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Research

Mcc Utilization In Developing Losartan Potassium And Hydrochlorothiazide Tablets Designs

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Abstract

This study aims to develop Losartan Potassium and Hydrochlorothiazide tablets using microcrystalline cellulose (MCC) as a primary excipient. The objective is to create a stable, effective formulation that ensures consistent drug release and therapeutic efficacy. Preformulation studies evaluated the physical, chemical, and mechanical properties of the active pharmaceutical ingredients (APIs) and their interaction with various excipients. The optimal formulation was identified through a series of trials, focusing on parameters such as bulk density, tapped density, angle of repose, and Carr's index. Tablets were prepared using wet granulation followed by compression, and the final product was evaluated for weight variation, hardness, friability, disintegration, and dissolution. Accelerated stability testing was conducted to assess the shelf life under various storage conditions. The results demonstrated that the tablets possessed excellent flow properties, uniform drug content, and acceptable physical characteristics. The dissolution profile indicated that the formulation achieved the desired release rate, meeting the USP specifications for both Losartan Potassium and Hydrochlorothiazide. The study concludes that MCC is an effective excipient for developing robust and reliable tablet formulations of Losartan Potassium and Hydrochlorothiazide, providing a viable option for hypertension management.

Keywords: Losartan Potassium, Hydrochlorothiazide, microcrystalline cellulose, tablet formulation, stability testing.

INTRODUCTION

Active pharmaceutical compounds (drugs) are used for the treatment ofa disease or for prophylactic purpose. An Active Pharmaceutical Ingredient (API) mayexist in solid, liquid or semisolid form. They are rarely prescribed to the patients as such i.e. without adding excipients, since the desired effect may not be obtained. Earlier, it was thought that excipients are inert in nature but, in recent time it is well known that excipients can greatly modify the intended effect of a drug. The API and excipients are suitably processed in pharmaceutical industry to convert them into dosage forms such as tablet, capsule, suspension, solution, etc. The selection of excipients and processing of drug excipients mixture is as important as API itself. Patient acceptability can be

improved by controlling the organoleptic properties.Dosage form provides desired therapeutic level of a drug. [A.Liberman, Lachmann, second edition].

Tablet

It is a solid dosage form each containing a unit dose of one or more medicament/s. Tablets are solid, flat or biconvex discs prepared by compressing a drugor a mixture of drugs with or without suitable excipients. Tablets may be swallowed whole or being chewed. Some are dissolved or dispersed in water beforeadministration. Some are put in oral cavity, where the active ingredient is liberated ata predetermined rate. Implants or passeries may also be presented in form of tablet. Tablet may vary in shape and differ greatly in size and weight depending on the amount of medicinal substance and the intended mode of administration. [A.Liberman,Lachmann, second edition].

Properties

The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in proper form, at or over the proper time and in desired location, and to have its chemical integrity protected to the point.So, the following properties are to be possed by the tablets Should be an elegant product having its own identity while being free of defects such as chips, cracks, discoloration, contamination and Should have the strength to withstand the rigors of mechanical shocksencountered in its production, packaging, shipping, and dispensing. Should have the chemical and physical stability to maintain its physicalattributes over time. Must be able to release medicinal agent(s) in the body in a predictableandreproducible manner. Must have a suitable chemical stability over time so as not to allow alterationof the medicinal agent(s).

Types of tablets

With advancement in technology and increase in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability,newer and more efficient tablet dosage forms are being developed.The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To understand each dosage form, tablets here are classified by their route of administration and by the typeof drug delivery system they represent within that route. [A.Liberman, Lachmann, second edition].

Oral tablets for ingestion

These tablets are meant to be swallowed intact along with a sufficient quantityof potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular.

Immediate release drug delivery systems

Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and othertechniques. The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenicmanipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Thus, the term excludes formulations which are adapted to provide for "modified","controlled", "sustained", "prolonged", "extended" or "delayed" release of drug.

In this context, the term "release" includes the provision (or presentation) of drugfrom the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. For gastrointestinal tract release, the release is under pH conditions such aspH=1 to 3, especially at, or about, pH=1. In one aspect of the invention a formulation as described herein with a compound of formula (I), or an acid addition salt thereof, in crystalline form releases drug under a range of pH conditions. In another aspect of the invention a formulation as described herein with a compound of formula (I), or anacid addition salt thereof, releases drug under pH conditions such as pH=1 to 3, especially at, or about, pH=1. Thus, formulations of the invention may release at least70% (preferably 80%) of active ingredient within 4 hours, such as within 3 hours, preferably 2 hours, more preferably within 1.5 hours, and especially within an hour (such as within 30 minutes), of administration, whether this be oral or parenteral.[Gabrielsson. J., et al., 2002]

Pharmacokinetics

In this consideration, study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so both rate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue,

disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugsincrease.

