# Design, Formulation and *In-vitro* Evaluation of Controlled Release Matrix Tablet of Simvastatin Containing Natural Polymer.

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## ABSTRACT:

The present investigation was aimed at designing controlled release matrix tablets of Simvastatin, using natural polymers like guar gum and xanthan gum in combinations of various concentrations, to produce a controlled release of Simvastatin to improve the efficacy and patient compliance and drug release profiles of the optimized formulation. The tablets' medication release adhered to zero-order kinetics. Due to its longer half-life and lower clearance rate compared to developed immediate-release tablets, controlled-release tablets were found to have a better degree of drug absorption, according to in vitro experiments. For a period of 12 hours, matrix formulations based on Xanthum gum displayed controlled release. Simvastatin tablets with controlled release showed better absorption than tablets with developed IR. Our findings imply that Simvastatin controlled-release tablets are an effective medication delivery methods that will overcome the drawbacks of conventional therapy.

**KEYWORDS:**Simvastatin, Controlled release matrix, Xanthun Gum, Direct compression, Zero order.

## INTRODUCTION:

Simvastatin is used in the treatment of hypercholesterolemia. In conventional treatment, Simvastatin is administered 2-3 times a day due to its shorter half-life. Controlled release (CR) products are fabricated to release the immediate release part to initiate therapeutic concentration employingan initial dose and then to offer Controlled release over the required period with the maintenance portion. For both conventional and new drug delivery methods, oral administration is the most helpful, widely used, and preferred mode of drug delivery for systemic activity. Patients and doctors alike favor tablets, which are the most widely used oral solid formulation on the market. There are numerous explanations for this, not the least of which would be patient acceptability and simplicity of administration. Conventional formulations must be given in various doses during long-term therapy for the management of chronic illness conditions, which presents several drawbacks. However, many therapeutic agents are subjected to extensive presystemic elimination when given orally due to gastrointestinal degradation and/or first pass hepatic metabolism, which results in low systemic bioavailability, shorter therapeutic activity durations, and the formation of inactive or toxic metabolites. Because they improve patient compliance, maintain uniform medication levels, reduce dosage and side effects, and expand the safety margin for high-potency pharmaceuticals, controlled-release (CR) tablet formulations are chosen for this type of therapy.[2]

Controlled release dosage forms may be defined as any drug or dosage form modification that prolonged and uniform release of a drug. A controlled-release dosage form aims to maintain therapeutic medication levels in the blood or tissues over a long period. Typically, zero-order release from the dose form is attempted to achieve this Zero-order release, also known as constant release rate, is the medication release from the dosage form that is unaffected by the quantity of the drug in the delivery system. A controlled-release tablet allows for a two or greater reduction in the frequency of drug delivery when compared to a prompt-release dose form. By enhancing the biopharmaceutical, pharmacokinetic, and pharmacodynamic aspects of the medicine, controlled-release products

outperform immediate-release dose forms. It has been shown that controlled-release dosage forms increase therapeutic effectiveness by maintaining a constant medication plasma concentration. Matrix-based CR tablet formulations are the most widely used controlled-release drug delivery methods due to how simple they are to formulate and the ease with which they can be produced on a large scale. When formulating pharmaceutical dosage forms, polymers are now an important tool for managing the release of medications. Numerous studies on the use of hydrophilic polymers in the manufacturing of CR matrix systems for different medications have been published in the literature for a long time.[6]

The use of polymeric materials for medical purposes has rapidly increased since the early 1950s. Polymers have long been utilized in the medical industry. Natural polymers continue to be desirable due to their cost-effectiveness, chemical flexibility, non-carcinogenicity, mucoadhesivity, biodegradability, and biocompatibility as well as their high drug holding capacity, high thermal stability, and ease of compression[10]. Its use as an excipient in hydrophilic drug delivery systems resulted from this. In the past few decades, numerous natural gums and mucilage, such as guar gum and other medicines, tragacanth gum, Xanthum gum, pectin, alginates, etc. in the development of a controlled release tablet dosage form.[5]

Simvastatin, a newer antihyperlipidemic agent, belongs BCS class-II agent. It is a specific inhibitor of HMG CoA. It is a prodrug and is hydrolyzed to its active β-hydroxyacid form, simvastatin acid, after administration. It is practically insoluble in water and other aqueous media. The very poor aqueous solubility and wettability of simvastatin give rise to difficulties in the design of pharmaceutical formulations and led to variable oral bioavailability. Thus, there is a need to increase the rate of dissolution. Hence, the study was carried out to formulate and evaluate the controlled release dosage form of Simvastatin as a model drug and had an aim those final batch formulation parameters should show prolonged drug release.

