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FORMULATION OPTIMIZATION OF IMMEDIATE RELEASE BILAYER TABLETS OF TELMISARTAN AND HYDROCHLOROTHIAZIDE

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Keywords:

Bilayer Tablets, Telmisartan, Hydrochlorothiazide, Wet Granulation, Seal Coating, Dissolution Efficiency

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ABSTRACT: The aim of the current investigation was to develop bilayered immediate-release tablets of Telmisartan (TEL) and Hydrochlorothiazide (HCTZ) for the treatment of hypertension. In contrast to monotherapy, the dual drug therapy of TEL (an angiotensin II receptor blocker) and HCTZ (diuretic) is connoted to have a cumulative antihypertensive effect. Additionally, it offers ameliorative patient adherence to fixed-dose combination therapy over monotherapy and diminishes pill burden and dose-related side effects. The preformulation studies were accomplished by determining the compatibility of model drugs with their respective excipients by FTIR studies. These studies unambiguously connoted nix chemical interaction of excipients with the chosen model drugs. The formulation development was achieved in phases comprising of preliminary screening, pre-optimization and optimization studies. The wet granulation technique was adopted for formulating bilayer tablets. For pre-optimization studies, five batches for each layer (T1-T5 for TEL and H1-H5 for HCTZ layer) were prepared. Based on the outcomes of pre-optimization, the formulation batches T2 and H5 were subsequently chosen for optimizing the varied process and formulation variables. The optimum bilayer formulation (T2H5) released drugs within 1 h (TEL-102.03% and HCTZ-101.03%) with individual layers. The super disintegrates attributing optimum immediate release characteristics were crospovidone (3.7% w/w) in TEL layer and sodium starch glycolate (1.66% w/w) in the HCTZ layer, respectively. The stability studies in conformity to ICH guidelines revealed a shelf life of 20 months. The study concluded that the bilayer tablets of TEL and HCTZ could be an alternative to a conventional dosage form for the treatment of hypertension.

INTRODUCTION: A drug substance can be incorporated into numerous dosage forms for the convenient and efficacious treatment of a disease. The enteral routes are preferred by the majority of the patients in which the dosage form is to be swallowed and the absorption of the drug into bloodstream takes place through small intestine [1, 2].

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Further, more owing to the well-established manufacturing methods used to produce solid oral dosage forms, they are cheaper to produce, making them the most cost-effective choice, in light of the importance of reducing overall prescribing costs, for prescribers and healthcare providers [3].

Among various dosage form designs, the bilayer tablet technology is a novel approach, widely practiced nowadays, to deliver two or more drugs in a single tablet unit orally. This system improves patient compliance, prolongs the action of the drug resulting in effective and efficient therapy along with better control of plasma drug levels. This technology can be a crucial way to avoid tablet

chemical incompatibilities between API's by physical separation. The development of different drug release profiles may also be facilitated by combining the effect of slow-release with the immediate-release formulations. This also improves treatment outcomes [4]. In the present investigation, the selected model drug Telmisartan is a potent, long-lasting, non-peptide antagonist of the Angiotensin II Type-1 (AT1) receptor that is indicated for the treatment of hypertension. The second model drug Hydrochlorothiazide is a thiazide diuretic used to increase excretion of sodium, potassium, and water [5]. It is indicated for the treatment of high blood pressure and to prevent strokes, heart attacks, and kidney problems. In a study conducted by Zaletel *et al.,* (2016), a fixed drug combination of TEL and HCTZ effectively decreased BP in patients with all grades of essential hypertension [6].

Furthermore, Ando *et al.,* (2009) showed that combination therapy of TEL with low dose HCTZ has superior antihypertensive effects as opposed to monotherapy [7]. Yet in another study, Bhushan (2014) showed that FDC of TEL and HCTZ effectively controls stage II hypertension [8]. Thus, it is evident from the literature that dual drug therapy comprising Telmisartan and Hydrochlorothiazide effectively controls essential hypertension. The success of a pharmaco-treatment essentially depends on the availability of the drug at the site of action in the living body. The drug should reach the target site at a concentration greater than the minimal effective concentration [9]. Telmisartan is a BCS class II drug that has very poor solubility in the physiological pH range of the gastrointestinal tract between pH 1 and 7 while hydrochlorothiazide degrades in alkaline conditions [10]. Additionally, both model drugs are water-insoluble, thus possess a greater challenge to attain the required bioavailability. Consequently, during the current investigation, the bilayer tablet technique was resorted to addressing these issues.

MATERIALS AND METHODS: The model drugs, namely Telmisartan, hydrochlorothiazide, and all excipients, were obtained as gift samples from Ind-Swift Ltd. Derabassi, Punjab.

Method: The poor aqueous solubility and incompatibilities between the selected model drugs may lead to drug instability and poor drug delivery, leading to decreased product performance [11]. As mentioned before, Telmisartan needs an alkaline environment, while hydrochlorothiazide degrades in an alkaline environment.

