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# FORMULATION AND EVALUATION OF SIMVASTATIN MATRIX TABLETS

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**Abstract:**
*Formulation and evaluation of the sustained release tablets of the Simvastatin. The before going to formulate the tablets the preformulation studies are carried out such as FTIR,calibration,organoleptic characters. The formulation is developed by using different types of the super disintegrates such as the hpmc and xanthin gum in different trails. The pre compression parameters such as angle of repose ,bulk density, true density, compressability index, these are found to be within the limits. The oral dispersible tablets of Nizatidine tablets are prepared by the direct compression method. The talc used as glidant and lactose used as lubricant mcc used as filler. The after development of oral dispersible tablets are undergo for evaluation parameters. Such as weight variation, thickness, friability, drug content, disintegration, and In vitro dissolution studies. They all are found in within range of limits. The in vitro drug release studies carried out by USP-II apparatus. The buffer medium 6.8 . The optimised formulation undergo for stability studies for 3 months .In stability studies the drug content and drug release studies carried out. These no degradation takes place in the drug content and drug release studies.*

***Key words:*** *Formulation, Evaluation of Simvastatin, matrix tablets*

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## INTRODUCTION:

Oral administration is the most suitable, widely used route of administration for both conventional and novel drug delivery systems. This route preferred for the systemic action of drugs. Several drugs have shown limited oral bioavailability due to their unfavorable physicochemical characteristics or absorption in specific sites [1]. In the case of chronic diseases, long term therapy, conventional formulations vital to be administered in numerous doses along these lines have a few burdens. Even. When administered orally, numerous therapeutic agents are subjected to wide pre-systemic elimination by first-pass hepatic metabolism and gastrointestinal degradation because of which low systemic bioavailability, the shorter extent of therapeutic effect and formation of inactive or harmful metabolites [2-3]. Matrix tablets composed of drug and polymer as release delaying material offer the simplest approach in developing a sustained release drug delivery system [4-6] Sustained-release (SR) tablet formulations are mostly preferred because of their better patient compliance, maintain uniform drug levels, moderate dose and side effects, and increase the safety boundary for high-potency drugs [7]. Simvastatin is an anti-hyperlipidaemic drug that widely used to control a high level of cholesterol in blood or hypercholesterolemia [8].

It is on the World Health Organization's List of Essential Medicines, which lists the Simvastatin most effective and safe medicines needed in a health system [9]. Synthetically derived from a fermentation product of the fungus Aspergillus terreus. Simvastatin inhibits hepatic hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate, the main step in cholesterol synthesis. This agent lowers plasma cholesterol and lipoprotein levels. Simvastatin modifies immune responses by suppressing MHC II (major histocompatibility complex II) on interferon gamma-stimulated, antigen-presenting cells such as human vascular endothelial cells.[10-13].

## MATERIALS AND METHODOLOGY:

### MATERIALS

Simvastatin Procured from**,** Provided by Chandra labs Hyderabad. Ethyl cellulose, Talc, Magnesium Stearate, Hydroxy propyl cellulose are Standard chemical Reagents

### METHODOLOGYPREFORMULATION STUDIES:

### ORAGANOLEPTIC CHARACTERS:

The pre formulation studies such as the colour, odour, taste can be done by visually.

### SOLUBILITY STUDIE:

The solubility studies are done by using various solvents such as the ethanol, methanol, acetone, and other organic solvents.

### DRUG AND EXCIPIENT COMPATABILITY STUDIES:

The drug and excipient compatability studies are done by FTIR Studies by using Kbr pellet method. First the 1 gm of the drug powder is taken under kept for the FTIR studies. The 1gm of drug and polymer take and kept under FTIR studies the peaks which are came for drug product the nearer to the drug the polymer peaks will come. If they are not came the drug and excipients are in compatable with each other.

### CONSTRUCTION OF CALIBRATION CURVE IN 6.8 BUFFER:

To take 10mg of Simvastatin active substance it is going to disperse in 10ml of water in volumetric it is 1000ppm.From 1000ppm to take 1 ml and it is disperse in 10ml of volumetric flask it is 100ppm.From that take 1 ml and make up to 10 ml in volumetric flask it is 10ppm.To check absorbance at 10ppm if the absorbance is high undergo for serial diluations like 1,2,3,4,5, ml and check the absorbance at 280 nm by using U.V visible spectroscopy.

### CONSTRUCTION OF CALIBRATION CURVE IN ETHANOL:

To take 10mg of Simvastatin active substance it is going to disperse in 10ml of ethanol in volumetric it is 1000ppm.From 1000ppm to take 1 ml and it is dispersing in 10ml of volumetric flask it is 100ppm.From that take 1 ml and make up to 10 ml in volumetric flask it is 10ppm.To check absorbance at 10ppm if the absorbance is high undergoing for serial dilutions like 1,2,3,4,5, ml and check the absorbance at 315nm by using U.V visible spectroscopy.

