ORIGINAL ARTICLE

Formulation and characterization of orodispersible tablet of glimepiride

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ABSTRACT

The present study is regarding, Glimepiride is one derivatives of sulfonyl urea used in the treatment of Type II DM which classified as class-II (BCS) of high permeability and low degree of solubility. The endeavor is to improve its solubility by solvent vaporization method to enhance the rate of dissolution of glimepiride. Soluplus (Polyvinyl caprolactampolyvinyl acetate-polyethylene glycol graft co-polymer) , PVP k40 (Polyvinylpyrrolidone) and PEG k5 are blended with the drug in various proportions (1:1,1:3) and prepared Soluplus1, Soluplus2, PEG1, PEG2, PVP1 and PVP2 as solid dispersion. The optimized formula of solid dispersion PVP1 is added to sodium starch glycolate and cross-carmellose. The disintegration profile will appear diminished in the drug release from the dosage form at a determined period of time. Differential scanning calorimetry appeared to a reduction in its crystallinity in solid dispersions. Scanning electron microscope and particle size analysis show a reduction in the drug particle size as solid dispersions. Fourier transform infrared spectroscopy does not show an interaction between them. Hence, that PVP1 batch will be considered from nine oral dissolving tablets dosage form. Finally, orally disintegrating tablets are estimated for various parameters; for instance, disintegration time, the content of the drug, wetting time, and *in vitro* release profile show a conventional result. The selected formula F6 shows a good result in disintegration time during 13-second and in-vitro drug release profile achieves 96% at the end of 40 minutes.

Key words: Glimepiride, orodispersible tablets, solid dispersions and solvent evaporation technique

INTRODUCTION

Orodispersible tablets (ODTs) are important in the pharmaceutical formulation for both over-the-counter drugs and prescription; they improve patient acceptability, low cost and simple methods. The disintegration of such dosage form is determined by the size and hardness of tablets.[1] Thus the goal of current study is to compress the component into tablet that characterized by fast dissolving through rapid disintegration and high drug release from the formula during a short period of time.[2] It is also considered as a single dose solid dispersion that used orally inside the mouth cavity, which dissolves in saliva with rapid onset of action. ODTs are produced by adding cross-povidone, sodium cross-carmellose, and sodium starch-glycolate.[3] There are different techniques used in the production of ODTs like lyophilization, mass

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extrusion, spray drying, molding, sublimation, and direct compression.[4]

The preparation of solid dispersion relies on the disintegration rate which can be enhanced by improve surface area to avoid the precipitation within the carrier, solid including in the solution and improve the wetting properties due to direct interaction with hydrophilic polymer carrier, to take a shape of a metastable crystalline structure.[5] Therefore adjusting the drug/polymer ratio and selecting the suitable method have direct effect on the type of solid dispersion and drug release behavior [6]

The polyethylene glycol (PEG) 5k, Soluplus, and polyvinylpyrrolidone (PVP) 40k are the foremost utilized polymer to carry solid dispersion and their capability to form atomic adduct compounds.[7] The presence of hydroxyl and carbonyl group tends to enhance water solubility, bioavailability, and stability.[8] Hence, the use of such polymers has a crucial role in improving the dissolution rate profile for the drug and consequently the absorption.[9] Glimepiride has low water solubility (<0.004 mg/ml) and dissolution properties may cause poor bioavailability.[10] Additionally, Glimepiride is a weak acid (pKa 6.2), and has low solubility in acidic media, so it is a challenge to overcome this issue by formulating Glimepiride as ODTs to obtain rapid release of the drug in the oral cavity with a few second to achieve a high percent of drug release from the formula.[11] Subsequently, to improve the therapeutic efficacy by enhancement of solubility and dissolution rate of Glimepiride.[12]

MATERIALS AND METHODS

Materials

Glimepiride was a gift from Al Warqaa Medical Store for Chemicals Baghdad and Soluplus, PVP 40k, and PEG 5k were purchased from Al-Noor Medical Store for Chemicals. Sodium starch glycolate and sodium croscarmellose are purchased from Al-Noor Medical store.

Method of preparation

Solvent evaporation technique was used in the preparation of glimepiride solid dispersion, where various formulas of glimepiride were prepared by solid dispersion technique and arranged into two proportions with each polymer PEG 5k, PVP 40k, and Soluplus. Precisely weighed amount of the drug with polymer; then homogenously mixed with an adequate volume of alcohol. The prepared solution was evaporated at room temperature to get dry solid dispersion at that point dried in a desiccator; the batches of solid dispersion are shown in Table 1. The yield solid was sieved through 65 meshes to ensure the equal consistency of particle size within the required range.[13]

Estimation of solid dispersion

Taking 10mg of prepared Glimepiride/polymer solid dispersion of (1:1 and 1:3) ratio and dilute with 50mL Ethanol of 95% using magnetic stirred for 1-hour then scanning at 217nm UV absorbance to obtain λmax as shown in figure 1 UV.[14] Then performing the solubility study, percentage yield, FTIR Spectroscopy, In-vitro study, scanning electron microscopy and thermal analysis (differential scanning calorimetry) to estimate the formulation of solid dispersion that assist in the selection of the optimize formula.[15]

Table 1: Solid dispersion batches preparation ratio of drug-polymer

Polymer	Formula	Ratio
PEG 5k	PEG1	1:1
	PEG2	1:3
PVP 40k	PVP1	1:1
	PVP2	1:3
Soluplus	Soluplus 1	1:1
	Soluplus 2	1:3

PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone

Preparation of orally disintegrating tablets

Glimepiride ODTs are prepared by combination of Na-starch glycolate and super-Na-crosscarmellose through direct compression method. The component are accurately weighed and passed through 50# sieve prior blending and placed into a glass mortar to mix consistently as shown in Table 2 the component of Glimepiride ODTs formula. The blend at that point is estimated for precompression parameters before the compression process.[16]

Estimation of precompression powder

The characterization study is performed by determining the angle of repose, tapped and bulk density, Carr's Index and Hausner ratio; to estimate the properties of the blend before compression.[17]

Estimation of orally disintegrating tablets

Weight variation test is carried out for the prepared tablets to determine the total differences in weight. The percentage of weight variation is obtained by taking the total weight of 20 tablets and the average weight difference with mean value of ±S.D.[18]

The hardness test was performed to determine the driving force required to break the tablet over an applied pressure. The hardness was obtained in kg about 3–5 kg/cm^2, which is palatable for uncoated tablets. The hardness test device was Monsanto hardness analyzer.[19]

Friability test is performed to determine the weight loss from the tablet and comparing the final weight with the original tablet. This test is important obtain the surface resistance during the packaging and transport. The device used is Roche Friabilator.[20]

Table 2: Formula for preparing orally disintegrating tablets of glimepiride

Material	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Batch PVP1 (mg)	85	85	85	85	85	85	85	85	85
Cross-Carmellose Na	-	-	10	15	10	15	10	12.5	15
SSG	12.5	10	-	-	10	5	5	5	-
MCC	117.5	120	120	115	110	110	115	112.5	115
Mannitol	33	33	33	33	33	33	33	33	33
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Talc powder	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Na-saccharin	1	1	1	1	1	1	1	1	1
Total	250	250	250	250	250	250	250	250	250

PVP: Polyvinylpyrrolidone, SSG: Sodium starch glycolate, MCC: Microcrystalline cellulose

Table 3: Identification and characterization of glimepiride

Tests	Results
Appearance	White to yellowish
Melting point	188-192°C
Nature	Crystalline powder
Solubility	In acid media at 25°C (<0.004 mg/ml)

Dissolution time analysis

The dissolution test apparatus type II USP was used to determine the rate of dissolution of the ODTs.[21] One tablet was set in each vessel of 1 liter 0.1 M HCL at 37 ± 2°C, and the sample is scanned at 217nm UV to obtain the average percent of drug release during 25-minute.[25]

Wetting test

The test was used to determine the wetting time by placing a tablet in a beaker; Each table should be weighted before and after fluid absorption to determine the difference in weight using sensitive electronic balance to obtain the percent of wetting according to the equation 1.[23]

$$R = Wa - Wd / Wd \times 100$$

Where Wa is tablet after water after and Wd is dry tablet.

In vitro study

The study was conducted *in vitro* to determine the drug release profile in phosphate-buffered saline (PBS) of pH 7 for 25.[24] Eight samples are tested triplicate using dissolution test apparatus type II (Digital DT 950 Series Dissolution Tester); the tablet is placed in 900mL phosphate buffer solution at 37±2°C and the sample is scanned at 217nm UV to obtain the average percent of drug release during 25-minute.[25]

RESULTS AND DISCUSSION

Solvent evaporation method is used to produce Glimepiride ODTs and the preformulation studies are performed for all the formula to obtain the data of organoleptic properties, angle of repose, Carr's 48. index, solubility analysis, λmax and calibration curve; which assist in the selection of best formula.

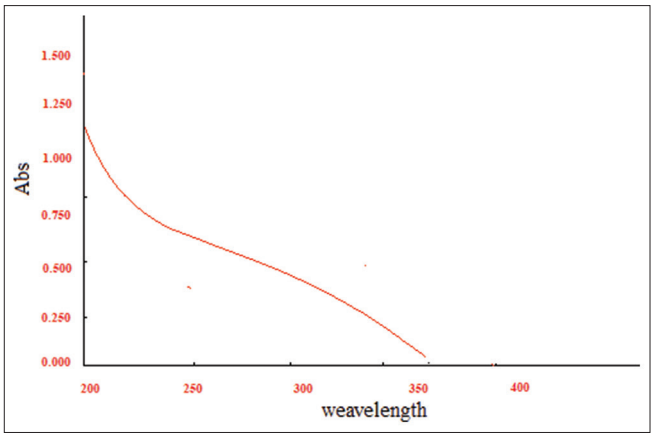

Figure 1: UV spectrum of Glimepiride in ethanol, UV: Ultraviolet

Preformulation studies

Characterization: Organoleptic properties were studied and are placed in Table 3.

λ max determination

UV spectrophotometer is used to determine λmax of the drug in different solvents as shown in Figure 1; the data of λmax in ethanol, water and PBS are placed in Table 4.

Calibration curve determination

The solution of 0.1mg/mL Glimepiride shows linear relation at maximum UV absorption, the data of the intercept, slope and R^2 are placed in Table 5; and the calibration curve of Glimepiride in PBS, water and ethanol are shown in Figures 2-4.

Fourier transform infrared spectroscopy spectroscopy

The characterizations of Glimepiride are appeared in Table 6. The data of wave numbers of Glimepiride are placed Table 7. FTIR stretching of C=O group at 1656-1715cm-1 and stretching of C-H bond at 2922cm-1 ; which slightly shifted in batch PEG1 ,PEG2 ,PVP1, PVP2,Soluplus1 and Soluplus2 at 2954, 2873,2837, 2886, 2939, 2933 cm-1 respectively. The boarded peak indicates a great interaction of H- bonds with PEG1, PVP1and Soluplus1 which cause a shift into the amorphous form; thus there is no change in the internal structure due to the compatibility of drug and polymers. FTIR analysis for Glimepiride, PVP1, PVP2, PEG1, PEG2, Soluplus 1 and Soluplus 2 are shown in Figures 4-10 respectively.