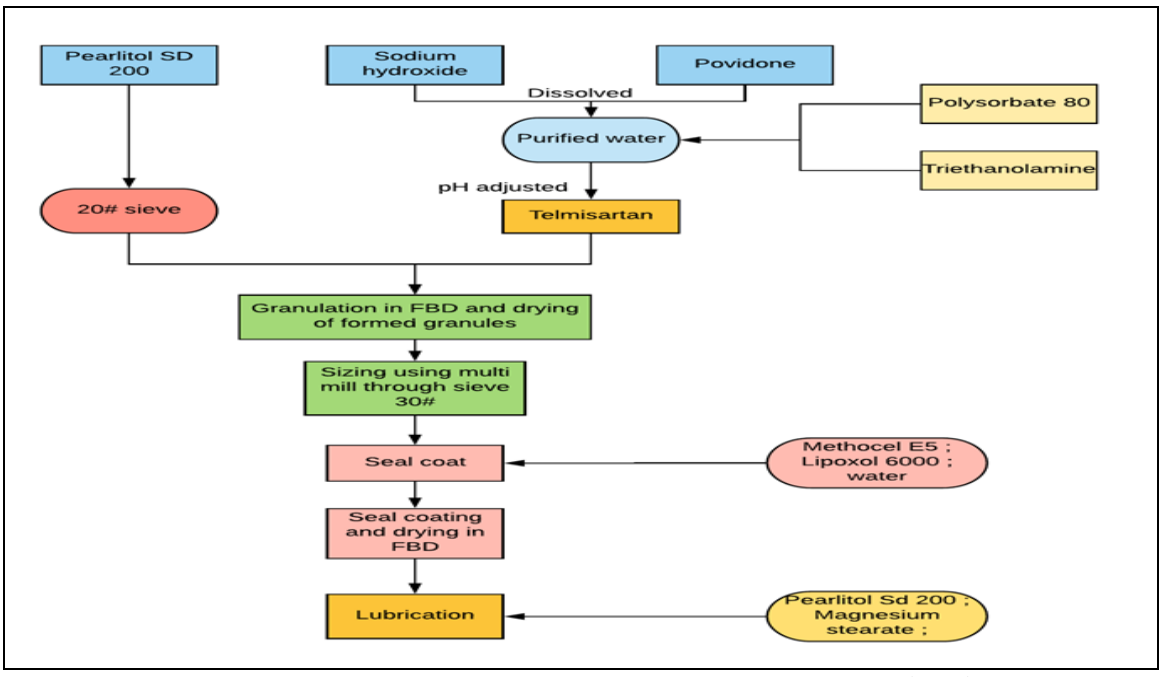

FIG. 1: FLOW CHART FOR THE PREPARATION OF TELMISARTAN (TEL) GRANULE

Thus, the combination of TEL and HCTZ is not feasible due to the incompatibility of HCTZ with basic compounds [12]. The bilayer tablet technology enables to overcome of this problem providing pH-

independent dissolution of the poorly water-soluble Telmisartan and also provides an immediate release of diuretic from a rapid disintegrating matrix containing superdisintegrants [5]. Furthermore, this structure also overcomes the stability problem caused by the incongruity of diuretics (HCTZ) with basic constituents of the Telmisartan formulation. The methods to formulate granules of TEL and HCTZ have been shown in **Fig. 1** and **2,** respectively.

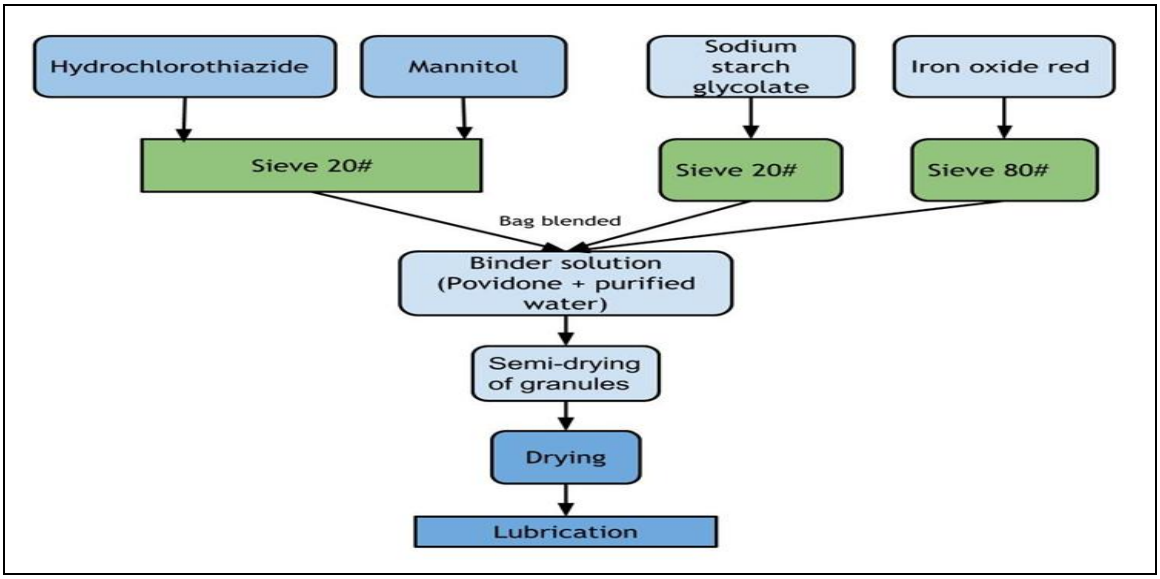

FIG. 2: PREPARATION OF HYDROCHLOROTHIAZIDE (HCTZ) GRANULES

Preliminary studies were aimed at the selection of an appropriate technique and ratio of excipients for the formulation of immediate-release bilayer tablet formulations. For this, tablets were collected at random from varied formulation batches which were subsequently subjected to several routine evaluation procedures pertaining to tableting including pre-compression parameters (bulk and tapped density, compressibility index, Hausner's ratio, angle of repose) and post-compression parameters (friability, hardness, thickness, length, disintegration time, drug release and drug content). Further, during pre-optimization studies, five more batches for each layer were prepared based on the best technique employed for each layer *i.e.*, wet granulation along with seal coating for TEL layer and wet granulation of HCTZ.

The tablet blends for both layers were coded (T1 T5 for TEL layer and H1-H5 for HCTZ layer respectively) suitably. Based on the outcomes of pre-optimization, the formulation batches T2 and H5 were subsequently chosen for optimizing process and formulation variables.

