Design and Development of (MDT) Mouth Dissolving Film of Promethazine HCL Using Natural Gums and polymers

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Abstract:

Natural polymers are biocompatible and can be used widely in pharmaceutical field. They are easily available and are nontoxic in nature. Natural polymers along with other drug delivery systems can be efficiently used in film formulation as well. Novel extracted polymer Taro and cassava it may be found to enhance the properties such as the tensile strength, *In vitro* disintegration time and the *In vitro* release of the film when used in combination with the semi synthetic polymer like HPMC E5 as per literature review. The main objective of the study was to formulate and evaluate mouth-dissolving film containing Promethazine HCL. The 3 and 4 % w/v HPMC E-5 and PVA films were prepared by casting method. Compatibility of Promethazine HCL with polymers was confirmed by FT-IR studies. Four films were evaluated for weight variation and thickness showed satisfactory results. Tensile strength, percentage elongation and folding endurance of the films The stability studies were performed for about 1 month. No significant changes were observed in the thickness, tensile strength, *In-vitro* disintegration and *In-vitro* drug release. The film (F2) Promethazine HCL,HPMC E-5 with Cassava Gum are given best result as compare to other showed maximum release within 3 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament.

Keywords: Promethazine MDT, Natural Polymer, Solvent casting method, Cassava Gum, Xanthan Gum.

INTRODUCTION

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal. Oral route is commonly used route for the delivery of the drugs till date as it bears various advantages over the other route of drug delivery, but oral drug delivery systems still a date need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms.[1] Many pediatric and geriatric patients who having difficulty in swallowing are unwilling to take solid preparations as a result of concern of choking. So, fast-dissolving drug-delivery systems came into existence in the late 1970's as another to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. It was developed on the basis of technology of the transdermal patch. The fast dissolving drug delivery system consists of a very thin strip that is just placed on the patient's tongue or any oral mucosal tissue, instantly wet by secretion the film rapidly hydrates and adheres onto the location. It then quickly disintegrates and dissolves to release the drug for oromucosal and intragastric absorption. Mouth dissolving films offers an elegant route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage.[2]

MATERIAL & METHOD

DRUG PROFILE

1. **Promethazine HCL**

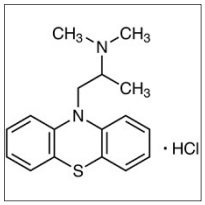


Fig.No.1. Promethazine HCL

Promethazine is used to prevent and treat nausea and vomiting related to certain conditions (such as before/after surgery, motion sickness). It is also used to treat allergy symptoms such as rash, itching, and runny nose. It may be used to help you feel sleepy/relaxed before and after surgery or to help certain opioid pain relievers (such as meperidine) work better.[3]

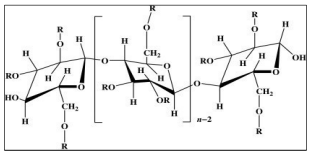
Excipient profile

HYDROXY PROPLY METHYL CELLULOSE HPMC

Synonyms: Hydroxy propyl methylcellulose, Lacril,Methocel, Propyleneglycol ether.

Chemical Name: Cellulose-2-hydroxy propyl methyl ether

Molecular Weight: Approx.,86000 Dalton (variable according to grade)



FigNo-2:HPMC

Xanthan Gum

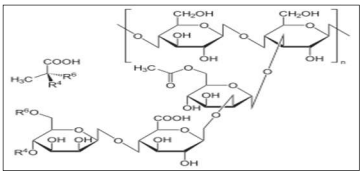


Fig.No.3. Xanthan Gum

Synonyms

Corn sugar gum; E415; Keltrol; merezan; polysaccharide B-1459; Xanthan Gum.

