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FORMULATION EVALUATION AND OPTIMIZATION OF METFORMIN HCl MATRIX TABLET USING NATURAL POLYMER

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Keywords:

Metformin HCl, Tamarind seed polysaccharides (TSP), Freeze-drying, Matrix tablet, Differential Scanning Calorimetry (DSC)

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ABSTRACT: Objectives: The main objective was to find out a suitable and effective natural release retardant, which can be used in matrix tablet preparation along with synthetic excipients. **Methods:** Tamarind seed polysaccharides (TSP) were isolated from *Tamarindus indica* by hot extraction method followed by freeze-drying and yield was found to be 16.85%. Microbial studies confirmed that TSP doesn't support microbial growth. Matrix tablet of Metformin HCl was prepared by using a wet granulation method with the help of TSP. Drug excipients compatibility was checked with the help of Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). At last, the release was compared with the marketed formulation. **Results:** The drug content of all the formulations ranged from 96.55% to 98.54%. Formulation F7 showed release up to 12 h. It was observed that as per increase in the polymer concentration, the release rate also increased. F6 formulation was found to be the optimized formulation. The F6 and marketed both the formulation followed the Higuchi model as n values came within the range of 0.5-1.00.

INTRODUCTION: Type - II diabetes is related to abnormal blood glucose, overweight, lipid disturbances, and blood pressure. For all this problem, oral hypoglycemic agents (OHAs) or insulin is often preferred. Biguanides particularly Metformin HCl enhance insulin-mediated glucose uptake and disposal in skeletal muscle and fat. It suppresses the hepatic gluconeogenesis and glucose output from the liver to lower blood glucose level [1]. It is having an oral bioavailability of 50%-60% in the fasting condition with a duration of action in between 6-8 h.

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The daily dose is 0.5 to 2.5 g with a plasma $t_{1/2}$ of 1.5-3 h [2, 3]. Matrix tablets are the oral solid dosage forms in which drug or active ingredient is homogeneously dispersed throughout the hydrophobic or hydrophilic matrices which act as release rate retardant. Furthermore, Metformin HCl presents formulation challenges due to its inherently poor compressibility, high dose, and high water solubility (> 300 mg/ml at 25 ºC).

It belongs to class III of Biopharmaceutical Classification System (BCS) having high water solubility and low permeability. For drugs that are highly water-soluble, both hydrophobic and hydrophilic matrices used for oral drug delivery system [4]. Polymers, which have high molecular mass each molecule of which consist of a very large number of single structural units joined together regularly. Natural polymers occur in nature and can be extracted.

They are water-based. Tamarind seed polysaccharides is also a naturally extracted polymer isolated from *Tamarindus indica*, possesses properties like high viscosity, broad pH tolerance, non-carcinogenicity, mucoadhesive nature, and biocompatibility [5].

MATERIALS AND METHODS: Tamarind seed polysaccharides (TSP) was obtained from the forest of Assam, district- Darrang. Metformin HCl was purchased from Yarrow Chem Products, Mumbai. USP I tapper of a USP tap density tester (Electro lab, model ETD-1020), vortex mixer (Lab-line Equipment's, India), Bench centrifuge (Remi, India), Brookfield viscometer (LVDV-E) (Brookfield Engineering Labs, Stoughton- USA), Perkin Elmer 2400 Semis II CHN analyzer, differential scanning calorimeter (JADE DSC, Perkin Elmer, and USA), Siemens D5000 X-ray Diffractometer (Siemens, Munich, Germany), IR spectrometer (Bruker Alpha FTIR). All other chemicals and solvents used were of analytical grade.

Isolation of Tamarind Seed Polysaccharides: Seeds of *Tamarindus indica* was collected and dried in sunlight. After that, seeds were crushed into powder and boiled with water at 45 °C to extract the polysaccharides. After boiling for 12 h, the supernatant liquids were collected and stored in a cool place. After the liquids become cooled acetone was added and freeze at -40 °C. Freeze materials then lyophilized to extract out the Tamarind seed polysaccharides [6].