Optimization of Process Variable for T2 and H5 Batch: The process variables which were optimized included seal coating process time and lubrication time for the T2 batch. The process variables optimized for H5 batch included blending time, lubrication time, and compression speed of rotary tablet machine. During this study, TEL optimized batches were encoded as T2a-T2e and for that of HCTZ were encoded as H5a-H5c, respectively **Table 1.**

TABLE 1: OPTIMIZATION OF PROCESS VARIABLES

Optimization of process variable for formulation T2		
Formulation code	**Process factor**	**Optimizing level**
T2a	Seal coating time (min)	100-115
T2b	Lubrication time (min)	5-10
T2c	Compression speed (rpm)	15-45
T2d	pH	8-12
T2e	Drying time (min)	200-210
Optimization of process variables for formulation H5		
Formulation code	**Process factor**	**Optimizing level**
H5a	Blending time (min)	12-17
H5b	Lubrication time (min)	5-15
H5c	Compression speed (rpm)	15-25

Optimization of Formulation Variable for T2 and H5 Batch: The critical formulation variables have an effect on the overall performance of the formulation.

Herein, the formulation variables (factors) *viz* concentration of polysorbate 80 (0.180.92% w/w) and methodical E5 (1.37-2.00% w/w) for TEL layer were optimized **Table 2.** For HCTZ layer, the concentration of SSG (0.83-1.25% w/w) and povidone (2.50-3.33% w/w) were optimized **Table 3.** TEL batches were encoded as AT1-AT3 while HCTZ batches as AH1-AH3

TABLE 2A: FACTOR COMBINATION AS PER EXPERIMENTAL DESIGN FOR OPTIMIZATION OF FORMULATION VARIABLE FOR TEL LAYER

Factor levels in coded form		
Formulation code	**X_1**	**X_2**
T2	+1	-1
AT1	-1	-1
AT2	-1	+1
AT3	+1	+1

TABLE 2B: TRANSLATION OF CODED LEVELS IN ACTUAL UNITS FOR TEL LAYER

Factor level	+1	-1
Concentration of polysorbate 80 (mg)	2.5	0.5
Concentration of methocel E5 (%w/w)	5.4	3.7
Tablet weight and other process parameters were kept constant as that of formulation T2		

TABLE 3A: FACTOR COMBINATION AS PER EXPERIMENTAL DESIGN FOR OPTIMIZATION OF FORMULATION VARIABLE FOR HCTZ LAYER

Factor levels in coded form		
Formulation code	**X_1**	**X_2**
H5	+1	-1
AH1	-1	-1
AH2	-1	+1
AH3	+1	+1

TABLE 3B: TRANSLATION OF CODED LEVELS IN ACTUAL UNITS FOR HCTZ LAYER

Factor level	+1	-1
Concentration of SSG (mg)	3	2
Concentration of povidone (%w/w)	8	6
SSG: Sodium starch glycolate; Tablet weight and other process parameters were kept constant as that of formulation H5		

***In-vitro* Dissolution Studies:** Phosphate buffer (900 ml) of Ph 7.5 ± 0.05 was used as the dissolution media for TEL while 0.1 M Hydrochloric acid (900 ml) for HCTZ. The dissolution buffer was placed in the vessel, and the apparatus was assembled (USP type II dissolution apparatus).

All the parameters, such as program, temperature, speed, time were set. Accurately weighed bilayered tablets (n = 6) of Telmisartan (40 mg) and hydrochlorothiazide (12.5 mg) were placed in each beaker of the dissolution apparatus. The apparatus was operated for a specified time at a specified rate 75 rpm of TEL and 50 rpm for HCTZ.

The samples 20 ml of dissolution fluids were withdrawn through a filter 0.45 µm at varied time intervals till 45 min for TEL and till 60 min for HCTZ. The samples collected were subsequently analyzed using HPLC [13].

Determination of Drug Content: The drug content of Telmisartan and hydrochlorothiazide in each preparation was calculated using equations 1 and 2, respectively.

$$\text{Percent assay} = A_T / A_S \times W_S / 100 \times 5 / 50 \times P / 100 \times 100 / W_T \times 50 / 5 \times 100 / 40 \text{ (Label claim)} \times \text{Avg. mass of the tablet.} \quad \text{…….(1)}$$

Where, A_T = Peak area of Telmisartan peak in each preparation, A_S = Mean peak area of six injections of TEL peak in standard preparation-I, W_S = Weight of working standard-I of TEL in mg, W_T = Weight of tablet powder taken in mg, P = Potency working standard (W.S) of TEL used in percent on as such basis.

$$\text{Percent assay} = A_T / A_S \times W_S / 100 \times 5 / 50 \times P / 100 \times 100 / W_T \times 50 / 5 \times 100 / 12.5 \text{ (Label claim)} \times \text{Avg. mass of the tablet} \quad \text{….(2)}$$

Where, A_T = Peak area of Hydrochlorothiazide peak in each preparation. A_S = Mean peak area of six injections of HCTZ peak in standard preparation-I. W_S = Weight of working standard-I of Hydrochlorothiazide in mg. W_T = Weight of tablet powder taken in mg. P = Potency working standard (W.S) of HCTZ used in percent on as such basis.

Stability Studies: Stability of pharmaceutical products refers to the capacity of the product or a given drug substance to remain within established specifications of identity, potency, and purity during a specified time interval [11]. The stability studies were conducted as per ICH guidelines [14] for final optimized formulation (T2H5) at distinct storage conditions (25 ± 2 °C / 60 ± 5/ RH, 30 ± 2 °C / 75 ± 5 / RH, 40 ± 2 °C / 75 ± 5 / RH).

The samples were kept in stability chambers for a period of six months. Moisture is considered to be one of the most important factors that must be controlled to minimize decomposition of solid dosage forms [9,] and thus the amount of water was determined in the samples after storing them at discrete storage conditions. Various other critical parameters were also evaluated (appearance, mean drug release, drug content, and total impurities. Furthermore, shelf-life prediction of the final formulation was performed (equations 3, 4, and 5) followed by ANOVA analysis.

$$\ln k = - E_A / R_T + \ln A \text{ ..... (3)}$$

$$\text{Log } k = - Ea / 2.303RT + + \log A \text{..... (4)}$$

Shelf life =Specification limit of impurity – Initial level of impurity/Rate of change of impurity per month....(5)

RESULTS AND DISCUSSION: To design optimum tablets choosing right excipients to play a vital role as they modify dissolution, solubility, and improve compatibility with the APIs [1]. Thus, the samples were assessed for drug-excipients compatibility studies, and it was found that all the samples remained physically unaltered throughout the study period of one month **Table 4** and **5** this indicated that no physical change was observed.

