INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN: 2320-2831

IJPAR |Vol.4 | Issue 2 | April-June-2015
Journal Home page: www.ijpar.com

Research article *Open Access*

Formulation and evaluation of carvedilol fast dissolving sublingual films

V.Kranthi kmar, Syed Umar Farooq,* M Vamshi Krishna, R srividya and Dr D Sudheer kumar

Departmnent of Pharmaceutics Care College of Pharmacy, Kakatiya University, Telangana, India.

***Corresponding author: Syed Umar Farooq**

ABSTRACT

Carvedilol, a non selective beta blocker is an antihypertensive drug which has oral bioavailability of 25-35% with conventional dosage forms due to first pass metabolism. The present study investigated the possibility of developing carvdilol fast dissolving sublingual films allowing fast, reproducible drug dissolution in the oral cavity, thus bypassing first pass metabolism to provide rapid onset of action of the drug. The fast dissolving films were prepared by solvent casting method. Low viscosity grades of HPMC E3 and HPMC E5 were used as film forming polymers. In this study Tween 80 was used as solubilising agent as well as plasticizer. All the film formulations (F1-F9) were evaluated for their thickness, weight variation, tensile strength, percentage elongation, folding endurance, in-vitro disintegration, drug content, in-vitro drug release and ex-vivo permeation studies. Disintegration time showed by the formulations was found to be in range of 25-50 sec. Formulation F7 was chosen as the best formulation which showed 96.65% in-vitro drug release within 5 min and 62.36% ex-vivo drug permeation within 60 min. The film showed an excellent stability at least for 45 days when stored at 40^0 C and 75% relative humidity.

Keywords: Carvedilol, Fast Dissolving Sublingual Films .sublingual route

INTRODUCTION

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, by passing the gastrointestinal tract and first-pass metabolism in the liver. The unique environment of the oral cavity offers its potential as a site for drug delivery. Because rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver. The continuous secretion of saliva results in rapid removal of released drug and this may desire that the oral cavity be restricted to the delivery of drugs, which have a short systemic circulation[1]. There has been increased demand for the novel dosage form to gain more patient compliance. Fast dissolving films recently have acquired great importance in the pharmaceutical industry due to their unique properties and specific advantages like no need of water for disintegration,

accurate dosing rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance[2]. Fast dissolving film is a type of drug delivery system, which when placed in the oral cavity it rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption, without chewing and intake of water[3]. This technology evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action[4,5]. This type of technology offer a convenient way of dosing medication, not to special population groups like paediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. The sublingual mucosa is relatively permeable due to thin membrane and large veins. It gives rapid absorption and instant bioavailability of drugs due to high blood flow [6,7]. As the fast-dissolving film is taken through the sublingual route, rapid absorption of drug is possible, which finally leads to quick onset of drug action and prevent the first pass-metabolism of the drug.

MANUFACTURE PROCESS OF FILMS[9]

One or more of the following process can be used combine to manufacture the mouth dissolving films.

- Solvent casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

SOLVENT CASTING METHOD

Fast dissolving films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in a suitable solvent then both the solutions are mixed and stirred and finally casted into the Petri plate and dried.

HOT MELT EXTRUSION

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder. The screw speed should set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3–4 min. The processing temperatures should be 800C (zone 1), 1150C (zone 2), 1000C (zone 3) and 650C (zone 4). The extrudate (T = 650C) then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion,

- -Fewer operation units
- -Better content uniformity
- -An anhydrous process

SOLID DISPERSION EXTRUSION

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

ROLLING

In rolling method a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes.

MATERIALS AND METHODS

MATERIALS

Carvedilol was procured from Dr. Reddy's laboratories, Hyderabad. Hydroxy propyl methyl cellulose (HPMC E3 and HPMC E5) from sjs pharma, Hyderabad. Tween 80 and ethanol were procured from SD fine chemicals, Mumbai. All the chemicals used were of analytical grade.

METHODS

In the present study, fast dissolving sublingual films of carvedilol were prepared by solvent casting method. Flat round shaped glass mould having surface area of 75.39cm^2 were fabricated for casting the films.

