FORMULATION & EVALUATION OF ORALLY DISINTEGRATION FILM USING PROMETHAZINE HCL

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INTRODUCTION

The oral course of treatment is the most popular due to its ease of administration, comfort, adaptability, patient consistency, and recognition. Many alternatives to the oral route of drug transportation have been made available for pediatric, geriatric, ill, and rebellious individuals using current creative innovations. Innovative advances have given rise to bioadhesive mucosal measuring structures such as tablets, gels, and fixes. Among the various portion structures, the use of polymeric films to deliver drugs into the buccal pit has recently demonstrated tremendous potential.[1] Orally degrading films (ODFs) immediately hydrate by splashing saliva after degradation and disintegration, releasing the dynamic pharmacological component from the measurement. The mouth-dissolving film is a coating made using hydrophilic polymers that quickly dissolve when exposed to spit. Oral disintegrating films and tablets are two different oral medicine delivery devices. This framework developed in the latter part of the 1970s as an alternative to traditional dose structures, such as fast-disintegrating tablets and containers, for elderly and young patients who had problems swallowing those structures.[2] The size of a typical orally degrading film is comparable to a postage stamp. The purpose of the Oral dissolving tablet presence at the commercial center was to provide patients with information on the proper organization, including warnings like "don't bite/don't swallow". Despite these restrictions, bites and gulps were frequently observed. However, orally degrading film liberated the majority from these catastrophes.[3]

MATERIAL & METHOD

Preparation of Mouth Dissolving Film (MDF)[4]

The Mouth dissolving film was prepared by solvent casting method. The weighed quantity of polymer was dissolved in the minimum quantity of distilled water and stirred to ensure the complete mixing of polymer. Then the drug was dissolved in that polymer solution with stirring. After that a sweetening agent was added to the solution and stirred properly. Finally, calculated quantity of plasticizer was added to the above mixture and kept for sonication till the solution became clear and free of bubbles.

After sonication, the solution was cast on the glass plate before pouring the solution glass plate is coated with butter paper. The glass plate was kept in a controlled temperature oven at 60 ºC for 24 hr for drying of the film. After the drying of films, it was peeled and cut into 2 cm × 2 cm (4 cm^2) size and stored in aluminum foil. These films were further subjected to various evaluation tests.[5]

Drug Excipient Compatibility Studies by Physical Observation

Excipients are substances which are included along with the active pharmaceutical ingredient (API) in dosage forms. Most excipients have no direct pharmacological action but are important for facilitating the administration, modulating the release of the active component and stabilizing API against degradation. However, inappropriate excipients can also give rise to inadvertent and/or unintended effects which can affect the chemical nature, the stability and the bioavailability of the API, and consequently, their therapeutic efficacy and safety. Studies of drug-excipient compatibility represent an important phase in identifying interactions between potential formulation excipients and the API in the development stage of all dosage forms. Physical incompatibility: We assess the change in the physical form of the formulation, like color changes, dissolution, solubility, sedimentation rate, liquefaction, phase separation or immiscibility.[6]

Table No 1: Drug Compatibility Study by Physical Observation

S.No	DRUG	DAYS	OBSERVATION
1	Promethazine Hcl	15	No change
2		30	No change
3		45	No change
4		60	No change

Drug and Polymers compatibility studies

Table No 2: Drug and Polymers compatibility studies

S.No	DRUG & EXCIPIENT	DAYS	OBSERVATION
1	Promethazine Hcl + HPMCE-	15	No change
2		30	No change

3	5+Taro Gum, Cassava, Xanthan Gum, Guar Gum, Sodium Alginate, Gum Tragacanth	45	No change
4		60	No change

DRUG EXCIPIENT COMPATIBILITY STUDIES

Fourier Transformed Infrared (FTIR) Spectroscopic Analysis

Fourier transform infrared spectroscopic (FTIR) analysis of the extracts was carried out using Shimadzu FTIR– 8400s Fourier transform infrared spectrophotometer, Japan. Methanol and aqueous extracts of Promethazine Hcl seed were oven-dried to get powders of the different solvent extracts used for FTIR analysis. The dried extracts powder (10 mg) were encapsulated in 100 mg of KBr pellet, to prepare translucent sample disc and analysis was carried out by scanning the samples through a wave number range of 400 to 4000 cm-1 with a resolution of 2 cm-1. FTIR analyses were performed and the different peaks present and possible chemical interactions were examined.[7]

