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Preparation and Evaluation of Bilayer Tablet For The Treatment Of Hypertension

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ABSTRACT

In the present scenario, combination therapy for various types of drugs is used for the disease management by the developed and developing countries. These combinations are also used for the long term treatment like hypertension, other cardiovascular diseases and diabetes. Over 90 to 95% of tablets are taken orally. Bilayer tablet design is the most popular now a days. This may lower the dosing frequency. These tablets have been designed to provide continuous release of the drug substances for complete duration of treatment. Metoprolol succinate and indapamide hemihydrate combination is used in the current study. In bilayer tablet dosage form, the 1st layer is meant with a prompt releasing and 2ndlayer is used as the persistent dose. Objective proposedinvestigation is formulating as well as develop bi-layer tablet, which contains metoprolol tartarate as immediate release part and indapamide hemihydrate as a sustained release part. Metoprolol tartarate is a selective β_1-blockeras utilized in managing of high BP, angina pectoris & congestive heart failure. Indapamide hemihydrate belongs to the class of diuretic/antihypertensive. It prevents the absorption of both Na^+ and K^+ cations from the kidney.

KEYWORDS: Bilayer tablet, hypertension, antihypertensive, indapamide hemihydrate, metoprolol tartarate

1. INTRODUCTION

In pharmaceutical companies, bilayer floating tablets are used to avoid chemical incompatibilities between the ingredients. It enables the development of different drug release profiles[1,2]. These tablets remain buoyant in the stomach. It does not affect the gastric emptying rate and prolongs the effect of tablet[3, 4]. These tablets have apparent density that is less than that of the fluid present in the stomach. These tablets increase the GRT and may control the fluctuations in drug plasma concentration[5,6]. Now a days, almost all countries are using the combination of drugs for disease treatment[7,8]. It can be used for the treatment of hypertension, diabetes and rheumatoid arthritics. It also helps in suppression of dose dependent problems. It has an advantage over monotherapy[9,10]. When two or more drug substances are combined, it helps to increase the patient convenience and compliance. As compared to conventional single layer tablets, bilayer tablets have certain important advantages[11,12]. By physical separation, these tablets avoid the chemical incompatibility of formulation components. It enables the controlled delivery of API with pre-determined release profile. These tablets are most suitable for combination of two drugs[13,14], consisting of first layeras priming dose or loading dose and the another layer as the sustained dose[16,17]. Such drug products are prepared for prolongingthe time of release of small amount of drug for some time on the upper part of the GIT and increase its bioavailability[18,19]. Researchers have invented the different types of dosage form like tablets, bilayer, trilayer, thiolate tablets, patches, microspheres, pellets, micro-particles, beads, floating ring capsule in situ gel etc. to enhance the performance of GIT drug delivery. [20, 21, 22]

1.1 Need of bilayer tablets

- For the combination of different drugs bilayer technique is used. It is also used for fixed dose administration. It prolongs the lifecycle of drug products.

- Actualsectional area of drug layers is modified by sand witching. It may be controlled by incorporating the drugs in one or more layers and making them to show the swelling and erodible behaviour for extended release.
- For the controlled release of drug, it should be separated from one layer to other layer.[23,24,25]

2. MATERIALS AND METHODS

Metoprolol tartarate and indapamide hemihydrate of pharmaceutical grade and all grades of polymers were obtained as gift samples. Analytical grades chemicals and reagents were used. Excipients which are used in this study are hydroxypropyl methylcellulose, Croscarmellose sodium, Magnesium stearate, Aerosil, Cross povidone, Starch, MCC, Sunset yellow, Talc, HPMC K4M, HPMC K100M, Lactose monohydrate, Starch, Sodium bicarbonate, PVP K-30 and Isopropyl alcohol.

2.1 Method of preparation of immediate release tablet:

The drug (metoprolol tartarate) was mixed with a suitable disintegrant for 20 mins and poured into a porcelain mortar. After that it was passed through the sieve (#60). Aerosil and magnesium stearate were used for mixing the blend. The direct compression method was utilized for tablet compression. Flat faced punch rotary tablet machine was used for this process.1% of magnesium stearate has been used to all the formulations. 5 to 8% of disintegrants were added to the tablets. The formula for immediate release layer is as represented in Table 1.

Table1:Formulation table of metoprolol tartarate IR tablet (I1 to I10)

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metoprolol tartarate	48	48	48	48	48	48	48	48	48	48
Croscarmellose sodium	5	x	10	5	20	x	25	10	x	15
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Colloidal SiO_2 (aerosil)	1	1	1	1	1.0	1.0	1.0	1.0	1.0	1.0
Cross povidone	5	10	15	20	x	30	x	10	35	15
Starch	5	10	15	5	10	5	20	25	5	10
MCC	52	32	22	42	42	32	42	12	15	17
Sunset yellow	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2

2.2 Method of preparation of floating sustained release tablet:

To prepare sustained release tablets, indapamide hemihydrate and HPMC were mixed with other excipients. The mixture was poured into porcelain mortar and stirred for about 10 mins. This preparation was used for the formation of wet mass by granulating fluid using iso-propyl alcohol (IPA). Damp mixture was sieved in sieve no.16; kept into an oven at a temperature of 50^0C. After the completion of drying, these granules are passed through sieve no. 12. Then around 5% to 8% magnesium stearate was mixed with the prepared granules. The flat-faced punch rotary tablet machine was used for the compression of tablets.The formula for sustained release layer as shown into Table2.

Table 2: Formulation table of indapamide hemihydrate floating SR tablet (S1 to S10)

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Indapamide hemihydrate	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65
HPMC K4M	85	45	x	x	60	55	45	45	35	x
HPMC K100M	-	40	60	55	x	x	x	x	10	35
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Colloidal silicon dioxide (aerosil)	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35
Lactose monohydrate	110	110	110	110	110	110	110	110	110	110
Starch	5	10	20	x	25	x	30	x	35	x
Sodium bicarbonate	5	10	20	30	40	50	x	60	x	30
Polyvinyl pyrrolidone (PVP K-30)	x	x	x	5	x	10	x	15	x	20
Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Iso-propyl alcohol (IPA)	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

2.3Method of preparation of bilayer tablet

From the optimized batch of metoprolol tartarate, (F4) [immediate release] and indapamide hemihydrate (F2) [sustained release] have been selected to formulate of 2-layer tablet. From the above procedure granules of indapamide hemihydrate and blend powder of metoprolol tartarate were prepared separately. The double rotary tablet press (D-tooling)with 12mm circularpunch& respective dyes were used to compressfinal blend.

