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FORMULATION DEVELOPMENT AND EVALUATION OF NADOLOL ORAL FAST DISSOLVING FILMS

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Abstract:

The main goal in the development of any drug formulation is to achieve the complete drug release within the time or prior to it. Most of the drug delivery systems are successful because of their safety, most convenient and most economical drug delivery with highest patient compliance. In this a very thin oral strap consisting of drug disintegrates very fastly in the mouth and releases the drug into circulation the oral cavity therefore absorbed into the systemic.

The aim of the present study is to formulate the oral fast dissolving films of Nadolol using HPMC K4M and HPMC E50 as film forming polymers, Propylene glycol as a plasticizer, Tween 80 as a surfactant, and Sodium saccharin as a sweetening agent. Nadolol with the other ingredients is dispersed in the polymer solution and films are prepared by solvent casting method. The prepared films were found to satisfy the mouth dissolving time and other film parameters like thickness, folding endurance, weight uniformity, surface pH, tensile strength and drug content. 2 x 2 cm of film is required to be placed on to patient tongue whereby film instantly gets wet by saliva, rapidly hydrates, adheres to tongue, rapidly disintegrates and dissolves to release the drug. Time required for the film to dissolve and release the drug is 26 seconds and 2 minutes respectively. From this, it can be concluded that the 'Oral-flash' release films can be regarded as a potential novel drug delivery system for poorly water soluble drugs.

Keywords: *Fast dissolving drug delivery, fast dissolving oral films (FDOFs), oral thin film (OTF), oral–flash release films, Nadolol , HPMC K4M, solvent casting method, poorly water soluble drugs.*

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INTRODUCTION:

Societal pressures to reduce healthcare costs, coupled with the pharmaceutical industry's need to maintain its economic incentive to develop new drugs, have required that the industry increase speed to market and reduce the number of failures and overall cost of new drug development. This need has made it imperative for the industry to use efficient, systematic approaches to both drug discovery formulation design.

Oral drug delivery known for decades is the most widely utilized routes for administration among all routes that have been explored for systemic delivery of drug via various pharmaceutical products of different dosage forms. Popularity of the route may be ease of administration as well as traditional belief that by oral administration the drug is well absorbed like food stuff ingested daily. Sustained release (S.R)/Controlled release (C.R) pharmaceutical products have over the past decade gradually gained medical acceptance and popularity since, their introduction into the market has received regulatory approval for marketing and their pharmaceutics superiority and clinical benefits over immediate release pharmaceutical products have been increasingly recognized. Sustained release oral dosage forms have brought new lease of life into drugs that have lost market potential due to requirement of frequent dosing, dose related toxic effects and gastro intestinal disturbance[1]. So far there were no oral formulations for the nadolol that is why new oral drug delivery system were formulated and evaluated.

It is a non-selective beta blocker used in the treatment of Hypertension. In its oral administration, Nadolol does not undergo first pass effect so that the drug is absorbed and shows it's therapeutic action immediately.It generally works by relaxing the blood vessels and slowing heart rate to improve the blood flow. Nadolol fall in class III of the Biopharmaceutics Classification System (BCS), which means the drug is highly water soluble, while showing a moderate permeability in the GI mucosa.

MATERIALS AND METHODS:

Chemicals:

HPMC PMC K_4M,HPMC $E_{50,}$ Propylene glycol, Tween 80, Alcohol, Methanol, PEG 4000, PEG 6000, Distilled water and Nadolol.

NADOLOL – PURE DRUG:

Construction of calibration curve of Nadolol:

Preparation of phosphate buffer pH 6.8:

Accurately weigh 6.80g of potassium dihydrogen orthophosphate and transfer into 1000 ml volumetric flask and add little amount of water and dissolve it. After weigh 1.56g of sodium hydroxide and transfer into same volumetric flask and dissolve. Finally made up to the volume with distilled water and adjust the pH with sodium hydroxide solution.

CALIBRATION:

Preparation of Standard solution:

Accurately weigh 10mg of drug and dissolve in 10 ml of methanol and made up to volume 100ml with buffer solution (1000µg/ml; Stock-A). From stock A 10ml of solution was pippeted out and made to 100mlwith buffer solution.

