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FORMULATION DEVELOPMENT AND INVITRO CHARACTERIZATION OF BILAYERED MATRIX TABLETS OF METOPROLOL TARTRATE AND METFORMIN HYDROCHLORIDE

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Abstract:

Diabetes Mellitus (T2DM) is one of the complex metabolic disorders with multiple effects. Hypertension is one of the major and common conditions that is associated with it. In the present study, attempts were made to formulate a dosage form which is a combination of both anti-diabetic and anti-hypertensive agents. Metoprolol tartrate was formulated in IR Layer using disintegrants and Metformin was formulated in CR layer using natural gums and Eudragit RLPO. The evaluation tests of both formulations were conducted and dissolution study of optimized bilayered formulation has revealed that the formulations can offer a bimodal release, i.e., Metoprolol was found to be 97.42% within 2 hrs and Metformin from CR layer was 98.45% at the end of 24 hrs. Kinetic studies showed good linearity with Zero order Kinetics (Regression coefficient-0.982) and Korsemeyer Peppas model for release mechanism (Regression coefficient-0.996, n-0.758) indicating super case II transport. Hence these bilayer formulations may be considered suitable for the treatment of Diabetes associated Hypertension.

Key Words: Bilayer tablets, Metformin Hydrochloride, Metoprolol tartrate, Combination therapy.

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INTRODUCTION:

Oral drug delivery proves to be the primary and most convenient mode of administration of molecules in terms of accessibility, compliance, ease and flexibility in design and so on. Certain shortcomings like poor drug stability, enzymatic and physiological barriers, repetitive dosing requirements, peak-trough profiles etc tend to limit the applications of peroral formulations. But, necessary modifications in the drug delivery systems like designing of sustained/extended/modified/controlled release systems can prove to enhance the efficacy with definite advantages over conventional administration of the same drugs [1], [2], [3], [4].

Diabetes Mellitus type 2, i.e., non-insulin dependent diabetes mellitus (T2DM), characterized by the levels of blood glucose deems to be a complex, chronic metabolic disorder or syndrome rather than a disease [5]. It is inherently one of the extremely accountable life threats ~ 463 million populations of the world health, hence demanding regular medical supervision and strategies for the reduction of multi-factorial risks [6], [7]. Longevity of the disease may cause macrovascular and microvascular complications that could seriously affect the quality of life of patients. Moreover, during the progression of T2DM, the effects of other metabolic diseases such as, obesity, hyperlipidemia, hypertension, renal failure and others become more incident. It is therefore possible that patients with chronic T2DM and other complications shall have to use a variety of drugs [8], [9], [10].

Combination therapy can be beneficial in these conditions where multiple medicinal agents need to be administered in a narrow time range. Multi-layered tablets prove to be a better therapeutic option with various features to ensure a successful delivery system [11, [12]. It is truly advantageous where two or more drugs with similar or different pharmacological activities can be given in a single formulation. This technology has advantages of achieving dual release profiles (like immediate release from one layer and controlled/sustained release from the other layer) and enhancing the stability of dosage form by combining compatible or incompatible drugs etc [13], [14], [15]. Diabetes and Hypertension are the most common co-existing disorders which may be fatal. Here, combination therapy is favourable which may confer the treatment of both the disorders simultaneously [16], [17].

Metoprolol tartrate is a cardio selective beta-blocker used in the management of hypertension, angina pectoris, and heart failure. The half-life of the Metoprolol deems to be 3-4 h [18]. Metformin hydrochloride is an orally administered biguanide and the first-line choice for the management of type 2 diabetes. It is a hydrophilic drug that shows incomplete absorption from the exhibiting an absolute bioavailability of 50 – 60 %. Plasma half-life of the drug is relatively short, i.e., 1.5-4.9 h and has reported gastrointestinal side effects like metabolic acidosis. It is usually administered in doses of approximately 1.5-2.5g/day, the initial dose being 500 mg [19], [20].

The present research focuses on the formulation of bilayer tablets of Metoprolol tartrate and Metformin hydrochloride in immediate and controlled release layers respectively, i.e., development of combination formulations of two different classes of drugs.

MATERIALS AND METHODS:

Materials:

Metoprolol tartrate was obtained as a gift sample from Siries laboratories, Vijayawada and Metformin Hydrochloride from Hetero drugs Ltd., Hyderabad. Okra Gum and sapota gum were extracted in the laboratory based on reported procedures. Eudragit RLPO was a gift sample from Aurobindo Pharma, Hyderabad. Polyplasdone XL, sodium starch glycolate and other excipients were procured from SD Fine Chemicals, Mumbai, India. Ethocel ™ (20 cps) was a gift sample from Dr. Reddy's Laboratories, Hyderabad.

METHODS:

Extraction of Okra Gum: Okra gum was extracted in the laboratory from the pods of *Abelmoschus esculentus*. Fresh pods were collected, cleaned and sliced and seeds were removed. The pieces were subjected to boiling after sufficient soaking on a water bath at 60-80˚C for 1 hour and left undisturbed for 2-3 hours. The slimy mixture was then filtered through layered muslin cloth and squeezed properly for complete extraction of mucilage and removal of unwanted pulp. The filtrate was then treated with excess of acetone to precipitate the mucilage. The mucilage was isolated, dried in hot air oven at 40-50˚C, collected and passed through sieve no.80 and stored in a desiccator for further uses [21], [22], [23].

