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# DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLET OF NITROGLYCERIN CONTAINING HYDROPHILIC POLYMERS

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## Summary

An experiment was designed to assess the feasibility of formulating low cost hydrodynamically balanced GIDS and to evaluate the in-vitro drug release performance controlling polymer to desirable release kinetics of nitroglycerine. Ten different formulations of nitroglycerin tablet were studied. Methocel K4, K15, K100 CR and Aerolac 100 SR were used in various concentrations with soluble and insoluble fillers. Drug release profile were analysed to first order and higuchi square root law to reveal the release kinetics perspective of nitroglycerin. The study showed that the weight variation varies from 0.78-2.45, the hardness and friability of tablets of all the batches was within the acceptable limits. In vitro drug release rate showed that increased the filler concentration in the formulation F-2, increased the released rate. From the high molecular weight of methocel showed the slow release of nitroglycerin in F-3. Decreased in Methocel K100 M concentrations increased the release rate. It was found from the formulation F-4, F-5, F-6 and F-10 that the development of nitroglycerin sustained release tablet for using the methocel K4 M in low concentration with higher soluble fillers was suitable. It was observed from different formulations that Methocel K4, K15, K100 M showed better performance in concentration of 25.88%, 38.7% and 19.4% respectively, whereas Aerolac SR 100 showed better performance in concentration of 84.26%. The data generated in this experiment indicate that modulation of hydrophilic polymer content in the controlling system would impart a significant impact on the rate and extent of drug release. A judicious combination of fillers and technical selection of polymers can maintain the release rate of nitroglycerin tablet. Among different polymers concentrations, 25% Methocel K4 M CR was found suitable for nitroglycerine matrix tablet. Further study can be done on different concentration of Aerolac SR for this drug.

Keywords: Nitroglycerin, sustained release, matrix, polymers, Methocel, Aerolac

## Introduction

Nitroglycerin that is also known as glyceryl trinitrate (GTN) has been used medically as a vasodilator to treat heart conditions for over a century, such as angina and chronic heart failure[1]. It is one of the oldest and most useful drugs for treating heart disease by shortening or even preventing attacks of angina pectoris. The oral route for drug delivery way is one of the most common methods. Oral route still remains the most popular for drug administration by virtue of its convenience to the patient and oral nitroglycerin has been used as an anti-anginal agent for more than a century[2].

For prolonging and controlling the rate of drug release, it is important to incorporate the drug in a suitable combination of polymers and fillers. Regular research is going on different types of polymers and fillers to find out the suitable combination for sustained release matrix tablets[3-4]. A number of polymers have been investigated to develop in situ gel-forming systems, due to the ability of these hydrogels to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross-linking[5-6]. Hydroxypropylmethylcellulose (HPMC) is the polymer most widely used as the gel-forming agent in the formulation of solid, liquid, semisolid and even controlled-release dosage forms[7]. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from these dosage forms are controlled by the hydration of HPMC, which forms a gel barrier through which the drug diffuses[8-9]. The adjustment of the polymer concentration, the viscosity grade and the addition of different types and levels of excipients with the polymers matrix can modify the drug release rate.

The sustained release dosage forms have been emerged with a view to deliver drug at a required rate, directed by the need of the body over the period of treatment. This system is simple and cost effective and flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance[10-11]. That is why the present research was designed to develop hydrodynamically balanced gastrointestinal delivery system using hydrophilic and hydrophobic matrix materials in tablet form and evaluate the in-vitro drug release performance of such system as a function of polymer level. The polymer content was varied accordingly to estimate a mixture model and the kinetics and mechanism of nitroglycerin release from such matrix has been explored and explained with the help of exponential equation.

## Materials and Methods

Ten formulations (F-1 to F-10) corresponding to the preparation of matrix tablets were studied. Tablet containing 2.6 mg of Nitroglycerin (5% dispersion), fillers, and lubricants were prepared by double compressing the blended powders, using a 27 punch station compression machine and 8 mm diameter flat punches. Compositions of nitroglycerin tablet are given in table 1.

For the evaluation of physical properties of the hydrophilic matrix tablets, like tablet weight, weight variation, determination of friability and hardness, 10 tablets were taken from the each formulation. In-vitro drug release studies from the prepared of matrix tablets were conducted using a six station USP XXII type II apparatus at 37±0.5°C and 100 rpm speed. The dissolution studies were carried out for 8 hours in phosphate buffer medium ($P^H$ 7.2) under sink condition. At every 1st hours, 2nd hours, 4th hours, and 8th hours intervals samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the constant volume. Samples were filtered to remove suspended, insoluble tablet components and appropriate dilution, the sample solution was analyzed at 210 nm for nitroglycerin by a High Performance Liquid Chromatography (HPLC). The amount of drug present in the samples was calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve. The drug release study was mainly performed for 8 hours because the total gastrointestinal transit time of nutrients

and dosage forms in humans approximately 8 hours. The experiment was design the sustained release of nitroglycerin tablets satisfied with the dissolution profile as 1st hour: between 20 to 35%, 2nd hour: between 35 to 65%, 4th hour: between 55 to 90%, 8th hour: not less than 85%. To analyse the mechanism of drug release from the matrix tablet, the release data were fitted to the following equation:

First- order equation[12]:

$$\ln (100-Q)=\ln 100- kt$$

Where Q is the percent of drug release at time t, and k is the release rate constant.

Higuchi's equation[13]:

$$Q= k2\ t1/2$$

Where Q is the percent of drug release at time t, and k2 is the diffusion rate constant.

## Results

Physical properties of tablets

The results of different formulations showed that the highest average weight was 187 and the lowest average weight was 144. The weight variation varies from 0.78-2.45% (Table 2).

