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Design of novel oral films as drug delivery system

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Abstract

The main aim of research work was to design novel fast dissolving films as a drug delivery system for treatment of severe hypertension and acute cases like angina pectoris. In present research work thin films of antihypertensive drug amylodipin besylate was prepared by using different concentration of polymers, plasticizers and super disintegrants. These prepared films were characterized on basis of thickness, folding endurance, tensile strength and dissolution time. On basis of study it was found that the optimized film dissolves within 60 sec. So the drug will dissolve quickly which will increase solubility and hence bioavailability of drugs.

Key-Words: Oral Films, DDS, Drug

Introduction

Some patients have difficulties in swallowing or chewing solid dosage which forms risk or fear of chocking so this is a major problem in the use of tablets. Oral dissolving film is a new drug delivery system for oral delivery of drug. Oral film a type of film which is used in acute condition such as pain, antiemetic, anti-migraine, anti-hypertension, congestive heart failure, and Asthma etc. oral dissolving film has gained popularity due to its availability in various size and shape [1]. Oral dissolving films are intended to disintegrate or dissolve within seconds. They offer advantages such as administration without water, rapid onset of action and convenience of dosing. For fast dissolving active pharmaceutical ingredients absorption is possible through the oral mucosa and may improve bioavailability [2].

The concept of oral dissolves film

- This delivery system consists of a thin film.
- After placing it on the top of the tongue, the film dissolves within seconds, promoting first pass metabolism as compared to tablet and other immediate release oral solid dosage forms, and may increase the bioavailability of drug [3].
- FDF dissolves in the mouth like a cotton candy.

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Advantages of oral dissolving film (ODF) over fast dissolving tablet (FDT)

- Accessibility of larger surface area that leads to quickly disintegrate and dissolution in the oral cavity within seconds [4].
- ODF is flexible so they are not as fragile and need not any kind of special package for protection during transportation and storage as compared to FDT.
- No need of water has led to better satisfactoriness amongst the dysphasic patients.
- No fear of chocking as compared to FDT.
- The large surface area available in the film dosage form allows rapid wettive by saliva then quickly disintegrates and dissolve and absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism and on increase the bioavailability [5].
- The dosage form can be consumed at any place and any time as per convenience of the individual. The first pass effect can be avoided, so a reduction in the dose which can lead to reduction in side effects associated with the molecule [6].
- Patients suffering from dysphagia, repeated emesis, hypertension, heart attack, asthma, motion sickness, paralysis and mental disorders prefer this dosage form as they are not capable to swallow large quantities of water.

Material and Methods

The amlodipin drug was obtained as gift samples from Amneal formulations, ahemdabad. The HPMC K-15,

Pullulan, cross povidone and cross carmellose sodium was obtained as a gift samples from trupati balaji formulations. Rest all material were purchased from Hi media and CDH laboratory. The all material was of analytical grade.

Preparation of Films By Solvent Casting Method

The all Solid Material properly weigh by pre calibrated electronic balance (Citizen) and all liquid materials were also measured properly. The all pre weighed material were mix properly on mechanical stirrer at controlled speed. The all material was added in solvent and then liquid material was added during stirring. The stirring speed of stirrer was kept at 200-500 RPM and temperature was set at 25-30^{0}c. The mixing was continue till clear, transparent solution was obtained. After complete mixing of all ingredients the clear solution was sonicated to remove dissolved air which may appear during mixing process. Three cycle of sonication of 5-10 sec was performed for complete removal of air. A 20.0 x8.0 cm sized Film casting glass reservoir was fabricated having depth of 0.5cm. This sized Film casting glass reservoir will produce forty 2.0x2.0 cm size films. Then the solution was carefully poured in to glass reservoir uniformly to ensure uniform thickness of film. Preliminary study suggests that 40 ± 1.0 ^{0}C for 12 hrs adequately dry the film. The drying of film was done under controlled evaporation to assure no air entrapped during the drying process. After complete drying of film, the film was carefully removed from glass reservoir. The removal was easily performed as already oil was used for lubrication. After complete removal of film it was ready to cut in appropriate size. After complete removal of films it was cut in to appropriate size for administration in oral cavity. The films were cut in to 2 X 2 cm ^{2}. [7]

Optimization of Films

The optimization was performed on basis of following three important factors:

- Selection of Film Forming Agents
- Selection of Plasticizers
- Selection of Super disintegrating agents

Two film forming agents and one co-film forming were selected for this research work. The concentration of film forming was important to form a proper thickness for appropriate packaging and handling of oral films. The two film forming agents like HPMC K15 and Pullulan at different concentration were taken. Concentration of film forming agent is optimized on the basis of thickness and appearance of film.[8]

Two film plasticizer and one co- plasticizer were selected for this research work. The concentration of plasticizer was important to tensile strength %age elongation and folding endurance of film. Concentration of plasticizer optimized on the basis of tensile strength %age elongation and folding endurance of film.

