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Orally Dispersible Tablet of Mesalazine: Formulation and Evaluation

Himanshu Rajendra Nikam[1,*], Yogesh B. Rokade[1]

Abstract

Oral disintegrating tablets (ODTs) have become increasingly more and more popular, particularly among elderly and pediatric patients who have difficulties with swallowing. The 5-aminosalicylic acid compound oral mesalazine, frequently referred to as mesalamine, is used to treat mild to severe ulcerative colitis and has a high percentage of success in causing and establishing response. Mesalazine has a topical therapeutic action at the location of the suffering colonic mucosa. The medication's disadvantage is that it is nearly insoluble in water, which results in poor solubility, GI absorption, and bioavailability. Therefore, the goal of this study is to create an oral disintegrating tablet of mesalazine by combining croscarmellose *(CM) with its kneading mixture and using* croscarmellose *as a super disintegrating agent. The present research has been undertaken with the aim to formulate and evaluate the oral dispersible tablet of mesalazine.*

Keywords: Colitis, ulcerative, oral dispersible tablet (ODT), mesalamine (Mesalazine/5-Amino Salicylic Acid), kneading mixture

INTRODUCTION

The most significant and convenient drug administration method is oral administration. Unique approaches to drug delivery (NDDS) have developed recently with the goal of improving patient compliance and the safety and effectiveness of medicinal compounds through formulation. Orally disintegrating tablets (OrDTs) are one such strategy that has produced a lot of fascination as a preferred substitute for conventional tablets and capsules over the previous three decades. The disadvantage of traditional tablets can be resolved by mouth-dissolving tablets (MDTs) or ODTs. Within a few seconds, the tablets dissolve, disintegrate, and disperse in saliva [1]. According to modified life-cycle management, simple dosage for pediatric, elderly, and mental patients with dysphagia, new ODT technologies satisfy a wide range of pharmaceutical and patient needs. In general, dysphagia affects around 35% of people and is related to several illnesses, including Parkinson's disease, mental illnesses, motion sickness, unconsciousness, water scarcity, etc. To address these issues, a unique medication delivery mechanism, like mouth-dissolving tablets, has been developed [2].

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The technology working on the production of ODTs affects their performance. The capacity of these tablets to dissolve quickly and provide in saliva, without the need for water, is an essential feature. Significant technological advancements have made it possible for ODT to carry out this special duty. The colon is where mesalazine or 5 amino salicylic acid is mostly absorbed in the liver; it undergoes ring-hydroxylation and N-acetylation before conjugating with glucuronic acid. The acetylator phenotype of the individual influences

the serum levels of mesalazine (5-amino salicylic acid) to some amount. A plasma mesalazine (5-amino salicylic acid) concentration of more than 20 µg/ml is associated with successful ulcerative colitis treatment. The majority of mesalazine is eliminated through the urine [3]. Treatment for multiple bowel disorders, including Crohn's disease, ulcerative colitis, amebiasis, colon cancer, local colonic pathology treatment, and systemic administration of protein and peptide medications. Its partition coefficient, the ratio of noctanol to pH phosphate buffer 7.4, equals 1.5.

It slightly dissolves in water and is insoluble in stomach fluid simulation. The combination of warfarin or methotrexate raises the chance of adverse effect. Considering the facts above, we have decided to use the kneading combination of croscarmellose in the weight ratio of 5-amino salicylic acid to CM to formulate an oral disintegrating tablet using the wet granulation method.

Include mesalazine (5-aminosalicylic acid, 5-ASA) in a formulation that is either slow-release or sustained release and is made up of 5-ASA molecules joined by an azo bond. Slow-release formulations are required to avoid 5-ASA being prematurely absorbed in the proximal portion of the small intestine, which would leave the more distal portions – where inflammation is frequently the worst – with insufficient 5-ASA availability [4].

