"FORMULATION AND CHACTERIZATION OF ORAL DISINTEGRATING NITROGLYCERINE FILM FOR THE TREATMENT OF ANGINA PECTORIS"

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Abstract:

Over the past few decades, tendency toward innovative drug delivery systems has majorly increased attempts to ensure efficacy, safety and patient acceptability. As discovery and development of new chemical agents is a complex, expensive and time consuming process, so recent trends are shifting toward designing and developing innovative drug delivery systems for existing drugs. Out of those, drug delivery system being very eminent among pediatrics and geriatrics is orally disintegrating films (ODFs). The main objective of the study was to formulate and evaluate mouth-dissolving film containing Nitroglycerine. The 3 and 4 % w/v HPMC E-5 and PVA films were prepared by casting method. Compatibility of Nitroglycerine 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) Nitroglycerine,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: Nitroglycerine, MDT, Natural Polymer, Solvent casting method, Xanthan Gum.

INTRODUCTION

Oral route of drug administration is a most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability. Regarding oral route of drug administration, many substitutes have continuously been presented by using recent novel technologies for pediatrics, geriatrics, nauseous and non-compliance patients. Bioadhesive mucosal dosage forms including adhesive tablets [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. Form: Thin oral strip placed on the tongue or oral mucosa. Mechanism: Instantly wets by saliva. Rapidly hydrates, adheres to the site. Quickly disintegrates and dissolves. Drug is released for oromucosal or intragastric absorption. Advantages: Bypasses first-pass metabolism, improving systemic bioavailability. Enhanced drug permeability due to rich vascular and lymphatic drainage in the oral mucosa. Provides a convenient and elegant route for systemic delivery.[2]

MATERIAL & METHOD

DRUG PROFILE

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 Gum

Preparation of Mouth Dissolving Film (MDF)

Form: Thin oral strip placed on the tongue or oral mucosa.

Mechanism:

Instantly wets by saliva.

Rapidly hydrates, adheres to the site.

Quickly disintegrates and dissolves.

Drug is released for oromucosal or intragastric absorption.

Advantages:

Bypasses first-pass metabolism, improving systemic bioavailability.

Enhanced drug permeability due to rich vascular and lymphatic drainage in the oral mucosa.

Provides a convenient and elegant route for systemic delivery.

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You said:

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 cm2) size and stored in aluminum foil. These films were further subjected to various evaluation tests

Preparation of Mouth Dissolving Film

Polymer Dissolution: Weighed amount of polymer is dissolved in minimum distilled water with continuous stirring. Drug Incorporation: Drug is added to the polymer solution and stirred thoroughly. Addition of Sweetener: A sweetening agent is added and mixed well. Plasticizer Addition: Calculated quantity of plasticizer is added. The mixture is sonicated to remove air bubbles and achieve clarity. Casting and Drying: The bubble-free solution is cast onto a glass plate. Dried in an oven at 60 °C for 24 hours. Cutting and Storage: Dried films are peeled and cut into 2 cm × 2 cm (4 cm²) pieces. Films are stored in aluminum foil. Evaluation: Prepared films are subjected to various evaluation tests..[8]

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 the surface of water and the time measured until the oral film was dissolved completely. 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 Nitroglycerine 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]

