WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 8, 1460-1467. Research Article ISSN 2277– 7105

FORMULATION, FABRICATION AND *IN-VITRO* EVALUATION OF FAST DISSOLVING ORAL FILM OF CILNIDIPINE

Nisha Kumari[1]*, Nishi Prakash Jain[1] and Jitendra Banweer[1]

Sagar Institute of Research, Technology & Science-Pharmacy, Near ISRO, Ayodhya Bypass Road, Bhopal (India)-462041.

Article Received on
30 May 2017,
Revised on 20 June 2017,
Accepted on 10 July 2017
DOI: 10.20959/wjpr20178-9010

***Corresponding Author**
Nisha Kumari
Sagar Institute of Research, Technology & Science-Pharmacy, Near ISRO, Ayodhya Bypass Road, Bhopal (India)-462041.

ABSTRACT

Patient compliance is an integral part of pharmaceutical research for better and sustained drug delivery. This is now essential for the pharmaceutical scientist to reconsider their research focus. The oral delivery of drugs is the most ideal route of administration due to ease of administration. This research work focus on development of Oral Fast Dissolving Films (OFDF), which has the unique property of rapidly dissolving and releasing the drug as soon as they come in contact with saliva. A new calcium channel blocker (CCB), Cilnidipine has an inhibitory action on the sympathetic N-type and L-type Ca^{2+}channels. Oral Fast Dissolving Films (OFDF) of Cilnidipine was prepared by solvent casting method with HPMC E-15 and Gum acacia (2.5%w/v) as film former, PEG-400 as plasticizer, Citric acid for producing more saliva while Sodium starch glycholate were taken as superdisintigrants. The prepared films were evaluated for Weight uniformity, Folding endurance, Tensile strength, Percent Elongation, Disintegration Test and Drug Content. All OFDFs of Cilnidipine were transparent and the thickness was varying from 185±0.167 µm to 250±0.236 µm. The weight of films (COF1 to COF9) was found to be in range of 104.8±0.216 to 116±0.141 mg and folding endurance found to be 256±2.645 to 289.6±1.154 times. The prepared films found to be 1.20±0.017 to 1.50±0.043 kg/cm^2 range of tensile strength. Disintegration time of all batches varies between 143.6±1.527 Sec. to 91.60±1.527 Sec. The prepared optimized batch of OFDF of Cilnidipine may be useful in Acute Hypertensive patients and other cardiac diseases patient.

KEYWORDS: Cilnidipine, calcium channel blocker (CCB), Oral Fast Dissolving Films

(OFDF), Hypertension, Cardiac diseases.

INTRODUCTION

Men and medicine are undividable from times civilization. Although the physical forms of medication have not changed considerably, the attitude of the public toward accepting medicines have changed with the time. Patient compliance is an integral part of research for better and sustained drug delivery. This is now mandatory for the pharmaceutical scientist to reconsider their research focus. The oral delivery of drugs is the most ideal route of administration due to ease of administration. Oral Fast Dissolving Films (OFDF), has the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva. Therefore, these dosage forms have lured the market for a certain section of the patient population. The novel drug delivery system such as Oral Fast Dissolving Films (OFDF) of new calcium channel blocker, Cilnidipine can provide and compliance to the patient with economical solution. Cilnidipine is a unique Ca^{2+} channel blocker with an inhibitory action on the sympathetic N-type as well Ca^{2+}channels. Cilnidipine has been elucidate to exert antisympathetic actions in various examinations from cell to human levels, in contrast to classical Ca^{2+} channel blockers. Furthermore, renoprotective and neuroprotective effects as cardioprotective action of Cilnidipine have been demonstrated in clinical practice or animal examinations. The ultimate aim of such systems is tailoring of the drug formulation to individual requirements under the control of patho-physiological or *in-vivo* conditions rather than *in-vitro* characteristics.

MATERIALS AND METHODS

Material

Cilnidipine was obtained from JB Chemicals and Pharmaceuticals, Mumbai. Hydroxy Propyl Methyl Cellulose E15, Sodium Starch Glycolate, Gum Acacia, PEG-400, Stevia and Citric Acid were purchased from CDH Pvt. Ltd. Mumbai. All the excipients and chemicals were used of Pharmaceutical grade.

Method

Procedure for preparation of Oral Fast Dissolving Film (OFDF) of Cilnidipine[1]

The solvent casting method is used for the preparation of oral fast dissolving film (OFDF) formulation as per Table No.1. The amount of polymer HPMC E-15 and Gum acacia (2.5%w/v) was dissolved in 5ml of water and kept for 24 hours for swelling at room temperature. Swelled solution homogeneously stirred for 30 minute with stevia, coloring

agent, citric acid and PEG-400 using magnetic stirrer. The Cilnidipine 100 mg were dissolved in 5 ml of water and mixed in the above prepared polymeric solution. Polymeric solutions were sonicated. The polymeric solution was poured for casting in a specifically designed glass mould for 20 strips (size 20 x 4 cm surface area) and then dried at 45±2^{o}C temperature in hot-air-oven for 24 hours. The dried film was carefully removed from the glass films and was cut into size required for testing. The prepared oral fast dissolving film were packed in aluminum foil and stored in air tight plastic bags till further use.