Characterization of Tamarind Seed Poly-saccharides:

Phytochemical Examination: Preliminary tests were performed to confirm the presence of polysaccharide by ruthenium red test and Molisch's test [7].

Organoleptic Properties: Properties like color, odor, taste, shape, touch, and texture were determined.

Composition of Polysaccharides: Considering glucose as standard, the total sugar content was estimated by the phenol-sulfuric acid analysis. Tests like Molisch tests, Fehling's test, and the iodine test was performed to determine the total carbohydrate content. UV- visible spectra and Barfoed test were undergone to determine the protein presence [8].

Micromeritic Properties of Polysaccharides: Isolated TSP powder was evaluated for bulk density, tap density, angle of repose, Hausner's ratio, and Carr's index.

Solubility Studies: The polysaccharides obtain from *Tamarindus indica* was evaluated for solubility in water, acetone, methanol, and ether as per Indian Pharmacopoeia specification.

Determination of Melting Point: Melting point was determined by a capillary tube in melting point apparatus.

Loss on Drying: LOD was carried out as per the method mentioned in Indian Pharmacopoeia [9].

pH of 1% Solution: The pH of the 1% TSP solution was measured using a digital pH meter.

Moisture Content: The moisture content of the powder was carried out by thermos gravimetric method using IR moisture balance.

Viscosity of 1% Solution: The viscosity of 1% solution was determined by Brookfield viscometer (LVDV-E) (Brookfield Engineering Labs, Stoughton- USA) using Spindle 62 at 0, 20, 40 and 60 rpm.

Determination of Swelling Index: This was done by taking 1.0 g quantity of in a 15 ml plastic centrifuge tubes, and the volume occupied was noted. Ten milliliters of distilled water was added to it, and the content was mixed on a vortex mixer (Lab-line Equipment, India) for 2 min. The mixture was allowed to stand for 10 min and immediately centrifuged at 1000 rpm on a bench centrifuge (Remi, India). The supernatant was carefully decanted, and the volume of sediment was measured. The swelling index was computed using the following equation.

$$S = (V2 - V1) / V1 \times 100$$

Where S is the % swelling capacity, V2 is the volume of the hydrated or swollen material, and V1 is the volume of the material before hydration. The experiment was repeated by using 0.1 N HCl and Phosphate buffer 7.4 in water [10].

Determination of Ash Value: 2 gm of polysaccharide (TSP) was weighed accurately in a previously ignited and tarred silica crucible. The material was then ignited by gradually increasing the heat to 500- 600 ℃ until it appeared white indicating the absence of carbon. It is then cooled in a desiccator, and total ash in mg per gm of air-dried material is calculated. To the crucible containing total ash, 25 ml of 2M HCl was added and boiled gently for 5 min, and then about 5 ml of hot water was added and transferred into the crucible. The insoluble matter was collected on an ashless filter paper. This was then washed with hot water until filtrate is neutral and the filter paper along with the insoluble matter was transferred into the crucible and ignited to constant weight. The residue was then allowed to cool and then weighed. The percentage of insoluble acid ash was calculated from the weight of the sample taken [11].

Microbial Content Determination: Total microbial content was determined by Streak plate (surface plating) method using agar plates.

Compatibility Studies:

FTIR Studies: The pure drug, Metformin hydrochloride and the physical mixture of pure drug with tamarind seed polysaccharides (TSP) powder, HPMC K 100M in the ratio 1:1 were subjected to IR spectral studies using FTIR spectrophotometer (Bruker Alpha FTIR)at the scanning range of 4000-400 cm^{-1}. [12]

DSC Studies: It is used to analyses thermal stress on drug and their mixture. Individual sample and 1:1 w/w physical mixture of the drug were weighed, and almost 5 mg was taken in the DSC pan and scanned in the temperature range of 50 to 300 ℃ in a nitrogen environment. A heating rate of 10 ℃ per minute was used, and the thermograph was reviewed for evidence of any interaction [13].

