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Preparation and In-Vitro Evaluation of Tizanidine Flash Oral Dispersible Tablet

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ORIGINAL STUDY

Preparation and In-Vitro Evaluation of Tizanidine Flash Oral Dispersible Tablet

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ABSTRACT

Background: Oral administration is the most common and preferred route for drug delivery. Oral dispersible tablets (ODTs) are solid dosage forms that disintegrate into saliva without the need for water. Tizanidine is a centrally acting muscle relaxant used to manage spasticity from spinal or brain injuries. Preparing it as a flash (ODT) tablet may enhance patient compliance and potentially improve bioavailability by bypassing part of the first-pass metabolism.

Methods: Six formulations of tizanidine flash tablets were developed using varying concentrations of mannitol (bulk-forming agent), glycine (to aid tablet collapse), and gelatin (matrix-forming agent). The formulations were evaluated for weight variation, friability, wetting time, disintegration time, and drug release.

Results: All formulations complied with pharmacopeial standards for weight variation and friability (0.75–0.94%). Wetting times ranged from 19 to 55 seconds. A strong correlation was observed between wetting and disintegration times. Notably, formula F6, which had the shortest wetting time, also showed the fastest disintegration and drug release. After 10 minutes, F6 released nearly 100% of the drug content, outperforming other formulations and conventional film-coated tablets. This enhanced performance is attributed to its lower gelatin content.

Conclusion: Tizanidine can be effectively formulated as a flash tablet, offering rapid disintegration and improved dissolution, potentially leading to faster onset of action and better patient compliance.

Keywords: Tizanidine, Flash tablets, Gelatin, Disintegration

1. Oral drug delivery system

The most popular and advised method of delivering drugs, including both liquid and solid dose forms, is orally.

Solid single-unit dose forms called oral dispersible tablets are meant to be consumed without water after being placed in the mouth and given time to dissolve in saliva [1].

Swallowing difficulties are common in all age groups, especially in the elderly, and can also be observed when taking conventional pills and capsules. Numerous serious illnesses, such as stroke, Parkinson's disease, AIDS, and other neurological conditions like cerebral palsy, are associated with this syndrome. ODT is suitable for geriatric, pediatric, and traveling patients because it requires no water to be consumed, making it easy to give [2].

Oral dispersible tablets have been studied for their ability to improve patient compliance and, by altering the drug's dissolving profile, increase the bioavailability of poorly water-soluble drugs. However, due to the quick disintegration of oral dispersible tablets, the active ingredient comes into contact with taste receptors, making a pleasant flavor essential to the patient's palatability. Therefore, one of the biggest challenges in producing ODT products correctly is disguising the taste of unpleasant active compounds.

In summary, oral administration of bitter active compounds via ODT formulations should result in greater patient compliance, improved palatability, and a favorable therapeutic outcome [3].

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A variety of techniques, including lyophilization, molding, freeze-drying, sublimation, rapid dissolving films, and direct compression, are used in the production of ODT that is available commercially. Even though ODT has a high degree of friability and no physical resistance, it disintegrates in around 30 seconds thanks to the lyophilization and shaping processes. Conversely, tablets made by direct compression break down more slowly but are less brittle [4].

2. Flash tablets

Lyophilization is the process of removing the solvent from a frozen suspension or solution containing medication and other excipients. An aqueous carrier solution is used to dissolve or disperse the medication. The premade blister pack wells are filled with mixture using a pump. The blister packets' medicinal solution is frozen using liquid nitrogen as as Zydis units. After that, they. shipped to their intended sites [5].

Lyophilized tablets offer improved absorption and bioavailability, are highly porous, and disintegrate rapidly. Higher temperatures and humidity will affect the ODT lyophilized product. A lyophilized tablet will dissolve rapidly on the tongue. The production process of freeze-drying is more expensive than ordinary tablet pressing [6].

Gelatin: In animal connective tissue, collagen partially breaks down to produce gelatin, a which is a white or yellowish, transparent, glossy solid [7].

It is extensively utilized in solid oral dosage forms, such as soft and hard gelatin capsules, since, when hydrated, it creates thermo-reversible gels with melting points between 35 and 37 ˚C, or just below body temperature. When flash tablets are prepared, it functions as a matrix-forming agent [8].

