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# FORMULATION AND EVALUATION OF BILAYER TABLETS OF GLIMEPIRIDE AND CAPTOPRIL

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## ABSTRACT

The present study is to establish bi-layer tablets of Glimepiride and Captopril, of which Glimepiride as immediate release and Captopril as sustained release layers. Immediate release layer was prepared by direct compression method by using cross povidone as disintegrant and sustained release layer was prepared by direct compression method by using HPMC K4 as polymer. Both powder blends of immediate and sustained release layers were evaluated for Bulk density, Tapped density, Compressibility index, Hausner ratio and Angle of repose. All the values were found within limit of standard. In vitro release studies were carried out by USP type 2 paddle apparatus. The result showed that polymer HPMC K4 in sustained layer controlled the release of drug. The formulation (F4) having immediate release layer produced immediate effect showing 99.6%drug release within 30minutes, followed by sustained release effect showing 96.8% drug release upto 12 hours. The present study concluded that Bilayer tablets of Glimepiride and Captopril can be a better alternative to conventional dosage form for providing immediate and sustained drug delivery.

**KEYWORDS:Bilayer tablet, Glimepiride, Captopril, Sustained Release, Higuchi equation.**

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# INTRODUCTION

Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction. The design of modified release drug product is to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval providing greater patient compliance and convenience. Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They are intended for oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in water before being administered and some are retained in the mouth, where the active ingredient "liberated". Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action. Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer [e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing] and the patient [e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of administration].[1]Bilayer tablet is the new era for the successful development of controlled release formulation. Bilayer tablet is better than the traditionally used dosage forms. Bi-layer tablet is suitable for sequential release of two drugs in combination. It is also capable of separating two incompatible drug substances. Of the two layers, one layer is immediate release as initial dose and second layer is maintenance dose. The immediate release layer delivers the initial dose, it contains superdisintegrants which promotes the drug release rate and attains the onset of action quickly (loading dose) whereas sustained release (maintenance dose) layer releases the drug in a sustained manner for a prolonged time period. In certain cases bilayer tablets have two sustained release layers of different drugs. Bilayer tablet is an improved technology to overcome the shortcoming experienced with the single layered tablet.[2]In the present scenario of pharmaceutical drug delivery system, conventional pharmaceutical dosage forms are being replaced by new drug delivery systems. The development in the field of API, excipients and tableting machines or processing equipments during the past decade has made tablet manufacturing a science and tablets the most commonly used dosage form. A combination of one or more active ingredients gains importance in recent years to treat the various forms of diseases or to get the different therapeutic actions, particularly from solid oral dosage form. [3]Bi-layer tablet is suitable for sequential release of two drugs in combination and separately two incompatible substances. Bilayer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of sustained delivery of active pharmaceutical ingredients with pre-determined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers.[4]

### *ADVANTAGES OF BILAYER TABLET DOSAGE FORM[5, 6]*

- Bilayer tablets can be designed in such manner as to modify release as either of the layers can be kept as extended and the other as immediate release.
- Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
- Separation of incompatible components.
- Prospective use of single entity feed granules.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odour and bitter taste can be masked by coating technique.
- Bilayer execution with optional single - layer conversion kit.

- Low cost compared to all other dosage form.
- Offer greatest precision and least content uniformity.
- Easy to swallow with least hang up problems.
- Flexible concept.
- Suitable for large scale production.
- Lighter and compact.
- Patient compliance is improved leading to improve drug regimen efficiency.
- They are unit dosage form and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and least content variability.
- Patient compliance is improved fewer daily dose are required compared to the traditional delivery system.

### *DISADVANTAGES OF BILAYER TABLET DOSAGE FORM*[7]

- Drugs with poor wetting, slow dissolution properties, optimum absorption, high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Difficult to swallow in case of children and unconscious patients.
- Adds complexity and bilayer rotary presses are expensive.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Cross contamination between the layers.
- Insufficient hardness, layer separation, reduced yield.

### *TYPES OF BILAYER TABLET PRESS*[8]

***i) Single sided tablet press.***
***ii) Double sided tablet press.***
***iii) Bilayer tablet press with displacement monitoring.***

#### *i) Single sided tablet press*

- The simplest design is a single sided press with both chambers of the doublet feeder separated from each other.
- Each chamber is gravity or forced fed with different power, the producing the two individual layers of the tablets.
- When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder.
- Then the entire tablet is compressed in one or two steps.

Limitations of single sided press:

- No weight monitoring/control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping, and hardness problems.
- This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of the lower tablet output.

**Figure 1**
***Single sided bilayer tablet press***

***ii) Double sided tablet presses***

- In most double sided tablet presses with automated production control use compression force to monitor and control tablet weight.
- The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer
- This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

**Figure 2**
***Double sided bilayer tablet press***

***iii)Bilayer tablet press with displacement***

- The displacement tablet weight control principle is fundamentally different from the principle based upon compression force.
- When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre- compression force.

***Advantages***

- Weight monitoring/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.
- Independence from the machine stiffness
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross-contamination between the two layers.Clear visual separation between the two layers and maximized yield.

