"Design and Development of Oral Disintegrating Film Using Carica Papaya"

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Abstract:

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the Parenterals and liquid orals.1 A fast dissolving oral film (FDOF) is defined as "an ultra-thin film containing active ingredient that dissolves or disintegrates in the saliva at a remarkably fast rate, within few seconds without the aid of water or chewing".2 Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration.3 It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin.4 FDO,Fs are useful in patients such as paediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing FDOFs are prepared using hydrophilic polymer that rapidly dissolves on the buccal cavity, Optimized F2 formulation was sealed in Aluminium packing laminated with polyethylene. Thickness(mm) 0.55, Folding endurance 180 Tensile strength(g/cm^2) 51.18±0.68 Dissolutiontime(min.) 1±0.20 *In-vitro* disintegration time(sec) 28±0.10 pH *6*.85±0.21 Drug content 99.55% and in stability studies Samples were kept at 40 c and 75% RH for 1 months. At the end of study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics.

Keywords: disintegration film, carica papaya, Physical incompatibility, mold,

Introduction

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the Parenterals and liquid orals.[1] A fast dissolving oral film (FDOF) is defined as “an ultra-thin film containing active ingredient that dissolves or disintegrates in the saliva at a remarkably fast rate, within few seconds without the aid of water or chewing”.[2] Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration.[3] It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin.[4] FDO,Fs are useful in patients such as paediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing FDOFs are prepared using hydrophilic polymer that rapidly dissolves on the buccal cavity, delivering the drug to the systemic circulation via buccal mucosa.[5] The fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability.[6] Oral route is the preferred and foremost utilized route of drug administration due to several reasons namely: convenience and cost-effective.[7] Film is well known among all oral dosage forms existing now a days since of its comfort of self- administration.

Carica papaya

Plants and plant-based products have been employed to prevent various human diseases since ancient times. Overall, approximately 80% population of the world depends directly on plants for the primary health care40. In India, about 45,000 plant species have been reported to possess medicinal properties.[8] Natural product or compounds isolated from the plant have shown a major advantage over synthetic drugs such as cost-effective, easy availability and show negligible side effects. Numerous studies have published the use of medicinal plants for the management of a wide range of Diseases. carica papaya Linn. From the Caricaseae family, is indigenous to Central America and South of Mexico, and commonly grown in India has been used for its medicinal properties around the world43. The papaya plant is perennial usually un branched, smooth stem and long-stalked leaves are having 5–6 lobes and can grow up to 20 m in height[9]. Different parts of papaya plant viz. fruit, bark, roots, seeds, peel, pulp, and leaf have many known therapeutic uses around the world Chronic diseases are becoming an increasingly serious hazard to public health, necessitating the implementation of nutrition-based strategies to combat them. It can be difficult to obtain medical care for certain disorders, and the consumption of staple functional foods is vital in terms of preventing such ailments. Medical care accounts for 10 to 20% of the changeable contributors to human health, whereas social determinants, specifically healthy eating habits, account for 80 to 90% of the adjustable contributors. Healthy plant-based diets are more environmentally friendly and are connected with a lower risk of obesity, type 2 diabetes mellitus, viral infections, and some malignancies, among other health benefits. When it comes to addressing chronic human diseases, functional agriculture, specifically the cultivation of functional food crops like papaya leaves (Carica papaya L.), has emerged as a new frontier in nutritional research. The creation of functional food crops employing cutting-edge technology in combination with approaches from crop science, food science, and preventive medicine is therefore a significant topic of research. *C. papaya L.* belongs to the family *Caricaceae* and is commonly known as papaya, pawpaw, and kates. It is a perennial horticultural shrub originated from Mesoamerican Centre, Central America, and southern Mexico and is mainly cultivated in the tropical and subtropical regions of Brazil, Australia, Malaysia, China, India.

