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# Formulation and evaluation of almotriptan controlled release pellets

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## ABSTRACT

The aim of the present study was to formulate and evaluate Almotriptan pellets. Almotriptan controlled release pellets were prepared by Solution layering technique by using croscarmellose and povidone in former case and three different polymers HPMC K 100, Ethyl cellulose and Eudragit RS 100 as rate controlling polymer in three different ratios like 1:1, 1:1.5 and 1:2 to achieve desired release in later case. Evaluation was performed according to the Pharmacopoeia standards including Drug excipients compatibility, Percentage yield, Particle size distribution, Drug content analysis and *in-vitro* release study. The best results were found to be using Almotriptan and Eudragit RS 100 in 1:2 ratios. A broad variety of drug release pattern could be achieved by variation of polymers ratios which was optimized to match the target release profile. In comparison of *in-vitro* release studies for different controlled release formulations, F9 releases 98.54% of drug at the end of 12$^{th}$ hour and was considered as best formulation. Stability study has shown no significant change in the drug content analysis and *in-vitro* dissolution study of best formulation even after 6 months.

**Keywords:** Almotriptan, Controlled release, Dissolution profile, *in-vitro* drug release, Stability studies.

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## INTRODUCTION

Pelletization can be defined as an agglomeration (size-enlargement) process that converts fine powders or particles of bulk drugs and excipients into small, free-flowing, more or less spherical units, and called pellets [1]. Granulation is also known as pelletization, agglomeration or spheronization, and the units obtained referred to as granules, pellets, agglomerates or spheroids [2]. The general terms "granulation" and "pelletization" sometimes used synonymously and no clear distinction is made between them. Generally, if a size-enlargement process produces agglomerates of a size distribution within the range of 0.1 to 2.0 mm and a high porosity (about 20-50%), the process may be called "granulation", and the resulting agglomerates are called granulates [3]. Pelletization is often referred to as a size-enlargement process that involves the manufacture of agglomerates with a relatively narrow size range, usually with mean size from 0.5 to 2.0 mm, named pellets [4]. Pellets have free-flowing properties and a low porosity (about 10 %). The term "spheronization" is more specific, usually associated with spherical units formed by a size-enlargement process that includes a spheronization step where extrudates or agglomerates are rounded as they tumble on a rotating frictional base plate, being named spheroids [5]. The objective of the present work includes To maintain the effective drug concentration levels in the blood for a longer time, patient compliance by reducing dosing frequency, To minimize side effects by maintaining the plasma drug concentration at the same level within a therapeutic range for the required period [6].

## MATERIALS & METHODS

The Almotriptan was purchased from Orchid Pvt Ltd, Chennai, Excipients like Hydroxy Propyl Methyl Cellulose K100 was procured from Himedia Laboratories Pvt. Ltd. Mumbai, Eudragit RS 100, Ethyl cellulose, Titanium Dioxide, Isopropyl Alcohol, PVP K-30 was procured from S.D. Fine Chem. Ltd. Mumbai. All other reagents used were of analytical grade.

### Methodology

**Drug-excipients compatibility studies by using FTIR:** FTIR spectra were recorded with a Thermo Nicolet Japan, in the range 450-4000 cm−1 using a resolution of 4 cm−1 and

16 scans [7]. Samples were diluted with KBr mixing Powder and pressed to obtain self-supporting disks. Liquid samples formulations were analyzed to form a thin liquid film between two KBr disks.

**Formulation of Pellets**

**Seal coating:** Non-parcel seeds (sugar pellets) (#22/#24) were procured from Aadhya Biotech Pvt Ltd. Due to high solubility, the sugar spheres immediately get dissolved in aqueous media without build-up of sufficient osmotic pressure in the core [8]. In order, to retard the dissolution rate of non-parcel seeds initially coated with 2% (w/w) HPMC E5 as a seal coat.

