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FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DESSOLVING 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 molecule 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 increasing 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 Superdisintegrants. 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.

KEYWORDS: Losartan potassium, nifedipine, super disintegrants, fast dissolving tablets (FDT_S).

INTRODUCTION

TABLET

A tablet is a pharmaceutical oral dosage form. Tablets are defined as solid unit dosage forms of a drug or drug with appropriate excipients. They are different in size and weight, depending on amount of medicinal substances and the intended mode of administration. I substance and intended method of administration. Contains a mixture of active substance and excipients, usually in powder form, pressed or deposited from a powder to solid dosage. [(1)]

FAST DISINTEGRATING/DISSOLUTION TBLETS (FDTs)

The most evident drawback of the commonly used oral dosage forms like tablets and capsules is swallowing, particularly in case of paediatric and geriatric patients. To meet these medical needs, pharmaceutical technologists have developed a novel oral dosage forms called orally disintegrating tablets (ODTs) or Fast disintegrating tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets (MDTs) which are rapidly broken down in saliva, usually in a 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 cavity of the mouth, saliva speedily penetrates into the pores to cause rapid tablet disintegration. Drug delivery systems (DDS) are a strategic tool for creating pay out markets, product life cycles and creating opportunities. [2]

ADVANTAGES OF FDTS

1. Easy administration for patients how are mentally ill, disabled and uncooperative.
2. No water needed.
3. Can design to live minimal or no residue in mouth.
4. It provided a pleasant mouth feel.
5. No chewing needed.
6. Better taste obtained by taste masking.
7. Improved stability, low sensitivity environmental condition.
8. First pass metabolism is reduced, thus offering improve bioavailability and thus reduced dose and side effect.[3]

Disadvantage

1. Drugs with relatively largely doses difficult to formulate into FDT e.g. antibiotic.
2. Patients who are concurrently anti cholinergic take medication, best for FDTs cannot be candidate.
3. Patient with shorans syndrome of dryness of mouth due to decrease saliva production may not be good candidate for this tablet formulation.[3]

HYPERTENSION

All patients with raise 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 puts them at risk of coronary heart disease, stroke and kidney failure. If the high blood pressure is certifying by accurate measurements on several time, drug treatment should be considered. [4]

ANTIHYPERTENSIVE DRUG

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

1. **Drug Name** Losartan Potassium

2. **Trade Name -** Cozaar

3. **Formula –** $C_{22}H_{22}ClKN_6O$

4. **Route of administration –** oral

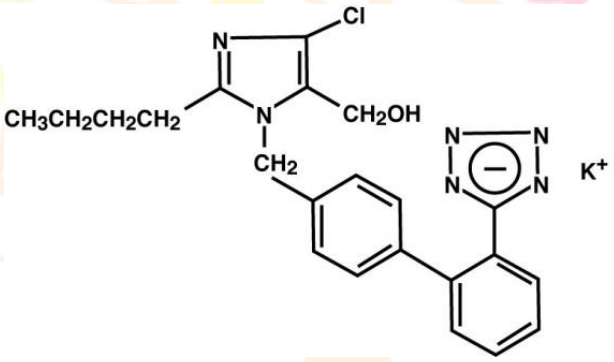
5. **IUPAC Name** – [2–butyl–4–chloro–1- ({4-[2-(2H -1,2,3,4–tetrazol5–yl)phenyl] phenyl} methyl)-1H–imidazol–5-yl]methanol

6. **Mol. mass** – 461 g/mol.

7. **Bioavailability-** 25-35%

8. **Half –life –** 1.5-2 hours

9. **Structure**



Losartan potassium

II.NIFEDIPINE

GENERAL DESCRIPTION[6]

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

1. Drug Name – Nifedipine

2. Trade Name – Adalat

3. IUPAC Name - 3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5- dicarboxylate.

4. Formula – $C_{17}H_{19}ClN_2O_6$

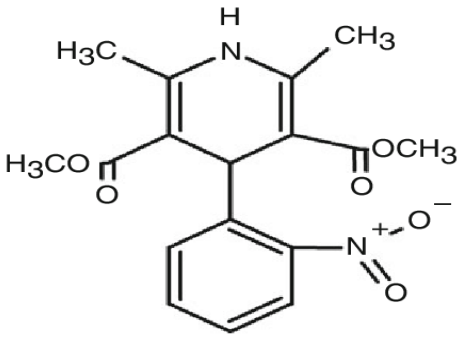
5. Route of administration – oral

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 is gifted to me by mordern laboratory aerosil sodium starch glycolate, talcum poweder, mannitol and cross-carmellose are available in modern instituted of pharmaceutical science.

METHOD

Method of preparation of fast dissolving tablet Losartan potassium and Nifedipine

Fast dissolving tablet was prepared by following steps.

Various batches of tablet 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 ingredient 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.

PREFORMULATIONS STUDY

ANGLE OF REPOSE

The angle of repose is defined as the maximum angle possible between the surface of the powder pile and the horizontal plane. Improper flow of powder is caused by the friction force between the particles and these frictional forces are determined by the angle of repose. [7]

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

Where,

θ = angle of repose.

h = height of pile.

r = radius of the base of 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 [7]

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

Where,

w = mass of powder,

vs_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. [7]

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

Where,

w = mass of powder,

v_t = bulk volume

CARR'S COMPRESSIBILITY INDEX

This is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density. It is calculated by [7]

Carr's Index = Tapped density – Bulk Density/ Bulk Density

HAUSNER'S RATIO

It denotes the flow properties of the powder and is measured by the ratio of tapped density to the bulk density. [7]

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

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

DRUG – EXICIPIENT INTERACTION STUDY

Physical observation of sample was done visually at every week for any change in the sample mixture foe 4 weeks. The compatibility of drug and various excipients was studied by thin layer chromatography (TLC) technique. For study purpose, 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 mobile phase, Methanol: Ammonia taken in the ratio of 70:30.

Table No: 13 Formula of Fast Dissolving Tablet (Mg)

SI.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 Numbers of Evaluation parameter was done by using standard methods as followed : Tablet Thickness, Uniformity of Weight, Tablet Hardness, Friability, In-Vivo Disintegration Test, Wetting Time, In Vitro Dispersion Time and Stability studies as per ICH guidelines

RESUELT AND DISCUSSION

ORGANOLAPTIC PROPERTIES

Table No: 15 properties of Losartan potassium and Nifedipine

S. NO.	Parameter	Observation of losartan potassium	Observationof nifedipine
01.	Colour	White	Yellowish
02.	Odour	Odourless	Odourless
03.	Taste	Better	Better

DRUG SOLUBILITY STUDIES

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

Table No: 15 Solubility of Nifedipine in Different Solvents

SI. 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 blend were conducted for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The two most important properties for a direct compression formula are good throughput and good compressibility. Inter particulate inter reaction that influence 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 gives powder, such a comparison is often used as an index of the capacity of the powder to flow. Help us with angle of repose gives important information about the flow characteristics of the powder mixture. Powder flow depends on three general areas: physical properties of the particle (e.g., shape, size, compressibility), the bulk properties (e.g. size distribution, compaction), and processing environment (e.g., storage, humidity),

DRUG INTERACTION STUDY

Table No: 16 Interaction study of Losartan Potassium

SI. 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: 17 interaction study of Nifedipine

SI. 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: 18 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: 19 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 per formulation studies of drug and excipients was performed. The Preformulation studies were carried out in terms of solubility profile, flow properties (drug). All the values of above mentioned found satisfactory for the formulation.

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