Section: Research Paper

Formulation Development and Evaluation of Immediate Release for The Treatment of Diabetes Mellitus of Teneligliptin

Pankaj Kumar Sharma[1], Rabnoor Alam[1]*, Kamini Sharma[1]

Raj Kumar Goel Institute of Technology (Pharmacy),5th KM Stone, Delhi-Meerut Road, Ghaziabad, Uttar Pradesh, India

***Corresponding Author**
RabnoorAlam
Raj Kumar Goel Institute of Technology (Pharmacy),
5th KM Stone, Delhi-Meerut Road,
Ghaziabad, Uttar Pradesh, India

Abstract

Teneligliptin instant release tablets were developed and evaluated as part of this study utilizing a wet granulation technique and various ratios of super-disintegrates and binder. It falls under Biopharmaceutical Classification System Class II. The results of the early pre-formulation experiments were found to be within the bounds. All of the aforementioned batches were made, and the granules' pre-compression characteristicssuch as loss on drying, bulk density, tapped density, and compressibility indexwere assessed. Tablets' weight fluctuation, thickness, hardness, and friability were assessed; the assay and disintegration time were found to be within acceptable ranges. The effects of several superdisintegrants were investigated during in vitro dissolutions in a 6.8 PH phosphate buffer. The formulation F8 revealed a 91% drug release within 30 minutes, according to dissolving studies, which were used to make the final formulation choice. In vitro drug release was demonstrated by formulation (F8), which contained 2% each of polyplasdone XL 10 and meglumine and 20% binder, according to similarity and difference characteristics. The in vitro drug release profile shows that there was an increase in drug release with increased concentrations of polyplasdone XL 10 and meglumine 2% and decreased binder concentration (20%). For the optimized batch, accelerated stability investigations were carried out, and the results showed that the drug content and in vitro dissolution were unchanged.

Keywords: Teneligliptin, Immediate Release Tablets, Wet Granulation Method, Dissolution Test, Stability Study.

Introduction

The need for new oral drug delivery system continues, due to poor patient acceptance for invasive methods, need for exploration of new market for drugs and coupled with high cost of disease

management. Developing new drug delivery techniques and utilizing them in product development is critical for pharma companies to survive this century. This is reflected by the fact that well over 80% of the drugs in the United States that are formulated to produces systemic effects are marketed as oral dosages forms [1].

Immediate release dosage form is those which disintegrate rapidly and get dissolved to release the medicaments [2]. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption [3]. This term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug [4].

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates [5]. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour. To enhance dissolution and hence bioavailability of any drug from immediate release tablets, disintegration is one of the important process. Few Super-disintegrants are available commercially as Croscarmellose sodium, Crospovidone and SSG [6].

Several Technologies are available to manufacture immediate release tablets. The most common preparation methods are moulding, lyophilisation or freeze drying, direct compression, spray drying and sublimation. Direct compression, is one of the techniques that requires the incorporation of a superdisintegrants into the formulation. Direct compression does not require the use of water or heat during the formulation procedure and is very sensitive to changes in the type and proportion of excipients and the compression forces, when used to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics [7].The objective of present study is to develop orodispersible tablets of teneligliptinusing different types of super disintegrants to enhance the disintegration and dissolution of teneligliptin to improve bioavailability of the drug.

Material and method

Teneligliptin was received as a gift sample from systoptic laboratories private limited (Delhi). Mannitol, magnesium stearic acid was obtained from central drug house (P) Ltd (New Delhi India). Microcrystalline Cellulose 101 (Avicel 101) grade was obtained from sherincrops solution. Starch 1500 & Maize Starch Ashland obtained from Aqualon functional ingredients. Poly plasdone XL 10 Crospovidone& Poly plasdone XL 100 Crospovidone were obtained fromsystoptic laboratories. Remaining all other chemicals was obtained fromSherincorps Solutions Inc., Indore, India. All chemicals and solvents used were of analytical grade.

Drug Excipient compatibility study

Compatibility studies were carried out to explore and forecast physicochemical interactions between drug substance and excipients by generating compatibility blends with varying ratios of excipients to drug premised on a tentative ideal weight. These mixtures were kept at 40 degrees Celsius and 75 percent relative humidity for one month. The drug-to-excipient ratio ranges from 1:1

to 10:1.The samples' physical features were examined compared to a control sample maintained at 4 ^{0} C for 7, 14, and 30 days.Chemical compatibility is determined by FTIR spectrometry, which is the most powerful approach for identifying the drug's functional groupsThe analysis was conducted using an FTIR (thermo Nicolet 670 spectrometer) in the frequency range of 4000-400cm2 resolution. The investigation involved the usage of a quantity equal to 1 gram of pure medicines. The disc (pellet) technique of potassium bromide was used in this investigation.

Method.

Wet granulation process is used to make immediate-release tablets.

Teneligliptin, Mannitol and Microcrystalline Cellulose (Accel- 101) were co-sifted through # 36 sieve and mixed thoroughly in a poly bag.

Transferred the sifted material into the RMG and mixed for 15 minutes.

Binder solution was prepared by dissolving Starch in purified water.

