# Bilayer Tablet of Atenolol and Simvastatin

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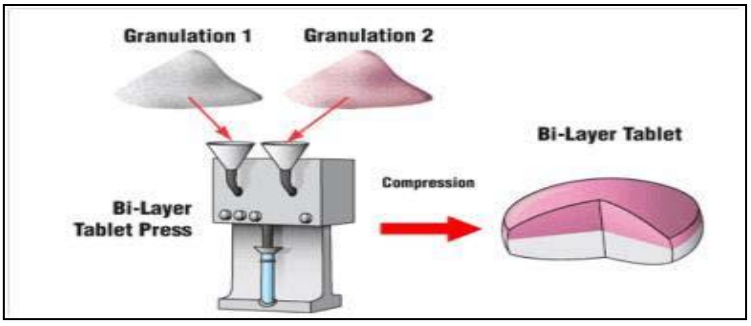
Introduction:-

**Abstract**: Bilayer tablets are planned by way of one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an sustained release form. The bilayer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers of two API. To manufacture sufficient tablet formulation, definite necessities such as sufficient mechanical strength and desired drug release profile must be meet. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

**Keywords**: - Bilayer, Compression, Release, tablet

**BILAYER TABLET** [26]

Now a days various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as pain, high LDL, various cardiovascular diseases, hypertension and diabetes etc. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over single dose therapy. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIS by physical separation. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug later as second dose or in an extended release or for both immediate release. Bi-layer tablets are tablet, made by compressing two different granulation feed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two layers. Bi-layer tablets are composed of two layers of granulation compressed together. They have the appearance of a like sandwich because the edges of each layer are exposed. General concept of bi-layer tablet technology is shown in following fig. No.1.




**Techniques for bilayer tablet** [24, 25, 26, 27]

- OROS® push pulls Technology
- L-OROSTM Technology
- EN SO TROL Technology
- DUREDAS™ Technology
- DUROS Technology

**Rationale behind formulation of bi-layer tablet** [1]

- Two chemically incompatible active pharmaceutical ingredients (APIs) can be formulated in a bilayer formulation.
- Two APIs or the same API with different release profiles can be delivered as a single bilayer tablet.(eg.One of immediate release and another extended release layer).
- Increased efficacy of the Active pharmaceutical components due to their synergistic effect.
- Combination of two or more APIs in a single bilayer tablet reduces the dosing unit burden thereby improving patient compliance

**Challenges in bilayer tablet formulation** [1]

- Cross contamination between the two layers.
- Reduced production yield because of to prevent cross contamination, dust collection is required which leads to losses.
- Sufficient mechanical strength to maintain its integrity and individual layer weight control
- Large tablet size, which can impact the swallow ability of the unit dose

**Advantages of bilayer tablet press with displacement monitoring**

- Weight monitoring and control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Maximum prevention of cross-contamination between the two layers.
- Clear visual separation between the two layers and maximum yield.

**Box-Behnken experimental design** [56]

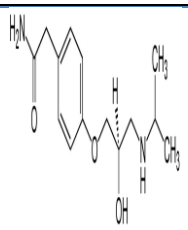
The Box-Behnken experimental design, developed by Box and Behnken in 1980, is a useful method for developing second-order response surface models. The Box-Behnken design is based on the construction of balanced incompleted block designs and requires at least three levels for each factor. We will try to explain the structure of Box Behnken design with three-factors. In Box-Behnken experimental design, the level of one of the factors is fixed at the center level while combinations of all levels of the other factors are applied. The level of the factor C was fixed and then, the combinations of all levels of the factors A and B were applied and subsequently, the same procedures were performed for the factors B and A, respectively. The last column of the design matrix contains center point values.

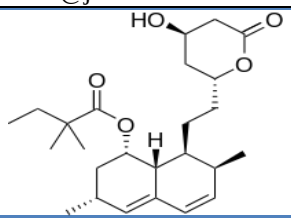
The selection of optimal levels for control factors in a system is called parameter design. The system can be a process or a product. Those factors that are within our control are called control factors. Additionally, there is a second group of factors that cause most variation in the response variable. Those factors are called noise factors and are uncontrollable factors in the system. The uncontrollability of these factors increases the variation in the response variable. The objective of robust parameter design is to create a design insensitive to the noise factors whose variation can not be eliminated or controlled. Noise factors are usually functions of environmental conditions. For example, the temperature and humidity of the room where the design is developed, if uncontrollable, are noise factors.

**DRUG PROFILE**

| **ATENOLOL** [36], [37] | |
|---|---|
| **Parameters** | **Description** |

| **SIMVASTATIN** [36], [37] | |
|---|---|
| **Parameters** | **Description** |

| | |
|---|---|
| **Structure** |  |
| **Molecular weight** | 266.33 |
| **Colour** | White |
| **Nature** | Crystalline |
| **Category** | Antihypertensive Agent, Adre |
| **Solubility** | Freely soluble in methanol & slightly soluble in water. |
| **Half life (Hrs)** | 7-8 |
| **Tmax (Hrs)** | 2-4 |
| **Log p** | 0.57 |
| **pKa** | 14.03 |
| **BCS class** | Class 3 |
| **Dose(mg)** | 50-100 |
| **Melting point** | 158-160$^{o}$C |
| **Marketed preparation** | Asomex AT, Calock Plus, Tenormin. |

| | |
|---|---|
| **Structure** |  |
| **Molecular weight** | 418.56 |
| **Colour** | White |
| **Nature** | Amorphous |
| **Category** | HMG-CoA Reductase inhibitor, Antihyperlipidemic |
| **Solubility** | Soluble in ethanol, methanol and insoluble in water |
| **Half life(Hrs)** | 2 |
| **Tmax (Hrs)** | 4 |
| **Log p** | 4.68 |
| **pKa** | 14.91 |
| **BCS class** | Class II |
| **Dose(mg)** | 10-80 |
| **Melting point** | 135-138$^{o}$C |
| **Marketed preparation** | Sivastin, Sinvacor, Lipex, Labistatin, Zocar. |

**List of Ingredients:-**

| Sr No. | Ingredients |
|---|---|
| **1** | Atenolol |
| **2** | Simvastatin |
| **3** | HPMC K100 M |
| **4** | Ethyl cellulose |
| **5** | Croscarmillose sodium |
| **6** | Mannitol |
| **7** | PVP K30 |
| **8** | Magnesium stearate |
| **9** | Talc |
| **10** | Ferric oxide red |

| | |
|---|---|
| **11** | Alcohol |
| **12** | Methanol |
| **13** | Sodium dihydrogen orthophosphate |
| **14** | Hydrochoric Acid |

**PREFORMULATION STUDY** (65-68)

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 determination.

**Identification and characterization of drug** (72)

- **Organoleptic characteristics**

The organoleptics characteristics of atenolol and simvastatin such as colour, odour and taste were studied.

- **Melting point**
- **FT-IR spectra**

**Determination of absorption maxima ($\lambda_{max}$) and preparation of calibration curves**

- The absorption maxima of drug Atenolol and Simvastatin was determine as follows:
- The standard stock solution was prepared by dissolving 10 mg of Atenolol and Simvastatin in different solvents (0.1N HCl of pH 1.2 and phosphate buffer pH 6.8) to make final concentration of 100 µg/ml.
- Different aliquots were taken from these stock solutions and diluted with same buffer solution used for preparation of stock solution separately to prepare series of concentrations from 05-25µg/ml of Atenolol and 02-12µg/ml of Simvastatin.
- The $\lambda_{max}$ of Atenolol and Simvastatin were found by UV spectrophotometry in different solvents (0.1N HCl of pH 1.2 and phosphate buffer pH 6.8) in the range of 200-400 nm.
- **The calibration curves were prepared as follows:**
- The standard stock solution was prepared by dissolving 10 mg of Atenolol and Simvastatin in different solvents (0.1N HCL of pH 1.2 and phosphate buffer pH 6.8) to make final concentration of 100 µg/ml.
- Different aliquots were taken from these stock solutions and diluted with same buffer solution used for preparation of stock solution separately to prepare series of concentrations from 05-25µg/ml of Atenolol and 02-12µg/ml of Simvastatin.
- The $\lambda_{max}$ of Atenolol and Simvastatin were found by UV spectrophotometry in different solvents (0.1NHCl of pH 1.2 and phosphate buffer pH 6.8) in the range of 200-400 nm.
- The calibration curves were prepared by plotting absorbance versus concentration of Atenolol and Simvastatin at practically found $\lambda_{max}$ in 0.1N HCL of pH 1.2 and phosphate buffer pH 6.8.

**DRUG –EXCIPIENT COMPATIBILITY STUDY** (67, 68, 72)

The purpose of drug/excipients compatibility consideration and practical studies is to define, as quickly as possible, real and possible interactions between potential formulation excipients and the API. This is essential risk reduction exercise early in formulation development. The drug-excipient incompatibility can alter the stability and/or the bioavailability of drugs thereby, affecting its safety and/or efficacy. So, while formulating a dosage form, it is important that the excipient used in formulation should be physically and chemically compatible with drug material. Compatibility study was carried out both in presence and absence of moisture. The compatibility study was carried out at

55°C for 14 days with in hermetically sealed glass container of individual drug and Drug: Excipient (1:1). The procedure for compatibility study was as follows-

**Ratio of drug (Atenolol) and its mixture with excipients for compatibility testing**

| Physical mixture | Ratio (Drug: excipient) | Total weight (mg) |
|---|---|---|
| **Drug** | 1 | 50 |
| **Drug+ Cros Carmellose** | 1 : 1 | 100 |
| **Drug+ Mannitol** | 1 : 1 | 100 |
| **Drug+ PVP K30** | 1 : 1 | 100 |
| **Drug+ Talc** | 20 : 1 | 52.5 |
| **Drug + Mag. Steareate** | 20 : 1 | 52.5 |

**Ratio of drug (Simvastatin) and its mixture with excipients for compatibility testing**

| **Physical mixture** | **Ratio (Drug: excipient)** | **Total weight (mg)** |
|---|---|---|
| **Drug** | 1 | 50 |
| **Drug+ Ethyl Cellulose** | 1 : 1 | 100 |
| **Drug+ HPMC K100 M** | 1 : 1 | 100 |
| **Drug+ Mannitol** | 1 : 1 | 100 |
| **Drug+ PVP K30** | 1 : 1 | 100 |
| **Drug + Talc** | 20 : 1 | 52.5 |
| **Drug + Mag. Steareate** | 20 : 1 | 52.5 |

**FORMULATION AND DEVELOPMENT**

**Preliminary screening for bilayer tablets**

**Trials for selection of disintegrant**
**Trial I:**

For the disintegrant screening following percent of the croscarmellose sodium used in the single layer of immediate release tablet of atenolol by the direct compression and wet granulation method. Following formula was used for the same,

Table.01Trial batch I for selection of disintegrant

| **Sr No.** | **Ingredient Name** | **Quantity taken (mg)** | **Catagory** |
|---|---|---|---|
| **1** | Atenolol (Drug) | 50 | API (Antihypertensive) |
| **2** | Croscarmellose Na | 3.6 | Superdisintegrant |
| **3** | PVP K30 | 9 | Binder |
| **4** | Mannitol | q.s.to 120 mg | Filler |
| **5** | Talc | 2 | Lubricant |
| **6** | Mg.Stearate | 7 | Lubricant |

For the above trial **8mm** punch were selected and tablet were formulated by direct and wet granulation technique.

