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Formulation development and evaluation of gastroretentive mucoadhesive tablets of glimepiride using natural polymers

Rahul Malasiya[1]*, Tarkeshwar P. Shukla[2]

[1]Student, Oriental College of Pharmacy, Bhopal, Madhya Pradesh, India

[2]Professor, Oriental College of Pharmacy, Bhopal, Madhya Pradesh, India

ABSTRACT

Glimepiride, a third-generation sulfonylurea is poorly soluble anti-diabetic drug. Currently, the use of natural gums and mucilage is of increasing importance in pharmaceutical formulations as valuable drug excipients. Natural plant-based materials are economic, free of side effects, biocompatible and biodegradable. The development of mucoadhesive sustained release drug delivery system is recommended in order to enhance the bioavailability. A mucoadhesive tablets were developed using the natural polymer sodium alginate and gum tragacanth. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. The tablets of glimepiride were prepared by direct compression method. Pre-compression parameters were evaluated. The tablets were evaluated for post-compression parameters such as thickness, hardness, average weight, friability and In vitro release studies. All the compositions were resulted in adequate pharmacopoeia limits. The varying concentration of polymers was found to affect on *in-vitro* drug release and mucoadhesive strength. *In vitro* drug release of gastro retentive tablet of glimepiride shown that the formulation F5 was found to be the best formulation as it releases 98.78%. Glimepiride in a sustain release manner for an extended period of time (up to 12 hrs).The release data was fitted to various mathematical models such as higuchi, korsmeyer-peppas, first order and zero order to evaluate the kinetics and mechanism of the drug release.Prepared tablets of glimepiride may prove to be a potential candidate for safe and effective controlled drug delivery over an extended period of time for gastro retentive drug delivery system.

Keywords: Glimepiride, Gastro retentive, Anti-diabetic drug, Direct compression method

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***Address for Correspondence:**

Rahul Malasiya, Oriental College of Pharmacy, Bhopal, Madhya Pradesh, India

INTRODUCTION

The last two decades mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining a formulation in intimate contact with the absorption site (e.g. buccal cavity) as mucosal membranes[1]. Mucoadhesive drug delivery systems have so far not reached their full potential in oral drug delivery, because the adhesion of drug delivery systems in the GI tract is insufficient to provide a prolonged residence time of delivery systems in the stomach or small intestine[2]. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate andprolonged contact at the site of administration[3]. Mucoadhesion and bioadhesion involves two materials in which at least one is biological in nature, held together for an extended period of time by interfacial forces. Alternately it is defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. Bioadhesion involves adhesion of the polymer with the biological membrane while mucoadhesion involves adhesion of the polymer with the mucus membrane. Adhesion as a process is simply defined as the "fixing" of two surfaces to one another[4]. Gastroretentive systems can remain in the gastric region for several hours and hence can significantly prolong the gastric residence time of drugs. Prolong gastric retention improves bioavailability, reduces drug wastage, and improves solubility for the drugs that are less soluble in the high pH environment[5]. Glimepiride is an oral blood glucose lowering drug belonging to the third generation sulphonylurea class that is currently available for treating hyperglycemia in non insulin dependent diabetes mellitus (NIDDM). Glimepiride is classified under class II according to biopharmaceutical classification systems [6]. Chemically glimepiride is identified as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3- pyrroline-1carboxamido) ethyl] phenyl] sulfonyl]-3-(trans4-methylcyclohexyl) urea [7]. It is practically insoluble in water having high cell permeability [8]. It is slightly soluble in methanol and showed favorable partition coefficients (1.8 in octanol/pH7.4buffer) [9]. The primary mechanism of action of

glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from the functioning pancreatic beta cells [10]. Metformin and glimepiride tablets simultaneously targets insulin resistance and insulin deficiency in type 2 diabetes, which may account for the greater effects on hyperglycemia [11].In recent years, natural polymers are growing rapidly and it continues to remain and important in the new formulation development of the controlled released dosage form[12]. Natural polymers are much safer than synthetic. They provide many applications in the formulation development of a new controlled release dosage form, such as binder, disintegrator, diluents and release modifier[13].Therefore, they needs a novel approach to enhance the use of natural polymers in the formulation development of controlled released dosage form, because of the ease availability at an affordable price, high safety margin and higher productivity. Hence, the present study is aimed to enhance the use of natural plant based polymer as a release modifier to develop Glimepiride gastroretentive mucoadhesivetablet. The purpose of this study is to investigate the sustain release properties of gum tragacanth. These polymers were used as modifier using model drug glimepiride[14].

