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FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE AND HYDROCHLORTHIAZIDE BILAYER TABLETS BY WET GRANULATION METHOD

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ABSTRACT: Metoprolol succinate extended-release tablet is a beta-1 (cardio-selective) adrenoceptor-blocking agent formulated to provide controlled and predictable release of metoprolol. Hydrochlorothiazide (HCT) is a well-established diuretic and antihypertensive agent, which promotes natruresis by acting on the distal renal tubule. The pharmacokinetics, efficacy, and safety/tolerability of the antihypertensive combination tablet, metoprolol extended release hydrochlorothiazide, essentially reflect the well-described independent characteristics of each of the component agents. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer as immediate release layer as initial dose and second layer as maintenance dose. The aim of present work was to develop a robust formulation of Bi-layer tablets of Metoprolol Succinate Extended Release and Hydrochlorthiazide Immediate Release using methocel as polymer and Cross-carmellose-sodium as super disintegrant respectively in two layers. The drug product developed to reduce Hypertension. Metoprolol Succinate is an antihypertensive (cardio selective b-blocker) used in the management of hypertension, angina pectoris and heart failure in doses ranging from 25 mg to 200 mg. Hydrochlorothiazide is a first line diuretic drug of the thiazide class which inhibits the reabsorption of sodium, potassium ions in the nephron of the kidney and produces Antihypertensive effect.

KEYWORDS: Extended release tablets, Antihypertensive, Bi layer tablets, Hydrochlorothiazide

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1.INTRODUCTION

Hypertension[1] is a chronic medical condition in which the blood pressure in the arteries is elevated. It is classified as either primary (essential) or secondary. About 90-95% of cases are termed primary be found and for remaining fraction of cases the causes are known like hyperlipidimia etc. Hypertension effects almost all organs of the body like kidneys, arteries, heart, or endocrine system. Hence, there is growing need for development of suitable medication to treat or manage hypertension. Anti-hypertensives are class of drugs which are used to manage hypertension. There are various classes of drugs which are used as antihypertensive like beta blockers, calcium channel blockers; ACE inhibitors etc., among all these, beta blockers are still being used as first line agents used for management of hypertension. Metoprolol succinate[2] is a beta1-selective (cardio selective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, at higher plasma concentrations, Metoprolol succinate also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol succinate has no intrinsic sympathomimetic activity and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Because of these desired pharmacodynamic properties, Metoprolol succinate is used popularly for management of hypertension. Metoprolol succinate belongs to class I category in BCS classification system, i.e. freely soluble & highly permeable. Because of good solubility and permeability, its bioavailability is more and half life is less. This results in multiple doses of Metoprolol succinate every day. Hence, continuous efforts are being made whereby number of doses of Metoprolol succinate can be minimized. This has resulted in formulation of Metoprolol succinate in to extended release form. Literature is flooded with reference in which various approaches are used for the formulation of extended release form of Metoprolol. These methods suffer from one or the other disadvantages. Hence, in the present work an attempt will be made in which formulation of Metoprolol succinate will be designed for extended release and it will be validated. Hydrochlorothiazide[3], abbreviated HCTZ, HCT, or HZT, is a diuretic drug of the thiazide class that acts by inhibiting the kidney's ability to retain water. This reduces the volume of the blood, decreasing blood return to the heart and thus cardiac output and, by other mechanisms, is believed to lower peripheral vascular resistance.

INTRODUCTION TO BILAYER TABLET

Oral ingestion[5,6,7] has long been the most convenient and commonly employed route of drug delivery due to its ease of administration. It is well known that modified release dosage forms may offer one or more advantages over immediate release formulations of the same drug. There are many ways to design modified release dosage forms for oral administration; from film coated pellets, tablets or capsules to more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. The design of modified

release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience[8,9]. The most common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period[10]. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance[11] . Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity[12].

METHODS OF GRANULATION

Granulation is the act or process of forming or crystallizing into small particles. Granules typically have a size range between 0.2 to 4.0 mm depending on their subsequent use. The granulation process combines one or more powder particles and forms a granule that will allow tableting or spheronization process to be within required limits. This way predictable and repeatable process is possible and quality tablets or pellets can be produced using tabletting or spheronization equipment [13,14,15]. Granulation is carried out for various reasons, one of those is to prevent the segregation of the constituents of powder mix. Segregation is due to differences in the size or density of the component of the mix. Normally, the smaller and/or denser particles tend to concentrate at the base of the container with the larger and/or less dense ones on the top. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule and segregation of granules will not occur.Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties. Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same powders are often more easily compacted. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granules[16,17,18].

Granulation techniques

In pharmaceutical industry, two types of granulation technologies are employed, namely, wet granulation and dry granulation.