The FTIR spectra of pure drugs (TEL and HCTZ) were also found concordant with their respective working standards, **Table 6.** Furthermore, FTIR spectra of physical mixtures of model drugs with their respective excipients showed no chemical interaction as the characteristic peaks of physical mixtures followed the same trajectory as that of the drug alone with minor differences. The flow properties of the granules can be arbitrated from discrete parameters, which included the angle of repose, compressibility index, and Hausner's ratio.

The values for the angle of repose, compressibility index (%), and Hausner's ratio for all prepared granules were found to be in the range of 28-36 °C, 9.25-22.03% and 1.10-1.28 respectively **Fig. 3, 4** and **5.** The bulk density was found to range between 0.44-0.56 g/cm^3 and tapped density between 0.54-0.64 g/cm^3 for all formulations. However, the flow properties of preliminary formulation batches (TPS1 and HPS1) and pre-optimization formulations (T2 and H5) showed good to excellent flow properties which can be attributed to use of optimum percent of seal coating material and lubricants **Table 7,** and **8** the formulation batches namely T2 and H5 were further optimized for process and formulation variables. The T2 optimized formulation of the first layer was then allowed for direct compression with various formulations for the second layer, **Table 9.** Here, crospovidone was used as a super disintegrant, showed better release when used in 3.70% w/w concentration. Crospovidone has high wicking propensity causing it to take up water. It swells without gelling and being non-ionic in nature; the disintegrant action is independent of the pH of the media [15, 16,] which was alkaline in the case of the TEL layer. For the second layer (H5), 1.66% w/w SSG sodium starch glycolate, proved to be optimum. SSG is the sodium salt of a carboxymethyl ether of starch, the mechanism of which has been attributed to its high rate of water uptake and rapid swelling property [15].

The varied pharma-cotechnical parameters for all the formulations *viz* average tablet weight (501.66 512.12 mg), friability (0.02-0.46%), disintegration time (5.23-6.89 min) and the hardness (70-90 N) were observed within the specified range [17]. Amongst all the formulations, T2H5 was considered as the best formulation. The drug content of the final optimized formulation T2H5 was found to be 99.05% and 102.56% for TEL and HCTZ **Fig. 6,** while the drug release was found to be 102.03% and 101.03% respectively **Fig. 7.** Furthermore, salient dissolution parameters *viz*. PD_{10}, PD_{30}, DE_{10} and DE_{30} inveterate the superiority of T2 (PD_{10} = 64.13%, PD_{30} = 99.11%, DE_{10} = 32.06% and DE_{30} 71.06%) and H5 batches (PD_{10} = 76.39%, PD_{30} = 90.03%, DE_{10} = 38.20% and DE_{30} = 69.18%), the same has been shown in **Fig. 8** and **9** respectively.

Such fitting inferences can be attributed to the addition of a non-ionic surfactant (polysorbate 80) and super disintegrates (crospovidone and SSG). The non-ionic surfactants (surfactants with an uncharged polar head group) are able to form micelle at a much lower concentration than ionic surfactants and have modifying effect on the rate of hydrolysis of drugs [18, 19], thus, enabling greater solubility. Furthermore, due to the uncharged nature, these surfactants are less sensitive to salt but quite sensitive to temperature.

The critical micelle concentration for such surfactants is generally much lower than that of corresponding charged surfactants and is generally less irritant as well as better tolerated [20]. The cumulative drug release of TEL and HCTZ from final optimized formulation T2H5 was fitted to various kinetic models. The release of TEL from T2H5 followed Hixon Crowell model (K_{HC} = 0.039 and R^2 = 0.816) while that of HCTZ followed Korsmeyer Peppas model (K_{HC} = 0.177 and R^2 = 0.991) **Fig. 10** and **11** following kinetic analysis, T2H5 was employed for stability studies at varied storage conditions (25 °C / 60% RH, 30 °C / 75%, and at 40 °C / 75% RH) for six months. All the critical parameters evaluated were within limits indicating T2H5 formulation was stable with no significant changes at the accelerated condition of temperature and humidity.

Furthermore, the energy of activation (E_a= 19.447.533) and rate constant (In A = 28.879) was calculated using equations 3 and 4. Eventually, the values of E_a and log A was put into Arrhenius equation (equations 3 and 4) at 25 °C (298 K) to estimate the shelf life of the final formulation in long term condition which was found to be 20 months **Table 10** in addition, ANOVA (Two factors without replication) was performed for mean drug release of TEL and HCTZ from T2H5 **Table 12.** The p values (p = 0.004 for TEL and p = 0.010) were less than alpha (α = 0.05) in case of storage conditions during stability testing leading to rejection of the null hypothesis (H_o). However, in the case of time periods (3 and 6 months), the p-values (p = 0.490 for TEL and p = 0.066) obtained were more than alpha (α = 0.05), leading to acceptance of null hypothesis (H_o).

TABLE 4: PHYSICAL APPEARANCE OF SAMPLES OF TEL DURING DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Sample details	Sample codes	25 °C / 60% RH (initial)	40 °C / 75% RH (1 week, 2 weeks and 1 month)
Drug (TEL)	T	White	Off - white
TEL + Crospovidone (Kollidon CL)	TA		
TEL + Mannitol	TB		
TEL + Polysorbate 80	TC		
TEL + HPMC E5	TD		
TEL + Magnesium stearate	TE		
TEL + Triethanolamine	TF		
TEL + Polyethylene glycol	TG		
TEL + Sodium hydroxide	TH		

Note: The colour of samples slightly changed from white to off white during the accelerated drug-excipients compatibility studies.

