

FORMULATION OF DUAL COMPONENT DRUG DELIVERY OF GLIMEPIRIDE AND METFORMIN HYDROCHLORIDE FOR IMMEDIATE AND SUSTAIN RELEASE

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ABSTRACT

The purpose of the present study was to design an inlayered tablet consisting of glimepiride core tablet for immediate release to produce immediate therapeutic effect, which was inserted inside the cup of metformin hydrochloride for sustained delivery of metformin hydrochloride. The inner core portion was designed using superdisintegrants for immediate release and the outer cup portion was designed as matrix formulations using polymers such as Hydroxy Propyl Methyl cellulose (HPMC) and Poly vinyl pyrrolidone [pvp(k)] to modulate the drug release .

The invitro dissolution kinetics followed Kosmeys–Peppas model via a non-fickian type diffusion controlled release mechanism for sustained release. XRPD study reveals that there were no interaction between the drug and polymers used in designing of in-layered tablets. All the rate data (K) were found to be significant at the level of p value ≤ 0.05 assessed by two tails ANOVA.

The in-vitro release profile shows the desired biphasic release behaviour. The glimepiride (in core fraction) was dissolved within 30mins, where as the metformin hydrochloride (cup fraction) was able to release more than 12 hrs from different formulations and $t_{1/2}$ were found to be 6.3hr, 6.9hr and 8.3hr from the formulations such as F1, F2 and F3 respectively, which indicate the suitability for patient compliance.

KEY WORDS: Core, Cup, In-layered Tablet, Sustained release, Interaction study, Statistical analysis.

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INTRODUCTION

Sustained drug delivery systems can improve patient compliance and provide extended periods of effective blood levels. In an approach, polymers and their blend are used in various formulations to achieve sustained drug release. Most thoroughly investigated and used natural polymers such as gum cordial¹, gum karaya² and synthetic agents such as carboxy polymethylene³, Hydroxy propyl methyl cellulose^{4, 5, 6} were investigated as hydrophilic matrices for sustained drug delivery. The designing of the oral controlled release matrix tablet using HPMC, as retardant for various drugs such as lamivudine⁷, diclofenac sodium⁸ and hydrophilic polymers⁸ including methyl cellulose, sodium carboxy methyl cellulose, sodium alginate were studied and found to be modifying the drug release rate.

The designing of drug delivery systems using core in cup technique^{9, 10} matrix core tablet in dual component delivery¹¹, bilayered tablets¹², donut shaped tablets^{13, 14} were tried for different drugs to sustained the drug release and found to be effective in managing patient compliance. The simple, accurate and economical spectrophotometric methods for simultaneous estimation¹⁵ of two component drug mixture of rosiglitazone maleate and glimepiride in a combined dosage forms were followed for the estimation of glimepiride and metformin hydrochloride core in cup tablets. In the present study designed to obtain an immediate / sustained drug release patterns developed core in cup tablet in which the core tablet consists of glimepiride(1mg/dose) mixed with crosslinked sodium starch glycolate as superdisintegrant designed for immediate release and the same composition of core tablet kept constant for each formulations. The formulations such as F1, F2 and F3 are found to be releasing the drug within 30 mins.

The cup portion of the tablet which consist of metformin hydrochloride (500mg/dose) formulated in the form of matrix with the blend of HPMC at different concentration such as 10%, 20% and 30% for formulations F1, F2 and F3 respectively and the concentration PVP(k) kept constant at 5% level. The most commonly used kinetic models because of their simplicity and applicability^{16,17} such as the zero order, Higuchi and Kosmeys –Peppas equation are applied for invitro drug release kinetic analysis. The drug release study assed by two tail ANOVA at the level of p value ≤ 0.5 and the release kinetics found to be following Kosmeys Peppas model fitting with a $t_{1/2}$ of 6.3hr, 6.9hr and 8.3hr respectively for formulations F1, F2 and F3 respectively indicating the drug delivery pattern may sustained up to 16 hrs, which is suitable for patient compliance.

The physicochemical compatibilities of the drug and the used excipients were studied by XRPD¹⁸. The result reveals that there were no interaction between the drug and polymers used in designing the in-layered tablets.

