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Original Article

GLIMEPIRIDE FAST DISINTEGRATING TABLETS: FORMULATION, EVALUATION AND *IN VIVO* DISINTEGRATION AND DYNAMIC STUDIES

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ABSTRACT

Objective: The main objective of the research was to formulate directly compressible fast disintegrating tablets of glimepiride by using different super disintegrants such as crospovidone, croscarmellose sodium, sodium starch glycolate and L-HPC in various concentrations.

Methods: The prepared tablets were evaluated for various tablet properties like weight variation, thickness, hardness, friability, taste, drug content, *in vitro* and *in vivo* disintegration time, and *in vitro* drug release, *in vivo* dynamic studies. Other parameters such as wetting time, water absorption ratio, and drug-excipient compatibility were also evaluated.

Results: The disintegration time of the optimized fast disintegrating tablet formulation was observed to be 12 s *in vitro* and 19.80 s *in vivo*. The correlation was observed between disintegration time and '*R*' for each of the four super disintegrants at the concentrations studied. Considering the '*R*' values and disintegration time, croscarmellose sodium was significantly superior compared to the other super disintegrants tested. Drug release was faster from formulations containing 25% croscarmellose sodium compared to the pure drug and without super disintegrant glimepiride tablet. FTIR studies did not indicate any excipient incompatibility, either during mixing or after compression. Optimized formulation exhibited good results in the decrease in blood glucose in rats when compared to the pure drug and marketed product.

Conclusion: Form the results if this study it can be concluded that prepared optimized fast disintegrating tablets of glimepiride are the better option to treat diabetes.

Keywords: Superdisintegrants, Fast disintegrating tablets, Disintegration time, Water absorption ratio, Wetting time, Dissolution, Dynamic studies

INTRODUCTION

The elderly constitute a major portion of today's population mainly because of increased life span of individuals. Physiological and neurological conditions, such as dysphasia, a risk of choking, and hand tremors are leading causes of patient non-compliance in the self-administration of conventional solid oral dosage forms [1].

Because of impaired swallowing ability, many elderly patients find it difficult to take some conventional dosage forms such as tablets and capsules. In order to overcome this problem, the development of solid dosage forms that disintegrate fast or dissolve even when taken orally without water is being undertaken, as well as travelling patients who may not have ready access to water and suitability for geriatric and pediatric patients and patients suffering from nausea, vomiting, those with mental disorders, the bedridden patients [2-4]. Many attempts having fast disintegrating behavior have been reported like lyophilizing, molding and compressing wet powders to construct highly porous structure. However, these methods require particular machines and are time-consuming techniques; moreover, the hardness of the products was not enough to stand the process of packaging and transportation. Therefore, direct compression is the simplest, most convenient and easiest way to produce fast disintegrating tablets with sufficient structural Integrity [5].

The technologies utilized for the manufacturing of FDTs have been reported. These includes vacuum drying, lyophilizing, molding and compressing wet powder to construct the highly porous structure, crystalline transition method, wet granulation method, and direct compression method, nanonization, mass extrusion, quick dissolve film [2, 6]. But these methods required the particular machines and the time-consuming techniques; the hardness of the products was not enough to stand up to the process of packaging and transportation. In order to overcome these problems direct compression is a convenient and cheap way to produce tablets with sufficient structural integrity [4].

The important factors for the fast disintegrating tablets (FDTs) are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution so that it can be absorbed. Fast disintegrating tablets constitute several excipients are involved in a complex series of dissolution that begins when the solvent contacts the solid and penetrates the tablet matrix [4, 5]. This requires not only that excipients should have high wettability, but also that the tablet structure should have a highly porous network. When conventional direct compression and granulation methods are employed, the porosity of the tablets is inversely related to the compression pressure. However, high compression pressure is needed to ensure adequate strength of the tablets. Thus, it is often difficult for the tablet to have porosity that allows fast water absorption while maintaining high mechanical strength. New strategies to increase tablet the porosity without sacrificing its mechanical performance are desired [7].

FDTs are also known as fast disintegrating, fast dispersing, rapid dissolving, and rapid melting, and or orodisperse tablets. The European Pharmacopoeia defines the term orodisperse as a tablet that can be placed in the mouth where it disperses or disintegrates fastly before swallowing [1, 8].

FDTs approved by United States Food and Drug Administration are classified as fast disintegrating tablets. The advantages of this dosage form over conventional tablets or capsules include ease of administration, patient compliance, and palatability. The fast disintegration of tablets inside the mouth renders possibly a certain degree of absorption throughout the buccal mucosa or the sublingual. The drug candidates that undergo pre-gastric absorption when formulated as FDTs may show increased dissolution. From the perspective of the pharmaceutical industry, FDTs may provide new business opportunities in the form of product differentiation, line extension and life cycle management, exclusivity, uniqueness, and patent life extension. The significant limitation of FDT formulations is product cost since manufacturing involves use of novel excipients

and technologies. In addition, the specialized packaging is necessary to withstand handling and transportation mechanics [1, 9].

The saliva plays an important role in the disintegration of FDTs and primarily secreted in the oral cavity by parotid, submandibular (submaxillary), sublingual glands, and also by numerous minor glands. Saliva is mainly composed of water (99.5% w/v) and the remaining 0.5 % w/v is constituted by dissolved compounds. The important components of saliva are inorganic electrolytes (0.2% w/v), gasses (CO_2, N_2, and O_2), nitrogen products, such as urea and ammonia, vitamin C, creatinine, and mucins (glycoprotein with high molecular weight which renders the saliva viscous and adhesive). The accepted range of normal salivary flow is comprised from about 0.1 to 0.2 ml/min and reaches 7 ml/min upon stimulation [1, 9].