Extraction of Sapota gum: Ripe fruit peels and pulp of *Manilkara zapota* were separated and seeds were removed. 500g of pulp was soaked in distilled water for 24h, with occasional stirring. The soaked pulp was further ground and kept for 24h for the release of mucilage, then the material was squeezed through muslin cloth to separate the marc from filtrate. Then acetone was added to the filtrate in a ratio (1:3) to precipitate the mucilage. The precipitated mass was

separated by washing twice with acetone. The mucilage was subjected to preliminary drying in open air for evaporation of acetone and finally dried in hot air oven at 40 powdered and passed through standard sieve no 80. The powdered mucilage was kept in a desiccator until further use [24], [25], [26].

Preformulation Study:

UV Spectrophotometric Analysis: Standard dilutions of Metoprolol pure drug were prepared in the range of 2–10 μg/mL in 0.1 N HCl and the absorbance values were determined at 221nm using a UV spectrophotometer (Analytical Technologies T60). The obtained values were plotted across concentrations into linear standard curves. Similar procedure was performed for Metformin Hydrochloride at 233 nm in Phosphate buffer, pH 6.8 and graphs were plotted to detect linearity.

Drug-Excipient Compatibility study: Compatibility between both the drugs and drugs with excipients was studied by Fourier Transform Infrared Spectroscopy [27]. The samples of individual drugs, combination and mixtures with excipients were analyzed by KBr disc pellet technique. The spectra obtained were evaluated for the presence of any impurities or incompatibility.

Preparation of Immediate release tablets of Metoprolol tartrate:

Immediate release Metoprolol tablets were prepared using Wet granulation method. The mixture of drug along with the other excipients was taken in a glass mortar and ground into fine powder. Sufficient portion of starch paste was then added and granules were prepared, dried and passed through 60#, further dried, mixed with required quantities of Magnesium stearate and talc and compressed using a rotary tablet compression machine (Saimach SMD 16, 10 mm oval) (Table 1).

Preparation of Controlled Release matrix tablets of Metformin Hydrochloride:

Metformin Hydrochloride matrix tablets were prepared by wet granulation method using natural polymers Okra gum, Sapota gum) and synthetic polymer Eudragit RLPO as matrix formers. Ethocel ™ was used for the design of backing layer. Weighed quantities of drug along with polymers and other excipients blended properly and Iso-Propyl Alcohol was used as a binder. The wet masses were screened through sieve #12, and after drying through sieve #44 to achieve a uniform size. Magnesium stearate and talc were then added and the mixtures were subjected to compression on a rotary tablet compression machine (Saimach SMD-16 station, 16 mm oval, biconcave tooling) (Table 2).

Table 1. Composition of Metoprolol tartrate Immediate release tablets (IM1-IM6)

INGREDIENTS	IM1	IM2	IM3	IM4	IM5	IM6
Metoprolol tartrate (mg)	25	25	25	25	25	25
Polyplasdone XL (mg)	5	7.5	10	-	-	-
Sodium starch glycolate (mg)	-	-	-	5	7.5	10
Micro crystalline cellulose (mg)	20	20	20	20	20	20
Dicalcium phosphate (mg)	45	42.5	40	45	42.5	40
Magnesium stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5
Talc (mg)	2.5	2.5	2.5	2.5	2.5	2.5
Starch paste (mg)	q.s	q.s	q.s	q.s	q.s	q.s
Total Tablet weight	100	100	100	100	100	100

Table 2. Composition of Metformin Hydrochloride Controlled release tablets (F1-F11)

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Metformin Hydrochloride (mg)	500	500	500	500	500	500	500	500	500	500	500
Okra gum (mg)	220	160	110	60	-	-	-	-	160	110	60
Sapota gum (mg)	-	-	-	-	220	160	110	60	60	110	160
Eudragit RLPO (mg)	-	60	110	160	-	60	110	160	-	-	-
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate (mg)	5	5	5	5	5	5	5	5	5	5	5
Talc (mg)	5	5	5	5	5	5	5	5	5	5	5
Ethocel Backing Layer	20	20	20	20	20	20	20	20	20	20	20
Total Tablet weight	730	730	730	730	730	730	730	730	730	730	730

Preparation of Bilayered tablets of Metoprolol and Metformin:

In order to prepare bilayer tablets, a series of characteristic evaluation tests were conducted for IR formulations and CR formulations separately. Based on the results, the formulations that have exhibited behavior in terms of physico-chemical, mechanical and release properties were selected as best formulations () and were formulated to bilayer tablets. To prepare bilayer tablets, firstly, the Ethocel layer was compression to form a thin and firm backing layer and then Metformin tablets were punched with lesser compression force. Then the immediate release Metoprolol granules were placed over the slightly compressed tablet and a hardness of 6-8 kg/cm^2 was imposed. The total weight of each bilayer tablet was adjusted to 830 mg, containing 25 mg of Metoprolol and 500 mg of Metformin. The prepared bilayer tablets were evaluated for various post-compression parameters and in vitro dissolution studies [28].