Saturated solubility of Glimepiride/Solid-dispersion

Solubility study is performed to enhance the bioavailability of poor water solubility drug.[19,20] Here, glimepiride solubility is compared with polymers solubility in water as shown in Figure 11 where the polymers appear higher

solubility in water. The solid dispersion of PVP1 and PVP2 have higher solubility than other batches due to formation of H-bonds with water to form amorphous structure to improve the drug release. The data of saturated solubility are recorded in Table 5 with mean value of ±S.D.

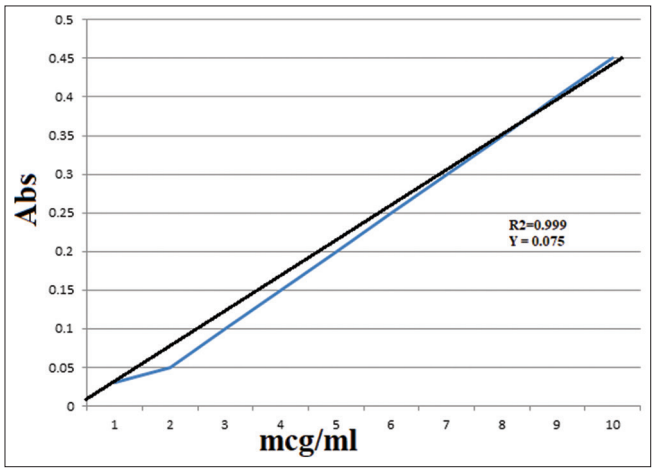

Figure 2: Drug/PBS calibration curve, PBS: Phosphate-buffered saline

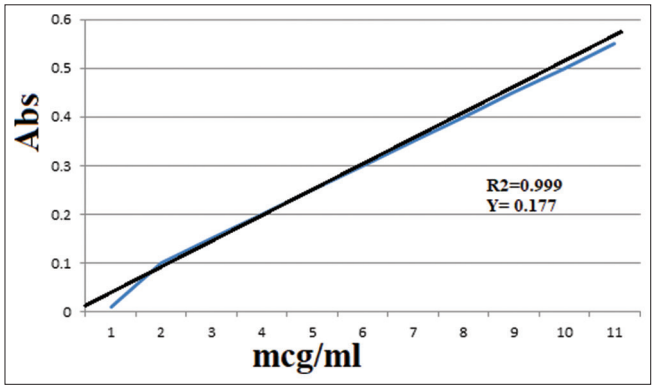

Figure 3: Drug/ethanol calibration curve

Percentage yield and drug content of the formulas

The obtained data of drug content and percentage yield by detecting the amount of drug in each formula using UV absorbance at 217nm where Soluplus 2 was the higher drug content than others because of the stuck nature of the polymer as shown in Table 8.

In vitro study

The drug release in PBS alone is 53.13% within 10 min, while with polymer PVP K-40 the percent of release profile increased to 73.4% and 58.2% for PVP1 and PVP2, respectively [Figure 12].

Thermal study differential scanning calorimetry

The test is important to determine the compatibility between the drug and excipients to obtain an accurate data about their interactions.

Interpretation of DSC thermograms data is shown in Figures 13-16 for pure drug, PVP1, PEG1 and S1 respectively below, the information about melting point shows a decline in

Table 4: λmax of maximum absorbance in various solvents

Solvent	λmax (nm)
Phosphate buffer solution 7	219
Water	218
Ethanol	217

Table 5: Glimepiride calibration curve in different solvents

Solvent	Slope	Intercept	R^2
Phosphate buffer 7	0.177	0.024	0.999
Water	0.086	0.016	0.999
Ethanol	0.075	0.095	0.999

