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# Formulation & Evaluation of Simvastatin Sustained Release Tablets by Using Different Polymers

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**Abstract** **Review Article**

***Purpose:*** The main objective of present research investigation is to formulate sustained release tablets of Simvastatin using different polymers. Simvastatin, an anti-hyperlipidemic agent belong BCS class-II agent. ***Methods:*** The SR tablets of Simvastatin were prepared employing different concentrations of HPMCK15M, xanthan gum and carbopol and tablets are prepared by using direct compression method. ***Results and discussion:*** Total six formulations are designed and evaluated for hardness, friability, thickness, % drug content and In-vitro drug release. From the results it was concluded that all the formulations are found to be within the pharmacopeia limits and in-vitro dissolution profiles of all formulation are subjected to different kinetic models, the statistical parameters like slope intercept and regression coefficient were calculated. ***Conclusion:*** It was concluded that the polymeric combination of HPMCK15M with xanthan gum in the ratio 1:1 was able to retarded the release of Simvastatin from the tablets to the24th hour and showed an ideal release pattern necessary for sustained release tablet.
**Keywords:** Simvastatin, Sustained release tablet, HPMCK15M, Xanthan gum and Carbopol.


## INTRODUCTION

Traditional drug delivery system[1] has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a formulation with control release that maintain a near-constant or uniform blood level. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

### Drawbacks of Conventional Dosage Forms

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

### Sustained release concept

Sustained release, sustained action, prolong action, controlled release, extended action, depot are terms used to identify drug delivery systems that are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of orally administer this period is measured in hours while in the case of injectables this period varies from days to months[2,3].

### Advantages of sustained release dosage forms:[4]

- Control of drug therapy is achieved.
- Rate and extent of drug absorption can be is modified
- Frequency of drug administration is reduced.
- Patient compliance can be improved.

### Disadvantages of sustained release dosage forms [5,6]

- It not permits prompt termination of therapy.
- Less flexibility in dose adjustment.
- These dosage forms are designed on the basis of average biological half-life.
- They are costly

## MATERIAL AND METHODS

Simvastatin, marketed under the trade name Zocor among others, is a lipid-lowering medication. It is used along with exercise, diet and weight loss to decrease elevated lipid (fat) levels. It is also used to decrease the risk of heart problems in those at high risk. It is taken by mouth. Simvastatin, the methylated form of lovastatin, is an oral anti-lipemic agent which inhibits HMG-CoA reductase. Simvastatin is used in the treatment of primary hypercholesterolemia and is effective in reducing total LDL-cholesterol as well as plasma triglycerides and apolipoprotein B.

**Formulation and development**

Pre-formulation characteristics: [7, 8] Preformulation testing is the first step in rational development of dosage forms of a drug substance. Preformulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, preformulation studies were performed for the obtained sample of drug for identification and compatibility studies.

Solubility: The solubility of a candidate drug may be the critical factor for determining its usefulness, since aqueous solubility dictates the amount of compound that will dissolve and therefore, the amount available for absorption. The solubility of the drug sample was carried out in different solvents (aqueous and organic).

Loss on drying: 1-2 g of sample of API was weighed and the powder was kept in a moisture balance apparatus at 105˚C, auto mode and the moisture content was calculated.

Flow Properties: Angle of repose, Bulk density, Tapped density and Compressibility index of API was done. Tablets were prepared by setting various concentrations of polymers and combination of polymers along with glidents and lubricants.