Glimepiride, 1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxami - do) ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl) urea, is a new oral sulfonylurea hypoglycemic agent for the treatment of non-insulin dependent (type II) diabetes mellitus.

It causes hypoglycemia by stimulating the release of insulin from pancreatic β cells and by increasing the sensitivity of the peripheral tissue to insulin. It also promotes the movement of sugar from the blood into the cells that need it. Glimepiride is practically insoluble in water (2.7×10^{-4} mg/ml at 25 °C) and belongs to "Class II" drugs in the Biopharmaceutical Classification System. It is likely to display low and irregular bioavailability following oral administration due to the low solubility [7].

In the present study our goal was to develop directly compressible fast disintegrating tablets of glimepiride by using different super disintegrants such as crospovidone, croscarmellose sodium, sodium starch glycolate and L-HPC in various concentrations and evaluate various tablet properties like weight variation, thickness, hardness, friability, taste, drug content, *in vitro* and *in vivo* disintegration time, and *in vitro* drug release, *in vivo* dynamic studies. Further, other parameters such as wetting time, water absorption ratio, and drug-excipient compatibility were also evaluated and the results were discussed.

MATERIALS AND METHODS

Materials

Glimepiride, Crospovidone(CP), Croscarmellose sodium(Ac-Di-Sol,CCS), Primogel (Sodium starch glycolate,SSG), Low-substituted hydroxyl propyl cellulose (L-HPC).

Microcrystalline cellulose (Avicel pH 102); Magnesium stearate; and colloidal silicon dioxide (Aerosil) were purchased from Qualikems fine chemicals; Streptozotocin was purchased from Himedia chemicals (Mumbai, India). All chemicals used in the study were of analytical grade.

Methods

Assignment of formulation codes

Various formulations of glimepiride fast disintegrating tablets (FDTs) were designed utilizing four super disintegrants, crospovidone (CP), croscarmellose sodium (CCS), sodium starch glycolate (SSG) and low-substituted hydroxyl propyl cellulose (L-HPC) each varied at different levels of concentration. All of the other ingredients were kept constant except diluents concentration varied. A total of such fourteen formulations prepared were designated with their codes and will be referred to the same in further sections. The assigned formulation codes were as follows: F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13 and F14 for formulations containing CP as the super disintegrant with concentrations of 5,10 and 15%, respectively. Similarly, CCS 5,10, 15, 20, 25 %, and SSG 5, 10, 15 % and L-HPC 5,10,15 % were the assigned codes for the formulations prepared with these respective super disintegrants at the percentage levels provided for above super disintegrants.

Preparation of glimepiride fast disintegrating tablets

Glimepiride fast disintegrating tablets were prepared by direct compression technique [5-7]. Each tablet was composed of 5 mg glimepiride, 1 mg of magnesium stearate as a lubricant, 0.5 mg colloidal silicon dioxide as a glidant, 0.5 mg orange flavor and various concentrations of the excipients as follows: either Ac-Di-Sol, Primojel or L-HPC and crospovidone as disintegrants; Avicel PH102 as diluents to complete the final weight of the tablet to 100 mg. Before compression, the previously sieved drug, diluent, glidant, and disintegrant were mixed in a glass mortar; then the lubricant was added, and mixing was continued for further 5 min. One hundred milligrams of powder mixture was manually filled into the 7 mm die and compressed into flat-faced tablets at hardness ranging from 2-4 kg/cm^2 using a 16-station single rotary tablet machine. Table. 1 shows the outlines of the compositions of various FDT formulations studied.

Evaluation of prepared glimepiride FDTs

Weight variation

Twenty tablets from each formula were randomly selected and was weighed individually using an electronic (Shimadzu, AUX 220, Japan) digital balance and mean of tablet weights was calculated. Results are presented as mean±standard deviation (*SD*).

Thickness variation

From all the prepared formulations, ten tablets from each formulation were taken randomly, and their thickness was measured with a digital vernier caliper (Mitutoyo Corp, Kawasaki, Japan). The mean±SD *values* were calculated. It should be controlled within±5 % variation of standard value.

Hardness and friability

Hardness or crushing strength of the tested FDT formulations was measured using the Monsanto hardness tester. The friability of a sample of 10 FDTs was measured utilizing a USP-type Roche friabilator (TA-024, Inco instruments& chemical ltd). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted, accurately reweighed, and percentage loss in weight (friability) was calculated.

Content uniformity

The FDT formulations were assayed for drug content. Ten glimepiride tablets were randomly selected from each formulation (containing 5 mg glimepiride) were weighed and pulverized to a fine powder in the mortar. The average weight of a tablet was calculated. A sufficient quantity equivalent to the average weight of tablet content was accurately weighed from the tablet powder and methanol was added to dissolve the active material and made up to the volume of 100 ml in a volumetric flask [12]. Then 1 ml of this solution was taken and put into another volumetric flask. Then it was completed to 25 ml with phosphate buffer pH 7.8. It was centrifuged for 10 min and supernatant was filtered through a 0.22 µm filter, and resulted supernatant solution absorbance value at 228 nm was determined using Systronics UV–Vis spectrophotometer 2202-India, and with the aid of the calibration equation drug amount in the sample was calculated.

Wetting time

The tissue papers were placed in a petri dish by folding it into five circular form in a 10 cm diameter. Petri dish containing ten milliliters of water with 0.5 % nigrosine, a water-soluble dye, was added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. The Tablet was carefully placed on the surface of the tissue paper in the center of the petri dish at 25 °C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time [1,3,14]. These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch and presented as mean±SD.

Water absorption ratio (R)

The weight of the tablet prior to placement in the petri dish was noted (w_b) utilizing a Shimadzu digital balance. The wetted tablet was removed and reweighed (w_a). Water absorption ratio, *R*, was then determined according to the following equation.

$$R=100\times(w_a-w_b)/w_b$$

Where w_b and w_a were tablet weights before and after water absorption, respectively.

