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THE FORMULATION OF ORODISPERSIBLE FILM OF CETIRIZINE BY CASTING METHOD

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ABSTRACT

Thin-film drug conveyance utilizes a dissolving film or oral medication strip to control drugs employing absorption in the mouth (Buccal or sublingual) and additionally through the small digestion tracts (enteric). A film is readied utilizing hydrophilic polymers that quickly disintegrate on the tongue or Buccal fossa, conveying the medication to the fundamental diffusion through disintegration when contact with the fluid is made. Slight film drug conveyance has arisen as a high-level option in contrast to the customary tablets, containers, and fluids regularly connected with a solution and OTC prescriptions. Comparative in size, shape, and thickness to a postage stamp, meager film strips are regularly intended for oral organization, with the client putting the strip on or under the tongue (sublingual) or along within the cheek (Buccal). These medication conveyance alternatives permit the drug to sidestep the principal past digestion in this way making the medicine more bioavailable. As the strip breaks up, the medication can enter into the circulation system enteric, Buccal or sublingual. Assessing the fundamental trans membrane medication conveyance, the Buccal mucous membrane is the favored locale when contrasted with the sublingual mucosa. Solvent Casting method use to prepare films. Cetirizine is an antihistamine that reduces the natural chemical histamine in the body. Histamine can produce symptoms of sneezing, itching, watery eyes, and runny nose. It is used to treat cold or allergy symptoms such as sneezing, itching, watery eyes, or runny nose. With the help of HPMC & PVA polymers the oral films formulated. Six batches were formulated with different types of concentration selected in it; and the films evaluated for

weight variation, content uniformity, folding endurance, thickness, surface pH, tensile strength, % elongation, % moisture absorption, %moisture loss *in vitro* disintegration and *in vitro* dissolution. While the film made up of 300mg HPMC polymer released 93.6% of drug within 2 minute which was the best results among them.

KEYWORDS: Oral Film, Sublingual Film, Cetirizine, HPMC, PVA, Solvent Casting, Buccal Film, Fast Dissolving Oral Film.

INTRODUCTION

The oral route is the most adaptable route for the conveyance of the medications to date as it bears different benefits over the other route of medication organization, yet oral medication conveyance frameworks actually need a few progressions to be made. So, Fast-dissolving drug-delivery systems came into existence in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms. Psychotic patients may spit out oral medication because of its undesirable taste or find injectable dosage form unacceptable or contraindicated. Also, a psychotic patient is agitated or shows difficulty in swallowing. Administration of oral disintegrating dosage forms offers an additional advantage for the treatment of patients with psychiatric disorders. Innovative work in the drug delivery segment has prompted progress of measurement structures from basic customary tablets or capsules to changed delivery tablets or cases to oral disintegrating films (ODT) to the new advancement of oral quick-dissolving films (OFDFs).

Fig. 1: Flow chart for the development of oral dosage forms.

The film is not difficult to deal with and direct, keeps a basic and advantageous packaging, reduces unpleasant taste, and is clear to manufacture put on the top of the floor of the tongue.

Mouth dissolving film is the most exceptional oral solid dosage form because of its adaptability/flexibility and comfort being used. Mouth dissolving films are oral solid dose

structures that crumble and disintegrate inside brief when set in the mouth without taking water orbiting. This dose structure permits the drug to sidestep the primary pass digestion so the bioavailability of medicine might be improved. Mouth dissolving film can improve the beginning of activity bring down the dosing and eliminate the fear of choking.

Orally disintegrating films (ODFs), when placed on the tongue, immediately hydrates by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form. ODFs are somewhat details that are usually arranged utilizing hydrophilic polymers empowering quick disintegration upon contact with salivation.

Fast disintegrating oral formulations are generally prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. Some of the quality attributes of films are as follows:
Easy transportation, good mechanical strength & stability Enhanced bioavailability due to bypassing hepatic first pass effect Ease of swallowing for geriatrics and pediatrics patients with dysphasia & upper respiratory disease.

