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DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLETS OF GLIMEPIRIDE

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ABSTRACT

The objective of the current study was to assess the feasibility of developing fast dissolving tablets of glimepiride for type-2 diabetic patients, by direct compression and sublimation techniques. The formulations were prepared by direct compression method using super disintegrants like crospovidone, croscarmellose sodium and hydroxy propyl cellulose. Formulations by sublimation technique were prepared using camphor. The prepared tablets were evaluated for weight variation, hardness, friability, drug content, wetting time, thickness and disintegration time. Dissolution studies were carried out with USP type II dissolution apparatus using phosphate buffer (pH 6.8) at 37 ± 0.5°C. The properties of the tablets did not show any significant variations and were found to have good physical integrity except with disintegration time and wetting time. In vitro release studies indicate higher drug dissolution rate in two formulations and were subjected to stability studies. The stability data suggested that the prepared formulations were stable during the study period. Given the excellent data, it can be concluded that the fast dissolving tablets of glimepiride can be formulated by direct compression and sublimation techniques.

INTRODUCTION

The pharmaceutical companies are focusing on the development of new drug delivery systems for existing drugs with an improved efficacy and bioavailability together with reduced dosage frequency to minimize side effects. Major reason for this approach is to overcome the expense in developing a new chemical entity, which is likely to be much higher. In this perspective, the primary choice in drug delivery development is the oral route, which has wide acceptance and represents higher percentage of total drug formulations [1]. Further, this route is the considered to be the best preferred route as it provides additional advantages such as ease of ingestion, pain free consumptions etc [2]. In general, oral formulation does not provide adequate compliance to all categories of patients and the demand for new formulations is increased in the past two decades. Recent advances in novel drug delivery systems aim to formulate dosage forms for convenient administration and better patient compliance. One such approach leads to the development of fast dissolving/disintegrating tablets [3,4]. Several drug molecules have been designed and formulated as fast dissolving tablets and are available in market, while many are awaiting the FDA approval [5]. Typically, these dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing [6,7]. The target populations for this dosage forms have generally been pediatric, geriatric and bedridden or developmentally disabled patients. Patients with persistent nausea, while traveling, or who have little or no access to water are also good candidates for these formulations [8]. The ease of administration of a fast-dissolving tablet, along with its pleasant taste, may encourage a patient to adhere to a daily medication regimen [9].

Glimepiride, an oral hypoglycemic agent, is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus [9]. It is a weak acid (pKa = 5.3), practically insoluble in water, and highly permeable (Class II drugs in accordance to biopharmaceutics classification system). After oral administration, glimepiride exhibit uniform, rapid and complete absorption. Its bioavailability is nearly 100%, relatively short elimination half-life of 2.0-3.3 h and exhibit peak drug levels (Cmax) at 2 to 3 hours [10-12]. Moreover, this drug is currently considered as one of the best choice for the elderly patients [13-15]. However, the administration of this drug in the conventional formulation (tablet) reduces the patient compliance in elderly patients, due to reduce in swallowing ability. To our knowledge there are no fast dissolving formulations for glimepiride is available in the market. Thus, there is a strong clinical need and market potential for a dosage form that will deliver glimepiride in a fast dissolving manner which in turn results in better patient compliance.

The objective of the current study was to develop a fast dissolving tablet formulations of glimepiride by direct compression and sublimation technique and its evaluation *in vitro*.

EXPERIMENTAL

Materials

Glimepiride, crospovidone, croscarmellose sodium, hydroxy propyl cellulose, microcrystalline cellulose, poly vinyl pyrrolidone (PVP K-30), aerosil, and camphor were purchased from Sigma-Aldrich, St Louis, MO, USA. All other chemicals and reagents used were of analytical grade.

Equipment

Double beam UV-visible spectrophotometer (Shimadzu, 1700, Japan), Dissolution test apparatus-Type II (Erweka, Germany), Friabilator (Erweka, Germany), Monsanto type tablet hardness tester (Campbell Electronics, India), Multi station rotary press (Erweka, Germany), Single pan balance (Shimadzu, AX200, Japan), Tablet disintegration apparatus (Erweka, Germany) were used in the current investigation.

