# Formulation and *in-vitro* evaluation of floating bilayer tablet of lisinopril maleate and metoprolol tartrate

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**Abstract**: The purpose of this study was to introduce the technology for the development of rate-controlled oral drug delivery system to overcome various physiological problems. Several approaches are being used for the purpose of increasing the gastric retentive time, including floating drug delivery system. Gastric floating lisinopril maleate and metoprolol tartrate bilayer tablets were formulated by direct compression method using the sodium starch glycolate, crosscarmellose sodium for IR layer. Eudragit L100, pectin, acacia as sustained release polymers in different ratios for SR metoprolol tartrate layer and sodium bicarbonate, citric acid as gas generating agents for the floating extended release layer. The floating bilayer tablets of lisinopril maleate and metoprolol tartrate were designed to overcome the various problems associated with conventional oral dosage form. Floating tablets were evaluated for floating lag time, drug contents and in-vitro dissolution profile and different kinetic release models were applied. It was clear that the different ratios of polymers affected the drug release and floating time. L2 and M4 showed good drug release profile and floating behavior. The linear regression and model fitting showed that all formulation followed Higuchi model of drug release model except M4 that followed zero order kinetic. From the study it is evident that a promising controlled release by floating bilyer tablets of lisinopril maleate and metoprolol tartrate can be developed successfully.

**Keywords**: Metoprolol tartrate, lisinopril maleate, bilayer floating tablets, polymers.

## INTRODUCTION

Within last 2 years tremendous advances occur in oral control drug delivery system. Gastric emptying time depend upon dosage form, fed and fast state of stomach. Normal gastric emptying ranges between 5min to 2hr. Drug with short half life are rapidly eliminated from body (Rangapriya *et al*., 2012).

In recent era various developed and developing countries are moving towards combination therapy to treat different diseases like hypertension, diabetes mellitus, CVD. Combination therapy requires low dose of two active ingredients, which may provide synergistic effect or additive effect resulting in decrease dose of drug, it may help in reducing fetal drug effect. Combination therapy may use to target specific organ or act through specific pathway which lead to decrease in side effects (Gadde *et al*., 2009).

Lisinopril is lysine derivative of enalapril (Banweer *et al*., 2010; Naveed *et al*., 2011). It is competitive inhibitor of angiotensin converting enzyme which inhibits conversion of angiotensin I into angiotensin II which is potent vasoconstrictor. Angiotensin II causes the release of aldosterone from adrenal cortex.

It also decreases the vesopressor activity (Talasila *et al*., 2012; Gaffar *et al*., 2011). Lisinopril belongs to BCS Class III drug (High solubility and low permeability).

Metoprolol is a beta1-selective (cardio selective) adrenoreceptor-blocking agent. It is indicated in for the treatment of hypertension, anginapectoris, heart failure and also for symptomatic heart failureof ischemic, hypertensive, or cardiomyopathic origin (Mujoriya *et al*., 2010).

The present work aims to develop a stable and optimized bilayer floating dosage form containing one immediate release drug Lisinopril maleate and another extended release floating metoprolol tartrate layer.

## MATERIALS AND METHODS

### *Preparation of lisinopril maleate immediate release layer*

Lisinopril and microcrystalline cellulose were mixed with super-disintegrants in pestle and mortar for 15 minutes, and then passed through sieve no 60. The blend was mixed with cab-O-sil and magnesium stearate. Then

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erythrosine red was added and compressed using 6mm punch.

***Preparation of sustained release metoprolol tartrate layer***

Sustained release layer was prepared by direct compression. All ingredients including drug were weighted accurately and pass through sieve no 60 separately. The drug and polymer mixed through small portion to get uniform blend. Finally mixture was blended with magnesium stearate and cab-O-sil and compressed using 11mm punch.

***Characterization of granules***

Prior to compression blend of formulation was evaluated for pre-compression parameters like bulk density, tapped density, carr's index and Hausner's ratio.