2.4Pre-compression parameters:

The micromeritic studies of granules of both the layers were determinedpertainingto untapped& tapped density, repose angle, compressibility index as well ashausner'sproportion.

2.4.1 Bulk density

An appropriately weightedquantity of powder has beenadded in graduated cylinder and then bulk vol. (v bulk)is noted. True density (ρ_b) wasdenoted as g/ml and calculated using the followingformula:

$$\rho_b = \frac{m}{Vb}$$

2.4.2 Tapped density

Precisely weighed amount of powder has been introduced in bulk density apparatus. The cylinder was hit every 2seconds from the height of 2.5 cm up to volume plateau. Tapped density (ρ_t)has beendetermined by utilising formula shown below:

$$\rho_t = \frac{m}{Vt}$$

2.4.3 Compressibility index

Carr's index is utilisedfor explaining flow behaviour of powders. It was expressed as percentage and determinedutilisingfollowingequation:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

2.4.4 Hausner's ratio

The hausner's ratio is used for measurement of flow of powder. It's determined by utilising method below:

$$\text{Hausner's ratio} = \frac{\rho t}{\rho b}$$

2.4.5. Angle of Repose

To determine angle of repose, fixed funnel technique is employed. Height(h) and radius (r) were noted and for determining angle of repose below mentioned formulationhas been utilised:

$$\text{Angle of repose } (^0) = \tan^{-1}\left(\frac{height of the pile}{radius of pile of powder}\right)$$

2.5Post compression parameters:

In order to assess tablets, several post-compression criteria were employed, such as weight fluctuation, disintegration & dissolution tests, thickness & hardness measurements, homogeneity of content, and friability.

Twenty pills were weighed individually to determine weight variance. Average weight of 20 tablets is computed. Single tablet weight was then contrasted with mean weight.The following formula was used to calculate the % deviation:

%deviation = (Mean weight-Individual weight) / Mean weight×100

To check hardness of prepared tablet, Monsanto hardness tester was used, for random 6 tablets. Kg/cm2was unit of measurement.

The friability test of tablets has been performed using 10 tablets after dusting them. Weighted tablets are kept into Roche friabilator & rotated for 4min duration with 25rpm. Using the formula, the residual weights of tablets were measured after dusting, and percentage of friabilityis determined:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} / 100$$

Vernier caliper has been used to determine thickness of the tablets. 10 random tablets were selected for this purpose.

USP standards for tablet content consistency were used to establish homogeneity of tablets' content. If quantity of medicine into every of 10 tested tablets is between 85 and 115 percent of label claim, tablet passes the test, as well as relative standard deviation (RSD) is less than or equal to 6 percent. USP disintegration test device was used to conduct immediate release layer disintegration test. 6 tubes holding 900 ml of filtered water were placed into beaker kept at 37±2°C and every pill was placed in one of tubes.Time taken by tablets for disintegrating and passing by mesh is recorded & taken as the disintegration time.

Swelling index was performed using dissolution testing apparatus, in whichtablets were placed for determining the swelling properties of tablet layer. It was conducted into an container having 900ml of 0.1N HCl sustained around temp. of 37^0 ± 0.5°C. The apparatus has beenrevolved for 30 minutes with 50rpm. The tablets are taken out, excess water was drained out and weight of swollen tablets isnoted. Swelling index is determined with:

$$\text{Swelling Index} = \frac{(\text{Initial weight of tablet} - \text{Final weight of swollen tablet}) \times 100}{\text{Initial weight of tablet}}$$

Floating property study was conducted for the bilayer tablets. For this, 1 tablet with every batch is kept in type II dissolution kit having 900ml of 0.1N HCl as media. The investigationis conducted withrevolving speed having 50rpm &temp of $37^0 \pm$ 0.5 ^{0}C. Time taken by the tablet for emerginguponsurface of the media& time durationwheretablet persistently remains onto surface of the media isrecorded as buoyancy laggingduration&overall float durationcorrespondingly.

The dissolution investigation of bilayer tablets had been carried by USP dissolution test II kit with 50 rpm. Studyisperformedusing 900ml of pH1.2 HCl buffer for initial 2hrs,trailed with pH7.2 phosphate buffer for the 16 hours of total timewithtemp of 37±0.5°C. Uponseveral time durations,5ml sample was inhibited, filtered &substituted by exact volume of dissolution media. Sampleshave beenappropriately diluted and analysis was done for metoprolol tartarate and indapamide hemihydrate content at 224 nm and 240nm respectively.

2.6 *In vivo* study for bilayer tablets:

The final batch of the formulated tablets was used for the animal study.In this study, 6 to 8 rabbits were used for the determination of different of pharmacokinetic parameters. The weight of the rabbits selected was 2.8 to 3.4 kg. Rabbits used were healthy and clean. In this experiment, rabbit has been fastened for around 12h to 15h. They consumed only water. 6 groups were taken for this test. Three groups received metoprolol tartarate and three groups received indapamide hemihydrate. Amongst the three groups, two groups received metoprolol tartarate formulation and one group was given pure drug. The same procedure was followed for indapamide hemihydrate. The doses were given orally. 2ml of sample was taken at every one hour and then centrifuged for 30mins at 2500 rpm. Anticoagulant was also used. After the completion of centrifugation, supernatant was taken and diluted appropriately. By using HPLC, these samples were analysed at 224 nm for metoprolol tartarate and at 240nm indapamide hemihydrate.

2.6.1 HPLC method

For the calibration of curve, peak area was taken from y axis and the drug plasma was taken on x axis. For the calibration of standard curve of metoprolol tartarate and indapamide hemihydrate, different concentrations were taken from 0 to 12µg/ml for metoprolol tartarate and 0 to 20 µg/ml for indapamide hemihydrate. In metoprolol tartarate, mobile phase ratio of methanol: phosphate buffer was (75:25) and for indapamide hemihydrate, mobile phase ratio of methanol: acetate buffer was (75:25). This method was used for the calculation and evaluation of regression lines and linearity. The wavelength selected for metoprolol succinate was 224 nm and that of indapamide hemihydrate was 240nm.