TABLE 5: PHYSICAL APPEARANCE OF SAMPLES (HCTZ) DURING DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Sample details	Sample codes	25 °C / 60% RH (initial)	40 °C / 75% RH (1 week, 2 weeks and 1 month)
HCTZ + Mannitol	H	White	White
HCTZ + Sodium starch glycolate	HA		
HCTZ + Povidone (Kollidon 30)	HB		
HCTZ + Magnesium stearate	HC		
HCTZ + Iron oxide red	HD		
HCTZ + Mannitol	HE		

Note: The colour of samples remained same *i.e.* white during the accelerated drug-excipients compatibility studies.

TABLE 6: INTERPRETATION OF FTIR SPECTRA OF PURE MODEL DRUGS

Interpretation of FTIR spectra of pure drug Telmisartan		
Reported peaks (cm^{-1})	**Observed peak (cm^{-1})**	**Inference**
3100-3050	3061.13	C = H stretching
1780-1650	1694.47	C = O stretching
1600-1475	1460.46	C = C aromatic stretching
1300-1000	1266.79	C - O stretching
900-690	891.42	C - H aromatic stretching
Interpretation of FTIR spectra of pure drug Hydrochlorothiazide		
Reported peaks (cm^{-1})	**Observed peak (cm^{-1})**	**Inference**
3500-3300	3362.69	N - H stretching
1660-1600	1604.43	C = C stretching
1300-1000	1222.43	C - O stretching
1300-1000	1059.72	C - O stretching
900-690	822.60	C - H aromatic stretching

TABLE 7: COMPOSITIONAL DETAILS OF TELMISARTAN LAYER OF BILAYER TABLET

Ingredients	Formulation composition (in % w/w)				
	T1	T2	T3	T4	T5
Dry mix					
Mannitol SD 200	58.51	59.25	60	60.74	60.74
Drug and binder solution					
Telmisartan	14.81	14.81	14.81	14.81	14.81
Sodium hydroxide	1.22	1.22	1.22	1.22	1.22
Polysorbate 80	0.18	0.55	0.92	1.29	1.66
Triethanolamine	4.44	4.44	4.44	4.44	4.44
Crospovidone	3.70	3.70	3.70	3.70	3.70
Purified water	Q.S				
Seal coat					
HPMC E5	2.11	1.74	1.37	0.81	0.44
PEG 6000 MD	0.18	0.18	0.18	-	-
Purified water	Q.S				
Lubrication					
Mannitol SD 200	12.33	12.33	12.33	12.33	12.33
Magnesium stearate	2.48	1.74	1.00	0.62	0.62
Total weight of telmisartan layer = 270 mg					

TABLE 8: COMPOSITIONAL DETAILS OF HYDROCHLOROTHIAZIDE LAYER

Ingredients	Formulation composition (in % w/w)				
	H1	H2	H3	H4	H5
Dry mix					
Hydrochlorothiazide	5.20	5.20	5.20	5.20	5.20
Mannitol	71.66	72.50	73.33	74.16	75.00
Sodium starch glycolate	0.83	0.83	1.25	1.25	1.66
Iron oxide red	0.08	0.08	0.08	0.08	0.08
Binder solution					
Povidone	5.83	5.00	4.16	3.33	2.50
Purified water	Q.S				
Lubrication					
Sodium starch glycolate	0.83	0.83	0.83	0.83	0.83
Mannitol SD 200	13.87	13.87	13.45	13.45	13.04
Magnesium stearate	1.66	1.66	1.66	1.66	1.66
Total weight of hydrochlorothiazide layer = 240 mg					