**Table 1**: Statistical approaches of the formulations

| | -1 | 0 | +1 | Mx |
|---|---|---|---|---|
| SSG | 1 | 2 | 3 | - |
| CC-Na | 1 | 2 | 3 | - |
| Acacia | 4 | 9 | 14 | 36 |
| Pectin | 4 | 9 | 14 | 36 |
| Eudragit | 8 | 18 | 28 | 36 |

***Apparent bulk density***

Powder to be compressed was weighed on analytical balance (m). This powder was then poured into graduated cylinder and volume of mixture was noted ($V_B$) (Pattanayak *et al*., 2011; Raffick *et al*., 2012). Bulk density was found as

$$P_B = \frac{M}{V_B}$$

***Tapped density***

Mixture present in graduated cylinder was then tapped for specific time interval or tapings. This volume is called tapped or true volume ($V_T$) (Pattanayak *et al*., 2011; Raffick *et al*., 2012). Tapped density was found as:

$$P_T = \frac{M}{V_T}$$

***Compressibility index***

Its value is expressed as percentage. It is an indirect measure of particle size distribution and cohesiveness of dry mixture. The percentage compressibility of the powder mixture was determined by the following formula (Pattanayak *et al*., 2011).

C.I = Tapped density – Bulk density / Tapped density

***Hausner's ratio***

Hausner's Ratio was measured to determine and confirm the rate of consolidation. It has no unit. It was calculated by the following formula (Pattanayak *et al*., 2011; Malpani *et al*., 2009)

Hausner's Ratio = Tapped density / Bulk density

***Angle of repose***

It is related to friction between particles of powder mix. Powder mix was allowed to pass through funnel, a cone was formed, height and diameter of that cone was measured and values were put in following equation (Shajan *et al*., 2012).

$\tan \theta = h / r$

***Post compression parameters***

*Physical appearance*

Tablets were evaluated for shape, size

***Thickness***

20 tablets were selected randomly from each batch and their thickness was measured with the help of Vernier calipers.

***Hardness***

Ten tablets were taken from each formulation and hardness was determining using hardness tester (Chitra *et al*., 2013).

***Weight variation***

Twenty tablets were accurately weighted on analytical balance. Average weight of all tablets was calculated. Weight individual tablets. Then compared the individual weight of tablet with average weight (Chitra *et al*., 2013).

***Friability***

Tablets were taken and weighed ($W_1$), and placed in drum of friability tester, run at 25rpm for 4 minutes. Tablets were then removed from drum, loose dust was removed with muslin cloth, weighed again ($W_2$) and percent friability was calculated by using following equation. Maximum allowed friability is 1% (Biswal *et al*., 2011; Shajan *et al*., 2012).

$$friability = \frac{w_1 - w_2}{w_1} \times 100$$

***Drug content uniformity***

Six tablets were grinded and weighted in pestle and mortar. Transfer 50 mg drug to 50ml of 0.1N HCl to prepare stock solution (1000mcg/ml). Then 10ml of stock solution was drawn and diluted with 100ml of 0.1N HCl (100mcg/ml). At the end 2ml from stock solution was drawn and diluted to 10ml. Check absorbance at 215nm by using UV-Visible spectrophotometer at 215nm (Gaffar *et al*., 2011).

Take 20 tablets. Powder them in pestle and mortar. Transfer powder having equivalent weight containing 75mg metoprolol to 150ml of ethanol and shake for 15min than cool it. Make final volume 200ml with ethanol. Filter using what man filter paper. Take 20ml filtrate add make final volume to 50ml with ethanol. Check absorbance at 274nm. Its limit is 95-105% (British Pharmacopeia, 2009).

