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FORMULATION AND DEVELOPMENT OF FAST DISINTEGRATING ORAL FILM

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ABSTRACT

The fast-dissolving drug delivery system is advancement for innovative formulation and development. The present study was aimed to formulate and evaluate fast dissolving oral films of Azilsartan Medoxomil using HPMC propylene glycol pvp k30 and fenugreek. The suitable plasticizer and its concentration were selected on the basis of flexibility, tensile strength and stickiness of the film. The films are prepared by Solvent casting and Hot melt extrusions method, characterized by palatability study and electron scanning microscopy. The films were evaluated for Palatability Studies, disintegration time, Folding endurance, swelling property, surface PH, Tensile Strength, Mouth dissolving time, Thickness, content uniformity and In-vitro dissolution studies. The F3 formulation has given 98.5% drug release within 3.41 minutes and has a tensile strength of 5.08(kg/mm2).

KEYWORDS: Azilsartan Medoxomil, HPMC, super disintegrants, fast dissolving oral film, solvent casting method.

INTRODUCTION

The Fast Dissolving Drug Delivery Systems was an advancement that came into existence in the early 1970's and combats over the use of the tablets, syrups, capsules which are the other oral drug delivery systems.[1] Fast Dissolving Drug Delivery Systems serves as a major benefit over the conventional dosage forms since the drug gets rapidly disintegrated & dissolves in the saliva without the use of water. It provides the direct entry into the systemic circulation thereby avoiding the hepatic first pass Effect and ease of administration. This delivery system consists of a thin film, is simply place below the tongue, instantly wet by saliva; the film rapidly dissolves.[3] Then it rapidly disintegrates and dissolves to release the medication for systemic absorption this fast dissolving action is primarily due to the large

surface area of the film, which wets quickly when exposed to the moist sublingual environment.[3] FDFs are useful in patients such as pediatrics, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic, attacks, or coughing for those who have an active lifestyle.

The advantages of the convenience of dosing and portability of mouth dissolving film have led to the wider acceptability of this dosage form by pediatric as well as geriatric patients. They also impart unique product differentiation, thus enabling the use of line extensions for existing commercial products.[2] This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of drugs. Also due to ease of transportation of mouth dissolving film than ODT helpful for reducing damage cost compared to ODT and other liquid formulation.[2]

Formulation of mouth dissolving film involves the application of both aesthetic and performance characteristics such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents.[3] From the regulatory perspectives, all excipients used in the formulation of oral drug strips should be approved for use in oral pharmaceutical dosage forms. Mouth dissolving films evolved over the past few years from the confection and oral care market in the form by consumers for delivering vitamins as well as personal care products.

Main objectives of the study are as follows:

1. To evaluate prepare Fast Dissolving Oral Strips containing Azilsartan medoxomil by different post- formulation parameters like uniformity thickness, foldability, weight variation, in-vitro disintegration time, in-vitro dissolution study etc.[5]
2. To carry out the comparative study of the in-vitro dissolution of prepared Fast Dissolving Oral Strips containng artificial super-disintegrant with prepared Fast Dissolving Oral Strips containing natural super-disintegrant.[5]

Materials

Azilasartan Medoxomil as active ingredient was received as a gift sample from Hetero Labs ltd, solan, HP, Hydroxy propyl methyl cellulose (HPMC) as a water soluble polymer, Sodium lauryl sulphate (SLS), Mannitol used as sweetening agent and Glycerol as humectant. HPMC,

SLS, Mannitol, pvp k30, fenugreek, sucralose, lactic acid, lemon grass oil, and Glycerol were procured from S.D. Fine chemicals Ltd Mumbai. All other chemicals used were of analytical grade.