The chemical composition of the drug or polymer, matrix structure, swelling, diffusion, erosion, release mechanism, and in vivo environment all play a role in dosage form development. Conductedto develop and access a controlled-release dosage form of simvastatin as a model medication, with the final batch formulation characteristics intended to demonstrate prolonged drug release.[9]

Designing an optimized formulation with an acceptable dissolving rate quickly and with the fewest number of trials is a crucial challenge. Numerous statistical experimental designs have been acknowledged as effective methods for enhancing the process variables.[11]

A centralcomposite factorial design was employed to systematically study the drug release profile. A centralcomposite full factorial design was employed to investigate the effect of two independent variables (factors), i.e. the amounts of Xanthum gum and Guar gum on the dependent variables.

## MATERIALS AND METHODS:

Simvastatin, Guar Gum, Xanthan Gum, Micro Crystalline Cellulose, Magnesium Stearate, lactose, and Talc were gift samples from Lupin Ltd. Pune

**Methods**

**Drug-Excipient Compatibility Studies:**

FTIR analyses were performed on the physical mixture of the pure drug and drug and excipients. The preparation of the pellets involved exerting 10 metric tonnes of pressure in a hydraulic press while the pure medication and its mixture with excipients were separately mixed with IR-grade potassium bromide in a ratio of (1:100). The pellets were then scanned in an FTIR instrument throughout a 4000-400 $cm^{-1}$ range

**Formulation of Simvastatin Controlled Release Matrix Tablets:**

Tablets containing 80 mg of Simvastatin were prepared, according to the formulae given in Table 1, by direct compression. The respective powders, namely Simvastatin, release-retarding polymer(s) Xanthum gum,) were passed through sieve no. 20, separately. Mixing of powders was carried out using a pestle and mortar for 10 min. Talc and magnesium stearate was then added to the mixed powders. Mixing was continued for another 3 min. Finally, 200 mg of each mixture was weighed and fed manually into the die of a single punch-tableting machine (Cemach Machineries Limited, India),equipped with flat-faced punches (8.0 mm), to produce the desired tablets. The hardness of the tablets was adjusted at 5 $kg/cm^2$ using a Monsanto hardness tester.

**Table. 1. Simvastatin Controlled release matrix tablet formulation.**

| Ingredients | Simvastatin | Guar Gum | Xanthum Gum | MCC | Mg. Sterate | Talc | Lactose | Total Wt. |
|---|---|---|---|---|---|---|---|---|
| **F1** | 80 | 11 | 5.86 | 30 | 2 | 2 | 69.14 | **200** |
| **F2** | 80 | 11 | 34.14 | 30 | 2 | 2 | 40.86 | **200** |
| **F3** | 80 | 2 | 10 | 30 | 2 | 2 | 74 | **200** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **F4** | 80 | 1.7 | 20 | 30 | 2 | 2 | 64.3 | **200** |
| **F5** | 80 | 20 | 30 | 30 | 2 | 2 | 36 | **200** |
| **F6** | 80 | 20 | 10 | 30 | 2 | 2 | 56 | **200** |
| **F7** | 80 | 2 | 30 | 30 | 2 | 2 | 54 | **200** |
| **F8** | 80 | 23.8 | 20 | 30 | 2 | 2 | 42.2 | **200** |
| **F9** | 80 | 11 | 20 | 30 | 2 | 2 | 55 | **200** |

**All quantities are expressed in are in mg.**

***In- vitro* evaluation of the prepared matrix tablets**

1. **Tablet Weight Variation:**

Twenty tablets were chosen at random and weighed precisely. Results are shown as mean values SD[7].

