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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF TOFISOPAM

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Mouth Dissolving Tablets, Fenugreek, Sodium Starch Glycolate

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ABSTRACT

Drug delivery system became sophisticated as pharmaceutical scientists acquire a better understanding of the physiochemical and biochemical parameters pertinent to their performances. Over the past three decades fast dissolving drug delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the fastest, safest, convenient and most economic method of drug delivery having the highest patient compliance and preferred over conventional tablets. The goal of this study was to formulated and evaluated mouth dissolving tablets of Tofisopam. The key to develop successful MDT formulations by direct compression method is to select a right superdisintegrant and compatible excipents depending upon the FTIR studies. Various formulations were prepared by direct compression method using different concentrations of Sodium starch glycolate (4 to 8mg)) as synthetic superdisintegrant and isolated mucilage of Fenugreek (4 to 8mg) as natural superdisintegrant. Formulations were evaluated for pre-compression and post-compression parameters like uniformity of weight, thickness, hardness, friability, drug content, wetting time, water absorption ratio, *in vitro* dispersion time, *in vitro* disintegration time and *in vitro* dissolution study. Results revealed that among the 6 formulations, the formulation FMT3 containing 8mg Fenugreek and formulation FMT6 containing 8mg Sodium starch glycolate was found to be promising formulation. FMT3 showed disintegration time of 25 seconds and the drug release was up to 98.82% in 7 minutes and FMT6 showed disintegration time of 38.53 seconds and the drug release was up to 95.25% in 7 minutes.

INTRODUCTION

Among all route of administration, oral route is most important and preferable route of administration of solid dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow; almost 50% of the population is affected by such problem[1]. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet and capsules when water is not available, also in elderly patients and children, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis[2]. The present study shows a crucial need of a new dosage form that can improve patient compliance. The Center for Drug Evaluation and Research (CDER), US FDA defined Mouth dissolving/disintegrating tablets (MDDTs) are "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Recently European Pharmacopoeia also adopted the term "Oro Dispersible Tablet" defined as uncovered tablet for buccal cavity, where it disperses before ingestion[3]. Mouth disintegrating tablets (MDT) are also known as fast dissolving, mouth dissolving, rapid-dissolve, quick disintegrating, orally disintegrating, rapimelt, orodispersible, melt-in-mouth, quick dissolving, porous tablets, EFVDAS or Effervescent Drug Absorption System[4]. In today's scenario MDTs are more preferred for patients suffering from diseases like antacids; muscle relaxants; hypertension; depression; nausea and vomiting (generally occurs in patients who are following chemotherapy, radiation therapy and surgery); heart attacks etc. The treatment of major disorder requires prolonged pharmacotherapy in order to resolve the current episode and reduce the risk for recurrence of disease symptoms. Such prolonged therapy requires considerable commitment on the part of patients to take their medication as prescribed. During the past decade, the MDT technology makes tablets dissolve or disintegrate in the mouth without additional water intake, has drawn a greater deal of attention. The tablets disintegrate into smaller granules or melt in the mouth from a hard solid structure to a gel like structure, allowing

by patients. The disintegration time for those tablets varies from a few seconds to more than a minute[5]. MDTs are not only formulated for people who have swallowing difficulties, but also are ideal for active people[6].

2.1 Advantages of Mouth Dissolving Tablets (MDTs):

MDTs offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include:

- **Patient compliance:** No need of water to swallow the dosage form. Hence, it is convenient for patients who are travelling and do not have immediate access to water. It is convenient to administer especially for geriatric, paediatric, mentally disabled and bed ridden patients who have difficulty in swallowing[7].
- **Enhanced bioavailability and stability:** Achieve increased bioavailability through pre-gastric absorption of drugs from mouth, pharynx and oesophagus as saliva passes down avoiding first pass metabolism. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability [8].
- **Rapid action:** Have rapid dissolution and absorption of the drug which will produce quick onset of action.
- **Accurate dosing*:*** Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for paediatric and geriatric patients[13].
- **Enhanced palatability:** Good mouth feel, especially for paediatric patients as taste masking technique is used to avoid the bitter taste of drug[9].
- **Cost effective:** Conventional processing and packaging equipments allow the manufacturing of tablets at low cost. No specific packaging required. It can be packaged in push through blisters[10].
- **Business Avenue:** Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management[11, 12].

