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FORMULATION AND EVALUATION OF EXTENDED-RELEASE TABLET OF TOLBUTAMIDE USING NATURAL BINDER

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ABSTRACT: The aim of present work was to formulate and evaluate extended release tablets of Tolbutamide using natural binders. Natural binders provides the tablet formulations with good hardness and friability. These binders prolongs the dissolution rate of some slightly soluble drugs and can be chosen as good candidate for sustained release. Tablets were prepared by direct compression method using different drug-polymer concentration. FT-IR study revealed that there was no chemical interaction between the drug and polymers used. Pre-compression and post-compression parameters complied with Pharmacopoeial limit for the tablets. Four different binders (tragacanth, gum acacia , guar gum, starch) were used in 3 different concentrations (25%, 50%, 75%) and was compared with the standard rate retardant polymer HPMC. The in vitro release study was performed and the results indicated that the formulation TEF8 (Guar Gum 50%) was found to be the optimized formulation which can extend the release up to a period of 24 hours. The kinetic release data showed that the optimized formulation followed zero order kinetics. From the stability studies it was clear that the formulation was stable after 2 months at accelerated condition of 40 °C±2 °C/75% RH±5% in a stability chamber.

KEYWORDS:- Tolbutamide, Natural binder, Extended release, Tablets

1. INTRODUCTION:

Oral drug delivery is the largest and oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration. Use of hydrophilic matrices for oral extended release of drugs is common practice in the pharmaceutical industry. However, also drugs with long half-life qualify if a reduction in steady state fluctuation is desired. With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non toxic for an extended period of time (1). To achieve better therapeutic action various types of drug delivery systems are available, out of which extended release systems are gaining much importance because of there wide advantages over others like ease of administration, convenience and non-invasiveness. (2) The maximum recommended daily dose of Tolbutamide in the United States is 2.5 g given in three doses with meals. Tolbutamide acts by decreasing hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake. Because of its shorter and variable biological half-life of 1.5—4.5 hr, it should be repeatedly administered (500 mg thrice a day) to maintain effective plasma concentration. In spite of its favorable clinical response and lack of significant draw backs, chronic therapy with Tolbutamide suffers from certain problems of which the most prominent is the high dose (1.5 – 2.0 g/day) low bio-availability (60%) and high incidence of gastrointestinal tract (GIT) side effect (30% case). (3, 4) Therefore, there were continued efforts to improve the pharmaceutical formulation of metformin hydrochloride in order to achieve an optimal therapy. These efforts mainly focus on extended release of drug. Administration of a extended release, once-a-day Tolbutamide dosage form could reduce the dosing frequency and improve patient compliance.

2. MATERIALS AND METHODS:

Tolbutamide was obtained from Yarrow Chem Pvt. Ltd., Mumbai, India. HPMC was obtained as gift samples from Loba Chem Pvt., Ltd. Mumbai. All other ingredients used throughout the study were of analytical grade and were used as received.

2.1 UV Spectroscopy: Stock solution of 1mg/ml of Tolbutamide was prepared by dissolving 100mg of drug in 100 ml of simulated gastric fluid (0.825M hydrochloric acid and 0.2% sodium chloride). The stock solution was serially diluted to get solutions in the range of 2- 10µg/ml and λmax of the solution was found out by scanning the solution from 200-400 nm using UV-VIS spectrometer. (5)

2.2 Compatibility Studies: IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymer. A physical mixture of drug and polymer was prepared and mixed with the suitable quantity of potassium bromide. About 100mg of mixture was compressed to form a transparent pellet using a hydraulic press at 6

tons pressure. It was scanned from 4000 to 400 cm^{-1} in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks. The IR spectrums of the sample and of the tolbutamide working/reference standard in the range of 4000 cm^{-1} to 400 cm^{-1} were taken by preparing dispersion in dry potassium bromide under the same operational conditions mentioned above. (6)

2.3 Pre-Compression Parameters

- Angle of repose
- Bulk Density
- Tapped Density
- Carr's Index
- Hausner's Ratio (7)

2.4 Formulation And Development: Extended-release tablets of tolbutamide were prepared by direct compression using different natural polymers like starch, Gum acacia, Guar Gum, Tragacanth and comparing with a standard rate retardant polymer HPMC at three different concentrations of polymers (25%, 50% and 75%).

Table 1: Preparation of Extended-release tablets using different natural

S. No.	Drug	Polymer	Polymer %
1	Tolbutamide	-	-
2		HPMC	25, 50, 75
3		Tragacanth	25, 50, 75
4		Guar Gum	25, 50, 75
5		Gum Acacia	25, 50, 75
6		Starch	25, 50, 75

The ingredients in the table above were accurately weighed and passed through sieve #60, then magnesium stearate and talc was passed through sieve #80. Then the materials were blended except magnesium stearate and talc for 20 minutes in ascending order. Later the powder mixture was blended with magnesium stearate and talc for 5 minutes. (8, 9)

Table 2: Formula for development of tablet

F. Code	Drug (mg)	HPMC (mg)	TR (mg)	GG (mg)	GA (mg)	ST (mg)	MCC (mg)	MS (mg)	Talc (mg)
TEF1	100	25	-	-	-	-	75	3	2
TEF2	100	50	-	-	-	-	50	3	2

TEF3	100	75	-	-	-	-	25	3	2
TEF4	100	-	25	-	-	-	75	3	2
TEF5	100	-	50	-	-	-	50	3	2
TEF6	100	-	75	-	-	-	25	3	2
TEF7	100	-	-	25	-	-	75	3	2
TEF8	100	-	-	50	-	-	50	3	2
TEF9	100	-	-	75	-	-	25	3	2
TEF10	100	-	-	-	25	-	75	3	2
TEF11	100	-	-	-	50	-	50	3	2
TEF12	100	-	-	-	75	-	25	3	2
TEF13	100	-	-	-	-	25	75	3	2
TEF14	100	-	-	-	-	50	50	3	2
TEF15	100	-	-	-	-	75	25	3	2

HPMC= Hydroxy Propyl Methyl Cellulose; TR= Tragacanth; GG= Gaur Gum; GA= Gum Acacia; ST= Starch; MCC= Microcrystalline Cellulose; MS= Magnesium stearate

2.5 Post Compression Parameters

2.5.1 Weight Variation: Weight variation test for the tablets was performed as per the IP procedure. Ten tablets were weighed individually, and the average weight was determined. The individual weight of all the ten tablets was noted. The percentage deviation of the individual weights from the average weight was then calculated.

