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Research Article

EFFECT OF NATURAL POLYMER ON RELEASE RETARDING RATE OF GLIMEPIRIDE SUSTAINED RELEASE TABLET

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ABSTRACT

Glimepiride is a primary III generation drug belonging to the class of sulphonylurea which shows the hypoglycaemic effect and is a very potent drug with a prolonged duration of action. It is given in doses of 1-8 mg once a day. The prime objective of this work was to formulate a sustained release matrix anti-diabetic tablet by using a natural polymer guar gum. Using this natural polymer, sustained release tablets of glimepiride were formulated by using wet granulation technique in various trials with the change in the concentration of polymers. The formulated granules were evaluated for pre-compression parameters like bulk density, tapped density, angle of repose, Hausner's ratio and compressibility ratio. The tablets were also evaluated for post-compression parameters like *in-vitro* swelling studies, uniformity weight, drug content hardness, friability, *in-vitro* dissolution study and kinetic data analysis. The results obtained indicated that the formulated tablets results are within the range. In comparison with all the formulations, it was observed that F2 showed optimum release for 12 hours in sufficiently sustained manner. The kinetic data analysis also proved that it followed the zero-order release and fitted in the Higuchi model with an r^2 value of 0.994.

Keywords: Natural Polymer, Guar gum, Glimepiride, Sustained-release tablets.

1. INTRODUCTION

Diabetes mellitus (DM) is metabolic and endocrine disorder characterized by hyperglycaemia, hyper-cholesterolemia and hypertriglyceridemia. More than 200 million people worldwide are suffering from DM which results due to insufficient insulin secretion or defects or both. The pancreas produces a hormone called insulin; it enables the absorption of glucose from the body cells. It leads to severe complications, if the cells do not absorb glucose from the body [1].

Glimepiride is a primary III generation drug belonging to the class of sulphonylurea which shows the hypo-glycaemic effect and is a very potent drug with a prolonged duration of action. The nature of the drug is weak with a pKa of 5.2. It belongs to class II of the BCS classification. The drug is insoluble in water and acidic environment but has high permeability. The oral bioavailability is nearly 100% with uniform, rapid oral absorption. The pharmacokinetics and dosage schedule supports sustain release formulations which are to be taken once a day for monitoring of blood glucose levels enhancing the compliance of the patient and efficacy. Half-life is approximately 5 hours and plasma protein binding is 99.5%. It is used in the treatment of type II diabetes *i.e. non*-insulin-dependent, and not used for type I diabetes as there is no production of insulin from pancreas [2, 3]. The mode of action of this drug is to increase the production of insulin from the beta-cells of the pancreas [4, 5]

There would be several drawbacks if multiple dosing is to be given for long term therapies for chronic conditions. Therefore, sustained-release tablet formu-lations are much desirable and preferred for such therapy. They are mainly framed for maintaining therapeutic tissue levels or blood levels of the drug for over some time with minimized systemic or local adverse effects. This kind of dosage forms helps in overcoming the drugs, having a short elimination half-life. The therapeutic efficacy can be still enhanced by using these matrices. Hence sustained release matrix tablets came into importance. The key performers in these systems are drug retarding polymers which are hydrophilic. They have good hydrating and swelling indices when they come in contact with aqueous media of the system which releases and prolongs the action of the drug that is dispersed or dissolved and is called a

matrix system. It can otherwise define as a gelling agent *i.e.* hydrophilic polymer, with one or more drugs [1, 2].

A recent investigation reveals that natural hydrophilic polymers application has gained importance because of its biocompatibility, non-toxic, biodegradable, cost-effective and ready availability [6, 7]

The present work aims to study the effect of natural gum on the formulation of sustained release matrix tablets of glimepiride. In the present work gum guar was used to formulate the tablet and evaluated for the retarding property.

2. MATERIAL AND METHODS

Glimepiride was obtained as a gift sample from Medley Laboratories, Mumbai. Guar gum was purchased from the local market and authenticated from the Department of Botany, Dr P. R. Ghogrey Science College, Dhule. Laboratory grade Dicalcium phosphate, Magnesium stearate, Talc, PVP K-30 were used for experiments. Perkin Elmer Lambda 25 UV spectro-photometer, Electrolab TDT-08L Dissolution apparatus USP type II and Oakton™ pH 700 pH meter were used in the analysis.