Wet granulation

In wet granulation, granules are formed by the addition of a granulation liquid onto a powder bed which is under the influence of an impeller (in a High shear granulator, screws (in a twin screw granulator) or air (in a fluidized bed granulator). The agitation resulting in the system along with the wetting of the components within the formulation results in the aggregation of the primary powder particles to produce wet granules. The granulation liquid (fluid) contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol either alone or in combination. The liquid solution can be either aqueous based or solvent based. Aqueous solutions have the advantage of being safer to deal with than solvents[19,20,21]. Water mixed into the powders can form bonds between powder particles that are strong enough to lock them together. However, once the water dries, the powders may fall apart. Therefore, water may not be strong enough to create and hold a bond. In such instances, a liquid solution that includes a binder (pharmaceutical glue) is required. Povidone, which is a polyvinyl pyrrolidone (PVP), is one of the most commonly used pharmaceutical binders. PVP is dissolved in water or solvent and added to the process. When PVP and a solvent/water are mixed with powders, PVP forms a bond with the powders during the process, and the solvent/water evaporates (dries). Once the solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules. The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which is subsequently dried[22,23,24].

Dry granulation

The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. In this process the primary powder particles are aggregated under high pressure. Sweying granulator or high shear mixer-granulator can be used for the dry granulation[25,26]. Dry granulation can be conducted under two processes; either a large tablet (slug) is produced in a heavy duty tabletting press or the powder is squeezed between two rollers to produce a sheet of materials (roller compactor, commonly referred to as a chilsonator). When a tablet press is used for dry granulation, the powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in varying degrees of densification. The roller compactor (granulator-compactor) uses an auger-feed system that will consistently deliver powder uniformly between two pressure rollers. The powders are compacted into a ribbon or small

pellets between these rollers and milled through a low-shear mill. When the product is compacted properly, then it can be passed through a mill and final blend before tablet compression[27].

TABLETS BY DIRECT COMPRESSION

Direct Compression is by far the easiest means of processing tablets, because it only involves the main steps of powder blending, lubrication and compaction. Because there is no granulation step to improve flow and compaction it is usually necessary to use excipients specifically designed for direct compression, and engineered to provide the necessary flow and compaction properties. Such materials are sometimes known as "filler-binders". Despite the availability of these materials, the utility of direct compression may be limited by the dose of drug to be tableted.

IMPORTANCE OF THE PRESENT METOPROLOL SUCCINATE AND HYDROCHLORTHIAZIDE COMBINATION

The aim of present study is to develop a bilayered tablet for management of Hypertension using Hydrochlorothiazide and Metoprolol succinate.The bilayered tablets gives biphasic drug release like loading dose of HCTZ and maintenance dose of Metoprolol succinate. The bilayered tablets are prepared using croscarmellose sodium as superdisintigrant for immediate released layer and different viscosity grades of hydrophilic polymers for sustained released layer, prepared tablets are evaluated for their physio-chemical properties.Bilayer tablet technology has been specially developed to provide two different release rates or biphasic release of a drug from a single dosage form . For these types of drugs,extended release formulations generally lead to a delayed appearance of effective plasma levels and they cannot provide a prompt disposition of the dose, while the immediate released formulation appears quickly after their administration. Combination drug therapy is recommended for treatment of hypertension to allow the medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each. The rational for combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure to achieve the goal to minimize dose dependent side effects and adverse reactions. When smaller doses of medication with different mechanism of action are combined, synergistic or additive effects on blood pressure are achieved and dose dependent side effects are minimized.HCTZ and Metoprolol succinate is from BCS class 4 and 1 respectively.Thus this poorly soluble compounds leads to high intra- and inter-subject variability and lack of dose proportionality and it resulting fluctuation in dosing with conventional dosage form. Thus the strong need for the development of sustained release bilayer is recognized to deliver loading dose of drug in the stomach, to reduce frequency of administration and to increase the efficacy of the drug by providing sustained action[28,29]. In the present study, a combination drug therapy of HCTZ and Metoprolol succinate is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses, by formulating the immediate and

sustained released layers of Bilayer tablets.Therapy with any combination of Metoprolol succinate extended release and Hydrochlorothiazide will be associated with both sets of dose independent side effects[30].

2. MATERIAL AND METHODS

The formulation chart is given below

Table 1: COMPOSITION OF IMMEDIATE RELEASE LAYER

SL.NO	INGREDIENTS	FORMULATION(mg)
1	Hydrochlorothiazide	12.5
2	Croscarmellose Sodium	12.5
3	Hydroxypropylmethyl Cellulose 3cps	5
4	Microcrystalline Cellulose	20
5	Aerosil	2
6	Magnesium Stearate	2
7	Iron Oxide	Tinge
8	**Weight of total immediate release layer(mg)**	**54**

Table 2 : COMPOSITION OF EXTENDED RELEASE LAYER

SL.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Metoprolol Succinate	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
2	HPMC K100M	47.5	95	142.5	47.5	95	142.5						
3	Ethyl Cellulose	27.5	27.5	27.5				27.5	27.5	27.5			
4	HPMC K4M				27.5	27.5	27.5				27.5	27.5	27.5
5	Kollidone SR							47.5	95	142.5	47.5	95	142.5
6	Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
7	Talc	2	2	2	2	2	2	2	2	2	2	2	2
8	**Weight of total extended release layer(mg)**	**127.5**	**175**	**222.5**	**127.5**	**175**	**222.5**	**127.5**	**175**	**222.5**	**127.5**	**175**	**222.5**
9	**Total weight of the tablet(mg)**	**181.5**	**229**	**276.5**	**181.5**	**229**	**276.5**	**181.5**	**229**	**276.5**	**181.5**	**229**	**276.5**

3. RESULTS AND DISCUSSION

PREFORMULATION STUDIES

4.1 Solubility Determination

Metoprolol Succinate is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane; practically insoluble in ethyl acetate, acetone, diethylether.