MATERIALS AND METHODS

Materials

Glimepiride were obtained as pure sample from m Dr. Reddy's Laboratories, Hyderabad, India as gift samples along with their analytical reports. MCC was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Sodium alginate, gum tragacanth and Talc were purchased from SD Fine Chem. Limited, Mumbai. Magnesium stearate was purchased from LobaChemie Pvt. Ltd, Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Determination of absorption maxima

A solution of containing the concentration 10µg/ ml was prepared in 0.1N HCl. UV spectrum was taken using Double beam UV/VIS spectrophotometer (Labindia-3000+). The solution was scanned in the range of 200-400nm.

FT- IR Study

FT- IR spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. Identification of Glimepiride was done by FTIR Spectroscopy. It was identified from the result of IR spectrum as per specification.

Preparation calibration curve

10mg of drug was accurately weighed and dissolved in 10ml 0.1N HCl in 10 ml volumetric flask, to make (1000µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100µg/ml) sub stock solution (2), and then final concentrations were prepared 5-25µg/ml with 0.1N HCl. The absorbance of standard solution was determined using UV/ VIS spectrophotometer (Labindia 3000+) at 232.0 nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

Method for preparation of glimepiride mucoadhesive matrix tablet

Direct compression was taken after to manufacture the mucoadhesive tablets of glimepiride[15]. Six different formulations (F1, F2, F3, F4, F5 and F6) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in table 1 and all the definition were utilized for encourage assessments parameters.

Pre compression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index and hausner's ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

$$\theta = \tan\text{-}1(h/r)$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [(TBD - LBD)/TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [16-18].

$$\text{Hausner's ratio} = \text{Tapped density/Bulk density.}$$

Evaluation of tablets

All the tablets were evaluated for following various parameters which includes [19,20].

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (--).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ max of 232 nm using 0.1 N HCl blank.

Hardness

For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Cadmach).

Friability

The friability of sample of 10 tablets was estimated utilizing a friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Swelling index

Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and 0.1 N HCl was used as medium, and the temperature was maintained at 37 ± 0.5°C. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 hours (W_2) [21]. Percent hydration (swelling index) was calculated using the following formula:

$$\textbf{Swelling index} = (W_2 - W_1) \times 100/W_2$$

Where W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet.

Determination of mucoadhesive strength

The working of a double beam physical balance formed the basis of the bioadhesion test assembly. The left pan was removed and hung with a stainless steel chain. A Teflon block with 1.5 in height and 1.5 in diameter was hung with the stainless steel chain to balance the weight of the other pan. The height of the total set up was adjusted to accommodate a glass container or beaker below it leaving a head space of about 0.5 cm in between. Block of 2 in height and 1.5 in diameter was kept inside the glass vessel, which was then positioned below the top hung Teflon block. Suitable weights were added on the right pan to balance the beam of the balance. The porcine gastric mucosa was attached with the mucosal side upward onto the lower Teflon block which was then placed in the glass vessel. Sufficient simulated gastric fluid was filled into the beaker so that the surface of the fluid just touches the mucosal surface to Teflon block. A tablet was fixed to the bottom portion of the cylindrical shaped base with 'feviquick' glue. The string with tablet was hung in such a way that the tablet was just in contact with the surface of the mucosal side of pig stomach when the balance was in a balanced position. The balance was left in a balanced position for fixed time of 5 minutes and then slowly weights were increased on the right pan until the tablet detaches from the surface of the intestinal mucosa. The weights on right side pan gave the mucoadhesive strength of the tablet in grams. From mucoadhesive strength, the bioadhesion force was calculated per unit area of the tablet as follows.

$$F=\frac{Ww \times G}{1000 \times A}$$

Where F is the bioadhesion force (kg/m/s^2), Ww is the mass applied (g), g is the acceleration due to gravity (cm/s^2) and A is the surface area of the patch (cm^2).