2.5.2 Thickness: Tablet thickness is important for tablet packaging; very thick tablets affect packaging either in blisters or plastic containers. (10)

2.5.3 Tablet hardness: Tablet hardness has been defined as the force required for breaking a tablet in a diametric compression test. A tablet was placed between two anvils of the hardness tester, force was applied to the anvils, and the crushing strength that caused the tablet to break was recorded. (11)

2.5.4 Friability test: The friability of the tablets were measured in a friability apparatus (Roche Friaberator VEGGO). Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes and then the tablets were dedusted and weighed (W_{final}). Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%. Determination was made in triplicate.

$$\textbf{\% Friability} = \left[\frac{W_{initial} - W_{final}}{W_{initial}} \right] X\ 100$$

2.5.5 Assay of tablet: Ten tablets were randomly weighed and crushed. Calculated the average weight and taken the powder equivalent to 10 mg of paliperidone base in a 100 ml volumetric flask. Add few ml simulated gastric fluid and sonicated for 30 minutes. Then volume made up to 100 ml with simulated gastric fluid. The 1mL of resultant solution diluted to 100mL with simulated gastric fluid and the absorbance was measured using UV spectrophotometer at 245.8nm. (12, 13)

2.5.6 In-vitro dissolution study:

- Instrument: USP XIX Dissolution rate test apparatus
- Type: II Paddle
- Medium: 500 ml simulated gastric fluid
- Temperature: 37±0.5°C.
- RPM: 50
- Testing time: 24 h
- Time points: 1, 2, 3, 4, 5, 6, 7, 8,9,24
- Amount withdrawn: 5 ml.
- λ max: 237 nm.

2.5.7 Release Kinetic Analysis: To study the release kinetics, data obtained from in-vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug released vs. time, first order as log cumulative percentage of drug remaining vs. time, and Higuchi's model as cumulative percentage of drug released vs. square root of time. (14-17)

2.5.8 Stability Studies: The prepared formulations which showed best results in vitro was selected and kept for stability testing for a period of three months. The tablets were kept at 40± 2°C/75% ± 5%RH in a stability chamber in packed condition. These samples were analyzed for color, hardness, assay, % moisture absorbed and in vitro drug release, at the end of first, and second month. Further these results were compared with the initial results to evaluate the stability of the product. (18)

3. RESULTS

3.1 Determination of λmax: The wavelength showing maximum absorbance (λ max) for Tolbutamide was determined by scanning the standard stock solution of the drug using UV visible spectrophotometer. The λ max was found to be 248 nm for tolbutamide which is in accordance with the data available in literature.

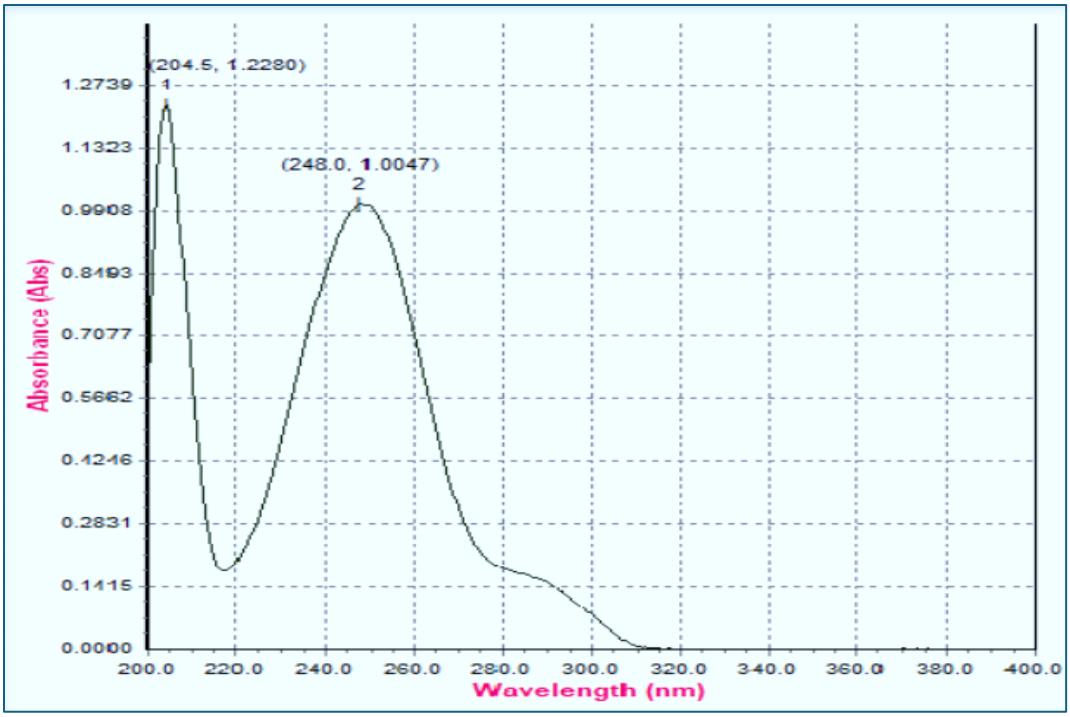

Figure 1: UV Spectra of Tolbutamide

3.2 Calibration Curve: The prepared sample was observed at λ max 248 nm at UV spectrophotometer. The calibration graph was plotted absorbance vs. concentration.