**Preparation of sustained Release Simvastatin tablets by Direct Compression-**

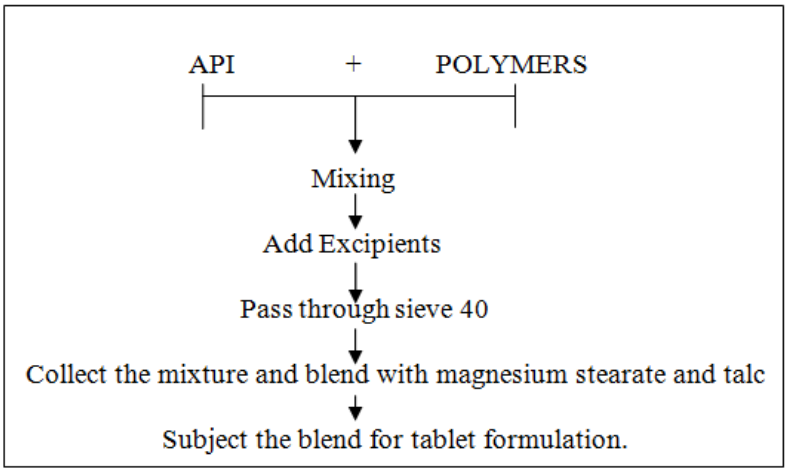


**Fig-1: Schematic representation for preparation of tablets By direct compression method**

**Formula Design**

**Table-1: Formula Design**

| INGREDIENTS | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| API (mg) | 40 | 40 | 40 | 40 | 40 | 40 |
| MCC (mg) | 165 | 165 | 165 | 165 | 165 | 165 |
| HPMCK15M (mg) | 30 | - | - | 15 | 15 | - |
| Carbopol (mg) | - | 30 | - | 15 | - | 15 |
| xanthan gum (mg) | - | - | 30 | - | 15 | 15 |
| Talc (mg) | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| Magnesium stearate (mg) | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| Total weight (mg) | 250 | 250 | 250 | 250 | 250 | 250 |

Tablet Compression: All formulations from $F_1$ to $F_6$ were compressed using 8mm oval shaped punches as per company requirement (caddmach compression machine).

**Evaluation parameters**

- Uniformity of weight
- Thickness
- Hardness
- Friability
- Disintegration
- Dissolution test

## RESULTS AND DISCUSSION

**Solubility Profile of Simvastatin**

**Table-2: Various Physico-chemical characteristics of Simvastatin**

| Sr.No | Drug Name | Melting point ($^0$C) | Solubility (mg/ml) | | |
|---|---|---|---|---|---|
| | | | WATER | ALCOHOL | CHLOROFORM |
| 1 | Simvastatin | 138 $^0$C | Insoluble | Soluble | Soluble |

Standard Calibration Curve of Simvastatin at 233.0 nm:

**Table-3: Absorbance data for calibration curve of Simvastatin in 6.8 pH Phosphate buffer**

| Conc (µg/ml) | Area |
|---|---|
| 2 | 0.292 |
| 4 | 0.525 |
| 6 | 0.715 |
| 8 | 0.901 |
| 10 | 1.081 |

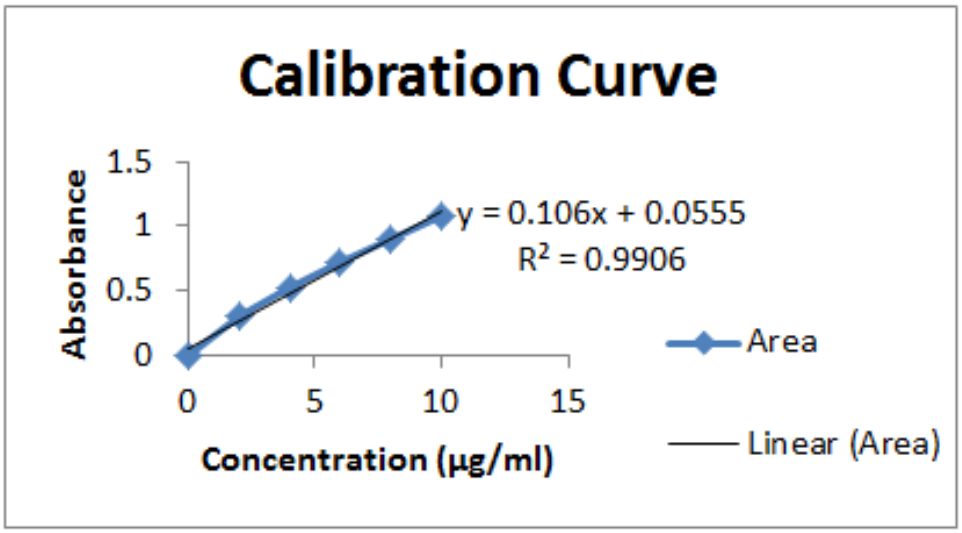


**Fig-2: Calibration curve for Simvastatin**

Evaluation of rheological characteristics of sustained release tablets of Simvastatin

