WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 14, 1029-1048. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF LOSARTAN POTASSIUM ORODISPERSIBLE TABLET USING NOVEL COPROCESSING METHOD

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Article Received on
26 June 2023,

Revised on 16 July 2023,
Accepted on 06 August 2023

DOI: 10.20959/wjpr202314-29299

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ABSTRACT

The oral route of administration is considered as the most widely accepted route. Oral dosage forms dissolve rapidly in saliva and can be swallowed without the need of drinking water Oro-Dispersible tablets constitute an innovative dosage form that overcomes the problems of swallowing and provides a quick onset of action. Losartan Potassium is an angiotensin II receptor antagonist. It suppresses the effects of angiotensin II at its receptors, thereby blocking the rennin-angiotensin system. The rennin-angiotensin system plays a crucial role in the control of blood pressure & thus plays an important role in hypertension. Losartan potassium has been selected as a model drug to study the effect of co-processed superdisintegrants by formulating it as an ODT. Co-Processing is defined as combining two or more excipients by an appropriate process. Co-Processing of excipients could lead to formation of excipients with superior properties compared with the simple physical mixture of their components or with individual components like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, low/no moisture sensitivity, reduced lubricant sensitivity & good machine ability even in high speed tableting machinery with reduced dwell times. The low bioavailability would increase as the drug is directly taken in systemic circulation & first pass metabolism is avoided & formulating it as an ODT causes rapid dissolution of drug & absorption, which may produce the rapid onset of action in the treatment of hypertension. Our

aim is to prepare ODT of this drug and avoid the complications occurring with conventional system. The proposed work is envisaged to carry out the preformulation, optimization, development of co-processed excipients and then formulation and evaluation of ODT.

1.0 INDRODUCTION

An orally disintegrating drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing. Most mouth-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. These are also called melt-in-mouth tablets, rapimelts, porous tablets, Oro-dispersible, quick dissolving or rapid disintegrating tablet. **Need for ODT's**, Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Dysphasia is seen to affect nearly 35%of the general population. This disorder is generally associated with number of medical conditions including strokes, Parkinson's disease, AIDS, Head and neck radiation therapy and other neurological disorders. As most drugs are unpalatable, mouth dissolving delivery systems usually contain the medicament in taste masked form so increased consumer choice, preferred by the patients. When swallowing convention tablet is difficult. It can be administered anywhere. It requires no water or chewing. Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and, psychiatric patients. No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water. Good mouth feels properly of ODDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients. Rapid dissolutionof drug and absorption which may produce rapid, onset of action. Administration to the patients who can not swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients. The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety. Rapid drug therapy intervention, No chewing needed, it provide better taste, improved stability, allows high drug loading. Ability to provide advantages of liquid medication in the form of solid preparation. New business opportunity like product

differentiation, product promotion, patent extension and life cycle management (Murray *et al*., 2003).

Co-processing in pharmaceutical industry developed back to the late 1980s with the introduction of co-processed microcrystalline cellulose and calcium carbonate. A similar principle was applied in developing silicified microcrystalline cellulose (SMCC), which is most widely used co-processed excipient. Major challenge for tablets and capsules manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations(>70%) contain excipients at higher concentration than active drug. In recent years drug formulation scientists have recognized that single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. Co-processing based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of the individual.co-processing excipients leads to the formulation of excipient granules with superior properties as compared with physical mixtures of components or individual components like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity and reduced lubricant sensitivity. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/ratio. For example, if a substance used as filler-binder has a low disintegration property, it can be Co-processed with another excipient that has good wetting property and high porosity because these attributes will increase the water intake, which will aid and increase the disintegration of tablets. One of the reasons for preparing the co-processed superdisintegrants was to avoid the problem of segregation. Many detailed studies of an excipient's chemical properties after coprocessing have proven that these excipients do not show any chemical change. Detailed studies of SMCC with X-ray diffraction analysis, solid-statenuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy, and C13 NMR spectroscopy have detected no chemical changes and indicate a similarity to the physicochemical properties of MCC. Controlled optimal particle size and particle-size distribution ensures superior flow properties of co-processed excipients without the need to add glidants. The particle-size range of these excipients was found to be similar to those of the parent excipients, but the flow of co-processed excipients was better than the flow of simple physical mixtures. Co-processed excipients have been used mainly in direct-compression tableting because in this process there is a net increase in the flow properties and

compressibility profiles and the excipient formed is a filler–binder. The compressibility performance of excipients such Cellactose, SMCC , and Ludipress have been reported to be superior to the simple physical mixtures of their constituent excipients (Schmidt et al., 1996). Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material. Most active drug substances are poorly compressible, and as a result, excipients must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent. Most co-processed products consist of a relatively large amount of brittle material such as lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material (Bolhius *et al*., 1993).

