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Development of sustained release formulation of glipizide using natural polymer from *Tamrindus indica* for better patient compliance

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ABSTRACT

The study was to design a drug product to reduce the frequency of dosing, increase therapeutic effectiveness and improvement in patient compliance, by developing sustained release matrix tablet of Glimepiride using tamrind gum as a release modifier. In current study tamrind gum is used as a polymer which is investigated for sustained release carrier. The pre-formulation studies of drug excipient mixtures were performed. The tablets formulated were evaluated by physicochemical studies, *in- vitro* drug release, kinetic studies and stability studies. Drug and polymers has no interaction as observed by FTIR and UV studies. All the physicochemical parameters of tablets were found in the limits. Glimepiride is used in the treatment type II diabetes mellitus and is a first third generation sulphonyl urea agent. The drug release pattern was studied for extended period of 12 hrs for the optimized formulations. The release of drug under kinetic studies showed that it follows first order models. The different tablet formulations were put to stability studies and it was observed that there were no significant changes in release pattern, physicochemical parameters and drug content. The present study result indicates the suitability of the tamrind gum polymer in the preparation of sustained release formulations of glimepiride.

Keywords: Sustained Release, Glipizide , Natural Polymer, *Tamrindus Indica*

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INTRODUCTION

Oral Drug Delivery is the most favorable route of drug delivery due to patient compliance, ease of administration and dose flexibility of formulation. Most of the drug delivery system available in the market is oral drug delivery systems. Historically also the oral drug administration has been the predominant route for drug delivery as approximately 50% of the drug delivery systems available in market are oral drug delivery systems.[1]

In recent years, natural polysaccharides are growing rapidly and it continues to remain and important in the new formulation development of the controlled released dosage form.[2] Natural polysaccharides 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.[3] Therefore , they needs a novel approach to enhance the use of natural polysaccharide 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 such as tamrind as a release modifier to develop Glimepiride sustained release tablet. The purpose of this study is to investigate the sustain release properties of tamrind. These polymers were used as modifier using model drug Glimepiride.[4]

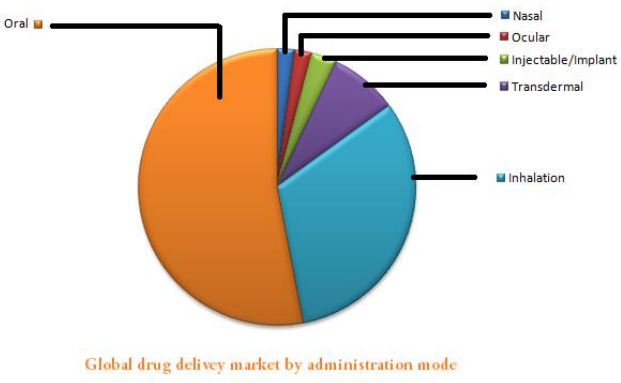

Figure 1: Global Drug Delivery Market by mode of Administration

MATERIAL & METHODS

Materials

Table 1: List of chemicals

S.No.	Ingredient	Application
1	Glimepiride	Active pharmaceutical Ingredient
2	Tamrind seeds	Polymer
3	Ethyl Cellulose	Polymer
4	MCC (Microcrystalline cellulose)	Filler
5	Lactose	Diluents
6	Talc	Lubricants
7	Magnesium Stearate	Glidant

Experimental Methods

Preparation of tablet formulations by direct compression method

Glimepiride tablet formulations were prepared by direct compression method.[5-7] The drug and excipients were weighed accurately mixed properly with trituration and then matrix tablets were prepared by direct compression. Each tablet contains 8 mg of Glimepiride[8].

Table 2: Formulation development of Glimepiride by direct compression method

Formulation code	Glimepiride (mg)	TSP (mg)	Ethylcellulose (mg)	MCC (mg)	Magnesium Sterate (mg)
F1	8	50	30	76	6
F2	8	100	30	76	6
F3	8	150	30	76	6
F4	8	200	30	76	6
F5	8	50	30	66	6
F6	8	100	40	66	6
F7	8	150	40	66	6

Drug-excipient compatibility studies

The pre-formulation during the development of solid dosage form the assessment of possible incompatibilities between an active drug substance and excipients.[9] Therefore, the pure drug and the formulations mixed with polymers were subjected to UV analysis and infra-red (IR) studies.