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1 N HCl was set into the dissolution flask maintaining the temperature of 37±0.5^{0}C and rpm of 75. One tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2 hours using 10ml pipette. The new disintegration medium (37^{0}C) was supplanted each time with a similar amount of the sample and takes the absorbance at 232nm using spectroscopy [22-26].

Mathematical treatment of *in-vitro* release data: The quantitative analysis of the qualities got in dissolution/release tests is simpler when mathematical formulas that express the dissolution comes about as an element of a portion of the measurement frames attributes are utilized.

1. Zero-order kinetics: The pharmaceutical dosage frames following this profile release a similar measure of medication by unit of time and it is the ideal method of medication release keeping in mind the end goal to accomplish a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Q_t = Q_o + K_o t$$

Where$Q_t$is the amount of drug dissolved in time t, $Q_o$is the initial amount of drug in the solution (most times, Q_o=0) and $K_o$is the zero order release constant.

2. First-order kinetics: The following relation expresses this model:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

Where$Q_t$is the amount of drug dissolved in time t, $Q_o$is the initial amount of drug in the solution and $K_1$is the zero order release constant.

Along these lines a graphic of the decimal logarithm of the released measure of drug versus time will be linear. The pharmaceutical dosage shapes following this dissolution profile, for example, those containing water-solvent drugs in permeable frameworks, discharge drug in a way that is corresponding to the measure of drug staying in its inside, in such way, that the measure of drug released by unit of time reduce.

3. Higuchi model: Higuchi built up a few theoretical models to ponder the arrival of water-solvent and low dissolvable medications in semi-strong or potentially strong grids. Mathematical expressions were acquired for sedate particles scattered in a uniform grid acting as the diffusion media.The simplified Higuchi model is expressed as:

$$Q = K_H . t^{1/2}$$

Where Q is the amount of drug released in time t and K_H is the Higuchi dissolution constant. Higuchi model describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be utilized to

portray the drug dissolution from a few kinds of modified release pharmaceutical dosage structures, for example, transdermal systems and mucoadhesivetablets with water-dissolvable drugs.

4. Korsmeyer-Peppas model: Korsmeyer *et al.* used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a\, t^n$$

Where $M_t/M_\infty$is fraction of drug released, a is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log M_t/M_∞ versus log time curve. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of *n* =0.5 for fickian diffusion and higher values of *n*, between 0.5 and 1.0, or *n* =1.0, for mass transfer following a non-fickian model. In case of a cylinder *n* =0.45 instead of 0.5, and 0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent *n* the portion of the release curve where $M_t/M_\infty < 0.6$should only be used. To use this equation it is also necessary that release occurs in a one-dimensional way and that the system width-thickness or length-thickness relation be at least 10. A modified form of this equation was developed to accommodate the lag time (*l*) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_{t-l}}{M_\infty} = a\,(t-l)^n$$

When there is the possibility of a burst effect, b, this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

In the absence of lag time or burst effect, l and bvalue would be zero and only at^n is used. This mathematical model, also known as Power Law, has been used very frequently to describe release from several different pharmaceutical modified release dosage forms.

RESULTS AND DISCUSSION

λ_{max} of glimepiride was found to be 232nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25µg/ml Fig.1. The melting point of glimepiride was 205-207ºC and Ft-IR spectra of pure drug shown in fig.2.

