Bulk Density) were determined by 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was placed into a 10-ml measuring cylinder.

After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The reading of tapping was continued until no further change in volume was noted. Using the following equation *LBD* and *TBD* was calculated:

LBD = Weight of the powder / volume of the packing.

TBD = Weight of the powder / Tapping volume of the packing.

**Compressibility index:** The compressibility index of the granules was determined by Carr's compressibility index:

Carr's index (%) = {(*TBD* – *LBD*) X 100}/*TBD*

**Total Porosity.** Total porosity was determined by measuring the volume occupied by a selected weight of powder (*Vbulk*) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space (*V*) :

Porosity (%) = *Vbulk* – *V/V bulk* × 100

**Drug Content.** Five tablets were weighed individually, and the drug was extracted with diluents. The solution was filtered through 0.45-µ membrane filter paper. The absorbance was measured at 275 nm after suitable dilution.

**TABLE 2: EVALUATION OF FORMULATION**

| Formulation | Loose bulk density (LBD) gm/ml | Tapped bulk density (TBD) gm/ml | Carr's index (%) | Hausner's ratio | Total porosity (%) | Moisture content (%) |
|---|---|---|---|---|---|---|
| F-1 | 0.38±0.02 | 0.52±0.03 | 26.92±.01 | 1.13±0.2 | 14.30±.01 | 2.44 |
| F-2 | 0.40±0.03 | 0.51±0.03 | 21.56±.02 | 1.23±.02 | 16.40±.02 | 2.45 |
| F-3 | 0.47±0.02 | 0.48±0.02 | 20.30±.01 | 1.01±.01 | 13.40±.01 | 1.43 |
| F-4 | 0.40±0.01 | 0.52±0.03 | 19.40±.01 | 1.05±.02 | 12.40±.02 | 1.83 |
| F-5 | 0.42±0.02 | 0.51±0.01 | 21.40±.03 | 1.14±.01 | 16.30±.03 | 1.92 |
| F-6 | 0.46±0.02 | 0.50±0.02 | 19.70±.02 | 1.15±.03 | 15.30±.02 | 3.43 |
| F-7 | 0.38±0.06 | 0.51±0.06 | 18.90±.02 | 1.21±.05 | 14.30±.03 | 2.93 |
| F-8 | 0.36±0.03 | 0-52±0.02 | 19.50±.01 | 1.09±.04 | 13.60±.01 | 1.93 |
| F-9 | 0.41±0.02 | 0.51±0.01 | 21.50±.02 | 1.21±.05 | 13.90±.02 | 2.00 |

**Physical evaluation of Indapamide Matrix Tablet:** The prepared tablets were subjected to thickness, weight variation test, hardness, friability, and drug content.

***In vitro* Dissolution Study:** The release study was carried out for 12 h using USP 2 paddle type dissolution apparatus. For dissolution medium gastric medium (pH 1.5) was required.

a) **Preparation of gastric medium (0.1 N HCl pH 1.5)**: For 0.1N HCl, 8.5 ml of Hydrochloric acid (37% v/v) was diluted with sufficient water to produce 1000 ml.

b) **Preparation of buffer medium (pH 6.8):** For pH 6.8 we had to use di sodium hydrogen phosphate with sufficient NaCl or phosphoric acid to adjust.

**Stability Studies:**

**Preparation of Standard Solution:** The standard stock of Indapamide (16ppm) was prepared by dissolving 32 mg of working standard in Methanol in 200 mL volumetric flask After sonication for 2 min and volume was made up to the mark with methanol. 5 mL aliquot from the standard stock solution of Indapamide was transferred in 50 mL volumetric flask, and the volume was made up to the mark with diluent.

**Sample Preparation:** Twenty tablets were weighed, their mean weight was determined, and they were crushed in a mortar. An amount of powdered mass Indapamide equivalent to 7.5 mg weighed. separate the Indapamide Tablets equivalent to 7.5 mg then add 10 ml solution of stock solution then add 40 ml methanol sonicate 30 min and make up to mark with diluent in 250ml volumetric flask.

**Stress Degradation Studies:**

- **Acid degradation**: Treated with 5ml 5 N HCl and heated on boiling water bath for 2 h then cool at room temperature after that add 5ml 5 N NaOH for neutralize the solution.