Preformulation studies[10]

Micromeritic properties[11,12]

Angle of repose

The funnel and cone method is employed in which the funnel is fixed. The funnel is held with its tip at a given height, h, 2cm above graph paper. With r being the radius, of base of conical pile, angle of repose can be determined by following equation:

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

Where, θ is the angle of repose,

h is height of pile;

r is radius of base of the pile

Bulk density and tapped density

The flow property of granules was determined by bulk density and tapped density. A quantity measured about 2gm of granules from each formula was introduced into the 10ml of measuring cylinder which was previously light shaken to break any agglomerates formed. After observation of initial volume, the cylinder was tapped down its own weight from the hard surface from a height of 2.5cm at 2 sec intervals.

L B D and T B D were calculated using formulas:

Bulk Density = W / VO

Tapped Density = W / VF

L B D: Weight of the powder/Initial volume of the packing

T B D: Weight of the powder/Final volume of the packing

Carr's Compressibility Index (CI)

Compressibility index is the measure that can be obtained from the bulk and tapped densities. A material having values of less than 20% has good flow property. The compressibility index was determined by Carr's Compressibility index

Carr's index (%) = [(TBD-LBD) * 100] / TBD

Where,

L B D: Weight of the powder / Volume of the packing

T B D: Weight of the powder / Tapped volume of the packing

Evaluation of Glimepiride sustained release matrix tablets[13,14]

Tablets were evaluated at various parameters such as weight variation, hardness, friability, drug content uniformity tablet and thickness, and *in-vitro* drug release with different media.

Weight variation

This is performed to ensure that a tablet contains the proper amount of drug. The USP weight variation test is perform by weighing 20 tablets collectively and individually, calculating the average weight. I.P. official limits of percentage deviation of tablet.

Tablet hardness:

The hardness of the tablet is calculated to observe breakage under storage conditions. Monsanto hardness tester was used to check the hardness of each batch of tablet. The hardness was calculated in unit of kg/cm^2. For testing hardness of batch of tablets, 5 tablets were chosen randomly and the average hardness of 5 determinations was recorded.

Friability:

Friability refers to loss in weight of tablets due to removal of fines from the surface of the tablets in the containers. Friability usually reflects poor cohesion of tablet ingredients.

Tablet thickness:

Vernier Callipers is used for calculation of thickness of tablets. It was determined by checking the thickness of ten tablets of each formulation batch.

D**rug content uniformity**

Drug content uniformity was calculated by using five tablets of each formulation and was weighed powdered. The quantity of powder was equivalent to 8 mg of the drug content. This equivalent weight of glimepiride was taken in the 100 ml volumetric flask and methanol was used as the extracting solvent and samples was analyzed spectrophotometrically by using UV/ Visible spectrophotometer at 228 nm.

In Vitro-Release Testing

Sustained release tablet formulation was subjected to In Vitro Release test by performing dissolution studies for all the formulations, employing 900ml of pH 6.8 phosphate buffer as the dissolution medium. The temperature of 37°C ± 0.6°c was maintained by the medium used for dissolution studies.

Stability studies

Stability of a drug defined as the ability of a particular formulation in a specific condition, to remain within its physical, chemical, therapeutically and toxicological specification. The reason of stability testing is to evaluate the quality of drug formulation which varies with time under the influence of various environmental conditions such as temperature, humidity, light.

RESULT & DISCUSSION

Determination of λ max of Glimepiride

The λ max of the Glimepiride was found to be 228 nm in methanol.

