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FORMULATION AND EVALUATION OF HERBAL FAST DISSOLVING BUCCAL FILM CONTAINING CURCUMIN

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ABSTRACT

The present work aimed at preparing fast dissolving buccal films of Curcumin solid dispersion, since Curcumin is a poorly soluble drug. The main aim of this is to provide quick onset of action, improved bioavailability and also to increase the patient convenience of administration. The rate of dissolution can be increased by incorporating the solid dispersed drug into film which are prepared by polyethylene glycol (PEG4000) and polyvinyl pyrrolidone (PVP k30) as polymers, Lycoat RS720 as a polymer and glycerine as a plasticizer using solvent casting method. The films were evaluated for their physiochemical parameters like disintegration time, surface pH, thickness, weight, percent moisture absorption, folding endurance, drug content and stability testing. It is concluded that as the ratio of drug to PEG 4000 or PVP k30 in solid dispersion increased the release rate increased, as the concentration of Lycoat RS720 increased the release rate decreased, as the concentration of glycerine increased the release rate increased and the solvent evaporation method gave greater drug release than fusion method. 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, Curcumin, Solid dispersion, Lycoat RS720, solvent casting method.

1. INTRODUCTION

There is always increasing demand for patient convenience. 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 which leads to high levels of patient compliance.[1] Generally geriatric, paediatric 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. Many paediatric 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. To overcome this problem a novel formulation i.e. oral fast dissolving films which is very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue (buccal /sublingual), instantly wet by saliva, and then film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication in mucosal cavity.[2] 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. 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.[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.[4] 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.[5]

A huge investigation exposed that turmeric and curcumin has an extensive variety of curative property such as antiinflammatory, antibacterial, antifungal, anticancer antispasmodic, antioxidant, antiamoebic, anti HIV, antidiabetic, antifertility etc. Curcumin, a golden color attained by Curcuma longa is been used from the time immemorial as a nutritional complement, coloring means, spice and also for therapeutic the purpose. It is also accounted that the curcumin is safe and sound up to 8g/day.[6] Curcuminioids, the oleoresins, resultant by ethanolic extraction of turmeric are mainly liable for golden colour and are believed liable

for the natural actions. In neutral and acidic situation curcumin shows bis keto form. In acidic condition curcumin performs as an influential hydrogen patron.[7] For improving solubility, dissolution behaviour and on set of action solid dispersion is one of the preferable techniques. It rivet a spreading of one or more drug component in an inert transporter or matrix in solid state set by melting, dissolution in solvent or melting solvent method. The method has been used for a broad range of weakly water soluble active ingredients such as Nimesulide, Tenoxicam, Nifedipine, Nimodipine etc.

The present work was aimed to improve the bioavailability and efficacy of Curcumin by preparing rapidly dissolving buccal films. Among varies techniques Solid dispersion have been used to increase the solubility and dissolution rate of poorly water soluble drugs, it is the most frequently and effectively used one. The methods used to prepare solid dispersion include fusion (melting) method, solvent evaporation method and solvent wetting method. 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 Hydroxyl propyl methylcellulose (HPMC).[7]

2. MATERIALS

Curcumin was obtained by the Sehat Pvt. Ltd., Gujarat, Himatnagar. PEG 6000, PVP K30, was obtained from Sigma – Aldrich, USA. Lycoat RS720 was obtained as a gift sample from Roquette pharma Pvt. Ltd, USA. Glycerin was obtained from GCC (UK), tartaric acid from Sun pharma Pvt. Ltd, Mumbai, India. Sorbitol, Polaxamer 407 was purchased from Loba Chemie Pvt.Ltd, Mumbai, India. All other chemicals used were analytical grade.

METHODS

2.1 Preformulation Studies

Preformulation studies characterize the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.

2.1.1. Drug-Excipients compatability study by FT-IR spectroscopy

FT-IR Spectroscopy of pure drug (Curcumin) and its formulations were carried out on Bruker FTIR16000 model to investigate any possible interaction between the drug and the utilized polymers (PEG 4000, PVP K30, Lycoat RS720). The compatibility of drug in the formulation was confirmed by comparing FTIR spectra of pure drug with FTIR of its formulation.