Methods

Preformulation Studies

To study the drug and excipients compatibility, active drug was blended with individual excipients in 1:1 ratio. It was filled in open glass vials and placed in incubators at 30°C/65% RH. Samples were observed for any physical changes at the end of 1st week, 2nd weeks, and 4th weeks. The chemical compatibility was assessed by thin layer chromatography.

Formulation of tablets

Fast dissolving tablets of glimepiride were prepared by direct compression and sublimation

method. All the ingredients were passed through standard sieves (#60 and #40), to obtain the particles size in range of 250 to 425 µm. The total weight of the formulation was kept constant (100 mg), while the amounts of other ingredients were varied. For direct compression the constituents in the given proportion (Table 1) were mixed by using mortar and pestle. The resultant mixture was compressed on a tablet punching machine with 6 mm flat round punches. In sublimation method the constituents in the given proportion (Table 2) were mixed and passed through sieve # 60. This was further lubricated with 1% w/w aerosil and magnesium stearate and tablets were prepared by using 16 station tablet punching machine with similar conditions. After the compression, the tablets were dried at 70 C for 30 min, to sublime the camphor.

Table 1: Composition (2 mg/tablet) glimepiride fast dissolving tablets by direct compression technique

Ingredients	Quantity in mg per tablet								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glimepiride	2	2	2	2	2	2	2	2	2
Micro crystalline cellulose	15	15	15	91	90	88			
Di basic calcium phosphate	71	71	71	-	-	-	91	90	88
Crospovidone	-	-	5	3	4	6	3	4	6
Croscarmellose sodium	5	-	-	-	-	-	-	-	-
Hydroxy propyl cellulose	-	5	-	-	-	-	-	-	-
Pre gelatinized starch	5	5	5	-	-	-	-	-	-
Poly vinyl pyrrolidone K30	-	-	-	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1

Table 2: Composition (2 mg/tablet) of glimepiride fast dissolving tablets by sublimation technique

Ingredients	Quantity in mg per tablet				
	FS-1	FS-2	FS-3	FS-4	FS-5
Glimepiride	2	2	2	2	2
Di basic calcim phosphate	87	86	85	84	83
Crospovidone	5	5	5	5	5
Camphor	2	3	4	5	6
Poly vinyl pyrrolidone K30	2	2	2	2	2
Aerosil	1	1	1	1	1
Magnesium stearate	1	1	1	1	1

Characterization of granules and tablets

The various granule characteristics like bulk density, tapped density, angle of repose and Carr's index were determined by standard procedures [16-17]. The weight variation of the tablets were performed by randomly selecting twenty tablets and weighed individually and together in a balance. Friability was tested using the friabilator. Briefly, preweighed tablets were allowed for 100 revolutions in 4 min and the percentage loss was calculated by reweighing the tablets. Hardness was tested by placing a tablet between the anvils and the crushing strength, which causes the tablet to break, was recorded. The wetting time was measured by placing five circular tissue papers (6.5 cm diameter) to simulate the tongue conditions in a petri dish with 6.5 cm diameter. Six milliliters of water containing eosin was added to the petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time. The disintegration time (DT) was determined by using disintegration test apparatus.

Drug release profile was evaluated *in vitro* using simulated salivary fluid as dissolution medium (pH 6.8) [18]. The temperature was maintained at 37 ± 0.5 C with a constant paddle rotation speed of 50 rpm. Samples (5 ml) were withdrawn at regular intervals, diluted and analyzed for glimepiride by UV spectrophotometric method at 225 nm as described by [19]. All the data obtained for dissolution was evaluated statistically by one way analysis of variance (ANOVA).

Stability studies

Short term stability studies were carried out for the selected formulations (kept in open glass vials) for a period of two months under the storage conditions of 25°C / 60% RH and 40°C / 75% RH [20].