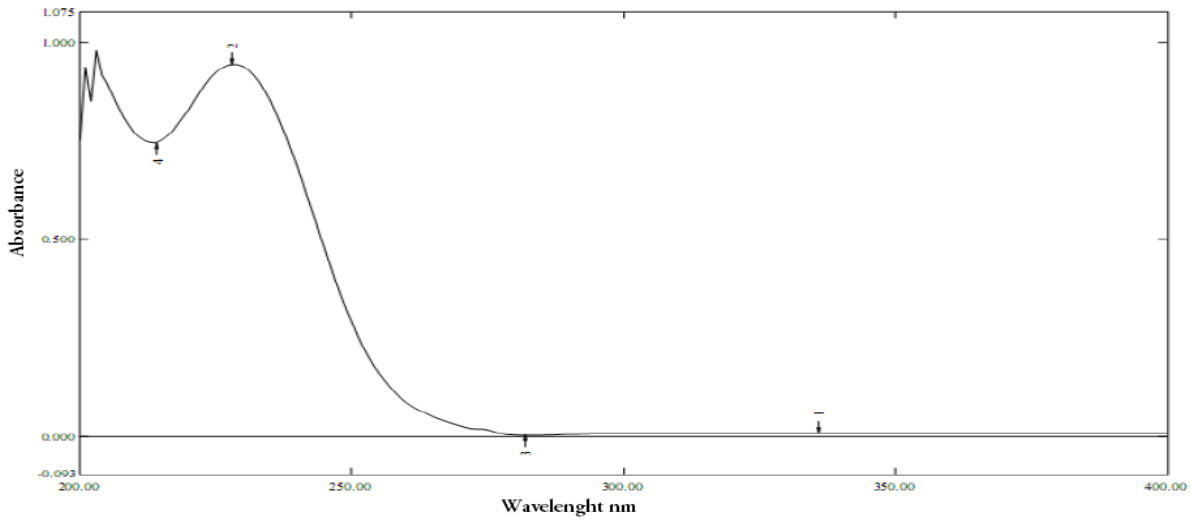

Figure 2: Glimepiride having λ max at 228 nm.

Compatibility study

Spectra of the pure drug, excipients and physical mixture were recorded in between 400 - 4000 wave number (cm^{-1}). In the FTIR spectral analysis there is no appearance or disappearance of any characteristic peaks of pure drug glimepiride and in the physical mixture which confirms the absence of chemical interaction between drug and polymers.

Pure drug Peak		Physical mixture Pea	
NH stretching at	3363 cm^{-1}	NH stretching at	3363 cm^{-1}
C-H stretching at	2942-2847 cm^{-1}	C-H stretching at	2938-2885 cm^{-1}
C=O stretching at	1711 cm^{-1}	C=O stretching at	1712 cm^{-1}
C-N stretching	1542 cm-1	C-N stretching at	1543 cm-1

