RESEARCH ARTICLE

Formulation and *In-vitro* Evaluation of Two Layers Tablet for Dual Release of a Model Drug

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ABSTRACT

Objective: Glimepiride is a third-generation sulfonylurea medication that has been used to treat type 2 diabetes (T2D) mellitus. It is class II drug according to the biopharmaceutical classification system (BCS) characterized with its low solubility and high permeability. Due to the drug's weak water solubility, its bioavailability is restricted by its dissolving rate. This study aimed to develop a bilayer tablet of glimepiride with one layer for immediate release (IR), a dose of 2 mg, a second layer for sustained release (SR), and a 4 mg dose Immediate release layer included solid dispersion of glimepiride .

Methods: Glimepiride solid dispersions were prepared utilizing four water-soluble carriers (poloxamer 188, polyethylene glycol (PEG6000), Kollicoat IR and soluplus) by solvent evaporation and fusion techniques at 1:1, 1:2, and 1:4 ratios and evaluated in 0.1 N of HCL buffer pH 1.2 with 1% of sodium lauryl sulphate (SLS) for 2 hours. utilizing a USP-II paddle-type dissolution apparatus containing 900 mL dissolution medium kept at 37 ± 0.5°C and 50 rpm. The sustained release layer of glimepiride bilayer tablet was prepared using various polymers, including HPMC K15, HPMC K4, xanthan gum, carbopol 934 and ethyl cellulose at 1:1, 1:2,1:3 ratios and combination of polymers in phosphate buffer pH 6.8 for 12 hours. The prepared solid dispersion of immediate release were evaluated by X-ray powder diffraction (PXRD), and fourier transform infrared spectroscopy for selected SD9. The FTIR spectroscopy analysis for selected formula (F24) of sustained layer, angle of repose, Hausner's ratio and Carr's Index were used to evaluate the flowability and compressibility of the formulation powders during the pre-compression investigations, while, thickness, hardness, weight variation, friability, drug content, for prepared tablets.

Results: The results revealed that SD9 at ratio (1:4 glimepiride: soluplus) was the optimal formula since 94% of drug released at 2 hours for immediate layer formula 24, which included ethylcellulose polymer in a 1:1 ratio in the sustained layer of the tablet, was chosen as the optimal formula out of another formula (F1–F28), This formula demonstrated acceptable sustained properties of the glimepiride over the course of 12 hours. and approximately 96% of the medication was released.

Conclusion: This study successed in designing bilayer tablets containing glimepiride solid dispersion formulation in the first immediate release layer and untreated pure drug formulation in the second layer for sustaining the release of the drug for a specific period of time to be used as the effective treatment of type II diabetes mellitus.

Keywords: Type II diabetes mellitus, Glimepiride, Immediate layer, Sustained layer, Solid dispersion, Solvent evaporation, FTIR spectroscopy.

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INTRODUCTION

For decades, oral drug delivery has been the most extensively used route of administration among all the ways investigated for systemic drug delivery *via* a variety of pharmaceutical products with varying dosage forms[1] Oral administration is the most convenient and widely used mode of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, lack of sterility requirements, and design flexibility for dosage forms.[2] Orally administered solid medicaments include powders, pills, sachets, capsules, and tablets . On the other hand, tablets and capsules now account for well over two-thirds of the overall number and cost of medications produced worldwide.[2] With many drugs, the primary objective of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non-toxic over a prolonged period of time.[3] The bilayer tablet concept has been used for a very long time to create sustained release formulations. This type of tablet has an immediate releasing layer and may contain a second layer (bilayer) to sustain drug release. The pharmacokinetic advantage is

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depend on the criterion that drug release from the immediate releasing layer causes a rapid increase in blood concentration. As the sustaining layer is released, however, the blood level is maintained at a steady state.[4] glimepiride is a sulfonyl urea-type oral hypoglycemic agent of third generation that is commonly used in the treatment of T2D. glimepiride's principal mode of action is to reduce blood glucose. Glimepiride's principal method of action is to stimulate the release of insulin from functional pancreatic cells. extra pancreatic effects may possibly contribute to glimepiride's action.[5] The drug enhances peripheral tissue's insulin sensitivity and increasing the number of glucose transporter molecules in the plasma membranes of peripheral muscle and adipose tissue, hence increasing glucose uptake. Furthermore, glimepiride stimulates glycogen synthesis and lipogenesis while inhibiting gluconeogenesis. Glimepiride is quickly and completely absorbed (100%) from the gastrointestinal tract upon oral administration, and its absorption is unaffected by meal intake, glimepiride is completely metabolised and has a half-life of 5–8 hours, converted to its cyclohexyl hydroxymethyl derivative by the hepatic cytochrome P450 2C9 isozyme. This is then metabolized to the carboxyl derivative by cytosolic enzymes. Metabolites are removed from the body through the urine and faeces.[6] Glimperide is classified as a class II drug by the BCS. For BCS Class II substances, dissolution is the rate-limiting step in drug absorption; thus, dissolution can be used to evaluate the adequacy of performance, with the stipulation that the dissolution test employed should reflect the *in-vivo* performance.[7] Utilizing solid dispersions of such therapeutic candidates in physiologically inert hydrophilic carriers has the potential to enhance their solubility and bioavailability. Solid dispersion (SD) is an effective solubilization technique for medicines with poor water solubility. Given that an SD is fundamentally a drug–polymer two-component system, the drug–polymer interaction governs its efficiency and development.[8]

MATERIALS AND METHODS

Chemicals

Glimepiride (Glm) as a gift from Santa cruz, USA. Kollicoate IR was purchased from Sigma chemical Co, USA, hydroxypropylmethyl cellulose K4M, Jiangsu yew pharmaceutics Co., ltd china. Poloxamer 188 Eastman Chemical Co. USA, Hyroxy propyl methyl cellulose k 15 Alpha chemical, India, Poly ethylene glycol 6000(PEG), Alpha chemical, india Soluplus, BASF pharmaceutical industries-Germany, Carbopol 934 p, ethylcellulose and xanthan gum are from Baoji guokang Co. Avicel PH 102 (Microcrystalline cellulose) from Shanghai ruizheng chemical Ltd, china. Sodium Lauryl sulphate, ethanol, methanol, sodium hydroxide, potassium dihydrogen orthophosphate, hydrochloric acid (HCL) disodium orthophosphate and dihydrogen sodium orthophosphate from Thomas Baker Pvt, Limited, India.. Lactose monohydrate and talc from Himedia, India, spray dried lactose and mannitol from Middle east laboratories Co. Limited (Iraq), crospovidone, magnesium stearate and sodium starch glycolate from Samara drug industry, Iraq.