Formulation of Matrix Tablets: Metformin HCl tablets were prepared by wet granulation technique. Sustained-release (SR) matrix tablets of Metformin HCl was prepared by using drug Metformin HCl, HPMC-K-100, PVP-K-30, microcrystalline cellulose, and tamarind seed polysaccharides. Tamarind seed polysaccharides were used as matrix-forming polymer, while microcrystalline cellulose was used as a filler to maintain the tablet weight. All ingredients were passed through a sieve #20, weighed and blended. The granules were compressed by a direct compression technique, using KBR (IR press), with the help of 10 mm flat punches.

Evaluation Parameters of Tablets: [14, 15]

Pre-Compression Studies of Granules: Various parameters like bulk density, tap density, angle of repose, Hausner's ratio, and Carr's index were determined.

Post-Compression Studies of the Prepared Formulations: Test for weight variation, hardness, friability, and thickness were determined for compressed tablets.

Drug Content Determination: Ten tablets of each formulation were powdered. Powder equivalent to 500 mg of Metformin hydrochloride was weighed and transferred to 100 ml volumetric flask, initially about 50 ml of phosphate buffer 6.8 was added and the flask was shaken thoroughly, and the volume was made up to 100 ml with the buffer solution. The resulting solution was filtered. From this, 5 ml was taken and diluted to 100 ml. From this, 2 ml was taken and diluted to 100 ml. From the resulting solution, drug content was estimated at 234 nm using UV spectrophotometer taking phosphate buffer as blank.

***In-vitro* Drug Release:** Drug release studies were carried out using USP type - II dissolution test apparatus, rotating paddle method (Electro lab, Mumbai, India). The study was conducted at 37 ℃ ± 5 ℃ and 50 rpm. The dissolution medium used was 900 ml of phosphate buffer pH 6.8 and study was carried up to 12 h 10 ml of sample was withdrawn at different time intervals and replaced with fresh medium to maintain sink condition. The withdrawn samples were diluted suitably, and drug release percentage was estimated spectrophotometrically at 234 nm, using phosphate buffer as blank [16].

Drug Release Kinetics:

Zero-Order Kinetics: Zero-order as a cumulative amount of Percentage drug released *vs.* time.

$$C = K0t$$

Where KQ is the zero-order rate constant expressed in units of concentration/time and t is the time in h.

First Order Kinetics: First order as cumulative log percentage of log (%) cumulative drug remaining *vs.* time.

$$\text{Log } C = \text{Log}C0 - kt/2.303$$

Where Co is the initial concentration of the drug, k is the first order constant, and t is the time.

Higuchi Model: Higuchi's model as a cumulative percentage of drug released *vs.* square root of time.

$$Q = Kt1/2$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, the drug release rate is proportional to the reciprocal of the square root of time

Korsmeyer Peppas Equations: Korsmeyer-Peppas equation used to determine the mechanism of drug release from the polymer matrix of the tablet as Log cumulative percentage of drug released *vs.* log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/Mo = Ktn$$

Selection of Optimized Formulation: The concentration of natural polymer in matrix tablet was optimized by study the properties of tablet and in vitro release profile. The effect of polymer concentration on release properties of matrix tablet was determined using different drug: polymer ratio. All the tablet parameter was evaluated for each formulation, and mathematical kinetics model for release profile was compared. The formulation which provides best release pattern with better tablet parameter selected as an optimized tablet.

RESULTS AND DISCUSSION:

Evaluation of Tamarind Seed Polysaccharides (TSP): The purity of polysaccharide was determined by undergoing phytochemical tests such as a test for alkaloids, proteins, fats & oils and amino acid whose outcome found to be absent. The purity was confirmed as the only carbohydrate was found to be present. Then the polysaccharide was characterized by various organoleptic properties such as color, odor, taste, touch, and texture are shown in **Table 2**. % yield of Tamarind Seed Polysaccharides (TSP) was found to be 16.85%.

Swelling index of the tamarind seed polysaccharides (TSP) was found to be high. The ability of swelling of any polysaccharide is based on its water retention capacity. The pH of the 1% w/v tamarind seed polysaccharides (TSP) was found to be 6.9. The melting point of polysaccharides was found to be 250 °C - 260 °C. Moisture content was found to be 8.10%, which results from good stability for pharmaceutical dosage forms.