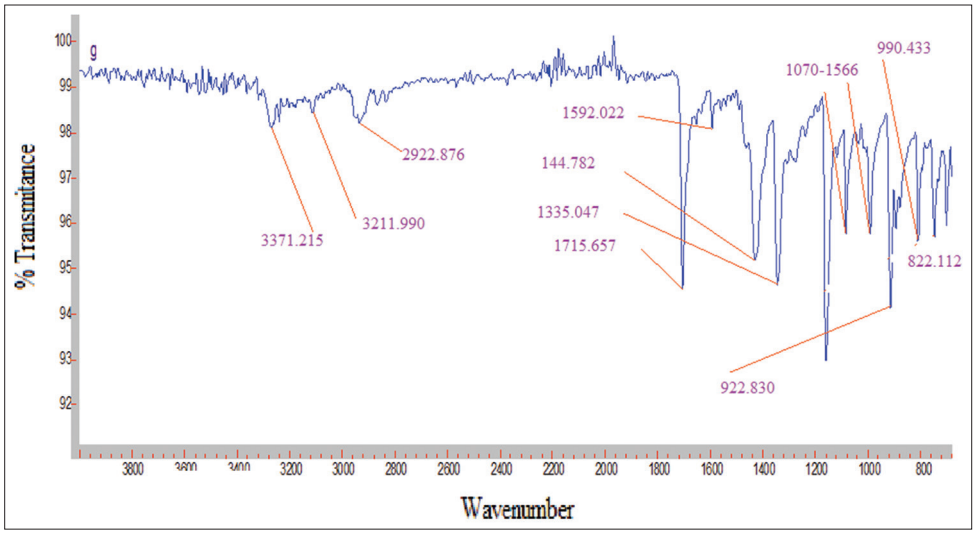

Figure 4: Fourier transform infrared spectroscopy pure glimepiride

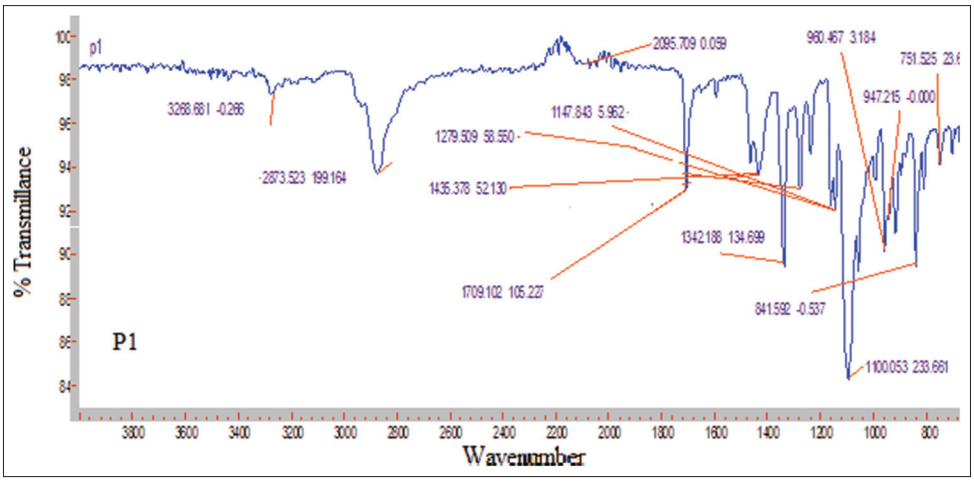

Figure 5: Fourier transform infrared spectroscopy PVP1. PVP: Polyvinylpyrrolidone

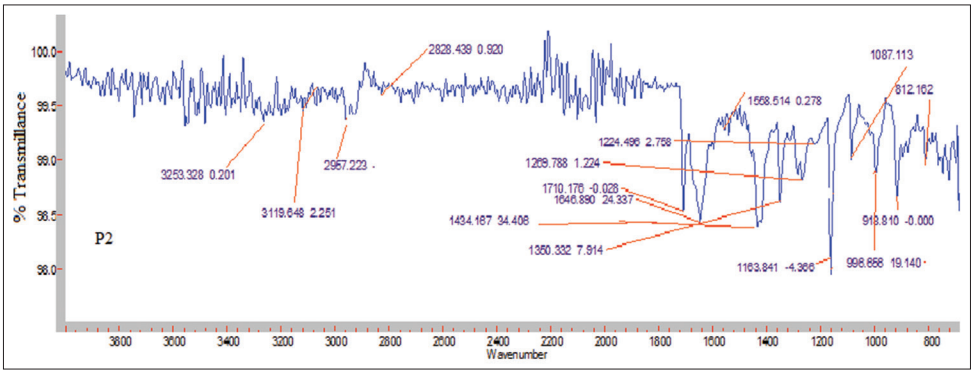

Figure 6: Fourier transform infrared spectroscopy PVP2. PVP: Polyvinylpyrrolidone