Preparation of working standard solutions (Calibration curve):

From the Stock-B pipette out 0.2ml (2µg/ml), 0.4ml (4µg/ml), 0.6ml (6µg/ml), 0.8ml (8µg/ml) and 1ml (10µg/ml) into 10 ml volumetric flasks and make the volume up to 10 ml with phosphate buffer (pH-7.5). The resulting working standard solutions absorbance was measured at 270nm and calibration curve was constructed.

DRUG – EXCIPIENT COMPATIBILITY STUDY:

Study was carried out using FTIR (BRUKER) where the spectra of the films were taken with and without the drug. The specific peaks of drug and the polymers were studied for the interactions.

TRIAL FORMULATIONS:

Nadolol Films:

- Films were prepared using solvent casting method.
- Polymer was soaked in water for 24hrs. Then the drug solution and other additives were added and stirred until we get a clear solution.
- Then it was poured into mould to cast films.
- Various trial formulations were performed.

Table 3.3.1: Formula for preparation of trial formulation films

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
01.	Nadolol (mg)	-	-	-	125	125	125	125	125
02.	HPMC K_4M (mg)	500	-	-	500	500	500	-	-
03.	HPMC E_{50} (mg)	-	-	500	-	-	-	-	-
04.	Methanol (ml)	-	-	-	-	-	16	-	10
05.	Tween 80 (mg)	500	500	500	500	500	500	500	500
06.	Propylene glycol (ml)	2	2	2	2	2	2	2	2
07.	Purified water (ml)	20	20	20	20	20	20	20	20

EVALUATION OF PREPARED FORMULATIONS:

Weight Variation: The film was cut into small pieces (2×2) and its weight was noted. Three trials were performed with each formulation and average was calculated and noted.

Thickness: The thickness of a film can be measured by screw gauge at different strategic locations (at least 4 locations). This is essential to determine uniformity n the thickness of the film as this is directly related to the accuracy of dose in the film.

Folding endurance test: Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of the times of the film is folded without breaking is computed as the folding endurance value.

Drug content: The film of area 2x2 cm2 was cut and dissolved in distilled water. Then solvent ethanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with distilled water to 100ml in 100ml volumetric flask. Then 1ml was withdrawn from the solution and diluted to 10ml.The absorbance of the solution was taken at relevant nm and concentration was calculated. By correcting dilution factor, the drug content was calculated

Dissolving time test: To find out actual time required for disintegration of the film, dissolve the prepared film in a suitable buffer and note down the time required to breakdown of the films.

In vitro Dissolution test: The dissolution studies was carried out in simulated saliva consisting of phosphate buffer (pH 6.8) dissolution behaviour of the film.

Surface p^H of films: The surface pH of the films was determined to know the possibility of side effects, *in vivo* as an acidic or alkaline pH may cause irritation to the buccal mucosa. It was determined by taking 3 films of each formulation and the films taken in a watch glass and were wetted with little water and pH was measured using pH meter and noted.

Stability studies: The stability study of the prepared films was carried out by storing films in an aluminium package for 30days at 40^0C and 75% R.H. The films were observed for physical change (form and colour), dissolving time and drug content.

RESULTS AND DISCUSSION:

In this study, an attempt has been made to design, formulate and evaluate the Nadolol oral dissolving films by solvent casting method.

