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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF THIOCOLCHICOSIDE

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Keywords:

MDT (mouth dissolving tablets), natural polymers, synthetic polymers, superdisintegrants

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ABSTRACT

The purpose of this present study was to formulate and evaluate the mouth dissolving tablets (MDTs) of Thiocolchicoside, posses muscle relaxant activity by comparing natural polymer (Modified Tragacanth Gum) and synthetic polymer (Sodium starch glycolate) used as superdisintegrants to achieve rapid onset of action, improves bioavailability and as to defeat the swallowing problems in patients.

The key to develop successful MDT formulations by the direct compression method is to select the appropriate superdisintegrants and compatible excipients determined by FTIR studies. Various formulations are prepared with different concentrations of Modified Tragacanth used as natural polymer and Sodium Starch glycolate as synthetic polymer by using direct compression method. Formulations F1-F4 are prepared with Modified Tragacanth Gum, F5-F8 are prepared with Sodium Starch glycolate. Pre and postcompression parameters were evaluated and the results were within specifications as per IP. When compared all eight formulations, F4 and F8 showed better results. Therefore formulation F4 was compared with F8, then F4 was selected as the best formulation as it showed good in-vitro disintegration time, in-vitro drug release, wetting property. When an increase in the concentration of super disintegrating agent (natural, synthetic) improves the drug release of the tablet.

INTRODUCTION

Oral route is the most preferable route for drug therapy due to their ease of ingestion, painless administration and mainly patient compliance[1-3]. But there is big disadvantage in oral administration i.e. dysphagia (difficulty in swallowing). Dysphagia is common among all age groups but it is mainly found in geriatrics and pediatrics[4]. Because children have underdeveloped muscular and nervous system and old patients have weak nervous and muscular system. It shows that about 50% of the population is affected by this issue, which results in a high occurrence of noncompliance and non-efficacious therapy. In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. In novel drug delivery system, there is new dosage form developed i.e. FDDDS (Fast dissolving drug delivery system). FDDS includes all mouth dissolving tablets, films, strips etc. Now a days, mouth dissolving tablets are very common in market because of their excellent patient compliance[5]. Mouth dissolving tablets defines as a solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water. According to European Pharmacopoeia, Orodispersible tablet as a tablet that to be placed in the mouth where it disperses rapidly before swallowing in less than three minutes. The purpose of formulating mouth dissolving tablets of Thiocolchicoside is to provide quick disintegration and increase the bioavailability of drug. Thiocolchicoside is a competitive $GABA_A$ receptor antagonist used as muscle relaxant with anti-inflammatory effects. In this present study, design of mouth dissolving tablets of Thiocolchicoside by comparing with natural (Modified Tragacanth Gum) and synthetic (Sodium starch glycolate) by direct compression technique[6-7] to achieve quick disintegration, to increase the water uptake within shorter wetting time. The direct compression is inexpensive and convenient for producing tablets of sufficient mechanical integrity. Researchers are looking for directly compressible agents which cannot improve only mechanical integrity of MDTs but also disintegrate the tablets in a few seconds in the oral cavity. In the present study Thiocolchicoside drug was used it is an anti-inflammatory, muscle relaxant and analgesic drug. Oral bioavailability of Thiocolchicoside is very low[8] i.e. 25%, it is because of high first pass metabolism degradation of the drug. Incorporating Thiocolchicoside in mouth dissolving tablets will help in bypassing the first pass metabolism and therefore its oral bioavailability will increase

significantly. Reduction in dose of the drug will also help in lowering the risk of side effects of drug. During research work all these objectives were achieved.

MATERIALS AND METHODS

Thiocolchicoside was recieved as gift sample from Associated Biotech, Baddi and Sodium starch glycolate was obtained from DFE Pharma, Banglore. Tragacanth gum were purchased from SD Chem, Mumbai. Other materials used were of analytical grade and procured from commercial sources.