Binder solution was added slowly to dry mix in Fluid Bed Drier bowl.

Dried the wet granulate in fluid bed dryer at an inlet temperature of 35° - 40°C till the desired LOD of 2.0 –3.0 %w/w was achieved.

Sifted the dried granules through # 22 sieves.

Polyplasdone XL was sifted through # 36 sieve and geometrically mixed and collected in a polybag.

Load the dried, sized granules in to the Octagonal blender and Blended for 20 minutes.

Magnesium stearate was sifted through # 56 sieve, added to the blend and mixed for 5 minutes.

Granules were compressed using compression machine with lubricated blend, employing appropriate punch tooling [8].

Evaluation of flow property of prepared granules

Angle of repose

The funnel method was used to determine the angle of repose of API powder [9]. Angle of repose is defined as the greatest feasible angle between the surface of a powder pile and the horizontal plane. The funnel was filled with the precisely measured powder combination. The funnel's height has been changed such that it is 2.5 cm above the surface level. The powder mixture is allowed to freely flow through the funnel and onto the surface. The diameter of the powder cone is measured, and the same operation is repeated three times, with the average value collected. Equation is used to determine the angle of repose [10].

Angle of Repose (θ) =Tan -1 (h/r)

Where, h = height of pile

r = radius of the base of the pile

θ = angle of repose.

Bulk density determination

A weighed quantity of the powder (W) is placed in a graduated measuring cylinder, the volume (V0) is measured, and the bulk density is determined using the formula [11].

Bulk density (BD) = W/ Vo

W=Weight of the powder

VO=Volume of powder

Tapped density determination

The powder sample undergoing examination was screened via sieve No.18, and a 100 mL graduated cylinder was filled with the weight of the sample, which was equal to 25 grammes. The mechanical tapping of the cylinder was done at a nominal rate for 500 times using a tapped density tester, and the tapped volume Vo was recorded. Vf is deemed tapped volume when the difference between two tapping volumes is less than 2%. The tapped density, Hausner's ratio, and Carr's Index were calculated using the volume of the mix [12].

Tapped density (TD) = W/ Vf g/ml

W=Weight of the powder

Vf=Volume of powder

Carrs index or % compressibility

Carr's index is often referred to as compressibility.It's linked to relative flow rate, cohesion, and particle size in an indirect way. The formula for calculating Carr's index was used [13].

Carr‟s Index(%) = (Tapped Density –Bulk Density) x100 /Tapped Density

Hausner ratio

Hausner's ratio, defined as the ratio of tapped density to bulk density, reveals the flow qualities of the powder [14].

Hausner‟s Ratio = Tapped density / Bulk density.

Evaluation of post compression parameter of prepared Tablet

1. **Thickness**
   Digital verniercallipers were used to measured the thickness of the tablets. The findings were averaged from ten individual pills from each batch. It should be within 5% of a standard value's range of variation [15].The outcomes were given in mm.

2. **Weight variation**
   Twenty tablets were haphazardly chosen from each bunch and separately gauged [16]. The standard deviation and average weight were computed. The test for weight variety is passed provided that not more than two of the singular tablet loads stray from the normal load by more than the permitted rate deviation and none deviate by over two times the rate shown.

3. **Hardness**
   To determine the average tablet hardness or crushing strength, ten tablets from each batch were chosen and their hardness was evaluated using a Digital hardness tester [17].

   Hardness should be in between 3-6 kg/cm^2.

4. **Friability**
   A Roche friabilator was used to determine the tablet's friability values [18].It is communicated in %. 20 tablets were at first gauged (starting weight) and moved to friabilator. Friabilator was worked at 25 rpm for 4 min. The following equation was used to compute the percentage friability. Friability of tablets under 1% was thought of as satisfactory.

   % Friability = initial weight - final weight ×100 Initial weight

5. **Disintegration Time**
   Six tablets were taken arbitrarily from each bunch and set in USP breaking down contraption crates, which is more than once drenched 30 times each moment into a thermostatically controlled liquid at 37°C and seen throughout the time portrayed in the singular monograph. The tablets must entirely disintegrate into a mushy mass with no discernible solid core in order to pass the test. Immediate delivery tablets ought to have the option to deliver the medication within 1min [19].

6. In vitro dissolution test

The disintegration investigations of the pre-arranged tablets were conveyed utilizing Electro lab device II[20].Disintegration was acted in 900 ml phosphate buffer of pH 6.8 at 37 ± 0.5°C at 50 rpm.An autosampler, coupled to the dissolution mechanical assembly was modified to pull out and supplant 10 ml of the disintegration media at 0, 5, 10, 15, and 30 min.Around 80% of the medication ought to be delivered inside 15 min.

Dissolution parameters

Medium	:	Phosphate buffer,
pH 6.8 Volume	:	900 ml
Apparatus	:	Dissolution apparatus type II of USP (paddle)
Rotation speed	:	75 rpm
Temperature	:	37 ±0.5°C

7. Drugs release Kinetic (Dependent Model Mothed)

The kinetics and mechanism of drug release from tablets are evaluated using mathematical models.Based on the correlation coefficient (r) value in several models, the model that best matches the release data is chosen.The model with the highest "r" value is judged to be the best fit to the release data [8].