2. **Tablet Thickness:**

Ten randomly chosen tablets were determined for thickness using a Verniercaliper. Results are shown as mean values SD[6].

3. **Friability Test:**

A tablet friability test instrument (Roche) drum was filled with ten randomly chosen tablets. The drum was set up to spin 100 times in 4 minutes. The tablets were taken out, dusted off, and precisely weighed. The weight loss percentage was determined[7].

**4. Hardness:**

The hardness of the prepared tablets was determined using Monsanto tablet hardness tester[6].

5. **Content Uniformity:**

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labeled drug content can be considered, as the test was passed[16].

6. **Drug Release Studies:**

In-vitro dissolution study for the Simvastatin controlled release tablets was carried out in USP type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium for the first two hours followed by phosphate buffer pH 6.8 at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn employing a syringe fitted with a pre-filter, and the volume withdrawn at each interval was replaced with the same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 239 nm using a UV Visible spectrophotometer after suitable dilutions[17].

**7. Kinetic modeling of drug release.**

The dissolution profile of all the formulations was fitted into zero-order, first-order, Higuchi and Korsmeyerpeppas models to ascertain the kinetic modeling of drug release

## RESULTS AND DISCUSSION:

**FTIR Study:**

The FTIR spectra of Simvastatin and powder of Simvastatin- excipients physical mixture were shown in Fig. 1, Fig. 2

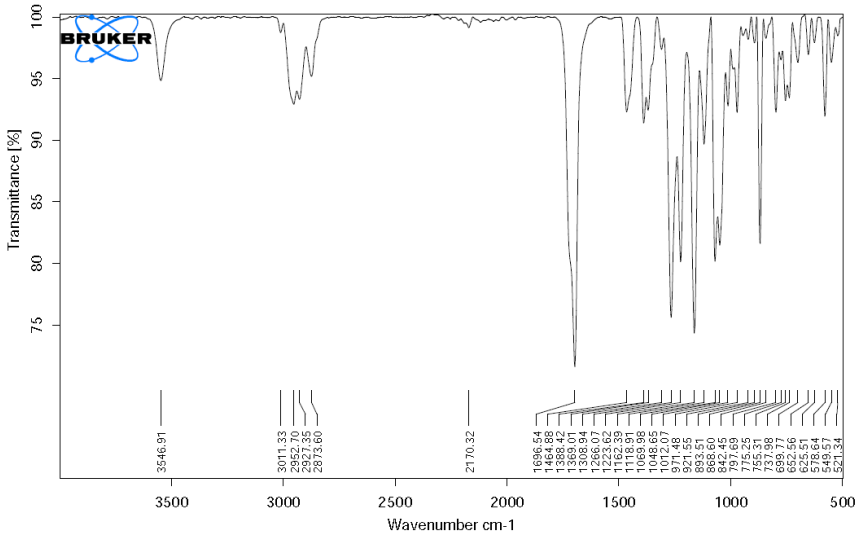


**Fig. 1: FTIR Spectra of Simvastatin**

The FTIR spectra Simvastatin pure drug and Simvastatin-excipients physical mixture showed the following characteristic peaks, 1266.37 cm-1 due to C-O bending vibrations, 1016.53 cm-1 due to C-O-C stretching vibrations, 1697.92 cm-1 due to C=O stretching vibrations, 2876 cm-1 due to O-CH3 stretching vibrations, 3546 cm- 1 due to O-H stretching vibrations, 2927cm-1 due to -CH2 stretching vibrations, 1464.88cm- 1 due to methylene bending vibrations, 1162cm-1 due to C-O-C-O stretching vibrations, 797cm- 1 due to C2H stretching vibrations, indicating all functional groups are intact. Hence, it is a confirmation that no chemical reactions have taken place amongst any of the constituents in the formulation.