Hydrochlorthiazide is slightly or very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dimethylformamide; n-butylamine; and solutions of alkali hydroxides; insoluble in ether, chloroform, and dilute mineral acids

4.2 Melting point determination

Metoprolol has a very low melting point around 136°C..

Hydrochlorothiazide has a melting point between 273° C-275° C.

4.3 IR Spectroscopy

The IR spectrum of Metoprolol Succinate pure drug was found to be similar to the standard spectrum of Metoprolol Succinate as in IP.The spectrum of Metoprolol succinate showed the following functional groups at their frequencies.Standard spectra of drugs were shown in following tables.

Compatability Studies

This work exemplifies a general method of studying the drug excipient interactions, with the aim of predicting rapidly and inexpensively the long term stability of their mixtures. We study the physico-chemical properties of a drug (Metoprolol Succinate) in the solid state and in different combinations with several excipients (HPMC,EthylCellulose,Kollidone). We compare the properties of pure compounds (untreated, or moisture/temperature conditioned) with those of binary mixtures drug:excipient which underwent the same treatment. The purpose is to find indications of interactions within the mixtures, which means a potential incompatibility of the excipient. Both morphological and thermal properties are sensitive to interactions which leave mostly unmodified the IR spectra and the X-rays patterns. In particular, we find that Metoprolol Succinate does not interact with either HPMC or Ethyl Cellulose or Kollidone.

FT-IR spectra:

Table 3: Pure drug

Functional groups	Wave number cm^{-1}
OH	3415.97 stretching
NH	1560.67 bending
-O-	1383.42 stretching
Aromatic ring	2930.28 stretching 639.53 bending

Table 4: Pure drug+HPMC

Functional groups	Wave number cm^{-1}
	3431.41 stretching
NH	1559.82 bending
-O-	1387.27 stretching
Aromatic ring	2929.34 stretching 639.68 bending

Table 5:Pure drug+Kollidone

Functional groups	Wave number cm^{-1}
OH	3386.72 stretching
NH	1559.76 bending
-O-	1399.45 stretching
Aromatic ring	2929.42 stretching 639.07 bending

Table 6:Pure drug+Ethylcellulose

Functional groups	Wave number cm^{-1}
OH	3448.12 stretching
NH	1560.25 bending
-O-	1392.85 stretching
Aromatic ring	2977.53 stretching 639.56 bending

Figure 1:FT-IR studies of Metoprolol succinate

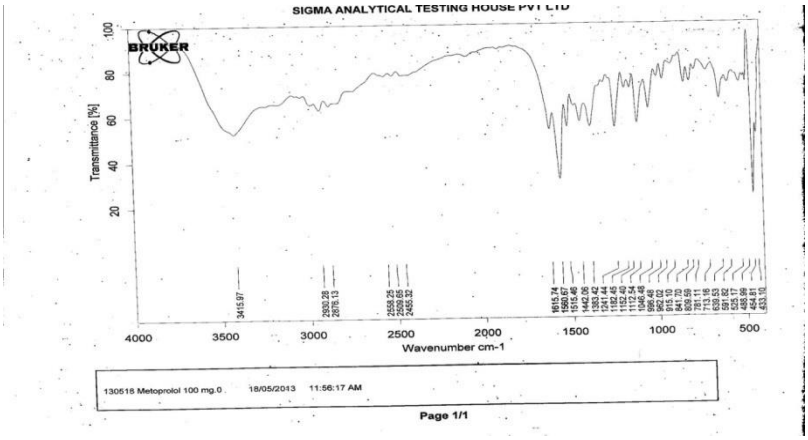
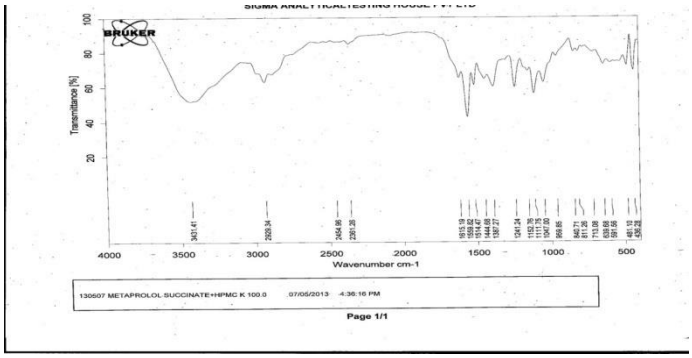