2.2 Patient factors: Mouth dissolving dosage forms are particularly suitable for patients, who for one reason or the other find it inconvenient to swallow traditional tablets and capsules with a glass of water[13]. These include the following:

- Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
- Paediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Travelling patients suffering from mot ion sickness and diarrhoea that do not have easy access to water.
- Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H_2 blockers, which are prescribed in order to avoid gastric ulceration.
- Mentally challenged patients, bedridden patients and psychiatric patients[14] .

3. MATERIALS AND METHODS

3.1 Materials

Tofisopam was obtained as a gift sample from (Concern Pharma, Ludhiana), microcrystalline cellulose & sodium starch glycolate (DFE Pharma, Bangalore), magnesium sterate, mannitol, spray dried lactose and talc (S D Fine Limited, Mumbai).

3.2 Methods

3.2.1 Extraction of fenugreek seeds

Fenugreek was used as natural superdisintegrant and compared with synthetic superdisintegrant such as (Sodium starch glycolate). It helps in improving the disintegration and dissolution rate of the tablet. Fenugreek was extracted using the following steps mentioned below:

- **Step 1:** Fenugreek seed (100mg) were ground to 100 mesh using a laboratory mill. The fine powder was extracted with boiling hexane in Soxhlet apparatus for 80 mins.
- **Step 2:** The obtained extract was treated with 95% ethanol (maintaining its boiling point) for 130 min in conical flask to remove the unwanted saponin.
- **Step 3:** Enzyme deactivation was initiated by refluxing the extract with 70% ethanol for 180 mins. The resulting mixture was repeatedly treated with ethanol to remove undissolved traces if necessary.
- **Step 4:** The residue was filtered through muslin cloth at room temperature.
- **Step 5:** The filtered residue was subjected to mechanical stirring at 700 rpm with addition of water for 8 hrs.
- **Step 6:** The obtained mixture was centrifuged at 2500 rpm for 12 min.

- **Step 7:** The supernatant contained crude fenugreek gum, which was decanted and precipitated by addition of ethanol (70%).
- **Step 8:** Finally, the gum precipitate was washed with acetone and pure fenugreek gum was oven dried.

3.2.2 Preparation of mouth dissolving tablets

Mouth dissolving tablets of Tofisopam were prepared by direct compression method, using synthetic superdisintegrant sodium starch glycolate and natural superdisintegrant fenugreek, in different ratios. Mannitol, Microcrystalline cellulose, Lactose, Talc and Menthol flavor were used to enhance the mouth feel. Following steps were used in the preparation of mouth dissolving tablets:

- **Step 1:** Weighed 50mg drug (Tofisopam) along with synthetic superdisintegrant (Sodium starch glycolate) and natural superdisintegrant (fenugreek) in mortar.
- **Step 2:** Microcrystalline cellulose, talc, mannitol, magnesium sterate, spray dried lactose and menthol flavour was added in a mortar and mixed with pestle. These ingredients were then passed through sieve no 80 to remove impurities.
- **Step 3:** The powders were compressed into tablets on tablet punching machine and weight of the tablets were 150mg.
- **Step 4:** The mouth dissolving tablets were prepared and collected.

Table 1: Formulation of Mouth Dissolving Tablets of Tofisopam

FC	FMT1	FMT2	FMT3	FMT4	FMT5	FMT6
Drug (Tofisopam)	50	50	50	50	50	50
Fenugreek	4	6	8	-	-	-
Sodium starch glycolate	-	-	-	4	6	8
MCC	46.5	44.5	42.5	46.5	44.5	42.5
Magnesium sterate	4	4	4	4	4	4
Talc	4	4	4	4	4	4
Mannitol	40	40	40	40	40	40
Flavour	1.5	1.5	1.5	1.5	1.5	1.5

4. PHYSICAL EVALUATION OF POWDER BLEND

4.1 Determination of Angle of Repose:

The flow property was determined by angle of repose which is maximum angle that can be attained between the free surfaces of powder heap with its horizontal plan. The formula for calculating angle of repose was:

$$\Theta = \tan^{-1} \frac{h}{r}$$

Values of θ less than 40°C indicate responsible flow property to the powder and value greater than 50°C indicates difficulty in flow. Table 1.4 shows the result obtained for angle of repose of all the formulations. All formulation showed the angle of repose within 20-30°. This indicated that all formulation showed good flow properties.