2.0 MATERIAL AND METHOD

2.1 Materials

The Losartan Potassium was obtained as gift sample from IPCA Lab's, Ratlam. All excipents are purchased form BASF analytical grade.

2.2 Methods

2.2.1 Formulation of ODT

ODT's were prepared by direct compression method by using the novel co-processed superdisintegrants, physical mixture of superdisintegrants and single superdisintegrants addition method. Tablets are compressed directly from powder blends of active ingredient and suitable excipients (including fillers, disintegrants, and lubricants). Firstly, drug was mixed with suitable amount of mixture of superdisintegrants properly. Then microcrystalline cellulose (MCC) was added and mixed thoroughly. This was followed by the addition of diluent. Then, the whole mixture was passed through sieve no. 60. Sweetening agent, talc, colloidal silicon dioxide and flavoring agent were then blended with the sieved mixture. Finally, the mixture was subjected to compression using single punch tablet compression machine (Kuchekar*et al.*, 2010).

Table 1: Ingredients used in formulation of ODT.

S. No.	Ingredients	Status	Acceptable limits of ingredients
1	Sodium starch glycolate (SSG)	Superdisintegrant	1-5 % w/w
2	Crospovidone (CP)	Superdisintegrant	1-5 % w/w
3	Microcrystalline	Directly	20-90% w/w (as

	cellulose (MCC)	compressible filler	filler)
4	Mannitol	Sweetening agent & Diluent	10-90 % w/w
5	Talc	Lubricant	0.25-10 % w/w
6	Colloidal silicon dioxide	Anti-adherent	0.1-0.5 % w/w
7	Aspartame	Sweetening agent	9mg/tablet
8	Peppermint Flavor	Flavoring agent	Q.S.

2.2.2 Optimization methodologies

It can be categorized into two classes, i.e., simultaneous optimization, where the experimentation is completed before the optimization takes place and sequential optimization where experimentation continues as the optimization study proceeds.

Factorial design

Factorial design (FD) is a system of experimental design which provides a means whereby the factors involved in a reaction or a process can be evaluated simultaneously and their relative importance assessed. It is thus a means of separating those factors which are important from which are not. It involves the variation of two or more levels. The technique establishes the relative order of importance of the factors, and can also indicate if the factors interact and if such interactions are significant. It involves studying the effect of all factors (n) at various levels (x), including the interactions amongst them with total number of experiments as X^n.

Variables

The development of a pharmaceutical formulation and the associated process usually involves several variables. These are the constituents or process characteristics of a formulation that can be altered to influence its performance. The independent variables are the formulation and process variables directly under the control of the formulator, e.g. Concentration of polymer. On the other hand, the dependent variables are the responses or characteristics of the finished product, e.g. Tablet. These are usually a direct function of the independent variables, e.g. Drug content uniformity, drug release profile etc. Formulation variable may be either quantitative or qualitative. Quantitative variables are those that can take numerical values and are continuous. On the other hand qualitative variables include the type of a polymer like superdisintegrant.

Experimental design

Experimental run or trial is a practical manipulation or series of manipulations carried out under defined conditions, resulting in the data for each of the response to be measured. Experimental design involves the arrangement of experiments in the design space such that the reliable and consistent information is achievable with minimum number of experiments.

The Hit and Trial method of experimental design was selected to investigate the effect of different parameters on the mean and variance of the process performance and to obtain an optimal, well-functioning process. It is a general method of problem solving, fixing things, or for obtaining knowledge. The method is called generate and test. This approach can be seen as one of the basic approach and is contrasted with an approach using insight and theory. It can be methodical in manipulating the variables in an attempt to sort through possibilities that may result in success. Itextends into a whole recursive sequence of levels, successively above each other in a systematic hierarchy. It is possible to use this method to find all solutions or the best solution, when a testable finite number of possible solutions exist. To find the best solution, one finds all solutions by the method just described and then comparatively evaluates them based upon some predefined set of criteria, the existence of which is a condition for the possibility of finding a best solution (Banker et al., 1995).