MATERIALS AND EQUIPMENTS

Table 1: List of chemicals

Raw Material	3randName	Source
Losartan potassium USP	-	Aurobindo Pharma Ltd
Hydrochlorothiazide USP	-	Aurobindo Pharma Ltd
Microcrystalline celluloseUSNF	Avicel PH101	FMC Biopolymer
Lactose monohydrate USNF	Pharmatose200	DMv International
Microcrystalline celluloseUSNF	Avicel PH200	FMC Biopolymer
Pre-gelatinised starch USNF	Starch 1500	Colorcon Asia Pvt.Ltd
Colloidal silicone dioxideUSNF	Aerosil 200	Degussia (EvonikIndustries)
Magnesium stearate USNF	-	Ferro International
OPADRY 20A52179 YellowIH	-	Colorcon Asia Pvt.Ltd

Table 2: List of equipments

S. No	Equipments	Manufacturer / Supplier
1.	Electronic Balance module-AUW2200	Shimadzu Corporation, Japan.
2.	pH Meter	Metler Toledo, India.
3.	UV-Visible Spectrophotometer (UV-1601), (UV-2550)	Shimadzu-Corporation, Japan.
4.	FT-IR Spectrophotometer 8300	Shimadzu-Corporation, Japan.
5.	Dissolution Apparatus Type 2	Venkel, USA
6.	Friability Test Apparatus (USP)	Electro Lab, ET-2, India.
7.	Hardness Tester	Pfizer Ltd.
8.	Tap Density Apparatus	Electro Lab ETD - 1020, India.
9.	Filter (0.22□m)	Millipore, UK
10.	Rapid Mixer Granulator (10L)	Sainath boilers, India
11.	Octagonal Blender (10L)	Gansons, India.
12.	Moisture Balance	Sartorius, Germany
13.	Vernier Caliper	Mitutoyo, Corps, Japan
14.	Fluidized Bed Dryer (5Kg)	Plam glatt pharma technologies, Maharastra
15.	Compression Machine (16 station)	Cadmach, India.
16.	Disintegration tester (USP)	Electro Lab, India
17.	Multimiller	Neomachine, Culcutta, India
18.	Analytical Sieve Shaker	Retsch, Culcutta, India
19.	HPLC	Shimadzu- S.S, Serses

METHODOLOGY

Preformultaion Studies

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such that the appropriate physical and chemical data is available to aid the selection of new chemical entities that enter the development process. During this evaluation, possible interaction with various inert ingredients intended for use in final dosage form is also considered. The following data must be considered.

Method

Compatibility study was performed by preparing compatibility blends at different ratios of different excipients with the drug, based on tentative average weight. These blends were stored at accelerated condition of 40^0C/75% RH. Controlsamples were stored at 40^0C. The ratio of drug to excipient varies from 1:1 to 1:10

depending on the purpose of use, and the samples were kept in double lined poly- bags. The samples were evaluated for any change in the physical characteristics with reference to its controlled sample stored at 40^0C for a period of 15 days. In the present study, the potassium bromide disc (pellet) method wasemployed. Chemical stability was confirmed by IR spectrometry.