**Coating Procedure of Controlled Release Pellets:** Slurry of Almotriptan with 6% Croscarmellose sodium, 1% povidone K-30 (w/w) and add 0.01% tween 80 were dissolved in 100ml acetone. The seal coated sugar pellets (Non-parcel seeds) (#22/#24) was preheated to about 35° C with gentle movement in a pan coater, and then sprayed prepared slurry coating % weight build up 30% w/w on sugar pellets while spraying the drug solution pan were allowed to rotate for about 10 mins until uniform drug loading occurs [9]. Spray rate, inlet air temperature were adjusted in such a way that the core bed reaches a temperature of about 35° C. Over wetting of the cores is to be avoided as it may cause agglomeration. After a complete quantity of the drug loading solution was consumed. The pellets were dried in a tray drier at about 45° C to a moisture content of <2%. The dried pellets were sized on a sifter to remove agglomerates, broken pellets and fine powder.

**Preparation of Coating solution:** Almotriptan and HPMC K 100, Ethyl Cellulose and Eudragit RS 100 were taken in 4 different ratios 1:1, 1:1.5, and 1:2 as per the table 01 were dissolved in 1:1 ratio of methanol and dichloromethane, Ethanol and Acetone and Acetone respectively [10]. Finally, added 0.1% Tween 80 and 0.5% PEG 400. The composition of the coating solution is coded with C1, C2, C3, C4, C5, C6, C7, C8, and C9. The solutions were filtered through nylon cloth and taken into the spray gun.

**Table 1: Composition of Coating Solution**

| Coating Batches | Drug: Polymer Ratio | Percentage of Coating (%) | Polymers used |
|---|---|---|---|
| F1 | 1:1 | 31 | HPMC K-100 |
| F2 | 1:1.5 | 32 | |
| F3 | 1:2 | 33 | |
| F4 | 1:1 | 31 | Ethyl Cellulose |
| F5 | 1:1.5 | 32 | |
| F6 | 1:2 | 33 | |
| F7 | 1:1 | 31 | Eudragit RS 100 |
| F8 | 1:1.5 | 32 | |
| F9 | 1:2 | 33 | |

**Coating Procedure:** Initially, Seal coated sugar pellets (Non-parcel seeds) (#22/#24) were taken and preheated to about 35°C with gentle movement in a pan coater, and then sprayed prepared Almotriptan, HPMC K 100, Ethyl Cellulose and Eudragit RS 100 of 4 different ratios 1:1, 1:1.5 and 1:2 on sugar pellets coating % weight buildup for 28%, 29%, 30% respectively, while spraying the solution pan were allowed to rotate until uniform drug, and polymer loading occurs [11].

**Table 2: Optimized Process variables for different stages of coating**

| Process Variables | Specifications |
|---|---|
| Inlet air temperature (°C) | 38-42 |
| Product bed temperature (°C) | 33-37 |
| Atomization air pressure (bar) | 1.2-1.5 |
| Spray rate (g/min) | 10-15 |
| Pan speed (rpm) | 10-15 |

**Evaluation studies**

**Percentage yield:** All the batches of controlled release Almotriptan pellets prepared by pan coating evaluated for percentage yield of the pellets [12]. The actual percentage yields of pellets calculated by using the following formula. The % yields of various batches of pellets.

$$\text{Percentage yield of pellets} = \frac{\text{The practical yield of pellets}}{\text{The theoretical yield of pellets}} \times 100$$

**Particle size distribution by sieve analysis:** Sieve analysis was done by using electromagnetic sieve shaker. A quantity of 25 g of pellets was taken on the top sieve, close with a plate and run the apparatus with 20 watts power for about 20 min. After that sieves were weighed and calculated the percentage of material remaining on each sieve [13]. The average particle sizes of the pellets analyzed by simple sieve analysis method. The particle sizes of the various batches of pellets.

