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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF GLICLAZIDE

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ABSTRACT
Mouth dissolving tablets is the fast growing and highly accepted drug delivery system, convenience of self administration, compactness and easy manufacturing. Gliclazide is a second generation anti-diabetic drug used for the treatment of type II diabetes. The drawback of the drug is, it is practically insoluble in water and so possesses poor solubility, GI absorption and bioavailability. Hence the objective of the work is to develop mouth dissolving tablets of gliclazide by direct compression method using three super disintegrants, viz., hypromellose, crospovidone and sodium starch glycolate at different concentrations with microcrystalline cellulose. The bland were examined for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The prepared tablets were evaluated for thickness, hardness, friability, and weight variation, content uniformity, wetting time, water absorption ratio, *in vitro* dispersion time, dissolution studies and FTIR studies. Twelve formulations F1 to F12 were prepared with three super disintegrants with different concentration. The optimum formulation was chosen and their optimum results were found to be in close agreement with experimental finding. Among three super disintegrants crospovidone F6 emerged as overall best formulation. Short term stability studies on the formulations indicated no significant changes in the drug content and *in vitro* dispersion time.
Keywords: Gliclazide, Mouth dissolving tablets, Superdisintegrants, Direct compression.

INTRODUCTION

Most of the oral pharmaceutical dosage form like conventional tablets and capsules are formulated but it was difficult to swallow for elderly and children. This problem is also applicable to active working or travelling people who do not have ready access to water[1]. Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating convenient dosage form to administration[2]. One such approach is mouth dissolving tablets (MDTs). A mouth dissolving tablet is a solid dosage form that disintegrates and dissolves in mouth without water within 60 seconds or less. The various technologies used to prepare MDTs include freeze drying and sublimation[3-4]. The commonly used superdisintegrants are hypromellose, crospovidone and sodium starch glycolate. In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence dissolution. When placed on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus, as the saliva passes down into the stomach. In such cases the bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both industry and academia. Their growing importance was underlined recently when European Pharmacopoeia adopted the term "Orodispersible tablet" as a tablet that to be placed in oral cavity where it disperse rapidly before swallowing[4]. Zydis, the best known of mouth dissolving / disintegrating tablet preparations was the first marketed new technology tablet. A zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin. In view of the above information, we have selected gliclazide, a second generation anti-diabetic drug to develop as a mouth dissolving tablets by simple and cost effective direct compression method using three super disintegrants, hypromellose, crospovidone and sodium starch glycolate at different concentrations with microcrystalline cellulose. But the problem with this potentially useful hypoglycemic agent is that it is practically insoluble in water. This limits its oral bioavailability with large individual variation. After oral administration it gets extensively metabolized by hydroxylation, N-oxidation and oxidation to several inactive metabolites. It is slightly soluble in water having half life 6-8 hrs[5]. The drug is neutral in nature, molecule weight 323.4, melting point about 181°C and partition coefficient 2.1.

MATERIALS AND METHODS

Gliclazide was obtained as gift sample from Aurobindo pharmaceuticals, Hyderabad, India. Sodium starch glycolate, hypromellose and crospovidone were obtained as gift sample from AET Laboratories Hyderabad. Microcrystalline cellulose and sodium bicarbonate were gift sample from LOBA Chemical Pvt. Ltd., Mumbai. All other chemicals used were of analytical reagent grade.

Preparation of mouth dissolving tablets of Gliclazide

Gliclazide tablets were prepared by direct compression method[6]. All the ingredients were passed through sieve No. 44 separately. Then the ingredients were weighed and mixed in geometrical order. The blend thus obtained was directly compressed using 8 mm round flat punch by rotary tablet compression machine. Twelve batches F1 to F12 were prepared with various proportions of super disintegrants (hypromellose, crospovidone and sodium starch glycolate) and microcrystalline cellulose shown in Table 1.

EVALUATION

Precompression Parameters

Prior to the compression into tablets, the blend was evaluated for properties such as;

Angle of repose

Angle of repose was determined by using funnel method[7]. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and the angle of repose (Θ) was calculated using the formula.

$$\Theta = \tan^{-1} (h / r)$$

Bulk density

Apparent bulk density (p_b) was determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula[7].

$$p_b = M / V_b$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (p_t) was calculated by using formula.

$$p_t = M / V_t$$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, an indication of the ease with which a material can be induced to flow was given by compressibility index (I)[7].

$$I = (V_0 - V_t / V_0)\ 100$$

Where, vo is the bulk volume and vt is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by the following method.

$$\text{Hausner ratio} = p_t / p_d$$

Where, p_t is tapped density and p_d is bulk density lower hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25)[7].

Post compression Parameters

Weight variation

Twenty tablets were selected at random and weighted individually. The individual weights were compared with average weight for determination of weight variation[7].

Friability

Friability of the tablets was determined by using Roche friabilator[7]. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were deducted using a soft muslin cloth and reweighed. The friability (f) was given by the formula.

$$F = (1-W_0 / W)\ 100$$

Where, W_0 is weight of the tablets before and W is weight of the tablets after test.

Hardness

Hardness was measured by using Monsanto hardness tester[7].