**Table 2**: Composition of lisinopril maleate immediate release layer

| | Statistical Designed formulations | | | | | | Compressed Formulations | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Batch code | F1 | F2 | F3 | F4 | F5 | F6 | F1(%) | F2(%) | F3(%) | F4(%) | F5(%) | F6(%) |
| Lisinopril maleate | - | - | - | - | - | - | 8.3 | 8.3 | 8.3 | 8.3 | 8.3 | 8.3 |
| SSG | 0 | +1 | +1 | -1 | 0 | +1 | 2 | 3 | 3 | 1 | 2 | 3 |
| CC-Na | 0 | +1 | -1 | +1 | +1 | 0 | 2 | 3 | 1 | 3 | 3 | 2 |
| Mg-Stearate | - | - | - | - | - | - | 4.1 | 4.1 | 4.1 | 4.1 | 4.1 | 4.1 |
| Cab-O-sil | - | - | - | - | - | - | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Erythrosine red | - | - | - | - | - | - | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| MCC | - | - | - | - | - | - | 82.6 | 80.6 | 82.6 | 82.6 | 81.6 | 81.6 |

**Table 3**: Composition of sustained release metoprolol tart rated layer

| Batch Code | M1 | M2 | M3 | M4 | M5 | M6 | M1 (%) | M2 (%) | M3 (%) | M4 (%) | M5 (%) | M6 (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metoprolol Tartrate | - | - | - | - | - | - | 34.7 | 34.7 | 34.7 | 34.7 | 34.7 | 34.7 |
| Acacia | - | Mx | - | 0 | -1 | +1 | | 36 | | 9 | 4 | 14 |
| Pectin | Mx | - | - | 0 | -1 | +1 | 36 | | | 9 | 4 | 14 |
| Eudragit L100 | - | - | Mx | 0 | +1 | -1 | | | 36 | 18 | 28 | 8 |
| Sodium bicarbonate | - | - | - | - | - | - | 17 | 17 | 17 | 17 | 17 | 17 |
| Citric acid | - | - | - | - | - | - | 8 | 8 | 8 | 8 | 8 | 8 |
| Avicel | - | - | - | - | - | - | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 | 1.8 |
| Aerosil | - | - | - | - | - | - | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| PVP | - | - | - | - | - | - | 1 | 1 | 1 | 1 | 1 | 1 |
| Mg-Streate | - | - | - | - | - | - | 1 | 1 | 1 | 1 | 1 | 1 |

**Table 4**: Pre-compression parameters of lisinopril maleate

| Batch Code | Bulk Density ±SD | Tapped Density ±SD | Hausner's Ratio | Car's Index | Angle Of Repose ±SD |
|---|---|---|---|---|---|
| L1 | 0.4973±0.009 | 0.5883±0.011 | 1.1829 | 15.46 | 19º94±2.093 |
| L2 | 0.4974±0.012 | 0.5600±0.029 | 1.1258 | 11.17 | 22º63'±1.402 |
| L3 | 0.5085±0.008 | 0.5927±0.023 | 1.1655 | 14.20 | 23º90'±1.103 |
| L4 | 0.4918±0.008 | 0.5809±0.017 | 1.181 | 15.33 | 25º63±0.802 |
| L5 | 0.5028±0.004 | 0.5806±0.006 | 1.1548 | 13.40 | 22º42±2.280 |
| L6 | 0.5232±0.005 | 0.5960±0.006 | 1.1390 | 12.21 | 24º90'±1.589 |

**Table 5**: Pre-compression parameters of metoprolol tart rate

| Batch Code | Bulk density ±SD | Tapped density ±SD | Hausner's ratio | Car's index | Angle of repose ±SD |
|---|---|---|---|---|---|
| M1 | 0.3846 ±0.043 | 0.4545±0.675 | 1.1817 | 15.37 | 24º30±0.044 |
| M2 | 0.4167±0.973 | 0.5000 ±0.387 | 1.1999 | 16.66 | 25º77±0.544 |
| M3 | 0.5000±0.424 | 0.6250 ±0.435 | 1.2500 | 20.00 | 28º56±0.453 |
| M4 | 0.3571±0.006 | 0.4545 ±0.654 | 1.2728 | 21.43 | 29º65±0.544 |
| M5 | 0.4762±0.065 | 0.5882 ±0.065 | 1.2352 | 19.04 | 27º29±0.654 |
| M6 | 0.4348±0.653 | 0.5263 ±0.076 | 1.2104 | 17.38 | 26º54±0.543 |