Figure no. 1 Carica papaya

Table no 1: List of Ingredients Used in Formulation with Category

S.N.	Ingredients	Category
1.	Carica Papaya	Antiemetic
2.	HPMC E5	Polymer
3.	Xantham gum	Polymer
4.	Gaur Gum	Polymer
5.	Sodium Alginate	Polymer
6.	Gum Tragacanth	Polymer
7.	Cassava Gum	Polymer
8.	Taro Gum	Polymer
9.	Glycerine	Plasticizer
9	Citric Acid	Salivary , Stimulating Agent
10	Aspartame	Sweetener
11	Distilled water	Solvent

RESULT AND DISCUSSION

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.[10] 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.

Table No 2: Drug Compatibility Study by Physical Observation

S.No	DRUG	DAYS	OBSERVATION
1	Carica Papaya	15	No change
2		30	No change
3		45	No change
4		60	No change

- **Drug excipient compatibility studies by FT-IR**

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 Carica papaya 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.

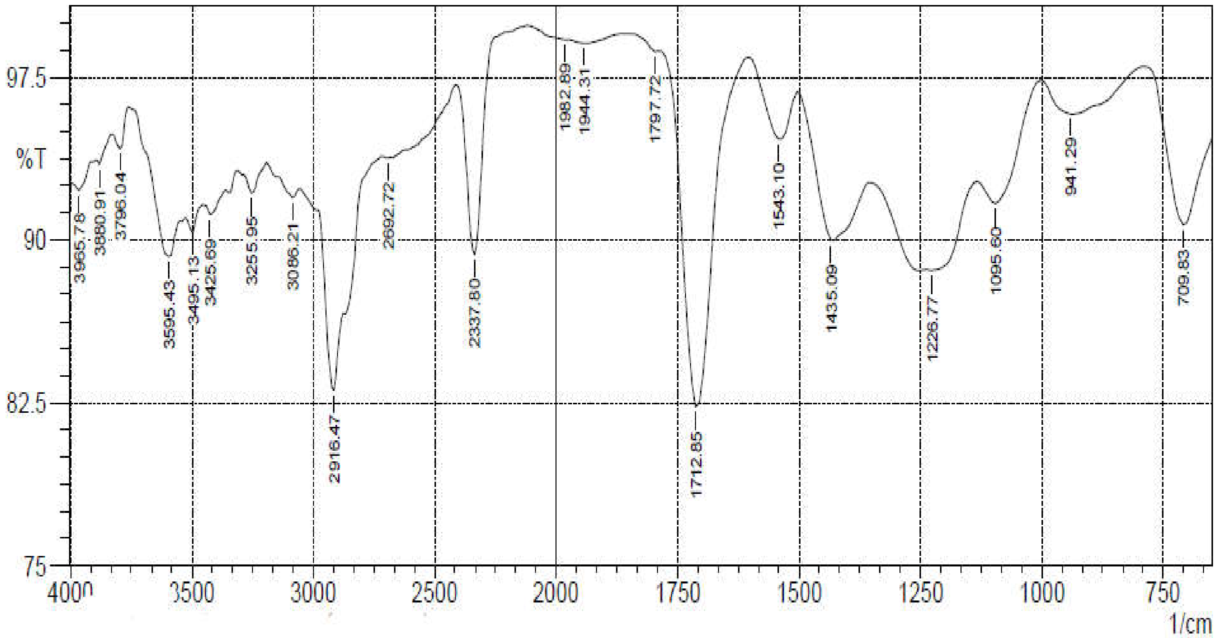


Figure 2: FTIR spectrum of methanol extract of C. papaya

Table 3: FTIR Interpretation of the methanol extract of the Carica papaya seed

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 3: FTIR Spectrum of aqueous extract of C. papaya seed