Preparation of Modified Tragacanth gum[9]

5gms of Tragacanth, 0.05gms tween80 and 1ml solution of hydrogen peroxide (30% w/v) were taken in 100ml of purified water and boiled for 15min. The mixture was allowed to cool and settle. The clear supernatant fluid was decanted and the sediment was washed repeatedly with water. Finally the sediment was collected by centrifuging at 2500RPM and dried at 800C for 4hrs. The dried product was ground to fine powder and passed through sieve no.200.

Preparation of Mouth dissolving tablets by Direct compression method[10]

Mouth dissolving tablets of Thiocolchicoside were prepared by direct compression as per the formula given in table1,2 .individual ingredients were passed through sieve no.60 separately. The drug and the ingredients were weighed and mixed in geometrical order and direct compressed to acquire tablets of 100 mg weight using flat face 8mm size punch by single punch tablet compression machine.

Table 1: Formulation of Thiocolchicoside Mouth Dissolving Tablets containing Modified Tragacanth gum prepared by direct compression method

Formulation / Ingredients	F1	F2	F3	F4
Drug (mg)	8	8	8	8
Modified Tragacanth Gum (mg)	4	6	8	10
Talc (mg)	7	7	7	7
Magnesium stearate (mg)	7	7	7	7
Mannitol (mg)	37	36	35	34
Lactose (mg)	37	36	35	34
Total (mg)	100	100	100	100

Table 2: Formulation of Thiocolchicoside Mouth Dissolving Tablets containing Sodium Starch glycolate prepared by direct compression method

Formulation / Ingredients	F1	F2	F3	F4
Drug (mg)	8	8	8	8
Sodium starch glycolate (mg)	4	6	8	10
Talc (mg)	7	7	7	7
Magnesium stearate (mg)	7	7	7	7
Lactose (mg)	37	36	35	37
Mannitol (mg)	37	36	35	37
Total (mg)	100	100	100	100

Post compression evaluation parameters for Mouth Dissolving Tablets:

After the manufacture of tablets of every batch were subjected to the following tests.

1. Shape and Color of Tablets

Prepared tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light[11].

2. Uniformity of Thickness

The thickness of the tablets can be measured by using vernier caliper[12]. Five tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

3. %Friability

To achieve % friability within limits for MDT is the challenges to the formulator since all methods of MDT are responsible for increasing the % friability values. Thus, it is necessary that this parameter should be evaluated and the results are within bound limits (0.1 to 0.9)[13]. Friability of mouth dissolving tablets was determined by using friabilator, 10 tablets from each batch were selected at random and weighed accurately. Tablets were then placed in the plastic chamber that rotates at 25 rpm dropping tablets from a distance of six inches with each revolution. The friabilator was then operated for 100 revolutions after that tablets were dusted and reweighed[14]. Friability can be calculated by using following equation.

$$\text{Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

4. Hardness

The limit of hardness of the MDTs is usually kept in lower range to facilitate early disintegration in the mouth. The hardness of the tablets was determined using Monsanto hardness tester[15]. It is expressed in Kg/cm^2. Five tablets were randomly picked from each formulation and the mean and the standard deviation values were calculated[16].

5. Wetting time

Wetting time of dosage form is related with the contact angle. Wetting time of MDT is another important parameter, which need to be assessed to give an insight into the the disintegration properties of the tablets, a lower wetting time implies a quicker disintegration of the tablet[17].

10 ml of distilled water containing Eosin, a water-soluble dye was placed in a petridish of 10cm diameter. Tablets were carefully placed in the centre of the petridish and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The test results are presented as mean value of three determinations[18].

6. Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation[19-20].

$$R = \frac{W_a - W_b}{W_a}$$

Where, W_b= Weight of tablet before water absorption

W_a= Weight of tablet after water absorption

7. Weight uniformity test

The tablets (10) were selected randomly from each formulation and weighed individually to check for weight uniformity. The Indian Pharmacopoeia allows a little variation in the weight of a tablet. The following Table 3 %age deviation in weight variation is allowed[21].

