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Formulation and Evaluation of Fast Dissolving Buccal Film Containing Isradipine Solid Dispersion

M. Sri rekha[1]*, SK. Shaheda Sultana[1], K. Mahathi[1], P. Parveen[1], B. Prathima[1], A. Seetha devi[1]
1. Hindu college of pharmacy, Guntur, Andhra Pradesh, India.

ABSTRACT

The present work aimed at preparing fast dissolving buccal films of Isradipine solid dispersion, since Isradipine is a poorly soluble drug and the rate of absorption is often controlled by the rate of dissolution. The purpose of developing a dosage form for a very quick onset of action and for improved bioavailability along with the convenience of administration i.e. without the problem of swallowing and using water. The rate of dissolution can be increased by incorporating the drug in a fast dissolving buccal film as a solid dispersion that prepared using polyethylene glycol (PEG4000) or polyvinyl pyrrolidone (PVP k30). The fast dissolving films of Isradipine solid dispersion were prepared by solvent casting method using Lycoat RS720 polymer and glycerin as a plasticizer. The formulated films were evaluated for their physiochemical parameters like disintegration time, surface pH, thickness & weight of the films, percent moisture absorption, folding endurance, drug content and stability testing. Different factors affecting the dissolution rate of solid dispersion and fast dissolving film were studied. It was seen that as the ratio of drug to PEG4000 or PVP k30 in solid dispersion increased the release rate increased and the solvent evaporation method gave greater drug release than fusion method. In fast dissolving film it was seen that as the concentration of Lycoat RS720 increased the release rate decreased and as the concentration of glycerin increased the release rate increased. Formulation F6 showed 98.89% drug release from the film within 7 minutes which is an essential character for faster absorption.

Keywords: Fast dissolving buccal film, Isradipine, Solid dispersion, Lycoat RS720, solvent casting method.

*Corresponding Author Email: rekhashankarsutari@gmail.com
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INTRODUCTION

There is always increasing demand for patient convenience and compliance related research. Among the various routes, the oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance.[1] About 60% of all the formulations are solid dosage form. The most popular oral solid dosage forms are tablets and capsules. Generally geriatric, pediatric and bedridden patient as well as travelling patients who may not have ready access to water experience difficulties in swallowing the conventional oral dosage form.[2] Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance.[3] To overcome this problem a novel formulation was developed i.e. oral fast dissolving films. Fast dissolving buccal film is new oral drug delivery system. This delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue (buccal/sublingual), instantly wet by saliva, then film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption.[4,5] This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment. Drug delivery via the oral mucosa is a promising route, when one wishes to achieve a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism.[1] Buccal films offer an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage. Also large surface area of absorption, easy ingestion & pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug delivery.[6,7] The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament[3]. 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, good mouth feel and improved patient compliance.[8,9] These films have potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also have been used for local action.[10,11] Among the plethora of avenues explored oral films gain more attention as it emerging new platform for pediatric and geriatric patients.[3] Oral fast dissolving films are useful for the pediatric and geriatric patients and also for the patients suffering from diarrhea, acute pain,

emesis, allergic attacks, cough, asthma, hypertension, congestive heart failure, migraine, mental disorder, bedridden patients etc. where an ultra rapid onset of action required[2,3]. Isradipine (dihydropyridine class) is a long-acting calcium channel blocker used as an anti-hypertensive and in the management of angina. Isradipine Like other calcium channel blockers, acts by relaxing the arterial wall smooth muscle, decreasing total peripheral resistance and hence reducing blood pressure; in angina it rises blood flow to the heart muscle.[4] Isradipine is a poorly soluble drug belongs to BCS class II and the rate of absorption is frequently controlled by the rate of dissolution. The rate of dissolution can be enhanced by incorporating the drug in a fast dissolving dosage form as a solid dispersion.[5] The half life of Isradipine is 8hrs and it undergoes hepatic metabolism. The absolute oral bioavailability is about 15-24%[12]. The present work was aimed to improve the bioavailability and efficacy of Isradipine by preparing rapidly dissolving buccal films. Solid dispersion is among varies techniques have been used to increase the solubility and dissolution rate of poorly water soluble drugs, it is the most frequently and effectively used one.[13] The methods used to prepare solid dispersion include fusion (melting) method, solvent evaporation method and solvent wetting method.[14] Different water-soluble carriers have been employed for preparation of solid dispersion; the most common ones are various grades of polyethylene glycols (PEG), polyvinyl pyrrolidone (PVP), β- cyclodextrin, lactose, and hydroxypropylmethylcellulose (HPMC).[15]

MATERIALS AND METHOD

Materials

Isradipine was obtained from Celon labs, Hyderabad. PEG 6000, PVP K30, and were obtained from Sigma – Aldrich, USA. Lycoat RS720 was obtained as a gift sample from Roquettepharma Pvt. Ltd,USA. Glycerin was obtained from GCC (UK), tartaric acid from Sun pharma Pvt. Ltd, Mumbai, India. Sorbitol, Polaxamer 407 was purchased from LobaChemie Pvt.Ltd, Mumbai, India. All other chemicals used were analytical grade and were used without purification. Distilled water was used in the study.

Methods

Preformulation Studies

Preformulation study may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. During this

evaluation, possible interaction with various inert ingredients intended for use in final dosage form was also considered.

Drug-Excipients compatability study by FT-IR spectroscopy

FT-IR Spectroscopy of pure drug (Isradipine) and its formulations were carried out on Bruker FT-IR16000 model to investigate any possible interaction between the drug and the utilized polymers (PEG 4000, PVP K30, Lycoat RS720). The samples were finely grounded with KBr to prepare the pellets under a hydraulic pressure of 600 psi and a spectrum was scanned in the wavelength range of 400 and 4000 cm-1 using Bruker FT-IR spectrophotometer. The compatibility of drug in the formulation was confirmed by comparing FTIR spectra of pure drug with FTIR of its formulation.

CONSTRUCTION OF CALIBRATION

Preparation of Standard Stock Solution

10 mg of Isradipine was accurately weighed and dissolved in 100ml volumetric flask containing phosphate buffer of pH 6.8 and subjected to sonication. The volume is made up to 100ml with pH 6.8 phosphate buffer to produce a concentration of 100µg/ml, which is a stock solution.

Determination of λ_{max}

Above solution was scanned between the range of 200-400nm by Shimadzu 1700 model UV spectrophotometer. From the scan it was concluded that the λ_{max} of Isradipine was 285nm.

Calibration curve of Isradipine in phosphate buffer of pH 6.8

From the standard stock solution aliquots 1ml, 2ml, 3ml, 4ml and 5ml were pipette out into 10ml volumetric flask .The volume was made up with phosphate buffer of pH 6.8 to get final concentration of 10, 20, 30, 40 and 50µg/ml respectively. The absorbance of each concentration was measured at λ_{max} 285nm using UV Visible spectrophotometer against blank (phosphate buffer of pH 6.8).

Preparation of Solid Dispersions

Melting method (fusion method)

Solid dispersion of Isradipine in PEG4000 or polyvinyl pyrollidone (PVP K30) containing three different ratios (1:1, 1:1·5 and 1:2 w/w) as seen in Table(1) were prepared by fusion method. Required amount of drug and polymer were mixed in china dish, the mixture was then heated using water bath at 70°C till it was completely melted, continues stirring during the melting was carried out to prevent the separation of the constituents. The melt was then rapidly solidified. The solidified mass was then crushed, size reduced in a mortar and pestle and sieved through 0.63 mm sieve. The product obtained was kept in a desiccator for further treatment.[16]

Solvent evaporation method

Solid dispersion of Isradipine in PEG4000 or PVP K30 containing three different ratios (1:1, 1:1·5 and 1:2 w/w) as seen in Table (1) were prepared by solvent evaporation method. Isradipine and the polymer were dissolved in 15ml of methanol. The solvent was stirred on magnetic stirrer at temperature 40°C and then evaporated in oven at 40°C. The solidified mass was then crushed, size reduced in a mortar and pestle, sieved through 0.63 mm sieve and stored in desiccators a for further treatment.[1]

Table 1: Different formulas of Isradipine solid dispersion

Formula code	Isradipine (mg)	PEG 4000 (mg)	PVPK30 (mg)	Method
SD1	500	500	-	Fusion
SD2	500	750	-	Fusion
SD3	500	1000	-	Fusion
SD4	500		500	Fusion
SD5	500		750	Fusion
SD6	500		1000	Fusion
SD7	500	500		Solvent evaporation
SD8	500	750		Solvent evaporation
SD9	500	1000		Solvent evaporation
SD10	500		500	Solvent evaporation
SD11	500		750	Solvent evaporation
SD12	500		1000	Solvent evaporation

Evaluation of Solid Dispersions

Drug content in solid dispersions

An accurately weighed and transferred 10 mg of solid dispersion into 100 ml volumetric flask and dissolved in phosphate buffer of pH 6.8. The volume was made up to the mark with phosphate buffer of pH 6.8. After suitable dilution, the absorbance of the above solution was measured at 285 nm using appropriate blank solution. The drug content of Isradipine was calculated using calibration curve.