***In vitro* disintegration time**

The disintegration of tablets was determined using a USP disintegration testing apparatus type II (Paddle, Electrolab ED-2L, India) with pH 6.8 phosphate buffer as a disintegrating medium. The medium was maintained at 37±0.5 °C throughout the test. Six tablets were placed into an apparatus and disintegration time was recorded [16]. Measurements were carried out in replicates (*n*=6) and mean±*SD* values were recorded.

***In vitro* dissolution studies**

The drug release was determined using USP standard dissolution tester, Apparatus II rotating paddle (Electrolab TDT-08L, India). Dissolution was carried out in 300 ml of phosphate buffer at pH 7.8. The paddle was rotated at 75 rpm at 37±0.5ºC. Aliquots of 5 ml were withdrawn and replaced with equal volumes of fresh phosphate buffer pH 7.8 at specified time intervals (5, 10, 15, 20, 30, 40, 50 and 60 min). Samples were adequately diluted, filtered through a 0.22 µm filter and analyzed with spectrophotometrically for their glimepiride in phosphate buffer pH 7.8 at 228 nm (Systronics UV–Vis spectrophotometer 2202-India). Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved. The experiments were done in triplicates (n=3) for each of the selected FDT formulae.

***In vivo* oral disintegration time**

The disintegration time of FDTs is measured utilizing the conventional tests for tablets that are described in the Pharmacopoeias. It is very difficult to assess the disintegration rate for the FDT with these tests due to its rapid disintegration rate even in a small amount of water. So, the disintegration rate obtained from the conventional disintegration tests appears not to be reflective of the disintegration rate in the human mouth. Because of this standard compendia test faces many disadvantages in the discrimination between different FDTs as their disintegration time is very short and also because of the strong agitation and large volume of water used during this test [24]. The measurements of disintegration time in the oral cavity were carried out in six healthy volunteers (mean age = 23.5±1.04 y). Prior to the test, all volunteers got a detailed briefing on purpose and protocol of this test. The institutional ethics committee approved the in the vivo study protocol, and each subject gave his written consent to participate. As per the protocol. Then they were asked to rinse their mouth with a cup of water (200 ml). The FDT was placed on the subject's tongue and immediately a stopwatch was started as soon as the tablet contacts the tongue. The subjects were instructed to move gently the tablet against the upper part of the mouth with their tongue and to cause a gentle tumbling action on the tablet [4, 17, 20]. It was emphasized to the subjects that this is a gentle motion without biting on the tablet or tumbling it from side to side. Immediately after the last noticeable granule had disintegrated, the time was recorded. The swallowing of saliva was prohibited during the test, and also, saliva was rinsed from the mouth after each measurement [15-18, 24].

***In vivo* pharmacodynamic studies**

Prepared glimepiride tablets were administered to male albino Wister rats to investigate the biological activity of new prepared optimized glimepiride tablet in comparison with the directly compressed tablet and pure drug.

Experimental design

Rats were divided into the following groups.

Group I: (Control group) consisted of 6 rats which served as control

Group II: (DCT group) consisted of rats they will be with the oral dose of the directly compressed tablet that is without super disintegrant (DCT).

Group III: (Pure drug): Consisted of 6 rats and they will be with the oral dose of the pure drug (Glimepiride).

Group IV: (Glimepiride formula group) consisted of 6 rats and they will be with the oral dose of glimepiride optimized tablet.

Preparation of reagents

Preparation of citrate buffer

0.1 M citrate buffer was prepared by dissolving 1.47 g of sodium citrate in 50 ml of deionized water; adjust the pH to 4.5 by using monohydrate citric acid solution.

Preparation of streptozotocin solution

Streptozotocin was prepared by dissolving required amount of Streptozotocin (it is calculated according to the body weight of individual rat) in required amount of citrate buffer.

Preparation of glucose solution

5% glucose was prepared by dissolving 5 g of glucose dissolved in 100 ml distilled water.

Induction of diabetes

Prior to the induction of diabetes, all the male albino rats of Wistar strain (150-250 g; 4-6 w old) were maintained under controlled conditions of light (12 h/24 h) and temperature (23±1ºC). The animals were fasted for overnight. A single dose of streptozotocin (40 mg/kg) was administered through intraperitoneal route to the Groups II, III and IV rats. While normal control rats were injected with buffer alone. Streptozotocin was dissolved in freshly prepared 0.1M citrate buffer pH (4.5). Streptozotocin injected animals were given 5 % glucose for 24 h to prevent initial streptozotocin-induced hypoglycemic mortality [15, 19].

Blood sampling

Blood samples were withdrawn from the animals after predetermined intervals 15 min, 30 min, 45 min, 60 min, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h through the tail vein.

Table 1: Composition of Glimepiride fast disintegrating tablets

Formulation	Glimepiride (mg)	CP (mg)	SSG (mg)	CCP (mg)	L-HP (mg) C	MCC (mg)	Mg stearate (mg)	Aerosil (mg)	Erythritol (mg)	Orange flavor (mg)
F1	5	5				87	1	1	0.5	0.5
F2	5	10				82	1	1	0.5	0.5
F3	5	15				77	1	1	0.5	0.5
F4	5	-	5			87	1	1	0.5	0.5
F5	5	-	10			82	1	1	0.5	0.5
F6	5	-	15			77	1	1	0.5	0.5
F7	5	-	-	5		87	1	1	0.5	0.5
F8	5	-	-	10		82	1	1	0.5	0.5
F9	5	-	-	15		77	1	1	0.5	0.5
F10	5	-	-	20		72	1	1	0.5	0.5
F11	5	-	-	25		67	1	1	0.5	0.5
F12	5	-	-	-	5	87	1	1	0.5	0.5
F13	5	-	-	-	10	82	1	1	0.5	0.5
F14	5	-	-	-	15	77	1	1	0.5	0.5

Determination of blood glucose levels

Blood glucose levels were determined using a glucometer. The blood samples were withdrawn for determination of blood sugar after 15 min, 30 min, 45 min, 60 min, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h. The blood sugar levels were then plotted against time.