Some special things about ODFs

Thin elegant film
Available in various size and shape
Unobstructed
Excellent mucoadhesion
Fast disintegration and rapid release.[1]

There are some limitation with ODFs as it difficulty in incorporating poorly water-soluble drugs, relatively smaller drug load given its smaller size and thickness, and sensitivity to humidity and temperature necessitating exclusive packaging Optimistically, recent studies have been addressing various limitations of oral films such as the possibility of incorporation of poorly water-soluble films into oral films by various particle engineering techniques. The most common limitations of the oral films are related to their instability in environments with high relative humidity.[2]

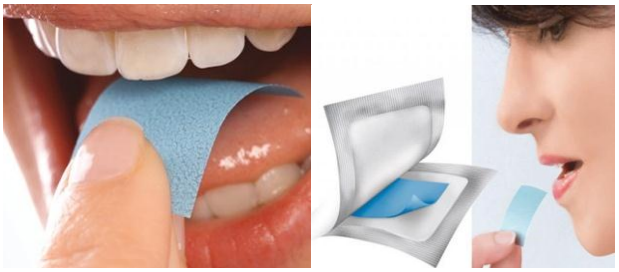


Fig. 2: Oral dispersible film.

Classification of oral films

There are three types of oral films

1. Flash release
2. Mucoadhesive melt away wafer
3. Mucoadhesive sustained-release wafers.[3]

Table 1: Different properties of oral films.

Properties	Flash Release Wafer	Mucoadhesive Melt Away Wafer	Mucoadhesive Sustained Release Wafer
Area	2-8	2-7	2-4
Thickness	20-70	50-500	50-250
Structure	Film:single layer	Single or multilayered system	Multi-layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, highly hydrophilic polymers	Low/ non-soluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particle	Suspension or solid solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingival (other region in the oral cavity)
Dissolution	Maximum 60 sec	Disintegration in a few minutes, forming gel	Maximum 8-10 hrs
Site of action	Systemic or local	Systemic or local	Systemic or local

Oral Disintegrating Films (Odfs)

The organization of ODFs has various benefits and some of them are as per the following:

1. Simplicity of gulping for geriatrics and pediatrics.
2. Advantageous for dysplasia patients experiencing issues in gulping tablets and cases.
3. Quick beginning of activity with expanded bioavailability due to bypassing hepatic first-pass impact and steadiness.
4. Simple transportation.
5. Advantageous and exact dosing. No need for water for an organization.

Advantages

- Pleasing and fresh mouthfeel.
- No risk of choking.
- Easy application-no swallowing and chewing difficulties.
- To avoid the first-pass metabolism.
- Administering an accurate dose is possible.
- For improved patient compliance, a small size is available.
- Rapid onset of action.
- It helps in enhancing stability
- It masks the bitter taste.
- Available in various sizes and shapes.
- Reduce gastrointestinal irritation.

Disadvantages

- Sometimes shows the fragile and granular property.
- Hygroscopic in nature thus must be stored in a dry place.
- Require special packaging for the product's stability and safety.
- The high dose cannot be incorporated into an oral film.
- Eating and drinking may be restricted.[4]

Mechanism of action

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, were 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 tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects.[5]

MATERIALS AND METHOD

API: Cetirizine hydrochloride

Polymers: Polyvinyl alcohol, Hydroxypropyl methyl-cellulose (HPMC)

Plasticizer: Glycerol

Sweeteners: Aspartame

The formulation of drug loaded films by casting method

Batch No.	Hpmc (Mg)	Pva (Mg)	Aspartame (Mg)	Glycerine	Cetirizine	Distilled Water	Stirring Speed (Rpm)	Stirring Time (Min)
1.	500	50	55	300mg	40mg	15ml	1000	15
2.	400	50	55	300mg	40mg	15ml	1000	15
3.	300	50	55	300mg	40mg	15ml	1000	15
4.	400	-	55	300mg	40mg	15ml	1000	15
5.	500	-	55	300mg	40mg	15ml	1000	15
6.	300	-	55	300mg	40mg	15ml	1000	15