Characterization of Individual films

Determination of thickness

Thickness of film was most important parameter because uniformity of thickness determined content uniformity of BFDOF. The thickness of film was determined by DIGITAL THICKNESS GAUGE (Moore & Wright, Germany) at stage when film is removed from the fabricated glass reservoir. The thicknesses of one batch were determined in nine different places to assured the uniformity.[9]

Size of film

Size of tongue is about 2.5 x2.0 cm, to provide sufficient space for dissolving in oral cavity by putting film on tongue for swishing or hydrating with saliva , size 2.0 x 1.5 cm were concluded as unit dose of BFDOF.

As per the guidance provided by Center for Drug Evaluation and Research (CDER) USFDA for Orally disinteragation films should be less than 30 seconds (half minute), that guidance were objective for this present study.This was a quality guideline for qualitative guideline for quality control test at development stage. [8]

A pharmacopeial disintegrating test apparatus (Labindia) were used to determining the disintegration time *in-vitro* (Fig-1.3)

Tensile Strength and %-Age Elongation Determination

The load [N] and elongation [%] were measured during tensile test by a Tensile Strength And %-Age Elongation testing apparatus (Winsar chennai).Each strip of film was cut and prepared so that 2.0x2.0 cm^2 remain for testing ,other portion were clamped between the tensioning tools.[7,10]

Folding endurance were determined by repeating folding of the oral dissolving films initially as in single layer and then finally for bilayer fast dissolving oral films.[11]

Folding endurance of the films is determined by automatic folding endurance apparatus. The final shaped oral films were analyzed in this apparatus individually for each batch.

Drug Content and Content Uniformity

As per pharmacopeial assay method the drug content and content uniformity were determined for each API during single layer optimization and during final batches of different combinations. Content uniformity was determined by selecting three samples of film.[12]

Taste Evaluation and Disintegration In Mouth

Taste acceptability was measured by a taste panel (n=5) and subsequently film sample held in mouth until disintegration, then spat out and the bitterness level was then recorded. The volunteers were asked to gargle with distilled water between the drug and film sample administration. The scale for the bitterness study was as follows: [8]

+ = very bitter
++ = moderate to bitter
+++ = slightly bitter
++++ = tasteless/taste masked
+++++ = excellent taste masking

Dissolution Test

A modified shaking water bath dissolution method was employed to determining the drug release profile of the film. The shaking water bath apparatus (100 strokes per minute) consist of a water bath, thermostatically controlled at 37±0.5 ºC and a mechanical shaker platform onto which bottle holder plate were positioned. Glass bottles (125ml), the secured holders of holder plate. 100 ml of PBS (Phosphate Buffered Solution) having the pH 6.5 equilibrated to37±0.5 ºC were used for dissolution medium. A specified time intervals, 2.0 ml aliquots of samples were taken out from each vessel (Three) using a syringe and filtered through 0.45 µ Millipore filter. An equal amount of fresh pH6.5 PBS were used to replaced into each vessels to ensure a constant volume of dissolution medium throughout the dissolution study.[8]

All dissolution samples were analyzed as predetermined specific wavelengths for individual API

Results and Discussion

Optimization of films

Batch MOF-III seems to produce desired thickness and weight of individual film was around 120 mg so for double layer it will be around about 250 mg. The batch was found transparent too. Thickness of this batch also suitable bilayer fast disintegration oral films aimed about 150µm, the thickness of all Batches lies between 62±2 to 118±6 µm. The result shows that as the concentration of film forming polymer increases, the thickness of films also increases. When thickness of films is less than it fails the folding endurance and thick films are not transparent in nature so MOF- III was selected as optimized concentration of film forming agents.

The tensile strength of all batches (Except MOF- XIX and XX) was found to be 0.758 to 1.141 Kg/cm^2. This shows that all films having good tensile strength. The mechanical properties of the film were studied by percentage elongation which was found 22.6 to 62.3. The batch having highest % elongation and appropriate tensile strength was selected.

Hence batch MOF-XIII were optimized with selection of PEG-4000 due to better tensile strengths high flexibility (folding endurance)

The results of this optimized batch were appropriate for envisaged oral film were as folding endurance 586±23, tensile strength 1.056 Kg/cm^2 and percentage elongation 62.3 were found.

The disintegration time was found out in range of 32±1 to 46±2. The disintegration time decreases as concentration of super disintegrants increases. The Batch having least disintegration time was selected so as to get less dissolution time of drugs.