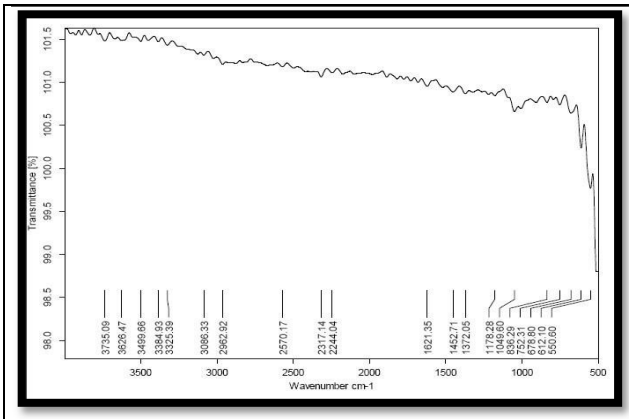
RESULT AND DISCUSSION

Drug Excipient Compatibility Studies by Physical Observation

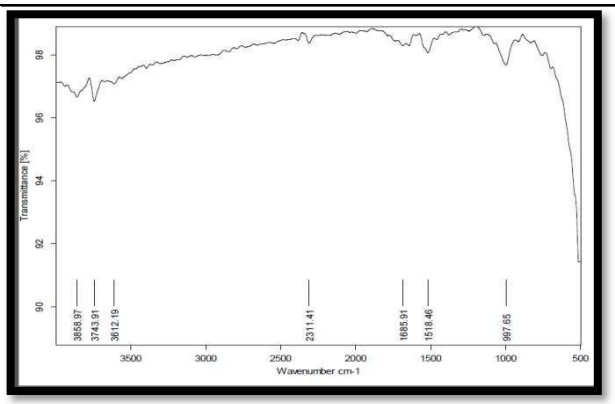
Nitroglycerine and HPMC E-5 and GUM was mixed in equal proportion and kept at 40 degree/ 75 % Rh condition give to two months. The physical properties (color change) will be every 15 days monitored regularly. The change in color of mixture will be considered as incompatibility.

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.



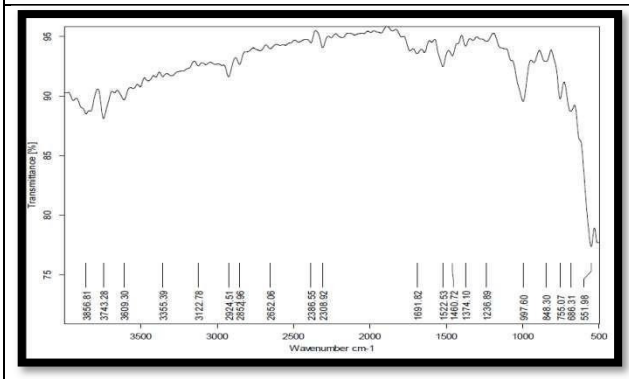
Graph 1: FTIR Report of Nitroglycerine



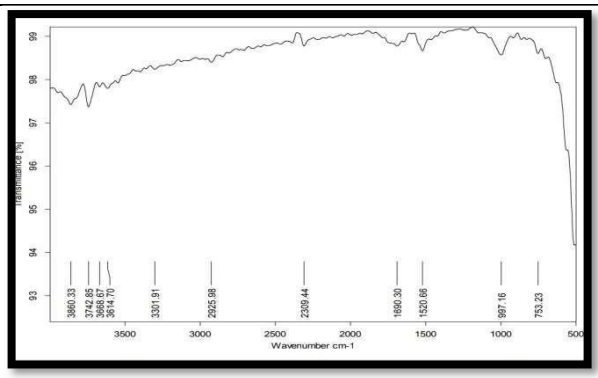
Graph 2: FTIR Report of Cassava Gum

Graph 3: FTIR Report of Taro Gum

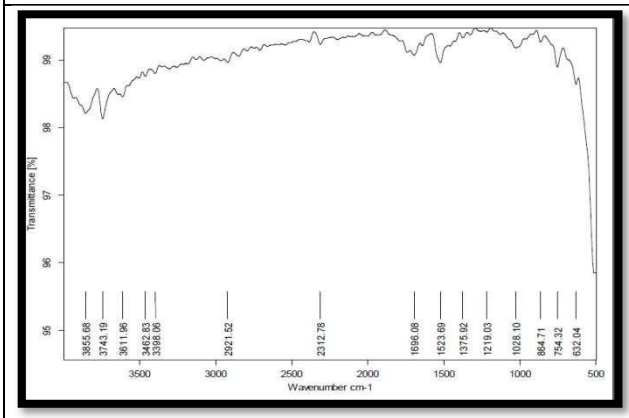
Graph 4: FTIR Report of HPMC E5+ Nitroglycerine



