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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 often used due to their cost-effectiveness and convenience of self-administration. For example, mouth dissolving tablets dissolve in saliva and may be eaten without the need for water. The pre-compression characteristics of a powder blend, weight variation test, thickness test, hardness, friability, drug content, wetting time, water absorption ratio, and disintegration time were used to evaluate the tablets. 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 tablet was prepared by Torsemide (Solid Dispersion), Crospovidone, Sodium starch glycocolate, Mannitol, Magnesium Stearate, Talc, and Aspartame in eight different batches (T1-T8 formulations).As a consequence, it was noted that the T7 formulation outperformed the others in terms of disintegration time, water absorption ratio, and wetting time.

Key Words:-Mouth Dissolving Tablet, 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 [1-4]. 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 [5]. Solid dosage forms also present

significant administration challenges in other patient groups, such as children, mentally challenged, bed ridden and uncooperative patients [6]. 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 [7-8].

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 [9]. 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 [10-11].

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. Becausepre-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 [12-13].

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.

Material & Method

Drug profile

Torsemide

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.[128]

Fig. 1: Chemical structure of torsemide

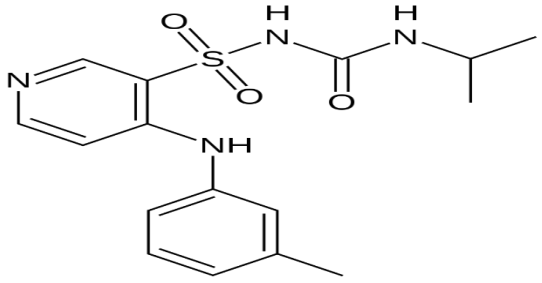


Table 1: Physico-chemical properties of torsemide

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	163-164ºC
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, compared to wet granulation technique, direct compression method yields higher productivity and better quality of tablets.

Direct compression was used to create the tablet softorsemide.Every formulation element listed in Table 1 was weighed appropriately and combined using a mortar and pestle.After a brief period of drying, this powder mixture was again mixed well and passed through a Sieve 60.Then, a blender was 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 80 mg 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

The powder combination formulation was evaluated using established methodologies for its various rheological characteristics. Three times (n=3) was the assessment conducted, and mean statistics were provided.

Bulk density

The bulk density and tapped density are assessed in order to calculate the blend-to-die filling rate. The bulk density was measured in accordance with the study report. Following the filling of the mixes into a measuring cylinder, the total volume was recorded. The powder mixture's gravity was determined using a digital weighing balance. The bulk density was ascertained using the formula below:

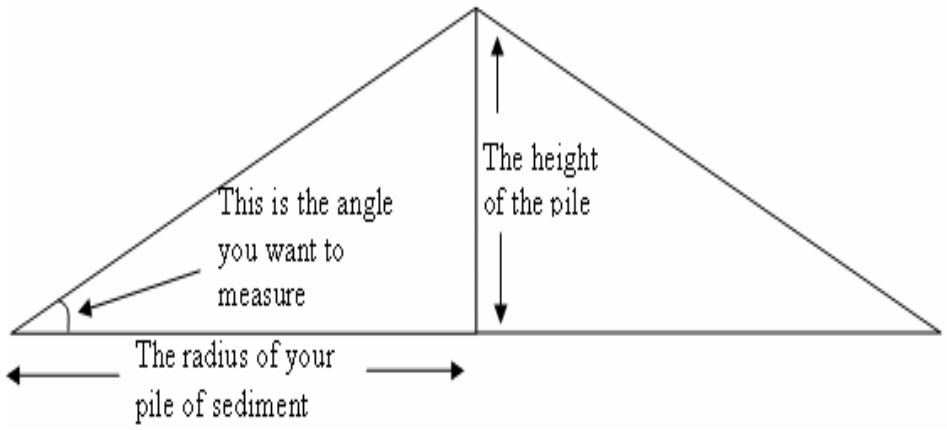
Bulk Density = Weight of the powder/Volume of the powder

Angle of repose

The fennel was positioned 6 cm above the graph paper in this procedure. The fennel was gradually eliminated from the powder kept on. The scale was used to calculate the heap's height. The following formula was used to calculate the angle of repose:

$$\theta=\tan^{-1}h/r$$

Where, h = height of heap of granularbed, 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

The formula below was used to calculate Hausner's ratio, which was then expressed as a percentage.

$$H=D_t/D_b$$

Where Dt denoted the powder's tapped density and Db denoted its bulk density

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 prepared powders were mixed with a lubricant (talc) and glideant (magnesium stearate) prior to compression into tablets.The powder was punched into tablets using 10 mm flat-faced punches with the aid of compression.

