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Research Article

Formulation Development & Evaluation of Mouth Dissolving Tablet of Torsemide

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ABSTRACT

The oral route of medication delivery is the most popular and generally recognized. Oral dose forms are frequently used since they are inexpensive and simple to administer on one's own. For example, mouth dissolving tablets dissolve in saliva and may be ingested without water. Torsemide is indicated for the treatment of oedema associated with congestive heart failure, renal, or hepatic diseases. This research is designed for fast release of drug for treatment of oedema. The tablets were prepared using Torsemide (Solid Dispersion), Crospovidone, Sodium Starch Glycolate, Mannitol, Magnesium Stearate, Talc, and Aspartame in eight different batches (T1-T8). The tablets were evaluated based on pre-compression characteristics of powder blend, weight variation test, thickness test, hardness, friability, drug content, wetting time, water absorption ratio, and disintegration time. According to the results, the T7 formulation outperformed the others in terms of disintegration time, water absorption ratio, and wetting time.

Key Words: Mouth Dissolving Table, Torsemide, formulations

Introduction

Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance. However, traditional tablets and capsules administered with a glass of water may be inconvenient or impractical for some geriatric patients because of changes in various physiological and neurological conditions associated with aging including difficulty in swallowing/dysphagia, hand tremors, deterioration in their eyesight, hearing, memory, risk of choking in addition to change in taste and smell. Solid dosage forms also present significant administration challenges in other patient groups, such as children, mentally challenged, bed ridden and uncooperative patients. Pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules [1-5].
Therefore, to cater the needs of such patients, recent advancements in technology have resulted in development of viable dosage alternatives popularly known as orally disintegrating tablets (ODTs).During the past decade, the FDT (fast dissolving tablet) technology, which makes tablets dissolve or disintegrate in the mouth without additional water intake, has drawn a great deal of attention [6]. The technology is also referred to as fast disintegrating tablet, fast dispersing tablet, rapid dissolve tablet, rapid melt tablet, quick disintegrating tablet, and orally disintegrating tablet. The FDT formulation is defined by the Food and Drug Administration (FDA) as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". The tablets disintegrate into smaller granules or melt inthe mouth from a hard solid structure to a gel like structure, allowing easy swallowing by the patients. The disintegration time for those tablets varies from a few seconds to more than a minute [7].

FDT is a desirable dosage form for patients with problems swallowing tablets or other solid dosage forms. It has advantages over oral solutions including better stability, more accurate dosing, and lower volume and weight. The dosage form can be swallowed as a soft paste or liquid, and suffocation is avoided because there is no physical obstruction when swallowed. Since the tablets disintegrate in the mouth, drugs can be absorbed in the buccal, pharyngeal, and gastric regions. Thus, rapid drug therapy intervention and increased

bioavailability of drugs might be possible. Because pre-gastric drug absorption avoids first pass metabolism, the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism [8].

Administration of FDTs is different from conventional tablets, and the FDTs should have several unique properties to accommodate the rapid disintegration time. They should dissolve or disintegrate in the mouth without water or with a very small amount of water as the disintegration fluid is the patient's saliva. The disintegrated tablet should become a soft paste or liquid suspension, which provides good mouth feel and enables smooth swallowing. "Fast dissolution" or "fast disintegration" typically requires dissolution or disintegration of a tablet within one minute [9-13].

Material & Method

Torsemide is a high-ceiling loop diuretic. The IUPAC name of torsemide is 1-[4-(3-methylanilino) pyridin-3-yl] sulfonyl-3-propan-2-ylurea. It is commonly used as an antihypertensive agent.

Table 1: Physico-chemical properties of torsemide

Chemical name	1-[4-(3-methylanilino) pyridin-3-yl] sulfonyl-3-propan-2-ylurea
Molecular formula	$C_{16}H_{20}N_4O_3S$
CAS number	56211-40-6
Molecular mass	348.4gm/mole
Physical appearance	White to off-white crystalline powder
Melting point	163-164°C
Log P	2.3
Solubility	Soluble in DMSO (18 mg/ml) and is insoluble in water

Therapeutic Indication
Torsemide is indicated for the treatment of oedema associated with congestive heart failure, renal or hepatic diseases.

Mechanism of Action
Since it is a loop diuretic's part, its mechanism of action is by the reduction of the demand of oxygen in thick ascending loop of Henle. It acts by the inhibition of Na+/K+/Cl- pump on the luminal surface of cell membrane. This is achieved as torsemide binds to the transport molecule's chloride ion-binding site.

