

Comparative Study of Mucoadhesive Vaginal Film and Tablet of Curcumin

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ABSTRACT

Vaginal candidiasis is a common condition and up to 75% of women suffer at least one episode of this infection during their life time. *Candida albicans* is the most important cause of this, accounting for over 80% of the infections. Curcumin is a phytochemical, a component of folklore medicine since ages. It has been investigated as anti-inflammatory, anticancer, antimicrobial, and antifungal. Mucoadhesion has been proposed for a variety of local as well as systemic purposes. Systems like tablets, films, gels, liquids and multiparticulates have been employed successfully. The objective of the present work was to formulate mucoadhesive vaginal film and tablet of Curcumin for the treatment of vaginal candidiasis, and compare their performance. Film was cast by solvent evaporation method while tablet was prepared by direct compression. Both formulations were designed by using Xanthan gum and HPMC K15M. Evaluation and comparison was accomplished through parameters like mucoadhesion, drug release and zone of inhibition. Mucoadhesive strength of film was better at 0.37 mJ. Drug release found was 90-95% for film while 80-85% for tablet in 12 h. Antimicrobial study of film showed better performance than tablet against *Candida albicans*. The study reflected mucoadhesive curcumin films would be a better choice than tablets for vaginal candidiasis.

Keywords: Vaginal infection, *Candida albicans*, Curcumin, Xanthan gum, HPMC, Mucoadhesion, Film, Tablet.

INTRODUCTION

Conditions causing inflammation of the vagina is generally referred to as vaginitis, one of the frequent gynaecological diseases. Candidiasis and bacterial vaginosis are the two most common causes of vaginitis. Vaginal candidiasis (VC) is a prominent reason for women requiring visit to a gynaecologist. As per the literature, almost 75% of all adult women population have at least one episode of vaginitis in their life time. It is also important to note that at least 50% of these women experience, one or more recurrent episodes of VC. Genus *Candida*, a type of yeast is pathogenic in human beings. *Candida albicans* is responsible for 90% vaginal fungal infection cases along with other *Candida* species, such as *Candida glabrata* and *Candida parapsilosi*¹. The increasing incidence of VC requires the need of an appropriate drug delivery approach for successful eradication of infectious agent, achieving higher drug levels at the site, avoidance of first-pass metabolism, a shorter regimen of therapy along with convenience and safety. The vaginal mucosa provides advantages such as large surface area, rich blood supply, a potential site for local and systemic therapy. Many classes have been reported eg contraceptives, antifungals, antivirals etc. Conventional vaginal dosage forms such as creams, foams, pessaries, and jellies have short residence time at the site of application as well as leakage and messiness, possibly resulting in reduced therapeutic effect and causing inconvenience to users¹⁴. Mucosal drug delivery systems may avoid these problems.

In addition to providing effective treatment of vaginitis, the formulation should adhere to vaginal mucosa in order to bring drug in contact with target tissues for sufficient period of time and prevent expulsion of formulation. Mucoadhesive polymers have the capability to adhere to mucous-epithelial surfaces and act as promising carrier to be used in the design of mucoadhesive vaginal drug delivery systems.

Curcumin is a major pigment of the *Curcuma* species, commonly used as a yellow colouring and flavouring agent in foods particularly in South Asia. The use of curcumin in traditional medicine and as a household remedy for various diseases, including biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis has been well documented. Curcumin has also been reported to possess anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antiarthritic, antibacterial, antifungal, antiprotozoal, antiviral, antipsoriatic, neuroprotective and anti-Alzheimer activities. Studies have shown that curcumin is nontoxic to humans. Work has been carried out on antifungal activity of curcumin against *Candida* and it was found that curcumin was 2.5 fold more potent than fluconazole at inhibiting the adhesion of *Candida albicans*, and it has synergistic antifungal effects with azoles and polyenes^{2,3}.

The objective of present work was to formulate mucoadhesive vaginal units viz. tablet and film of

curcumin projected for the treatment of vaginal candidiasis.

MATERIALS

Curcumin as gift sample was courtesy Sava Health Care Pvt Ltd, Pune, India. Hydroxypropylmethyl cellulose (HPMC K15M) and Xanthan gum (Pure, Food Grade) were purchased from Colorcon Asia, Goa, India and Research-Labs FineChem Industries, Mumbai, India respectively. PEG 400 (Research-Labs FineChem Industries, Mumbai, India), Acetone (Universal Labs, Mumbai, India). Magnesium stearate and talc (Loba Chemie, Mumbai, India) were procured from local market. Water used was distilled in house.