**FORMULATION TABLE OF SIMVASTATIN SUSTAINED RELEASE TABLETS**

**Table No 1 : showing formulation table of Simvastatin**

| Ingridients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Simvastatin** | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| **HPMCK4M** | 5 | - | 5 | 10 | - | 10 | 20 | - | 20 | 20 |
| **Stearic acid** | - | 5 | 5 | - | 10 | 10 | - | 20 | 20 | - |
| **Cross povidone** | 5 | 5 | 5 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Mcc** | 236 | 236 | 231 | 226 | 226 | 216 | 216 | 216 | 196 | 206 |
| **Talc** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Magnesium stearate** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Total wt** | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

**SIMVASTATIN TABLETS PREPARED BY USING DIRECT COMPRESSION METHOD:**

**Dispensing:** The drug and all ingredients are dispensed above mentioned in table.

**Mixing:** All ingredients are mixing except adding Mg.Strate and talc

**Seiving:** The drug and all ingredients undergo for sieving in sieve no:40

**Mixing:** After sieving the drug and expect Mg. Stearte and talc all ingredients are mixed together.

**Compression:** After mixing the all along with mg.stearte and talc they undergo for punching in a multi compression mission

**POST COMPRESSION PARAMETERS:**

**WEIGHT VARIATION TEST:**

The post compression parameters in that weight variation study is done. The weight variation is done by the taking 20 tablets. First to take the individual weight for 20 tablets. Finally to take final weight of the group of 20 tablets by using the Essae electronic balance. None of the individual Tablet weight should be less than 90% and more than 110% of the average weight.

Calculated by using the following formula;

$$\text{Weight variation} = \frac{(\text{Weight of Tablet-Average weight})}{\text{Average weight of Tablet}} \times 100$$

**HARDNESS:**

The after formulation of the tablets the post compression parameter such as the hardness was done by using the Monsanto hardness tester. Hardness defined as the it indicates the capability of a tablet to withstand mechanical shocks while handling. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

**THICKNESS:**

The thickness of the tablets is done by using Digital venire calipers. By using this the diameter of the tablets are done. Five tablets were used, and average values were calculated.

**FRIABILITY TEST:**

The formulated tablets are under kept for the friability test. The friability can be done by the using friability apparatus that is Roche Friabilator (USP EF-2 Electrolab.). It is expressed in percentage (%). The friability is done by the taking 10 tablets and they first weight that is initial weight of the tablets. After that the tablets are kept in the fribilator. The friability operator started the rpm set for 4mins at 50 rpm about to 100 revaluations.

$$\%F = 100\ (1\text{-}W0/W)\ \%$$

Friability of tablets less than 1% are considered acceptable.

***IN-VITRO* DRUG RELEASE STUDIES:**

The In-vitro drug release studies are performed by the using USP type II apparatus paddle method. For In - vitro drug release studies 6.8 buffer is used the dissolution volume is 900ml.The room temperature is 37±5ºC. The time interval is 10mins.The drug will release up to the 10 hrs The 1ml of sample is taken into the bowl it is replaced by the fresh sample for maintain

of the sink conditions. The sample is analysed in U.V visible spectroscopy at 315nm.

**STABILITY STUDIES**

Stability studies protect the maintenance of product quality, safety and efficacy throughout the shelf life are contemplated as pre-requisite for the acceptance and approval of any pharmaceutical substance. These studies are appropriate to be conducted in a planned way following the guidelines issued by ICH, WHO and or other agencies. Importance of different technologies followed for stability testing of pharmaceutical substances, guidelines issued for stability testing and other aspects.

## RESULTS AND DISCUSSION:

**ORGANOLEPTIC CHARACTERS:**

**Table No 2: showing results of organoleptic characters**

| **Properties** | **Results** |
|---|---|
| Description | crystalline powder |
| Taste | bitter taste |
| Odour | mild, characteristic odor |
| Colour | White |

**SOLUBILITY STUDIES**

**Table No 3: Solubility of the Simvastatin in various solvents**

| **Solvent** | **Solubility properties of drug** |
|---|---|
| Water | Slightly Soluble |
| Alcohol | Soluble |
| chloroform | Soluble |
| acetone | soluble |

**CALIBRATION CURVE OF THE SIMVASTATIN IN PH 6.8 BUFFER**

**Table No 4: showing calibration values of Simvastatin**

| **Concentration (µg/ml)** | **Absorbance in pH 6.8 buffer** |
|---|---|
| 0 | 0 |
| 1 | 0.177 |
| 2 | 0.392 |
| 3 | 0.563 |
| 4 | 0.741 |
| 5 | 0.921 |

