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Research Article

Formulation and Evaluation of Mouth Dissolving Tablet Glimepiride by Direct Compression Method

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ABSTRACT

Fast dissolving tablets emerge as one of the popular and widely accepted dosage forms, especially for pediatric patients because of incomplete development of the muscular and nervous system and a case of geriatric patients suffering from Parkinson's disorder or hand tremors. Few solid dosage forms like capsules and tablets are present days facing the problems like difficulty in swallowing (dysphagia), resulting in many incidences of non-compliance and making the therapy ineffective. Oral dosage form and oral route are the most preferred route of administration for various drugs have limitations like first-pass metabolism, psychiatric patients, bed ridden and uncooperative patients. Glimepiride is a second generation sulfonylurea of oral hypoglycaemic drug that stimulates the ß-cells of the pancreases to secrete insulin. The mouth dissolving tablets were prepared by direct compression technique. The drug- excipient compatibility studies were performed by Fourier Transform Infrared spectroscopy (FTIR). Physicochemical characteristics and *In-vitro* drug dissolution tests were performed. The *In-vitro* drug release pattern and the dissolution data was treated with mathematical modeling accelerated stability studies were also carried out to the optimized formulation (F-6). The FTIR studies revealed that drugs were compatible with the Superdisintegrants used. The optimized formulations were found to have good physicochemical and *In-vitro* release properties. The *In-vitro* dissolution data was perfectly fitting to zero order and the release of drug from the formulation followed Higuchi's release. The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions.

INTRODUCTION

In the past several years, there has been rapid development in the number of fast disintegrating tablets available in pharma market. The mouth dissolving tablet was described as tablet intended to be placed in the mouth that subsequently disperses rapidly before swallowed by patient [1]. A mouth dissolving tablet is generally recognized as a solid dosage form containing a medicinal substance that disintegrates rapidly and dissolves in mouth without water. Mouth dissolving tablets are also known as quick dissolves, fast melts; melt in the mouth, rapimelts, fast dissolving, rapid dissolve, or orally dissolving tablets. These formulations have increase acceptance because patients, old and young find them convenient and easy to use.

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In addition, pharmaceutical manufactures can differentiate their products by offering new dosage forms [2]. Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing, conventional dosage forms such as tablet when water is not available [3].

Orally disintegrating tablets offer great advantages for patients having difficulty in swallowing. The condition in which patient suffers from difficulty in swallowing is known as

'Dysphagia'. It is common among all age groups, especially in elderly patients. Disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy.

Advantages of mouth dissolving tablet dosage form include administration without water, accuracy of dosage, alternative to liquid dosage forms, easy portability, ideal for geriatric patients and rapid onset of action. Traditional tablets and capsules administered with 250mL of water may be inconvenient for patients. The concept of mouth dissolving / disintegrating tablets emerged from the desire to provide patient with more conventional means of taking this medication when drinking water is not available.

When administered an *In-situ* suspension is created in the oral cavity as the tablet disintegrates and is subsequently swallowed. The time for disintegration of orally disintegrating tablets are generally considered less than one minute.

Several technologies are available to manufacture MDTs. The most common preparation methods are moulding, lyophilization or freeze drying, cotton candy, spray drying, sublimation and direct compression.

Desired Characters for Mouth Dissolving Tablets [4]

- The tablet should be to administer without water.
- Any unpleasant taste should be masked.
- Disintegration should take place within seconds.
- Tablet should have a pleasing mouth feel without grittiness.
- Leave minimal or no residue in the mouth after oral administration.
- The formulation should be stable to environmental conditions such as humidity and temperature.
- The manufacturing cost should be economic.

Advantages of Mouth Dissolving Tablets [5]

- Ease of administration to patient such as pediatric, geriatric and psychiatric patients who have difficulty in swallowing.
- Highly convenient feature for patients during traveling and do not have immediate access to water, since it needs no water for administration.
- Mouth dissolving tablet produces quicker onset of action due to rapid disintegration and dissolution.
- It helps drugs to get absorbed from the mouth, pharynx and esophagus when passing to stomach with saliva.
- Improved bioavailability can be obtained as absorption takes place.

Disadvantages of Mouth Dissolving Tablets [5]

MDT's have following drawbacks:

- The tablets may leave unpleasant taste and / or grittiness in mouth if not formulated properly
- Mouth dissolving tablets need special packing for properly stabilization and safety of stable product.