ORAL MUCOSA

The oral cavity is composed of up of the floor of the mouth, lips, cheek, tongue, and hard and soft palates. The buccal, sublingual, gingival, palatal, and labial mucosa are all parts of the oral mucosa, which is the lining of the oral cavity. Approximately 60% of the oral mucosal surface area is made up of the buccal, sublingual, and ventral tongue mucosal tissues. Closely packed epithelial cells make up the upper quarter to one-third of the oral mucosa. The tongue's taste receptors are among the many sensory receptors found in the oral mucosa. The oral cavity has three different types of oral mucosa: the buccal mucosa, which is the lining mucosa, is in the sublingual area (the floor of the mouth) and the outer oral vestibule (Figure 1) [5].

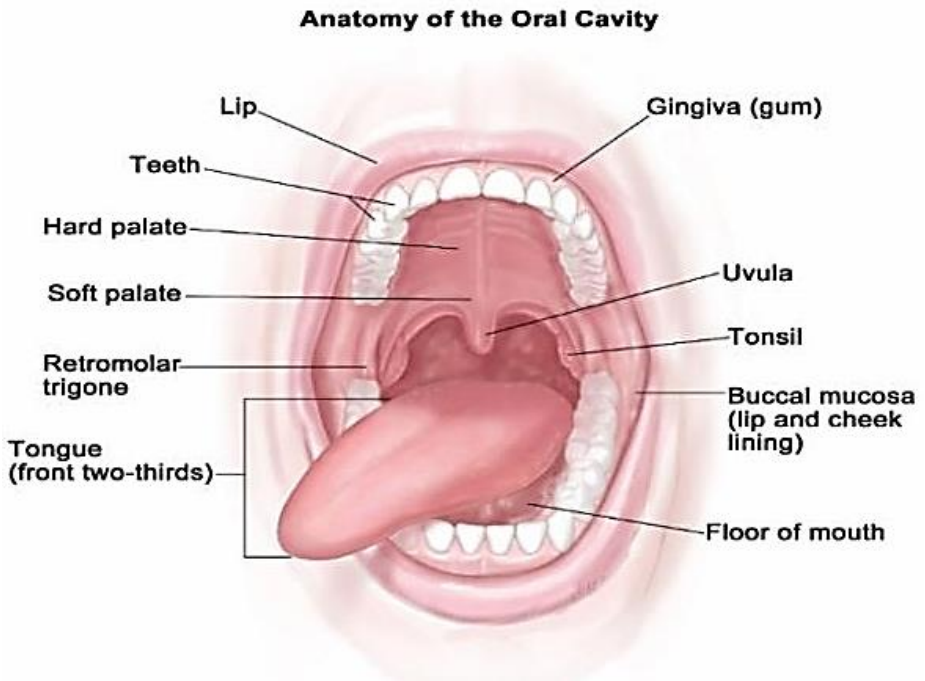

Figure 1. Oral mucosa.

In an adult human, the lining mucosa consists up around 60% of the oral mucosal lining's surface area, followed by the masticatory mucosa at 25% and the specialized mucosa at 15%.

ORALLY DISINTEGRATING DOSAGE FORMS

The need to give patients more traditional ways to take their medication gave rise to the idea of oral disintegrating dose forms. It is interesting to acknowledge that over the past ten years, there has been a significant growth in demand for ODDFs, especially among pediatric and elderly patients who have trouble swallowing traditional tablets and capsules. As a result, they avoid prescriptions, which leads to a high rate of ineffective treatment [6]. Swallowing traditional solid dosage forms becomes challenging when a patient has abrupt episodes of coughing, recurrent episodes of vomiting, or motion sickness. In these circumstances, oral disintegrating dosage forms can be a useful substitute method of medication delivery [7].

As the saliva travels down, the medication may then be absorbed from the pharynx, esophagus, or other parts of the GIT. In these situations, bioavailability is noticeably higher than that of the typical tablet dosing form [8].

Advantages of Orally Disintegrating Tablets

- Avoiding the hepatic first-pass effects.
- Suitable for geriatric and pediatric patients.
- A large amount of blood supply.
- Potentially rapid systemic delivery.
- Easy to use for patients with dysphagia.

Disadvantages

- Drugs get wiped away by saliva.
- Needs to be formulated for a palatable taste.
- Somewhat limited surface area.
- Oral mucosa permeation is a barrier.