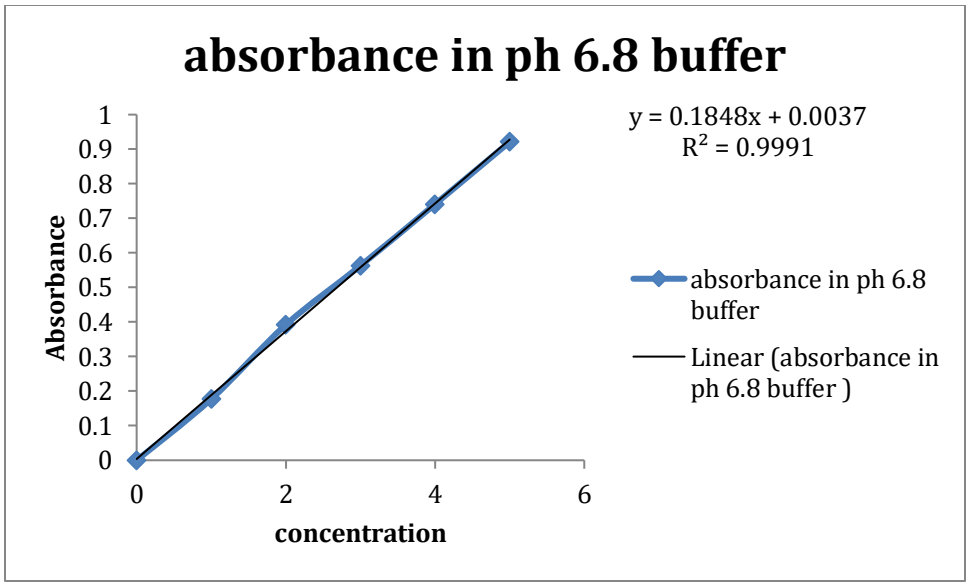


**Fig. No1: showing picture of the calibration plot in 6.8 buffer**

**CALIBRATION CURVE OF THE SIMVASTATIN IN METHANOL**

**Table. No 5: showing calibration values in methanol**

| Concentration (µg/ml) | Absorbance in methanol |
|---|---|
| 0 | 0 |
| 1 | 0.14 |
| 2 | 0.29 |
| 3 | 0.45 |
| 4 | 0.63 |
| 5 | 0.78 |