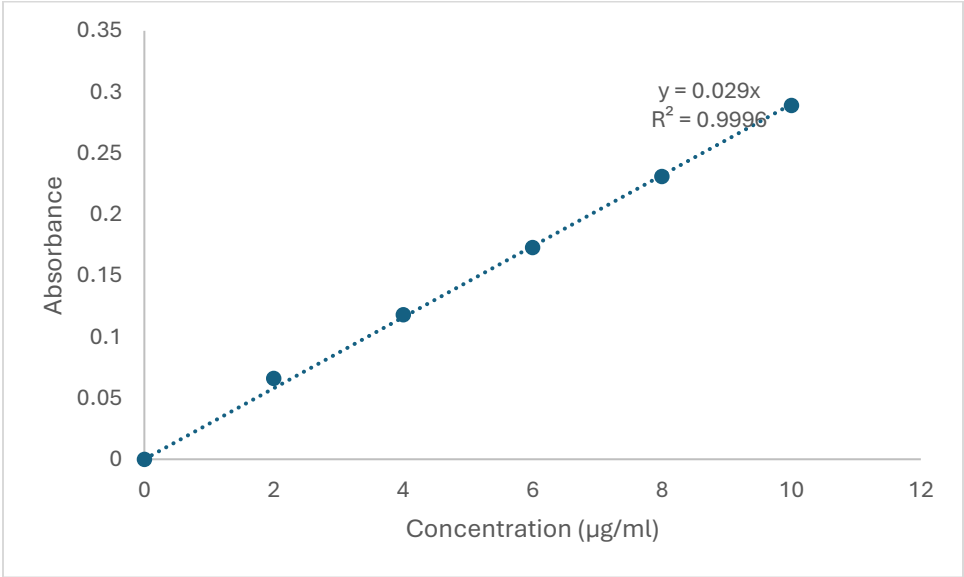

Figure 2: Calibration Curve of Tolbutamide

3.3 Compatibility studies: IR spectra matching approach was used for detection of any possible chemical interaction between the drug and the polymer. The samples were prepared by pressed pellet technique. The IR spectra was determined using Aligant

Technology. The scanning range was between 500- 4000cm^{-1}. The spectrum obtained was shown in figure 3.

