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DEVELOPMENT AND OPTIMIZATION OF GLICLAZIDE SUBLINGUAL TABLETS BY USING CO-PROCESSED EXCIPIENT TO TREAT TYPE II DIABETES

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ABSTRACT

Gliclazide is a sulfonylurea antidiabetic drug approved for the treatment of type II diabetes. The objective of the work was to formulate fast disintegrating sublingual tablets of Gliclazide for the potential emergency treatment of type II diabetes. An attempt has been made to prepare fast dissolving tablets of Gliclazide using a novel co-processed excipient (LUDIFLASH) which composes 90% mannitol, 5% kollidon CL-SF, 5% kollicoat SR 30D. Four different groups of formulations (F1, F2, F3, F4) with variation in concentration of co processed excipient and a separate formulation (F5) containing cross-povidone were prepared by direct compression method. The pre and post compression parameters were evaluated for each formulation and found to be satisfactory. The studied sublingual tablet F4 shows a lesser T50% compared to pure drug and F5 formulation. The F4 also indicates the fast dissolution and disintegration rate of the optimized Gliclazide sublingual tablet, which is prerequisite for rapid management of type II diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a metabolous distract resulting from a disturbance in insulin secretion, insulin action, or both. Diabetes is a chronic disease that happens either when the pancreas does not produce adequate insulin or when the body cannot effectively make use of insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycaemia, or conjured up blood sugar, is a common effect of ungoverned diabetes and over time leads to severe damage to many of the body's systems, especially the nerves and blood vessels. Gliclazide is a sulfonylurea derivative chemically *N-(hexahydrocyclopenta[c]pyrrol-2(1H)-*

ylcarbamoyl)-4 methyl benzene sulfonamide used as an oral hypoglycemic agent. Its classification has been uncertain as literature uses it as both a first-generation and second-generation sulfonylurea. It is marketed as Diamicron and Dianorm in India. Gliclazide energizes insulin secretion from pancreatic β-cells, reduces hepatic gluconeogenesis, and turns down blood glucose concentrations. It also inhibits platelet aggregation at therapeutic doses[1].

The sublingual dosage form offers fast eject of drug from the formulation and it reaches the systemic circulation directly, various techniques can be used to formulate rapidly disintegrating or dissolving tablets[2]. Direct compression is one of these techniques which require incorporation of a super disintegrant into the formulation, or the use of highly water-soluble excipients or co-processed excipient to attain fast tablet disintegration. Co-processing is another way that new excipients are referring market without undergoing the rigorous safety testing of a completely Modern chemical. It can be defined as combining two or more established excipients by an appropriate process. Co-processing of excipients could direct to the formation of excipients with superior properties equated to the simple physical mixtures of their ingredients. The main aim of co-processing is to get a product with added value related to the ratio of its functionality/price. Development of co-processed directly compressible adjuvant starts with the selection of the excipients to be combined, their targeted proportion, selection of preparation method to get optimized product with hoped physico-chemical parameters and it ends with minimizing avoidance with batch-to-batch variations[3, 4].

Ludiflash(Coprocessed Mannitol): Ludiflash is an advanced, unique co-processed blend of 90% mannitol, 5% crospovidone and 5% polyvinyl acetate dispersion stabilized with povidone, specifically designed for orodispersible formulations. This sugar-free composition provides a pleasant, creamy mouth feel without a chalky or grainy sensation[5]. Direct compression does not require the employment of water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications. Extremely fast tablet disintegration would be required to enhance the release of Gliclazide from tablets for rapid absorption by the sublingual mucosa blood vessels. It was decided that Gliclazide could be formulated into fast-disintegrating tablets for sublingual administration as potential emergency treatment of Type II diabetes mellitus. This could be accomplished by selecting the appropriate pharmaceutical excipients in the correct proportion, in combination with

optimal manufacturing techniques. The purpose of this study was to develop a sublingual Gliclazide tablet formulation having good bioavailability.

MATERIALS AND METHODS

Gliclazide was obtained Aurobindo Pharmaceuticals. Ludi-flash was obtained from Wei Ming Pharmaceutical Mfg. Co.ltd, Taiwain. Mannitol, lactose DCL, magnesium stearate, talc, saccharine sodium was procured from S.D. Fine Chemicals Pvt. Ltd., Mumbai, India. Cros povidone was obtained from Amit Cellulose products, Puna. All the chemicals and solvents used were of analytical grade.

Preparation of Gliclazide sublingual tablets

The Sublingual tablets of Gliclazide were designed as per the composition given in Table 1 and prepared by direct compression technology. All the ingredients were passed through sieve No. 40 separately. The drug, co-processed excipients (LUDIFLASH) and other ingredients were blended thoroughly using a mortar and pestle for 10min to obtain a homogenous mixture. The flow properities of powder blends were evaluated by determined angle of repose bulk density (BD) and tapped density (TD), Carr's index (CI) and Hausner's ratio. Finally, power blends were lubricated with magnesium stearate (2%w/w) and talc (1%w/w) for additional 5 min. The powder blend was weighed for individual quantities and compressed on 6mm flat–faced punch of a R&D Tab Press10STN tablet machine (CHEMACH).) The pre compression parameter of powder blends[6] was given in Table 2.