2.6.2 Establishment of *in vitro-in vivo* correlation (IVIVC) for bilayer matrix tablets

For the formulation of bilayer tablets, predicting*in vitro-in-vivo* association was most significant. In *in-vitro* conditions*,* drugs have low release. Present study shows the optimization of metoprolol tartarate and indapamide hemihydrate bilayer floating matrix tablets. The pharmacokinetics of drugs followed one-compartment open model.

3. RESULTS AND DISSCUSSIONS

3.1 Standard curve of metoprolol tartarate and indapamide hemihydrate

Standard curve of metoprolol tartarate was found to be linear (1 to 16 µg/mL) in pH 1.2 HCl buffer as shown in figure 1.

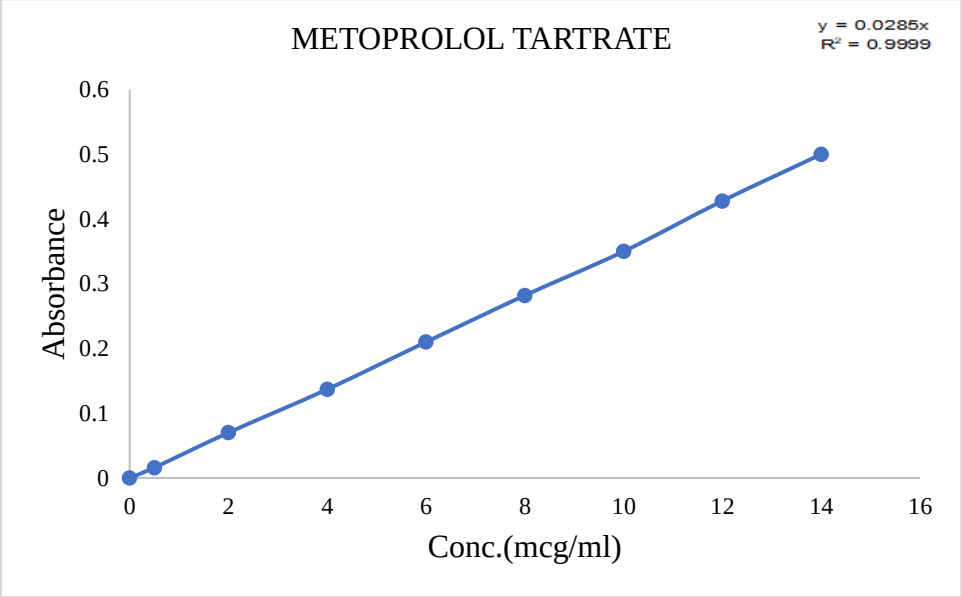

Fig1: Calibration curve of metoprololtartarate

Standard curve of indapamide hemihydrate was found to be linear (1 to 14 µg/mL) in pH 1.2HCl buffer as shown in Figure 2.

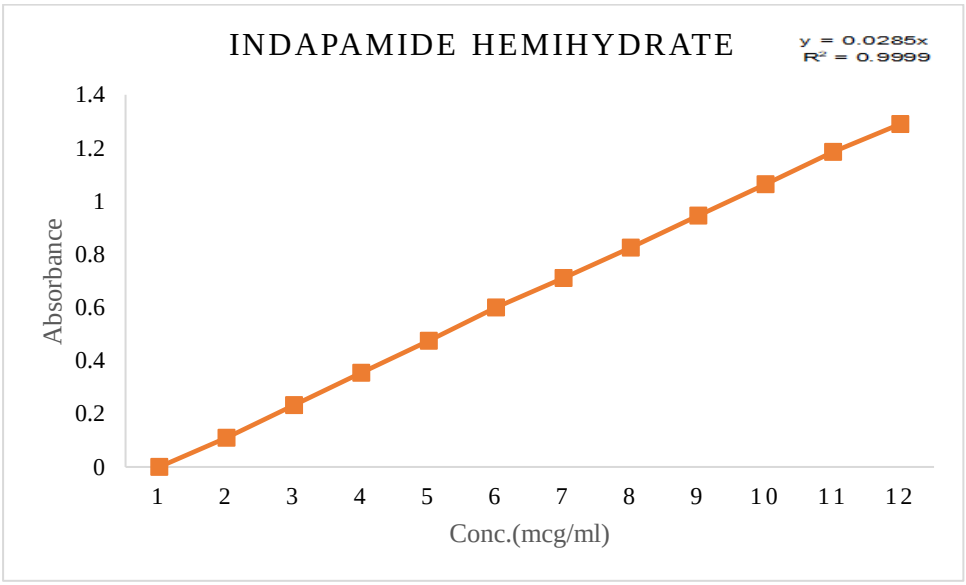

Fig2: Calibration curve of indapamide hemihydrate

Standard curve of indapamide hemihydrate was found to be linear (1 to 12 µg/mL) in pH 7.2phosphate buffer as depicted in Figure 3.