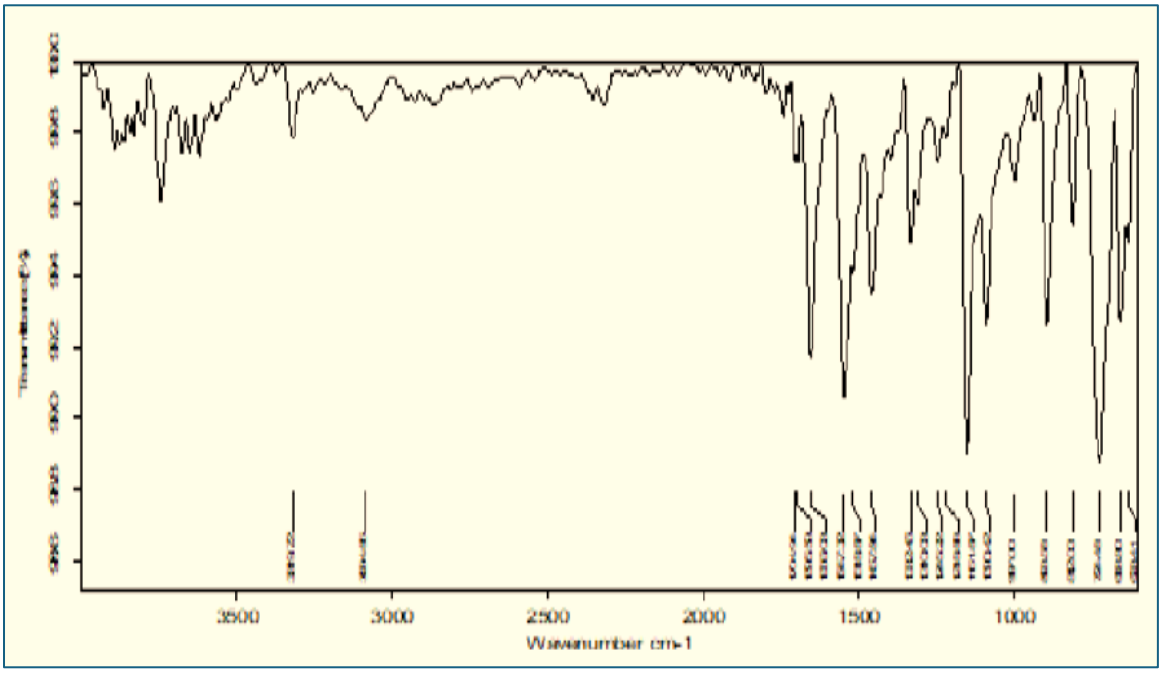

Figure 3: FTIR Spectra of Tolbutamide

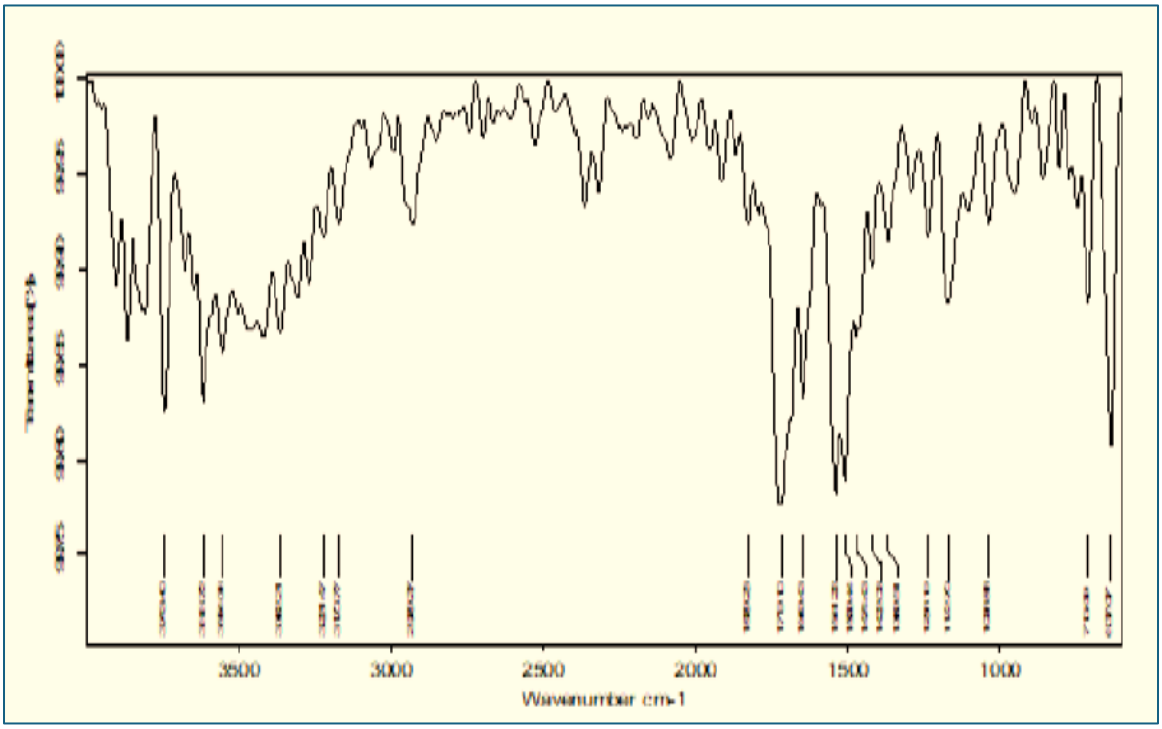

Figure 4: IR spectra of Tolbutamide with Excipients

3.4 Precompression Parameters: The preformulation parameters like angle of repose, bulk density, tapped density and compressibility index and Hausner's ratios were studied to evaluate the flowability and compressibility of the powder formulations. This indicates the granules have good flow character and have good compression property. All the results are within the prescribed limits.

Table 3: Results of Pre-compression parameters

F. Code	Angle of Repose	Hausner's Ratio	Carr's Index	Tapped Density	Bulk Density
TEF1	27°13'	1.29	19.11	0.776	0.563
TEF2	28°45'	1.26	18.76	0.567	0.602
TEF3	30°32'	1.36	22.65	0.665	0.612
TEF4	29°45'	1.47	21.75	0.854	0.544
TEF5	32°11'	1.41	23.23	0.869	0.621
TEF6	31°56'	1.28	24.12	0.853	0.579
TEF7	33°22'	1.29	26.76	0.854	0.604
TEF8	34°45'	1.26	15.54	0.629	0.623
TEF9	35°99'	1.32	26.34	0.739	0.721
TEF10	32°78'	1.41	24.09	0.628	0.632
TEF11	32°29'	1.38	29.11	0.589	0.545
TEF12	35°23'	1.29	28.47	0.603	0.593
TEF13	32°78'	1.33	19.76	0.599	0.634
TEF14	29°56'	1.33	24.57	0.784	0.589
TEF15	35°71'	1.21	23.21	0.803	0.454

3.5 Evaluation Of Post Compression Parameters: The tablets were evaluated for thickness, hardness, friability, average weight and assay.

Table 4: Results of Post compression parameters of Prepared tablets

F. Code	Hardness (kg/cm^2)	Average wt (mg)	Friability (%)	Thickness (mm)	Assay %
TEF1	5.3	203.15	0.453	5.76	95.56
TEF2	4.8	204.5	0.412	5.43	94.11
TEF3	5.0	200.6	0.411	6.52	96.54
TEF4	3.9	197.6	0.342	4.71	95.18
TEF5	4.2	201.6	0.312	5.75	96.11
TEF6	4.1	206.2	0.312	7.33	97.54
TEF7	5.0	202.5	0.265	6.59	90.65

TEF8	4.8	205.3	0.165	6.62	97.56
TEF9	4.6	205.8	0.299	5.74	91.88
TEF10	4.5	199.8	0.312	5.63	95.71
TEF11	4.9	203.7	0.254	4.70	96.76
TEF12	5.1	202.5	0.231	5.56	97.08
TEF13	4.8	206.6	0.245	6.62	97.67
TEF14	4.4	208.5	0.289	5.65	97.15
TEF15	4.6	207.9	0.301	5.72	95.89

3.6 In vitro Dissolution Study of Tablets: Tolbutamide controlled release tablets were formulated using 5 different polymers in the percentage of 25%, 50%, and 75%. A total of 15 formulations were made using these polymers by direct compression method & 24 hours dissolution studies were carried out.