Methods

Immediate Layer Prepared using Solid Dispersion Technique

- By Solvent Evaporation Method

Methanol was employed as the solvent to make the solid dispersions in this approach. For each three distinct drug: soluplus ratios were developed (1:1, 1:2 and 1:4). The soluplus and drug were dissolved separately in the needed amount of methanol and combined mechanically, after which the solvent was evaporated using a rotary evaporator at decreased pressure. The dried solid dispersions were collected, ground in a mortar and pestle, and sieved (0.36 mm sieve) before being kept in desiccators until later usage. The same procedure was employed to prepare solid dispersion using kollicoate IR polymer except that ethanol is used as a solvent instead of methanol. The optimum drug to polymer ratios as compared to the physical mixture of the same weight drug: carrier ratio and pure glimepiride. The comparison studies included measuring *in-vitro* release study.[9] Tables 1 to 3 shows the drug carrier weight ratios in solid dispersion and physical mixing.

- By fusion method

The required amount of glimepiride and carrier in 1:1, 1:2, and 1:4 ratios was weighted firstly. Accurately amount weighted carrier (poloxamer 188) was melted in a porcelain dish at temperature above melting point of carrier 57°C and amount of glimepiride previously weighed was added with thorough mixing for 1–2 minute until obtaining homogeneous mixture followed by quick cooling using ice bath. The dried mass was pulverized, passed through mesh sieve (0.36 sieve) and stored in a desiccator to be use later. The same procedure was employed to prepare solid dispersion with PEG6000 polymer. The optimum drug to polymer ratio was compared to the physical mixture of the same-weight drug: carrier ratio and pure glimepiride. The comparison studies included measuring solubility and *in-vitro* release studies. Table 1 shows the drug carrier weight ratios in solid dispersion and physical mixing.[10]

Preparation of Sustained Layer of Glimepiride

All of the formulations were made using the direct compression method, and the components (drug, polymers, and excipients) are listed in Table 2. To achieve a homogeneous mixture, drug, polymers, and excipients (excluding glidants and lubricants) were individually passed through mesh 0.36 mm and then combined for 15 minutes. After adding the specified amount of magnesium stearate and talc, the materials were mixed for another 5 minutes before being compressed using an 8 mm flat punch tableting machine. The model drug formulations' physical parameters were then analyzed.[11]

Bilayer Tablet Preparation

Using an 8 mm flat-faced punch, bilayer tablets were created. The mixture for the sustained-release layer was put into the die cavity. Direct compression was used to compress the material lightly (8 tons/cm^2). The lower layer is created with an 8mm flat punch tableting machine, which was previously

Table 1: Formulation code of glimepiride solid dispersions and physical mixtures prepared with different carriers

Formulation codes	*Carrier*	*Drug: carrier ratio (w/w)*	*Method of preparation*
SD1	PEG6000	1:1	Fusion method
SD2		1:2	Fusion method
SD3		1:4	Fusion method
PM1		1:4	Physical mixture
SD4	Poloxamer 188	1:1	Fusion method
SD5		1:2	Fusion method
SD6		1: 4	Fusion method
PM2		1:4	Physical mixture
SD7	Solupus	1:1	Solvent Evaporation
SD8		1:2	Solvent Evaporation
SD9		1:4	Solvent Evaporation
PM3		1:4	Physical mixture
SD10	Kollicoate IR	1:1	Solvent Evaporation
SD11		1:2	Solvent Evaporation
SD12		1:4	Solvent Evaporation
PM4		1:4	Physical mixture

Table 2: Formulas of glimepiride sustained release layer tablet

Ingredient	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*	*F11*	*F12*	*F13*	*F14*	*F15*
Glimepiride	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Hpmc (15)	15	30	45	60	----	----	----	-----	10	30	----	----	------	-----	15
Crospovidone	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Xanthan gum	----	----	----	----	15	30	45	60	10	10	20	----	-----	-----	15
Carbopole934	-----	-----	-----	-----	-----	------	-----	------	-----	----	----	15	30	45	15
Avicel pH102	111	96	81	66	111	96	81	66	106	86	106	111	96	81	81
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Subtotal(mg)	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
Ingredient	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27	F28		
Glimepiride	4	4	4	4	4	4	4	4	4	4	4	4	4		
Crospovidone	15	15	15	15	15	15	15	15	15	15	15	15	15		
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3		
HPMCK4	15	30	45	60	22.5	33.75	22.5	33.75	---	---	---	22.5	33.75		
Xanthan gum	---	---	---	---	22.5	11.25	---	---	---	---	---	---	---		
Carbopole934	---	---	---	---	---	---	22.5	11.25	---	---	---	---	---		
Ethyl cellulose	---	----	---	---	---	---	---	---	15	30	45	22.5	11.25		
Avicel pH102	111	96	81	66	81	81	81	81	111	96	81	81	81		
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2		
Subtotal(mg)	150	150	150	150	150	150	150	150	150	150	150	150	150		
Total weight (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200		

compressed to the required uniform layer of powder with low compression force. The upper punch was elevated after compression, followed by the mixture of the immediate release layer was put into the die, which contained an initial layer of a sustained release and the final bilayer tablet is made up and a compression force of 12 tons/cm^2.[12]

Determination of Glimepiride λ_{max}

Stock solutions of glimepiride (40 ug/mL) in different dissolution media. In HCl (PH 1.2) and phosphate buffers (pH 6.8 and 7.4) were prepared then diluted to obtain (20 ug/mL) and scanned by UV-visible spectrophotometer over the wavelength range (400–200) nm, and the λ max of the drug was determined in each dissolution media.[13]

