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Research Article

FORMULATION AND *IN-VITRO* EVALUATION OF ORO-DISPERSIBLE TABLETS OF TENELIGLIPTIN

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ABSTRACT

Objective: Teneligliptin is a newly advanced oral dipeptidyl peptidase 4 inhibitor used for the treatment of type 2 diabetes mellitus (T2DM) in adults alongside exercise and diet. In this study, Teneligliptin oro-dispersible tablets (ODTs) were developed to improve solubility and bioavailability.

Methods: In the present work, using various superdisintegrants such as Croscarmellose sodium, Sodium Starch Glycolate (SSG), and Crospovidone, a total of nine formulations of Teneligliptin ODTs were developed by the direct compression method. All the developed formulations were subjected to *in vitro* characterization and studied for various physicochemical properties, drug release studies, and release kinetics. The physical stability study was conducted on the optimized formulation for 6 months.

Results: All the developed formulations met the pharmacopoeial limits for weight variation, hardness, friability, and drug content. Among nine formulations, the F9 formulation showed the fastest disintegration time of 15 sec and 99.12% of drug release within 15 min. Based on the wetting time, disintegration, and drug release studies, the F9 formulation was selected as the optimized formulation. Further, the F9 formulation was stable for 6 months.

Conclusion: Teneligliptin ODTs were successfully prepared by the direct compression method using Croscarmellose sodium, SSG, and Crospovidone as superdisintegrants. The optimized formulation F9 showed the highest drug release and was stable for 6 months.

Keywords: Diabetes mellitus, oro-dispersible tablets, Superdisintegrants, Disintegration time, *In vitro* release.

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INTRODUCTION

Poor patient acceptability of invasive procedures, the need to investigate new medication markets, and the high expense of illness management have all contributed to the ongoing demand for innovative oral drug delivery systems [1].

An oro-dispersible medication delivery system is one of the most common ways to improve bioavailability and patient compliance [2]. Over the past three decades, more research has been conducted on oro-dispersible tablets (ODTs) than on conventional tablets and capsules because of their superior patient compliance, stability, and solubility. ODTs break down rapidly, typically in a matter of seconds, when placed in the mouth [3]. They dissolve rapidly because of their porous and melting character. The standard processes used to manufacture orally disintegrating tablets include sublimation, direct compression, tablet molding, and freezing and drying. ODTs have a very quick reaction time and takes a few seconds to a minute to disintegrate.

Teneligliptin is a recently developed oral dipeptidyl peptidase 4 inhibitor that is used in conjunction with diet and exercise to treat type 2 diabetes mellitus in adults. The chemical name of Teneligliptin is ([2S,4S]-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl)-3-thiazolidinyl-methanone [4,5]. It has limited solubility and limited absorption, which leads to low bioavailability of the drug [6]. The objective of the present study was to develop ODTs of Teneligliptin using different types of superdisintegrants to enhance the disintegration and dissolution of Teneligliptin to improve the bioavailability of the drug.

MATERIALS AND METHODS

Teneligliptin was received as a gift sample from Dr. Reddy's Laboratories Private Limited, Hyderabad. Magnesium stearate, Microcrystalline sodium, Sodium Starch Glycolate (SSG), Crospovidone, Croscarmellose sodium, Talc, and all other ingredients were purchased from Yarrow Chemicals and Pharmaceuticals (Mumbai, India).

Drug-excipient compatibility study

Differential scanning calorimetry (DSC 4000, PerkinElmer) was used to evaluate drug-excipient compatibility. A sample weighing 5–15 mg was placed in a punctured DSC aluminum pan and scanned over a temperature range of 50–300°C. The system was cooled using liquid nitrogen, and nitrogen gas was used as the purge. The heating rate was maintained at 10°C/min.