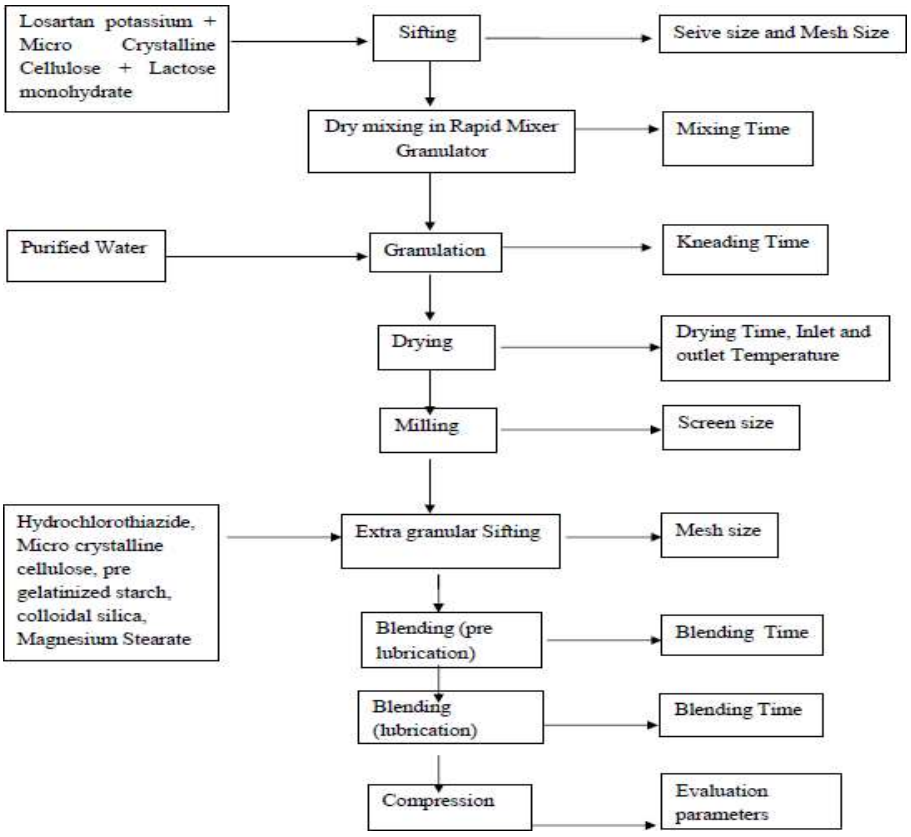
Working Formula

The various materials used in the formulation of different strength were mentioned in table 3.

Table 3: Formulation table

S.No	INGREDIENTS	50/12.5	100/25
	INTRAGRANULAR		
1	Losartsan potassium	50	100
2	Microcrystalline cellulose	35	70
3	Lactose mono hydrate	113.5	227
4	Purified water	QS	QS
	EXTRAGRANULAR		
5	Hydrochlorothiazide	12.5	25
6	Microcrystalline cellulose	22	44
7	Pre gelatinized starch	14.5	19
8	Colloidal silicone dioxide	1.25	2.5
9	Magnesium stearate	1.25	2.5
	WEIGHT OF CORE TABLET	**250**	**500**
	Coating material		
10	OPADRY YELLOW	7.5	15.0
	WT. OF COATED TABLET	**257.5**	**515.0**

Components Process In process Controls



Evaluation parameters

Pre-compression Characteristics

Angle of Repose

Angle of repose is used to determine the flow properties of powders, pellets or granules. The method to find angle of repose is to pour the powderon a conical heap on a level, flat surface and measure the included angle with the horizontal.

Tan θ = h/r

Where,

h = height of the heap,r = Radius of the heap

Table 4: Angle of repose I.P limits

Angle Of Repose	Powder Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

Bulk Density

Bulk density of a compound various substantially with the method ofcrystallization, milling or formulation. Bulk density is determined by pouring presievedgranules into a graduated cylinder via a large funnel and measure the volume and weight.

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

Tapped Density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which isoperated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

$$\text{Tapped density} = \frac{\text{weight of granules}}{\text{Tapped volume of granules}}$$

Carr's Index

Carr's index is measured using the values of bulk density and tappeddensity. The following equation is used to find the Carr's index.

$$CI = \frac{(TD\text{-}BD) \times 100}{TD}$$

Where,

TD = Tapped densityBD = Bulk density

Moisture Content (Or) Water by Kf

Take around 50ml of methanol in titration vessel of Karl Fischer titrator and titrate with Karl Fischer reagent to end point.In a dry mortar grind the pellets to fine powder .Weigh accurately about 0.5 g of the sample, transfer quickly to the titration vessel, stirr to dissolve and titrate with Karl Fischer reagent to end point.

$$\text{Moisture content} = \frac{V \times F \times 100}{\text{Weight of Sample in Mg}}$$

Where,

F= factor of Karl Fischer reagent.

V= volume in ml of Karl Fischer reagent consumed for sample titration.

Post-Compression Characteristics

Drug content

Three tablets were crushed and quantity equivalent to 45mg will be taken and determined using 0.1M Hcl with UV spectrophotometer.