***In-vitro* dissolution studies**

Dissolution study was performed for all the prepared solid dispersion by using USP-II paddle apparatus. Samples equivalent to 5mg of Isradipine were added to the 900 ml of phosphate buffer of pH6.8 at 37 ± 0.5°C and stirred at 50 rpm. An aliquot of 5 ml was withdrawn at different time intervals 5, 10, 15, 20, 30, 40, 50 and 60 mins with a syringe filter. The withdrawn volume was replaced immediately with the same volume of fresh medium in order to keep total volume constant. The filtered samples were assayed spectrophotometrically at 285 nm using phosphate buffer of pH 6.8 as blank. The mean of at least three determinations were used to calculate the

drug release.[18] The solid dispersion showing better dissolution profiles was selected and used in the preparation of fast dissolving buccal films.

Preparation of Fast Dissolving Films

Six formulations were prepared (F1-F6), with their composition shown in Table (2), using solvent casting method as seen in Figure (1).[19] The films were prepared using a Lycoat RS720 polymer and Glycerin as a plasticizer in different concentrations to study the effect of Polymer and plasticizer concentration on the physicochemical properties. Each film with surface area approximately 6 cm2 as seen in Figure (2) is loaded with 16mg solid dispersion which is equivalent to about 5 mg of Isradipine. The area and number of films prepared for each batch can be calculated as follows:

Total area of petri dish = 71 cm2

Each film area = 2×3 = 6 cm2

Number of films in batch =71/6 =11.8

Approximately 12 films

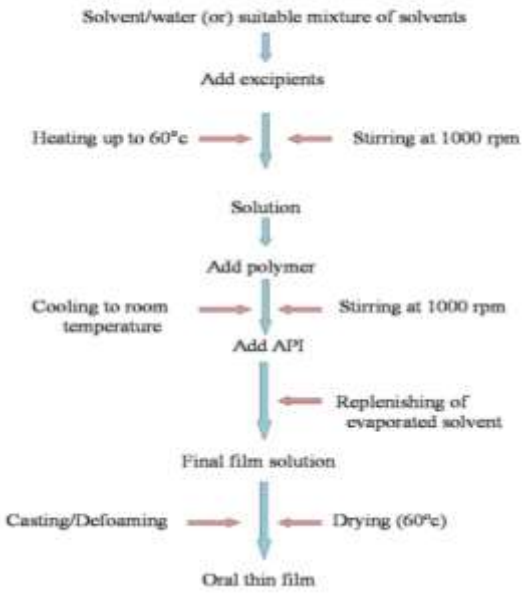

Figure 1:

Figure 2: The prepared buccal films

Table 2: Different formulas of Isradipine solid dispersion buccal films.

Substances (mg)	Formula code					
	F1	F2	F3	F4	F5	F6
Isradipine solid dispersion	16	16	16	16	16	16
Lycoat RS720	40	45	50	40	40	40
Glycerin	10	10	10	7.5	15	20
Tartaric acid	4	4	4	4	4	4
Poloxamar 907	2	2	2	2	2	2
Sorbitol	4	4	4	4	4	4
Water (mL)	10	10	10	10	10	10

Evaluation of Fast Dissolving Film

Visual inspection

Properties such as homogeneity, color, transparency and surface of the oral films were evaluated for all the prepared oral films.[20]

Weight variation

The weight variation of the buccal film was done by weighting twenty films individually and the average weight was calculated. For the film to be accepted, the weight of not more than two films deviate from the average weight by no more than 7.5% and no film deviates by more than 15%.[21]

Thickness measurements

The thickness of each film was measured at five different locations (centre and four corners) using micrometer screw gauge. The data are represented as a mean± Standard deviation (SD) of three replicate determinations.[22] This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.[18]

Folding endurance test

It gives an indication about brittleness of the film. The folding endurance of randomly selected films was determined by repeatedly folding one film at the same place till it break or folded maximum 250 times and the values were reported.[23]

Surface pH

The surface pH of fast dissolving film was determined in order to find out the possible any *in-vivo* side effects. Commercially available pH strips were used for this purpose. The film to be tested was placed in a petri dish and was slightly wetted with water. The pH was measured with pH strip in contact with the surface of the oral film. The average of three determinations for each formulation was determined.[24]

Swelling index

The studies for swelling index of the film are conducted in stimulated salivary fluid. The film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing the film is submerged into 50 ml of stimulated salivary medium contained in a mortar. Increase in weight of the film is determined at each interval until a constant weight is observed. The degree of swelling is calculated using the following formula.[25]

$$\mathbf{SI = W_t - W_o / W_o}$$

Where SI is the swelling index,

W_t is the weight of the film at time "t", and

W_o is the weight of film at t = 0

Percentage moisture absorption (PMA)

The PMA test was carried out to check the physical stability of the mouth dissolving film at high humid conditions. Three films were taken, weighed accurately and placed in a desiccator containing saturated solution of aluminum chloride, keeping the humidity inside the desiccators at 79.5 % RH. After 72 hours the films were removed, weighed and percentage moisture absorption was calculated by using the following formulae.[25]

PMA = (Final weight – Initial weight)/ Initial weightx 100

Disintegration time

The disintegration time was measured using modified disintegration method. For this purpose a petri dish was filled with 10 ml of water. The film was carefully put in the centre of petri dish. The time for the film to completely disintegrate in to fine particles was noted in Table 3.[26]

Drug content

Drug content of all films was determined by UV-Spectrophotometric method. For this 2x3 cm2 strip was dissolved in 100ml of phosphate buffer of pH 6.8 and solution was stirred for 1 hr on a magnetic stirrer. The solution was filtered and absorbance was recorded at 285 nm. Drug content was calculated by using standard curve of drug.[18]

***In-vitro* Dissolution Study**

The *in vitro* dissolution test was carried out in USP-II a paddle dissolution apparatus. In order to mimic the *in vivo* adhesion and to prevent the film strips from floating, each film strip was fixed to a rectangular glass slab and placed at the bottom of the dissolution vessel prior to starting the dissolution test. The dissolution test was performed using 300 ml of simulated salivary fluid (pH 6.8 phosphate buffer) maintained at 37±0.5°C and stirred at 50 rpm. Samples of 5 ml were withdrawn at 1, 3, 5, 7, 10, 15, 20, 25, 30, 45 and 60min, and the same volume was replenished with fresh buffer. The samples were filtered through a 0.45µm membrane filter and analyzed by UV visible spectrophotometer at 285 nm.[27,28]. The optimized formulation (F6) from the results of *in vitro* dissolution study was further evaluated for *ex vivo* permeation, stability studies and characterization by DSC.