**Drug Content Analysis:** Drug content of pellets were determined by U.V spectrophotometer, pellets containing 40 mg equivalent of the drug transferred to a 100ml volumetric flask containing pH 7.4 phosphate buffers. For ensuring complete solubility sonication done for 30 mins filtered through Whatman filter paper [14]. The filtrate was analyzed by U.V spectrophotometer after appropriate dilution at 227 nm. The drug content analyses of various batches of pellets.

***In-vitro* drug release study:** Almotriptan 40mg equivalent weight of controlled release (30 mg) pellets were filled in '0' size hard gelatin capsule by hand filling capsule Machine and drug release studies were carried out for each formulation by using Dissolution test apparatus Type I. The data obtained from the *in-vitro* dissolution studies were subjected for kinetic treatment to obtain the order of release and the best fit model [15]. The *in-vitro* studies of various batches of pellets.

**Pharmacokinetics of Drug Release Mechanism**

The results of *in-vitro* release profile obtained for all formulations were plotted in modes of data treatment as follows:

**Zero-order kinetics**: The pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change [16] and no equilibrium conditions are obtained can be represented by the following equation. $Q_t = Q_o + K_o t$

**First order kinetics:** To study the first order release

kinetics the release rate data were fitted to the following equation: Log $Q_t$ = log $Q_o$ + K t / 2.303

**Higuchi model:** Higuchi developed several theoretical models to study the release of water-soluble and low soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions obtained for [17] drug particles dispersed in a uniform matrix behaving as the diffusion media, the equation is $Q_t = K_H . t_{1/2}$

**Korsmeyer and Peppas Release model:** To study this model, the release rate data fitted to the following equation F = $M_t$ / M = K.$t_n$

**Stability study:** The ICH guidelines for evaluation of stability data describe when and how extrapolation should consider while proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by available data from the stability under the long-term storage condition [18].

