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LISINOPRIL AS IMMEDIATE RELEASE AND METOPROLOL AS SUSTAINED RELEASE BILAYERED TABLETS: FORMULATION AND EVALUATION

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Abstract:

The development of a logical diagnostic strategy for drug estimate is the focus of this work. Pre-detailed consideration is given to readings of drug excipient similarity for excipient determination. making tablets using different polymers for drug delivery. to assess the pre- and post-pressure parameters of the detailed tablets. Analysis of the selected scheme's stability. Metoprolol, lisinopril, and the drug excipients blend were visible in the IR range. It was determined in the current analysis that there is no compound interaction between metoprolol, lisinopril, and the polymers used. It can be seen from the figure that there were no changes to these principal tops in the IR spectra of the mixture of drugs and polymers, suggesting that there were no physical interactions as a result of some bond creation between the drugs and polymers. This further supports the reliability of pure medication and the similarities between them and excipients.

Keywords: Lisinopril, Metoprolol, Bilayer Tablet, IR Spectra, Immediate release tablet.

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INTRODUCTION:

The rise of an upgraded method of drug delivery system has received a lot of recognition in the last 20 years. The basic logic for controlled drug delivery is to alter the pharmaco- dynamics and pharmaco-kinetics of pharmacologically active compound by use of new drug delivery systems and pharmacological parameters essential in the selected route of introduction. Rate controlled dosage form less or not at all, a property of the drug molecules inherent kinetic properties. Thus, the design of controlled release systems necessity is a thorough understanding of the pharmaco-kinetics and pharmacodynamics of the drug Lisinopril Dehydrate. It has been employed as a pharmaceutical active agent for the treatment of hypertension. It shows high solubility in gastric pH and rapid fall in intestinal pH. The biological half-life is 12 hours. The dosing regimen is twice or four times a day. The amount of blood the heart pumps and the amount of resistance to blood flow in the arteries both have a role in the abnormal condition of the heart known as hypertension. A single dose of Lisinopril Dehydrate to a certain plasma profile is preferred for the treatment of hypertension, which may require ongoing medication delivery to the heart. It is required to design an osmotically controlled release tablet of lisinopril dehydrate because a conventional formulation may require a high dosing frequency to keep the medicine within the therapeutic concentration. A beta-selective adrenergic receptor antagonist called metoprolol is used to treat a variety of cardiovascular conditions. The current study's goal was to create several Metoprolol formulations for immediate and sustained release.The medicine Metoprolol tartrate was chosen because it reaches its peak plasma concentration after 1.5 to 2 hours of an oral dose, but because of its short half-life (between 3 and 4 hours), the therapeutic plasma concentration can only be sustained if Metoprolol tartrate is used often.
Due to the absence of an initial bolus dose, sustained release formulations are unable to deliver immediate relief. Metoprolol tartrate is a good choice for the formulation of bi layer tablets due to these properties. Preparing a bilayer tablet of metoprolol tartrate that has both an immediate release layer and a sustained release layer is necessary (SRL). Therefore, the primary goal of this research was to create various Metoprolol Tartrate Immediate and Sustained Release formulations and choose the most effective formulation for making bi-layer tablets. There are several researcher worked on formulation and evaluation of bilayer drug delivery system.(1,2,3,4,5,6,7).

This work refers to the creation of a logical diagnostic plan for drug estimation. Drug excipient similarity readings for excipient determination are a pre-detailed consideration. preparation of tablets using various polymers for drug delivery. to evaluate the detailed tablets' pre- and post-pressure parameters. Stability analysis of the preferred scheme.

METHODOLOGY:

1. Formulation Development:

Bi-layer tablet preparation:

- Preparation of Immediate release layer of Lisinopril by the method of direct compressoin.
- Preparation of Sustain release Layer of Metoprolol by method of wet granulation.

2. Evaluation Studies:

Evaluation of granules

- Determination of bulk density and tapped density

Evaluation Of Tablet: Thick-ness, Hardness, Friability, Weight variation, Content Uniformity, Swelling Study, In-vitro Release Study

3. Stability Study:

Preparation of Immediate Layer of Lisinopril by Direct Compression Method

Steps to be followed-Weigh all the ingredients in essential amount, Transfer all ingredients into a mortar, triturate for 10minutes pending to get fine particles and sieve the material. (#60),Then transfer the substance into mixer for proper distribution of treatment in blend for10minutes.Then calculation of lubricant is done, mix fine, Then perform the micrometric properties (Pre-compression studies) lastly compression is done.

