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Formulation, Development and Evaluation of Fast Dissolving Tablet of Losartan Potassium and Nifedipine

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ABSTRACT

Fast-dissolving tablet format designed to allow administration of an oral dose form in the absence of water or fluid intake. The tablets rapidly dissolve or disintegrate in the saliva. Formulation research is oriented towards increasing the efficacy of existing drug molecules thought novel concepts of drug delivery. Losartan potassium and Nifedipine widely used as an antihypertensive drug. The aim of this study was to improve the solubility of Losartan potassium and Nifedipine and increase its disintegration time by formulation of fast-dissolving tablets by direct compression method and various ratios of cross povidone (CP) cross carmellose sodium (CCS) sodium starch glycolate (SSG) as Super disintegrants. The tablet pre-compression parameter e.g. angle of repose, bulk density, tapped density, carr's compressibility index and hausner's ratio and post compression parameter like drug content uniformity, hardness, wetting time, friability, thickness, disintegration time, were evaluated for each formulation and found satisfactory.

INTRODUCTION

Tablet

A tablet is a pharmaceutical oral dosage form. Tablet is defined as the solid unit dosage forms of medicament or medicaments with suitable excipients. They are different in size and weight, depending on the amount of medicinal substances and the intended mode of administration. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into solid dose.

Fast Disintegrating / Dissolution Tablets (FDTs)

The most evident drawback of the commonly used oral dosage forms like tablets and capsules is swallowing, particularly in case of pediatric and geriatric patients. To deliver these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as orally disintegrating tablets (ODTs) or Fast disintegrating tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets (MDTs) which break up rapidly in saliva, usually in a matter of seconds, without the need to take water. Drug dissolution and reduction as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms. When such tablets are put in the oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration. Drug delivery systems (DDS) are a strategic tool for paying out markets, laying out product life cycles and generating opportunities.

Hypertension

All patients with raised blood pressure should be inspired to have a healthy lifestyle. Even though there are benefits from weight loss, salt and alcohol reduction and exercise, these lifestyle changes may be deficient to control a patient's blood pressure. This leaves them at risk of coronary heart disease, stroke and renal failure. If the high blood pressure is certified by accurate measurements on several times, drug treatment should be considered.

Antihypertensive Drug

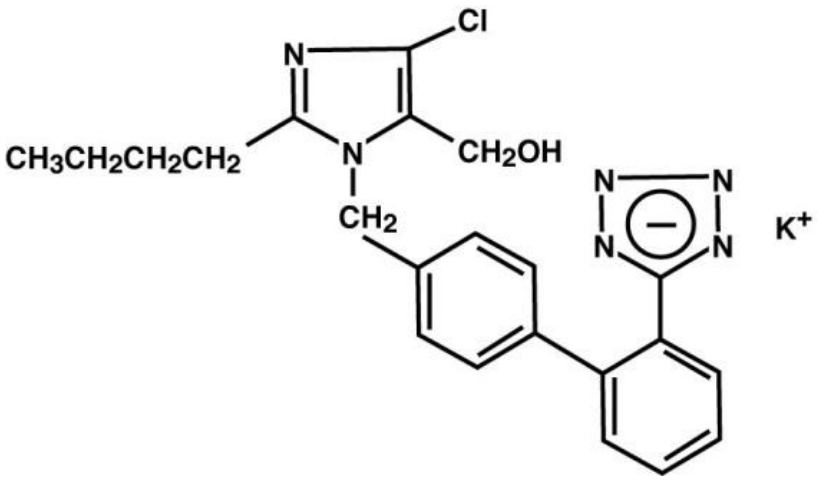
Antihypertensive is a category of drugs that are used to treat hypertension. Antihypertension therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that a reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the

likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many group of antihypertensive, which low blood pressure by different means. Among the most important and most widely used medications are diuretics, calcium channel blockers, ACE inhibitors, angiotensin 2 receptor antagonists and beta blockers.