## RESULTS AND DISCUSSION

### Compatibility studies

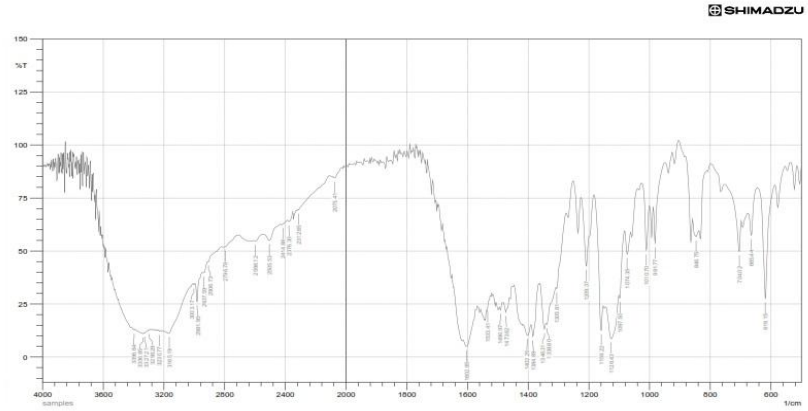


**Figure 1: FTIR spectra of Almotriptan**

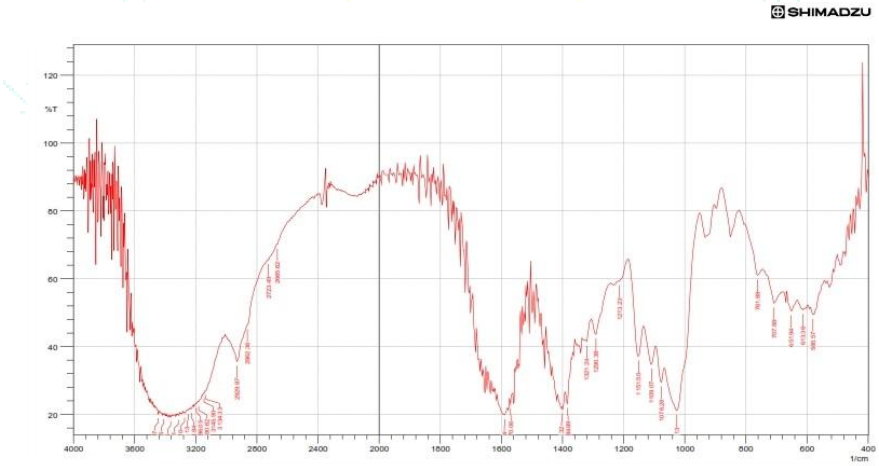


**Figure 2: FTIR spectra of Mixture of compound**

**Table 3: Interpretation data of FTIR spectra of Drug and Excipients**

| Almotriptan | | | |
|---|---|---|---|
| S. No. | Interpretation | IR absorption bands ($cm^{-1}$) | |
| | | Characteristic peak | Observed peak |
| 1. | (s)= C-H bend | 1000-650 | 666, 685 |
| 2. | (s)C-O stretch | 1320-1000 | 1017 |
| 3. | (m) C-C stretch (in-ring) | 1500-1400 | 1413 |
| Mixture of compound | | | |
| 1. | (s)= C-H bend | 1000-650 | 794 |
| 2. | (s, b) N-H wag | 910-665 | 823 |
| 3. | (m) C-N stretch | 1250-1020 | 1154 |
| 4. | (m) C-C stretch (in-ring) | 1500-1400 | 1496 |
| 5. | (m) C-H bend | 1470-1450 | 1434 |
| 6. | (m) N-H bend | 1650-1580 | 1595, 1626 |

**Evaluation Studies**

**Percentage yield of pellets:** The percentage yields of Almotriptan pellets calculated. The percentage yields of Almotriptan pellets of controlled release formulations F1 to F9 was found to be in the range of 83.12% to 94.97% as shown in table 04.

**Drug Content:** Percentage drug content of Almotriptan pellets of controlled release F1-F9 of all formulations determined by UV spectrometric method. The Drug content Analysis of controlled release formulations F1 to F9 was found to be in the range of 89.44 ± 0.8 % to 99.90 ± 0.3 %. The drug content analysis of pellets was found to be within the limits as per IP were shown in table 05.

**Sieve Analysis Method**

**Table 4: Particle Size distribution data of Almotriptan Pellets**

| Formulation Code | Nominal mesh Aperture size (µm) | % Wt. of Pellets Retained | Cumulative % of Pellets Retained |
|---|---|---|---|
| F1 | 1000 | 0 | 0 |
| | 850 | 9 | 9 |
| | 710 | 83.5 | 92.5 |
| | 355 | 7 | 99.5 |
| F2 | 1000 | 0 | 0 |
| | 850 | 8 | 8 |
| | 710 | 81 | 89 |
| | 355 | 9 | 98 |
| F3 | 1000 | 0 | 0 |
| | 850 | 8 | 8 |
| | 710 | 87 | 95 |
| | 355 | 4 | 99 |
| F4 | 1000 | 0 | 0 |
| | 850 | 9 | 9 |
| | 710 | 85 | 94 |
| | 355 | 5 | 99 |
| F5 | 1000 | 0 | 0 |
| | 850 | 10 | 10 |
| | 710 | 83.5 | 93.5 |
| | 355 | 5 | 98.5 |
| F6 | 1000 | 0 | 0 |
| | 850 | 6 | 6 |
| | 710 | 85 | 91 |
| | 355 | 8 | 99 |
| F7 | 1000 | 0 | 0 |
| | 850 | 7 | 7 |
| | 710 | 84 | 91 |
| | 355 | 7.7 | 98.7 |
| F8 | 1000 | 0 | 0 |
| | 850 | 7 | 7 |
| | 710 | 86 | 93 |
| | 355 | 6 | 99 |
| F9 | 1000 | 0 | 0 |
| | 850 | 8 | 8 |
| | 710 | 87 | 87 |
| | 355 | 4 | 99 |