Pharmacokinetics
Absorption
Its oral bioavailability is high. It is mostly higher than 80% regardless of the condition of the patient. Absorption is unaffected by using it with food concomitantly. It attains its max. concentration in serum within an hour of administration.

Distribution
Torsemide's distribution volume is 0.2 L/kg. It has a great affinity for the proteins of plasma with plasma binding as high as 99% of the administered dose.

Metabolism
Extensive metabolism of torsemide occurs in the liver. The amount of dose that does not undergo metabolism is only 20% which is recovered in the urine. Metabolized via the hepatic CYP2C8 and CYP2C9 mainly by reactions of hydroxylation, oxidation and reduction to 5 metabolites. The major metabolite, M5, is pharmacologically inactive. There are 2 minor metabolites, M1, possessing one-tenth the activity of torsemide, and M3, equal in activity to torsemide.

Excretion
Processing of torsemide occurs mainly via liver and therefore, excretion of almost 70% of the dose which is administered occurs by this route. Excretion occurs from faeces. On the other hand, only 20-30% of the administered dose is found in the urine. It has an average half-life of 3.5 hrs.

Contraindications
It is contraindicated in such cases as high amount of triglyceride in the blood, extreme loss of body water, gout, low amount of potassium in the blood, hardening of the liver, hearing loss, high amount of uric acid in the blood, azotemia, ascites, acid base imbalance of the blood toward the basic side, decreased blood volume, absence of urine formation.

FORMULATION DEVELOPMENT OF MOUTH DISSOLVING TORSEMIDE TABLET

As a result, the direct compression approach outperforms the wet granulation technique in terms of productivity and tablet quality. The direct compression approach was used to make the tablet softorsemide. Every item listed in formulation table 1 was weighed appropriately and combined with a mortar and pestle. After a short period of drying, this powder mixture was thoroughly mixed once again and run through Sieveno60.The blend was then used for additional processing.

Table 2: Formulation of mouth dissolving torsemide tablets

Ingredients	T1	T2	T3	T4	T5	T6	T7	T8
Torsemide(SDA) (Eq 20mg drug in 80mg solid dispersion)0	80	80	80	80	80	80	80	80
Crospovidone	2	2	2	2	4	4	4	4
Sodium starch glycolate	2	3	4	5	2	3	4	5
Mannitol	13	12	11	10	11	10	9	8
Mg.Stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Aspartame	1	1	1	1	1	1	1	1
Theoretical Weight	100	100	100	100	100	100	100	100

Evaluation of Pre-Compression Characteristics of Powder Blend

Standard protocols were used to evaluate the powder mixture's various rheological characteristics. Three times (n=3) the assessment was conducted, and the mean results were presented.

Bulk density

The pace at which the mix fills the die is determined by evaluating the bulk density and the tapped density. According to the study article, the bulk density was assessed. A measuring cylinder was filled with the mixes, and the total volume was then recorded. he powder mixture's gravity was determined using a digital weighing balance. The bulk density was calculated using the following formula:
Bulk Density = Weight of the powder/Volume of the powder

Angle of repose

The fennel was positioned 6 cm above the graph paper throughout this procedure. The fennel was powdered and then carefully removed. The height of the heap was measured using the scale. The following formula was used to calculate the angle of repose:
$\theta=\tan^{-1}h/r$
Where, h= height of heap of granular bed, r = radius of heap of granular bed.

Flow property	Angle of Repose (Degrees)
Excellent	25 –30
Good	31 –35
Fair – aid not needed	36 – 40
Passable – mayhang up	41 – 45
Poor – must agitate, vibrate	46 – 55

Hausner's ratio

Hausner's ratio was calculated by using following formula and it was expressed in percentage
$H=D_t/D_b$
Where D_t denoted the tapped density of the powder D_b denoted the bulk density of the powder

Carr's index	Flow Character	Hausner's Ratio
= 10	Excellent	1.00-1.11
= 11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Compression of powders into tablets
The glidant (magnesium stearate) and lubricant (talc) were combined with the prepared powders prior to compression into tablets. The powder was compressed and then punched into tablets using flat-faced punches with a 10 mm diameter.