2.2 Construction of Calibration

2.2.1Preparation of Standard Stock Solution

10 mg of Curcumin 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.

2.2.2. Determination of λ max

Above solution was scanned between the range of 200-800nm by Shimadzu 1700 model UV spectrophotometer. From the scan it was concluded that the λmax of Curcumin was 421nm.

2.2.3. Calibration curve of Curcumin 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 421 nm using UV Visible spectrophotometer against blank (phosphate buffer of pH 6.8).

2.3. Preparation of Solid Dispersions

Melting method (fusion method)[8]

Solid dispersion of Curcumin 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.

Solid dispersion of Curcumin 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. Curcumin 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.

Table. 1: Formulation of Curcumin solid Dispersion.

Formulation code	Curcumin (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	Solvent evaporation
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

2.4. Evaluation of Solid Dispersions

2.4. 1. Drug content in solid dispersions

An accurately weighed 10 mg of solid dispersion was transferred 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 421 nm using appropriate blank solution.

2.4. 2. *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 Curcumin 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. The same volume volume was replaced with fresh buffer in order to maintain sink conditions. The samples were assayed spectrophotometrically at 421nm using phosphate buffer of pH 6.8 as blank.18 The solid dispersion showing better dissolution profiles was selected and used in the preparation of fast dissolving buccal films.

3. 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 "Fig. 1".[12] 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. Each film with surface area approximately 6 cm^2 as seen in "Fig: 2" is loaded with 16mg solid dispersion which is equivalent to about 5 mg of Curcumin. 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

Suitable mixture of solvents to this excipients are added

↓

Heated upto 60^0C and strirred at 1000rpm and forms Solution

↓

Add polymer and cooled to room temperature and stirred at 1000rpm

↓

Add API and allowed for evaporation of solvent

↓

Final Film Solution is defoamed and casted and dried at 60^0C

↓

Oral thin film is formed

"Fig. 1" Solvent Casting Method

Fig. 2: Films prepared.

Table. 2: Formulation of Curcumin solid dispersion buccal films.

Ingrediants (mg)	F1	F2	F3	F4	F5	F6
Curcumin solid Dispersion	16	16	16	16	16	16
Lycoat RS 720	40	45	50	40	40	40
Glycerin	10	10	10	7.5	15	204
Tartaric acid	4	4	4	4	4	4
Polaxamer 907	2	2	2	2	2	2
Sorbitol	4	4	4	4	4	4
Water (ml)	10	10	10	10	10	10

4. Evaluation of Fast Dissolving Film

4.1 Visual inspection: Properties such as homogeneity, colour, transparency and surface of the oral films were evaluated for all the prepared films.[10]

4.2. Weight variation

The weight variation of the buccal film was done by weighing 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 not more than 7.5% and no film deviates by not more than 15%.

4.3 Thickness measurements

The thickness of each film was measured at five different locations (centre and four corners) using micrometer screw gauge. 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.[9]

4.4 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.

4.5 Surface pH

The surface pH of film was determined in order to find out any possible 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.

4.6 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 pre-weighed 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.

SI = Wt – Wo / Wo

Where SI is the swelling index,

Wt is the weight of the film at time “t”, and

Wo is the weight of film at t = 0

4.7 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.

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

4.8 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.

4.9 Drug content: Drug content of all films was determined by UV-Spectrophotometric method. For this 2x3 cm^2 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 421nm. Drug content was calculated by using standard curve of drug.[9]

***4.10 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 421 nm. 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.

***4.11 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.[11]

4.12. 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.

5. RESULTS AND DISCUSSION

5.1 Drug- Excipients compatibility by FTIR spectroscopy

All the above characteristic peaks of drug in all other spectra of formulation of Curcumin solid dispersion and fast dissolving buccal film appear almost at the same wave number. From the results as shown in "Fig: 3" 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 Curcumin, indicates there was no interaction between drug and utilized polymers.

