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FORMULATION DESIGN AND OPTIMIZATION OF MOUTH DISSOLVE TABLETS OF GLIPIZIDE

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Abstract

Aim: The aim of this work was to prepare and evaluate mouth dissolving tablets of glipizide with sodium starch glycolate (ssg), crospovidone and pregelatinized starch. we attempted to formulate mouth dissolving tablets of anti- diabetic drug glipizide by direct compression technique.

Methods: Fast dissolving tablets of the Sodium Starch Glycolate (SSG), Crospovidone and Pregelatinized starch were prepared by direct-compression method in different concentrations. Six formulations having superdisintegrants at different concentration levels were prepared to assess their efficiency and critical concentration level. The tablets were evaluated for crushing strength, disintegration time, wetting time, friability, drug content and drug release.

Results: Dissolution profile indicated that the complete drug release in 20 min from all the formulation tested. The results of multiple regression analysis revealed that in order to obtain a fast dissolving tablet of the Pregelatinized starch. Different types of evaluation parameters for tablets were used. Tablets containing Pregelatinized starch showed with excellent *in vitro* and *in vivo* dispersion time and drug release, as compared to other formulations.

Conclusion: This investigation has demonstrated that satisfactory fast Pregelatinized dissolving tablets can be formulated. It also showed the potential of experimental design in understanding the effect of formulation

variables on the quality of fast dissolving tablets. Fast dissolving tablets of glipizide, an antidiabetic drug can be formulated by addition of superdisintegrants, thus providing the benefits of patient compliance, rapid onset of action, and good stability

Keywords: Direct compression, glipizide, superdisintegrants, Sodium Starch Glycolate, Crospovidone and Pregelatinized starch

Introduction

Glipizide is an anti-diabetic drug (sulfonylurea-type) used along with a proper diet and exercise program to control high blood sugar. It is used in patients with type 2 diabetes (non-insulin-dependent diabetes)[1]. It works by stimulating the release of your body's natural insulin. Controlling high blood sugar helps prevent heart disease, strokes, kidney disease, blindness, and circulation problems, as well as sexual function problems (impotence). Mechanism of action is produced by blocking potassium K^+ channels in beta cells of islets of Langerhans. The increase in calcium will initiate more insulin release from each beta cell. It increases the concentration of insulin in the pancreatic vein. By this, it decreases glucose concentration[5].Out of all the orally administered dosage forms; tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of change of various physiological functions associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy. The pediatrics and geriatrics patients are of particular concern. To overcome this, dispersible tablets [2] and fast-disintegrating tablets [3] have been developed. Molded tablets dissolve completely and rapidly. However lack of strength and taste masking are of great concern [3].Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets [4]. Therefore, direct compression appears to be a better option for manufacturing of tablets.

The fast disintegrating tablets prepared by direct compression method, in general, are based on the action established by super disintegrates such as sodium starch glycolate, crospovidone and pregalatinized starch.

The objective of the present work is to develop fast dispersible glipizide tablets and to study the effect of functionality differences of superdisintegrants on the tablet properties [5]. Fast-disintegrating tablets are gaining prominence as new drug-delivery systems. These dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing. [6]

The objective of this study was to enhance safety and efficacy of drug molecule, achieve better compliance, solve the problem of difficulty in swallowing, enhance onset of action, and provide stable dosage form.

Materials and Methods

Glipizide was received as a gift sample from Mehta Chemicals (Mumbai, India). Crospovidone, sodium starch glycolate, and Micro crystalline cellulose were gifted by Alembic Ltd. All reagents and solvents used were of analytical grade.

Preparation of mixing blend of drug and excipients

The superdisintegrants (Crospovidone, sodium starch glycolate and pregalatinized starch starch) in varying concentration (05-10%) were used to develop the tablets. All the ingredients (shown in [Table 1]) were passed through mesh no. 60. All the ingredients were co-ground in a pestle motor for 5 minutes. The mixed blend of excipients was compressed using a single-punch machine to produce convex-faced tablets weighing 150 mg each, with diameter of 8 mm. A minimum of 50 tablets were prepared for every batch. [7][8]

Table-1: Formulation of Acelclofenac FDTs by Direct compression method.