Preparation of Films by Solvent Casting Method

The HPMC & PVA as nominative quantity was dissolved in 10ml of distilled water & 5ml distilled water respectively. By using magnetic stirrer; individually both kept aside for a 15min. After that both the solution was mixed in the required quantity. Drop by drop plasticizer added homogeneous way & aspartame was added to the mixture also for sweetening. After that cetirizine drug was loaded in the mixture. For the removal of bubbles the solution was kept aside for few minutes and then cast into the petridish (9 cm^2 area). Petridishes were kept at maintained room temperature for a few hrs and then kept in a hot air oven for 24hrs at 40°C. After drying films were removed and cut into the desired size i.e.2×2 cm^2, packed in aluminum foils and kept for further use.

Evaluation of Drug Loaded Optimized Film

The oral fast dissolving films were evaluated for their dissolution, Organoleptic characteristics and mechanical properties like thickness, dryness, tensile strength and folding endurance, transparency, disintegration time, surface pH, moisture loss, moisture uptake and uniformity of drug content were also evaluated.

Organoleptic evaluation

All the films were inspected visually for appearance, smoothness and uniform distribution of drug in film. The formulated fast dissolving oral films were evaluated for Organoleptic characteristics like color, odor and shape.[6]

Thickness

By using vernier caliper; average thickness was determined. The three films were selected randomly & the thicknesses of films were measured in four corners & five different unique central point.

Folding endurance & Transparency

The folding of film takes place repeatedly from the same place till it breaks down.Folding endurance to determine mechanical properties of film. The number of times the film is folded without breaking is calculated as the folding endurance value. This parameter was checked simply by visual inspection of films.

Percentage (%) moisture loss

Moisture loss was determined by weight variation. Initial weight of the film was determined and afterward film was kept in a desiccator containing silica for about 72 h. Films were then taken out and weighed.

Percentage moisture loss is calculated by using the following formula as below.16

$$\% \text{ Moisture Loss} = [\text{Initial weight} - \text{Final weight} / \text{Final weight}] \times 100. \quad (7)$$

Drug content

Drug Content of oral fast dissolving films were determined by standard assay method taken for 6 individual samples as per the test procedures. The acceptance value of the test is less than 15 in accordance with all pharmacopoeia. A film of size 1 cm square was cut and kept in 100 ml of volumetric flask containing solvent. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution and then filtered. The drug was determined spectroscopically after appropriate dilution and dilutions were measured at 232 nm to get Absorbance.

Percentage elongation

The increase in the length of a film when it is pulled under standard conditions of stress just before the point of break is known as percent elongation. Randomly 3 films were selected from each formulation and initial length was measured. Films were pulled manually until it was broken. Then final length was observed and average percentage elongation was determined. Percentage elongation was calculated from the formula mentioned below.

$$\text{Percentage of Elongation} = [\text{Increase length} / \text{Initial length}] \times 100$$

Disintegration time

The disintegration time of the film prepared using different polymers was determined visually in a beaker of 25 ml distilled water with shaking every 10 sec. The disintegration time of each patch was noted.[8]

Surface pH

The film kept in a Petri dish was moistened with 5 ml of distilled water and kept for a few minutes. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min.[9]

Surface texture

Surface texture of cetirizine was studied by SEM analysis. The surface morphology of pure APIs cetirizine and optimized films of cetirizine were observed by scanning electron microscopy.

Uniformity of weight

Three different films of the individual batch are weighed and the average weight was calculated. The dried films were weighed on digital balance. The films exhibited uniform weight. The data of the individual weights are shown in the Table. From this studies the films exhibited uniform weight and there was no deviation in the weight of any formulation.[10]

Percentage moisture absorption (PMA)

The moisture absorption studies carried out at 75% relative humidity. % moisture up take increases when PVA and HPMC concentration increases, because of hydrophilic nature of those polymers. The % moisture absorbance is maximum for F_1 because the concentration of the polymer is more.[7]

In vitro dissolution studies

The dissolution was carried out for different experimental trials. The various results that are obtained are tabulated below. Dissolution studies are carried out in the following media.