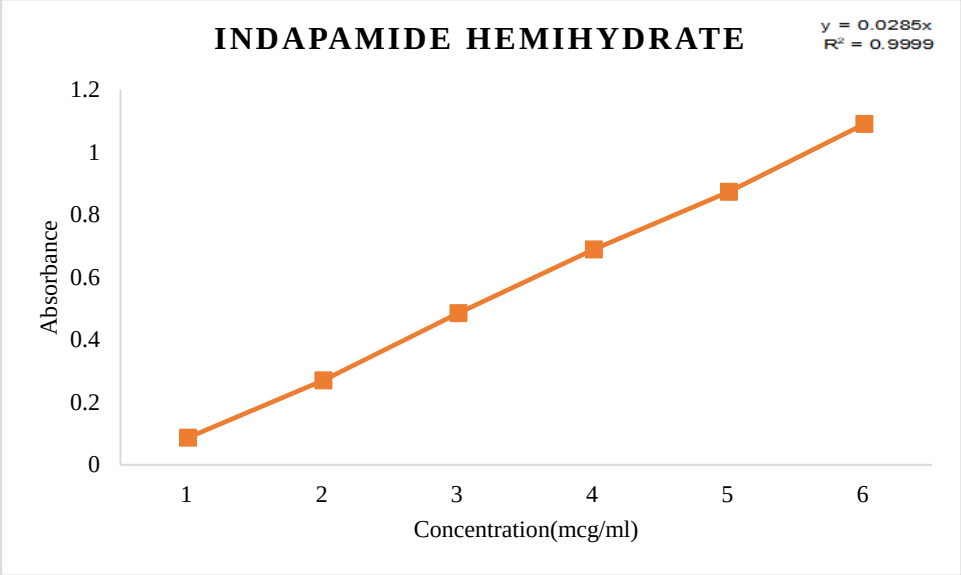

Fig3: Calibration curve for indapamide hemihydrate using pH 7.2phosphate buffer

3.2 Pre-compression and post compression parameter of immediate and sustained release tablet

The pre-compression constraints of prepared granules like angle of repose, untapped & tapped density, Carr's index & hausner's ratio of all batch of immediate release & sustained release were obtained &outcomeshave been depicted into Table-3 & 5 respectively.

Outcomes for postcompression parameters of sustained release (indapamide hemihydrate) and immediate release (metoprolol tartarate) bilayer tablets are depicted in Table 4 and 6.

Table3:Results of pre-compression parameter of IR powder blend of metoprolol tartarate (n=3)

Batch	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index(%)	Hausner's ratio
F1	29.58±0.18	0.28±0.17	0.30±0.029	14.59±0.016	1.10±0.04
F2	30.56±0.14	0.28±0.16	0.31±0.028	8.88±0.012	1.12±0.023
F3	30.15±0.15	0.28±0.14	0.29±0.030	12.63±0.014	1.20±0.017
F4	29.35±0.18	0.29±0.16	0.30±0.028	10.48±0.015	1.16±0.016
F5	30.45±0.19	0.28±0.13	0.31±0.027	8.37±0.017	1.18±0.05

F6	31.82±0.16	0.28±0.17	0.30±0.029	7.55±0.018	1.19±0.016
F7	30.55±0.14	0.27±0.18	0.29±0.028	8.52±0.016	1.10±0.012
F8	29.45±0.16	0.29±0.19	0.30±0.025	11.02±0.014	1.09±0.007
F9	30.59±0.17	0.30±0.17	0.31±0.026	10.56±0.013	1.08±0.006
F10	31.25±0.19	0.31±0.18	0.30±0.023	9.15±0.015	1.03±0.004

Table 4:Results of post compression parameters of immediate release layer of metoprololtartarate

Formulation I	Weight (in mg) n=20	Thickness (in mm) n=10	Hardness (in kg/cm^2) n=6	Friability(in %) n=10	Disintegration time (in secs) n=6	Drug content (in %) n=20	Swelling index in 1 hour (in %) n=6
F1	120±1.3	2.26±0.04	5.56±0.01	0.34	35.38±6.55	100.0	12.3
F2	105±1.5	2.35±0.01	4.20±0.51	0.20	53.18±13.99	99.5	12.9
F3	120±1.8	2.29±0.03	3.01±0.10	0.66	36.67±5.60	101.2	13.2
F4	125±1.5	2.19±0.05	2.26±0.38	0.30	190.52±35.25	100.7	13.5
F5	125±1.2	2.40±0.06	4.20±0.01	0.38	79.69±24.38	99.5	13.4
F6	130±1.3	2.25±0.04	4.20±0.18	0.59	108.85±16.19	100.5	13.1
F7	140±1.4	2.30±0.03	4.90±0.19	0.76	55.52±14.30	99.5	13.6
F8	110±1.3	2.15±0.04	3.85±0.37	0.58	55.56±34.2	98.52	13.3
F9	110±1.2	2.28±0.06	2.25±0.39	0.56	109.25±33.56	99	12.6

F10	110±1.4	2.56±0.09	3.45±0.22	0.35	115.89±3 3.86	100.56	12.8

Table5:Outcomes of pre-compression parameter of SR powder blend of indapamide hemihydrate

Batch	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index(%)	Hauser's ratio
F1	27.36±0.17	0.478±0.15	0.192±0.28	9.25±0.17	1.10±0.23
F2	27.25±0.16	0.480±0.13	0.168±0.26	13.59±0.16	1.15±0.15
F3	28.45±0.15	0.481±0.12	0.195±0.35	18.48±0.15	1.20±0.16
F4	27.65±0.13	0.489±0.11	0.165±0.33	9.45±0.12	1.21±0.17
F5	29.98±0.12	0.258±0.14	0.178±0.22	8.48±0.11	1.25±0.01
F6	27.75±0.15	0.148±0.15	0.156±0.28	8.49±0.11	1.09±0.03
F7	30.65±0.16	0.359±0.12	0.264±0.26	10.2±0.17	1.45±0.05
F8	30.65±0.19	0.300±0.13	0.278±0.27	10.3±0.16	1.25±0.13
F9	29.34±0.17	0.245±0.14	0.233±0.29	10.56±0.15	1.35±0.12
F10	29.38±0.12	0.359±0.15	0.215±0.35	8.48±0.14	1.46±0.12

Table 6:Results of post compression parameters of SR layer of indapamide hemihydrate