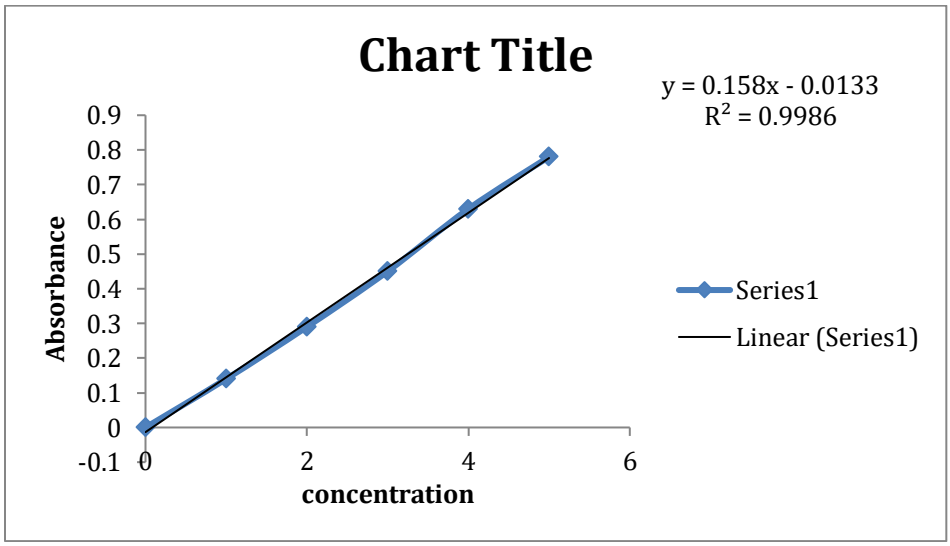


**Fig. No 2: showing calibration plot in methanol**

**FTIR STUDIES:**

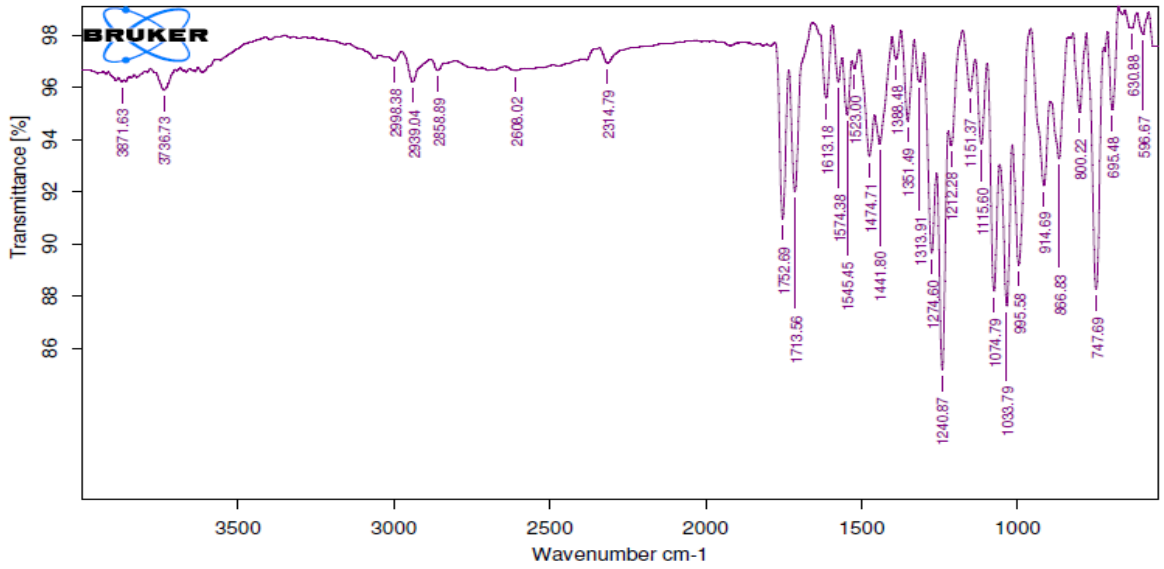


**Fig. No 3: pure spectra of the Simvastatin**

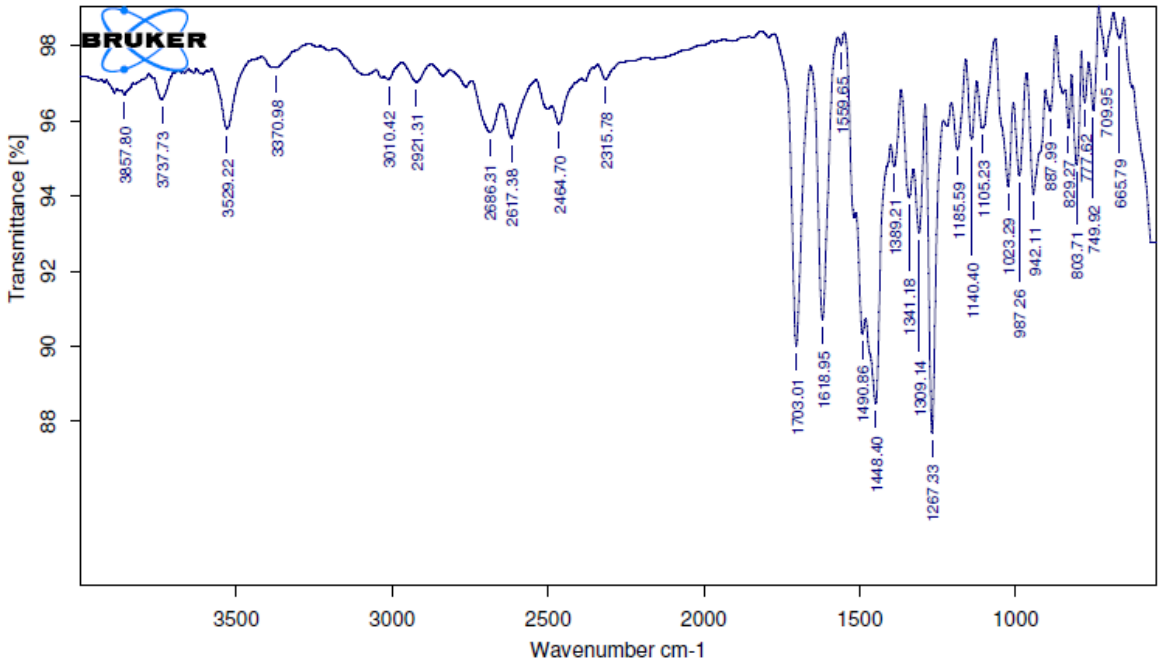


**Fig. No 4: The fig shows the FTIR spectra of the drug and polymer blend**

**PRE-COMPRESSION PARAMETERS**

**Table. No 6: showing values of the pre compression parameters**

| Formulation | Angle of repose (θ) | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| F1 | 25.38±0.13 | 0.40±0.02 | 0.50.02 | 20±0.13 | 1.25±0.01 |
| F2 | 22.52±0.28 | 0.44 ±0.02 | 0.56±0.04 | 20±0.04 1. | 1.27±0.01 |
| F3 | 27.19±0.19 | 0.44±0.00 | 0.54±0.01 | 18.61±0.11 | 1.22±0.02 |
| F4 | 28.51±0.16 | 0.45±0.01 | 0.55±0.01 | 18.33±0.15 | 1.22±0.01 |
| F5 | 23.60.21 | 0.41±0.01 | 0.50±0.00 | 18±0.05 | 1.21±0.02 |

**Discussion:** The all the F1-F5 formulations pre compression parameters such as the angle of repose, bulk density,tap density,husners ratio,compressability index all comes under the within range of limits. All the formulations fallow the good flow.

**Table. No 7: showing values of the pre compression parameters**

| Formulation | Angle of repose (θ) | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| F6 | 24.38±0.13 | 0.38±0.02 | 0.48.02 | 20.83±0.13 | 1.26±0.01 |
| F7 | 23.52±0.28 | 0.39 ±0.02 | 0.47±0.04 | 17.02±0.04 1. | 1.20±0.01 |
| F8 | 24.19±0.19 | 0.39±0.00 | 0.45±0.01 | 13.33±0.11 | 1.15±0.02 |
| F9 | 22.51±0.16 | 0.40±0.01 | 0.44±0.01 | 9.09±0.15 | 1.1±0.01 |
| F10 | 23.60.21 | 0.40±0.01 | 0.46±0.00 | 13.04±0.05 | 1.15±0.02 |

**Discussion:** The all the F6-F10 formulations pre compression parameters such as the angle of repose, bulk density, tap density,husners ratio,compressability index all comes under the within range of limits. All the formulations fallow the good flow.