Functional category

Stabilizing agent; Suspending Agent; Viscosity-Increasing Agent.[4]

Guar Gum

Chemical composition

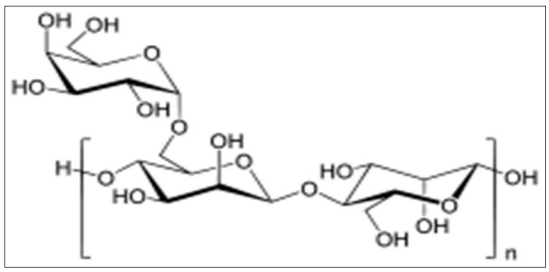


Fig.No.5. Guar Gum

Guar Gum also called Guaran, is a Galactomannan polysaccharide extracted from Guar beans that has thickening and stabilizing properties useful in food, feed, and industrial applications.The guar seeds are mechanically dehusked, hydrated, milled and screened according to application. It is typically produced as a free-flowing, off-white powder.[5]

GLYCERINE

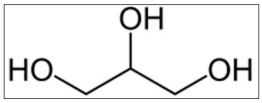


Fig.No.6. Glycerine

CITRIC ACID

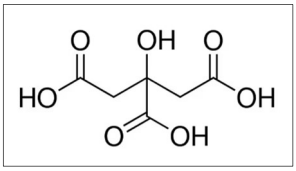


Fig.No.7. Citric Acid

ASPARTME

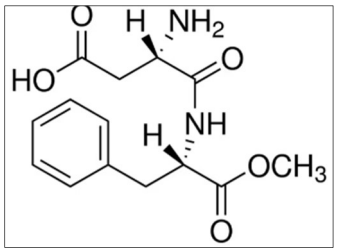


Fig. No 8 Aspartame

SODIUM ALGINATE

Synonyms

Algin; alginic acid; sodium salt; E401; kelcosol; keltone; manucol;manugel;pronova; satialgine-H8.

Molecular weight - 1828

Functional category

Stabilizing Agent ; Suspending Agent; Tablet and Capsule Disintegrant; Tablet Binder; Viscosity-Increasing agent.[6]

PROCUREMENT OF DRUG

Table No. I: Procurement of drug

S. NO	DRUG	MANUFACTURED AND SUPPLIED BY
1	Promethazine HCL	Research-Lab Fine Chem Industries Mumbai 400 002 (INDIA)

Table No. 2: Procurement of Excipient

S. NO	DRUG	SUPPLIED BY
1	HPMC E5	Central Drug House
2	Xanthum gum	Central Drug House
3	Gaur Gum	Central Drug House

4	Sodium Alginate	Central Drug House
5	Gum Tragacanth	Central Drug House
6	Citric acid	Central Drug House
7	Glycerine	Central Drug House
8	Aspartme	Central Drug House

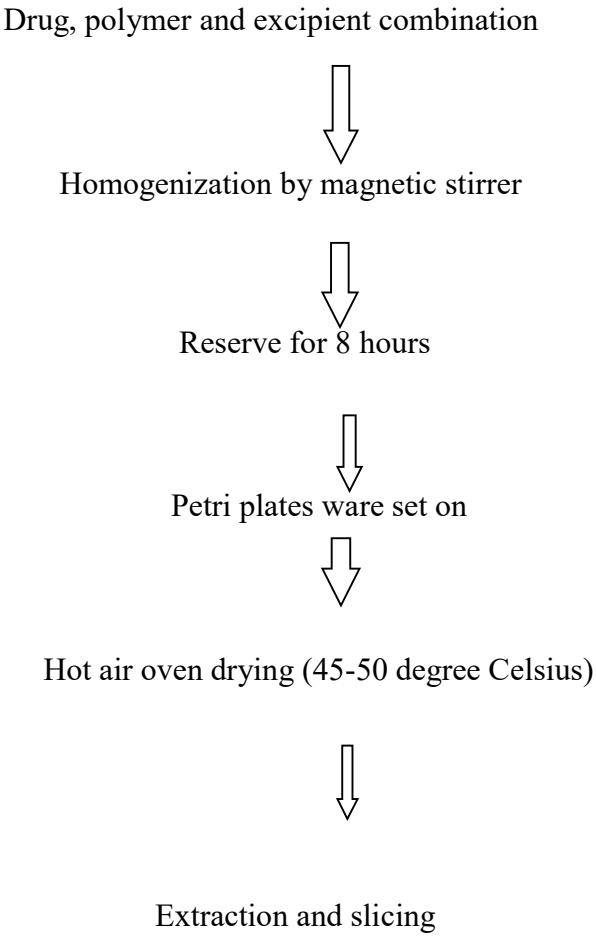
Fig No.9 Taro Gum **Fig No.10: Cassava Gu**

Preparation of Mouth Dissolving Film (MDF)

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. [7] 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. 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.[8]

Solvent casting method

The process of preparing MDFs by solvent casting typically involved the following steps:



Composition of batches from polymer screening

Different- different polymers and gum used for preparation of mouth dissolving film. Films ware the prepared by solvent casting method. They are screened for the film forming capacity. Disintegration time and appearance.[9]

Composition of batches for plasticizer screening

Different plasticizers used for preparation of mouth dissolving film. They are screened for the film forming capacity. The disintegration time and appearance.[10]

Evaluation parameters of mouth dissolving film

Folding Endurance.