Formulation	Weight (in mg) n=20	Thickness (in mm) n=10	Hardness (in kg/cm^2) n=6	Friability (in %) n=10	Disintegration time (in secs) n=6	Drug content (in%) n=20	Swelling index in 1hour (in %) n=6

n							
F 1	210±7.8	3.32±0. 06	4.5±0.3 0	0.5 84	35.38±6.55	100.60±0. 68	12.4
F 2	220±6.5	3.25±0. 05	5.0±0.0 5	0.6 23	53.18±13.99	101.9±0.5 8	12.8
F 3	215±7.7 5	3.34±0. 06	5.2±0.3 5	0.7 89	36.67±5.60	101.8±0.4 4	13.3
F 4	205±6.9	3.45±0. 05	5.3±0.4 5	0.6 54	55.52±35.25	102.6±0.5 6	13.4
F 5	240±7.9	3.65±0. 08	5.1±0.6 5	0.3 57	79.69±24.38	101.7±1.4 8	13.6
F 6	230±4.3	3.35±0. 06	4.1±0.3 5	0.4 58	54.85±16.19	100.8±0.5 0	13.8
F 7	230±6.7	3.45±0. 05	5.2±0.4 5	0.0 36	55.52±14.30	101.3±0.5 6	13.7
F 8	235±6.9	3.36±0. 08	4.6±0.2 5	0.4 58	55.56±34.2	100.9±0.6 7	13.5
F 9	195±7.8	3.14±0. 04	6.4±0.3 5	0.3 69	60.25±33.56	101.8±0.8 6	12.6
F 1 0	200±5.9	3.63±0. 06	4.4±0.6 5	0.7 53	65.89±33.86	101.9±0.8 2	12.7

3.3 Dissolution test of immediate and sustained release tablet:

The *in-vitro* drug releasing profiles of metoprolol tartarate & indapamide hemihydrate bi-layer tablets are shown in Figure 4 to 7.On the basis of drug release data, the batch F4 of metoprolol tartarate IR part and F2 formulation of indapamide hemihydrate SR part exhibited best drug release amongst other formulation batches.The sustained release effect was achieved byincorporating two release rate retarding polymers such as HPMC K4M and HPMC K100M that releasing drug with precise manner with steady interval of time. Therefore the two formulations were combined together form bi-layer tablet, whose drug release study was performed and selected further for stability analysis.

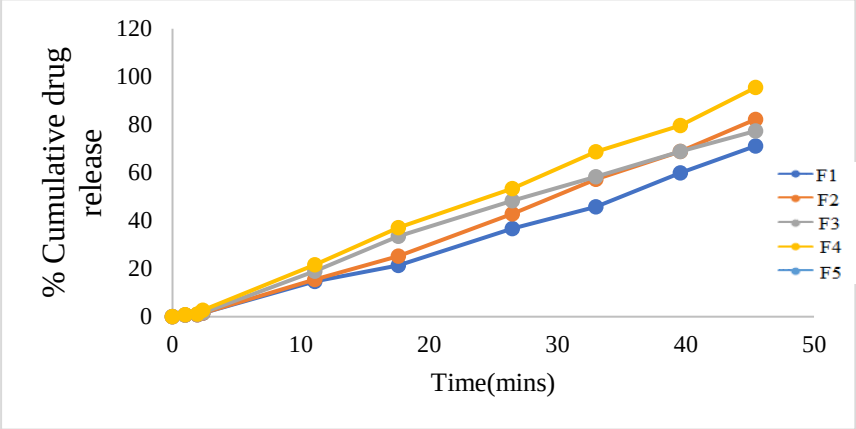

Figure 4: Dissolution test of metoprolol tartarate IR tablets (F1 to F5)

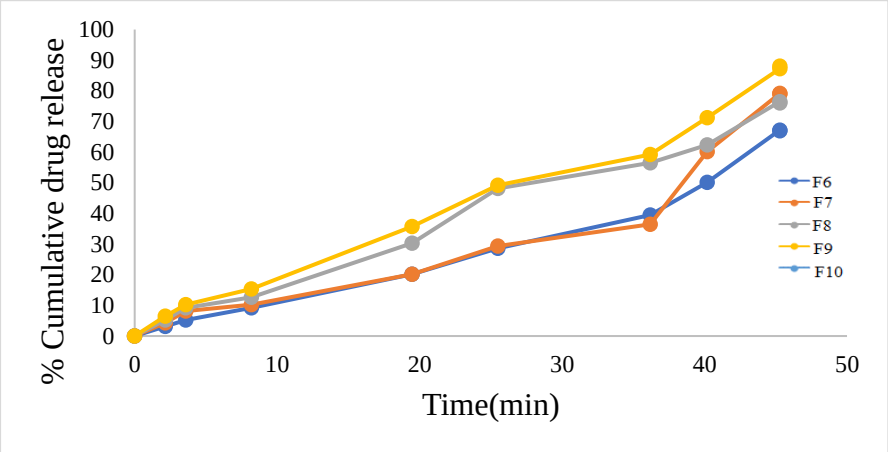

Figure 5: Dissolution test of metoprolol tartarate IR tablets (F6 to F10)

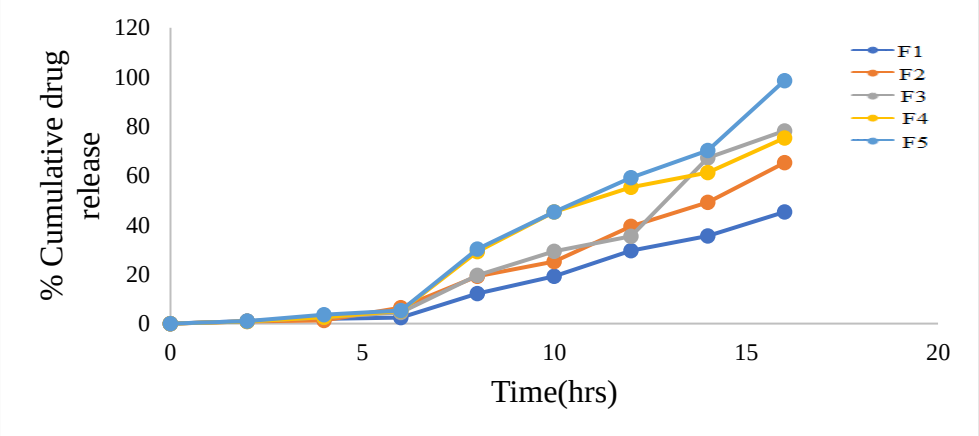

Figure 6:Dissolution test of indapamide hemihydrate SR tablets (F1 to F5)