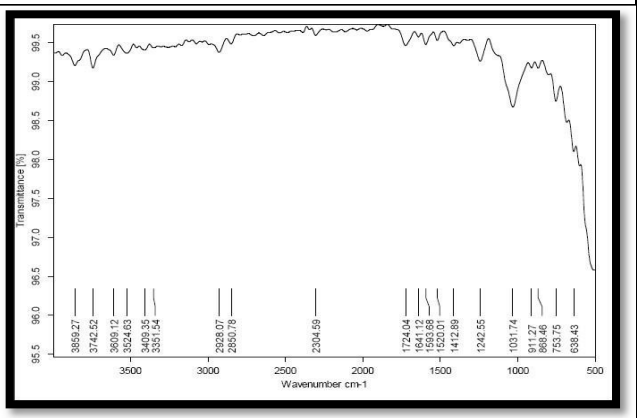
Graph 5: FTIR Report of Cassava Gum + Nitroglycerine



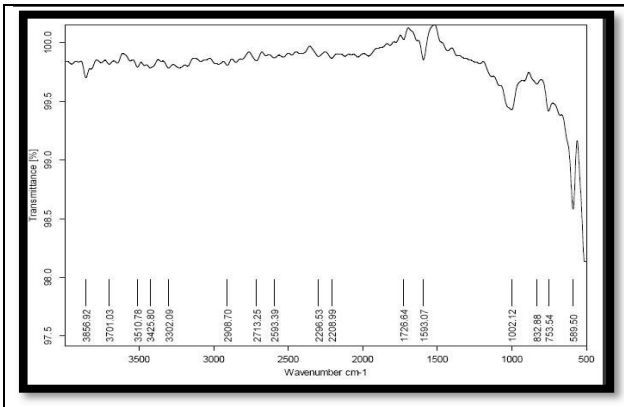
Graph 6: FTIR Report of Taro Gum + Nitroglycerine



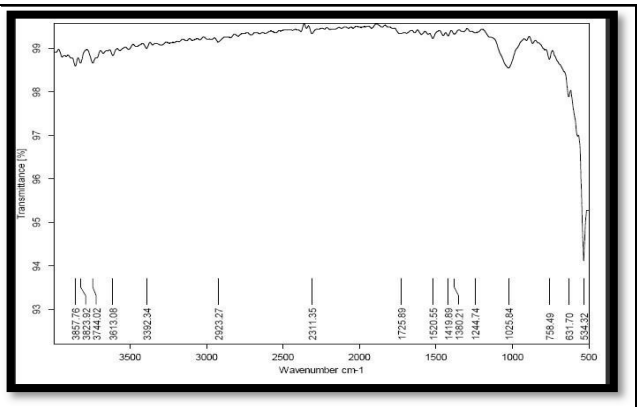
Graph 7: FTIR Report of Guar Gum + Nitroglycerine



Graph 8: FTIR Report of Gum Tragacanth + Nitroglycerine



Graph 9: FTIR Report of Sodium Alginate + Nitroglycerine



Graph 10: FTIR Report of Xanthan Gum + Nitroglycerine

Standard Calibration Curve of Nitroglycerine in Phosphate Buffer (pH 6.8)

Table No. XXII: Standard Calibration Curveof Nitroglycerine

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

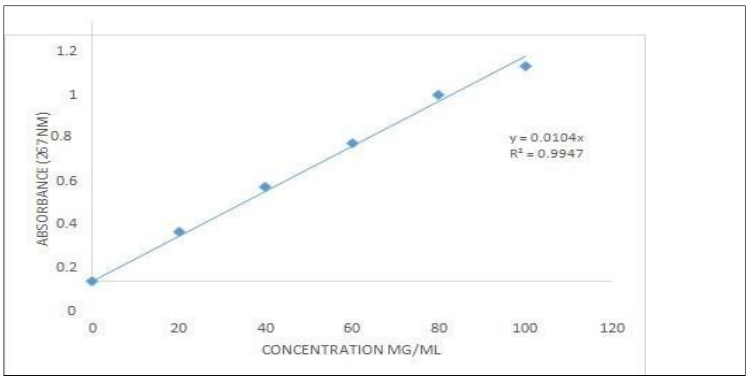


Fig. No. 11. Standardgraphof Nitroglycerine

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

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 = πr^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	Nitroglycerine	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: 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%