***In vitro* characterization of IR and CR tablets:**

Determination of Pre-Compression parameters:

Pre-compression parameters or micromeritic properties such as Angle of repose, Compressibility index of the prepared IR and CR granules were evaluated by reported methods and the results were tabulated.

Determination of Post-Compression parameters [29], [30]:

The prepared IR and CR tablets were subjected to the following physico-chemical, mechanical and release properties.

Thickness: Randomly selected 10 tablets for each batch were evaluated for thickness using vernier calipers.

Hardness: It is the force required to break a tablet and is indicative of its mechanical strength during handling and shipping. 10 tablets from each batch were selected and hardness was determined by Monsanto hardness tester and is indicated in units of kg/cm^2.

Uniformity of Weight: Twenty tablets were selected randomly from each batch and weighed individually. Average of such total weights was calculated and the % deviation was calculated using the equation-

% Weight variation = [(Individual weight – average weight) / (Average weight)] * 100

The percentage deviation in weight variation should fall within the USP limits (±5%).

Drug Content: Five tablets from each batch were taken randomly and crushed in a mortar. From the mixture, samples equivalent to individual dose of the drug (25 mg of Metoprolol for IR tablets and 500 mg for CR tablets) were weighed and are taken into 100 ml volumetric flasks. To this, little amount of methanol was added to dissolve the contents and volume was made up to the mark with concerned media (0.1 N HCL and Phosphate buffer, pH 6.8. The samples were placed in a sonicator for 24 hours, filtered and absorbances were measured spectrophotometrically. The drug content should range between 90 and 110% of the standard [31].

In vitro Dissolution Studies:

The release of drugs from different batches of prepared IR and CR tablets was individually studied using USP type-II dissolution test apparatus (Electrolab TDT-08L). The dissolution media used were 900 ml of 0.1 N HCl for immediate release layer and 900 mL of 0.l N HCL followed by Phosphate buffer, pH 6.8 for CR tablets. Temperature was maintained at 37 ± 0.5˚ C and the stirring rate was 50 rpm. The samples were withdrawn at regular intervals for 2 hrs for IR Tablets and up to 24 hours for CR tablets and withdrawn volume were replaced with fresh medium to maintain sink conditions. The collected samples were filtered using Whatmann filter paper and observed using spectrophotometer at respective λ_{max} (221 nm for Metoprolol in IR tablets and 232 nm for Metformin in CR tablets) against a blank (respective medium) [32].

Kinetics of Drug release:

The data obtained from the dissolution study was used to study the dissolution behavior, order and mechanism of drug release. This can be performed through kinetic analysis by fitting into various models namely Zero order, First order, Higuchi's square root, Hixson-Crowell and Korsemeyer Peppas [33].

Evaluation of bilayered tablets:

The Evaluation parameters of bilayer tablets were performed according to I.P. specifications. Parameters such as weight variation were performed by taking average weight of 20 tablets and hardness test was performed by Monsanto hardness tester. Thickness of the tablet was measured using vernier calipers.

In vitro drug release studies of bilayer tablets were carried out using USP dissolution apparatus type II in 900 mL of 0.1 N HCl for first 2 hrs and in 900 mL of Phosphate buffer, pH 6.8 up to 24 hrs. The medium in bowl was replaced with another medium which was preferred for dissolution of controlled release layer. The collected samples were filtered and observed in UV spectrophotometer [34], [35].

RESULTS AND DISCUSSION:

In the present research, bilayered tablets of Metoprolol tartrate and Metformin were formulated with specific compositions of polymers and EC backing layer.

Preformulation study:

UV Spectrophotometric analysis: The Standard solutions of Metoprolol tartrate have shown maximum absorbance at 221nm in 0.1 N HCL and Metformin at 233 nm in Phosphate buffer, pH 6.8 respectively. Standard calibration curves were plotted for both and the regression coefficient values were 0.996 and 0.998 respectively relating to a better linearity (Fig.1, Fig.2, and Fig.3).

