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FORMULATION OF LOSARTAN AND HYDROCHLOROTHIAZIDE ORODISPERSIBLE TABLETS FOR IMMEDIATE ONSET OF ACTION BY USING SUPER DISINTEGRANTS

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ABSTRACT

The objective of this research was to formulate an immediate release tablets containing combination of Losartan and Hydrochloro thaizide for rapid action , by using a suitable binders and super-disintegrants.Faster disintegration of the tablet administrated orally minimizes absorption time and improves its bioavailability in less time. The main aim of IR technology is to achieve improved bioavailability, rapid onset of action, chemical stability and patient convenience and compliance. The tablets were prepared by direct compression and FTIR studies indicates that there were no incompatibility between the drugs losartan ,hydrochlorthiazide and formulation excipients.among the different formulations F7 was found to be optimed formulae which faster rate of drug release with increased bioavailability thus combination of losartan and hydrochlorthiazide were effectively formulated

KEYWORDS: losartan, hydrochlorthiazide, FTIR, superdisintegrants.

INTRODUCTION

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, ease of administration lead to high levels of patient compliance.

Fig 1: Fast dissolving tablets (1)

Fast-disintegrating and fast-dissolving tablets are becoming popular as novel delivery systems for drug administration. They are more convenient for children, elderly patients, patients with swallowing difficulties, and in the absence of potable liquids. The most desirable formulation for use by the elderly is one that is easy to swallow easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-disintegrating dosage forms.[1,2]

Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution.[2,3] Combination of losartan and hydrochlorthiazide and is used for treating high blood pressure. Losartan is an oral medication that belongs to a class of drugs called angiotensin recptor blockers (ARBs). Losartan (more specifically, the chemical formed when the liver converts the inactive losartan into an active chemical) blocks the angiotensin receptor. By blocking the action of angiotensin, losartan relaxes the muscles, dilates blood vessels and thereby reduces blood pressure.[4]

MATERIALS AND METHODS

Losartan and hydrochlorthiazide were received as gift samples from hetero labs and avicel ph 102, cross caremellose sodium, magnesium sterate, starch, pvp k 30 all of analyticl grade obtained from merck specialities pvt ltd, Mumbai, india.

METHODOLOGY

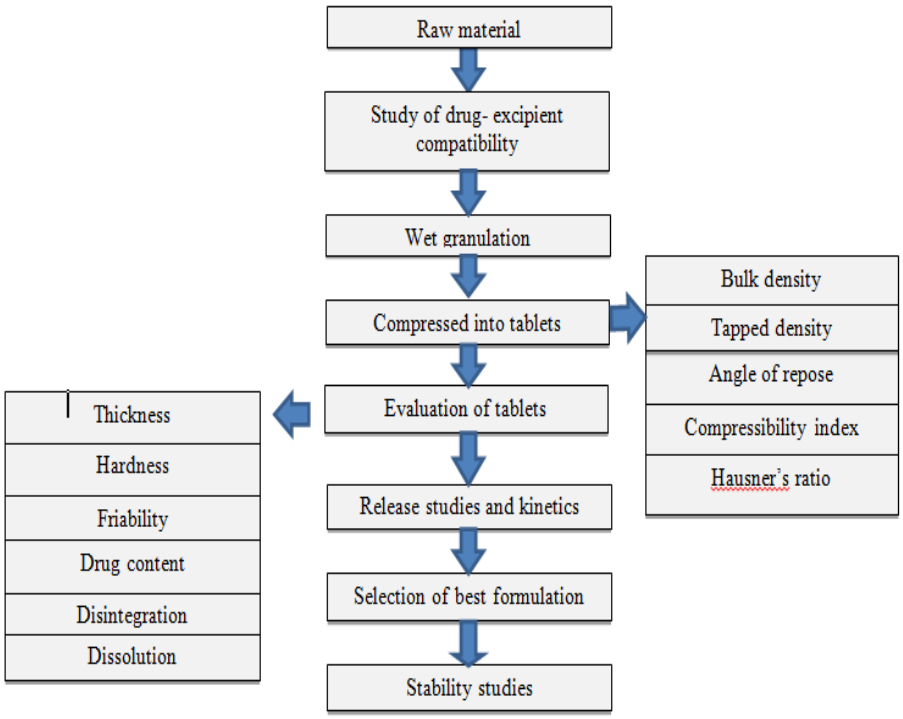

Fig: 2 Flow chart representing the process involved in the preparation of tablets[5]

Flow Properties

Bulk density

Bulk density was determined by pouring gently 20 gm of sample through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density = weight of sample in gram /volume occupied by the sample

Tapped density

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%. A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and taped density is calculated using following formula.