I. Losartan potassium

General description

1. **Drug Name -** Losartan Potassium
2. **Trade Name –** Cozaar
3. **Formula –** $C_{22}\ H_{22}\ ClKN_6O$
4. **Route of administration –** oral
5. **IUPAC Name** – [2–butyl–4–chloro–1- ({4-[2-(2H -1,2,3,4–tetrazol5–yl)phenyl] phenyl} methyl)-1H–imidazole–5-yl]methanol
6. **Mol. mass** – 461 g/mol.
7. **Bioavailability-** 25-35%
8. **Half–life –** 1.5-2 hours
9. **Structure**

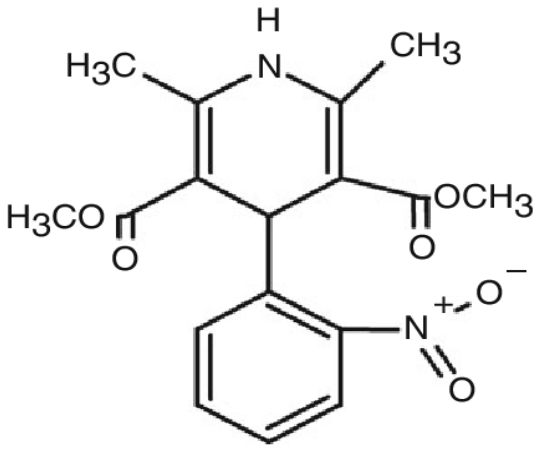


II. Nifedipine

General description

Nifedipine is an odorless, yellow crystalline tasteless Powder. Nifedipine is water insoluble. Chemically Nifedipine is a Dihydropyridine Calcium Channel Blocker.

1. **Drug Name –** Nifedipine
2. **Trade Name – A**dalat
3. **IUPAC Name-** 3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.
4. **Formula –** $C_{17}H_{19}CIN_2O_6$
5. **Route of administration –** oral
6. **Mol. mass –** 345.335g/mol
7. **Half-life –** approximately 2 hours
8. **Solubility –** poorly water-soluble
9. **Structure -**



EXPERIMENTAL MATERIALS

MATERIALS

Losartan potassium and nifedipine are given to me by modern laboratory, aerosil, sodium starch glycolate, talcum powder, mannitol and cross-carmellose are available in the modern

institute of Pharmaceutical Science.

METHOD

Method of preparation of fast dissolving tablet Losartan potassium and Nifedipine

Fast dissolving tablet was prepared by following the steps.

Various batches of tablets were prepared using the formula depicted in table. Nine (9) batches (F_1-F_9). The screened quantities of Losartan Potassium and Nifedipine, Crospovidone, sodium starch glycolate, cross-carmellose sodium, Mannitol, Aerosil, sodium saccharine, sodium benzoate, were transferred into a mortar and mixed intimately with a pestle. The ingredients of each batch passed through a #44 mesh screen prior to mixing. Screened quantities of talc were added stepwise and mixed thoroughly. The powder blend was slugged using a tableting machine and the resulting tablets. Tablets from various batches were evaluated for post-compression parameters. Sixty tablets were prepared per batch.

Preformulation Study

Angle of repose

The angle of repose is defined as the maximum angle possible between the surface of a pile of the Powder and horizontal plane. The improper flow of powder is due to frictional force between the particles and these frictional forces are quantified by angle of repose.

$$\tan\theta = \frac{h}{r}$$

Where,

θ = angle of repose.

h = height of pile.

r = radius of the base of the pile**.**

Bulk Density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and cohesiveness of particles. Mathematically it is defined as:

$$\text{Bulk Density } (\rho_b) = w/v_b$$

Where,

w = mass of powder,

v_b=bulk volume.

Tapped Density

Tapped density is defined as the mass of a powder divided by the tapped volume. It was determined by mechanically tapping the measuring cylinder and the volume was noted.

$$\text{Tapped Density } (\rho_t) = w/v_t$$

Where,

w = mass of powder,

v_t = bulk volume

Carr's Compressibility Index

It is also one of the simple methods to evaluate the flow property of a powder by comparing the bulk density and tapped density. It is calculated by

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Bulk Density}}$$

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Drug – excipient interaction study

Physical observation of the sample was done visually every week for any change in the sample mixture for 4 weeks.

The compatibility of the drug and various excipients was studied by thin layer chromatography (TLC) technique. For study purposes, losartan potassium 10 mg was mixed thoroughly by mortar and pestle with excipient in ratio of 1:5 respectively and placed in tightly closed glass vials. All the vials were kept at 40^0c for 4 weeks. The samples were analyzed by physical observation and thin-layer chromatography before and after storage.

Mobile phase preparation: for the mobile phase, Methanol: Ammonia taken in the ratio of 70:30.