**Table 6**: Post compression paramrters of lisinopril maleate

| Batch Code | Tablet Thickness | Tablet Diameter | Tablet hardness ($Kg/cm^2$) | Weight variation | Percentage friability (%age) | Drug content | Disintegration Time |
|---|---|---|---|---|---|---|---|
| L1 | 3.63±0.187 | 6.65±0.361 | 4.76±0.098 | 120.76±0.745 | 0.50 | 99.5±0.738 | 33.16±1.078 |
| L2 | 3.84±0.195 | 6.85±0.465 | 4.97±0.078 | 120.33±1.345 | 0.09 | 97.68±0.112 | 37.5±0.43 |
| L3 | 3.04±0.835 | 6.56±0.654 | 4.83±0.021 | 121.93±1.002 | 0.35 | 96.08±1.281 | 51.5±0.556 |
| L4 | 3.9±0.260 | 6.43±0.342 | 4.22±0.054 | 120.03±1.105 | 0.44 | 95.24±0.346 | 23.33±0.543 |
| L5 | 3.62±0.773 | 6.12±0.077 | 4.78±0.056 | 121.39±0.485 | 0.98 | 98.88±1.161 | 42.33±0.567 |
| L6 | 3.33±0.123 | 6.09±0.154 | 4.96±0.987 | 121.85±1.305 | 0.84 | 96.26±0.524 | 25.8±0.454 |

***Disintegration test***

Disintegration apparatus was used. One tablet was placed in each six baskets, disk was inserted and operated for specified period of time using at 37°C. Then time required disintegrating the tablet was calculated (Raffick *et al*., 2012).

***Floating behaviour***

Floating behavior of the tablet was also studied and it was determined from floating lag time. Floating lag time is the time interval between the entry of tablet in the dissolution medium and its buoyancy to top of medium. It was observed visually using USP II dissolution apparatus and dissolution media for 12 hr (ziyaur *et al*., 2006).

***Swelling index***

WU%= Wt. of swollen tablet- Initial Wt. of tablet/ Initial Wt. of tablet X 100

Where "WU" means water uptake, tablets were removed periodically from the dissolution medium and were weighted for weight gain after draining that is swelling behavior (Girish *et al*., 2007).

**Fig. 1**: Formulated bilayer tablets.

***In vitro drug release studies***

*In vitro* drug release studies were carried out by using USP Type II Dissolution Apparatus. Dissolution test was carried out by using 900ml of 0.1N HCl (pH=1.2) at 37±0.2°C at 50 rpm for lisinopril maleate. Draw aliquot of solution at 10, 15, 20, 30, 40, 50 and 60 min and replace aliquot with fresh dissolution medium to maintain constant volume. Check absorbance spectrometric ally at λ max 215nm for lisinopril maleate (Sharmin *et al*., 2012; Raffick *et al*., 2012).

*In-vitro* drug release studies were carried out by using USP Type II Dissolution Apparatus. Dissolution test was carried out by using 900ml of 0.1N HCl for 2hr and 6.8 phosphate buffers for 10hr at 37±0.2°C at 50 rpm for metoprolol tartrate layer. Aliquate of solution was drawn at 1, 2, 4, 6, 8, 10 and 12hr and replace aliquot with fresh dissolution medium to maintain constant volume. Check absorbance spectrometric ally at λmax 274 nm for metoprolol tartrate (Sharmin *et al*., 2012; Raffick *et al*., 2012).