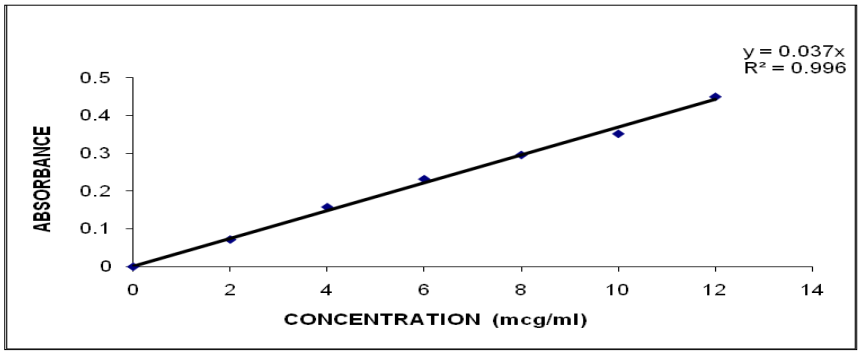

Fig.1. Calibration curve of Metoprolol tartrate in 0.1N HCl at 221 nm

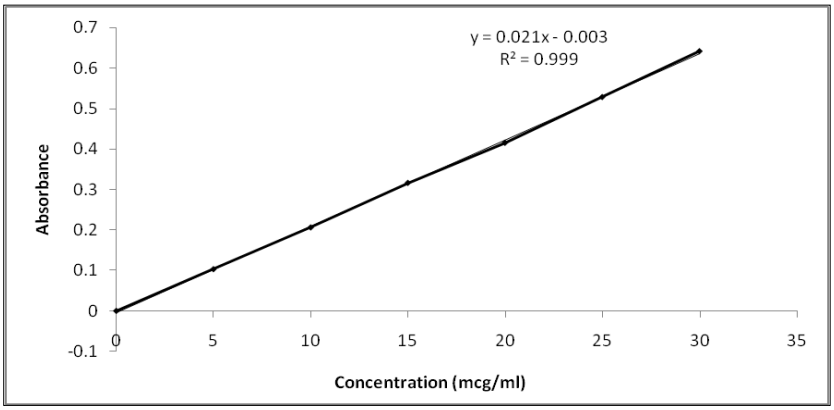

Fig.2. Calibration curve of Metformin Hydrochloride in 0.1N HCl at 228 nm

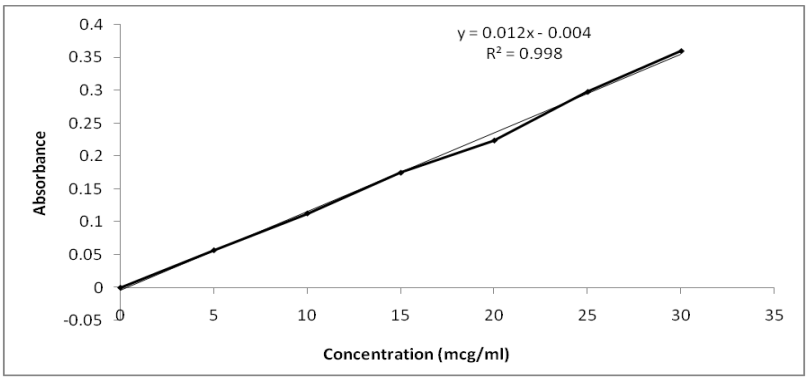

Fig.3. Calibration curve of Metformin Hydrochloride in Phosphate buffer at 233 nm

Drug-Excipient Compatibility study: The FTIR spectra of Metformin Hydrochloride and Metoprolol tartrate were analysed and shown in Figures 4 and 5. For Metformin, The following characteristic bands observed C=N-(stretching) 1629.55 cm^{-1} ,1655.59 cm^{-1}, 1669 cm^{-1}, C-N- (stretching) 1061.62 cm^{-1},1029.48 cm^{-1}, 1030.77 cm^{-1}, N-H- (stretching) 3397.96 cm^{-1},3378.67 cm^{-1},3394.1 cm^{-1}, in each case. For Metoprolol, bands observed were -OH stretching 3629.5 to 3902.3 cm^{-1}, -NH stretching 3397.95 cm^{-1}, -OH bending 1400.32 cm^{-1}.
It was inferred that no significant incompatibility could exist between drugs and excipients.