2.1. Compatibility study of Drug-Excipients

Infra-red spectroscopy was conducted over a range of 400-4000 cm^{-1} and the spectrum was recorded. The pellets were prepared using potassium bromide by dispersing the drug into it and by compressing into discs by applying the required pressure for 3min in a hydraulic press. The formed pellet was kept in FT-IR [1, 2].

2.2. *In-vitro* swelling behaviour of formulated tablets

The formulated tablets were assessed for the swelling index. The tablet was weighed individually (W1) and placed in a petri dish containing phosphate buffer of pH 7.8 and incubated at 37±0.5°C. For every two hours, regularly the tablet was taken from the petri dish and kept on a filter paper such that the excess surface water was removed and then reweighed (W2).

$\% SI = [(W2 - W1)/W1] \times 100$

2.3. Formulation of matrix tablets:

Wet granulation technique was used for the formulation of matrix tablets. The drug, guar gum, dicalcium phosphate were mixed and granulated with the aid of granulating agent PVP K-30. Then the damp mass was passed through sieve no. 44 and dried in an oven at 50°C. After drying, granules are sifted through sieve no.22. Lubrication of granules was done with magnesium stearate and talc. Then the tablets were compressed using a tablet punching machine [1, 2].

Table 1: Formulations for the Matrix Tablets

Ingredients (mg)	F1	F2	F3	F4	F5
Glimepiride	2	2	2	2	2
Guar Gum	2	5	7	9	11
Dicalcium phosphate	171	168	166	164	162
Magnesium stearate	2	2	2	2	2
Talc	3	3	3	3	3
PVP K-30	20%	20%	20%	20%	20%
Total	200	200	200	200	200

2.4. Evaluation of granules

The parameters such as tapped density, angle of repose, bulk density Hausner's ratio, and compressibility index are evaluated for the granules.

2.5. Evaluation of formulated tablets [8, 9]

2.5.1. Weight variation

All the twenty tablets were weighed initially and individually. The average weight of the tablets is calculated and then the standard deviation.

2.5.2. Thickness

Thickness of individual tablet was measured by using Vernier callipers (20 tabs).

2.5.3. Hardness

From each batch, three tablets were selected and the hardness of the tablets was checked using a Monsanto hardness tester.

2.5.4. Friability

Initially, twenty tablets were weighed and placed in the Roche friability apparatus and rotated at 25 rpm for 4

min. After the revolutions, the tablets were dusted and weighed again. It was measured using the formula:
% Friability = {(Initial weight-Final weight)/ Initial weight} x 100

2.5.5. Uniformity of drug content

Uniformity was determined by taking an accurate weight amount of powdered glimepiride (10 mg). The equivalent weight was transferred into a volumetric flask. The absorbance was measured by UV- visible spectrophotometer at 229 nm.

2.6. *In-vitro* dissolution test

Dissolution studies were performed using the USP-II paddle apparatus. Phosphate buffer of pH 7.8 was taken as dissolution medium and 900ml was taken in each of the dissolution vessels. The temperature was maintained at 37±0.5°C. The formulated tablet was placed in each of the vessels and rotated at 75rpm speed for 12 hours. Aliquots were taken at definite intervals of time of 5ml each and replaced the same amount of volume with the fresh buffer medium. At 229nm the samples were analysed spectrophotometrically using UV-spectro-photometer.

2.7. Kinetic Data Analysis

The kinetic data analysis is an important parameter for understanding the release mechanism of the drug from the formulation. Even though it is a complicated process yet it is possible in matrix formulations. The models such as diffusion and exponential equations, zero-order, first-order equations which is a model-dependent approach as per the literature are used. From the zero-order and first-order kinetics the order of release pattern can be known and the mechanism of release pattern by Higuchi equation and Peppas-Korsemeyer equation.

3. RESULTS AND DISCUSSION

3.1. Compatibility Study using FTIR analysis:

There is no appearance or disappearance of any peak of drug glimepiride in the mixture mixed physically. There is little change in percentage transmittance, may be due to crystalline change. Hence it confirms that there is no chemical interaction between drug and polymer [10, 11].

3.2. *In vitro* swelling behaviour of formulated tablets:

The percentage swelling index was calculated for all the formulated tablets based on their swelling behaviours and results were ranging from 23.92 to 74.01. It was seen from the results that the swelling capacity was increasing with an increase in polymer concentration [12, 13].