Table No: 1 Formula of Fast Dissolving Tablet (Mg)

Sr.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
01.	Losartan	25	25	25	25	25	25	25	25	25
02.	Nifedipine	10	10	10	10	10	10	10	10	10
03.	Sodium starch glycolate	42	44	46	-	-	-	-	-	-
04.	Crospovidone	-	-	-	42	44	46	-	-	-
05.	Cross carmellose sodium	-	-	-	-	-	-	42	44	46
06.	Mannitol	105	105	105	105	105	105	105	105	105
07.	Aerosol	2	2	2	2	2	2	2	2	2
08.	Talc	6	6	6	6	6	6	6	6	6
09.	Saccharin	2	2	2	2	2	2	2	2	2
10.	Sodium benzoate	2	2	2	2	2	2	2	2	2

Evolution of Tablets

Size and Shape

The size and shape of the tablet can be dimensionally described, monitored and controlled.

1. Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded

using a micrometer.

2. Uniformity of Weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

3. Tablet Hardness

The hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. The hardness of the tablet of each formulation was determined using the Monsanto Hardness tester.

4. Friability

It is measured of the mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A pre-weighed tablet was placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of the test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as;

%Friability = loss in weight / Initial weight x 100.

5. In-Vivo Disintegration Test

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37°C ± 2°C was used as a disintegration media and the time in seconds was taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

6. Wetting Time

The method reported by Yunixia was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID =6.5 cm)

containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined.

7. In Vitro Dispersion Time

In vitro dispersion time was measured by dropping a tablet in a beaker containing 0.1 N HCL 6.8PH. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed.

8. Stability studies as per ICH guidelines

Stability is an essential factor of the quality, safety and efficacy of drug product. In theory stability of pharmaceutical preparation should be evaluated by exposing the product to normal shelf life conditions for years of extended periods. Generally, the rate of decomposition is slow at room temperature. So such a method is time-consuming and un economical. Therefore, in practice methods are devised to accelerate the rate of degradation by keeping the products at higher temperatures.

Accelerated stability studies are used to predict the shelf life of product by accelerating the rate of decomposition, preferably by increasing the temperature. Stability testing provides evidence that the quality of drug substance changes with time under the influence of various environmental conditions such as temperature, relative humidity, etc. Stability studies consist of a series of tests in order to maintain an assurance of stability of drug product, namely maintenance of drug product packed in specified packaging material and stored in established storage conditions within the determined time period.

Result and discussion

Organoleptic properties

Table No: 2 properties of Losartan potassium

Sr. NO.	Parameter	Observation
01.	Colour	White
02.	Odour	Odourless
03.	Taste	Better

Table No: 3 properties of Nifedipine

Sr. NO.	Parameter	Observation
01.	Colour	Yellowish
02.	Odour	Odourless
03.	Taste	Better

Drug solubility studies

The solubility of Nifedipine was checked in different solvents. Which are shows in following table.

Table No: 4 Solubility of Nifedipine in Different Solvents

Sr. No.	Solvent	Solubility(mg/ml)
01.	Water	0.001
02.	Acetone	302.7
03.	Ethanol	13.81
04.	Chloroform	81.6
05.	Methanol	32

Pre-compression parameters of all formulations blends were conducted for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The two most important attributes for the direct compression formula are good flow and good compressibility. Interparticulate inter-reaction that influences the bulking properties of powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder, such a comparison is often used as an index of the ability of the powder to flow. The angle of repose gives important information about the flow characteristics of the powder mixture. The powder flow depends on three general areas: the physical properties of the particle (e.g., shape, size, compressibility), the bulk properties (e.g. size distribution, compaction), and the processing environment (e.g., storage, humidity),

Drug interaction study

Table No: 5 Interaction study of Losartan Potassium

Sr. No.	Parameter	Initial	After 4 week	Observation
1.	Pure drug	White	No change	No change
2.	Drug + Cross Carmellose sodium	White	No change	No change
3.	Drug + Sodium starch glycolate	White	No change	No change
4.	Drug + Cross povidone	White	No change	No change
5.	Drug + Mannitol	White	No change	No change
6.	Drug + Aerosil	White	No change	No change
7.	Drug + Talc	White	No change	No change
8.	Drug + Saccharine	White	No change	No change
9.	Drug + Sodium benzoate	White	No change	No change