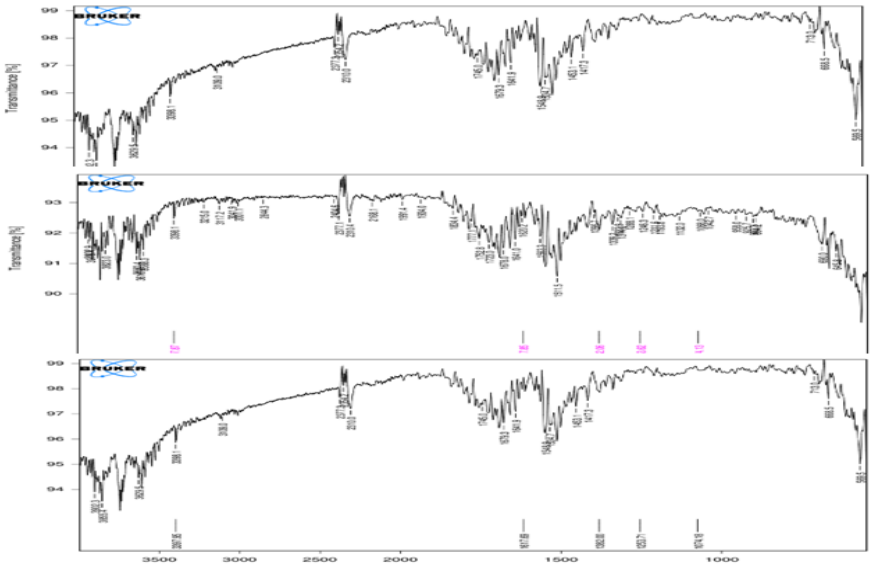

Fig.4. FTIR Spectra of Metoprolol tartrate

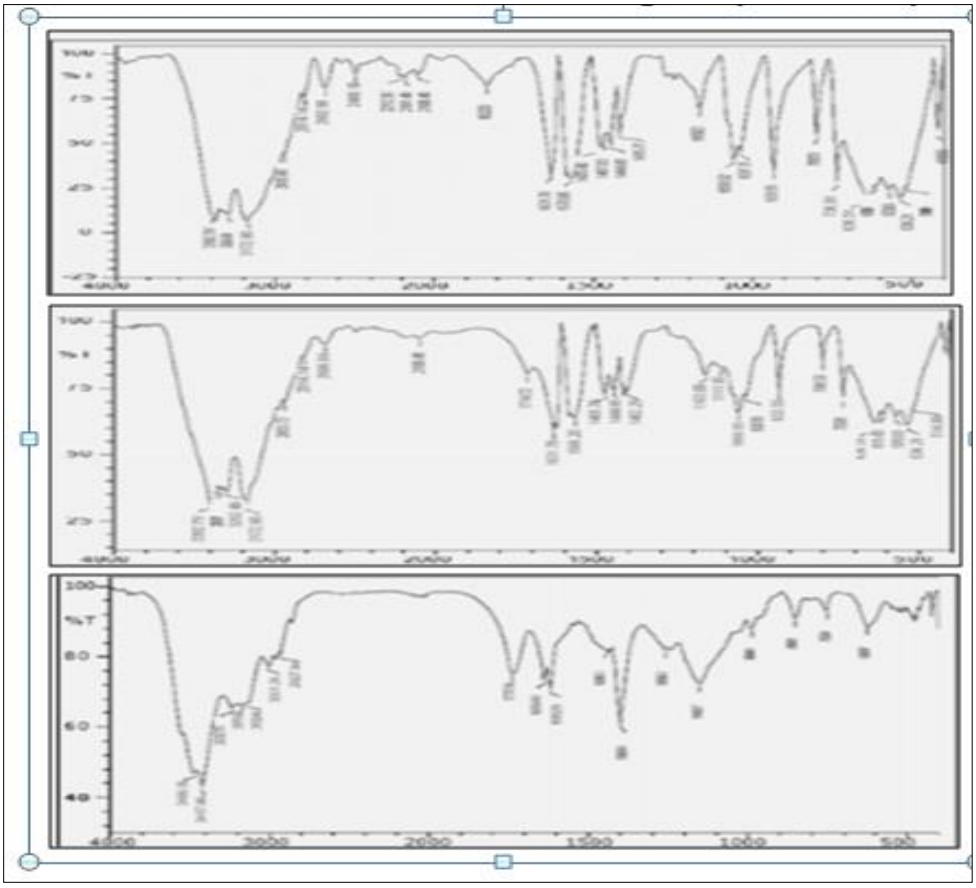

Fig.5. FTIR Spectra of Metformin Hydrochloride

Pre-compression Parameters of IR and CR formulations:

Metoprolol IR and Metformin CR tablets were formulated by wet granulation method and the granules were evaluated for flow properties (Table 3, Table 4). Almost all the formulations exhibited fair to passable flow to ensure good compression.

Table 3. Precompression Flow properties of IR Formulations

Formulation	Angle of Repose (˚)	% Compressibility (Carr's Index)
IM1	28.15±0.14	11.90±0.14
IM2	27.21±0.23	12.56±0.17
IM3	26.12. ±0.21	12.68±0.14
IM4	27.46±0.15	14.48±0.27
IM5	26.57±0.26	13.34±0.34
IM6	27.14±0.45	11.63±0.15

Table 4. Precompression Flow properties of CR Formulations

Formulation	Angle of Repose (˚)	%Compressibility
F1	31.02±0.15	16.33±0.12
F2	28.13±0.24	15.28±0.14
F3	26.5 ±0.06	15.03±0.18
F4	24.08±0.23	14.56±0.18
F5	28.16±0.15	15.65±0.1
F6	27.3±0.4	15.4±0.45
F7	25.11±0.25	14.7±0.21
F8	25.09±0.16	14.03±0.16
F9	29.15±0.14	16.21±0.13
F10	26.01±0.07	15.7±0.1
F11	25.1± 0.22	14.12±0.13

All the values are indicative of mean± S.D (n=3)

Post-Compression parameters:

The prepared IR and CR tablets were evaluated for their Physical appearance, mechanical strength and chemical integrity (Table 5, Table 6). Results of all the formulations were found to be in compendial limits.