Adequate hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. The result showed that, none of the formulation showed hardness range not less than 30 N. The hardness was between 39.6± 2.15N to 159.1± 3.24N. Highest hardness was observed in Methocel polymer and lowers was observed in Aerolac. In the formulation F-7 and F-9 where Aerolac SR 100 was used, showed the lower average hardness and these were 39. 8±3.0 and 39.6± 2.2 N. Friability is important for the tablet to resist attrition. A maximum loss of not more than 1% generally is considered acceptable for most products by British Pharmacopoeia. All the batches of tablets showed friability below 0.25%, which is well below the acceptable norm of 1%. Lowest friability was observed in F-5 that was 0.154 (Table 2).

**Dissolution and drug release profile in different orders**

The effect of content level of various sustained release polymer and different type of fillers are contain the formulation on the release profile of nitroglycerin are illustrated in figure-1 to figure-4. In vitro drug release depends on several factors, such as manufacturing process, type of excipients and polymers and amount of drug. Results showed that modulation of hydrophilic polymer content in the controlling system would impart a significant impact on the rate and extent of drug release. It was observed that, as the percentage of controlling polymer was increased, the release of active ingredient was consequently decreased. It was also observed that, as the percentages of water soluble excipients were increased, the release of active ingredients was respectively increased. The drug release data of ten different formulations were plotted in First order and Higuci order and their concentration coefficient were determined graphically to identify their mechanism (Figure-4 and 5). It was observed that most of the regression followed the first order. The correlation coefficients of different kinetics are showed in Table 3.

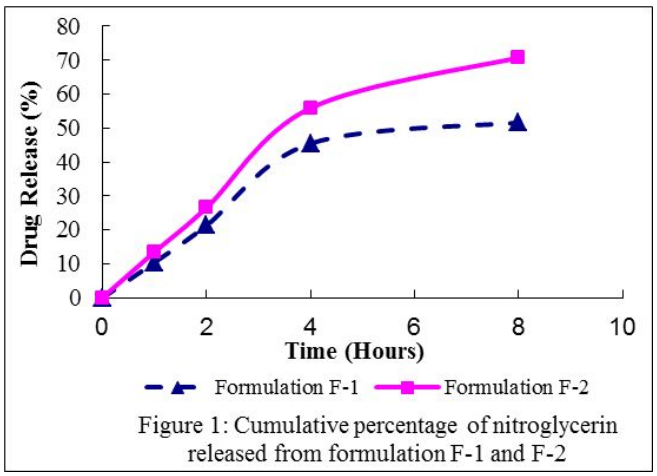


Figure 1: Cumulative percentage of nitroglycerin released from formulation F-1 and F-2

**Release profile of formulations F-1 and F-2**

Figure-1 illustrated that F-1 and F-2 contains 45% and 38.7 % of Methocel K15M CR premium and same quantity of insoluble fillers and lubricants but soluble filler were different. After dissolution, result

showed that F-1 was fewer nitroglycerins liberated in desire in-vitro dissolution. It was observed that F-2 showed higher present (70.75) of nitroglycerin release in 8th hours, where as in F-1 it was only 51.60%. In formulation F-2, decreased in polymer concentration and increased the filler concentration, increased in the release of nitroglycerin. It was found that the formulation F-1 was slow release the nitroglycerin in desire time period while the release rates was increased in F-2 but it could not comply the specified range. None of these formulations showed desire nitroglycerin release with time. Data was analysis by different equation and different formulation shows the different kinetics. F-1 follows the higuchi equation to cumulative release of nitroglycerin but F-2 follows the first order kinetics (Figure 5 and 6).

**Release profile of Formulations F-3 and F-8**

Figure-2 illustrated that F-3 and F-8 contains 27% and 19.41% of Methocel K100 M CR premium respectively. During the 1st hour it was released only 7.81% in F-3 and at the end of 8th hour it was found 49.36% of nitroglycerin that was very low then the expected limit. On the other hand, F-8 showed that in the 1st hour 16.76% nitroglycerin were released and at the end of 8th hour it was found 61.45% of nitroglycerin. This indicated that the combination of polymer and filler in F-3 and F-8 were not suitable to release the maximum amount of nitroglycerine from the matrix tablet because of the slow diffusion of the drug from the core.

From the high molecular weight polymer of methocel showed the slow released of nitroglycerin in F-3 where the polymer concentration was lower in the formulation F-8. However F-8 contains lower quantity polymer but increased the soluble filler quantity, increased the release rate of nitroglycerin. Data was analysis by different equation and different formulation shows the different kinetics. F-3 follows the first order kinetics equation to cumulative release of nitroglycerin but F-8 follows the higuchi equation (Figure 5 and 6).

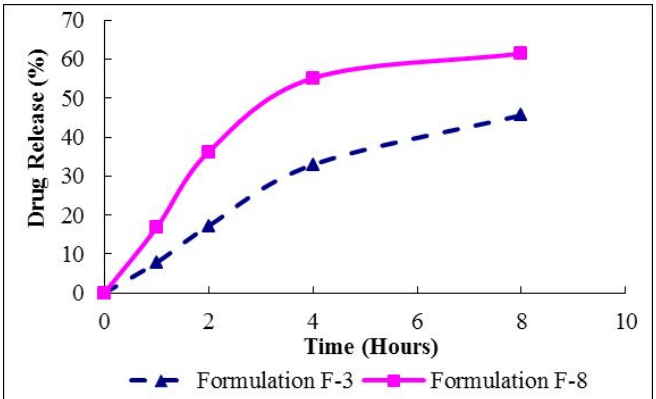


Figure 2: Cumulative percentage of Nitroglycerin released from formulation F-3 and F-8