Formulation development of Teneligliptin ODTs [7]

In the present study, oral dispersible tablets of Teneligliptin were formulated using the direct compression method. All ingredients listed in Table 1 were accurately weighed and processed in a geometrical mixing order. Teneligliptin, mannitol, and the selected superdisintegrants were first passed through a #22 sieve and blended for 15 min. Magnesium stearate, previously sieved through a #60 mesh, was then added and mixed with the blend for an additional 5 min. The final mixture was compressed into tablets weighing 100 mg each using 8 mm round flat punches on a 16-station rotary tablet press. The composition of the formulations is detailed in Table 1.

Evaluation of Teneligliptin ODTs [8]

Weight variation

All the formulations were evaluated for uniformity of weight. Twenty tablets were randomly selected from each formulation and weighed using a Shimadzu digital balance. The mean standard deviation values were calculated.

Table 1: Composition of Teneligliptin oro-dispersible tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Teneligliptin	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose	45	40	35	45	40	35	45	40	35
Croscarmellose sodium	5	10	15	--	--	--	--	--	--
Sodium Starch Glycolate	--	--	--	5	10	15	--	--	--
Crospovidone	--	--	--	--	--	--	5	10	15
Mannitol	23	23	23	23	23	23	23	23	23
Aspartame	2	2	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100

Hardness

The Monsanto hardness tester was used to measure the hardness of tablets. A tablet is placed in the hardness tester, and the force needed to crush it is measured. The tablet takes longer to dissolve because of its increased hardness. Compared to other tablets, ODTs are less firm. Uncoated tablets with a hardness of about 3–5 kg/cm^2 are deemed adequate, and the force is expressed in kilograms.

Friability

The Roche friabilator is used to measure a tablet's mechanical strength. The tablets were dropped six inches apart with each revolution in a plastic chamber that rotates at a rate of 25 revolutions/min. The tablets are swapped out in the friabilator for a minimum of 4 min. After the test, the tablets are reweighed and dusted. The percentage decrease in tablet weight is used to quantify friability.

% Friability = (loss in weight/Initial weight) × 100

Drug content

Tablets were randomly selected, weighed, and finely powdered, and the quantity of powder equivalent to one tablet was added to the pH 6.8 Phosphate buffer solution in a conical flask and placed on a rotary shaker. An aliquot of the solution was centrifuged, and the supernatant was filtered. Absorbance of the resulting supernatant solution was measured. The concentration of the drug present in one tablet was calculated.

Disintegration Test

Six tablets were used in the test, which was conducted at 37°C with distilled water as the disintegration medium. The amount of time in seconds it took for the tablet to completely dissolve and leave no solid mass in the device was noted.

Wetting Time

The wetting time of a fast-dissolving oral tablet is another crucial aspect to look into to comprehend capillarity and, in turn, the disintegration characteristics of the tablet. The tablet will dissolve more quickly if the wetting time is shorter. The given approach was used to compute the wetting time. A piece of tissue paper that had been folded twice was put in a small Petri dish (I.D=6.5 cm) with 10 mL of water. A pill was placed on the tissue paper and left to absorb the entire liquid. The time required for the tablet to become fully moistened was recorded in seconds.

Thickness

The tablet's thickness was measured using a Vernier caliper. A tablet was placed between two Vernier caliper arms to measure thickness, and the tablet's thickness was noted in millimeters (mm).

Dissolution Test

The most popular and effective option for the ODTs dissolution test is the USP 2 paddle device, which has a paddle speed of 50 rpm. Samples (5 ml) were collected at predetermined time intervals (5,10, and 15 min), replaced with an equal volume of fresh medium, filtered through a Whatman filter paper, and analyzed with a Ultraviolet-Visible spectrophotometer at 245 nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved.

Drug release kinetics study

The kinetics and mechanism of drug release from tablets are evaluated using various mathematical models. The cumulative amount of drug release from the formulated tablets was fitted to Zero-order kinetics, First-order kinetics, Higuchi's model, and Korsmeyer–Peppas model to characterize the *in vitro* drug release mechanism.