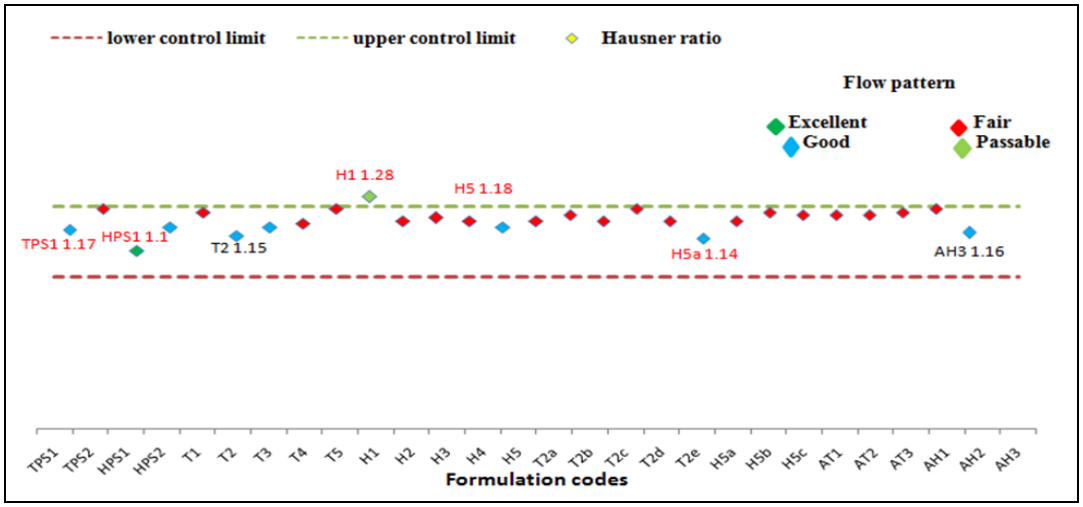

FIG. 3: COMPARISON OF CARR'S INDEX VALUES FOR FORMULATIONS PREPARED DURING VARIED STAGES

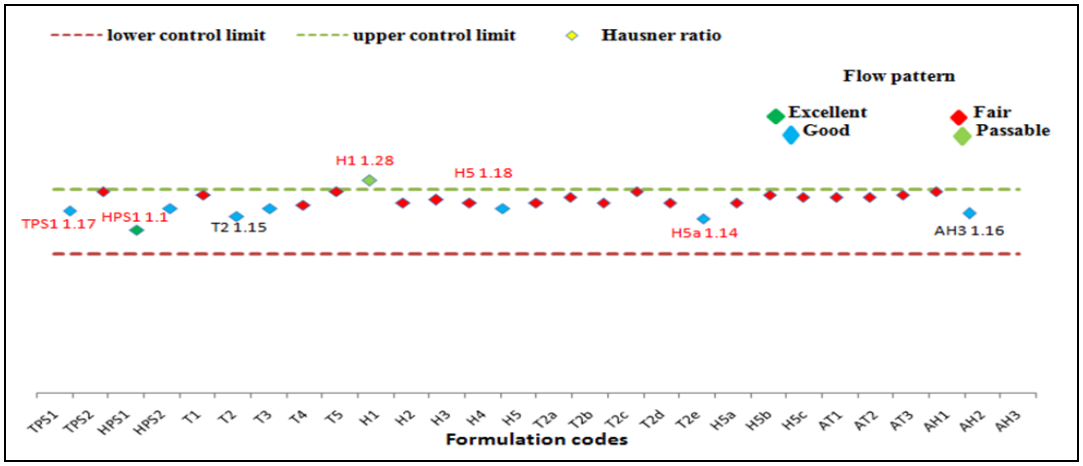

FIG. 4: COMPARISON OF HAUSNER'S RATIO FOR FORMULATIONS PREPARED DURING VARIED STAGE

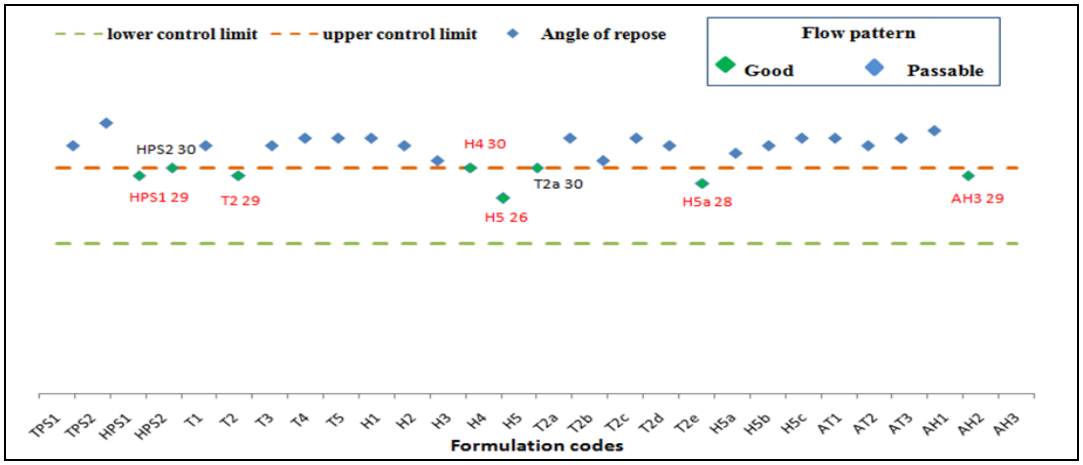

FIG. 5: COMPARISON OF ANGLE OF REPOSE FOR FORMULATIONS PREPARED DURING VARIED STAGES

TABLE 9: POST COMPRESSION PARAMETERS OF BILAYER TABLETS OF TELMISARTAN AND HYDROCHLORO-THIAZIDE

F. C	Weight variation (mg) Mean ± S. D (n=20)	Hardness (N) Mean ± S. D (n=10)	Thickness (mm) (Mean ± S.D) (n=10)	Friability (%) (Mean ± S. D) (n=10)	Disintegration time (min) (Mean ± S. D) (n=6)
T2-H1	504.36 ± 0.44	80 ± 0.12	3.59 ± 0.33	0.11 ± 0.11	5.23 ± 0.11
T2-H2	508.11 ± 0.78	70 ± 0.11	3.45 ± 0.14	0.46 ± 0.23	6.74 ± 0.01
T2-H3	501.66 ± 0.36	71 ± 0.01	3.49 ± 0.61	0.63 ± 0.15	5.41 ± 0.11
T2-H4	505.01 ± 0.51	80 ± 0.04	3.60 ± 0.47	0.34 ± 0.04	6.89 ± 0.12
T2-H5	512.12 ± 0.35	90 ± 0.13	3.63 ± 0.38	0.02 ± 0.00	5.43 ± 0.11
B.R	501.66-512.12	70-90	3.45-3.63	0.02-0.63	5.23-6.89

B. R: Broad range; F. C: Formulation codes; N: Newton; min: min; S. D: Standard deviation

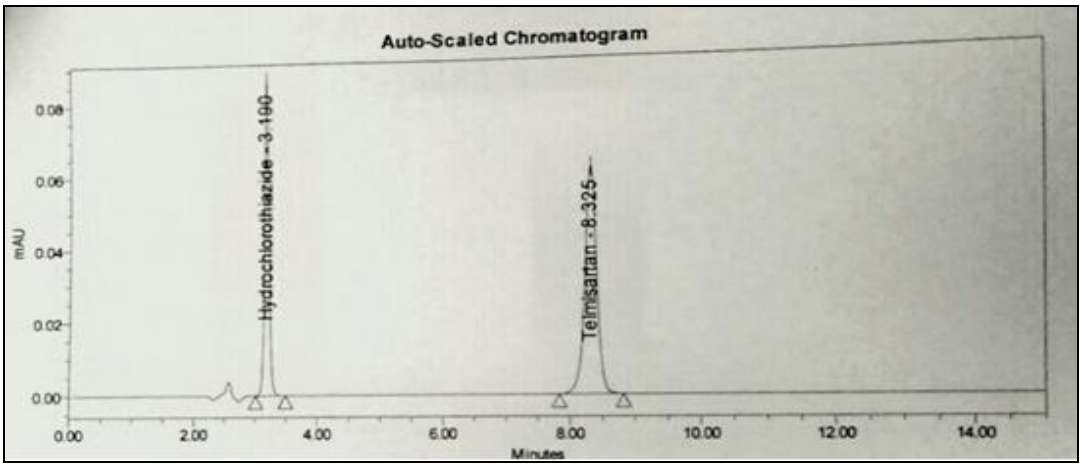

FIG. 6: HPLC CHROMATOGRAM OBTAINED FOR CONTENT UNIFORMITY OF FOMULATION (T2H5)