Evaluation of compression characteristics of tablets

Once tablets are formulated, it is necessary to verify that the dosage form is appropriate for the intended therapeutic outcome. The evaluation of compression tables is done using a variety of parameters. Using standard procedures, the prepared tablets' thickness, friability, hardness, weight variation, and dissolution test were assessed.

Weight variation test

Each of the 20 tablets was weighed individually during this process. By calculating average mean, the average weight of a single tablet was determined. It has been said on IP that no more than two tablets result in noticeably different weight. According to IP note, none of the unique weights shall deviate from the mean weight by more than twice the proportion stated in the monographs.

Thickness test

We measure the tablet thickness in micrometres using the helpvernier calliper. Three readings were averaged, and the mean result was reported (n=3).

Hardness test

The hardness of prepared tablets was measured using the Monsanto Hardness Tester. The kg/cm2 measure was used to calculate the hardness. Three readings were taken, with an average recorded.

Friability test

The abrasion rate of prepared tablets was determined using the Roche friabilator. Twenty pills are kept in the friabilator chamber; weigh each one. For four minutes, the friabilator was rotated at a speed of 25 rpm. After the rotation of the stabiliser tables was finished, the

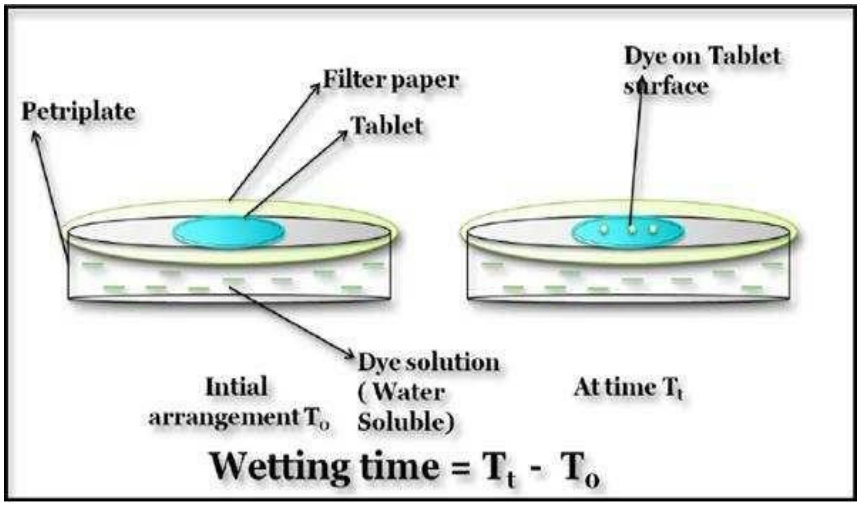
weights were weighed, and the percentage of weight reduction was computed using a formula.

Drug content

To ascertain the drug content, the three tablets were crushed with a pestle into a fine powder in a mortar. A single tablet's worth of powder was swallowed and dissolved in phosphate buffer at a pH of 6.8. Using a UV-visible spectrophotometer, determine the absorbance of a diluted sample of tromemide at 260 nm. The medication content was determined using the standard calibration curve.