MATERIALS AND METHODS

Materials

Glimepiride is a gift sample from Saimirra Info pharma Pvt Ltd, Chennai, Sodium starch glycolate, Crospovidone, Crosscarmellose sodium is a Superdisintegrant, MCC act as a Diluent, SLS act as a surfactant, Orange flavor as a flavoring agent, Aspartame is a sweetening agent, Colloidal silicon dioxide as a Lubricant, Magnesium stearate as a Glidant.

Methods [6, 7]

Various techniques have been developed for the formulation of Mouth dissolving tablets or Orodispersible tablets.

- Freeze drying/ lyophilization
- Tablet Moulding
- Spray drying
- Sublimation
- Direct compression
- Mass extrusion

Preparation of Mouth Dissolving Tablets [8]

The drug, diluents, sweetening agent, superdisintegrants, glidant, lubricant and flavor were passed through sieve no.80. The drug was mixed with of diluent, superdisintegrant, Aspartame, orange flavor by Geometric mixing 30 minutes. The drug mix added sifted Colloidal Silicon dioxide and mixed well for 10 minutes to get a uniform pre-lubricated blend. To the pre-lubricated blend sifted Magnesium stearate was added and mixed for 3 minutes to obtain final blend. The blend was compressed in 10 station compression machine with single punch to obtain Glimepiride Mouth dissolving tablets.

Table 1: Formulation of glimepiride mouth dissolving tablets

S.NO	INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Glimepiride	5	5	5	5	5	5	5	5	5
2	Sodium starch glycolate	5	10	15	-	-	-	-	-	-
3	Crospovidone	-	-	-	5	10	15	-	-	-
4	Croscarmellose sodium	-	-	-	-	-	-	5	10	15
5	Microcrystalline cellulose	85	79	73	85	79	73	85	79	73
6	SLS	1	2	3	1	2	3	1	2	3
7	Orange flavor	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
8	Colloidal silicon dioxide	1	1	1	1	1	1	1	1	1
9	Aspartame	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
10	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

The tablet obtained was studied for compatibility and evaluated for post compression parameters.

Formula of Various Formulations of Mouth Dissolving Tablets

Precompression Parameters

The granule blend was evaluated for flow characteristics viz. angle of repose, bulk density, tapped density, compressibility index, Hausner ratio.

Bulk Density[9]

Apparent bulk density (Db) was determined by pouring 25g of the weighed blend into a graduated cylinder of tap density apparatus and untapped apparent volume Vb was noted. The bulk volume (Vb) and weight of the powder (M) was calculated using formula:

$$Db = \frac{M}{Vb}$$

Where, Db= Bulk density in g/cm, M= Weight of powder in gm, Vb= Bulk volume in cm.

Tapped Density

It is ratio of total mass of powder to the tapped volume of the powder. After noting down the bulk density , the cylinder was tapped for 300 times and tapped volume was noted. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured.

$$Dt = \frac{M}{Vt}$$

Where, Dt = Tapped Density in g/cm, M= Weight of powder in gm, Vt= Volume after tapping in cm

Compressibility Index [10]

The simplest way of measurement of free flow of powder is compressibility. The indication of the ease with a material can be induced to flow is given by compressibility index.

$$CI = \frac{(pt - pb)}{pt} \times 100$$

Where, CI= Compressibility Index in %
Pt= Tapped density of powder
Pb= Bulk density of powder

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow.

$$HR = \frac{pt}{pb}$$

Where HR= Hausner Ratio, pt= Tapped density, pb= Bulk density

Angle of Repose [11]

Angle of repose was determined by fixed funnel method. The blend was poured was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated. It is the maximum angle possible between the heap of the pile and base

$$\text{Angle of repose} = \tan\frac{h}{r}$$

h= Height of heap in cm, r= Radius of pile in cm.

Post Compression Parameters

Appearance

The appearance of a tablet involves measurement of number of attributes like tablet shape, size, color, presence or absence of an odor, taste, surface texture, physical flaws for

control of lot uniformity and tablet to tablet uniformity.

Uniformity of Weight [12]
Weigh 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage prescribed and none deviates by more than twice that percentage.

Tablet Diameter [13]
The tablet was measured using venire caliper in mm.

Tablet Thickness
The tablet thickness was measured using venire in mm. It should be controlled within ±5% variation of standard value.

Hardness [14]
The tablet crushing load, the force required to break to tablet into halves by compression was determined by using Monsanto hardness tester.

Friability Test [15]
Friability of the tablets checked by using Roche Friabilator. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed 25rpm for 4 minutes. Tablets were then de-dusted, re-weighed and then percentage loss in weight (friability was calculated.