Figure 2:FT-IR studies of Metoprolo succinate+HPMC K100M



igure 3:FT-IR studies of Metoprolol succinate+ Kollidone

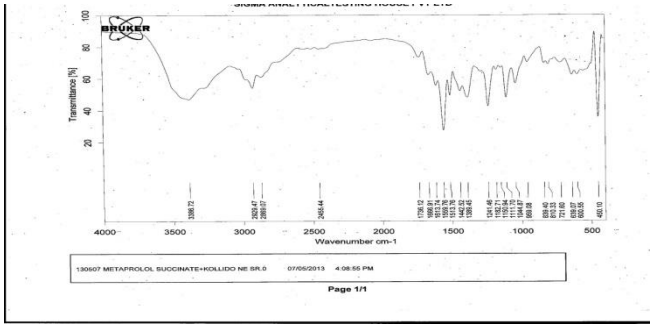
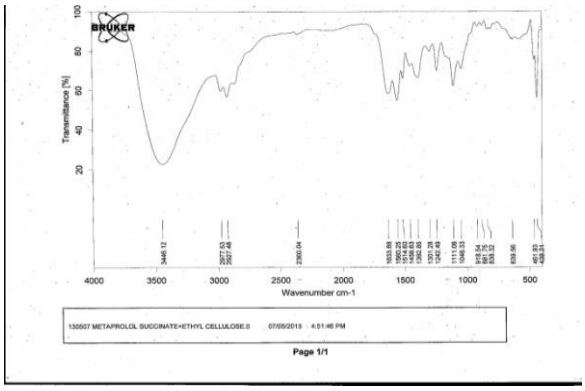


Figure 4: FT-IR studies of Metoprolol succinate+Ethylcellulose



4.4 Determination of absorbance maximum of Metoprolol Succinate in 6.8 ph buffer and Hydrochlorthiazide in 0.1N HCl:

Standard solution of Metoprolol succinate(10µgm/ml) was scanned in the range of 200-400nm and showed maximum absorbance at 222nm

Standard solution of Hydrochlorthiazide(10µgm /ml) was scanned in the range of 200-400nm and showed maximum absorbance at 225nm

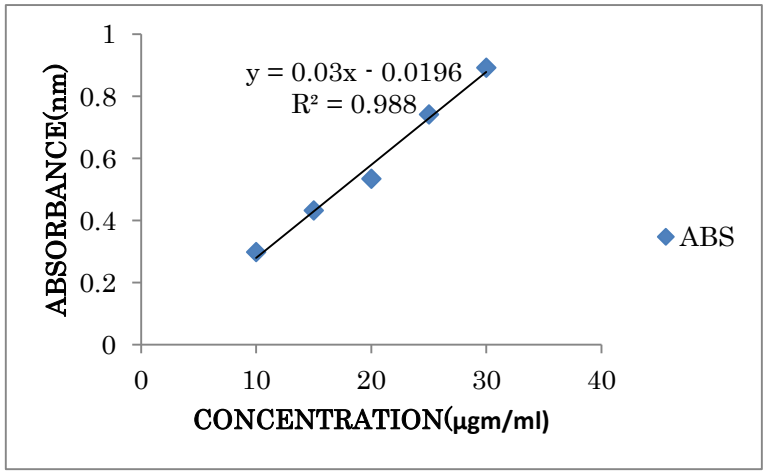
When observed under UV, it was found that specific wavelength was to be taken whose absorbance was maximum.

Standardization

Metoprolol Succinate in 6.8 P^H buffer

Absorbances of the drug solutions containing 10-30ppm of Metoprolol Succinate in phosphate buffer 6.8 was shown in the table.The calibration curve was found to be in the range of 10-30ppm at 222nm with slope,regression of 0.03,0.988.

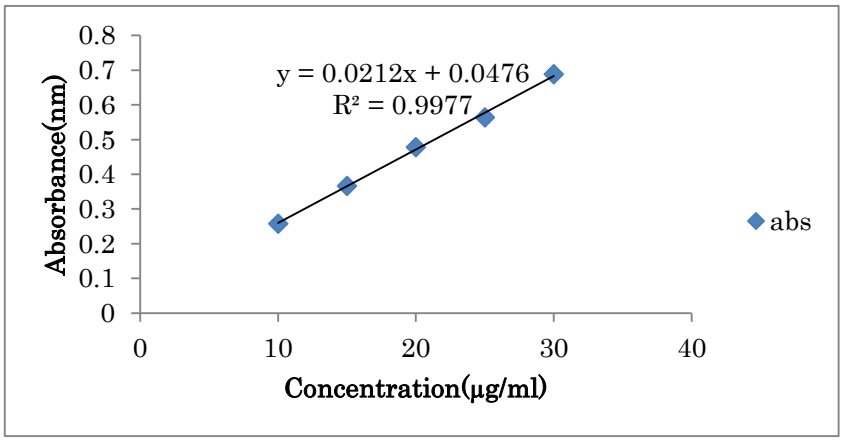
Figure 5 : Standard curve of Metoprolol succinate in 6.8P^H buffer



Metoprolol Succinate in 0.1N HCl

Standard solution of Metoprolol succinate(10µgm/ml) was scanned in the range of 200-400nm and showed maximum absorbance at 222nm.Absorbances of the drug solutions containing 10-30ppm of Metoprolol Succinate in 0.1N HCl was shown in the table.The calibration curve was found to be in the range of 10-30ppm at 222nm with slope,regression of 0.212,0.997.