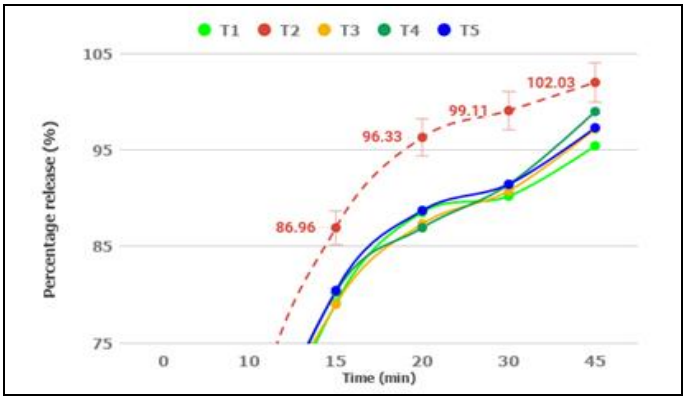

FIG. 7A: TEL FORMULATIONS (T1-T5)

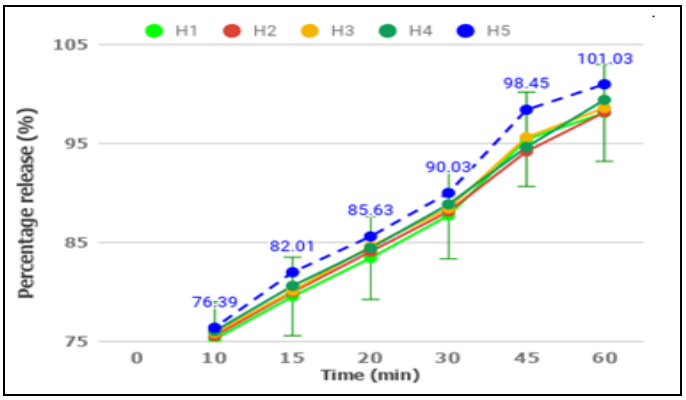

FIG. 7B: HCTZ FORMULATIONS (H1-H5)

FIG. 7: DISSOLUTION PROFILES OF TELMISARTAN AND HCTZ FORMULATIONS

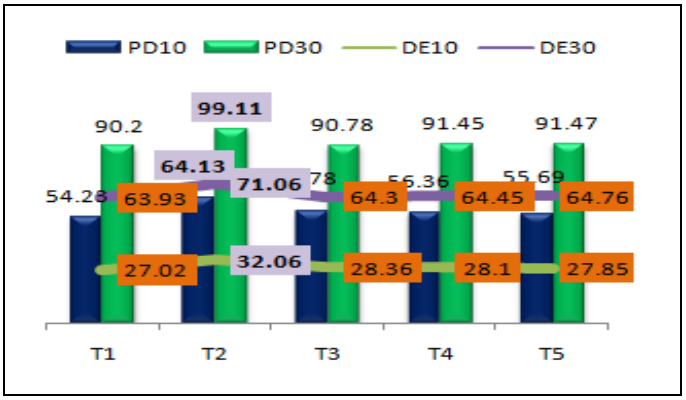

FIG. 8: COMPARATIVE DISSOLUTION PARA-METERS OF TEL FORMULATIONS T1-T5

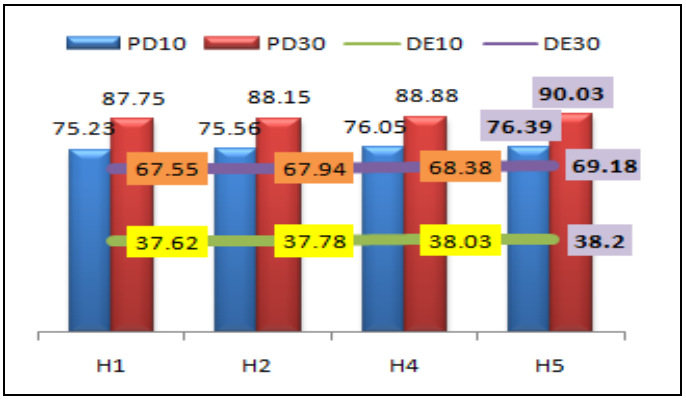

FIG. 9: COMPARATIVE DISSOLUTION PARA-METERS OF HCTZ FORMULATIONS H1-H5

TABLE 10: STABILITY STUDY DATA OF FINAL OPTIMIZED FORMULATION (T2H5)

Stability study data of TEL layer in final optimized formulation					
Storage condition	**Time period**	**Mean drug released (%) Mean ± S. D (n=3)**	**Drug content (%) Mean ± S. D (n=3)**	**Water content (% w/w) Mean ± S. D (n=3)**	**Total impurities (%) Mean ± S. D (n=3)**
Initial		102.03 ± 0.06	96.80 ± 0.12	0.76 ± 0.14	0.25 ± 0.03
25 ± 2 °C/60 ± 5% RH	3M	102.00 ± 0.14	95.93 ± 0.45	0.34 ± 0.00	0.34 ± 0.00
	6M	101.36 ± 0.12	95.80 ± 0.21	1.00 ± 0.17	0.39 ± 0.12
30 ± 2 °C/75 ± 5% RH	3M	100.23 ± 0.23	95.79 ± 0.12	1.01 ± 0.22	0.45 ± 0.01
	6M	100.06 ± 0.58	95.15 ± 0.45	1.23 ± 0.05	0.65 ± 0.11
40 ± 2 °C/75 ± 5% RH	1M	98.12 ± 0.36	95.65 ± 0.17	1.27 ± 0.04	0.66 ± 0.13
	3M	97.25 ± 0.25	95.36 ± 0.09	1.16 ± 0.01	0.72 ± 0.14
	6M	97.45 ± 0.21	95.05 ± 0.12	1.23 ± 0.44	0.80 ± 0.30
Stability study data of HCTZ in final optimized formulation					
Storage condition	**Time period**	**Mean Drug released (%) Mean ± S. D (n=3)**	**Drug Content (%) Mean ± S. D (n=3)**	**Water content (%w/w) Mean ± S. D (n=3)**	**Total Impurities (%) Mean ± S. D (n=3)**
Initial		101.03 ± 0.31	101.01 ± 0.02	0.76 ± 0.12	0.25 ± 0.03
25 ± 2 °C/ 60 ± 5% RH	3M	101.00 ± 0.52	101.10 ± 0.05	0.98 ± 0.14	0.34 ± 0.00
	6M	100.95 ± 0.28	100.68 ± 0.11	1.00 ± 0.12	0.39 ± 0.12
30 ± 2 °C/75 ± 5% RH	3M	100.96 ± 0.41	100.89 ± 0.01	1.01 ± 0.11	0.45 ± 0.01
	6M	100.23 ± 0.60	101.21 ± 0.23	1.23 ± 0.33	0.65 ± 0.11
40 ± 2 °C/75 ± 5% RH	1M	100.20 ± 0.11	100.00 ± 0.01	1.27 ± 0.14	0.66 ± 0.13
	3M	100.23 ± 0.14	100.65 ± 0.05	1.16 ± 0.21	0.72 ± 0.14
	6M	99.90 ± 0.01	100.03 ± 0.11	1.23 ± 0.01	0.80 ± 0.30