- **Alkali degradation**: Treated with 5ml 5 N NaOH and heated on boiling water bath for 2 h then cool at room temperature after that add 5ml 5 N HCl for neutralize the solution.

**Stability Procedure:** RP-HPLC method for monitoring of the photochemical stability of Indapamide, An isocratic HPLC chromatographic condition was described for determination of Indapamide in presence of its degradation products. As the method could effectively separate the drug from its degradation products, it can be used as a stability-indicating one. The chromatographic separation was achieved on Amzone C18, 150 mm × 4.6 mm column. The mobile phase consisted of a mixture of Buffer: Acetonitrile: Methanol (45:25:30), (Buffer Solution**:** 6 g of Potassium dihydrogen phosphate was accurately weighed an dissolved in 1000 mL of Milli Q water added 2ml Triethaylamine then adjusting pH 3 with Ortho phosphoric acid ). UV detection was performed at 285 nm with flow rate of 1 mL/min. The method was validated for linearity, precision, robustness, LOD, LOQ, specificity, accuracy and all this parameters found to be satisfactory. Indapamide was exposed to day light and the presence of degradation products was observed. The drug was subjected to acid hydrolysis, base hydrolysis, oxidation, dry heat, and photolysis to apply stress conditions.

There were no other co eluting, interfering peaks from excipients, impurities, or degradation products due to variable stress conditions, and the method was specific for determination of perindopril and indapamide in the presence of degradation products.

The method was validated in terms of linearity, precision, accuracy, specificity, robustness, and solution stability. The linearity of the proposed method was investigated in the range of 7.5-17.5 µg/mL ($r^2$ = 0.9992) for indapamide.

Degradation products produced as a result of stress studies did not interfere with the detection of indapamide, and the assay can thus be considered stability indicating.

**Data analysis.** To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$C = kot$ …….. …… (1)

Where, K0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$LogC0 - LogC = kt / 2.303$ …… (2)

Where, C0 is the initial concentration of drug and K is first order constant.

$Q = Kt^{t1/2}$ ..... (3)

Where, K is the constant reflecting the design variables of the system.

$Q_0^{1/3} - Qt^{1/3} = K_{HC}\, t$..... (4)

Where, Qt is the amount of drug released in time t, $Q_0$ is the initial amount of the drug in tablet and $K_{HC}$ is the rate constant for Hixson-Crowell rate equation.

The following plots were made: Cumulative *%* drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) log cumulative % drug release vs. log time (korsmeyer model) and cube root of drug % remaining in matrix vs. time (Hixson-crowell cube root law).

**Mechanism of Drug Release:** Korsmeyer *et al.,* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$Mt / M\infty = Kt\, n$ ..... (5)

Where, $Mt / M\infty$ is the fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in the following table for cylindrical shaped matrices: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n) Overall solute diffusion mechanism

0.45 Fickian diffusion

0.45 < n < 0.89 Anomalous (non-Fickian) diffusion

0.89 Case-II transport

n > 0.89 Super case-II transport

**RESULTS:** The purpose of the present study is to develop and characterize the extended release matrix tablets of indapamide. Tablets were prepared by direct compression method. Methocel K15M CR & Methocel K100 LVCR polymers were used as rate retarding agents in nine formulations (F1-F9).

The granules were evaluated for angle of repose (26.78±.01 to 29.25±0.03), loose bulk density (0.39±0.02 to 0.52±0.03 g/ml), moisture content (<4.0%), Carr's index (18.66% - 26.47%), total porosity (12.7±0.04 – 16.3± 0.03)% and weight variation /assay (1.35- 1.65 mg/tablet).

The tablets are subjected to average weight (198 – 210 mg), weight variation test, hardness (4.10-4.6 kg-cm), friability (0.9 to 0.03) and *in vitro* dissolution studies. The granules showed satisfactory flow properties, compressibility and drug content. All the properties were compiled with pharmacopoeial specifications for test parameters. The dissolution study was carried out for 12 h using USP paddle method in both acidic and buffer media (**Table 3**).