Table 3: IP Limits for Weight Uniformity of Tablets

Average weight of a tablet	Percentage deviation
80 mg or less	10
More than 80 mg and less than 250 mg	7.5
250 mg or more	5

In all the formulations the tablet weight was more than 80 mg and less than 250 mg, hence maximum of 7.5% difference is allowed.

8. *In-vitro* disintegration time

The disintegration time of the prepared mouth dissolving tablets was determined by using USP disintegration test apparatus containing 900ml phosphate buffer pH 6.8 as a disintegrating media maintained at $37^0C \pm 2^0C$. Time was noted when all the fragments of mouth dissolving tablet passed through the screen of the basket. A mean of three determinations was recorded and reported in seconds, as *in-vitro* disintegration time[22].

9. % Drug content determination

Five tablets were selected randomly and average weight was calculated. Tablets were crushed in mortar and accurately weighed amount of average tablet was taken from the rushed blend. Then, samples were transferred to three 100ml volumetric flasks and were diluted up to mark with phosphate buffer solution, 6.8 pH. The content was shaken periodically. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 260 nm against blank reference.

10. *In-vitro* drug release study

Dissolution of the tablet of each batch was carried out using USP XXIII dissolution type II apparatus using paddle at 50 rpm. 900ml of phosphate buffer solution, pH 6.8 was filled in a dissolution vessel and the temperature of the medium was set at 37 ± 2^0C. 5 ml of sample was withdrawn at predetermined time interval of 1min, 3min, 5min, 7min, 9min and 11min and same volume of fresh medium was replaced. These samples were analyzed by an UV spectrophotometer at 260 nm using phosphate buffer solution, pH 6.8 as blank solution. The drug content was calculated using the equation generated from standard calibration curve. The percent cumulative drug release was calculated[23].

Dissolution test parameters for Mouth Dissolving Tablets of Thiocolchicoside

Medium : 900 ml of 6.8 pH phosphate buffer solution

Rpm : 50

Time : 1, 2,3,4,5,6,7,8,9,10 min.

Apparatus : Paddle

λ_{max} : 260nm

Temperature : 37^0 C ± 0.5^0 C

RESULTS AND DISSCUSSION

Pre compressional evaluation parameters:

1. Physical Evaluation

Polymeric dispersions were evaluated for various micromeritic properties.

1.1 Bulk density and Tapped density

The bulk densities of the powder blends of all the formulations ranged from 0.34 to 0.54 gm/cc. The Tapped densities of the powder blends of all the formulations ranged from 0.52 to 0.67 gm/cc in Table 4.

1.2 Angle of repose (θ)

It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane. Values ranged from 20º 33′ to 30º 16′ angle of repose (< 30) indicate good flow properties of granules, and it was observed to be within the pharmacopoeias limits (Table 4,5).

1.3 Compressibility index and Haunsner's ratio

The Hausners ratio values ranged from 1.14 to 1.25. Evaluated values were Less than 1.25 Indicating Good flow. It means that the powder flow properties were within the pharmacopoeias limits. The Carr's index values ranged from 12 to 20% in table 4,5.

Table 4: Pre-compression parameters of powder blend of Modified Tragacanth gum

Parameter	F1	F2	F3	F4
Loose bulk density(gm/cc)	0.520	0.514	0.512	0.540
Tapped bulk density(gm/cc)	0.616	0.606	0.626	0.623
Angle of repose θ (^{0})	30^0 16'	26^0 02'	21^0 06'	24^0 23'
Compressibility index(%)	15.50	15.18	18.20	13.3
Hausner's ratio	1.18	1.17	1.22	1.15

Table 5: Pre-compression parameters of powder blends containing Sodium Starch Glycolate

Parameters	F5	F6	F7	F8
Loose bulk density(gm/cc)	0.503	0.510	0.545	0.522
Tapped density(gm/cc)	0.623	0.640	0.624	0.636
Angle of repose θ (^{0})	20^0 33'	25^0 80'	24^0 52'	25^0 20'
Compressibility index(%)	19.7	20.3	12.6	17.91
Hausner's ratio	1.21	1.25	1.14	1.05