Mathematical models are

1) Zero order release model
2) First order release model
3) Higuchi release model
4) Korsmeyer – peppas release model

8. Wetting Time

The measurement structure's wetness season is influenced by the contact point. The wetting time of an oral dissolving tablet, which reveals information about capillarity and, consequently, the characteristics of how quickly the tablet will deteriorate, is another important trademark to examine. The tablet may likely disintegrate more quickly if the soaking time is shorter.The wetting time was determined using the method that was provided.A small Petri dish with an ID of 6.5 cm and 6 ml of room temperature water was filled with a piece of tissue paper that had been folded over twice.A tablet was embedded on the tissue paper and given permission to hold the entire fluid. The following section was then preserved as the amount of time it took to completely dampen the tablet.

RESULT AND DISCUSSION

Evaluation of Granules:

Table 1: Formulation table of teneligliptin tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Teneligliptin	20	20	20	20	20	20	20	20	20
Mannitol	1	1	1	1	1	1	1	1	1
Magnesium steric acid	1	1	1	1	1	1	1	1	
Microcrystalline Cellulose 101	46	41	46	41	46	41	46	41	44
Starch 1500	------	------	10	15	-----	10	-------	15	10
Maize starch	10	15			10		10		
Polyplasdone XL 10	20	20	20	20	20	20	20	20	20
Meglumine	1	1	1	1	1	1	1	1	1
Lactose monohydrate	1	1	1	1	1	1	1	1	1
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	100	100	100	100	100	100	100	100	100

Table 2: Preformulation studies

S.No.	Test	Specification	Result
1	Description	White to Light Tan Solid	White powder
2	Solubility	Freely soluble in methanol and DMSO, slightly soluble in ethanol, very slightly soluble in water	Complies
3	Loss on drying	Not more than 0.5%	0.35%
4	Melting point	188-190 °C	189.2 °C
5	Drugs identification	Performed by FTIR	Found group identification
6	Identification of λmax max	Based on highest peak	Found at 243.5 nm