Table 1.2: Grading of powder according to angle of repose

S. No	Angle of Repose (Θ)	Type of flow
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Passable
4.	>40	Very Poor

4.2 Bulk Density: Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$\rho_b = \frac{M}{V_b}$$

4.3 Tapped Density: The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the formula:

$$\rho_t = \frac{M}{V_t}$$

4.4 Compressibility Index: The simplest way for measurement of flow of powder is its compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follow:

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

4.5 Hausner Ratio (%): Hausner ratio is the ratio of tapped density to the bulk density. It was measured by pouring the weighed powder into a measuring cylinder and the initial volume was noted and then it was subjected to 500 tappings from a height of 2 inches. Haunser's ratio was calculated by noted tapped density and poured density values shown in Table 1.4. Evaluated values were less than 1.25 indicating good/free flowing. It means that the powder flow properties were within the pharmacopoeias limits.

Table 1.3: Hausner's Ratio

S. No	Hausner's Ratio	Property
1.	0-1.25	Free flowing
2.	1.25-1.6	Cohesive powder

Table: 1.4: Pre-Compression Parameter of Tofisopam Mouth Dissolving Tablets

FC	FMT1	FMT2	FMT3	FMT4	FMT5	FMT6
Angle of Repose (θ)	27.25± 0.50	25.96± 0.75	28.70± 0.35	25.35± 0.89	29.05± 0.15	31.50± 0.65
Bulk Density (g/cm^3)	0.584± 0.009	0.625± 0.007	0.611± 0.006	0.627± 0.005	0.633± 0.005	0.574± 0.012
Tapped Density (g/cm^3)	0.666± 0.007	0.718± 0.008	0.711± 0.010	0.714± 0.011	0.715± 0.011	0.649± 0.003
Compressibility Index (%)	12.212± 0.005	12.957± 0.005	14.051± 0.010	12.220± 0.004	11.447± 0.015	11.499± 0.004
Hausner's Ratio	1.126± 0.392	1.134± 0.544	1.136± 0.765	1.112± 0.795	1.129± 1.233	1.117± 0.782

5. RESULTS AND DISCUSSIONS

5.1 Evaluation of Mouth Dissolving Tablets

Shape and Colour of Tablets

Randomly picked tablets from each formulation batch examined under lens for shape and in presence of light for colour. The tablet showed round shaped, white in colour. There was no change in colour and odour of the tablets in all the formulations. This indicated that all the excipients used were compatible with the drug and did not cause any chemical reaction that affects the properties of formulation.

Thickness Test

The thickness of the tablets was measured by using Vernier caliper by picking the tablets randomly. The values were almost uniform in all formulations. Thickness was found to be in the range of 2.07±0.12mm to 2.41±0.02mm respectively. Uniformity in the values indicated that formulation was compressed properly. The mean values were shown in Table 1.5.

Hardness

Hardness test was performed by Monsanto hardness tester. Hardness was maintained to be within 2.713± 0.16 to 3.04± 0.15 kg/cm^2. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform and posses good mechanical strength with sufficient hardness. The results were tabulated in Table 1.5.

Friability

Friability was found well within the approved range (<1%) in all the formulation. Friability was in between 0.53% to 0.73%. Results revealed that the tablets possessed good mechanical strength. The results were tabulated in Table 1.5

Weight variation

All the tablets passed weight variation test as the percentage variation was within the pharmacopoeia limit of ±7.5%. It was found to be from 146 mg to 152 mg. The weight of all the tablets was found to be uniform. This was due good flow property and compressibility of all the formulations. The percent weight variation for all the formulations were tabulated in Table 1.5.

Wetting Time

The wetting time of the tablets was measured using a very simple process. Five circular tissue papers of 10cm diameter were placed in a Petri dish with a 10cm diameter. Ten millilitres of water containing a water soluble dye (crystal violet) was added to the Petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time. All tests are summarized in Table 1.5.

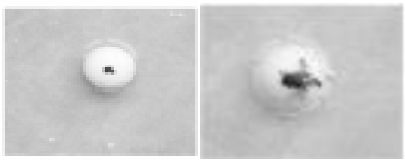

Figure 1.1: Wetting Time

***In vitro* Dispersion Time**

Tablet was added to 10ml of phosphate buffer pH 6.8 and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed. The dispersion time was found to be in the range of 26.33-68.66.

Figure 1.2: Dispersion test of tablet

***In vitro* Disintegration Time**

In this test the time required for complete dispersion of a tablet was measured. The tablets were subjected to the evaluation of disintegration time and the results ranged from 25 to 62 seconds. Based on the in-vitro disintegration time, formulation FMT3 and FMT6 were found to be promising and showed a dispersion time of 25.66 and 38.56 seconds respectively.