MATERIALS AND METHODS

Manufacturing Process for core Tablet

Glimepiride and lactose were mixed geometrically in polybag and pass through a #60 mesh screen. Lake of brilliant blue and starch mixed and pass through #100 mesh screen. Both are mixed as a dry mix in a polybag for 5 mins. Binder solution consists of PVP k-30 in purified water added to dry mix and mixed properly in a granulator up to 10mins. Screening was done by 12 mm screen; the granules were dried at 60⁰ C approximately. The blend of above granule, Sodium starch Glycolate and Mag-stearate were finally compressed using 8mm round flat type punches with rotary tablet machine.

Manufacturing Process for Cup portion

The required quantity of metformin hydrochloride, HPMC and PVP(k) were mixed properly for 5 mins in a blender. The binder solution consist of isopropyl alcohol in water were added to the dry mix and screened by 12 mm mesh, to get the wet granules which is dried at 60⁰ C temperature with tray dryer. The above dry granules were lubricated with Mag-stearate and compressed with 12mm round and flat type punches using rotary tablet machine.

Analytical test for inlayered tablet

The diameter thickness of inlay tablet was measured by slide calipers. The hardness measured by Monsanto hardness tester. The friability test was conducted using Roche friabilator. The weight uniformity were determined from randomly selected 20 tablets from each batches.

Drug Content Determination in the Prepared Formulations

The equivalent weight of 100mg glimepiride and metformin hydrochloride from the powdered tablet were dissolved in 100 ml of methanol and diluted with methanol to get 10.0 µg/mL (Theoretical weight) The content uniformity were determined by using U.V-VIS spectrophotometer at λ_{max} 228 nm and 237 nm for glimepiride and metformin hydrochloride respectively with refer to the standard curve.

Preparation of Standard Curve

Different concentration of drug sample such as 1 ppm, 2 ppm, 5 ppm, 8 ppm, 10 ppm, 15 ppm, 20 ppm, 30 ppm and 40 ppm solutions of glimepiride and a concentration of 1 ppm, 2 ppm, 5 ppm, 8 ppm, 10 ppm, 15 ppm, 20 ppm, 30 ppm, 40 ppm, 50 ppm and 100 ppm solution of metformin hydrochloride were prepared with methanol and the O.D. of their respective solutions were measured with U.V-Vis spectrophotometer (Shimadzu 1800 UV/VIS spectrophotometer) at λ_{max} of 228nm and λ_{max} of 237nm respectively for glimepiride and metformin hydrochloride. The standard curve of O.D. versus concentration was drawn as follows:

In vitro drug release studies of all formulation

The in vitro drug release were measured by using USP type I dissolution apparatus (Veego:VDS-6DR) at 100rpm in 750 mL of 0.1N HCl for 2 hour subsequently addition of 0.2 M Tribasic sodium phosphate to make the pH 6.8 maintained up to 12 hour. Dissolution fluid maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. 5 ml of the sample were withdrawn at predetermined time and the same volume being replaced to make equilibrium volume of dissolution fluid. Then the concentration released with respect to time were determined referring the standard curve for the respective drugs using U.V- Visible spectrophotometer at λ_{max} of 228 nm and λ_{max} of 237 nm respectively for glimepiride and metformin hydrochloride. To analyze the mechanism of drug release from the data obtained from the drug release studies were analyzed according to Equations 1, 2, and 3 following zero-order, Higuchi, Korsmeyer-Peppas model respectively:

$$Mt/M_{\infty} = K_0 t \quad \text{---1}$$

$$Mt/M_{\infty} = K_H t^{1/2} \quad \text{---2}$$

$$Mt/M_{\infty} = K_p t^n \quad \text{---3}$$

Where Mt/M_{∞} is the fraction of drug released at time t .

K_0 , K_H and K_p are the release rate constants for equation 1, 2 and 3 respectively.

The n is the diffusion exponent indicative of mechanism of drug release.