Table 2: FTIR analysis of drug-excipient compatibility

Peak in pure drug	Functional group	Type of vibration	Peak in physical mixture
3372.27	Amine(N-H)	Stretch(medium)	3370.00
2934.66	Aromatic(C-H)	Stretch(medium)	2931.00
1674.50	Amide(C=O-NH2)	Stretch(strong)	1674.39
1080.92	Sulfoxide	Stretch(strong)	1081.72
1543.09	Aromatic(C=C)	Stretch(weak, multiple)	1543.62

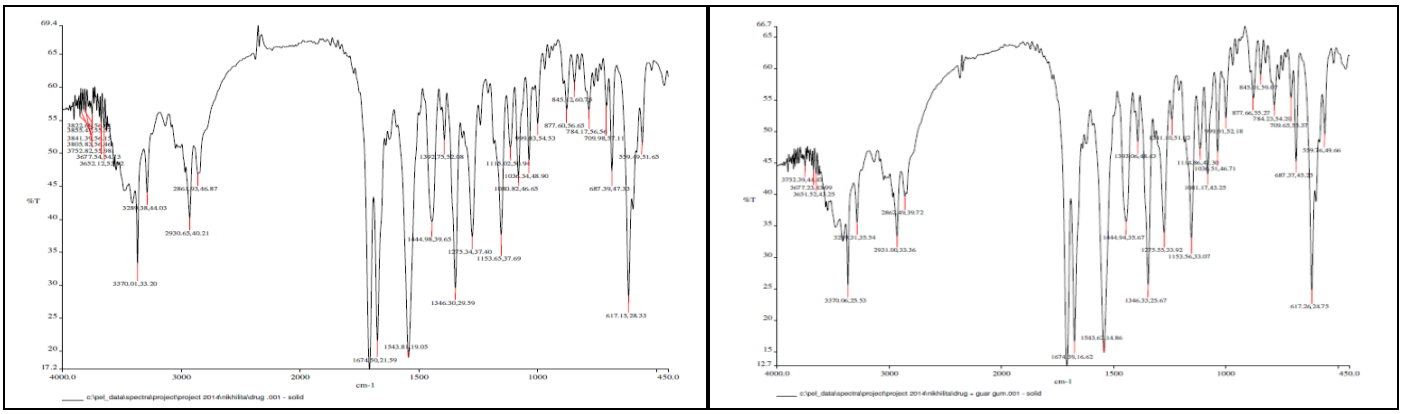

Fig. 1: FTIR Spectra for Drug and Drug-excipient

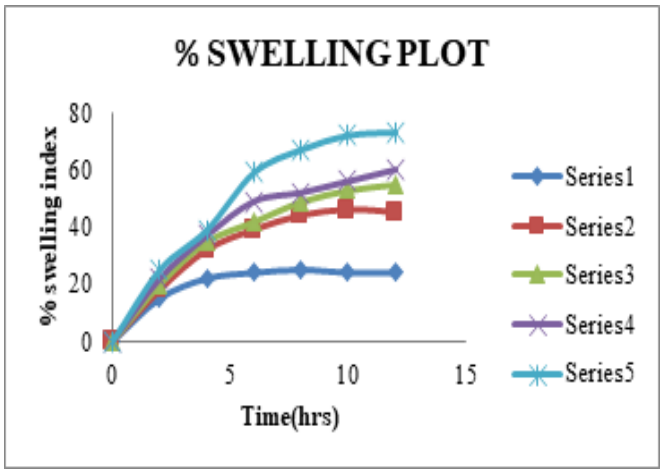

Fig. 2: *In-vitro* swelling of prepared tablets

3.3. Evaluation of formulated granules

The prepared granules were evaluated for their flow properties. The angle of repose ranged from 28.77± 0.23 to 31.25±0.17 which indicate that it ranged from excellent to good flow properties. The compressibility index ranged from 17.42 to 18.88 and Hausner's ratio from 1.21 to 1.23. Hence it indicates that they have good flow properties [14, 15].

3.4. Evaluation of formulated tablets

The formulated tablets were evaluated for thickness, hardness, friability, weight variation, and drug content. It was found that variation of weight in tablets were found to be ranging from 199.3±0.58 to 200.2±0.82, thickness ranging from 2.9±0.34 to 3.1±0.32, hardness from 6.8±0.20 to 7.0±0.12 (limit=≥6kg/cm2) and friability ranging from 0.28±0.03 to 0.51±0.01(less than 1%). The drug content of formulated tablets was in the range of 98±1.02 to 101±0.98. The results were found to be within acceptable limits [16, 17].