Figure 6: Standard curve of Metoprolol succinate in 0.1 HCl



Hydrochlorthiazide in 0.1N HCl

Standard solution of Hydrochlorthiazide (10µgm/ml) was scanned in the range of 200-400nm and showed maximum absorbance at 225nm.Absorbances of the drug solutions containing 2-6 ppm of Hydrochlorthiazide in 0.1N HCl was shown in the table.The calibration curve was found to be in the range of 2-6ppm at 225nm .

Figure 7: Standard curve of Hydrochlorthiazide in 0.1 HCl

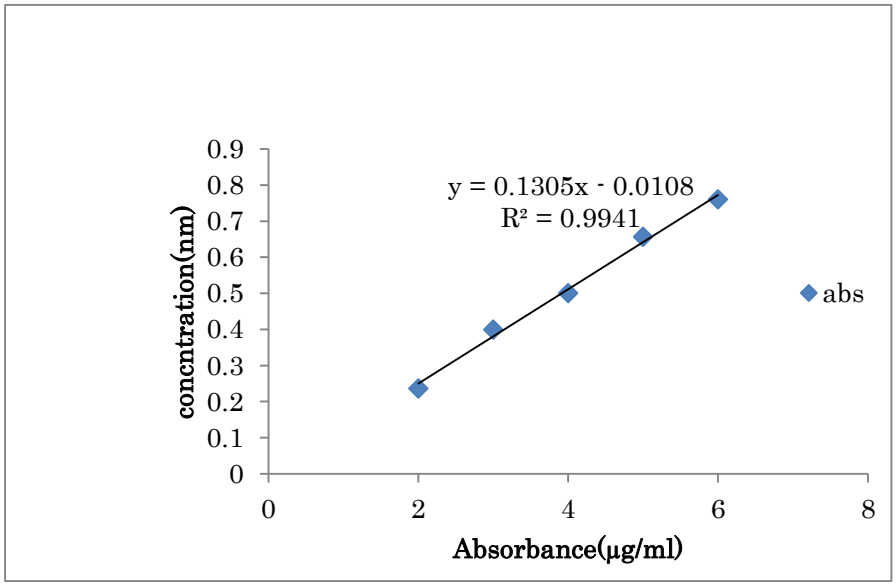


Table 7: Preformulation values of Metoprolol succinate

FORMULATIONS (Metoprolol Succinate)	BULK DENSITYgm/ml	TAPPED DENSITY gm/ml	COMPRESSIBILITY INDEX(%) (5-25)	HAUSNER'S RATIO (1-1.6)	ANGLE OF REPOSE (θ) (25-65)
F1	0.554	0.678	18.367	1.225	23.72
F2	0.534	0.633	15.63	1.184	19.29
F3	0..569	0.68	16.279	1.194	24
F4	0.595	0.677	12	1.136	22.5
F5	0.597	0.66	9.54	1.105	21.6
F6	0.636	0.777	18.14	1.221	27.8
F7	0.462	0.806	42.6	1.744	26
F8	0.51	0.806	42.6	1.58	27.2
F9	0.518	0.611	15.217	1.179	22.4
F10	0.484	0.624	22.5	1.29	21.1
F11	0.485	0.628	22.72	1.294	23.5
F12	0.462	0.644	28.2	1.393	22.1

Table 8: Preformulation values of Hydrochlorthiazide

PREFORMULATION STUDIES	F1(HYDROCHLORTHIAZIDE)
ANGLE OF REPOSE(θ)	30.2
BULK DENSITY(gm/ml)	0.307
TAPPED DENSITY(gm/ml)	0.385
COMPRESSIBILITY INDEX(%)	20.26
HAUSNER'S RATIO	1.25

Table 9: Postformulation values

FORMULATIONS	HARDNESS (kg/sqcm)± SD	FRIABILITY(%)	WEIGHT VARIATION(mg)	ASSAY(%)
F1	4.0±0.17	0.4	179.5	96.5
F2	4.5±0.17	0.41	225	98.01
F3	4.5±0.12	0.27	272.8	98.5
F4	4.5±0.15	0.49	180	96
F5	4.0±0.12	0.45	227.5	97.89

F6	5±0.18	0.21	276	98.03
F7	4.5±0.15	0.39	178.3	97.02
F8	5.0±0.15	0.31	227.5	97.7
F9	4.0±0.16	0.29	276.9	92.8
F10	3.5±0.12	0.45	179.8	95.6
F11	4.5±0.14	0.51	228.8	98.01
F12	4.5±0.18	0.5	275.5	98

Table 10: Dissolution Data (Metoprolol Succinate)