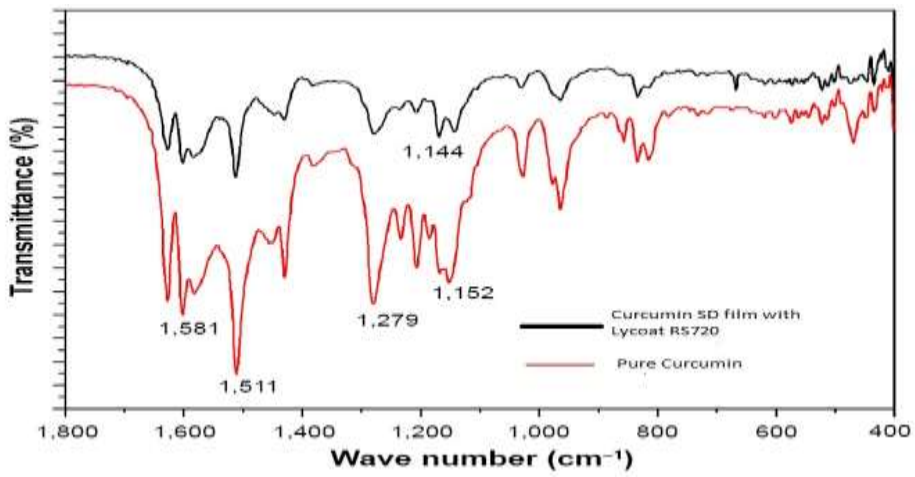

Fig. 3. FT-IR Spectra of Pure Curcumin and Curcumin SD Film with Lycoat RS720.

5.2. Calibration curve of Curcumin in Phosphate buffer of pH 6.8

Table: 3 Calibration curve of Curcumin in Phosphate buffer pH6.8

Concentration (µg/ml)	Absorbance(nm)
0	0
10	0.037±0.04
20	0.079±0.02
30	0.126±0.005
40	0.171±0.008
50	0.211±0.006

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

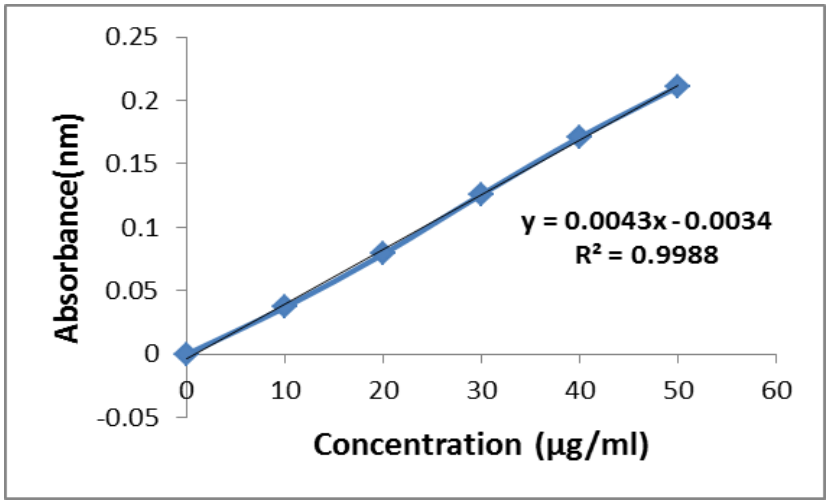

Fig. 4. Standard plot of Curcumin in Phosphate buffer of pH 6.8.

5.3. 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 Curcumin Solid Dispersions with PEG 4000 and PVP K30.

Formulation code	Drug content	Formulation code	Drug content
SD 1	87.12±0.02	SD7	96±0.12
SD 2	86.6 ±0.37	SD8	97.3±0.04
SD 3	87±0.55	SD9	99.3±0.32
SD 4	88. ±40.63	SD10	93.6±0.23
SD5	87.6±0.41	SD11	99.00.43
SD6	86.3±0.73	SD12	97.05±0.71

5.4. In-vitro dissolution studies

The prepared solid dispersion formulations were subjected to *in-vitro* dissolution studies and studied for variables affecting the dissolution profile of Curcumin. 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.