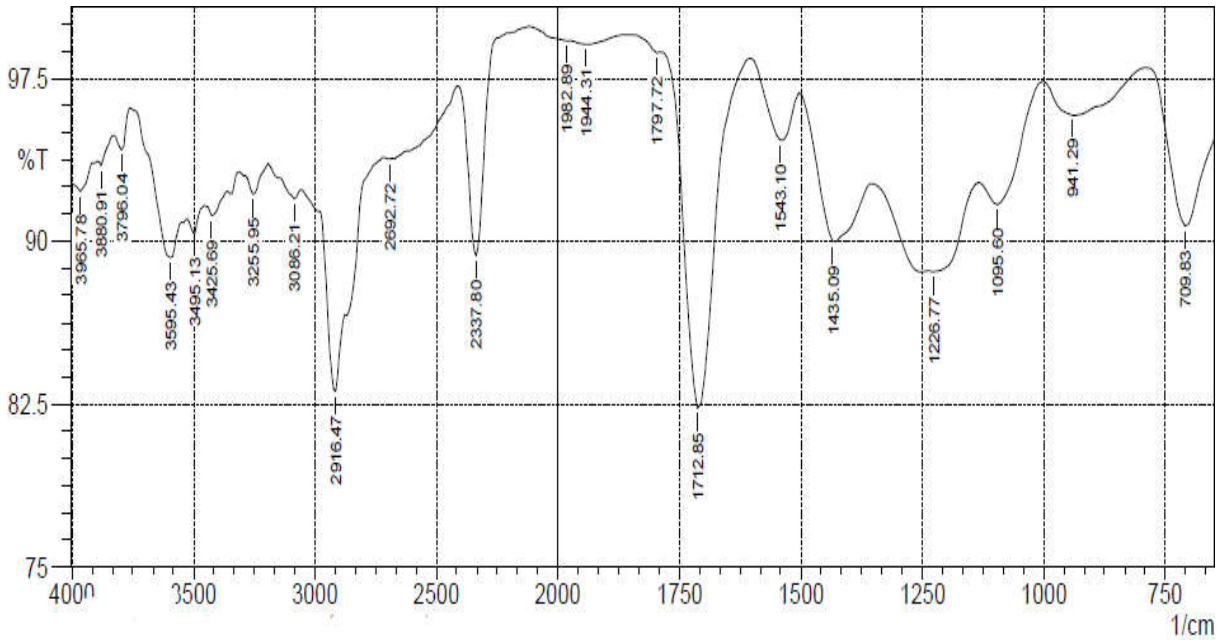


Figure no.1: FTIR spectrum of methanol extract of Promethazine Hcl

Table 3: FTIR Interpretation of the methanol extract of the Promethazine Hcl

S/NO	Test sample (cm^{-1})	Reference standard (cm^{-1})	Functional group Assignment	Identified Compounds
1	709.83	665-730	C=C bend	Alkene
2	941.29	915-995	C=C bend	Alkene
3	1095.6	1150-1085	C-O stretch	Ether
4	1226.77	1200-1275	C-O stretch	alkyl aryl ether
5	1435.09	1395-1440	O-H bend	carboxylic acid
6	1543.1	1500-1550	N-O stretch	nitro compound
7	1712.85	1705-1725	C=O stretch	aliphatic ketone
8	1797.72	1770-1800	C=O stretch	Halide
9	1944.31	1900-2000	C=C=C stretch	Allene
10	1982.89	1900-2000	C=C=C stretch	Allene
11	2337.8	2275-2349	O=C=O stretch	Carbonate
12	2692.72	2500-3000	O-H stretch	carboxylic acid
13	2916.47	2840-3000	C-H stretch	Alkene
14	3086.21	3080-3140	C-H stretch	Alkene
15	3255.95	3250-3330	N-H stretch	Amine
16	3425.69	3400-3500	N-H stretch	Amine
17	3495.13	3400-3500	N-H stretch	Amine
18	3595.43	>3500	O-H stretch	Alcohol
19	3796.04	>3500	O-H stretch	Alcohol
20	3880.91	>3500	O-H stretch	Alcohol
21	3965.78	>3500	O-H stretch	Alcohol