Table 1.5: Evaluation Parameters of Mouth Dissolving Tablets

Ingredients	**FMT1**	**FMT2**	**FMT3**	**FMT4**	**FMT5**	**FMT6**
Thickness (mm)	2.313± 0.022	2.076± 0.121	2.329± 0.089	2.414± 0.025	2.361± 0.061	2.295± 0.066
Weight (mg)	148.46± 0.731	152.13± 0.66	150.93± 1.45	146.235± 0.602	147.33± 0.322	149.4± 0.264
Hardness (kg/cm^2)	2.713± 0.156	2.913± 0.200	3.043± 0.150	3.003± 0.090	2.800± 0.191	2.990± 0.101
Friability (%)	0.823± 0.051	0.64± 0.05	0.536± 0.030	0.626± 0.045	0.653± 0.081	0.856± 0.041
In vitro Disintegration Time (s)	51.66± 2.51	62.66± 2.51	25.66± 2.08	41.66± 2.51	66.33± 3.12	38.56± 2.08
Wetting Time (s)	47.33± 6.02	57.66± 3.51	18.66± 2.51	38.33± 3.51	55.66± 6.11	32.33± 2.08
In vitro Dispersion Time (s)	57.33± 1.52	65.20± 2.10	27.33± 2.08	48.30± 2.64	68.66± 2.08	31.33± 2.51

***In Vitro* Dissolution studies**

In Vitro dissolution studies for all the fabricated tablets was carried out using USP paddle method at 50 rpm in 900 ml of Phosphate buffer (pH 6.8) as dissolution media, maintained at 37±0.5^{0}C. 5ml of aliquot was withdrawn at the specified time intervals filtered through whatmann filter paper and assayed spectrophotometrically at 312 nm. An equal volume of fresh medium, which was pre-warmed the constant volume throughout the test. The various kinetic

treatments were given to the dissolution data. The *in vitro* permeation data obtained were subjected to a zero order and first order kinetics to understand the release profile and release mechanism. When a graph of the cumulative percentage of the drug released from the tablet against time was plotted, zero order release was linear in such a plot, indicated that the released rate was independent of concentration. The zero order kinetics models data are shown in Table 1.6 and graphically in Figure 1.3. The first order kinetics models data are shown in Table 1.7 and graphically as Figure 1.4.

Table 1.6: *In Vitro* Release Data of Tofisopam Tablets

Time (min.)	Cumulative Percentage Drug Released					
	FMT1	FMT2	FMT3	FMT4	FMT5	FMT6
0.000	0.000	0.000	0.000	0.000	0.000	0.000
1.000	61.03	68.75	77.58	70.96	57.72	74.27
2.000	67.03	70.33	84.63	74.22	64.66	77.99
3.000	73.88	72.98	89.51	76.89	69.43	85.04
4.000	78.70	80.73	95.52	85.66	73.12	92.13
5.000	80.23	81.73	98.25	90.54	75.72	94.84
6.000	81.13	82	98.65	91.02	76.12	95.11
7.000	81.64	82.62	98.82	91.45	76.75	95.24