Thickness

Thickness was measured by using digital Vernier calipers[7].

Wetting time and water absorption ratio

A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a petridish containing 6 ml of simulated saliva pH 10, a tablet was put on the paper ,the time required for complete wetting was measured[8-15]. The wetted tablet was taken and weighed. Water absorption ratio (R) was determined by using following equation.

$$R = 100 \times (W_a - W_b) / W_b$$

Where, W_b is weight of tablet before water absorption and W_a is weight of tablet after water absorption.

Content uniformity

Ten tablets were weighed and powdered. The powder equivalent to 5 mg of gliclazide content was determined by measuring the absorbance at 226 nm after appropriate dilution[9-10].

***In vitro* dispersion time**

One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5^{0}C and time required for complete dispersion was determined[11-15].

***In vitro* dissolution study**

In vitro dissolution of gliclazide mouth dissolving tablets were carried out by USP paddle method type II apparatus (Electrolab, Model- TDT- 08L) at 37±0.5^{0}C, taking 900 ml of phosphate buffer pH 6.8 as a dissolution medium. Speed of rotation of paddle was set at 50 rpm. Absorbance of sample was measured at 226 nm by using UV spectrophotometer[9].

Short term stability studies

Short term stability studies on the promising formulations F6 were carried out by storing the tablets at 40±2^{0}C and 75±5% RH over a 3 month period. At intervals of 1month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time[10].

RESULTS AND DISCUSSION

Twelve formulations of gliclazide were prepared by direct compression method with varying concentration of three super disintegrants, sodium starch glycolate, crospovidone and hypromellose with microcrystalline cellulose. The slight bitter taste of the drug has been masked by using aspartame. A total of twelve formulations were designed. The powder blend was evaluated the physical properties such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio were tabulated in Table 2. The angle of repose between 31^0 34" to 33^0 72", this indicates passable flowability, the percentage compressibility index and hausner's ratio were within the limits (< 15%). The prepared tablets were evaluated for hardness, friability, thickness, weight variation, content uniformity were shown in Table 3. The drug content was found to be in the range of 98 to 100 (acceptable limits) and the hardness of the tablets was found to be 2.8 to 3.2 kg / cm^2 were tabulated in Table 3. Friability below 1% was indicating good mechanical resistance of tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in the presence of little amount of water were also found within the limits. *In vitro* dispersion test was done for all the formulation. Tablet disintegration was affected by the wicking and swelling of the disintegrants from the 12 formulations F6 (crospovidone) shown less disintegration time, 24 seconds when compared with others super disintegrants. Water absorption ratio for F6 was 84% it shows good water absorption capacity. *In vitro* drug release studies of gliclazide prepared tablets F1 to F12 using different super disintegrating agents by different concentrations. The maximum drug release for the formulation F1, F2, F3 and F4 using different concentration of hypromellose, at the end of the 15 minutes are 97%, 97%, 96% and 93% were shown in Figure 1 respectively for the formulations F5, F6, F7 and F8 using crospovidone at different concentrations. The drug release was found to be 94%, 97%, 94% and 97% at the end of 15 minutes. It concluded that F6 formulation gives maximum drug release within 10 minutes respectively for the formulation F9, F10, F11 and F12 using sodium starch glycolate at different concentrations. The drug release was found to 85%, 83%, 85% and 82% at end of 15 minutes from these three different super disintegrating agent 4% W/W crospovidone formulation F6 show good drug release. The graph were plotted cubic root of 100 cubic root of drug remained vs. time, the drug release for the optimized formulation F6 according to Hixon and Crowell equation. From the results drug release of F6 formulation shows Hixons and Crowell mechanisms. It indicates a change in the surface area and diameter of the tablet with the progressive dissolution of tablet as the function time. IR spectroscopic studies indicated that the drug was compatible with all the excipients. The IR spectrum of F6 showed all the characteristic peaks of gliclazide pure drug, thus confirming that no interaction of drug occurred with the components of the formulation. Short term stability studies of the above formulations indicated that there were no significant changes in drug content and *in vitro* dispersion time at the end of 3 month period ($p < 0.05$).

CONCLUSION

The mouth dissolving tablets of gliclazide were prepared by direct compression method using three super disintegrants, viz., hypromellose, crospovidone and sodium starch glycolate at different concentrations with microcrystalline cellulose were used along with sodium bicarbonate and citric acid as effervescent agent. Among these formulations(F1 to F12) tablets containing 4% crospovidone F6 formulation were optimized due to its fast *in vitro* dispersion when compare to other formulations and 97% drug release with in 15 min.

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Table 1: Formulation of Gliclazide Mouth Dissolving Tablets

Ingredients (mg)*	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Gliclazide	5	5	5	5	5	5	5	5	5	5	5	5
Hypromellose	2	4	6	8	_	_	_	_	_	_	_	–
Crospovidone	–	_	_	_	2	4	6	8	_	_	_	_
Sodium starch glycolate	_	_	_	_	_	_	_	_	2	4	6	8
Microcrystalline cellulose 101	86	84	82	80	86	84	82	80	86	84	82	80
Aspartame	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100	100	100	100

*All the quantities expressed are in mg/tablet.