Table 5. Post-compression parameters of IR Formulations

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Drug Content (%)
IM1	99.69±0.14	2.14±0.26	1.53 ±0.72	87.23±0.42
IM2	101.82±0.22	2.63±0.32	2.13±0.66	91.32±0.31
IM3	98.42±0.14	2.96±0.44	2.22±0.45	98.41±0.22
IM4	98.35±0.12	2.28±0.53	2.24±0.21	102.5±0.61
IM5	100.52±0.11	2.44±0.72	2.15±0.65	87.41±0.31
IM6	97.43±0.21	2.56±0.52	2.14±0.55	100.2±0.51

Table 6. Post-compression parameters of CR Formulations

Formulation	Average Wt (mg)	Hardness (kg/cm^2)	Thickness (mm)	Drug Content (%)
F1	742.25±3.15	6.03±0.15	5.34±0.23	96.22±0.42
F2	748.11±1.23	6.26±0.14	5.14±0.45	92.45±0.58
F3	732.2 ±4.14	6.82±0.17	5.08±0.31	99.12±0.2
F4	729.54±1.05	7.05±0.13	5.26±0.22	101.3±0.05
F5	735.56±2.10	6.43±0.15	5.02±0.74	100.0±0.82
F6	726.48±4.21	7.15±0.44	5.35±0.03	97.64±0.36
F7	738.72±3.36	7.53±0.29	5.7±0.34	93.4±0.19
F8	728.82±2.08	7.31.±0.11	5.21±0.64	101.55±0.76
F9	729.43±0.64	7.92±0.12	5.14±0.14	98.51±0.09
F10	732.05±1.05	8.25±0.15	5.24±0.14	100.3±0.25
F11	740.07±0.75	8.72±0.12	5.05±0.08	99.82±0.15

All the values are indicative of mean± S.D (n=3)

***In vitro* dissolution study:**

Dissolution studies were performed to study the release of Metoprolol from IR tablets (IM1-IM6) and Metformin Hydrochloride from CR formulations (F1-F11).

IR formulations of Metoprolol were prepared using disintegrants Polyplasdone and Sodium starch glycolate in different ratios. Dissolution study was performed in 0.1N HCl for a period of 2 hours. The profiles as a function of % drug released were plotted versus time and the results are summarized (Table 7, Figure 6). It can be seen from the results that formulation IM4 was optimum formulation with a release of 98.57 % ±3.66 % after 2 hours and considered for further bilayer mechanism.

CR formulations of Metformin were prepared using varying drug: polymer ratios using rate modifying natural polymers like Okra gum, Sapota gum, synthetic Eudragit RLPO in combination.

Ethyl Cellulose was used to form a thin, constant backing layer to the matrix tablets to provide uni-directional movement, which is a primary concern for controlling the drug release. Dissolution profiles were represented by cumulative percentage of drug released at each sampling intervals and summarized in Tables 8. From the results it can be observed that formulation F10 that exhibits a drug release of 99.46 % ±2.71% over a period of 24 hrs was selected to be best formulation and formulation into bilayer tablets (Table 8, Figure 7).

Table 7. *In vitro* drug release data for IR tablets

Time (min)	Cumulative Drug released (%)					
	IM1	IM2	IM3	IM4	IM5	IM6
0	0	0	0	0	0	0
5	17.03 ±4.09	21.70 ±4.42	28.27 ±4.88	24.08 ±3.48	29.08 ±3.48	37.46 ±3.10
10	29.65 ±5.12	32.82 ±3.59	40.91 ±4.09	38.20 ±6.06	40.20 ±6.06	48.02 ±6.58
15	35.42 ±2.25	43.46 ±5.98	51.55 ±5.24	46.08 ±5.01	49.08 ±5.01	58.45 ±7.01
30	48.93 ±3.42	59.85 ±6.26	62.53 ±3.01	58.83 ±4.28	58.83 ±4.28	74.54 ±3.12
45	60.06 ±5.18	67.01 ±2.24	78.46 ±3.21	66.90 ±6.61	76.90 ±6.61	87.34 ±4.80
60	71.22 ±3.21	75.52 ±3.12	86.54 ±2.90	75.75 ±5.26	85.52 ±5.26	97.75 ±3.01
90	79.14 ±3.08	84.48 ±2.98	98.95 ±1.69	83.04 ±3.12	94.04 ±3.12	……
120	83.28 ±1.56	95.79 ±2.48	.....	98.57 ±3.66	……	……