TABLE 1: COMPOSITION OF METFORMIN HCl TABLET (mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCl	500	500	500	500	500	500	500	500	500
Polymer (TSP)	50	100	150	200	250	300	350	-	-
HPMC K100	-	-	-	-	-	-	-	100	200
MCC	330	280	230	180	130	80	30	280	180
PVP K 30	10	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total	900	900	900	900	900	900	900	900	900

TABLE 2: ORGANOLEPTIC PROPERTIES OF POLYSACCHARIDES

Organoleptic properties	Results
Colour	Brown
Odor	Odorless
Taste	Tasteless
Shape	Irregular
Touch and Texture	Hard and rough

The solubility behavior of the polysaccharide was carried out which shows that the polysaccharide is soluble in warm water, sparingly soluble in cold water, whereas insoluble in methanol, acetone& ether. The ash values are measured as high values of ash indicates a low level of purity and adulteration of sand and other earthy matter such as carbonates. Here the total ash values for polysaccharide was found to be 1.6050, and the acid insoluble ash value was found to be 0.0996, which indicates a high level of purity as the values were found to be very low. The microbial test for the polysaccharide was performed, and the count

was found to be within limit; thus, microbial contamination is not a risk factor for product degradation. The properties such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose are referred to as properties of the powder to adhere together for better compressibility in a pharmaceutical formulation. Compressibility index (CI) values up to 15% usually result in good to excellent flow properties, and value above 25% are often sources of poor tableting qualities. The values are found to be within the limit and are believed to serve for good flow properties and compressibility. The angle of repose was found to be 29.45, which indicates good flow properties, and all these are shown in **Table 3**. The viscosity of 1% solution of tamarind seed polysaccharides (TSP) was found to be 1250, 620, 420 and 90 Centipoise (cP) at 0, 20, 40, 60 rpm respectively and shown in **Fig. 1**.

TABLE 3: EVALUATION PARAMETERS OF TAMARIND SEED POLYSACCHARIDES (TSP)

Parameters	Results
% yield	16.85
Swelling index (%v/v) water	196
0.1N HCl	220
Phosphate buffer 6.8	455
Loss on drying (%w/w)	11
Moisture Content (%w/w)	8.10
Total ash (%w/w)	1.6050
Acid insoluble ash (%w/w)	0.0996
Water soluble ash (%w/w)	0.8218
pH	6.9
Melting Point	250-260 °C
The angle of repose (Degree)	29.45
Bulk density (g/cc)	0.63
Tapped density (g/cc)	0.83
Compressibility index (%)	24.17
Hausner's ratio	1.03

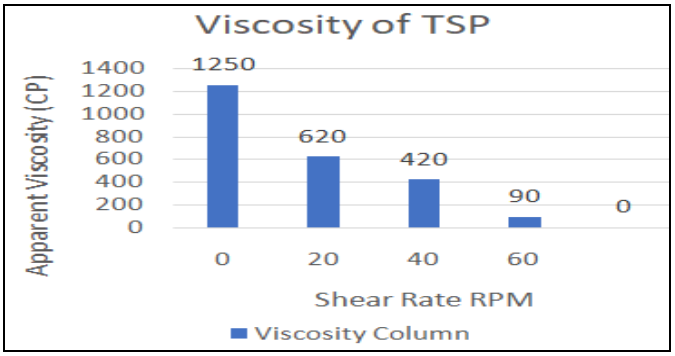

FIG. 1: VISCOSITY DIAGRAM FOR POLYSACCHARIDES

Drug-Excipients Compatibility Study:

Differential Scanning Calorimetry: After mixing Metformin HCl and tamarind seed polysaccharides (TSP) onset shifted to 221.74 °C and peak is 228.72 °C, which is acceptable as shown in **Fig. 2**.