Glycine: The most researched amino acid in medication delivery is glycine, which is the most basic amino acid [9]. Is typically used as a freeze-dried co-substitute in protein formulations because it can provide a strong, elegant cake with a porous structure in the final lyophilized product [10].

Tizanidine: Tizanidine is a central nervous system-acting muscle relaxant. It is a myotonolytic medication used to treat spasticity in people with brain or spinal injuries. It functions as a central alpha-2 adrenoceptor agonist. It is an antispastic medication with a more favorable tolerance profile and an efficacy like baclofen [11].

The major objectives of the present work are the development of oral dispersible tizanidine flash tablets which may participate in improving the performance of the intended drug by the decrease of the first-pass effect by introduction to the oral cavity, may increase the bioavailability of tizanidine and, possibly, reduce the time to peak plasma concentration, thereby shorting the latency of therapeutic effect.

3. Material and methods

3.1. Preparation of calibration curve of tizanidine HCl

To prepare the tizanidine HCl calibration curves, a Shimadzu 1800 UV visible spectrophotometer was used in phosphate buffer pH 6.8. Tizanidine hydrochloride (50 mg) was weighed precisely and then added to a 50 ml volumetric flask. The remaining volume was filled up with phosphate buffer (pH 6.8) to obtain a 1000 μ g/ml stock solution of tizanidine HCl. From the stock solution serial dilutions of 10,8.3, 6.25,5,3 μ g/ml were prepared.

3.2. Preparation of TZN flash tablets

To prepare TZN flash tablets, 100 milliliters of water were used to completely hydrate the necessary weight of gelatin. A magnetic stirrer was used to obtain the clear gelatin solution. Gelatin solution was used to dissolve the weights of glycine, 80 mg of TZN, and mannitol, as shown in Table 1. Following the pouring of the resultant dispersion into each of the 0.5 ml pockets of a tablet blister pack, a TZN dose of 4 mg per tablet was achieved. The blister packets, with ten tablets each, were placed in a deep freezer set at –22 ˚C for a whole daya and then by lyophilization for 24 hrs with condenser temperature of –45˚C and pressure of 7×10^{-2} mbar. used to

Table 1. Formulation of different TZN flash tablets.

No Formulas	TZN mg	Gelatin	Mannitol	Glycine
F1	4	40	100	50
F2	4	40	120	50
F3	4	40	140	50
F4	4	40	120	60
F5	4	50	120	50
F6	4	30	120	50

remove the water, and then follow the flash tablets stored in desiccators to prevent any impact from the environment, particularly moisture. It is possible to prevent flash pills from becoming gritty in the mouth [11].

4. Evaluation of flash tablets

4.1. Weight variation

Twenty tablets from each formulation were chosen at random, and the average weight of each tablet was calculated by weighing it individually on an electronic scale. The following formula was used to determine the percentage weight variation of twenty tablets:

$$\text{percentage weight variation} = \left(\text{individual weight} - \text{average weight}/\text{average weight}\right) \times 100.$$

The tablets were deemed acceptable after meeting USP requirements [12].

4.2. Friability

Twenty pre-weighed tablets were tested for friability using a friabilator (Erweka, Germany); the device was susceptible to 100 revolutions. The friability is represented by the weight loss percentage. If the percentage loss was less than 1%, the tablets were approved. The following formula was used to determine the tablets' % friability [13]:

$$\text{percent friability} : \text{Initial weight} - \text{Final weight} / \text{Initial weight} \times 100$$

4.3. Wetting time

The test was carried out by wetting the tablet fully on the surface of the filter paper, which was placed in a straightforward feeding glass dish with an appropriate volume of dye solution. The wetting time was determined by taking the length of time needed to completely wet the tablet [14].

4.4. Disintegration time

Six tablets were placed in 300 ml distilled water at 37 ± 0.5 °C using a disintegration tester apparatus. The time consumed for full disintegration of tablets was recorded [14].

4.5. Dissolution test

Using the USP II dissolution device, the rate of TZN dissolution from several flash tablet formulations was determined. The dissolving media (300 ml phosphate buffer pH 6.8) was kept at 37 ± 0.5 °C, and the paddle rotation was set to 100 rpm. Five-milliliter aliquots of each were taken at pre-arranged intervals of two, five, ten, fifteen, and twenty minutes. The samples were measured for absorbance at 320 nm, and the corresponding concentrations were computed [15].

