FORMULATION, DEVELOPMENT AND EVALUATION OF DISPERSIBLE TABLET OF ANTI DIABETIC DRUG

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ABSTRACT

Last few decades, the remarkable advancement in the drug delivery system has been done; the oral route remains the importance and picks up the safest route of drug delivery. Regardless of striking advancements in the oral route medication, Linagliptin an anti-diabetic drug belonging to BCS class-III, inhibits the enzyme, dipeptidyl peptidase-4 (DPP-4). The concept of formulating fast dissolving tablets containing linagliptin offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability. Fast dissolving tablets of linagliptin were prepared by direct compression methods and blend was evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The tablets were prepared by using croscarmellose sodium and sodium starch glycolate, as superdisintegrants in different concentration along with microcrystalline cellulose. Total six formulations were prepared and evaluated for hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and *invitro* drug release. *In-vitro* dissolution studies are performed by using phosphate buffer pH 6.8 at 75 rpm by paddle method. Overall, the formulation F5 containing of croscarmellose sodium was found to be promising and has shown a disintegration time 53±5 sec. The stability studies were performed for two months (accelerated studies) as per ICH guidelines. The optimized formulation (F5) showed no significant variations for the tablets parameters and it was stable for the specified time period. Thus results conclusively demonstrated successful masking of taste and fastest disintegration of the formulated tablets in oral cavity.

Keywords: Linagliptin, Fast dissolving tablets, Superdisintegrants, Pre-compression.

INTRODUCTION

Diabetes mellitus is a chronic disease that involves the metabolic and endocrine system of the body and careful considerations of both pharmacological and non-pharmacological interventions are inevitable, because a failure of proper dose and dosage form can lead to critical situations such as hypoglycemic

coma and hyperglycemia [1]. Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. It is estimated that 70% of the population is affected by this problem [2]. Recent advances in novel drug delivery systems (NDDS) aimed to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is fast dissolving tablets (FDT) [2-5]. Linagliptin, chemically named as (R)-8-(3-Aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydro-purine2, 6-dione with a molecular formula $C_{25}H_{28}N_8O_2$ and molecular weight 472.553 g/mol is one of the prominent anti-hyperglycemic agents of selective DPP-4 (Dipeptidyl peptidase-4) enzyme inhibitor to prevent post-prandial hyperglycemia [6,7]. With a prolonged terminal half-life of approximately 12 hours, inhibition of DPP-4 activity by linagliptin is sustained, which indicates the appropriateness of once-daily dosing [8] and immediate release tablet dosage form with its rapid drug release performance serves the purpose of quick entry of this drug molecule into the systemic circulation since, most of the anti-glycemic drugs are taken just before the meal [9]. Drug release from tablets depends on the release profile of the disintegrant and starch is the most commonly used one in tablet formulation which does not exhibit superior performance in terms of faster drug release [10]. In this experiment, an attempt was made to improve Linagliptin fast dissolving tablets formulation by implementing varying concentrations of super-disintegrants (CCS and SSG) to aid faster disintegration, dissolution, and absorption of the drug to achieve prompt hypoglycemic action.

MATERIALS AND METHODS

Materials

Linagliptin was a gift sample from Hetero Drugs Ltd., (Hyderabad, India). Sodium Starch glycolate and Sodium croscarmellose was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. Lactose, talc and magnesium stearate was procured from Central Drug House (P) Ltd. New Delhi. All other solvents and chemicals used were of analytical grade.

Preparation of tablets of Linagliptin

Fast dissolving tablets of linagliptin (5mg) were prepared by direct compression method after incorporating different superdisintegrants such as, croscarmellose sodium (Ac-Di-Sol) 10, 15, and 20 mg, sodium starch glycolate in different concentrations 10, 15, and 20 mg for optimization of best formulation [11]. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh 60. Magnesium stearate (6mg) as lubricant and talc (5 mg) as glidant and microcrystalline cellulose as bulking agent (124, 119, 114, 124, 119 and 114mg) were added in a final step and mixed, this blend was subjected to analysis of

pre-compression parameters which included angle of repose, bulk density, tap density, carr's index and hausner's ratio. The blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Six formulations of linagliptin granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablet weighing 150 mg was obtained. Composition of tablets is mentioned in Table 1.

Table 1 Composition of Linagliptin fast dissolving tablets

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Linagliptin	5	5	5	5	5	5
Sodium Starch glycolate	10	15	20	--	--	--
Croscarmellose sodium	--	--	--	10	15	20
Microcrystalline cellulose	124	119	114	124	119	114
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	150	150	150	150	150	150

Evaluation of fast dissolving tablets of PRE

Pre-compression parameters

Angle of repose (θ)

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$Tan\ \theta = h/r$$

$$\theta = tan\text{-}1\ (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$LBD\ (Loose\ Bulk\ Density) = Mass\ of\ Powder/Volume\ of\ Packing$$

$$TBD\ (Tapped\ Bulk\ Density) = Mass\ of\ Powder/Tapped\ Volume\ of\ Packing$$

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

$$Carr's\ index\ (\%) = [(TBD - LBD)/TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [12].