Ex-Vivo Permeation Studies

Ex- vivo skin permeation study was performed by using a Franz diffusion cell with a receptor compartment capacity of 10 ml. The receptor compartment of the diffusion cell was filled with phosphate buffer of pH 6.8. Porcine buccal mucosa membrane was mounted between the donor and receptor compartment. The formulated film of 1×1cm diameter was cut and placed over the porcine oral mucosa membrane. The donor compartment was then placed and fixed over it with the help of rubber bandages. The whole assembly was placed on a magnetic stirrer, and the solution in the receptor compartment was continuously stirred. The temperature was maintained at 37 ± 2ºC. Samples of 1 ml were withdrawn at time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 minutes and were analyzed at 285 nm spectrophotometrically for drug content against blank. The receptor phase was replenished with an equal volume of phosphate buffer each time the sample was withdrawn. The percentage of the released drug was calculated and plotted against time.[29]

Figure 3: Franz diffusion cell for *ex vivo* permeation study

Stability Studies

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as

temperature, humidity and light. For this films were packed in laminated aluminum foil and were subjected to conditions of 40°C, 75% RH in stability chamber (Environmental test chamber, CAT No. MSW-127)for a period of 45 days. The samples were withdrawn after 45 days and analyzed for drug content.

Characterization of Film by DSC

The physical state of the drug in the formulation was characterized by using differential scanning calorimeter (DSC 60, Shimadzu Corporation, Japan). Analysis was performed by heating 10 mg of sample on aluminum crimp pans at a rate of 10^0c/min in a nitrogen atmosphere (50ml, min-1) using Differential Scanning Calorimeter.

RESULTS AND DISCUSSION

Drug- Excipients compatibility by FTIR spectroscopy

Pure drug Isradipine showed sharp characteristic peaks at 3657 cm^{-1}(O-H stretching), 2924 cm^{-1} (C-H stretching), 1731 cm^{-1} (C=O stretching), 1645 cm^{-1} (C=N stretching), 1541 cm^{-1} (N-H bending), 1238 cm^{-1} (C-N vibrations). All the above characteristic peaks of drug appear in all other spectra of formulation of Isradipine solid dispersion and fast dissolving buccal film almost at the same wave number. From the results it was concluded that there was no appreciable change in position and intensity of peaks in all the formulations with respect to IR spectrum of pure Isradipine, indicates there was no interaction between drug and utilized polymers.

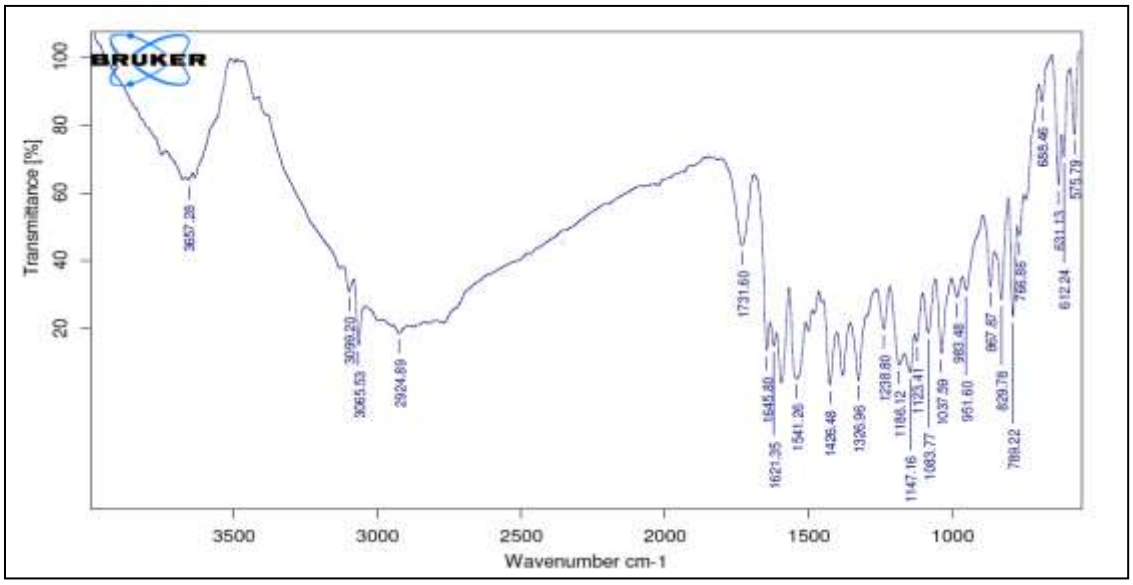

Figure 4: FT-IR spectrum of pure Isradipine

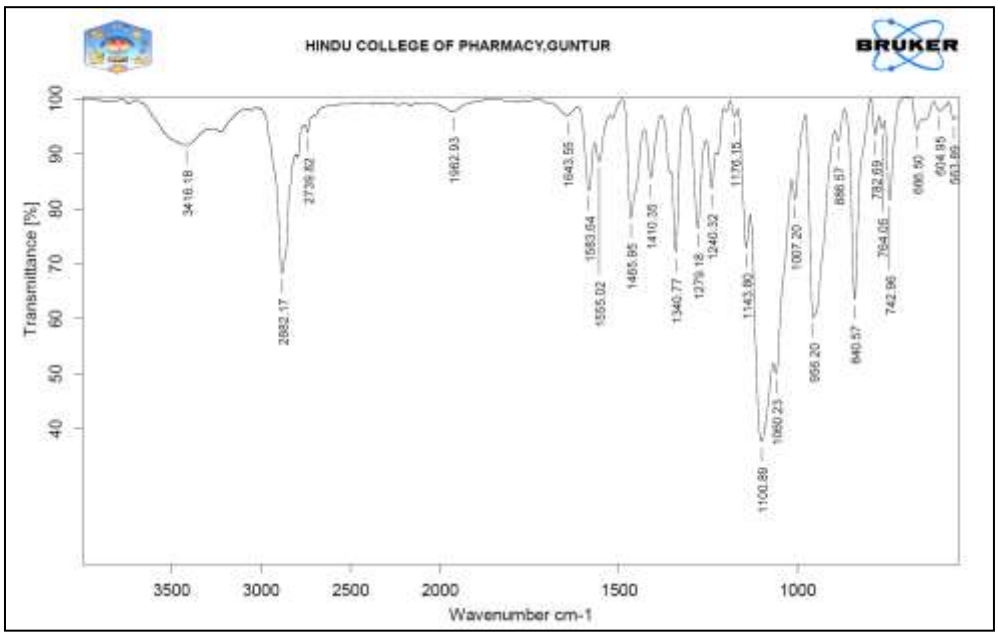

Figure 5: FT-IR spectrum of Solid dispersion

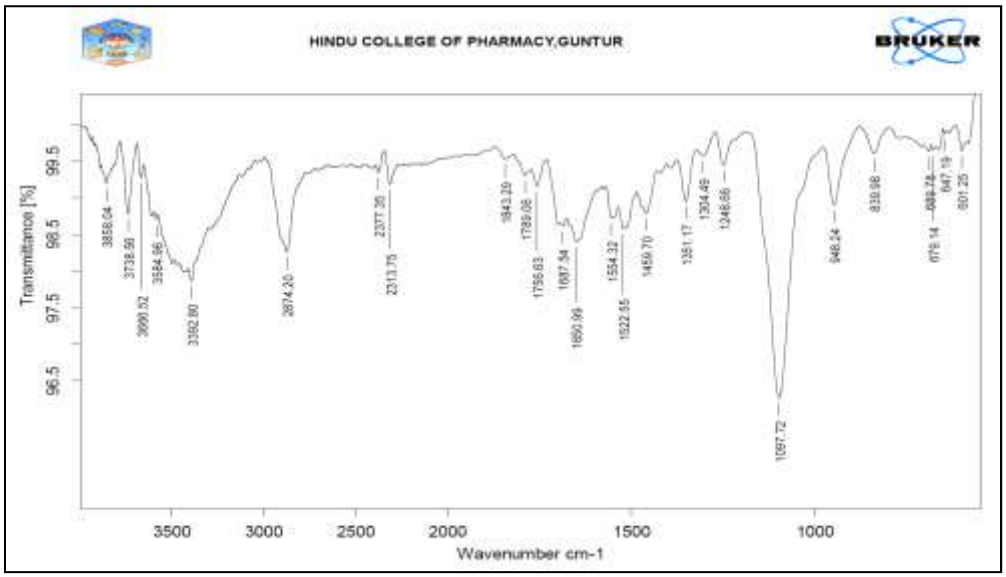

Figure 6: FT-IR spectrum of fast dissolving buccal film with Lycoat RS720

Calibration curve of Isradipine in Phosphate buffer of pH 6.8

Table 3: Absorbance-concentration profile for standard curve of Isradipine

Concentration (µg/ml)	Absorbance (nm)
0	0
10	0.037 ±0.004
20	0.079±0.002
30	0.126±0.005
40	0.174±0.008
50	0.211 ± 0.006