**Table-4: Evaluation of Pre Compression Parameters**

| Formulation Code | Bulk density (gm/ml) | Tapped density (gm/ml) | Compressibility index % | Hausner's Ratio | Angle of repose (°θ) |
|---|---|---|---|---|---|
| $F_1$ | 0.6000±0.033 | 0.6154±0.014 | 2.5000±0.012 | 1.0256±0.023 | 29±0.041 |
| $F_2$ | 0.4643±0.019 | 0.5416±0.021 | 14.2857±0.008 | 1.1666±0.012 | 28±0.031 |
| $F_3$ | 0.4727±0.036 | 0.5416±0.013 | 12.7272±0.017 | 1.1458±0.007 | 28±0.022 |
| $F_4$ | 0.4527±0.021 | 0.5382±0.018 | 15.8730±0.027 | 1.1886±0.011 | 29±0.041 |
| $F_5$ | 0.4489±0.042 | 0.5550±0.021 | 19.1176±0.031 | 1.2363±0.029 | 34±0.11 |
| $F_6$ | 0.4687±0.012 | 0.5555±0.016 | 15.6250±0.016 | 1.1852±0.022 | 27±0.23 |

All the values expressed as mean ±S.D, n=3

**Evaluation of Post-Compression Parameters**

**Table-5: Evaluation of Post-Compression Parameters**

| Formulation Code | Hardness of tablets (kg/cm2) | Friability of Tablets* (%) | Weight variation (mg ±SD) | Thickness | Percentage drug content per tablet* (%) |
|---|---|---|---|---|---|
| F1 | 4.9±0.10 | 0.3±0.02 | 748±2.5 | 3.4±0.01 | 103.02±0.4 |
| F2 | 4.6±0.08 | 0.5±0.013 | 752±1.3 | 3.3±0.012 | 102.23±0.9 |
| F3 | 4.9±0.12 | 0.4±0.016 | 750±2.7 | 3.3±0.011 | 98.99±0.83 |
| F4 | 4.4±0.06 | 0.7±0.012 | 747±2.0 | 3.4±0.011 | 101.06±0.6 |
| F5 | 4.6±0.15 | 0.4±0.006 | 750±1.3 | 3.2±0.013 | 100.35±0.22 |
| F6 | 4.8±0.13 | 0.4±0.014 | 753±1.7 | 3.4±0.012 | 99.85±0.27 |

All the values expressed as mean±S.D, n=3

**In-vitro drug release of various formulations**

Drug release studies were carried out by using USP type II (paddle) apparatus. 900 ml of 6.8 phosphate buffer was used as dissolution medium and the basket was rotated at 50 rpm at temperature (37ºC ± 0.5ºC). Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analyzed using HPLC.

The in-vitro dissolution studies are done to obtain the cumulative drug release profile of the drug and to procure the optimized formulation among all to undergo the stability and other evaluation parameters.

**Table-6: Dissolution studies**

| TIME (Hrs) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 35 | 37 | 32 | 30 | 34 | 29 |
| 4 | 58 | 49 | 45 | 42 | 41 | 47 |
| 8 | 76 | 66 | 63 | 66 | 60 | 63 |
| 16 | 89 | 95 | 89 | 88 | 86 | 84 |
| 24 | 100 | 99 | 100 | 97 | 93 | 97 |