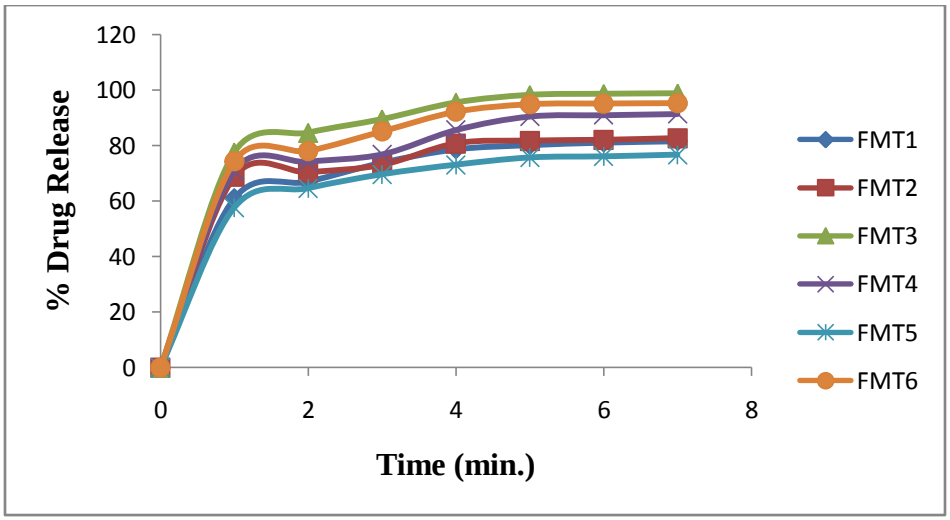

Figure 1.3: *In Vitro* Release curve of Tofisopam Tablet Zero Order Release

Table 1.7: *In Vitro* Log % Drug Retained Data of Tofisopam Tablets

Time (min.)	Log Cumulative Percentage Drug Retained					
	FMT1	FMT2	FMT3	FMT4	FMT5	FMT6
0	2	2	2	2	2	2
1	1.590	1.494	1.350	1.462	1.626	1.410
2	1.505	1.472	1.186	1.411	1.548	1.342
3	1.416	1.431	1.020	1.431	1.485	1.174
4	1.328	1.284	0.651	1.284	1.429	0.895
5	1.296	1.263	0.243	1.263	1.385	0.712
6	1.275	1.255	0.211	0.953	1.378	0.667
7	1.263	1.240	0.223	0.931	1.366	0.638

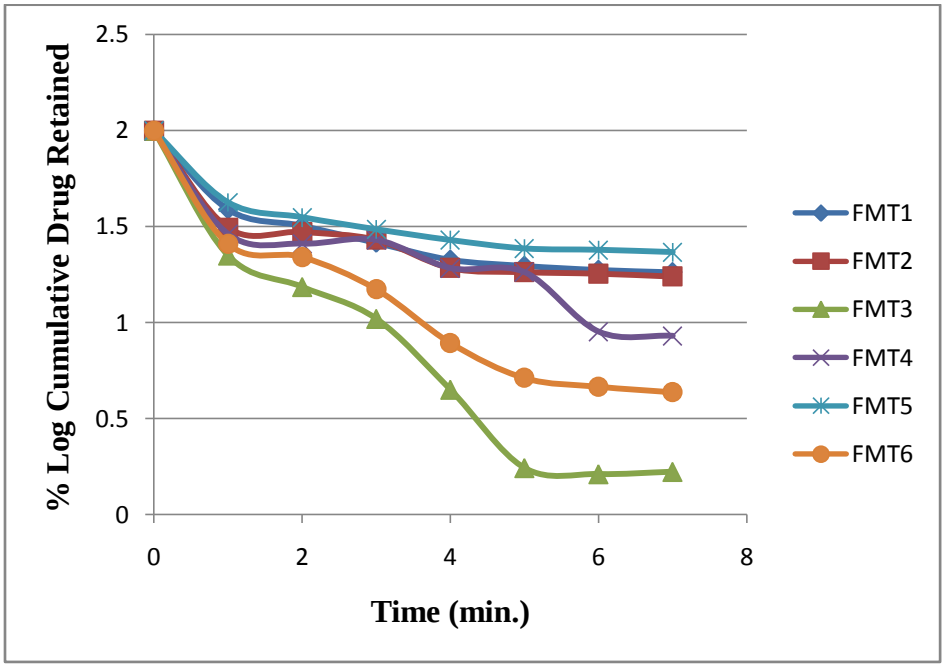

Figure 1.4: In Vitro Drug Retained Curve of Tofisopam Tablet First Order

The order of drug release was found to be**:**

FMT3> FMT6> FMT4> FMT2> FMT1> FMT5

The formulation with fenugreek (natural superdisintegrant) showed maximum release than the tablets with Sodium starch glycolate. The release data obtained were subjected for the kinetic treatment to know the type and order of drug release. The obtained data from *in- vitro* Drug release study are tabulated and represented in Table 1.8 as:

(a) Cumulative percentage drug release v/s Time (Zero order release kinetics)

(b) Log cumulative percentage drug retained v/s Time (First order release kinetics)

Table 1.8: Fit of various Kinetic Models for Mouth Dissolving Tablets of Tofisopam

Formulation Code	Zero Order			First Order		
	Intercept	R^2	K(mg/min)	Intercept	R^2	K(mg/min)
FMT1	35.60	0.578	8.528	1.769	0.768	0.088
FMT2	38.78	0.518	8.173	1.733	0.708	0.086
FMT3	45.20	0.544	10.04	1.749	0.926	0.254
FMT4	39.33	0.585	9.502	1.784	0.849	0.126
FMT5	33.97	0.566	7.927	1.786	0.734	0.074
FMT6	42.30	0.566	9.863	1.747	0.905	0.183

Drug Content

Randomly selected tablets were weighed and powdered in a glass mortar pestle. The weight equivalent to 50mg drug (Tofisopam) was weighed and dissolved in 5 ml of methanol in volumetric flask, the volume was adjusted to 100 ml with phosphate buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. Content in was determined spectrophotometrically at 312 nm.