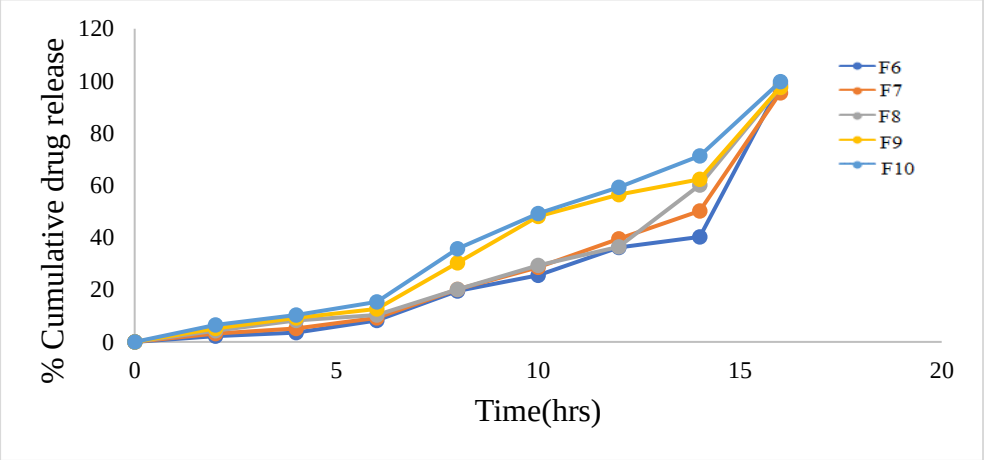

Figure 7:Dissolution test of indapamide hemihydrate SR tablets (F6 to F10)

3.4 Dissolution study of optimized bilayer tablet:

The % cumulative drug release v/s time (hours) plots for optimized batch of bilayer tablet were prepared as shown in Figure 8 to 10.

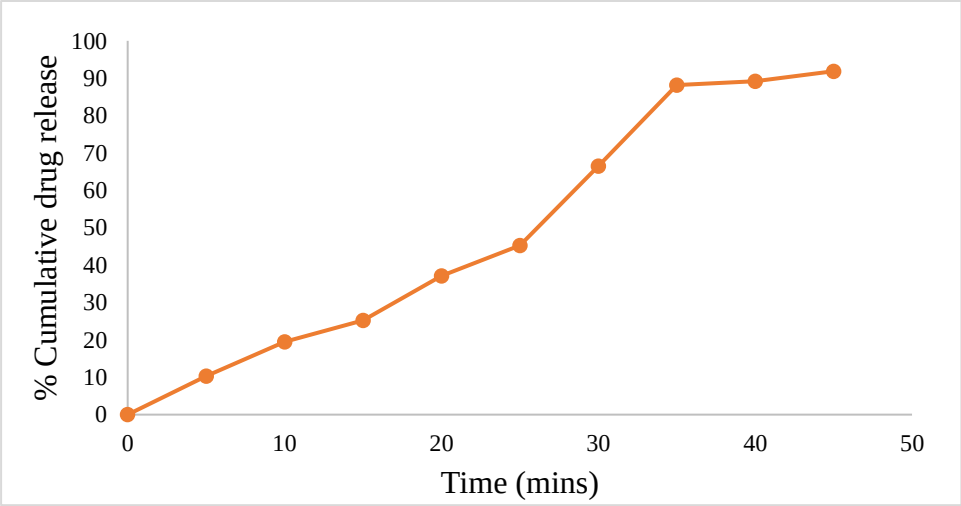

Figure 8:Metoprololtartarate release from Bi-layer Tablet

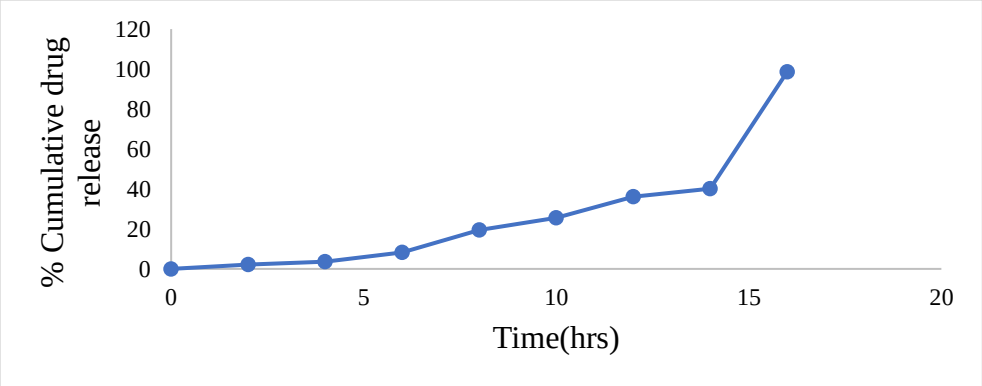

Figure 9:Indapamide hemihydrate release from Bi-layer Tablet

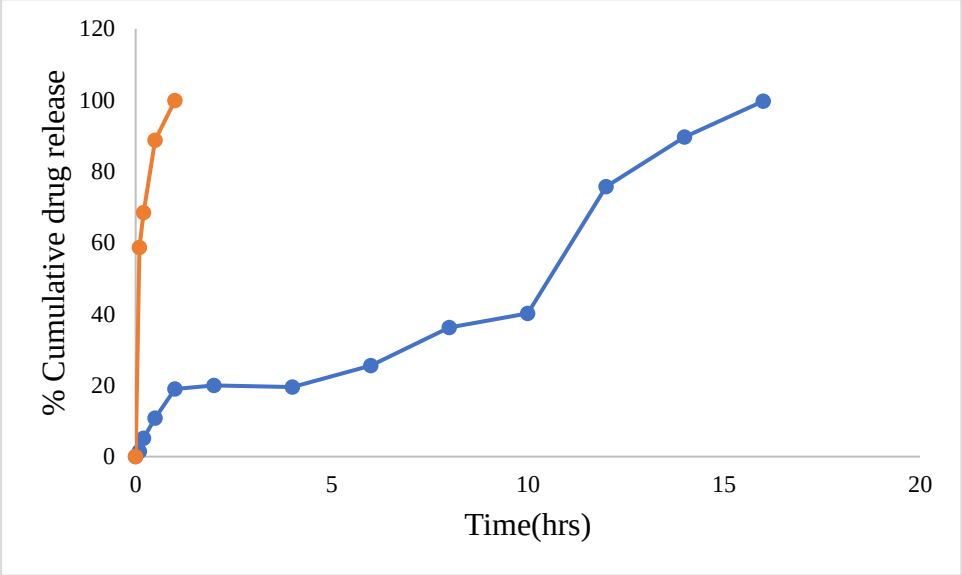

Fig10: Dissolution study of bilayer tablet

3.5 Post compression parameters of Bi-layer Tablet

The results for post compression parameters of sustained release (indapamide hemihydrate) and immediate release (metoprolol tartarate) bilayer tablet dosage formis depicted into Table7.