Stability studies

The stability studies of ODTs were performed on the optimized formulation for 6 months according to ICH (International Conference on Harmonization) guidelines. The tablets were kept under accelerated conditions of temperature and humidity, 35°C±5°C and 75%±5%, respectively. All the physical and *in vitro* tests were performed, and any significant changes were observed.

RESULTS AND DISCUSSION

DSC study was conducted to determine the compatibility between drugs and excipients. The study revealed that no interactions were found with the drug and physical mixture, as the endothermic peak was observed at 208°C for pure drug and 211°C for physical mixture, respectively (Fig. 1 and 2).

Following formulation development, the tablets were evaluated for various post-compression parameters. The results for weight variation, hardness, thickness, and friability were all found to be within the pharmacopeial limits as presented in Table 2. The weight variation of all the developed formulations ranged between 9.03 and 101.6 mg. Friability was found between 0.10-0.13% for all formulations, which was less than the official value of friability, i.e., less than 1%, indicating that tablets had good mechanical strength and did not show any unnecessary breakdown of the particles. Hardness and thickness were present within the limits. Disintegration time, 15 to 45 sec, and wetting time, 21 to 75 sec, were noted for each formulation. Results had clearly revealed that the disintegration time was even less than 1 min for all nine formulations. As the concentration of disintegrants increased, the disintegration time also decreased [9,10]. The formulation developed with more amount of Crospovidone (F9) disintegrated within 15 sec compared to other formulations such as F7 and F8. The results of both wetting time and disintegration time studies were in agreement, indicating that all formulations would definitely disintegrate in the oral cavity within the specified time period [11].

Uniformity of drug content in all of the formulations was also assessed to ensure dose. The analysis proved that drug contents in all of the formulations remained within the range of 97.1% to 100.1%. These results were within prescribed limits, proving a uniform and proper distribution of the drug among all the ODTs.

Table 2: Post-compression parameters of Teneligliptin oro-dispersible tablets

Formulation	Weight variation (mg)	Hardness (Kg/cm²)	Thickness (mm)	Friability (%)	Wetting time (sec)	Disintegration time (sec)	Assay (%)
F1	100.5±1.12	3.21±0.2	5.1±0.02	0.12±0.01	75.6±3.1	45.2±2.4	97.1±1.2
F2	101.0±1.37	3.42±0.1	5.2±0.05	0.11±0.03	59.5±2.3	41.4±3.1	98.3±2.3
F3	101.6±1.41	3.58±0.1	4.9±0.01	0.13±0.02	42.8±1.2	34.2±2.9	99.7±1.5
F4	100.2±1.25	3.27±0.2	5.3±0.03	0.10±0.01	52.4±3.5	33.1±3.1	98.2±1.1
F5	99.03±1.01	3.42±0.3	5.0±0.13	0.12±0.04	41.7±3.9	24.4±2.3	99.3±2.6
F6	100.1±1.12	3.18±0.2	5.1±0.07	0.10±0.02	25.3±2.1	18.1±1.6	100.1±1.4
F7	101.3±1.03	3.53±0.1	5.2±0.04	0.11±0.03	56.1±4.7	44.3±4.1	99.2±1.3
F8	100.7±1.38	3.29±0.2	4.9±0.02	0.13±0.01	46.4±3.9	23.2±2.2	97.4±2.7
F9	101.5±1.09	3.63±0.2	5.1±0.01	0.12±0.02	21.3±2.1	15.3±1.4	99.7±3.1

*Data given in mean ± SD, n=3. SD: Standard deviation.