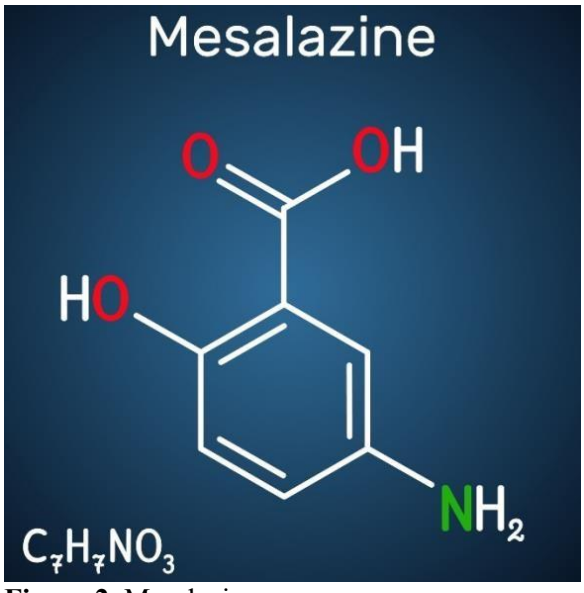

Figure 2. Mesalazine.

DRUG AND EXCIPIENTS PROFILE

Drug: Mesalazine (5-Amino Salicylic Acid)

- *Source:* 5-aminosalicylic acid (5-ASA) or mesalazine is primarily derived from a prodrug called sulfasalazine, which is then broken down by bacteria in the colon to release the active 5-ASA molecule (Figure 2).
- *Molecular Formula:* $C_7H_7NO_3$.

- *Molecular Weight*: 153.135 g/mol.
- *IUPAC Name:* 5-amino-2-hydroxybenzoic acid.
- *Boiling Point: 275–280°C.*
- *Functional Category:* non-steroidal anti-inflammatory drug (NSAID). It is used to treat inflammatory bowel disease (IBD) and ulcerative colitis (UC).

STRUCTURAL FORMULA

Clinical Pharmacology

It is thought to inhibit the cyclooxygenase and lipoxygenase pathways, which lowers the production of leukotrienes and pro-inflammatory prostaglandins [9]. Likewise associated with colon inflammation, the peroxisome proliferator activated receptor-g has been found to be a target of 5-ASA activity [10]. The optimal mesalazine formulation would increase the active drug's distribution to the colonic mucosa while minimizing systemic absorption in the upper gastrointestinal tract. The intestinal epithelial cells' N-acetyltransferase 1 (NAT 1) enzyme acetylates ingested 5-ASA to produce the inactive metabolite N-Ac-5ASA. After that, this metabolite is either released back into the intestinal lumen and eliminated in the faeces or absorbed systemically and eliminated in the urine [11].

Therapeutic Uses

This systematic review will quantify the pharmacokinetic profiles of oral mesalazine formulations and pro-drugs used in the treatment of ulcerative colitis. Similar ranges of systemic absorption of 5ASA as shown by plasma pharmacokinetics, 24-hour urinary excretion of total 5ASA, and fecal excretion of 5ASA when used in the treatment of irritable bowel disease.

Adverse Effects

The most common adverse effects include headache, nausea, diarrhea, constipation, myalgia, arthritis, and stomach discomfort. Interstitial nephritis and pancreatitis are uncommon but dangerous adverse effects [12].

Excipients

- *Microcrystaline cellulose phosphate:*
  - *Molecular Formula:* $(C_6H_{10}O_5)$ n.
  - *Molecular Weight:* 36,000 grams/mole.
  - *IUPAC Name:* 2-{[4,5-dihydroxy-2-(hydroxymethyl)-6-methoxyoxan-3-yl]oxy}-6(hydroxy methyl)-5-methoxyoxane-3,4-diol.
  - *Boiling Point:* 667.9°C.
  - *Functional Category:* Superdisintegrants.
  - *Structural Formula:* (Figure 3).