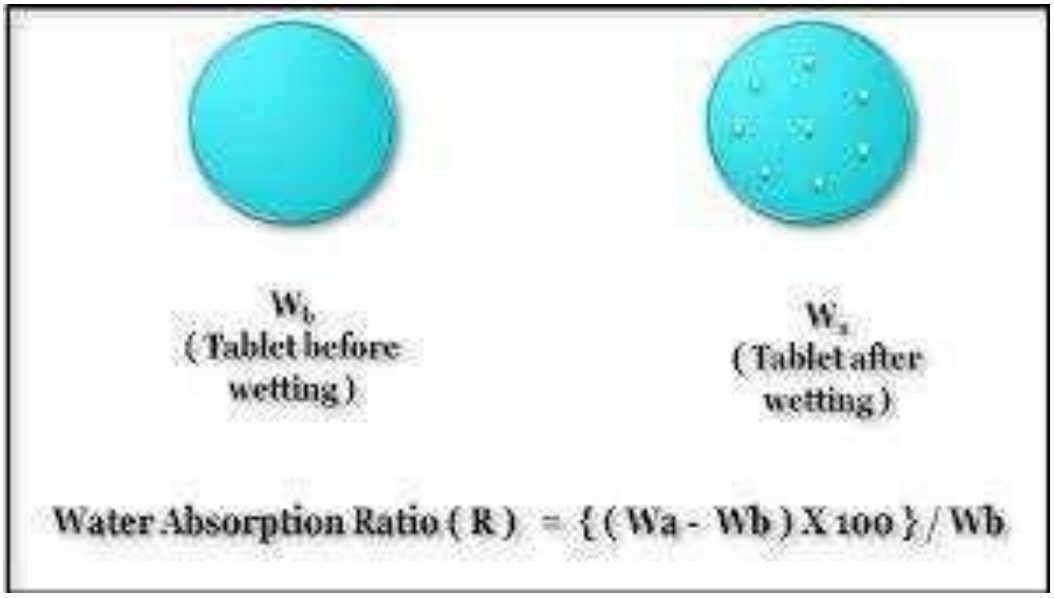
Wetting time

By placing the tablets in the Petri dish, which contained six millilitres of purified water and two folded pieces of tissue paper, the amount of time needed to fully wet the tablets was calculated.



Water absorption ratio procedure

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



RESULT

Various formulations' bulk and tapped densities were calculated. The bulk density ranges from 0.473 to 0.483, while the tapped density ranges from 0.467 to 0.513. The results showed that the Compressibility Index ranged from 11.39 to 14.09 and the Hausner's ratio was between 1.12 and 1.19. Angle of repose showed good to exceptional powdered mix flow characteristics (Table 6.6). Direct compression techniques can be used to create mouth-dissolving tablets, according to Torsemide's pre-compression research.

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

Parameters	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**
Mean Angle of 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
Mean Apparent bulk density* (g/cm^3)±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
Mean Tapped bulk density* (g/cm^3)±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
Compresibility 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 displayed in tables is an average of three calculations

Evaluation of mouth dissolving tablet of Torsemid

The evaluation of the physicochemical properties of the Torsemide mouth dissolving tablet produced the following findings. The tablet's thickness and width are included in its dimensions. All formulations were found to range in thickness from 3.21 to 3.62. Table observations show that all formulations' tablet weights fell within 305 ± 1 mg, which is below USP limitations. The hardness of the tablet of all 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 friability result implied that all formulations could survive shocks. UV spectroscopy was used to measure the homogeneity of the 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 and sent to industry scientists; the results showed successful trials. According to Table and Fig., the wetting duration was 17.79 to 35.07 seconds, and the water absorption ratio was 39.24 to 73.38 seconds (Table 6.9 and Fig. 6.10).When the concentrations of crospovidone and sodium starch glycolate were increased, the wetting time of Torsemide mouth dissolving tablets was prolonged. The concentration of ropidogonine and sodium starch glycolate was increased by decreasing the water absorption of Torsemide mouth dissolving tablets.

The disintegration time of mouth dissolving tablets ranges from 38.21 to 22.36 seconds (Table and Fig).When the concentration of rospovidone and sodium starch glycolate was increased, the disintegration time of Torsemide mouth dissolving tablets was shortened. According to the results above, the T7 formulation outperformed the others in terms of disintegration time, water absorption ratio, and wetting time. Furthermore, the T8 formulation showed the best water absorption ratio and the lowest disintegration and wetting times. This parameter increases due to gelling and its consequent viscosity producing effects.