A combination of SGS (250 mg) and Crosscarmilose (50 mg) were able to disintegrate oral film within 32 seconds, Hence MOF-XXX were selected for further study.

ASOF-SI (Amlodipine single layer oral film) was the optimized batch of Amlodipine 5mg. ASOF-SI was able to disintegrate within 35 seconds with thickness of 79±5 µ m. This single layered oral film was showing appropriate folding endurance (523±12), %-age elongation (46) and tensile strength (1.098 Kg/cm2).The weight of each film were 125±2 mg.

Characterization of films

Determination of Thickness

The thickness of all Batches lies between 79±5 to 106±4 µm. The result shows that The films was sufficient thin so as to dissolve within 40 sec.

Tensile Strength and % Elongation Determination

The tensile strength of all Formulations was found to be 0.916 to 1.214 Kg/cm^2. This shows that all films having good tensile strength.

The mechanical properties of the film were studied by % elongation which was found 38 to 63. The all formulation shows appropriate % elongation.

Disintegration Time

The disintegration time was found out to be 35±1. The disintegration time is sufficient to get less dissolution time of drugs.

Drug Content

The Drug Content of all Optimized batches of each individual drug was determined from three different positions.

The drug Content of all Batches was found to be 98.6 ±0.6 which shows good content uniformity of all drugs throughout the film.

Taste Evaluation and Disintegration In Mouth

Taste masking was evaluated by human panel volunteers. The taste masking of all formulation was evaluated by human panel volunteers. A result shows

that excellent taste masking was found in all formulations.

***In vitro* dissolution studies**

All dissolution samples were analyzed as predetermined specific wavelengths for individual API.

Conclusion

The objective of present research work was to develop fast dissolving oral films which in turn will increase dissolution and increase bioavailability of drug. After all the experimental procedure it was concluded that all formulations were prepared successfully and prepared formulations were stable. The drug release data reveals that the bioavailability was also increased which will reduce the dose and increased patient compliance.

Hence it can be concluded that developed dosage form is better alternative dosage form for antihypertensive drug and for acute conditions like angina pectoris by increasing bioavailability of drugs and improves patient compliance.

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Table 1: Optimization of Film forming agents with their formulation code

Name of Ingredients	Formulation codes with weight of ingredients									
	MOF-I	MOF-II	MOF-III	MOF-VI	MOF-V	MOF-VI	MOF-VII	MOF-VIII	MOF-IX	MOF-X
API	-	-	-	-	-	-	-	-	-	-
HPMC K15	2400	3000	3600	4200	4800	-	-	-	-	-
Pullulan	-	-	-	-	-	2400	3000	3600	4200	4800
Gum Acacia	200	200	200	200	200	200	200	200	200	200
Glycerine	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
Peg-4000	150	150	150	150	150	150	150	150	150	150
DBP	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml
SSG	200	200	200	200	200	200	200	200	200	200
Sucralose	120	120	120	120	120	120	120	120	120	120
Citric Acid	120	120	120	120	120	120	120	120	120	120
DM Water Qs	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32mL	32mL	32mL	32mL

Table 2: Optimization of Plasticizers with their formulation code

Name Of Ingredients	MOF-XI	MOF-XII	MOF-XIII	MOF-XVI	MOF-XV	MOF-XVI	MOF-XVII	MOF-XVIII	MOF-XIX	MOF-XX
API	-	-	-	-	-	-	-	-	-	-
HPMC K15	3600	3600	3600	3600	3600	3600	3600	3600	3600	3600
Gum Acacia	200	200	200	200	200	200	200	200	200	200
Glycerin	-	-	-	-	1.0ml	1.2ml	1.4ml	1.6ml	1.6ml	2.0ml
PEG-4000	75	100	125	150	-	-	-	-	-	-
DBP	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml
SGS	200	200	200	200	200	200	200	200	200	200
Sucralose	120	120	120	120	120	120	120	120	120	120
Citric Acid	120	120	120	120	120	120	120	120	120	120
DM Water Qs	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml

Table 3: Optimization of Superdisintegrants with their formulation code

Name Of Ingredients	MOF-XXI	MOF-XXII	MOF-XXIII	MOF-XXVI	MOF-XXV	MOF-XXVI	MOF-XXVII	MOF-XXVIII	MOF-XXIX	MOF-XXX	MOF-XXX
API	-	-	-	-	-	-	-	-	-	-	
HPMC K15	3600	3600	3600	3600	3600	3600	3600	3600	3600	3600	3600
Gum acacia	200	200	200	200	200	200	200	200	200	200	200
PEG-4000	125	125	125	125	125	125	125	125	125	125	125
DBP	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1 ml
SGS	200	300					150	150		250	250
CS	-	-	200	300	-	-	150	-	150	50	
CP	-	-	-	-	200	300	-	150	150	-	50
SucralosE	120	120	120	120	120	120	120	120	120	120	120
Citric acid	120	120	120	120	120	120	120	120	120	120	120
DM Water QS	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml	32 ml