Table 3: Pre-compression parameters of glimepiride sustained release layer

Formula no	*Angle of repose*	*Bulk density (gm/cm^3)*	*Tapped density (gm/cm^3)*	*Carr's index*	*Hausner ratio*	*type of flow rate*
F1	31.06 ± 2.1	0.316 ± 0.02	0.365 ± 0.01	13.42 ± 0.98	1.15 ± 0.08	Good
F2	33.94 ± 1.65	0.335 ± 0.01	0.389 ± 0.03	13.88 ± 0.1.3	1.16 ± 0.06	Good
F3	37.2 ± 2.56	0.374 ± 0.4	0.462 ± 0.02	19.04 ± 1.02	1.23 ± 0.09	Fair
F4	38.03 ± 2.15	0.351 ± 0.02	0.424 ± 0.02	17.22 ± 1.1	1.20 ± 0.07	Fair
F5	32.28 ± 1.26	0.370 ± 0.15	0.426 ± 0.04	13.14 ± 0.5	1.15 ± 0.06	Good
F6	36.23 ± 1.8	0.357 ± 0.05	0.428 ± 0.03	16.58 ± 0. 82	1.19 ± 0.08	Fair
F7	39.28 ± 1.4	0.385 ± 0.02	0.475 ± 0.03	18.94 ± 0. 66	1.23 ± 0.09	Fair
F8	41.64 ± 2.2	0.374 ± 0.02	0.483 ± 0.02	22.5 ± 0. 6	1.26+0.05	passable
F9	42.115 ± 1.5	0.349 ± 0.02	0.446 ± 0.03	21.74 ± 0.8	1.27 ± 0.04	passable
F10	39.23 ± 2.1	0.360 ± 0.01	0.451 ± 0.05	20.177 ± 0. 3	1.25 ± 0.05	Fair
F11	37.17 ± 1.75	0.357 ± 0.01	0.447 ± 0.04	20.13 ± 0.63	1.252 ± 0.01	Fair
F12	36.87 ± 2.85	0.370 ± 0.02	0.452 ± 0.04	18.14 ± 1.2	1.22 ± 0.016	Fair
F13	36.73 ± 1.2	0.371 ± 0.03	0.45 ± 0.02	17.55 ± 0.51	1.21 ± 0.09	Fair
F14	33.27 ± 1.8	0.321 ± 0.07	0.367 ± 0.03	12.53 ± 0.74	1.14 ± 0.07	Good
F15	34.43 ± 1.2	0.345 ± 0.09	0.398 ± 0.06	13.3 ± 0.7	1.153 ± 0.03	Good
F16	35.8 ± 2.9	0.371 ± 0.03	0.45 ± 0.04	17.55 ± 1.4	1.21 ± 0.1	Fair
F17	29.33 ± 1.4	0.341 ± 0.03	0.38 ± 0.03	10.26 ± 0.5	1.11 ± 0.05	Excellent
F18	30 ± 2.3	0.321 ± 0.01	0.364 ± 0.02	11.81 ± 0.3	1.13 ± 0.06	Good
F19	34.65 ± 1.8	0.341 ± 0.02	0.382 ± 0.01	10.73 ± 0. 5	1.12 ± 0.05	Good
F20	37.12 ± 2.41	0.373 ± 0.04	0.461 ± 0.03	19.08 ± 0. 8	1.23 ± 0.06	Fair
F21	36.03 ± 2.16	0.352 ± 0.03	0.423 ± 0.09	16.78 ± 0. 4	1.20 ± 0.08	Fair
F22	30.43 ± 1.18	0.324 ± 0.01	0.363 ± 0.4	10.74 ± 0.62	1.12 ± 0.04	Good
F23	31.43 ± 1.26	0.368 ± 0.03	0.434 ± 0.02	15.2 ± 0.5	1.17 ± 0.06	Good
F24	26 ± 1.26	0.321 ± 0.03	0.358 ± 0.01	10.33 ± 51	1.11 ± 0.04	Excellent
F25	28.31 ± 1.15	0.327 ± 0.06	0.368 ± 0.07	11.14 ± 0.32	1.12 ± 0.02	Good
F26	32 ± 2.3	0.352 ± 0.15	0.412 ± 0.02	14.5 ± 0.56	1.17 ± 0.05	Good
F27	33 ± 1.4	0.347 ± 0.31	0.409 ± 0.21	15.158 ± 0.12	1.17 ± 0.08	Good
F28	36.86 ± 0.95	0.369 ± 0.01	0.456 ± 0.04	19.07 ± 0.28	1.23 ± 0.07	Fair

Evaluation of the Prepared Solid Dispersion

- *In-vitro* dissolution study

The USP type II (paddle type) dissolution test apparatus was used for the *in-vitro* dissolution investigation (Cosmo Lab). At 37°C and a rotation speed of 50 rpm, 900 mL of 0.1 N HCl dissolving media (pH 1.2) was used. 2 mg of glimepiride and an equivalent amount from solid dispersions and physical mixtures were separately placed in a dissolution vessels for 120 minutes, and 5 mL samples were withdrawn and replaced with the same volume of fresh medium at appropriate time intervals (5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes) to keep the sink condition constant. Samples were then filtered and spectrophotometrically analyzed at determined λmax for glimepiride. For each run test, the technique was repeated three times, and the mean and standard deviation were computed.[14]

Factors Affecting the Dissolution Rate of Solid Dispersions

- Effect of Drug: Carrier Ratios

The effect of the drug: carrier ratio on the drug solubility was evaluated using the formulas (SD1-SD3), (SD4-SD6), (SD7-SD9), and (SD10-SD12). Dissolution tests were used to study the influence of drug:carrier ratio on drug dissolution and release.

- Effect of Carrier Type

Solid dispersions SD3, SD6, SD9, and SD12 formulas were used to study the influence of carrier type (PEG6000, poloxamer 188, soluplus, and Kollicoat IR) on Glimepiride solubility by comparing phase solubility changes, as well as the effect of carrier type on drug dissolution and release.

Characterization of the Selected Solid Dispersion in the Immediate Layer

- FTIR

Glimepiride, Soluplus and SD9 samples (equal to approximately 2 mg of glimepiride) were pulverized, mixed with dry potassium bromide and pressed into discs using a hydraulic press. The discs were examined using FTIR spectroscopy (4000–400 cm^{-1})[15]

- PXRD

The extent of crystallinity for pure drug, optimum formula of solid dispersion, and physical mixture was measured using a PXRD system (Shimadzu, Japan) equipped with Cu radiation

(λ = 1.54060 A°) at a voltage of (40 Kv) and a current of (30 mA). The instrument was set to continuous scan mode, and samples were evaluated in the range (5-80◦) with a step size of 0.05° at a scanning speed of (5◦/min) and axis number (2θ)[16] completed at Nano center in the University of Technology in Baghdad

Angle of Repose

The fixed funnel method was used to estimate the angle of repose of powders. Granular materials were poured from a funnel at a height of 2 cm onto a specified base with known roughness attributes. To reduce the influence of falling particles, the funnel is either fixed or slowly raised while the conical shape of the material heap is growing. When the heap reaches a certain height, the material pouring is stopped. The angle of repose is then calculated using the inverse tangent (arctan) rule, which involves measuring the average radius of the produced conical shape and the maximum height of the heaped material, and then calculating the arctan of the maximum height to average radius ratio.[16] The angle of repose was computed by measuring the diameter of the powder cone and applying the following equations.[17]

$$Tan\ \theta = h/r \quad \text{----- Equation (1)} \quad \theta = tan^{-1}\left(h/r\right) \quad \text{------ Equation(2)}$$

where θ = angle of repose, h = is the height of the resultant powder cone, and r = radius the of the powder cone.