**TABLE 3: % RELEASE OF FORMULATIONS**

| Time | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 13.62 | 12.03 | 14.6 | 12.25 | 11.2 | 15.2 | 12.2 | 14.08 | 15.3 |
| 4 | 43.3 | 40.5 | 40.6 | 43.3 | 39.6 | 40.1 | 38.2 | 38 | 45.12 |
| 6 | 43.5 | 44 | 39.25 | 44 | 44 | 44.1 | 40.1 | 46.13 | 55.12 |
| 8 | 45 | 48 | 49.5 | 51.2 | 46 | 49 | 44 | 57.6 | 57.6 |
| 12 | 65 | 65 | 60.75 | 75.15 | 66.8 | 61.5 | 68 | 64 | 64.78 |

**DISCUSSION:** The release mechanism are explained by zero, first order, higuchi, korsmeyer –peppas and hixon-crowell method.Primarily nine formulations were prepared by using the variation amount of two polymers, Methocel K15M, Methocel K100LV CR in a ratio of F1(25%, 20%), F2(25%, 15%) F3(25%, 10%) F4(20%, 20%) F5(20%, 15%) F6 (20%, 10%) F7(15%,20%) F8(15%, 15%) F9(15%, 10%). The tested formulations were shown the non-Fickian mechanism. Among the formulation, F-6 and F-8 exhibited BP specification where diluents was starch 1500. In this study, the percentage friability for all the formulations was below 1%, indicating that the friability was within the official limits.

All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability. Except the proposed formulation F-7 (using 15% Methocel K15M and 20% Methocel K100M) all formulations fails to exhibit official drug release (Table 3) than other formulations for 12 h period. This polymer has been well known to retard the drug release by swelling in aqueous media. A polymer's ability to retard the drug release rate is related to its viscosity. However, processing factors including particle size, hardness, porosity and compressibility index etc. Also affect the release rate of drug from tablets. The hydration rate of HPMC depends on the nature of the substituent like hydroxypropyl group content. Hence, Methocel was used because it forms a strong viscous gel in contact with aqueous media, which may be useful in controlled delivery of drugs. The drug release data obtained were extrapolated by Zero order, Higuchi, First order, Korsmeyer-Peppas and Hixson-Crowell equations to know the mechanism of drug release from these formulations (**Table 4**).

**TABLE 4: INTERPRETATION OF RELEASE RATE CONSTANTS AND R-SQUARE VALUES FOR DIFFERENT RELEASE KINETICS OF F-1 TO F-9:**

| Formulation | Zero order | | Higuchi | | Korsmeyer-Peppas | | Hixson- Crowell | |
|---|---|---|---|---|---|---|---|---|
| | $K_0$ | $R^2$ | $K_h$ | $R^2$ | n | $R^2$ | $K_{hc}$ | $R^2$ |
| F1 | 7.607 | 0.87 | -3.01 | 0.92 | 0.79 | 0.84 | 4.46 | 0.85 |
| F2 | 6.54 | 0.93 | -4.10 | 0.94 | 0.86 | 0.86 | 4.51 | 0.91 |
| F3 | 8.42 | 0.87 | -2.63 | 0.95 | 0.75 | 0.87 | 4.45 | 0.88 |
| F4 | 5.18 | 0.93 | -6.09 | 0.92 | 0.93 | 0.88 | 4.46 | 0.92 |
| F5 | 5.61 | 0.91 | -4.90 | 0.93 | 0.87 | 0.87 | 4.54 | 0.92 |
| F6 | 8.34 | 0.96 | -2.40 | 0.96 | 0.75 | 0.92 | 4.43 | 0.92 |
| F7 | 5.34 | o.92 | -5.17 | 0.92 | 0.87 | 0.89 | 4.58 | 0.91 |
| F8 | 7.29 | 0.90 | -4.09 | 0.95 | 0.83 | 0.91 | 4.47 | 0.92 |
| F9 | 10.54 | 0.82 | -2.17 | 0.93 | 0.79 | 0.83 | 4.33 | 0.79 |

$k_0$ = zero-order rate constant; $k_H$ = Higuchi rate constant; $R^2$ = Correlation coefficient

In this experiment, the *in vitro* release profiles of drug from all these formulations could be best expressed by Higuchi's equation, as the plots showed highest linearity ( $R^2$= 0.97 to 0.99). To confirm the diffusion mechanism, the data were fitted into comparatively high slope (n) values of >0.6, which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion. Hence, diffusion coupled with erosion might be the mechanism for the drug release from Methocel based matrix tablet (**fig. 1-3**).