Optimized batch (ASOF-SI)

Table 4: Optimized composition of Amlodipine Films

S.No.	Name of Ingredients	Composition
1	Amlodipine	200 mg
2	HPMC k15	3600
3	Gum acacia	200
4	Peg-4000	125
5	DBP	0.1ml
6	SSG	250
7	CS	50
8	Sucralose	120
9	Citric acid	120
10	Colorant (orange)	Qs
11	Flavour (orange)	Qs
12	DM water qs to	32 ml

Table 5: Drug Content of Optimized batches of different Drugs

S.No.	Formulation Code	Drug Content
1	ASOF-SI	98.6 ±0.6

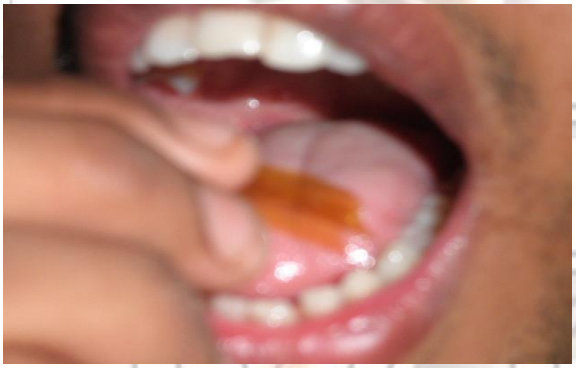

Fig. 1 (A)

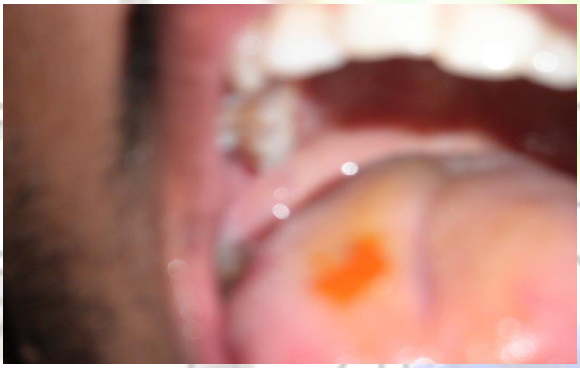

Fig.1 (B)

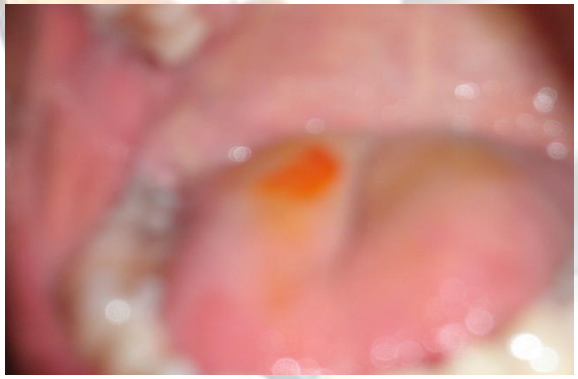

Fig. 1 (C)

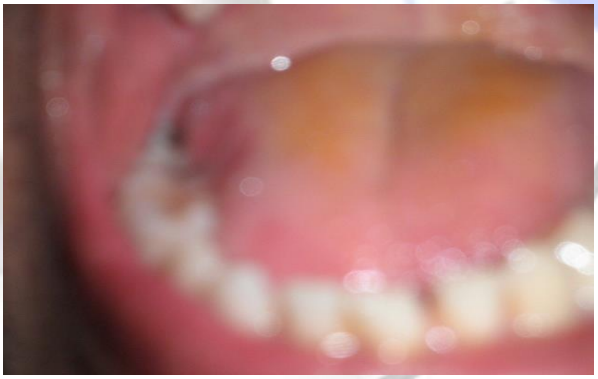

Fig. 1 (D)

Fig. 1: Disintegration of films in humans at different time
A- 0 sec **B.** 10 Sec **C.** 30 sec **D.** 45 sec **E.** 60 sec

Table 6: % Cumulative release profile of Optimized batches of different Drugs

S.No	Time in minutes	% Cumulative Drug Release of Amlodipin
1	0	0.0
2	5	31.43±0.6
3	10	76.55±0.8
4	15	91.23±1.2
5	20	94.87±0.9
6	25	94.96±0.8
7	30	95.54±0.9
8	40	96.54±1.1
9	50	96.55±0.8
10	60	96.55±0.7