Figure. 2: FTIR Spectrum of Promethazine Hcl

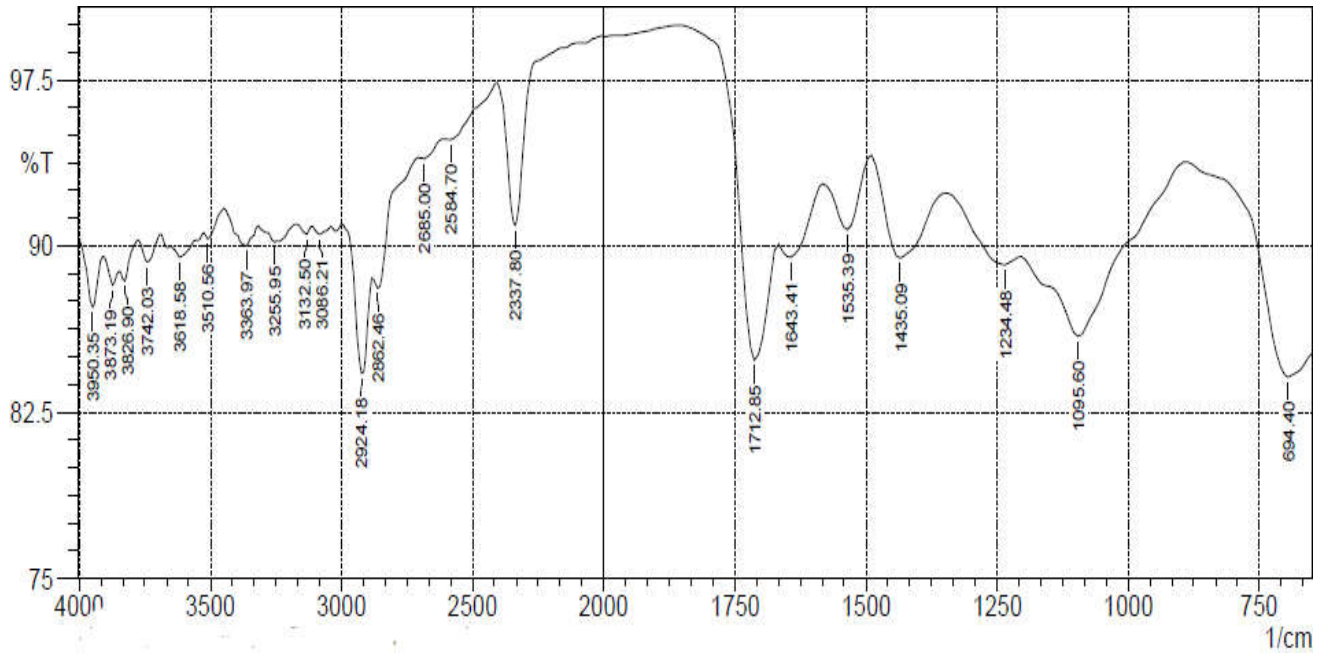
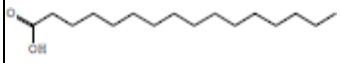
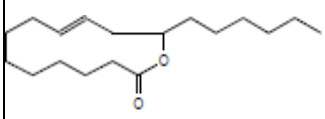
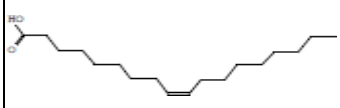


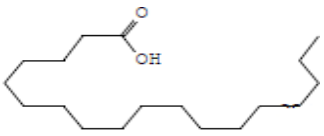
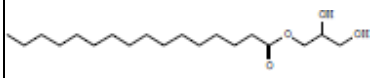
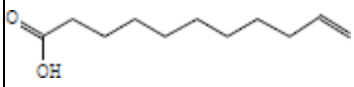
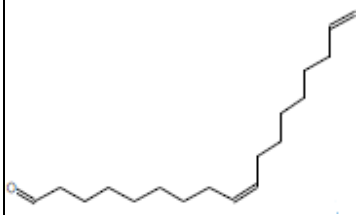
Table 4: FTIR Interpretation of the aqueous Promethazine Hcl