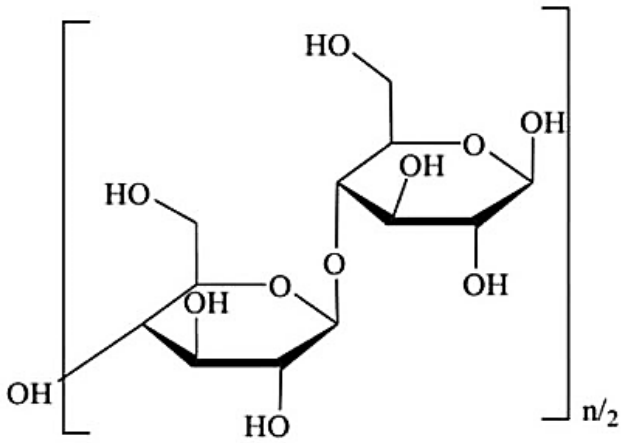

Figure 3. Microcrystalline cellulose.

Dicalcium Phosphate

- *Molecular Formula:* $CaHPO_4$.
- *Molecular Weight:* 136.06 g/mol.
- *IUPAC Name:* Calcium hydrogen phosphate.
- *Boiling Point:* 158°C.
- *Functional Category:* Fillers (enhances bulk of dosage form).
- *Structural Formula:* (Figure 4).

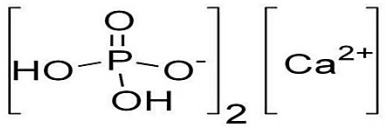

Figure 4. Dicalcium phosphate.

Maize Starch

- *Molecular Formula:* $(C_6H_{10}O_5)$ n.
- *Molecular Weight:* 342.30 grams/mole.
- *IUPAC Name:* 2-(hydroxymethyl)-6- {[4,5,6-trihydroxy-2-(hydroxymethyl) oxan-3yl] oxy} oxane-3,4,5-triol.
- *Functional Category:* Binder.
- *Structural Formula:* (Figure 5).

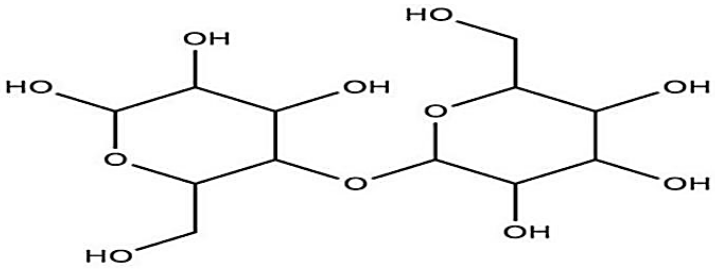

Figure 5. Maize starch.

Talc

- *Molecular Formula:* $Mg_3Si_4O_{10}(OH)_2$.
- *Molecular Weight:* 379.27 grams per mole (g/mol).
- *IUPAC Name:* Trimagnesium; 1,3,5,7-tetraoxido-2,4,6,8,9,10-hexaoxa-1,3,5,7 tetrasilatricyclo [3.3.1.13,7] decane; dihydroxide.
- *Functional Category:* Lubricant.
- *Structural Formula:* (Figure 6).

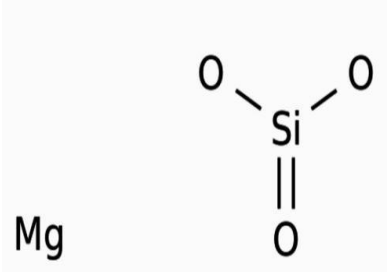

Figure 6. Talc.

Polyvinylpyrrolidone

- *Molecular Formula:* (C_6H_9NO) n.
- *Molecular Weight:* 10,000 g/mol.
- *IUPAC Name:* Polyvinylpyrrolidone.
- *Functional Category:* Binder.
- *Structural Formula:* (Figure 7).