Determination of flow properties of drug

Angle of repose

Angle of repose is defined as the maximum angle between the surface of the pile of the powdered sample and horizontal plane. Angle of repose is an important parameter to study the flow property analysis of any powdered formulation with respect to their frictional forces. Angle of repose was measured by thefixedfunnelmethod employed a funnel that was secured with its tip at a given height H, above graph paper, placed on a flat horizontal surface. Powder was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel, then further it was calculated by the below given formula:

Angle of repose (tan ɵ) = Height of the pile (h)/ Radius of thepile(r)

tan (ɵ) = h/r

ɵ= tan $^{-1}$ h/r

Where,

tanɵ=angle of repose,

h=height from funnel tip to the base of cone;

r= radius of cone of granules (Lachman*et al*., 1987; Aulton*et al*., 2007).

Table 5.4: Angle of repose of drug.

Material	Angle of repose
Losartan potassium	35^0 21'± 0.223

5.1.2 Drug excipient interaction studies

a) Differential scanning calorimetry (DSC Analysis)

Compatibility of the drug with excipients was determined by differential scanning calorimetry (DSC) analysis. This study was carried out to detect any change on chemical constitution of the drug after combination with the excipients. The samples were taken for DSC study- drug plus excipients were carried out using differential scanning calorimeter JADE PARKIN ELMERE (Pyris 6 DSC). Zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 5mg sample was hermetically sealed in aluminum pans and heated at constant rate of 10 °C/ min over a temperature range of 40 to 320°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/ min and the observations are depicted in below Figure 5.4 (a) and Figure 5.4 (b):

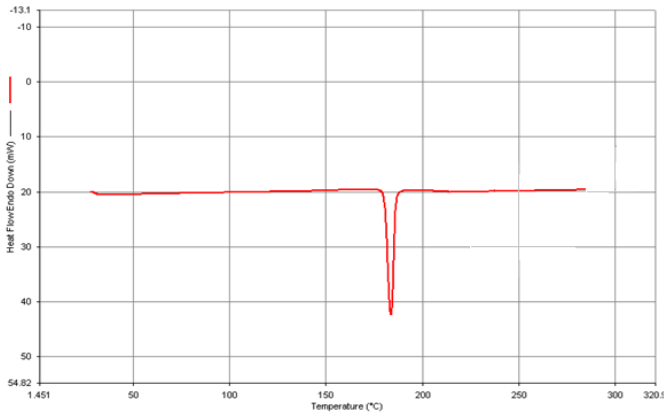


Figure 5.4 (a) DSCthermogram of drug.

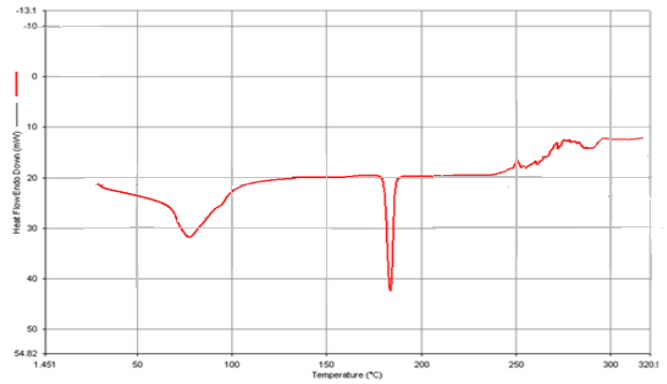
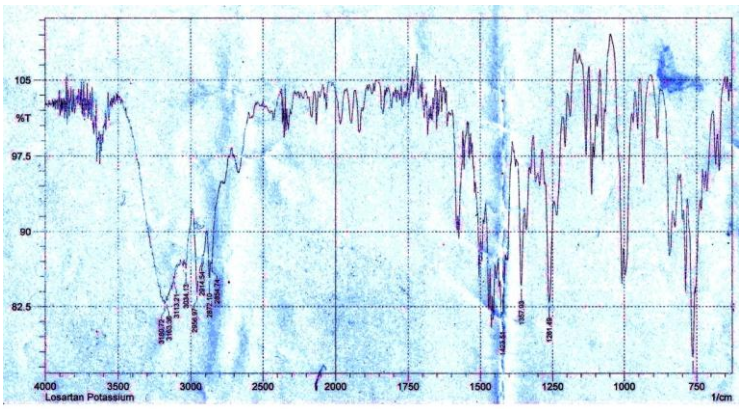