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

In-Vitro **Disintegration Time** [16]
The disintegration of tablet was determined using a USP disintegration testing apparatus type-II (Paddle) with water 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. Measurements were carried out in replicates (n=6) and mean±SD values were recorded.

In- Vitro **Dispersion Time** [17]
Tablet was added to 10 mL Water at 37±0.5°C and time required for complete dispersion was noted. Three tablets from each formulation were randomly selected for the test.

Wetting Time [18]
The tissue papers were placed in a petri dish by folding it into five circular form in a 10cm diameter. Petri dish containing ten milliliters of water with sunset yellow 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. These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch and presented as mean± SD.

Water Absorption Ratio
The weight of the tablet prior to placement in the petri dish was noted (Wb) utilizing a digital balance. The wetted tablet was removed and reweighed (Wa). water absorption ratio, was determined using the following equation.

$$R = \frac{(W_a - W_b)}{W_b} \times 100$$

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

Moisture Uptake [19]
Ten tablets from each formulation were kept in desiccators over calcium chloride at 37°C for 24h. The tablets were then weighed and exposed to 75% Relative Humidity, at room temperature for 3 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the dessicator 3 days. Tablets were weighed and the percentage increase and the percentage increase in weight was recorded.

Chemical Properties of The Tablet
Assay [20]
The amount of drug was determined by blank correction method. Accurately weighed samples (n=3) equivalent to 10mg of drug was taken in a 100mL volumetric flask, a volume of 20mL methanol was added and sonicated for 20 min to dissolve the drug. The volume was made to 100mL with pH 7.8 buffer solution. The dispersion was filtered using 0.45µm membrane filter. A 10mL of aliquot of the above solution was taken and diluted to 100mL with buffer solution. The absorbance of sample solution was determined at 228nm against carrier blank.

Uniformity of Drug Content [21]

The MDT formulations were assayed for drug content. Ten glimepiride tablets were randomly selected from each formulation (containing 5mg glimepiride) were weighed and pulverized to a fine powder in the mortar. The average weight of a tablets was calculated. A sufficient quantity equivalent to the average weight of the tablet content was accurately weighed from the tablet powder and methanol was added to dissolve the active material and made up to volume of 100mL in a volumetric flask. Then 1mL of this solution was taken and put into another volumetric flask. Then it was completed to 10mL with phosphate buffer 7.8. It was centrifuged for 10 min and 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.

***In-Vitro* Drug Release** [22]

In-vitro dissolution studies for various batches on tablets were performed in phosphate buffer (pH 7.8) at 37±0.5°C Using USP II rotating paddle apparatus (VEEGO Dissolution tester) at 75rpm. All the formulations were subjected to dissolution. 10mL of the samples were withdrawn at time intervals 2, 4, 6, 8, 10, 12, 14 and 16 minutes. The sample was filtered through Whatman paper (0.45µ size). The volume of the dissolution fluid was adjusted by replacing 10mL of dissolution medium after each sampling. The absorbance of the solution was measured at 228 nm using dissolution medium as a standard. The concentration of Glimepiride was calculated by using standard calibration curve.

Stability Study of the Tablet Formulation [23]

The stability study of the prepared Glimepiride tablets was performed by exposing to accelerated stability conditions and detecting the physical and chemical changes on tablets. In addition, the suitability of the packaging system can be evaluated by filling 100 tablets per 40 CC HDPE bottle and 2g silica gel canisters were added to each bottle as desiccant. The neck space of the bottle was occupied by rayon to minimize mechanical stress on tablets during handling. Each bottle was then thermally sealed and capped by a 33mm CRC cap. The bottles were charged into a stability chamber at 40±2°C/75±5% RH. Samples were withdrawn after 1 month exposure. Tablets were evaluated physically by all the previously mentioned tests.

RESULT AND DISCUSSION

Characterisation of Drug

The received samples were identified by various tests.

Organnoleptic Properties

Colour: A white or almost white powder.

Odour: Odourless

Solubility: Soluble in dimethyl formamide, slightly soluble in methanol, insoluble in water.

Melting point:

The Melting point was determined by using capillary tube method. The melting point of glimepiride was found to be 207°C.

Chemical Compatibility Studies:

There is no interaction with the drug and excipients.

Pre-fomulation Studies

Evaluation of Granule Blends

The flow property of the granule blends is an important parameter to be measured since it affects the uniformity of dose.