- Bulk Density (Db)

Bulk Density The apparent bulk density was obtained by inserting pre-sieved granules in a graduated cylinder, weighing and measuring the volume as it is. The following equation is used to compute bulk density.[18]

Db = (Mass powder)/Powder Bulk Volume --- Equation 3

- Tapped Density (Dt)

The tapped volume was determined by tapping the powder against a hard surface. After 100 taps in a graded measuring cylinder, the volume remained steady., and the following equation was used to compute it.[18]

Dt = (Powder Mass)/(powder Tapped volume) ----- Equation 4

- Carr's index (compressibility index) and Hausner's ratio calculation[19]

The powder sample was placed into a measuring glass cylinder, and the volume of untapped material was measured, then the volume of tapped material was measured after each tap cycle until the volume remained constant, and the Carr's index was determined using the equation: Carr's index= (Tapped density - Bulk density) ÷ (Tapped density) ×100 ----- Equation 5

- Hausner's Ratio

The Hausner's ratio displays the powder material's flow characteristic. It's the ratio of the powder's tapped density to its bulk density, and it's calculated using the equation below: Hausner's ratio= Tapped density ÷ Bulk density = Dt/Db ---------- Equation 6

Evaluation of the Prepared Bilayer Tablets (Post Compression Parameter)

- Hardness Test

The hardness test was performed using a "Monsanto" hardness tester with five tablets chosen at random and fitted sufficiently between the spindle and the anvil via their diameter. By rotating the knurled knob, the pressure on the tablet is increased until the tablet falls apart. The force needed to break the tablet (in kilograms) from the scale has been recorded.[20]

- Friability Test

The study began with a total weight of 10 tablets, which was recorded as the beginning weight (Wi). All of the tablets in the friability tester's drum and apparatus were rotated at 100 rpm for a period of time {4 minutes (25 rpm for 1 minute)}. After that, the tablets were de-dusted and reweighed; this is thought to be the final result weightage (Wf). Tablets that lose no more than 1% of their weight are generally regarded as appropriate. Friability was measured as a percentage. The following formula was used to calculate% friability:

% friability= {(W intial –W final)/W intial)} x100% ---- Equation (7)

Where % Friability is the proportion of friability, W initial = tablet weight before the test.

W final = after-test weight of tablets.[21]

- Thickness Test

A vernier caliper was used to determine the thickness of the tablets. Three tablets from each formula were used, calculated average values and standard deviations (SD).[22]

- Weight Variation Test

The weight variation test was conducted by weighing twenty tablets at random from each batch and calculating average weights.If no more than two tablets go outside the percentage restriction (5%) and none of the tablets differ by more than twice the percentage limit(10 %), the tablet passes the test.[23]

The average weight of tablets = (Total weight of tablets)/ (Number of tablets) Equation 8

% Deviation=(Average weight -Individual weight)/ (Individual weight) X 100 Equation 9

- Drug Content Uniformity

Five tablets were crushed and powdered in a mortar. In 100 mL of 0.1N HCl, an amount equal to the average weight of the produced tablets was dissolved and sonicated for 15 minutes. Whatman filter was used to filter the solution. A 1-mL of the filtrate was diluted to 10 mL with 0.1 N HCl in a suitable measuring flask, and the drug content was determined by measuring the absorbance at the glimepiride's λ_{max} using a UV-visible spectrophotometer. In the USP states monograph, the criteria of content uniformity achieve if the amount of active component in each tablet is within 85–115% of the value on the label percent of the total.[25]

Characterization of Sustained Layer

- *In-vitro* Dissolution Study

The *in-vitro* dissolution investigation was conducted utilizing a USP type II (paddle type) dissolution test device (Cosmo Lab). In a dissolution vessel, one tablet of each produced formula was inserted. A medium containing 900 mL USP buffer solutions at pH 6.8 (phosphate buffer solution) was used. The medium

was kept at 37 ± 0.5℃ with a rotational speed of 50 rpm. At 0 m, 15 m, 30 m, 45 m, 1 hours, 2,3,4,5,6,7,8,9,10,11 and 12 hours, 5 mL of dissolving sample was taken and refilled with equal volume to maintain sink condition. The absorbance of the samples was measured spectrophotometrically at λ_{max} of drug after they were filtered using Whatman filter paper (filter syringe 0.45 µm). A calibration curve made from pure glimepiride samples was used to determine the concentration of each sample. For each run test, the procedure was repeated three times and the mean and standard deviation were calculated (24) hardness, friability, disintegration time were also determined according to established protocols. All the brands complied with the official specification for friability, uniformity of weight, disintegration time and drug content. UV spectroscopic and RP-HPLC methods were validated for the parameters like linearity, accuracy, precision and robustness. Potency was determined by using these two methods. Potency obtained from UV method and HPLC methods were found similar with paired t test. Dissolution test results were subjected to further analysis by difference factor (f1).

- Drug-excipients Compatibility Study

This study was conducted on the selected formula using FTIR spectroscopic analysis in order to rule out any drug-excipient interactions that may occur during the formulation process. The potassium bromide discs were made by compressing the powder in a hydraulic press and analyzing within the specified ranges (4000–400 cm^{-1}).[25]

Variable Affecting Glimepiride Release from Sustained Layer

- The Effect of Polymer Type

The influence of polymer type on drug release qualities was studied using formulas (2, 6, 14, 17, and 25) containing HPMC15, xanthan gum, Carpobol, HPMCK4M, and ethylcellulose, respectively. The polymer concentration in these formulations was kept constant at 20% (w/w).

- The Effect of Polymer Concentration

In this study, ethylcellulose was employed in formulas (24, 25, and 26) at 10, 20, and 30% (w/w) concentrations, respectively. The purpose of using a varied amount of polymer was to see how changing the polymer concentration within the tablet influenced medication release.

- Selection of the Optimum Formula

The best formula was chosen depending on the smallest amount of polymer that could be used and which formula could provide sustained release during dissolution for a long time**.**

- Statistical Analysis

The experimental results were expressed as the mean of triplicate samples with a standard deviation and compared using one-way analysis of variance (ANOVA) when the difference was less than ($p < 0.05$), it was regarded as statistically significant; however, it was considered non-significant ($p > 0.05$).