S/NO	Test sample (cm^{-1})	Reference standard (cm^{-1})	Functional group Assignment	Identified Compounds
1	694.4	665-730	C=C bend	Alkene
2	1095.6	1070-1150	C-O stretch	ether compound
3	1234.48	1200-1275	C-O stretch	alkyl aryl ether
4	1435.09	1395-1440	O-H bend	carboxylic acid
5	1535.39	1500-1550	N-O stretch	nitro compound
6	1643.41	1638-1648	C=C stretch	Alkene
7	1712.85	1705-1725	C=O stretch	aliphatic ketone
8	2337.8	2275-2349	O=C=O stretch	Carbonate
9	2584.7	2550-2600	S-H stretch	Thiol
10	2685	2500-3000	O-H stretch	carboxylic acid
11	2862.46	2850-3000	C-H stretch	alkane

12	2924.18	2850-3000	C-H stretch	alkane
13	3086.21	3000-3100	C-H stretch	Alkene
14	3132.5	3080-3140	C-H stretch	Alkene
15	3255.95	3250-3330	N-H stretch	Amine
16	3363.97	3300-3400	N-H stretch	Amine
17	3510.56	>3500	O-H stretch	Alcohol
18	3618.58	>3500	O-H stretch	Alcohol
19	3742.03	>3500	O-H stretch	Alcohol
20	3826.9	>3500	O-H stretch	Alcohol
21	3873.19	>3500	O-H stretch	Alcohol
22	3950.35	>3500	O-H stretch	Alcohol

Table no 5. Compounds identified in aqueous Promethazine Hcl

Peak No	Retention time	Formula	Molecular weight	Compound Name	Area%	Structure
1	15.974	$C_{16}H_{32}O_2$	256	n-Hexadecanoic acid	7.55	
2	16.966	$C_{18}H_{32}O_2$	280	13-Hexyloxacyclotridec-10-en-one	1.19	
3	17.718	$C_{18}H_{34}O_2$	282	Oleic acid	30.21	

4	17.868	$C_{18}H_{36}O_2$	284	Oleic acid	5.28	
5	18.905	$C_{19}H_{38}O_4$	330	Hexadecanoic acid, 2,3-dihydroxpropyl ester	2.37	
6	19.512	$C_{11}H_{20}O_2$	184	Undecylenic acid	40.33	
7	20.412	$C_{18}H_{34}O$	266	9-Octadecenal	7.09	
8	22.345	$C_{18}H_{32}O$	264	9,17-Octadecadienal, (Z)-	5.98	

The number of peak values revealed by FTIR spectroscopic analysis of Promethazine Hcl demonstrated the presence of functional groups which are indicative of secondary metabolites and other bioactive compounds. The presence of these compounds in Promethazine Hcl seed extract underscores its ability to possess biological activity.[8] This is in line with the work of Maobe and Nyarango, (2013) who reported that these functional groups confirm the presence of secondary metabolites and other phytochemical components present in plants.

Differential Scanning Calorimetric (DSC) Graph of Promethazine Hcl

Current study was carried out on Thermal Analysis Equipment (DSC), Make and Model: Perkin STA 8000. Analysis was carried out at heat from 50 °C to 500 °C at 20 °C/min rate with suitable cooling attachment with thermocouple sensor Pt-Pt/Rh. For the analysis sample Weight taken 7.654 mg.