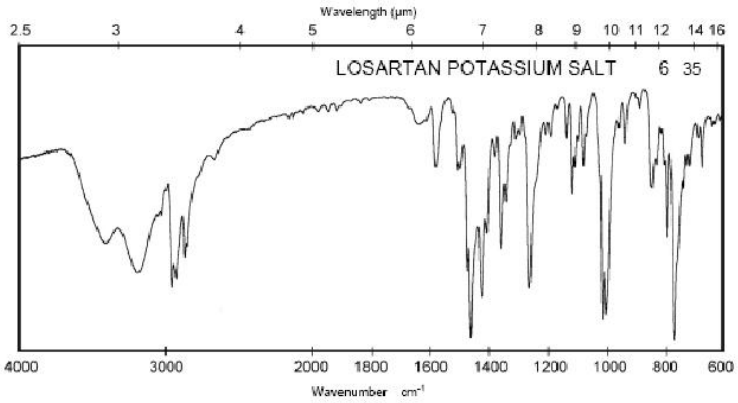
Figure 5.4 (b) DSC thermogram of drug + CP + SSG.

Drug Excipient Intreaction by FTIR

Identification of drug was done by FTIR spectroscopy. Infrared spectrum of any compound gives information about the group present in particular compound. An infrared spectrum of drug was taken using KBr pellets. Small quantity of drug was mixed with oil and one drop was placed between KBr pellets and scattered uniformly. The pellets were placed in holder and an infrared spectrum was taken. The infrared spectral assignment of Losartan potassium was obtained by FTIR (Jasco-470 plus), which showed the characteristic peaks of various functional groups of drug Figure 1(a) which matches with the standard spectrum of drug Figure 1(b):



FTIR Spectrum of formulatio



FTIR spectra of drug (Standard)

Table 2: Formulation of ODT's.

Ingredients (mg)	Formulation code				
	F_1	F_2	F_3	F_4	F_5
Losartan potassium	25	25	25	25	25
Sodium starchglycolate	-	8	-	-	-
Crospovidone	-	-	8	-	-

Physical mixture (CP + SSG)	-	-	-	8	-
Co-processed mixture (CP+SSG)	-	-	-	-	8
MCC	40	40	40	40	40
Mannitol	121	113	113	113	113
Aspartame	6	6	6	6	6
Talc	4	4	4	4	4
Colloidal silicon dioxide	2	2	2	2	2
Peppermint flavor	2	2	2	2	2
Total	200	200	200	200	200

Where,

F_1. Control Batch (No Superdisintegrant)

F_2: Tablet formulation containing Sodium Starch Glycolate

F_3: Tablet formulation containing Crospovidone

F_4: Tablet formulation containing Physical Mixture of Superdisintegrants

F_5: Tablet formulation containing Co-processed Mixture of Superdisintegrants

Table 3: Dissolution profile of ODTs.

Time (min)	Cumulative % drug release of different formulations				
	F_1	**F_2**	**F_3**	**F_4**	**F_5**
0	0	0	0	0	0
2	1.9±0.10	55.49±2.20	67.38±2.47	77.24± 2.89	84.69± 2.67
4	5.2±2.5	62.45±3.5	76.58±2.32	83.19±2.00	97.55 ±1.65
6	10.9±2.84	72.26 ±3.3	89.67±2.47	94.08±2.65	98.90±0.66
8	15.5±3.88	82.11 ±2.8	94.97±2.30	98.29±0.79	-
10	20.23±2.12	96.59 ±0.75	98.05±0.84	-	-
SD ± (n=3)					

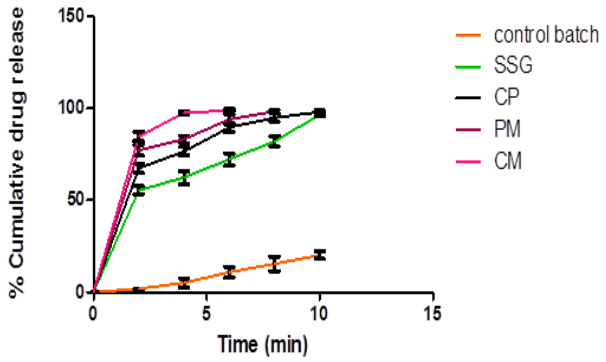


Figure 2: Dissolution profile of ODTs.