**Release profile of formulations F-4, F-5, F-6 and F-10**

Figure-3 illustrated that F-4, F-5, F-6 and F-10 contains 42%, 32.36%, 29.12% and 25.88% of methocel K4 M CR and 22.65 %, 32.36%, 35.59% and 38.83% of soluble filler lactose respectively. Among these four formulations, it was observed that F-10 showed highest percentage of nitroglycerin release compare to other formulations. It was found that F-4 released 23.78% nitroglycerin after 1st hour of dissolution and at the end of 8th hour it was only 72.08%. On the other hand, in F-5 the percentage of drug release was not increased significantly compare to F-4. At the end of 8th hour it was found 84.29% of nitroglycerin has been liberated that was not up to the desire limit. However, in F-6 it was found that the percentage of drug released from the matrix tablet during the 1st, 2nd, 4th and 8th hours of dilution were within the desire limit. At the end of 8th hour it was found 87.90% of nitroglycerin has been liberated. Highest percentage of nitroglycerine was released in the F-10 than three other formulations with the similar type of polymer. In this formulation 26.17% nitroglycerin was released after 1st hour of dissolution. After 2nd and 4th hour it was 46.80% and 75.93% respectively while the extended limit of 35% to 55% and 55 to 90%. At the end of 8th hour it was found 96.63 % of nitroglycerin has been liberated from the matrix tablet.

Results indicated that when the polymer concentration was decreased and soluble filler was increa-

sed, the release rate of nitroglycerin was increased in each formulation. It can be said that the development of nitroglycerin sustained release tablet for using the hydrophilic polymers in low concentration with higher soluble fillers is recommended. Data was analysis by different equation and different formulation shows the different kinetics. F-4 followed the higuchi equation and F-5, F-6, F-10 followed first order kinetics equation to cumulative release of nitroglycerin.

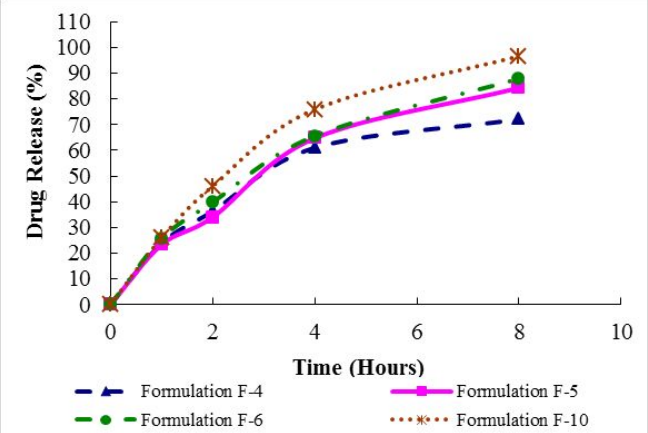


Figure 3: Cumulative percentage of Nitroglycerin released from formulation F-4, F-5, F-6 and F-10

**Release profile of formulations F-7 and F-9**

Figure-4 Illustrated that in F-7 and F-9 different concentration of Aerolac-SR-100 were used. It was found that F-7 was less niroglycerin liberated in 1st, 2th, 4th hour and 8th hour than the F-9. It was observed that release rate of nitroglycerin were more or less similar at 1st and 2nd hours in both formulations. However distinct differences were observed from the 4th and 8th hours. Formulation nine was more nitroglycerins liberated because of the decrease of the concentration of polymers. At the end of 8th hour it was found 78.90% of nitroglycerin has been liberated in F-7 whereas it was 89.14% in F-9.

It can be said that the development of nitroglycerin sustained release tablet for using the hydrophilic polymers in low concentration is suitable. Equations showed that F-7 followed higuchi order on the other hand F-9 follows first order kinetics equation to cumulative release of nitroglycerin (Figure 4 & 5).

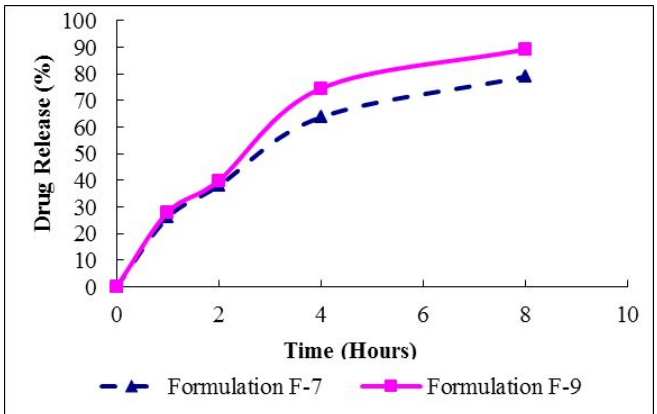


Figure 4: Cumulative percentage of Nitroglycerin released from formulation F-7 and F-9

## Discussion

Nitroglycerin formulations generated by the modification of nitroglycerin release rates from matrix system. The presence of soluble filler (Lactose) or insoluble filler (Microcrystalline Cellulose) affect the release rate of nitroglycerin from various hydrophilic polymers.

The study showed that the highest average weight was 187 and the lowest average weight was 144. The weight variation varies from 0.78 - 2.45%. In case of weight variation test, it found that no tablet fell outside the USP limit. On the contrary small variations were found in all cases. It indicates the precision of weight variation test of all the batches. The hardness of tablets of all the batches was within the acceptable limits. However it was found that higher hardness of tables with methocel compare to aerolac SR. In all the batches showed the friability below 0.25% this was well below the acceptable limit of one present.