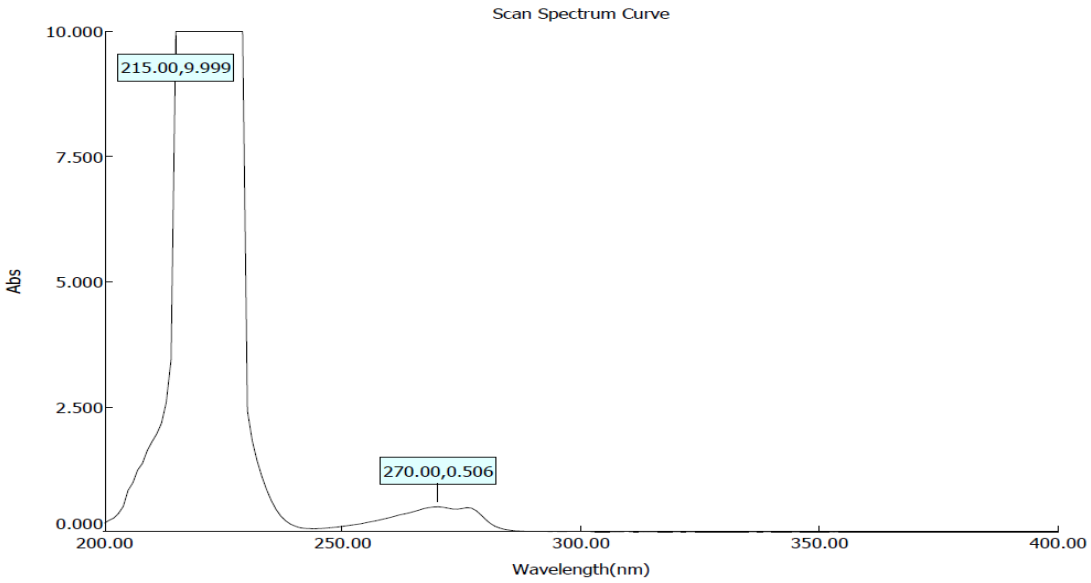
STANDARD CALIBRATION OF NADOLOL:

Standard calibration curve of Nadolol in phosphate 6.8 pH buffer was drawn by plotting absorbance v/s concentration. The λ_{max} of Nadolol in phosphate buffer was determined to be 270nm as shown in Fig. 4.1.1. The absorbance values were tabulated in Table 4.1.1. Standard calibration curve of Nadolol in the Beer's range between 2-10 µg/ml is shown in Fig.4.1.2.

Table 4.1.1. Calibration Table of Nadolol

Conc (µg/ml)	Absorbance
0	**0**
20	0.098
40	0.163
60	0.237
80	0.338
100	0.450

Fig 4.1.1 Spectrum of Nadolol.



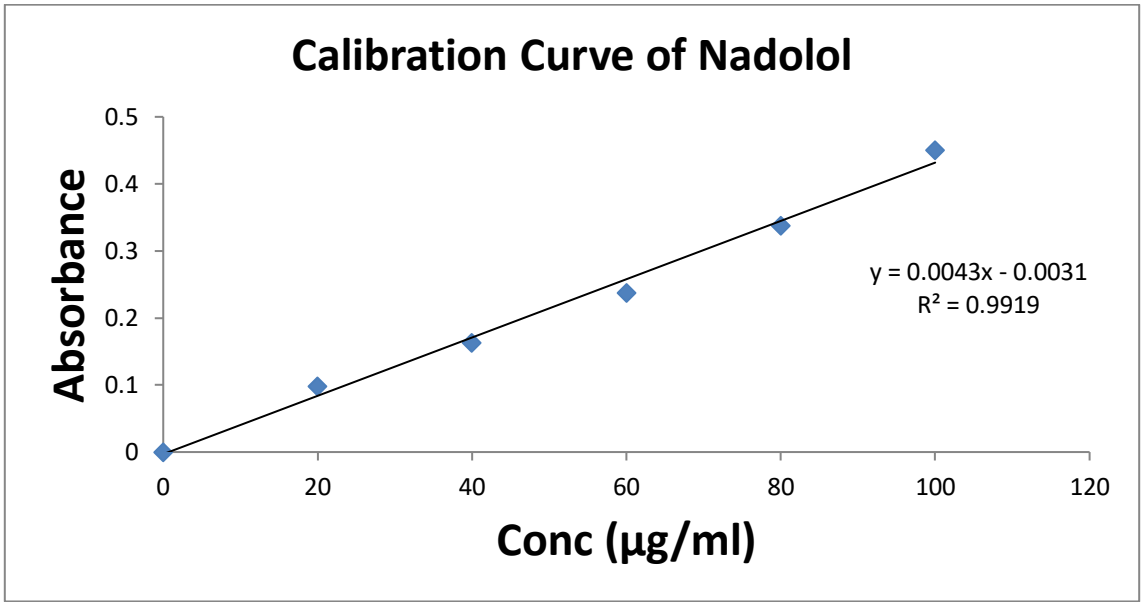


Fig 4.1.2 Standard Calibration Curve of Nadolol in pH 6.8 phosphate buffer

DRUG – EXCIPIENT COMPATIBILITY STUDY:

Drug – excipient compatibility study was carried out using FTIR. The spectra of the pure drug, the physical mixture containing polymer and final film were taken, the FTIR spectra were as below. Since there were no absence and presence of peaks in the physical mixture and final formulation compared with that of pure drug indicates that the drug is compatible with selected polymer and other excipients.