## RESULTS

The results of pre-compression evaluation parameters are shown in (tables 4 and 5). All the pre-compression evaluation parameters were within the USP Pharmacopoeia limits

***In vitro drug release studies of lisinopril maleate***

***Percentage drug release of lisinopril maleate from formulation L1-L3 in 0.1N HCl***

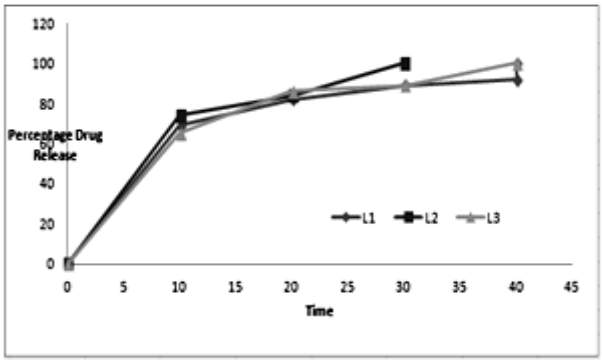


**Fig. 2**: *In vitro* drug release studies of lisinopril maleate formulation L1-L3

***Percentage drug release of lisinopril maleate from formulation L4–L6 in 0.1N HCl***

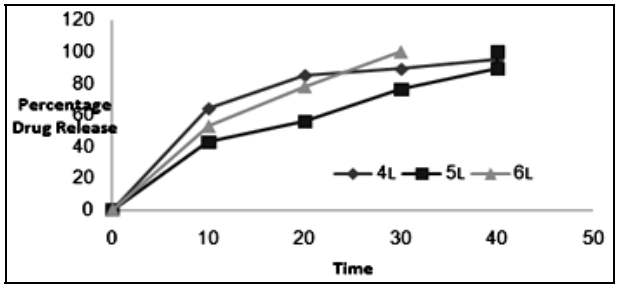


**Fig. 3**: *In vitro* drug release studies of lisinopril maleate formulation L4-L6

***In-vitro drug release studies of metoprolol tartrate from formulations M1-M3 in 0.1N HCl for 2hr and 6.8 phosphate buffer for 10hr***

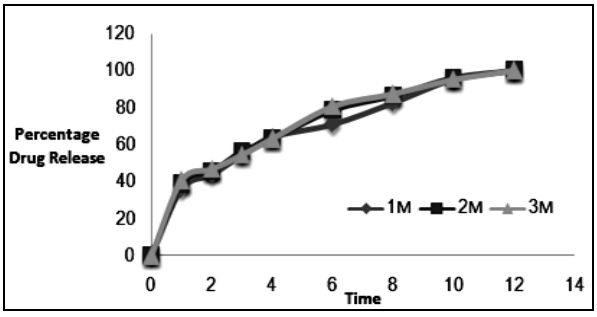


**Fig. 4**: *In vitro* drug release studies of metoprolol tartrate from formulations M1-M3 in 0.1N HCl for 2hr and 6.8 phosphate buffer for 10hr

**Table 7**: Post compression parameters of metoprolol tartrate

| Batch Code | Tablet Thickness | Tablet Diameter | Tablet Hardness (Kg/cm$^2$) | Weight variation |
|---|---|---|---|---|
| M1 | 5.43±0.187 | 11.62±0.060 | 11.96±0.02 | 695.76±0.577 |
| M2 | 6.54±0.195 | 10.55±0.095 | 10.97±0.008 | 696.33±1.527 |
| M3 | 5.10±0.835 | 11.56±0.086 | 7.89±0.078 | 695.65±1.875 |
| M4 | 5.9±0.660 | 11.63±0.07 | 6.89±0.009 | 696.43±1.307 |
| M5 | 6.32±0.873 | 11.64±0.047 | 9.99±0.009 | 695.43±0.624 |
| M6 | 5.32±0.33 | 10.57±0.101 | 11.96±0.012 | 696.84±1.615 |

**Table 8**: Post compression parameters of metoprolol tartrate

| Batch Code | Percentage friability (%age) | Drug content | Floating Lag Time (minutes) | Swelling Index (%) |
|---|---|---|---|---|
| M1 | 0.36 | 96.62±0.142 | 3.03 | 0.86 |
| M2 | 0.43 | 97.10±0.671 | 3.17 | 0.73 |
| M3 | 0.27 | 97.02±0.537 | 3.21 | 0.82 |
| M4 | 0.47 | 98.43±0.701 | 3.53 | 0.91 |
| M5 | 0.24 | 96.44±0.480 | 3.31 | 0.79 |
| M6 | 0.25 | 97.65±0.991 | 3.38 | 0.89 |