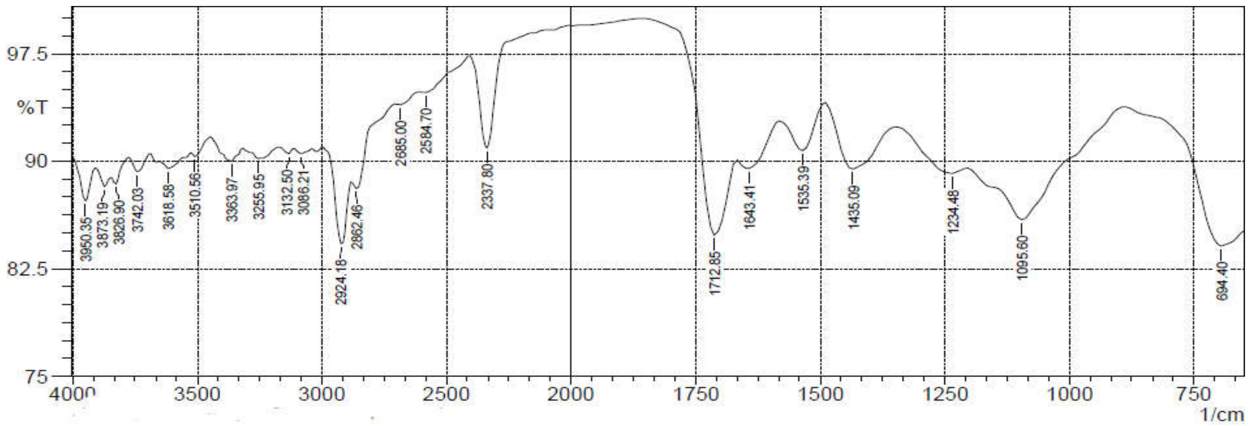
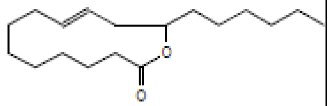
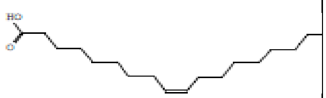
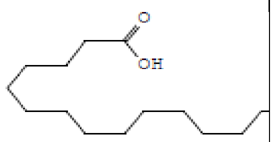
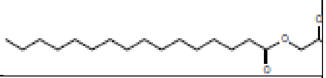


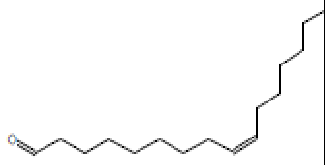
Table 4: FTIR Interpretation of the aqueous extract of the *Carica papaya* seed

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 extract of *Carica papaya* seed

Peak No	Retention time	Formula	Molecular weigh t	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	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 Carica papaya seed extracts demonstrated the presence of functional groups which are indicative of secondary metabolites and other bioactive compounds. The presence of these compounds in Carica papaya seed extract underscores its ability to possess biological activity. 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 Carica Papaya

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.