Methods

1. Solvent casting

In solvent casting method the water-soluble ingredients are dissolved to form a clear viscous solution.[5] The API and other agents are dissolved in smaller amounts of the solution and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum.[5] The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

In this method, firstly the water-soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is incorporated with the API dissolved in suitable solvent. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.[5]

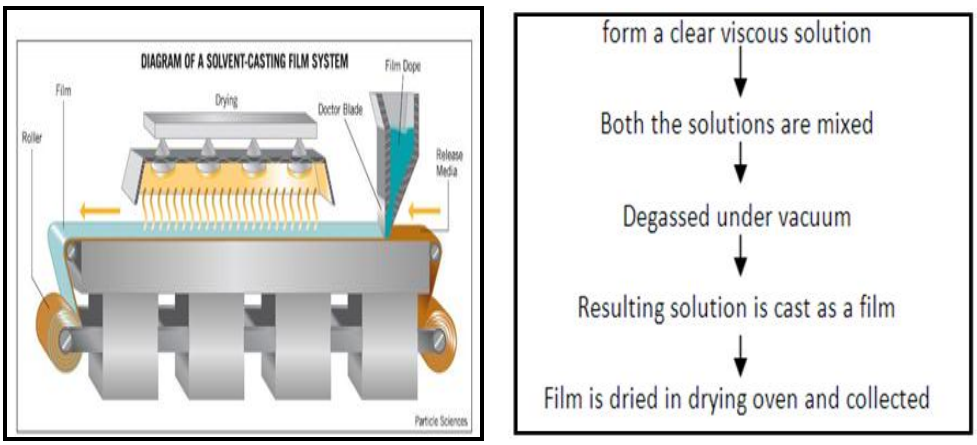

Fig. 1: Solvent casting apparatus and procedure.[5]

2. Hot melt extrusions: In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the Extruder having heaters melts the mixture.[5] Finally, the melt is shaped into films by the dies. There are certain benefits of hot melt extrusion. Advantages of hot melt extrusion for film formation include-

• No requirement on the compressibility of the active ingredients.[5]

• More uniform dispersion of the fine particles due to intense mixing and agitation causing suspended drug particles to de-aggregate in the molten Polymer.[5]

• The bioavailability of the drug substance could be improved when it is dispersed at the molecular level in hot melt extruded dosage forms.[5]

The hot melt extrusion process has recently gained acceptance in the pharmaceutical industry. Building on Knowledge from the plastics industry, formulators can extrude combinations of drugs, polymers, and plasticizers into various final forms to achieve desired drug release profiles. The benefits of using HME over traditional processing techniques include:

• Better content uniformity.

• An anhydrous process.

• A dispersion mechanism for poorly soluble drugs.

• A low energy alternative to high-shear granulation.

• Less processing time compared with conventional wet granulation.

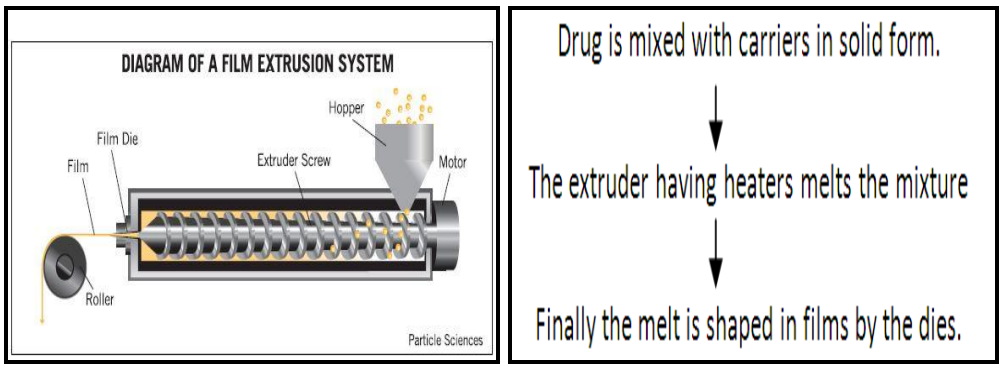

Fig. 2: Film extrusion apparatus and procedure.[5]

RESULTS AND DISCUSSION

Palatability Studies

The study was divided into 4 days, with two treatments and two phases on each day. There was a washout period of 2 h between the two phases on the same day. Prior to the study, the volunteers were required to gargle their mouth with 200 mL of distilled water.[6] One ODF film (2× 3 cm) was placed on the tongue of the volunteer. The volunteers were requested to record the disintegration time of the ODF and gave the score based on the parameters, namely taste, aftertaste, mouthfeel, ease of handling and acceptance as presented in Table 4.[6] The volunteers were told to spit out the test sample, followed by rinsing their mouths with 200 mL of distilled water. In each phase of the study, one ODF formulation was given to all the 4 volunteers. Another two ODF formulations were given to the volunteers the next day.