Tapped density = Wt. of sample in gm / Tapped volume

Compressibility Index and Hausner ratio

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the Compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

Relation of flow property with HR & CI

C.I=tapped-untapped*100/tapped.

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Angle of Repose

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose= $\tan^{-1}$ (h/r)

Where,

h = height of a pile (2 cm)

r = radius of pile base.

Fourier Transform Infrared Spectroscopy (FTIR) Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

DEVELOPMENTOF CALIBRATIONCURVE FOR HYDROCHLOROTHIAZIDE

Hydrochlorothiazide was weighed accurately100mg using digital analytical balance and transferred to 100 ml volumetric flask,dissolved in water and the final volume was made upto100ml with0.1NHcl to get a stock solutionA.From the stock solutionA,10 ml was pipette outin 50ml volumetric flask and the final volume was made upto 50ml with hydrochloricacid(Hcl)buffer of pH 1.2 to get a stock solutionB.From the stock solution

B,further dilution was made with hydrochloric acid buffer of 0.1NHcl in10ml volumetric flasks to get the solutions in the range of 2-12µg/ml concentration and absorbance was recorded at 258nm against suitable blank using UV-Visible spectrophotometer.

FORMULATION DEVELOPMENT

Direct compression

Accurately weighed amounts of drug, polymer, disintegrants and diluent were mixed geometrically in a mortar. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate and for 2 minutes and compressed into tablets on a 16-station rotary tableting machine using 9mmround, flat-faced punches.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations.

Table: 1 Formulation

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Losartan	25	25	25	25	25	25	25
Hydrochloro thiazide	12.5	12.5	12.5	12.5	12.5	12.5	12.5
PVPK 30	12.5	12.5	--	--	12.5	12.5	12.5
Starch	--	--	12.5	12.5	--	--	--
CCS	12.5	--	12.5	--	--	--	--
CP	--	12.5	--	12.5	18.75	25	31.25
Talc	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Magnesium stearate	6.25	6.25	6.25	6.25	6.25	6.25	6.25
MCC	175	175	175	175	168.75	162.50	156.25
Total weight	250	250	250	250	250	250	250

EVALUATION OF TABLETS[9]

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

Physical appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Hardness

The force required to break the tablet is measured in kilograms. The small and portable hardness tester measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet.

Tablet size and Thickness

The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers.

Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

The percentage friability was determined by the formula
% Friability = $(W_1-W_2) / W_1 X 100$
W_1 = Weight of tablets before test
W_2 = Weight of tablets after test

Weight variation of Tablets

All the prepared tablets of Naratriptan were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits.[10]

Disintegration test

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time in-vitro and in-vivo, several methods were proposed, developed and followed at their convenience. One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2^{o}c and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

DISSOLUTION TEST

Dissolution

It is the amount of the solid substance that goes into the solution per unit time under standard conditions of the temperature and pressure.

- **METHOD**

Dissolution media was taken as 0.1N HCL, 900ml was placed in the vessel and the USP apparatus –II (paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 ± 0.5°C. Tablet was placed in the vessel, the apparatus was operated for 60min at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed using UV. The absorbance of solution was recorded at 234nm and 256nm using buffer as blank.The result was calculated as Percentage drug release of Losartan and Hydrochlorothaizide.

STABILITY STUDIES[10]

FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human life.The ICH tripartite guidelines have established long term stability testing to be done at 25^0C/60%RH for 12 months. Accelerated stability testing should be done at 40^0 C/75%RH for 6 months and stability testing at intermediate storage conditions should be done at 30^0C/65%RH. The following table shows different storage conditions and period of stability testing.