PREPARATION OF CARVEDILOL SUBLINGUAL FILMS

Carvedilol sublingual films were prepared by solvent casting technique using different excipients[11]. Different concentration of excipients was used to

prepare different group of sublingual films. The polymer solution was prepared by dissolving weighed quantities of polymer in 10ml of ethanol taken in a beaker. The drug was dissolved in 5ml of ethanol and added to the above polymeric solution along with tween 80 as a plasticizer, thoroughly mixed to form a homogenous mixture. The volume was made up to 20ml with ethanol. The beaker was covered with aluminum foil and the solution was stand for some time to remove air bubbles. The prepared solution of 10ml was taken and poured in to a glass Petridish having the surface of 75.39cm^2 and kept it in a vacuum oven at a temperature 50^0c for 2 to 3hrs. The films were removed by peeling and cut in to 2×1cm ($2cm^2$) so that each film contained 3.125mg of drug and these films were packed in self-sealing cover.

DETERMINATION OF ABSORPTION MAXIMA

A spectrum of the working standards was obtained by scanning from 200- 400 nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 241nm. Hence all further investigations were carried out at the same wavelength.

PROCEDURE FOR PREPARATION OF 6.8 PH PHOSPHATE BUFFER

Potassium Dihydrogen Orthophosphate 0.2m

dissolves 27.21g of potassium dihydrogen orthophosphate in water and dilute with water to 1000ml.

SODIUM HYDROXIDE 0.2 M

Dissolve sodium hydroxide in water to produce a 40 to 60 % w/v solution and allow it to stand. Taking precautions to avoid absorption of carbon dioxide split off the clear supernatant liquid and dilute with carbon dioxide free water, a suitable volume of the liquid to contain 8.0 g of NaOH in 1000ml.

PROCEDURE FOR CONSTRUCTION OF CARVEDILOL IN 6.8 PH PHOSPHATE BUFFER

Accurately weighed amount of 100 mg of carvedilol was dissolved in a mixture of 50ml of methanol and 50ml of buffer. From this primary stock solution 5 ml was transferred to another volumetric flask and made up to 50 ml with 6.8 pH phosphate buffer, from this secondary stock solution concentrations of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg /ml, 12 µg /ml and 14 µg /ml were prepared. The absorbance was measured at 241 nm by using a UV-Visible spectrophotometer.

PROCEDURE FOR CONSTRUCTION OF CARVEDILOL IN 7.4 PH PHOSPHATE BUFFER

Accurately weighed amount of 100 mg of carvedilol was dissolved in a mixture of 50ml of methanol and 50ml of buffer. From this primary stock solution 10ml was transferred to another volumetric flask and made up to 100ml with 7.4 pH phosphate buffer, from this secondary stock solution 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg /ml, 12 µg /ml, 14 µg /ml and 16 µg /ml were prepared. The absorbance was measured at 241 nm by using a UV-Visible spectrophotometer.

DRUG- EXCIPIENTS COMPATIBILITY STUDIES

FT-IR spectrum of the drug and drug in the presence of the polymers was recorded and the characteristic peaks of carvedilol were identified as N-H stretching at 3339 cm^{-1}, C-O stretching at 1017 cm^{-1}, O-H stretching at 3615 cm^{-1} and C-O-C stretching at 1174. Carvedilol optimized formulation exhibits respective peaks at 3458 cm^{-1}, 1254 cm^{-1}, 3336 cm^{-1} and 1062 cm^{-1}. It was observed that there were no changes in the main peaks in the FT-IR spectra of drug, polymers and excipients. Hence, it was concluded that no physical or chemical interactions of carvedilol with polymers and excipients.

EVALUATION OF CARVEDILOL FILMS

THICKNESS

The thickness of film of each formulation was measured by screw gauge at different positions of film and average thickness was calculated.

WEIGHT VARIATION

$2cm^2$ film was cut at three different places in the cast film. The weight of each filmstrip was taken and weight variation of all formulations was calculated. It was calculated on an electronic weighing balance.

FOLDING ENDURANCE

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value[12]. A small strip of 4cm^2 was taken for this test by folding the film at same plane repeatedly until a visible crack was observed.