The formulation F-1 and F-2 contains different percentage of polymer and same quantity of insoluble fillers and lubricants. After dissolution it was found that F-1 was less nitroglycerin liberated in desire in-vitro dissolution but the change in formulation F-2 decreased in polymer concentration but increased the filler concentrations increased the release of nitroglycerin. Lactose may create void spaces in the insoluble polymer structure that result in increased nitroglycerin release.

The formulations F-3 and F-8 with Methocel K100 M showed that, the high molecular weight of methocel showed the slow release of nitroglycerin. However, though the F-8 contains lower quantity of polymer, it was observed that release rate of nitroglycerin increased with increasing the quantity of soluble filler. So it said that the decrease in Methocel K 100 M CR polymer concentration increase the release rate of the nitroglycerin. Sung, *et al.*[8] also reported that a greater drug release rate was observed with lower HPMC/lactose ratios.

The formulation F-4, F-5, F-6 and F-10 contains 42%, 32.36%, 29.12% and 25.88% of methocel K4 M CR respectively and 22.65%, 32.36%, 35.59% and 38.83% of soluble filler lactose respectively. It was observed that release rate of nitroglycerin tables increased with decreasing the concentration of polymer and increasing the soluble filler. The findings also supported by the previous reports[14]. An experiment with adinazolam mesylate by Sung, *et al.*[8] found that K4M formulations exhibited greater drug release rate than the K15M and K100M. Similar findings was observed by Bharatbhai[15] and reported that as the viscosity of HPMC increase, the rate of release of antidiabetic drugs was decreased. The authors also reported that K100M showed the lowest release rate. In some previous research it was also found that the release rate of the ranolazine drug from the matrix tablets decreased with an increase in polymer proportion because of an increase in the gel strength as well as formation of a gel layer with a large diffusional path. This could have caused a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate [16-17]. So it said that the development of nitroglycerin sustained release tablet for using the hydrophilic methocel K4 M CR polymers in low concentration with higher soluble fillers is recommended.

Aerolac-SR-10 contains different concentration in different formulation. It was found that F-7 showed less percent of niroglycerin release in 1$^{st}$, 2$^{th}$, 4$^{th}$ hour and 8$^{th}$ hours than the formulation of F-9. Formulation nine showed more nitroglycerin release because of the decrease of the concentration of polymers. Tapan[18] conducted an experiment on diazepam drug formulated with polyethylene glycol as a solid dispersion to increase aqueous solubility and dissolution of drug where the author used croscarmellose sodium and aerolac to achieve rapid disintegration of tablets. It was found that low concentration of Aerolac-SR-10 polymers may also suitable for the development of nitroglycerin sustained release tablet.

## Conclusion

In conclusion it is said that Methocel K4, K15, K100 M CR showed better performance in concentration of 25.88%, 38.7% and 19.4% respectively. Aerolac SR 100 showed better performance in concentration of 84.26%. The data generated in this experiment indicate that various polymer has a great effect on the release rate of nitroglycerin tablet. This different concentration of polymer level and fillers are responsible for the release rate of nitroglycerin. A judicious combination of fillers and technical selection of polymers can maintain the release rate of nitroglycerin tablets. Among different polymers concentrations, Methocel K4 M CR with 25% inclusion level was found suitable for nitroglycerine matrix tablet. Further study can be done on different concentration of aerolac SR.

## Acknowledgements

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| Ingredients Name | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 | F-9 | F-10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Nitroglycerin | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 |
| MethocelK-15 M CR Premium (HPMCE) | 70 | 60 | - | - | - | - | - | - | - | - |
| MethocelK-100MCR Premium | - | - | 40 | - | - | - | - | 30 | - | - |
| MethocelK-4MCR Premium | - | | - | 65 | 50 | 45 | - | - | - | 40 |
| Aerolac-SR 100 (Ethylcellulose+HPMC) | - | - | - | - | - | - | 160 | - | 150 | - |
| Avicel PH-101 | 50 | 50 | 50 | 50 | 50 | 50 | - | 50 | - | 50 |
| Lactose | 30 | 40 | 50 | 35 | 50 | 55 | 23.5 | 70 | 23.5 | 60 |
| Mg Stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Purified Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Colloidal Silicone Dioxide (Aerosil-200) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

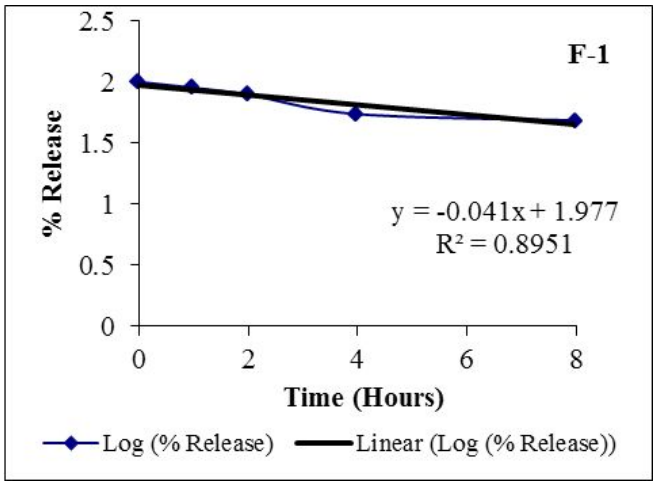
Table-1: Nitroglycerin tablet composition in different formulations (mg)