**Trial II:**

For the trial II 4, 6, 8 and 10 percent of the croscarmellose Na was used and tablet were formulated by the wet granulation method. Following formula was used for the same,

Table.02 Trial batch II for selection of disintegrant

| **Ingredients/Batch** | **F1 (mg)** | **F2 (mg)** | **F3 (mg)** | **F4 (mg)** |
|---|---|---|---|---|
| Atenolol | 50 | 50 | 50 | 50 |
| Croscarmellose sodium | 4.8 **(4%)** | 7.2 **(6%)** | 9.6 **(8%)** | 12 **(10%)** |
| PVP K30 | 9 | 9 | 9 | 9 |
| Mannitol | q.s.to 120 | q.s.to 120 | q.s.to 120 | q.s.to 120 |
| Talc | 2 | 2 | 2 | 2 |
| Mg.Stearate | 7 | 7 | 7 | 7 |

For the above trial 8mm punch were selected and tablet were formulated by wet granulation technique.

**Trials for selection of Polymers**
**Trial I:**

For the polymer screening following percent of the Ethyl cellulose and HPMC K100 M used in the single layer of sustained release tablet of simvastatin by the dry and wet granulation method. The concentration of the HPMC K100 M in F1 to F6 batch were **20%, 10%, 20%,0%, 35%, 20%.** and Ethyl cellulose in F1 to F6 batch were **10%, 20%, 0%, 20%, 20%, 35%** taken. Following formula was used for the same,

Table 03.Trial batch I for selection of polymers

| **Ingredient (mg) (180 mg)/tab** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
|---|---|---|---|---|---|---|
| Simvastatin | 20 | 20 | 20 | 20 | 20 | 20 |
| HPMC K100 M | 36 **(20%)** | 18 **(10%)** | 36 **(20%)** | - **(0%)** | 63 **(35%)** | 36 **(20%)** |
| Ethyl Cellulose | 18 **(10%)** | 36 **(20%)** | - **(0%)** | 36 **(20%)** | 36 **(20%)** | 63 **(35%)** |
| PVP K30 | 9 | 9 | 9 | 9 | 9 | 9 |
| Mannitol | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 |
| Mg.Stearate | 7 | 7 | 7 | 7 | 7 | 7 |

For the above trial **8mm** punch were selected and tablet were formulated by wet granulation technique.

By the above formulation the **F1 batch** found to good result as per the sustained release criteria by the **wet granulation method.** So we try near by polymer concentration trial batch

**Trial II:**

For the polymer screening in Trial no.II following percent of the Ethyl cellulose and HPMC K100 M used in the single layer of sustained release tablet of simvastatin by the dry and wet granulation method. The concentration of the Ethyl cellulose in F1, A1 and A2 batch were 10%, 13% and 5% in both dry and wet granulation method. And HPMC K100 M in F1, A1 and A2 batch were 20%, 17% and 25% in both dry and wet granulation method taken. Following formula was used for the same,

Table.04 Trial batch II for selection of polymers

| Ingredient (mg) /Batch (180 mg per Tab) | F1 | A1 | A2 |
|---|---|---|---|
| Simvastatin | 20 | 20 | 20 |
| HPMC K100 M | 36 **(20%)** | 30.6 **(17%)** | 45 **(25%)** |
| Ethyl Cellulose | 18 **(10%)** | 23.4 **(13%)** | 9 **(5%)** |
| PVP K30 | 9 | 9 | 9 |
| Mannitol | q.s. 180 mg | q.s. 180 mg | q.s. 180 mg |
| Talc | 2 | 2 | 2 |
| Mg. Stearate | 7 | 7 | 7 |

For the above trial 8mm punch were selected and tablet were formulated by wet granulation technique.

**Trials for bilayer tablet methodology**
**Trial I:**

For the combine disintegrant and polymer release screening following percent of the croscarmellose sodium, Ethyl cellulose and HPMC K100 M used in the bilayer layer of immediate release and sustained release tablet of atenolol and simvastatin by the direct compression and wet granulation method. Following formula was used for the same in that Croscarmellose were used 6% and HPMC K100 M as a 20% and Ethyl cellulose as a 7.5%.

**Formula for Atenolol**

Table 1.Trial batch for bilayer tablet methodology

| Sr No. | Ingredient Name | Quantity per Tab (mg) | Catagory |
|---|---|---|---|
| 1 | Atenolol (Drug) | 50 | API |
| 2 | Croscarmellose Na | 7.2 **(6%)** | Disintegrant |
| 3 | PVP K30 | 6 | Binder |
| 4 | Mannitol | q. s. up to 120 mg | Filler |
| 5 | Talc | 4.8 | Lubricant |
| 6 | Mg.Stearate | 3.6 | Lubricant |

**Formula for Simvastatin**

Table.06 Trial batch for bilayer tablet methodology

| Sr No. | Ingredient Name | Quantity per Tab (mg) | Category |
|---|---|---|---|
| 1 | Simvastatin | 20 | API |
| 2 | HPMC K100 M | 30 (20%) | Polymer |
| 3 | Ethyl Cellulose | 11.25 (7.5%) | Polymer |
| 4 | PVP K30 | 6 | Binder |
| 5 | Mannitol | q.s.up to 150 mg | Filler |
| 6 | Talc | 6 | Lubricant |
| 7 | Mg. Stearate | 4.5 | Lubricant |

For the above trial 8mm punch were selected and tablet were formulated by wet granulation and dry granulation technique.

**OPTIMIZATION**

**Statistical experiment design** [56], [73]

A three-level, three-factor Box Behnken design of response surface methodology was employed for the formulation optimization using statistical software, Design expert version 9.0.1 (Stat-Ease Inc., Minneapolis, MN). Three components ie. Disintegrant, two polymers were screened from preliminary experimental work and used for optimization study as independent variables. These components tested at three different concentrations. Total 17 formulations including 5 replicates of central points were prepared to investigate the influence of screened three excipients on disintegration time for immediate release and polymer release for sustained release tablet of bilayer tablet.

Experimental response values were analyzed by multiple linear regressions to calculate the polynomial equations. Adjusted $R^2$ ($R^2$adj) values were calculated to evaluate the polynomial fits. The F-statistic was used to identify statistically significant terms. Significant effects were evaluated by the analysis of variance at $p < 0.05$. Less significant regression coefficients were progressively eliminated to maximize the $R^2$ adjusted parameter. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient of variation (CV), the multiple correlation coefficient ($R^2$); adjusted multiple correlation coefficient (adjusted $R^2$); and the predicted residual sum of square (PRESS), proved by design expert software.

Table07.Box-Behnkenexperimental design for three variables [56]

| Run | Variable 1 | Variable 2 | Variable 3 |
|---|---|---|---|
| **1** | -1 | -1 | 0 |
| **2** | +1 | -1 | 0 |
| **3** | -1 | +1 | 0 |
| **4** | +1 | +1 | 0 |
| **5** | -1 | 0 | -1 |
| **6** | +1 | 0 | -1 |
| **7** | -1 | 0 | +1 |
| **8** | +1 | 0 | +1 |
| **9** | 0 | -1 | -1 |
| **10** | 0 | +1 | -1 |
| **11** | 0 | -1 | +1 |
| **12** | 0 | +1 | +1 |
| **13** | 0 | 0 | 0 |
| **14** | 0 | 0 | 0 |
| **15** | 0 | 0 | 0 |
| **16** | 0 | 0 | 0 |
| **17** | 0 | 0 | 0 |

Table 08 .Levels of independent variable used for experiment

| Independent Variable | Lowest level (-1) | Middle level (0) | Highest level (+1) |
|---|---|---|---|
| **Croscarmelose Sodium (%)** | 4 | 6 | 8 |
| **Ethyl Cellulose(%)** | 5 | 7.5 | 10 |
| **HPMC K100 M (%)** | 15 | 20 | 25 |

Table09. Formulation runs as per DOE with used variables

| F. no. | Croscarmellose Sodium(%) | Ethyl Cellulose(%) | HPMC K100 M | Total wt. (mg) |
|---|---|---|---|---|

| | | | (%) | |
|---|---|---|---|---|
| **1** | 4 | 5 | 20 | 270 |
| **2** | 8 | 5 | 20 | 270 |
| **3** | 4 | 10 | 20 | 270 |
| **4** | 8 | 10 | 20 | 270 |
| **5** | 4 | 7.5 | 15 | 270 |
| **6** | 8 | 7.5 | 15 | 270 |
| **7** | 4 | 7.5 | 25 | 270 |
| **8** | 8 | 7.5 | 25 | 270 |
| **9** | 6 | 5 | 15 | 270 |
| **10** | 6 | 10 | 15 | 270 |
| **11** | 6 | 5 | 25 | 270 |
| **12** | 6 | 10 | 25 | 270 |
| **13** | 6 | 7.5 | 20 | 270 |
| **14** | 6 | 7.5 | 20 | 270 |
| **15** | 6 | 7.5 | 20 | 270 |
| **16** | 6 | 7.5 | 20 | 270 |
| **17** | 6 | 7.5 | 20 | 270 |

Responses obtained from the reduced equation, an equation containing only statistically significant terms, are used for drawing response surface plots to visualize the impact of changing variables. The optimum point may be identified from the plot and replicate trials may be run to verify the prediction of optimum response.