Evaluation of compression characteristics of tablets
Following tablet formation, it is necessary to verify that the dose form is appropriate for the intended therapeutic response. Compression tablets are evaluated using a variety of parameters. Using standard procedures, the prepared tablets' thickness, friability, hardness, weight variation, and dissolution test were assessed.

Weight variation test
The 20 pills were weighed individually throughout this procedure. By considering the average mean, the average weight of one pill was determined. According to I.P., no more than two pills result in noticeable weight. I.P. notes that there are more than two different weights from the mean weight, and none of them should be significantly different from the percentages stated in the monographs.

Test of thickness
We measure the tablet thickness in micrometres using a help vernier calliper. Three readings were averaged, and the mean values were reported (n=3).

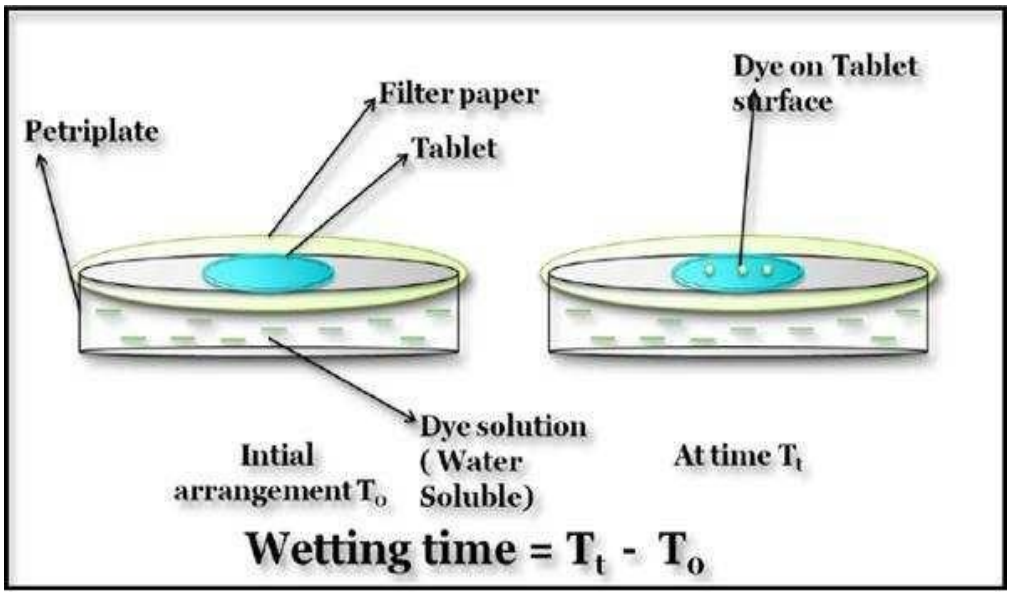
Test of hardness
The hardness of the prepared tablets was assessed using the Monsanto hardness tester. The hardness was measured in kilogram's per square centimeter. Three readings were taken, and the average was recorded.

Test of Friability
The abrasion rate of the prepared tablets was measured using the Roche friabilator. Weigh the twenty pills that are stored in the friabilator chamber. For four minutes, the friabilator was rotated at 25 rpm. Weights were taken once the rotation was finished, and the % weight reduction was computed using a method.

Content of drugs
The three pills were ground into a fine powder in a mortar and pestle to determine the drug concentration. Powder that was dissolved in phosphate with a pH of 6.8 and had the weight of one tablet. Make use of a UV-visible spectrophotometer to determine the absorbance of a diluted torsemide sample at 260 nm. The standard calibration curve was used to determine the drug content.