Variables affecting the dissolution profile

5.4.1. Effect of solid dispersion formation

It was seen that the release of Curcumin increased significantly when it was 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.

5.4.2. Effect of drug to polymer ratio: Formulations SD7-SD12 was 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.

5.4.3. Effect of polymer type: Formulations SD9and SD12 was 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.

4.4.4. Effect of method of solid dispersion preparation

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.

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.

5.5. 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 5.

5.5.1 Visual inspection

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

5.5.2. Weight variation

The observed results of Weight variation test are shown in Table 5. 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.

5.5.3. 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 5). 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.

5.5.4. 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.

5.5.5. 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.

5.5.6. Swelling index

The swelling percentage of the formulated films was observed in phosphate buffer of pH 6.8 and results were shown in Table 5. From the results it was concluded that as the concentration of polymer increases, swelling index of fast dissolving film increases.

5.5.7. Percentage moisture absorption (PMA)

The observed results of PMA are shown in Table 5. 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.

5.5.8. 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 cm^2 constant area of the film.

5.5.9. 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 5: The physicochemical parameters of buccal thin films of Curcumin

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±0.40	6.5±0.09	31.9±0.50	2.3±0.01	96.7±0.47	58.0±0.01
F2	79.3±0.33	0.6±0.01	52±0.71	6.74±0.12	44.8±0.60	2.56±0.06	99.28±0.90	73.0±0.04
F3	85.6±0.34	0.9±0.01	44.3±0.63	6.04.56±	51.5±0.71	4.42±0.01	100.29±0.20	95.4±0.33
F4	73.3±0.23	0.73±0.02	51.3±0.3	6.6±0.04	26.1±0.69	2..05±0.06	96.51±0.80	45.1±0.01
F5	79.3±0.45	0.36±0.03	65.1±0.23	6.73±0.03	36.3±0.41	3.93±0.08	97.22±0.90	46.2±.023
F6	83.6±0.36	0.30±0.24	76.3±0.56	6.69±0.03	44.0±0.10	5.34±0.06	99.71±0.36	47.0±0.01

5.5.10. *In-vitro* release studies

The formulated films were subjected for *in vitro* dissolution studies and the results were shown in Table 6 and "Fig: 5". 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. 6: *In vitro* drug release profiles of fast dissolving buccal films.

Time (min)	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	Curcumin Tablet
0	0	0	0	0	0	0	0
1	49.05	47.26	44.26	42.18	54.19	55.88	0.5
3	65.88	54.52	52.02	56.82	68.23	72.34	1.2
5	78.53	63.79	60.17	67.31	85.34	90.56	2.41
7	83.74	77.23	72.28	80.54	94.43	99.89	5.33
10	90.96	85.51	80.13	90.13	99.93		8.92
15	98.87	92.37	88.69	95.43			13.56
20	99.87	100	95.55	99.96			19.52
25			100.0				26.34
30							33.96
40							41.23
50							47.86
60							57.42