Post compressional evaluation parameters:

i. **Hardness**: The hardness of all the formulations ranged from 2.8 to 2.95 kg/cm2.The pharmacopoeias limit for hardness is 3-5 kg/cm^2. Hence all the formulations passed the test for hardness (Table-6,7).

ii. **Weight variation**: The weights of the tablets were between 98 to 101 mg, as the weight of the tablet is 100mg, the weight variation limit is ± 7.5%.The pharmacopoeias specification for weight variation limit is ±7.5%, for uncoated tablets weighing more than 80mg but less than 250mg. Hence all the formulations passed the weight variation test (Table-6,7).

iii. **Thickness**: The thickness of all the formulations was between 2.67 to 2.89 mm which was, according to the pharmacopoeias specifications. Tablet mean thickness was almost uniformly in all the formulations (Table-6,7).

iv. **Friability:** The friability of all the formulations was determined, and the values were in the range from 0.49 to 0.63 %.Friability below 1% were an indication of good mechanical resistance of the tablets. Hence all the formulations were within the pharmacopoeias limits (Table-6,7).

v. **Drug content**: The drug content uniformity was performed for all the 10 formulations and results are tabulated in Table-6,7. Three trials from each batch were analyzed by using spectrophotometer. Average value and standard deviations of all formulations were calculated.

vi. **Wetting time:** All the formulations were evaluated for wetting time and the values ranged from 20 and 39 seconds. Among the ten formulations, F4 and F8 were found to be better and showed a dispersion time of 20 and 23 seconds (Table-6,7).

vii. **Disintegration test:** The tablets were subjected to the evaluation of disintegration time and the results ranged from 29 to 49 sec. Among these results formulations F4 and F8 were shows a lesser dispersion time of 1 min respectively (Table-6,7).

Table 6: Post-compression parameters for Formulations containing Modified Tragacanth gum

S.No.	Parameters	F1	F2	F3	F4
1.	Hardness(gm/cm^2)	2.5±0.133	2.4±0.111	2.80±0.139	2.74±0.141
2.	Thickness(mm)	2.59±0.002	2.65±0.002	2.50±0.003	2.62±0.001
3.	Uniformity of weight(mg)$^{\#}$	99.8±3.0	101.1±3.0	98.4±3.5	100.8±3.2
4.	Friability(%)$^{\#}$	0.451±0.002	0.372±0.001	0.492±0.002	0.401±0.002
5.	Wetting time(sec)**	35.10±0.06	24.39±0.009	39.34±0.14	20.54±0.07
6.	Water absorption ratio(%)**	85.05±1.2	80.16±1.4	72.10±0.6	86.04±1.7
7.	Disintegration time(sec)**	35±0.666	30±0.999	34±0.817	29±0.139

#Results of one batch

**Each value was an average of three determinations(n=3)

Table 7: Post-compression parameters for Formulations containing Modified Tragacanth gum

S.No.	Parameters	F5	F6	F7	F8
1.	Hardness(gm/cm^2)	2.89±0.121	2.94±0.134	2.95±0.149	2.75±0.150
2.	Thickness(mm)	2.78±0.002	2.52±0.001	2.89±0.002	2.72±0.003
3.	Uniformity of weight(mg)$^{\#}$	98.4±3.1	100.2±2.8	99.6±2.5	100.6±3.1
4.	Friability(%)$^{\#}$	0.474±0.001	0.63±0.001	0.371±0.002	0.352±0.001
5.	Wetting time(sec)**	25.14±0.06	22.31±0.004	27.29±0.14	23.21±0.05
6.	Water absorption ratio(%)**	73.60±1.2	86.43±1.8	84.50±1.2	87.08±1.3
7.	Disintegration time(sec)**	39±0.121	34±0.093	32±0.754	39±0.701