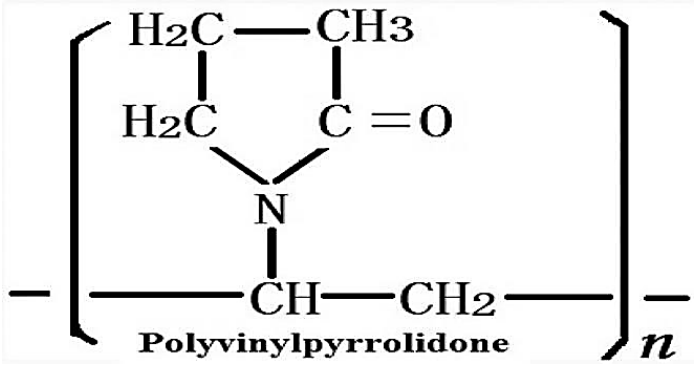

Figure 7. Polyvinylpyrrolidone.

Mannitol

- *Molecular Formula:* ($C_6H_{14}O_6$).
- *Molecular Weight:* 182.172 g/mol.
- *IUPAC Name:* hexane-1,2,3,4,5,6-hexol.
- *Functional Category:* Sweeteners and Sugar based Excipients.
- *Structural Formula:* (Figure 8).

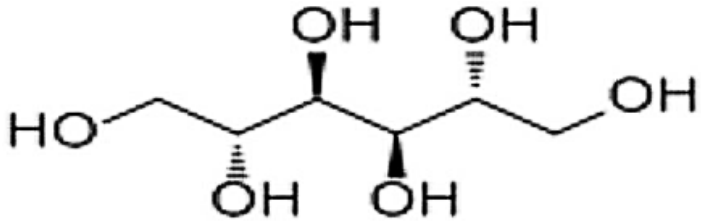

Figure 8. Mannitol.

Croscormellose

- *Molecular Formula:* $C_8H_{16}O$.
- *Molecular Weight:* 240.21 g/mol.
- *IUPAC Name:* Sodium carboxymethyl cellulose.
- *Boiling Point:* 223°C.
- *Functional Category:* Superdisintegrant.
- *Structural Formula:* (Figure 9).

Magnesium Stearate

- *Molecular Formula:* Mg(C18H35O2)2 (Figure 10).
- *Molecular Weight:* 591.27 g/mol.
- *Iupac Name:* Magnesium octadecanoate.
- *Boiling Point:* 359.4°C.
- *Functional Category:* Lubricants.
- *Structural Formula:* (Figure 9).

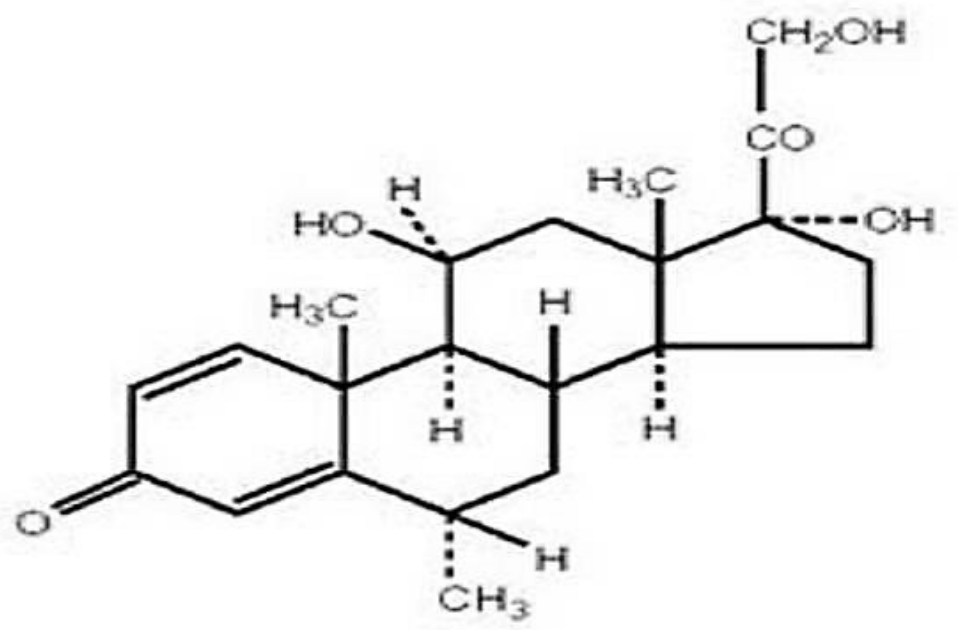

Figure 9. Croscormellose.