**Figure 3**
***Bilayer tablet press with displacement***

## MATERIALS AND METHODS

Glimepiride and Captopril were gifted samples obtained from GPT Pharma Hyderabad, HPMC K100, HPMC K4M, polyvinylpyrollidone, Ethyl cellulose gifted by Sisco research laboratories Pvt.Ltd Mumbai. Starch, Micro Crystalline Cellulose, Magnesium Stearate, Talc gifted by S.D. Fine Chem. Ltd, Mumbai. Cros Povidone, Cross Carmellose Sodium, Sodium Starch Glycolate gifted by ESSELfine chem. Mumbai.

***Formulation of Immediate release layer (Glimepiride)***

Immediate Release tablets of Glimeperide were prepared by direct compression method. The concentrations of the ingredients shown in the table 3. All the ingredients were weighed accurately. The drug was mixed with excipients, except magnesium stearate and talc. The powder mixtures were blended for 20 minutes to have uniform distribution of drugs in the formulation. Then, magnesium stearate and talc were added and mixed for not more than 1 min (to ensure good lubrication). The powder blend was evaluated for pre-compression parameters (Angle of Repose, Loose Bulk Density, Tapped Bulk Density, Carr's Index, Hausner's Ratio). The results are mentioned in the table 1. After the evaluation of pre-compressed parameters, about 150 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 8mm round surface punches. The tablets are evaluated for parameters such as hardness, friability and thickness.

***Formulation of Sustained Release layer ( Captopril)***

The sustained release tablets of Captopril were prepared by direct compression method. As shown in Table 4. All the ingredients were weighed accurately. The drug was mixed with excipients, Microcrystalline cellulose, polymer and binder were blended for 20 minutes to have uniform distribution of drug in the formulation, followed by addition of Magnesium Stearate and talc (to ensure good lubrication). The mixtures were then further blended for 10 min. The powder blend is evaluated for pre-compression parameters (Angle of Repose, Loose Bulk Density, Tapped Bulk Density, Carr's Index, Hausner's Ratio). The results are mentioned in the table number 2. About 200 mg of the resultant powder blend was fed into the die of

single punch machinery and compressed using 8mm round surface punches. The tablets are evaluated for parameters such as hardness, friability and thickness.

***Pre-formulation studies***

The preformulation studies of both Glimepiride and Captopril were evaluated for various physical properties individually and the values were presented in the table 1and 2. From the table 1 it is observed that the powder blends of Glimepiride has good flow properties. From the table 2, it is observed that the powder blends of Captopril have excellent flow properties. From the results in the tables 5 and 6 it was evident that all the tablets of Glimiperide and Captopril have complied with the official requirements of uniformity of weight, hardness, thickness and friability.

**Table 1**
***Preformulation studies of Glimepiride powder blend***

| Formulations | Angle of Repose (θ) | Loose Bulk Density (g/ml) | Tapped Bulk Density (g/ml) | %Compressibility | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | 26.09 | 0.37 | 0.42 | 11.90 | 1.14 |
| **F2** | 24.78 | 0.35 | 0.40 | 12.50 | 1.14 |
| **F3** | 25.45 | 0.32 | 0.37 | 13.51 | 1.16 |
| **F4** | 28.13 | 0.37 | 0.42 | 11.90 | 1.14 |
| **F5** | 27.46 | 0.34 | 0.38 | 10.53 | 1.12 |
| **F6** | 26.08 | 0.34 | 0.39 | 12.82 | 1.15 |

**Table 2**
***Preformulation studies of Captopril powder blend***

| Formulations | Angle of Repose (θ) | Loose Bulk Density (g/ml) | Tapped Bulk Density (g/ml) | %Compressibility | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | 27.31 | 0.34 | 0.39 | 12.82 | 1.15 |
| **F2** | 25.23 | 0.31 | 0.36 | 13.89 | 1.16 |
| **F3** | 26.09 | 0.37 | 0.42 | 11.90 | 1.14 |
| **F4** | 24.89 | 0.33 | 0.38 | 13.16 | 1.15 |
| **F5** | 26.54 | 0.32 | 0.37 | 13.51 | 1.16 |
| **F6** | 25.01 | 0.36 | 0.41 | 12.20 | 1.14 |

**Table 3**
***Preparation of immediate release layer tablets of Glimepiride***

| Ingredients (mg) | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ |
|---|---|---|---|---|---|---|
| **Glimepiride** | 4 | 4 | 4 | 4 | 4 | 4 |
| **CP** | 7.5 | -- | -- | 11.25 | -- | -- |
| **CCS** | -- | 7.5 | -- | -- | 11.25 | -- |
| **SSG** | -- | -- | 7.5 | -- | -- | 11.25 |
| **Starch** | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| **Magnesium stearate** | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 |
| **Talc** | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 |
| **MCC** | 123.5 | 123.5 | 123.5 | 119.75 | 119.75 | 119.75 |
| **Total weight(mg)** | 150 | 150 | 150 | 150 | 150 | 150 |