TENSILE STRENGTH

This mechanical property was evaluated using Instron universal testing instrument (Model F. 4026), Instron Ltd., Japan, with a 5 Kg load cell. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the top clamps at a rate of 100 mm/min pulled the strips; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Tensile strength is the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross sectional area of fractured film from the following equation[13]:

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}$$

PERCENTAGE ELONGATION

The percentage elongation was measured by measuring the distance between the tensile grips of

The tensile strength testing machine before and after the fracture of the film, then the percentage elongation of the films was computed with the help of the formula given below:

$$\%E = D_f - D_0/D_0 \times 100$$

Where:-

%E = Percentage elongation

D_0 = Distance between the tensile grips before the fracture of the film.

D_f = Distance between the tensile grips after the fracture of the film

DISINTEGRATION TEST

The disintegration time is the time when the film starts to break or disintegrates. One film of each formulation was taken in a petridish containing 25 ml of pH 6.8 phosphate buffer and disintegration time was determined visually with swirling every 10sec.

DRUG CONTENT UNIFORMITY

This parameter was determined by dissolving three films of dimension 2 x 1 cm^2 from each formulation in 10 ml of methanol. From this, 0.1ml was taken and diluted to 10ml with 6.8 pH phosphate buffer. The absorbance was measured at 241nm using an UV spectrophotometer.

DISSOLUTION TEST OF CARVEDILOL SUBLINGUAL FILMS

Drug release from Carvedilol sublingual films was determined by using dissolution test United States Pharmacopoeia (USP) type II (paddle).

Dissolution medium	**:** 6.8 pH phosphate buffer
Volume	**:** 900 ml
Temperature	**:** at 37^{0}C± 0.5^{0}C
Speed	**:** 50 rpm

5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (2, 5, 10, 20, and 30minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV- spectrophotometer. The concentration was calculated using standard calibration curve.

EX-VIVO PERMEATION STUDIES

This was performed by application of the film on freshly cut porcine sublingual mucosa. The porcine tissue was fixed on the one side of the measuring cylinder and this was dipped in a beaker filled with 300 ml of P^H 7.4 phosphate buffer which was maintained at 37^{0}C. Stirring was maintained with a magnetic bead at 50 rpm. The film was kept on mucosa from other side of measuring cylinder and filled with 10ml of pH 6.8 phosphate buffer. Samples were withdrawn at suitable time intervals (10, 15, 30, 45 and 60 minutes) and replacing the same amount with the fresh medium[14]. The percentage of drug permeated was determined by measuring the absorbance in UV-Visible spectrophotometer at 241nm.

Figure no 1: Ex-vivo permeation study of optimized formulation Stability studies

A stability study of optimized formulation was carried out for 45 days at 40^0C/75%RH. The films were observed for physical change, drug content and percentage drug release. The fast dissolving sublingual films of carvedilol showed no significant change in terms of physical characteristics, drug content and percent drug release at above mentioned stability condition.