**Table 5: Yield of pellets and % Drug content Analysis data of prepared pellets**

| Formulation Code | Yield of Pellets | Drug content |
|---|---|---|
| F1 | 83.12 | 91.22 ± 0.5 |
| F2 | 87.26 | 95.19 ± 0.3 |
| F3 | 92.46 | 92.10 ± 0.6 |
| F4 | 87.12 | 89.44 ± 0.8 |
| F5 | 90.18 | 95.51 ± 0.8 |
| F6 | 91.71 | 91.20 ± 0.2 |
| F7 | 85.65 | 94.60 ± 0.3 |
| F8 | 90.56 | 92.81 ± 0.5 |
| F9 | 94.97 | 99.40 ± 0.3 |

Each value represents the mean ± standard deviation (n=3)

***In-vitro* Dissolution Study:** *In-vitro* release studies of all Formulations from F1 to F9 were compared, among all the formulations F9 shows best release rate with 98.23 % at the end of 12hrs in which contains drug and Eudragit RS 100 ratio 1:2 shown in table 06 & figure 03.

**Table 6: *In-vitro* Drug Release Data Almotriptan controlled release pellets**

| Time (Hrs) | Cumulative % Drug Release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 1 | 15.65 | 14.60 | 10.34 | 12.32 | 13.73 | 19.98 | 10.13 | 13.36 | 18.16 |
| 2 | 20.12 | 19.66 | 23.76 | 23.65 | 21.21 | 28.12 | 17.56 | 20.45 | 26.44 |
| 3 | 44.68 | 29.56 | 38.65 | 38.73 | 38.73 | 33.63 | 22.87 | 31.76 | 35.33 |
| 4 | 49.56 | 33.87 | 43.76 | 46.36 | 42.96 | 48.16 | 38.45 | 39.12 | 49.76 |
| 5 | 54.53 | 43.56 | 48.75 | 54.76 | 59.74 | 53.53 | 42.21 | 46.26 | 54.96 |
| 6 | 65.32 | 58.87 | 53.54 | 62.26 | 62.28 | 68.32 | 57.87 | 51.83 | 65.18 |
| 7 | 74.97 | 65.14 | 58.54 | 69.27 | 69.73 | 72.97 | 61.65 | 66.12 | 71.84 |
| 8 | 69.74 | 71.86 | 63.34 | 70.56 | 71.95 | 79.74 | 72.63 | 73.76 | 78.04 |
| 9 | 79.83 | 78.56 | 68.21 | 75.21 | 78.35 | 83.83 | 79.18 | 78.96 | 81.54 |
| 10 | 82.43 | 80.76 | 73.58 | 81.29 | 83.32 | 87.43 | 86.28 | 84.14 | 88.18 |
| 11 | 89.51 | 89.28 | 78.49 | 88.29 | 89.51 | 91.51 | 91.86 | 90.24 | 91.66 |
| 12 | 91.28 | 93.56 | 88.78 | 92.28 | 95.29 | 96.38 | 97.64 | 94.16 | 98.23 |