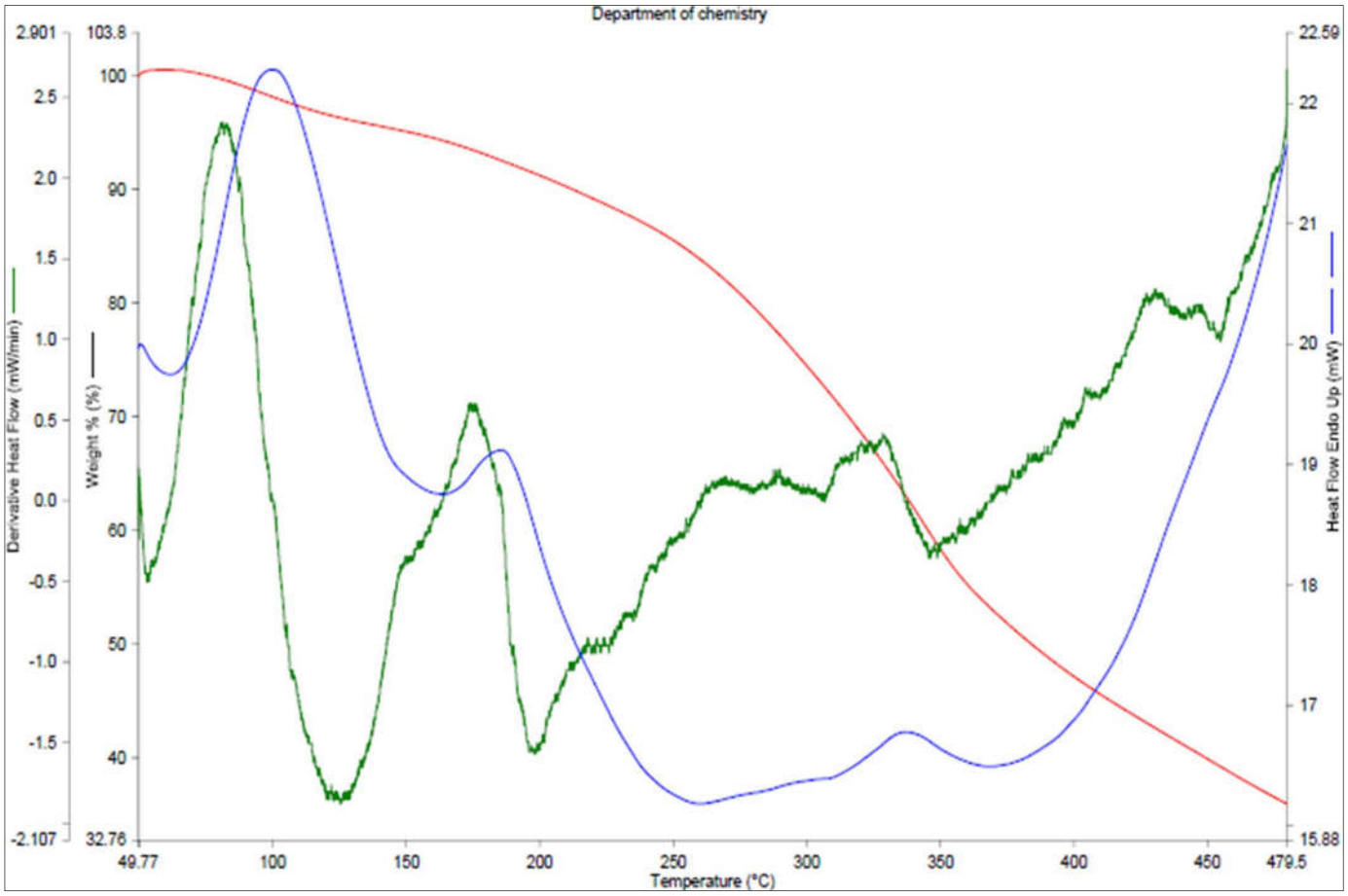


Figure 3. DSC Thermogram of the of *Promethazine Hcl*

INTERPRETETION OF DSC

The Thermal analysis method is a powerful tool for study of the effects of reaction atmosphere on thermal chemical characteristics for plant leaves sample. In Differential Scanning Calorimetric (DSC) analysis results show that in DSC curve, Endothermic peak at 101 °C is attributed to dehydration/Water loss from surface and pores of the powder sample. Step at 215 °C is associated with second order phase transition such as Glass Transition and it should be further confirmed in second heating (During heat- cool- heat cycle). Endothermic peak at 336 °C is associated protease thermal

decomposition. In further analysis there is possibility of degradation of lignin between 450-800 °C by further extending the analysis temperature.[9]

- **Evaluation of Extracted Polymer**

Table No.6 : Characteristic of Extracted Natural Taro Gum & Cassava Gum

PARAMETERS		TARO GUM	CASSAVA GUM
Solubility		Forms viscous colloidal solution in hot water, insoluble in acetone, ethanol,methanol, DMSO and ether.	Forms viscous colloidal solution in hot water, insoluble in acetone, ethanol, methanol, DMSOand ether.
Powder Characteristics	Bulk Density	0.7692 g/cc	0.7580g/cc
	TappedDensity	0.5455 g/cc	0.5060g/cc
	Angle ofRepose	25^0C	16.19^0C
pH		6.88	6.50
Loss On Drying		15.6%w/w	16.2w/w
Specific gravity (1% w/v solution)		0.9937g/ml	0.9530g/ml
Viscosity (0.1% w/v, in water)		0.93cps	0.90cps