EVALUATION OF POST COMPRESSION PARAMETERS OF TABLETS

Tablet Thickness: Dimension of the tablets was measured by using a vernier caliper. Four tablets of each formulation were picked out randomly and its thickness was measured individually.

Weight Variation Test: Weight variation test was conducted by selecting 10 tablets randomly for each formulation and weighed on the electronic balance. Calculate the standard deviation as per procedure described in I.P[7].

Hardness: Six tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester (Dolphin.TM). The mean values and standard deviation for each batch were calculated.

Friability: Friability indicates the ability of a tablet to withstand mechanical shocks while handling. Six tablets from each batch were examined for friability by using CAT.NO-1015-C friabilator (Dolphin.TM) and the equipment was run for 4 min at 25 revolutions per minute. The tablets were taken out and reweighed. Percent friability (f) was calculated by using the following formula[8].

$$F= ((W_{initial}) - (W_{final})) \div W_{initial} \times 100\ \%$$

Friability of less than 1 % is considered acceptable

Drug Content Uniformity: Five tablets were powdered and weigh accurately equivalent to 30mg of gliclazide and transferred into a 100 ml volumetric flask. Initially, 10 ml of methanol was added and shaken for 10 minutes. Then, the volume was made up to 100 ml with methanol. Subsequently, the solution in the volumetric flask was filtered, and 1 ml of the filtrate was suitably diluted and analyzed for drug content using UV-spectrophotometer (UV-1690) at 224.1nm

Disintegration Time: The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus (SUNBIM India) containing 900ml distilled water. . The time required to obtain complete disintegration of all the tablets were noted.

***In-vitro* drug release study**

The *in vitro* dissolution studies of Gliclazide sublingual tablets were carried out in USP- type II dissolution test apparatus. The drug release study was carried out in 900ml phosphate buffer (pH 6.8) as the dissolution medium with agitation speed 50 rpm, maintained at 37±0.5^{o}C. At predetermined time intervals 5ml of samples were drawn and filtered through Whattmann filter paper. The volume withdrawn at each interval was substituted with same quantity of fresh dissolution medium. The samples were analyzed for drug release by measuring the absorbance at 224.1nm in UV- spectrophotometer. All the studies are conducted triplicate. The amount of drug present in the sample was calculated with the help of appropriate calibration curve constructed from reference standards. Dissolution profiles for various formulations were in Figure 4.

Stability study: The stability of optimized formulation was determined by storing the formulation at accelerated temperature 40 ^{0}C, 3months and compared the physical

appearance, tensile strength, drug content and dissolution profile of the optimized formulation with previous results.

RESULTS AND DISCUSSION

Table 1 Compositions of different sublingual tablets of Gliclazide

Ingredients (mg per tablet)	F1	F2	F3	F4	F5
Gliclazide	30	30	30	30	30
Ludiflash	5%	10%	15%	20%	-
Crospovidone	-	-	-	-	80
Mannitol	-	-	-	-	50
Sodium Saccharine	10	10	10	10	10
Microcrytalline cellulose	134	114	94	74	24
Magnesium Stearate	4	4	4	4	4
Talc	2	2	2	2	2
Total weight	200	200	200	200	200

Table 2 Pre-compression parameters sublingual tablets of Gliclazide

Formulation code	Angle of repose(^{0})	Bulk density(g/cc)	Tapped density(g/cc)	Carr's index (%)	Hausner ratio
F1	27	0.520	0.579	10.18	1.0-1.11
F2	28	0.507	0.530	4.33	
F3	27	0.502	0.524	4.19	
F4	28	0.508	0.531	4.33	
F5	25	0.481	0.496	3.02	

Table 3 Post-compression parameters sublingual tablets of Gliclazide

Formulation code	Tablet thickness (mm)	Average weight(mg)	Hardness kg/cm^2	Friability (%)	Drug content (%)	Disintegration time(sec)	Dissolution efficiency (%) (de50)
F1	2.1±0.01	201± 0.8	4.6±0.32	0.74±0.08	98.83±0.6	60±0.4	90.98
F2	2.0±0.13	200± 1.6	4.2±0.29	0.60±0.12	98.18±0.5	55±0.2	93.00
F3	2.1±0.14	199± 1.5	4.5±0.27	0.33±0.04	98.82±0.4	40±0.5	94.13
F4	2.0±0.5	199± 1.2	4.1±0.49	0.40±0.05	99.05±0.3	25±0.6	98.48
F5	2.0±0.6	201± 1.3	4.2±0.24	0.56±0.19	98.87±0.4	35±0.7	90.24