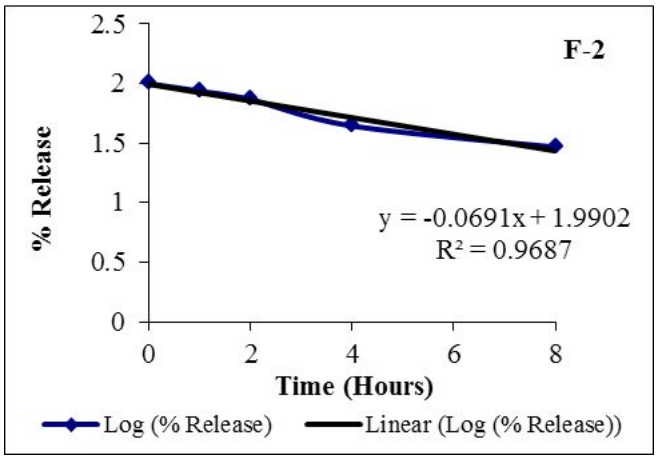
| Formulation | Average Weight | Weight Variation | Average Hardness | Average Friability |
|---|---|---|---|---|
| F-1 | 155.09 | +2.45%, -2.18% | 150.9±4.37 N | 0.22±0.032 |
| F-2 | 154.97 | +0.7937%, -1.142% | 157.4±2.46 N | 0.222±0.024 |
| F-3 | 144.77 | +1.54%, -1.22% | 159.1± 3.24N | 0.225±0.014 |
| F-4 | 154.53 | +0.951%, -0.8606% | 98.6± 4.32N | 0.197±0.020 |
| F-5 | 155.05 | +1.257%, -1.322% | 96.9± 3.96N | 0.154±0.024 |
| F-6 | 154.10 | +1.233%, -1.362% | 96.0± 4.17N | 0.167±0.034 |
| F-7 | 187.48 | +0.8107%, -0.789% | 39.8± 2.99N | 0.228±0.020 |
| F-8 | 154.10 | +1.2329%, -1.363% | 157.8± 2.32N | 0.236±0.025 |
| F-9 | 178.50 | +1.961%, -1.961% | 39.6± 2.15N | 0.223±0.017 |
| F-10 | 155.05 | +1.902%, -1.967% | 95.9± 4.13N | 0.2±0.019 |

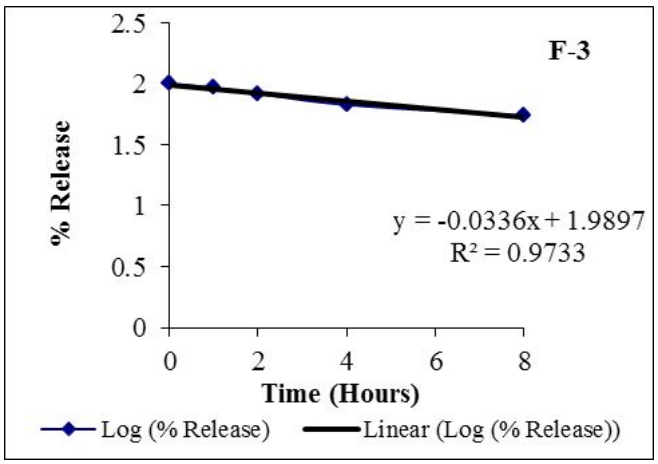
Table-2: Average weight, weight variation, hardness and friability of nitroglycerine tablets in different formulations

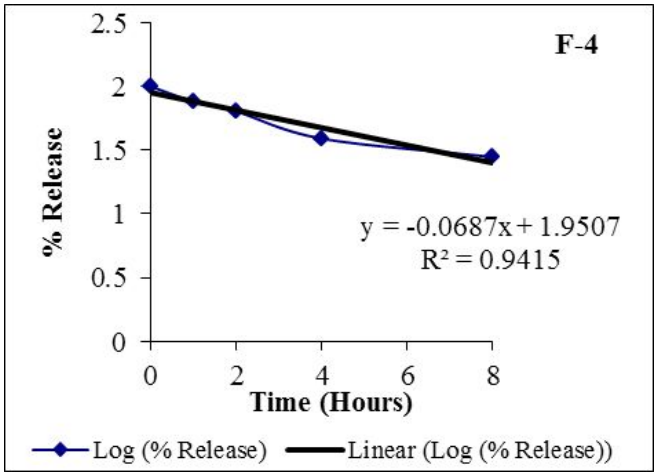
| Multiple co-efficient of determination ($r^2$) | | |
|---|---|---|
| Code | First order | Higuchi |
| F-1 | 0.8951 | 0.9274 |
| F-2 | 0.9687 | 0.9459 |
| F-3 | 0.9733 | 0.9551 |
| F-4 | 0.9415 | 0.976 |
| F-5 | 0.9934 | 0.9901 |
| F-6 | 0.9995 | 0.985 |
| F-7 | 0.9754 | 0.9452 |
| F-8 | 0.8727 | 0.9452 |
| F-9 | 0.9829 | 0.9711 |
| F-10 | 0.9916 | 0.9805 |

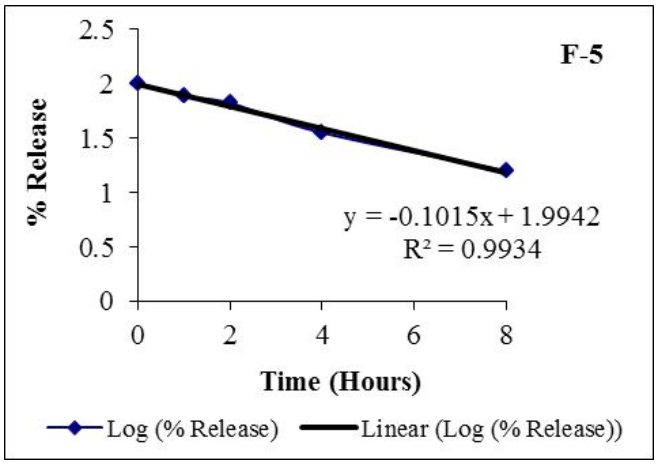
Table-3: Drug release data of different formulations in different kinetics order