Box Behnken model gives the optimized formula which could be used to form better Bilayer tablet of atenolol and simvastatin. It was used to make 30 tablet batch of optimized formula and evaluated for various parameters.

**Final formulation of bilayer tablets**
**Purpose** –Forulation, development and optimization of bilayer tablet of atenolol immediate release and simvastatin sustained release tablet.

**Formulation**

After the design and development of technique, final formulation of bilayer tablet was prepared. The formulation of bilayer tablet of atenolol and simvastatin was prepared in the following manner.

**Immediate release:**

Immediate release layer of atenolol was prepared by wet granulation method. In that we taken Atenolol-50 mg, PVP K30-5%, Zink oxide red-0.15%, Mg.Stearate-3%, Talc-4% and Mannitol as a filler constant only variation takes place in Croscarmellose sodium.

**Sifting-** All ingredient ie. Atenolol, croscarmellose sodium, mannitol, PVP K30, Zink oxide Red, talc and Mg.Stearate were sifted through #60 mesh separately.

**Blending-** Mix geometrically atenolol, croscarmellose sodium, mannitol and PVP K30 for about 15 min in mortor pestle.

**Granulation-** To this mixture mix ethanol as granulating vehicle.Formulation of wet mass and pass through sieve #20 and dried at room temperature.

**Lubrication-** The above granules were lubricated with Mg.Stearate and talc for 3 min.

**Sustained Release:**

Sustained release layer of Simvastatin was prepared by wet granulation method. In that we taken Simvastatin-20 mg, PVP K30-5%, Mg.Stearate-3%, Talc-4% constant and Mannitol as a filler, variation takes place in HPMC K100 M and Ethyl cellulose.

**Sifting-** All ingredient ie. Simvastatin, Ethyl Cellulose, HPMC K100 M, mannitol, PVP K30, talc and Mg.Stearate were sifted through #60 mesh separately.

**Blending-** Mix geometrically Simvastatin, Ethyl Cellulose, HPMC K100 M, mannitol and PVP K30 for about 15 min in mortor pestle.

**Granulation-** To this mixture mix ethanol as granulating vehicle.Formulation of wet mass and pass through sieve #20 and dried at room temperature.

**Lubrication-** The above granules were lubricated with Mg.Stearate and talc for 3 min.

**Bilayer tablet formulation:**

Bilayer tablet were prepared by combining immediate and sustained release layer.

For the preparation of dual component formulation, the die of the tablet machine was filled manually with the weighted amount of the sustained release layer component. Then sustained release component was compressed lightly by using 8 station rotary tablet compression machine ie. JMD-4-8, Jaguar and the immediate release granules were added and on upper side add precompressed low hardness sustained release tablet. The dual component compressed tablet system were prepared by wet granulation technique.

**Process parameter:**

**Punch size:** 8mm diameter, Flat round shape.

**Tablet wt:** Total weight 270 mg

**Sustained release layer-**150 mg,

**Immediate release layer-**120 mg.

**EVALUATION STUDY**

**Table no 10 Evaluation parameters**

| **Pre compression study** | **Post compression evaluation** (Evaluation of Bilayer Tablet) |
|---|---|
| Angle of Repose | Friability testing |
| Bulk density | Weight variation test |
| Tapped density | Hardness testing |
| Carr's compressibility index | Diameter and thickness of the tablet |
| Hausners ratio | Content uniformity |

**Dissolution test of bilayer tablet**

Dissolution test of bilayer tablet of atenolol and simvastatin was performed by using Dissolution apparatus of Electrolab, in that we taken pH 1.2 medium for first 2 hrs and then 6.8 phosphate buffers **(by addition of 50ml of 2M Dibasic Sodium Phosphate)** medium. The dissolution study was carried out for about 12 hrs at 37.5 ºC and 50 rpm by using USP type 2 apparatus. 5 ml sample were

withdraw from dissolution medium at every 5 min interval up to 45 min and sink condition were maintained for the immediate release layer. After that 5 ml sample withdraw per hour and sink condition were maintained for sustained release layer in between the same the medium converted 1.2 pH to 6.8 pH phosphate buffer after two sampling. Samples were diluted to with respective phosphate buffer of 1.2 and 6.8 pH. Its absorbance was measured on UV spectrophotometer. Drug release was calculated and results were note down.

## RESULT AND DISCUSSION

## PREFORMULATION STUDY

### Identification and characterization of drug
### Organoleptic characteristics

The organoleptics characteristics of Atenolol and Simvastatin such as colour, odor, and taste were studied. Colour of drug was found to be yellow. Taste of the drug was identified simply by taste sensation on tongue drug was found to be bitter in taste.

Table.11 Organoleptic properties of Atenolol and Simvastatin

| Organoleptic Properties | Standard | Observation |
|---|---|---|
| **Colour** | White Crystalline | White Crystalline |
| **Odour** | Odourless | Odourless |
| **Taste** | Bitter | Bitter |

### Melting point

Melting point of drug Atenolol and Simvastatin was determined by capillary method. The temp at which drug goes in the liquid state was consider as a melting point of Atenolol and Simvastatin. Practically it was found that drug get melts at 160 ºc and 138 ºc respectively. Reported melting point of the drug Atenolol and Simvastatin is 158-160ºc and 135-138ºc respectively.

### FT-IR spectra

FT-IR spectra of Atenolol were taken on IR spectrophotometer by simply placing small amount of drug in powder form on selenium bromide crystal. In a spectra peak for carbonyl group(c=o group) was seen at 1631.34 $cm^{-1}$ and peak for nitrile group (C-H) was found at a 1407.40 $cm^{-1}$. FT-IR spectra of Atenolol was found as follows,

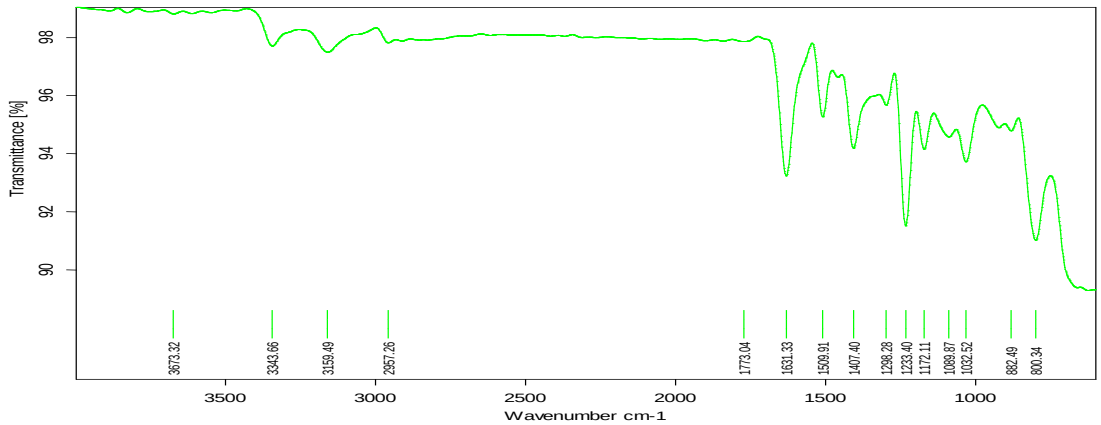



Table12.IR ranges and functional group present Atenolol

| Functional group | Type of vibration | Frequency ($cm^{-1}$) | |
|---|---|---|---|
| | | Standard | Observed |
| **O-H** | Stretching | 3550-3200 | 3343.66 |

| | | | |
|---|---|---|---|
| **N-H** | Stretching | 3200-2800 | 3158.39 |
| **C-H Methyl** | Stretching | 3000-2840 | 2957.26 |
| **C=O(Amines)** | Stretching | 1680-1630 | 1631.33 |
| **C-H** | Bending | 1450-1375 | 1407.40 |

FT-IR spectra of Simvastatin were taken on IR spectrophotometer by simply placing small amount of drug in powder form on selenium bromide crystal. In a spectra peak for ester group(c=o group) was seen at 1706.96cm-1 and peak for lactone group (C-O-C) was found at a 1260.31 cm-1. FT-IR spectra of Simvastatin was found as follows

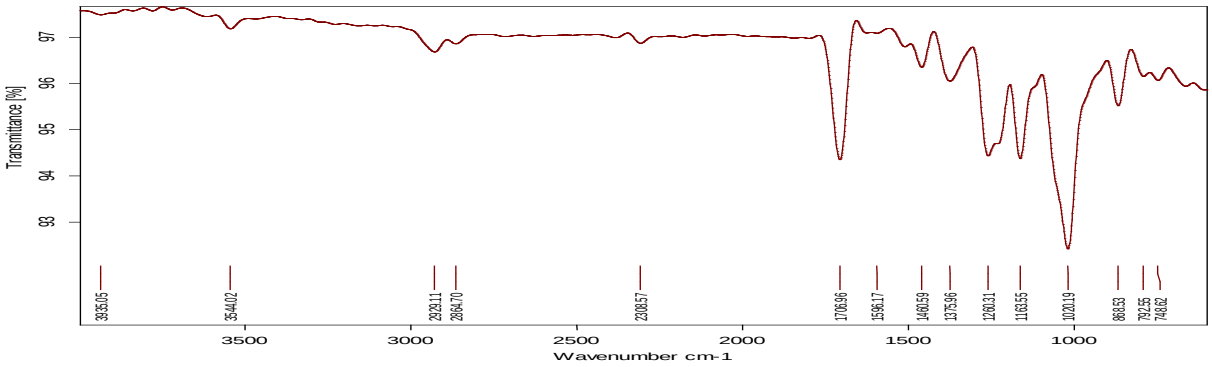



Table13.IR ranges and functional group present in Simvastatin

| **Functional group** | **Type of vibration** | **Frequency ($cm^{-1}$)** | |
|---|---|---|---|
| | | Standard | Observed |
| **O-H** | Stretching | 3550-3200 | 3544.02 |
| **C-H methyl** | Stretching | 3000-2840 | 2929.11 |
| **C=O ester** | Stretching | 1725-1705 | 1706.96 |
| **Lactone-C-O-C** | Stretching | 1310-1250 | 1260.31 |
| **C-O** | Stretching | 1085-1000 | 1020.19 |

**Determination of absorption maxima ($\lambda_{max}$) and calibration curve plot**

**The absorption maxima ($\lambda_{max}$) of drug Atenolol**

The absorption maxima ($\lambda_{max}$) of drug Atenolol in 0.1 N HCl and 6.8 pH buffer, when scanned from 400 nm to 200 nm was found to be 224 nm practically. Theoretically absorption maxima ($\lambda_{max}$) in 0.1 N HCl and 6.8 pH buffer are 226 nm.