Table 2: Precompression Parameters of Gliclazide Mouth Dissolving Tablets

Formulations	Angle of repose	Bulk density	Tapped density	Percent compressibility index	Hausner Ratio
F1	31^0 58”	0.51	0.67	16.8	1.31
F2	33^0 67”	0.31	0.35	14.3	1.12
F3	31^0 46”	0.27	0.34	19.3	1.25
F4	32^0 32”	0.23	0.28	16.5	1.21
F5	31^0 78”	0.25	0.29	11.8	1.16
F6	32^0 87”	0.32	0.38	16.9	1.18
F7	33^0 24”	0.36	0.42	15.9	1.17
F8	33^0 72”	0.37	0.46	10.8	1.24
F9	32^0 62”	0.25	0.31	17.6	1.25
F10	32^0 97”	0.28	0.33	14.6	1.18
F11	31^0 34”	0.33	0.39	18.7	1.18
F12	32^0 53”	0.28	0.35	13.0	1.25

Table 3: Evaluation of Gliclazide Mouth Dissolving Tablets

Formulations	Hardness Kg/cm^2	Friability (%)	Thickness (mm)	Content Uniformity (%)	Wetting Time (s)	*In vitro* Dispersion time (s)	Water Absorption ratio (%)
F1	2.86±0.02	0.90	2.48±0.02	98.46±0.6	92±0.81	54±1.24	66.3± 0.54
F2	3.26±0.07	0.79	2.44±0.02	98.86±0.6	63±0.21	40 ±1.34	71.3± 0.56
F3	3.10±0.11	0.69	2.51±0.04	99.47±1.8	42±0.24	38 ±1.32	77.4± 0.45
F4	2.98±0.05	0.94	2.49±0.02	99.75±1.6	55±0.25	53 ±1.26	74.6± 0.64
F5	2.88±0.01	0.64	2.55±0.06	99.86±0.9	30±0.85	44 ±1.26	80.1 ±0.88
F6	3.10±0.12	0.64	2.48±0.05	100.46±0.9	34±0.92	24 ±1.04	84.3± 0.78
F7	2.80±0.15	0.73	2.49±0.08	98.46±0.7	63±1.12	53 ±1.25	77.3± 0.24
F8	2.96±0.01	0.89	2.58±0.06	98.46±1.5	35±0.13	58 ±1.24	72.0± 0.45
F9	2.80±0.03	0.78	2.55±0.03	99.25±1.2	68±1.24	45± 0.98	62.6± 0.65
F10	2.94±0.02	0.84	2.51±0.02	100.46±0.9	71±0.25	58 ±1.12	59.6± 0.48
F11	2.83±0.05	0.74	2.50±0.08	100.70±1.6	69±0.87	56 ±1.54	53.8± 0.95
F12	3.12±0.05	0.89	2.57±0.06	98.46±0.8	53±1.00	54 ±1.25	49.0± 0.35

*Average of three determinations

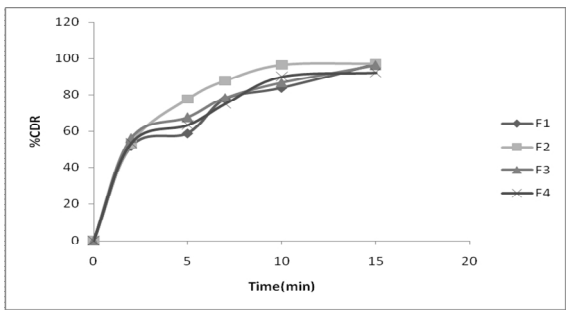

Figure 1: *In Vitro* Dissolution Profile of Hypromellose (F1-F4)

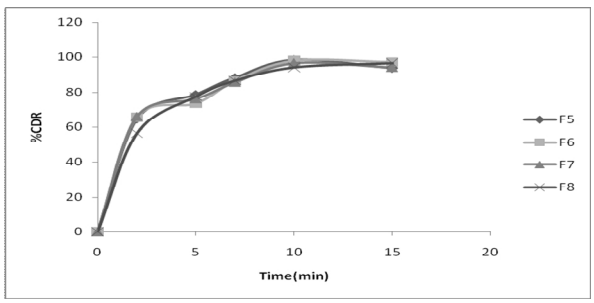

Figure 2: *In Vitro* Dissolution Profile of Crospovidone (F5-F8)

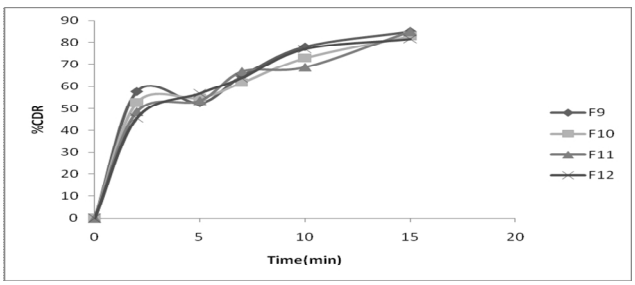

Figure 3: *In Vitro* Dissolution Profile of Sodium Starch Glycolate (F9-F12)

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