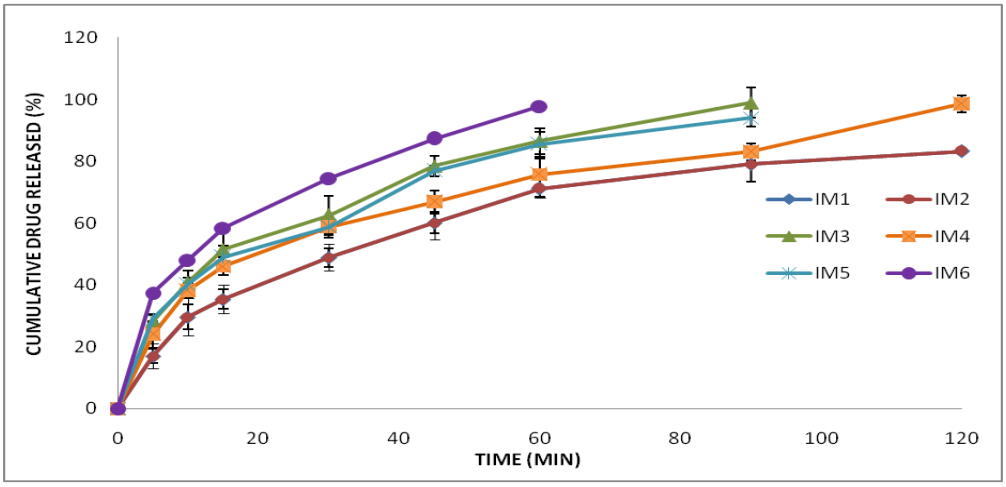

Fig.6. *In vitro* drug release of Metoprolol from IR tablets

Table 8. In vitro drug release data for CR tablets

TIME (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0	0	0	0	0
1	15.23 ± 2.26	10.34 ± 2.26	7.91 ± 3.16	2.70 ±4.31	18.35 ± 2.26	11.58 ±3.06	9.63 ±3.03	3.61 ±1.24	8.18 ±4.31	4.18 ±4.31	3.12 ±1.24
2	21.82 ±4.09	17.21 ±4.09	12.5 ±3.64	7.53 ±2.46	25.08 ±2.14	21.25 ±3.67	15.45 ±2.44	6.20 ±2.23	16.82 ±4.09	7.71 ±3.46	5.71 ±2.23
4	31.82 ±4.09	29.45 ±3.24	21.61 ±5.72	15.18 ±2.82	38.31 ±5.3	32.5 ±2.00	25.17 ±3.81	11.43 ±3.56	28.40 ±6.08	14.43 ±2.82	9.65 ±3.56
6	43.40 ±6.08	36.76 ±3.01	28.85 ±6.26	21.85 ±3.4	52.35 ±3.11	41.16 ±3.01	32.62 ± 3.07	17.35 ±2.05	39.38 ±4.53	21.63 ±3.4	14.35 ±2.05
8	59.83 ±4.53	51.52 ±3.46	42.18 ±3.24	28.54 ±3.75	65.52 ±2.01	53.16 ±3.01	40.16 ±3.24	23.55 ±1.64	52.09 ±3.55	29.42 ±3.31	21.55 ±1.64
10	76.06 ±4.21	64.68 ±2.72	55.52 ±4.12	32.77 ±5.01	81.86 ±5.27	62.21 ±2.55	57.52 ±4.12	29.04 ±4.12	61.72 ±5.32	39.48 ±3.01	28.62 ±4.12
12	89.50 ±5.32	75.87 ±5.66	67.4 ±4.98	41.09 ±2.64	90.18 ±2.09	78.68 ±2.72	69.73 ±3.83	35.48 ±2.9	72.68 ±3.13	51.43 ±2.16	34.61 ±2.9
16	98.53 ±3.13	91.03 ±2.14	79.53 ±3.51	58.74 ±2.11	99.64 ±2.09	91.87 ±5.66	83.72 ±3.31	47.08 ±3.08	84.57 ±2.65	63.74 ±2.11	45.45 ±3.08
20	---	98.65 ±3.08	96.41 ±2.04	75.85 ±1.46	---	98.61 ±1.49	96.29 ±3.83	68.21 ±2.07	99.12 ±2.71	78.85 ±1.46	65.29 ±2.07
24	---	---	---	98.53 ±2.71	---	---	---	82.53 ±1.53	---	99.46 ±2.71	87.2 ±1.91

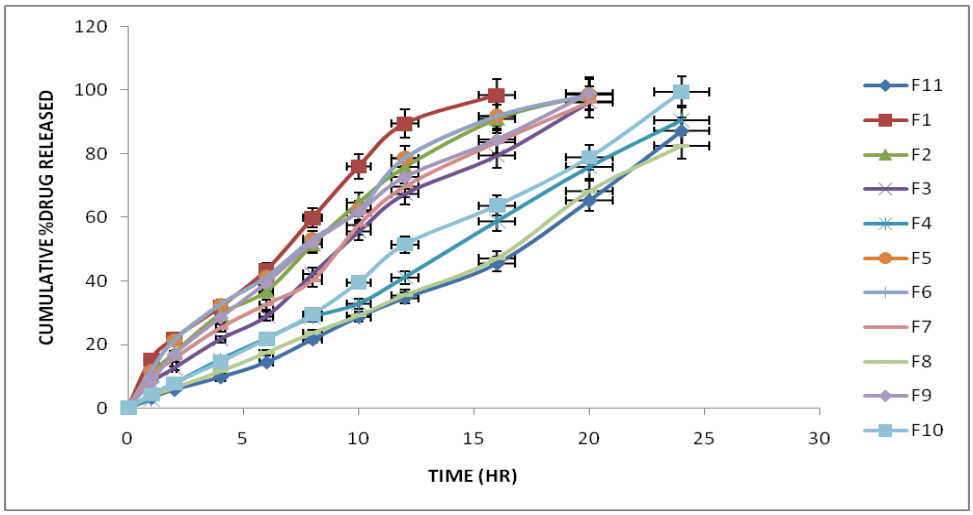

Fig.7. *In vitro* drug release of Metformin from CR tablets

Drug release Kinetics:

The data obtained from drug release studies was analysed for order and mechanism of release by best-fit method. Values of regression coefficient (R^2) were considered important for the determination of release kinetics. Results of kinetic analysis of CR formulations are represented in Table 9.