To determine folding endurance, a film is cut and rapidly folded at the same placetill it broke. The number of times the film could be folded at the same placewithout breaking gives the value of folding endurance.

Weight Variation

Tenfilmswererandomlyselectedandtheiraverageweightwasweighed.Individual films were weighed and compared with the average weight for thedeviation.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Thickness

A micrometer screw gauge was used to measure the film thickness. In order toobtain uniformity of film, thickness is measured at5 different locations. Thethickness of the film should be less than 5 %.

Surface pH Value

The pH value was determined by one mouth dissolving film in the 10ml water measuring the pH of the solution. All the strip determination of the pH value.

TensileStrength

Tensilestrengthisthemaximumstressappliedtoapointatwhichthestripspecimenbreaks.It is calculated bythe formulation was evaluated by a digital tensile strength tester.[11]

$$\text{Tensilestrength} = \frac{\text{LoadatFailure} \times 100}{\text{Strip Thickness} \times \text{Strip Width}}$$

***In-vitro* Disintegration Studies**

2 ml of distilled water was placed in the petri dish and one film was added on thesurfaceofwaterandthetimemeasureduntiltheoralfilmwasdissolvedcompletely. The *In-vitro* disintegration time of fast dissolving films was noted.[12]

Drug Content

The formulated mouth dissolving film was dissolved in 100 ml volumetric flask of containing 0.1N HCL. One ml of stock solution was further the diluted to 10ml with 0.1N HCL .The

absorbance of this solution was noted. The calibration curve of different concentration of Promethazine HCL in 0.1 N HCL. Drug content of the film ware determination by using UV-VIS Spectroscopy.

Stability Studies

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized F2 formulation was sealed in Aluminum packing laminated with polyethylene. Samples were repeat 4^0c and75% RH for 3 months. At the end of study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics.[13]

***In-vitro* Dissolution Studies**

It was determined visually in a glass beaker filled with 25 ml distilled water with swirling every 10seconds. The time at which film started to break or disintegrate was recorded as the *in-vitro* disintegration time. It was performed in triplicate.[14]

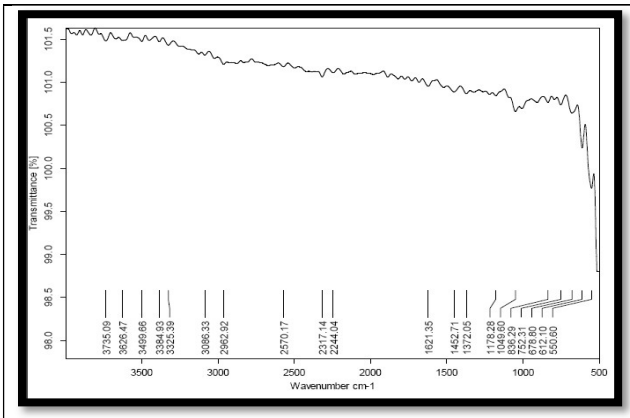
RESULT AND DISCUSSION

Drug Excipient Compatibility Studies by Physical Observation

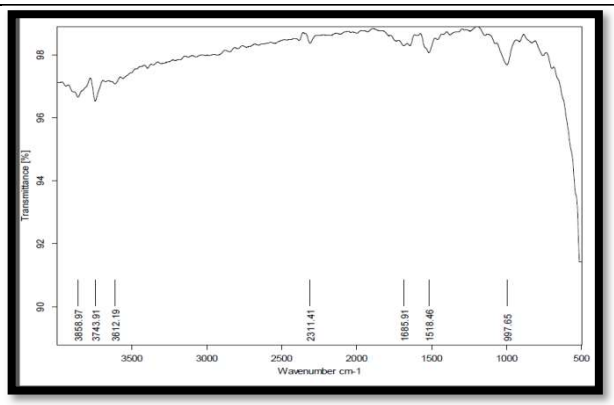
Promethazine HCL and HPMC E-5 and GUM was mixed in equal proportion and kept at 40 degree/ 75 % Rh condition give to two months. The physical properties (color change) will be every 15 days monitored regularly. The change in color of mixture will be considered as incompatibility.