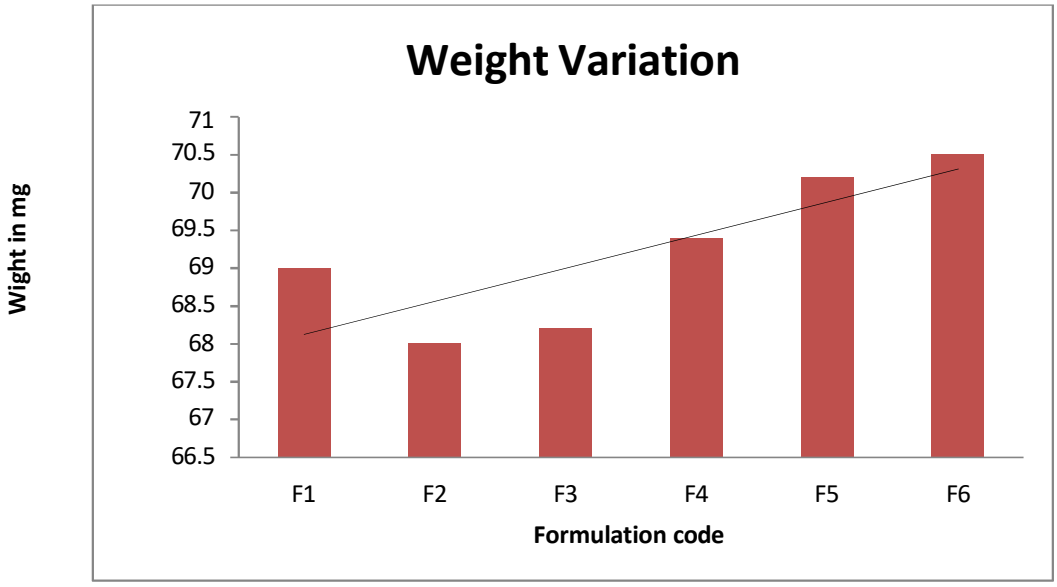


Fig. No. 23. Weight Variation Graph

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* Dissolution of 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