The same procedure was repeated up to 4 days to complete the evaluation of all the eight formulations.(Table no.4).[6]

Thickness

The thickness of the film is determined by screw gauge or micrometer at different points of the films. This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.[13]

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below.[13]

Tensile strength = Load at breakage/ Strip thickness × Strip Width.[13]

Surface pH of the film

Surface pH of films is determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films. The change in the color of pH paper was observed and reported.[13]

Swelling property

Film swelling studies are conducted using simulated saliva solution. Each film sample is weighed and placed in a pre-weighed stainless steel wire mesh. The mesh containing film sample is submerged into a 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed.

The degree of 0 swelling was calculated using the parameter.

S.I = Wt – Wo/Wo

Where S.I is the swelling index, Wt is the weight of the film at a time "t", and Wo is the weight of film at t = 0.[15]

Assay/ Content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopeias.[10] Content uniformity is determined by estimating the API content in an individual strip. Limit of content uniformity is 85–115 percent.

Disintegration time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips.[13] Although no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at the development stage. Pharmacopoeia disintegrating test apparatus may be used for this study.[13] Typical disintegration time for strips is 5–30 DT results show in (table no.3).

Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to the tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed are show in (table no.3).[13]

Folding Endurance

It was measured by folding the film at the same place repeatedly until a visible crack is Observe. This gives an indication of brittleness of the film are show in (table no.3).[13]

Weight variation of the film

2x3 cm film was cut from different locations in the cast film. The weight of each film strip was taken and the weight variation was calculated.[17]

Palatability Evaluation

As such, development of a taste-masking formulation is highly favorable. The results of the palatability evaluation and statistical analysis results are presented in Table 4. Formulation1 containing 7 mg sucralose was slightly sweet in taste. Formulation 3 had the highest score and was significantly different from the other formulations.[17] The effectiveness of sucralose in masking bitter taste can be explained by its powerful sweetness, which is 600–1,000 times sweeter than sucrose. The taste of formulation B (contained only flavouring agent), was not significantly different when compared with formulation A (control). The presence of flavouring agent alone showed no taste-masking effect(Table no.4).[17]

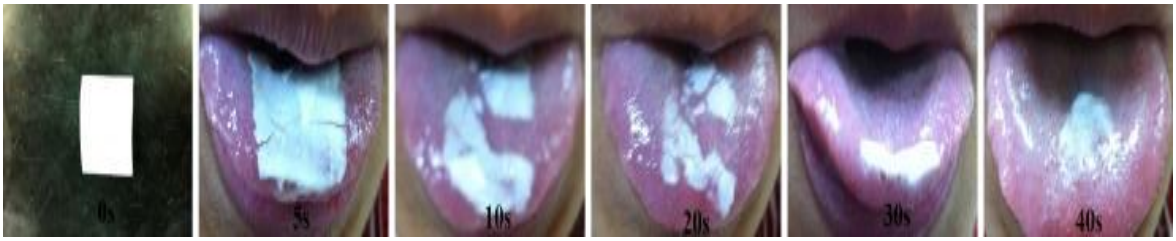

Fig. 3: Physical Evaluation of Oral Strip.

In-Vitro Study

The formulation of fast dissolving strip with synthetic super disintegrant showing faster drug release as compared to the formulation containing natural super disintegrant and combination of both.[17] (Refer the table no.3).

Scanning Electron Microscopy

The scanning electron micrographs are presented in Fig. 5. It can be seen that the surface of ODF was more coarse and rough with the incorporation of flavour when compared with ODF without sweetener and flavour. With incorporation of sweetener and flavour the coarseness and roughness of ODF surface was more obvious Refer to (Fig.no.5).

Table 1: Formulation table.

Formulation code	Film No. I (Artificial superdisintegrant)	Film No. II (Natural super disintegrants)	Film No. III (Combination of both)
Azilsartan medoxomil	40mg	40mg	40 mg
Sucralose	7mg	7mg	10mg
Propylene Glycol	75 mg	75 mg	75 mg
Mannitol	20mg	20mg	20mg
HPMC	200 mg	200mg	200mg
Lactic acid	10 mg	10 mg	10 mg
PVP K30	25 mg	-	12.5 mg
Fenugreek	-	25 mg	12.5 mg
Lemon Grass oil	q.s.	q.s.	q.s.
Sodium lauryl sulphate	q.s.	q.s.	q.s.