Drug excipient compatibility studies by FT-IR

A Fourier Transform- Infra red spectrophotometer (Spectrum BX series, 51658, Perkin Elmer BX, UK) equipped with spectrum v2.19 software was used to study the non-thermal analysis of drug and drug - excipient (binary mixture of drug: excipient 1:1 ratio) compatibility.



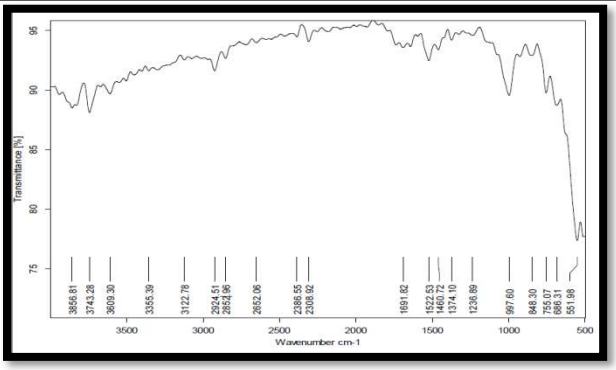
Graph 1: FTIR Report of Promethazine HCL



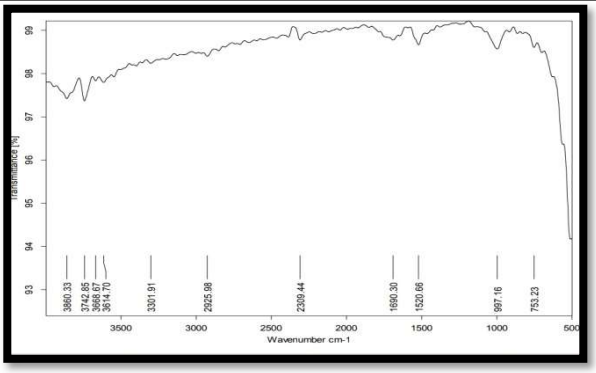
Graph 2: FTIR Report of Cassava Gum

Graph 3: FTIR Report of Taro Gum

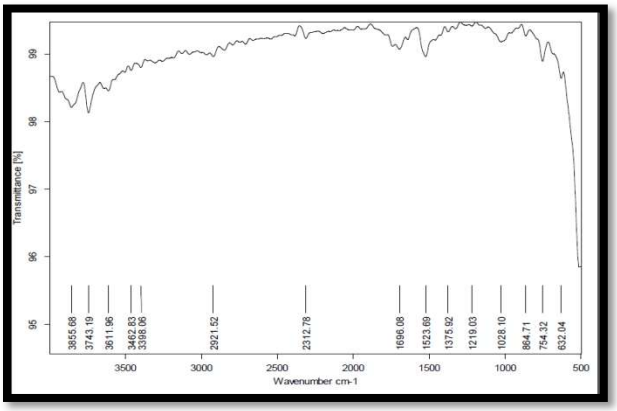
Graph 4: FTIR Report of HPMC E5+ Promethazine HCL



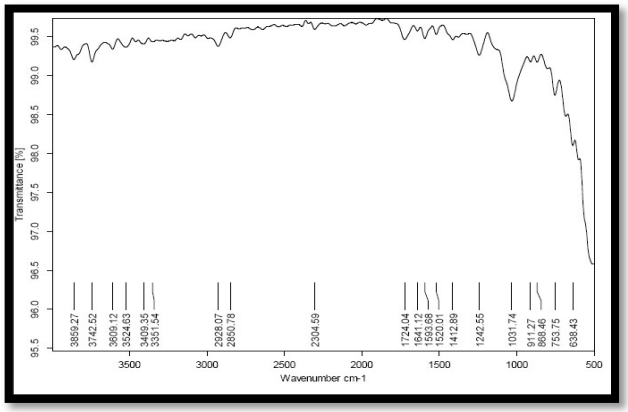
Graph 5: FTIR Report of Cassava Gum + Promethazine HCL