3.5. In-vitro dissolution study

The in-vitro dissolution test was conducted for the formulated sustain release matrix tablets. In USP-II apparatus (paddle) of speed 75rpm and temperature of 37±0.5°C it dissolution was performed using a buffer of pH7.8. The results showed a good sustained release profile which was dependent upon polymer concentration. In all of the five trials conducted, the trail F2 showed the best result of 96% release in 12 hrs. [18]

3.6. Kinetic study

The results of dissolution data are fitted to kinetic study in order to determine the release order and the mechanism of the formulation. It was interpreted by using the above zero order, first order, Higuchi plot and Korsemeyer - Peppa's plot. It was seen that the drug release order followed zero-order kinetics with an R2 value of 0. 940. The mechanism of release of drug was well fitted in the Higuchi plot with an R2 value of 0.997 [19].

Table 3: Preformulation parameters for formulated granules ready for compression

Formulations	Angle of repose (°)	Bulk ensity (g/ml)	Tapped density (g/ml)	Compressibility Index	Hausner's ratio
F1	31.25±0.17	0.531±0.01	0.647±0.02	17.93±0.06	1.22±0.05
F2	29.19±0.18	0.520±0.03	0.641±0.07	18.88±0.07	1.23±0.02
F3	28.77±0.23	0.510±0.01	0.629±0.01	18.91±0.02	1.23±0.02
F4	29.54±0.14	0.526±0.02	0.637±0.03	17.42±0.03	1.21±0.08
F5	30.61±0.19	0.505±0.05	0.644±0.03	18.81±0.05	1.23±0.09

Table 4: Evaluation of formulated prepared tablets

Formulations	Weight variation (mg±SD)	Thickness (mm±SD)	Hardness (kg/cm^2±SD)	Friability (%±SD)	Drug content (%±SD)
F1	199.8±0.91	3.1±0.32	6.9±0.14	0.51±0.01	98±1.02
F2	200.2±0.82	3.0±0.45	7.0±0.12	0.32±0.05	99±1.12
F3	200.1±0.12	3.0±0.56	6.9±0.18	0.41±0.08	101±0.98
F4	201.4±0.72	2.9±0.34	6.8±0.20	0.28±0.03	99±1.00
F5	199.3±0.58	3.0±0.23	6.9±0.13	0.35±0.01	100±1.32