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

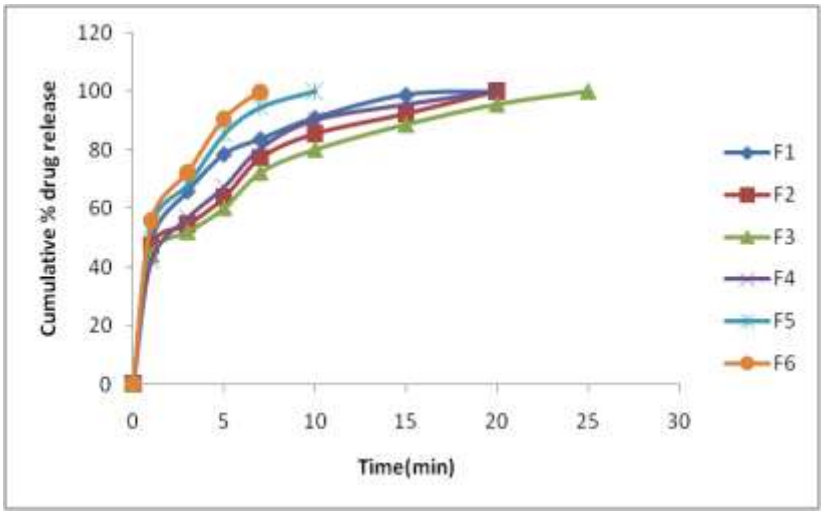

Fig. 5: *In vitro* drug release profiles of fast dissolving buccal film.

Variables affecting the dissolution profile of fast dissolving film

Effect of polymer concentration

Figure 6 shows the effect of changing concentration of Lycoat RS720 on the release of Curcumin 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 from "Fig: 6" 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 behaviour 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 Curcumin 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 glycerine increased from 7.5% to 20% the release rate increased significantly as seen in "Fig: 7". 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.

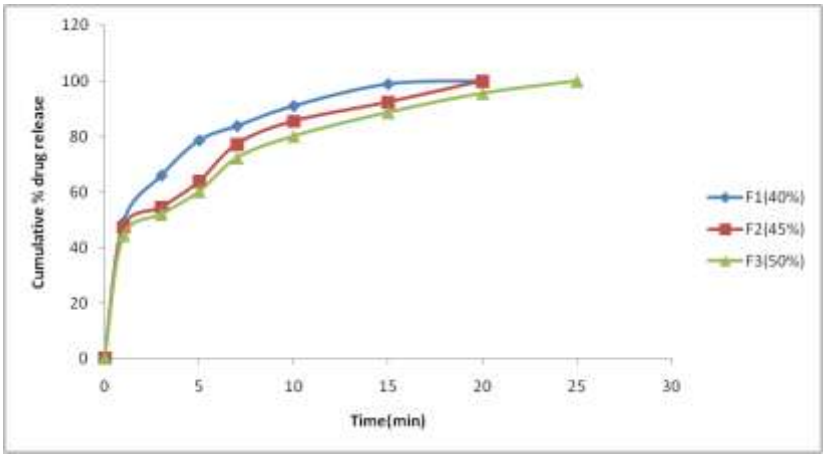

Fig. 6. The effect of polymer concentration on the release of Curcumin from the fast dissolving buccal film.

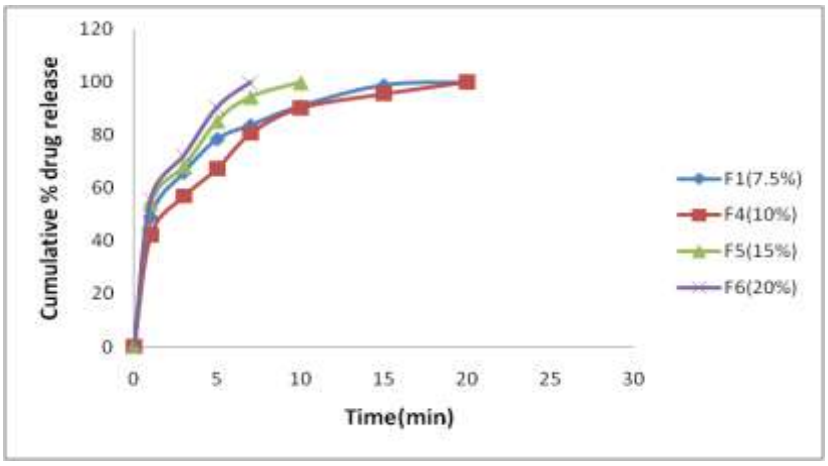

Fig. 7. The effect of plasticizer (glycerin) concentration on the release of Curcumin from the fast dissolving buccal film.

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 *ex-vivo* permeation study, stability testing and characterization by DSC.

Comparison between the release profiles of Curcumin fast dissolving film (F6) and Curcumin oral tablet: As shown in "Fig: 8" a comparison was made between the release profiles of Curcumin fast dissolving film (F6) and Curcumin 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.