Table-1: Composition Of Lisinopril

S. No.	(INGREDIENTS)	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
1	Lisinopril	20	20	20	20	20	20	20	20
2	(SSG)Sodium Starch Glycolate	4	6	8	--	--	--	--	--
3	HPMC	--	--	--	4	66	8	--	--
4	Ethyl cellulose	--	--	--	--	--	--	4	6
5	(MCC)Microcrystalline cellulose	73	71	69	73	71	69	73	71
6	Yellow Ferric oxide	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
7	Aerosil-200	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
8	Magnesium stearate	2	2	2	2	2	2	2	2
	Total Weight	100	100	100	100	100	100	100	100

Preparation of Sustain release Layer of Metoprolol by Wet Granulation Method:
The tablets each containing 500mg of Metoprolol were made by method of wet granulation. The manufacturing process involves following steps they were

1) **Sifting:** Drugs, super disintegrating agents, (MCC) and diluents are sifted using #40 meshsieve (stage 1).

2) **Preparation of Binder**

3) **Granulation**

a) **Dry mixing:** The drug and diluents after stage 1(one) were mixed properly to ensure the uniformity of premix blend, several drug diluents were taken with selected ratio of super disintegrating agents(s) which were previously sifted using #60 mesh for 5 min and then premixes were mixed.

b) **Granulation:** Granules were made by adding binding and granulation and the wet masswere passed through sieve no.#18.

c) **Drying:** The produced granules were dried at 50°C -60°C for 60 min in a hot-air oven.

4) **Sizing:** Dried granules of Metformin Hcl are passed through 20 mesh sieves.

5) **Lubrication:** These granules were blended with lubrication mixture (sodium sterylfumarate and aerosil) for 5min in polythene bag.

6) **Compression:** After the lubrication granules went for compression using 16 station rotary tablet machine, equipped with round punches of 8.7 mm diameter and flat-face

Table-2: COMPOSITION OF METOPROLOL

S. No.	(INGREDIENTS)	A1	A2	A3	A4	A5	A6	A7	A8	A9
1	Metoprolol	500	500	500	500	500	500	500	500	500
2	Methocel 40-101	50	100	--	--	--	--	50	50	--
3	Methocel k15m pcg	--	--	50	100	--	--	50	--	50
4	Microcrystalline Cellulose	95	55	95	55	95	55	55	55	55
5	Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
6	Sodium Steryl fumarate	3	3	3	3	3	3	3	3	3
7	Talc	2	2	2	2	2	2	2	2	2
	Total Weight	650	650	650	650	650	650	650	650	650

To determine tap density and bulk density

a) Bulk Density

Bulk density is defined as the powdered mass divided by volume of bulk.Following equation can be used for its calculation:

Weight of sample taken× 1 /Noted Volume = Bulk density

b) Tap density

A precisely weighed amount of powder (W) was poured into the graduated cylinder and measurement of volume was noted.

Weight of sample taken×1 / tapped volume

here,

Final volume = (Vf) Initial volume = (V0) **Tablet EvaluationVariation of weight**

20 tablets were randomly picked by each batch and individually weight is measured. Theaverage weight and standard-deviation of 10+10 (20) tablets were calculated.

Thickness

20 tablets were randomly picked from each batch and there width or thick-ness was measuredby using the instrument (vernier caliper). After measuring mean was found out from thickness of 3 tablets from each batch.

Hardness

Hardness means the ability of a tablet to tolerate mechanical shocks or wear and tear during handling. Monsanto hardness tester was used to test the hardness of the tablets. . It was expressed in kg/cm2. 3 tablets were randomly selected and hardness of the tablets were to bedetermined.

Friability

- To evaluate the effect of shock and friction friability test is performed, which may often cause tablet to break,chip or cap. For this Roche-friabilator was used.
- 20 tablets were picked, weighed and placed in the Roche-friabilator, where the operation was carried out for 4 minutes at 25 rpm. Tablets were de-dusted and weight is measured again after revolution. Compressed tablets should not loose more than 1% of their weight.

Uniformity of Content

- From each batch 20 tablets were taken and crushed into powder and weighed precisely equivalent to 0.1 g bi-layered tablet. Then dissolve the weighed powder into 0.1 L of 0.1 NNaOH solution by stirring it for atleast 12-15 minutes.
- 1 ml of solution was pipetted into 10 mililitre volumetric flask, and 1 mililitre of 5% Ninhydrin solution was added, boiling is done for 3 minutes to this solution, then leave it for cooling, atlast distilled water is added to make up to the volume.
- By using reagent blank immediate analyzing is done by taking the drug absorbance at suitable wavelength.

