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Formulation And Evaluation Of Ticagrelor Oral Disintegration Flim

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ABSTRACT

The development of oral disintegration films (ODFs) as an alternative to conventional oral dosage forms has gained increasing attention due to their convenience and ease of administration. In this study, Ticagrelor FDFs were prepared by the solvent casting method and evaluated using *in vitro* studies. The prepared formulations showed a uniform distribution of the drug throughout the film and effective release when compared to other formulations by drug release study.

The prepared films were found to be homogenous, yellowish in color, and flexible. The results shows that thickness, tensile strength, and the concentration of the film significantly influenced the ODF dissolution time. The surface pH of all the selected formulations was around neutral pH, indicating that there will be no irritation to the oral mucosal cavity.

The folding endurance values provide important information about the mechanical properties of ODFs and can help in selecting the most suitable formulation for use. The dissolution test value comparison showed that F2 and F6 are similar in terms of drug release and F5 and F1 have very different drug release profiles. Based on the results, it can be concluded that ODFs have promising potential dosage form for the delivery of Ticagrelor, F2 and F6 were identified as most successful formulation of this study

Keywords: Solvent casting method, Ticagrelor, HPMC, in vitro dissolution test.

INTRODUCTION

The oral route is currently the most used method for drug delivery since it has a number of advantages over other drug administration methods.

The most popular dosage form for medications is the oral route because it is straightforward to organise, unobtrusive, adaptable, patient-consistent, and enjoyable .Since oral drug administration is widely accepted, up to 50–60% of all dosage forms are given orally. Solid dose forms are preferred because they are simple to administer, precise in their amount ,allow for self-medication, reduce pain, and most significantly, increase patient compliance.

Tablets and capsules are the most often used solid dose forms. However, for some patients, the inability to take these dose forms is one of their drawbacks.Currently,35%ofthegeneralpopulationexperiencesdysphagia,or difficulty swallowing. Water consumption is crucial for properly swallowing oral dose forms. People frequently find it difficult to swallow standard dosage forms, such as when water is not available. The advantages of both liquid and traditional tablet formulations are combined in mouth dissolving drug delivery systems (MDDDS), a new generation of formulations that also provides additional benefits above both standard dosage forms.

To make ticagrelor drug administration more convenient and to increase patient compliance ,the current research study developed a taste-masked ODF of the medication that disintegrates in 30 seconds. Water consumption is crucial for properly swallowing oral dose forms People frequently find it difficult to swallow standard dosage forms, such as when water is not available. Due to these factors, there has been a lot of interest in tablets that quickly dissolve or disintegrate in the oral cavity. The goal of the current study was to create a taste-masked ODF of ticagrelor dissolving within 30 seconds to increase patient convenience and compliance

Taste masking is the perceived elimination of an unpleasant taste that would otherwise be there. Finding a universal inhibitor of all bitter-tasting compounds that has no effect on other taste modalities like sweetness or saltiness would be the best way to lessen or suppress bitterness. Mouth Dissolving Tablets (MDTs) are ingested without water dissolve in thesaliva.MDT save several advantages over traditional tablets, including easy manufacture ,self-administration and compactness

Flow Chart for the Development of Oral Solid Dosage forms

Conventional oral dosage forms (tablets, capsules)

↓

Modified release tablets and capsules

↓

Fast dissolving tablets and capsules

↓

Fast dissolving oral thin Film·

Mucus, which is composed of proteins and carbohydrates, is a layer of 40–50 cells that makes up the oral mucosal epithelium. The gums, tongue, and base of the mouth all have mucosal thicknesses between 100 and 200 m. The submucosal layer secretes a tiny quantity of mucus,gel-like fluid that is 90%– 99water-insoluble glycoprotein, and other substances such proteins, enzymes, electrolytes, and nucleic acids . The clinical effectiveness of novel immediate release (IR) systems over traditional products is clear. Among these technologies, mouth-dispersing films, oral patches, and wafers have demonstrated more effective drug delivery.

Fast-dissolving oral films (FDOF) are a safe and clinically superior dose form to traditional dosage forms. Usefulness of FDOF has been researched in relation to some chronic disorders,such as depression and emesis.FDOFs allow for taste masking, fast salivary dissolution or disintegration, and swallowing without water] . A quick onset of action can be possible due to the drug's fast release into the oral cavity. Some medications can avoid first-pass metabolism if they are absorbed through the oral mucosa, which may increase their bioavailability.