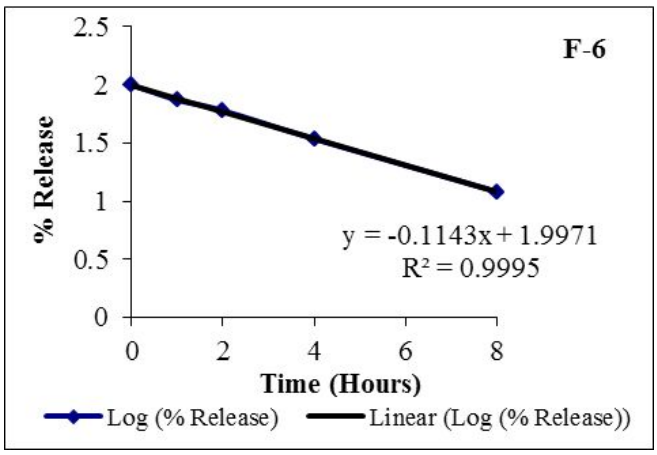

F-1
% Release
y = -0.041x + 1.977
R² = 0.8951
Time (Hours)
Log (% Release)
Linear (Log (% Release))


F-2
% Release
y = -0.0691x + 1.9902
R² = 0.9687
Time (Hours)
Log (% Release)
Linear (Log (% Release))


F-3
% Release
y = -0.0336x + 1.9897
R² = 0.9733
Time (Hours)
Log (% Release)
Linear (Log (% Release))


F-4
% Release
y = -0.0687x + 1.9507
R² = 0.9415
Time (Hours)
Log (% Release)
Linear (Log (% Release))


F-5
% Release
y = -0.1015x + 1.9942
R² = 0.9934
Time (Hours)
Log (% Release)
Linear (Log (% Release))


F-6
% Release
y = -0.1143x + 1.9971
R² = 0.9995
Time (Hours)
Log (% Release)
Linear (Log (% Release))

