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Research Article

FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM AND HYDROCHLORTHIAZIDE CONVENTIONAL RELEASE TABLETS

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ABSTRACT:
The losartan potassium and hydrochlorthiazide tablets are prepared by using low substituted HPC as disintegrant. The addition of diuretics to angiotensin II receptor blockers will potentiate the action of angiotensin receptor blockers. The tablets are formulated using wet granulation technology using purified water as granulating agent. The tablets are evaluated for their weight, thickness, hardness, friability, disintegration and dissolution. A total of seven batches are punched and the first six are rejected as they do not complied with the specifications and the seventh batch is complied with all the specifications. The disintegrant used in the innovator product is croscarmellose and the disintegrant in the present study is low substituted hydroxy propyl cellulose. The dissolution profile of the optimised batch is compared with the innovator and the percentage drug release of the innovator product is 97% but it is increased to 99% as the disintegrant is changed.

KEYWORDS: Losartan Potassium, Hydrochlorthiazide, Diuretics, Disintegrant.

INTRODUCTION

The oral route of drug administration is the most important route of administering drugs for systemic effect. About 90% of drugs used to produce systemic effects are administered by oral route. When a new drug is discovered one of the first questions a pharmaceutist asks is whether or not the drug can be effectively administered for its intended effect by the oral route.

The drugs that are administered orally, solid oral dosage form represent the preferred class of products. The reasons for this preference are as follows. Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self administered by the patient.

Method of preparation of tablet:

Wet granulation:

Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction. The wet granulation technique employs a solution, suspension, or slurry containing a binder, which is usually added to the powder mixture; however, the binder may be incorporated dry into the powder mix, and the liquid may be added by itself. The method of introducing the binder depends on its solubility and on the components of the mixture. Since, in general the mass should merely be moist rather than wet or pasty, there is a limit to the amount of solvent that may be employed. Therefore, when only a small quantity is permissible, the binder is blended in with the dry powders initially; when a large quantity is required, the binder is usually dissolved in the liquid. The solubility of the binder also has an influence on the choice of methods, since the solution should be fluid enough to disperse readily in the mass. The liquid plays a key role in the granulation process .liquid bridges are developed between particles, and the tensile strength of those bonds increases as the amount of liquid added is increased. These surface tension forces and capillary pressure are primarily responsible for initial granule formation and strength. Once the granulating liquid has been added, mixing continues until a uniform dispersion is attained and all the binder has been activated. During granulation, practices and agglomerates are subjected to consolidating forces by action of machine parts and of inter particulate forces. Granulation in large blenders requires 15min to an hour. The length of time depends on the powder mixture and the granulating fluid, and upon the efficiency of the mixer. A rough way of determining the end point is to press a portion of the mass in the palm of the hand; if the ball crumbles under moderate pressure, the mixture is ready for the next stage in processing, which is wet screening. Granulation may be considered as a size enlargement process during which small particles are formed into larger, physically strong agglomerates in which original particles can still be identified. High shear forces in high speed mixers are widely used in the pharmaceutical industry for wet granulation. Processing parameters were shown to affect the growth rate of granules in the high-shear wet granulation. The main objective of granulation is to improve flow properties and compression characteristics of the mixture to prevent segregation of the constituents. Though this technique is old for the product of compressed tablet, this method is being used because of the content uniformity[1,2].

Angiotensin receptor blockers :

Mechanism of action

These substances are AT_1-receptor antagonists – that is, they block the activation of angiotensin II AT_1 receptors. Blockage of AT_1 receptors directly causes vasodilation, reduces secretion of vasopressin, and reduces production and secretion of aldosterone, amongst other actions. The combined effect reduces blood pressure.

The specific efficacy of each ARB within this class depends upon a combination of three pharmacodynamic and pharmacokinetic parameters. Efficacy requires three key PD/ PK areas at an effective level; the parameters of the three characteristics will need to be compiled into a table similar to one below, eliminating duplications and arriving at consensus values; the latter are at variance now.

Diuretics

Mechanisms of diuretic drugs

Diuretic drugs increase urine output by the kidney (i.e., promote diuresis). This is accomplished by altering how the kidney handles sodium. If the kidney excretes more sodium, then water excretion will also increase. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect). The reason for this is that one nephron segment can compensate for altered sodium reabsorption at another nephron segment; therefore, blocking multiple nephron sites significantly enhances efficacy.

Thiazide diuretics, which are the most commonly used diuretic, inhibit the sodium-chloride transporter in the distal tubule. Because this transporter normally only reabsorbs about 5% of filtered sodium, these diuretics are less efficacious than loop diuretics in producing diuresis and natriuresis. Nevertheless, they are sufficiently powerful to satisfy most therapeutic needs requiring a diuretic. Their mechanism depends on renal prostaglandin production.