Table 3: Drug release kinetics of all the developed Teneligliptin oro-dispersible tablets

Formulation	Zero order	First order	Higuchi order	Peppas order
F1	0.9306	0.9045	0.9451	0.9229
F2	0.9319	0.9016	0.9418	0.9218
F3	0.9343	0.9031	0.9435	0.9246
F4	0.9321	0.9029	0.9429	0.9235
F5	0.9352	0.9013	0.9414	0.9258
F6	0.9329	0.9042	0.9465	0.9241
F7	0.9312	0.9059	0.9459	0.9263
F8	0.9335	0.9036	0.9427	0.9225
F9	0.9361	0.9027	0.9469	0.9239

The drug release studies were conducted for all the developed formulations. Formulations F1–F3 were developed with Croscarmellose sodium, F4–F6 formulations were developed with SSG, and F7–F9 formulations were developed with Crospovidone. The results had shown that the release of the drug was in the range of 81–99% for all 9 formulations in 15 min. The results indicated that Crospovidone is the strongest among other superdisintegrants, resulting in the fastest disintegration time than Croscarmellose sodium and SSG [12,13] (Fig. 3-5). Formulation F9 showed the highest drug release, 99.12% within 15 min, compared to F7 and F8. Because a larger amount of Crospovidone disintegrates the dosage form rapidly (15 sec) and releases the drug completely within 15 min. Whereas, F7 and F8 formulations could not release the complete drug due to the low concentration of superdisintegrant. As the concentration of superdisintegrant increased, the disintegration time decreased, and a greater amount of drug was released [14,15]. Based on the disintegration time, wetting time, and drug release studies F9 formulation was considered the optimized formulation and used for further studies.

The drug release mechanism from Teneligliptin ODTs was analyzed using various kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas equations. The correlation coefficients (R^2 values) obtained for all selected formulations were sufficiently high to evaluate the release pattern. Zero-order kinetics showed R^2 values ranging from 0.9306 to 0.9361, while First-order kinetics ranged from 0.9013 to 0.9590. The Higuchi model exhibited values between 0.9414 and 0.9469, and the Peppas model values were in the range of 0.9218–0.9263. Among these, the Higuchi model demonstrated the best fit, indicating that the drug release from the tablets primarily followed a diffusion-controlled mechanism. This behavior can be attributed to the rapid diffusion of the drug through the porous matrix of the ODTs. These results suggest a good fit with all kinetic models, indicating consistent release behavior. The detailed kinetic data are presented in Table 3.

Stability studies were conducted on the best formulation, F9, for 6 months. The tablets were kept under accelerated conditions of temperature and humidity. The tablets were evaluated for all the required evaluation parameters. Over the period, the tablets did not exhibit any physical changes such as color change, friability, and hardness (Table 4).

The results also indicated that there were no significant variations in drug content and in vitro drug release up to 6 months [16,17]. It means that the optimized formulation F9 was considered stable under accelerated conditions of temperature and humidity (Table 4).