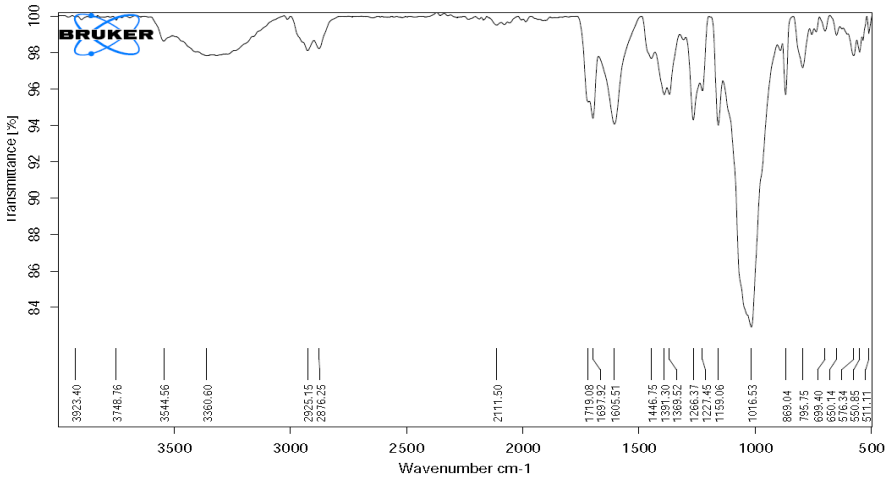


**Fig. 2: FTIR Spectra of Simvastatin -Excipients Physical Mixture**

**Differential scanning calorimetry (DSC):**

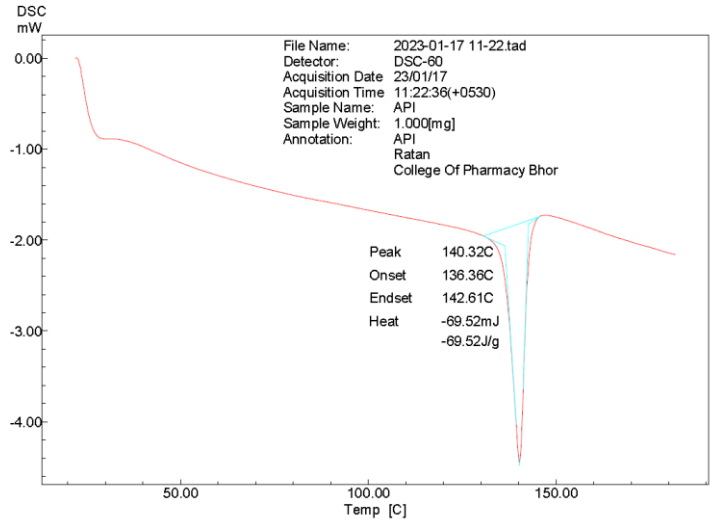


**Fig. 3: DSC of Simvastatin**

**Pre-Compression evaluation of Powder**:

Granules of all formulations were evaluated for angle of repose, bulk density, tap density, compressibility index, and Hausner's ratio.

**Table. 2. Evaluation of Powder**

| Formulation | Bulk density (g/cm3) | Tapped density ($g/cm^3$) | Compressibility index (%) | Hauser's ratio | Angle of repose (θ) |
|---|---|---|---|---|---|
| F1 | 0.44±0.04 | 0.50±0.04 | 12.00±0.4 | 1.13±0.2 | 25.17 |
| F2 | 0.45±0.01 | 0.50±0.02 | 10.00±0.1 | 1.11±0.4 | 26.22 |
| F3 | 0.40±0.02 | 0.45±0.01 | 11.11±0.3 | 1.125±0.1 | 22.29 |
| F4 | 0.47±0.05 | 0.53±0.03 | 11.32±0.4 | 1.12±0.3 | 23.7 |
| F5 | 0.44±0.06 | 0.51±0.05 | 13.72±0.2 | 1.151±0.4 | 24.22 |
| F6 | 0.41±0.02 | 0.46±0.02 | 10.86±0.1 | 1.12±0.2 | 22.78 |
| F7 | 0.47±0.03 | 0.54±0.01 | 12.96±0.5 | 1.14±0.3 | 23.26 |
| F8 | 0.53± 0.05 | 0.59±0.03 | 10.16±0.2 | 1.11±0.2 | 23.74 |
| F9 | 0.47±0.04 | 0.54±0.02 | 12.96±0.1 | 1.14±0.1 | 24.22 |

**Post-Compressional Studies:**

Simvastatin-controlled release matrix tablets were developed employing natural matrix-forming polymers guar gum and Xanthum gum by the direct compression method. The incorporation of Mg Stereate and talc in the designed systems was suggested to impart superior flow and enhance powder compaction in direct compression.