Table no. 2: Parameters and Score in Palatability Study.[17]

Parameter Score					
Taste	**Aftertaste**	**Mouthfeel**	**Ease of handling**	**Acceptance**	**1**
Very bitter	**Very bitter**	**Gritty and irritating**	**Very brittle**	**Very poor**	**2**
Bitter	**Bitter**	**Gritty**	**Brittle**	**Poor**	**3**
Slightly bitter	**Slightly bitter**	**Slightly gritty**	**Does not break**	**Acceptable**	**4**
Sliightly sweet	**Sliightly sweet**	**Smooth**	**Flexible and easy to handle**	**Good**	**5**
Very sweet	**Very sweet**	**Very smooth**	**Very easy to handle**	**Very good**	**6**

Table 3: Evolutionary parameters of Fast dissolving oral strips of Azilsartan medoxomil.

Parameters	Formulation no.1	Formulation no.2	Formulation.3
Thickness (mm)	0.96 ± 0.01mm	0.98 ± 0.01 mm	0.98 ± 0.01 mm
Weight variation (mg)	328 ± 1.52	330 ±1.53	335 ±1.53
Tensile strength (kg/mm^2)	4.86	4.89	5.08
Surface pH	6.8	6.7	6.8
Swelling property	25.51	24	28.60
Content uniformity (%)	104.7	101.34	101.73
Disintegration time (min.)	3.20	4.01	3.41
Dissolution test (sec.)	215	256	286
Folding Endurance	>250	>250	>250

Table no. 4: *In-situ* palatability study.

Palatability parameters	F1	F2	F3
Taste	5.0 ± 0.1	5.0 ± 0.5	6.0 ± 0.4
Aftertaste	5.0 ± 0.4	5.0 ± 0.6	4.0 ± 0.2
Mouthfeel	4.0 ± 0.2	4.0 ± 0.2	5.0 ± 0.2
Ease of handling	4.0 ± 0.2	4.0 ± 0.2	3.0 ± 0.8
Acceptance	3.0 ± 0.1	4.0 ± 0.3	3.0 ± 0.2
Statistical analysis (Kruskal–Wallis test)	$p < 0.05$	$p < 0.05$	$p < 0.05$

Table no. 5: Calibration curve of Azilsartan medoxomil in Phosphate Buffer PH 6.8.

Sr. no.	Concentration mcq/ml	Absorbance
1	5	0.52
2	10	0.99
3	15	1.63
4	20	2.27
5	25	2.88

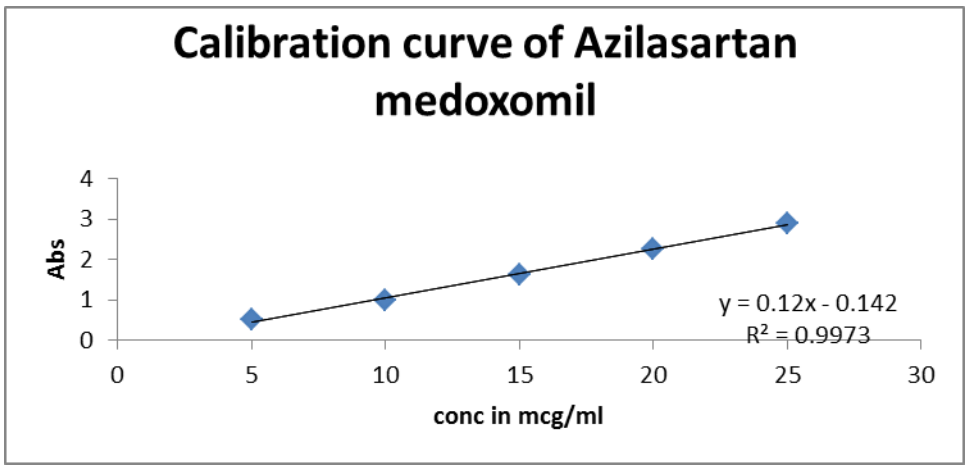

Fig. 4: Calibration graph of Azilsartan medoxomil in Phosphate Buffer.