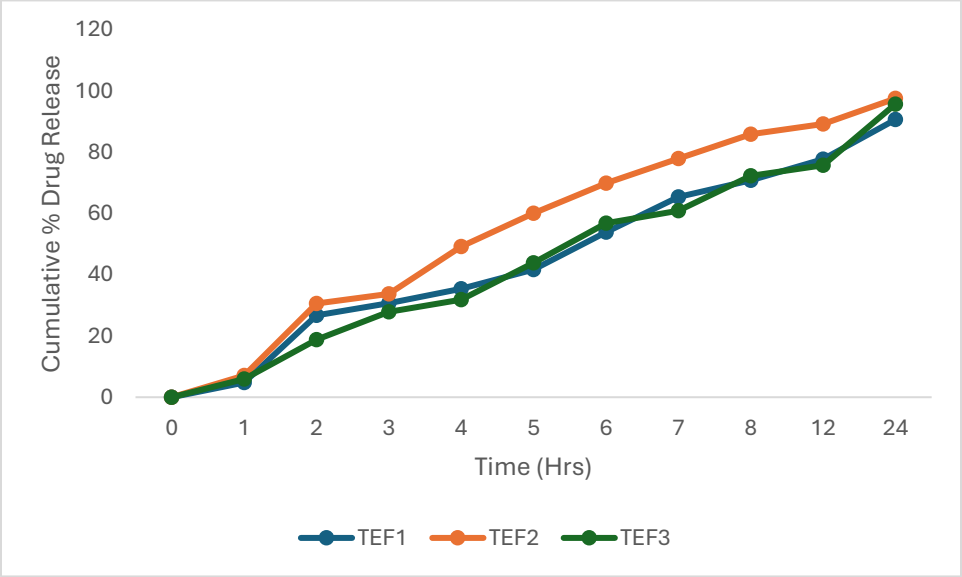

Figure 5: Dissolution graph of HPMC (TEF1, TEF2, TEF

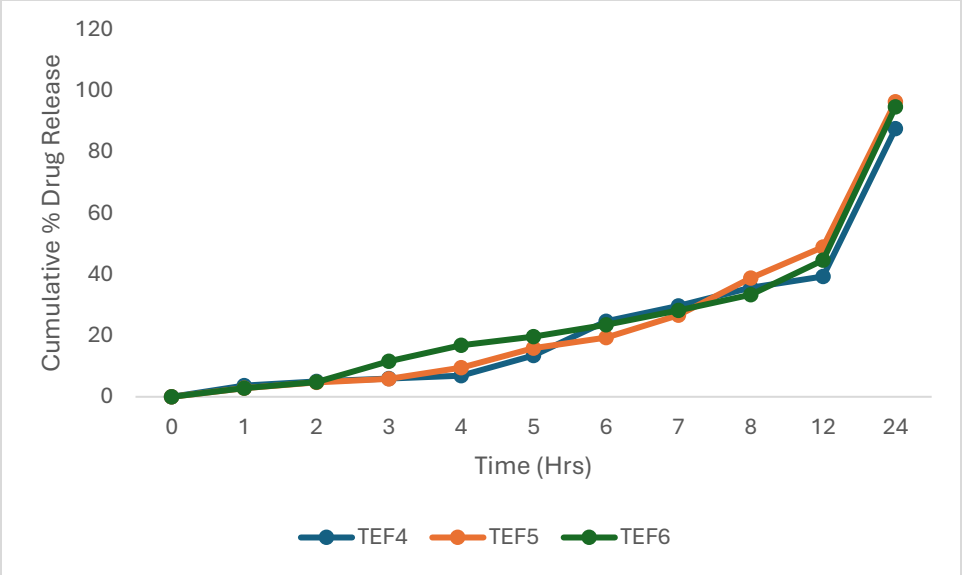

Figure 6: Dissolution graph of tragacanth (TEF4, TEF5, TEF6)

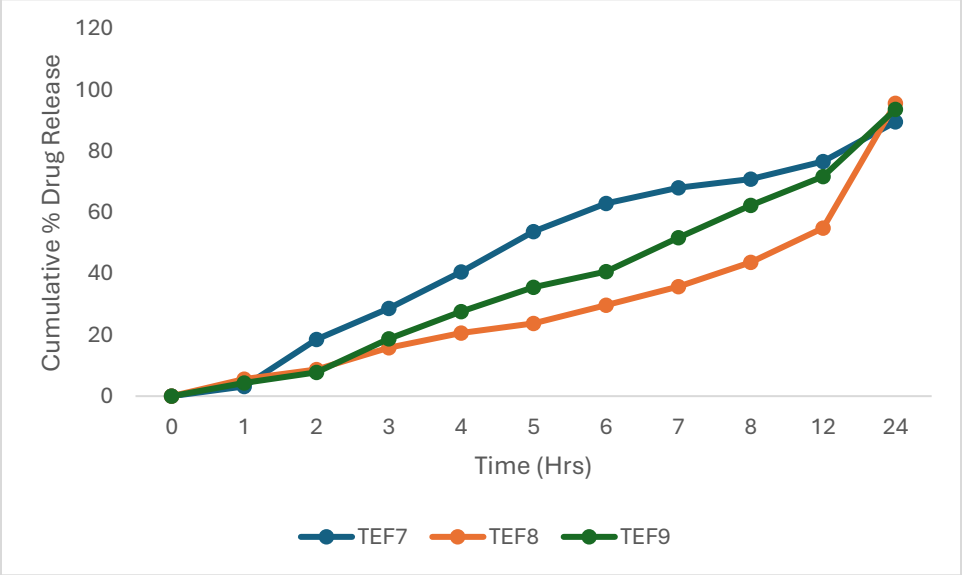

Figure 7: Dissolution graph of Guar Gum (TEF7, TEF8, TEF9)