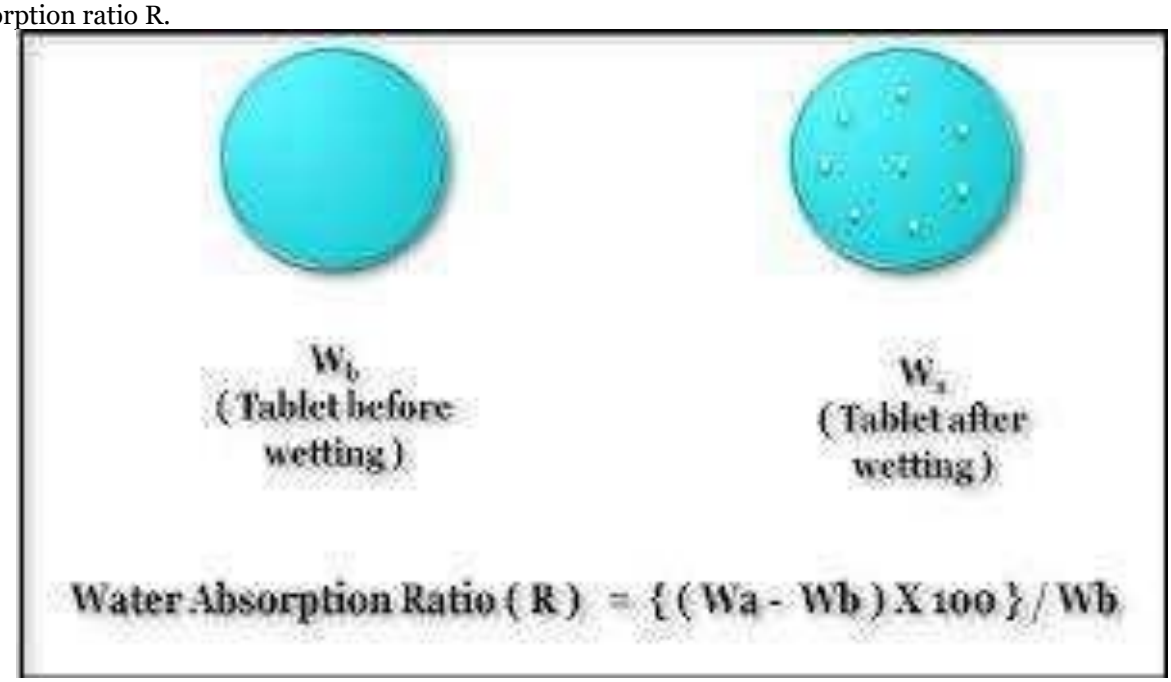
Time spent wetting

The tablets were placed in a Petri dish to determine the wetting time. The Petri dish contained tissue paper that had been folded twice and six milliliters of purified water. The amount of time needed for tablets to fully wet was measured.



Water absorption ratio procedure

The water absorption ratio was calculated using the wetting time. Equation was used to calculate the water absorption ratio R.



RESULT

The tapped density and bulk density of several formulations were calculated. Bulk density ranges between 0.473 and 0.483, whereas tapped density ranges between 0.467 and 0.513. The compressibility index ranged from 11.39 to 14.09, while Hausner's ratio was between 1.12 and 1.19. Angle of repose showed that the powdered mix had acceptable to exceptional flow characteristics (Table 6.6).

According to Torsemide's pre-compression research, mouth-dissolving tablets may be made using direct compression techniques.

Table 3: Data of pre-compression characteristics of Torsemide powder blend

Parameters	T1	T2	T3	T4	T5	T6	T7	T8
MeanAngleof repose*±S.D.	36° 25' ± 0.02	29° 36' ± 0.11	31° 28' ± 0.05	30° 57' ±0.08	29° 91' ± 0.09	31° 43' ± 0.13	34° 72' ± 0.21	38° 14' ± 0.05
MeanApparentbulkdensity * (g/cm³)±S.D	0.473 ±0.02	0.565 ±0.04	0.547 ±0.06	0.513 ±0.01	0.574 ±0.03	0.519 ±0.06	0.538 ±0.04	0.558 ±0.04
MeanTappedbulkdensity* (g/cm³)±S.D.	0.565 ±0.03	0.689 ±0.01	0.672 ±0.03	0.621 ±0.06	0.698 ±0.04	0.625 ±0.03	0.645 ±0.02	0.672 ±0.02
ompresibility Index*(%)	12.74	15.09	17.11	17.39	14.89	15.36	16.59	19.34
Hausner's Ratio*	1.14 ± 0.01	1.17 ± 0.02	1.20 ± 0.04	1.21 ± 0.02	1.17 ± 0.05	1.18 ± 0.02	1.20 ± 0.05	1.23 ± 0.03

*Value shown in tables is mean of three determinations

Evaluation of mouth dissolving tablet of Torsemide.

The following are the findings of an evaluation of the physicochemical properties of the oral dissolving tablet of torsemide. The tablet's thickness and width are included in its dimensions. All formulations were determined to be between 3.21 and 3.62 in thickness. The tablet weights of all formulations were found to be below USP limitations, ranging from 305 to 1 mg, according to the table.The hardness of the tablets in the autumn batches ranged from 3.05 to 3.73 (Kg/cm2), which is within acceptable bounds as reported in the literature. Because the proportion of friability was less than 1%, the result of friability indicated that all formulations could survive shocks.UV spectroscopy was used to determine the homogeneity of content, and all formulations showed drug content ranging from 97.61 to 99.25%.