Evaluation of Oral Fast Dissolving Film of Cilnidipine

Visual Inspection[2]

Oral fast dissolving films were inspected manually for their transparency and air bubble.

Thickness[3]

The thickness of the drug loaded patch was measured in different points by using a digital micrometer (6 locations) and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared films.

Weight uniformity[4]

The prepared films were dried in oven at 45±2° for 24 hrs before testing. A specified area of film is to be cut in different parts of the film and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Folding endurance[5]

A strip of specific area was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Tensile strength[6]

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.

$$\text{Tensile Strength} = \frac{\text{Load at breakage}}{\text{Film thickness} \times \text{Film width}}$$

Percent Elongation[7]

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.

$$\% \text{ Elongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}}$$

Disintegration Test[8]

Disintegration of orally fast dissolving films requires U.S.P. disintegration apparatus. The disintegration time limit of 180 seconds or less for orally disintegrating tablets applied to fast dissolving oral fast dissolving films. Disintegration time will vary depending on the formulation but typically the disintegration range from 60 to 180 seconds. Although, no official guidance is available for oral fast disintegrating films, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating test apparatus may be used for this study.

Drug Content[9]

A randomly selected one oral fast dissolving film of Cilnidipine was dissolved in approximately 90 ml of phosphate buffer (6.8 pH) and Sonicated the mixture for 2 minutes, then volume makeup to 100 ml with phosphate buffer (6.8 pH) . The solution then filtered and volume makeup to 100 ml by phosphate buffer (6.8 pH). To determine the drug content of Cilnidipine, 5 ml of solution were withdraw and diluted up to 10 ml by phosphate buffer (6.8 pH). The absorbances of diluted solution of Cilnidipine were determined by UV spectrophotometer at λ_{max} 275nm. The drug content was determined with suitable formula.

RESULT AND DISCUSSION

Cilnidipine oral fast dissolving films were prepared and evaluated for Transparency, Thickness, Weight uniformity, Folding endurance, Tensile Strength, Percentage elongation, Disintegration and Drug content. All the OFDFs were transparent, the thickness were varies between 185±0.167 µm to 250±0.236 µm. The formulation (COF5) shows thickness values 205±0.089 µm there was no more significant difference in SD. The weight variations of the OFDFs were not found to be more variance in all the batches. The weight of films (COF1 to COF9) was found to be in range of 104.8±0.216 to 116±0.141 mg, the weight of formulation (COF5) was 110±0.109 mg. The SD value was not significantly varies and it indicated that formulation (COF5) was meet the criteria for the weight variation. Folding endurance for all

the formulation was found to be 256±2.645 to 289.6±1.154 times. It shows that all formulation had a good plasticity. The prepared films found to be 1.20±0.017 to 1.50±0.043 kg/cm^2 range of tensile strength. All the formulations were evaluated for the drug content. The formulation (COF5) shows maximum amount of drug i.e. 99.618±0.011 percent and less amount of drug content than other formulation was found in COF7. Disintegration time of each formulation was determined. It was varies in range between 143.6±1.527 Sec. to 91.60±1.527 Sec. The disintegration time for the formulation COF5 was found to be 108.3±0.577 sec.

In Vitro Dissolution study

Dissolution studies of all the batches were carried out in phosphate buffer (pH 6.8) as a dissolution medium. The in vitro drug release studies of formulations COF1 to COF9 had performed, the maximum drug release was found to be 93.5% in formulation COF5 whereas minimum amount of drug release was found to be 89.1% in formulation COF7. The % Cumulative drug release of all formulations of oral fast dissolving films Cilnidipine have determined. From the drug release studies of all formulations, the formulation COF5 showed maximum drug release 93.5% at 25 minutes and was considered to be optimized formulation. The drug release from the oral fast dissolving films was dependent on concentrations of superdisintegrants, HPMC E15 and plasticizers such as polyethylene glycol.

Based on regression coefficient (r^2) values it was observed that release of Cilnidipine from formulation COF5 are best expressed by Higuchi diffusion equation and Zero order kinetics.

Table No. 1: Formulation table for oral fast dissolving films of Cilnidipine.