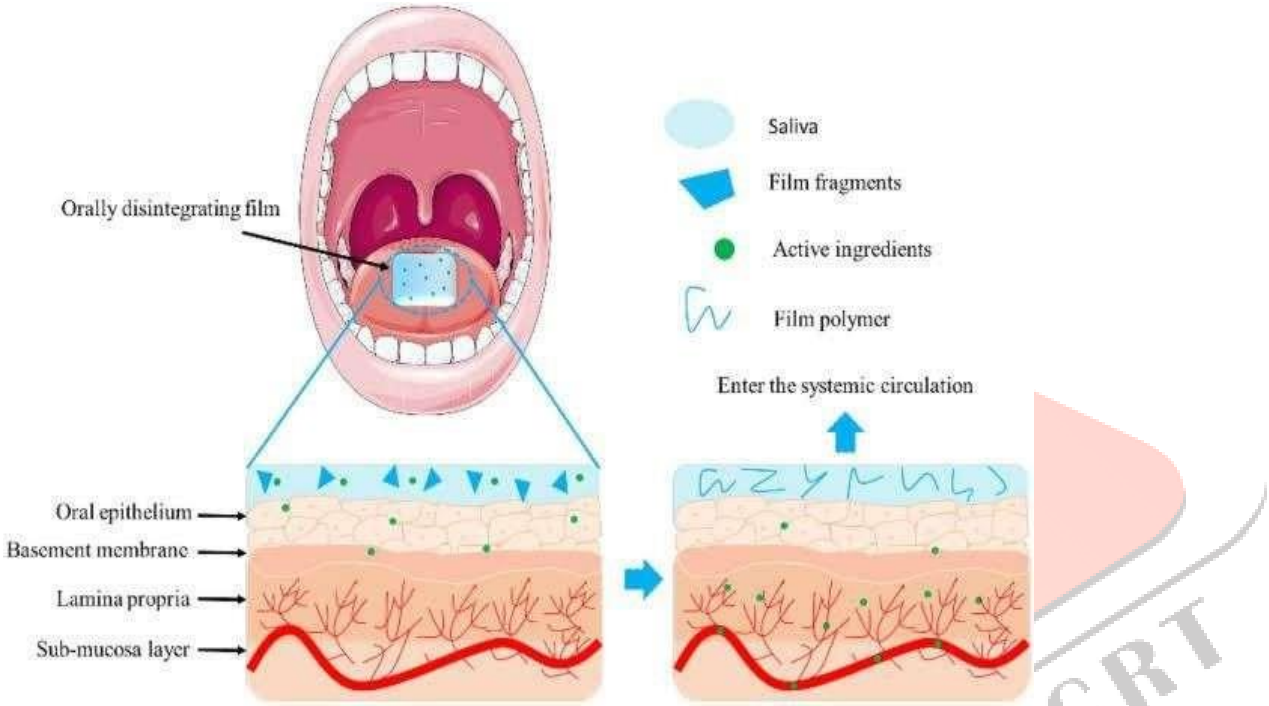
Buccal absorption might be very helpful for people with migraines, for instance. However, due to the quick onset of action, some
patients may feel sleepy.

Many pharmaceutical companies have focused their research efforts on creating new dosage forms for previously prescribed medications .

Formulation of ODF

ODF is primarily made up of plasticizers, active substances, and additional additives such surfactants, sweeteners, taste- masking agents, and compounds that stimulate salivation. The common materials used for ODF development and their primary functions are present edin the following sections·

When compared to commercially available immediate release tablets, which demonstrated a 22-second in vitro disintegration time and >95% drug releasein10minutes,drug-loaded films made of the appropriate plasticizer and the chosen polymers demonstrated excellent film forming capacity, good folding endurance, and after 10 minutes, on 30.4%



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A combination of sucralose and mono ammonium glycerrhizinate, which produces a prolonged sweetness profile, successfully masks the bitter active in the films' pleasant flavour, which ranges from 30 to 40 mg in weight·