MATERIALS AND METHODS

The various materials used in the formulation are given in Table no.1

Table: 1 Materials

S.NO	RAW MATERIALS	MANUFACTURER
1	Losartan potassium	aurobindopharmaltd.,Hyderabad
2	Hydrochlorthiazide	aurobindopharmaltd.,Hyderabad
3	Aerosil 200 pharma	Signet Chemicals, Mumbai
4	Lactose Monohydrate	Colorcon, Mumbai
5	Avicel 102	Signet Chemicals, Mumbai
6	HPMC	Aurolab, Madurai
7	Starch 1500	Signet Chemicals, Mumbai
8	Avicel 101	Signet Chemicals, Mumbai
9	Low substituted hydroxyl propyl cellulose	Colorcon Verna Industrial estate area, Goa
10	Magnesium stearate	SD Fine Chemicals limited, Mumbai

DRUG PROFILE

LOSARTAN POTASSIUM:

Losartan potassium is an angiotensin II receptor (type AT_1) antagonist. Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted into a carboxylic acid metabolite. Losartan metabolites have been identified in human plasma and urine. In addition to the carboxylic acid metabolite, several metabolites are formed[3].

Molecular Formula : $C_{22}H_{22}ClKN_6O$

Molecular Weight : 461.0

Chemical name :

2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Solubility:

It is freely soluble in water, soluble in alcohols, and slightly soluble In common organic solvents, such as acetonitrile and methyl ethyl ketone.

HYDROCHLORTHIAZIDE:

Molecular Formula : C7H8ClN3O4S2

Molecular Weight : 297.74

Chemical name :

2H-1,2,4-Benzothiadiazine-7-sulfonamide,6-chloro-3,4-dihydro-,1,1-dioxide.

6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [58-93-5].

Solubility: Very slightly soluble in water, soluble in aqueous solutions of Inorganic bases, e.g. sodium hydroxide / ammonium hydroxide, and in organic bases like n-butylamine

Uses:

This medication is used to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Hydrochlorothiazide is a "water pill" (diuretic) that causes you to make more urine. This helps your body get rid of extra salt and water. This medication also reduces extra fluid in the body (edema) caused by conditions such as heart failure, liver disease, or kidney disease. This can lessen symptoms such as shortness of breath or swelling in your ankles or feet

Formulae:

The excipients used in the preparation are given in table no. 2.

Table-2

Sl.No.	Chemicals	F1	F2	F3	F4	F5	F6	F7
1	Losartan potassium	100	100	100	100	100	100	100
2	HCTZ	12.5	12.5	12.5	12.5	12.5	12.5	12.5
3	Avicel 101	70	70	60	50	40	30	30
4	L- HPC	-	-	-	-	12.5	15.0	15.0
5	Avicel 200	-	-	-	10	20	30	30
6	Starch 1500	10.0	12.5	15.0	20.0	25.0	25.0	30.0
7	HPMC	10	10	10	12.5	-	-	-
8	Aerosil 200 Pharma	90	90	90	-	-	-	-
9	Pharmatose DCL 11	-	-	-	80	80	80	80
10	Magnesium Stearate	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Granulating fluid								
11	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Preparation of LOSARTAN/HCTZ tablets by wet granulation method:

Sifting:

Microcrystaline Cellulose (Avicel PH 101) and Lactose Monohydrate (Pharmatose 200M) sifted separately through # 40 mesh(ASTM,425 µm) in both batches. In 1 st batch losartan potassium sifted through #40 mesh and in 2nd batch through #30 mesh to improve the sifting process[4].

Dry Mixing:

Sifted materials were loaded into Rapid Mixer Granulator and dry mixing was carried out for 5+5+5 minutes in 1st batch and in 2nd batch for 10 min with Impeller at slow speed.Unit dose samples were collected and submitted for analysis.The results found to be satisfactory within the acceptable limits.

Granulation:

Granulation fluid(Purified water-fluid uptake-10%) was added over a period of 5-6 min with impeller at slow speed in 1st batch and in 2nd batch the fluid was added in 3min10sec.Kneading was done for 2 min in 1st batch and in 2nd batch to have better granules Kneading was done for 30 sec with impeller at slo9w speed in both batches.

Drying:

Drying was carried out in Fluidized Bed Drier at an inlet temperature of 55±5°c in 1st batch and in 2nd batch drying was carried out with an inlet temperature of 60±5°c to have a better control of drying.Loss on Drying of the granules at the end of drying was found to be 3.98%w/w(lot I) and 3.81%w/w(Lot II) in 1st batch and in 2nd batch 3.85%w/w against limit of 3.0-5.0%w/w.

Sifting & Milling:

Dried granules were sifted through #30 mesh(ASTM,600µm) & retentions milled through 1.0mm screen at medium speed,knives forward configuration.Milled granules were sifted through #30 mesh(ASTM<600µm).The retentions were milled through 1.0mm screen at fast speed,knives forward.Ensured all the material passed through 30 mesh(ASTM<600µm) in both batches[5].