Fourier transforms infrared spectroscopy (FTIR)

Drug excipient incompatibility was studied by Fourier transform infrared spectroscopy. FTIR studies were performed on drug, Croscarmellose sodium, physical mixture and the optimized formulated compressed tablet using Shimadzu IR Prestige FTIR Spectrophotometer Prestige, India. The samples were analyzed for wave numbers 4000 and 400 cm.

RESULTS AND DISCUSSION

Formulation rationale

The objective of a directly compressible fast disintegrating tablet is that it disintegrates or disperses in the saliva within a matter of seconds. The super disintegrants form the core of FDT formulations. Crospovidone (CP), croscarmellose sodium (CCS), sodium starch glycolate (SSG) and Low-substituted hydroxyl propyl cellulose (L-HPC) are four of the most commonly used and highly effective super disintegrants currently included in solid dosage formulations. In this study, CP, CCS, SSG and L-HPC in the glimepiride FDT formulations was evaluated at different concentrations. Other formulation components were kept constant except diluent concentration.

CP polymers are densely cross-linked homopolymers of *N*-vinyl 2-pyrrolidones. CP rapidly absorbs liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration due to their porous particle morphology. One researcher in his research study reported, in addition, to its unique particle size and morphology, disintegrant properties of CP are not affected by pH and consequently being non-ionic does not bind to ionic drug moieties, it can also be used as a solubility enhancer to improve dissolution and, unlike other super disintegrants, does not form a gel at higher concentrations [1].

CCS is cross-linked carboxymethyl cellulose sodium; Its unique fibrous nature imparts excellent water-wicking properties and cross-linking makes it a hydrophilic and highly absorbent material resulting in excellent swelling properties. CCS swells rapidly up to 4–8 times its original volume in contact with water. Similar to CP, it is also used as a dissolution aid.

SSG, a sodium salt of carboxymethyl ether of starch. Disintegration occurs as a result of rapid uptake of water followed by rapid and enormous swelling, which is its primary mechanism of action [1, 12, 13]. SSG may swell up to 300 times its original volume in water.

L-HPC (Low-substituted hydroxypropyl cellulose) is partially substituted hydroxypropyl ether of cellulose in which a small proportion of the three hydroxyl groups contained in the β-o-glucopyranosyl ring of the cellulose is etherified with propylene oxide. While highly substituted hydroxypropyl ether of cellulose is soluble in both water and alcohols, L-HPC is insoluble in these solvents, but it swells in water. Different grades are available that differ in hydroxyl propyl content and in particle size [21, 22].

Avicel PH102 was included in the formulation as a disintegrant and a diluent. This grade of microcrystalline cellulose is powder in nature and commonly used direct compression filler. Owing to excellent compressibility, it is widely added in tablet formulations to improve hardness and prevent capping.

Colloidal silicon dioxide (Aerosil®), which acts both as a glidant and lubricant, also helps in appreciably decreasing tablet friability. This may be due to Aerosil® helping in restoring the bonding properties of the excipients.

Evaluation of the prepared glimepiride FDTs

All the glimepiride tablet formulations containing these four super disintegrants at different concentrations were evaluated. Weight variation and thickness are within mean±7.5 % and mean±5 %, respectively. FDT should disintegrate rapidly upon placement in the mouth, yet possess sufficient structural integrity to withstand handling without substantial breakage. Thus, tablet properties such as hardness, and friability are closely linked to causing rapid tablet disintegration.

The hardness of all the prepared tablets was in the range of 2.3±2.9 kg/cm^2 for all the fast disintegrating tablets.

The friability is a measurement of the tablet's physical strength. It was stated that an acceptable friability for dispersible tablets ranges from 0.52 % to 0.73 %. All the prepared formulation had no tablet was cracked, split or broken in either formula.

Content uniformity was found to be good where the percentage of drug content was found to be in the range of 96 % to 98 %.

Disintegration time is an important criterion for selecting an optimum FDT formulation. Several methods have been described for evaluating *in vitro* and *in vivo* disintegrating time of FDT formulations. *In vitro* disintegrating time was determined following the procedure described in a previous section [6, 17]. According to the compendia standards, FDT should disintegrate within 3 min when examined by the test for the disintegration of tablets and capsules [22].

Table 2: Evaluation of glimepiride fast disintegrating tablets

Formulation	Weight variation* (mg)	Thickness** (mm)	Hardness** kg/cm^2	% Friability** (%)	Drug content*** (%)
F1	95.14±1.21	2.2±0.2	2.5±0.06	0.52±0.12	96±0.7
F2	98.97±1.14	2.21±0.14	2.3±0.08	0.68±0.20	97.2±0.4
F3	99.73±0.87	2.1±0.12	2.4±0.2	0.72±0.15	95.8±0.56
F4	96.10±0.87	2.2±0.08	2.6±0.18	0.59±0.12	97.4±0.8
F5	101.01±0.96	2.4±0.13	2.4±0.1	0.73±0.14	97.8±0.3
F6	99.16±0.9	2.3±0.18	2.6±0.12	0.67±0.17	98±0.27
F7	96.9±0.7	2.2±0.2	2.8±0.1	0.55±0.12	96.8±0.8
F8	98.4±1.1	2.1±0.1	2.2±0.2	0.54±0.09	95.8±0.55
F9	98.1±0.97	2.3±0.12	2.6±0.1	0.64±0.13	97.8±0.47
F10	98.4±1.1	2.2±0.1	2.7±0.13	0.69±0.12	97.8±0.68
F11	99.75±0.89	2.2±0.18	2.8±0.08	0.72±0.11	98±0.37
F12	98.4±0.92	2.1±0.2	2.9±0.12	0.58±0.10	96.2±0.43
F13	99.14±0.99	2.1±0.08	2.5±0.14	0.69±0.11	96.6±0.86
F14	98.5±0.91	2.2±0.06	2.4±0.2	0.71±0.10	96±0.075