Table7:Results of post compression parameters of bi-layer tablet

Batch code	Weight (in mg) n=20	Thickness (in mm) n=10	Hardness (in kg/cm^2) n=6	Friability (in %) n=10	Drug content (in %) n=20
0	345±0.18	5.44±0.13	4.534±0.78	0.29	98.75±0.68 (MT-IR) 99.32±0.46 (IH-SR)

The mean weight of bilayer tablet had been observed as 345 mg with friability less than 1%. The hardness of the tablet was 4.534 kg/cm^2 and thickness was obtained to be 5.44 mm.The drug content was 98.75% for metoprolol tartarate and 99.32% for indapamide hemihydrate. The % cumulative drug release of metoprolol tartarate and indapamide hemihydrate from bilayer tablet at the end of 16 hours was found to be 98.76and 99.26% respectively.

In vitro buoyancy parameters of bilayer tablet are shown in table 8.The buoyancy lag time (BLT) was 20 minutes with total floating time (FT) of 12.33 hours.

Table 8: In vitro buoyancy parameters of bilayer tablet

Formulation code	Total Floating time (hours) n=3	Matrix integrity n=6	Swelling index in 1hour (%) n=6	Buoyancy lag time (minutes) n=3
0	12.33 ±0.58	++	12.45	20±2

3.6 Stability studies

Six tablets were used for the stability studies. The results show thattablets were stable at 40°C/ 75%RH for 6 months. After stability study, dissolutiontesting of bi-layer tablets was performedand the profile is as shown in Figure 11 and Figure12 for metoprolol tartarate and indapamide hemihydrate respectively.

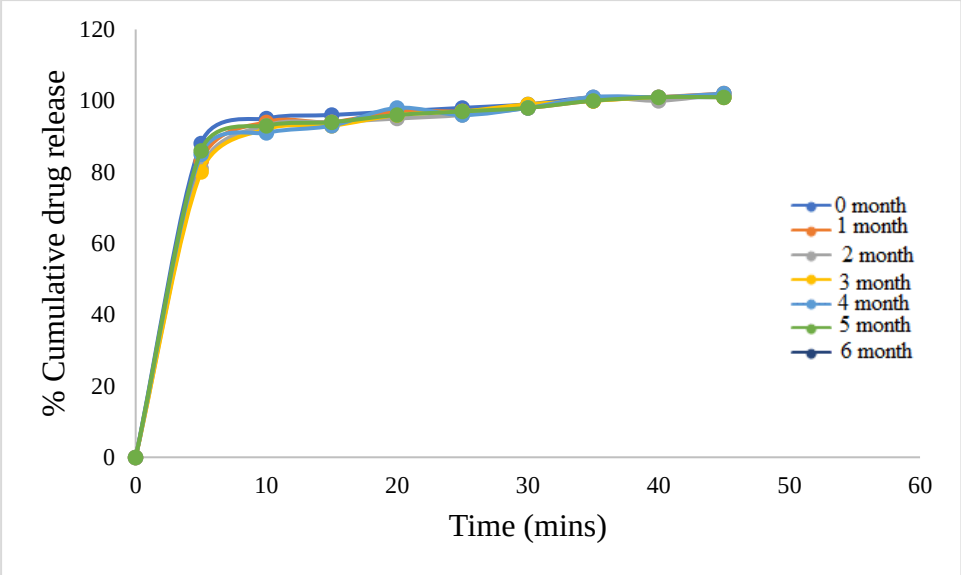

Figure 11:Metoprololtartarate release from bi-layer tablet after stability study

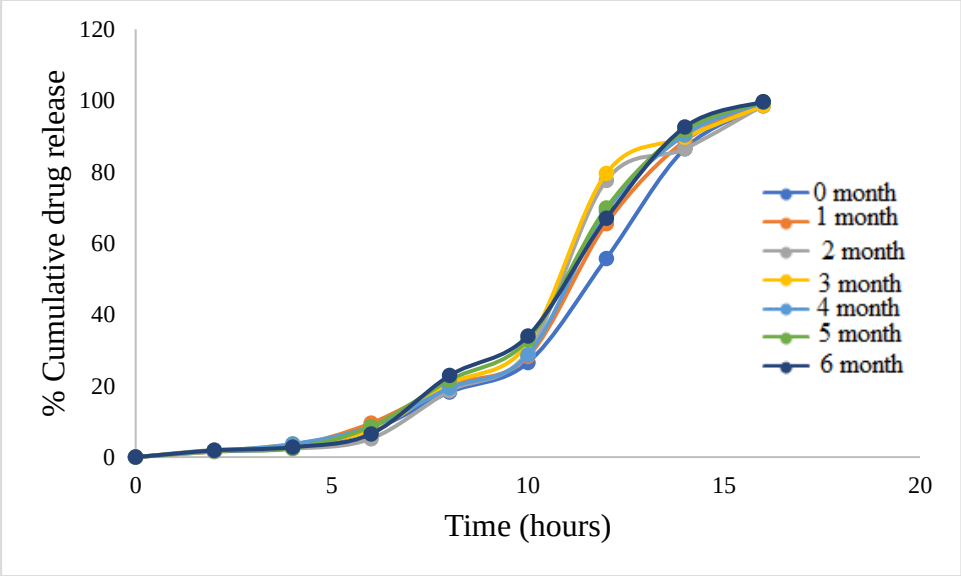

Fig12:Indapamide hemihydrate release from bi-layer tablet after stability study

3.7 Results of *in-vivo* studies of bilayer tablet and IVIVC

The various pharmaco-kinetic parameters such peak plasma concentration (C_{max}), time of peak concentration (t_{max}), area underneath curve (AUC), plasma half life ($t_{1/2}$) & elimination rate

constant (K_E)have beenfound& are shown in Table 9. The drug plasma concentration profiles of metoprolol tartarate and indapamide hemihydrate are represented in Figure 13 and 14.