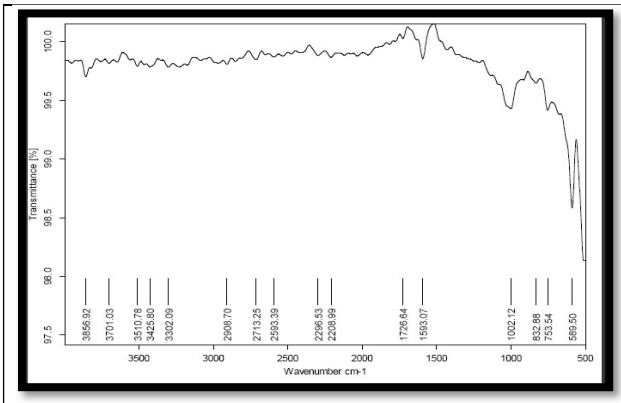
Graph 6: FTIR Report of Taro Gum + Promethazine HCL



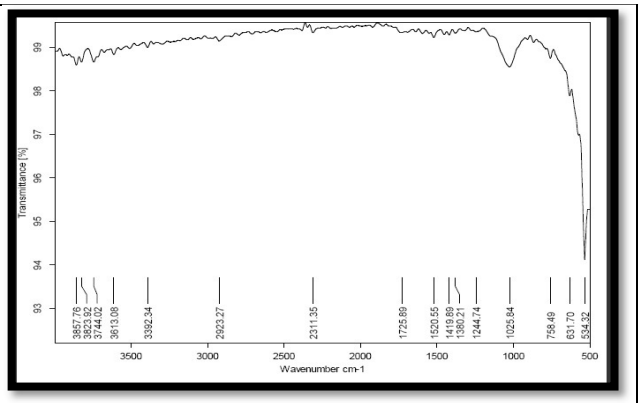
Graph 7: FTIR Report of Guar Gum + Promethazine HCL



Graph 8: FTIR Report of Gum Tragacanth + Promethazine HCL



Graph 9: FTIR Report of Sodium Alginate + Promethazine HCL



Graph 10: FTIR Report of Xanthan Gum + Promethazine HCL

Standard Calibration Curve of Promethazine HCL in Phosphate Buffer (pH 6.8)

Table No. XXII: Standard Calibration Curveof Promethazine HCL

S.No	Concentrationµg/ml	Absorbance(267nm)
1	20	0.228
2	40	0.436
3	60	0.641
4	80	0.864
5	100	0.998

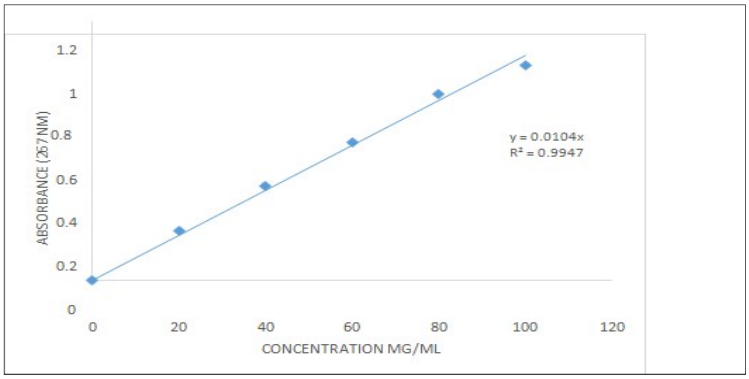


Fig. No. 11. Standardgraphof Promethazine HCL

Preparation of Mouth Dissolving Film (MDF)

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 they are used for preparation of mouth dissolving film.

Table No. 3: Composition of Batches for Polymer Screening Without Drug (gm& ml)

Trial code	HPMC E-3	HPMC E-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. Preparation of Final Optimized Formulation of Mouth Dissolving Film Without Drug

Table No. 4: Final Optimized Formulation of Mouth Dissolving 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

Formulated Oral Film of 2×2cm^{2}Dimension with Formulation Code

Fig. No.12 THG (F1)

Fig.No.13 CHG (F2)

Fig.No.14 XHG (F3)

Fig No.15 SHG (F5)

Fig. No.16 GtHG (F6)

All film Shot on oneplus 48MP+50MP

Evaluation Results for Batches

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

Dose Calculation

Diameter of the plate =9.5cm

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

Area of 1 film = 4cm^2

Dose of drug per film =10mg

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

$$= \frac{10 \times 70.88}{}$$

Drug to be added in one batch = 0.177.2g

Formulation development of final optimized oral mouth dissolving film

Mouth dissolving film are prepared using HPMC and different gums polymer.