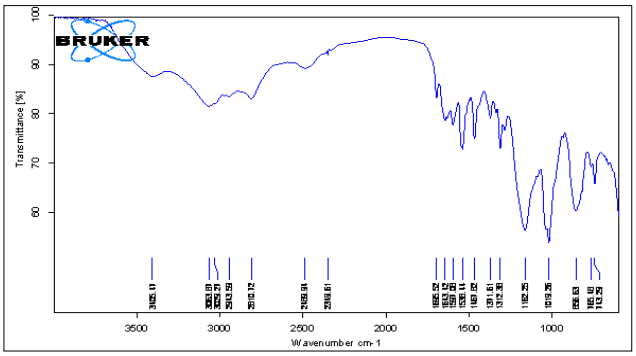

Figure 2: FT-IR spectra of pure Glimepiride

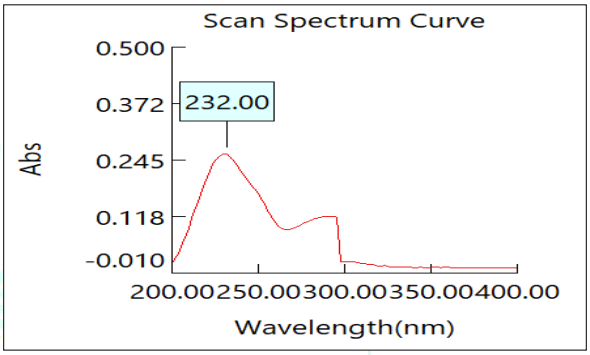

Figure 1: Determination of λ_{max} of Glimepiride

Tablet powder blend was subjected to various pre-compression parameters Table 2. The bulk density of all the formulations was found to be in the range of 0.421to 0.457 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.525 to 0.562 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 18.683to 19.810which shows that the powder has good flow properties. All the formulations have shown the Hauser's ratio ranging between 1.230to 1.247 indicating the powder has good flow properties.

Table 1: Result of pre-compression properties of glimepiride

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner's ratio
F1	0.421	0.525	19.810	1.247
F2	0.422	0.526	19.772	1.246
F3	0.436	0.538	18.959	1.234
F4	0.452	0.558	18.996	1.235
F5	0.457	0.562	18.683	1.230
F6	0.442	0.551	19.782	1.247

The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 4.9±0.2to 5.2±0.1kg/cm² and the friability values were less than 0.9% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 2.1±0.1 to 2.2±0.1mm. All the formulations satisfied the content of the drug as they contained 98.69±0.32to 99.56±0.45 % of glimepiride and good uniformity in drug content was observed. Thus all the physical attributes of the

prepared tablets were found be practically within control. In the present study 6 formulations with variable concentration of polymers (MCC, sodium alginate, gum tragacanth and gaur gum) were prepared by direct compression method and evaluated for physicochemical properties. The results of swelling index, and bioadhesion strength were given in Table 4, 5. The tablets were evaluated for in vitro dissolution studies in 0.1N HCl for 12 hours. The results of in-vitro drug release revealed that the glimepiride was released in a controlled manner from all the formulations where formulation F5 showed maximum drug release i.e. 98.78% at the end of 12th hour. The results of release studies of formulations F1 to F6 are shown in Table 6 and Figure 3. The *in vitro* drug release data of the optimized formulation F5 was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Peppas model was maximum i.e. 0.979 hence indicating drug release from formulations was found to follow Peppas order kinetics Table 7, 8 & Fig. 4-7.

Table 2: Results of post compression properties of glimepiride matrix tablets

Formulation code	Thickness* (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	2.1±0.1	5.1±0.2	149±4	0.852±0.008	98.85±0.35
F2	2.2±0.1	5.2±0.1	155±5	0.845±0.007	99.45±0.35
F3	2.1±0.2	5.1±0.1	150±4	0.825±0.004	99.56±0.45
F4	2.2±0.1	4.9±0.2	152±3	0.785±0.008	98.74±0.85
F5	2.2±0.2	5.1±0.2	153±4	0.658±0.009	98.85±0.65
F6	2.2±0.1	5.2±0.3	148±5	0.785±0.007	98.69±0.32