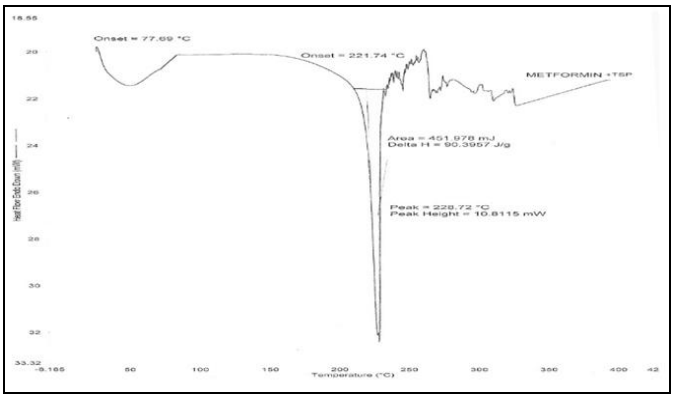

FIG. 2: DSC OF METFORMIN HCL AND TSP

Fourier Transform Infrared Spectroscopy (FTIR): FT-IR Spectroscopy studies of Metformin HCl, Metformin HCl with polysaccharide and only polysaccharide was carried out separately to find out the compatibility of the Metformin HCl with the polymer. The FT-IR spectra of pure Metformin HCl showed characteristics peak at for the presence of respectively which are also present in the combination of Metformin HCl and polymer indicating the compatibility of Metformin HCl with Tamarind Seed Polysaccharides polymer, shown in **Fig. 3**.

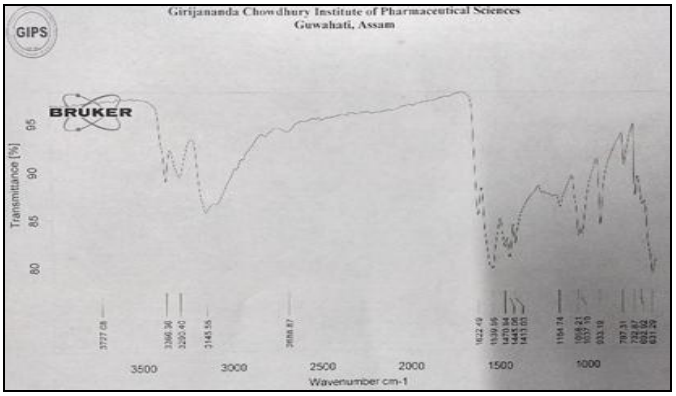

FIG. 3: FTIR STUDY OF DRUG AND POLYMER

Evaluation of Tablets: Before preparing the batches of tablets, several pre-compression parameters were evaluated for the granules used in the formulation of tablets. Some of the pre-compression parameters evaluated were the angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index and mentioned in **Table 4**. The tablet formulations were evaluated for thickness, hardness, friability, weight variation, % of drug content, and shown in **Table 5**.

TABLE 4: PRE-COMPRESSION PARAMETERS OF ALL GRANULES

Formulation code	Angle of repose (ɵ°)	Bulk Density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)
F-1	22.45	0.456	0.534	1.09	9.02
F-2	23.67	0.461	0.578	1.16	11.23
F-3	25.21	0.421	0.532	1.05	9.67
F-4	23.87	0.498	0.578	1.17	12.44
F-5	24.44	0.454	0.545	1.09	11.06
F-6	26.01	0.429	0.578	1.20	13.32
F-7	24.56	0.478	0.588	1.27	16.53
F-8	26	0.498	0.591	1.07	10.76
F-9	28.23	0.467	0.567	1.23	11.03

TABLE 5: POST COMPRESSION PARAMETERS FOR ALL FORMULATIONS

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation	% of Drug content
F-1	4.2±0.02	4.5±0.2	0.23±0.01	907±0.6	97.55±0.27
F-2	4.2±0.04	4.8±0.2	0.26±0.02	906±0.5	97.33±0.48
F-3	4.3±0.02	4.8±0.8	0.25±0.01	908±0.3	96.55±0.78
F-4	4.4±0.03	5.2±0.4	0.18±0.04	907±0.01	97.62±0.44
F-5	4.3±0.04	5.6±0.4	0.16±0.06	905±0.05	98.54±0.58
F-6	4.2±0.02	6.2±0.1	0.11±0.01	906±0.04	98.56±0.18
F-7	4.2±0.05	5.9±0.5	0.14±0.03	906±0.06	98.35±0.45
F-8	4.3±0.02	6.4±0.3	0.8±0.07	906±0.04	96.58±0.48
F-9	4.2±0.03	5.8±0.7	0.13±0.01	907±0.03	98.54±0.36

Drug Release: Maximum % cumulative drug release was observed in F5. Minimum % cumulative drug release was observed in F1. The concentration of polymer varies the release of the drug and shown in **Table 6**.