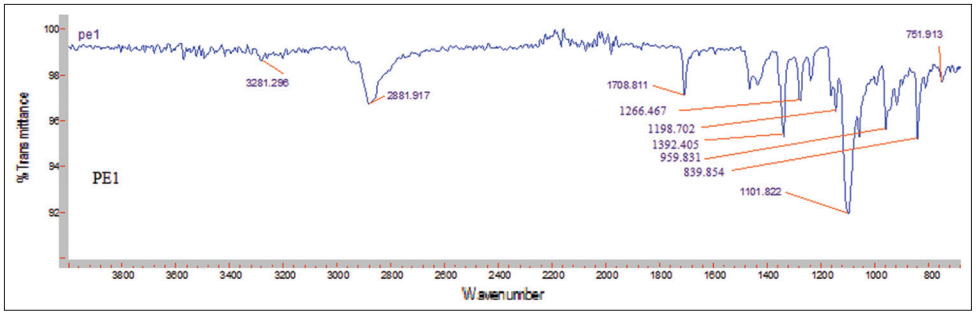

Figure 7: Fourier transform infrared spectroscopy PEG1. PEG: Polyethylene glycol

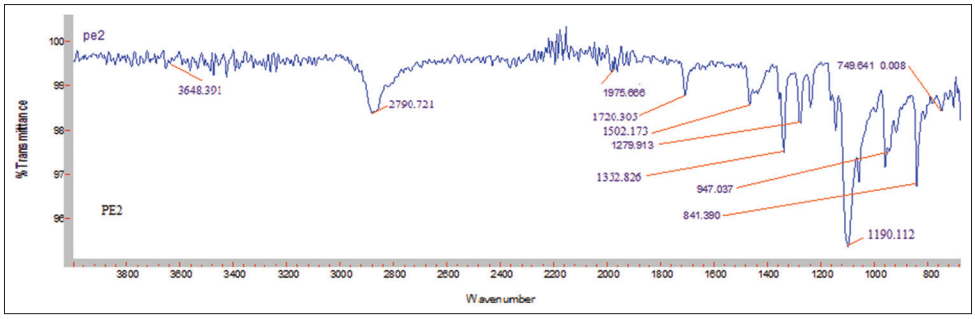

Figure 8: Fourier transform infrared spectroscopy PEG2. PEG: Polyethylene glycol

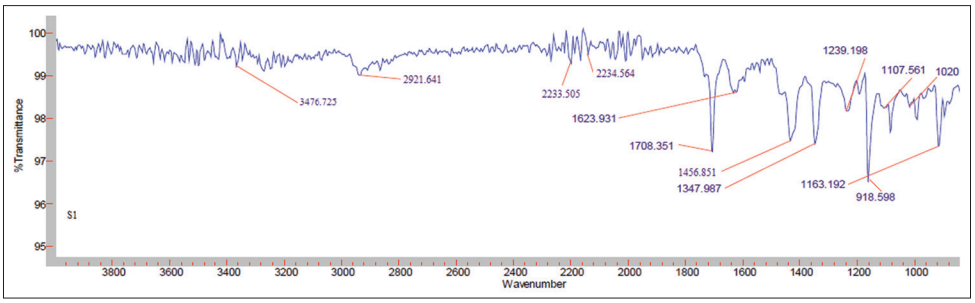

Figure 9: Fourier transform infrared spectroscopy Soluplus 1

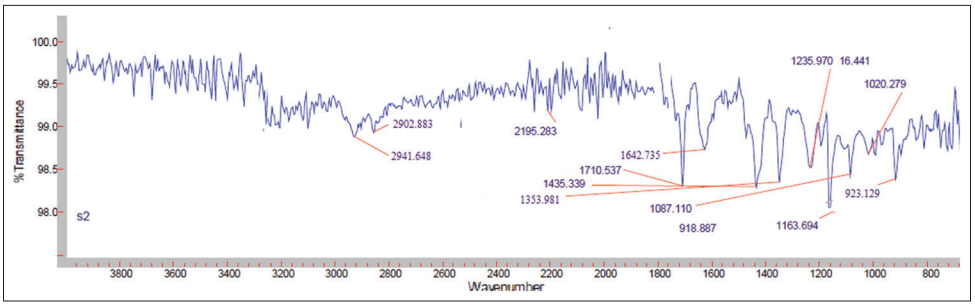

Figure 10: Fourier transform infrared spectroscopy Soluplus 2

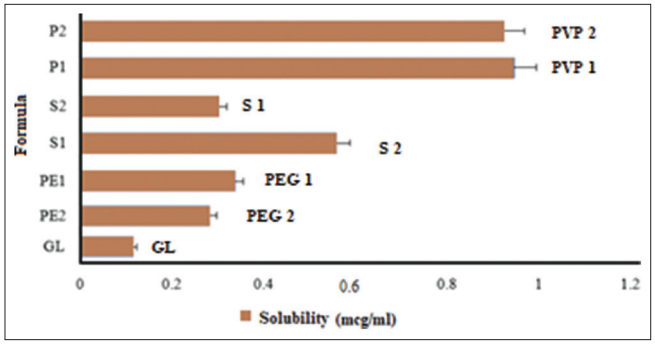

Figure 11: Saturation solubility of glimepiride and batches PEG1, PEG2, PVP1, PVP2, Soluplus 1, and Soluplus 2, PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone

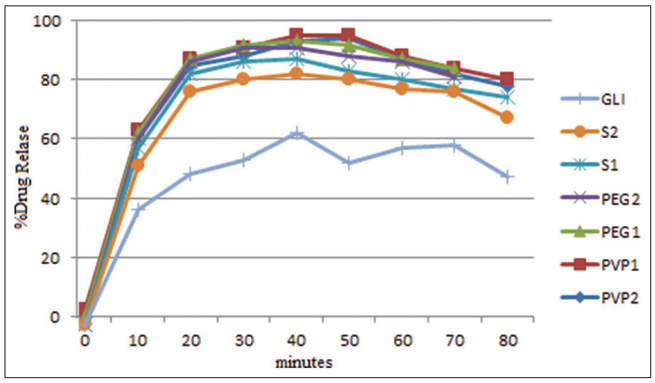

Figure 12: Drug release profile of glimepiride

PVP1 with less M. P than pure drug; 75.3°C and 191.8°C that's mean the endothermic reaction of the formula PVP1 with reduction in the temperature of the thermograms

Table 6: Percentage yield and drug content

Formula	Drug content	Percentage yield
PEG1	80.2	23.32
PEG2	81.3	25.90
PVP1	69.2	35.21
PVP2	64.6	33.43
Soluplus 1	75.4	22.32
Soluplus 2	85.6	18.26

PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone

Table 7: Peaks characterization for pure glimepiride

Functional group	Reference wave number (cm^{-1})	Obtained wave number (cm^{-1})
OH	3250-3400	3371.215
C-H Stretch	2750-3100	2922.876
C=O (carbonyl)	1656-1715	17165.657
-C=C-Aromatic	1450-1650	1592.022
Para substituted	825-935	822.112

Table 8: Glimepiride and solid dispersion batches (saturation solubility)

Formula	Saturated solubility
Glimepiride	0.1202±0.008
PEG1	0.3972±0.008
PEG2	0.3628±0.005
PVP1	0.9571±0.005
PVP2	0.9121±0.003
Soluplus 1	0.3309±0.002
Soluplus 2	0.6298±0.005

PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone

Table 9: Values of precompression study

Batches	Angle repose (θ)	Hausner's ratio	Bulk (g/ml)	Tapped (g/ml)	Carr's index
F1	29.2	1.22	0.54	0.69	17.91
F2	28.1	1.12	0.56	0.66	16.32
F3	27.4	1.23	0.53	0.64	16.61
F4	26.5	1.19	0.58	0.68	15.43
F5	28.3	1.17	0.61	0.67	18.45
F6	27.8	1.18	0.57	0.67	16.82
F7	24.9	1.24	0.59	0.70	14.99
F8	28.5	1.16	0.56	0.71	15.37
F9	26.6	1.17	0.55	0.69	15.48

Table 10: Preformulation values

Formulas	Thickness (mm)	Hardness (kg/cm²)	Weight (mg)	Friability	Disintegration time (s)
F1	3.26±0.12	3.41±0.167	248±1.02	0.37±0.010	18±1.22
F2	2.74±0.27	3.49±0.124	251±1.05	0.43±0.023	22±1.35
F3	2.91±0.13	3.50±0.100	248±1.10	0.78±0.113	17±1.11
F4	3.88±0.25	3.60±0.200	251±1.32	0.62±0.311	17±1.40
F5	2.92±0.35	3.60±0.200	248±1.23	0.65±0.336	22±1.00
F6	2.32±0.42	3.36±0.057	250±1.15	0.42±0.007	13±1.72
F7	2.73±0.24	3.43±0.057	248±1.03	0.73±0.100	14±0.64
F8	2.23±0.45	3.40±0.264	252±1.23	0.75±0.025	20±1.00
F9	3.63±0.37	3.62±0.154	250±1.35	0.47±0.005	21±1.26

Table 11: Oral dispesrable tablets estimation values

Formula	Percentage drug content	Wetting time	Percentage H_2O absorption ratio	Percentage drug release
F1	98.23±0.774	21±1.12	52.32	42±5
F2	96.54±0.253	23±1.46	59.65	39±1
F3	97.32±0.422	18±1.32	57.72	31±7
F4	98.74±0.567	13±1.15	59.52	45±3
F5	96.76±0.321	25±1.23	57.61	37±1
F6	99.36±0.582	15±1.54	59.85	44±1
F7	98.81±0.518	20±0.21	59.65	36±2
F8	98.21±0.773	21±0.78	59.69	28±3
F9	97.39±0.691	19±1.22	58.43	31±2