Weight Variation

The USP weight variation test will be run by weighing 20 tablets individually, calculating theaverage weight, and comparing the individual tablet weights to the average. The tablets met the USP tests that were not more than 2 tablets were outside the percentage limit and no tablets differed by more than 2 times the percentage limit.

Table 5: Weight Variation Tolerance For Uncoated Tablets

S.No.	Average Weight Of Tablets (Mg)	Maximum Percentage Difference Allowed
1	130 or less	10
2	130 to 324	7.5
3	More than 324	5

Hardness

Hardness of the tablets will be determined by breaking it between the second and third fingers with thumb being as a fulcrum. There will be a sharp snap the tablet will be deemedto have acceptable strength. Hardness of the tablets will be determined by Stokes Monsanto Hardness Tester and the hardness should be found within the rangeof 3.5-5.5 kg/cm².

Friability

The friability of tablets will be determined by Roche Friabillator. 20 tablets weretaken and weighed. After weighing the tablets were placed in the Roche Friabillator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25RPM for minutes dropping the from a distance of six inches with each revolution. After operation the tablets were de-dusted and reweighed.

Friability is determined by

$F=100(1-Wo/Wt)$

Where,

Wo= weight of tablets before friability test.Wt= weight of tablets after friability test.

Content Uniformity

In this test, 30 tablets were randomly selected contained for sample, and 10 the tablets candesartan cilexetil should contain not less than 85.0 % and not more than 115.0 % of the label claim. If one unit outside the range of 85 to 115% of the label claim and no units is outside 75 to 125% or if RSD> 6% or if both conditions prevail, test 20 additional units.

Thickness

The thickness of a tablet will be the only dimensional variable related to the process. 10 tablets were measured for their thickness and diameter with a Caliper, Thickness Gauge. Average thickness and diameter were calculated.

Disintegration Test

Disintegration time is considered to be one of the important criteria inselecting the best formulation. For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. Place one tablet into each tube and suspend the assembly in to the1000ml beaker containing water maintained at 37 ± 2ºC and operate the apparatus for 30 seconds. Remove the assembly form the liquid. Observe the tablets, if one ortwo 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 by HPLC:		**Dissolution parameters**
Parameters		**Settings**
Type	-	Apparatus 2(paddle type)
Medium	-	Distilled water
Volume	-	900 ml
RPM	-	50

Temperature - 37 ± 0.5^0 C
Time - 90 minutes

Dissolution means the process by which solid substance enters in the solvent to yield a solution. It is controlled by the affinity between the solid substance and the solvent. It is a process in which a solid substance solubilises in a given solvent that is mass transfer from thesolid surface to the liquid phase.

Standard preparation

About 50mg of LP and HCTZ working standard was accurately weighed and transferred into a 100ml volumetric flask. To that about 30ml of dissolution medium was added and sonicated for about 3 minutes with intermediate shaking to dissolve and finally diluted to the 100ml with dissolution medium and mixed well. Further 5ml of the resulting solution was diluted to 50ml with dissolution medium. Again 5ml of the resulting solution was diluted to 50ml with dissolution medium and mixed well.

Sample preparation

The dissolution test apparatus was kept as per the above conditions. One tablet was placed in each dissolution bowl and the apparatus was ruined. After Specified time interval 10 ml aliquot was withdrawn from zone midway between the top of rotating paddle and surface of dissolution medium and 1cm away from the wall of jar, the solution was filtered through 0.45□ membrane filter, rejecting the first few ml of the filtrate, intoa separate test tube. Further 5ml of the resulting solution was diluted to50ml with dissolution medium. Again 5ml of the resulting solution was diluted to 50mlwith dissolution medium and mixed well.

Stability Studies

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less thana predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

Objective of the study

The purpose of stability testing is to provide evidence on how the quality of a drugsubstance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. The International Conference on Harmonization (ICH) guidelines titled "StabilityTesting of New Drug substance and Products" describes the stability test requirements for drug registration for drug registration applications in the European Union, Japan and The United States of America. ICH specifies the length of study and storage conditions.

Table 6: Storage Conditions

Study	Storage condition	Minimum time period covered bydata atsubmission.
Long trm	25ºC ± 2 ºC/ 60% RH ± 5%RH	12 months
Intermediate	30ºC ± 2 ºC/ 65% RH ± 5%RH	6 months
Accelerated	40ºC ± 2 ºC/ 75% RH ± 5%RH	6 months

Stability studies were carried out at 40^0 c/75% RH for the selected formulation for the period of two month.