TABLE 6: CUMULATIVE PERCENT DRUG RELEASE DATA

Time (h)	% Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	21.58±0.94	19.96±0.75	16.87±0.05	13.92±0.88	11.53±0.25	14.34±0.75	13.21±0.75	8.507±0.13	12.16±0.06
1	44.15±0.25	36.35±0.56	26.92±0.69	25.52±0.44	21.02±0.44	26.22±0.56	23.27±0.44	22.28±0.06	24.04±0.88
1.5	57.65±0.25	55.12±0.05	42.04±0.88	39.58±0.94	38.50±0.25	41.06±0.25	41.00±0.25	38.10±0.38	38.53±0.25
2	75.44±0.31	61.45±0.13	54.63±0.81	45.35±0.56	56.74±0.19	54.07±0.31	50.41±0.06	49.71±0.94	51.60±0.38
3	84.86±0.19	75.44±0.31	63.14±0.63	51.39±0.44	66.79±0.88	58.71±0.94	57.09±0.75	61.10±0.56	59.20±0.13
4	93.58±0.99	87.32±0.13	69.25±0.81	57.79±0.88	73.12±0.05	65.60±0.56	63.77±0.44	72.56±0.25	61.52±0.44
5		97.24±0.19	83.53±0.25	74.39±0.63	78.67±0.69	73.26±0.63	72.49±0.19	79.24±0.19	65.53±0.25
6			94.35±0.38	84.86±0.19	84.86±0.19	77.83±0.94	77.90±0.25	83.60±0.56	73.82±0.13
8				91.19±0.31	90.28±0.25	85.00±0.81	83.60±0.56	88.94±0.31	76.21±0.75
10					98.08±0.94	91.19±0.31	92.60±0.56	94.21±0.75	87.96±0.94
12						98.01±0.63	97.59±0.75	97.80±0.69	97.24±0.19

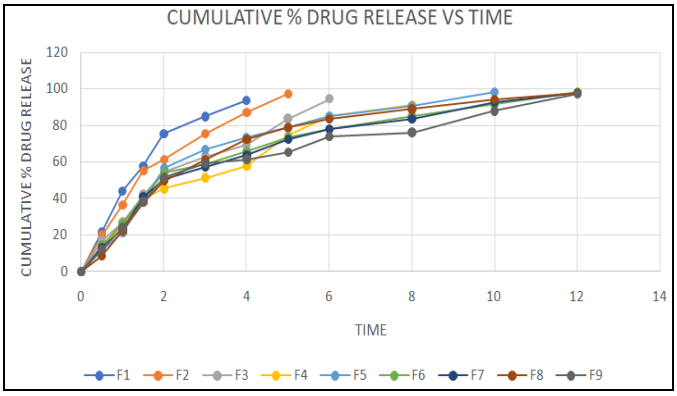

FIG. 4: CUMULATIVE % DRUG RELEASE CURVE

The *in-vitro* dissolution studies were carried out for all the formulations from F1-F9 in USP apparatus type II using dissolution mediums phosphate buffer pH 6.8. The release data were noted for 12 h for all the formulated batches. The result showed that with the varying concentration of polymer, the release of the drug showed a sustained pattern. Formulation F1 containing 10% of the polymer showed 4 h to release 93%, *i.e.* approximately 100% of the drug.

Similarly, the formulations F2, F3, F4, F5 got released at 5, 6, 8, 10 h and F6, F7, F8, F9 showed sustained release pattern till 12 h approximately 98%. Thus, with increase % of the polymer, the release time was seen to be extended together with a polymer. It was confirmed that by increasing the

concentration of polymer the release of drug is extended because of slower erosion and increased viscosity which kept the gel network intact for 12 h with a higher proportion of polysaccharide and release profile shown in **Fig. 4**.