Table 2: ICH Guidelines for stability study

Study	Storage Condition	Duration
Long term	25±2°C, RH 60±5%	12 months
Intermediate	30±2°C, RH 65±5%	6 months
Accelerated temperature	40±2°C, RH 75±5%	6 months

RESULTS AND DISCUSSIONS

SPECTROSCOPIC STUDIES[7]

Determination of λ max

A solution of 10µg/ml of Losartan potassium was scanned in the range of 200 to 400nm. The drug exhibited a λmax at 234 nm in 0.1N HCl and had good reproducibility.Correlation between the concentration an d absorbance was found to be near to 0.999, with a slope of 0.0608 and intercept of 0.0134.

Calibration curve of Losartan potassium inpH0.1N Hcl

Table 5.1 shows the calibration curve data of Losartan potassium in pH 0.1N HCl at 234nm. Fig. 5.2shows the standard calibration curve with a regression value of 0.999, slope of 0.0608 and intercept of 0.0134in simulated gastric fluid pH 0.1N Hcl. The curve was found to be linear in the concentration range of 2-12µg/ml.

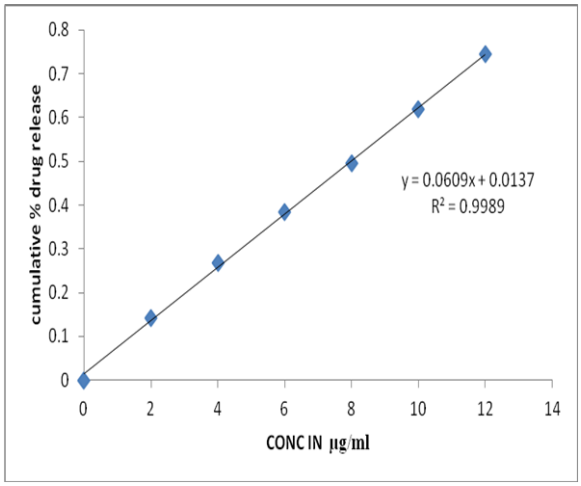