2.2.3 Evaluation of optimized batch of odt

The formulated Orodispersibletablets with co-processed excipients (batch F5) were evaluated for different parameters like general characteristic, uniformity of weight, hardness test, friability test, wetting time, water absorption ratio, *in vitro* dispersion test, in vitro dispersion drug release, disintegration test and drug release profile.

General characteristics

General appearance of tablet, its visual identity size, shape, color of the tablet was evaluated visually (I.P. 1996) and thickness was measured by Vernier Caliper instrument and the result obtained is mentioned in Table 4:

Table 4: General attributes of ODT.

Formulation Code	Description	Thickness(mm)
F5	Off White, circular shaped tablets	2.80±0.06
SD ± (n=3)		

Drug Content Uniformity of ODT

An accurately weighed quantity of crushed tablets equivalent to 25 mg of active drug was taken in 100 ml volumetric flask and dissolved in 100 ml phosphate buffer saline (pH 6.8). Appropriate dilution of the resulting solution were prepared and assayed for drug content using a UV Spectrophotometer at 231 nm. Each sample was analyzed in triplicate. All the tablets contain 100±5% of drug. All the batches of tablets were passed in the test according to Indian Pharmacopoeia 1996 and the observation showed in below Table 5:

Table 5: Drug content of ODT.

S. No.	Formulation code	Drug content
1.	F5	98.99 ± 0.472
SD ± (n=3)		

Weight variation test

In this test, 20 tablets of each batch were collected arbitrarily during compression and weight of individual tablet was measured (I.P. 1996).None of the tablets deviated from the average weight by more than ±5 % (USP XX). Tablets prepared by all formula, complies the pharmacopoeias specification for uniformity of weight. All the batches of tablet passed in uniformity of weight test according to Indian Pharmacopoeia 1996. The results are tabulated in Table 6:

Table 6: Weight variation test of ODT.

S. No.	Formulation Code	Average weight (mg)	Result
1.	F5	202.32±1.45	P ass
SD ± (n=3)			

Table 7: Standard range of weight variation test (I.P. 1996).

Average weight of Tablets (mg)	Maximum percentage difference allowed
80 or less	10
80 – 250	7.5
More than 250	5

Limit: Weight of all individual tablets should be in the limit of average wt± 5%.

Crushing test

A significant strength of mouth dissolve tablet is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of crushing strength for a mouth dissolve tablet is usually kept in a lower range to facilitate early disintegration in the mouth. The crushing strength of the tablet was measured using conventional Monsanto hardness tester. The force that causes a diameter failure (clear breaking) of tablet was taken as indicator of the tablet strength (Lachman *et al*., 1987, Aulton*et al*., 2007). The result obtained is tabulated in below Table 8:

Table 8: Crushing strength of ODT.

S. No.	Formulation	Hardness (Kg/cm^2)
1.	F5	3.14±0.50
SD ± (n=3)		

Friability test

To achieve % friability within limits for a mouth dissolving tablet is a challenge to the formulator since all methods of manufacturing of mouth dissolve tablet are responsible for increasing the % friability values. Thus, it is obligatory that this parameter should be evaluated.

This test was carried out by using tablet friability test apparatus (Roche fribilator). Six tablets were weighed initially and then pre weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines (using no. 60 mesh screen) and the

percentage of weight loss was calculated using following formula (Lachman*et al*., 1987; United State Pharmacopoeia (USP 2003). The result obtained is tabulated in below Table 9:

$$\% \text{ Friability} = \frac{\text{Wt. of 20 tablets before rotation} - \text{Wt. of 20 tablets after rotation} \times 100}{\text{Wt. of 20 tablets before rotation}}$$

Table 9: Friability of ODT.

S. No.	Formulation Code	Friability (%)
1.	F5	0.55 ± 0.015
SD ± (n=3)		

3.0 RESULT AND DISCUSSION

Over the past three decades ODTs have gained much attention as preferred to conventional oral dosage form such as tablets and capsules because of the numerous advantages like administration without water, accuracy of dosage, easy portability, alternative to liquid dosage form, ideal for pediatric and geriatric patients and rapid onset of action. These oral dosage forms dissolve rapidly in saliva and can be swallowed without the need of drinking water Oro-Dispersible tablets constitute an innovative dosage form that overcomes the problems of swallowing and provides a quick onset of action. The major claim of Oro-dispersible tablet is to increase its bioavailability as compared to the traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from formulations in where the drug dissolves quickly in saliva 2 to 10 seconds.