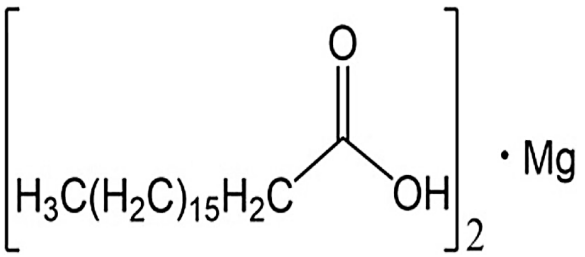

Figure 10. Magnesium stearate.

PREPARATION OF ORAL DISPERSIBLE TABLET

- *Kneading Mixture:* Mesalazine ODTs developed applying a specific kneading mixture, mesalazine: Croscarmellose, which produced a significantly improved in vitro dissolving rate as any additional kneading mixtures. To produce a smooth, moist mass, the measured quantity of drug and polymer mixture was placed in a mortar and triturated with a small amount of methanol. After 45 minutes of kneading, the bulk was dried in an oven set to 35°C until its weight remained constant. After the dried mass was ground up and sieved through #100, the powder fraction that was obtained was put stored in glass vials which contained 30 milliliters [13]. Mesalazine ODTs were made utilising a specific kneading mixture, namely mesalazine: Croscarmellose, which showed a markedly better in vitro dissolving rate than all other kneading mixes. To choose a tablet with the best ODT properties, several formulations were examined.
- The chosen formulation that met every official requirement. Sieve number 30 was used to filter the kneading combination of mesalazine and croscormellose, MCCP, croscormellose, and DCP. After that, a 10% starch solution was used as a binding agent to granulate the mixture.
- The granules were obtained by passing the wet mixture through #30. For roughly 20 minutes, the moist granules were dried in an oven set to 60°C.
- Talc, mannitol, and magnesium stearate were added to the dry granules and thoroughly mixed. The blend's micromeritic qualities were adequate.
- A rotary punch machine with eight stations was then used to compress the blend using 5 mm flat punches.

Formulation Table

This table is for preparing oral dispersible tablets for each containing 20 mg of drug (Table 1).

Table 1. Formulation table.

S.N.	Ingredient	Quantity
1	Mesalazine	20 mg
2	Microcrystaline cellulose phosphate	67 mg
3	Dicalcium phosphate	10 mg
4	Maize starch	10 mg
5	Talc	10 mg
6	Polyvinylpyrrolidone	10 mg
7	Mannitol	60 mg
8	Croscormellose	3 mg
9	Mango flavor	0.1 mg
10	Magnesium stearate	10 mg

Pre-Compression Evaluation

The various blend properties that need to be examined before compression. Along with a few specialized tests, the evaluation parameters of the tablets listed in the Pharmacopoeias must be evaluated [14].

- *Angle of Repose:* The funnel method is used to determine the angle of repose. The precisely weighed mixture is transferred into a funnel. The funnel's height takes place so that the tip of the funnel just touches the top of the mix pile. The drug-excipient mixture (in the form of a solid dispersion) is permitted to freely flow to the surface of the funnel. The following formula is used to determine the powder cone's diameter and angle of repose.

Formula

$Tan\ \Theta = h/r$

where, h is the height of cone and r is radius cone base.

Bulk Density

A weighed amount of blend is poured into a graduated cylinder, and the weight and volume are measured to calculate the apparent bulk density. Bulk density can be calculated by using following formula

- *Bulk Density:* Weight of the powder / Volume of the packing.
- *Tapped Density:* A graduated cylinder with a known mass of drug-excipient combinations is placed to determine it. The cylinder is allowed to drop 10 cm from a height at 2-second intervals onto a hard surface under its own weight. The tapping keeps going until there is no more audible variation.

Tapped Density = (Weight of the powder / volume of the tapped packing)

- Compressibility Index: The blends' compressibility index is established using the compressibility index.