Table 3: Results of Swelling Index of glimepiride matrix tablets

Formulation Code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	20.23	45.65	64.56	73.25
F2	23.32	46.65	68.85	75.65
F3	24.56	47.78	65.56	74.58
F4	28.56	52.23	67.78	79.85
F5	26.65	50.45	69.98	80.21
F6	28.56	53.14	68.85	78.25

Table 4: Results of determination of bioadhesionstrength

S. No.	Formulation Code	Force of Adhesion
1.	F1	0.62
2.	F2	0.65
3.	F3	0.70
4.	F4	0.48
5.	F5	0.72
6.	F6	0.65
7.	F7	0.68
8.	F8	0.74
9.	F9	0.85

Table 5: *In-vitro* drug release study of matrix tablets

Time	% Cumulative Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	45.56	42.23	40.27	38.98	35.56	30.33
1	65.85	56.69	53.23	42.32	40.23	36.65
1.5	78.89	71.32	69.98	55.65	45.65	40.23
2	98.89	89.98	75.56	69.98	52.32	45.65
3	-	98.65	86.65	81.12	65.85	50.65
4	-	-	97.78	89.98	73.32	57.78
6	-	-	-	98.89	79.98	63.32
8	-	-	-	-	84.65	72.23
12	-	-	-	-	98.78	75.65

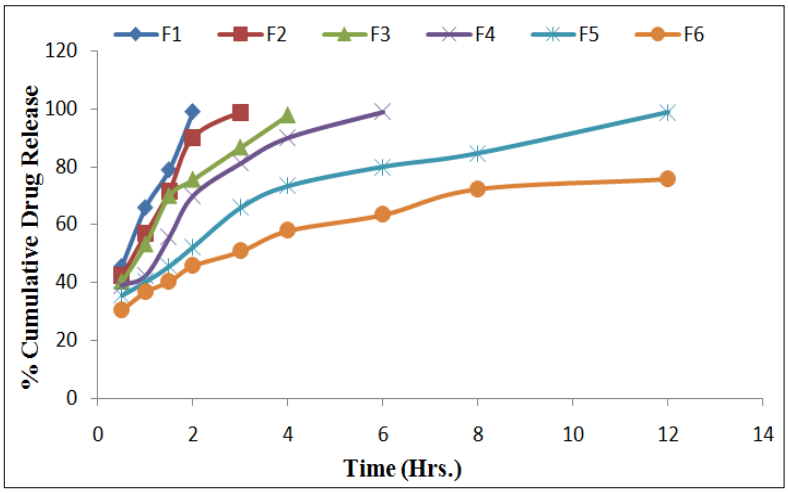

Figure 3: *In-vitro* drug release study of matrix tablets

Table 6: *In-vitro* drug release data for optimized formulation F5

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	35.56	1.551	64.44	1.809
1	1	0	40.23	1.605	59.77	1.776
1.5	1.414	0.301	45.65	1.659	54.35	1.735
2	2	0.602	52.32	1.719	47.68	1.678
3	2.449	0.778	65.85	1.819	34.15	1.533
4	2.828	0.903	73.32	1.865	26.68	1.426
6	3.464	1.079	79.98	1.903	20.02	1.301
8	0.707	-0.301	84.65	1.928	15.35	1.186
12	1	0	98.78	1.995	1.22	0.086

Table 7: Regression analysis data of glimepiride matrix tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
F5	0.896	0.916	0.964	0.979