***CP: crospovidone, CCS: Cross caramellose sodium,***
***SSG: Sodium starch glycolate,***
***MCC- Micro crystalline cellulose.***

**Table 4**
***Preparation of Sustained Release layer tablets of Captopril***

| Ingredients(mg) | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ |
|---|---|---|---|---|---|---|
| **Captopril** | 25 | 25 | 25 | 25 | 25 | 25 |
| **HPMC K100** | 20 | 30 | -- | -- | -- | -- |
| **EC** | -- | -- | 20 | 30 | -- | -- |
| **HPMC K4M** | -- | -- | -- | -- | 20 | 30 |
| **PVP K30** | 5 | 5 | 5 | 5 | 5 | 5 |
| **Talc** | 4 | 4 | 4 | 4 | 4 | 4 |
| **Magnesium stearate** | 4 | 4 | 4 | 4 | 4 | 4 |
| **MCC** | 142 | 132 | 142 | 132 | 142 | 132 |
| **Total weight (mg)** | 200 | 200 | 200 | 200 | 200 | 200 |

***MCC- Micro crystalline cellulose,***
***EC – Ethyl cellulose,***
***PVP- Poly vinyl pyrrolidine,***
***HPMC – Hydroxy Propyl methyl cellulose.***

# RESULTS AND DISCUSSION

### *Drug excipients compatability studies by FT-IR*

Infrared spectrum was taken (FT-IR, spectrum RX 1, Perkin Elmer Ltd, Swizerland) by scanning the sample in potassium bromide discs. The samples of pure drugs and their bilayer tablet blend were scanned individually demonstrating that the excipients selected were compatible with the drugs.