RESULTS AND DISCUSSION

The aim of the present study was to develop fast dissolving tablets of glimepiride by direct compression and sublimation methods. Compatibility studies using thin layer chromatography showed that glimepiride was highly compatible with all the excipients used (Data are not shown). The granule properties for all the formulations were determined and given in Table 3. There was no significant difference ($P>0.05$) in granule properties prepared by two methods when analyzed statistically. Further, the physical properties of the tablets did not show any significant variations and were found to have good physical integrity except with DT

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and wetting time (Table 4). Amongst the diluents and disintegrates used in the study, tablets that were formulated (direct compression) using crospovidone exhibited quicker disintegration than the use of croscarmellose sodium and hydroxy propyl cellulose. The drug content of all formulations was found to be in the the range of 94.50% to 98.53%.

Table 3: Characteristics of glimepiride granules for different formulations

Formulations	Granule properties			
	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose	Carr's index
F-1	0.56 ± 0.018	0.68 ± 0.012	33.06 ± 1.066	19.40 ± 0.459
F-2	0.54 ± 0.017	0.65 ± 0.044	28.52 ± 0.846	18.32 ± 0.912
F-3	0.58 ± 0.017	0.68 ± 0.021	25.72 ± 0.958	13.26 ± 0.569
F-4	0.50 ± 0.024	0.62 ± 0.014	34.82 ± 1.024	23.00 ± 0.451
F-5	0.53 ± 0.015	0.62 ± 0.020	25.26 ± 0.659	26.30 ± 0.569
F-6	0.58 ± 0.014	0.69 ± 0.017	23.32 ± 1.123	19.68 ± 0.372
F-7	0.62 ± 0.018	0.72 ± 0.018	34.82 ± 1.066	23.00 ± 0.884
F-8	0.57 ± 0.022	0.65 ± 0.019	28.56 ± 1.024	25.60 ± 0.561
F-9	0.54 ± 0.015	0.67 ± 0.022	30.58 ± 0.453	19.50 ± 0.236
FS-1	0.54 ± 0.013	0.67 ± 0.021	32.07 ± 0.617	19.40 ± 0.245
FS-2	0.52 ± 0.017	0.63 ± 0.014	28.56 ± 0.813	17.40 ± 0.398
FS-3	0.59 ± 0.015	0.68 ± 0.009	25.72 ± 0.914	13.23 ± 0.419
FS-4	0.50 ± 0.016	0.65 ± 0.022	34.82 ± 1.021	23.00 ± 0.579
FS-5	0.52 ± 0.014	0.60 ± 0.015	20.12 ± 1.019	16.82 ± 0.375

Each values are the mean ± SE (n = 3).

Table 4: Characteristics of glimepiride tablets prepared by direct compression and sublimation technique