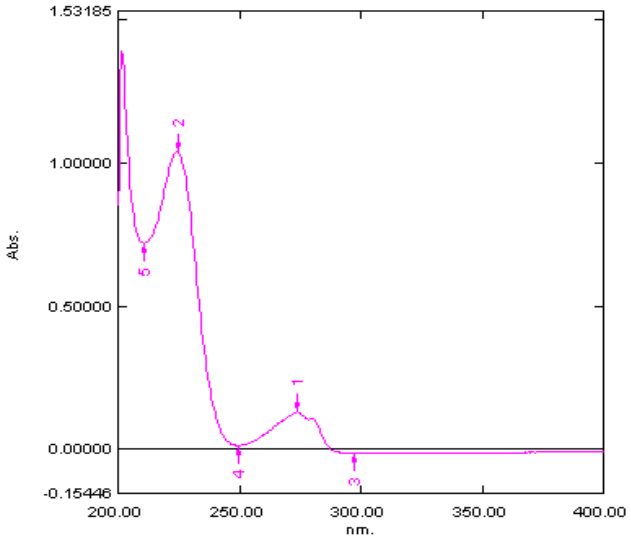



Figure.Absorbation spectrum of Atenolol in 0.1 N HCl (pH- 1.2)

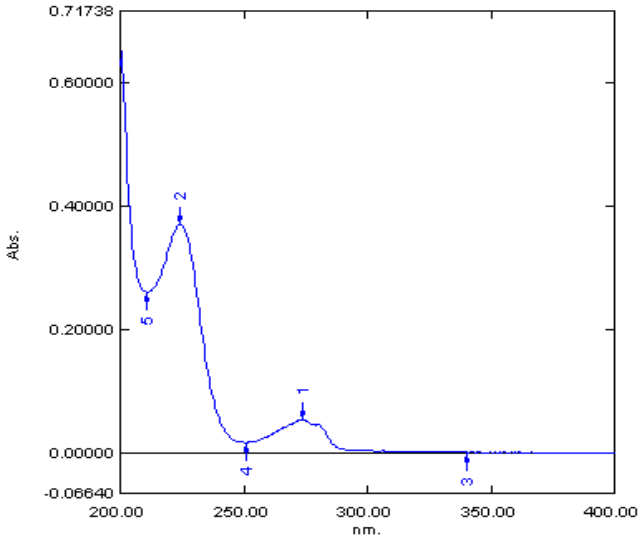



Figure.Absorbation spectrum of Atenolol in phosphate buffer (pH- 6.8)

**The absorption maxima ($\lambda_{max}$) of drug Simvastatin**

The absorption maxima ($\lambda_{max}$) of drug Simvastatin in 0.1 N HCl and 6.8 pH buffer, when scanned from 400 nm to 200 nm was found to be 238.50 nm practically. Theoretically absorption maxima ($\lambda_{max}$) in 0.1 N HCl and 6.8 pH buffer is 238.0 nm.

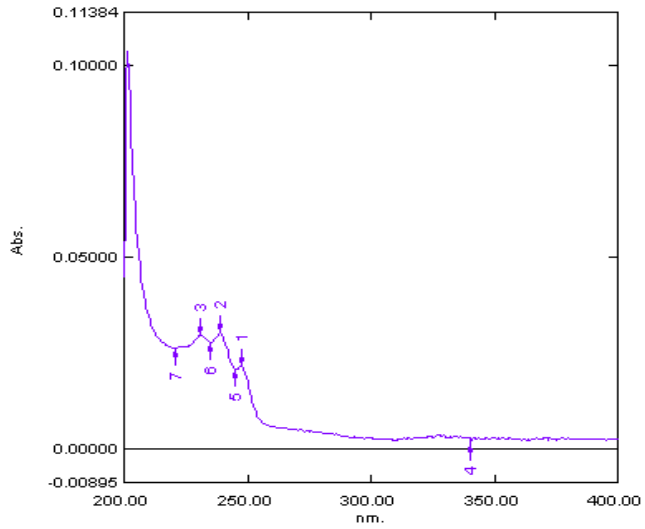



Figure.Absorbation spectrum of Simvastatin in 0.1 N HCl (pH- 1.2)

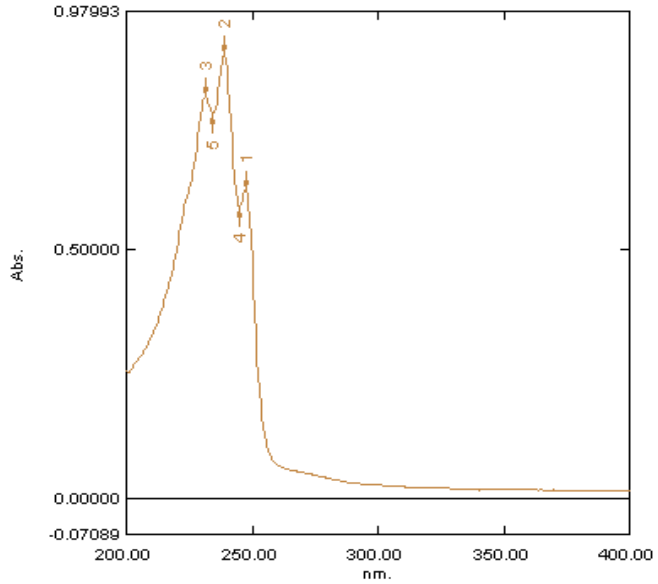



Figure.Absorbation spectrum of Simvastatin in phosphate buffer (pH- 6.8)

**Calibration curves for drug Atenolol**

The drugs used in the treatment of hypertension have to passes through gastric and intestinal fluid. Hence it was necessary to study the release study of atenolol in gastric fluid of pH 1.2 along with intestinal fluid of pH 6.8. In order to study their release study the calibration curves for atenolol in HCl of pH 1.2 and phosphate buffer of pH 6.8 were developed.

Table14.Absorption table of Atenolol in different buffer solutions

| Concentration (µg/ml) | Absorbance | |
|---|---|---|
| | 0.1N HCl (1.2 pH) | 6.8 pH Buffer |
| 5 | 0.197 | 0.098 |
| 10 | 0.401 | 0.213 |
| 15 | 0.613 | 0.315 |
| 20 | 0.828 | 0.438 |
| 25 | 1.04 | 0.572 |

The calibration curve for atenolol in 0.1 N HCl and 6.8 pH buffers was prepared by plotting absorbance versus concentration at practically obtained λmax 224 nm. Calibration curve was plotted in triplicate manner. Concentration ranges selected were of 5,10,15,20,25µg/ml. The calibration curve of atenolol in 0.1 N HCl of pH 1.2 and 6.8 pH buffer was found as follows

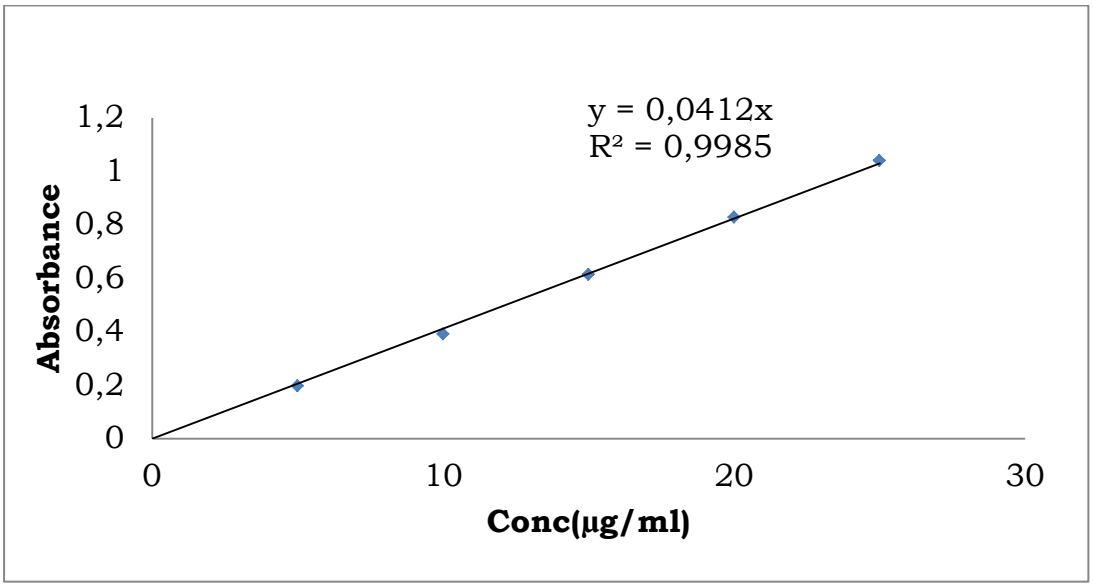
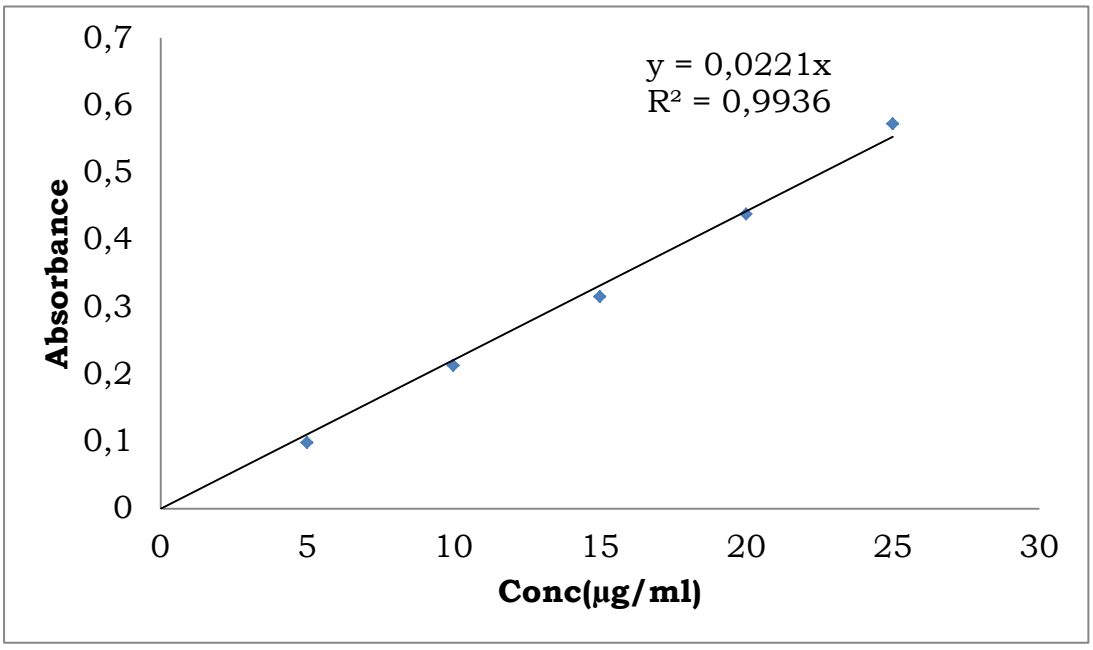