***FTIR Spectra of Glimepiride(pure drug)***

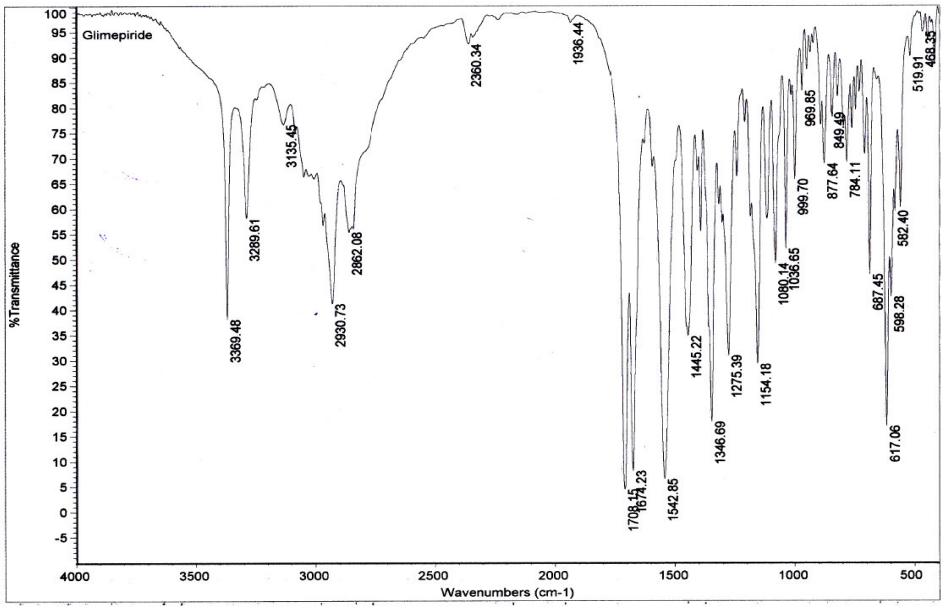


**Figure 4**
***FTIR spectra of Glimepiride pure drug***

***FTIR Spectra of Captopril (pure drug)***

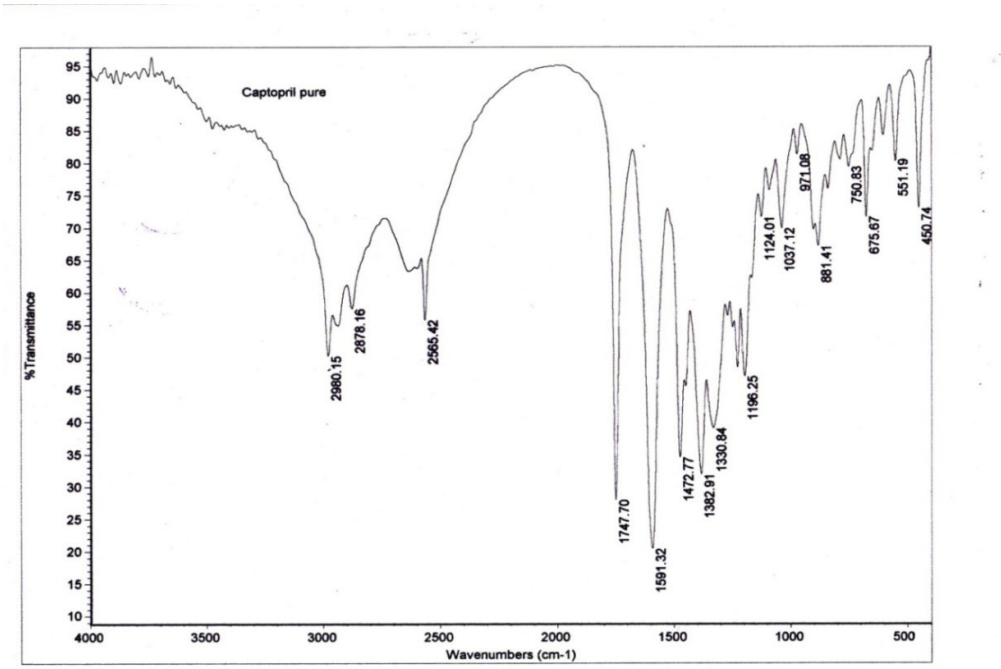


**Figure 5**
***FTIR spectra of Captopril pure drug***

### *FTIR Spectra of Bi-Layered Tablet*

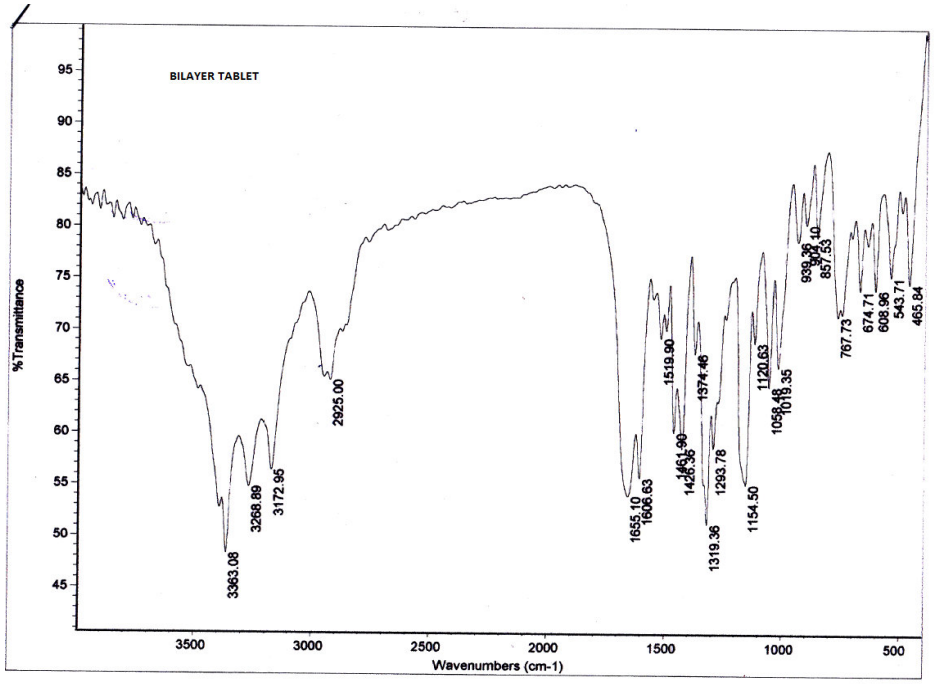


**Figure 6**
***FTIR spectra of Bi-Layered Tablet***

### *Evaluation studies of tablets*

**Table 5**
***Evaluation of Glimepiride tablets***

| Formulations | Average weight (mg) | Hardness $Kg/cm^2$ | Thickness (mm) | Friability (%) |
|---|---|---|---|---|
| **F1** | 150 | 3.3 | 2.9 | 0.36 |
| **F2** | 148 | 3.8 | 2.4 | 0.38 |
| **F3** | 151 | 3.6 | 2.6 | 0.42 |
| **F4** | 150 | 3.5 | 2.7 | 0.36 |
| **F5** | 149 | 3.9 | 2.2 | 0.40 |
| **F6** | 150 | 3.8 | 2.3 | 0.35 |

**Table 6**
***Evaluation of Captopril tablets***

| Formulations | Average weight (mg) | Hardness | Thickness (mm) | Friability (%) |
|---|---|---|---|---|
| **F1** | 201 | 4.6 | 2.80 | 0.38 |
| **F2** | 198 | 5.4 | 2.51 | 0.41 |
| **F3** | 200 | 5.1 | 2.61 | 0.37 |
| **F4** | 199 | 4.8 | 2.74 | 0.42 |
| **F5** | 201 | 5.0 | 2.67 | 0.45 |
| **F6** | 200 | 5.3 | 2.56 | 0.43 |

Based on the invitro release study of Glimepiride tablet (Table 7 ) the formulation F4 was considered optimized one. Based on the invitro release study of Captopril tablet the formulation F5 (Table 8) was considered to be optimized one.The data obtained from invitro release study of F5 formulation of Captopril was fitted to various mathematical models like Higuchi. Peppas model andfirst order.With the optimized layers of Immediate and Sustained Release blends, bilayer tablets were compressed and invitro dissolution studies were carried out.The Immediate release drug(Glimepiride) showed 99.9% release in 30 minutes and the Sustained Release drug (Captopril) showed 97.1% release in 12 hrs.