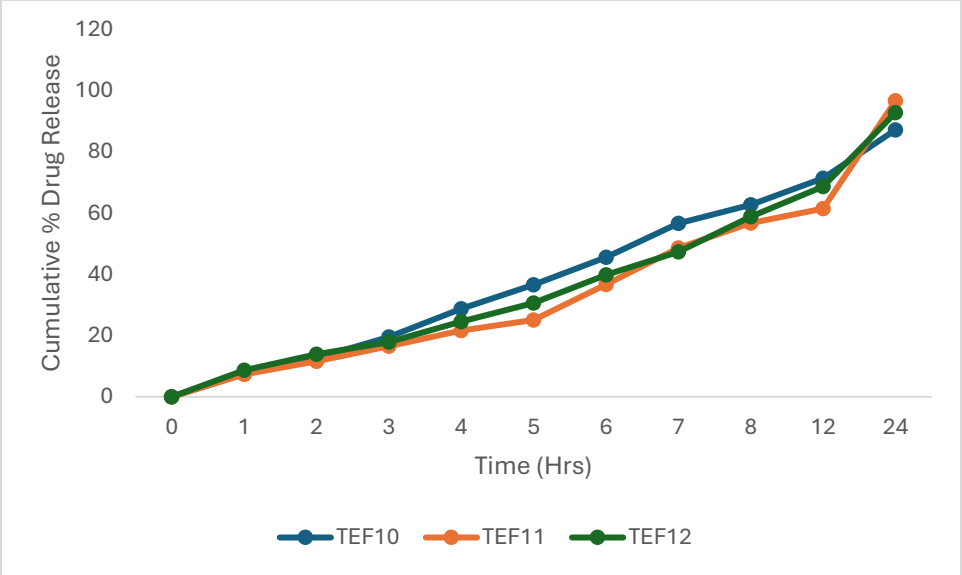

Figure 8: Dissolution graph of Gum acacia (TF10, TF11, TF12)

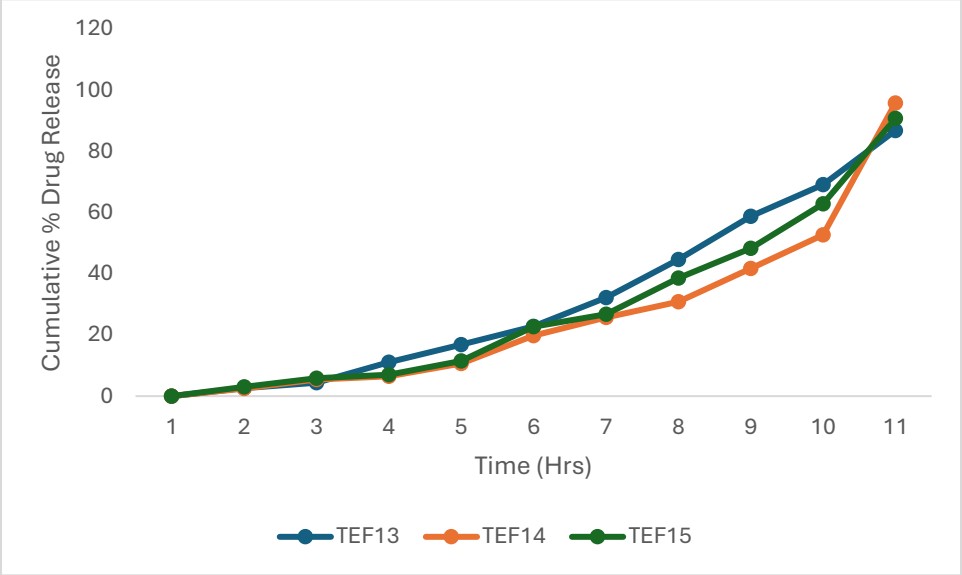

Figure 9: Dissolution graph of Starch (TF13, TF14, TF15)

3.7 Drug Release Kinetics analysis: The in-vitro drug release data of the optimized formulation was subjected to kinetic analysis by plotting various kinetic equations like zero order, first order and Higuchi plot.

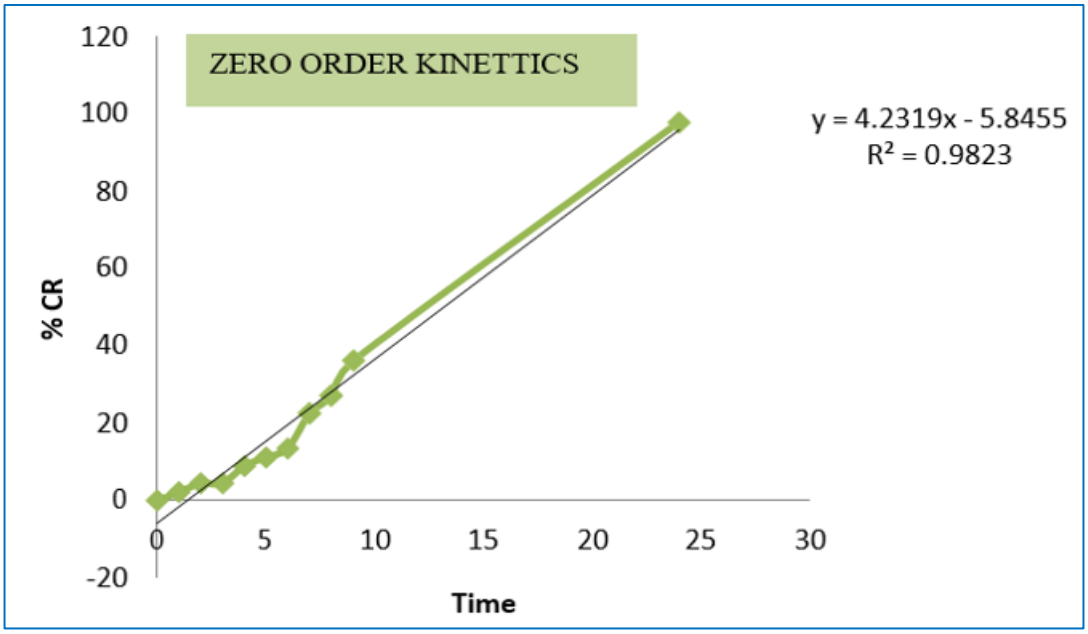

Figure 10: Zero order plot (TEF8)