(In hrs) Percentage drug release

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	12.7	15	13.6	13.2	14.6	15.8	17.4	14.5	11.2	14.5	16	13.6
4	38.2	41.4	39.8	38.4	40.6	42	45.4	40.9	37.5	38.6	43	30.2
8	56	61.6	58.1	57.6	61.3	63.7	67.6	59.6	56.5	48.9	64.7	51.4
10	67.8	81.3	74.6	70.12	74.9	80.4	82.9	80.4	76.6	79.01	83.1	78.6
12	92	99.8	94.3	88	95.6	99.9	98	90.9	86	92	99.5	88.4

Figure 8 : Time Vs % drug release of F1,F2,F3

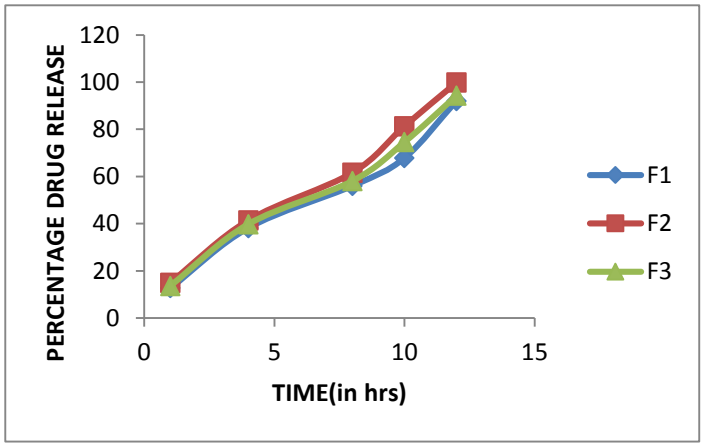


Figure 9 : Time Vs % drug release of F4,F5,F6

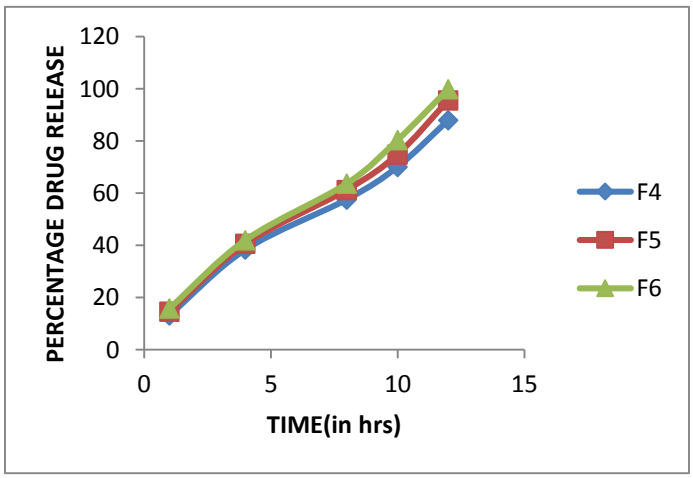


Figure 10: Time Vs % drug release of F7,F8,F9

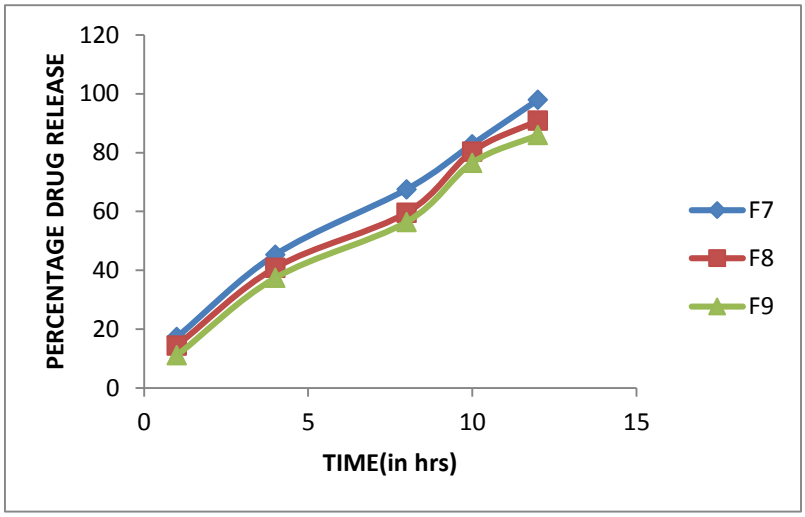


Figure 11:Time Vs %drug release of F10,F11,F12

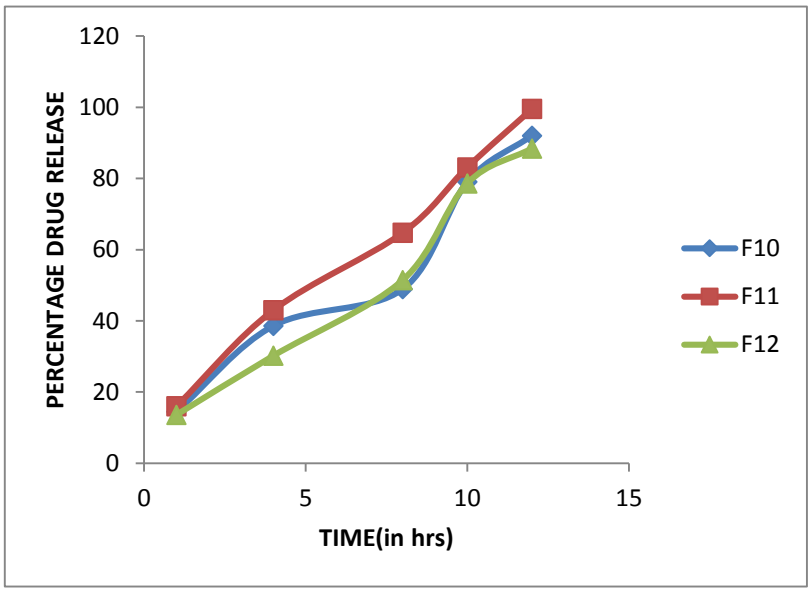


Table 11: Dissolution Data (Hydrochlorthiazide)

TIME (in min)	% Drug release
	F1% (HCTZ)
15	57.53
30	72.48
45	80.14
60	85.31

4.8 KINETIC PROFILE

Table 12: Zero order kinetics- %Drug release verses Time(Metoprolol succinate)

Time(hrs)	F2(%DR)	F6(% DR)	F7(%DR)	F11(%DR)
1	15	15.8	17.4	16
4	41.4	42	45.4	43
8	61.6	63.7	67.6	64.7
10	81.3	80.4	82.9	83.1
12	99.8	99.9	98	99.5

Table 13: First order kinetics-log(100-%Drug release) verses Time

Time(hrs)	F2 log(100-%DR)	F6 log(100-%DR)	F7 log(100-%DR)	F11 log(100-%DR)
1	1.929	1.925	1.916	1.924
4	1.76	1.76	1.73	1.75
8	1.584	1.559	1.51	1.547
10	1.271	1.292	1.232	1.227
12	-0.69	-1	0.301	-0.301

Table 14 : Zero order kinetics- %Drug release verses Time(Hydrochlorthiazide)

TIME (in min)	% Drug release
15	57.53
30	72.48
45	80.14
60	85.31

Table 15: First order kinetics-log(100-%Drug release) verses Time (Hydrochlorthiazide)

TIME (in min)	log(100-% Drug release)
15	1.62
30	1.43
45	1.29
60	1.16

Table 16: Higuchi plot-√Time Verses % Drug release

√Time(hrs)	F2(%DR)	F6(%DR)	F7(%DR)	F11(%DR)
1	15	15.8	17.4	16
2	41.4	42	45.4	43
2.828	61.6	63.7	67.6	64.7
3.162	81.3	80.4	82.9	83.1
3.464	99.8	99.9	98	99.5

Table 17: Hixon crowell plot-√(100-%Drug release)⅓ verses Time

TIME(hrs)	F2√(100-%DR)⅓	F6 √(100-%DR)⅓	F7√(100-%DR)⅓	F11√(100-%DR)⅓