Hausner's ratio = Tapped density/Bulk density.

Evaluation of Tablets

Shape and color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Hardness

Tablet hardness was measured by using Pfizer hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations and results were expressed in Kg/cm^2.

Friability test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, de dusted and reweighed. The friability was calculated as the percentage weight loss. % friability was calculated as follows

$$\% \text{ Friability} = (W1 - W2) \times 100/W1$$

Where W1 = Initial weight of the 10 tablets, W2 = Final weight of the 10 tablets after testing.

Friability values below 0.5-1% are generally acceptable.

Weight variation test

To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

Uniformity of drug content

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F6) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this

Solution take 1 ml and Diluted up to 100 ml with Phosphate buffer pH 6.8 and the drug content was determined spectrophotometrically at 294nm.

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows: A tablet placed in dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml Phosphate buffer pH 6.8. The samples withdrawn were assayed spectrophotometrically at 294nm using UV visible spectrophotometer. The release of drug was calculated with the help of standard curve of linagliptin[13-15].

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time) [16-18].

RESULTS AND DISCUSSION

In this experiment, all 6 formulations indicated good flow properties as the Carr's index was within the range of 16.759- 19.538, Hausner's ratio 1.201-1.243 and Angle of Repose 41-43 (Table 2) since, Carr's index up to 20, Hausner's ratio less than 1.25 and Angle of Repose less than 40 indicate fair to excellent flow properties of granule [19]. Uniform thickness was found in the range of 1.29±0.21-1.36±0.14 in manufactured tablets of 6 formulations. In terms of weight variation average percentage of deviation of formulated tablets was found within the limit. Also, below 1% friability was observed in experimented formulations that comply with the compendial specifications. Moreover, uniformity in the hardness of the tablets was also observed (Table 3). Disintegration time evaluation is incredibly vital for fast dissolving tablets as it assists swallowing and additionally plays an important role in increasing drug absorption, hence promoting bioavailability. The disintegration time of prepared tablets was within the range. All formulated tablets in this study provided better disintegration time. The disintegration time for optimized formulation was found to be 53±5 sec (Table 4). This significant difference in disintegration time can be attributed to the use of super-disintegrants. The tablets were evaluated for in vitro dissolution

studies in phosphate buffer pH 6.8 for 10 min. The results of the optimized formulation F5 showed maximum drug release i.e. 98.12 % at the end of 10 min. The results of release studies of formulations F5 was shown in (Table 5). The *in vitro* drug release data of the optimized formulation F5 was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Korsmeyer's models was maximum i.e. 0.998 hence indicating drug release from formulations was found to follow zero order kinetics release (Table 6).

Table 2 Results of pre-compression parameters of Linagliptin

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
F1	0.458	0.568	19.366	1.240	42^0
F2	0.449	0.557	19.390	1.241	42^0
F3	0.452	0.543	16.759	1.201	41^0
F4	0.463	0.569	18.629	1.229	42^0
F5	0.453	0.563	19.538	1.243	43^0
F6	0.474	0.578	17.993	1.219	43^0

Table 3 Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.5±0.2	0.658±0.045	155±5	1.35±0.25	98.45±0.41
F2	3.6±0.3	0.745±0.035	150±6	1.32±0.23	98.96±0.23
F3	3.4±0.2	0.854±0.041	145±4	1.36±0.14	99.05±0.25
F4	3.5±0.1	0.675±0.023	153±7	1.29±0.21	98.74±0.26
F5	3.7±0.1	0.778±0.025	148±5	1.36±0.23	99.85±0.54
F6	3.6±0.2	0.721±0.032	149±2	1.34±0.25	98.74±0.58

Table 4 Results of Disintegration time of formulations

Formulation code	Disintegration Time (Sec.)
F1	85±5
F2	75±6
F3	65±4
F4	69±3
F5	53±5
F6	62±4

*Mean ± SD (n=3)

Table 5 *In-vitro* drug release data for optimized formulation F5

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0.000	56.65	1.753	43.35	1.637
5	2.236068	0.699	76.65	1.885	23.35	1.368
10	3.162278	1.000	98.12	1.992	1.88	0.274

Table 6 Regression analysis data

Batch	Zero Order	First Order
	R²	R²
F5	0.998	0.927

CONCLUSION

Thus from the whole research work it can be concluded that, the oral fast dissolving tablet of linagliptin were formulated and evaluated for various parameters. From the compatibility studies by IR of drug it was found to be compatible with other formulation excipients. All evaluation parameter were within specification. The croscarmellose sodium shown faster drug release than sodium starch glycolate. Formulation F5 release maximum drug within the 10mins.ie. 98.12% and shown minimum disintegration time i.e. 53sec than other formulation and hence considered best formulation. It was concluded that superdisintegrants addition technique is a useful method for preparing fast dissolving tablets by direct compression method.

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