**POST COMPRESSION PARAMETERS FOR F1-F5 FORMULATIONS**

**Table. No 8: showing post compression parameters of F1-F5**

| Formulation | Weight variation | Thickness (mm) | Hardness ($Kg/cm^2$) | Friability (%) | Drug content (%) | Disintigration (mins) |
|---|---|---|---|---|---|---|
| F1 | 299±1.02 | 2.50±0.01 | 3.2±0.06 | 0.232 | 87.24±0.22 | 35 |
| F2 | 298±0.08 | 2.6±0.00 | 3.8±0.06 | 0.246 | 89.57±0.42 | 38 |
| F3 | 298.002 | 2.5±0.01 | 3.71±0.00 | 0.386 | 90.43±0.13 | 30 |
| F4 | 299±0.003 | 2.00±0.01 | 3.65±0.06 | 0.326 | 92.83±0.42 | 28 |
| F5 | 299±0.08 | 2.10±0.01 | 3.65±0.10 | 0.446 | 92.86±0.32 | 28 |

**POST COMPRESSION PARAMETERS FOR F6-F10 FORMULATIONS**

**Table. No 9: showing post compression parameters of F1-F5**

| Formulation | Weight variation | Thickness (mm) | Hardness (Kg/cm$^2$) | Friability (%) | Drug content (%) | Disintigration (mins) |
|---|---|---|---|---|---|---|
| F6 | 299±1.02 | 2.40±0.01 | 3.4±0.06 | 0.232 | 93.24±0.22 | 25 |
| F7 | 298±0.08 | 2.2±0.00 | 3.1±0.06 | 0.256 | 94.57±0.42 | 26 |
| F8 | 301.002 | 2.3±0.01 | 3.2±0.00 | 0.226 | 96.43±0.13 | 25 |
| F9 | 300±0.003 | 2.00±0.01 | 3.0±0.06 | 0.226 | 99.83±0.42 | 24 |
| F10 | 300±0.08 | 2.50±0.01 | 3.1±0.10 | 0.256 | 96.86±0.32 | 25 |

**IN –VITRO DRUG RELEASE STUDIES FOR ALL FORMULATIONS**

**Table No 10: showing in vitro drug release studies**

| Time in hrs | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 10.23 | 12.65 | 15.89 | 18.56 | 20.56 | 22.32 | 22.52 | 21.65 | 22.15 | 23.21 |
| 3 | 18.35 | 25.65 | 28.36 | 30.56 | 35.62 | 40.53 | 41.53 | 42.62 | 45.15 | 48.65 |
| 4 | 75.35 | 50.36 | 55.68 | 56.12 | 57.65 | 57.65 | 56.72 | 58.56 | 59.12 | 58.52 |
| 6 | 89.35 | 60.78 | 64.65 | 68.42 | 70.56 | 70.55 | 71.62 | 72.62 | 78.32 | 79.22 |
| 8 | 100.33 | 80.41 | 70.42 | 74.74 | 79.56 | 80.18 | 81.43 | 82.65 | 92.63 | 89.23 |
| 10 | 105.65 | 85.96 | 80.75 | 82.23 | 85.65 | 89.83 | 89.53 | 89.65 | 98.65 | 96.23 |

**ALL COMPARATIVE GRAPH**

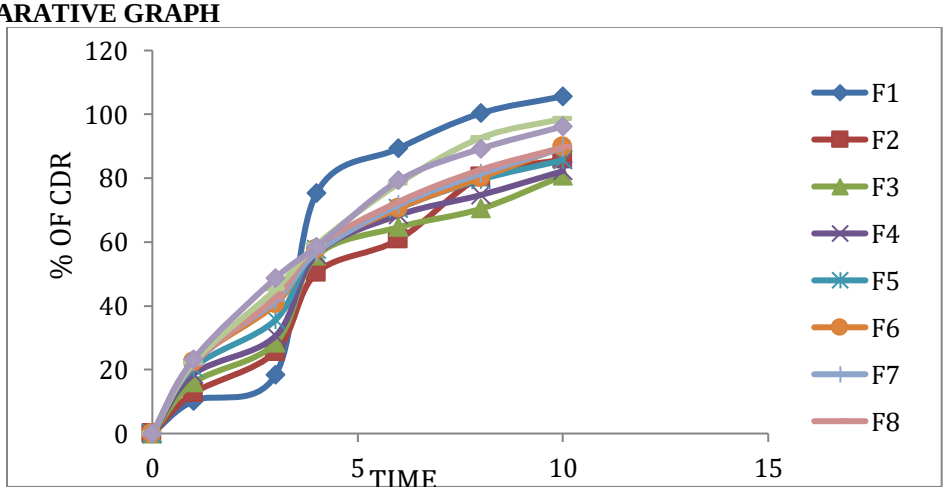


**Fig. No 5: showing picture of in vitro drug release studies comparative graph**

**COMPARATIVE GRAPHS FOR F1-F5:**

| Time in hrs | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 10.23 | 12.65 | 15.89 | 18.56 | 20.56 |
| 3 | 18.35 | 25.65 | 28.36 | 30.56 | 35.62 |
| 4 | 75.35 | 50.36 | 55.68 | 56.12 | 57.65 |
| 6 | 89.35 | 60.78 | 64.65 | 68.42 | 70.56 |
| 8 | 100.33 | 80.41 | 70.42 | 74.74 | 79.56 |
| 10 | 105.65 | 85.96 | 80.75 | 82.23 | 85.65 |