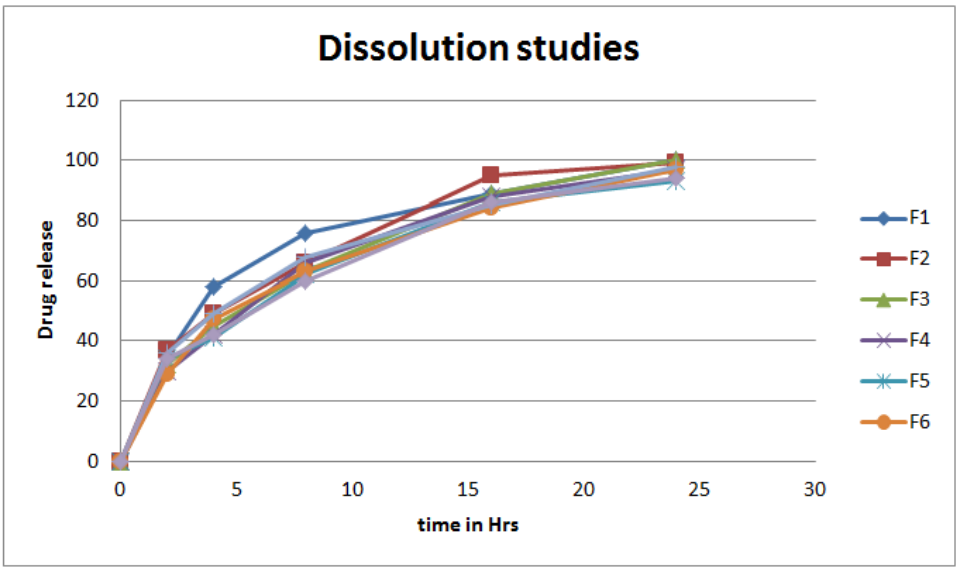


**Fig-3: In-Vitro Dissolution studies**

**Kinetic studies for optimized ($F_5$) formula**

**Table-7: Kinetic studies for optimised ($F_5$) formula**

| Time | Log Time | Square root of Time | Cumulative % Drug Released | Log Cumulative % Drug Released | Cumulative % Drug Remained | Log Cumulative % Drug Remained |
|---|---|---|---|---|---|---|
| 0 | - | 0 | 0 | 0 | 100 | 2 |
| 2 | 0.3010 | 1.414 | 34 | 1.5341 | 66 | 1.8198 |
| 4 | 0.6020 | 2 | 41 | 1.612 | 59 | 1.770 |
| 8 | 0.9030 | 2.828 | 62 | 1.7923 | 38 | 1.5797 |
| 16 | 1.204 | 4 | 86 | 1.9344 | 14 | 1.1461 |
| 24 | 1.380 | 4.898 | 93 | 1.9684 | 7 | 0.845 |