Table No. 5: Preparation of final optimized formulation of Mouth Dissolving 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 -10 mg

Evaluation Parameter of Final Feruled of Mouth Dissolving Film

Table No. 6:Evaluationparameters

Formulations	**Thickness(mm)**	**Foldingendurance**	**Tensilestrength(g/cm^2)**	**Dissolution time(min.)**	***In-vitro*disintegrationtime(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 Mouth dissolving film with drug

Fig. No.17 THG **Fig. No.18 CHG**

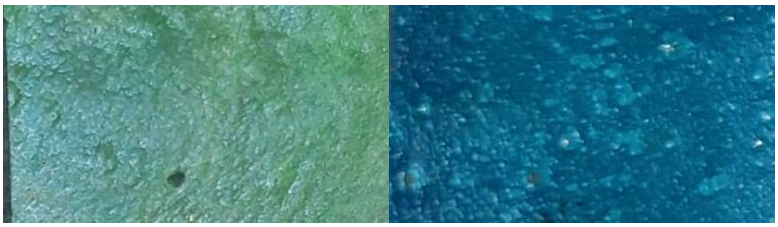


Fig. No.19 XHG F3 **Fig. N0 20 GHG F4**

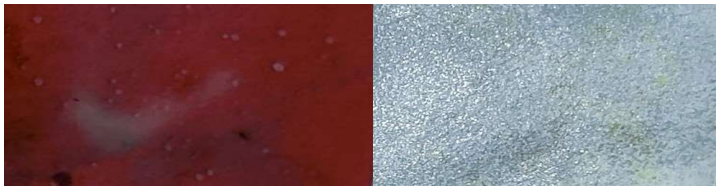


Fig. NO.21 SHG F5 **Fig. No.22 GtHG F6**

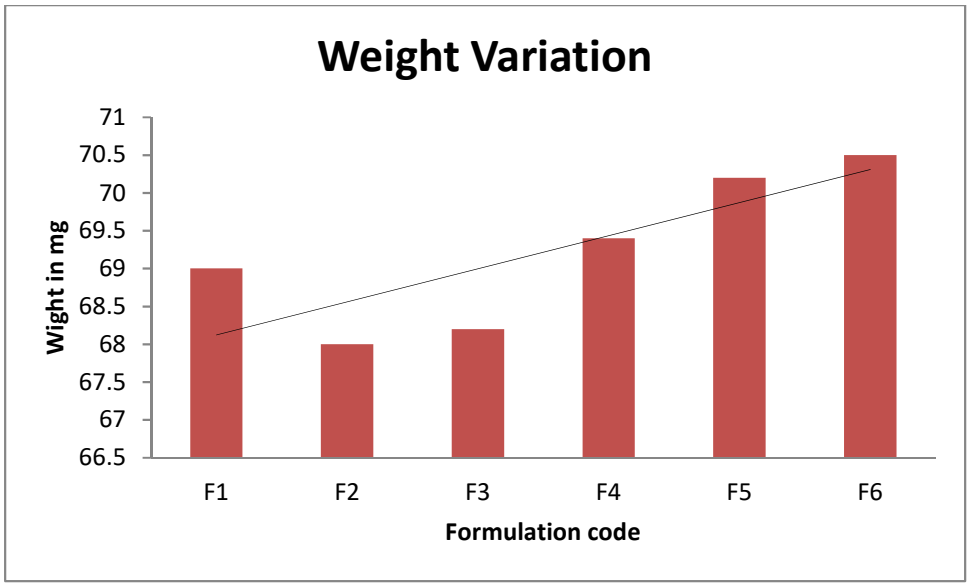


Fig. No. 23. Weight Variation Graph

In-vitro Disintegration Studies

2 ml of distilled water was placed in the petri dish and one film was added on thesurfaceofwaterandthetimemeasureduntiltheoralfilmwasdissolvedcompletely.Thein-vitro disintegration time of fast dissolving films of all formulations given in Table and fig.