1	4.39	4.38	4.35	4.37
4	3.88	3.87	3.79	3.84
8	3.37	3.31	3.18	3.28
10	2.65	2.69	2.57	2.56
12	0.58	0.46	1.25	0.79

Table 18: Korsmeyer peppas equation-log Time verses log % Drug Release

Log Time	F2(log%DR)	F6(log%DR)	F7(log%DR)	F11(log%DR)
0	1.176	1.198	1.240	1.204
0.602	1.617	1.623	1.657	1.633
0.903	1.789	1.804	1.829	1.810

DISCUSSION

Evaluation of Tablets

The formulation consists of two layers extended release layer of Metoprolol succinate and immediate release layer of Hydrochlorothiazide. Developed trials were taken and evaluated for pre compression and post compression parameters of bilayer tablets.

Extended release layer of Metoprolol succinate

In the present study, the release extended layer of Metoprolol succinate was designed with the dose of 181.5mg,229mg,276.5mg. The granules were prepared by wet granulation technique using HPMC as binder. HPMC K100M and HPMC K4M were used as drug release retardants for extended release layer of Metoprolol succinate, Microcrystalline cellulose was used to balance the weight of the tablet. The weight of Metoprolol succinate layer for all formulations was kept constant at 47.5mg. Bulk Density and tapped density for Metoprolol succinate extended release granules were found to be between 0.462 to 0.636 and 0.611 to 0.806 respectively. Compressibility index and Hausner's ratio were obtained in the range of 12 to 42.6 and 1.105 to 1.744 respectively. Angle of repose was observed in the range of 19°29' to 27°8'. In vitro dissolution study of the formulation containing polymer in different concentration were compared. In formulation, F - 1 to F - 3 the ER layer consist of HPMC K100M and Ethylcellulose, F – 4 to F - 6 the ER layer consist of HPMC K100M and HPMC K4M ,and the weight of the tablet was balanced with Microcrystalline cellulose. The release of drug in F – 2 & F - 6 was found to be within the internal specification limit. F7 toF9 consists of kollidone & EC and F10 to F12 consists of kollidone & HPMC K4M.