The instruments used in this study included UV/Vis Spectrophotometer (Shimadzu UV1601, Japan), FTIR Spectrophotometer (Shimadzu 8400, Japan), XRD (Advance D8), Texture analyser (Brookfield, India) pH meter (Digisun Electronics, Mumbai, India), Magnetic stirrer (Remi equipments, Mumbai, India), Dissolution apparatus (Lab India Analytical Instruments Pvt. Ltd. Bangalore, India) and Hot air oven (Labline Instruments, Kochi, India), Tablet machine (Minipress-1674, Rimek, India).

Methods

Solubility

Solubility of the drug was determined in different media (water, methanol, acetate buffer pH 4.2 and Stimulated vaginal fluid). Accurately weighed drug was transferred in volumetric flasks containing different solvents, well shaken and sonicated for 30 min until saturation was achieved.

FTIR Spectroscopy

For the identification of the sample of curcumin and to rule out interaction between drug and excipients IR absorption scan was performed.

DSC

Thermography of the drug and formulation was performed using DSC for the identification purpose and it would be also helpful for the evaluation of possible interactions in the chemical samples and the formulations.

XRD

XRD study of drug and formulation was performed for the determination of morphological nature of drug and excipient in plane and formulation forms.

Preparation of simulated vaginal fluid (SVF)

SVF was prepared using 900 mL water, NaCl (3.51 g), KOH (1.4 g), Ca(OH)₂ (0.22 g), bovine serum albumin (0.018 g), lactic acid (2.00 g), acetic acid (1.00 g), glycerol (0.16 g), urea (0.4 g) and glucose (5.00 g) and stirred well until complete dissolution occurred. The pH of the SVF was then adjusted to pH 4.5 using 0.1 N HCl with final volume adjustment to 1 L^{3,19}.

UV absorption (λ_{max} determination)

Calibration curve of Curcumin in SVF

Accurately weighed 10 mg of Curcumin was added to a 100 mL volumetric flask having 25 mL acetone. Volume was made up to 100 mL with SVF to yield 100 µg of the drug/mL. This solution was used as stock solution. Serial dilution of the stock solution gave solutions with

concentration in the range of 2-10 µg/mL. The absorbance was measured for each solution at the λ_{max} 417 nm using the UV/Vis spectrophotometer. A graph was plotted of absorbance v/s concentration. This would be used as calibration curve.

Preparation of vaginal film

Method of solvent casting was employed to formulate Curcumin films. Varying concentrations of HPMC K 15 M and Xanthan gum were used to prepare batches CF1-CF9. Table 1 contains the composition of prepared mucoadhesive films. HPMC K15 M and Xanthan gum dispersion was prepared in 20 mL distilled water, by stirring for 4hr, utilizing a mechanical stirrer. Weighed quantity of drug was dissolved in acetone separately. This was then mixed gradually with the polymer dispersion with continuous agitation. Propylene glycol was incorporated as a plasticizer while stirring. The ensuing solution was set aside at room temperature to produce good clarity, free from bubbles. This solution was carefully introduced onto a Teflon surface on which a stainless steel ring of 6 cm diameter and 1 cm height was placed to define a confinement. The Teflon surface had been arranged to horizontal plane with the help of a spirit level. The Teflon and ring had perfect contact not allowing leakage of the viscous solution. A fixed quantity (15 mL) of the solution was carefully poured. Observed for absence of leaking. The ring enclosing the pool of the drug-polymer solution was covered with an inverted funnel to permit controlled evaporation of solvent at room temperature and at the same time not allowing air turbulence and entry of air borne dust. It required overnight drying. Dried films were carefully detached not to introduce stress in the film and inspected for any defects and air bubbles. The curcumin film was packed in zip lock poly bag and stored in an airtight glass container to maintain the integrity and plasticity of the patches. The formulae for Curcumin mucoadhesive films are represented in Table 1^{1,2,4,6}.

Preparation of vaginal tablet

Pre-formulation for tablet

It was planned to go for tab compression following the method of direct compression which is a common industrial practice. For this, flow and compressibility are important. Thus, this was studied for the formulation powder components and their blends. They were sieved through # 80/120 (125-177 µ) individually and while blended.