Formulation	Tablet properties						
	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)	Weight Variation (mg)	DT in (sec)	Wetting time (sec)
F-1	3.40 ± 0.38	0.45 ± 0.01	3.19 ± 0.14	96.40 ± 1.66	3.06 ± 1.01	22.29 ± 2.29	37.60 ± 3.57
F-2	3.40 ± 0.55	0.38 ± 0.01	3.20 ± 0.12	94.50 ± 1.35	4.22 ± 1.33	23.38 ± 2.27	30.30 ± 2.75
F-3	3.42 ± 0.58	0.36 ± 0.01	3.18 ± 0.03	96.50 ± 2.16	3.15 ± 1.44	13.62 ± 2.16	17.60 ± 2.30
F-4	3.43 ± 0.60	0.42 ± 0.01	3.22 ± 0.44	96.25 ± 3.69	2.81 ± 1.33	16.17 ± 1.27	22.57 ± 3.30
F-5	3.44 ± 0.47	0.34 ± 0.01	3.19 ± 0.42	96.50 ± 3.46	2.45 ± 0.76	16.29 ± 0.82	26.28 ± 3.89
F-6	3.41 ± 0.49	0.32 ± 0.01	3.24 ± 0.48	98.50 ± 2.41	3.73 ± 1.24	10.41 ± 2.41	20.12 ± 3.75
F-7	3.45 ± 0.47	0.45 ± 0.01	3.27 ± 0.54	94.84 ± 2.78	2.82 ± 1.72	15.58 ± 0.79	21.21 ± 3.89
F-8	3.46 ± 0.55	0.38 ± 0.01	3.17 ± 0.49	96.34 ± 2.66	1.42 ± 0.64	14.13 ± 2.36	20.55 ± 1.92
F-9	3.48 ± 0.53	0.35 ± 0.01	3.19 ± 0.54	95.25 ± 2.44	2.01 ± 1.29	14.91 ± 2.39	23.64 ± 2.27
FS-1	3.53 ± 0.44	0.45 ± 0.01	3.21 ± 0.52	96.40 ± 2.99	3.12 ± 1.72	15.08 ± 2.45	24.54 ± 2.57
FS-2	3.53 ± 0.65	0.36 ± 0.01	3.19 ± 0.44	94.50 ± 2.85	3.93 ± 1.84	17.23 ± 0.90	15.04 ± 2.31
FS-3	3.54 ± 0.49	0.34 ± 0.01	3.23 ± 0.56	94.89 ± 1.89	1.85 ± 1.05	14.87 ± 1.41	22.58 ± 2.31
FS-4	3.52 ± 0.53	0.43 ± 0.01	3.10 ± 0.55	98.53 ± 1.89	1.34 ± 1.65	10.33 ± 2.29	19.00 ± 1.30
FS-5	3.55 ± 0.54	0.32 ± 0.01	3.33 ± 0.49	96.20 ± 2.12	3.48 ± 1.82	9.33 ± 2.28	14.32 ± 3.87

Each values are the mean ± SE (n = 3).

Figure 1 shows the in vitro drug release profiles of the formulations prepared by direct compression. It is apparent from the figure that the drug release profiles of formulations were comparable. However among the formulations, F-6 showed better dissolution when assessed for the t_{90} (90% release) and A_{10} (amount released in 10 min) values. It is also observed that all the formulations show full release in the study period (20 min). The t_{90} values were found to be 18, 17, 14, 19, 17, 11, 17, 16, 16 and 17 min for formulations F1 to F9, respectively.

Figure 2 shows the *in vitro* drug release profiles of formulations prepared by sublimation technique. Here too the drug release by the formulations did not show any significant difference ($P>0.05$) in release rate. However, among the formulations, FS-5 showed better dissolution when assessed for the t_{90} (90% drug release) and A_{10} (amount released in 10 min) values. It is also observed that all the formulations show full release in the study period (20 min). The t_{90} values were found to be 16, 16, 15, 13 and 12 mins for formulations FS-1 to FS-5, respectively. Based on these results, formulations F-6 and FS-5 were selected as the best formulations and were further tested for stability studies.

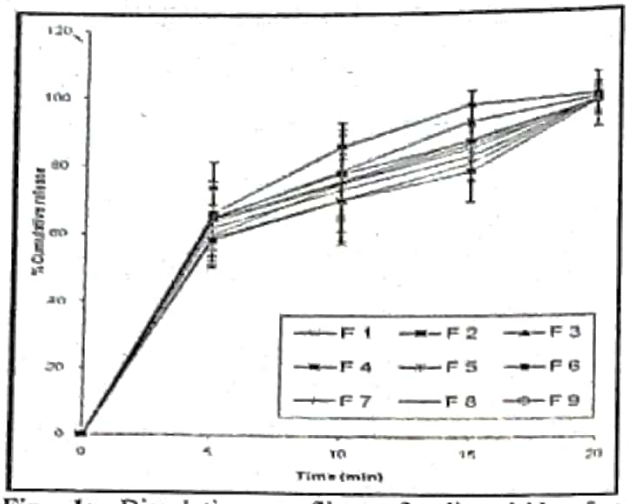

Fig. 1: Dissolution profiles of glimepiride fast dissolving tablets prepared by direct compression method. Each data = the mean ± SE of six experiments.