***Invitro dissolution studies of Immediate release tablet (Glimepiride)***

**Table 7**
***Dissolution studies of Glimepiride***

| Time in mins | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| **5** | 26.2 | 23.0 | 18.9 | 36.9 | 35.4 | 30.4 |
| **10** | 35.3 | 39.7 | 30.2 | 60.8 | 66.9 | 59.4 |
| **15** | 75.8 | 76.4 | 58.9 | 85.7 | 79.4 | 70.2 |
| **30** | 89.0 | 87.9 | 77.9 | 99.6 | 99.3 | 86.5 |
| **45** | 98.7 | 99.0 | 87.2 | -- | -- | 99.5 |

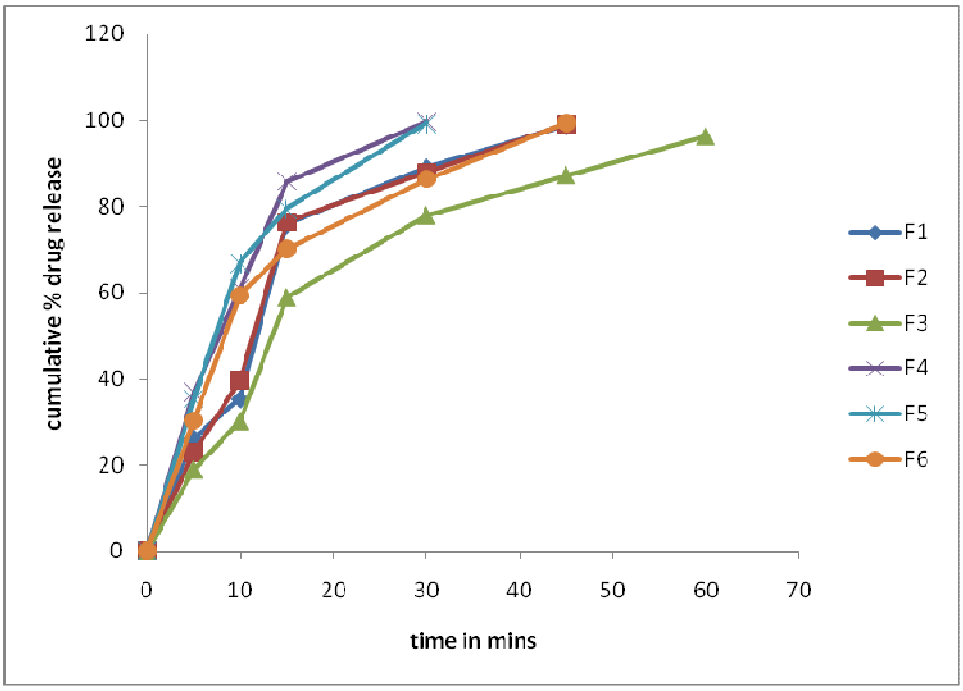


**Figure 7**
***Dissolution graph for glimepiride***

*In-Vitro Dissolution Studies of Sustained release tablets (Captopril)*

**Table no 8**
***Dissolution studies of Captopril***

| Time(hrs) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **Dissolution medium 0.1N HCL** | | | | | | |
| 1 | 25.7 | 15.7 | 12.09 | 7.57 | 8.5 | 7.3 |
| 2 | 34.0 | 27.8 | 19.7 | 15.8 | 10.6 | 11.2 |
| **6.8pH phosphate buffer** | | | | | | |
| 3 | 41.1 | 43.8 | 29.3 | 20.3 | 29.8 | 15.8 |
| 4 | 67.8 | 57.3 | 44.8 | 39.7 | 43.9 | 27.0 |
| 5 | 93.8 | 83.9 | 50.7 | 48.5 | 56.7 | 33.8 |
| 6 | 99.4 | 92.8 | 58.9 | 51.4 | 64.0 | 52.8 |
| 8 | -- | 97.0 | 67.3 | 65.6 | 87.8 | 77.9 |
| 12 | -- | -- | 77.8 | 70.4 | 96.8 | 85.8 |