5. Results and discussion

5.1. Calibration curve of TZN in phosphate buffer pH 6.8

Fig. 1 shows the developed calibration curves of TZN in phosphate buffer pH 6.8. When the absorbance was plotted against the concentration, a straight line was formed with a large coefficient of determination. According to this, the calibration curve over the concentration range complies with Beer's law.

5.2. Weight variation

All prepared formulas were within USP limited, which not more than two of the individual weights deviated from the average weight by more than 7.5% [16] as Table 2.

5.3. Friability

The prepared TZN formulations showed friability that oscillated between 0.61 and 0.92%, within the permissible range of less than 1%. Various lyophilized formulations demonstrated no shattering or cracking following tumbling and the computed percentage weight loss, suggesting that the formed tablets were undamaged and workable [17].

5.4. Wetting time

The wetting times of each TZN formulation were assessed; the results are shown in Table 4, with an average wetting time of between 55 and 19 seconds for all formulations.

The porous nature of the matrix, which permits quick liquid absorption by capillary action and produces rapid volume and shorter wetting time formulation, may be the cause of the short wetting time of TZN formulations [18]. Additionally, it was noted that formula F6, which had the shortest wetting time, also had the shortest disintegration time, indicating

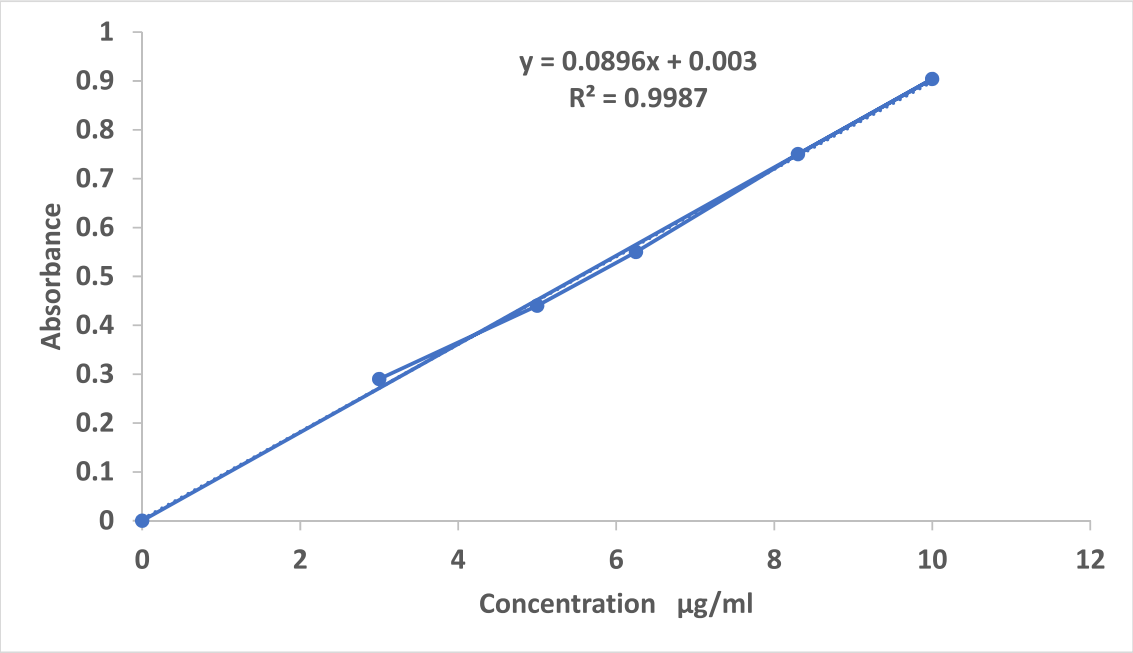

Fig. 1. Calibration curve of TZN in phosphate buffer pH 6.8.

Table 2. Weight variation test.

Formula	Upper (mg)	Lower (mg)
Formula 1	199.8 ± 0.3	188.6 mg ± 0.24
Formula 2	218.4 ± 0.13	211.9 mg ± 0.43
Formula 3	238.3 ± 0.16	226.3 ± 0.44
Formula 4	226.5 ± 0.27	219.4 ± 0.14
Formula 5	230.1 ± 0.32	221.3 ± 0.28
Formula 6	209.3 ± 0.11	202.9 ± 0.55

Table 3. Friability test.