**Table No 11: Comparative Graphs for F1-F5**

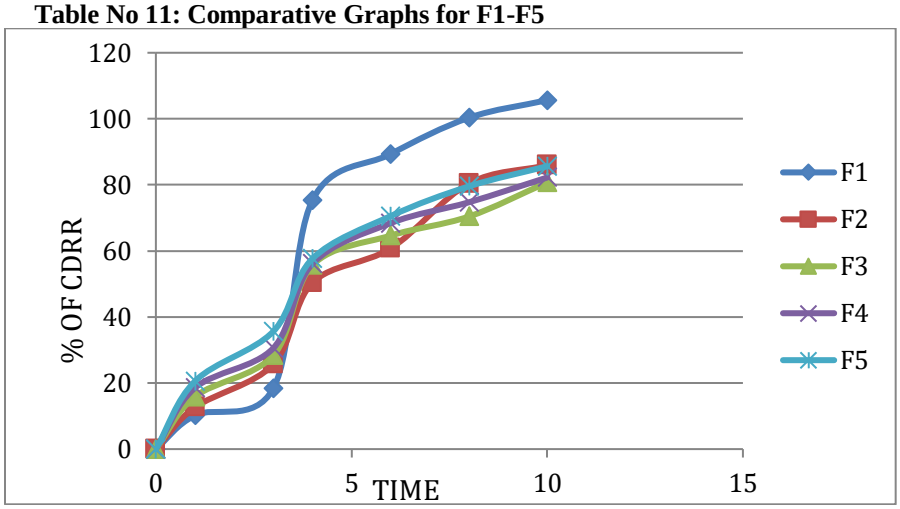


**Fig .No 6: Picture showing all Comparative drug release profile F1-F5**

**COMPARATIVE GRAPHS FOR F6-F10:**

| Time in hrs | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 22.32 | 22.52 | 21.65 | 22.15 | 23.21 |
| 3 | 40.53 | 41.53 | 42.62 | 45.15 | 48.65 |
| 4 | 57.65 | 56.72 | 58.56 | 59.12 | 58.52 |
| 6 | 70.55 | 71.62 | 72.62 | 78.32 | 79.22 |
| 8 | 80.18 | 81.43 | 82.65 | 92.63 | 89.23 |
| 10 | 89.83 | 89.53 | 89.65 | 98.65 | 96.23 |

**Table No 12: Comparative Graphs for F6-F10**

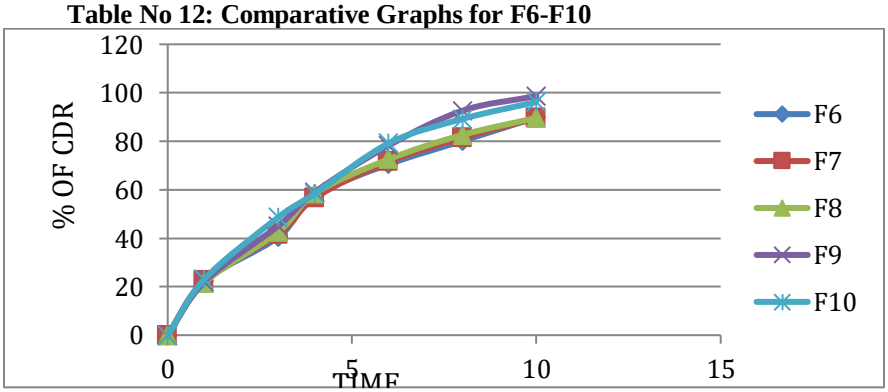


**Fig. No 7: Picture showing all Comparative drug release profile for F6-F10Kinetic profile data:**

**KINETIC STUDIES**

| Time | %cdr | Log T | √T | Log%cdr | ARA | Log%ARA |
|---|---|---|---|---|---|---|
| 0 | 0 | 1 | 0 | 0 | 100 | 2 |
| 1 | 22.15 | 0 | 1 | 1.34537373 | 77.85 | 1.89125862 |
| 3 | 45.15 | 0.47712125 | 1.73205081 | 1.65465775 | 54.85 | 1.73917663 |
| 4 | 59.12 | 0.60205999 | 2 | 1.77173443 | 40.88 | 1.61151089 |
| 6 | 78.32 | 0.77815125 | 2.44948974 | 1.89387268 | 21.68 | 1.33605928 |
| 8 | 92.63 | 0.90308999 | 2.82842712 | 1.96675166 | 7.37 | 0.86746749 |
| 10 | 98.65 | 1 | 3.16227766 | 1.99409709 | 1.35 | 0.13033377 |