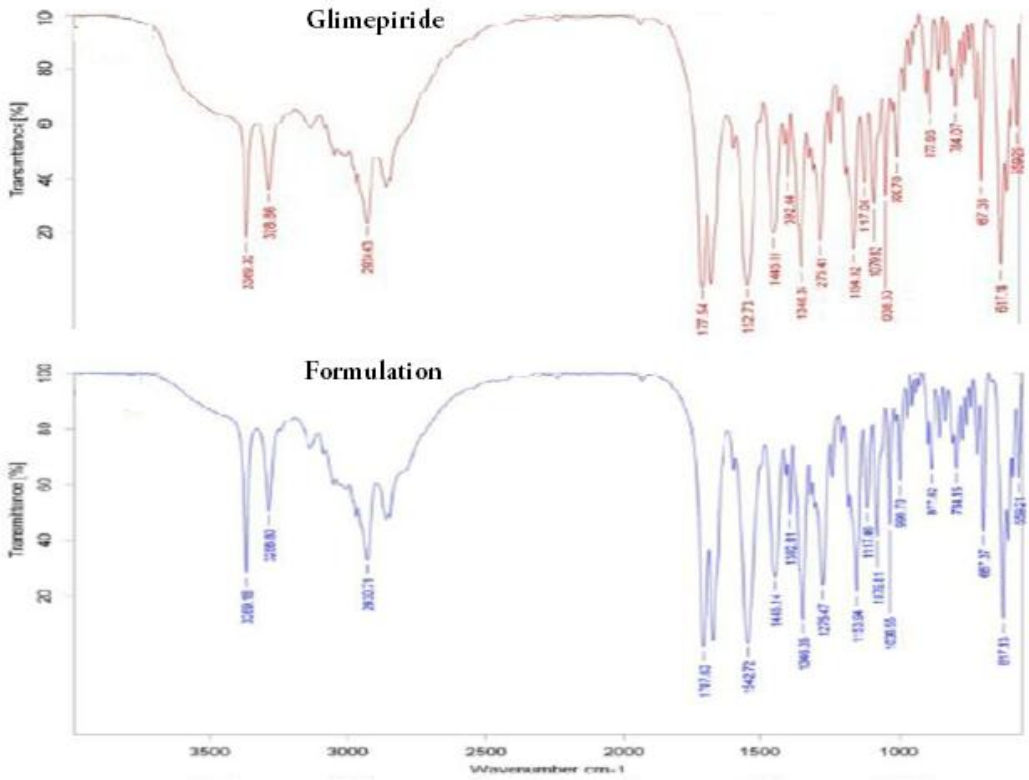

Figure 3: IR Spectra of the drug and formulation

Micromeritic properties

The pre-formulation studies was conducted by evaluation of granules by angle of repose, bulk and tapped density, compressibility index and Hausner's ratio. Results of all the pre-compressional parameters performed on granules for formulations shown in Table No. 3 & 4.

The range for angle of repose for the granules of all the formulations was found to be from 21º.28'±0.04 to 26º.19'±0.05. The results of angle of repose (<30) indicates good flow properties of the powder.

Table 3: Results of physical evaluation of Pre-compression blend using angle of repose.

Formulation	F1	F2	F3	F4	F5	F6	F7
Angle of repose (Degree ± SD)	22°.11' ±0.03	21°.31' ±0.05	24°.13' ±0.01	26°.19' ±0.05	21°.28' ±0.04	25°.23' ±0.03	26°.17' ±0.05

Table 4: Results of physical evaluation of Pre-compression blend using density.

Formulation	F1	F2	F3	F4	F5	F6	F7
Bulk Density (g/ml±SD)	0.232 ±0.01	0.219 ±0.03	0.248 ±0.05	0.231 ±0.07	0.218 ±0.02	0.229 ±0.04	0.232 ±0.01
Tapped Density (g/ml±SD)	0.264 ±0.06	0.260 ±0.02	0.289 ±0.03	0.260 ±0.01	0.266 ±0.04	0.262 ±0.02	0.279 ±0.06

Compressibility index range was found to be 11.92±0.07 to 14.77±0.04 % for the granules of all the formulations. The Hausner's ratio results were found to be lesser than 1.25 which indicates better flow properties. This was further supported by lower compressibility index values.

Table 5: Results of Pre-compression blend using Carr's index & Hausner's ratio.

Formulations	F1	F2	F3	F4	F5	F6	F7
Carr's Index (%± SD)	14.63 ±0.03	14.59 ±0.05	13.09 ±0.04	12.02 ±0.01	12.64 ±0.03	13.57 ±0.07	11.32 ±0.03
Hausner's ratio (%± SD)	1.18 ±0.01	1.18 ±0.01	1.14 ±0.03	1.13 ±0.07	1.16 ±0.01	1.13 ±0.07	1.15 ±0.03

Physical evaluation of tablets[14]

Following organoleptic properties *viz*. colour, odour and shape were carried out after compression which demonstrated various quality control tests. All formulations **(F1 to F7)** were expressed as white, odorless, concave, round and flat.[15]

Evaluation of prepared tablets[15]

The tablets were evaluated with respect to hardness of different formulations and it was found uniform within the range of 3.25±0.21 to 4.01±0.43 kg/cm^2.

Tablet's strength of different formulations is measured by friability. Acceptable limit for conventional compressed tablets is that it loses of weight less than 1%. All the tablet formulations showed acceptable formulation technical properties.[8,10]

Table 6: Results of sustained release tablet formulations

S.No.	Formulation	F1	F2	F3	F4	F5	F6	F7
1	Diameter (mm)± SD	7.76 ±0.023	7.85 ±0.001	7.82 ±0.003	7.91 ±0.013	8.01 ±0.017	7.89 ±0.018	7.98 ±0.021
2	Thickness (mm)± SD	3.7 ±0.01	4.0 ±0.05	4.1 ±0.03	3.8 ±0.03	4.0 ±0.08	3.9 ±0.01	4.1 ±0.05
3	Weight variation (mg)	322.91 ±0.23	323.73 ±0.71	325.28 ±0.61	325.75 ±0.24	324.79 ±0.22	322.56± 0.32	323.79 ±0.59
4	Hardness (kg/cm2)	7.4 ±0.01	7.9 ±0.02	8.0 ±0.02	6.6 ±0.03	6.9 ±0.01	7.2 ±0.08	6.2 ±0.08
5	Friability (%)	0.63 ±0.005	0.53 ±0.005	0.61 ±0.024	0.73 ±0.055	0.64 ±0.021	0.73 ±0.02	0.56 ±0.00
6	Drug content (%)	98.46 ±0.031	100.12 ±0.011	98.13 ±0.13	99.77 ±0.076	99.89 ±0.067	98.91 ±0.088	100.55 ±0.021