RESULTS AND DISCUSSION

Determination of Glimepiride λ_{max}

The diluted solution of glimepiride was scanned with a UV spectrophotometer in 0.1 N HCl (pH 1.2), phosphate buffers (pH 6.8) and (pH 7.4) spanning a wavelength range of 200–400 nm, with the λ^{max} recorded at 228 nm in all three solutions.[26]

Factors Affecting Dissolution Rate of Solid Dispersions

Effect of Drug: Carrier Ratio

The formulas (SD1-SD3), (SD4-SD6), (SD7-SD9), and (SD10-SD12) were used to study the influence of drug:carrier ratio on drug dissolution as shown in Figure 2 (a-d). The dissolution rate obtained from solid dispersion formulations was attributed to several factors as reduction in particle size, formation of higher energy metastable state with higher degree of amorphization of the drug, improved wetting properties, local solubilization of the carrier at the diffusion layer, increased porosity, and the formation of intermolecular hydrogen bonding between the drug and the carrier. For soluplus solid dispersion release was 79% at 1:1 ratio of SD7 formula, when the ratio was increased to 1:2 the release was 87% for SD8 formula and 94% for 1:4 ratio of formula SD9 produced the highest release of glimepiride during the initial stage of dissolution. Where formulations SD3, SD6, SD9 and SD12 at 1:4 ratio which were prepared using solvent evaporation and fusion method using four different carriers (i.e., PEG 6000, Poloxamer 188, Soluplus and Kollicoate IR) demonstrated the greatest release

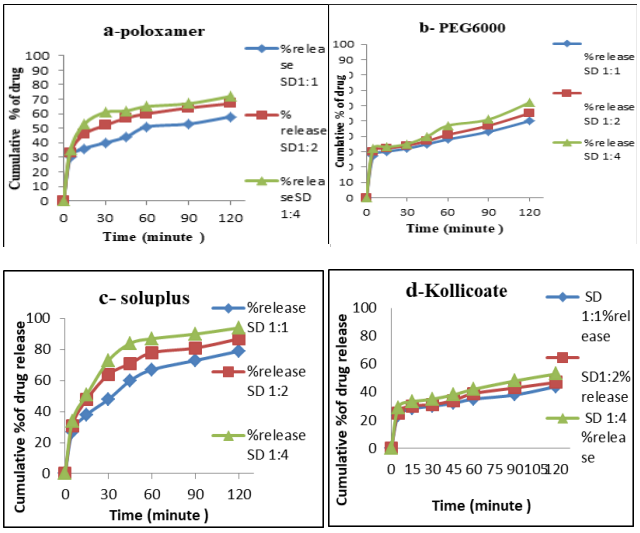

Figure 1: Effect of carrier ratio on the release of glimepiride

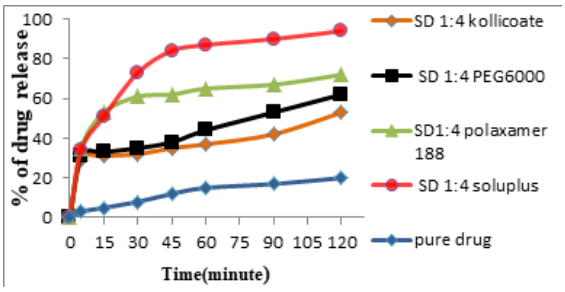

Figure 2: Effect of polymer type SD on the release of glimepiride.

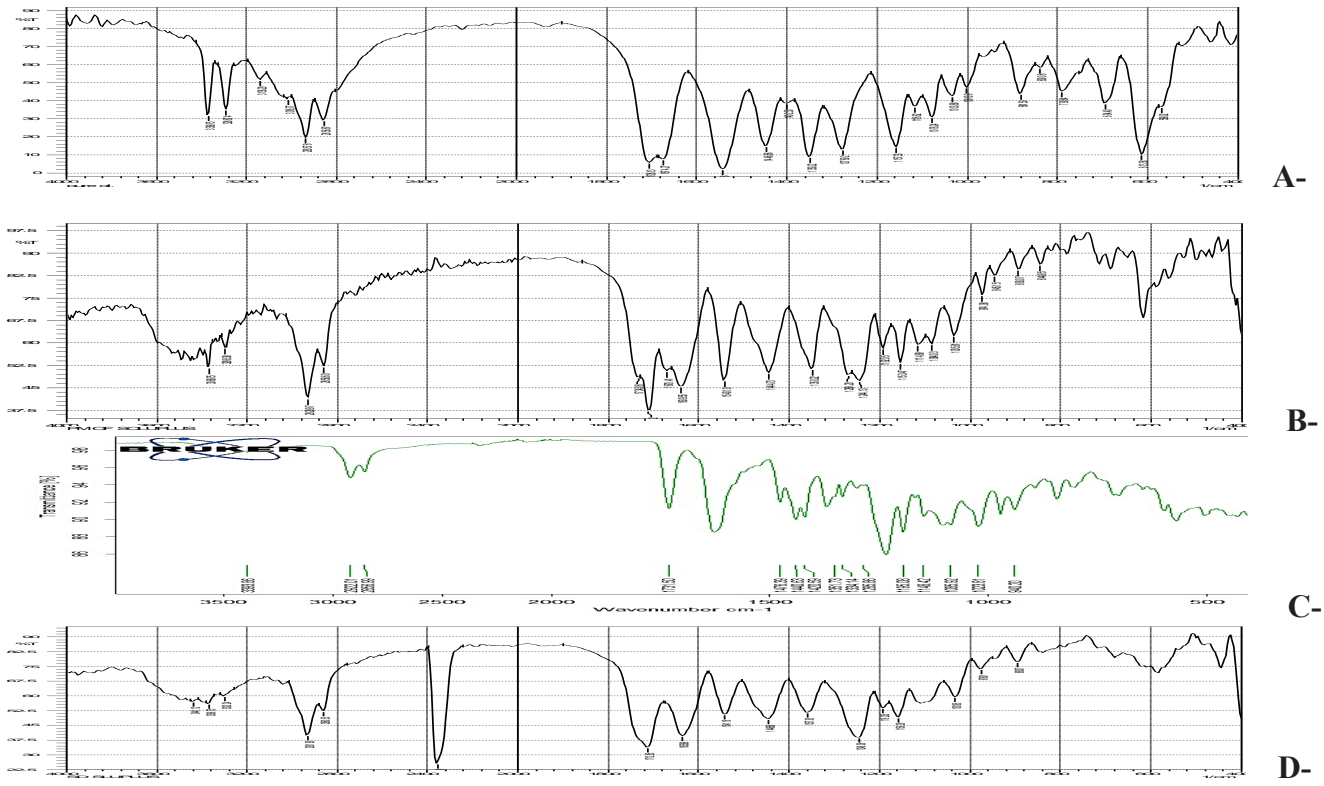

Figure 3: Effect drug carrier ratio on the release of glimepiride from solid dispersions.