Scanning Electron Microscopy: Oral strip presented roughness in the surface. All other blends (fig. a,b and c) and polymers presented very homogeneous surface. Roughness at fig.c surface in films made with HPMC blends has already observed, in general, the micrograph cross section HPMC of films displayed an irregular and rough structure. The micrograph results suggested good compatibility (fig.a) among the polymers, without micro phase separation, however HPMC in combination with other polymers, presented surface modification in rugosity.

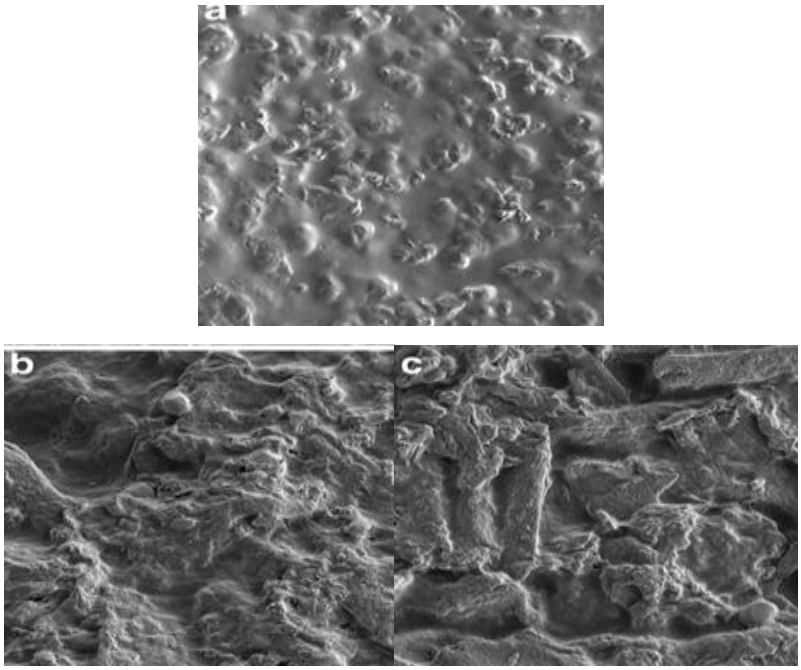

Fig. 5: Scanning Electron Microscopy.

CONCLUSION

The mass uniformity, thickness, folding endurance, surface pH, % elongation, and Tensile Strength values of films were evaluated and were found to be comparable to those of standard limiting values. The prepared films possessed no cracks on their surfaces and were cut into 2×3 cm pieces.[11] The various parameters evaluated for all the formulated films are represented in the table: The weight of films varied from 328 to 335±1.53 mg and they exhibited a thickness of approximately 0.98±0.01 mm. We did not observe any substantial increase in thickness with respect to variations in weight attributed to the addition of disintegrants. However, we did observe that the thickness of all formulations (F1–F3) showed a slight increase in thickness as compared to the thickness of formulation F1, with super disintegrants. The folding endurance varied between >250 times, which is considered the sign of good flexibility. The surface pH of all the formulations was around neutral (pH 6–7) and

hence no irritation would be caused to the buccal cavity. All the formulations contained more than 95 to 105% of the drug, as observed by the drug-content study, which indicated that the formulations were satisfactory for further study.

Drug delivery system has become an important subject in the past few decades. Development of fast dissolving drug delivery system has significantly boosted the pharmaceutical market by extending product life cycles.[13] With the advancement in fast disintegrating dosage form, it has solved problems encountered in the administration of drugs to pediatric and elderly population, that constitute a major proportion of world's population. To overcome the difficulty in swallowing conventional tablets, the scientist has developed innovative drug delivery system such as fast-dissolving drug delivery system. These can be administered any time without water leading to their suitability to mentally ill, bedridden patients as well as geriatric and pediatric population. The benefits in terms of patient compliance, rapid onset of action and bioavailability make this delivery system as a dosage form of choice in the current market.[19]

The prepared films were found to be uniform, flexible and 90% of the drug was released from the F1 film within 3.20 minutes which was desirable for fast absorption. Later stability studies of this formulation were indicating that there was no degradation of the formulation at high temperature and humidity conditions. It was indicating that this formulation was stable. From the present investigation, it can be concluded that oral thin film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for the general population.[15]

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