Figure 3: Standard graph of Losartan potassium in 0.1N Hcl

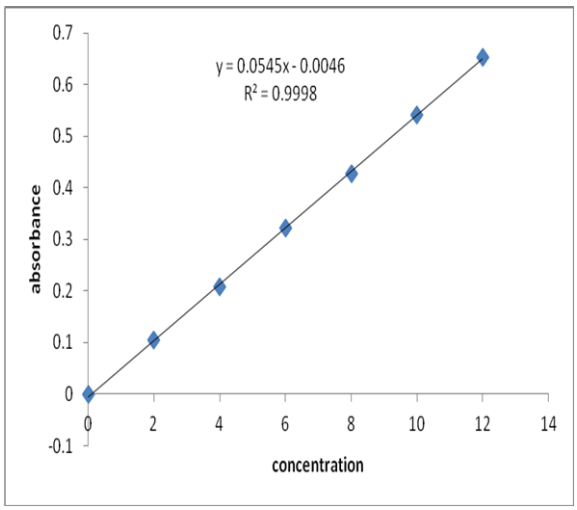

Fig no-3 calibration curve of Hydrochlorothiazide at 258nm

DRUG EXCIPIENT COMPATIBILITY STUDIES

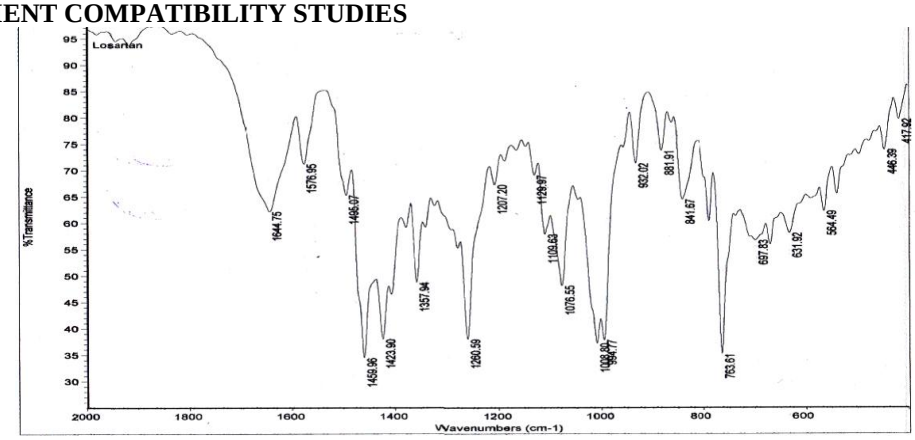

Fig no 4: FTIR Spectra of Losartan

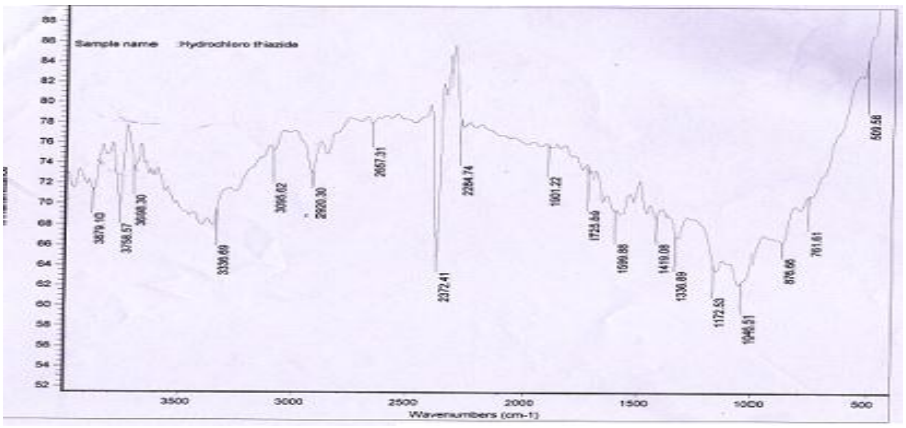

Fig no 5: FTIR Spectra of Hydro chlorothiazide

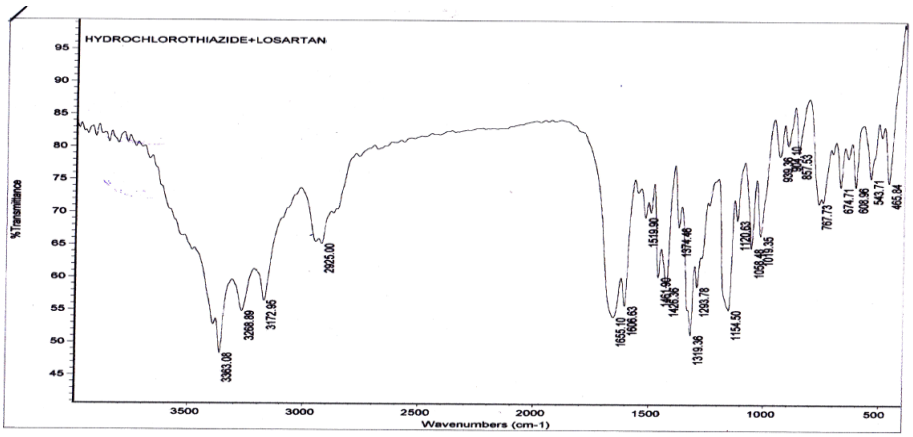

Fig no 6: FTIR Spectra of Hydrochlorothaizide + Losartan optimized formulation

Evaluation of Blend

Table: 3. Bulk density, Tapped density, % Compressibility index, Hausner ratio and Angle of repose. (Precompression studies).

Formulation code	Bulk density (gm /ml)	Tapped density (gm/ml)	Hausner ratio	Carr's index (%)	Angle of repose (θ)
F1	0.541	0.691	1.276	16.62	34^0
F2	0.484	0.615	1.27	14.30	33^0
F3	0.710	0.873	1.251	12.714	31^0
F4	0.712	0.870	1.206	15.126	32^0
F5	0.718	0.871	1.223	14.513	30^0
F6	0.410	0.483	1.178	15.113	32^0
F7	0.420	0.462	1.131	15.010	35^0