**Table No 13: table showing kinetic studies**

**ZERO ORDER REACTION**

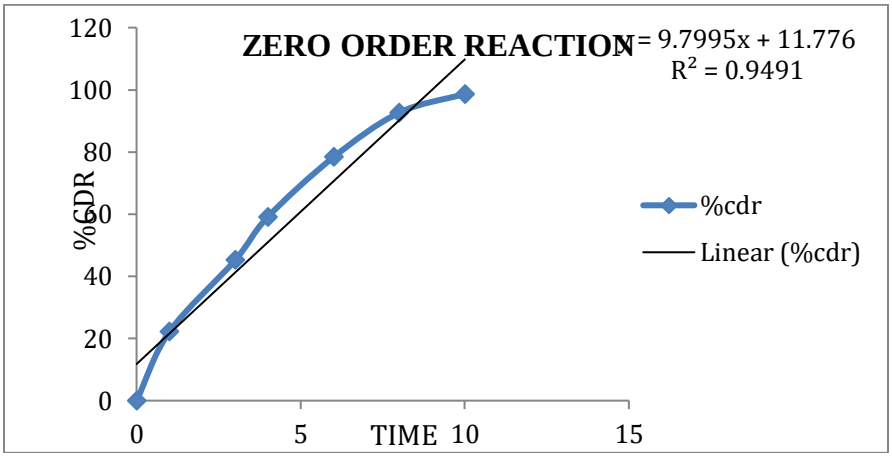


**Fig.No:8 showing picture of zero order reaction**

**FIRST ORDER REACTION**

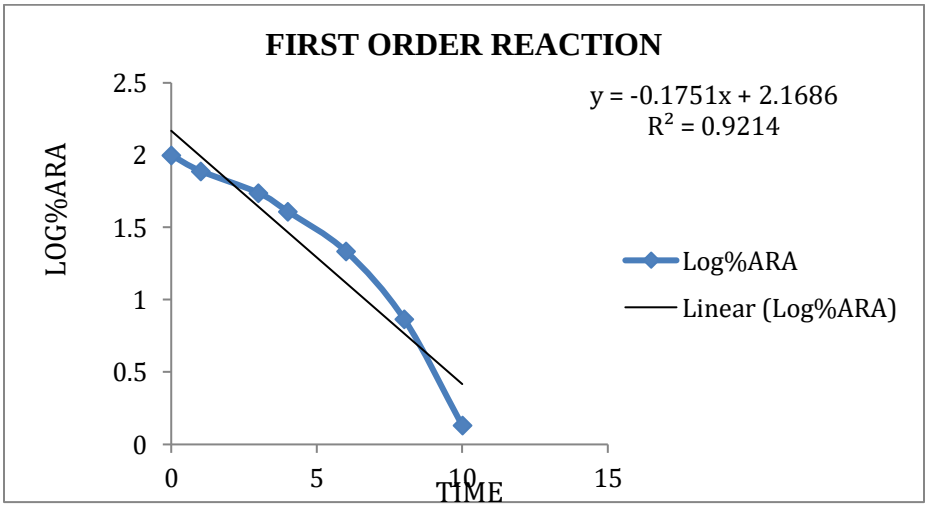


**Fig.No: 9 showing picture of First order Reaction**

**HIGUCHI EQUATION**

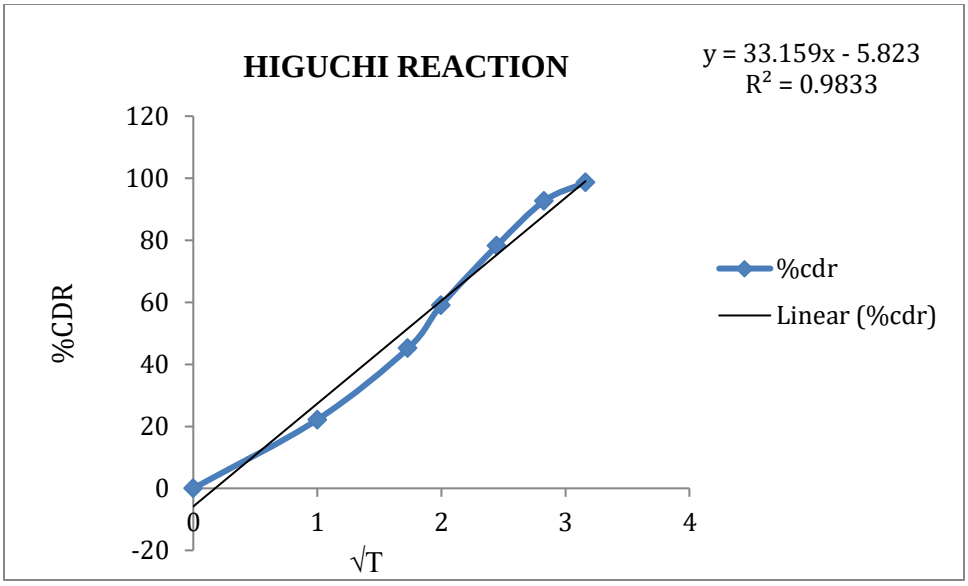


**Fig.No:10 showing picture of higuchi**

**KROSS MAYER PEPPAS**

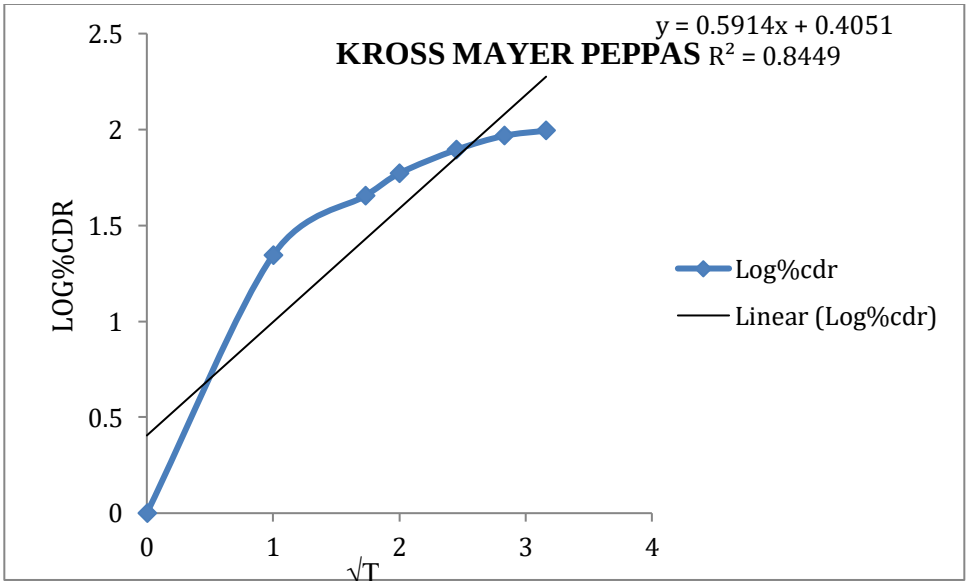


**Fig.No:11 showing picture of krossmayer peppas**

**STABILITY RESULTS:**

**STABILITY SAMPLES ARE STORED AT**

- Accelerated: 40±2$^0$C/75±5% RH
- Intermediate: 30±2$^0$C/65±5% RH
- Long term: 25±2$^0$C/60±5% RH

**TESTING INTERVALS**

- Accelerated: Initial, 3 months.

**Table No 14: Results of stability studies of optimized formulation F-9**

| Formulation Code | Parameters | Initial | 1st month | 2nd month | 3rd month | Limits as per Specifications |
|---|---|---|---|---|---|---|
| F-9 | $25^0$C/60%RH % Release | 98.65 | 99.7 | 97.56 | 99.53 | Not less than 85 % |

**Discussion:** It was concluded that stability studies of the optimized F9was carried out using the samples at temperatures $40^0C \pm 2^0C$/ 75% ± 5%RH for a period 3 month the Simvastatin tablets are observed and there is no significant change in the release characteristics and physicochemical properties.

**SUMMARY**

Formulation and evaluation of the sustained release tablets of the Simvastatin. For development of the tablets different excipients are used. The used various excipients are the HPMC K4M, Xanthin gum, pvpk30, Mg.sterate, Talc, MCC used as the diluents, Mg.sterate used as the lubricants. Talc is used as Glidant.

For formulation design the literature review is carried out. The drugs selection and the polymer selection is based on the collection of review literature. The polymers choosing also carried out by the review literature.

Before going to development the pre formulation studies are done such as the color ,odor, taste, solubility studies .The drug and the excipient compatability studies are done by using the FTIR studies.