Results are the mean of 20 observations±SD; **Results are the mean of 10 observations±SD, ***Results are the mean of 3 observations±SD

From the observation the increasing, the super disintegrant concentration resulted in a decrease in disintegrating time as depicted in fig. 1. The disintegrating time of formulations containing CCS were lower than those containing SSG,CP and L-HPC which might be attributed due to its rapid water-absorbing nature involving both capillary and swelling mechanisms, and delayed disintegration time for other super disintegrates due to their tendency to gel more than Croscarmellose sodium.

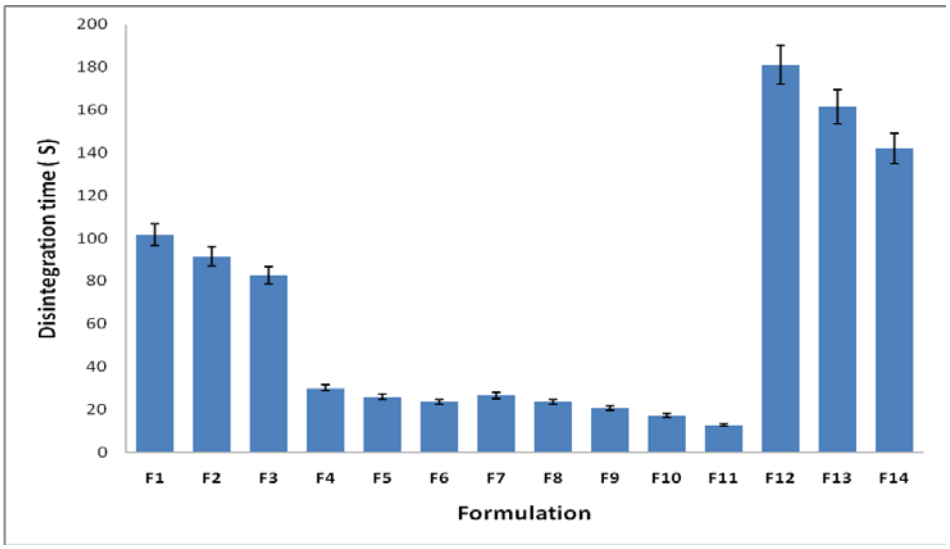

Fig. 1: Disintegrating time for various formulations (n=6, mean±SD)

The mechanism involved in Croscarmellose sodium is when it comes into contact with water it swells to a large extent to disintegrate the tablets. Also, it has fibrous nature that allows intra-particulate as well as extra-particulate wicking of water even at low concentration levels. In the case of crospovidone has excellent wicking nature and pronounced hydration, though it swells only to a small extent with little tendency to gel formation, and disintegrate rapidly but into larger masses of aggregated particles [2-4].

Because disintegration time of tablets contained crospovidone was delayed resulting the filling up of tablet porosity with formulating magnesium stearate which possessed hydrophobic property. Observed results suggested that the disintegrants added into tablet formulations might cause the penetration behavior of water in the tablet, and the penetration rate of water would be altered [5, 6]. The *in vitro* disintegration time for all formulation was found to be 12-142 s.

Wetting time and water absorption ratio for the prepared glimepiride FDTs

All the formulations were wetted within an acceptable time of less than 1 min, where F4, F5, F6, F7, F8, F9, F10, and F11 were wetted in 36±0.89, 32.6±1.3, 29.5±1.04, 34.5±1.87, 30.8±1.16, 27±0.89, 21.5±1.04 and 19.85±0.75 s respectively. However, the longest wetting time was taken by F1, F2, F3, F12, F13 and F14 which were 105.3±1.9, 96.8±1.8, 86±1.4, 187.5±1.04, 160.3±1.6 and147.1±1.16 s, respectively. It was also observed that formula F11 which had the least wetting time also had the minimum disintegration time showing a strong correlation between disintegration times and wetting time.

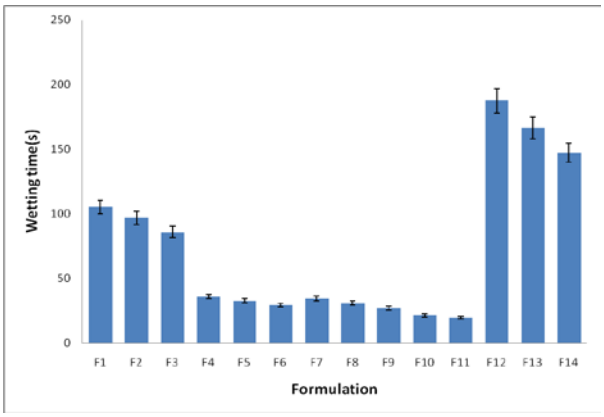

Fig. 2: Wetting time for various formulations (n=6, mean±SD)

Fig. 2 shows in details the main effects of each additive on the tablets' wetting time. Regarding the effect due to disintegrants (fig. 3), they can be arranged in ascending order as follows: Ac-Di-Sol<Primojel<CP<L-HPC with mean wetting time values of 26.7, 32.7, 96 and 164.9 s, respectively.