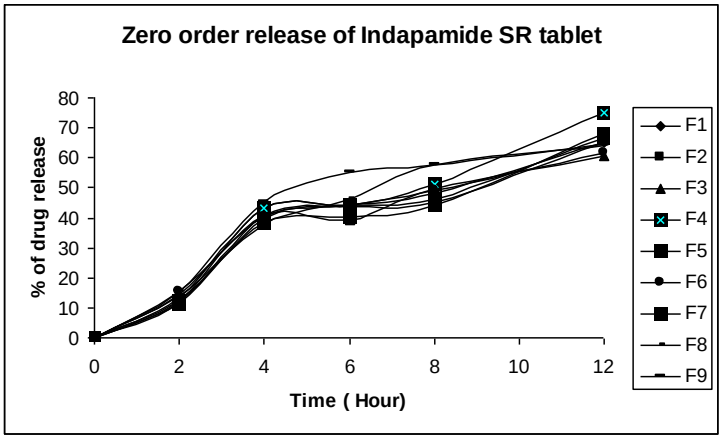


**FIGURE 1: ZERO ORDER RELEASE PROFILE OF FORMULATIONS**

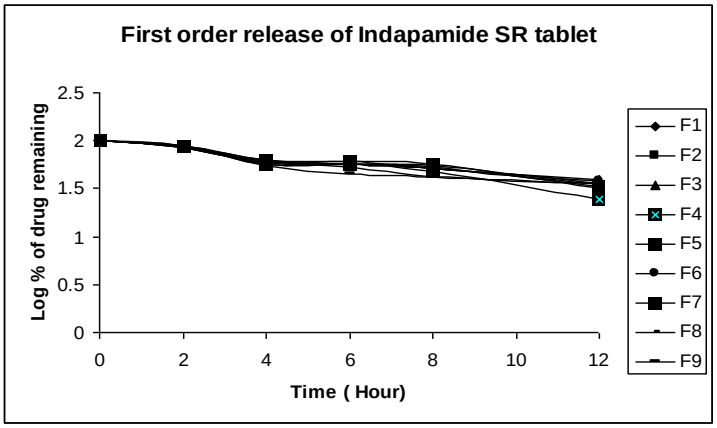


**FIGURE 2: FIRST ORDER RELEASE PROFILE OF FORMULATIONS**

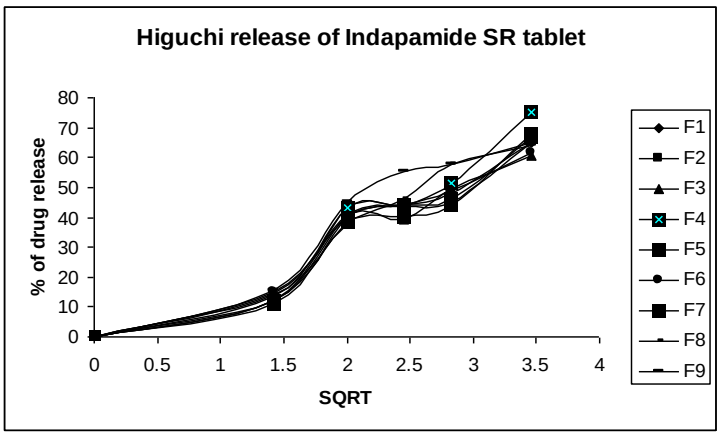


**FIGURE 3: HIGUCHI RELEASE PROFILE OF FORMULATIONS**

**CONCLUSION:** The experiment revealed that Methocel K15M CR and Methocel K100 LVCR in varying proportions control the Indapamide release effectively for 12 h; hence the formulations can be considered as a once daily sustained release tablet of Indapamide which was comparable to theoretical release profile. In most cases the release kinetics of Indapamide from the matrix tablets appeared to follow Higuchi and Korsmeyer-Peppas equation which indicated that the drug was released from the matrix tablets predominantly by diffusion. Further study on the Indapamide sustained release is required to obtain *in vivo* data of these formulations. The optimized formulations (F-7) may be used for the development of Indapamide sustained release tablet for commercial production in order to combat against essential hypertension and mild-to-severe chronic heart failure.

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