Table 1.9: Drug Content in the Mouth Dissolving Tablet of Tofisopam

Formulation Code	Drug Content (%)
FMT1	97.2%
FMT2	98.78%
FMT3	99.4%
FMT4	96.6%
FMT5	96.84%
FMT6	99.24%

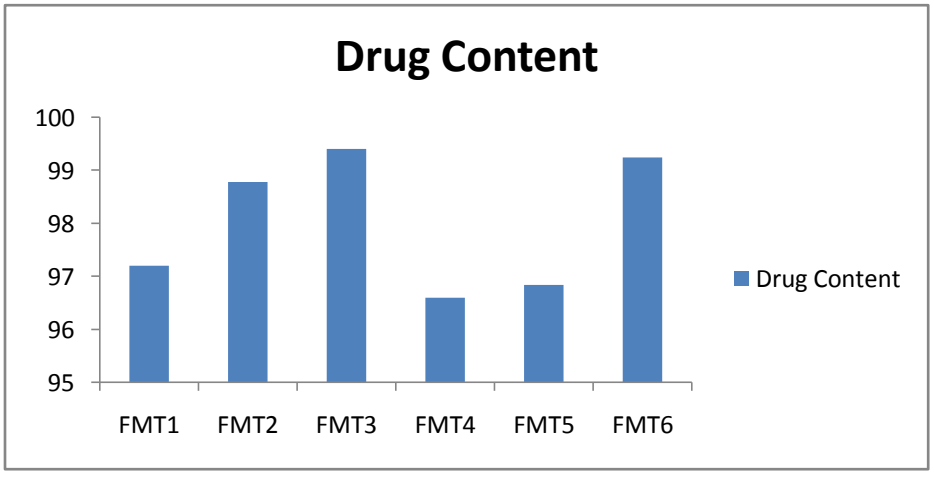

Figure 1.5: Graphical representation of drug content in mouth dissolving tablets

6. CONCLUSION

The present study was an attempt to develop a novel mouth dissolving product. The main objective of present investigation was to design, prepare and evaluate mouth dissolving tablets of Tofisopam, an anti- anxiety drug to reduce its hepatic first pass metabolism, enhancing its bioavailability and thus reducing its side effects making its patient compliance. Initially six formulations were prepared FMT1, FMT2, FMT3 using natural superdisintegrant (fenugreek) and remaining FMT4, FMT5, FMT6 using synthetic superdisintegrant (Sodium starch glycolate) along with binders, lubricants and flavouring agents. These tablets can disintegrate and dissolve rapidly when placed in the oral cavity.

These tablets were evaluated for their organoleptic (Color, odor, Taste), physical (Size, Shape, Texture) and quality control parameters (Diameter, Thickness, hardness, Friability, Disintegration Time and Wetting Time).

The drug release was found as:

FMT3 > FMT6 > FMT4 > FMT2 > FMT1 > FMT5

On the basis of drug release it was observed that the formulation containing 8% fenugreek (formulation FMT3) showed the maximum release of 98.82% and 8% Sodium starch glycolate (formulation FMT6) showed the maximum release of 95.24% in 7mins. The regression co-efficient (r^2) value of FMT3 formulation was found to be 0.544 and 0.926 for zero order and first order model respectively. It can be concluded that all the formulations follow first order kinetics and formulation FMT3 showed best drug release for first order kinetics. Hence mouth dissolving tablets can be successfully prepared by using natural superdisintegrant, maintaining their disintegration time less than 1minute, which provide faster effect and better patient compliance. The tablets may be helpful for geriatric and paediatric patients experiencing difficulty in swallowing conventional tablets, which leads to poor patient compliance. Thus, it was concluded that the method designed for mouth dissolving tablet of tofisopam using natural superdisintegrant formulation is simple, rapid, cost effective and highly efficient.

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