RESULTS AND DISCUSSION

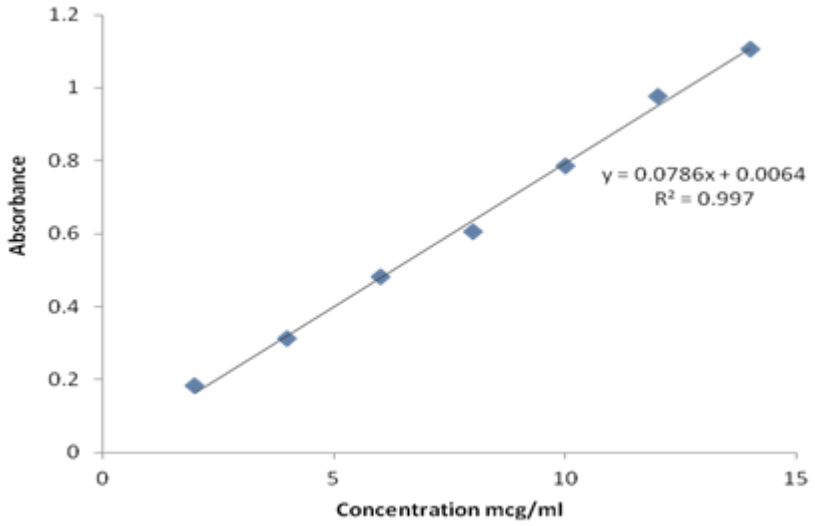


Figure no2: Calibration Curve of Carvedilol in pH 6.8 phosphate buffer

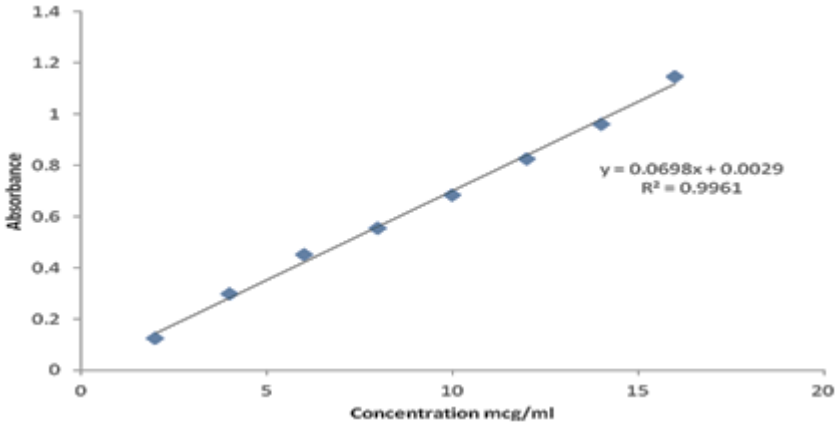
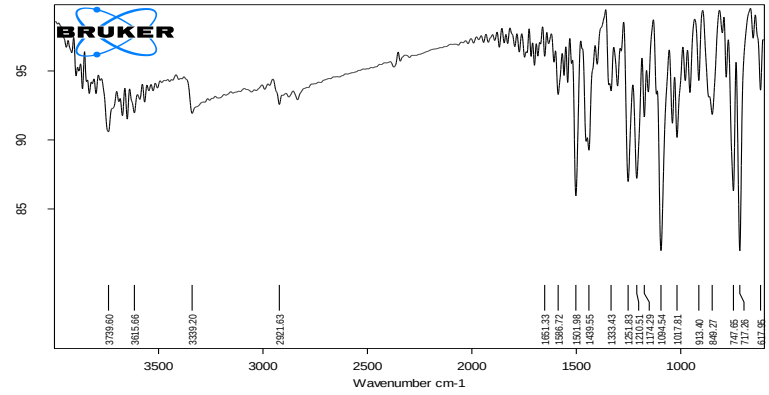
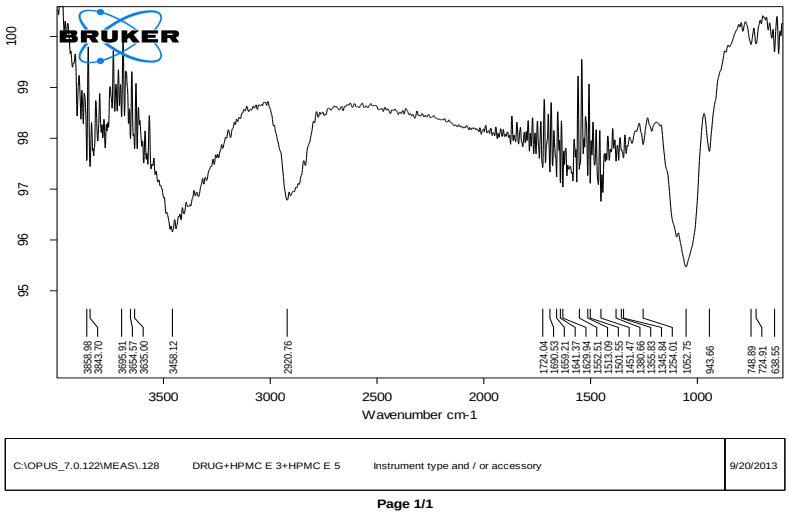