Medium: Distilled water

Type of apparatus: USP - II (paddle type)

RPM: 50 rpm

Volume: 150 ml

Temperature: 37ºC± 0.50C.[11]

RESULTS AND DISCUSSION

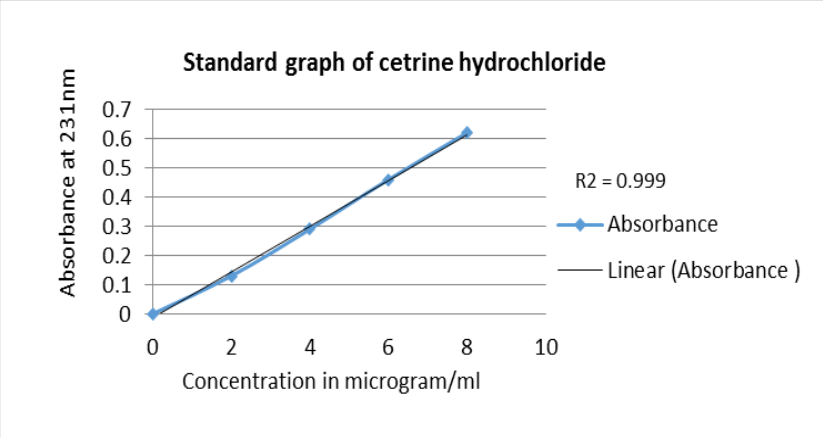
Preformulation studies of API

Characteristics	Results
Organoleptic evaluation	White crystalline powder, odorless
Solubility analysis	Freely soluble in water; while insoluble in inorganic solvents
Melting point	110-115º

Calibration curve of cetirizine hydrochloride

Development of cetirizine linearity curve by using UV spectrophotometry at λmax 231 nm in distilled water.

Concentration (mg/ml)	Absorbance
0	0
2	0.13
4	0.29
6	0.46
8	0.62
10	0.77



Formulation	F1	F2	F3	F4	F5	F6
Weight Variation(mg)	990± 0.0026	988± 0.0010	983± 0.0015	879± 0.0015	874± 0.0015	867± 0.0019
Thickness (mm)	0.35± 0.15	0.30± 0.07	0.29± 0.004	0.25± 0.015	0.23± 0.005	0.19± 0.005
Folding endurance	292± 0.0154	289± 0.060	281± 0.015	265± 0.014	258± 0.015	261± 0.013
Surface pH	6.98± 0.010	6.95± 0.030	6.90± 0.005	6.87± 0.015	6.83± 0.001	6.79± 0.015
% Drug content	90.6± 0.005	91.00 0.001	94.4± 0.0015	97.3 0.013	98.1± 0.015	99.67± 0.030
Disintegration time	55± 0.52	48± 0.57	45± 1.52	38± 1.00	32± 1.00	28±1.52
Tensile strength kg/cm²	173 ± 0.55	163± 0.05	155± 0.25	90± 0.55	87± 0.75	82± 0.95

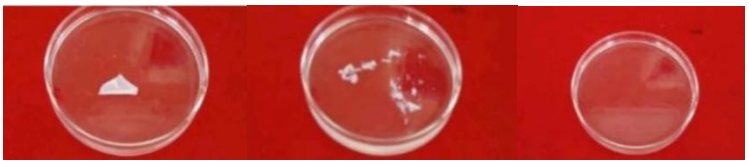
% Moisture loss	2.65± 0.038	2.1± 0.0589	2.59± 0.087	2.06± 0.005	1.95± 0.26	1.58± 0.036
% Moisture absorption	4.10± 0.25	4.01± 0.14	3.89± 0.025	3.54± 0.026	3.45± 0.015	3.15± 0.025
% Elongation	17.09± 0.25	14.89± 0.22	13.75± 0.86	12.90± 0.001	11.08± 0.013	10.57± 0.013