Extra granular Materials Sifting:

Microcrystalline Cellulose(Avicel PH 200)sifted through #30 sieve(ASTM 600µm), Pregelatinized Starch(stach 1500) & Low Substituted HYDROXYPROPYL Cellulose(L-HPC(LH-11)) sifted through #40 sieve(ASTM 425µm) Magnesium stearate was sifted through #60 mesh(ASTM,25.0µm) in both batches[6].

Prelubrication:

Sifted Extra granular material was added into Octagonal Blender and mixed for 5+5+5 min in 1st batch and in 2nd batch for 10 min in which unit dose samples were collected and submitted for analysis. The results found to be satisfactory within the acceptable limits.

Lubrication:

Sifted magnesium state was added into Octoganal blender and mixed for 3 min in both batches.Unit dose samples were collected and submitted for analysis. The results found to be satisfactory within the acceptable limits[7].

Inprocess blend analysis is complying with the proposed specifications.

Compression:

Compression was done on 16-station compression machine.All physical parameters were found consistent.

Coating :

In the first batch, during coating gun jamming, rough surface and shade variation was observed. As recommended by the formulation research from second batch onwards %w/w solids was decreased from 12%w/w to 10%w/w and coating efficiency was decreased from 90% to 80%. Coated tablets are complying with the drug product release specifications.

Coating procedure:

Pan Speed (RPM)	10-14
Air Pressure (kg/cm^2	2-2.5
Blower Air Volume (CFM)	30
Solid Content (%)	12-15
Baffels	4
Tablet Weight	150gm
Bed Temperature (°C)	35-40
Spray Nozzle (mm)	1
No. of Spray Gun	1
Inlet Air temperature(°C)	70

EVALUATION OF TABLETS:

The important parameters in the evaluation of tablets can be divided into physical and chemical parameters.

Physical appearance:

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, color, presence or absence of odour, taste, surface texture and consistency of any identification marks.

Hardness test:
This is the force required to break a tablet in a diametric compression. Hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture. The tablet hardness of 5 kg is considered as suitable for handing the tablet[8].

Tablet size and Thickness:
Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging[9].

Friability:
This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

Disintegration test:
For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type conventional release tablets are tested for disintegrating time.

Construction of Calibration curve of Losartan Potassium
Accurately weighed 100 mg of Losartan potassium and transferred into 100 ml of volumetric flask and dissolved in small quantity of methanol and diluted with 6.8 phosphate buffer up to the mark to give stock solution 1 mg/ml. 1 ml was taken from stock solution in another volumetric flask and diluted up to 100 ml to give a stock solution 10 µg/ml. Further dilutions were made from 2-40 µg/ml with 6.8 phosphate buffer and absorbance was measured at 235 nm.

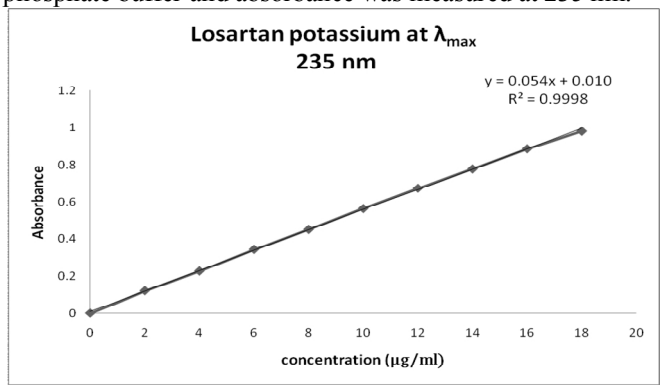

Fig.1 Calibration curve of Losartan potassium

INVITRO DISSOLUTION STUDIES OF TABLETS:
Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 900ml of pH 6.8 phosphate buffer as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 1 hr in pH 6.8 phosphate buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was with drawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 235 nm using uv-spectrophotometer[10].

Dissolution parameters:
Apparatus -- USP-II,
Dissolution Medium -- pH 6.8 phosphate buffer
RPM -- 50
Sampling intervals -- 5, 10, 15, 20, 30 and 45.
Temperature -- 37°c + 0.5°c

RESULTS & DISCUSSION:
The preformulation studies for API and blend for various formulations are given in Table no.3 and Table no.4 respectively.