#Results of one batch

**Each value was an average of three determinations(n=3)

viii. **In-vitro Release studies:**

Tablets were Prepared with modified Tragacanth (F1-F4), Sodium Starch Glycolate (F5 to F8), respectively. Hence, when compared to all eight formulations, F4 and F8 shows better results. It was observed that all the mouth dissolving tablets showed an in vitro release of 80-100% by the end of 5-10 min. The in-vitro dissolution profile indicated faster and maximum drug release from formulations F4 and F8. The in-vitro drug release profiles in zero order were plotted in Figures 1,3 and tabulated in Table-8,10. The log % drug retained profiles in first order were plotted in Figure 2,4 and tabulated in Table 9,11.

Table 8: *In-Vitro* Release of mouth dissolving tablets containing Modified Tragacanth gum

S.NO	Times in min.	% Drug release			
		F1	F2	F3	F4
1.	**1**	5.82±0.04	9.92±0.12	19.87±0.10	20.60±0.11
2.	**2**	17.33±0.09	15.02±0.16	35.42±0.15	39.01±0.50
3.	**3**	25.53±0.12	40.85±0.09	49.70±0.17	54.24±0.31
4.	**4**	54.30±0.05	61.02±0.44	64.2 ±0.06	67.12±0.25
5.	**5**	60.54±0.36	75.61±0.03	86.45±0.03	79.31±0.33
6.	**6**	73.15±0.02	89.82±0.13	94.07±0.26	86.09±0.09
7.	**7**	85.72±0.03	92.19±0.38	95.44±0.04	96.87±0.27
8.	**8**	86.04±0.02	92.45±0.10	95.34±0.21	97.25±0.01
9.	**9**	86.11±0.15	92.50±0.23	95.52±0.04	97.29±0.45
10.	**10**	86.14±0.01	92.55±0.19	95.65±0.11	97.31±0.12

*Each value was an average of three determinations

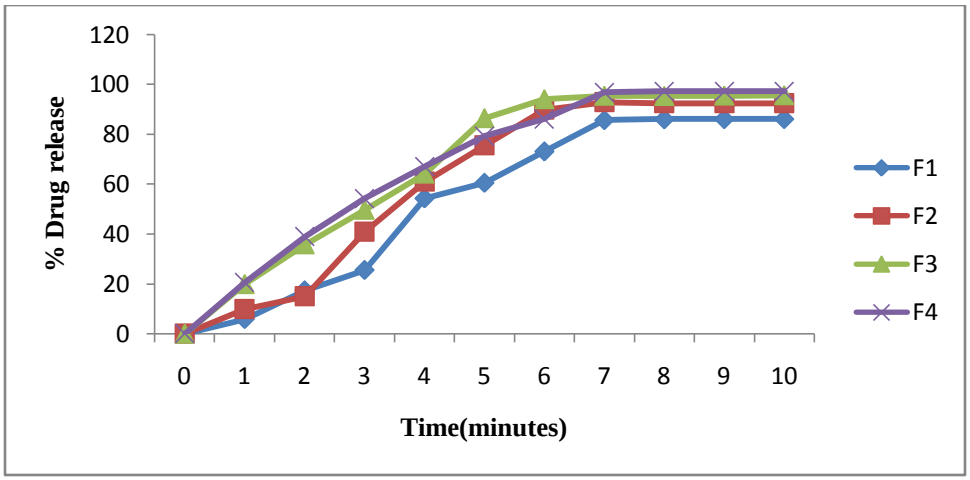

Figure 1: *In-vitro* release of Mouth Dissolving Tablets containing Modified Tragacanth gum for zero order

Table 9: In vitro log% Drug Retained Data of Thiocolchicoside Mouth Dissolving Tablets using Modified Tragacanth gum