All values represent mean ± standard deviation (SD), n=3

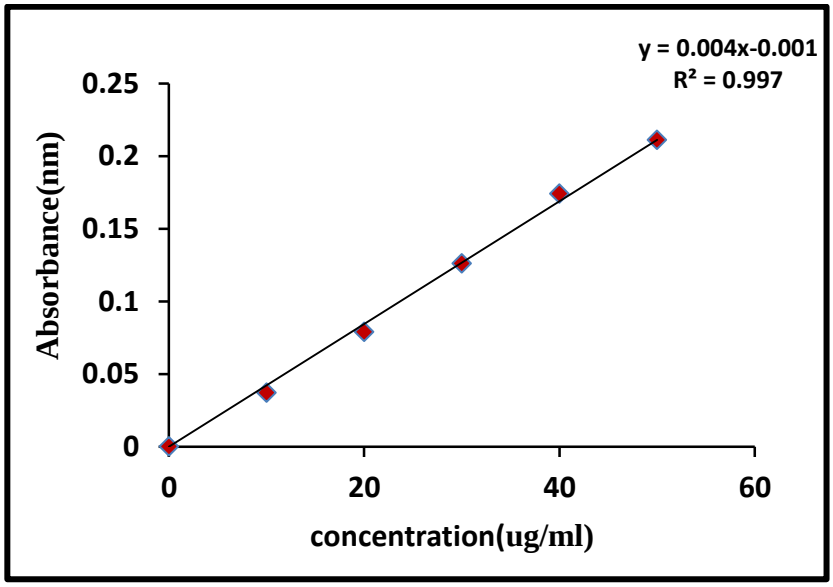

Figure 7: Standard plot of Isradipine in Phosphate buffer of pH 6.8

Drug content in solid dispersions

The drug content of the prepared solid dispersions was found to be in the range 87.12-99.30%. All preparations met the criteria of British Pharmacopeia content uniformity (85- 115) %. On this basis, it was found that the drug was dispersed uniformly throughout the solid dispersion. The results indicating that application of the solvent evaporation method was the best method for the preparation of solid dispersions with high content uniformity.

Table 4: Drug content of Isradipine solid dispersions with PEG 4000 and PVP K30

Formula code	Drug content	Formula code	Drug content
SD1	87.12±3.02	SD7	96.00±1.00
SD2	86.60±2.37	SD8	97.34±0.32
SD3	87.60±1.55	SD9	99.30±0.23
SD4	88.40±1.63	SD10	93.60±0.43
SD5	87.6±2.41	SD11	99.01±0.40
SD6	86.32±1.73	SD12	97.05±0.71

***In-vitro* dissolution studies**

The prepared solid dispersion formulations were subjected to *invitro* dissolution studies and studied for variables affecting the dissolution profile of Isradipine. The results were depicted in Figure 8. From the *In-vitro* release data, it was concluded that among all the formulations solid dispersion SD9 made by solvent evaporation method showed maximum drug release i.e. 97.06% at 60 min.

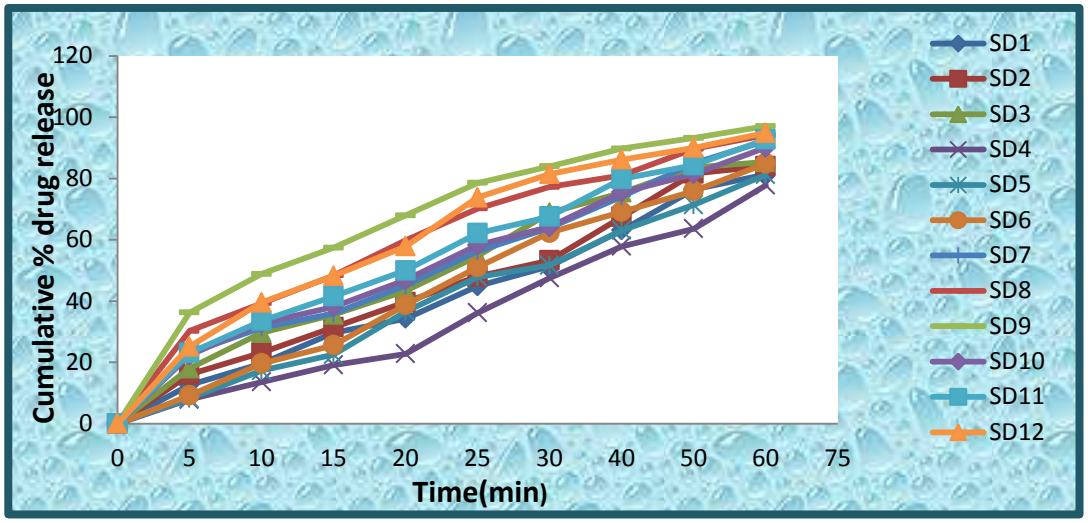

Figure 8: Drug release profiles of Isradipine solid dispersions

Variables affecting the dissolution profile

Effect of solid dispersion formation

Figure (9) showed the effect of solid dispersion formation on the release of Isradipine. It was seen that the release of Isradipine increased significantly when it formulated as a solid dispersion. 97.06% of drug was released from solid dispersion at 60 minutes in comparison with 58.34% of drug release when it is found in free form. The increased dissolution rate from solid dispersion may be due to reduction in particle size to molecular level when the carrier brings the drug into the dissolution medium. The presence of carrier may also prevent aggregation of fine drug particles thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer resulting in increased interfacial tension between the medium and drug and, hence, the higher dissolution rate. The presences of carrier polymer also inhibit crystal growth of the drug which facilitates faster dissolution.[30]

Effect of drug to polymer ratio

Formulations SD7-SD12 were used to study the effect of drug to polymer ratio and results were showed in Figure (10,11). It was seen that as the amount of PEG4000 (or) PVP increased the release rate increased significantly. It was observed that as the ratio of (drug: PEG4000 or PVP) increased from 1:1to 1:2 the drug release was increased, where at 60 minutes 92.29% and 97.06% of drug released from (1:1) and (1:2) of (drug:PEG4000) solid dispersion respectively, while 90.10% and 94.87% of drug was released from (1:1) and (1:2) of (drug: PVP) solid dispersion respectively. Since both polymers of PEG4000 and PVP are water soluble carriers, so increase their amount in solid dispersion leading to increase the wettability and dispersibility of drug from the dispersion resulting in increased dissolution of drug.

Effect of polymer type

Formulations SD9and SD12 were used to study the effect of polymer type on the release of drug from solid dispersion where PEG4000 and PVP were used in SD9and SD12 respectively. It was observed that 97.06% of drug was released from SD9 where as 94.87% drug was released from SD12 at 60 min. From the results it was concluded that the release of drug from solid dispersion containing PEG4000 was greater than that of solid dispersion containing PVP, this may be due to the more water solubility and hydrophilicity of PEG4000 than PVP.

Effect of method of solid dispersion preparation

Figure (13) shows the effect of method of preparation of solid dispersion on the release of Isradipine, formulations SD3 and SD9 are used for this purpose. It was observed that 85.40% of drug was released at 60 min from solid dispersion SD3 made by fusion method where as 97.06% drug was released at 60 min from solid dispersion SD9 made by solvent evaporation method. From the results it was concluded that more drug release from solid dispersion made by solvent evaporation method than solid dispersion made by fusion method.