in comparison to other ratios (1:1 and 1:2) after the same period of time. It was suggested that increasing the carrier concentration in the solid dispersion formulation resulted in increasing the drug's solubility.[27]

Effect of Carrier Type

Solid dispersions SD3, SD6, SD9, and SD12 formulas prepared at drug: carrier ratio 1:4 were used to study the influence of carrier type (PEG6000, Poloxamer 188, Soluplus, and Kollicoat IR, respectively) on drug dissolution and release as shown in Figure 1, formulas SD6 and SD9 prepared using poloxamer 188 and soluplus respectively produced the highest percentage release of drug during the initial stage of dissolution; approximately 72% for SD6 and 94% for SD9 of glimepiride were released throughout 120 minutes, where 62 and 53% for SD3 and SD12 prepared using PEG6000 and kollicoat IR, respectively during the same period. The dissolution rate was significantly greater ($p < 0.05$) in solid dispersion formulations than in pure medication. This increase in solubility can be attributed to Soluplus ® micellar solubilization characteristics. Soluplus® has a critical micelle concentration (CMC) of 0.0007% (w/v) at 37°C. As a result, the concentrations of soluplus in all of the solid dispersions investigated were more than the critical micelle concentration.[28] Poloxamer 188 polymer is also thought to generate monomolecular micelles. It reduces the interfacial tension between the medication and the dissolving media.[29] PEG 6000 is a second-generation solid dispersion as compare with soluplus and poloxamer 188 which are a third generation, and its effect on glimepiride dissolution is explained by the creation of zones of high concentration of dissolved polymer on the surface of drug,[30] Kollicoat IR has high hydrophilic character, which enhances the drug's water penetration and solubility to maintain its supersaturation. The dissolution rate of Kollicoat IR was significantly slower than that of poloxamer 188, PEG600, and soloplus. This is because the amount of Kollicoat IR used is insufficient to maintain supersaturation.[31]

Selection of the Best Formula

The optimal solid dispersion formula was chosen depending on the results of *in-vitro* dissolution tests, and was subjected to further investigation. Solid dispersion with soluplus (SD9) at ratio 1:4 was chosen as the selected formula due to its acceptable properties and high percentage of drug release; about 94% of the drug was released at the end of 120 minutes.

Characterization of Pure Drug, Polymer, Physical Mixture and the Selected Solid Dispersion Formula

FTIR

FTIR spectra of glimepiride, soluplus, physical mixture and the selected solid dispersion formula are presented in Figure 3. The characteristic peaks related to the functional group of glimepiride were amide stretching at 3388 cm^{-1} and 3288 cm^{-1}, sulphonyl group stretching at 1348.29 cm^{-1}, carbonyl (C=O) stretching at 1708 cm^{-1}, (C-H) stretching at 2931 cm^{-1},(C=C) stretching at1543 cm^{-1} and (C-N) stretching vibration at 1276 cm^{-1},[32] while the Soluplus spectra include C=O stretching at 1740 and 1641 cm^{-1}, and O-H (alcohol) stretching at 3394 cm^{-1}. FTIR spectroscopy was used to study the compatibility

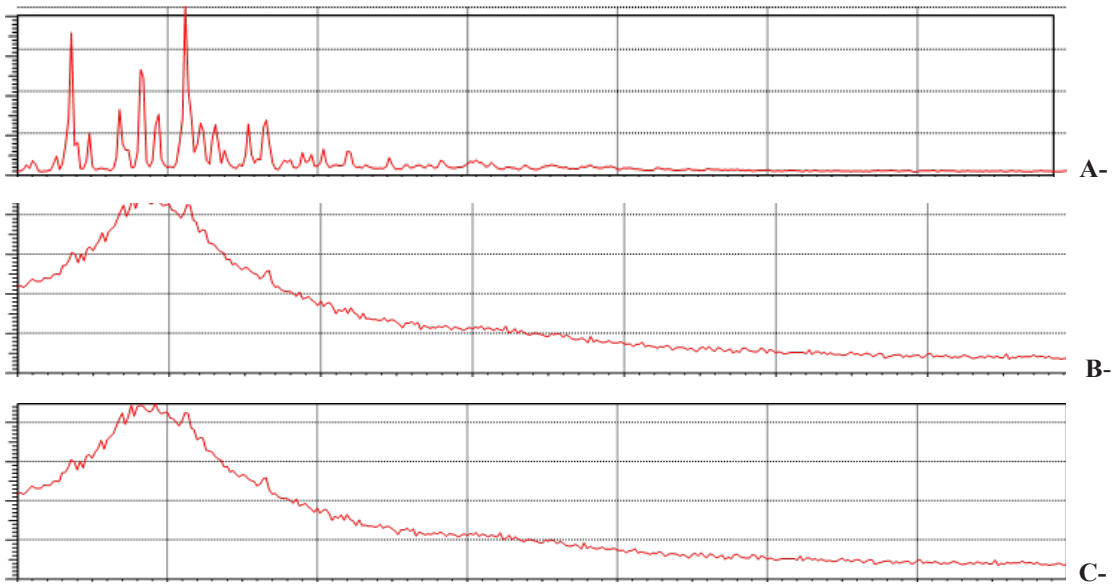

Figure 4: X-Ray diffraction pattern of (a) Glimepiride (b) Physical mixture (C) Solid dispersion (selected formula SD9).