Immediate release layer of Hydrochlorothiazide

The immediate release layer of Hydrochlorothiazide was designed with the dose of 12.5mg. The weight of hydrochlorothiazide layer for all the formulations were kept constant at 54mg. Bulk density and tapped density for Hydrochlorothiazide immediate release granules were found to be between 0.307 and 0.385 respectively. Compressibility index and Hausner's ratio were obtained in the range of 20.26 and 1.25 respectively. Angle of repose was observed as 30.2. The results indicate that the granules possessed good flow property and compressibility. Postformulation studies reveal that hardness and friability were found in the range of 4.0-5.0 and 0.21-0.51 respectively.Weight variation was said to be in limits which is not less than 5% and assay valves were in the rasnge of 92.8-98.5.

Dissolution:

The drug release of F2,**F6** ,F7,F11 at the end of 12th hour was found to be 99.8%,**99.9%,**98%,99.5% for Metoprolol succinate and 85.31% for hydrochlorothiazide at 1 hour. The drug release of optimized formulations were found to be increased when compared with the standard drug.

Release kinetics study for optimized bilayer tablet

The kinetics of drug release was determined based on korsmeyer - peppas equation obtained by in vitro dissolution data to various kinetics models. Accordingly the R^2 value of F2,**F6**,F7,F11 were found to be 0.9874,**0.9903**,0.993,0.9923 respectively for Zero order for Metoprolol and **0.942** for

Hydrochlorthiazide, 0.793,**0.8774**,0.776,0.6686 for first order for Metoprolol and **0.992** for Hydrochlorthiazide ,0.9607,**0.9664**,0.985,0.9783 for Higuchi, 0.9966,**0.9985**,0.9979,0.9979 for korsmeyer-peppas and 0.8006,**0.7884**,0.9028,0.8435 for Hixson-crowell cube root plot. The n value of korsmeyer peppas was found to between 0.658-0.6865.Hence the formulation follows zero order kinetics with anomalous diffusion or non fickian diffusion.

Table 19:R^2 values

Formulation	R^2	R^2	R^2	R^2	R^2	
	Zero order	First order	Higuchi	Hixon crowell	Korsmeyer peppas	N
F2	0.9874	0.798	0.9607	0.8006	0.9966	0.6865
F6	0.9903	0.8774	0.9644	0.7884	0.9985	0.6761
F7	0.993	0.776	0.985	0.9028	0.9979	0.658
F11	0.9923	0.6686	0.9733	0.8435	0.9989	0.677

From the above results and discussions, I have observed that F-6 was found to be optimized and has passed the prescribed limits for pre and post for formulation studies with a dissolution rate of 99.9%.

Table 20: Data of optimized formulation F-6

Preformulation studies	**Metoprolol succinate**	**Hydrochlorthiazide**
Bulk density(gm/ml)	0.56	0.307
Tapped density(gm/ml)	0.6	0.385
Carr's index(%)	14.8	20.26
Hausner's ratio	1.1	1.25
Angle of response(^{o})	27.8	30.2
Post formulation studies		
Hardness(kg/$cm^{2)}$	5	
Friability(%)	0.21	
Weight variation	276	
Dissolution (%)	99.9	
Kinetic profile	**R^2**	
Zero order	0.9903	0.942
First order	0.8774	0.992
Higuchi equation	0.9644	
Hixon crowell equation	0.7884	
Korsemeyer-peppas equation	0.9985(**n**=0.6761)	

4. CONCLUSION

Metoprolol succinate extended release/hydrochlorothiazide (metoprolol ER/HCT) tablets lower blood pressure in hypertensive patients. The blood pressure reductions are dose related and represent additive antihypertensive contributions from the component agents. The likelihood of controlling elevated blood pressure with the combination product is greater than with the component agents employed as monotherapies, even in patients with more severe levels of hypertension. The combination also provides an option to treat with lower doses of the individual agents. Metoprolol ER/HCT is generally well tolerated, reflecting the characteristics of the components, but it also reflects the same safety profiles including the admonition to avoid abrupt cessation of treatment in patients with or at risk for underlying coronary artery disease. Physicians might also consider that low dose combination products provide an option to intervene with well-tolerated treatments early in the course of hypertension and might well help patients avert more intractable hypertension. Certainly, this combination approach expands the population likely to respond to antihypertensive therapy compared with single agent treatment. It included about the hypertension disease profile,description about the drugs Metoprolol succinate and Hydrochlorthiazide, knowing about tablet dosage form and advantages of bilayer tablets over conventional dossage form,importance of present combination and objective of present projectIt shows the abstracts of different articles and journals collected in order to give an idea for the present title. done including selection of raw materials, compatability studies, preformulation studies, manufacturing of bilayer tablet, postformulation studies, invitro dissolution, kinetic profiles etc. the results obtained such as values of preformulation studies, postformulation studies,values and graphs of dissolution data,zero & first order kinetics, higuchi, hixon-crowell, korsmeyer and peppas plots and regression values of the kinetics studies.

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CONFLICT OF INTEREST

Authors have no conflicts of interest.

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