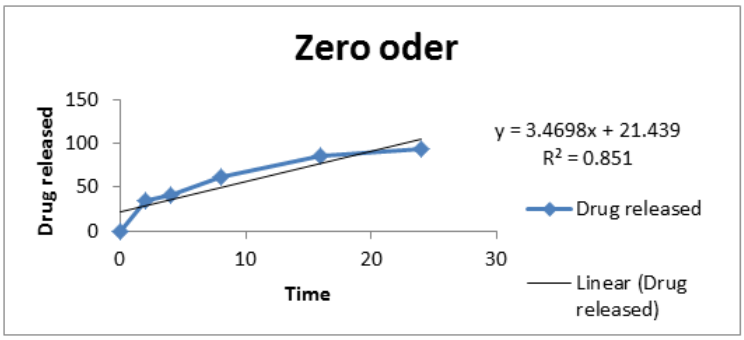


**Fig-4: Zero Order Kinetics**

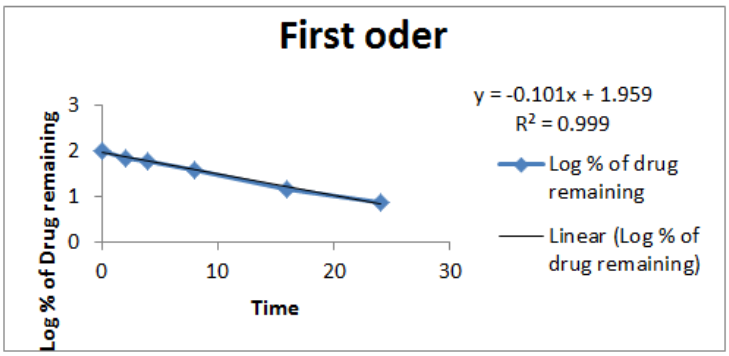


**Fig-5: First Order Kinetics**

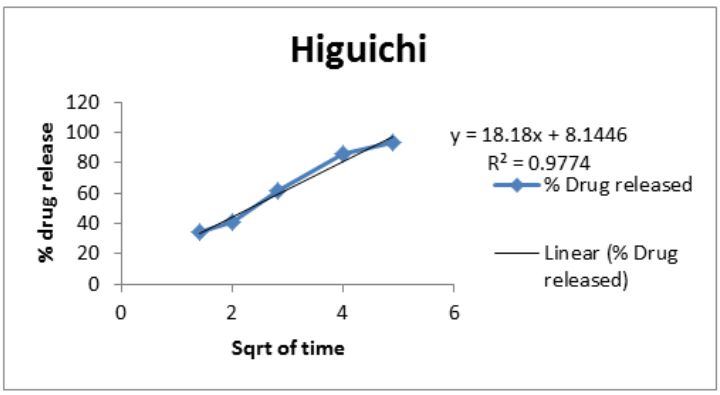


**Fig-6: Higuichi model**

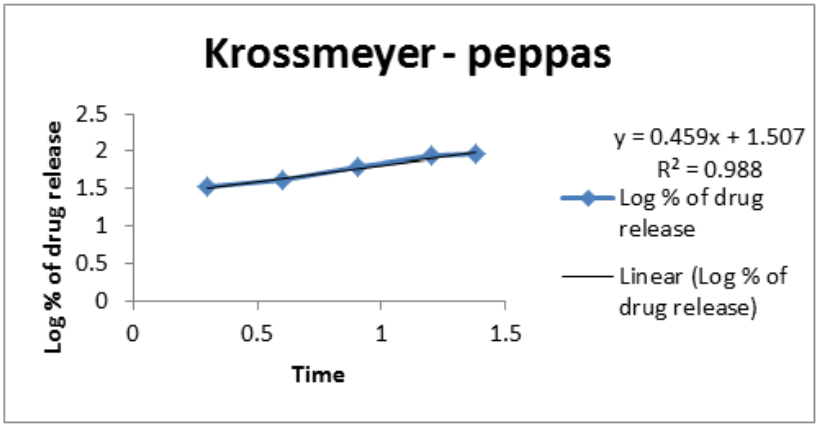


**Fig-7: Krossmeyer-Peppas model**

## DISCUSSION

- In present study an attempt to made to prepare a sustained release formulation of antibacterial agent simvastatin by using different polymers like xanthan gum, HPMC, and carbopol with different concentrations to obtain sustained release.
- When the active ingredient combines with other ingredients and stored it shows some incompatibilities which alters the drug color, odor etc. The studies relating the drug-excepient compatibility are shown in table no.15, all are mixed in 1:1 ratio and are stored under certain conditions initially and then at a room temperature of 55°C for about 2 weeks. Then after 2 weeks by maintaining the temperature and relative humidity conditions like 40±2°C /70±5 % RH they are stored up to 4 weeks.
- The prepared drug and excipient mixtures were evaluated at various intervals for related substances by HPLC as per the conditions and time intervals. Then after checked for any incompatibilities no characteristic change in the color of the powder and no additional degradation of the product were observed.
- The pre-compression parameters are conducted to various formulations F1, F2, F3, F4, F5, F6 which shows bulk densities 0.60, 0.46, 0.47, 0.45, 0.44, 0.46, (gm/ml) respectively. The tapped densities of these different formulations are obtained as 0.61, 0.54, 0.54, 0.53, 0.55, 0.55, (gm/ml) respectively. The compressibility indexes of these formulations are found to be 2.5, 14.2, 12.72, 15.8, 19.11, and 15.62 respectively. The hausner's ratio of these formulations are obtained through the values of bulk densities and tapped densities they are found to be 1.0, 1.16, 1.14, 1.18, 1.23, 1.18 respectively.
- These parameters are performed before the compression starts in order to determine the flow of blend from hopper to die. These are also carried out mainly to determine the powder flow characteristics which play a major role in the formulation of tablets. All the powders are nearly within the limit values representing the flow characteristics of the active ingredient is good. Drug release studies were carried out by using USP type II (paddle) apparatus. 900 ml of 6.8 phosphate buffer was used as dissolution medium and the basket was rotated 50 rpm at temperature (37$^{o}$C ± 0.5$^{o}$C). Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analyzed using HPLC.
- The drug release profiles are obtained for the innovator drug and various formulations F1, F2, F3, F4, F5, F6 and the optimized formulation trail F5 shows the cumulative % drug release 34,41,62,86,93 respectively shown in table no.6. The innovator drug shows drug release 34, 42,60,86,94 respectively. These are carried out at certain intervals of time duration 2, 4, 8, 16, 24(hours). Of all the formulations held trail F5shows cumulative % drug release after 24th hour similar to that of innovator. So it is considered as the optimized formulation in this work. Fig No. 4 indicates graph plotted by taking time on x-axis and the cumulative % drug release on y-axis describing in-vitro drug release profiles of innovator and different formulations of API. This trail is further used to carry out the evaluation parameters and they also undergo stability studies under certain conditions.
- Samples kept under stability studies were evaluated for every time interval up to 3 months. In which description, uniformity of weight, hardness, thickness, assay and dissolution studies were done. The assay values at initial, first month, second month are 99.92%, 99.83%, 99.79% respectively indicating the developed formula was stable at extreme storage conditions and the values were within the limits.

## CONCLUSION

From this present study, it was concluded that the polymeric combination of HPMCK15M with xanthan gum in the ratio 1:1 was able to retarded the release of Simvastatin from the tablets to the 24th hour

and showed an ideal release pattern necessary for sustained release tablet.

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