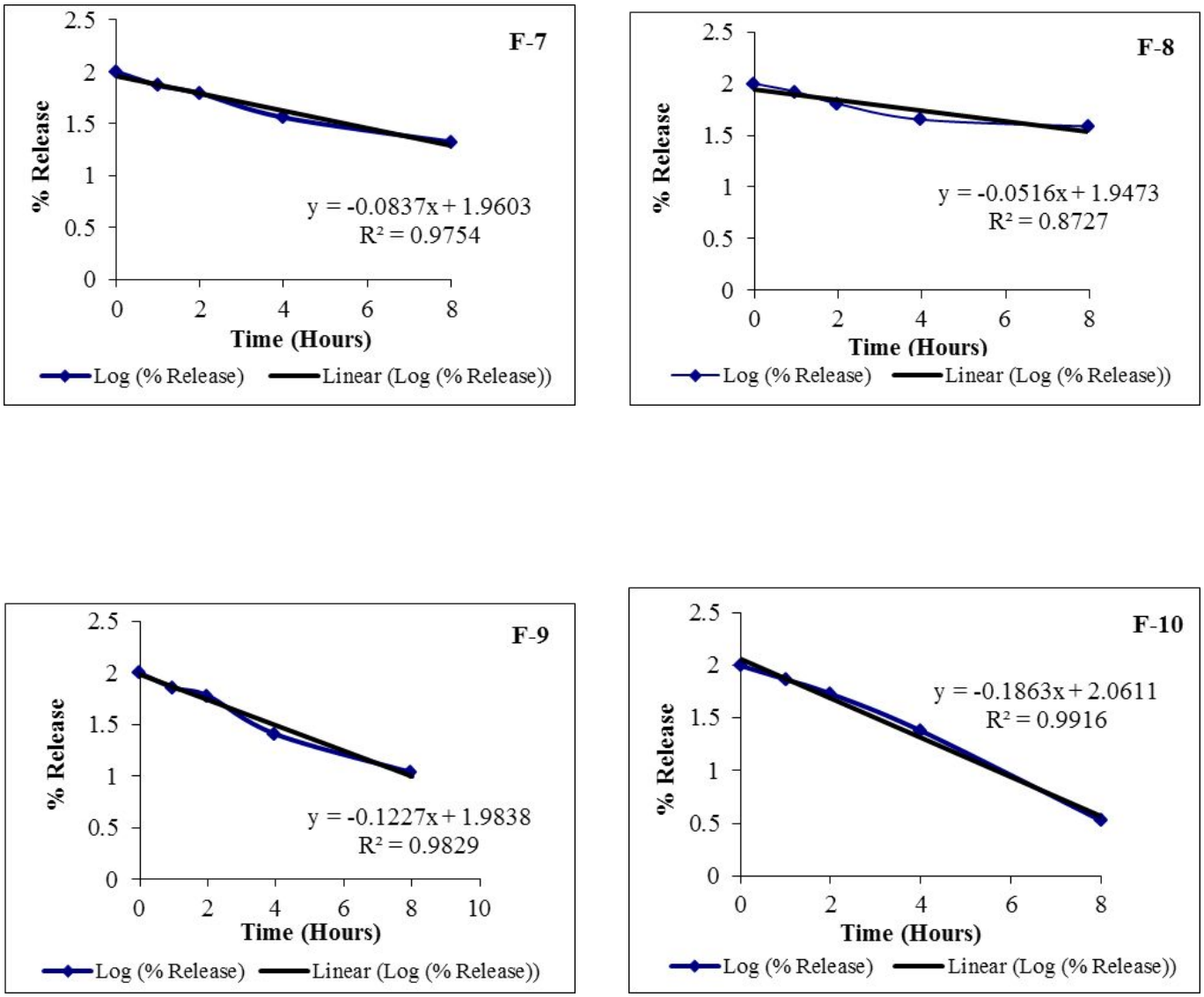
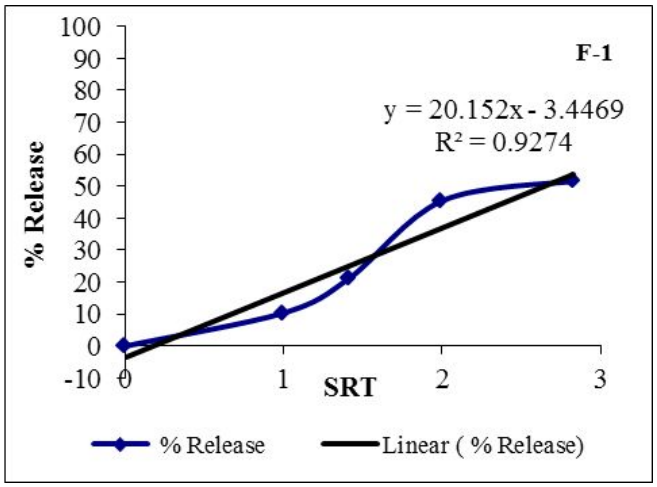
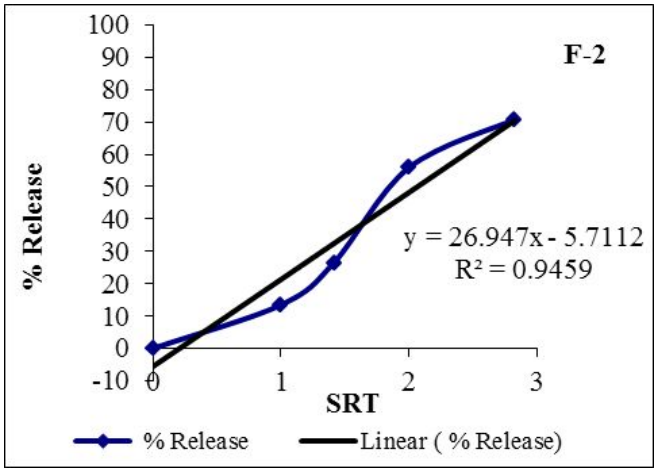
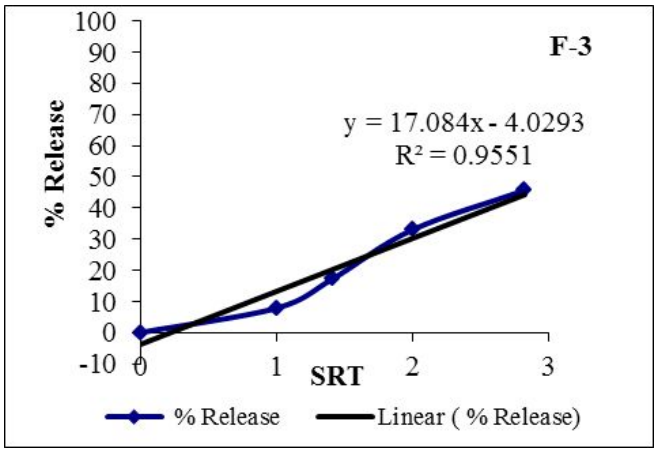
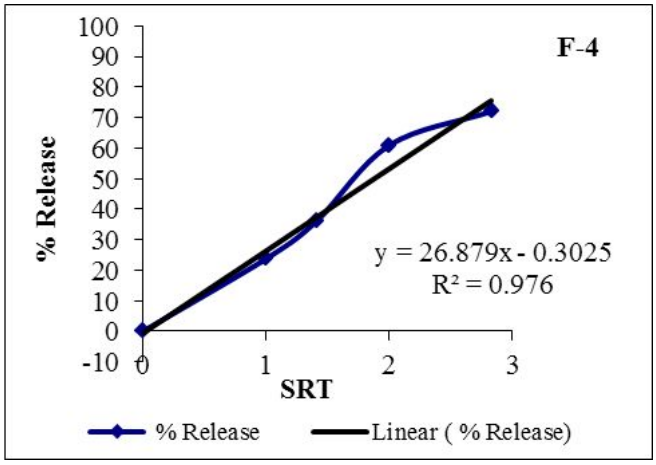


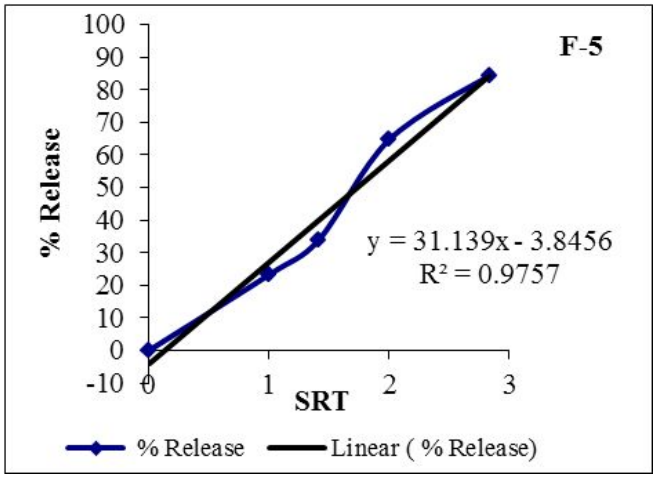

Figure 5: First order kinetics on nitroglycerine release in different formulations