Time	Log Cumulative % Drug Retained			
	F1	F2	F3	F4
0	2	2	2	2
1	0.764	0.996	1.298	1.313
2	1.238	1.176	1.549	1.597
3	1.407	1.611	1.696	1.734
4	1.734	1.785	1.807	1.826
5	1.782	1.878	1.936	1.899
6	1.864	1.953	1.973	1.934
7	1.933	1.964	1.979	1.986
8	1.934	1.965	1.979	1.987
9	1.935	1.966	1.980	1.988
10	1.935	1.966	1.980	1.988

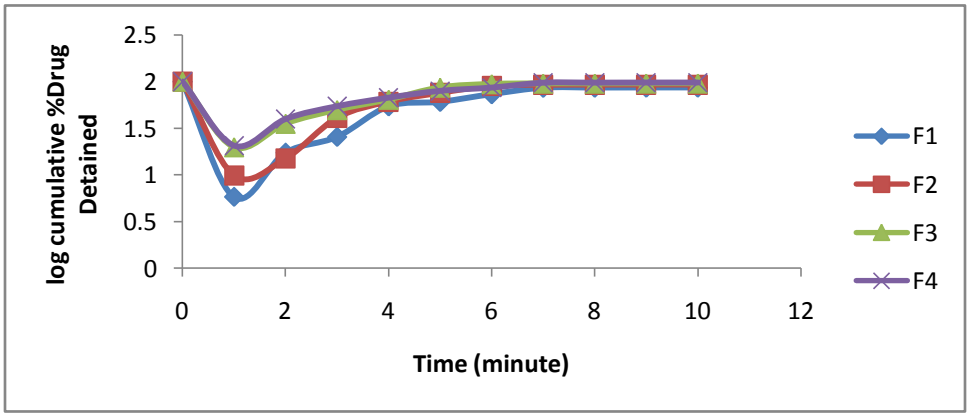

Fig 2: *In-vitro* drug retained curve of Thiocolchicoside from Mouth Dissolving Tablets using Modified Taragacanth for first order (Batches F1 to F4)

Table 10: *In-Vitro* Release of mouth dissolving tablets containing Sodium Starch glycolate

S.NO.	Times in min.	% Drug Release			
		F5	F6	F7	F8
1.	1	5.14±0.12	8.28±0.34	20.49±0.05	22.68±0.12
2.	2	16.03±0.02	25.49±0.11	32.82±0.06	38.24±0.20
3.	3	29.57±0.67	49.80±0.12	58.80±0.04	58.43±0.63
4.	4	60.90±0.58	60.62±0.12	75.93±0.01	79.57±0.41
5.	5	65.05±0.15	75.44±0.06	84.01±0.04	86.92±0.16
6.	6	75.71±0.09	82.50±0.14	93.09±0.02	94.12±0.45
7.	7	79.12±0.06	87.86±0.11	94.12±0.01	95.93±0.26
8.	8	83.92±0.01	90.43±0.04	94.20±0.08	96.17±0.27
9.	9	83.94±0.08	90.56±0.21	94.32±0.12	96.22±0.05
10.	10	83.98±0.02	90.62±0.16	94.32±0.03	96.31±0.02