The physicochemical properties of the tablets are summarized in Table 3. The thickness of all tablet batches ranged from 2.1 ± 0.43 to 2.5 ± 0.43 mm. All the tablet formulae showed acceptable properties and complied with the pharmacopoeial specifications for weight variation, drug content, and friability. The weight of the tablets ranged from 198 ± 0.41 to 199 ± 0.12 mg. Drug uniformity results were found to be good among different batches; the percentage of drug content ranged from 95.72 ± 0.19% to 99.58 ± 0.46. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance.

**Table.3. Post-Compressional Evaluation of Tablet.**

| Formulation | Weight Variation mg | Hardness $Kg/cm^2$ | Friability % | Thickness mm | Content uniformity % |
|---|---|---|---|---|---|
| F1 | 198 ± 0.67 | 6.12 ± 0.37 | 0.45 ± 0.26 | 2.3± 0.43 | 99.25± 0.51 |
| F2 | 199 ± 0.12 | 6.71 ± 0.14 | 0.25 ± 0.15 | 2.5 ± 0.43 | 99. 58 ± 0.46 |
| F3 | 199 ± 0.42 | 6.13 ± 0.67 | 0.37 ± 0.18 | 2.3 ± 0.43 | 98.64 ± 0.12 |
| F4 | 198 ± 0.63 | 5.12 ± 0.12 | 0.39 ± 0.21 | 2.2 ± 0.43 | 98.30 ± 0.10 |
| F5 | 201 ± 0.16 | 6.51 ± 0.46 | 0.36 ± 0.38 | 2.4 ± 0.43 | 97.55 ± 0.26 |
| F6 | 199 ± 0.38 | 6.53 ± 0.81 | 0.38 ± 0.41 | 2.1 ± 0.43 | 97.21 ± 0.62 |
| F7 | 198 ± 0.41 | 6.16 ± 0.31 | 0.39 ± 0.26 | 2.3 ± 0.43 | 97.14 ± 0.62 |
| F8 | 199 ± 0.31 | 6.58 ± 0.56 | 0.42 ± 0.29 | 2.3 ± 0.43 | 98.23 ± 0.39 |
| F9 | 199 ± 0.51 | 6.15 ± 0.35 | 0.41 ± 0.36 | 2.2 ± 0.43 | 95.72 ± 0.19 |

***In -Vitro* Drug Release Studies:**

The In-vitro dissolution study for the Simvastatin controlled release tablets was carried out in a USP type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium for the first two hours followed by phosphate buffer pH 6.8 at 50 rpm and temperature 37±0.5°C. The drug release profiles depending on the concentration of retardant polymer present in the matrix tablets. The Drug release profiles are shown in Figure 4. Out of all 9 formulations only F2 can control drug release up to 12hr and also satisfies official specifications of USP for controlled release tablets i.e. NMT 20% of the labeled amount of drug is getting released in first 2 hr., NLT 50% in 6hr.& NLT 80% in 12hr of the labeled amount of drug.