F. C: Formulation codes; RH: Relative humidity; TEL: telmisartan; Note: In the entire course of stability studies the appearance of the tablets remained white (as initial) F. C: Formulation codes; HCTZ: Hydrochlorothiazide; RH: Relative humidity; Note: In the entire course of stability studies the appearance of the tablets remained light pink (as initial)

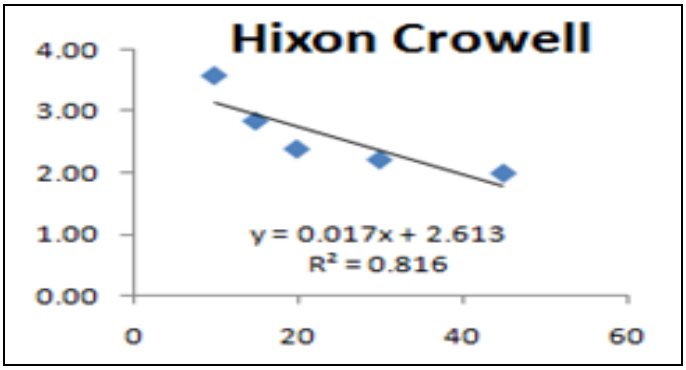

FIG. 10: KINETIC MODELING AS APPLIED TO T2H5 FORMULATION (TEL)

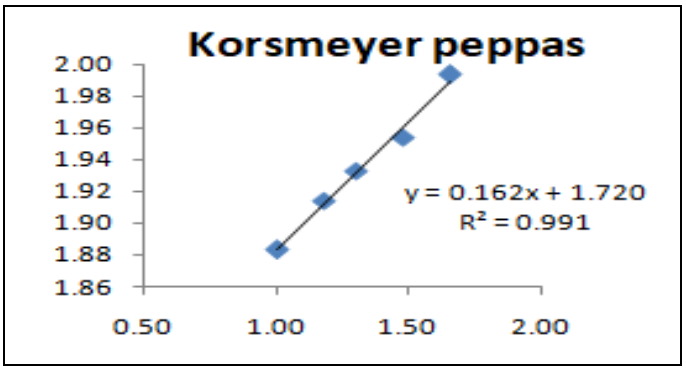

FIG. 11: KINETIC MODELING AS APPLIED TO T2H5 FORMULATION (HCTZ)

TABLE 11: SHELF LIFE ESTIMATION OF FINAL FORMULATION T2H5

Storage conditions	Initial percent impurity in formulation T2H5 (%)	Limit (as per USP)	Percent impurity (in 6 months)	Value of E_a, log A and K
40 ± 2 °C/75 ± 5% RH			0.80	E_a = 19447.533
30 ± 2 °C/75 ± 5% RH	0.25	NMT 1%	0.65	Log A = 28.879 K = 0.016
Shelf life = 20 months				

Ea: Energy of activation; K: Rate of change of impurity per month; log A: logarithmic scale of rate constant; RH: Relative humidity

TABLE 12: ANALYTICAL VARIANCE DETERMINATION OF FINAL FORMULATION T2H5

ANOVA: Two-factor without replication (TEL)						
Source of variation	**SS**	**D f**	**MS**	**F**	**P-value**	**F. crit**
Storage conditions	19.278	2	9.639	108.772	0.009	19.000
Time period	0.062	1	0.062	0.699	0.490	18.512
Error	0.177	2	0.088			
Total	19.517	5				
ANOVA: Two-factor without replication (HCTZ)						
Source of variation	**SS**	**D f**	**MS**	**F**	**P-value**	**F. crit**
Storage conditions	14.883	2	7.441	91.124	0.010	19.000
Time period	0.020	1	0.204	0.249	0.666	18.512
Error	0.163	2	0.081			
Total	15.067	5				

CONCLUSION: The wet granulation technique was successful in formulating bilayer tablets consisting of antihypertensive drugs for antihypertensive therapy. Agents such as solubilizing agents used in the TEL layer, *i.e.*, polysorbate 80, enhanced the effective solubility of hydrophobic drug Telmisartan. Furthermore, disintegrant agent *i.e.*, crospovidone and sodium starch glycolate, played a significant role in the immediate disintegration of TEL and HCTZ layer, respectively. The results of stability studies aided in proving that the developed bilayer formulation (T2H5) was stable even at the accelerated condition of temperature and humidity, indicating that the developed formulation. Thus, it was concluded that this novel approach might provide a potential opportunity for oral delivery of drugs, and this combination of drugs can successfully be given to treat hypertension.

Still, numerous future perspectives in context to these drugs can be explored further.

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