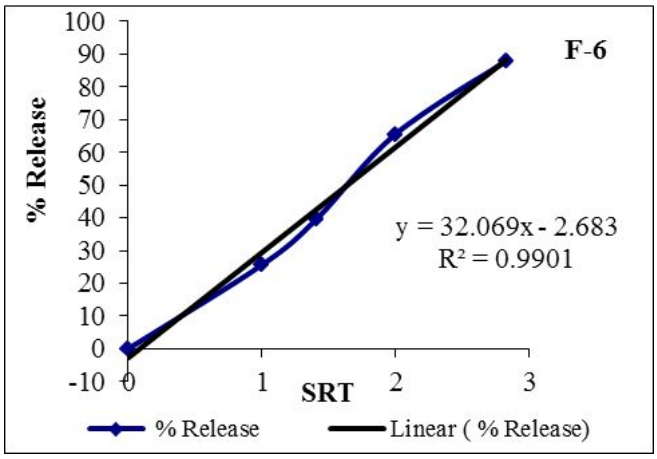

F-1
y = 20.152x - 3.4469
R² = 0.9274
% Release
SRT
% Release
Linear ( % Release)


F-2
y = 26.947x - 5.7112
R² = 0.9459
% Release
SRT
% Release
Linear ( % Release)


F-3
y = 17.084x - 4.0293
R² = 0.9551
% Release
SRT
% Release
Linear ( % Release)


F-4
y = 26.879x - 0.3025
R² = 0.976
% Release
SRT
% Release
Linear ( % Release)


F-5
y = 31.139x - 3.8456
R² = 0.9757
% Release
SRT
% Release
Linear ( % Release)


F-6
y = 32.069x - 2.683
R² = 0.9901
% Release
SRT
% Release
Linear ( % Release)

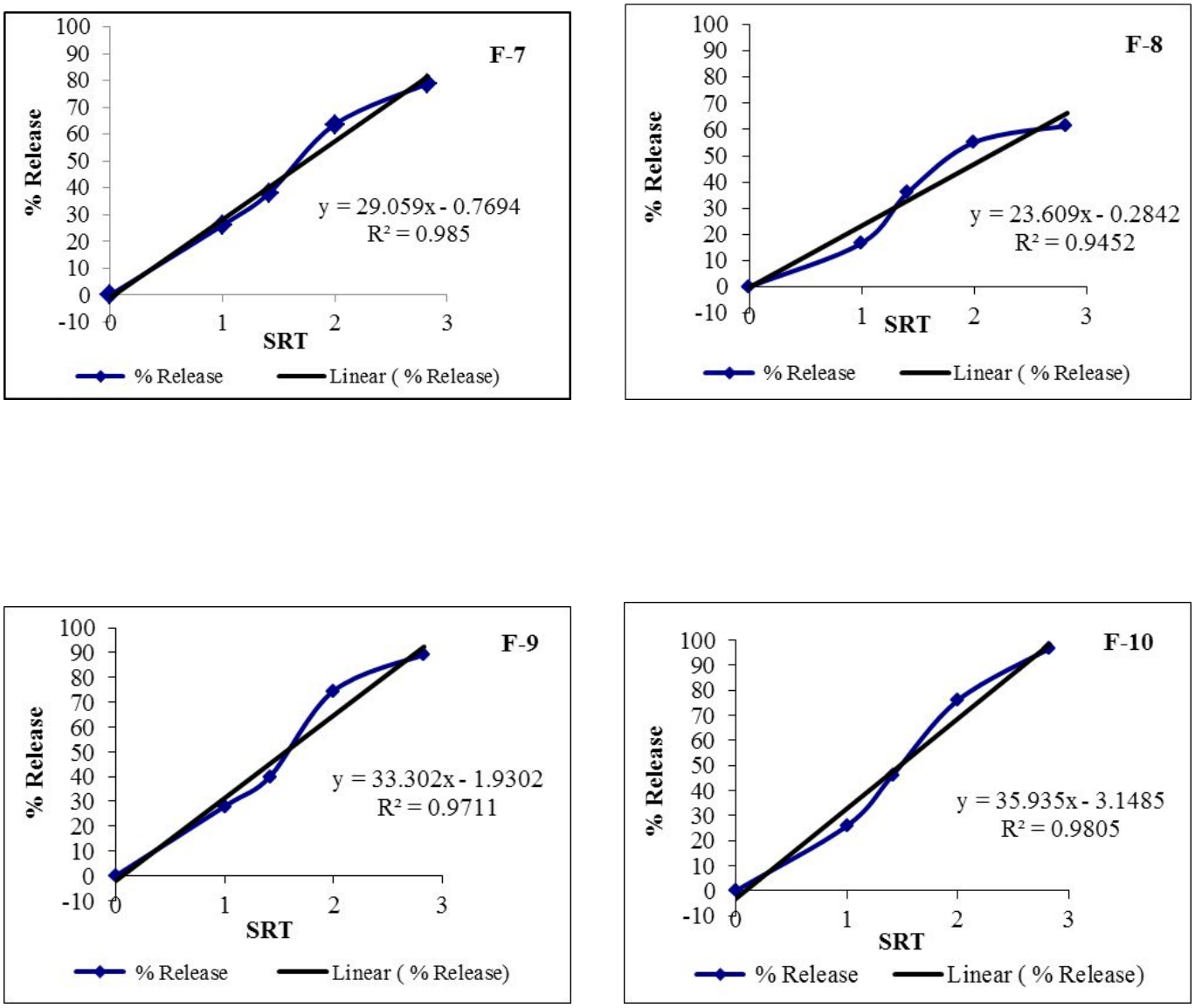



Figure 6: Higuchi square root order on nitroglycerine release in different formulations