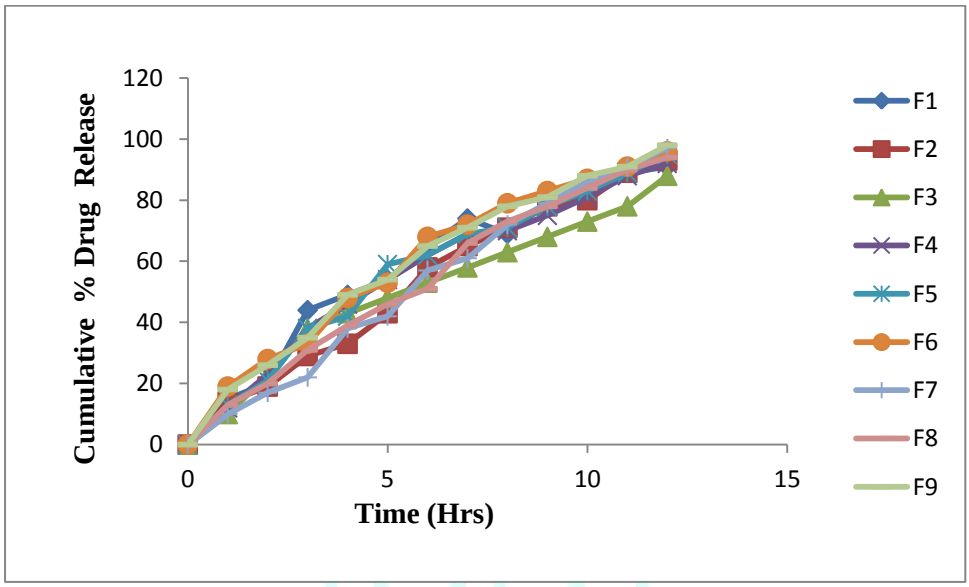


**Figure 3: *In-vitro* drug release Profiles of Formulations F1-F9**

**Kinetic Models Data Analysis:** The results of dissolution data fitted to various drug release kinetic equations like Zero order, First order, Higuchi model and Korsmeyer-Peppas. F1, F2, F3, F4, F5, F6, F7, F8, formulations were followed Korsemeyer-Peppas with correlation coefficient $R^2$= 0.9689, 0.9814, 0.9326, 0.9936, 0.971, 0.9576, 0.9781, 0.9613, 0.9684, 0.9575 and 0.9838 respectively. F9 formulation shown both Zero order and Korsmeyer-Peppas models with $R^2$=0.9929 and 0.989 respectively, and follows non-fiction mechanism and Zero order release with n= 0.957, remaining all formulations F1-F8 were found to follow anomalous diffusion mechanism with n= 0.5 to 1 when applied to Korsmeyer-Peppas kinetic model were tabulated in Table 7.

**Table 7: *In-vitro* drug release kinetics Correlation coefficient data and diffusion exponent data of F1-F9 formulations**

| Formulation code | Correlation Coefficient values ($R^2$) | | | | Diffusion Exponent value (n) |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi | Korsemeyer-Peppas | |
| F1 | 0.9668 | 0.9538 | 0.9765 | 0.9689 | 0.5443 |
| F2 | 0.9814 | 0.8997 | 0.9442 | 0.9331 | 0.596 |
| F3 | 0.9801 | 0.8562 | 0.9262 | 0.9326 | 0.6255 |
| F4 | 0.9526 | 0.961 | 0.9831 | 0.971 | 0.5051 |
| F5 | 0.9576 | 0.9509 | 0.9812 | 0.9726 | 0.5179 |
| F6 | 0.9713 | 0.9143 | 0.9775 | 0.9781 | 0.5596 |
| F7 | 0.989 | 0.9251 | 0.9664 | 0.9684 | 0.659 |
| F8 | 0.9915 | 0.9009 | 0.9529 | 0.9575 | 0.6916 |
| **F9** | **0.9929** | **0.8506** | **0.9806** | **0.989** | **0.957** |

**Stability Studies:** Stability studies were carried out for formulation F9 as per ICH guidelines. *In-vitro* drug release study of the standard are compared with test release for the 2nd month, 4th month and 6th-month data, and dissolution data comparison. It showed good stability and the values were within permissible limits as shown in figure 4 & Table 8.