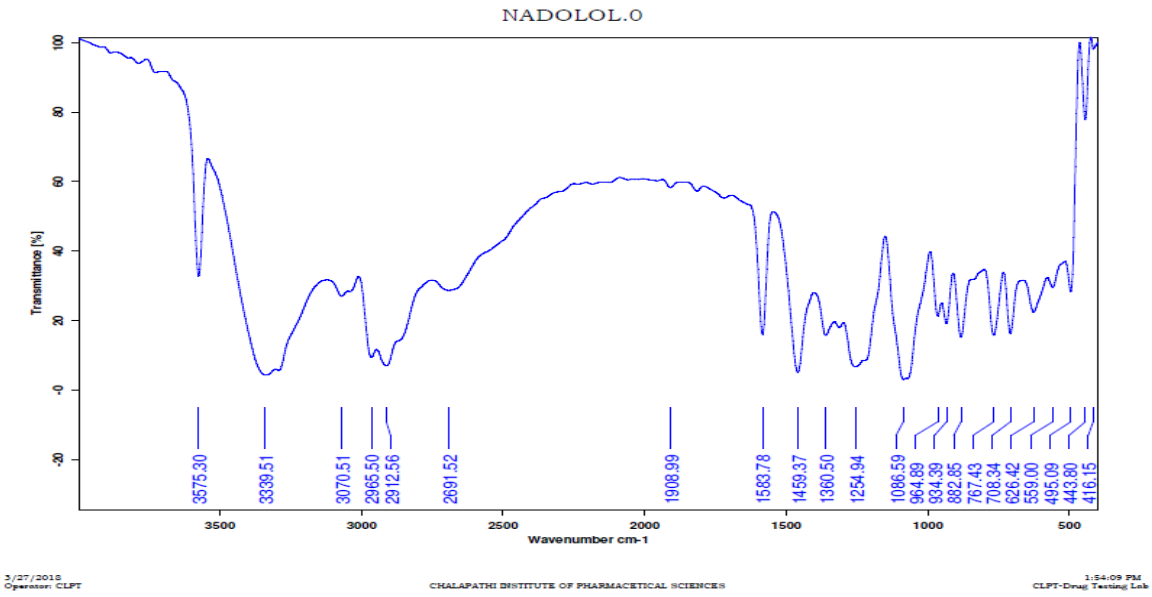


Fig 4.2.1 FTIR spectrum of pure Nadolol

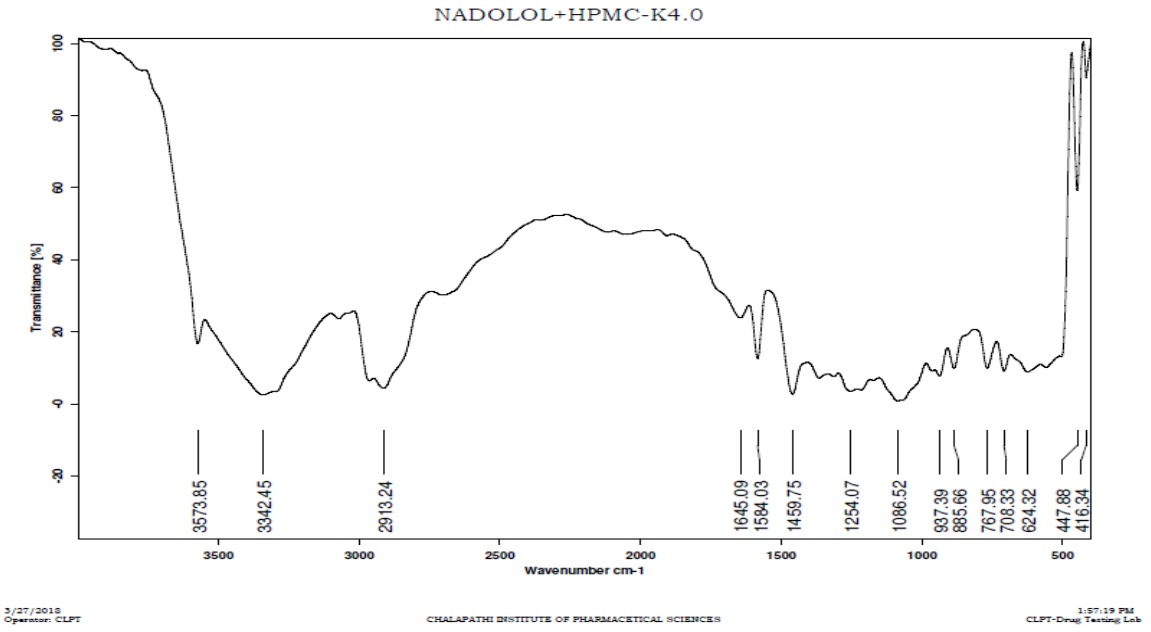


Fig 4.2.2 FTIR spectrum of physical mixture.

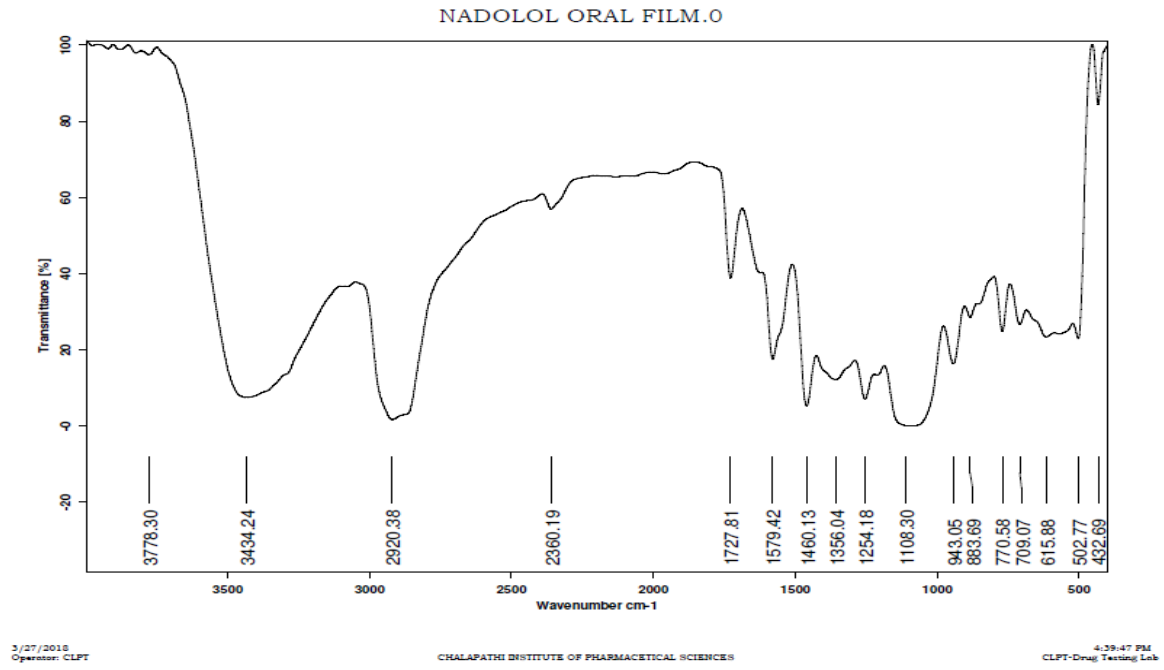


Fig 4.2.3 FTIR spectrum of final film.

TRIAL FORMULATIONS:

Selection of polymer:

Based on the literature review and availability of polymers, we have formulated blank films using three different polymers namely HPMC K_4M and HPMC E_{50}. Of all the three polymers film forming capacity, was found to be satisfactory with both.

Selection of best formulation:

Films were casted using the best two polymers and the film with HPMC K_4M showed good drug release.

Of all the 8 formulations, F5 was considered as best one based on various evaluation tests and *in vitro* drug dissolution studies.

Fig 4.3.2: Best formulation (F5)

EVALUATION OF FORMULATIONS:

Weight variation:

Films were cut into pieces, their weights were measured and average weight with standard deviation were calculated and given in the following Table 4.4.1.