**Table 9**: Kinetic models for formulation M1-M6

| Kinetics Models | | M1 | M2 | M3 | M4 | M5 | M6 |
|---|---|---|---|---|---|---|---|
| Zero Order | $R^2$ | 0.973 | 0.963 | 0.959 | 0.974 | 0.980 | 0.976 |
| | $K_0$ | 5.814 | 5.723 | 5.641 | 8.006 | 11.806 | 5.723 |
| First Order | $R^2$ | 0.916 | 0.911 | 0.917 | 0.941 | 0.879 | 0.927 |
| | $K_i$ | 0.038 | 0.036 | 0.035 | 0.070 | 0.047 | 0.037 |
| Hixon Crowell Cube Root | $R^2$ | 0.902 | 0.934 | 0.92 | 0.961 | 0.961 | 0.905 |
| | $K_s$ | 0.321 | 0.325 | 0.321 | 0.282 | 0.275 | 0.316 |
| Higuchi Model | $R^2$ | 0.992 | 0.992 | 0.985 | 0.950 | 0.961 | 0.996 |
| | $K_H$ | 26.751 | 26.472 | 26.059 | 36.025 | .53494 | 26.350 |
| Korsmeyer Peppas Model | $R^2$ | 0.990 | 0.988 | 0.976 | 0.737 0.916 | 0.990 | 0.990 |
| | n | 0.426 | 0.407 | 0.394 | 0.737 | 1.639 | 0.410 |

***In-vitro drug release studies of metoprolol tartrate from formulations M4-M6 in 0.1N HCl for 2hr and 6.8 phosphate buffer for 10hr***

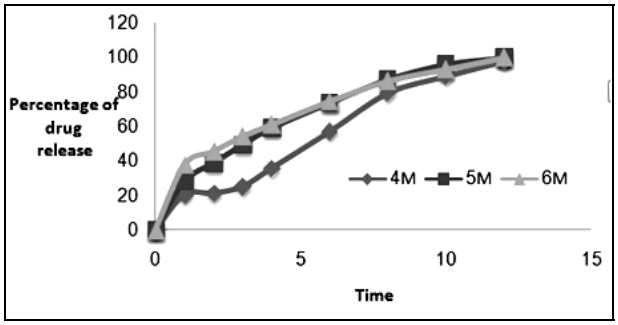


**Fig. 5**: *In vitro* drug release studies of metoprolol tartrate from formulations M4-M6 in 0.1N HCl for 2hr and 6.8 phosphate buffer for 10hr

## DISCUSSION

Different formulations of lisinopril maleate and metoprolol tartrate were formulated by using combination of immediate release and sustained release polymers which include Eudragit L 100, acacia , pection, SSG and CC-Na. All formulations were evaluated for pre-compression and post compression parameters as shown in tables 4-8. The intra-gastric floating (IGF) bilayer tablets were uniform and round in shape. Metoprolol tablets were white in color where as lisinopril tablets were pink. There was uniform color distribution and no mottling was observed. The results of physicochemical characterizations are shown in (tables 6 and 7). The thickness of IGF tablets was measured by calibrated dial calliper. Tablet mean thickness and diameter (n=20) were almost uniform in all the formulations and values for tablets ranged from 3.04±0.835to 3.9±0.260 and 6.09±0.154to 6.85±0.465mm respectively for lisiniopril maleate and 5.10±0.835 to 6.54±0.195 and 10.55±0.095 to 11.64±0.047 respectively for metoprolol tartrate layer. The standard deviation values indicated that all the formulations were within the range and show uniform thickness. The average weight of each formulation was recorded. The values were almost uniform and lie within the USP specifications. The values tablets ranged from 120.03±1.105to 121.93±1.002mg for lisinopril maleate and 695.43±0.624 to 696.84±1.615 for metoprolol tartrate