Table 3: identification with FTIR

S.No.	Type of stretching vibrations	Frequency (cm^2)
1	Aromatics (C-H)	3300

2	C-H	3100
3	N-H	3400

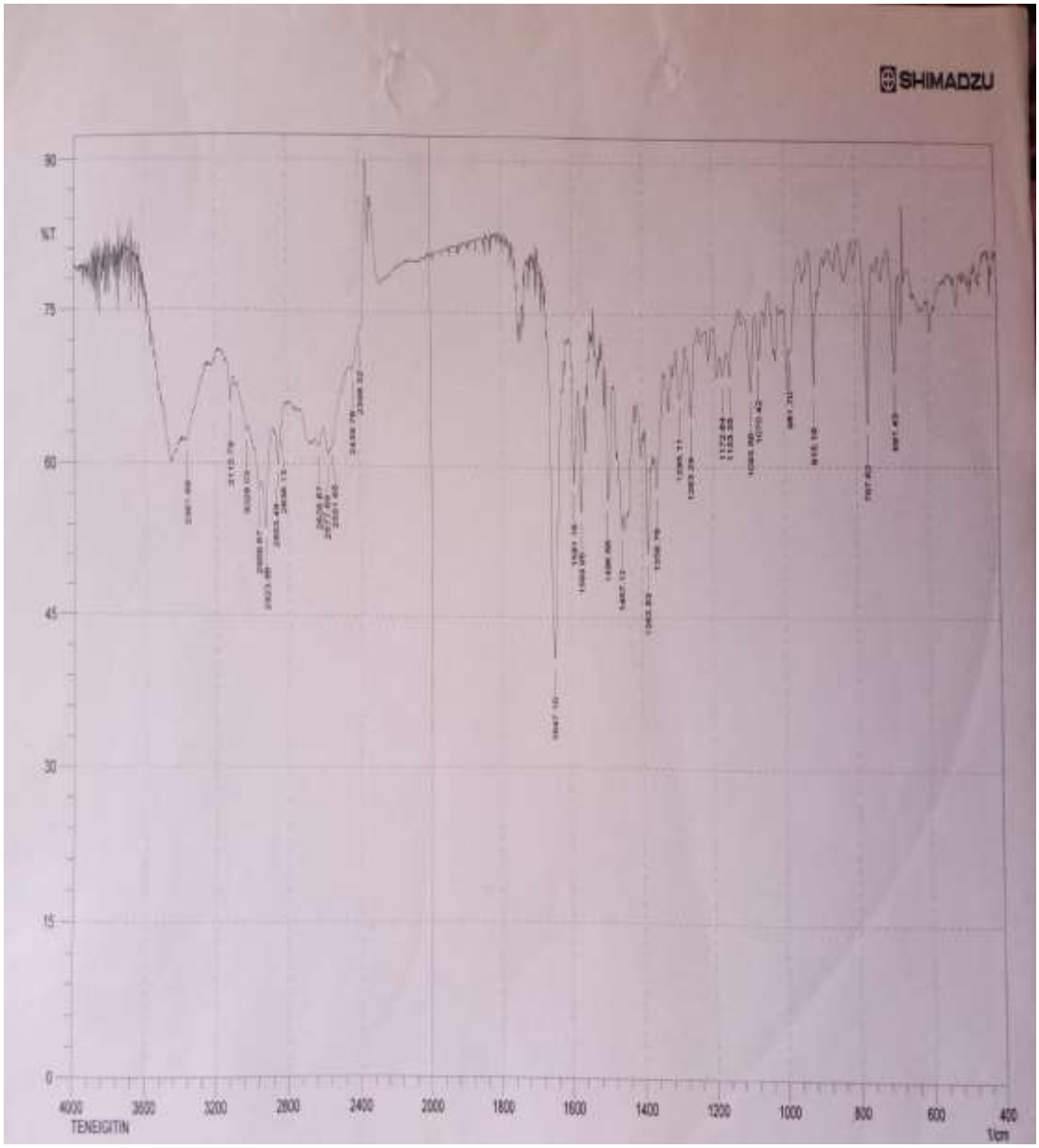

Fig 1: IR Spectra of pure drug sample (teneligliptin)

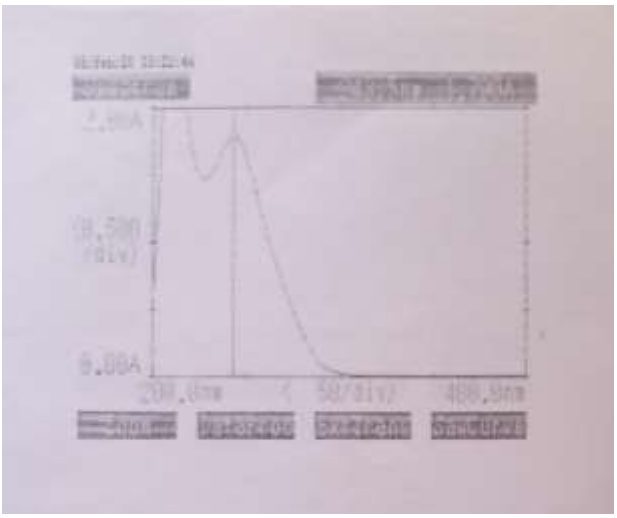

Fig 2: Spectral analysis of teneligliptin in methanol

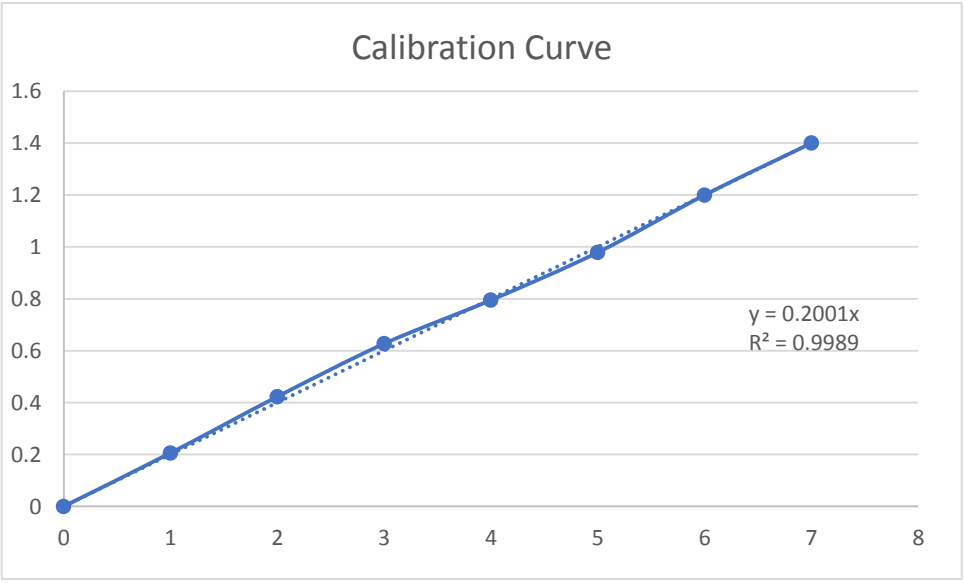

Fig 3: Calibration curve of teneligliptin in methanol

Table: Statical parameter derived from calibration curve

Statistical Parameter	In methanol
R^2	0.9997
Slope	0.2001
Equation line	Y= 0.2001x+0.9997

Table 4: Evaluation of Pre compression Parameter

Batch No.	Bulk density	Tapped density	Carr's index	Hausner Index
F1	0.25	0.294	14.147	1.176
F2	0.277	0.312	11.217	1.126

F3	0.263	0.33	20.303	1.254
F4	0.238	0.25	32	1.470
F5	0.227	0.32	29.503	1.418
F6	0.266	0.30	13.355	1.154
F7	0.272	0.31	13.650	1.158
F8	0.260	0.3	13.333	1.153
F9	0.279	0.31	11.428	1.129