Table 4.4.1: Weight variation test results

Weight	F1	F2	F3	F4	F5	F6	F7	F8
W1(mg)	10.6	9.7	10.3	44.5	60.3	70.9	75.6	50.7
W2(mg)	10.4	9.3	10.5	50.6	55.4	75.5	69.7	54.3
W3(mg)	9.8	9.4	10.2	48.7	50.2	68.4	72.8	53.5
Avg(mg)	10.2	9.4	10.3	47.93	55.3	71.6	72.7	52.83
S.d	0.416	0.2082	0.1527	3.1214	5.05	3.6	2.95	1.89

Thickness:
The thickness of the film was measured using screw gauze and the average thickness of the film was given in the Table 4.4.2.

Table 4.4.2: Thickness results

Thickness	F1	F2	F3	F4	F5	F6	F7	F8
T1(mm)	0.9	0.8	0.7	0.6	0.5	0.8	0.8	0.6
T2(mm)	0.9	0.9	0.7	0.6	0.5	0.8	0.9	0.8
T3(mm)	0.9	0.8	0.8	0.7	0.6	0.7	0.8	0.9
T4(mm)	0.8	0.7	0.8	0.8	0.6	0.7	0.9	0.8
Avg(mm)	0.875	0.8	0.75	0.675	0.55	0.75	0.85	0.775

Folding endurance test:
Folding endurance of the film was determined by repeatedly folding a small strip of the film at the place till it broke and the folding endurance was found to be about 258±10.675. Almost all the films showed the same folding endurance values.

Drug content uniformity:
Nadolol oral dissolving films were prepared with the aim to have a uniform dispersion of the drug throughout the film. In each case three 2×2 films were cut and average drug content was calculated. The drug dispersed in the range of 95.15 ± 1.143 to 99.02±1.355 suggesting that the drug was uniformly dispersed throughout the film.

Dissolving time test:
Dissolving time was noted for all the films and for the final film it was found to be 26sec.

In vitro Dissolution test:
The main aim of formulating oral dissolving films was to attain fast dissolution of the drug (i.e. in about 5 minutes). The required dissolution profile of the prepared films was obtained as the prepared Nadolol films showed complete drug release within 3 minutes. The dissolution profile of Nadolol oral dissolving films was compared to that of marketed Nadolol tablets.

Table 4.4.6.1: %Drug release comparison between films(F1-F8)

TIME(SEC)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
30	12.5	13.59	20.9	23.02	25.022	30.52	52.03	57.98
60	37.65	39.375	23.02	28.215	28.215	45.65	60	66.98
90	43.92	41.85	30.3	42.815	58.59	54.65	71.32	78.23
120	50.2	55.4	33.48	47.07	65.9	78.9	89.09	98.97
150	54.4	54.4	55.4	55.44	96	110	131.78	168.9