Losartan Potassium is an angiotensin II receptor antagonist. It suppresses the effects of angiotensin II at its receptors, thereby blocking the rennin-angiotensin system. The rennin-angiotensin system plays a crucial role in the control of blood pressure and thus plays an important role in hypertension. Losartan Potassium is emerged in the management of essential hypertension with lower incidence of side effects like cough. It is readily absorbed and undergoes rapid hepatic metabolism.

Losartan potassium has been selected as a model drug to study the effect of co-processed superdisintegrants by formulating it as an ODT; because it is an effective antihypertensive drug and cause gastrointestinal disorders, neutropenia, pancreatitis etc. and low bioavailability. The low bioavailability would increase as the drug is directly taken in systemic circulation & first pass metabolism is avoided and formulating it as an ODT causes rapid dissolution of drug and absorption, which may produce the rapid onset of action in the

treatment of hypertension. Hence, our objective is to prepare ODT of this drug and avoid the complications occurring with conventional system.

Oral drug delivery has been the most widely utilized route of administration among all the routes because of certain advantages such as unit dosage form, low cost, cheapest for packaging etc. apart from these advantages this route suffers from different drawbacks like patient noncompliance, slower onset of action, drug adverse interaction with GIT and therapeutic failure that limits its use. In order to overcome these drawbacks of conventional drug delivery there is need of development of new drug delivery system or modified drug delivery system. The objective of study was to formulate an Orodispersible tablet. Recent advances in novel drug delivery system aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. The proposed work is envisaged to carry out preformulation, optimization, formulation and evaluation of ODT.

Investigation of preformulation parameters is intended to identify those physicochemical properties that may influences the formulation design, method of preparation and pharmacokinetic- biopharmaceutical properties of the resulting product. Preformulation testing is the first step in the rational development forms of a drug substance.

The Losartan Potassium was obtained as gift sample from IPCA Lab's, Ratlam. The physical appearance i.e. color, odor and taste of the drug were found to be white, odorless and slightly bitter. The organoleptic properties were found to comply with the prescribed standards.

Melting point of the drug was determined by using melting point apparatus and it was found to be ranging from 183.7 - 184.5 °C, this range of melting point complied with the prescribed range for it i.e. 183.5-184.5 °C. This parameter showed that the drug was authentic as losartan potassium.

FTIR analysis of drug was done in Plethico Pharmaceuticals, Kalaria and it was found that the sample drug IR spectrum bands matched with the standard spectrum bands. The drug sample showed characteristic absorption bands i.e. functional group peaks at1576.78cm^{-1} (Presence of nitrogen and N=N stretching), 1586.02 cm^{-1} (COO stretching), 3163.36cm^{-1} (N-H stretching), 1357.93cm^{-1}(Presence of chloride of benzene), 763.84 cm^{-1}(C-Cl stretching), 2956.97cm^{-1} (CH stretching). IR characteristics mentioned for sample drug were found to be

in compliance with the standard drug characteristics. The sample was authentified as losartan potassium.

UV spectrum of sample drug in methanol (scanned in the range of 200-400nm) showed absorption maxima at 231 nm, which was found to comply with the standard reference drug absorption maxima (Moffat *et al.*, 2005, Indain Pharmacopoeia 2007). The marketed tablet LOSANORM containing 25 mg of active drug was also scanned in the same range and the absorption maxima was also found at 230 nm. The drug sample was indicated to be authentic and devoid of impurities by UV analysis.

DSC identification of drug sample was done by PERKIN ELMERE at RGPV, Bhopal and the thermogram depicted that the prominent endothermic peak was observed at 185 °C, which represents melting point of drug and also complied with the prescribed standard value for it, that is 184-185°C. Thus sample was identified as losartan potassium.

Flow properties of the drug i.e. bulk density and tapped density were determined as per procedure and were found to be 0.363, gm/ml, 0.485 gm/ml. angle of repose of the drug was determined by fixed funnel method. It was found to be 35^0 21', lying in the range > 34, this indicated that the drug has poor flow properties.

Compressibility of the drug was expressed in the terms of Carr's index and Hausner's ratio. The value of Carr's index and Hausner's ratio were found to be 25.155 % belonging to the prescribed range; 23-35 and 1.336 lying in between the range; 1.26-1.35, which also indicated that drug was having poor flow properties.