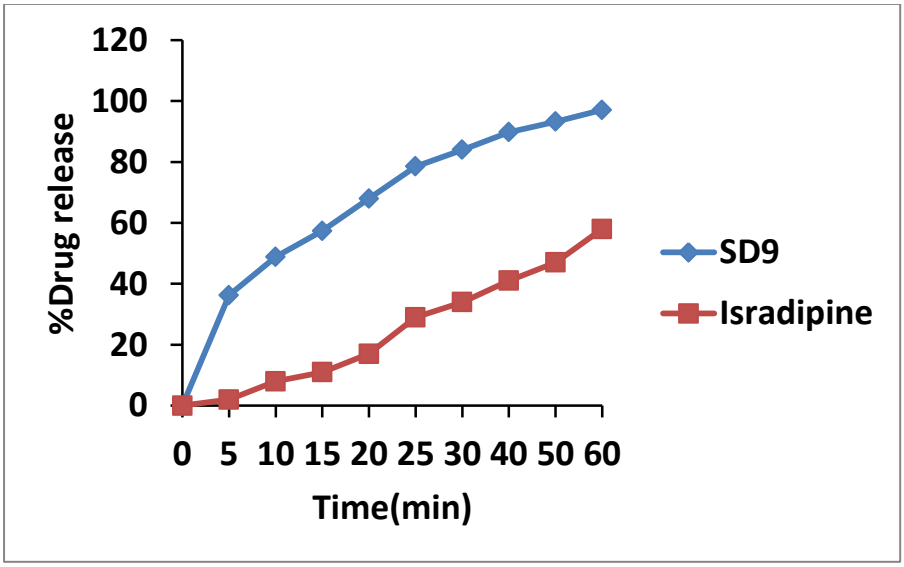

Figure 9: The effect of solid dispersion formation on the release profile.

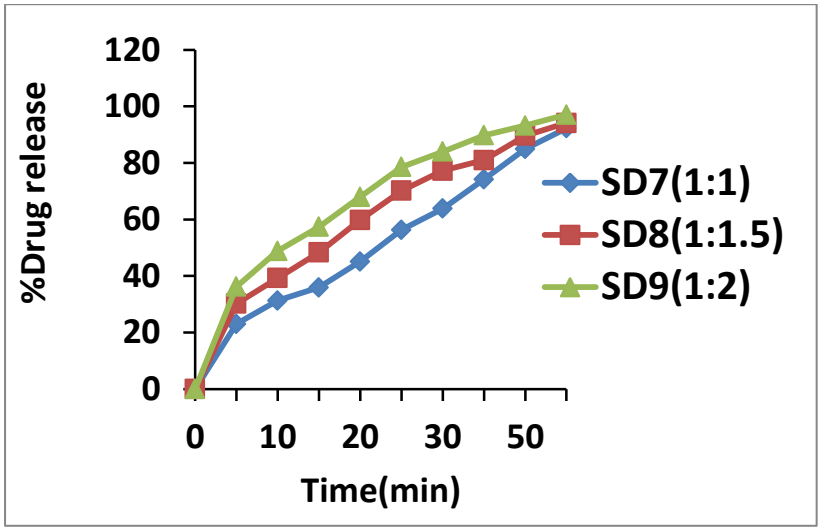

Figure 10: The effect of (Isradipine: PEG4000) ratio on the release profile.

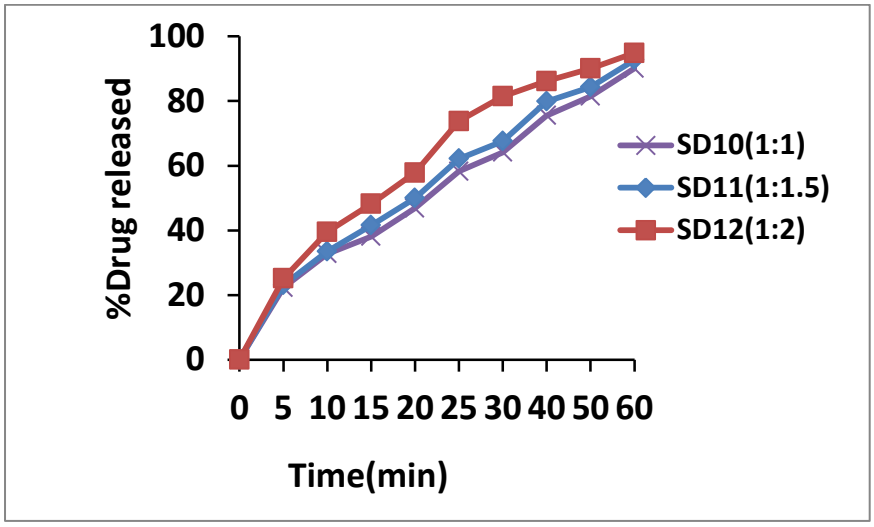

Figure 11: The effect of (Isradipine: PVP) on the ratio on the release profile

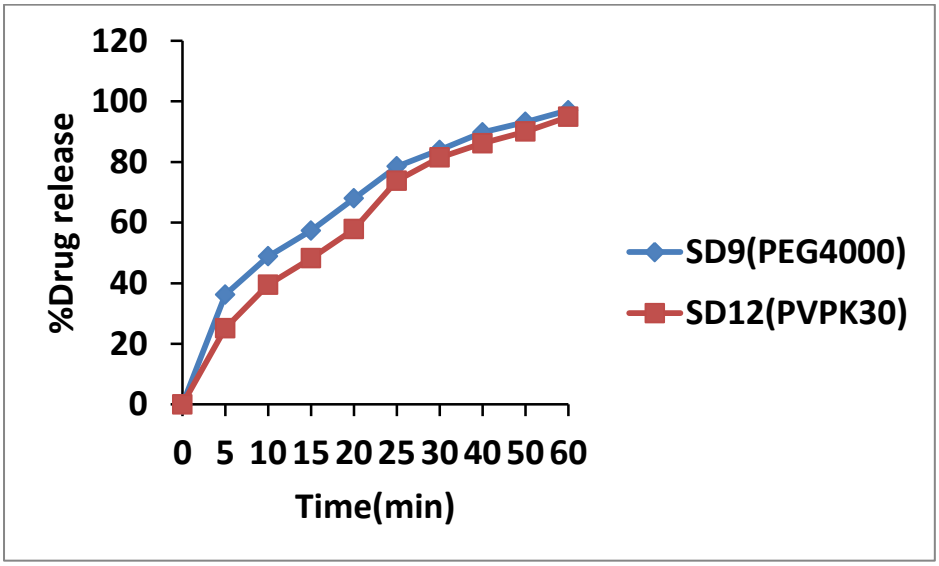

Figure 12: The effect of polymer type release profile.

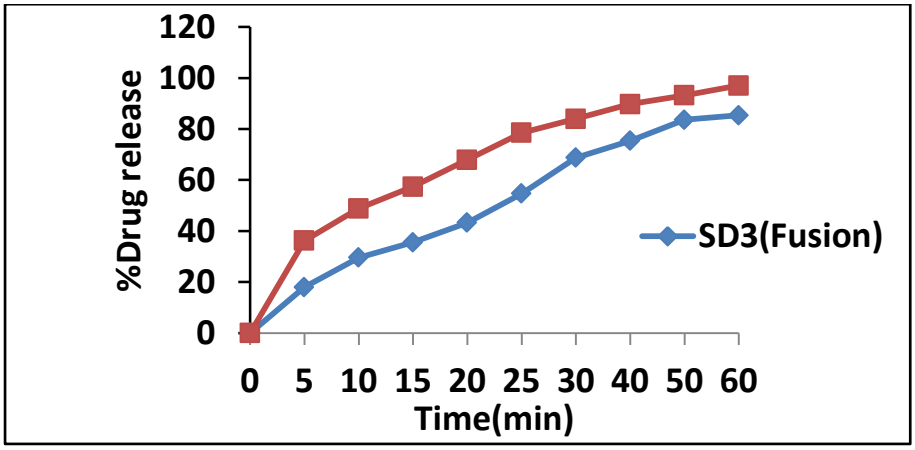

Figure 13: The effect of method of preparation of Solid dispersion on the release profile.

Therefore it can be concluded that SD9 formulation showed high drug content 99.30% and improved dissolution profile i.e. 97.06% at 60 min. So, it was selected as an optimized solid dispersion and further used in the preparation of fast dissolving buccal films.

Evaluation of fast dissolving films

All the prepared fast dissolving buccal films were evaluated for their physiochemical parameters like disintegration time, surface pH, thickness & weight of the films, PMA, folding endurance, drug content and the values are shown in Table 7.

Visual inspection

All the films prepared were found to be flexible, smooth, non sticky, homogenous, yellow colored and transparent with no visible particulate matter.