***In- Vitro* Release study-**

- By using Tablet dissolution test apparatus in-vitro drug release studies were carried out USPat 50 rpm. The dissolution medium contained 900 ml of Standard buffer pH 1.2 for the first 120 minutes, and pH 7.4 for remaining period of time.

- Temperature maintained at 37ºC then sample of 5 mililitre was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced.

- From that 5 mililitre sample, 1 ml sample was taken out and kept in a 10 ml volumetric flask, to it add 1 ml of 5 % Ninhydrin solution and 1 ml of 0.1 N NaOH solution, boil it for180 second at water bath, cooling is done in room temperature and the volume is made up with distilled water.

- At suitable wavelength the diluted samples were assayed.

Swelling study

- Due to liquid absorption by the tablet it gets swelled which results in increase in volume and

RESULTS & DISCUSSION:

weight. Due to saturation of spaces between capillary or macromolecules, liquid uptake takes place.

- Binding with large molecule takes place when the introduction of liquid takes place bypores. Which results in breaking of hydrogen bond and particle swelling takes place.

- The increasing in size of swelling can be calculated in terms of percentage weight gained bythe tablet.

- One tablet was weighed for each batch and placed in a Petri dish containing 0.025 L of 6.8buffer pH solution. After some interval the tablet was picked from beaker and removal of extra amount of buffer is done by the use of filter paper. Weighing is again done up to 10-13hours.

Stability studies:

- Stability studies evaluates the success of an effective product or formulation.

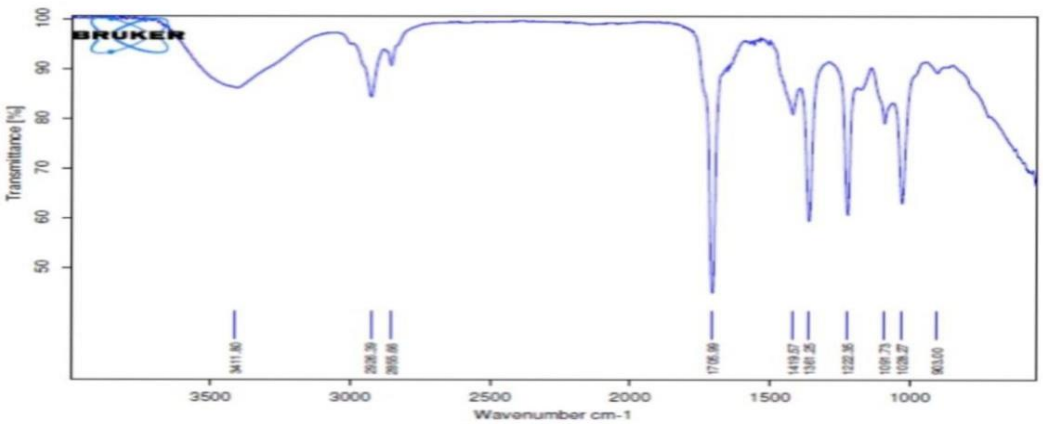
- The previously made bi-layered tablets were placed on tubes of plastic containing desiccant and stored in ambient condition, Like at room temperature, 38ºC-42º C and in fridge at 2-8ºC for a 3 months period.

Table-3: API Characterization of Lisinopril

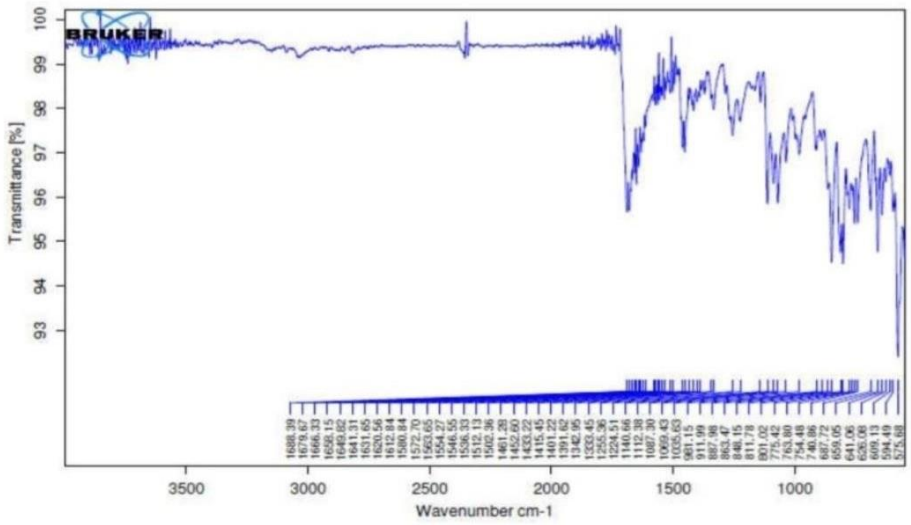
S. No.	API Characterization	RESULTS
1	Physical Appearance	White to pale white,crystalline powder
2	Taste	Tasteless
3	Smell	No smell
4	Melting point	160°C
5	Solubility	Its soluble, sparingly soluble and partially soluble in water, methanol and ethanolrepectively.