Method

The selected formulations were strip packed. They were then stored at 40^0 C/75%RH for one month and evaluated for their physical appearance, drug content and in vitrodispersion time at specified intervals of time. When significant change occurs at any time during 6 months testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.
In general significant change for a drug product is defined as

- A 5% change in assay from its initial value; or failure to meet the acceptancecriteriafor when using biological or immunological procedures.
- Any degradation products exceeding its acceptance criterion.
- Failure to meet the acceptance criterion for appearance, physical attributes,and functionality test. E.g. Hardness, dose delivery per actuation; however some changes in physical attributes may be accepted under acceleratedcondition andas appropriate for the dosage form.
- Failure to meet the acceptance criterion for pH.

- Failure to meet the acceptance criterion for dissolution for 12 dosage units.
- Storage conditions are maintained as stated in ICH guidelines. The globalizationand increase in worldwide trade in recent years has led to theneed for international drug approvals and unification of regulatory requirements and evaluation products.
- ICH has already a number of harmonized guidelines providing guidance ongeneration of data that would be acceptable in European Union, Japan, and USA.

Evaluation

A systematic approach should be adopted in the presentation and evaluation of thestability information, which should include as appropriate, results from the physical, chemical and microbiological tests, particular attributes of the dosage form. Thepurpose of the stability study is to establish based on testing a minimum of three batchesof drug product, a shelf life and storage instruction applicable to all future batches of the drug product manufactured and packaged under similar circumstances.

Any evaluation should consider not only the assay but also the degradation products and other attributes, where appropriate attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performances.

Formulation of stability study batches

Two batches were taken using optimized formula to check the reproducibility characters as shown in optimized formulation and to load the samples for stability testing of tablets according to ICH guidelines for different time periods. For the stability reproducible batch of selected formulation was used.

RESULTS

Evaluation of physico-chemical properties of pure drug

Table 7: Results of loss on drying of LP and HCTZ bulk drug

S.No	Test	Specification / limits	Observations
1	Loss on drying(LP)	Not more than 0.3%w/w	0.2%w/w
2	Loss on drying(HCTZ)	Not more than 0.3%w/w	0.2%w/w

Table 8: Results of evaluation of LP and HCTZ bulkpowder

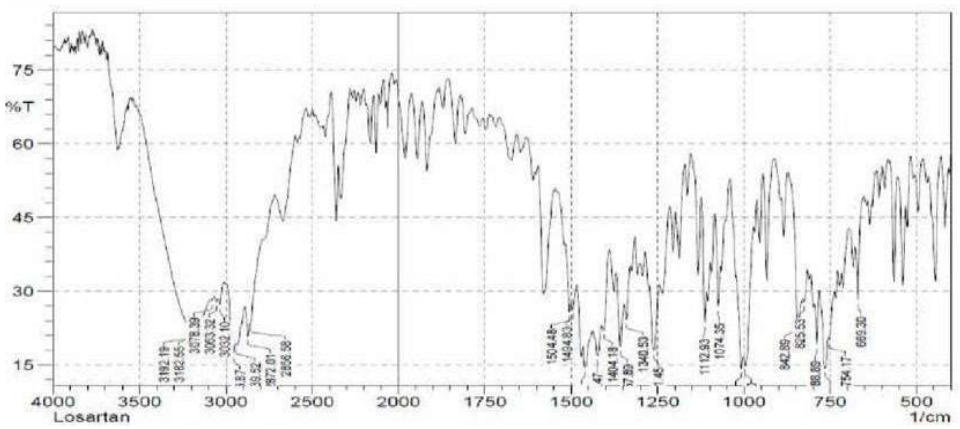
S.No	Material	BD (g/ml)	TD* (g/ml)	CI*(%)	HR*	ıngleOf Repose*
1	Losartan Potassium	0.442	0.610	27.50	1.379	34.42^0
2	Hydrochlorothiazide	0.641	0.745	20.23	1.235	32.54^0