Table 5: Evaluation of post compression parameters

Batch No.	**Average weight (mg)**	**Hardness ($kg/cm^{2)}$**	**Thickness (mm)**	**Friability (%)**	**D.T (min)**	**Assay (%)**
F1	99.58±1.43	2.13±0.268	2.75±0.01	0.24	1.2	97.8
F2	99.9±1.32	2.76±0.272	2.27±0.05	0.17	1.50	99.4
F3	100.2±1.34	2.115±0.37	2.06±0.02	0.21	55 sec	98
F4	99.83±1.41	3.065±0.356	2.176±0.08	0.23	1.03	101.8
F5	100.0±1.35	2±0.215	2.71±0.07	0.18	50 sec	99.7
F6	100.23±1.48	2.7±0.304	2.29±0.013	0.19	1.04	98.9
F7	99.51±1.38	2.1±0.308	2.156±0.016	0.20	39 sec	102.3
F8	99.96±1.33	3.05±0.215	2.235±0.012	0.22	42 sec	99.9
F9	100.25±1.44	2.18±0.402	2.245±0.015	0.18	1.09	99.1

Evaluation of tablets

The normal load of the table was viewed as in the spectrum of 100.25±0.44 to 99.58±1.43 mg. Thickness in the spectrum of 2.245±0.015 to 2.75±0.01 mm, Hardness 3.065±0.356 to 2±0.215 kg/cm^2, and friability were 0.24 to 0.17%. The disintegration time of the tablet is reached 39 sec to 1.50 min and analyzed in the scope of 97.8 to 102.3%. From the above outcome, all the formulations showed uniform thickness, the hardness of the tablet was palatable and the rate of friability for all the detailing was below1% demonstrating that friability is inside as far as possible. Great and uniform drugs content (>99) was seen inside the bunches of various tablet formulations.

In vitro Dissolution Studies

Tablet mixes were ready and micrometric reads up were done for those mixes. Pre-compressional boundaries, for example, bulk density, tapped density, compressibility index, and Hauser‟s index for actual combinations of immediate delivery definitions (F1 - F9) were assessed. The calibration curve was built having a regression value of 0.9997. Test upsides of the formulation were seen in the scope of 97.8 to 102.3%. Similarity studies were performed and it was seen that every one of the fixings utilized was viable with the d. Formulation (F8) was formed by including 2 % polyplasdone XL 10 and magnesium steric acid each and 20% binder. The outcomes showed disintegration down was inside limits and 100 percent drug discharge was viewed as in 30min. Thus, plan (F8) was taken as an upgraded definition. Sped-up security reads were performed for this bunch. Measure and disintegration read were performed for the advanced plan (F-8) at various time spans. Every

one of the boundaries was viewed as agreeable, disintegration studies were performed and it was observed that detailing F8 has shown the best outcomes.

Table 6: Dissolution profile of different formulation (F1-F3)

Time (min)	F1	F2	F3
5	22.49±0.13	18.61±0.67	29.9±0.28
10	35.70±0.59	33.18±0.89	49.1±0.25
15	41.2±0.49	38.62±0.59	57.9±0.035
20	47.1±0.48	43.64±0.53	64.7±0.73
30	52.7±0.52	49.94±0.72	78.23±0.14
45	57.6±0.55	54.7±0.22	82.7±0.83
60	79.9±0.32	72.4±0.64	91.7±0.23

Table 7: Dissolution profile of different formulation (F4-F6)

Time (min)	F4	F5	F6
5	27.4±0.73	21.85±0.55	18.98±0.56
10	43.8±0.25	39.54±0.26	34.89±0.05
15	51.6±0.37	42.032±0.77	41.54±0.36
20	58.6±0.29	50.99±0.59	46.58±0.78
30	69.17±0.89	53.98±0.47	48.94±0.48
45	74.7±0.39	58.89±0.32	56.47±0.25
60	84.14±0.83	82.07±0.38	79.64±0.71

Table 8: Dissolution profile of different formulation (F7-F9)

Time (min)	F7	F8	F9
5	33.03±0.56	33.03±0.28	27.67±0.63
10	54.61±0.23	65.68±0.39	45.178±0.023
15	59.6±0.46	76.64±0.33	58.96±0.37
20	68.09±0.42	82.39±0.85	69.83±0.16
30	79.90±0.29	91.86±0.42	81.64±0.34
45	84.42±0.53	99.03±0.78	84.87±0.21
60	93.13±0.89	99.52±0,54	92.12±0.16