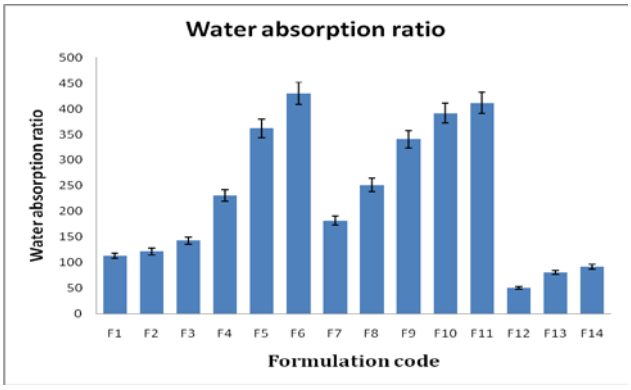

Fig. 3: Water absorption ratio for various formulations (n=3, mean±SD)

From the Fig.3. it was observed that the formulae are containing Primojel as disintegrant had higher mean water absorption ratio than Ac-Di-Sol, CP and L-HPC, and took more time for wetting of tablets than Ac-Di-Sol this high water uptake lead to less patient convenience while taking the FDTs. Wetting is closely related to the inner structure of the tablets and the hydrophilicity of excipients. Primojel shows its disintegration effect by the mechanism of ''swelling". Ac-Di-Sol shows its disintegration action by ''wicking" (due to its fibrous structure) and swelling with minimum gelling. It had the minimum wetting time and the minimum water absorption ratio. Increased porosity of Ac-Di-Sol provides pathways for the penetration of fluids into tablets resulting in ''wicking" through capillary action causing faster disintegration of tablets [1, 18, 24].

***In vitro* dissolution studies**

The drug release time for the crospovidone formulations was found at the F1, F2, and F3 are at 10 min (22.47±0.41), (28.34±0.25), and (30.62±0.24) respectively. From the above observations, it is concluded that F3 formulation gives maximum drug release within 10 min (fig. 4).

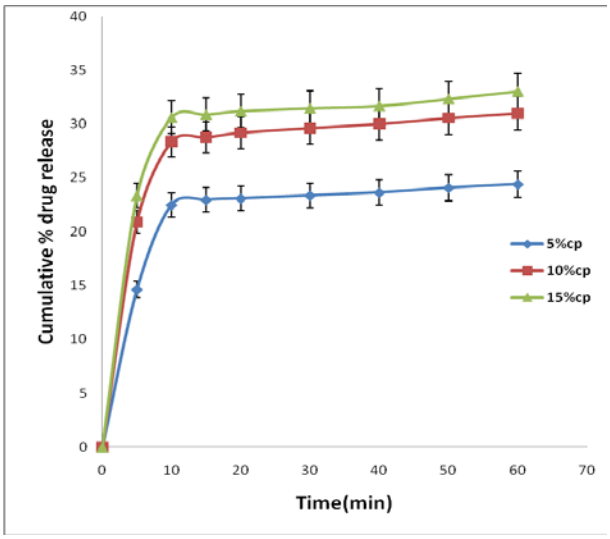

Fig. 4: *In vitro* drug release studies on prepared tablets at different concentrations of Crospovidone (n=3, mean±SD)

The maximum drug release time for the sodium starch glycolate formulations was found at the F4, F5, and F6 are 5 min (29.1±0.32) (37.1±0.48)(48.3±0.48) 60 min (39.33±0.43), 60 min (45.68±0.32), and 60 min (56.49±0.33) respectively. The initial drug release for formulation F4 at 5 min is 29.78±0.32. From the above observations, it is concluded that by increasing the concentration of Sodium starch glycolate, the drug releases at a faster rate (fig. 5).

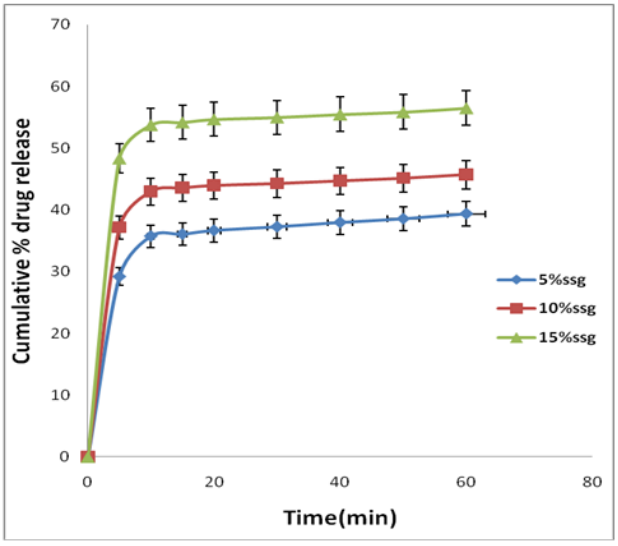

Fig. 5: *In vitro* release studies of prepared tablets at different concentrations of sodium starch glycolate (n=3, mean±SD)

The drug release time for the formulations was found at the F7, F8, F9, F10, and F11 are at 10 min (44.90±0.16), 10 min (50.19±0.32), 10 min (62.96±0.32), 10 min (70.17±0.33) and 10 min (84.74±0.32) respectively. From the above observations, it is concluded that F11 formulation gives maximum drug release within 10 min (fig. 6).

The drug release for the formulations F12, F13, and F14 are at 60 min (20.40±0.09), 60 min (22.12±0.41), 60 min (25±0.43) respectively. From the above observations, it is concluded that F14 formulation gives maximum drug release (Fig.7). The release of the drug rate was delayed when compared with other super disintegrant formulations [9, 11].