PHYSICOCHEMICAL PARAMETERS

Mechanical properties Evaluation

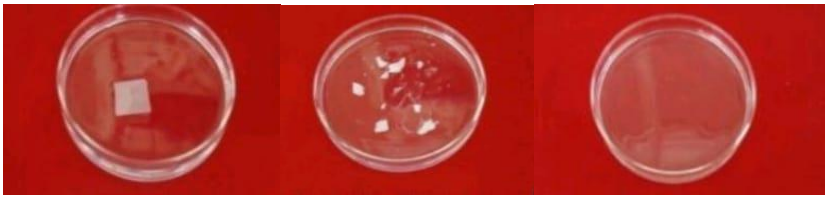
- **Films Thickness:** The thicknesses of the films were increased as the total quantities of the polymers are increased. From these studies the films showed uniformity in their thickness the thickness of the films ranges from 0.19-0.35mm.
- **Folding endurance:** The folding endurance was measured manually for the prepared films. A strip of film 2x2cm was cut evenly and repeatedly folded at the same place till it is broken. The number of times the film could be folded at the same place without breaking gives the exact value of folding endurance. The folding endurance of the film was found to between 261-292.
- **Surface pH:** Neutral or close to neutral pH is beneficial for the films. So a combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the film. The pH of all the films were found to be around 6.8 that is close to the neutral pH.
- **Percentage drug content:** The drug content was analyzed by spectrophotometrically at 231nm for cetirizine. The drug content analysis of the formulations have showed that the process employed to prepare films in this study was capable of giving films with uniform drug content and minimum batch variability. The drug content of the films ranges from 90.6%-99.67%.
- **Uniformity of weight:** Two different films of individual batch are weighed And then average weight was calculated. From this studies its shows that the films shows uniform weight and there is not more deviation in the any formulations.
- **In vitro disintegration time:** The films were placed in the tube of the container and disintegration time was recorded. The disintegration time for the formulation F6 was found to be is 28seconds.

The following diagrams shows disintegrating pattern.

a. 

HPMC+PVA+Cetirizine Disintegrating starts at 25-30 sec

(BEFORE DISINTEGRATION)

b. 

HPMC+Cetirizine Disintegrating starts at 15-20 sec

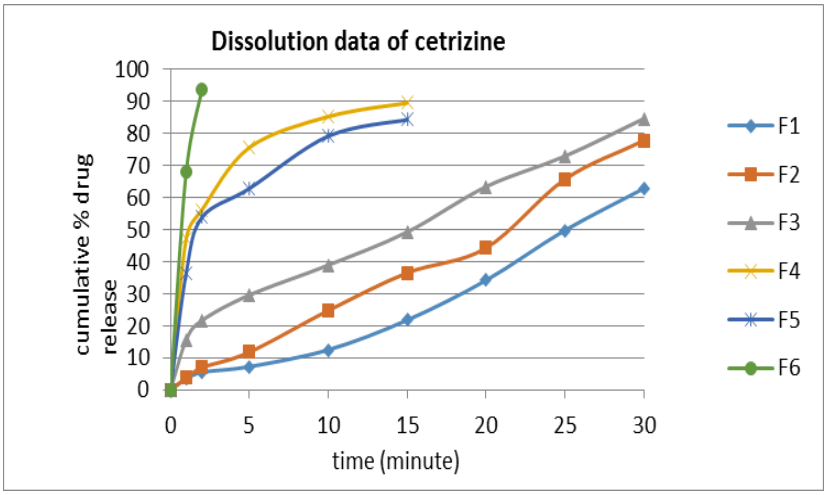
(AFTER DISINTEGRATION)

- **Tensile strength and percent elongation (%elongation):** By using Hounse field universal testing machine tensile strength was determined. Percent elongation of films gives information of how much a specimen can elongate before it breaks. It was carried out by Hounse field universal testing machine. The percentage elongation at break point is measured on scale and the data of the percentage elongation is presented in table.
- **Percentage Moisture Absorption (PMA):** The %moisture absorbance is maximum for F1 because the concentration of the polymer is more.
- **Percentage Moisture Loss (PML)**: The moisture loss studies carried in a desiccator containing anhydrous calcium chloride. All the films showed least percentage moisture loss. The percentage moisture loss is maximum for F1 because the concentration of the polymers is more.
- **In vitro dissolution studies:** Maximum drug release was observed in F6 that is 93.65% within 2 minute.