ODFs are thin films that quickly dissolve and have an area of 5 to 20 cm2, in which hydrophilic polymer is used to integrate the medicine as a matrix. Up to 15 mg of the active pharmaceutical component may be included with various excipients, such as plasticizers, colourants, sweeteners, and taste-muffling agents. Plasticizer lowers the glass transition temperature of polymers by improving the workability, spreadability, and flexibility of fims

DRUG PROFILE

TICAGRELOR

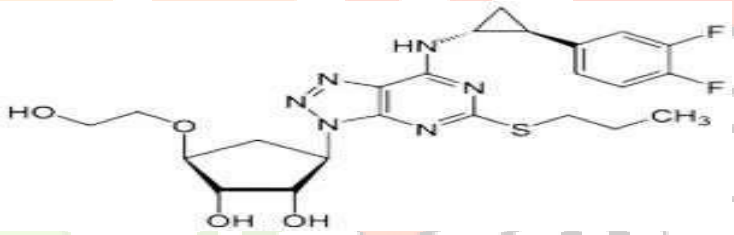
Ticagrelor is classified as an anti-platelet aggregator, which reversibly binds to the P2Y12 receptor and acts by antagonizing the binding of adenosine phosphate to the P2Y12 receptor resulting in decreased uptake of adenosine. Itis a direct-acting and immediate-release drug taken orally. Both the active drug and its metabolite have approximately equal potencies. **Figure 1** represents the structure of the Ticagrelor.

Ticagrelor is administered along with aspirin in cases of strokes, myocardial infarctions, and other acute coronary syndromes.1 It is a tasteless drug being poorly soluble.The drug also has a reported bioavailability of 36%. Ticagrelor is a BCS class IV drug having low Solubility and low permeability. Ticagrelor is one of the modest drugs prescribed in cases of Acute Coronary Syndrome, owing to its irreversible binding to the P2Y12 receptor.8 AstraZeneca got the approval for ticagrelor in 2011 by the FDA.9 Ticagrelor has a loading dose of 180 mg followed by 90 mg twice daily.

MOLECULAR FORMULA: C23H28F2N6O4S

MOLECULAR WEIGHT: 522.567g/mol

STRUCTURE



Polymer Profile

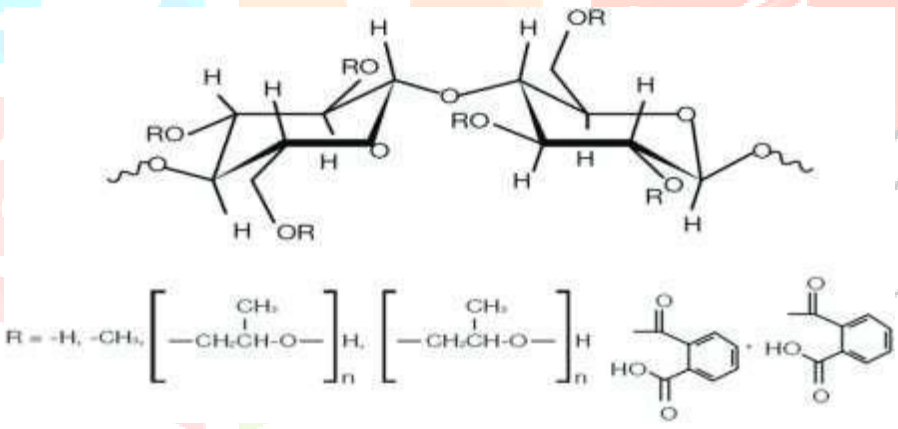
Hydroxypropylmethylcellouse [HPMC]

PubChem CID	57503849
Structure	Find Similar Structures
Molecular Formula	C56H108O30
Synonyms	HPMC Hydroxypropylmethylcellulose HYDROXYPROPYLMETHYL