Table No.7 : *In-vitro*Dissolutionof F2 Formulation of Oral Film Mouth Dissolving

S.No.	Time(mins)	Absorbance (267nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amountrelease	Cumulative drug release
1.	0.5	0.049	4.71	21.20	21.2	21
2.	1.0	0.083	7.98	35.91	36.0	36
3.	1.5	0.135	12.98	58.41	58.4	58
4.	2.0	0.156	15.1	67.5	68.0	68

5.	2.5	0.198	19.03	85.67	86.0	86
6.	3.0	0.225	21.63	97.36	97.3	97

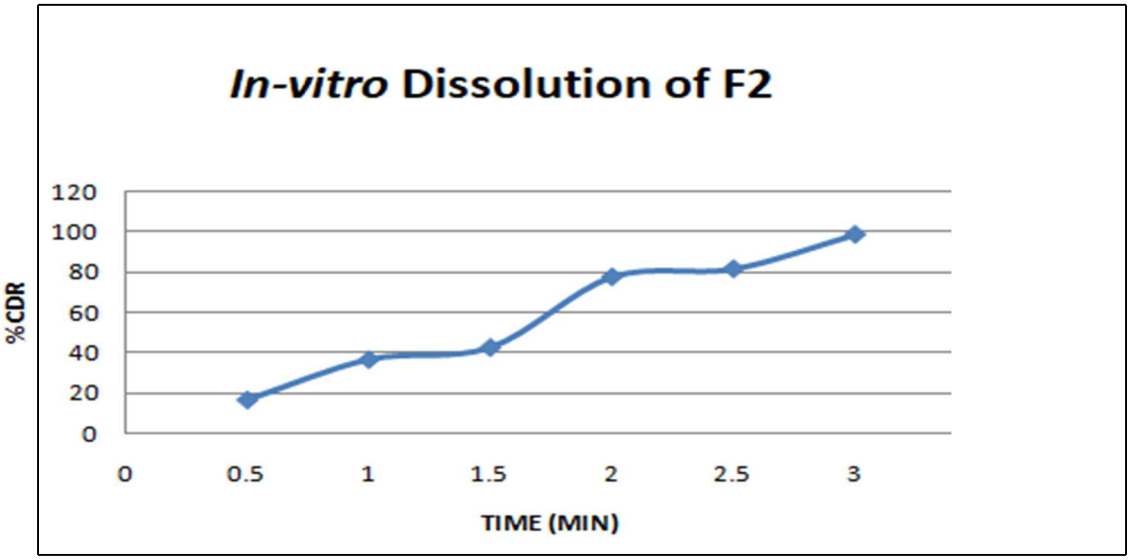


Fig. no. 24: *In-vitro*Dissolution of F2

Stabilitystudies (F2)

ThestabilitystudieswerecarriedoutaccordingtoICHtoassessthedrugformulation stability. Optimized F2 formulation was sealed in Aluminium packing laminated with polyethylene. Samples werekeptat40cand75%RHfor1 months. At the end of study period, the formulation was observed for change inphysicalappearance, color,drugcontentand drugreleasecharacteristics.

Table No. 8 :Stability studies [Condition (40°C/75%RH)] (F2)

S.No	Parameters	Initial	After 1month
1.	Thickness(mm)	0.55±0.02	0.59±0.02
2.	FoldingEndurance	180±1.2	180±1.2

3.	Tensile Strength(gm/cm^2)	51.18±0.68	50.15±0.60
4.	*in-vitro* Disintegration time(sec)	28±0.10	27.89±0..20
5.	*in-vitro* Dissolution Rate(%)	1±0.20	55±0.15

DISCUSSION

The present investigation was undertaken to formulate Mouth dissolving film for the treatment of antiemetic problems. F1-F6 were carried out with HPMC E-5cps, glycerin, aspartame and flavor. The films were clear and transparent. The thickness was uniform.The flexibility was good. The films shown good mechanical properties. Accordingto theassayresult the drugwas properlyloaded inthe film. F2 were carried out with HPMC E-5 and gum .The films shows good appearance in all the formulations. F2 shown good mechanical properties and less disintegration time of 20 seconds. All the parameters of film were found to be satisfactory. And the dissolution profile was found to be desirable and reproducible. The stability studies were performed for about 1 month. No significant changes were observed in the thickness, tensile strength, *In-vitro* disintegration and *In-vitro* drug release. The film (F2) Promethazine HCL,HPMC E-5 with Cassava Gum are give best result as compare to other showed maximum release within 3 minutes indicating the rapid drug release profile which entails in faster onset of action forthe medicament. Therefore the oral films have considerable advantage over the conventional dosage forms by using natural biocompatible polymers.

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