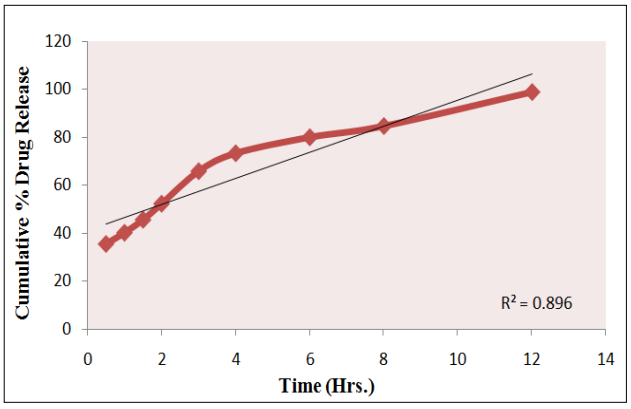

Figure 4: Zero order release Kinetics

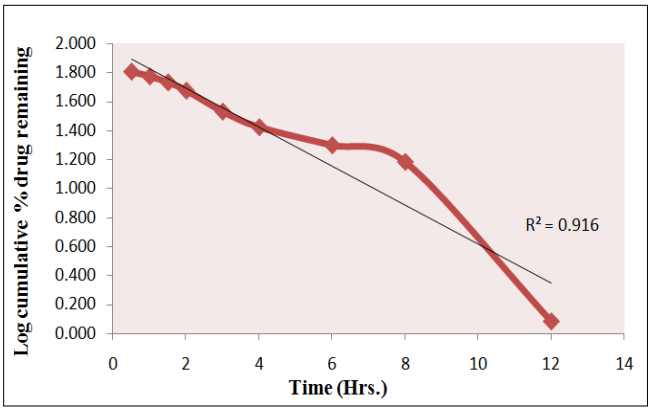

Figure 5: First order release kinetics

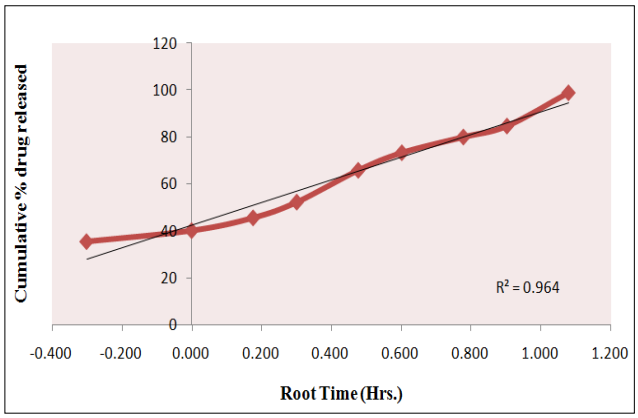

Figure 6: Higuchi release Kinetics

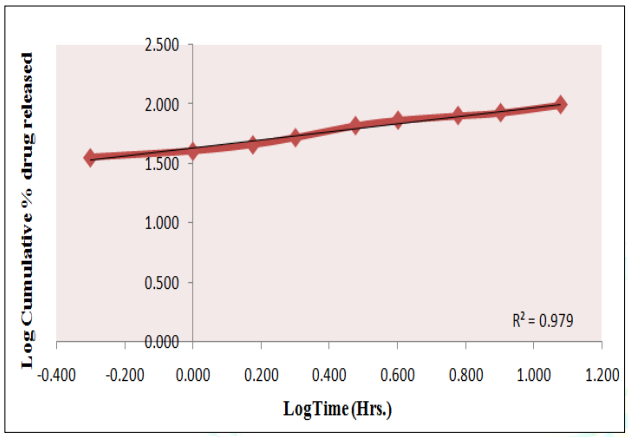

Figure 7:Korsmeyer-Peppas release Kinetics

CONCLUSION

Direct compression methods can be used alternatively for wet granulation, because it is an easier, simplified and economical method of manufacturing of tablets. A number of research articles are available which are evident that the direct compression is a preferred method of tableting. The present research work was successful in improving the efficacy of glimepiride oral therapy as the drug release was extended for 12 hours thus reducing dosing frequency thereby improving patient compliance. The gastroretentive mucoadhesivematrix tablets of glimepiride were prepared by direct compression method. Kinetic modeling showed that best fit model was the Korsmeyer–Peppas model, with non-Fickian diffusion tending towards zero-order release, indicating that the tablets can be successfully employed as a once daily, oral, controlled-release drug delivery system. The high bioadhesive strength of the tablets increases its gastrointestinal residence time and eventually improves the extent of bioavailability. However, proper balancing between the different levels of polymers is necessary to attain proper bioadhesion.

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