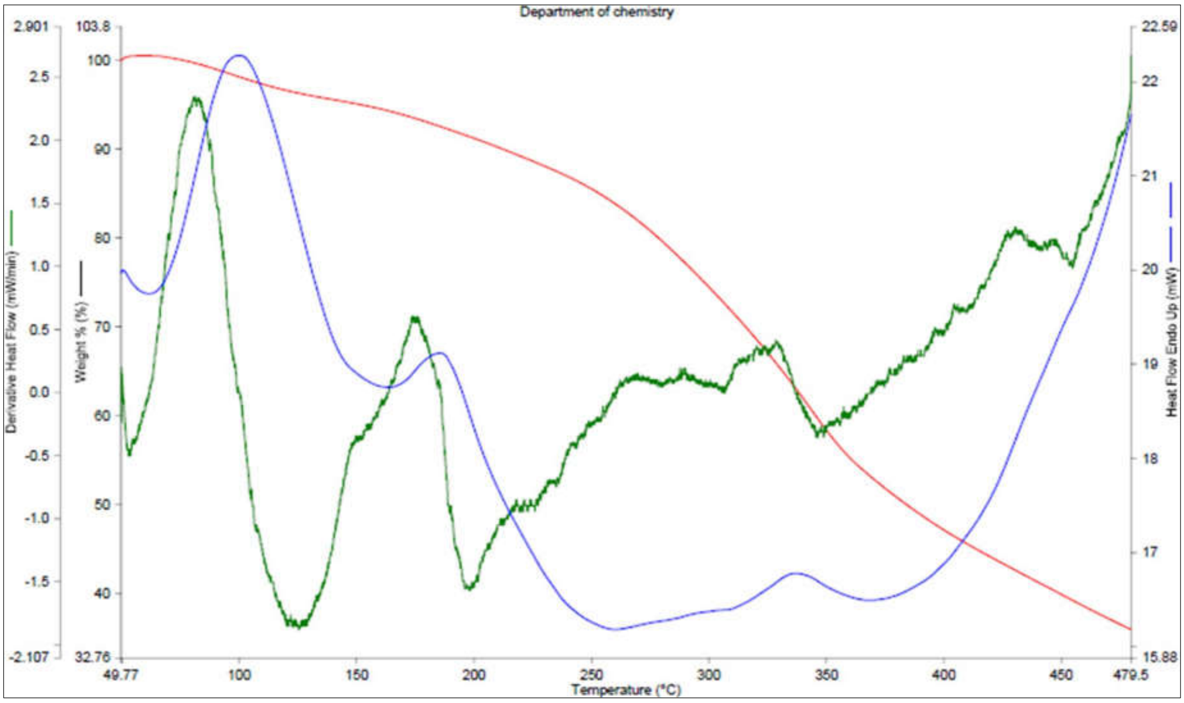


Figure 4. DSC Thermogram of the of *C. papaya*

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

- **Evaluation of Extracted Polymer**

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

PARAMETERS		TARO GUM	CASSAVA GUM
Solubility		Forms viscous colloidalsolution 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
	Tapped Density	0.5455 g/cc	0.5060g/cc
	Angle of Repose	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.

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

Trial code	HPMCE-3	HPMC E-5	HPMC E-15	HPMC E-50	Glycerin	Citric acid	Aspartame	DistilledWater
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.[11] They are evaluated and screening for appearance and dryness. Film formed ware transparent, dry. Film forming capacity is high as compared to another polymer. HPMC E-5, F6 is best formation of film and HPMC E- 3 ,F2 and HPMC E-15 F9 is not formed film.

Table No.8: Evaluation Results for Polymer Screening

Sr.No.	Trial code	Disintegration Time (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

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. 9: Evaluation Results for Batches

Sr.No.	Trial code	Disintegration Time (Sec.)	Surface Texture	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 No.

f. 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 =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 is prepared using HPMC and different gums polymer.

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.[12] 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.[13] The viscous solution was degassed under vacuum; the resulting bubble free solution was poured onto glass mold of size 3-inch X 3 inch, which was placed over a flat surface. The mold was kept for 12hrs at room temperature for drying. The film was removed from the mold and preserved in a butter paper and in a desiccator.[14]

Table No. 10: Preparation of final optimized formulation of Oral disintegration film with Drug (gm & ml)

S. NO.	Ingredient	F1	F2	F3	F4	F5	F6
1	Carica Papaya	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. 11: 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

Fig. No.5 THG **Fig. No. 6 CHG**

a. Weight Variation

Table No. 12: Data of Weight Variation of Optimized Film Weight of 20shape (2X2 cm^2)