Preparation of Oral disintegration film (ODF)

a. Composition of Batches from Polymer Screening Without Drug

Different polymers are used in HPMCE-3, HPMC E-5, HPMC E-15 and HPMC E-50 theyare used for preparation of Oral disintegration film.[10]

Table No 7: Composition of Batches for Polymer Screening Without Drug (gm& ml)

Trial code	HPMCE-3	HPMCE-5	HPMC E-15	HPMC E-50	Glycerin	Citric acid	Aspartame	Distilled Water
F1	0.40	----	----	----	0.8	0.01	0.04	Qs
F2	0.50	----	----	----	0.8	0.01	0.04	Qs
F3	0.60	----	----	----	0.8	0.01	0.04	Qs
F4	----	0.40	----	----	0.8	0.01	0.04	Qs
F5	----	0.50	----	----	0.8	0.01	0.04	Qs
F6	----	0.60	----	----	0.8	0.01	0.04	Qs
F7	----	----	0.40	----	0.8	0.01	0.04	Qs
F8	----	----	0.50	----	0.8	0.01	0.04	Qs
F9	----	----	0.60	----	0.8	0.01	0.04	Qs

b. Evaluation Result for Polymer Screening

Oral film by using different HPMC grades were formed. They are evaluated and screening for appearance and dryness. Film formed ware transparent, dry. Film forming capacity is high as compared to other polymer. HPMC E-5, F6 is best formation of film and HPMC E- 3 ,F2 and HPMC E-15 F9 is not formed film.[11]

Table No.8: Evaluation Results for Polymer Screening

Sr.No.	Trial code	DisintegrationTime (Sec.)	Surface Texture	Transparency
1	F1	96±0.10	Rough	Transparent
2	F3	55±0.18	Smooth	Transparent
3	F4	45±0.20	Smooth	Transparent

4	F5	67±0.15	Smooth	Transparent
5	F6	20±0.08	Smooth	Transparent
6	F7	30±0.25	Smooth	Transparent
7	F8	50±0.30	Rough	Transparent

c. Composition of batches for plasticizer screening without drug

Different plasticizer are used in PEG-200,PEG-400 and glycerin in used areplasticizer screening.

Table No.9: Composition of Batches for Plasticizer Screening WithoutDrug (gm & ml)

Trial Code	HPMC E-5	PEG 200	PEG 400	Glycerin	Citric Acid	Aspartame	Distilled Water
F1	0.60	0.5	----	----	0.01	0.04	Qs
F2	0.60	0.8	----	----	0.01	0.04	Qs
F3	0.60	1	----	----	0.01	0.04	Qs
F4	0.60	----	0.5	----	0.01	0.04	Qs
F5	0.60	----	0.8	----	0.01	0.04	Qs
F6	0.60	----	1	----	0.01	0.04	Qs
F7	0.60	----	----	0.5	0.01	0.04	Qs
F8	0.60	----	----	0.8	0.01	0.04	Qs
F9	0.60	----	----	1	0.01	0.04	Qs

d. Evaluation Results For Plasticizer Screening Without Drug

Oral film using the plasticizer screening of formulation of film. They are evaluated and screening for appearance and dryness. Film formed ware transparent, dry and flexibility of the film. Film forming capacity is high as compared to other plasticizer.[12] Glycerin are the best formation of the film F8 is

best formation of the film and PEG200, PEG400

F1-F2 formulation are not formed.

Table No .10: Evaluation Results for Plasticizer Screening

Sr.No.	Trial code	DisintegrationTime (Sec.)	Surface Texture	Transparency
1	F3	95±0.15	Rough	Transparent
2	F4	50±0.05	Smooth	Transparent
3	F5	60±0.08	Smooth	Transparent
4	F6	55±0.20	Rough	Transparent
5	F7	45±0.12	Smooth	Transparent
6	F8	30±0.10	Smooth	Transparent
7	F9	85±0.08	Smooth	Transparent

e. Preparation of Final Optimized Formulation of Oral disintegration film WithoutDrug

Table No. 11: Preparation of Final Optimized Formulation of Oral disintegration film Without Drug (gm & ml)