The post-compression results of Torsemide mouth dissolving tablets suggested that the tablet 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
	0.28	0.19	0.24	0.27	0.29	0.22	0.20	0.25

Friability (%)*	± 0.02	± 0.01	± 0.03	± 0.01	± 0.05	± 0.06	± 0.02	± 0.01
Tablet Hardness (Kp)*	3.29 ± 0.06	3.18 ± 0.03	3.51 ± 0.06	3.05 ± 0.04	3.62 ± 0.07	3.21 ± 0.05	3.73 ± 0.03	3.42 ± 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

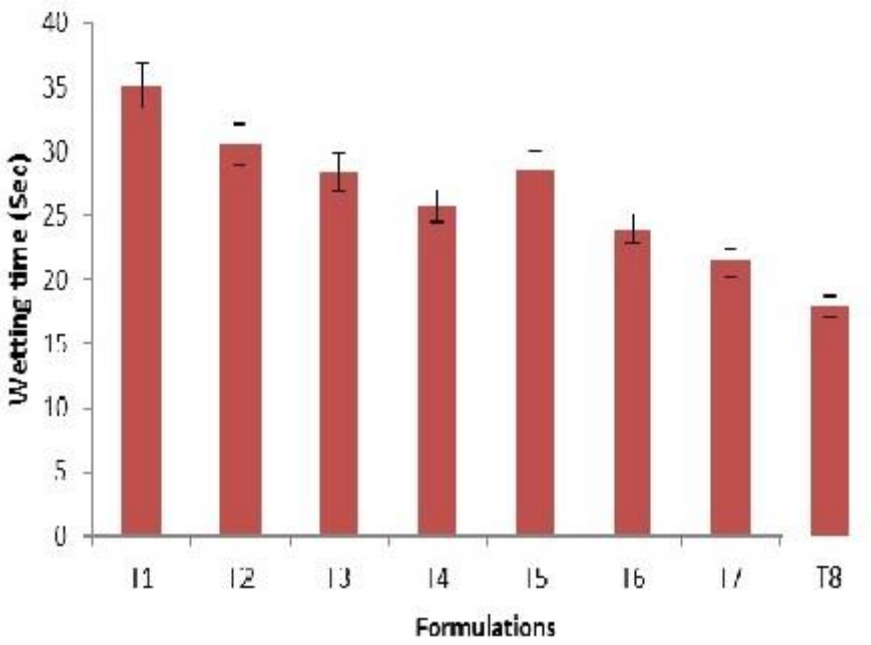


Fig 2: Wetting time of Torsemide mouth dissolving tablets

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

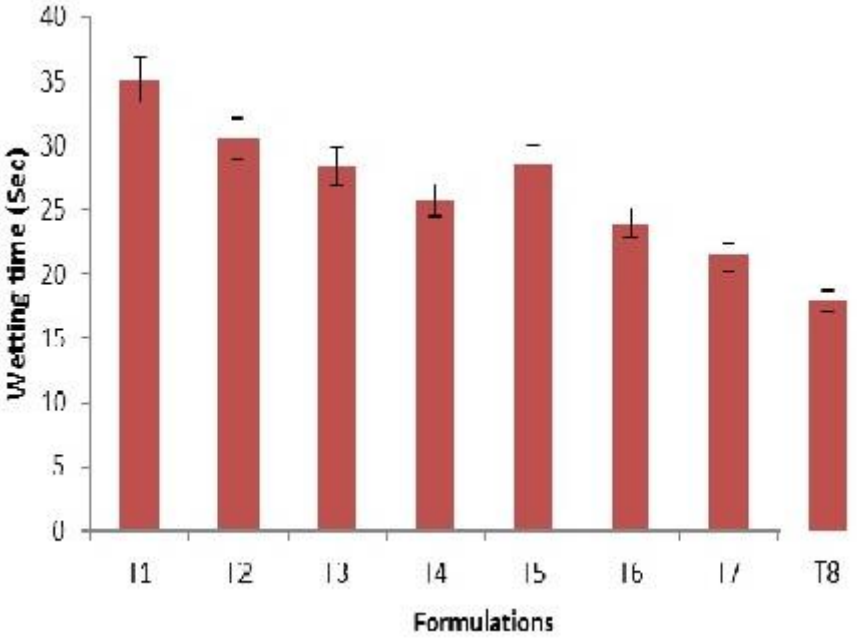


Fig 3: Water absorption ratio of Torsemide mouth dissolving tablets

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

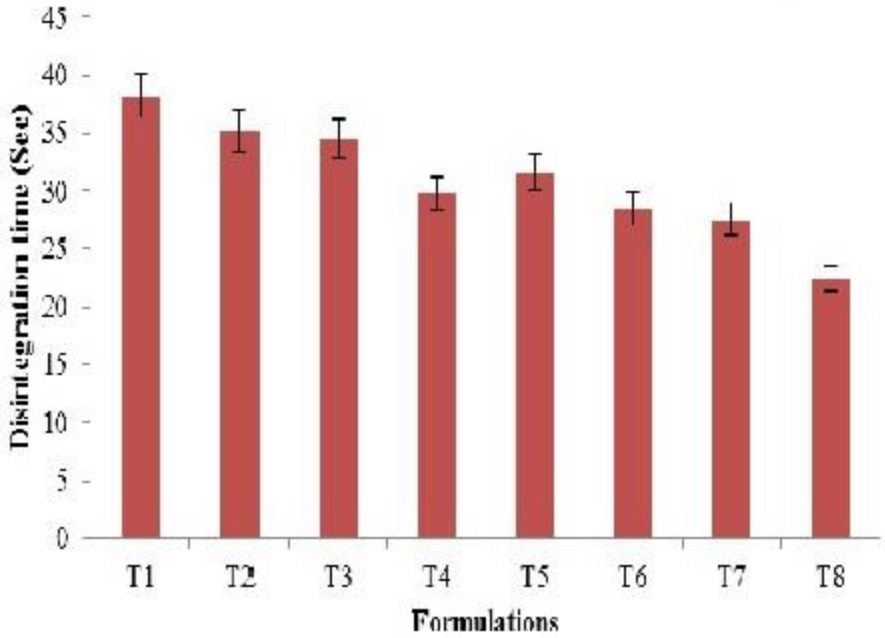


Fig 4: Disintegration time of Torsemide mouth dissolving tablets

Summary & Conclusion:-

Oral administration of therapeutic agents is still the favoured option due to its high degree of patient compliance, correct dose, low cost of therapy, self-medication, non-invasive manner, and convenience of administration. Direct compression was used to create the tablet softorsemide. Every formulation element listed in the table was weighed appropriately and combined using a mortar and pestle. After a brief period of drying, this powder mixture was again mixed well and passed through a Sieve 60.After that, blenders were used for additional processing.

The evaluation of the physicochemical properties of the Torsemide mouth dissolving tablet produced the following findings. The tablet's thickness and width are included in its dimensions. All formulations were found to range in thickness from 3.21 to 3.62. Table observations