Table 9: Results of evaluation of hygroscopicity of LP and HCTZ bulk powder

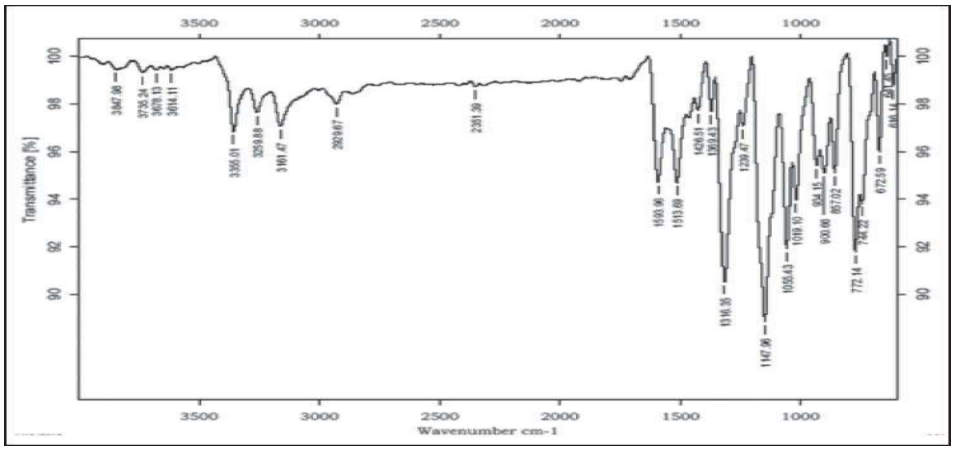
Experiment	Observation
Hygroscopcity	No Hygroscopic

Drug Excipient Compatibility Studies

The IR Spectra of both the drugs and the mixture of excipients and their tabletsare given in the Graph no 1 to 4.All the samples were scanned at the resolution of 4 cm^{-1} over the wave number region3500-500cm^{-1} using KBr disk method. This KBrdisks where formed by taking Drug and KBr in a ratio of 1:100 respectively. Then this mixture was mixed well in mortar for three to five min. A very small amount of this mixture was uniformly spread and sandwich between the pellets and pressed usingKBr pellet press at a pressure of 20,000 psi for 1 min. The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region.



Graph 1: FT IR spectrum for the pure sample of losartan potassium infingerprint region



Graph 2: FT IR spectrum for the pure sample of Hydrochlorothiazide infingerprintregion

Evaluation of granules

Based on the inference from the excipient compatibility studies, the compatible excipients were used for formulation development of tablets which were further evaluated for various parameters. The micromeritic properties such as angle of repose, Hausner's ratio, bulk density, tapped density and Carr's index of LP and HCTZ blend was studied. Theoverall results were tabulated in the table. The value of Bulk density indicates good packing characters. The Compressibilityindex (CI) of the optimized formulation were found to be below 20, indicating good flow properties of granules which were further analysed by determining the angle of repose for all granules, it ranged between 25^0 to 27^0 which indicates good flowproperties of granules.

Table 10: Evaluation of granules of LP and HCTZ

TRIAL	LOD(%m/m)	BD	TD	CI	HR
1	4.8	0.61	0.82	25.60	1.33
2	3.2	0.62	0.78	20.50	1.25
3	3.0	0.62	0.75	17.33	1.20
4	2.9	0.61	0.74	17.56	1.21
5	2.7	0.62	0.76	18.42	1.21
6	2.7	0.64	0.79	18.98	1.23

Table 11: Particle size distribution of LP and HCTZ

Seive no.	% cumulative retains					
	Trial 1	**Trial 2**	**Trial 3**	**Trial 4**	**Trial 5**	**Trial 6**
20	8	1	1	1	1	1
30	13	6	10	9	10	11
40	23	10	24	23	24	22
60	39	19	48	40	41	40
80	54	27	58	56	57	61
100	66	46	69	69	68	69
120	90	49	74	75	76	76
200	99	61	80	85	86	87
Plate	100	100	100	100	100	100

***In Vitro* Dissolution Study of LP and HCTZ tablets**

Apparatus : Dissolution Apparatus USP Type II
Medium : De aerated water, 900ml
Speed : 50 RPM
Time : 90 min
Temperature : $37 \pm 0.5\ ^0C$

Stability studies

Accelerated stability testing condition (40 c/75%RH)

Table 12: Losartan potassium and Hydrochlorothiazide tablets 50/12.5 mg

Time	1 month		2 months		3 months	
(min)	**LP**	**HCZ**	**LP**	**HCZ**	**LP**	**HCZ**
5	20.4	18.37	19.2	17.91	18.2	17.54
10	32.5	27.62	31.8	25.83	31.6	24.67
15	44.8	40.4	43.4	39.7	42.9	38.1
30	58.75	53.47	56.38	51.82	55.31	50.18
45	79.56	77.21	78.31	76.12	77.29	75.43
60	94.92	91.43	94.13	90.12	93.24	89.74