Formulation Batches of OFDFs									
INGREDIENT	**COF1**	**COF2**	**COF3**	**COF4**	**COF5**	**COF6**	**COF7**	**COF8**	**COF9**
Cilnidipine (mg)	100	100	100	100	100	100	100	100	100
HPMC E15(mg)	1400	1400	1400	1400	1400	1400	1400	1400	1400
Acacia (mg)	50	50	50	75	75	75	100	100	100
PEG 400 (mg)	60	60	60	60	60	60	60	60	60
Stevia (mg)	60	60	60	60	60	60	60	60	60
Citric acid (mg)	60	60	60	60	60	60	60	60	60
SSG (mg)	300	400	500	300	400	500	300	400	500
Colour/flavour	QS	QS	QS	QS	QS	QS	QS	QS	QS
Water (ml)	QS	QS	QS	QS	QS	QS	QS	QS	QS

Table No. 2: Evaluation table for oral fast dissolving films of Cilnidipine.

Evaluation Parameter				
Formulation	**Transparency**	**Thickness (µm)**	**Weight uniformity (mg)**	**Folding endurance**
COF1	Transparent	185±0.167	104.8±0.216	256±2.645
COF2	Transparent	200±0.141	107.5±0.141	237±1.732
COF3	Transparent	215±0.209	115.2±0.228	207.3±1.527
COF4	Transparent	192±0.189	106.6±0.368	303±2.000
COF5	Transparent	205±0.089	110±0.109	282±1.000
COF6	Transparent	240±0.141	115.4±0.167	235.6±2.516
COF7	Transparent	197±0.089	107.9±0.089	350±1.000
COF8	Transparent	215±0.109	112.5±0.189	320±1.732
COF9	Transparent	250±0.236	116±0.141	289.6±1.154

*All values expressed in mean ±SD, (n=3).

Table No. 3: Evaluation table for oral fast dissolving films of Cilnidipine.

Evaluation Parameter				
Formulation	**Tensile Strength (kg/cm^2)**	**Percent Elongation (%)**	**Disintegration Time (Second)**	**Drug Content (%)**
COF1	1.20±0.017	26.4±0.360	143.6±1.527	98.310±0.005
COF2	1.11±0.010	26.5±0.300	129.6±1.527	98.746±0.013
COF3	1.00±0.017	26.3±0.100	56.60±0.577	98.201±0.043
COF4	1.42±0.026	32.6±0.100	166.0±1.000	97.765±0.022
COF5	1.32±0.015	33.2±0.200	108.3±0.577	99.618±0.011
COF6	1.25±0.010	33.7±0.200	73.00±1.000	99.400±0.007
COF7	1.64±0.051	35.1±0.100	186.6±1.527	95.585±0.018
COF8	1.55±0.43	25.4±0.200	124.0±1.000	97.547±0.012
COF9	1.50±0.043	35.3±0.152	91.60±1.527	98.528±0.011

Table No. 4: Drug Release Profile of oral fast dissolving films of Cilnidipine

%Cumulative Drug Release Profile of Oral Fast Dissolving Films									
Time (min.)	**COF1**	**COF2**	**COF3**	**COF4**	**COF5**	**COF6**	**COF7**	**COF8**	**COF9**
0	0	0	0	0	0	0	0	0	0
10	16.5	15.6	14.1	13.1	15.1	18.2	12.5	13.2	13.8
20	46.2	53.5	56.5	41.6	45.2	59.2	39.5	44.1	46.1
30	77.6	82.6	86.1	64.5	68.2	81.2	61.6	71.2	72.4
40	83.3	91.3	93.2	78.2	84.2	91.3	75.6	81.9	84.6
50	88.4	91.2	93.1	86.2	92.4	93.2	82.1	85.2	88.2
60	91	91.1	93.1	91.1	93.5	93.1	89.1	91.2	92.1

Table No. 5: Curve Fitting Data for the Release Rate Profile of Formulations

Formulation	R^2 Value of Different Models		
	Zero Order	First Order	Higuchi Matrix
COF1	0.869	0.969	0.912
COF2	0.814	0.900	0.893
COF3	0.801	0.896	0.882
COF4	0.940	0.986	0.911
COF5	0.924	0.972	0.915
COF6	0.810	0.943	0.914
COF7	0.947	0.987	0.909
COF8	0.903	0.981	0.907
COF9	0.896	0.981	0.908

CONCLUSION

From the present research work is Formulation, Fabrication and *in-vitro* Evaluation Cilnidipine oral fast dissolving films for oral drug delivery, the following points can be concluded:

- The films prepared were elegant in appearance and smooth surface.
- The film was dissolving in mouth in seconds.
- The weights of films were uniform.
- The thicknesses of films were very less and uniform
- The films had good flexibility.
- The films show uniform tensile strength.
- The drug was distributed throughout the films uniformly.

More than 93% of the drug was released from all the formulations at the end of *in-vitro* drug release. From the result and conclusion of the research work we can summarize that Cilnidipine can be delivered via oral route. Hence product of research work OFDFs of Cilnidipine will be useful to treat the Acute Hypertensive patients.

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