Table-4: API Characterization of Metoprolol

S. No.	API Characterization	RESULTS
1	Physical Appearance	White
2	Taste	Taste-less
3	Smell	No smell
4	Melting point	120°C
5	Solubility	It is freely soluble in water; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2- propanol; practically insoluble in ethyl-acetate, acetone, diethyl ether and heptane.



Fourier Transformation Infra-red (FTIR) analysis of Lisinopril
(Fig-3)



(Fig-4)

Table-5: Characteristic Peaks and frequency of pure drug

Wave no. (cm-1)	Functional group	Pure drug
1500-2000	C-H Bending	1144 cm-1
1000-1500	C=C Stretch	1069 cm-1
1000-1500	C=O Stretch	775 cm-1
1000	C-H Stretch	609 cm-1

DISCUSSION: The Characteristic stretching of NH-OH at 3199cm-1 confirmsthe presence of Lisinopril.

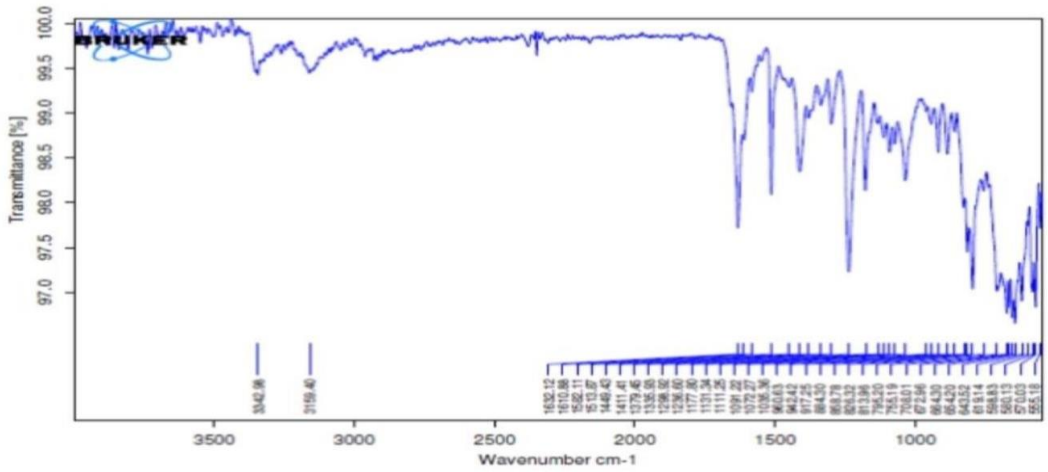
Fourier Transformation Infra-red (FTIR) analysis of Metoprolol

Table-6: Characteristic Peaks and frequency of pure drug

Wave no. (cm-1)	Functional group	Pure drug
3500-3000	C-H Bending	3411 cm-1
3000-2500	C=C Stretch	2928 cm-1
2000-1500	C=O Stretching	1726 cm-1
1500-1000	C-H Stretch	1028 cm-1

DISCUSSION: The presence of N-H primary and secondary stretching andcharacteristic C-N stretching confirms Metoprolol drug.

FT-IR graph for Bi-layer optimized formulation



(Fig-5)

Table-7: Characteristic Peaks for optimized formulation

S. No.	CharacteristicsPeaks	Frequency Range (cm-1)	Frequency (cm-1)
1	OH Stretching	3500-3000	3342.98
2	OH Bending	1000-1500	858.36
3	C-H Stretching	2500-2000	1610.25

DISCUSSION:

The IR range of Metoprolol , Lisinopril and Drug Excipients blend was appeared. In the current investigation, it had been concluded that there is not any compound cooperation between Metoprolol , Lisinopril and thepolymers utilized.From the fig. it was seen that there were no adjustments in these primary topsin IR spectra of blend of medication and polymers, which appear there were no physical collaborations as a result of some bond development among medication and polymers.This further affirms the trustworthiness of unadulterated medication and similarity of them with excipients.

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