Figure.Calibration curve for atenolol in 0.1 N HCl




Calibration curve for atenolol in 6.8 pH buffer

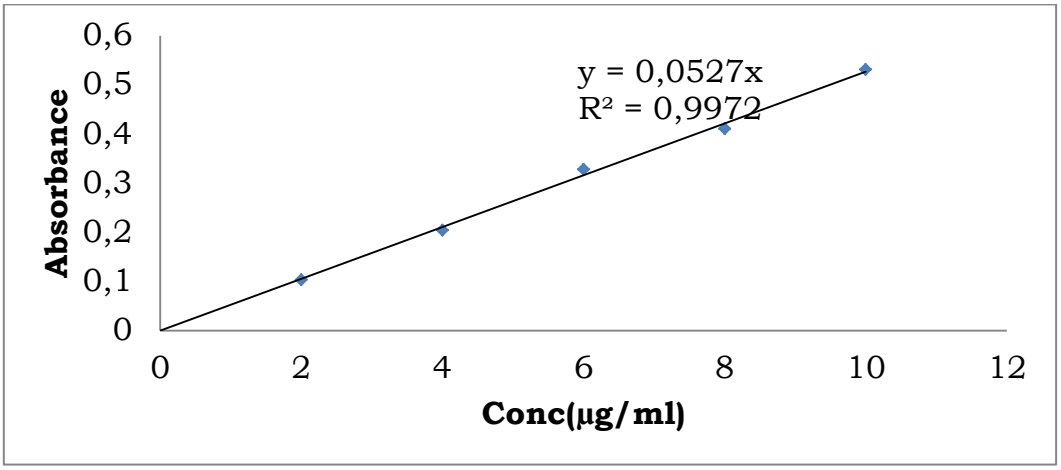
**Calibration curves for drug simvastatin**

The drugs used in the treatment of Antihyperlipidemic have to passes through gastric and intestinal fluid. Hence it was necessary to study the release study of simvastatin in gastric fluid of pH 1.2 and intestinal fluid of pH 6.8. In order to study their release study the calibration curves for simvastatin in HCl of pH 1.2 and phosphate buffer of pH 6.8 were developed.

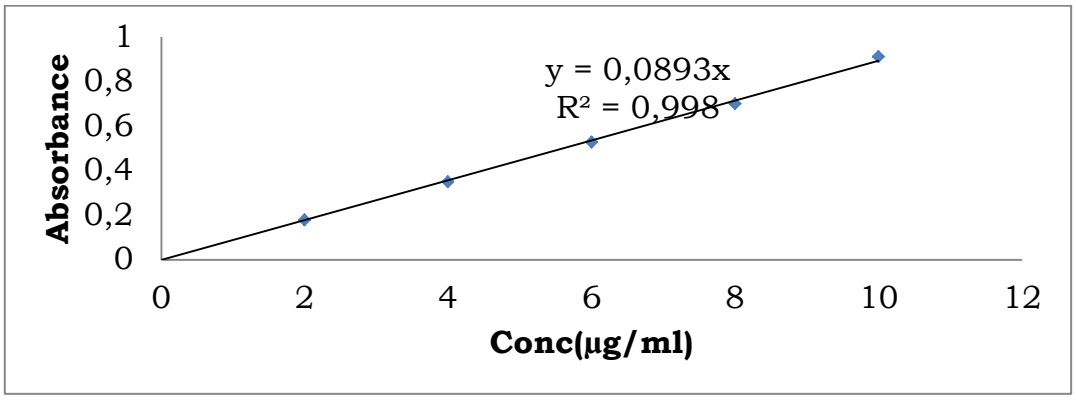
Table15.Absorption table of Simvastatin in different buffer solutions

| Concentration (µg/ml) | Absorbance | |
|---|---|---|
| | 0.1N HCl (1.2 pH) | 6.8 pH Buffer |
| 2 | 0.103 | 0.179 |
| 4 | 0.204 | 0.349 |
| 6 | 0.328 | 0.528 |
| 8 | 0.411 | 0.701 |
| 10 | 0.531 | 0.912 |

The calibration curve for simvastatin in 0.1 N HCl and 6.8 pH buffer was prepared by plotting absorbance versus concentration at practically obtained λmax 238.50 nm. Calibration curve was plotted in triplicate manner. Concentration ranges selected were of 2, 4, 6, 8, 10µg/ml. The calibration curve of simvastatin in 0.1 N HCl of pH 1.2 and 6.8 pH buffer was found as follows,




Calibration curve for simvastatin in 0.1 N HCl




Calibration curve for simvastatin ( phosphate buffer pH- 6.8)

**COMPATIBILITY STUDY**

Physical and chemical Compatibility study was carried out both in presence and absence of moisture at 55º C in hot air oven for 14 days. The drug-excipients mixtures were observed for physical incompatibilities such as colour change, liquefaction, caking, and Gas formation and chemical incompatibilities with the help of FT-IR study. The results obtained at each day in presence and absence of moisture were given in following table-

Table16.Compatibility study of drug (Atenolol) excipients mixture (without moisture)

| Drug + Excipient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Croscarmellose sodium | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mannitol | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| PVP K30 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Talc | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mag. Stearate | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

No change (-); caking (#); liquefaction- (*); gas formation- (¥)

Table17.Compatibility study of drug (Atenolol) excipient mixture (with moisture)

| **Drug + Excipient** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Croscarmellose sodium | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mannitol | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| PVP K30 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Talc | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mag. Stearate | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

No change (-); caking (#); liquefaction- (*); gas formation- (¥)

Table18.Compatibility study of drug (Simvastatin) excipient mixture (without moisture)

| **Drug + Excipient** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ethyl Cellulose | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| HPMC K 100 M | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mannitol | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| PVP K30 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Talc | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mag. Stearate | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

No change (-); caking (#); liquefaction- (*); gas formation- (¥)

Table19.Compatibility study of drug (Simvastatin) excipient mixture (with moisture)

| **Drug + Excipient** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ethyl Cellulose | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| HPMC K100 M | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mannitol | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| PVP K30 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Talc | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Mag. Stearate | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

No change (-); caking (#); liquefaction- (*); gas formation- (¥)

**FORMULATION DEVELOPMENT**

**Trials for selection of disintegrant**

Initially formulas of tablets were set by varying concentration of disintegrant i.e. croscarmellose sodium.

**Trial I:**

For the disintegrant screening following percent of the croscarmellose sodium used in the single layer of immediate release tablet of atenolol by the direct compression and wet granulation method. Following formula was used for the same,

Table20.Trial batch I for selection of disintegrant

| Sr No. | Ingredient Name | Quantity taken (mg) |
|---|---|---|
| 1 | Atenolol (Drug) | 50 |
| 2 | Croscarmellose Na | 3.6 |
| 3 | PVP K30 | 9 |
| 4 | Mannitol | q.s.up to 120 mg |
| 5 | Talc | 2 |
| 6 | Mg.Stearate | 7 |

**Significance:**

Croscarmellose were used as main disintegrant agent and one batch were prepared and evaluated their effects on disintegration time of tablet.

- By the above tablet formulation the DT and drug release was not achived in the immediate release criteria.
- Formula containing 3% of the croscarmellose sodium.
- The average DT recorded as 4.30min.

**Trial II:**

For the trial II 4,6,8 and 10 percent of the croscarmellose Na was used and tablet were formulated by the wet granulation method. Following formula was used for the same,

Table21.Trial batch II for selection of disintegrant

| Ingredients/Batch | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) |
|---|---|---|---|---|
| Atenolol | 50 | 50 | 50 | 50 |
| Croscarmellose sodium | 4.8 **(4%)** | 7.2 **(6%)** | 9.6 **(8%)** | 12 **(10%)** |
| PVP K30 | 9 | 9 | 9 | 9 |
| Mannitol | q.s.to 120 | q.s.to 120 | q.s.to 120 | q.s.to 120 |
| Talc | 2 | 2 | 2 | 2 |
| Mg.Stearate | 7 | 7 | 7 | 7 |

**Significance:**

- Four different concentrations were taken of croscarmellose sodium as disintegrant ie.4%, 6%, 8% and 10%.
- 4% croscarmellose sodium shows 4min average DT. Hence this conc. Not achieved the actual DT as per immediate release criteria.
- 6% croscarmellose sodium shows up to 3 min average DT. So this batch considered for the next optimization batch formulas.
- Also 8% of croscarmellose sodium shows DT within limits ie. average time shows 2.10 min.So this batch also considered for the optimization formula.