Various tablet indicators, including as flow property, dimension hardness, drug content, etc., were computed under the guidance of industrial experts and resulted in successful testing.

According to Table and Figure, the wetting time and water absorption ratio were 17.79 to 35.07 seconds and 39.24 to 73.38 seconds, respectively (Table 6.9 and Figure 6.10).As the concentration of crospovidone and sodium starch glycolate increased, the wetting time of Torsemide mouth dissolving tablets increased as well.By increasing the concentration of crospovidone and sodium starch glycolate, the water absorption of Torsemide mouth dissolving tablets was reduced.

Oral dissolving tablets have a disintegration time of 38.21 to 22.36 seconds (Table and Fig).By increasing the concentration of crospovidone and sodium starch glycolate, the disintegration time of Torsemide mouth dissolving tablets was shortened.

According to the results above, the T7 formulation outperformed other formulations in terms of wetting time, water absorption ratio, and disintegration time. Furthermore, the T8 formulation showed the best water absorption ratio and the shortest wetting and disintegration times. Due to gelling and the ensuing viscosity-producing effects, this parameter rises.

Torsemide mouth dissolving tablets' post compression results suggested that the formulation's composition was adequate.

Table 4: Evaluation of Torsemide mouth dissolving tablets

Parameters	T1	T2	T3	T4	T5	T6	T7	T8
Uniformity ofweight (mg)*	305.20 ± 1.12	304.17 ± 1.07	304.84 ± 2.01	305.07 ± 1.81	304.6 ± 1.92	305.51 ± 1.25	304.30 ± 1.58	305.42 ± 1.34
Thickness (mm)*	3.21 ± 0.01	3.50 ± 0.04	3.10 ± 0.03	3.34 ± 0.02	3.17 ± 0.01	3.27 ± 0.05	3.41 ± 0.03	3.62 ± 0.04
Friability (%)*	0.28 ± 0.02	0.19 ± 0.01	0.24 ± 0.03	0.27 ± 0.01	0.29 ± 0.05	0.22 ± 0.06	0.20 ± 0.02	0.25 ± 0.01
Tablet Hardness	3.29 ±	3.18 ±	3.51 ±	3.05 ±	3.62 ±	3.21 ±	3.73 ±	3.42 ±

(Kp)*	0.06	0.03	0.06	0.04	0.07	0.05	0.03	0.04
Assay(%)	98.37 ± 0.15	99.25 ± 0.72	98.74 ± 0.12	99.18 ± 0.34	97.61 ± 0.53	98.24 ± 0.79	99.15 ± 0.47	98.05 ± 0.25

*Average of three times measure

Table 5: Evaluation of wetting time of Torsemide mouth dissolving tablets

Formulation	Wetting time (Sec)
T1	35.07±0.02
T2	30.52±0.05
T3	28.36±0.12
T4	25.73±0.19
T5	28.46±0.08
T6	23.91±0.17
T7	21.32±0.09
T8	17.79±0.13