X-Ray Powder Diffraction

The X-Ray powder diffraction¹⁸ patterns were obtained at room temperature using a PW1710 X-ray diffractometer (Philips, Holland) with Cu as anode material and graphite monochromatic, operated at a voltage of 35 kV, current 20 mA. The samples were analyzed in the 2θ angle from $5^{\circ} 2\theta - 70^{\circ} 2\theta$ and the process parameters were set as scan step size of $0.02^{\circ} (2\theta)$, scan step time of 0.5s.

RESULTS

In this study different formulation of in-layered tablets such as F1, F2 and F3 were prepared consist of common core tablet containing 1mg glimepiride drug and the cup portion containing constant weight of 500mg metformin hydrochloride with variation in composition of the polymers of 10%, 20% and 30% respectively with other such excipients whose composition kept constant (**Table 1**). The analytical properties of the prepared tablets were studied (**Table 2**) and found to be having consistent quality.

The in-vitro drug release studies of the prepared tablets were performed both in simulated gastric fluids (0.1N HCl) for 2 hrs and continued in changing pH of 6.8 phosphate buffer up to 12 hrs.

The release pattern of glimepiride (core fraction) from the formulation (**fig-3**) indicates that 90% of the drugs released from all the formulations within 30 mins, indicating the suitability of providing immediate therapeutic effect.

The release pattern of metformin hydrochloride (cup portion) from all the formulations (**fig-4**) shows that the formulation able to sustain the drug releases up to 12 hrs. The $t_{1/2}$ values 6.9, 8.3 and 6.4 hrs for the formulations F1, F2 and F3 respectively indicates the sustainability of drug release and among them F2 will be the best one in prolonging drug delivery.

The XRPD spectrum of pure glimepiride shows that the drug was of crystalline in nature as demonstrated by numerous peaks. Numerous diffraction peaks of glimepiride were observed at $13.46^\circ 2\theta$, $14.67^\circ 2\theta$, $16.73^\circ 2\theta$, $18.16^\circ 2\theta$, $19.22^\circ 2\theta$, $21.04^\circ 2\theta$, $21.50^\circ 2\theta$, $22.95^\circ 2\theta$ and $26.37^\circ 2\theta$ (finger print region) etc. Indicating crystalline glimepiride. Diffraction peaks of metformin Hydrochloride observed at around $12.197^\circ 2\theta$, $17.629^\circ 2\theta$, $22.32^\circ 2\theta$ and $23.223^\circ 2\theta$, among all peaks, peak at $22.325^\circ 2\theta$ is prominent which is not found in excipient rather we observed in the formulation which clearly indicates that there is no change in atomic spacing of that drug. Peak of $17.62^\circ 2\theta$ and d-spacing of 5.03 [\AA] also found in formulation scan. For excipients (placebo) scanning was done at the range of 0-40 2θ positions. It has been observed that major peaks of excipients found also in formulation scan. Those are like the peak at 2θ of 19.13° having d-spacing of 4.63 [\AA] also found same order in formulation. Like that the peaks at $19.5^\circ 2\theta$ and $20.008^\circ 2\theta$ having d-spacing at 4.53 and 4.4 [\AA] respectively were also found in formulation, all the powder characterization at atomic reveals that there is no such interaction among the drugs or polymers. Diffraction peaks of glimepiride and metformin Hydrochloride pure drug are present in formulation. So there is no such interaction among drugs and excipients.

DISCUSSION

The study describes the formulation of a core in cup design, incorporates both immediate and modified release drug for increased therapeutic efficacy and patient compliance. The inlay tablets were prepared by wet granulation techniques using purified water and Isopropyl alcohol as a solvent tried many times for the good release behavior by HPMC K-100 M and PVP(k) 30 D as polymer.

The in-vitro drug release pattern (**Figure 3**) shows that all the formulations shows the release of glimepiride within 30 mins which fulfills the requirements for immediate therapeutic effect followed by sustained release of metformin hydrochloride (**Figure 4**) following Kosmeyer's-Peppas bestfit model, which is analysed by two tails ANOVA significant at p value ≤ 0.05 level. The $t_{1/2}$ such as 6.3hr, 6.9hr and 8.3hr for the formulations F1, F2 and F3 respectively. The in-vitro drug release kinetics (**Table 3**) suggests that among the formulations F3 is suitable for sustaining the drug delivery of metformin hydrochloride for longer period of time and is significant to be utilized for core in cup tableting technology.