Table 2: Evaluation of pre-compression parameters of powder blend

S.no	Formulation	Bulk density	Tapped density	Carr's index	Hausner's ratio (%)	Angle of repose(ø)
1	F1	0.424	0.558	24.01	1.32	30°,02'
2	F2	0.41	0.553	25.85	1.34	29°,17'
3	F3	0.406	0.523	22.37	1.28	29°,44'
4	F4	0.39	0.537	27.37	1.37	29°,15'
5	F5	0.38	0.509	25.34	1.33	28°,37'
6	F6	0.39	0.485	19.58	1.24	28°,25'
7	F7	0.39	0.534	26.96	1.36	30°,06'
8	F8	0.39	0.473	17.54	1.21	30°,17'
9	F9	0.39	0.464	15.94	1.18	29°,45'

It is a character related to Interparticulate friction or resistance to movement between particles. Improper powder flow is due to frictional forces between the particles. The blend have angle of repose between 28°,25'±0.02 to 30°,17'±0.02 which indicates good flow characters.

In-Vitro Dissolution Study

The formulation F6 with Crospovidone 15% exhibited faster release of drug when compared to formulations with SSG and CCS. The *In-vitro* drug release of the end of 10 minutes for formulation F3, F6 and F9 was 44.36%, 63.40%, and 43.82% respectively. At the end of 14 minutes the drug release of F3 and F9 were 74.53% and 78.58%. Formulation F5 released 99.97% at the end of 16 minutes. Optimized formulation was found to be F6.

Table 3: Evaluation of Post compression parameters

Formulation	Uniformity of Weight (mg)	Tablet Thickness (mm)	Tablet Diameter (mm)	Hardness	% Friability
F1	99.6±0.3	3.07 ±0.02	6.24±0.02	2.48±0.07	0.55±0.04
F2	100.25±0.1	3.05 ±0.04	6.27±0.04	2.5 ±0.06	0.57±0.07
F3	100.25±0.10	3.05 ±0.02	6.25±0.04	2.52±0.03	0.53±0.08
F4	99.95±0.02	3.07 ±0.04	6.23±0.02	2.52±0.05	0.44±0.03
F5	100.4±0.4	3.06 ±0.04	6.25±0.03	2.48±0.08	0.41±0.03
F6	99.85±0.1	3.17 ±0.06	6.27±0.05	2.52±0.06	0.4±0.05
F7	100.20±0.5	3.07 ±0.05	6.22±0.05	2.52±0.03	0.55±0.06
F8	100.25±0.04	3.08 ±0.07	6.25±0.05	2.52±0.1	0.53±0.05
F9	99.7±0.05	3.09 ±0.05	6.24±0.04	2.52±0.13	0.56±0.03

Table 4: Evaluation of Post compression parameters

Formulation	*In-Vitro* Disintegration Time	Wetting Time	Water Absorption Ratio	Assay	% Drug Content
F1	10 ±1.23	25±5	59.74±11	97.43 ±0.03	96.01 ±0.03
F2	62 ±6.54	17±4	61.07±0.54	97.86±0.05	96.49±0.05
F3	80 ±4.65	10±3	66.43±1.93	98.04±0.30	97.29±0.30
F4	5 ±3.00	16±4	93.62±4.31	99.71±0.04	98.58±0.04
F5	7±3.01	13±2	87.28±8.5	97.86±0.36	98.50±0.36
F6	10 ±5.56	09±4	96.29±0.67	99.42±0.05	99.50±0.05
F7	20 ±5.00	30±6	55.56±0.51	97.56±0.03	95.59±0.03
F8	65 ±4.26	15±4	65.28±1.85	97.72±0.07	97.45±0.07
F9	84 ±5.01	10±3	78.58±2.54	97.86±0.1	96.12 ±0.1

Table 5: *In-vitro* dissolution study

Time (Minutes)	% Cumulative Drug Release								
F	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
2	4.73	4.47	4.47	4.34	3.45	5.75	2.68	4.47	3.06
4	11.25	10.61	10.99	9.84	10.09	15.34	9.51	11.76	8.86
6	20.83	18.53	20.96	21.01	18.92	28.76	19.02	22.11	17.34
8	31.96	29.40	31.83	34.67	30.55	46.02	29.99	35.02	29.55
10	44.48	42.31	44.36	50.18	44.4	63.40	42.82	49.73	43.82
12	59.19	58.80	58.29	67.56	61.23	81.43	53.33	64.81	60.58
14	75.74	76.44	74.53	81.84	80.53	99.58	74.68	80.28	78.58
16	92.55	94.60	95.49	96.32	99.97	-	92.27	96.26	97.41