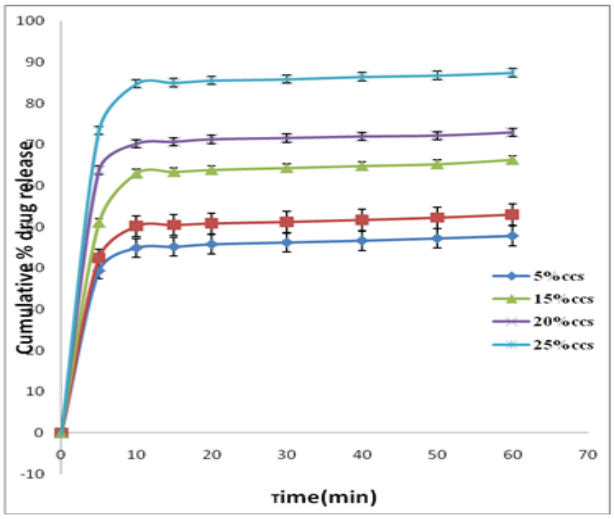

Fig. 6: *In vitro* release studies of prepared tablets at different concentrations of Croscarmellose sodium (n=3,mean±SD)

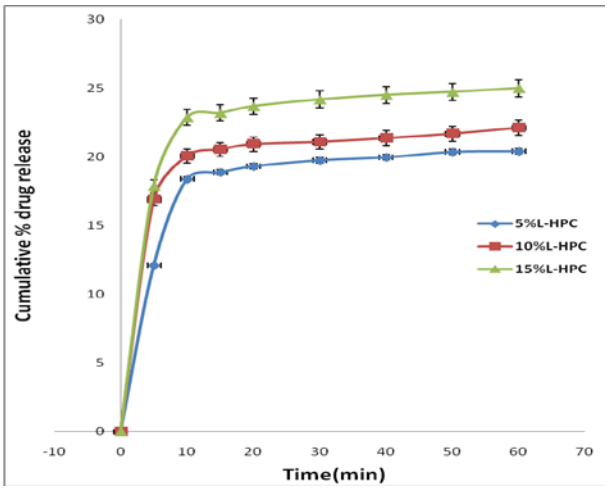

Fig. 7: *In vitro* release studies of prepared tablets at different concentrations of L-HPC (n=3, mean±SD)

In vitro dissolution studies showed that the comparison of drug released rate from the F3, F6, F11and F14 formulations within 10 min. The F3 formulation containing crospovidone in the concentration of 15 % showed minimum disintegration time of 82.6 s, wetting time of 86 s and 23.3 % drug and 33.04% drug was released within 5 and 60 min respectively. The F6 formulation containing sodium starch glycolate in the concentration of 15 % showed minimum disintegration time of 23.5 s, wetting time of 29.5 s and 48.3 % drug, 53.1 % and 56.04 % drug was released within 5,10 and 60 min respectively.

The F11 formulation containing croscarmellose sodium in a concentration of 25 % showed minimum disintegration time of 12.8 s, wetting time of 19.8 s and 73.4 % drug, 84.7 %and 87.4 % drug was released within 5,10 and 60 min respectively. The F14 formulation containing L-HPC in the concentration of 15 % showed minimum disintegration time of 142 seconds, wetting time of 147.6 s and 17.8 % drug, 22.8 % and 25 % drug was released within 5,10 and 60 min respectively. The optimized formulation of F11 was compared with F3, F6, F14 and the dissolution parameters of three formulations are shown in and fig. 8.

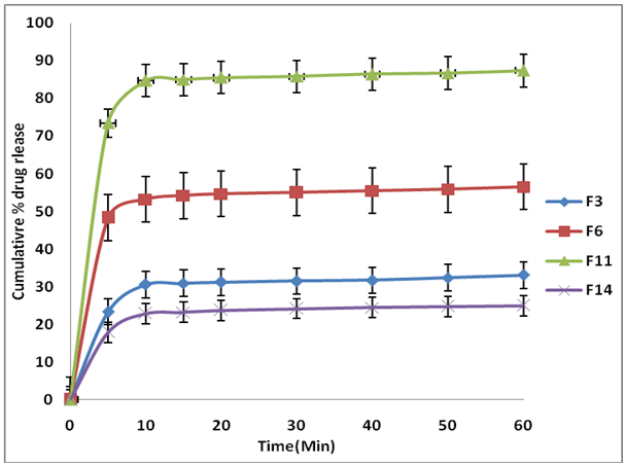

Fig. 8: *In vitro* drug release studies on prepared tablets, comparison of F3, F6, F11 and F14 formulations (n=3, mean±SD)

In vitro dissolution studies showed that more than 50 % of the drug was released from the F6, F9, F10, F11 formulations within 5 min. The F11 formulation containing croscarmellose sodium in a concentration of 25 % showed minimum disintegration time of 12 s, wetting time of 19.80 s and 73 % drug and 84.7 % drug was released within 5 and 10 min respectively.

The optimized formulation of F11 was compared with the Pure drug (Plain powder), a tablet without super disintegrant (DCT) and the dissolution parameters of three formulations are shown in fig. 9.

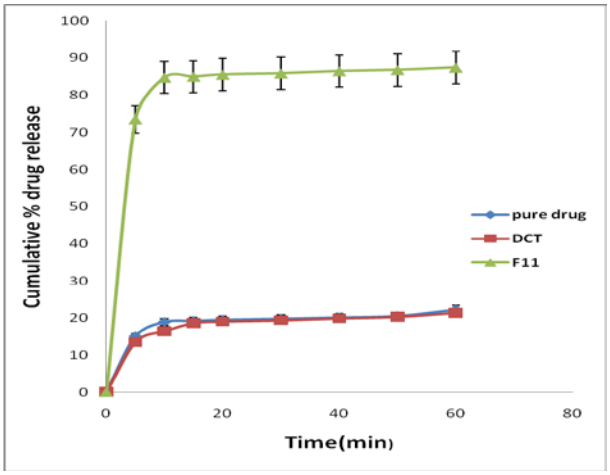

Fig. 9: *In vitro* drug release studies on prepared tablets, comparison of pure drug, DCT and F11 formulations (n=3, mean±SD)

In vivo disintegration time

Considering wetting time, water absorption ratio, *in vitro* disintegrating time, and cumulative % drug released, formulations containing CCS were considered to be better than those containing SSG, CP and L-HPC. F11 (CCS 25%) was considered as the optimal FDT formulation among all of the 14 formulations tested in this study and selected for *in vivo* disintegration studies. The test was performed as discussed in an earlier section [21,24].