The XRPD analysis indicates that there were no drug-drug and drug-excipients interactions. Therefore the selected polymers are suitable for designing the drug delivery system using the core in cup technique for immediate and sustained drug delivery.

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Table 1: Composition of different formulations

Glimepiride Core fraction (common for all formulations)		Metformin Hcl Cup fraction			
Ingredients mg per tablet		Formulation-F1		Formulation-F2	Formulation-F3
		Ingredients	mg per tablet	mg per tablet	mg per tablet
Glimepiride	1	Metformin Hcl	500	500	500
Lactose	50	HPMC K-100 M	50	100	150
Mannitol	30	pvp k 30D	25	25	25
Sodium starch glycolate	7	-----	-----	-----	-----
Binder	Q.S.	Binder	Q.S.	Q.S	Q.S
Mag-Stearate	2	Mag-Stearate	10	10	10
Lake Brilliant Blue	Q.S.	-----	-----	-----	-----

Table 2: Analytical tests for Inlayered tablet

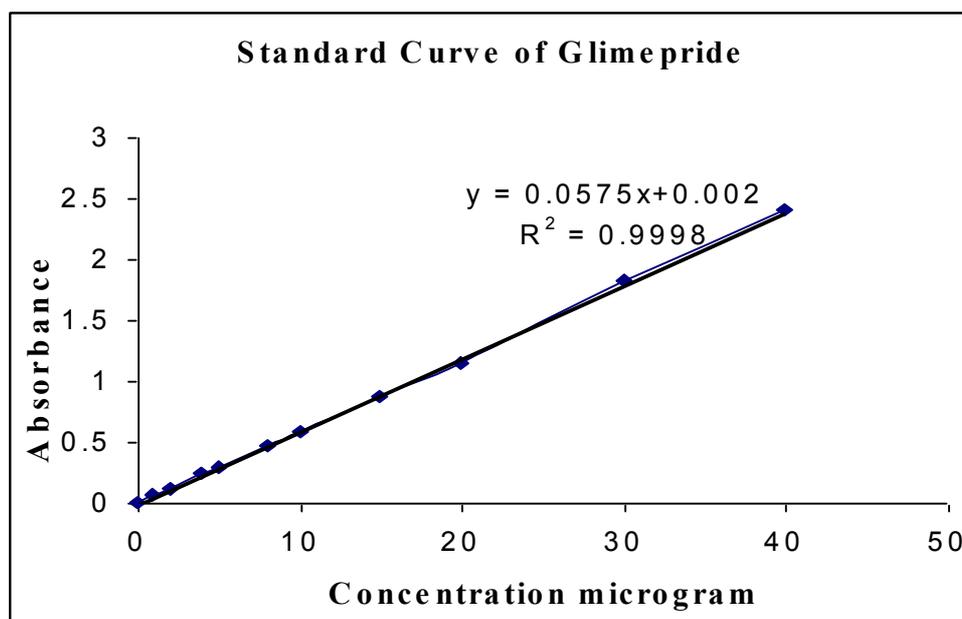
Trial name	Avg wt in mg	Thickne ss (in mm, n=10)	Hardne ss in (kg/cm ² ; n=6)	% Friability n=10	% Drug content G-glimepiride,	% Drug content ,M-Metformin Hcl
G(core tab)	90.06	2.1±0.01	4±0.5	0.45	98± 0.8	---
F1(inlay tab)	675.04	5.7±0.00	4±0.5	0.21	98±0.7	95 ±0.5
F2(inlay tab)	725.58	5.8±0.02	4±0.0	0.21	98±0.8	97±0.7
F3(inlay tab)	775.25	5.9±0.04	4±0.5	0.34	98±0.4	96±0.9

G: Glimepiride core tablet, F1: Formulation containing Metformin Hydrochloride cup with 10% HPMC, F2: Formulation containing Metformin Hydrochloride cup with 20% HPMC, F3: Formulation containing Metformin Hydrochloride cup with 30% HPMC.