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

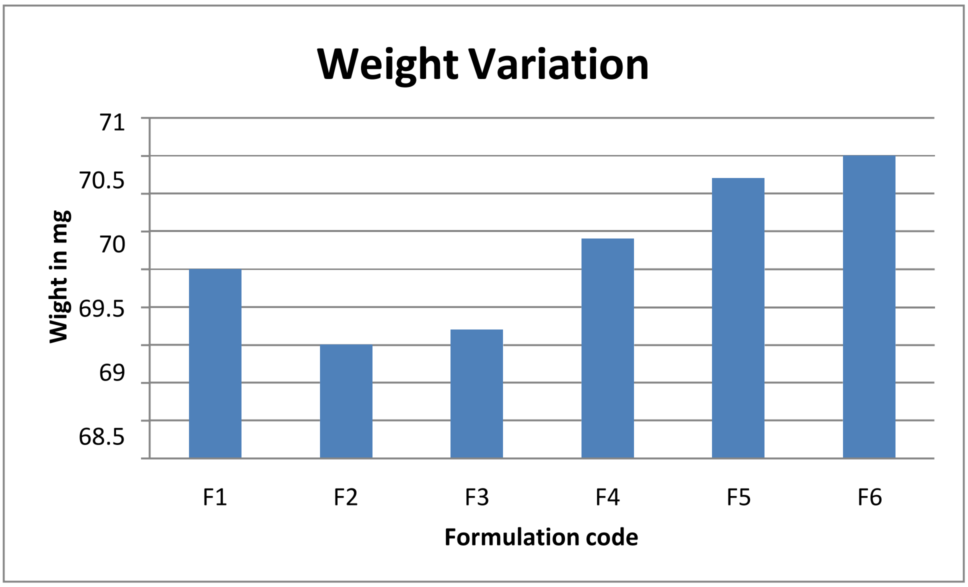


Fig. no. 6. Weight Variation Graph

a. *In-vitro* Disintegration Studies

2 ml of distilled water was placed in the petri dish and one film wasadded 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 of all formulations given in Table and fig.

Table No 13: *In-vitro* Dissolution of F2 Formulation of Oral FilmMouth Dissolving

S.No.	Time (mins)	Absorbance (267 nm)	Concentration µg/ml	Amount release mg/ml	Cumulative amount release	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

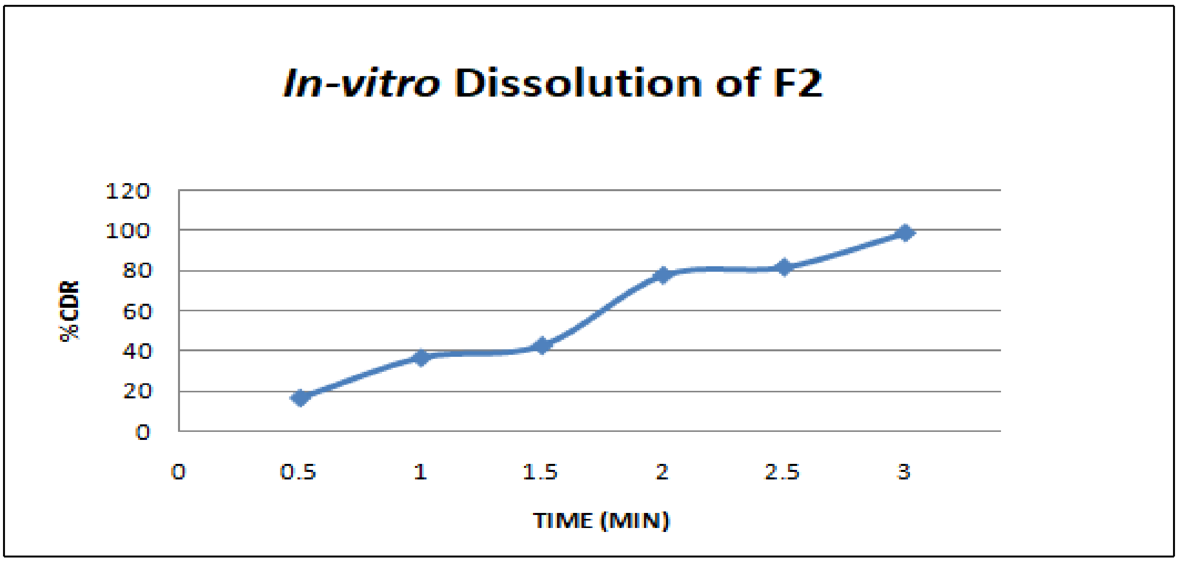


Fig. no.7. *In-vitro* Dissolution of F2

b. Stability studies (F2)

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 kept at 40 c and 75% RH for 1 months. At the end of study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics.

Table No.14: Stability studies [Condition (40°C/75%RH)] (F2)

S.No	Parameters	Initial	After 1 month
1.	Thickness (mm)	0.55±0.02	0.59±0.02
2.	Folding Endurance	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

Reference

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