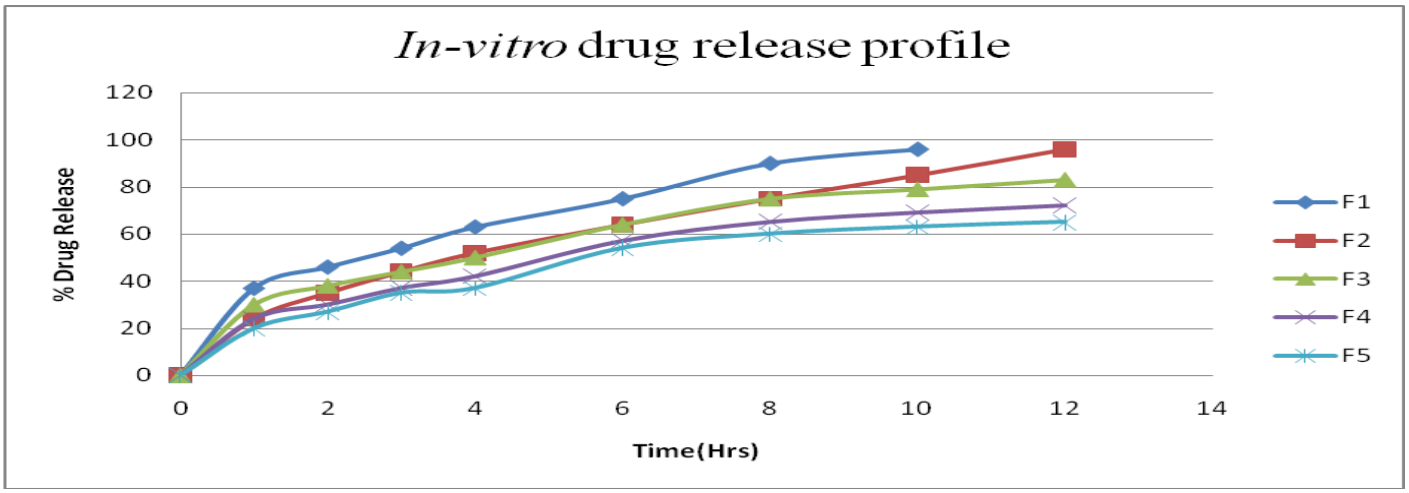

Fig. 3: *In-vitro* drug release from prepared tablets

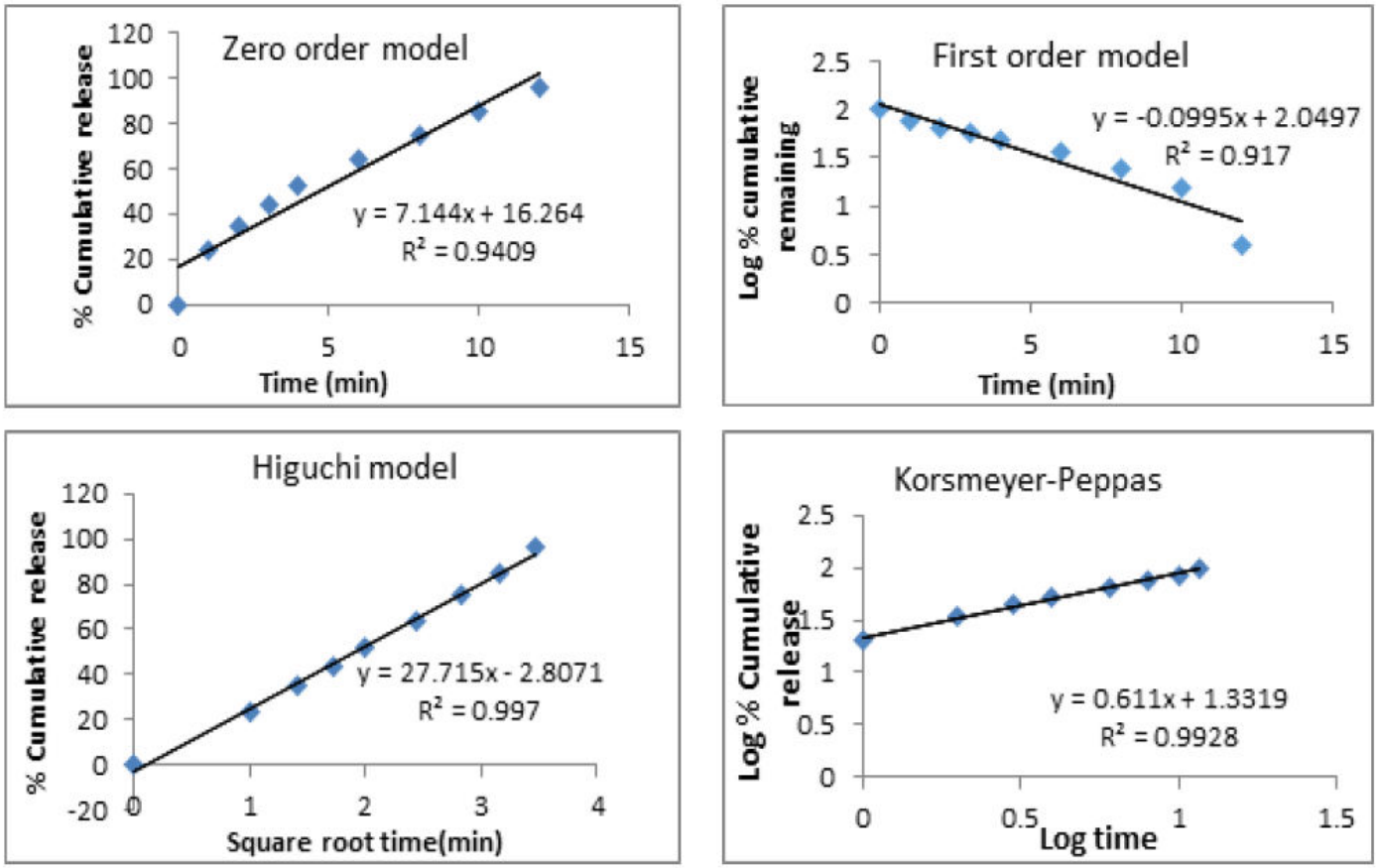

Fig. 4: Kinetic study of prepared tablets using Zero-order kinetics, First order kinetics, Higuchi Model and Korsmeyer-Pepps model *In-vitro* drug release from prepared tablets

4. CONCLUSION

From the above results, it can be concluded that guar gum as the natural polymer is suitable for the sustain release matrix tablet of the anti-diabetic drug, Glimepiride. It has good swelling property as well as flow properties. The drug release profile was best suited in F2 where the optimum release was found. The optimized kinetic data analysis showed that it followed the zero-order kinetics and the mechanism of the release of the drug in the Higuchi plot.

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