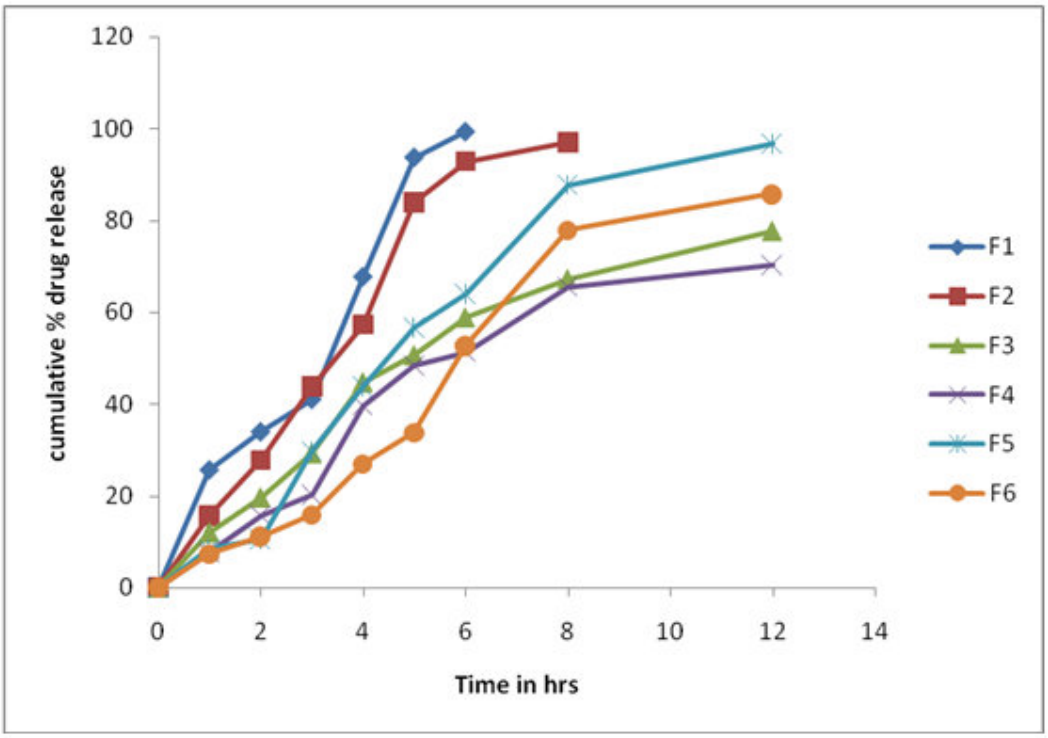


**Figure 8**
***Dissolution graph for sustained release formulations***

### *Invitro dissolution studies of Bilayer tablet*

**Table 9**
***Dissolution profile of bilayered tablet***

| S.NO | Sampling time | Percentage drug released (%) | |
|---|---|---|---|
| | | GLIMEPIRIDE | CAPTOPRIL |
| 1 | 15mins | 86.5 | 3.2 |
| 2 | 30 mins | 99.9 | 4.9 |
| 5 | 1hr | -- | 7.0 |
| 6 | 2hr | -- | 10.1 |
| 7 | 3hr | -- | 30.5 |
| 8 | 4hr | -- | 42.8 |
| 9 | 5hr | -- | 55.9 |
| 10 | 6hr | -- | 67.8 |
| 11 | 8hr | -- | 89.0 |
| 12 | 12hr | -- | 97.1 |

### *KINETIC RELEASE MODELS*

**Table 10**
***Release kinetics for formulation for sustained release tablet (captopril)***

| | ZERO | FIRST | HIGUCHI | PEPPAS |
|---|---|---|---|---|
| | % CDR Vs T | Log % Remain Vs T | %CDR Vs √T | Log C Vs Log T |
| Slope | 8.29272 | -0.11128413 | 30.34942883 | 1.434981223 |
| Intercept | 1.84832 | 2.156825431 | -16.6360224 | 0.575980624 |
| Correlation | 0.988210211 | -0.93644580 | 0.960563684 | 0.909061635 |
| $R^2$ | 0.97655942 | 0.876930746 | 0.922682591 | 0.826393055 |