S. NO.	Ingredients	F1	F2	F3	F4	F5	F6
1	HPMC	0.60	0.60	0.60	0.60	0.60	0.60
2	Taro Gum	0.20	----	----	----	----	----
3	Cassava Gum	----	0.20	----	----	----	----
4	Xanthan Gum	----	----	0.20	----	----	----
5	Guar Gum	----	----	----	0.20	----	----
6	Sodium Alginate	----	----	----	----	0.20	----
7	Gum Tragacanth	----	----	----	----	----	0.20
8	Glycerin	0.8	0.8	0.8	0.8	0.8	0.8
9	Citric Acid	0.01	0.01	0.01	0.01	0.01	0.01

10	Aspartame	0.04	0.04	0.04	0.04	0.04	0.04
11	Distilled water	Qs	Qs	Qs	Qs	Qs	Qs

All film Shot on oneplus 48MP+50MP

f. Evaluation Results for Batches

Oral film was Prepared and evaluated Film F1, F2, F3, F5 and F6 give best formation of thefilm and F4 Guar Gum film was not formed.

Table No. 12: Evaluation Results for Batches

Sr.No.	Trial code	DisintegrationTime (Sec.)	SurfaceTexture	Transparency	Tensile Strength (g/Cm2)
1	F1	95	Rough	Transparent	8.25±0.0.025
2	F2	50	Smooth	Transparent	9.20±0.0120
3	F3	60	Smooth	Transparent	10.4±0.0.015
4	F5	55	Rough	Transparent	12.04±0.0.100
5	F6	45	Smooth	Transparent	11.50±0.0.065

Once the polymer and its quantity were finalized, the type of plasticizer was screened. two plasticizers were screened for the selection at the same concentration (20% w/w). the evaluation results for batches are shown. in Table.

g. Dose Calculation

Diameter of the plate =9.5cm

Area of the plate $= \pi r^2$ =70.88cm^2

Area of 1 film = 4cm^2

Dose of drug per film =2 mg

$$\text{Drug to be added in one batch} = \frac{\text{Dose of drug per film} \times \text{Area of petri plate}}{\text{Area of one film}}$$

$$= \frac{2.0 \times 70.88}{4}$$

Drug to be added in one batch = 35.44 g

Formulation development of final optimized oral Oral disintegration film

Oral disintegration film are prepared using HPMC and different gums polymer.[13] Water soluble polymers are dissolved to form homogenous solution. Drug and other water soluble components are allowed to dissolve in small amount of water. Both solutions are mixed with each other with continuous stirring. Entrapped air bubbles are removed by applying vacuum. Solution formed is casted on nontreated surface. Subjected for drying and cut in pieces. Film was prepared by using polyvinyl alcohol by casting method. The specified amount PVA was dissolved in 7ml of water and was kept aside for 10min for swelling of polymer. Further required aspartame was dissolved separately in 2ml of hot water and specified quantity of menthol was dissolved in 1ml of ethanol were added to the polymer solution under continues stirring. 225 mg of drug was dispersed in polymer solution. Glycerin and poly-sorbate 80 were added to the polymer solution. Solution was mixed thoroughly using magnetic stirrer. The viscous solution was degassed under vacuum; the resulting bubble free solution was poured onto glass mould of size 3 inch X 3 inch, which was placed over a flat surface. The mould was kept for 12hrs at room temperature for drying. The film was removed from the mould and preserved in a butter paper and in a desiccators .

Table No.13: Preparation of final optimized formulation of Oral disintegration film With Drug (gm & ml)

S. NO.	Ingredient	F1	F2	F3	F4	F5	F6
1	Promethazine Hcl	0.177	0.177	0.177	0.177	0.177	0.177
2	HPMC E-5	0.60	0.60	0.60	0.60	0.60	0.60
3	Taro Gum	0.20	----	----	----	----	----
4	Cassava Gum	----	0.20	----	----	----	----
5	Xanthan Gum	----	----	0.20	----	----	----
6	Guar Gum	----	----	----	0.20	----	----

7	Sodium Alginate	----	----	----	----	0.20	----
8	Gum Tragacanth	----	----	----	----	----	0.20
9	Glycerin	0.8	0.8	0.8	0.8	0.8	0.8
10	Citric Acid	0.01	0.01	0.01	0.01	0.01	0.01
11	Aspartame	0.04	0.04	0.04	0.04	0.04	0.04
12	Distilled water	Qs	Qs	Qs	Qs	Qs	Qs