Weight variation

The observed results of Weight variation test are shown in Table 7. The results reveal that the weight of the films varied with polymer concentration. Increase in polymer concentration resulted in increase in weight of the film, but the increase was marginal.

Thickness measurements

Thickness of fast dissolving film depends on the concentration of polymer. Thickness of all mouth dissolving film was measured with micrometer screw gauge. The thickness was found to vary between 0.3 to 0.9 mm with very low standard deviation value (Table 7). A very low standard deviation value is indicating that the method used for the formulation of films gives films of uniform thickness and hence dosage accuracy in each film can be ensured. The results of thickness measurement indicating that as the concentration of polymer increases, thickness of fast dissolving film increases.

Folding endurance

Folding endurance gives an indication of about brittleness of the film. The folding endurance values of the prepared films ranged from 44.3 to 76.3 percent. The optimized F6 film was found to have folding endurance of 76.3%. The results showed that as the concentration of plasticizer increases, folding endurance of fast dissolving film increases.

Surface pH study

The surface pH of all the films was found between 6.5-6.7. The surface pH of all the formulations were close to the neutral pH, which indicated that films may have less potential to irritate the buccal mucosa, and hence more acceptable by the patients.

Swelling index

The swelling percentage of the formulated films was observed in phosphate buffer of pH 6.8 and results were shown in Table 7. From the results it was concluded that as the concentration of polymer increases, swelling index of fast dissolving film increases.

Percentage moisture absorption (PMA)

The observed results of PMA are shown in Table 7. The polymers used in the FDF formulations are expected to affect their moisture sorption properties. The percentage moisture uptake varied between approximately 2.3%-5.5%, with an overall trend of increase in moisture uptake with the increase in both plasticizer level and polymer ratio.

Drug content uniformity

Drug content in the films was evaluated and the values were found to be between 95.71 to 100.29 %. All the films were found to contain an almost uniform quantity of the drug, as per content uniformity studies indicating reproducibility of the technique. As per the USP requirements, the films found to meet the criteria for content uniformity (85- 115) %of the label claim. No significant difference in the drug content among the films indicated that the drug was dispersed uniformly throughout the 6 cm2 constant area of the film.

Disintegration time

It was observed that *in-vitro* disintegration time varies from 45-95 sec for all the formulations. *In-vitro* disintegration time of the films was found to be increased with increasing the concentration of the polymer, because high concentration of polymer resulted in a thicker gel upon contact with the medium, resulting in longer disintegration time. It was also found that the disintegration time increased none significantly on increasing the concentration of glycerin (plasticizer) from 7.5% to 20%. All the formulations found to gave minimum disintegration time as compared to other dosage forms, which is desirable for faster absorption.

Table 7: The physicochemical parameters of buccal thin films of Isradipine

FC	Weight (mg)	Thickness (mm)	Folding endurance (%)	Surface pH	Swelling index (%)	PMA	Drug content (%)	Disintegration time (sec)
F1	75.6±1.34	0.56±0.02	57.0±4.0	6.50±0.09	31.9±2.50	2.30±0.01	96.70±2.47	58.0±1.00
F2	79.3±2.33	0.60±0.01	52.0±7.0	6.74±0.03	44.8±2.60	2.56±0.06	99.28±5.90	73.0±4.00
F3	85.6±2.34	0.90±0.01	44.3±6.3	6.56±0.12	51.5±1.71	4.42±0.01	100.29±2.20	95.3±1.33
F4	73.3±2.33	0.73±0.02	51.3±1.3	6.60±0.04	26.1±0.69	2.05±0.06	96.51±3.80	45.0±1.00
F5	79.3±2.33	0.36±0.03	65.0±1.0	6.73±0.04	36.3±0.41	3.93±0.08	97.22±3.90	46.3±2.30
F6	83.6±1.24	0.30±0.01	76.3±2.3	6.69±0.03	44.0±4.10	5.34±0.06	99.71±1.36	47.0±4.00

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

***In-vitro* release studies**

The formulated films were subjected for *in vitro* dissolution studies and the results were shown in Table 8. Among the six formulations prepared, formulation F6 was found to release 99.89% drug with in 7 min which is desirable for faster absorption and rapid onset of action.

Table 8: *In vitro* drug release profiles of fast dissolving buccal films

Time (min)	Cumulative % Drug release						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**Isradipine tablet**
0	0	0	0	0	0	0	0
1	49.05±0.36	47.31±0.85	44.26±0.23	42.18±0.52	54.19±0.62	55.88±0.35	0.50±0.02
3	65.88±0.26	54.52±0.26	52.02±0.61	56.82±0.61	68.23±0.12	72.34±0.94	1.20±0.05
5	78.53±0.53	63.79±0.65	60.17±0.95	67.31±0.29	85.34±0.12	90.56±0.16	2.41±0.08
7	83.74±0.12	77.23±0.94	72.28±0.59	80.54±0.49	94.43±0.15	99.89±0.25	5.33±0.12
10	90.96±0.26	85.51±0.56	80.13±0.48	90.13±0.25	99.93±0.26	-	8.92±0.09
15	98.87±0.54	92.37±0.15	88.69±0.61	95.43±0.16	-	-	13.56±0.14
20	99.87±0.69	100.00±0.18	95.55±0.26	99.96±0.49	-	-	19.52±0.15
25	-	-	100.00±0.31	-	-	-	26.34±0.26
30	-	-	-	-	-	-	33.96±0.18
40	-	-	-	-	-	-	41.23±0.23
50	-	-	-	-	-	-	47.86±0.23
60	-	-	--	-	-	-	57.42±0.56

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

Figure-14

Figure-15

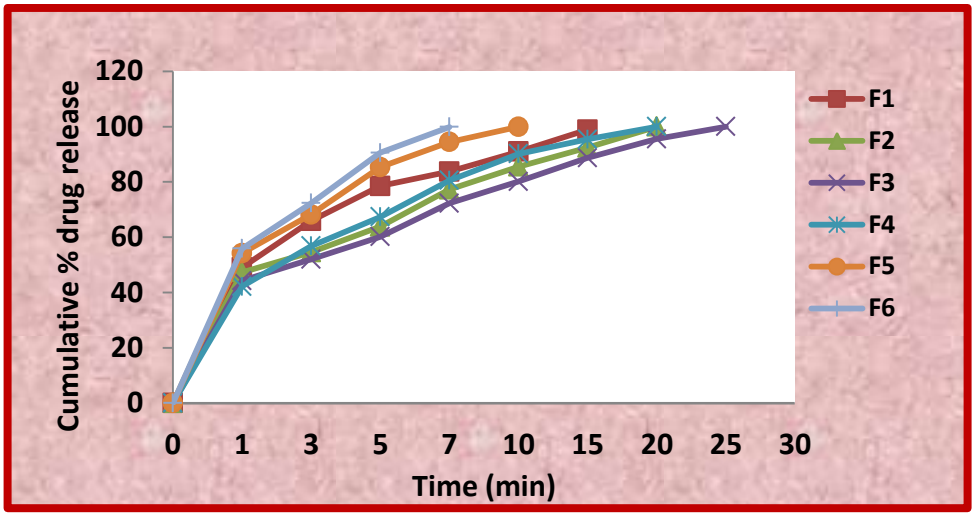

Figure 16: *In vitro* drug release profiles of fast dissolving buccal films

Variables affecting the dissolution profile of fast dissolving film

Effect of polymer concentration

Figure 17 shows the effect of changing concentration of Lycoat RS720 on the release of Isradipine where (40, 45, 50)% of Lycoat RS720 were used in formulations (F1,F2,F3) resulting in a release of (90.96, 85.51, 80.13)% in 10 minutes respectively. It was seen that as the concentration of the polymer increased, the drug release was found to be decreased due to the increase in the time required for wetting and dissolving the drug molecules present in the polymer matrices. This finding was also supported by the swelling behavior of the films where the maximum swelling was seen with formulations containing high proportion of polymer, although the marked increase in surface area can promote drug release but the increase in diffusion path length of the drug may paradoxically delay the release.