Ingredients(mg)	F1	F2	F3	F4	F5	F6
Glipizide	10	10	10	10	10	10
Sodium starch glycolate	5	10	--	--	--	--
Pregelatinized starch	--	--	5	10	--	--
Crospovidone	--	--	--	--	5	10
Micro crystalline cellulose	130	125	130	125	130	125
Talc	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3
Total	150	150	150	150	150	150

Evaluation of tablets

Prepared tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche friabilator), weight variation, *in vitro* dispersion time, wetting time and drug content. [9],[10] *In vitro* dissolution studies of fast-dissolving tablets were performed by using type II apparatus as specified in United State Pharmacopoeia at 100 rpm; and Sorenson's buffer (pH, 6.8), 900 mL, was used as dissolution medium. Temperature of dissolution medium was maintained at 37°C ± 0.5°C. Aliquot of dissolution medium was withdrawn at a specific time interval and it was filtered. Absorption of filtered solution was checked by UV spectroscopy (Shimadzu, Japan), and drug content was determined from standard calibration curve. Dissolution rate was studied for all designed formulations and conventional tablet. [12]

Hardness [11]

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Friability [11]

The friability of a sample of 20 tablets was measured using Roche friabilator (Electrolab, Mumbai, India). Twenty tablets were weighed, rotated at 25 rpm for 4 minutes.

Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. Friability below 1% was considered acceptable.

Weight variation test [11]

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

In vitro disintegration time [11]

The disintegration time of the tablet was measured in water (37±2°C) according to disintegration test apparatus with disk. The time in seconds taken for the complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds. Three tablets from each batch (formulation) were tested for the disintegration time calculations.

Wetting time [12]

A piece of tissue paper folded twice was placed in a small petridish (ID= 6.5 cm) containing 6 ml of simulated saliva pH 6.8, a tablet was put on the paper, and the time for complete wetting was measured.

Drug Content [12]

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 20mg of glipizide was dissolved in 100ml of pH 7.4 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 276nm using UV-Visible spectrophotometer (UV 1601 Shimadzu, Japan).

In vitro dissolution profile [13]

Dissolution studies were carried out by USP paddle method at 37+ 0.50 c, taking 900ml of phosphate buffer pH 7.4 as a dissolution medium. Speed of rotation of paddle was set

at 50 rpm. Absorbance of sample was measured at 276 nm by spectrometrically

Result and Discussion

The use of superdisintegrants for preparation of fast-dissolving tablets is highly effective and commercially feasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well.

Prepared fast-dissolving tablet gets dispersed in the mouth quickly and releases the drug early as compared to its formulated conventional tablet. Three different superdisintegrants sodium starch glycolate, Crospovidone,

and Pregalatinized starch Starch - The order of enhancement of the dissolution rate with various superdisintegrants was found to be were tried to achieve fast dispersion of tablets Crospovidone >Sodium starch glycolate >Pregelatinized starch. The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 3.2 kg/sq cm. Friability values below 1% were an indication of good mechanical resistance of the tablets. Formulations prepared by sublimation method were found to be more friable. All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weight variation in all the six formulations was found to be 150mg, which was in pharmacopoeial limits of ±7.5% of the average weight. The percentage drug content of all the tablets was found to be between 99.87 % of glipizide which was within the acceptable limits. The wetting time for all the six formulations was performed in triplicate. In vitro dispersion is a special parameter in which the time taken by the tablet to produce complete dispersion is measured. Tablets were prepared with sodium starch glycolate F-1 to F-2, Pregalatinized starch Starch F-3 to F-4 and crospovidone F-4 to F-6. The wetting time, in vitro dispersion time of the tablets were also considerably reduced in tablets containing, Pregalatinized starch Starch which may be attributed due to the wicking type of disintegrates (Pregalatinized sStarch) formed thus facilitating the disintegrates to bring about faster disintegration. Formulation parameter evaluated [Table 2]. However, tablets containing pregalatinized starch showed the fastest disintegration, as shown in [Figure 1]. Characteristics of tablets are tabulated in [Table 3]. *In vitro* dissolution studies for F4 confirmed the results. F4 tablet showed good dissolution efficiency and rapid dissolution. The study shows that the dissolution rate of glipizide can be enhanced to a great extent by direct-compression technique with the addition of superdisintegrants, which gives quick relief from emesis.