Table 3: Drug release kinetics of experimental formulations

Formulation	Zero order		Higuchi		Kosmeys-Peppas		$t_{1/2}$ (hr)
	r^2	$K(h^{-1})$	r^2	$K(h^{-1})$	r^2	$K(h^{-1})$	
F1	0.4606	7.8849	0.9263	23.8519	0.9592	32.0458	6.3
F2	0.8141	7.2814	0.9929	21.6171	0.9964	23.1972	6.9
F3	0.7636	5.9946	0.9816	17.88	0.9904	19.347	8.3

F1: Formulation with 10% HPMC; F2: Formulation with 20% HPMC; F3: Formulation with 30% HPMC. All the rate data (K) were found to be significant at the level of p value ≤ 0.05 assed by two tails ANOVA.

**Figure 1: Standard Curve for Glimepiride**

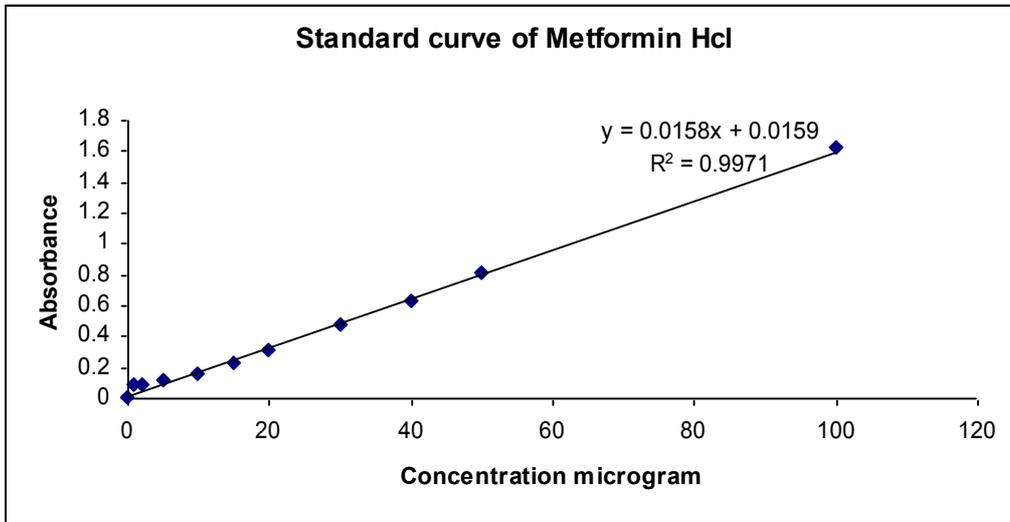


Figure2:StandardCurveforMetforminHcl

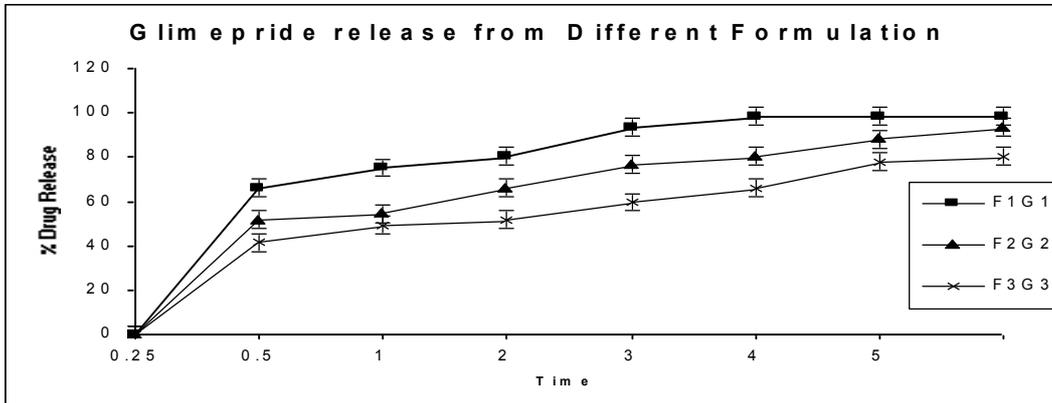


Figure 3: Release profile of Glimepiride From Different Formulation

F1G1-Formulation F1 with Glimepiride; F2G2-Formulation F2 with Glimepiride; F3 G3-Formulation F3 with Glimepiride.