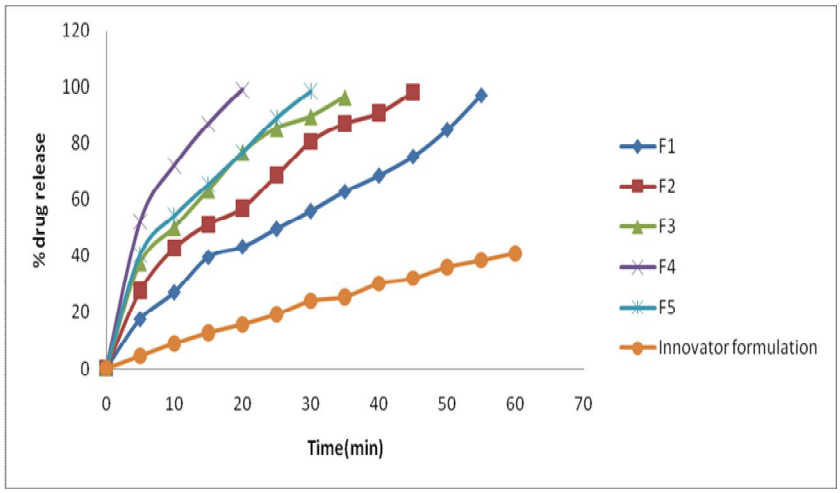

FIGURE 1 In- Vitro drug release profile of sublingual tablets of Gliclazide

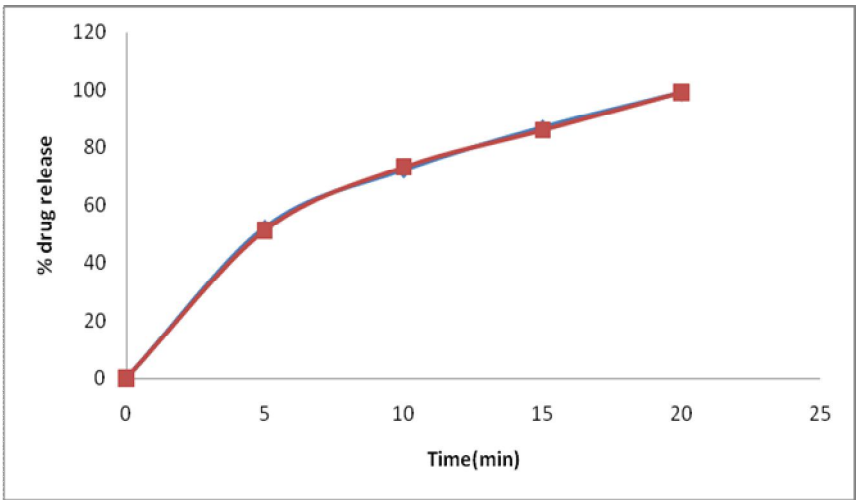

Figure 2 Dissolution profile of optimized formulation(F4) for stability studies

Gliclazide sublingual tablets were prepared by direct compression method according to the composition given in Table 1. The powder blends were characterized with respect to angle of repose, bulk density and tapped density. The angle of repose of powder blend was less than 21^0 indicate relative good flow behavior. The physical properties of powder blends were given in Table 2. The prepared sublingual tablets were assessed for hardness, friability, thickness, uniformity of the weight and content uniformity. The average weight of the Sublingual tablets was found to be in the range of 199-201mg. The hardness of the sublingual tablets was determined to be in the range of 4.9 - 6.8 kg/cm^2. The friability of all the formulations was less than 1%. The average thickness of tablets was in the range of 2.0-2.1mm. The drug content was found to be uniform in formulated tablets and was found to be within 99±2% of labeled claim. Evaluation data of sublingual tablets were shown in Table 3.

The hardness and friability values indicted good handling properties of the prepared tablets. The formulation F4 was quickly disintegrated compared to other Formulations F1, F2, F3 and F5. The disintegration time of the tablets were given in table 3.The prepared sublingual tablets were studied to *in vitro* dissolution studies. The formulation F4 releases the drug within 20 min with high dissolution efficiency. The *in vitro* drug release data of all formulations was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, Higuchi's and Korsmeyer -peppas models to ascertain the mechanism of drug release. All formulations follow zero order to release the drug. The t50% value of F4 formulation is equated with the commercial oral tablet. The stability study of optimized formulation shows showed similar physical appearance, tensile strength, drug content and drug release profile. The comparative dissolution profile of F4 formulation before and after stability study was shown in Figure 2.

CONCLUSION

The approach of the present study was to develop Gliclazide sublingual tablets by using co-processed excipient and physical mixture with different ratios. Among all the 5 formulations, F_4 formulation (drug with Ludiflash) ratio (20%) for immediate release formulation showing drug release in 20 min than the F_5 formulation with physical mixture and the formulation having good stability.

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