TABLE- 3 : API RESULTS

BULK DENSITY gm/ml	TAPPED DENSITY gm/ml	CARR'S INDEX (%)	HAUSNER'S RATIO	ANGLE OF REPOSE (Θ)
0.362	0.612	42	1.64	30.1

TABLE - 4 : BULK DENSITY, COMPRESSIBILITY INDEX, HAUSNER'S RATIO, ANGLE OF REPOSE OF LOSARTAN AND HCTZ BLEND

S.NO	FORMULATION CODE	BULK DENSITY(g/ml)		COMPRESSIBILITY INDEX (%)	HAUSNER'S RATIO	ANGLE OF REPOSE (DEGREES)
		Untapped	Tapped			
1	F_1	0.382	0.439	34.46	1.56	25.0
2	F_2	0.410	0.461	36.39	1.59	28.6
3	F_3	0.428	0.486	38.43	1.62	29.3
4	F_4	0.431	0.457	44.6	1.72	28.6
5	F_5	0.426	0.460	40.35	1.65	30.5
6	F_6	0.412	0.491	41.8	1.67	32.6
7	F_7	0.391	0.445	40.17	1.65	29.1

The various evaluation test results are given in table no.5

TABLE-5 : EVALUATION TESTS OF LOSARTAN AND HCTZ TABLETS FOR DIFFERENT FORMULATIONS

S. NO	FORMULATION CODE	HARDNESS OF TABLETS	THICKNESS OF TABLETS	FRIABILITY OF TABLETS	DISINTEGRATION TIME OF TABLETS	DISSOLUTION PROFILE OF TABLETS
1	F1	4.18	4.45	0.400	22.50	85
2	F2	4.28	4.43	0.286	20.03	90
3	F3	4.35	4.40	0.467	19.11	93
4	F4	4.42	4.41	0.466	13.55	94
5	F5	4.90	4.43	0.525	12.85	94
6	F6	5.76	4.41	0.458	11.52	96
7	F7	6.48	4.42	0.393	11.25	99

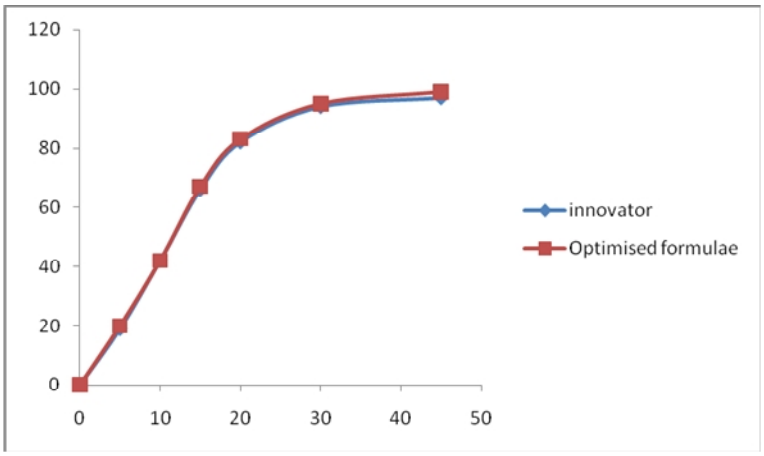

FIG 2 :COMPARISON OF *INVITRO* DISSOLUTION PROFILE OF INNOVATOR *VS* OPTIMISED FORMULATION IN PHOSPATE BUFFER MEDIUM

SUMMARY

The tablets are prepared using wet granulation technology and the resulted tablets are evaluated for their hardness, weight variation, thickness, friability, disintegration dissolution etc..,

In F1 batch the granules are cohesive even after drying for about 20 min. the loss on drying greater than 3%. The compressed tablets are evaluated for disintegration, the disintegration time in deviating from specifications.

In F2 batch to overcome these problems the binder concentration increased so that the agglomerates are decreased than the F1 trial.

In F3 further concentration of binder is increased to decrease the moisture content present in the final blend.

In F4 the microcrystalline cellulose 101 and 200 are added in various concentrations and the amount of starch is further increased to avoid problems like cohesive mass and to obtain LOD less than 3%.

In F5 the disintegrant is chained to low substituted hydroxyl propyl cellulose as it is found to be better than the previous and even the binder is increased.

In F6 the microcrystalline cellulose 101 and 200 are added in equal concentration to overcome the cohesive mass. The results are found to satisfactory.

Even though the results are satisfactory in F6 the concentration of binder is further increased to obtain the better results and the results are good.

The tablets from F7 complies all the specifications for the evaluation tests. The dissolution profile of F7 batch was complied with the innovator and found to be equal with that of innovator.

Then the F7 batch samples are kept for stability studies and are found to be good after three months.

CONCLUSION

The stable robust quality of losartan potassium and hhydrochlorthiazide conventional tablets are formulated. The formulated tablets are compared with the specifications of the innovator and the optimised formulation complies with the specifications.

The disintegrant used in the formulation is low substituted hydroxyl propyl cellulose which is different from that of the innovator and even the binder differs from the innovator even though the specifications of the evaluation are complied as per the specifications and dissolution results are better than that of the innovator.

The optimised formulation is kept for stability studies and the results are good

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