CELLULOSE

Molecular Weight	1261.4

Structure



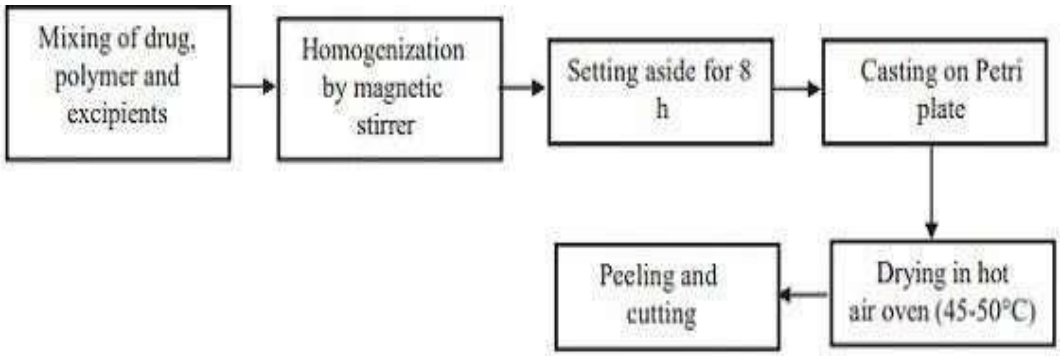
MATERIALS AND METHODS

Formulation of ODF

Solvent casting method:

The most popular technique for creating ODFs is solvent casting, which involves dissolving drugs, polymers,

and excipients in deionized water . The excipient and API mixture is cast onto a surface, dried, and then cut to the required size. The suspension made up of API, Polymer, and Plasticizer needs to be degassed to produce a homogeneous film and thickness. The suspension is then introduced into a vacuum to release trapped air bubbles, placed in a Petri dish or Teflon plate, and allowed to dry after a period of time. For ODF manufacturing using the solvent casting method, there are various process parameters. The temperature during drying must be managed. Low temperature should be employed in the formulation of thermosensitive APIs in order to create the proper viscosity and produce a film. The remaining solvents have a considerable impact on the mechanical and stability properties of ODF. Therefore, it is important to monitor and assess the ODF residual solvent .



Flow chart of solvent casting method

FORMULATION

Sl.No	Formulation	Drug (mg)	HPMC (mg)	Albumin (mg)	Surfactant (mg)	Plasticizer (mg)	Sweetening Agent (mg)	Saliva Stimulating Agent (mg)	Preservative (mg)
1	F1	25	80	-	0.2	2	10	1	1
2	F2	20	75	-	0.2	2	10	1	1
3	F3	15	65	15	0.2	2	10	1	1
4	F4	30	70	-	0.2	2	10	1	1
5	F5	25	70	10	0.2	2	10	1	1
6	F6	25	60	-	0.2	2	10	1	1

RESULT AND DISCUSSION

Evaluation Parameter

pH

Formulation	pH measured
F1	6.44
F2	6.93
F3	6.35
F4	6.91
F5	6.12
F6	6.97

The surface pH of all the selected formulation was ranging between 6.1 to 7; since surface pH of the film was found to be around neutral pH, there will not be any kind of irritation to the oral mucosal cavity.

Tensile strength

Batch code	Tensile strength (kg/mm^2)
F1	0.90
F2	0.86
F3	1.10
F4	0.89
F5	0.96
F6	1.20

The tensile strength values range from 0.86 to 1.20 kg/mm2. Batch F3 has the highest tensile strength value of 1.10 kg/mm2, followed by batch F6 with a value of 1.20 kg/mm2. Batch F2 has the lowest tensile strength value of 0.86 kg/mm2.

Thickness

Batch Code	Thickness(mm)
F1	0.270mm
F2	0.365mm
F3	0.290mm
F4	0.256mm
F5	0.287mm
F6	0.302mm

The thickness values for the six batches of oral disintegration films (ODFs) ranged from 0.256mm to 0.365mm. The thickest film was F2 with a thickness of 0.365mm, while the thinnest film was F4 with a thickness of 0.256mm.

The thickness of ODFs is an important parameter as it affects the disintegration time and drug release rate of the films. Thicker films may take longer to disintegrate and release the drug, while thinner films may disintegrate too quickly, leading to incomplete drug release.

Based on the thickness values, it can be observed that F2 may take longer to disintegrate and release the drug compared to the other formulations, while F4 may disintegrate too quickly, leading to incomplete drug release. However, the other formulations have thickness values that are relatively close to each other, which suggests that they may have similar disintegration times and drug release rates.

Folding Endurance

Batch code	Folding Endurance
F1	280
F2	245
F3	305
F4	170
F5	162
F6	386

The folding endurance values for the six different formulations of oral disintegration films (ODFs) of ticagrelor were measured to assess their mechanical properties. The folding endurance values ranged from 162 to 386. It was observed that formulations F3 and F6 had the highest folding endurance values, indicating better mechanical properties, whereas formulations F4 and F5 had the lowest folding endurance values,

indicating weaker mechanical properties. The folding endurance values of formulations F1 and F2 were also relatively lower compared to F3 and F6.