On comparison of order of release, it was found that almost all the formulations exhibited zero order release (R^2- 0.987 for F10) and Korsmeyer-Peppas equations were plotted and the value of diffusion exponent 'n', 0.758 indicates that the diffusion was 'non-fickian'. Hence, by considering the dissolution data and results of kinetic analysis, F10 was selected to be optimized formulation.

Table 9. Kinetics of drug release

Formulation	Zero order	First order	Higuchi	Korsemeyer- Peppas	
	R^2	R^2	R^2	R^2	n
F1	0.958	0.911	0.988	0.990	0.453
F2	0.965	0.976	0.916	0.997	0.52
F3	0.973	0.917	0.991	0.991	0.632
F4	0.962	0.980	0.978	0.978	0.548
F5	0.945	0.936	0.996	0.995	0.623
F6	0.931	0.920	0.991	0.992	0.67
F7	0.973	0.917	0.961	0.986	0.72
F8	0.962	0.980	0.972	0.992	0.432
F9	0.945	0.936	0.996	0.986	0.58
F10	0.987	0.920	0.971	0.992	0.758
F11	0.957	0.942	0.918	0.987	0.56

Evaluation of Bilayer tablets: Bilayer tablets of Metoprolol and Metformin were prepared after selection of optimized formulations from IR formulations and CR formulations. The prepared tablets were evaluated for their post-compression properties and results were observed to be satisfactory within the limits. From the results, the release of Metoprolol from IR layer was found to be 97.42% after 2 hrs and 98.45% after 24 hrs. The release of Metformin in the first 2 hours was found to be negligible owing to the presence of backing layer.

Table 10. Post compression parameters of Bilayer tablets

Formulation	Hardness (kg/cm^2)	Avg. Weight (mg)	Thickness (mm)	Drug content (%)
BM	8.25±0.15	732.05±1.05	9.52±0.14	100.3±0.25

Table 11. In vitro dissolution study of Bilayer tablets

Time (hr)		Drug Release (%)
IR LAYER	0	0
	0.5	12.65±4.15
	1	35.30 ±2.40
	1.5	68.21±4.07
	2	97.42±2.35
CR LAYER	3	2.18±1.15
	4	5.24±3.27
	5	12.57±2.28
	6	21.92±3.12
	8	35.60±2.04
	10	48.05±5.26
	12	64.20±4.71
	14	73.29±2.30
	16	85.12±2.01
	24	98.45±1.73

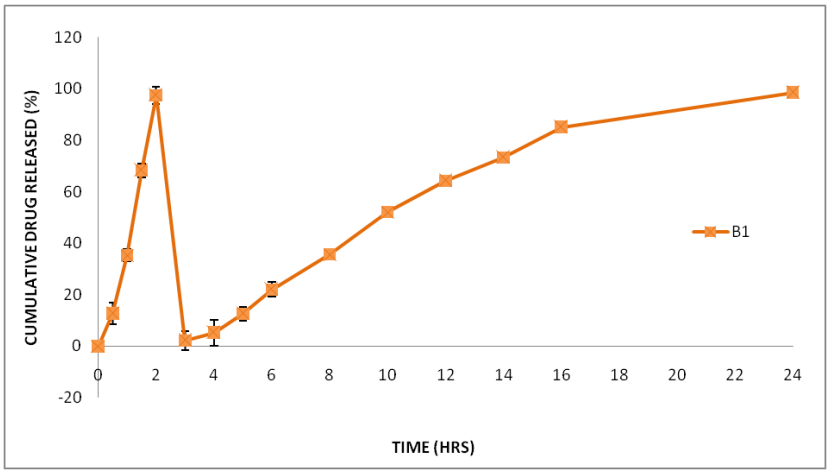

Fig 8. *In vitro* release of Metoprolol and Metformin from Bilayer tablets

CONCLUSIONS:

The current research demonstrated the successful formulation and evaluation of bilayer tablets with drugs belonging to two different categories. Immediate release tablets of Metoprolol tartrate were prepared using disintegrants Polyplasdone XL, Sodium starch glycolate and controlled release formulations using Okra gum, Sapota gum and Eudragit RLPO. All the evaluation tests have shown that pre and post compression parameters were within the official limits.

In vitro release studies reveal that IM4 of IR formulations and F10 of CR formulations were suitable for the formulation into bilayer tablets. In bilayer tablets, the release of Metoprolol was found to be 97.42% within 2 hrs and Metformin from CR layer was 98.45% at the end of 24 hrs. Release kinetics showed good linearity by best fitting in to Korsemeyer peppas and zero order kinetics for CR layer. From the above study, it can be concluded that the prepared bilayer tablets achieve the objective of treating the diabetes and hypertension with the sequential release of two drugs. It can be used as a better alternative to reduce pill burden and enhance patient compliance.

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