- In 10% of croscarmellose sodium concentration DT shows within limits but having problem of friability, so this concentration were not considered for next trials.
- By the above formulation the DT were achived in the 6 and 8% concentration of the croscarmellose sodium.

**Trials for selection of polymers**
**Trial I:**

For the polymer screening following percent of the Ethyl cellulose and HPMC K100 M used in the single layer of sustained release tablet of simvastatin by the dry and wet granulation method. The concentration of the HPMC K100 M in F1 to F6 batch were **20%, 10%, 20%,0%, 35%, 20%.** and Ethyl cellulose in F1 to F6 batch were **10%, 20%, 0%, 20%, 20%, 35%** taken. Following formula was used for the same,

Table22.Trial batch I for selection of polymers

| **Ingredient (mg) (180 mg)/tab** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
|---|---|---|---|---|---|---|
| Simvastatin | 20 | 20 | 20 | 20 | 20 | 20 |
| HPMC K100 M | 36 **(20%)** | 18 **(10%)** | 36 **(20%)** | - **(0%)** | 63 **(35%)** | 36 **(20%)** |
| Ethyl Cellulose | 18 **(10%)** | 36 **(20%)** | - **(0%)** | 36 **(20%)** | 36 **(20%)** | 63 **(35%)** |
| PVP K30 | 9 | 9 | 9 | 9 | 9 | 9 |
| Mannitol | q. s. | q. s. | q. s. | q. s. | q. s. | q. s. |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 |
| Mg.Stearate | 7 | 7 | 7 | 7 | 7 | 7 |

**Significance:**

- Six different batches having different concentrations were taken.
- In the F1 batch best result was found and matches with sustained release criteria ie.**Q3 (30-40%), Q6 (70-80%) and Q9 (90-100).**
- But in F2 batch there was higher concentration of the Ethyl cellulose so the release was decrease ie.25% in 12 hrs.
- In F3 batch there was only 20% HPMC so the release was found to be very quick and 100% release was found to be in 7 hrs.
- In F4 batch there was only 20% Ethyl cellulose so the release was found to be very low and found to be only 15% in 12 hrs.
- Also in F5 and F6 batch there was higher concentration of Ethyl cellulose ie.20% and HPMC ie.35% so the release was found to be low.so,
- By the above formulation the **F1 batch** found to best result as per the sustained release criteria by the **wet granulation method.**

**Trial II:**

For the polymer screening in Trial no.II following percent of the Ethyl cellulose and HPMC K100 M used in the single layer of sustained release tablet of simvastatin by the dry and wet granulation method. The concentration of the Ethyl cellulose in F1, A1 and A2 batch were **10%,13% and 5%** in both dry and wet granulation method**.** And HPMC K100 M in F1, A1 and A2 batch were **20%, 17% and 25%** in both dry and wet granulation method taken. Following formula was used for the same,

Table23.Trial batch II for selection of polymers

| **Ingredient (mg) /Batch** | **F1** | **A1** | **A2** |
|---|---|---|---|
| Simvastatin | 20 | 20 | 20 |
| HPMC K100 M | 36 | 30.6 | 45 |

| | | | |
|---|---|---|---|
| Ethyl Cellulose | 18 | 23.4 | 9 |
| PVP K30 | 9 | 9 | 9 |
| Mannitol | q. s. 180 mg | q. s. 180 mg | q. s. 180 mg |
| Talc | 2 | 2 | 2 |
| Mg. Stearate | 7 | 7 | 7 |

**Significance:**

- As per the previous trial F1 batch was found to best and this batch shows best result in this trial also.
- But the A1 batch shows low result due to higher concentration of 13 % Ethyl cellulose.
- In A2 batch the release shows to be slight decrease but it was best result.
- By the above formulation the **F1 and A2 batch** found to best result as per the sustained release criteria by the **wet granulation method.**
- Hence we conclude that the concentration of **Ethyl cellulose** is not useful above the **10%** of the total formula and also below **5%** is not useful for the sustained release criteria. So we use that level in our optimization for the ethyl cellulose.
- And also for the HPMC K100 M we conclude that the maximum concentration level for the same is 25% is beneficial in optimization formula and the lower level is the 15% for gaining the sustained release criteria.

**Trials for bilayer tablet methodology**
**Trial I:**

For the combine disintegrant and polymer release screening following percent of the croscarmellose sodium, Ethyl cellulose and HPMC K100 M used in the bilayer layer of immediate release and sustained release tablet of atenolol and simvastatin by the direct compression and wet granulation method. Following formula was used for the same

**Formula for Atenolol**

Table24.Trial batch for selection of methodology

| Sr No. | Ingredient Name | Quantity per Tab (mg) | Category |
|---|---|---|---|
| 1 | Atenolol | 50 | API |
| 2 | Croscarmellose sodium | 7.2 **(6%)** | Disintegrant |
| 3 | PVP K30 | 6 | Binder |
| 4 | Mannitol | q.s.120mg | Filler |
| 5 | Talc | 4.8 | Lubricant |
| 6 | Mg.Stearate | 3.6 | Lubricant |

**Formula for Simvastatin**

Table25.Trial for bilayer tablet methodology

| Sr No. | Ingredient Name | Quantity per Tab (mg) | Category |
|---|---|---|---|
| 1 | Simvastatin | 20 | API |

| | | | |
|---|---|---|---|
| 2 | HPMC K100 M | 30 (20%) | Polymer |
| 3 | Ethyl Cellulose | 11.25 (7.5%) | Polymer |
| 4 | PVP K30 | 6 | Binder |
| 5 | Mannitol | q.s.up to 150 mg | Filler |
| 6 | Talc | 6 | Lubricant |
| 7 | Mg. Stearate | 4.5 | Lubricant |

**Significance:**

- In above Formulation 6% of croscarmellose sodium, 7.5% of Ethyl cellulose and 20% of HPMC K100 M was used and shows best result as per the immediate and sustained release criteria shown in USP.
- By the above formulation trial the batch found to best result as per the immediate and sustained release criteria by the **wet granulation method.**
- But by the dry granulation capping problem observed, and both layer not stick properly. So we can't use dry granulation technique for further research.
- Another problems like capping, mottling, lamination and cracking were observed and solve by concern remedies in another trials of placebo.
- Hence we conclude that the concentration of **Ethyl cellulose** is not useful above the **10%** of the total formula and also below **5%** is not useful for the sustained release criteria. So we use that level in our optimization for the ethyl cellulose.
- And also for the HPMC K100 M we conclude that the maximum concentration level for the same is **25%** is beneficial in optimization formula and the lower level is the **15%** for gaining the sustained release criteria.

**OPTIMIZATION**

The purpose of this trial was to determine the optimum level of three selected excipients by using Box Behnken experimental design.

**Precompression characterization**

All the batches were found to have good flow property. All the formulations were shown reproducible result in terms of flow property of powders.

Table26.Precompression characteristics of formulations for Atenolol

| Batch No. | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr's Index (%) | Hausner's Ratio | Angle of Repose (θ) |
|---|---|---|---|---|---|
| IR1 | 0.357 | 0.428 | 17.58 | 1.17 | 25.32 |
| IR2 | 0.346 | 0.413 | 16.22 | 1.19 | 27.22 |
| IR3 | 0.355 | 0.409 | 16.80 | 1.15 | 26.45 |

Table27.Precompression characteristics of formulations for Simvastatin.

| Batch No. | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr's Index (%) | Hausner's Ratio | Angle of Repose (θ) |
|---|---|---|---|---|---|
| SR1 | 0.353 | 0.423 | 16.54 | 1.19 | 25.32 |
| SR2 | 0.364 | 0.440 | 17.27 | 1.20 | 23.48 |
| SR3 | 0.361 | 0.435 | 17.01 | 1.20 | 27.60 |
| SR4 | 0.397 | 0.462 | 14.06 | 1.17 | 19.35 |
| SR5 | 0.392 | 0.460 | 14.78 | 1.17 | 22.43 |

| | | | | | |
|---|---|---|---|---|---|
| SR6 | 0.360 | 0.425 | 18.05 | 1.18 | 31.12 |
| SR7 | 0.349 | 0.415 | 15.90 | 1.18 | 28.35 |
| SR8 | 0.355 | 0.397 | 10.57 | 1.11 | 21.43 |
| SR9 | 0.353 | 0.423 | 16.54 | 1.19 | 25.32 |

**Post compression characterization**

For the 17 batches all the evaluation parameters was carried out. Hardness was sufficient to pass the friability test. There was no sign of lamination during friability test. The weight variation test was also passed by all the 17 batches.

Table28.Postcompression characteristics of formulations

| Batch No. | Avg. Tablet wt. (mg) | Thickness (mm) | Hardness ($kg/cm^2$) | Friability (%) | Drug content(%) | |
|---|---|---|---|---|---|---|
| | | | | | Atenolol | Simva |
| F1 | 270.91±1.12 | 4.35±0.07 | 8.20 | 0.86 | 98.23 | 96.45 |
| F2 | 268.85±0.69 | 4.30±0.10 | 7.50 | 0.42 | 96.32 | 98.75 |
| F3 | 269.15±0.89 | 4.41±0.18 | 8.00 | 0.78 | 96.28 | 97.46 |
| F4 | 272.11±1.19 | 4.44±0.21 | 7.70 | 0.52 | 99.45 | 94.86 |
| F5 | 270.85±2.10 | 4.39±0.15 | 8.00 | 0.86 | 95.64 | 99.12 |
| F6 | 271.13±1.85 | 4.30±0.08 | 8.10 | 0.63 | 94.89 | 97.56 |
| F7 | 269.10±1.13 | 4.38±0.15 | 7.80 | 0.41 | 100.89 | 93.56 |
| F8 | 269.82±0.75 | 4.32±0.12 | 8.30 | 0.90 | 97.28 | 94.86 |
| F9 | 271.56±1.72 | 4.41±0.11 | 7.70 | 0.83 | 97.56 | 99.23 |
| F10 | 268.54±1.28 | 4.44±0.19 | 7.90 | 0.70 | 101.56 | 97.50 |
| F11 | 271.64±0.87 | 4.39±0.17 | 8.00 | 0.93 | 95.86 | 95.89 |
| F12 | 270.28±1.03 | 4.37±0.13 | 7.60 | 0.77 | 102.11 | 93.78 |
| F13 | 268.56±0.42 | 4.40±0.10 | 7.80 | 0.85 | 96.58 | 95.56 |
| F14 | 269.49±1.28 | 4.33±0.15 | 7.70 | 0.78 | 97.28 | 99.78 |
| F15 | 273.10±0.85 | 4.39±0.09 | 8.10 | 0.83 | 98.46 | 98.85 |
| F16 | 271.63±1.56 | 4.31±0.20 | 7.80 | 0.70 | 99.18 | 97.68 |
| F17 | 272.15±1.19 | 4.38±0.09 | 8.20 | 0.61 | 97.58 | 98.56 |