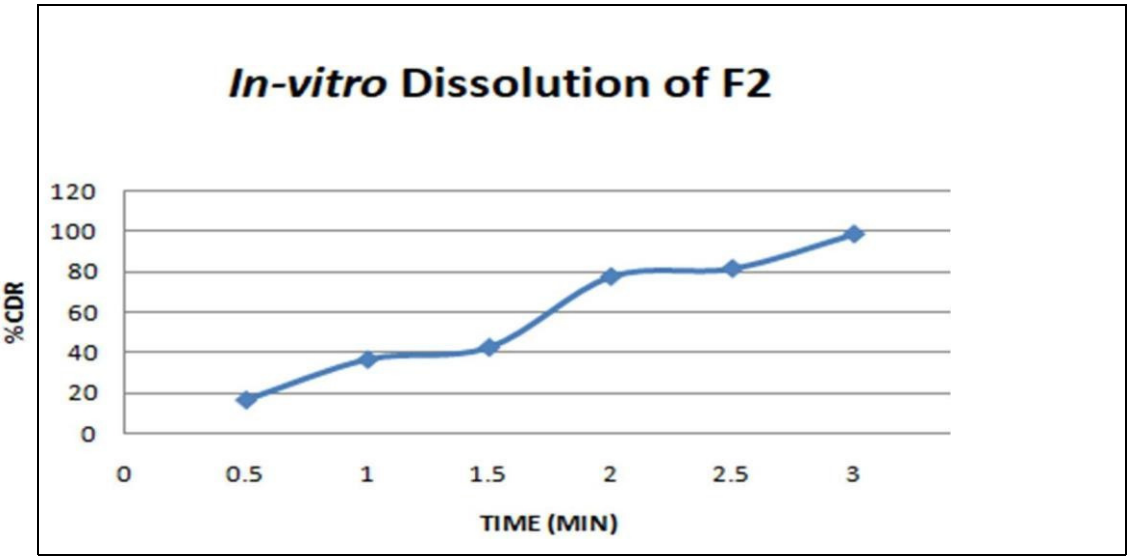


Fig. no. 24: *In-vitro*Dissolution of F2

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) Nitroglycerine,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.

Reference

1) Ali M.S et.al „Formulation and Evaluation of Fast Dissolving Oral Films of

Diazepam‟ Jr of Pharmacovigilance, 2016 vol 4(3), p.no 1-5.

2) Alka Tomar et.al „Formulation and Evaluation of Fast Dissolving Oral Film of Dicyclomine as potential route of buccal delivery‟ Int Jr Dr De &Res Jun 2012, vol 4(2), p.no 408-417.

3) Anjum Pathan et.al „Formulation and Evaluation of Fast Dissolving Oral Film of Promethazine hydrochloride using different surfactant‟ Int Jr Ph &Bio Sci, 2016 vol 3(1), p.no 74-84.

4) Aulton ME, Wells TI, pharmaceutics: the science of dosage from design. London, England: churchil; livingstone; 1998.

5) Bhyan B.,Jangra S, Kaur M, Sing H. Orally Fast Dissolving Films: Innovations In Formulation and Technology. International Journal of Pharmaceutical Sciences Review and Research, 2011, 9: 50-56.

6) British Pharmacopoeia. Electronic Edition, Crown Inc., London, 2007.

7) Buchi. N et.al „Development and Evaluation of Fast Dissolving Films of Sumatriptan Succinate for better therapeutic efficacy‟ Jr App Ph Sci, Aug 2013 vol 3 (8), p.no 161- 166.

8) Chen, M., Tirol, et.al “Film Forming Polymers In Fast Dissolve Oral Films” AAPS Annual meetingsposters and papers, T3200, 2006.

9) Deepthi.A et.al „Formulation and Evaluation of Fast Dissolving Thin Films.

10) Desai.P et.al „Design and evaluation of fast dissolving film of Domperidone‟ Int Res Jr Ph 2012, 3(9), P.NO 134-135.

11) Rakesh Tiwle “An Exhaustive Review On Solubility Enhancement For Hydrophobic Compounds By Possible Applications Of Novel Techniques.” Science Alert –Trends Research In Applied Science And Research. 7(8): 596-619; 2012.

12) Juliano, C., Cossu, M., Pigozzi, P., Rassu, G., Giunchedi, P., 2008. Preparation, in vitro characterization and preliminary in vivo evaluation of buccal polymeric films containing chlorhexidine. AAPS Pharm.Sci.Tech. 9, 1153-1160.

13) Dr. Arunakumari et.al „Design and Evaluation of Losartan Potassium Fast Dissolving Films‟ Int Jr Inn Ph Res, 2014, vol 5 (4) p.no 431-439.

14) PATEL M. Dasharath and Dharmendrasinh V. Dabhi. Development and characterization of Oral Dissolving Film For Nitroglycerine 2014, 4728-4740.

15) Patel M.Dipal et.al „Formulation and Evaluation of Fast Dissolving Film Of Cetirizine & Dextromethorphan‟ Int Jr Ph Sci &Nanotech, 2016, vol 9 (3) p.no 3305-

3311.

16) Joshi, P., Patel, H., Patel V., Panchal, R., 2012. Formulation development and evaluation of mouth dissolving film of domperidone. J. Pharm. Bioallied Sci.108, 9-