Figure no 3: Calibration curve of Carvedilol in pH 7.4 phosphate buffer



FT-IR characteristic peaks of pure drug



FT-IR characteristic peaks of Drug + HPMC E3 + HPMC E5

Table no 1: Formulation of sublingual films

INGREDIENTS	F1 1:4	F2 1:5	F3 1:6	F4 1:4	F5 1:5	F6 1:6	F7 1:4	F8 1:5	F9 1:6
CARVEDIOL(mg)	117	117	117	117	117	117	117	117	117
HPMC E3(mg)	468	585	702	-	-	-	234	292.5	351
HPMC E5(mg)	-	-	-	468	585	702	234	292.5	351
TWEEN 80(%w/w of polymer)	30	30	30	30	30	30	30	30	30
ETHANOL(ml)	20	20	20	20	20	20	20	20	20

Table no 2: Evaluation of physicochemical parameters of fast dissolving films of Carvedilol

Formulation Code	Thickness (mm)	Weight variation (mg)	Tensile strength (kg/cm^2)	Percentage elongation	Folding endurance (No. of folds)
F1	0.246±0.041	48.5±0.98	0.625±0.54	4.92±0.85	125
F2	0.314±0.052	48.62±0.95	0.697±0.45	5.54±1.56	130
F3	0.385±0.068	51.24±0.84	0.702±0.96	8.36±0.54	142
F4	0.315±0.046	49.25±1.10	0.634±0.84	6.89±0.65	132
F5	0.426±0.063	52.47±1.15	0.712±0.14	8.47±0.78	136
F6	0.496±0.078	54.85±0.84	0.754±0.98	10.92±0.42	145
F7	0.324±0.098	49.65±1.12	0.684±0.45	6.96±1.25	142
F8	0.465±0.054	52.24±0.74	0.712±0.24	7.56±1.35	144
F9	0.492±0.084	53.21±1.45	0.732±0.17	10.68±0.45	154

Data represents mean ± S.D (n=3).

Table no 3: Disintegration time and drug content of films loaded with carvedilol

Formulation code	Disintegration time sec (starts)	Drug content (%)
F1	25±1.45	97.67±0.45
F2	32±1.85	96.56±0.78
F3	38±1.14	92.10±0.45
F4	28±1.36	94.85±0.65
F5	34±1.98	92.86±1.47
F6	38±1.65	91.12±0.45
F7	26±0.98	97.14±0.98.
F8	38±0.45	94.48±0.59
F9	48±1.78	95.45±1.78

Data represents mean ± S.D (n=3).

Table no 4: Comparative percent drug release profiles of formulations with HPMC E3- F1 to F3

Time (min)	F1	F2	F3
2	85.68±0.86	76.56±1.74	72.65±0.47
5	96.02±1.45	95.47±0.65	93.22±1.14
10	79.20±0.47	58.58±0.98	57.41±0.36
20	75.16±1.68	46.44±1.45	52.14±1.45
30	70.87±1.25	45.65±1.02	50.48±1.65

Data represents mean ± S.D (n=3).

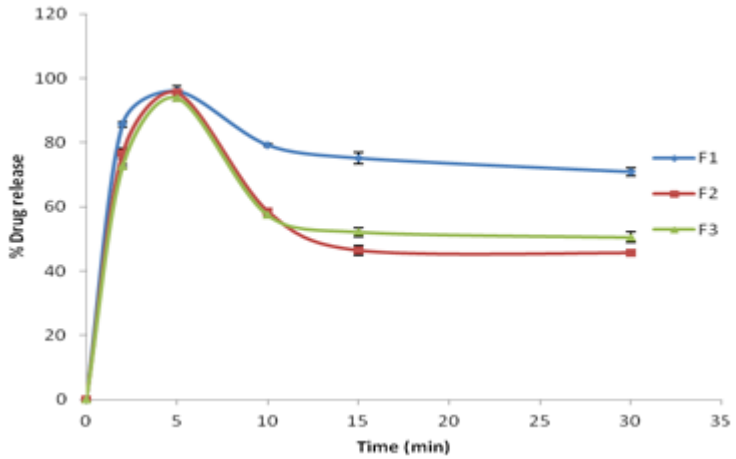


Figure no 4: Comparative percent drug release profiles of formulations with HPMC E3- F1 to F3

Table no 5: Comparative percent drug release profiles of formulations with HPMC E5- F4 to F6.