Table-2: Formulation parameter.

Formulation	Hardness Kg/cm^2 (±SD), n=3	Friability (%)(±SD) (n=6)	Drug content (mg%) (±SD) (n=10)	Wetting time(sec) (±SD) n=3	Weight variation (±SD) n=20
F1	3.2 ±0.13	0.66±0.8	99.82±0.4	32.14±1.8	150.15±1.7
F2	3.2±0.11	0.66±0.15	99.85±0.5	65.14±1.7	150.16±1.5
F3	3.2±0.11	0.59±0.11	99.56±0.6	74.15±1.6	150.18±1.9
F4	3.2±0.14	0.59±0.3	99.87±0.8	75.82±1.8	150.02±1.8
F5	3.2±0.15	0.64±0.12	99.77±0.7	48.12±1.5	150.06±1.7
F6	3.2±0.11	0.64±0.12	99.63±0.5	42.12±1.4	150.08±1.6

Table 3: Dissolution parameters of directly compressible fast dissolving tablets.

Formulation code	**after 2.5min % Release**	**after 5min % Release**	**after 10min % Release**	**after 15min % Release**	**after 20min % Release**
F1	39.12	56.19	81.26	91.26	95.37
F2	39.53	57.43	81.74	91.43	95.11
F3	42.41	58.95	82.93	92.81	96.21
F4	43.54	58.68	83.37	93.51	97.47
F5	41.13	56.72	80.24	90.67	93.58
F6	41.39	57.41	81.98	91.23	94.69

Formulation % Release

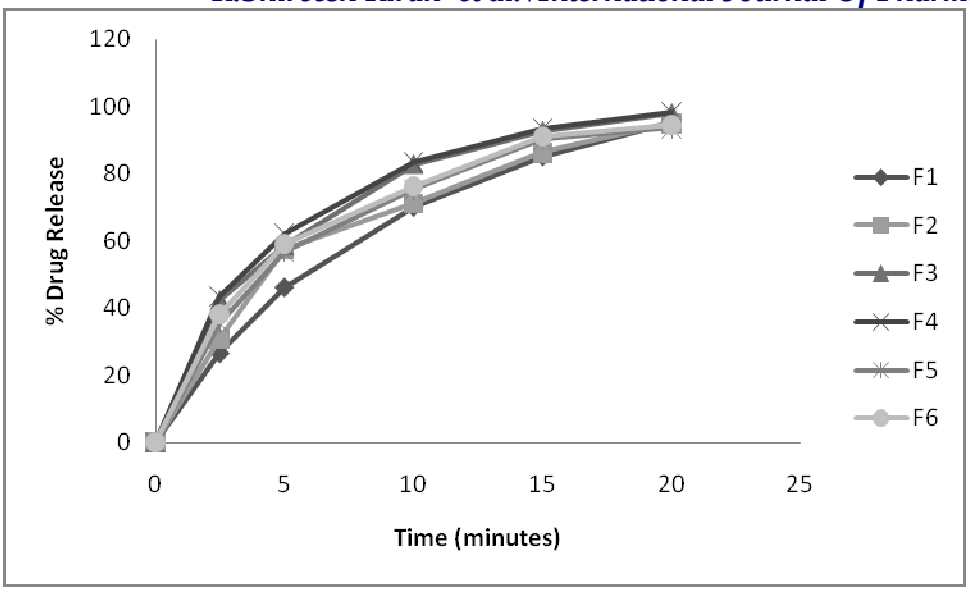

Fig-1: Dissolution Parameters of fast dissolving tablets.

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