**Table.4. % Drug release study of 9 formulations of Simvastatin**

| Time (hrs.) | PH Medium | Formulations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 % | F2 % | F3 % | F4 % | F5 % | F6 % | F7 % | F8 % | F9 % |
| 0 | PH 1.2 (Simulated Gastric Fluid) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | | 1.36 | 5.99 | 2.03 | 2.56 | 2.09 | 2.13 | 2.36 | 2.46 | 1.86 |
| 1 | | 4.26 | 12.08 | 5.25 | 5.29 | 5.25 | 5.32 | 5.55 | 5.55 | 4.75 |
| 2 | | 7.75 | 19.03 | 8.55 | 8.25 | 8.85 | 8.48 | 8.98 | 8.82 | 7.78 |
| 3 | PH 6.8 (Simulated Intestinal PH) | 14.24 | 26.62 | 12.04 | 11.68 | 15.27 | 12.04 | 15.14 | 12.78 | 11.81 |
| 4 | | 21.20 | 34.31 | 15.67 | 15.17 | 22.03 | 15.74 | 22.00 | 17.04 | 16.24 |
| 5 | | 24.73 | 42.13 | 19.43 | 19.03 | 28.95 | 19.67 | 29.12 | 21.53 | 21.10 |
| 6 | | 29.45 | 50.12 | 23.29 | 23.23 | 36.14 | 25.89 | 36.31 | 26.69 | 26.72 |
| 7 | | 34.78 | 58.18 | 30.48 | 28.09 | 43.33 | 32.81 | 43.53 | 33.28 | 33.35 |
| 8 | | 39.90 | 66.33 | 37.71 | 34.98 | 50.69 | 40.04 | 50.82 | 40.50 | 40.60 |
| 9 | | 44.76 | 74.55 | 45 | 42.27 | 57.98 | 47.32 | 58.18 | 48.16 | 48.62 |
| 10 | | 49.82 | 82.81 | 52.35 | 50.55 | 65.33 | 54.75 | 65.70 | 56.41 | 57.11 |
| 11 | | 54.98 | 91.16 | 60.41 | 59.61 | 72.72 | 63.00 | 73.42 | 65.10 | 66.46 |
| 12 | | 60.24 | 99.55 | 69.66 | 75.22 | 81.01 | 72.59 | 82.04 | 75.02 | 76.38 |

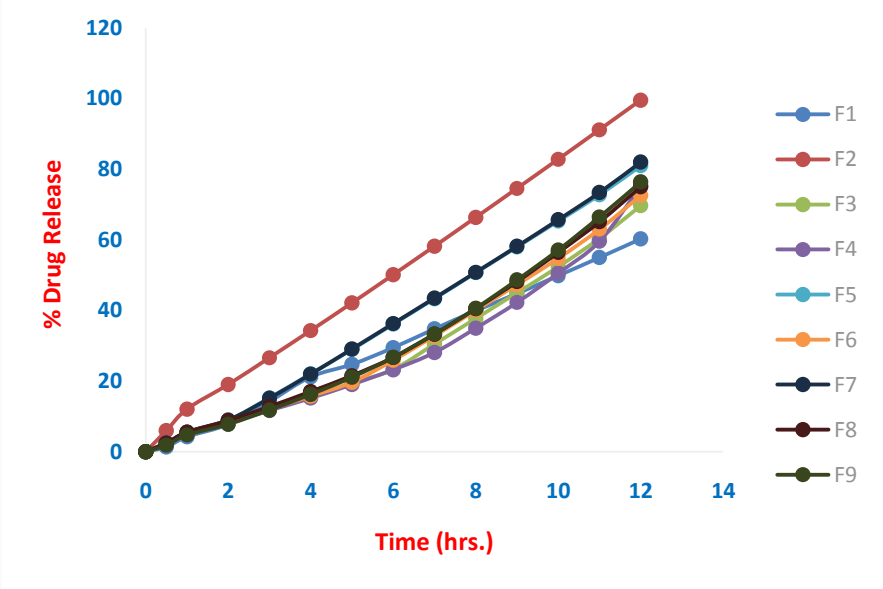


**Fig.4: % Drug release of 9 Formulation of Simvastatin controlled release tablets**

The drug release data were analyzed as per zero order, first order, Higuchi equation, and Korsmeyer Peppas equation models to know the order and mechanism of drug release from prepared matrix tablets. When the release data were analyzed as per zero and first order, models the correlation coefficient ($R^2$) values were relatively higher in the zero-order model with all Matrix tablets formulated indicating that the drug release from all these tablets followed zero-order kinetics.