*Each value was an average of three determinations

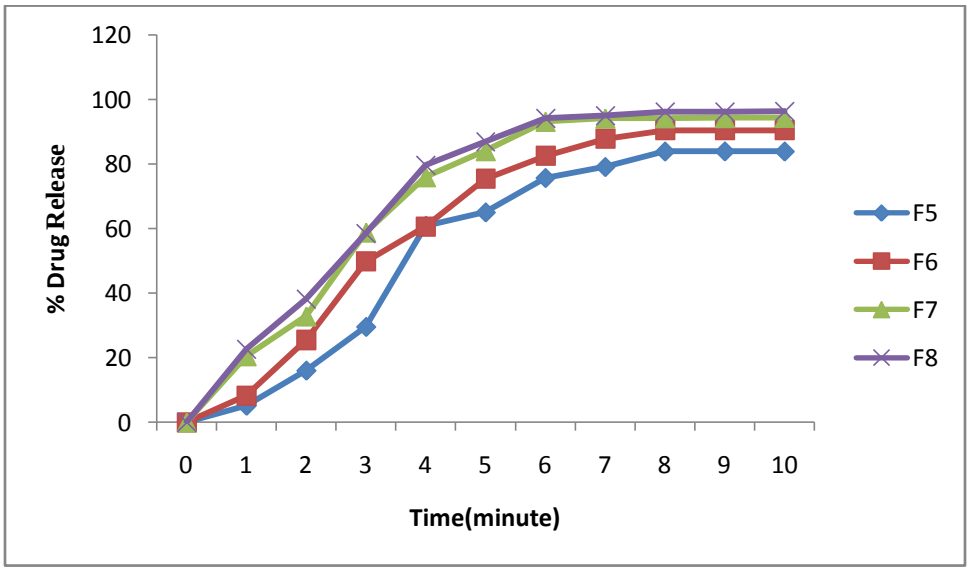

Figure 3: *In-vitro* release of Mouth Dissolving Tablets containing Sodium Starch glycolate

Table 11: In vitro log% Drug Retained Data of Thiocolchicoside Mouth Dissolving Tablets using Sodium Starch Glycolate

Time	Log Cumulative % Drug Retained			
	F1	F2	F3	F4
0	2	2	2	2
1	0.710	0.918	1.311	1.355
2	1.204	1.406	1.516	1.582
3	1.470	1.697	1.769	1.766

4	1.784	1.782	1.880	1.900
5	1.813	1.877	1.924	1.939
6	1.879	1.916	1.968	1.973
7	1.898	1.943	1.973	1.981
8	1.923	1.956	1.974	1.983
9	1.923	1.956	1.974	1.983
10	1.924	1.957	1.974	1.983

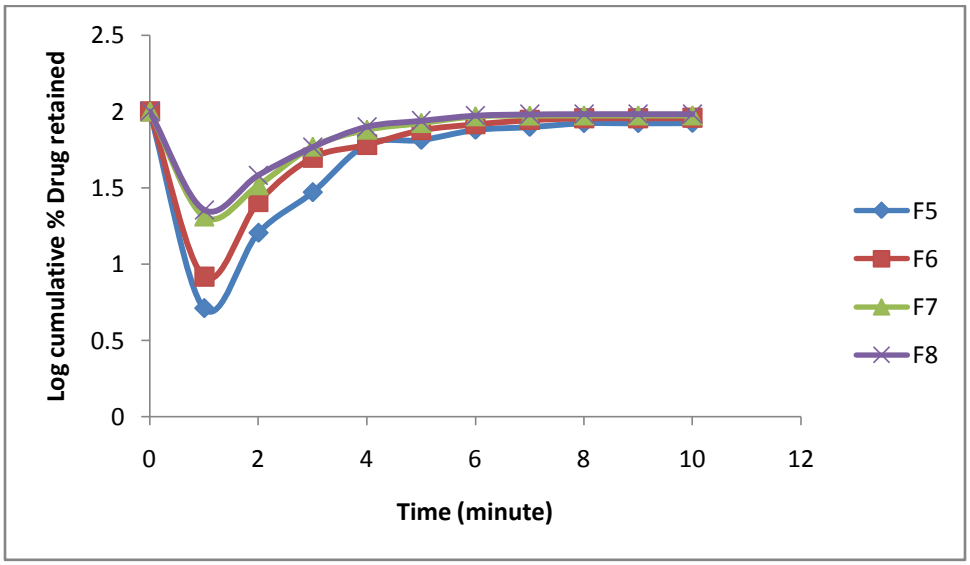

Fig 5.4: *In-vitro* drug retained curve of Thiocolchicoside from Mouth Dissolving Tablets using Sodium Starch Glycolate for first order (Batches F5 to F8)

As the concentration of the polymer increases, there was a decrease in the disintegration time and increase in dissolution rate of the drug. From drug release studies, it was noticed that increase in concentration of the super disintegrating agent increases the drug release. Therefore formulation F4 was compared with F8. Then F4 was selected as the best formulations as it showed good, in-vitro drug release, wetting property, in-vitro disintegration time and pre compression and post compression results were within the limits as given in official references.