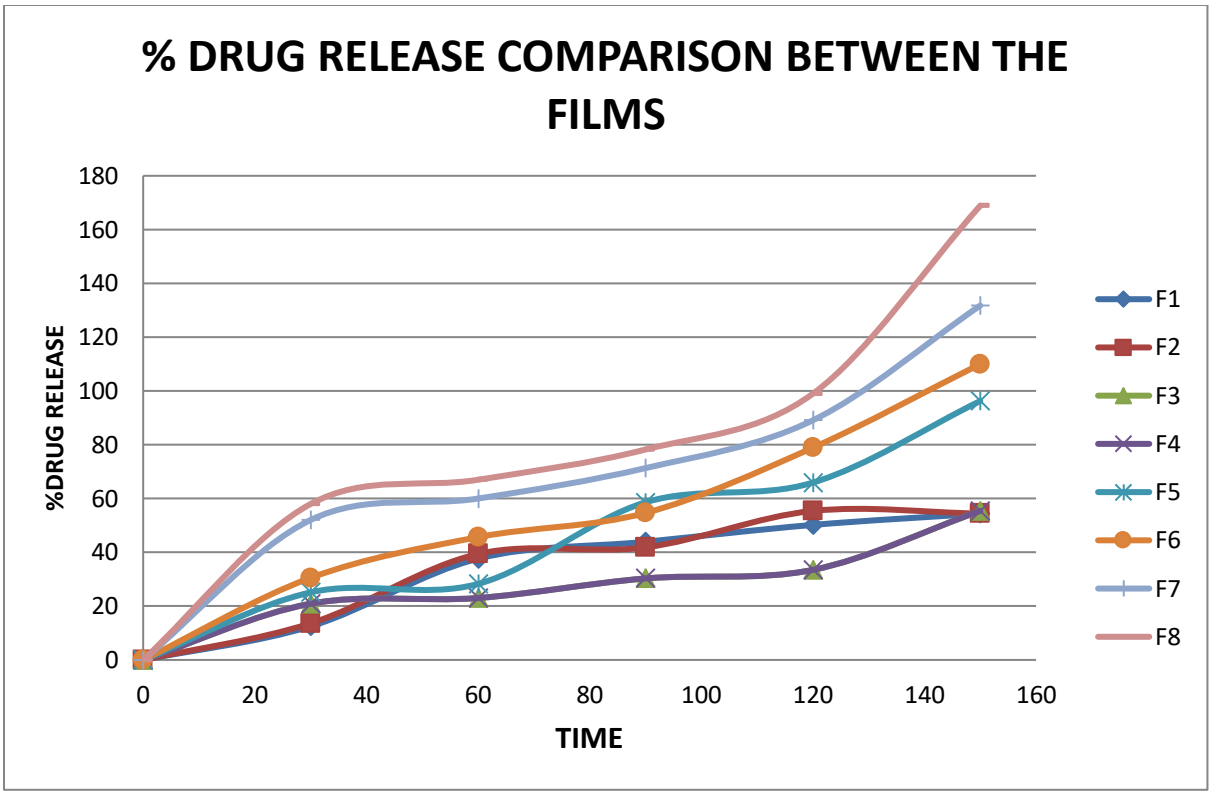


Fig 4.4.6.1: %Drug release comparison between films (F1-F8)

The dissolution profile of formulation F5 is as follows

Table 4.4.6.2: Drug dissolution profile of formulation F5

Time (sec)	Absorbance	Conc (µg/ml)	Amt (mg)	% D.R	% D.U	log % D.R	log % D.U
30	0.024	5.581	5.002	25.01%	74.99%	1.39	0.114
60	0.048	11.16	10.044	50.22%	49.78%	1.70	0.176
90	0.064	14.8837	13.395	66.975%	33.025%	1.825	0.748
120	0.078	18.1395	16.325	81.625%	18.375%	1.911	0.832
150	0.092	21.39	19.251	96.255%	3.745%	1.983	0.991

Surface pH of the films:
pH of the film was measured and was found to be in between 6.2- 6.8 for all the formulations.

Stability Studies:
Fast dissolving films of Nadolol were found to be physically and chemically stable as they shown no significant change in terms of physical characteristics (no discolouration and no change in shape), dissolving time and drug content under the kept storage conditions.

Table 4.4.8: Stability studies results.

S.No	Characteristic Property	Observation
01.	Colour	Transparent
02.	Folding endurance	256
03.	pH	6.4
04.	Dissolving time	30 sec
05.	*In vitro* dissolution	97.5% and 98.3% at 2 and 4 min respectively

CONCLUSIONS:

The prepared Nadolol oral films F5 was more effective and was evaluated for folding endurance, thickness, weight variation test, surface pH, content uniformity, dissolving time, &*in vitro* dissolution. Drug and excipients studies were done using FTIR. Oral films of Nadolol were formulated using HPMC E50, HPMC K_4M as a film forming agent and propylene glycol as plasticizer. The solvent casting method was used for the preparation of films. As the drug solubility was found to be limited solid dispersions were prepared using PEG 6000 as hydrophilic carrier by solvent evaporation method. No drug–excipients interaction was observed. The characterization studies depict the purity of drug & all the excipients used in the formulation. The IR spectrum of mixture of Nadolol with all other excipients does not show any changes which indicate its compatibility with other excipients.

Finally we conclude that the prepared Nadolol oral films f_5 shows the optimum bioavailability and all the evaluation parameters were clear thus they can be used as an alternative dosage forms for the bioavailability.

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