Evaluation of Tablets

Table 4:Post compression studies

Formulation code	Weight variation	Hardness (kg/cm^2)	Friabilty (%)	Thickness (mm)	Content uniformity	Disintegration Time (min)
F1	248	6.4	0.72	2.6	99.28	3.1
F2	249	6.3	0.68	2.6	97.16	2.6
F3	249	5.8	0.69	2.7	101.1	2.4
F4	248	5.6	0.66	2.75	97.68	2.7
F5	248	5.7	0.68	2.6	99.41	2.3
F6	250	6.4	0.65	2.62	98.19	1.4
F7	250	6.0	0.63	2.6	100.6	1.0

In -vitro drug release study

Table 5: Dissolution Values

Time	F1		F2		F3		F4		F5		F6		F7	
(Mn)	L	HCT	L	HCT	L	HCT	L	HCT	L	HCT	L	HCT	L	HCT
5	13.36	8.60	20.0	11.86	15.78	9.80	25.0	14.81	30.64	15.92	33.80	14.70	48.90	15.80
10	25.60	17.91	33.14	28.62	28.89	19.76	48.71	32.40	52.10	38.60	59.10	32.21	64.71	45.66
15	33.38	21.71	50.31	40.18	38.90	30.32	56.61	43.31	65.64	58.9	67.20	60.01	81.18	62.86
30	56.67	38.84	68.76	6315	67.72	43.40	70.68	64.32	75.51	70.14	80.0	72.60	97.20	77.41
45	60.01	59.94	76.51	69.09	74.40	63.13	81.14	71.05	82.63	78.80	93.67	81.44	--	80.70
60	79.89	68.80	80.04	79.46	82.0	77.49	86.60	87.70	87.50	88.06	--	90.0	--	96.64

L (Losortan) And Hct (Hydrochlorthiazide)

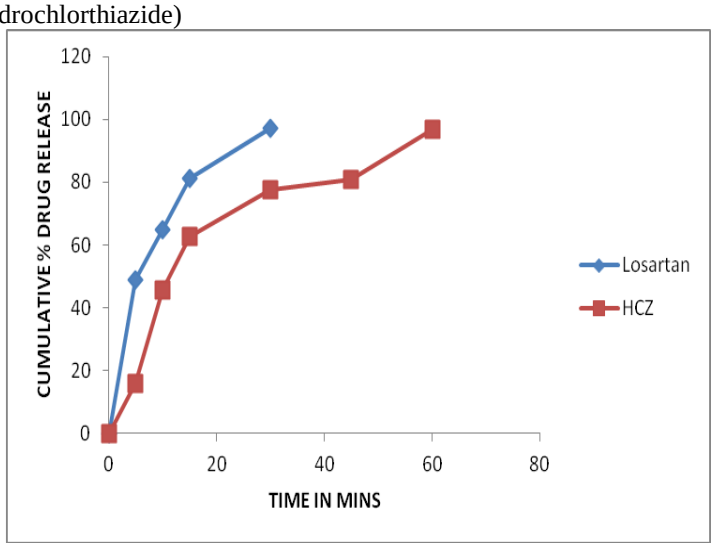

Figure 7. Cumulative % drug released formulations F7

Stability Studies

There was no significant change in physical and chemical properties of the tablets of formulation F-7 after 3 Months. Parameters quantified at various time intervals were shown.

Table 6 Results of stability studies of optimized formulation F-7

S.NO	Parameters	Initial	1 month	2 month	3 month	Limits as per specification
1	40^0C/75% RH % Release	100.6	99.52	97.79	96.56	Not less than 85 %
2	40^0C/75% RH Assay Value	100.6	99.96	96.22	96.00	Not less than 90 % Not more than 110 %

CONCLUSION

In the present work, immediate release tablets of containing combination of Losartan and Hydrochloro thaizide for rapid action were prepared by direct compression method. All the tablets were subjected to weight variation, drug content uniformity, and hardness,

and friability, disintegration time, dissolution, drug excipients interaction and short-term stability studies. Formulation F7 showed good results than rest of the formulations in pre and post compression studies.The average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared. Formulation F7 displayed maximum drug release which shows Losartan drug release of 97.2 % in 30min and Hydro chlorothaizide drug release of 96.64% in 60mins.IR-spectroscopic studies indicated that there are no drug–excipients interactions.

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