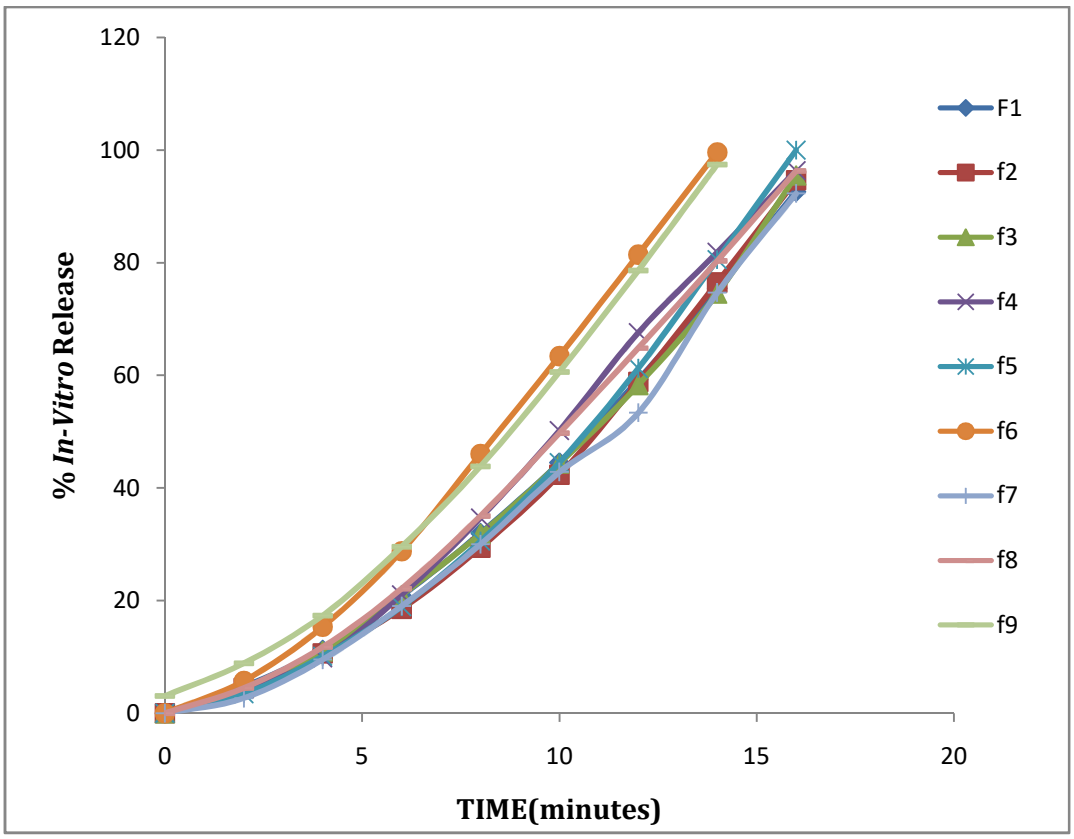

Figure 1: Percentage *in-vitro* drug release of glimepiride mouth dissolving tablets

Stability Data for Optimized Formulation (Cumulative % Drug Release of Optimized formulation) – F6 at (40±2°C/75±5% RH)

Table 6: Stability data for Optimized Formulation

Time (min)	Initial	After 30 Days
2	5.75	4.28
4	15.34	15.01
6	28.76	26.12
8	46.02	45.06
10	63.40	64.85
12	81.43	82.58
14	99.58	99.12

CONCLUSION

No significant changes in Physical appearance, uniformity weight of tablet, thickness, tablet diameter, % friability, *In-vitro* disintegration time, assay, drug content and *in-vitro* drug release. From the *In-vitro* drug release study, it was revealed that the formulations, various superdisintegrants of Sodium starch glycolate, Crospovidone, Crosscaremellose sodium. The F6 Formulation (Crospovidone) showed drug release of 99.58% at the end 14 minutes, with % Purity of the formulation 99.42±0.05 %W/W respectively. The formulation F6 had good *In-Vitro* Disintegration time (5 seconds), *In-vitro* Dispersion Time (8 Seconds) and water Absorption ratio (96.29±4.31%) when compared to other formulations. The *In-vitro* release kinetics study of the optimized formulation F6 was found to be zero order release kinetics Stability studies of the optimized formulation F6 no significant changes in Physical appearance, uniformity weight of tablet, thickness, tablet diameter, % friability, *In-vitro* disintegration time, Assay, Drug content and *In-vitro* drug release.

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