Table No: 6 Interaction Study of Nifedipine

Sr. No.	Parameter	Initial	After 4 week	Observation
01.	Pure drug	Yellowish	No change	No change
02.	Drug + Cross Carmellose sodium	Yellowish	No change	No change
03.	Drug + Sodium starch glycolate	Yellowish	No change	No change
04.	Drug + Cross povidone	Yellowish	No change	No change
05.	Drug + Mannitol	Yellowish	No change	No change
06.	Drug + Aerosil	Yellowish	No change	No change
07.	Drug + Talc	Yellowish	No change	No change
08.	Drug + Saccharine	Yellowish	No change	No change
09.	Drug + Sodium benzoate	Yellowish	No change	No change

Table No: 7 Evaluation of mixed blend of drug

(Losartan potassium and Nifedipine) and excipients

Formulation code	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio
S1	29.13 ± 0.52	0.57±0.015	0.68 ± 0.003	16.5 ± 0.004	1.19 ± 0.16
S2	27.32 ± 0.32	0.58 ± 0.024	0.69 ± 0.002	15.9 ± 0.02	1.18 ± 0.17
S3	29.52 ± 0.12	0.56 ± 0.052	0.68 ± 0.014	17.6 ± 0.017	1.21 ± 0.02
S4	28.11 ± 0.07	0.59 ± 0.02	0.68 ± 0.018	13.2 ± 0.015	1.15 ± 0.021
S5	30.01±0.25	0.60 ± 0.15	0.73 ± 0.001	17.6±0.011	1.21±0.018
S6	29.26 ± 0.15	0.60 ± 0.041	0.71 ± 0.007	15.2 ± 0.031	1.18 ± 0.001
S7	30.17 ± 0.11	0.60 ± 0.034	0.69 ± 0.005	14.4 ± 0.005	1.16 ± 0.007
S8	26.63 ± 0.7	0.59 ± 0.019	0.67 ± 0.012	16.8 ± 0.016	1.19 ± 0.005
S9	29.22 ± 0.52	0.56 ± 0.020	0.67 ± 0.031	17.9 ± 0.02	1.21 ± 0.031

Post-compression parameter study

Table No: 8 post compression parameter study

Formulation code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Wetting time(sec)
01.	192.6 ±0.136	2.8 ± .017	2.9 ± 0.025	0.63	23 ± 0.23
02.	201.6 ± 0.126	2.11 ±0.11	2.9 ± 0.052	0.90	19 ± 0.21
03.	198.1 ±0.143	2.9 ±.015	3.9 ± 0.016	0.73	17 ± 0.32
04.	202.3 ±0.124	2.16± .015	2.9 ± 0.058	0.8	24 ± 0.46
05.	198.6 ± 0.135	2.15 ±.028	3.0 ± 0.041	0.9	22 ± 0.34
06.	204.3 ±0.144	2.11± .031	3.0 ± 0.36	0.5	25 ± 0.40
07.	178.9±0.137	2.10± .021	2.9±0.050	0.8	23 ± 0.26
08.	194.4 ± 0.146	2.11± .015	2.8 ±0.031	0.3	24 ± 0.53
09.	202.8±0.143	2.9±0.4	2.8 ± 0.027	0.6	21 ± 0.47

Conclusion

The pre-formulation studies of drug and excipients was performed. The preformulation studies were carried out in terms of solubility profile, and flow properties (drug). All the values of above mentioned found satisfactory for the formulation.

Summary

The present work is a formulation, development and evaluation of fast dissolving tablet of Losartan potassium and nifedipine. Which is used in the treatment of hypertension.

The formulation known as fast dissolving tablet was developed with the aim to deliver the Losartan potassium and nifedipine as immediate release and extend the drug release for a second for better extended clinical effect. Their characteristic advantages such as administration without water, anywhere, anytime lead to solubility to geriatric and pediatric patients. The benefits, in term of patient compliance, rapid onset of action, increase bioavailability, and good stability make these tablets popular as a dosage of choice in the market.

1. The Losartan potassium and nifedipine were formulated as mouth dissolving tablets using super disintegrants by direct compression.

2. The bitter taste of Losartan and nifedipine was masked by adding mannitol to the formulations.

3. The physical parameters estimated i.e. weight uniformity, hardness, disintegration time, and drug contain were highly uniform.

4. The in vitro drug release studies were conducted for all the orodispersible tablet formulations in 0.1 N HCL 6.8 P^H phosphate buffer media.

5. The dissolution of the tablet of the formulation containing SSG as a super disintegration was more rapid than the other tablet formulation.

6. The order of dissolution rate for various orodispersible tablets with various super disintegrants CP<CCS<SSG.

7. All the dissolution parameters estimate and indicate the faster dissolution of the drug from an orodispersible tablet than that of a pure drug.

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