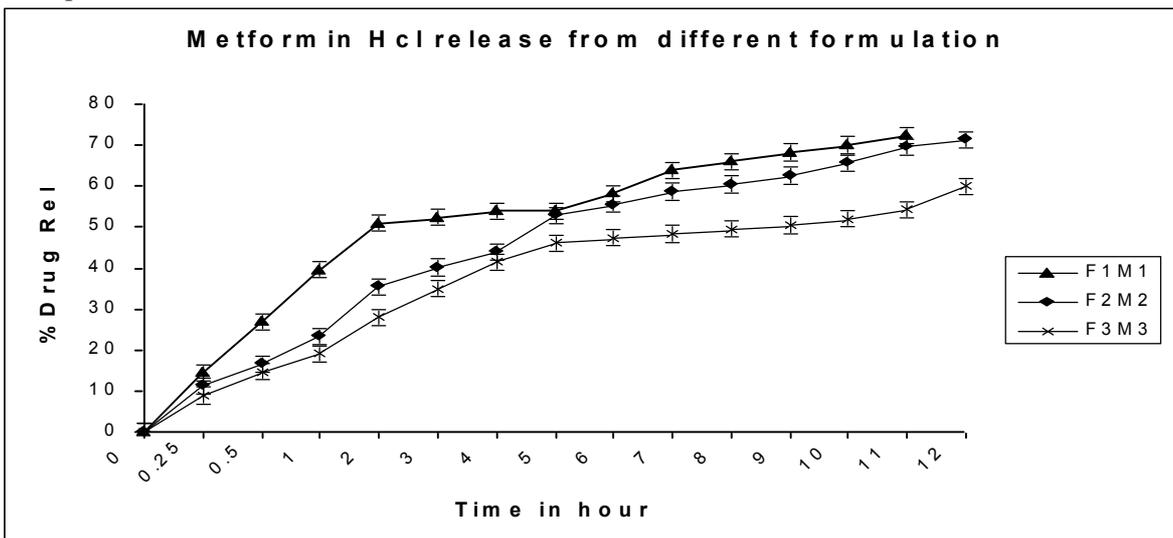


Figure 4: Release profile of Metformin Hcl From Different Formulation

F1M1- Formulation F1 with Metformin Hcl; F2M2- Formulation F2 with Metformin Hcl; F3M3- Formulation F3 with Metformin Hcl.