The disintegration time of FDTs containing F11 (CCS 25%) was measured in the mouths of six healthy male human volunteers as per the protocol. Complete disintegration was achieved at 13.1, 13, 14.6, 16.1, 13.1, and 15.6 s, respectively (mean±SD, 14.25 and 0.79 s). The same formulation was administered thrice to each individual, and the average of triplicate measurements represents an individual oral disintegrating time. The Results were depicted in Table. 3. Based on these data, this *in vivo* study demonstrates the applicability of the formulated FDT for potential commercial use.

Table: 3 *In vivo* disintegrating time for optimized formulation (n=3, mean±SD)

Human volunteers	*In vivo* disintegrating time (S)
1	23±0.12
2	26±0.25
3	20±0.36
4	24±0.56
5	26±0.39
6	25±0.45

In vivo pharmacodynamic studies

The blood glucose levels were determined by using blood glucose test stips (Gluco chek) with a glucometer. Blood samples were collected at predetermined intervals, i.e. 15 min, 30 min, 45 min, 60 min, 2 h, 4h, 6 h, 8 h, 12 h, 24 h. The results are shown in the fig. 7. Blood glucose levels were reduced considerably in the group II and group III rats treated with DCT (without super disintegrant) and pure drug within 4 h is up to 60 %. The reduction in blood glucose levels was significant in group IV rats treated with optimized FDT formulation. Blood glucose levels were decreased in 2 h (Fig.10). The rapid decrease of blood glucose levels in group IV rats might be due to the rapid absorption of the drug and rapid onset of action from the optimized fast disintegrating tablet showed good dynamic activity.

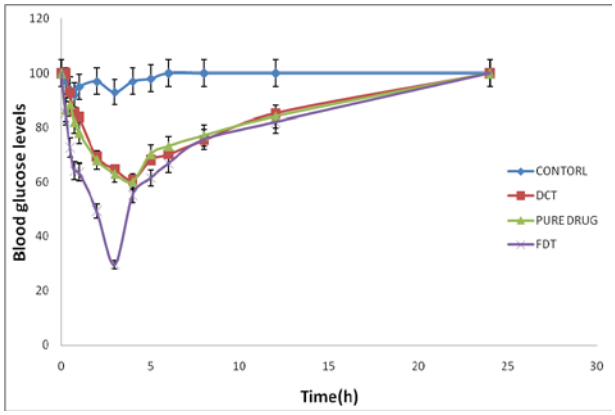

Fig. 10: Percentage of blood glucose level decrease in diabetes induced rats on oral administration of the pure drug, FDT powder, DCT powder (Without superdisintegrants tablet). (n=3, mean±SD)

Fourier transforms infrared spectroscopy

The characteristic FTIR spectra of Glimepiride, Croscarmellose sodium, Physical mixture, Tablet were shown in Fig.8. The stabilizing interaction between the OH-group of glimepiride (Hydrogen bonded at ~ 3367 cm^{-1}) and C-H stretch in the alkanes (2929 cm^{-1}) and C=C stretch in the alkenes (1674 cm^{-1}) and NO_2 symmetrical stretch group of nitro compound (1346 cm^{-1}) were found to remain unchanged in all of the Croscarmellose sodium, Physical mixture, tablet.

Croscarmellose sodium showed peaks at OH-stretch (Hydrogen bonded at ~ 3566 cm^{-1}) and C-H stretch in the alkanes (2920 cm^{-1}) and C=C stretch in the alkenes (1670 cm^{-1}) and NO_2 symmetrical stretch group of nitro compound (1375 cm^{-1}). Physical mixture

showed peaks at OH-stretch (Hydrogen bonded at ~ 3369 cm^{-1}) and C-H stretch in the alkanes (2922 cm^{-1}) and C=C stretch in the alkenes (1674 cm^{-1}) and NO_2 symmetrical stretch group of nitro compound (1346 cm^{-1}). Tablet showed peaks at OH-stretch (Hydrogen bonded at ~ 3367 cm^{-1}) and C-H stretch in the alkanes (2916 cm^{-1}) and C=C stretch in the alkenes (1674 cm^{-1}) and NO_2 symmetrical stretch group of nitro compound (1373 cm^{-1}).

In the optimized formulations, the presence of all the characteristic peaks of the Glimepiride indicates a lack of any strong interaction between the drug and the excipients.

CONCLUSION

From the experimental results, it can be concluded that the fast dissolving system can be formulated using different super disintegrants like Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium and L-HPC by Direct Compression technique. The FTIR Spectra revealed that Croscarmellose Sodium and excipients used were compatible with the drug. The formulated tablets showed compliance for various physiochemical parameters viz. hardness, friability, weight variation, content uniformity and disintegration and dynamic studies. The drug content was within an acceptable range which ensured dose uniformity in the formulation. The *in vitro* studies revealed that formulation F11 showed maximum drug release and drug content. The water absorption ratio revealed that Formulation F11 showed best wetting time results. On the basis of release drug disintegration and wetting studies, it can be concluded that the formulation F11 is the optimum formulation. *In vivo* pharmacodynamic study demonstrated that there is a decrease in blood glucose levels in diabetes-induced rats within 2 h and showed good dynamic activity. From the above-obtained data it concluded that fast disintegrating tablets of glimipiride are better formulations to treat diabetes.

CONFLICT OF INTERESTS

Declared none

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