Drug Content

Five tablets were selected randomly and average weight was calculated. Tablets were crushed in mortar and accurately weighed amount of average tablet was taken from the rushed blend. Then, samples were transferred to three 100ml volumetric flasks and were diluted up to mark with

phosphate buffer solution, 6.8 pH. The content was shaken periodically. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 260 nm against blank reference. The percentage of drug content was given in the Table 12.

Table 12: Drug Content in the Mouth Dissolving Tablets of Thiocolchicoside

Formulation Code	Drug Content (%)
F1	96.01
F2	90.38
F3	94.04
F4	98.05
F5	92.73
F6	93.81
F7	95.34
F8	97.45

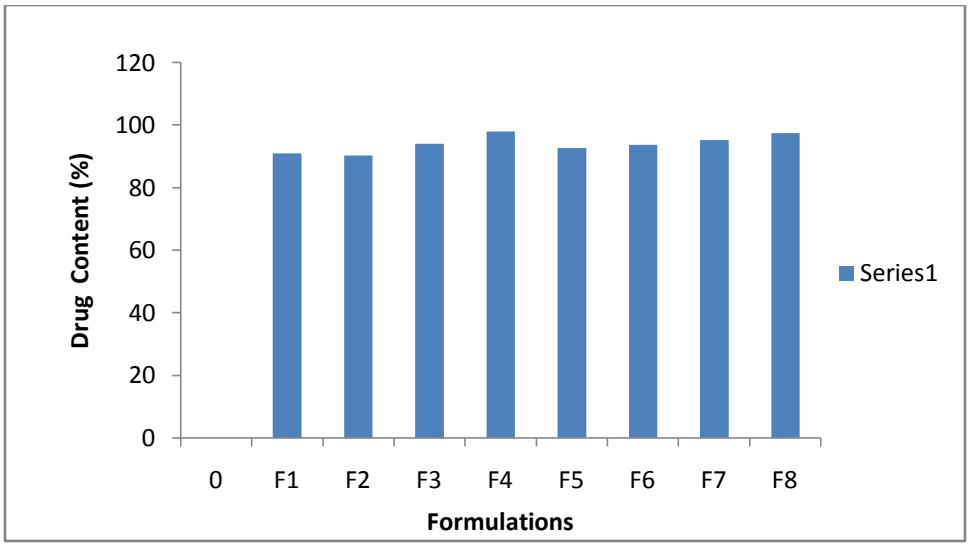

Fig 5.5: Bar graph of Drug Content of all formulations (F1-F8)

CONCLUSION

In the present study, mouth dissolving tablets were prepared using natural superdisintegrants (Modified Tragacanth gum) and synthetic superdisintegrants (Sodium Starch Glycolate). Direct compression method was selected to prepare mouth dissolving tablets of Thiocolchicoside. Evaluation parameters such as hardness, friability, weight variation and drug content indicate that values were within limits as given in official references for all formulations. The formulation F4 contains natural superdisintegrants (Modified Tragacanth gum) and F8 contains synthetic

superdisintegrants (Sodium Starch Glycolate) which leads to absorption of water resulting in fast swelling of polymers. It causes the in-vitro dispersion within 30 seconds. In-vitro drug release study was carried out and based on the results; F4 and F8 were identified as the best formulations among all the formulations and in vitro release profiles was more than 95% within 10 minutes.

F4 > F8 > F3 > F7 > F2 > F6 > F1 > F5

This proves that the increase in composition of superdisintegrants results the increase in drug release of the tablets.

After comparing both formulations F4 and F8, F4 was identified as the best formulation which was prepared using natural superdisintegrant.

Thus, mouth dissolving tablets of Thiocolchicoside can be successfully prepared by both superdisintegrants, maintaining their disintegration time less than one minute, which provides rapid onset of action and better patient compliance.

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