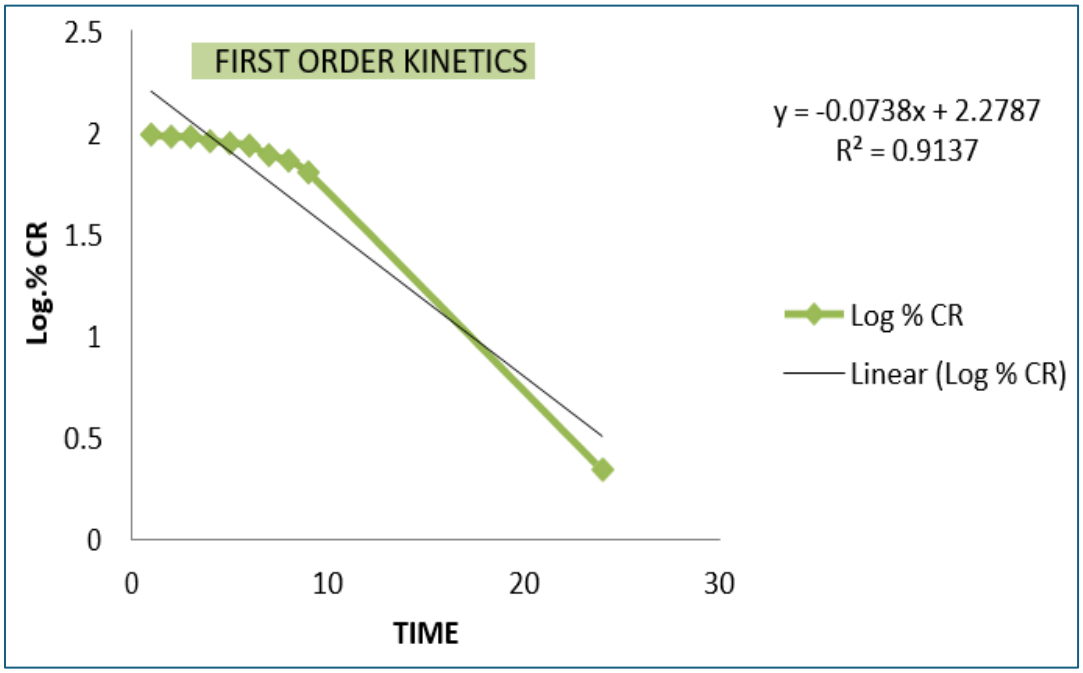

Figure 11: First order plot (TEF8)

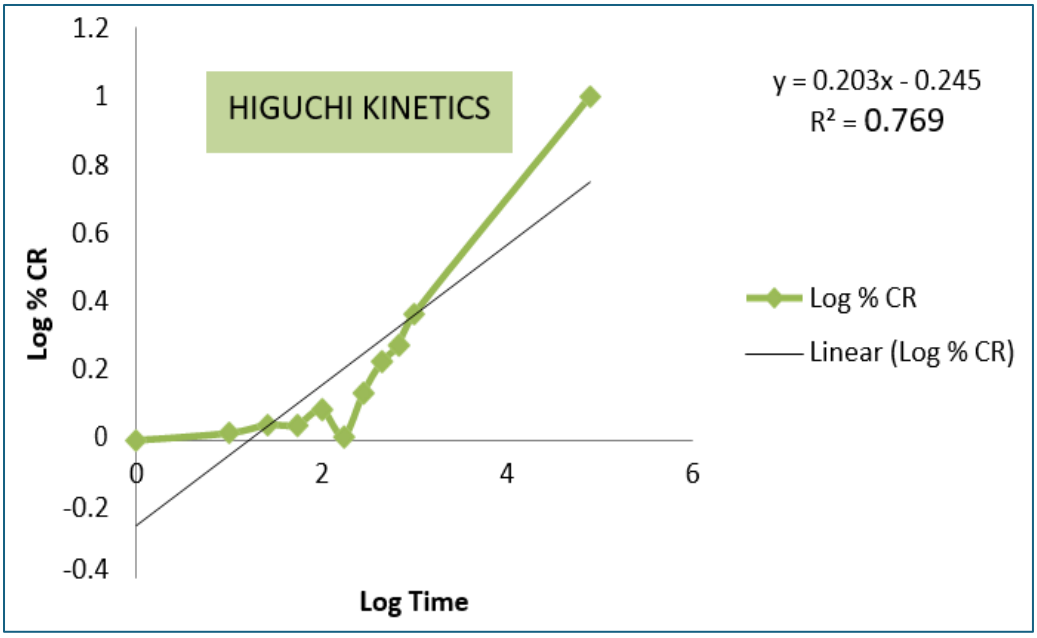

Figure 12: Higuchi plot (TEF8)

Table 5: Result of kinetic analysis

Formulation	Zero Order (R2)	First Order (R2)	Higuchi Kinetics (R2)
TEF8	0.995	0.913	0.769

Mechanism of drug release data can be assessed by plotting the drug release data in linear, exponential and power equations. From the regression co-efficiant value, it may follow zero order kinetics.

3.8 Stability Study: Here the tablets were loaded at accelerated condition at 40 °C±2 °C/75% RH±5% in a stability chamber. Samples were withdrawn at 30th and 60thday and evaluated for the physical appearance, drug content and dissolution characteristics. The stability analysis data were given in table above. The result showed that storage at 40 ºC had no effect on the hardness, disintegration time and dissolution time.

Table 6: Stability study of formulation TEF8 (Tolbutamide + Guar gum 50%)

S. No.	Parameters	Initial	30th Day	60th Day
1	Physical Appearance	Whitish Grey	Whitish Grey	Whitish Grey

2	Drug Content (%)	97.56	97.21	96.89
3	Dissolution	95.62	95.32	95.12

4. DISCUSSION

The drug was observed visually for its appearance, state, color, and odor. The solubility of raw drug was determined by dissolving in distilled water, methanol and phosphate buffer pH 6.8. The drug was practically insoluble in the water, soluble in methanol and phosphate buffer p H 6.8. It was found to be 128.5ºC which was within the specification range of standard. So it confirmed Tolbutamide present in raw material of drug. The percentage loss on drying for tolbutamide was found to be 0.1%.