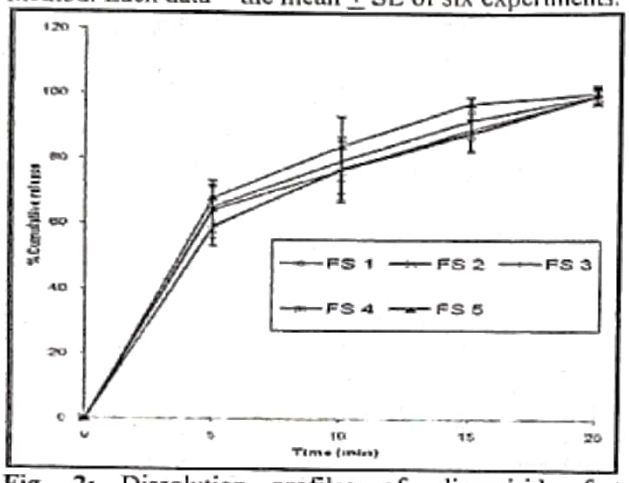

Fig. 2: Dissolution profiles of glimepiride fast dissolving tablets prepared by sublimation technique. Each data = the mean ± SE of six experiments.

The formulation F-6 and FS-5 showed a residual drug content of 96.28% and 95.84 %, respectively after two months when stored at 25°C / 60% RH. Similarly, the residual amount was found to be 97.15% and 94.22 % for formulations F-6 and FS-5, respectively when stored at 40°C / 75% RH for two months. These results indicated that the selected formulations are stable under the experimental conditions.

CONCLUSION

Fast dissolving tablets of glimepiride were prepared by direct compression and sublimation method and were evaluated for tablet properties and subjected to *in vitro* drug release studies. The tablet properties of the prepared formulations indicated good physical integrity and drug content, irrespective of the method of preparation. Similarly, the *in vitro* dissolution profile did not show much difference in the amount of drug release, among the formulations. However, the rate of drug dissolution was comparatively higher in formulation F-6 and FS-5. Moreover, the stability data indicated that these two formulations were stable during the study period. Thus this study concluded that fast dissolving tablets of glimepiride can be prepared by direct compression and sublimation technique as well.

RECOMMENDATIONS

In vivo studies are recommended to get further insight in to the efficiency of the selected formulations. Further, the formulation composition selected in the current study could be utilized for developing fast dissolving tablets of other drugs.

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تطوير وتقييم أقراص جليميبيرايد السريعة الذوبان

بندر الضبيب
قسم العلوم الصيدلية كلية الصيدلة الإكلينيكية ، جامعة الملك فيصل الاحساء
المملكة العربية السعودية

تهدف الدراسة الحالية لتقييم جدوى تطوير أقراص جليميبيرايد لمرضى السكري من النوع الثاني المعدة بواسطة الكبس المباشر وتقنية التسامي. وقد تم إعداد المستحضر الصيدلاني عن طريق تقنية الكبس المباشر باستخدام مواده مسهلة لتفكيك المستحضر مثل كروسبوفيدون ، كروسكار ميلوز ، هيدروكسي بروبيل السليلوز. وقد تم إعداد صياغات إخرى بواسطة تقنية التسامي باستخدام الكامفور كمعامل لعملية التسامي.

وقد تم تقييم المستحضرات المعدة من التقنيتين السابقتين بواسطة معايير عالمية. و إجريت دراسات الذوبانية بواسطة جهاز بستور الادويه الأمريكي وباستخدام فوسفات معادلة الحموضة (درجة الحموضة ٦.٨) في درجة حرارة ٣٧م°.

وقد وجدنا أنه لا يوجد أي اختلاف بين المستحضرات في الخصائص الفيزيائية عدى الوقت اللازم لتفكيك المستحضر. وقد اثبتت الدراسات المخبرية سرعة ذوبان الدواء في المستحضرين (Fs-5) و (F-6) .

وقد أجتاز المستحضرين إختبار الثباتية بنجاح. وخلص هذا البحث الى أن عقار جليميبيرايد يمكن تصنيعه بواسطة الكبس المباشر وتقنية التسامي.