In-vitro-dissolution data for oral thin films formulation of cetirizine

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	3.46	3.79	15.63	47.28	36.55	68.21
2	5.54	6.99	21.69	56.23	53.86	93.65
5	7.28	11.79	29.61	75.67	62.87	-
10	12.53	24.78	38.98	85.32	79.23	-
15	21.79	36.53	49.29	89.58	84.34	-

20	34.21	44.28	63.45	-	-	-
25	49.82	65.74	72.97	-	-	-
30	62.88	77.82	84.68	-	-	-



DISCUSSION

The aim of this work was to create oral films to deliver the medication at oral cavity for quick release. HPMC and PVA were chosen as film forming polymers. Films appearance was found to be white in colour, smooth & soft because of glycerol as a plasticizer gives a flexible films.

Thicknesses of films were measured with the help of vernier calipers. The thickness of films varies from 0.19mm to 0.35mm. The variation was occurred due to the presence of polymers. The assayed drug content in various formulation varied between 90.6% to 99.6%. The folding endurance varies from 261 to 292. These shows films have good strength. The average weight of the film was found to be between 867mg and 990mg.Uniformity of weight was found to be maximum for formulation F1 (990mg) whereas uniformity of weight observed to be minimum for formulation F6 (867 mg). These weight varies maybe due to the concentration of polymers. Film of formulation F1 containing high amounts of HPMC and PVA showed more time for drug release than films of all other formulations, which might be due to high viscosity of the PVA. All the films are disintegrated within 60 seconds and less than that. Tensile strength was found to be increased with increasing polymer concentration. The disintegration time varies from 28 to 55sec in different formulations. While the maximum time was taken by F1(55sec) and minimum time was taken by F6(28sec).

The release rate of Cetirizine increased with decreasing concentration of HPMC as in F4,F5 and F6 respectively.

HPMC is more hydrophilic and it can swell rapidly, therefore decrease of HPMC 3cps content improves the drug release in F6. The surface pH was found to be close to neutral in all the formulations. The average range varies from 6.79 to 6.98. This all are more comfortable because it is less irritable in mucous membrane.

Percentage elongation was found to be maximum for formulation F1(17.09%) whereas, minimum for formulation F6 (10.57%). Moisture loss was determined by placing the films in dessicator containing silica for 3 days. Moisture loss of the different films was found to be varying from 1.58% to 2.65%.

Detailing F6 showed moderately high rate of release of cetirizine which is because of fast expanding and disintegration of HPMC. Further, the increment in release of medication delivery could be clarified by the capacity of the hydrophilic polymers to retain water, subsequently advancing the disintegration, and thus the delivery, of the profoundly water dissolvable medication. Also, the hydrophilic polymers would drain out and subsequently, make more pores and channels for the medication to diffuse out of the device. Formulation F1 which contains high measures of HPMC and PVA gets dissolved gradually. In this way higher grouping of PVA can't be consolidated into such details for guaranteed drug discharge.

CONCLUSION

The principle objective of the examination was to formulate and evaluate mouth dissolving film containing cetirizine hydrochloride. HPMC and PVA films were set up by solvent casting technique. Tensile strength, percentage elongation and folding endurance of the films were increased with increase in the concentration of polymer due to increase in the elasticity nature of the polymer. The dissolution rates were also increased with the increase in the concentration of the polymer as the film-forming polymers are hydrophilic in nature.

Films with only HPMC as a polymer showed the maximum drug release. Hence it can be concluded that, Mouth dissolving film-containing cetirizine can be prepared by casting method. Formulation containing 300mg of HPMC film possess required tensile strength, folding endurance and percentage elongation and *in-vitro* drug release of 93.6% within 2 minute.

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