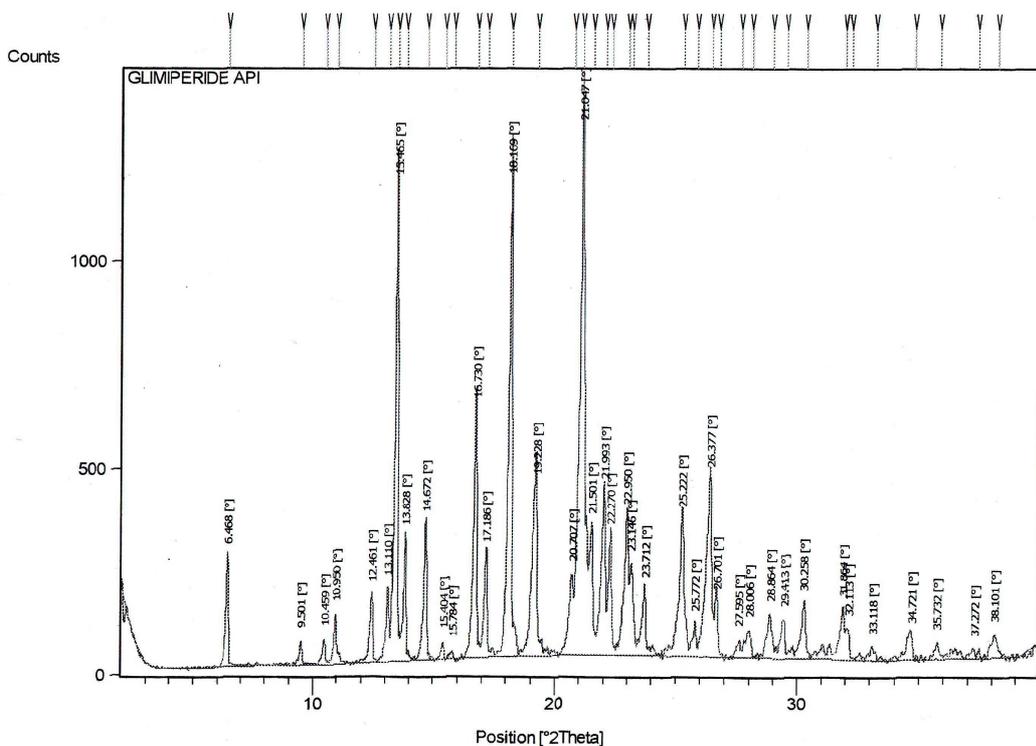


Figure 5: XRD of Glimepiride

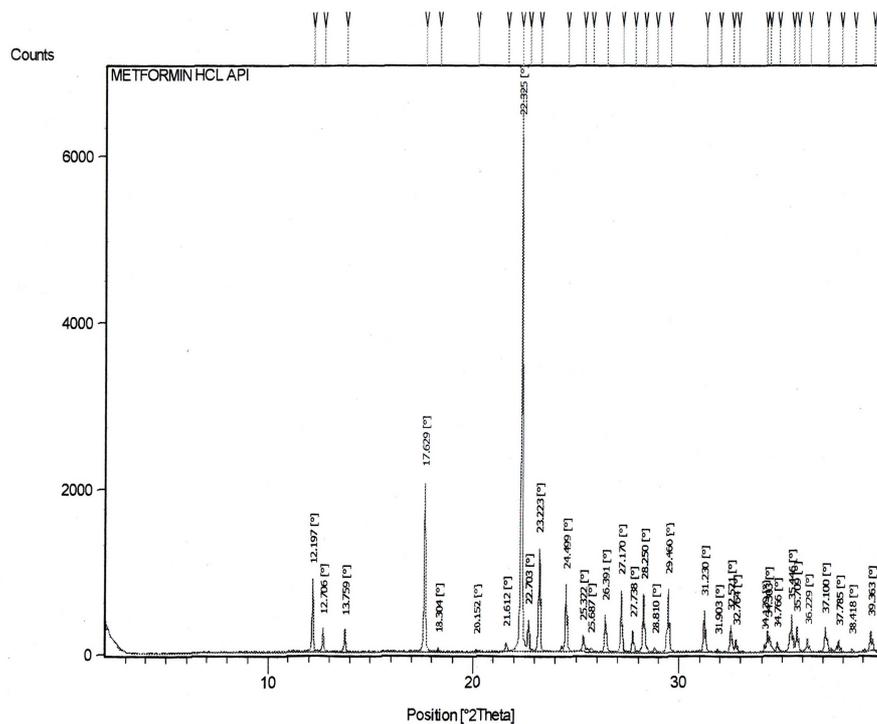


Figure 6: XRD Metformin HCl

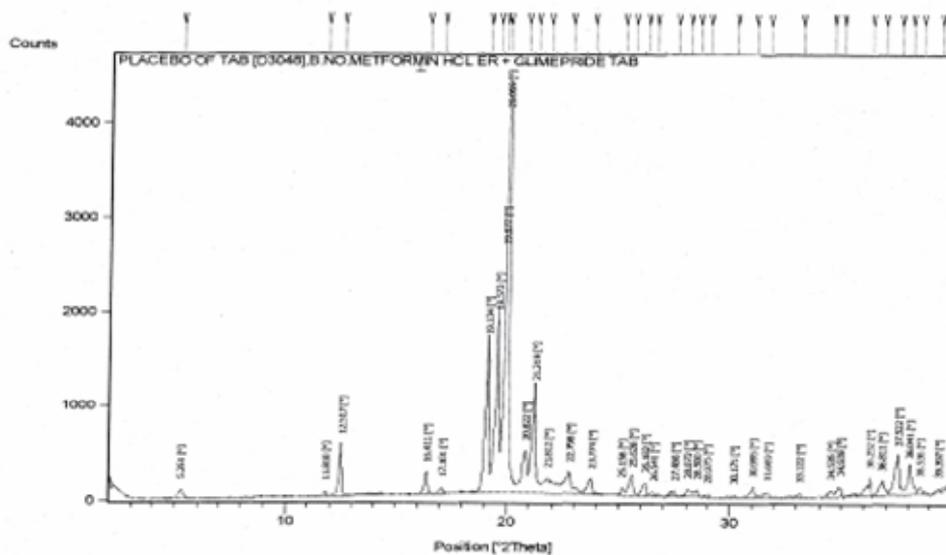