Formula	Initial wt (gram)	Final wt (gram)	Percentage of error
Formula 1	3.897	3.861	0.92%
Formula 2	4.290	4.255	0.81%
Formula 3	4.688	4.659	0.61%
Formula 4	4.490	4.453	0.82%
Formula 5	4.485	4.447	0.84%
Formula 6	4.094	4.065	0.73%

Table 4. Wetting time test.

Formula	Time (second)
Formula 1	45
Formula 2	55
Formula 3	39
Formula 4	35
Formula 5	40
Formula 6	19

Table 5. Disintegration time test.

Formula	Time (min)
Formula 1	1.46
Formula 2	2.20
Formula 3	1.12
Formula 4	1.56
Formula 5	2.18
Formula 6	0.34

a significant relationship between the two variables [19].

5.5. Disintegration time

All the TZN formulations were evaluated for their disintegration time, the results are shown in Table 5 ranging (0.34–2.20 min). Show the lowest time in F6 due to gelatin content [20].

5.6. In Vitro dissolution study

Fig. 2 shows an in vitro drug release profile of TZN formulations which all the formulation shows 100% drug release within 20 minutes.

Concerning the cumulative release curve, it was found that, in comparison to other formulas, the cumulative release from F6 after 10 minutes was almost 100%. This result could be explained by a close relationship between the amount of dissolution and the disintegration time. This makes sense because the

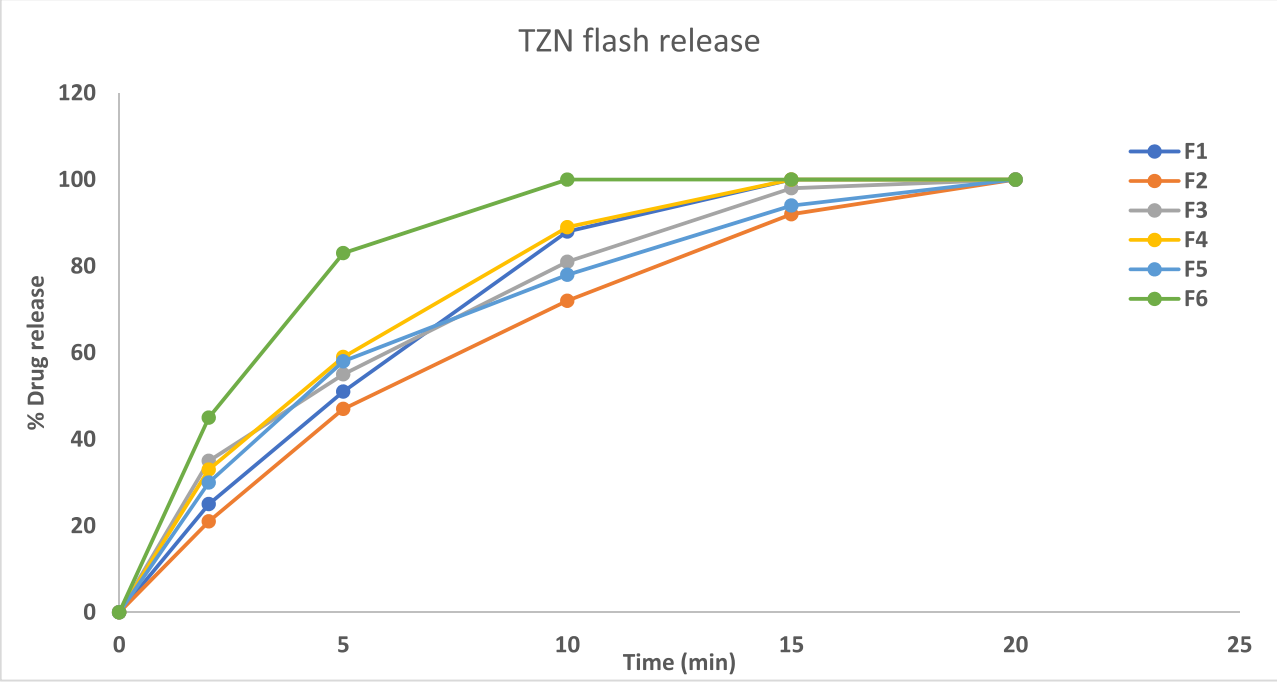

Fig. 2. Comparative dissolution profile of formulations F1–F6.