Table 4: Post compression parameters of glimepiride bilayer tablet

No of formula	*Thickness (mm)*	*Hardness (kg/cm^2)*	*Friability (%)*	*Weight variation (mg)*	*Content uniformity (%)*
F 1	3.81 ± 0.015	3.82 ± 0.37	0.406	199.3 ± 0.38	98.4 ± 1.45
F2	3.86 ± 0.011	4.01 ± 0.15	0.382	199.4 ± 0.27	99.2 ± 1.41
F3	3.84 ± 0.011	4.26 ± 0.23	0.373	198.9 ± 0.22	98.5 ± 1.54
F4	3.85 ± 0.015	4.9 ± 0.35	0.374	199.2 ± 0.39	99.4 ± 1.8
F5	3.81 ± 0.02	4.1 ± 0.2	0.354	200.2 ± 0.32	98.5 ± 2.23
F6	3.82 ± 0.036	4.27 ± 0.15	0.251	198.8 ± 0.45	99.46 ± 1.52
F7	3.77 ± 0.011	5.46 ± 0.12	0.352	198.5 ± 0.3	98.2 ± 2.34
F8	3.78 ± 0.042	6.06 ± 0.31	0.347	199 ± 0.64	99.6 ± 1.23
F9	3.79 ± 0.015	6.13 ± 0.4	0.327	199.1 ± 0.76	99.8 ± 1.76
F10	3.78 ± 0.025	6.26 ± 0.15	0.285	198.5 ± 0.48	96.4 ± 2.3
F11	3.79 ± 0.017	5 ± 0.25	0.267	198.2 ± 0.8	97.13 ± 3.62
F12	3.80 ± 0.04	3.9 ± 0.26	0.358	200 ± 0.46	97.5 ± 2.22
F13	3.76 ± 0.02	4.3 ± 0.2	0.361	198.3 ± 0.21	99.7 ± 1.56
F14	3.74 ± 0.061	5.23 ± 0.15	0.677	198.3 ± 0.33	96.5 ± 3.31
F15	3.73 ± 0.045	5.12 ± 0.17	0.632	199.1 ± 0.63	98.4 ± 1.21
F16	3.69 ± 0.05	3.9 ± 0.32	0.656	198.2 ± 0.54	98.53 ± 1.7
F17	3.76 ± 0.07	4.6 ± 0.55	0.73	198.8 ± 0.46	97.8 ± 2.4
F18	3.74 ± 0.08	5.21 ± 0.6	0.67	199.1 ± 0.3	96.9 ± 3.4
F19	3.76 ± 0.04	5.7 ± 0.05	0.568	198.25 ± 0.12	97.25 ± 2.9
F20	3.78 ± 0.09	5.32 ± 0.65	0.754	198.43 ± 0.53	98.13 ± 1.9
F21	3.73 ± 0.046	5.84 ± 0.41	0.462	199.31 ± 0.41	99.1 ± 1.6
F22	3.71 ± 0.09	5.67 ± 0.53	0.63	198.6 ± 0.15	98.6 ± 2.5
F23	3.72 ± 0.4	4.8 ± 0.73	0.346	199.4 ± 0.61	97.8 ± 1.9
F24	3.74 ± 0.06	5.1 ± 0.42	0.334	200 ± 0.182	99.2 ± 1.46
F25	3.75 ± 0.03	5.6 ± 0.74	0.583	198.4 ± 0.22	96.7 ± 3.8
F26	3.76 ± 0.05	6.1 ± 0.86	0.83	197.3 ± 0.34	98.45 ± 1.6
F27	3.72 ± 0.09	5.75 ± 0.78	0.645	198.2 ± 0.41	97.4 ± 2.8
F28	3.73 ± 0.061	5.4 ± 0.38	0.621	199.1 ± 0.62	96.6 ± 2.8

between the drug and carrier (soluplus) used in the formulation SD9 and that the carrier has no effect on structure of the drug, indicating that there was no chemical interaction.[33]

PXRD

The PXRD was used to characterize the solid state of the medication and solid dispersion in order to determine the crystalline nature of glimepiride, the physical mixture, and the solid dispersion SD9 at drug: soluphus weight ratio (1:4). Pure glimepiride's diffraction spectrum revealed that the substance is crystalline in form, as seen by several sharp peaks. As illustrated in Figure 4, some variations in the glimepiride peak positions were found in SD9. In solid dispersion, peak intensity was also lowered some variations in the glimepiride peak positions were found in SD9. In solid dispersion, peak intensity was also lowered.[34] The highest peak intensity was 3528 counts in the case of pure glimepiride; however, it was only 1892 in the case of physical mixing and 820 in the case of SD9. The proportional decrease in diffraction strength of glimepiride in SD 9 at these angles indicates that the crystals have decreased in size.

Pre Compression Parameter

Angle of repose for immediate release layer 29.74. ± 1.23, Carr's Index was 13.54 ± 0.95, Hausner's Ratio was 1.156 ± 0.05, bulk density and tapped density were0.332 ± 0.03 and 0.384 ± 0.02, respectively; and for the sustained release layer formulas were summarized in Table 3. The angle of repose varied between 26 and 42°; these values are within the pharmacopeia-recommended range. Furthermore, the additional glidants increase the flowability of the powder by reducing inter particulate friction. The Carr's index and Hausner's ratio for the immediate release layer mix were 13.54 and 1.156, respectively, indicating a favorable flow property and for sustained release layer blends for formulas (F1-F28) ranged from 10.26 to 22.5% and 1.11 to 1.21%, respectively, indicating a good to poor flow property.[35]

Evaluation of the Prepared Bilayer Tablets(Post Compression Parameter)

All tablets were found to be uniform in thickness. As indicated in Table 4, the thickness of prepared bilayer tablets ranged between (3.69 ± 0.05 and 4.21 ± 0.03 mm). This small variance in tablet weight was attributed to die fill homogeneity, adequate flow characteristics, uniform pressure, and appropriate punch action. The hardness was determined using a Monsanto hardness tester and it was in range of (3.82 ± 0.37kg/cm2 to 6.26 ± 0.15) for uncoated tablets demonstrating that the tablets possess sufficient strength to withstand handling and mechanical stress. The total weight loss of the bilayer tablets following the friability test was between 0.251 and 0.83%, which is less than 1%, total weight reduction which was related to the presence of avicel. All produced tablet formulas pass the weight variation test within the USP limitations (5%). It was determined to be between (197.34 ± 0.2 and 200.2 ± 0.46) due to adequate mixing and the absence of particle agglomeration. The USP test standards state that the glimepiride concentration should not be less than 90% and not more than 110% of the reported quantity of active medication. The percentage of active ingredient in all formulations was determined to be between 96.4 ± 2.3% and 99.8 ± 1.76 %. These findings demonstrated that the produced dosage form contained the active component in a uniform distribution and at an appropriate dose.[36]

Drug-excipients Compatibility Study

The FTIR spectra of glimepiride, ethylcellulose and F24 are presented in Figure 6. The characteristic peaks related to the functional group of glimepiride were amide stretching at 3388 cm^{-1} and 3288 cm^{-1}, sulphonyl group stretching at 1348.29 cm^{-1}, carbonyl (C=O) stretching at 1708 cm^{-1}, (C-H) stretching at 2931 cm^{-1}, (C=C) stretching at1543 cm^{-1} and (C-N) stretching vibration at 1276 cm^{-1}[32] while ethylcellulose reveals absorption bands for the stretching vibrations –C–O–C– (1054 cm^{-1}) and –CH stretching vibrations 2929 and 2973 cm^{-1}, –CH bending (1379 cm^{-1}), and –OH stretching (3395 cm^{-1})[37]. Similar peaks were obtained in the comparable physical combinations of glimepiride and ethylcellulose of formula (F24), NH stretching at 3369.3 cm^{-1}, C-H stretching at 2915 cm-1, (C=O) stretching at1706 cm^{-1}, (C-N) stretching at 1276.84 cm^{-1} and (C=C) stretching at 1545 cm^{-1}. The lack of significant alterations in the FTIR peaks' wavenumbers indicates almost no interaction between glimepiride and the excipients utilized in preparing this formula.