Figure 7: XRD of excipients (placebo)

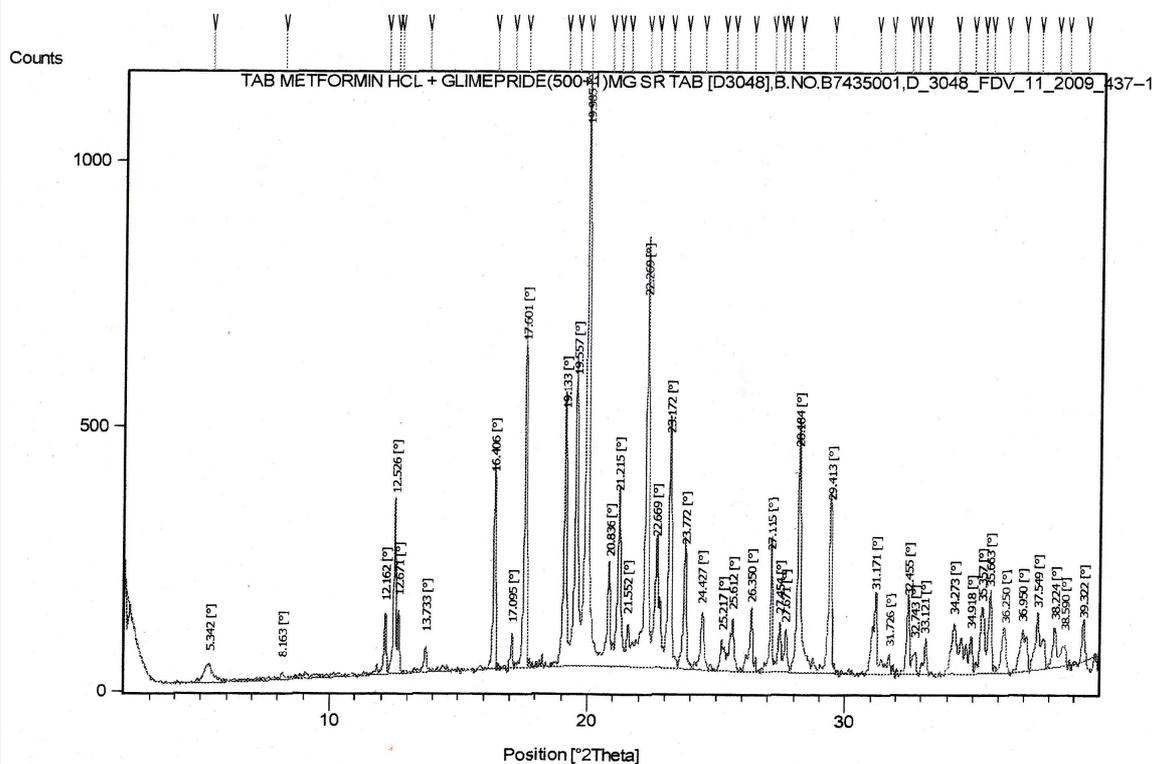


Figure 8: XRD of Glimepiride and Metformin Hydrochloride Inlayered Tablet

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