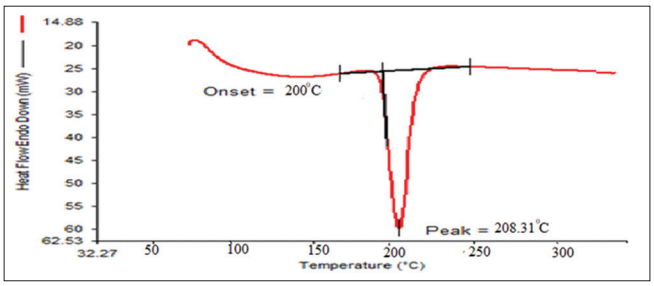

Fig. 1: Differential scanning calorimetry thermogram of pure drug Teneligliptin

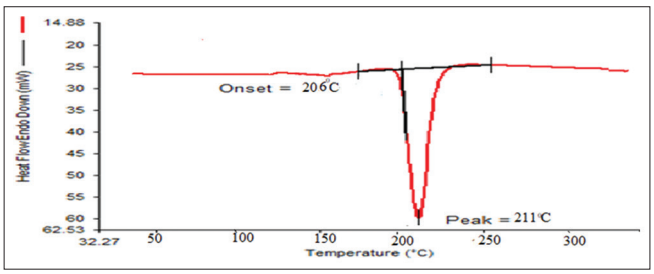

Fig. 2: Differential scanning calorimetry thermogram of physical mixture

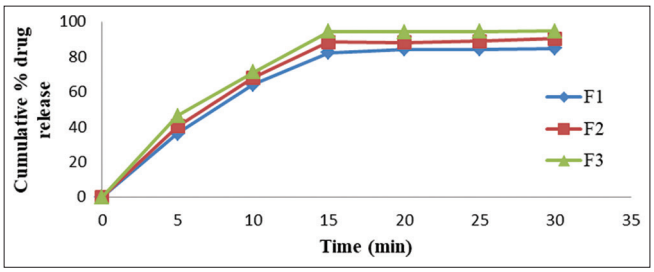

Fig. 3: Dissolution profiles of Teneligliptin prepared with Croscarmellose sodium (F1–F3). Data given in mean ± SD, n=3. SD: Standard deviation

Table 4: Stability studies of optimized formulation (F9 formulation)

Time (Months)	Color change	Friability (%)	Hardness (kg/cm²)	Drug content (%)	Drug release (%)
0	No	0.12	3.63±0.2	99.7	99.12
1	No	0.12	3.63±0.4	99.8	99.34
3	No	0.11	3.63±0.3	99.6	99.25
6	No	0.12	3.63±0.1	99.7	99.03

*Data given in mean ± SD, n=3. SD: Standard deviation

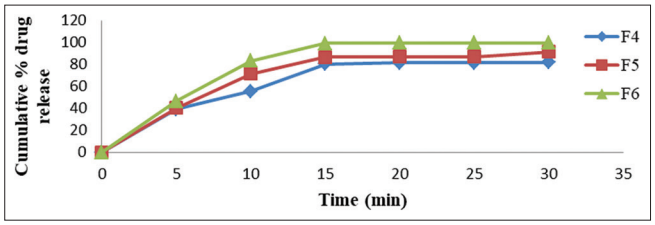

Fig. 4: Dissolution profiles of Teneligliptin prepared with Sodium Starch Glycolate (F4–F6). Data given in mean ± SD, n=3. SD: Standard deviation

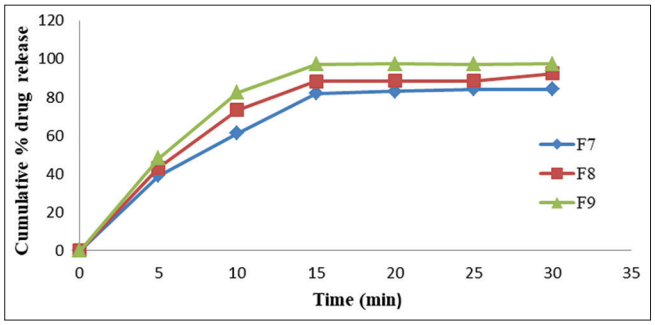

Fig. 5: Dissolution profiles of Teneligliptin prepared with Crospovidone (F7–F9). Data given in mean ± SD, n=3. SD: Standard deviation

CONCLUSION

Among all the formulations developed, Crospovidone demonstrated the most effective disintegration performance, achieving a disintegration time of less than 15 sec. DSC studies confirmed the compatibility of the selected excipients with Teneligliptin. Drug content across all formulations remained within the acceptable range, ensuring dose uniformity. A total of nine formulations were prepared using the direct compression method, incorporating superdisintegrants such as Croscarmellose sodium, Sodium Starch Glycolate, and Crospovidone. Based on comprehensive evaluation parameters - including dissolution profile, disintegration time, and wetting time - formulation F9 was identified as the optimized formulation. It exhibited the highest *in vitro* cumulative drug release, along with rapid disintegration and wetting characteristics, making it the most suitable candidate for further development.

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AUTHORS' CONTRIBUTIONS

All the authors have equally contributed to the article.

CONFLICT OF INTEREST

There is no conflict of interest.

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