The wavelength showing maximum absorbance (λ max) for Tolbutamide was determined by scanning the standard stock solution of the drug using UV visible spectrophotometer. The λ max was found to be 248 nm for tolbutamide which is in accordance with the data available in literature.

The data given in the table shows the characteristic peaks detected in the IR spectrum of pure drug, tolbutamide. The spectra of the pure drug and the spectra of the drug mixed with polymer are compared for the presence or absence of characteristic peak. It was found that the spectra of the drug with polymer showed all the characteristic peak of tolbutamide suggesting that there is no compatibility problem between the drug and polymer.

The precompression parameters like angle of repose, bulk density, tapped density and compressibility index and Hausner's ratios were studied to evaluate the flowability and compressibility of the powder formulations. The tapped density and bulk density was found to be in the range of 0.567 to 0.869 gm/cm^3 and 0.455 to 0.721 gm/cm^3. The compressibility and hausner's ratio were found to be 15.54% to 29.11% and 1.21 to 1.47. This indicates the granules have good flow character and have good compression property. All the results are within the prescribed limits.

The tablets were evaluated for thickness, hardness, friability, average weight and assay. The thickness of the formulated tablets was found to be in the range of 4.70 mm to 7.33 mm. Hardness and friability was found to be 3.9-5.3kg/cm^2 and 0.165- 0.412% which indicates the tablet has adequate mechanical strength. Weight variation of the tablets was found to be within the specified limits. The drug content of all the formulations ranged from 90.65-97.76% indicating the presence of an acceptable amount of drug in the formulations.

Cumulative percentage drug release for the different concentration of HPMC (25%, 50%,75%). Formulation TEF1, TEF2, TEF3 containing the different concentrations of

HPMC are taken. The TEF1 and TEF2 do not show the drug release up to the desired period of time. In case of formulation TEF2 containing HPMC (50%) also showed prolonged release but could not prolong the release for desired time.

Cumulative percentage drug release for the different concentration of tragacanth (25%, 50%, 75%). For formulation TEF5 containing 50% polymer the cumulative release was found to be 48.89% in 12 hr and 96.35% at 24 hours. The increase in polymer content delays the drug release as the polymer is hydrophilic and swellable polymer which produces increased swelling with increase polymer which might have increased diffusional path length for the drug to get diffuse across the membrane.

Cumulative percentage drug release for the different concentration of Gaur Gum (25%, 50%, 75%). The decrease in drug release rate as the concentration of the polymer increases may be attributed to the presence of a highly water soluble compound. It is seen that there is a faster rate of polymer swelling and a large increase in gel thickness to prevent immediate tablet disintegration, and thus controlling the diffusion of the drug.

Cumulative percentage drug release for the different concentration of Gum Acacia (25%, 50% and 75%). These formulations were able to extend and control their release pattern to desired period of time. The drug release rate was found to be decreased when concentration of polymers was increased. This may be due to increased swelling of the polymer when concentration is increased which leads to increased viscosity of the medium and thus increases the mean diffusional path length of the drug molecule to get released into the diffusion medium.

Cumulative percentage drug release for the different concentration of Starch (25%, 50%, 75%) is given the table below. In vitro dissolution data showed that these are not the best candidate for once daily dosage form as the release of the drug is not up to the desired extent. After 24 hours, the release of the drug was found to be 86-95% only. As a result, these formulations cannot be considered as optimized formulation.

From the in vitro dissolution data of the 15 formulations, almost all the formulations have the release up to the extended period of time. From these formulations TEF8 was chosen as the optimised formulation because of their extent their release up to 24 hours. All other post compression parameters like bulk density, tapped density, angle of repose, compressibility index and hausner's ratio are up to the specified limits.

The in-vitro drug release data of the optimized formulation was subjected to kinetic analysis by plotting various kinetic equations like zero order, first order and Higuchi plot. The kinetic analysis data of the formulation was shown in the table. The kinetic model that best fits with the release data of formulation was evaluated by the correlation coefficient (R^2) values. According to the values obtained higher linearity was observed with linear plot (zero order) with R2 value of 0.955. Thus, the formulation may follow zero

order drug release. Mechanism of drug release data can be assessed by plotting the drug release data in linear, exponential and power equations. From the regression co-efficiant value, it may follow zero order kinetics.

Here the tablets were loaded at accelerated condition at 40 °C±2 °C/75% RH±5% in a stability chamber. Samples were withdrawn at 30th and 60th day and evaluated for the physical appearance, drug content and dissolution characteristics. The stability analysis data were given in table above. The result showed that storage at 40 ºC had no effect on the hardness, disintegration time and dissolution time.

5. CONCLUSION

Extended-release tablets of Tolbutamide were Successfully prepared by direct compression method using 5 different natural polymers like starch, Gum acacia, Guar Gum, Tragacanth at three different concentrations of polymers (25%, 50% and 75%). Preformulation studies were carried out to study the nature of API & its compatibility with polymer and excipients including polymer. The result shows there was no interaction of API with all the excipients including polymer. The formulated tablets were assessed for both pre-compression and post compression parameters as per requirement of standards and the results were complied with the pharmacopeia specification. Out of 15 formulations, TEF8 with 50% of Guar Gum Concentration could give rise to tablets exhibiting Extended drug release.

Thus it concluded that the polymer Guar gum and other excipients selected for the formulation were not only compatible with Tolbutamide but also work on its ramification which may related to high blood plasma concentration levels and use of natural polymer will also lessen the toxic effect of Tolbutamide which occurs in the conventional drug delivery. The action of Guar gum as a natural polymer for the development of extended release drug delivery will be used as a biocompatible source.

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