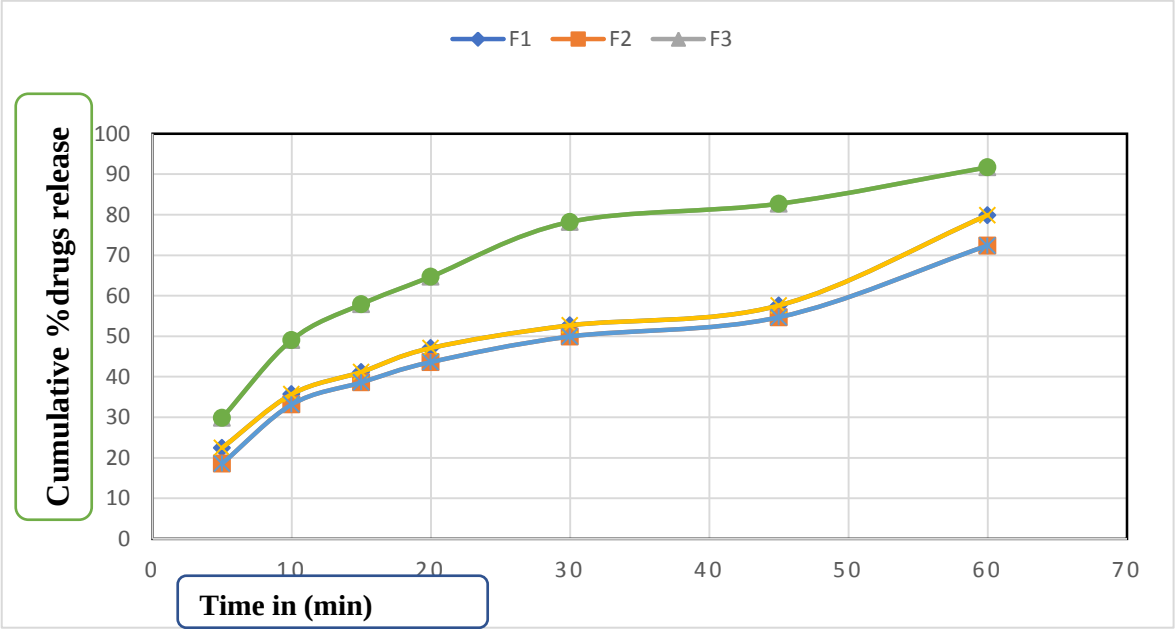

Fig 4: In vitro drug Release Profiles of F1-F3 Formulations

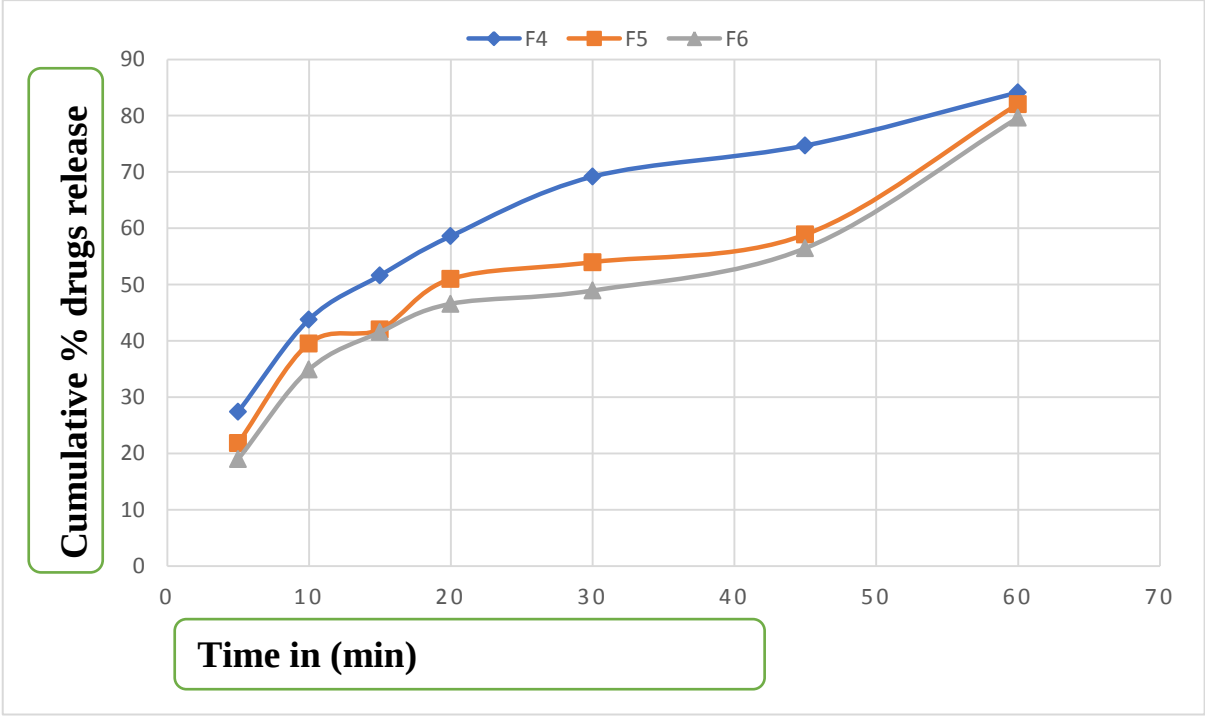

Fig 5: In vitro drug Release Profiles of F4-F6 Formulations

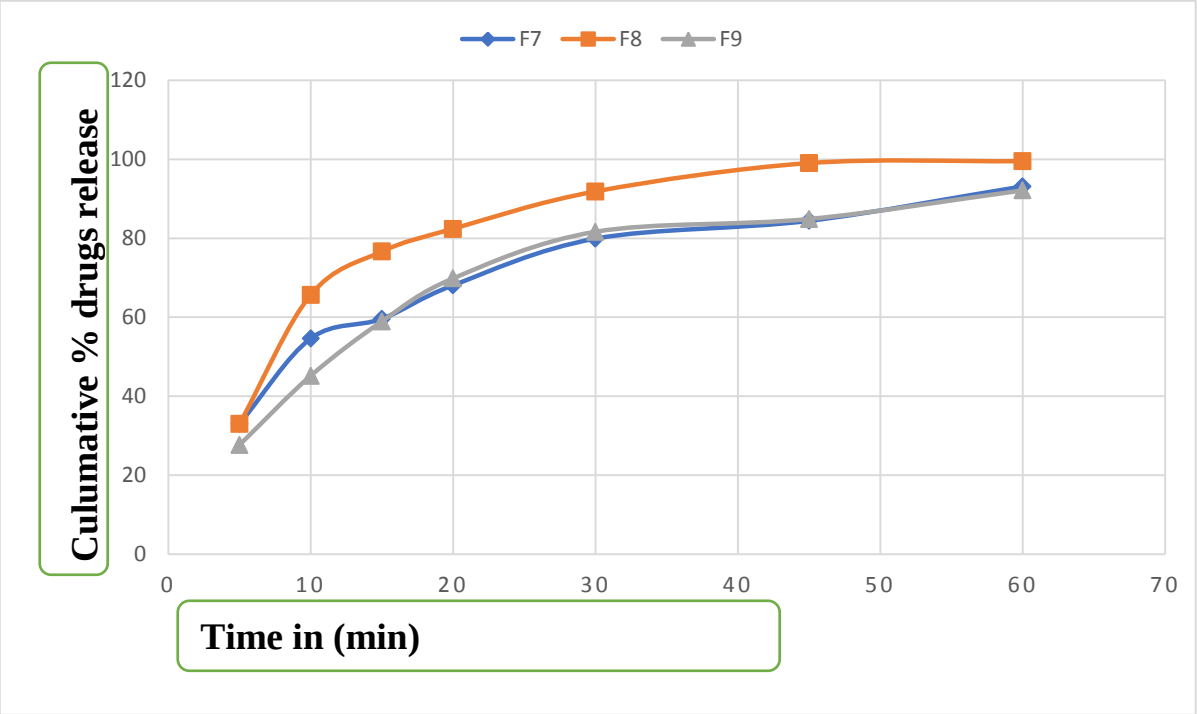

Fig 6: In vitro drug Release Profiles of F6-F9 Formulations

Table 9: Drugs release Kinetic & Mechanism

Formulation	Zero order	First order	Higuchi order	KorsmeyPeppas Order
F1	0.9316	0.9056	0.9461	0.9319
F2	0.9316	0.9056	0.9461	0.9319
F3	0.9316	0.9056	0.9461	0.9319
F4	0.9316	0.9056	0.9461	0.9319
F5	0.9316	0.9056	0.9461	0.9319
F6	0.9316	0.9056	0.9461	0.9319
F7	0.9316	0.9056	0.9461	0.9319
F8	0.9316	0.9056	0.9461	0.9319
F9	0.9316	0.9056	0.9461	0.9319