In-vitro drug release study

The formulated matrix tablets of glimepiride were evaluated by release profile as illustrated in table and figure. The *in-vitro* release of Glimepiride depends on swelling behavior of the tablets, higher the tablet swells the lesser amount of drug release. The *in-vitro* release study was performed in 0.1 N HCl for initial first 2 hrs, and then by phosphate buffer pH 6.8 and study was continued for 24 hour.[14]

Table 7: *In-vitro* drug release profile of Glimepiride sustain release matrix tablets

Time (Hrs)	Drug Release (Cumulative percentage)						
	F1	F2	F3	F4	F5	F6	F7
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	24.31±0.07	17.41±0.21	16.74±0.11	11.11±0.23	20.55±0.34	17.45±0.65	15.83±0.59
3	57.27±0.07	34.32±0.08	32.35±0.17	31.22±0.41	38.21±0.17	34.15±0.01	32.29±0.16
6	71.31±0.22	47.24±0.01	47.32±0.22	42.33±0.09	50.54±0.27	47.36±0.34	42.13±0.27
9	90.61±0.17	67.37±0.43	64.87±0.39	58.47±0.21	71.88±0.06	68.34±0.63	63.23±0.33
12	99.13±0.34	78.27±0.13	72.44±0.76	64.24±0.45	82.41±0.76	78.69±0.46	76.28±0.38
15	--	91.37±0.21	86.88±0.55	81.27±0.09	96.42±0.57	91.37±0.76	89.69±0.31
18	--	99.68±0.09	91.79±0.47	86.35±0.25	99.68±0.09	95.55±0.65	91.11±0.57
21	--	--	99.46±0.57	94.34±0.27	--	99.88±0.58	95.43±0.31
24	--	--	--	99.32±0.32	--	--	98.22±0.12

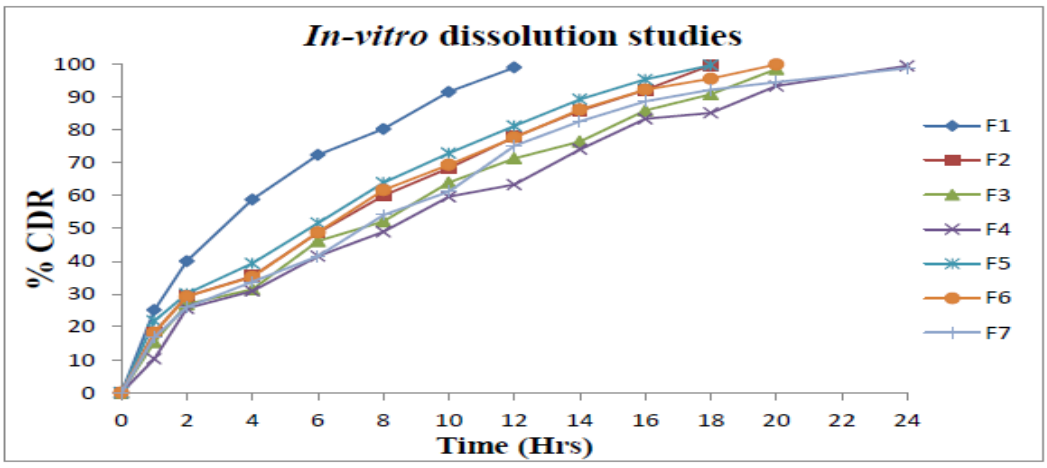

Figure 4: Dissolution profile of Glimepiride for formulations F1 to F7

CONCLUSION

On the basis of results of *in-vitro* drug release two best formulations F4 and F7 were selected as the best formulations. The formulations were subjected to various evaluation parameters like physical appearance, hardness, friability and drug content, invitro drug release. The outcome of the evaluation shows that there was no significant variation in result was observed in physical apprearance, hardness, friability, drug content and drug release during the whole duration of the study. It was found by three month stability studies that there was no significant change observed in the API. The inference is that formulations so prepared are physically and chemically stable.

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