Variable Affecting Glimepiride Release from Sustained Layer

The Effect of Polymer Type

Formula 2, which contains HPMC15, demonstrated full drug release after 7 hours. These findings could be explained by the relatively It is widely established that this polymer retards medication release in aqueous media through swelling.[38] Formula 6 containing Xanthan gum (20%) demonstrated 68% of drug released after 7 hours. Due to its hydrophilic nature this lead to the formulation matrix's slow hydration rate and generation a gel with thick layer. The formula F14 contains carbopole 934; 71% of the drug release. The Carbopol considerably swelled resulting in matrix expansion. Additionally, a substantial gel layer formed. As increase the gel thickness, liquid penetration and medication release are slowed.[39] Formula 17 which contains 20% HPMCK4, has been shown to delay the release of glimepiride for only six hours as the drug is completely released; hydrophilic characteristic of HPMC enables dissolving media to penetrate the network structure of the polymer chain unable of retaining their integrity over a longer period of time.[38] Formula (F25), which contains ethyl cellulose (20% w/w), demonstrated a delay in drug release, with 84 % of glimepiride being released within 12 hours as shown in Figure 6A, ethyl cellulose inhibits drug release by preventing solvent molecules from penetrating the system due to the hydrophobic nature of the ethyl cellulose on the tablet's surface, the release rate decrease as the proportion of ethyl cellulose increases[40] tap density, compressibility index and angle of repose. The tablets were evaluated for post

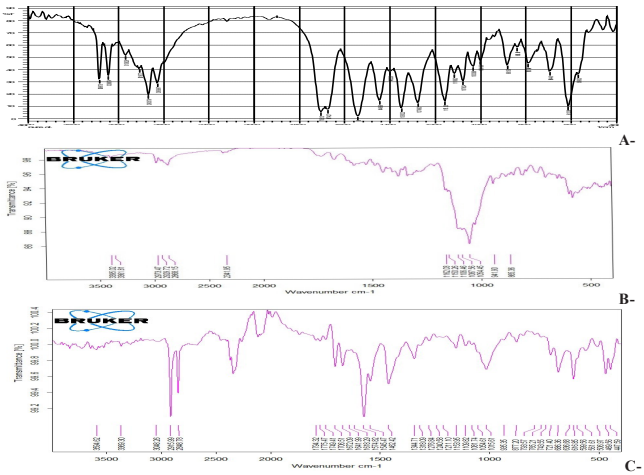

Figure 5: FTIR spectra of (A.) Glimepiride (B.) ethylcellulose (C.) formula 24.

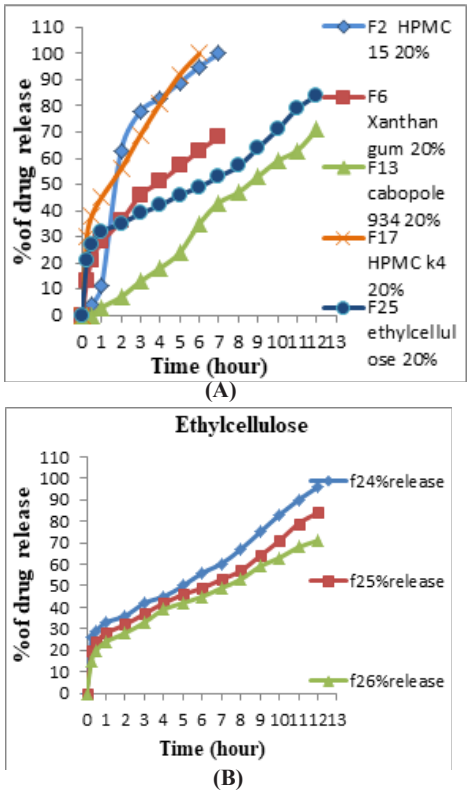

Figure 6: (A) Effect of polymer type (B) Effect of polymer concentration on on the release of glimepiride from sustained release layer.

compression parameter such as hardness, thickness, diameter, weight variation, drug content uniformity and friability. In vitro drug release studies were performed by using USP type II apparatus (paddle method.

The Effect of Polymer Concentration

When a 10% polymer concentration was utilized, formula (24) successfully controlled the release of glimepiride over a 12 hour period by increasing the polymer concentration up to 20 and 30% w/w in formulas (25 and 26), respectively, it was discovered that increasing the polymer concentration results in a decrease in the percentage of releasing drug which was 96, 84 and 71% for formulas F24, F25 and F26 respectively, this decrease is statistically significant ($p < 0.05$), as can be shown in Figure 6B. The highest percentage of polymer results in lower a porosity of the matrix, which leads to slower rate of drug release, drug release reduced as the quantity of ethyl cellulose polymer increase due to a decrease in solvent molecule penetration into the system caused by the hydrophobic nature of the ethylcellulose on the tablet surface[41] diltiazem HCl, and investigate its drug release mechanism. Method: Diltiazem HCl was chosen because of its high water solubility. Tablets containing the drug were prepared by direct compression method using different matrix ratios of ethyl cellulose (EC).

Selection of the Optimum Formula

Due to its acceptable qualities, formula F24 was chosen as the selected formula. Approximately 96% of the medication was released after 12 hours. The optimal formula was chosen based on the minimum amount of polymer required to produce sustained release during dissolution for an extended period of time.

CONCLUSION

The present study successed in designing bilayer tablets containing glimepiride solid dispersion formulation in the first immediate release layer and untreated pure drug formulation in the second layer for sustaining the release of drug for specific period of time to be used as the effective treatment of T2DM. The solubility of a poorly soluble drug like glimepiride can be enhanced by using solid dispersion technique prepared by different methods like solvent evaporation method and fusion method using four different polymers (poloxamer 188, PEG 6000, soloplus and Kollicoat IR). the best results were achieved with a solid dispersion created using drug: soloplus at a ratio of 1:4. All formulated bilayer tablets produced met the required specifications for hardness, thickness, friability, and weight variation . The best formula for sustained released layer of tablet was Formula (F24) using glimepiride and ethyl cellulose at 1:1 ratio, which showed approximately 96% of glimepiride released in 12 hours. An FTIR analysis indicated no chemical interactions between the medicine and any of the formula's excipients.

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