Time (min)	F4	F5	F6
2	84.98±0.84	77.47±1.02	71.65±0.47
5	95.90±0.47	93.64±1.08	91.98±1.47
10	78.25±1.14	70.12±0.84	62.45±1.89
20	68.54±0.69	64.97±0.78	60.12±0.14
30	60.49±0.47	59.28±1.09	56.42±0.47

Data represents mean ± S.D (n=3).

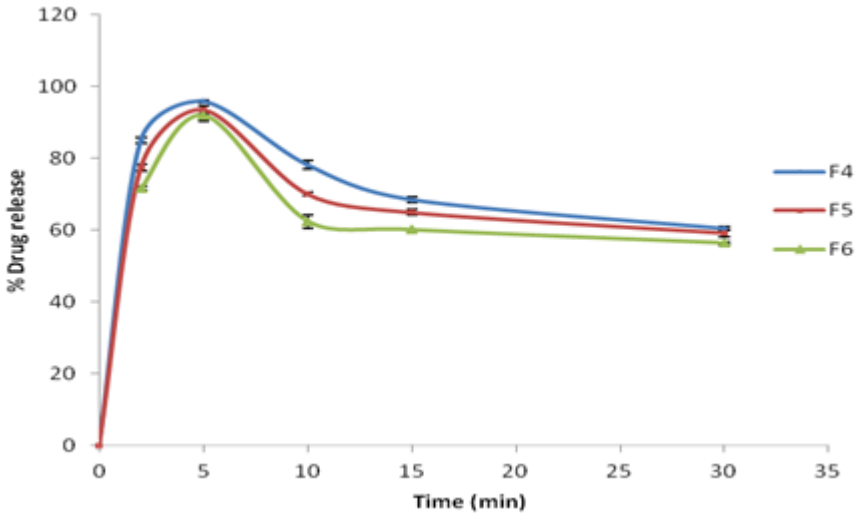


Figure no 5: Comparative percent drug release profiles of formulations with HPMC E5- F4 to F6.

Table no 6: Comparative percent drug release profiles of formulations with HPMC E3+ HPMC E5- F7 to F9.

Time (min)	F7	F8	F9
2	75.96±1.14	72.98±1.01	69.84±0.74
5	96.65±0.65	94.85±1.36	92.48±0.65
10	63.02±0.98	53.85±0.47	45.14±0.47
20	60.54±0.47	52.70±0.69	40.55±1.12
30	48.52±1.74	42.40±1.42	40.14±0.98

Data represents mean ± S.D (n=3).

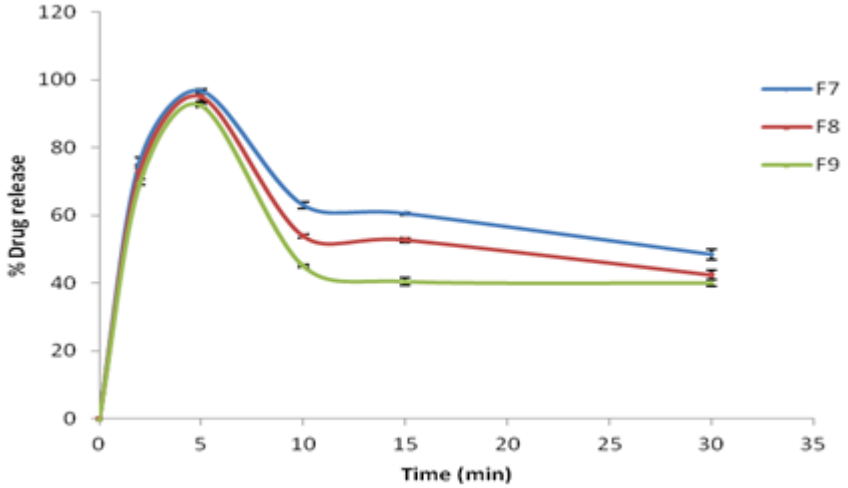


Figure no 6: Comparative percent drug release profiles of formulations with HPMC E3+ HPMC E5- F7 to F9