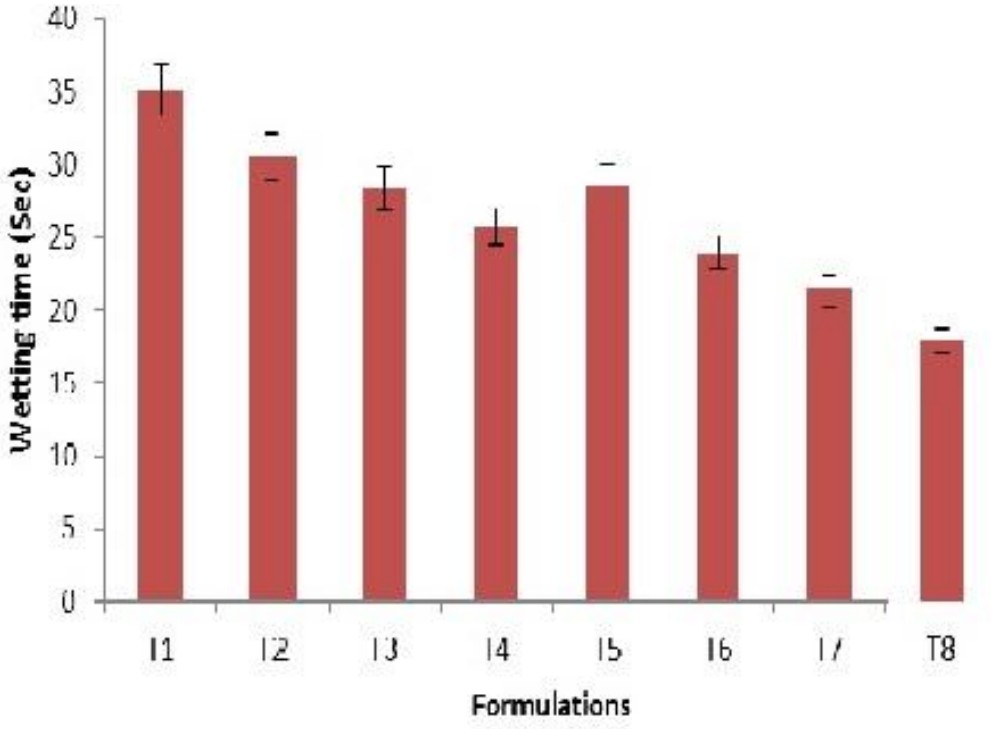


Fig 1: Wetting time of Torsemide mouth dissolving tablets

Table 6: Evaluation of Water absorption ratio of Torsemide mouth dissolving tablets

Formulation	Water absorption ratio
T1	39.24±1.01
T2	46.83±1.24
T3	52.64±0.78
T4	64.71±1.37
T5	50.57±1.29
T6	61.27±0.97
T7	68.19±1.07
T8	73.38±1.15

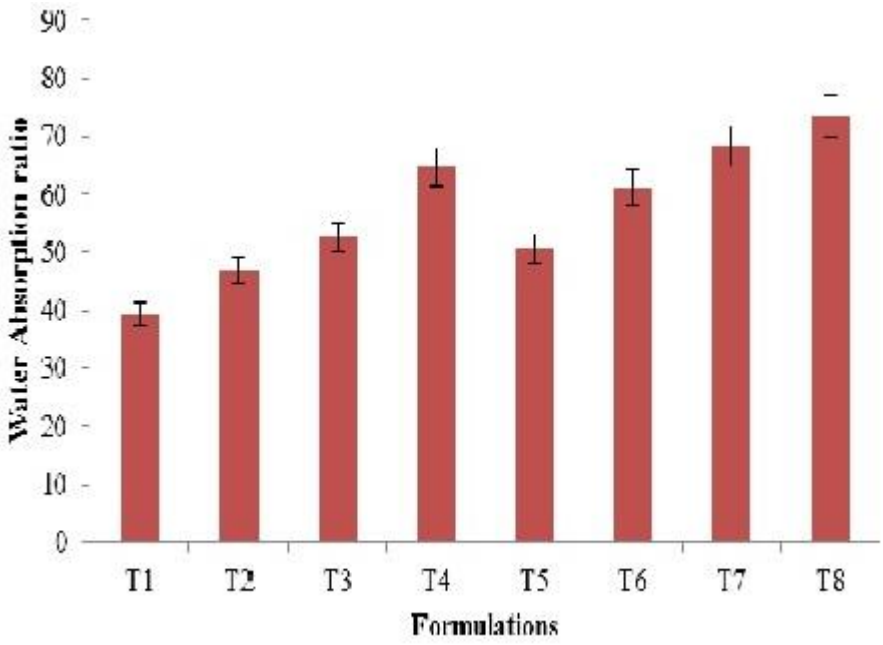


Fig 2: Water absorption ratio of Torsemide mouth dissolving tablets

Table 7: Evaluation of *in-vitro* disintegration time of Torsemide mouth dissolving tablets

Formulation	*In-vitro* disintegration time (sec)
T1	38.21±0.08
T2	35.18±0.12
T3	34.52±0.07
T4	29.73±0.08
T5	31.61±0.19
T6	28.45±0.09
T7	27.58±0.10
T8	22.36±0.05