Figure 7: Zero order release model

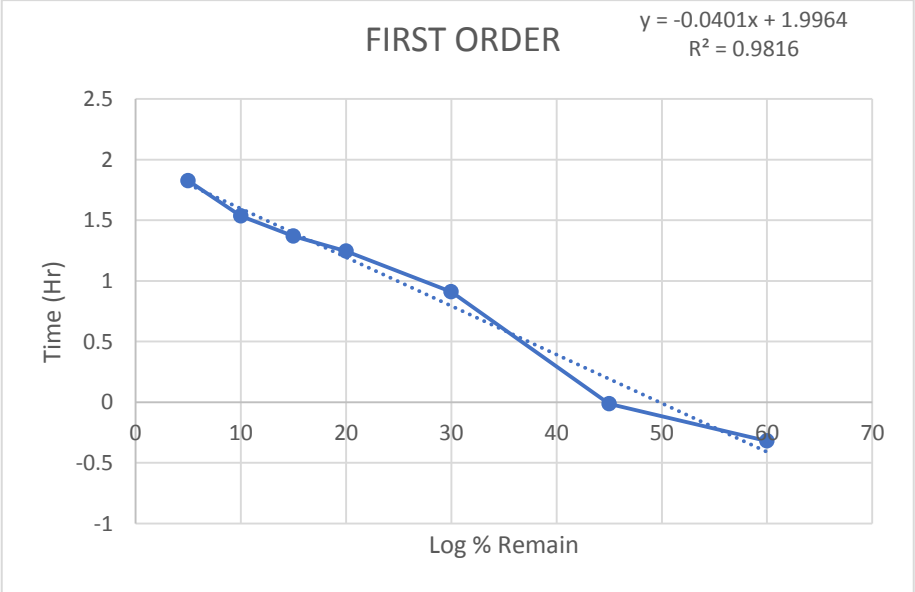

Figure 8: First order release model

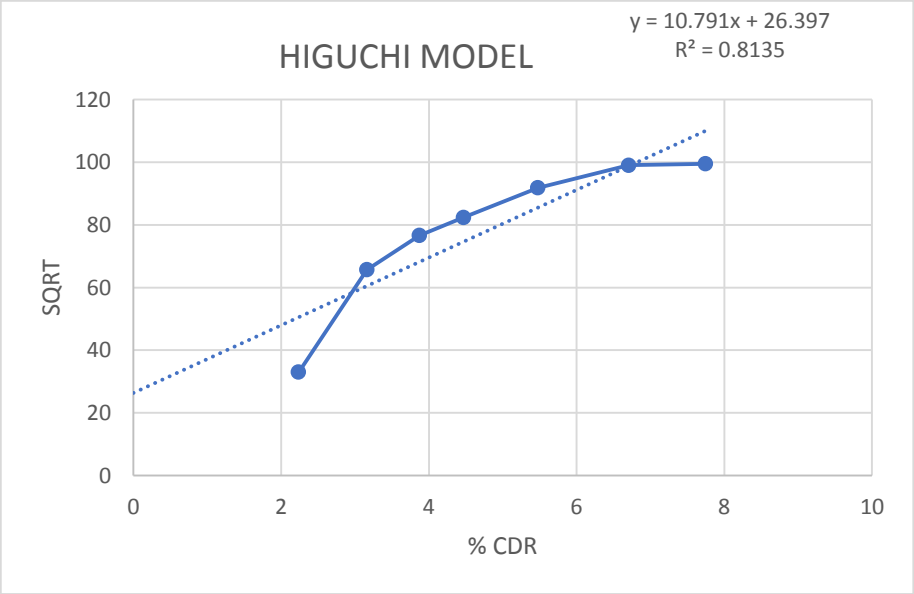

Figure 9: Higuchi release model

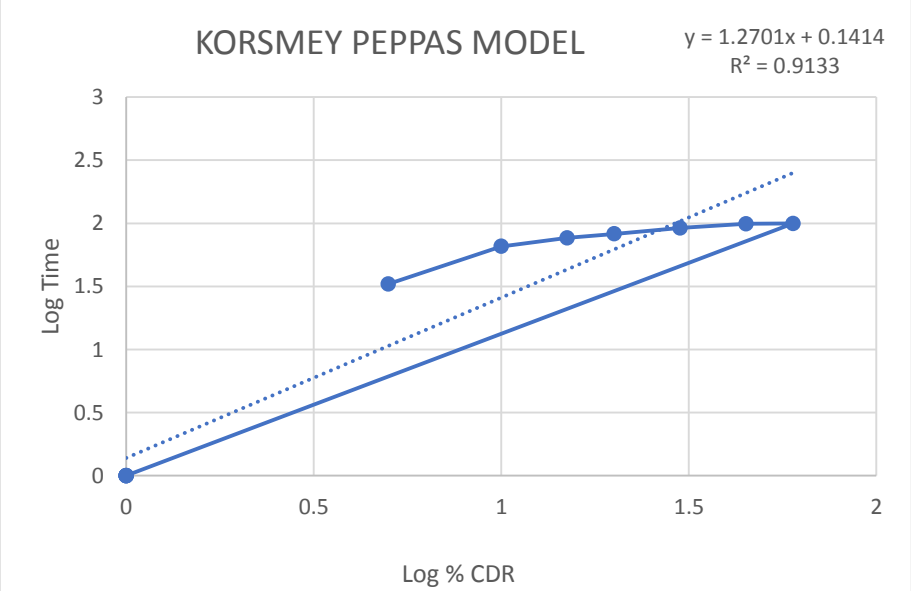

Figure 10: Korsmeypeppasrelease model

Stability research

According to ICH recommendations, stability testing on the chosen formulation (F8) was performed. indicated that over the study period, the tablets did not exhibit any physical changes, such as color change, friability, or hardness. At the end of 30 days, the drug content was discovered to be greater than 99%. This suggests that the formulation F8 tablets were reasonably stable under

accelerated storage circumstances. However, the produced product must be established for two years in real life for stability tests.

Table 10: Accelerated stability studies of optimized formulation (F8) At 40 ± 2^0 c &75±5%RH

S.NO.	Time period	% Drug release			
		Time (min)			
		10	15	20	30
1	Initial	63±0.23	83±0.72	92±0.28	98±0.32
2	1st month	65.7±0.58	82.2±0.69	92±0.53	99.7±0.17
3	2nd month	65.6±0.26	82.3±0.66	91.5±0.68	99.6±0.44
4	3rd month	65.3±0.36	81.8±0.32	91.4±0.47	99.3±0.54

CONCLUSION

From the aforementioned experimental findings, it can be inferred that several ratios and combinations of superdisintegrants and binders can be used to create quick-release tablets of teneligliptin. We chose F8 as the optimal formulation based on the dissolving profile and physical features. Compared to other formulations, formulation (F8) demonstrated complete drug release in 30 minutes and fair flow characteristics. Furthermore, the formulations F8, which are governed by first-order kinetics, show that Super case II transport was responsible for the release.

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