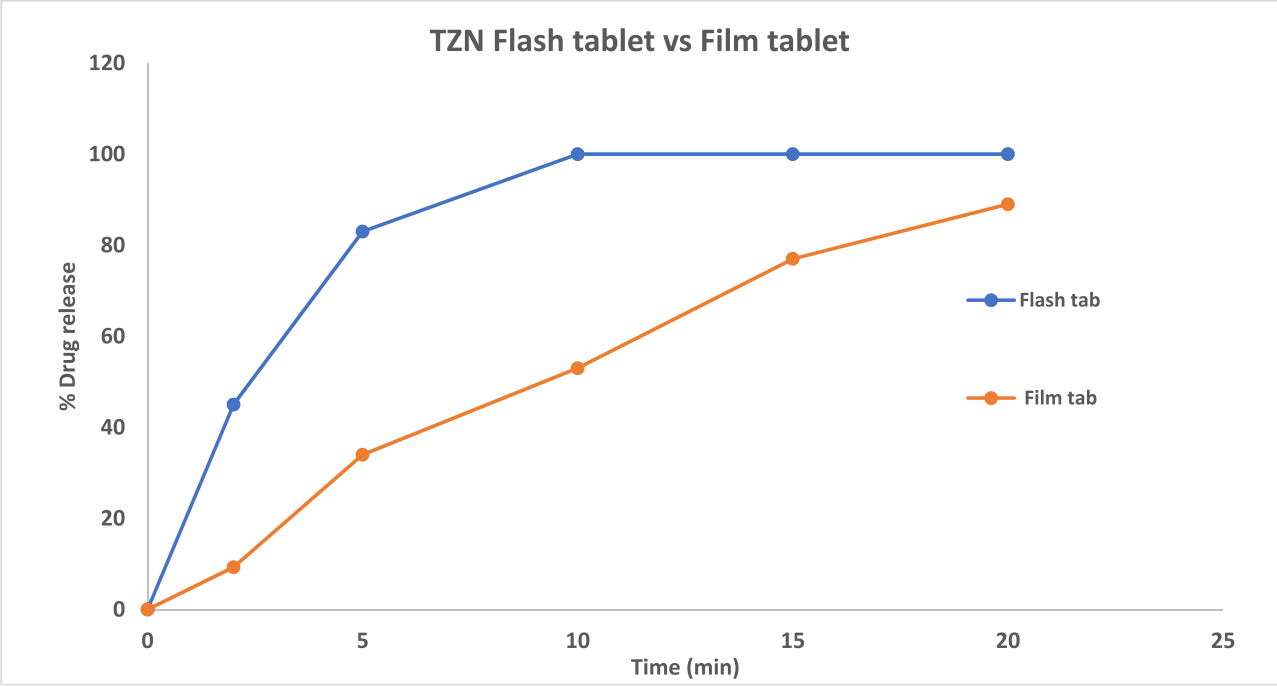

Fig. 3. A comparison of the dissolution profile of the prepared tizanidine flash tablet (F6) with tizanidine film tablet.

drugs with the shortest disintegration times release their contents at a faster rate because they have less gelatin in their formulas than other drugs [21]. An increase in gelatin concentration causes the polymer chain to relax, which reduces hydrogel swelling and ultimately lowers drug release [22].

The conventional film-coated market tablet of Tizanidine was compared with the best formulated (F6). The in vitro release of market product TZN was 53% at 10 min, whereas formulation flash tablet was 100% as in Fig. 3, showing significant (p-value $>$ 0.05) due to flash tablets are rapid wetting, rapid disintegration,

and final rapid drug release in compare with ordinary film-coated tablets.

6. Conclusions

Tizanidine flash tablets may be an appropriate choice for individuals who have trouble swallowing or who are unable to swallow regular pills with water, in addition to having a quicker onset of action than regular tablets. With mannitol, gelatin, and glycine, the formulated tizanidine flash tablet can be produced in this study with acceptable features (i.e., pharmaceutical properties) to improve the dissolution profile. The results indicated that formula 6 was the most effective since it was the selective formula, had the least amount of gelatin, a low wetting time (19 s), a low disintegration time (34 s), and a 100% release duration of 10 minutes. The dissolving profile of the (F6) was superior to that of the regular film-coated tablet.

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