**Table 8: Comparison of dissolution data of best formulation F9 subjected to stability study with the standard release**

| Time (Hrs) | Cumulative % drug release of best formulation | | | |
|---|---|---|---|---|
| | Standard | After two months | After four months | After six months |
| 0 | 0 | 0 | 0 | 0 |
| 1 | 38.16 | 36.86 | 37.02 | 35.78 |
| 2 | 46.44 | 45.01 | 44.72 | 46.03 |
| 3 | 55.33 | 54.0 | 53.76 | 54.05 |
| 4 | 59.76 | 58.07 | 57.86 | 57.11 |
| 5 | 64.96 | 63.21 | 62.81 | 63.04 |
| 6 | 69.18 | 67.78 | 68.14 | 67.66 |
| 7 | 73.84 | 72.10 | 71.86 | 73.01 |
| 8 | 78.04 | 77.92 | 76.10 | 75.88 |
| 9 | 83.54 | 82.13 | 81.90 | 83.30 |
| 10 | 87.18 | 86.88 | 85.34 | 85.02 |
| 11 | 92.66 | 89.22 | 91.03 | 90.93 |
| 12 | 98.54 | 97.06 | 96.58 | 95.86 |

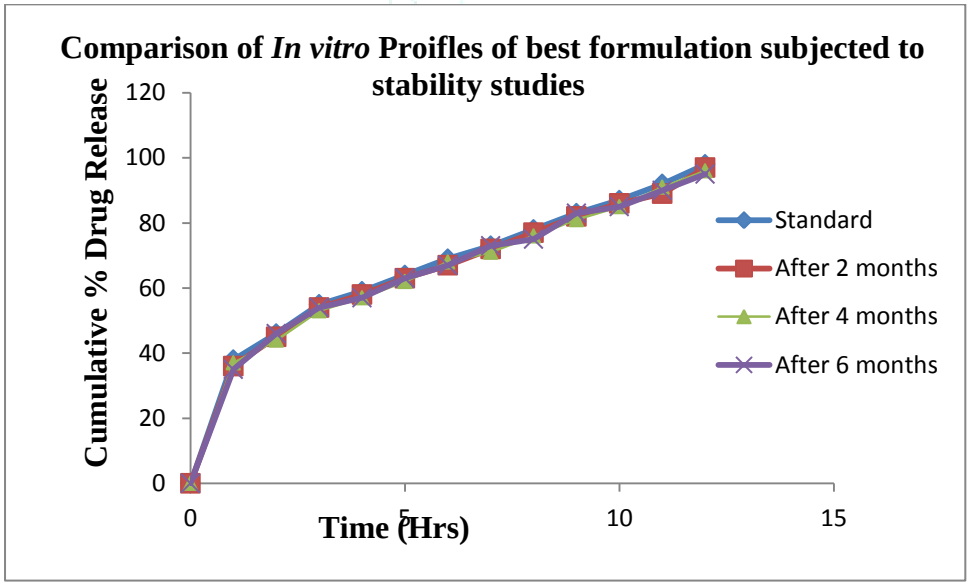


**Figure 4: Drug release pattern of the best formulation during stability study for every two months up to 6 months**

## CONCLUSION

FTIR Spectroscopy results determined compatibility of the Almotriptan, Polymers, and Excipients showed that the Almotriptan is compatible with all Polymers. All Nine formulations from F1-F9 containing HPMC K 100, Ethylcellulose and Eudragit RS 100 in 3 different ratios (drug: polymer) 1:1, 1:1.5 and 1:2 prepared. It concluded that after *in-vitro* Dissolution study among nine formulations from F1-F9, Combination of Almotriptan and Eudragit RS 100 F9 formulation ratio 1:2 shown the best result for 12 hrs. All the formulations were subjected to model fitting analysis to know the order and mechanism of drug release from the formulations by treating the data according to zero – order, first – order, Higuchi and Peppas equations. The data clearly shows that the release kinetics revealed that the formulation F9 follows both the Zero order and Korsmeyer-Peppas model with non-fickian diffusion mechanism. Stability studies were conducted for best formulation F9 at 25$^0$C/60% and 40$^0$C/75% RH for six months at every two months interval. The results revealed that no significant changes in drug content analysis and *in-vitro* dissolution study, thus indicating that formulation F9 was stable.

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