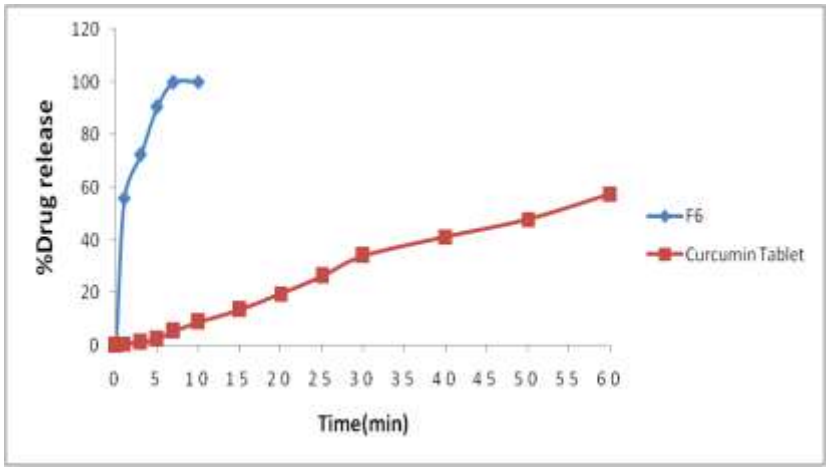

Fig. 8. Comparison between the release profiles of Curcumin fast dissolving buccal film (F6) and Curcumin oral tablet.

5.5.11. *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 7 and "Fig: 9".

Table. 7. *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

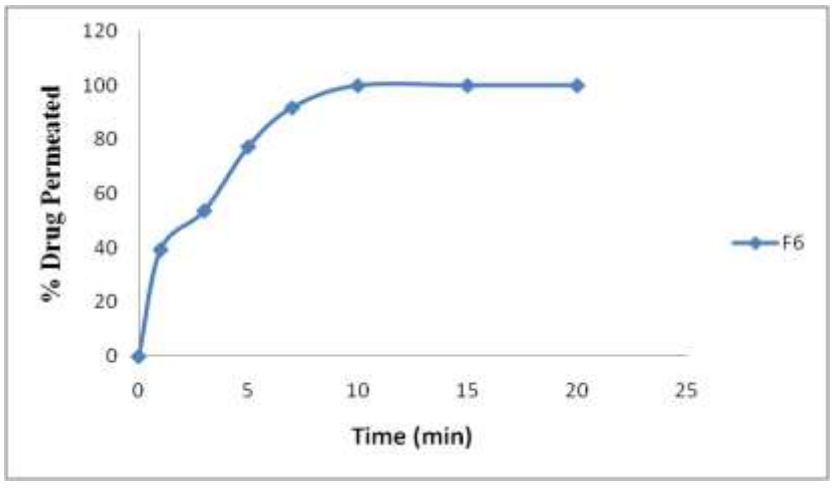

Fig. 9. *Ex-vivo* Permeation Study of Formulation F6.

5.5.12. Stability studies

The results of stability study are shown in Table 8. 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. 8: Stability Study for Formulation F6.

Parameter	Initial	After 45 days on 40^0C 75% RH
Appearance	**Yellow, transparent**	**Slight yellow, transparent**
Weight	83.6±1.24	80.1±0.31
Folding endurance	96.3±2.30	84.7±1.9
Surface pH	6.69±0.03	6.56±0.01
Disintegration time (sec)	47±4.0	50.2±0.66
Drug content (%)	99.71±1.36	98.67±0.56

6. CONCLUSION

99.89% of drug was released from F6 film within 7 minutes which was desirable for fast absorption. Hence fast dissolving films of Curcumin was the most suitable dosage form for clinical use in the treatment of mouth ulcers, where a quicker onset of action for a dosage form is desirable along with the improved bioavailability and convenience of administration. Thus curcumin films can be easily administered by paediatrics and geriatrics that are under the medication of Curcumin.

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