Effect of plasticizer concentration

Formulations F1&F4-F6 were used to study the effect of plasticizer (glycerin) concentration on the release of Isradipine from the fast dissolving film, where (7.5, 10, 15&20)% of glycerin were used in formulations (F4, F1, F5&F6) respectively. It was seen that as the concentration of glycerin increased from 7.5% to 20% the release rate increased significantly as seen in figure (18). It was seen that at 5 minutes the release rate increased from 67.31% to 90.56% when the concentration of glycerin increased from 7.5% to 20%. Since glycerin is water soluble, it will diffuse out of polymeric films into aqueous media generating void spaces in the film through which diffusion occurs more readily. The result being accelerated release profile of the active ingredient.

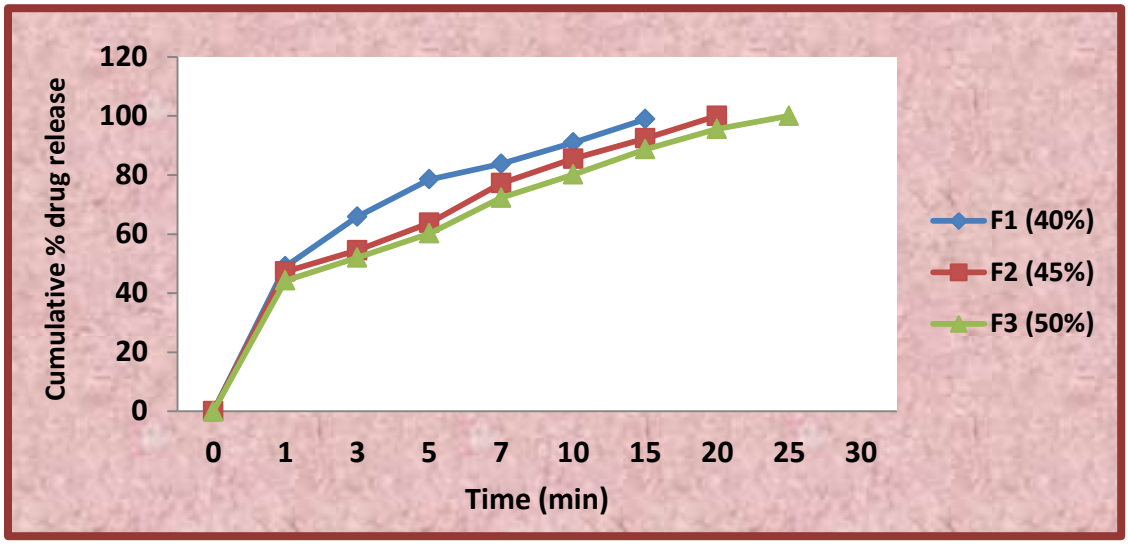

Figure 17: The effect of polymer concentration on the release of Isradipine from the fast dissolving buccal film.

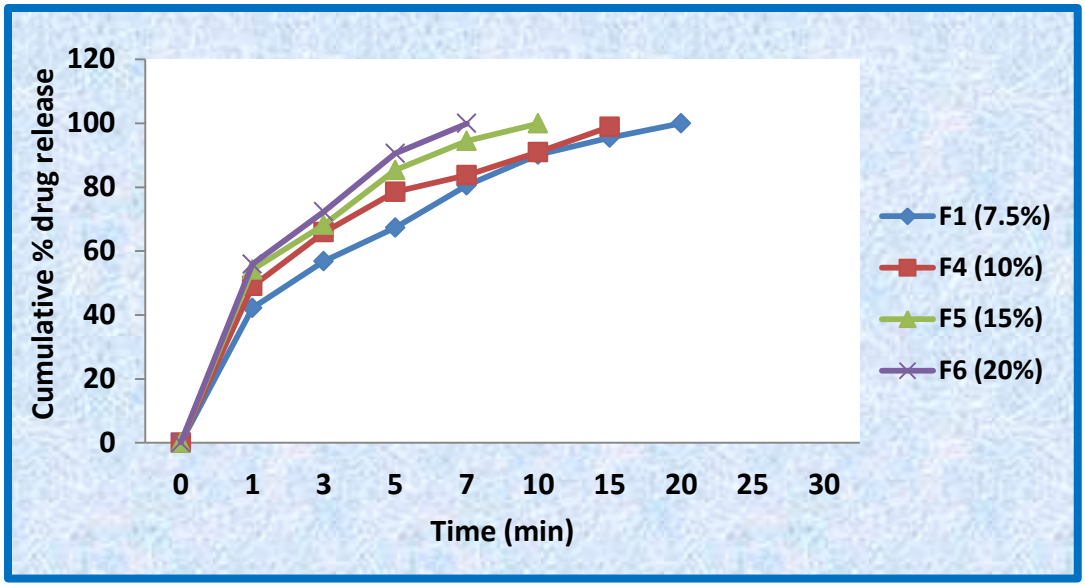

Figure 18: The effect of plasticizer (glycerin) concentration on the release of Isradipine from the fast dissolving buccal film.

Among the six formulations prepared, formulation F6 was found to be the best formulation in terms of drug release 100% within 7min which is desirable for faster absorption. So, formulation F6 was selected as a best formulation and further evaluated for exvivo permeation study, stability testing and characterization by DSC.

Comparison between the release profiles of Isradipine fast dissolving film (F6) and Isradipine oral tablet

As shown in figure 19 a comparison was made between the release profiles of Isradipine fast dissolving film (F6) and Isradipine oral tablet. It was found that there was significant increase in

the release rate when formulated as fast dissolving buccal film, 99.89 % drug release within 7min in comparison to 57.42% release in 60min indicating the satisfactory of fast dissolving film formulation that can be used as an alternative to the oral tablet.

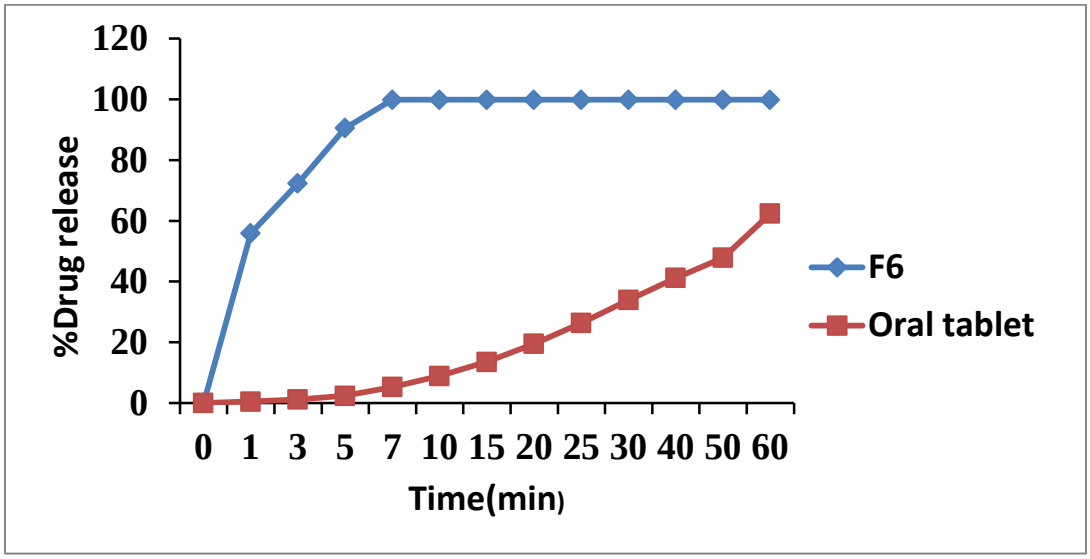

Figure 19: Comparison between the release profiles of Isradipine fast dissolving buccal film (F6) and Isradipine oral tablet.

***Ex-vivo* permeation studies**

Ex-vivo permeation study was performed on the F6 formulation because it gives the maximum drug release among all formulations. The percentage of the drug permeated was calculated and plotted against time and the results are shown in Table 9 and Figure 20.