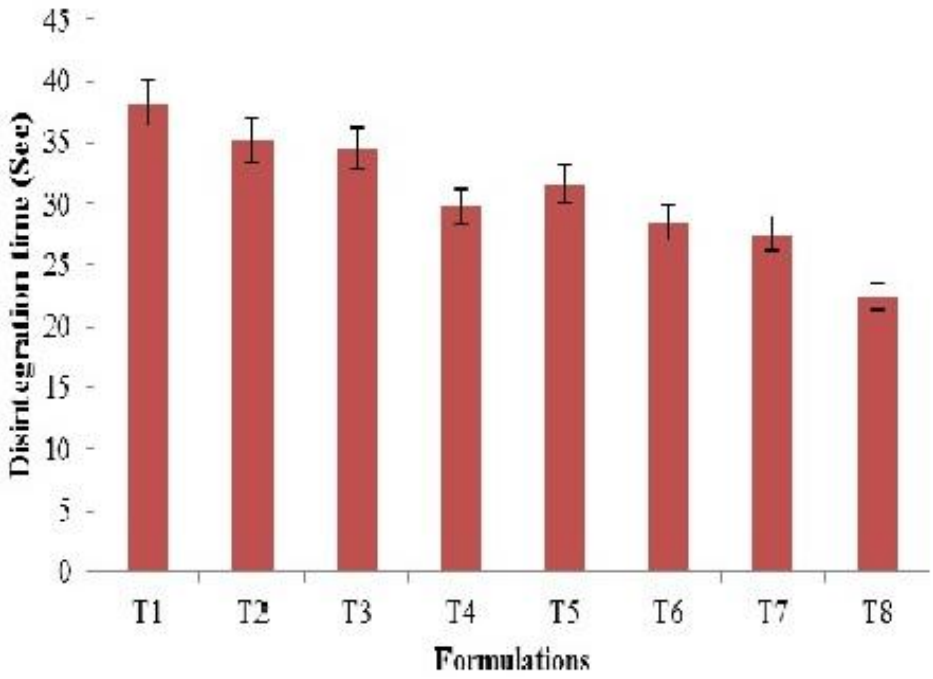


Fig 3: Disintegration time of Torsemide mouth dissolving tablets

Summary & Conclusion

Because of its precise dose, cheap cost, self-medication, non-invasive approach, and convenience of administration, which results in a high degree of patient compliance, the oral route is still the recommended technique for administering therapeutic substances. The direct compression approach was used to make the tablet softorsemide. Every item listed in the formulation table was weighed appropriately and combined in a mortar and pestle. After a short period of drying, this powder mixture was thoroughly mixed once again and run through Sieveno60.Blends were then utilized for additional processing.
The following are the findings of an evaluation of the physicochemical properties of the oral dissolving tablet of torsemide. The tablet's thickness and width are included in its dimensions. All formulations were determined to be between 3.21 and 3.62 in thickness.

The tablet weights of all formulations were found to be below USP limitations, ranging from 305 to 1 mg, according to the table. The hardness of the tablets in the autumn batches ranged from 3.05 to 3.73 (Kg/cm2), which is within acceptable bounds as reported in the literature. Because the proportion of friability was less than 1%, the result of friability indicated that all formulations could survive shocks. UV spectroscopy was used to determine the homogeneity of content, and all formulations showed drug content ranging from 97.61 to 99.25%.
Various tablet indicators, including as flow property, dimension hardness, drug content, etc., were computed under the guidance of industrial experts and resulted in successful testing.
The water absorption ratio and wetting time were determined to be 1739.24 to 73.38 seconds (Table 6.9 and Fig. 6.10) and.79 to 35.07 seconds (Table and Fig.), respectively. As the concentration of crospovidone and sodium starch glycolate increased, the wetting time of Torsemide mouth dissolving tablets increased as well.By increasing the concentration of crospovidone and sodium starch glycolate, the water absorption of Torsemide mouth dissolving tablets was reduced. Oral dissolving tablets have a disintegration time of 38.21 to 22.36 seconds (Table and Fig).By increasing the concentration of crospovidone and sodium starch glycolate, the disintegration time of Torsemide mouth dissolving tablets was shortened. According to the results above, the T7 formulation outperformed other formulations in terms of wetting time, water absorption ratio, and disintegration time. Furthermore, the T8 formulation showed the best water absorption ratio and the shortest wetting and disintegration times. Due to gelling and the ensuing viscosity-producing effects, this parameter rises. Torsemide mouth dissolving tablets' post compression results indicated that the formulation's composition was adequate.

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