The formulation is developed by the using direct compression method.The formulation is prepared by using different excipients .The excipients are hpmc and xanthin gum in various compositions for drug to release in 10hrs. The pre compression parameters are done such as the bulk density ,tap density, compressability index, Hauners ratio, Angle of repose. The all parameters are come under within range good flow. The post compression parameters are done such as the harness, thickness, weight variation, friability, disintegration.

The evaluation parameters of the optimised formulation F9 tablets values:

The weight variation of matrix tablets, 300mg

The hardness of the matrix tablets, 3.1**(Kg/cm$^2$)**

Thickness of the matrix tablets, 2.50mm

Disintegration of the matrix tablets,25 mins

Friability of the matrix tablets, 0.256 %

In-vitro drug dissolution studies of the oral dispersible tablets, 98.65%

The all parameters come under acceptable criteria within range of limts. The In-vitro drug release studies are done by USP-II apparatus paddle method. The optimised formulation F9gives the prolong release upto 10hrs the drug release

**CONCLUSION:**

Formulation and evaluation of the sustained release tablets of the Simvastatin. The before going to formulate the tablets the Preformulation studies are carried out such as FTIR, calibration, organoleptic characters. The formulation is developed by using different types of the super disintegrates such as the hpmc and xanthin gum in different trails. The pre compression parameters such as angle of repose, bulk density, true density, compressibility index, these are found to be within the limits. The oral dispersible tablets of Nizatidine tablets are prepared by the direct compression method. The talc used as glidant and lactose used as lubricant mcc used as filler. The after development of oral dispersible tablets are undergo for evaluation parameters. Such as weight variation, thickness, friability, drug content, disintegration, and In vitro dissolution studies. They all are found in within range of limits. The in vitro drug release studies carried out by USP-II apparatus. The buffer medium 6.8 . The optimised formulation undergo for stability studies for 3 months .In stability studies the drug content and drug release studies carried out. These no degradation takes place in the drug content and drug release studies.

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