**Drug release profile**

The result of dissolution study of formulations F1 to F17 was showed in the following table**.**

Table 29.Dissolution profile of formulations

| Batch No. | Conc. Of IR | | | Conc. Of SR at Time (Q3,Q6,Q9) | | |
|---|---|---|---|---|---|---|
| | 15 min | 30 min | 45min | 3 hrs | 6hrs | 9hrs |
| F1 | 25.46 | 56.13 | 86.62 | 34.59 | 79.13 | 92.45 |
| F2 | 31.14 | 69.15 | 98.56 | 35.10 | 78.00 | 98.62 |
| F3 | 22.76 | 48.45 | 87.45 | 25.20 | 54.82 | 76.52 |
| F4 | 37.49 | 67.25 | 99.58 | 25.79 | 57.45 | 73.42 |
| F5 | 23.16 | 49.25 | 85.15 | 36.85 | 69.56 | 91.24 |
| F6 | 32.76 | 71.85 | 98.12 | 37.49 | 79.12 | 89.91 |
| F7 | 25.35 | 57.89 | 86.19 | 22.98 | 62.45 | 86.73 |
| F8 | 33.96 | 70.12 | 99.74 | 20.12 | 63.23 | 81.59 |
| F9 | 30.56 | 61.23 | 91.71 | 46.11 | 85.12 | 99.31 |
| F10 | 32.35 | 59.66 | 93.56 | 25.51 | 64.67 | 84.24 |
| F11 | 29.45 | 57.78 | 93.89 | 23.56 | 69.36 | 78.56 |
| F12 | 27.56 | 59.39 | 93.45 | 21.22 | 48.48 | 68.45 |
| F13 | 28.39 | 62.36 | 92.18 | 27.56 | 74.87 | 89.49 |
| F14 | 31.35 | 65.87 | 93.45 | 28.51 | 75.61 | 90.11 |
| F15 | 27.56 | 61.86 | 93.70 | 28.23 | 73.12 | 86.26 |
| F16 | 32.45 | 56.89 | 93.10 | 28.67 | 73.18 | 89.10 |
| F17 | 21.75 | 55.45 | 92.81 | 29.31 | 74.45 | 90.19 |

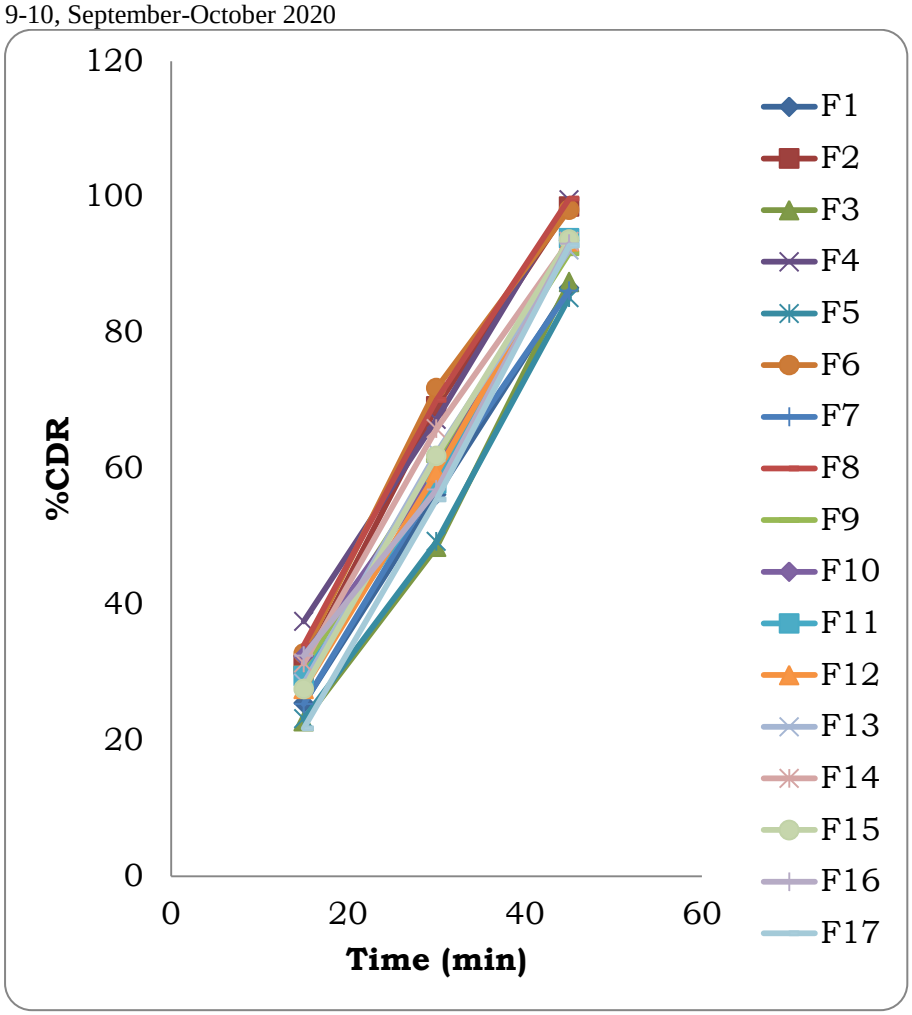
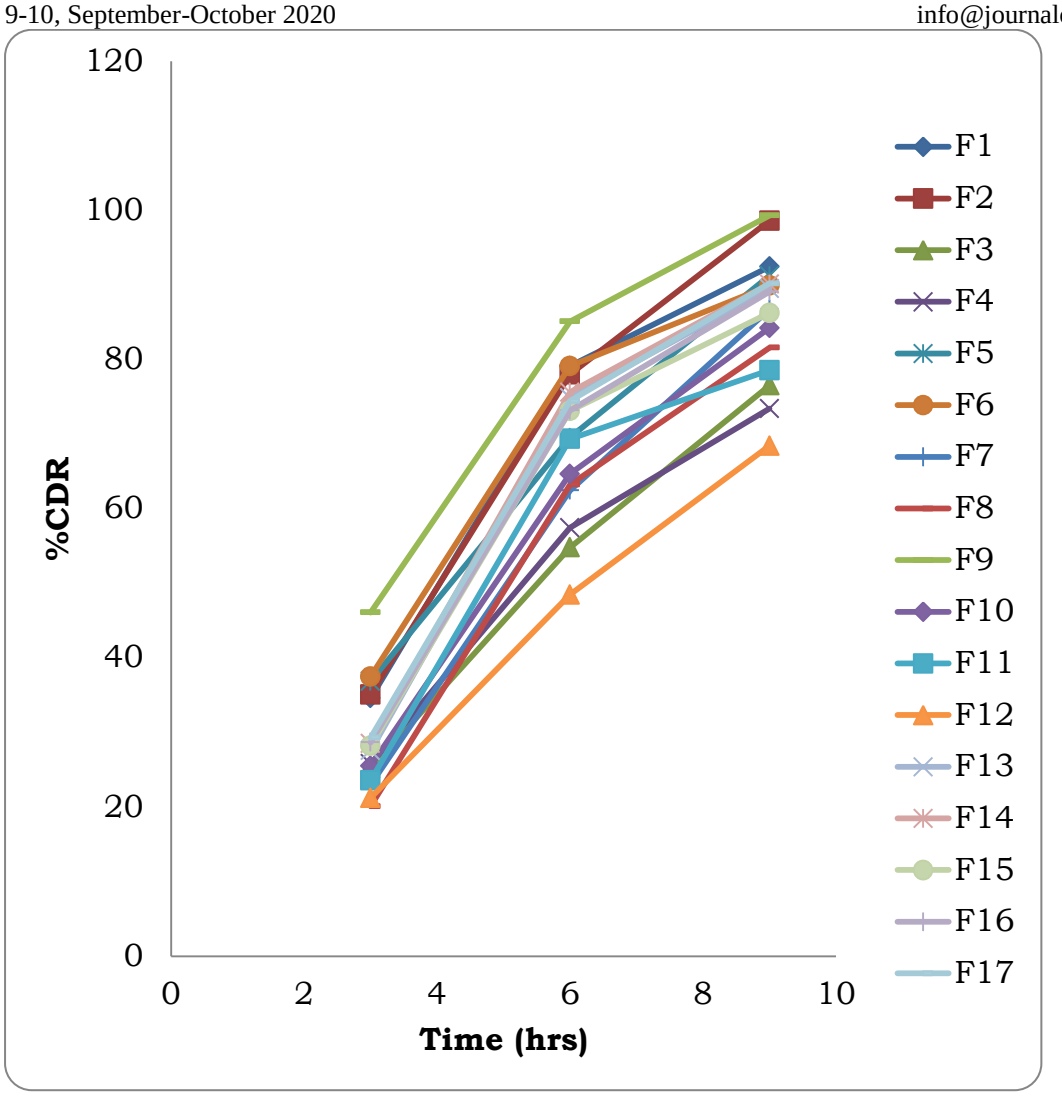



Figure 1.Dissolution profile of Atenolol (F1-F17)




**Optimized formula**

From the set target variables, the software calculates and predicts the formula which achieved the set target as near as possible. Optimize formula was showed in the following table.