Qualitative Solubility of active drug was determined in various aqueous and non aqueous solvents. The drug was found to be freely soluble in methanol, soluble in distill water, freely soluble in Isopropyl Alcohol, soluble in phosphate buffer saline (pH6.8), soluble in ethanol and dimethyl formamide. The drug was found to be soluble in methanol and in organic solvents also. The nature of drug was lipophilic but due to salt formation it was also exhibited hydrophilic nature and soluble in distill water.

Loss on drying was found out to be 0.30 %, which is also under the specified range i.e. not more than 0.50 %.

Partition coefficient of drug was determined by using octanol : water system as per procedure and was found out to be 3.5,which indicated that the drug has been more partitioned in lipophilic phase but due to salt formation it exhibited good solubility in water also.

Drug excipients compatibility study was performed by physical observation, IR analysis, and DSC analysis. No change was found in the physical appearance of drug sample after 3 weeks on the exposure room temperature, refrigerator and were observed at 50^{o}C. No appreciable change was noticed in terms of there physical characteristics. This indicated drug to be compatible with excipients.

IR spectrum and DSC thermogram of the drug with excipients were found to be matchable with the reported IR spectrum and DSC themogram for losartan potassium. IR spectrum of drug with excipients combination showed characteristic functional group peaks as given by pure drug sample.

DSC thermogram of combination sample exhibited an endothermic peak in the range of 184-185° C, which encloses the value of melting point of the pure drug sample. This showed no change in the drug moiety and also its compatibility with the excipients.

For the quantitative estimation of the drug the calibration curve of the drug were prepared in phosphate buffer (pH 6.8) in the concentration range of 2-20 µg/ml, methanol and distill water, A straight line with Regression coefficient (r^2) = 0.999, 0.998, 0.993, value in phosphate buffer (pH 6.8), methanol and distilled water was obtained respectively which indicated that drug follows Beer's –lamberts' law and showed linearity in curves.

Optimization study was done on the basis of experimental design**.** On the basis of optimization study, it was concluded that physical mixture and co-processed mixture of superdisintegrants in the ratio of 1:1 (4%) appeared to be the best ratio among all the prepared three different ratios (1:1, 1:2, 1:3), on the basis of flow properties. By comparing the 1:1(4%) ratio of physical mixture and co-processed mixture of excipients on the basis of Angle of repose, Hausner's ratio and Carr's index, it was observed that 1:1 ratio of co-processed excipients showed good flow properties.

Formula for ODT's was developed by experimental designing, five batches were prepared, one with optimized ratio of co-processed excipients, one with optimized ratio of physical mixture of superdisintegrants, one with crospovidone (4%), one with sodium starch glycolate

(4%) and one with no superdisintegrants i.e. control batch and further the appropriate ingredients were selected and ODT's were prepared by direct compression method.

Precompression parameters of prepared granules were found out and the results shoed that the batch F5 i.e. co-processed excipients batch showing the best result when compared with other batches on the basis of Angle of repose, Carr's index, Hausner's ratio etc.

ODTs were compressed and evaluated experimentally on the basis of four parameters i.e. drug content uniformity, *in vitro* dispersion time, disintegration time and *in vitro* dissolution rate and the results obtained which showed that the ODT prepared with 1:1 ratio of co-processed excipients (batch F5) were best among all the batches as it showed less disintegration time of 20.27 seconds, *in vitro* dispersion time 22.16 seconds, almost completely released the drug i.e.98.90 % in six minutes and also showed highest drug content of 98.99%. Further the evaluation of this optimized batch was done on some more different parameters and stability study was performed.

Formula for preparation of ODT was suitably designed by selecting appropriate ingredients in an appropriate concentrations and direct compression method was used. Formulation and optimization of ODT was done according to experimental design by appropriately selecting different selection parameters called as experimental factors.

Evaluation of optimized batch of ODT was done on different parameters like general characteristics, which involved physical appearance and thickness of the prepared ODT, and it was found out that the thickness was 2.88 ± 0.06 mm calculated by vernier caliper instrument and concluded that the thickness of the tablet was under the prescribed standard range for ODT, then it was evaluated for crushing strength by Monsanto hardness tester and was found out 3.14 ±0.50Kg/cm^2 which was also under the prescribed range for Oro-dispersible tablet i.e.2.5-3.5 Kg/cm^2.