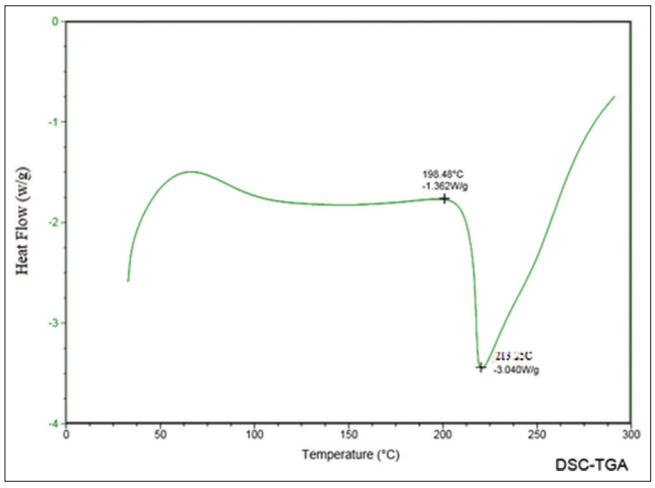

Figure 13: Differential scanning calorimetry pure glimepiride

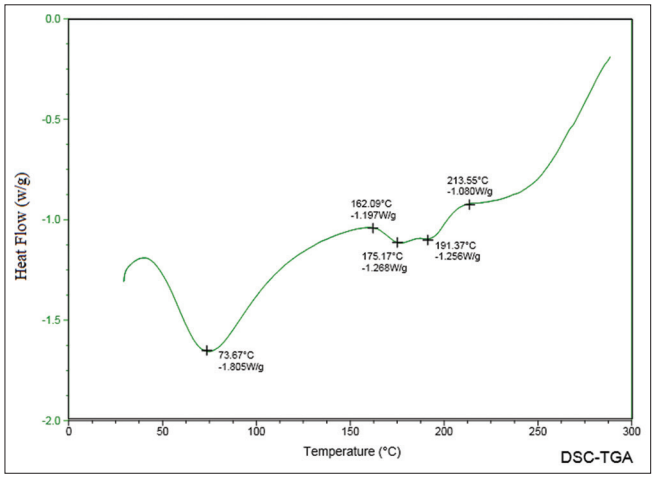

Figure 14: Differential scanning calorimetry polyvinylpyrrolidone

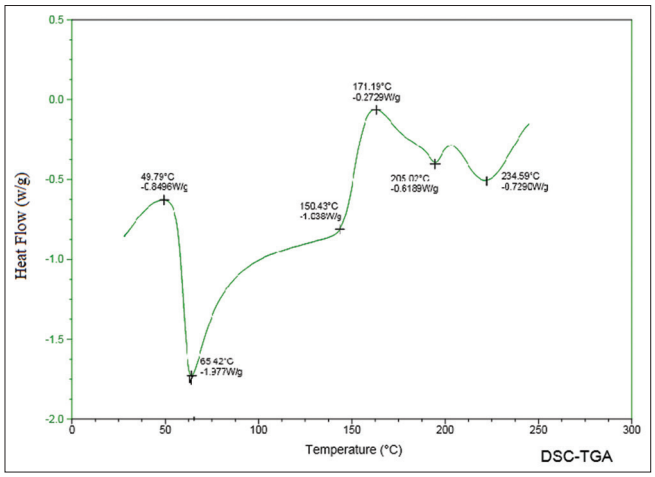

Figure 15: Differential scanning calorimetry polyethylene glycol

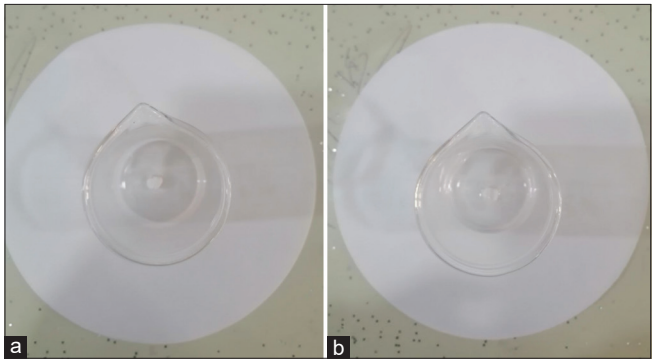

Figure 17: Water absorption. (a) Before, (b) After water absorption

peak area; that gives an indication in the faster dissolution rate because of the reduction in crystallinity and rapid dissolving, when compared with a pure drug, on the other hand, there is the same change in the thermograms shows in Figures 13-16; show a reduction in M. P of Soluplus 1 as compared to the unadulterated Glimepiride likely due to diminish in the size crystillinty. The melting point of formula Soluplus 1 and PEG1 is found to be 174.23°C and 168.17°C. The inhibition in crystallinity is ascribed to interaction drug particles with polymer matrix through using the solvent evaporation technique which gives a result about the compatibility of both together.

Estimation of orally disintegrating tablets formulas

Study of precompression parameters

Table 9 shows the results of precompression parameters of compression technique in the presence of super disintegrant at various ratios. The reduction in size of granules and angle of repose can improve the flowability and increase in the surface area; the data have determined with mean value of ±S.D.

Estimation of glimepiride orally disintegrating tablets

The obtained data of ODTs are shown in Table 10; the thickness ranges between 2.23±0.45 to 3.88±0.24 mm, the less the thickness

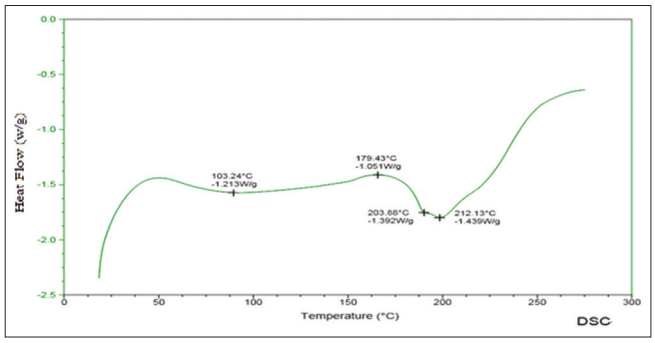

Figure 16: Differential scanning calorimetry Soluplus

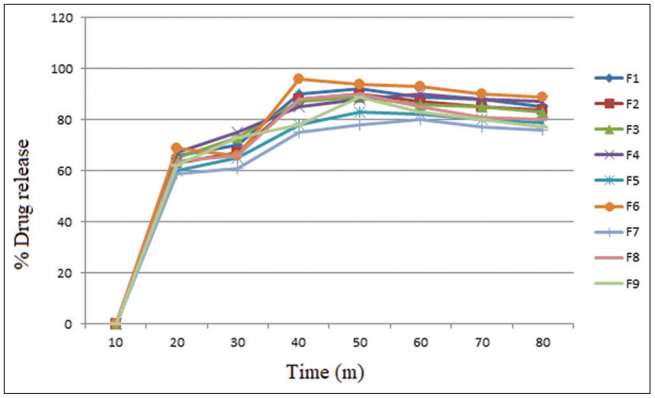

Figure 18: Percentage release profile

Table 12: Drug release profile

Time (min)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
10	66	63	65	67	60	69	59	64	62
20	70	67	73	75	65	66	61	66	73
30	90	88	87	85	78	96	75	88	78
40	92	90	89	88	83	94	78	90	89
50	89	87	86	90	82	93	80	85	83
60	88	85	85	88	80	90	77	81	80
70	85	84	83	87	79	89	76	80	77

shows a good product quality. The hardness test is not more than 4.00 ± 0.200 kg/cm^2 for accepted range. Weight variation is within the accepted limit of 248 ± 1.030–252 ± 1.23 mg. The friability values for all formulas are less than 1.0% which fall in range of 0.37%-0.78% and have good mechanical strength. Table 11 illustrates the values for the estimation study.

The disintegration time for all formulas is ranged between 13 to 22 seconds, F6 shows the rapid disintegration time within 13 seconds.

Figure 17 shows water absorption of the ODTs. The data have determined with mean value of ±S.D., percentage of drug release from 28 to 44% for F6 as shown in Table 11.

In vitro orally disintegrating tablets release profile

Fgure 18 illustrates the Release profile in-vitro study by using

dissolution rate apparatus USP2 test to obtain the dissolution time for the ODTs in PBS 7 media at 37°C, for F6 about 69% after 10 minutes and maximum release achieved 95.3% after 40 minutes; figure 18 illustrates the release profile, while the remaining formulas the burst release is started after 10 minutes less than 40% and the maximum release after 40 minutes is less than 90% as shown in Table 12.