Table no 7: Ex-vivo drug permeation of optimized formulation (F7)

Time in Min	Percent Drug Release
10	17.48
15	28.54
30	38.47
45	54.55
60	62.36

Table no 8: Stability study of optimized formulation for drug content

Parameter	Testing period	
	Initial	After 45days
Drug content (%)	97.14±0.98	95.84±0.46

Table no 9; Stability study of optimized formulation for percent drug release

S.No	Time (min)	Percent Drug Release	
		Initial	After 45days
1	2	75.96±1.14	74.68±0.48
2	5	96.65±0.65	94.12±0.78
3	10	63.02±0.98	61.78±1.02
4	20	60.54±0.47	58.47±0.45
5	30	48.52±1.74	42.78±0.95

Data represents mean ± SD (n=3)

DISCUSSION

EVALUATION PARAMTERS

THICKNESS

The thickness of films in each batch was measured. The difference in thickness was observed that the thickness of film increased with the amount of polymer increases. All the formulations were found to have thickness in the range of 0.546-0.765mm.

WEIGHT VARIATION

The individual weight of each type formulation was measured and the average weight of entire film was calculated. It was observed that the weight of entire film sample was uniform.

PERCENTAGE ELONGATION

It was observed that the percentage elongation increased with increase in polymer concentration in formulation

FOLDING ENDURANCE

All the films showed good folding endurance greater than 150 which indicated that all the films have good flexibility.

TENSILE STRENGTH

The tensile strength of film increased with the increase in the amount of polymer used in formulation.

DISINTEGRATION TIME

The in-vitro disintegration time of all films varied between 25 and 50 sec. It was observed that the disintegration time of films affected by thickness of film. The disintegration time of film increased with increase in the amount of polymer.

IN-VITRO DISSOLUTION

The in vitro drug release studies were performed for the formulations 1-9 by USP paddle apparatus, using 900 ml of pH 6.8 phosphate buffers as medium at 50rpm and temperature at 37°C ± 0.5 °C. In-vitro drug release studies were carried out using USP dissolution test apparatus type II. The dissolution results of formulations from F1 to F9 revealed that initially the drug released was above 90% in 5min but in further studies the cumulative release was declined. The rapid release of drug indicated the efficacy of the formulations. HPMC was most suitable as a film forming material and it provided

fast dissolution of films that were not sticky. HPMC E3 and HPMC E5 are low molecular weight polymers and rapidly soluble in nature. These polymers have an added advantage that they are non-ionic in nature. Tween 80 was used as a solubilizing agent as well as plasticizer in formulations, which enhanced the rapid solubility and dissolution of drug in dissolution medium. In in-vitro studies the further decrease in drug release was due to the precipitation of drug in dissolution media above saturation solubility of drug. The effect of polymer level and type of a polymer had no significant effect on the precipitation of drug.

OPTIMIZED FORMULATION

To optimize a formulation many factors are to be considered and evaluated. Factors like physical, mechanical and drug dissolution characteristics are generally considered in optimization. In this study 9 formulations were developed and optimized to get an optimum formula by considering above mentioned properties. The formulations developed with HPMC E3 polymer showed poor mechanical properties compared to HPMS E5 and mixture of HPMC E3 and HPMC E5 but the dissolutions studies reveal there was no significant effect of polymer type on dissolution characteristics. Based on the studies it was concluded that a formulation which was having a good mechanical property and optimum dissolution profile to be taken as optimized formula. By comparing all formulations, formulation F7 (1:4) was chosen as the best formulation.

EX-VIVO STUDIES

The ex-vivo study of formulation F7 was performed through porcine mucosa by using pH 7.4 phophate buffers. It was observed that the ex-vivo permeation studies through porcine mucosa was as fast as the in vitro drug release and the formulation F7 exhibited the release of the drug above 60% in 60min.

STABILITY STUDIES

Stability studies for the optimized formulation were carried out for 45 days at 40^0C/75%RH. The films were observed for physical change, drug content and percentage drug release. The fast dissolving sublingual films of carvedilol showed no significant change in terms of physical characteristics, drug content and percent drug release at above mentioned stability conditions.

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