The ability of ODFs to withstand repeated folding without breaking is crucial for ensuring that the film remains intact during handling, transportation, and usage. Therefore, formulations F3 and F6 with higher folding endurance values may be more suitable for practical use. On the other hand, formulations F4 and F5 with lower folding endurance values may be more prone to breakage, making them less desirable for practical use. Overall, the folding endurance values provide important information about the mechanical properties of ODFs and can help in selecting the most suitable formulation for use.

Dissolution Test

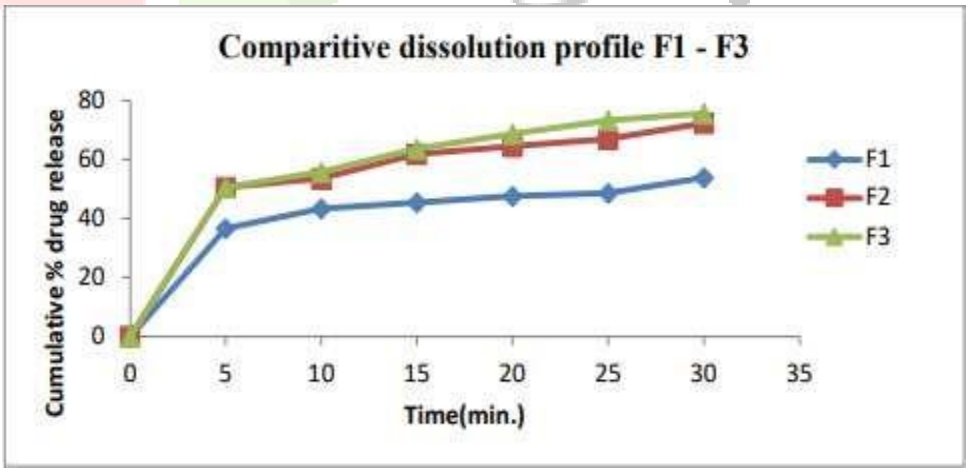
To generate a dissolution test value comparison for oral disintegration film, we can plot the cumulative drug release for each formulation (F1 to F6) against time. [Dissolution test value comparison for oral disintegration film]

Cumulative % Drug Release						
TIME (mins)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	**0**	**0**	**0**	**0**	**0**	**0**
5	36.53± 1.25	50.48± 1.12	50.53± 1.24	52.63 ±1.64	53.58 ±1.10	69.35± 1.15
10	43.34± 1.10	58.56± 1.17	55.78± 1.20	54.28 ±0.98	57.68 ±0.99	78.93± 0.98
15	45.38± 0.86	61.78± 1.15	63.59± 0.85	64.53 ±0.86	63.86 ±1.51	85.93± 1.12
20	47.53± 0.95	64.48± 1.12	68.68± 0.97	72.53 ±1.52	70.57 ±1.10	88.93± 0.99
25	48.56± 1.15	66.89± 0.97	73.23± 0.85	74.98 ±1.12	77.13 ±1.12	90.75± 1.52
30	53.83± 1.12	75.35± 0.98	75.63± 1.15	78.13 ±0.98	79.25 ±1.12	97.56± 0.85

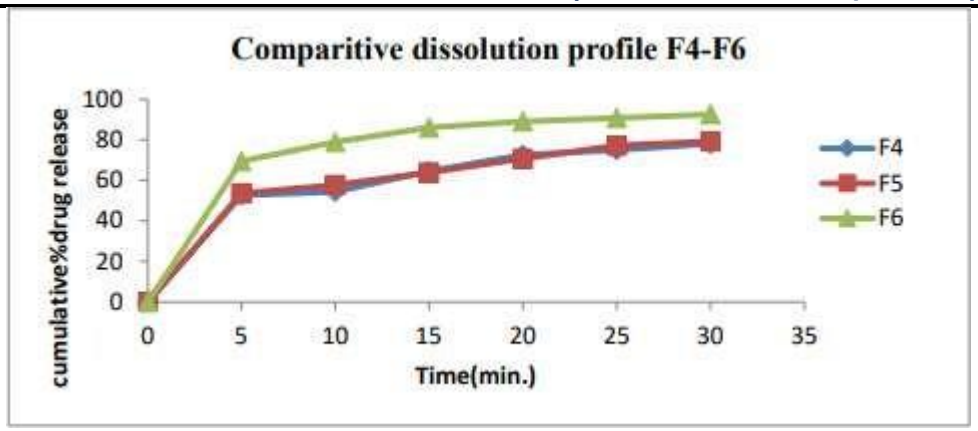
From the table, we can observe that:

- F1 and F2 have similar drug release profiles, with F2 showing a slightly higher drug release at later time points.
- F3 and F4 have similar drug release profiles, with F3 showing a slightly higher drug release at later time points.
- F5 and F6 have very different drug release profiles, with F5 showing a much slower drug release compared to F6. Based on this dissolution test value comparison, we can conclude that:
- F2 and F6 are similar in terms of drug release, and choosing between the two would depend on other factors such as cost or formulation feasibility.
- F3 and F4 are also similar in terms of drug release, and choosing between the two would depend on other factors such as stability or taste.
- F5 and F6 are very different in terms of drug release, and choosing between the two would depend on the desired pharmacokinetic profile and therapeutic effect.

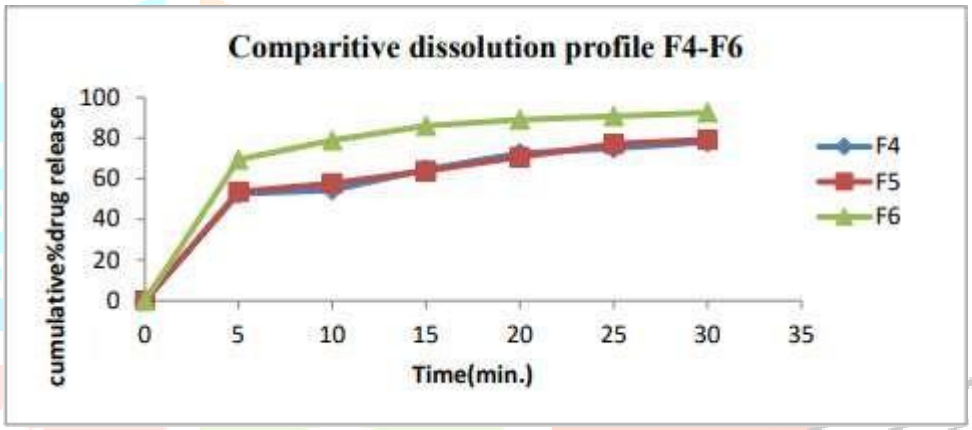
Ticagrelor FDFs were prepared by solvent casting method evaluated by *in vitro* studies. The prepared formulation showed uniform distribution of drug throughout the film. In vitro dissolution of prepared FDFs F2 and F6 shows effective release when compared to the other formulation. The drug polymer concentration released the complete drug in 7mins. The formulation F3 and F4 released only 80% of the drug in 10mins. As per results of evaluation tests the F2 and F6 formed good peelable film. The prepared films were found to be homogenous, and flexible. HPMC as a film former produced a smooth film surface,The concentration of the film former influenced the viscosity of the film matrix. The viscosity of the film matrix increases with the increase in the concentration of film former, therefore lengthen the disintegration time of ODF . produced a significantly faster disintegration time of ODF compared to the other four formulas . These results revealed that film thickness and tensile strength significantly influenced the ODF disintegration time.



Formulation F1 to F3



Formulation F4 to F6



Formulation F4 to F6

Summary and Conclusion

Ticagrelor ODFs showed effective drug release, and their properties were influenced by film thickness, tensile strength, and the concentration of the film former. The dissolution test value comparison showed that F2 and F6 were the most effective formulations in terms of drug release, while F3 and F4 released only 80% of the drug in 10mins. Film thickness was found to be 0.365mm for formulation F2, 0.302mm for formulation F6 while F2 is the thickest film, it can be observed that F2 may take longer to disintegrate and release the drug compared to the other formulations and tensile strength was found to be 0.86 *kg/mm2* for formulation F2, 1.20 *kg/mm2* for formulation F6, F6 had an highest tensile strength compared to F2, it can be observed that F2 has highest concentration of polymer. Hence the F2 formulation was found to be the best formulation and recommended for *in-vivo* study.

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