Optimization of Tablets: The R^2 value and model constant of the corresponding mathematical model were given in **Table 7**. From the zero-order and First-order plot it can be easily understood that with an increasing percentage of polymer, the more retardation of drug release occurred as seen in F1 to F7. The best release was seen in the case of F6. But linearity was observed with Higuchi equation indicating that drug release by diffusion through swellable matrix. The n values of the formulations were found to be 0.9313.

Thus as the n value of F6 falls in the range of 0.5-1.0, it follows anomalous non-fickian drug diffusion occurs *i.e.* combination of both diffusion or swelling as well as erosion mechanism in case of Higuchi model. So F6 can be considered as optimized formulation.

TABLE 7: KINETIC PARAMETERS OF ALL FORMULATIONS

FA	Zero-order		First Order		Higuchi Model		Korsmeyer-Peppas Model	
Code	K_0	R^2	K_1	R^2	K_H	R^2	n	R^2
F1	17.766	0.8448	0.4643	0.5448	48.422	0.9568	0.8367	0.9292
F2	15.358	0.8835	0.3463	0.4368	47.535	0.9661	0.5228	0.9078
F3	13.36	0.9182	0.3141	0.5377	36.535	0.9624	0.7734	0.9601
F4	11.144	0.9518	0.2641	0.5281	35.878	0.9714	0.5693	0.9621
F5	9.5112	0.7915	0.2314	0.4949	33.324	0.929	0.6762	0.8881
F6	7.2352	0.7808	0.1986	0.4429	26.65	0.9313	0.6844	0.8534
F7	5.5837	0.6962	0.0996	0.3711	27.04	0.8811	0.4637	0.7846
F8	6.4099	0.7175	0.1039	0.4439	29.00	0.9002	0.6818	0.8098
F9	5.5539	0.848	0.1165	0.4444	28.244	0.9564	0.7329	0.8947
Marketed	7.6347	0.8478	0.0931	0.4021	29.457	0.9597	0.5001	0.9098

The R^2 values for the marketed formulation were also carried out as given in **Table 7**. The marketed formulation was found to follow Higuchi model thus, and the values falls in the range of 0.5-1.00 which indicates it follows anomalous non-fickian drug diffusion occurs, *i.e.* combination of both diffusion or swelling as well as erosion mechanism in case of Higuchi model. Thus F6 was compared with the marketed formulation, and the release was found to be equivalent with that of the standard marketed formulation.

Stability Study: The stability study of optimized tablets (F6) was carried out according to ICH guidelines at 40°C ± 2°C/75 ± 5% RH for three months by storing the samples in stability chamber and result displayed in **Table 8**. [17]

TABLE 8: STABILITY STUDIES DATA

Formulation	Duration of Period	Drug Content (%)	Hardness (Kg/cm^2)	Friability (%)
F6	One Month	98.44±0.18	6.1±0.8	0.14±0.02
	Two Month	98.21±0.23	6.1±0.5	0.14±0.06
	Three Month	98.02±0.21	6.1±0.1	0.15±0.02

CONCLUSION: The research work was carried out successfully. The tablets were prepared by wet granulation technique using different drug-polymer ratios. Before compression, the granules were evaluated for pre-compression parameters, and then the tablets were evaluated for post-compression parameters. The results were found satisfactory for some of the formulations. Then *in-vitro* release studies were carried out for 12 h, and the release studies showed release approximately 100%. From which formulation F6 with polymer concentration, 30% was found to be optimized formulation as it showed better-sustained release of the drug. With the values obtained from drug release with time different release kinetics model equations were carried out and depicted in **Table 7**, it was found that the optimized formulation F6 and marketed formulation both followed Higuchi model of release, *i.e.* anomalous non-fickian drug diffusion occurs, *i.e.* combination of both diffusion or swelling as well as erosion mechanism as the values came within the range of 0.5-1.00.

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CONFLICTS OF INTEREST: Nil

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