layer. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±5% of the weight. The hardness of all formulations was in the range of 4.22±0.054 to 4.97±0.078kg/cm2 for lisinopril maleate and 6.89±0.009 to 10.97±0.008 for metoprolol tartrate. The values of standard deviation indicate that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness. The friability values of prepared tablets are given in (Table 6 and 7). All the values are below 1% indicating that the tablets of all formulations are having good compactness and showing enough resistance to the mechanical shock and abrasion. The content uniformity was performed for all six formulations. The percent drug content of tablets was found to be in between 95.24±0.346to 99.5±0.738% of lisinopril maleate and 96.44±0.480 to 98.43±0.701 for metoprolol tartrate. In-Vitro Dissolution studies were carried out and data was fitted into various drug release kinetic equations. Most of the formulation followed Higuchi Model of drug release.

Formulation L1 containing 2% SSG and 2% CC-Na show 75% drug release after 30min and 100% drug release after 40min. The same results were also obtained while and evaluation of bilayer tablets of lisinopril and gliclazide using SSG and CC-Na for IR lisinopril maleate layer (Gaffar, 2011). Fig. 2 shows drug release from IR lisinopril maleate layer. The presence of super-disintegrants lead to an increase in the release rate of lisinopril maleate. Regarding L2 containing 3% SSG and 3% CC-Na showed77% drug release in 10min, 100% drug release in 30min. same results were also reported during formulation of IR lisinopril maleate layer (Gaffar, 2011). Concerning L3 containing 3% SSG and 1% CC-Na showed 64% drug release in 10min, 97% drug release after 40min. Similar results were also predicted while formulating sustained release bilayer tablets of propranolol hydrochloride (Patra *et al*., 2007). However formulation L 4 and 5 containg 1% SSG, 3% CC-Na and 2% SSG, 3% CC-Na showed 60% and 45% drug release after 10min and 100% drug release after 40min. These results were agreement with previously published work (Kulkarni *et al*., 2010; Jayaprakash *et al*., 2011). Formulation L6 containing 3% SSG and 2% CC-Na showed 51% drug release in 10min and 98% drug release in 30min. Same results were also predicted by (Remya *et al*., 2010), while formulating bilayer tablets of ibuprofen and methocarbamol. Sustained release formulations M1 to M3 containing different concentration of hydrophilic and hydrophobic polymer showed 35-46% drug release after 1hr and 94-100% drug release after 12hr. Similar facts and findings were also reported by (Baloğlu & Şenyiğit, 2010). However, formulations M4-M6 showed 19-34% drug release after 1st hr, 82-87% drug release after 10hr and 91-100% drug release after 12hr. These results were agreement with the research work of (Junaid *et al*., 2014)

***Kinetic models for formulation M1-M6***

Lisinopril maleate Formulation L2 released 100% drug release in 30min and metoprolol tartrate showed 100% drug in 12hrs, as shown in figs. 2-4. The results of dissolution studies of formulation L2 and M4 composed of floating layer and sustained release layer were promising. The releases from both the formulations were quite similar as predicted while studying release pattern of sustained release layer only. The optimized formulation L2 release better in 30minutes with rapid disintegration time and M4 followed zero order release kinetic and drug release was controlled by the anomalous type of diffusion process. Metoprolol tartrate release from floating tablet was largely reliant on polymers swelling and drug diffusion.

## CONCLUSION

Floating bilayer tablet was prepared by using direct compression method. Floating bilayer tablet was formulated to provide sustained release effect of drug using combination of different polymers. Lisinopril maleate showed good abrupt release whereas metoprolol tartrate showed better sustained drug release. From the results it was concluded that floating bilayer tablet of lisinopril and metoprolol can be formulated for the cardiovascular diseases. Further biowaiver studies could be conducted to develop in-vitro in-vivo correlation.

## ACKNOWLEDGEMENTS

The authors are thankful to Werrick Pharmaceuticals Pvt. Ltd., Islamabad for providing Lisinopril maleate, CCL Pharmaceuticals Pvt., Ltd., Lahore for Metoprolol Tartrate and Unexo Labs. Pvt., Ltd., Lahore, Pakistan for excipients and chemicals.

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