show that all formulations' tablet weights fell within 305 ± 1 mg, which is below USP limitations. The hardness of the tabletofall 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 friability result implied that all formulations could survive shocks. UV spectroscopy was used to measure the homogeneity of the 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 and sent to industry scientists; the results showed successful trials. According to Table and Fig., the wetting duration was 17.79 to 35.07 seconds, and the water absorption ratio was 39.24 to 73.38 seconds.When the concentrations of crospovidone and sodium starch glycolate were increased, the wetting time of Torsemide mouth dissolving tablets was prolonged. The concentration of ropidogonine and sodium starch glycolate was increased by decreasing the water absorption of Torsemide mouth dissolving tablets. Oral dissolving pill disintegration times vary from 38.21 to 22.36 seconds (Table and Fig).When the concentration of rospovidone and sodium starch glycolate was increased, the disintegration time of Torsemide mouth dissolving tablets was shortened.

The T7 formulation demonstrated exceptional wetting time, water absorption ratio, and disintegration time, as observed from the above results in contrast to alternative formulations. Furthermore, the T8 formulation showed the best water absorption ratio and the lowest disintegration and wetting times. This parameter rises as a result of gelling and the viscosity-producing effects that follow. The post-compression results of Torsemide mouth dissolving tablets suggested that the ingredients utilised in the tablet formulation were adequate.

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