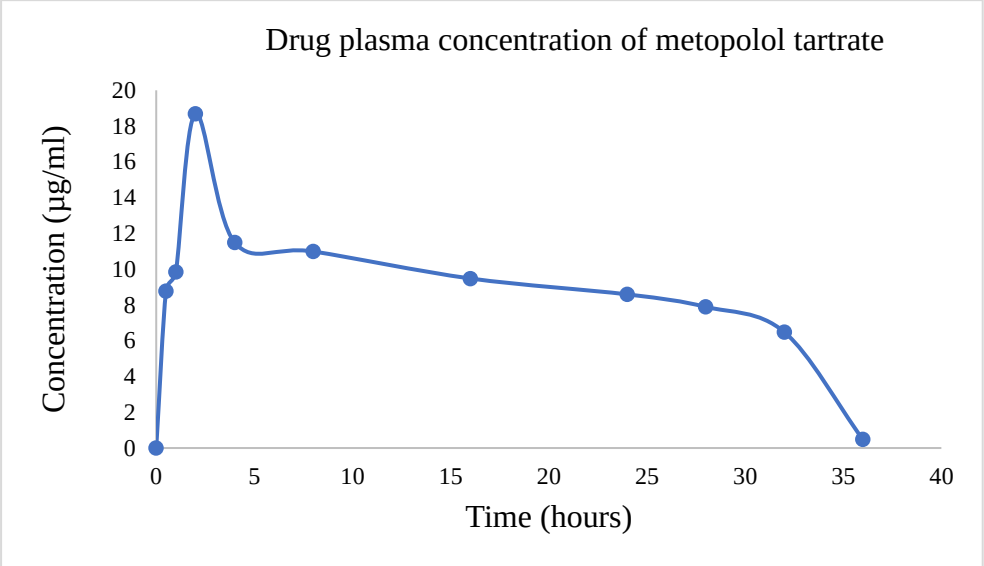

Figure 13: Drug plasma concentration for optimized formulation of metoprololtartarate

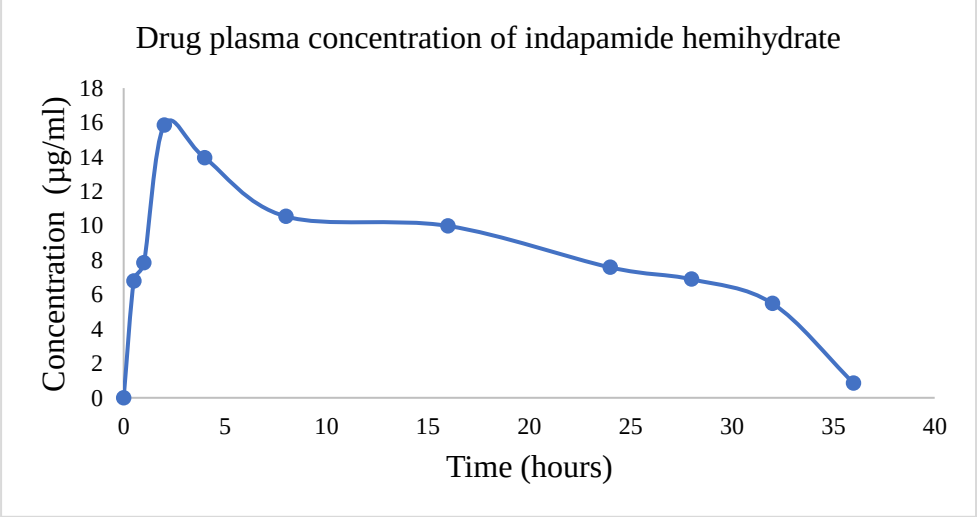

Figure 14: Drug plasma concentration for optimized formulation of indapamide hemihydrate

Table 9: Pharmacokinetic parameters obtained from in-vivo studies

Pharmacokinetic parameters	Optimized formulation (metoprolol tartarate)	Optimized formulation (Indapamide hemihydrate)
C_{max} (µg/ml)	12.85±1.85	90±1.24
t_{max}(hour)	1.85±0.96	4.0±0.21
$T_{1/2}$ (hour)	4.49	8.67

K_E ($hour^{-1}$)	0.159	0.236
AUC_{0-t}(µg-hour/ml)	298.93	380.49
$AUC_{0-\alpha}$(µg-hour/ml)	295.48	350.29

4. CONCLUSION & SUMMARY:

Current study has been conducted for developing and characterizing bi-layer tablets of metoprolol tartarate and indapamide hemihydrate for the management of hypertension. The oral way is mostly favoured route for drug administration.Optimized formulation of batch F4 of metoprolol tartarate and batch F2 in indapamide hemihydrate were used for the formulation of optimized batch of bilayer tablets.

Under post compression parameters, the hardness of the tablets varied between 3 to 5 kg/cm^2 and thickness was found to be 2.5 to 3mm. The weight of bi-layer tablets is observed as 345 mg. Friability of the tablets was less than 1%. The floating lag time (FLT) was greater than 10 hours. The drug constituent of tablets obtained was more than 98% for both the formulations. Duration taken to 50% of drug for getting released ($t_{50\%}$) & $\%CR_{16hrs}$was intothe limits of 0.9 to 10hrs & 59.45$\pm$4.59 to 99.99$\pm$0.09% respectively.

Consistency research of bilayer tablet was performed under ICH rules & it was noted as optimized batch had been steady for 6 months. Hydrophilic polymers were utilised for preparation of tablets and physicochemical characteristics such as powder flow characterization, assay, hardness, thickness, drug dissolution, buoyancy &*in vivo* studies of optimized batchwas performed.

The animal study was performed by using HPLC technique. For the accuracy of drug estimation and detection of sample were done by this analytical method. The drug plasma concentration data from blood of rabbits gives precious results of both the drugs (metoprolol tartarate and indapamide hemihydrate). The pharmacokinetic properties of both the drugs were easily determined.

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