Table 13: Losartan potassium and Hydrochlorothiazide tablets 100/25 mg

Time	1 month		2 months		3 months	
(min)	**LP**	**HCZ**	**LP**	**HCZ**	**LP**	**HCZ**
5	21.3	18.92	20.17	17.54	19.42	17.21
10	35.6	28.14	33.51	27.92	33.12	27.14
15	42.37	38.17	41.24	38.36	40.16	37.23
30	55.12	50.17	54.29	49.83	53.87	48.43
45	81.43	75.86	80.75	74.12	79.12	73.79
60	93.19	89.37	92.37	88.18	91.89	88.06

Extra granular materials sifting

Sifting: Sieve Losartan potassium, lactose monohydrate, microcrystalline celluloseseparately throughASTM mesh #30.

Dry mixing: Sifted materials are loaded to rapid mixer granulator and dry mixing was carried out up to 15minutes with impeller at slow speed, 6 point unit dose samples collected in duplicate after 5,10, 15 minutes of mixing intervals and submitted for analysis in the first trail for optimisationOptimum time for dry mixing is determined to be 10 minutes based on the RSD values. From the second trail drymixing is done for 10 minutes.

Granulation: The granulating fluid was added over a period of 4 to 5 minutes with impeller fast speed and chopper off. Kneading was done with impeller and chopper at slow speedfor 30 seconds, followed by impeller and chopper at slow speed for 30 seconds for thefirst trail, by incresing the kneading time to 1 minute sticking problem is solved in thesecond batch.

Drying: Drying was carried out at an inlet temperature of $60^0\ C \pm 5^0\ C$ in fluidised bed dryer till theloss on drying of granules is 2.0-3.5 % w/w.

Sifting and milling: Dried granules are sifted through #18 mesh and retentions milled through multimill using 1.0mm screen at slow speed, knives forward direction. Milled granules weresifted through #18 mesh and retentions were milled through 1.5mm screen at mediumspeed, knives forwarddirection and sifted through #18 mesh. Dissolution problem is optimised by changing the mesh size to #24 and using the 1.0 mm screen in the third trail Sift Microcrystalline cellulose (Avicel P^H 200), Colloidal silicon dioxide USNF (Aerosil 200), Hydrochlorothiazide and pregelatinizedstarch (starch 1500) through 600 µm sieve (ASTM mesh no # 30). Sift magnesium stearate through 250 µm sieve (ASTM mesh no # 60).

Blending (Prelubrication)

Load the milled granules into low shear blender. Load resifted Microcrystallinecellulose (Avicel P^H 200), Colloidal silicon dioxide USNF (Aerosil 200), Hydrochlorothiazide and pregelatinized starch (starch 1500) into low shear blender containing milled granules. Mix for 15 min. Load sifted magnesium stearate into low shear blender and lubricate for 5 min. Optimum time for pre lubrication is determined to be 10 minutes based on the RSD values. From the second trail pre lubrication is done for 10 minutes.

Blending (Lubrication)

Load megnesium stearate to the pre lubricated materials in octagonal blender and blend for3min, 5 min and 7 min Optimum time for lubrication is determined to be3 minutes based on the RSDvalues. From the second trail lubrication is done for 3 minutes.

Compression

Compression of Losartan potassium and Hydrochlorothiazide tablets wereperformed and the turret speed has been optimised to 20 – 25 r.p.m in the trail 4 and the hardness studieshave been performed to check the minimum and the maximum limits of the compression parameters. Dissolution rate of tablets were complying with the drug product release specifications.

After compilation of the data generated during the Process Optimization of Losartan Potassium and Hydrochlorothiazide tablets 50/12.5 and 100/25mg USPstudied and results shows that the critical parameters identified at developmental stageof formulation were reproducing at Process Optimization batches. However the following changes are recommended in various stages of manufacturing process for executing the Test batch / Pilot scale batches.

- Dry mixing, pre lubrication, lubrication time optimisation
- Kneading time increased to overcome the sticking problem
- Change of mesh and sieves to overcome the dissolution problem
- Turret speed is optimised to 20 – 25 rpm

CONCLUSION

The study concludes that MCC is an effective excipient for developing robust and reliable tablet formulations of Losartan Potassium and Hydrochlorothiazide, providing a viable option for hypertension management.

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