**Table 5: Mathematical Modelling and Release Kinetics of Simvastatin Controlled Release Matrix Tablets**

| Formulation | Mathematical models (Kinetics ) | | | |
|---|---|---|---|---|
| | Zero-order correlation coefficient R2 | First order correlation coefficient R2 | Higuchi Model correlation coefficient R2 | Korsmeyer Peppas correlation coefficient R2 |
| F1 | 0.9810 | 0.9854 | 0.9695 | 0.993 |
| F2 | 0.9995 | 0.9268 | 0.9678 | 0.9968 |
| F3 | 0.9480 | 0.9222 | 0.893 | 0.9848 |
| F4 | 0.9810 | 0.8267 | 0.848 | 0.973 |
| F5 | 0.9959 | 0.9439 | 0.9451 | 0.9969 |
| F6 | 0.9480 | 0.9257 | 0.8979 | 0.9846 |
| F7 | 0.9810 | 0.9233 | 0.9414 | 0.9957 |
| F8 | 0.9786 | 0.9191 | 0.907 | 0.9863 |
| F9 | 0.9480 | 0.9136 | 0.8963 | 0.9894 |

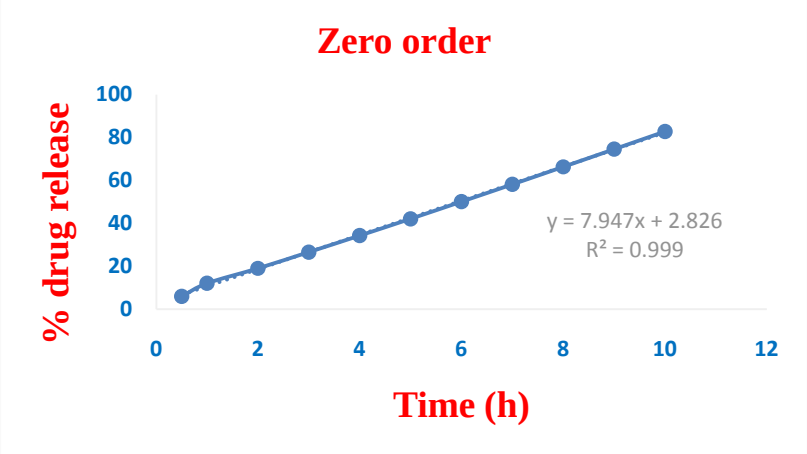


**Fig.5: Best fit model (Zero Order) of Formulation F2 of Controlled Release Matrix Tablet.**

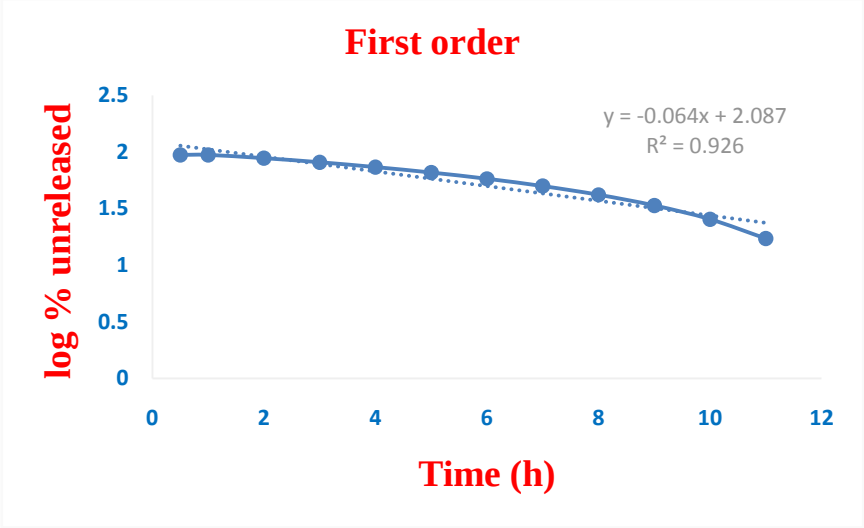


**Fig.6: Best fit model (First Order) of Formulation F2 of Controlled Release Matrix Tablet.**

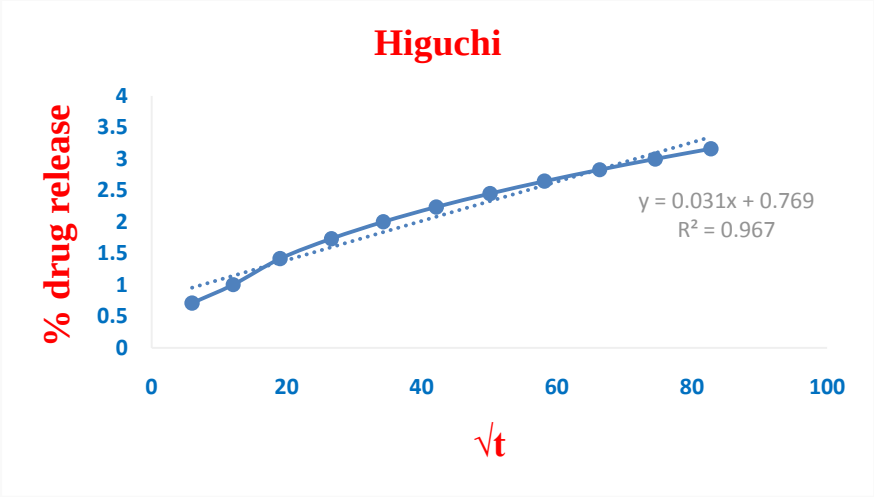


**Fig.7: Best fit model (Higuchi Model) of Formulation F2 of Controlled Release Matrix Tablet.**

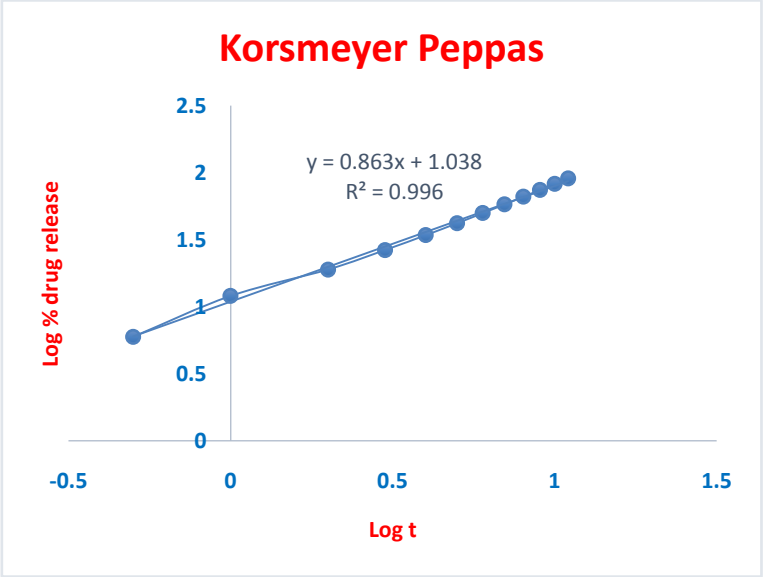


**Fig.8: Best fit model (Korsmeyer Peppas) of Formulation F2 of Controlled Release Matrix Tablet.**

When the release data were analyzed as per Mathematical models (Kinetics ) the correlation coefficient ($R^2$) values were relatively higher in the zero-order model with matrix formulated indicating that the drug release from all tablets followed zero order kinetics.

## CONCLUSION:

Controlled-release matrix tablets of Simvastatin were successfully developedemploying natural polymers. Among all the formulations, Constant and long period of drug release for 12hrs was observed in formulation F2. Hence, F2 was taken as the optimized formulation. From the above results, F2 was found suitable for controlled release. The optimized formulation followed the Zero-order drug release mechanism. The present research work investigates the applicability of Polymers such as Xanthan gum in the design and development of controlled-release tablet formulation of simvastatin utilizing the central composite factorial design. From the results, it was clearly understood that as the retardant (Xanthun Gum) Concentration increases the release rate of the drug was retarded. This may improve patient compliance by reducing the dosing frequency. Which will ultimately improve the therapeutic outcome.

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