Table30.Formula for optimized batch of Atenolol

| Sr. No. | Ingredients | Quantity (mg) |
|---|---|---|
| 1 | Atenolol | 50 |
| 2 | Croscarmellose sodium | 7.4 |
| 3 | PVP K30 | 6 |
| 4 | Mannitol | q. s. up to 120 mg |
| 5 | Talc | 4.8 |
| 6 | Mg.Stearate | 3.6 |
| | Total wt. | 120 |

Table31.Formula for optimized batch of Simvastatin

| Sr. No. | Ingredients | Quantity (mg) |
|---|---|---|
| 1 | Simvastatin | 20 |
| 2 | HPMC K100 M | 8.02 |
| 3 | Ethyl Cellulose | 30 |

| | | |
|---|---|---|
| 4 | PVP K30 | 6 |
| 5 | Mannitol | q.s.up to 150 mg |
| 6 | Talc | 6 |
| 7 | Mg. Stearate | 4.5 |
| | Total wt. | 150 |

## EVALUATION OF OPTIMIZED FORMULA BATCH

### Precompression study

Table32.Precompression characteristics for atenolol optimized formulation

| Flow properties | Optimize Batch | | | Mean ± S.D. (n=3) |
|---|---|---|---|---|
| | A1 | A2 | A3 | |
| Bulk density (g/cm$^3$) | 32.00 | 32.20 | 32.00 | 32.06±0.115 |
| Tapped density (g/cm$^3$) | 29.70 | 30.10 | 29.50 | 29.76±0.305 |
| Compressibility (%) | 7.18 | 6.52 | 7.81 | 7.17±0.645 |
| Angle of repose (θ) | 15.20 | 15.00 | 16.40 | 15.50±0.521 |

Table33.Precompression characteristics for simvastatin optimized formulation

| Flow properties | Optimize Batch | | | Mean ± S.D. (n=3) |
|---|---|---|---|---|
| | A1 | A2 | A3 | |
| Bulk density (g/cm$^3$) | 35.10 | 35.60 | 36.20 | 35.50±0.130 |
| Tapped density (g/cm$^3$) | 30.80 | 31.20 | 32.10 | 31.4±0.240 |
| Compressibility (%) | 6.52 | 6.82 | 7.45 | 6.84±0.530 |
| Angle of repose (θ) | 16.10 | 15.70 | 16.50 | 15.50±0.498 |

### Post compression study

### General appearance

The general appearance of a tablet, its visual identity and overall "elegance" is essential for consumer acceptance. Includes in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency.

Table34.Postcompression characteristics for optimized formulation

| Parameters | Optimize Batch | | | Mean ± S.D. (n=3) |
|---|---|---|---|---|
| | A1 | A2 | A3 | |
| Avg. Tablet wt. (mg) | 270.50 | 271.20 | 269.70 | 270.40±0.90 |
| Thickness (mm) | 4.35 | 4.40 | 4.38 | 4.37±0.09 |
| Hardness (kg/cm$^2$) | 7.50 | 8.10 | 7.90 | 7.80±0.15 |
| Friability (%) | 0.85 | 0.60 | 0.75 | 0.78±0.45 |
| % CU (Atenolol) | 98.65 | 97.86 | 99.56 | 98.69±0.012 |
| %CU (Simvastatin) | 97.86 | 96.85 | 98.86 | 97.85±0.015 |

(CU- Content Uniformity)

### Drug release profile

Dissolution study showed that all the three formulations percentage drug release more than 95% in 45 min for immediate release layer and in 9 hrs for sustained release layer. The result of dissolution study of formulations A1 to A3 was shown in following table.

Table35.Drug release of optimized formulation

| Time | | Percent Drug release (%DR) | | | Mean±SD (n=3) |
|---|---|---|---|---|---|
| | | A1 | A2 | A3 | |
| % CDR of Atenolol | 15 min | 31.24 | 33.15 | 36.76 | 33.71 |
| | 30 min | 70.14 | 68.45 | 72.98 | 70.52 |
| | 45 min | 96.24 | 98.73 | 97.80 | 97.59 |
| % CDR of Simvastatin | 3 hrs | 33.55 | 36.10 | 31.83 | 33.82 |
| | 6 hrs | 73.85 | 79.79 | 75.19 | 76.27 |
| | 9 hrs | 95.42 | 98.62 | 96.15 | 96.73 |

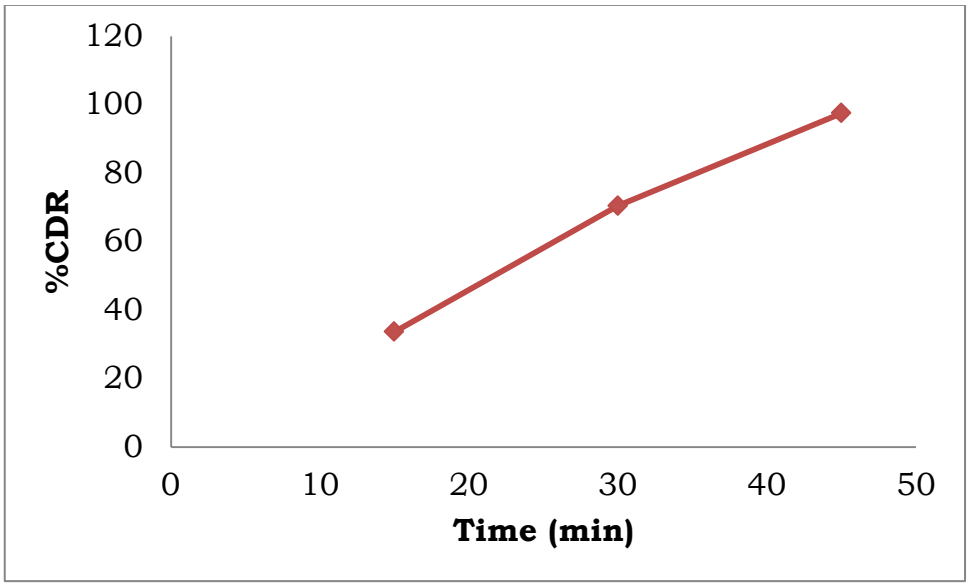



Figure.Dissolution Profile for atenolol of optimized batch

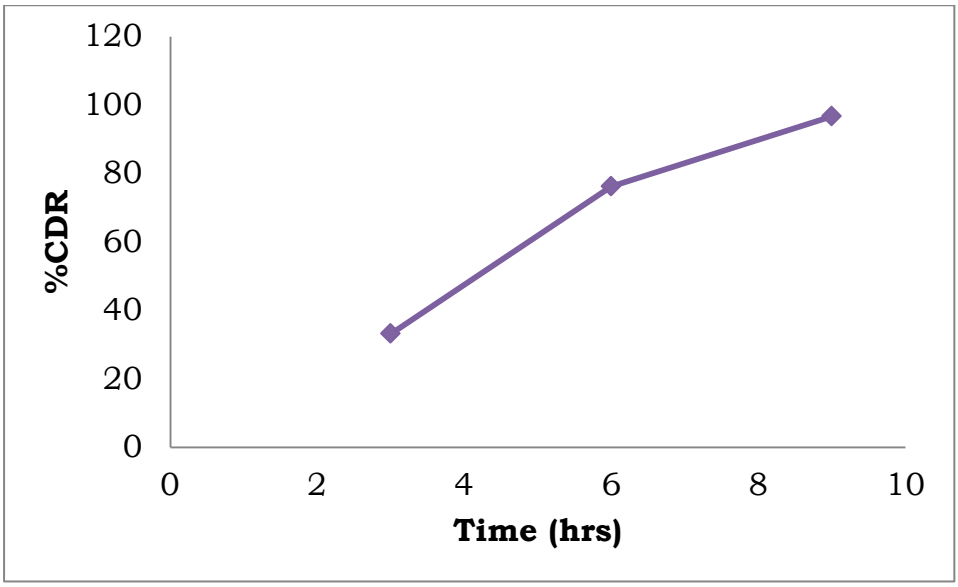


Figure.Dissolution Profile for simvastatin of optimized batch

**SUMMARY AND CONCLUSION**

Bi-layer tablet is suitable for sequential release of two or one drugs in combination. The aim of present study work is the design and development of bilayer tablet of Atenolol and Simvastatin. The drugs candidate selected for bilayer tablet as it is having one of antihypertensive and another is antihyperlipidemics in action. By formulating bilayer tablet combination of two APIs i.e. Atenolol and Simvastatin having two different actions reduces the dosing unit burden there by improving patient compliance.

Hypertension and dyslipidemia are conditions that coexist on a regular basis. In a recent study utilizing data from the third National Health and Nutrition Examination Survey (NHANES III), it was estimated that almost 15% of US adults (representing approximately 30 million persons) have both hypertension and dyslipidemia. It was also shown that more than 60% of patients with hypertension also have dyslipidemia; conversely, approximately 50% of patients with dyslipidemia have hypertension. Hypertension and hypercholesterolemia are the two leading risk factors for heart disease, which is the leading cause of death worldwide. So we formulated the new design of combination therapy for the same as above.

Conclusions drawn from the investigation are summarized below,

- IR spectra revealed that, the drug sample was pure.
- There was no interaction between excipients and drug. Excipients selected for bilayer tablet compatible with atenolol and simvastatin. The IR analysis indicates that there was no drug-excipient interaction.
- From preliminary screening of three excipients croscarmellose sodium, ethyl cellulose and HPMC selected according to their contribution in the formulations by studying release pattern as per immediate and sustained release criteria.
- Response surface method (RSM) can be successfully utilized for optimization of the batches. The selected independent variables disintegrant and polymers have significant effect on the dependent variable such as release concentration.
- From RSM it was predicted that,
  - If the amount of disintegrant i.e. croscarmellose sodium was increased then the drug release concentration also increases.
  - If the amount of ethyl cellulose was increases the release concentration decreases and also hardness increases.
  - If the amount of HPMC was increases up to high level release decreases and not obey the sustained release criteria, but the center point of the level obey the criteria.
  - According to point prediction study optimum concentration levels of the formulation composition of croscarmellose sodium (7.4mg), ethyl cellulose (8.02mg) and HPMC K100 M (30mg) was found to fulfill the maximum requirement of an optimum release concentration as per target variables.
  - Precompression and postcompression characterization of optimized batch was done and all the parameters pass the standards.
- The *in-vitro* dissolution study shows the drug release of immediate release layer 93.80 to 98.73% in 45 minutes and 95.42 to 98.62% of sustained release layer in 9 hrs.

It is concluded that a combination of different polymers concentration levels and hardness of tablet are important for making bilayer tablet of atenolol and simvastatin without any special apparatus.

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