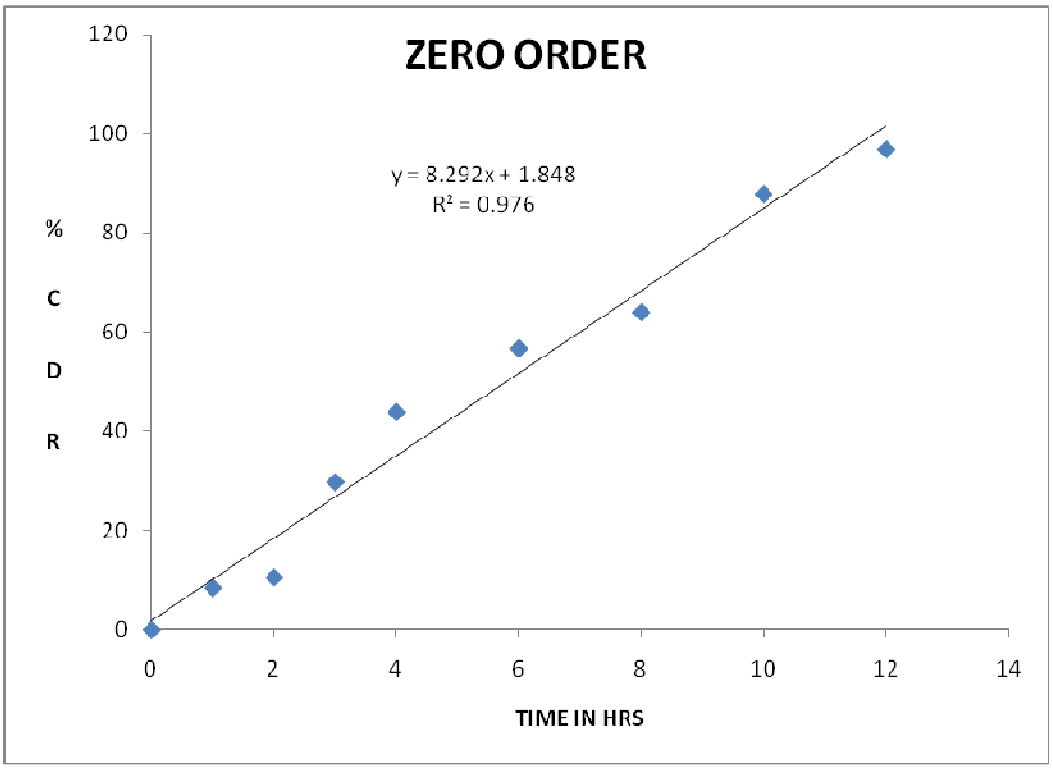


**Figure 9**
***zero order release graph for F5 sustained release formulation***

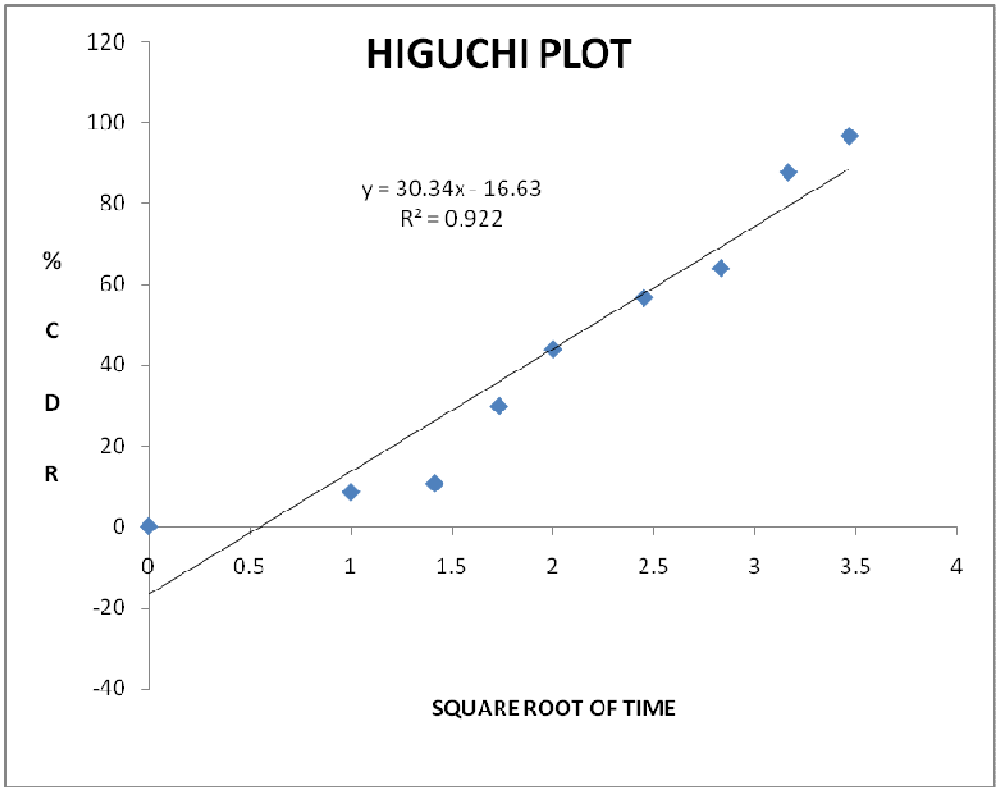


**Figure 10**
***Higuchi model graph for F5 sustained release formulation***

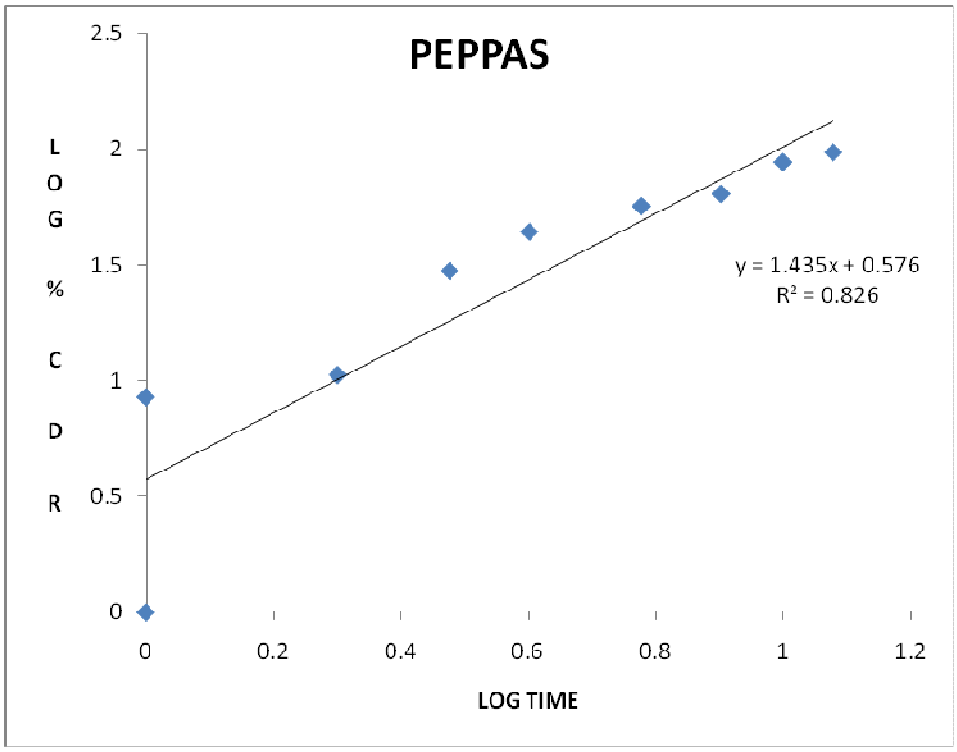


**Figure 11**
***peppas model for F5 sustained release formulation***

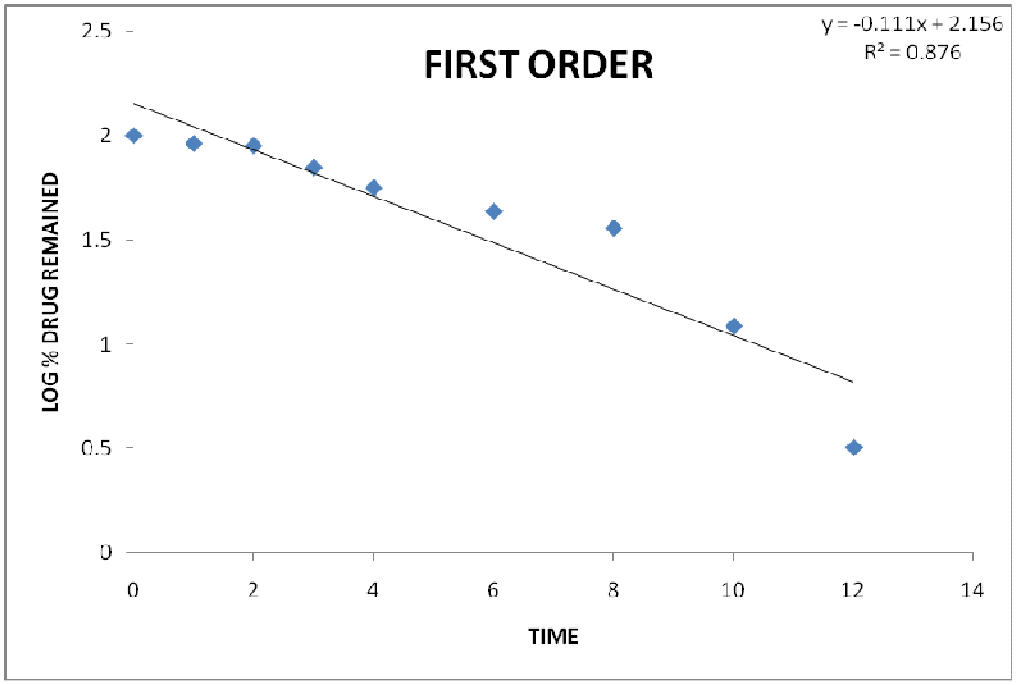


**Figure 12**
***First order release graph for F5 sustained release formulation***

## CONCLUSION

The Bilayered tablets containing immediate release layer of Glimepride and Sustained Release layer of Captopril were successfully prepared by direct compression method.Various formulations were prepared and evaluated with an aim of presenting Glimepiride as immediate release and Captopril as sustained release for improving the patient's compliance. The physiochemical evaluation results for the powdered blends of all trials passed the official limits in angle of repose, compressibility index, Hausner ratio.The prepared Immediate Release layer tablets and Sustained Release layer tablets also maintained the physiochemical properties such as thickness, hardness and friability. The optimized formulation F4 of IR Glimepiride contains the average thickness of 2.7mm, average hardness of 3.5 kg/cm$^2$, average weight of 150mg and friability of 0.36%. The optimized formulation F5 of SR formulations contains the average thickness of 2.67mm, average hardness of 5 kg/cm$^2$, average weight of 200mg and friability of 0.45%.The optimized formulation (F4) of immediate release drug (Glimepiride) released 99.6% of the drug in 30minutes. The optimized formulation (F5) of sustained release drug (Captopril) released 96.8% of drug in 12hrs. The dissolution study was carried out for the optimized bilayer tablet and it correlates with the drug release of individual release layer formulations.Based on the outcome of above studies it is concluded that the bilayer tablets prepared by direct compression method for immediate and sustained release Glimepiride and Captopril is a perfect and effective formulation for the treatment of Diabetis and Hypertension.

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