The following formula can be used for calculating the compressibility index:

Compressibility Index (%) = [(TD – BD) x *100] / TD]*

- *Hausner's Ratio*: Hausner's ratio can be used to define a comparable index to show the flow characteristics. The following formula can be used to determine Hausner's ratio:
- Hausner's ratio = (Tapped density x 100)/ (Poured density).
- Hausner's ratio <1.25 – Good flow = 20% compressibility index.
- 1.25 – Poor flow =33% compressibility index.

Evaluation of Tablets

- The following quality control tests were performed on each of the developed ODTs (Shyamala et al., 2002, Bradoo et al., 2001, & Makino et al., 1993) [15]:
- *Weight Variation:* To make sure that the weight of the tablets in a batch is consistent, the weight variation test is conducted. Initially, the average is determined by calculating the total weight of 20 pills from each formulation. To ascertain the weight variance, the specific weight of each tablet is also ascertained [16].
- *Hardness:* A tablet's strength can be determined by its hardness. The force needed to break the tablet during testing is measured. For uncoated tablets, a hardness of roughly 3–5 kg/cm^2 is considered adequate, and the force is expressed in kilograms. Monsanto, Pfizer, and other hardness testers evaluate the hardness of ten tablets from each formulation.
- *Friability Test:* Friability is the weight loss of the tablet in the container as a result of the surface being cleared of small particles. To determine the tablet's resistance to abrasion during handling, packing, and moving, a friability test is conducted. The Roche friabilator is used to determine whether the tablets are friable. Each batch of 20 tablets should be weighed before being placed in a Roche friabilator that rotates for four minutes at 25 rpm. After dusting every tablet, reweigh it [17]. The following formula can be used to determine the percentage of friability:

  $\%\ Friability = [(W1 - W2)100]/W1$

  where, W1= Weight of tablet before test, W2 = Weight of tablet After test
- *Disintegration Test:* The six glass tubes in the USP disintegration equipment are "three long, open at the top, and held against ten" screen at the basket rack assembly's bottom end. Each tube contains one tablet, and the basket rack is poisoned in a one-liter beaker of distilled water at 37 2°C so that the tablets sink no more than 2.5 cm from the beaker's bottom and stay below the liquid's surface as they rise.
- *In-Vitro Dissolution Test: The* USP Type II Apparatus (Paddle type) is used to conduct an in-vitro dissolution investigation at 50 rpm. 900 milliliters of phosphate buffer pH 6.8 are used as the dissolving media, which is kept at 37 ± 0.5°C. At predetermined intervals of two minutes, remove a 10-milliliter aliquot of the dissolving medium and filter. A suitable analytical technique is used to determine the amount of medication dissolved [18].

RESULTS AND DISCUSSIONS

The present study was the formulation and evaluation of oral dispersible tablets of mesalazine drug.

Table 2. Precompression evaluation.

S.N.	Parameter	Results
1	Angel of repose	27.35
2	Bulk density	0.62
3	Tapped density	0.74
4	Compressibility index	16.21
5	Hausner's ratio	1.19

The evaluation parameters were coming under results, like the angle of repose, bulk density, tapped density, Compressibility index, Hausner's ratio, weight variation, hardness, friability test, disintegration test and in-vitro dissolution test. The present work was the formulation and evaluation of oral dispersible tablet. The prepared formulation was good solubility and bioavailability (Tables 2 and 3).

Table 3. Formulation evaluation of Oral dispersible tablet.

S.N.	Parameter	Results
1	Weight variation:	99.50
2	Hardness:	3.6 kg/cm * 2
3	Friability test:	0.8
4	Disintegration test:	3 min
5	In-Vitro dissolution test	58.12

CONCLUSIONS

The present Formulation has shown craved result, therefore, these oral dispersible tablets formulation can be used as antiulcer activities. In this research work ODTs of mesalazine were successfully formulated by direct compression method using superdisintegration addition method. The flow properties of the formulation powder have good flow property which is an important aspect for the ODT formulations. The most effective technique to develop ODTs is the direct compression method. Additionally, this approach saves a great deal of money and time.

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