Table 9: *Ex-vivo* Drug Permeation Data of Formulations F6

Time(min)	% Drug permeated
0	0
1	39.37
3	53.73
5	77.28
7	91.69
10	99.85
15	99.87
20	99.87

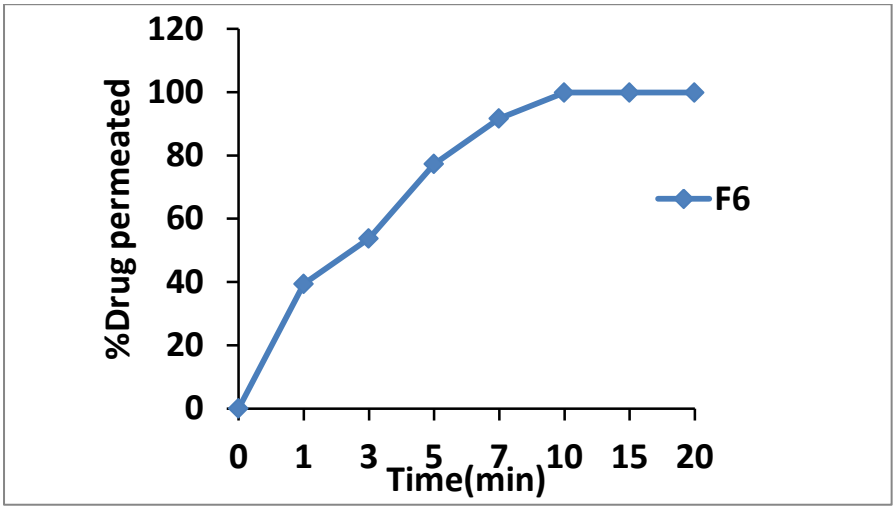

Figure 20: *Ex-vivo* Permeation Study of Formulation F6

Characterization of buccal film by DSC

DSC thermo graphic studies were carried out on Isradipine pure drug and formulation F6. The sharp endothermic peak for pure Isradipine drug indicates crystalline nature of Isradipine where as broad endothermic peaks for formulation indicates the conversion of Isradipine from crystalline structure to amorphous state while preparing solid dispersionwhich resulting in enhanced dissolution.

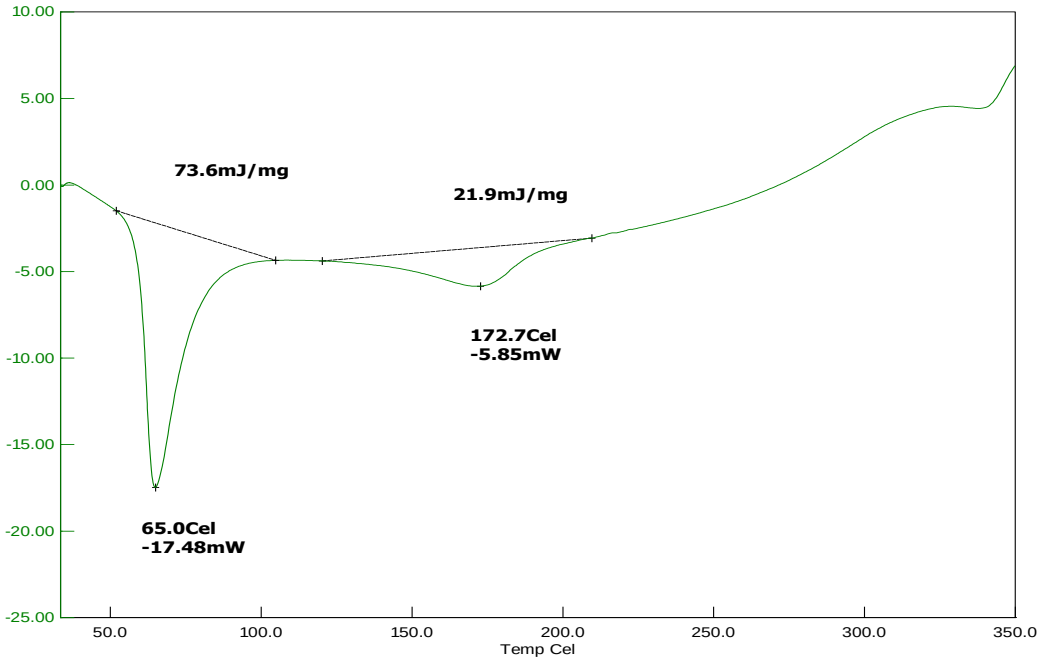

Figure 21: DSC of pure Isradipine pure drug

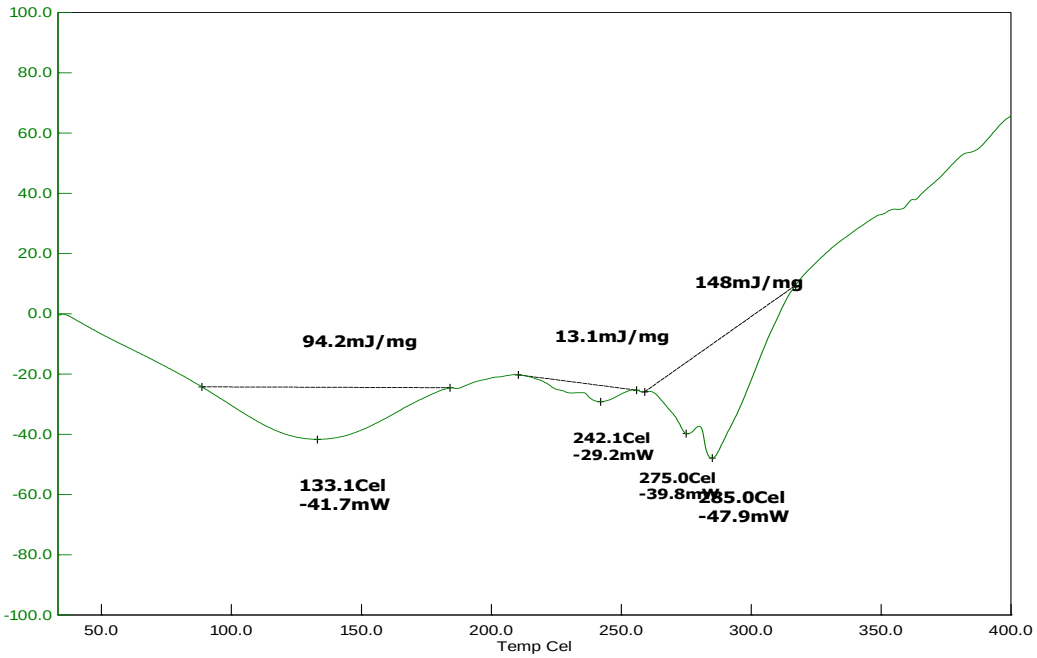

Figure 22: DSC of F6 Isradipine buccal film

Stability studies

The results of stability study are shown in Table 10. No significant changes were observed in folding endurance, surface pH, disintegration time and drug content but appearance was changed from yellow to slight yellow after 45 days storage at 40°C, 75% RH. The results indicating that the drug loaded buccal films of formulation F6 showed stability at accelerated stability conditions i.e. 40°C&75% RH.

Table 10: Stability Study for Formulation F6

Parameter	Initial	After 45 days on 40°C 75% RH
Appearance	Yellow, transparent	Slight yellow, transparent
Weight (mg)	83.6±1.24	80.1±0.31
Folding endurance (%)	96.3±2.30	84.7±1.90
Surface pH	6.69±0.03	6.56±0.01
Disintegration time(sec)	47.0±4.0	50.2±0.66
Drug content (%)	99.71±1.36	98.67±0.56

CONCLUSION

Isradipine was successfully formulated as solid dispersion and then orally fast dissolving films for better patient compliance and effective therapy. An optimization approach through design of experiments was adopted to select the optimum formulation parameters that produce fast dissolving buccal film of Isradipine with desirable properties. 99.89% of drug was released from F6 film within 7 minutes which was desirable for fast absorption. Hence fast dissolving films of

Isradipine was the most suitable dosage form for clinical use in the treatment of hypertension, where a quicker onset of action for a dosage form is desirable along with the improved bioavailability and convenience of administration. Thus fast dissolving buccal films were prepared and characterized for enhanced dissolution rate and easy administration to special categories of patients under the medication of Isradipine such as geriatrics who feel difficult to swallow.

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