Area of the film -2 X 2cm^2 Dose of drug per film -2 mg

Evaluation Parameter of Final Feruled of Oral disintegration film

Table No. 14: Evaluation parameters

Formulations	Thickness(mm)	Folding endurance	Tensile strength (g/cm^2)	Dissolution time(min.)	*In-vitro* disintegration time(sec)	*pH*	Drug content
F1	0.58	175	48.41±0.50	1.15±0.10	25±0.12	6.25±0.1	98.25%
F2	0.55	180	51.18±0.68	1±0.20	28±0.10	6.85±0.21	99.55%
F3	0.59	160	62.04±0.25	1.25±0.21	20±0.24	6.20±0.4	97.15%
F4	0.51	150	54.25±0.24	2.05±0.25	31±0.21	6.50±0.6	98.45%
F5	0.53	145	53.68±0.33	1.50±0.10	35±0.54	6.65±0.8	98.00%
F6	0.52	168	52.33±0.74	1.55±0.14	35±0.74	6.70±1.0	97.80%

Final formulated Oral disintegration film with drug


a. Weight Variation

Data of Weight Variation of Optimized Film Weight of 20shape (2X2 cm²)

Formulations	Weight variation (mg)
F1	69±1.25
F2	68±1.50
F3	68.2±0.50
F4	69.4±0.88
F5	70.2±0.66
F6	70.5±1.15

REFERENCE

1. Abdelbary, G., Eouani, C., Prinderre, P., Joachim, J., Reynier, J. P., & Piccerelle, P. H. (2005).Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. *International journal of pharmaceutics*, 292 (1), 29-41.
2. Aguilar-Díaz JE ,García-Montoya E ,Pérez-Lozano P ,Suñe-Negre JM ,Miñarro M ,TicóJR . The use of the SeDeM Diagram expert system to determine the suitability of diluents–disintegrants for direct compression and their use in formulation of ODT. Eur J Pharm Biopharm 2009;73:414–23 .
3. Aguilar-Díaz JE ,García-Montoya E ,Pérez-Lozano P ,Suñé-Negre JM ,Miñarro M ,TicóJR . SeDeM expert system a new innovator tool to develop pharmaceutical forms. Drug Dev Ind Pharm 2014;40:222–36 .
4. Aguilar-Díaz JE ,García-Montoya E ,Suñe-Negre JM ,Pérez-Lozano P ,Miñarro M ,TicóJR . Predicting orally disintegrating tablets formulations of ibuprophen tablets: an application of the new SeDeM-ODT expert system. Eur J Pharm Biopharm 2012;80:638– 48 .
5. Akseli I ,Xie J ,Schultz L ,et al.A practical framework toward prediction of breaking force and disintegration of tablet formulations using machine learning tools. J Pharm Sci 2017;106:234–47
6. Al-Khattawi A ,Mohammed AR . Compressed orally disintegrating tablets: excipients evolution and formulation strategies. Expert Opin Drug Deliv 2013;10:651–63 .
7. R. Madhavi, V. S. Murthy, A. P. Rani, and Y. M. Kumar, ―Formulation and evaluation of taste masked oral disintegrating tablet of cefixime based on cyclodextrin binary systems,‖Journal of Global Trends in Pharmaceutical sciences, vol. 5, no. 2, pp. 1738–1746, 2014.
8. Baber, N. (1994). International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH).*British journal of clinical pharmacology*, 37(5), 401-404.
9. Bhowmik D ,Chiranjib B ,Krishnakanth P ,Chandira RM . Fast dissolving tablet: an overview. J Chem Pharm Res 2009;1:163–77
10. Bandari S ,Mittapalli RK ,Gannu R . Orodispersible tablets: an overview.

Asian J Pharm 2014;2 .

11. Battu S. K., Repka M. A., Majumdar S., Madhusudan R. Y., Drug Dev.Ind. Pharm., 33, 1225-1232 (2007).
12. Bhardwaj S, Jain V, Sharma S, Jat RC and Jain S: Orally disintegrating tablets: a review Drug Invention Today 2010; 2(1): 81-88.
13. Bhati, R., Nagrajan, R. K. (2012). A detailed review on oral mucosal drug delivery system.*International Journal of Pharmaceutical Sciences and Research*, 3(3), 659.