The friability of ODT was found out by Roche friabilator and was calculated as 0.55 ± 0.015 %, which was also under the standard prescribed range i.e. < 1%, Indian Pharmacopoeia 2007. Uniformity of weight was calculated by weight variation test and was concluded that the tablet passed this test, the data obtained is 202.32 mg (average weight) which was under the limit i.e. ± 5 %.

Drug content study was performed according to Indian Pharmacopoeia and was found out 98.99 ± 0.472 % which showed that the drug content of ODT was under the prescribed standard range i.e. 100 ± 5 %. Disintegration test was performed by Disintegration Test Apparatus and was found out that the tablet did not leave any residue on the mesh screen, which proved that it passed the test and the disintegration time was found out 20.27 sec, which showed rapid disintegration and thus absorption of the drug.

Wetting time, water absorption ratio and *in vitro* dispersion time was found out 24.22 ±0.81 seconds, 90.84 ±1.41 % and 22.16 ± 1.05 seconds, which showed rapid wetting and thus absorption of drug in the oral cavity and results obtained was under the standard prescribed range i.e. < 60 seconds and 100 ± 5 %. *In vitro* dispersion drug release was found out 72.13±1.21, which showed greater amount of drug release just after the drug dispersion in an oral cavity.

Finally the *in vitro* drug release study (% CDR) was performed and the data obtained was 98.90 ± 0.66 % in six minute which was very high as compared to other batches of ODT and showed almost complete drug release in a less amount of time, which signified the role of ODT.

Thus according to the values of all evaluatory parameters, it was found out that the batch F5 i.e. containing co-processed excipients (sodium starch glycolate with crospovidone) in the ratio of 1:1 (4 %), was best superdisintegrants among all the three i.e. physical mixture of superdisintegrants (sodium starch glycolate with crospovidone) in the ratio 1:1 (4 %), with 4 % crospovidone and with 4 % sodium starch glycolte as they needed more time for disintegration, dispersion and less amount of drug release up to six minutes (showed in optimization study).

On the basis of stability study of optimized formulation i.e. F5 of co-processed superdisintegrants (crospovidone with sodium starch glycolate), 1:1 ratio (4 %), it was concluded that there was no significant change in the values of evaluation parameters before and after the stability study. The parameters like drug content, *in vitro* drug release, drug content, disintegration time and crushing strength did not showed variable amount of changes and the results for them after fifteen and after thirty days are mentioned, disintegration time were found out 21.78 ± 0.89 (after fifteen days), 21.89 ± 0.75 (after one month), the drug content after fifteen days was 98.94 ± 0.604 and after one month was 98.90 ± 0.731. The

crushing strength found out after fifteen days was 3.19 ± 0.42 and after one month was 3.23 ± 0.28 .Stability study was performed according to ICH guidelines 2002 and the stability study was conducted at 40°C ± 2°C/75%± 5% relative humidity as per guideline. Thus after performing stability study it was concluded that the formulation was indicated to be stable as there was no appreciable changes in the critical parameters of formulation i.e. drug release, disintegration time, drug content and crushing strength. Showed that there was no appreciable change in the drug release after performing stability study of optimized ODT formulation and ODT was stable and will provide rapid onset of action and better therapeutic efficacy.

4.0 SUMMARY AND CONCLUSION

Conclusion

From the present work, it was concluded that orodispersible tablet of losartan potassium can be prepared by direct compression using novel co-processed superdisintegrants which imparts rapid action, increased bioavailability. The formulation of ODT of losartan potassium has been found to be capable of overcoming the gastric side effects associated with the drug and also imparts rapid drug release by avoiding hepatic first pass metabolism which was shown *in vitro* drug release profile. The result of evaluation parameters suggested that co-processed mixture of crospovidone and sodium starch glycolate in the 1:1 ratio (4%) w/w was best to generate efficacious ODTs as compared with the simple physical mixture and individual added superdisintegrant in the same ratio.

Thus ODT of losartan potassium will be beneficial for patients and can be regarded as novel approach as compared with the conventional dosage forms of drug available in market. Undoubtedly the availability of various technologies and manifold advantages of Orodispersibletablets will surely enhance the patient compliance, low dosing, and rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near future. Orodispersible tablet of Losartan potassium will open new business opportunity like product differentiation, product promotion, patent extension and life cycle management.

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