CONCLUSION

Glimepiride ODT is prepared by using direct compression method as solid dispersion in the presence of super-disintegrant to enhance the dissolution rate of the tablets in oral cavity and increase the drug release profile through initial burst release from the matrix due to the swelling of the polymer in the presence of fluid to disintegrate the ODTs with a few second. The selection of F6 as a best formula is based on the collected data regarding high drug content and rapid drug release from the formula.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Zhang L, Yang J, Chen XQ, Zan K, Wen XD, Chen H, *et al*. Antidiabetic and antioxidant effects of extracts from Potentilla discolor Bunge on diabetic rats induced by high fat diet and streptozotocin. J Ethnopharmacol 2010;132:518-24.
2. Mythili MD, Vyas R, Akila G, Gunasekaran S. Effect of streptozotocin on the ultrastructure of rat pancreatic islets. Microsc Res Tech 2004;63:274-81.
3. Kohli A, Verma S Jr., Sharma A Jr. Psychogenic polydipsia. Indian J Psychiatry 2011;53:166-7.
4. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem 2006;52:112-9.
5. Kamiyama T, Iseki K, Kawazoe N, Takishita S, Fukiyama K. Carbamazepine-induced hyponatremia in a patient with partial central diabetes insipidus. Nephron 1993;64:142-5.
6. Thompson P Jr., Earll JM, Schaaf M. Comparison of clofibrate and chlorpropamide in vasopressin-responsive diabetes insipidus. Metabolism 1977;26:749-62.
7. Conceição J, Adeoye O, Cabral-Marques H, Concheiro A, Alvarez-Lorenzo C, Lobo JM. Orodispersible carbamazepine/hydroxypropyl-β-cyclodextrin tablets obtained by direct compression with five-in-one co-processed excipients. AAPS Pharm Sci Tech 2020;21:39.
8. Koner JS, Rajabi-Siahboomi AR, Missaghi S, Kirby DJ, Perrie Y, Ahmed J, *et al*. Conceptualisation, development, fabrication and *in vivo* validation of a novel disintegration tester for orally disintegrating tablets. Sci Rep 2019;9:12467-9.
9. Matsui R, Uchida S, Namiki N. Combination effect of physical and gustatory taste masking for propiverine hydrochloride orally disintegrating tablets on palatability. Biol Pharm Bull 2015;38:17-22.
10. Alshehri SM, Park JB, Alsulays BB, Tiwari RV, Almutairy B, Alshetaili AS, et al. Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology. J Drug Deliv Sci Technol 2015;27:18-27.
11. Kukulka M, Nudurupati S, Perez MC. Bioavailability, safety, and pharmacodynamics of delayed-release dexlansoprazole administered as two 30 mg orally disintegrating tablets or one 60 mg capsule. Therap Adv Gastroenterol 2016;9:770-80.
12. Szymańska-Chargot M, Cybulska J, Zdunek A. Sensing the structural differences in cellulose from apple and bacterial cell wall materials by Raman and FT-IR spectroscopy. Sensors (Basel) 2011;11:5543-60.
13. Daniel MC, Astruc D. Gold nanoparticles: Assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. Chem Rev 2004;104:293-346.
14. Gill P, Ghalami M, Ghaemi A, Mosavari N, Abdul-Tehrani H, Sadeghizadeh M. Nanodiagnostic method for colorimetric detection of *Mycobacterium tuberculosis* 16S rRNA. Nanobiotechnol 2008;4:28-35.
15. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev 2007;59:617-30.
16. Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. Pharm Glob 2011;3:001-7.
17. Tambe A, Mokashi P, Pandita N. Ex-vivo intestinal absorption study of boswellic acid, cyclodextrin complexes and poloxamer solid dispersions using everted gut sac technique. J Pharm Biomed Anal 2019;167:66-73.
18. Muller RH, Jacobs C, Kayer O. Nanosuspension for formulation of poorly soluble drugs. In: Nielloud F, Marti-Mesters G, editors. Pharmaceutical Emulsion and Suspension. New York: Marcel Dekker; 2000. p. 383-407.
19. Lipinski CA. Avoiding investment in doomed drugs, is poor solubility an industry wide problem? Curr Drugs Dis 2001;4:17-9.
20. Sekiguchi K, Obi N. Studies on absorption of eutectic mixtures. I.A comparison of the behavior of eutectic mixtures of sulphathiazoleand that of ordinary sulphathiazole in man. Chem Pharm Bull 1961;9:866-72.
21. Topaloğlu Y, Yener G, Gönüllü U. Inclusion of ketoprofen with skimmed milk by freeze-drying. Farmaco 1999;54:648-52.
22. Ishikawa T, Watanabe Y, Utoguchi N, Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter-taste-masked granules by the compression method. Chem Pharm Bull (Tokyo) 1999;47:1451-4.
23. Lindenberg M, Kopp S, Dressman JR. Classification of orally administered drugs on the world health organization model list of essential medicines according to the biopharmaceutical classification system. Eur J Pharm Biopharm 2004;58:265-78.
24. Bredenberg S, Duberg M, Lennernäs B, Lennernäs H, Pettersson A, Westerberg M, *et al*. *In vitro* and *in vivo* evaluation of a new sublingual tablet system for rapid oromucosal absorption using fentanyl citrate as the active substance. Eur J Pharm Sci 2003;20:327-34.
25. Gole D, Savall T, Ma LF, Greenwood D, Wilkinson P, Davies, J. (2005). U.S. Patent Application No. 10/638,822.