Flow properties

Bulk Density

Bulk density (BD) and tapped bulk density (TBD) were determined. A convenient quantity of powder accurately weighed was lightly introduced in to a 100 mL measuring cylinder. The volume was noted as bulk vol. The cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 5 sec intervals. This tapping was continued until no further change in volume was noted. The volume was noted as tapped vol. BD and TBD were calculated using the following equations.

Bulk density = Weight of powder / Bulk Volume - (1)

Tapped density = Weight of powder / Tapped Volume - (2)

Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is an index to evaluate the BD and TBD of a powder and the efficiency with which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = [(TBD - BD) \times 100] / TBD - (3)$$

Hausner Ratio

It is calculated from BD and TBD.

$$\text{Hausner ratio} = TBD / BD - (4)$$

Angle of repose

The angle of repose of powder blend was determined by the funnel method. Accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel would just touch the apex of the heap of powder. The test powder was allowed to flow through the funnel freely on to a paper surface. The diameter of the powder cone was measured when the formed heap touched the tip of the funnel stem. Angle of repose (θ) was calculated using the following equation.

$$\tan \theta = h / r - (5)$$

Where, h and r are the height and radius of the powder cone.

Preparation of Curcumin mucoadhesive vaginal tablets

Direct compression method was used to prepare Curcumin mucoadhesive vaginal tablets containing 20% curcumin and weighing 500 mg each using a 10 station rotary press (Minipress-1674, Rimek, India) fitted with round, flat faced 12 mm tooling. Composition of the formulations is listed in Table 5. To obtain a homogenous blend the powders were processed through # 80/120 prior to and after by mixing in a mortar-pestle^{3,6,7,8}.

Evaluation of Mucoadhesive Films

Physical appearance

Patches were physically inspected for colour, clarity and possible defects.

Thickness uniformity

A digital vernier calliper (Digimatic, India) was utilized to measure the thickness. Mean and standard deviation values were calculated.

Uniformity of weight

The film was cut into portions of size 2x2 cm² and weighed individually. Mean and standard deviation values were calculated.

Folding endurance

A ribbon of film (2x4 cm²) was cut and repetitively folded lengthwise at the centre by 180° till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance^{4,5,6}.

Tensile strength

The tensile strength was determined by a Tensile Strength Tester (Ubique 2006-218-LED, Pune, India). Three strips of film (5 x 0.5 cm) were cut. They were marked with ink 2 cm apart and 1 cm from each end. The thickness and breadth of strips were noted at the three marked sites and average values were taken. Each strip was clamped in the machine such that the markings were visible. Incremental stress load was applied. The change in dimension and break load were observed¹⁸.

Tensile strength relates to breaking force. It was calculated using the following formula.

$$(S) = \frac{m \times g}{b \times t}$$

Where, S = Tensile strength in dynes/cm²

m = mass in grams (the stress load applied).

g = acceleration due to gravity (980 cm/sec²).

b = breadth of strip in centimetres.

t = thickness of strip in centimetres.

Strain relates to change in Dimensions. It is calculated from change resulting in a size after the force is applied compared to its original size. Strain can be given as,

$$\text{Strain (E)} = \frac{L - L_0}{L_0}$$

Where, L = length after force was applied

L₀ = Original length.

Drug content

A square piece of film measuring 2 x 2 cm was immersed in a beaker containing 100 mL of SVF. The content was stirred by an ultrasonicator to dissolve the patch. Suitable aliquots were made and filtered. The absorbance of the filtered solution was found out by using the UV-visible spectrophotometer at the λ_{max} 417 nm⁵.

Surface pH

A 2% (w/v) agar plate was prepared by dissolving agar in warm water and pouring into a petridish to solidify at room temperature. The test patch was left to swell for 1 hour on the surface of the agar plate. Surface pH was then measured by means of pH paper placed on the surface of the swollen patch. Mean of three readings was recorded^{4,5}.

Moisture uptake

Three desiccators were used for the study, one for drying a patch, second for 58% RH and third for 79% RH. Saturated solution of sodium bromide and aluminum chloride at RT (30° C) was used for the 58% RH and 79% RH respectively¹⁸.

The patches were dried in a desiccator containing calcium chloride for 24 hours (room temperature 30°C) and then weights were noted. The patches were then kept in the desiccators of 58% RH and 79% RH respectively. They were equilibrated at respective RH for 48 hours and percent moisture uptake was calculated by using following formula.

Moisture Uptake %

$$= \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percent elongation

The percent elongation at break in the Tensile Strength Tester was measured by formula given below.

$$\text{Elongation \%} = \frac{L - L_0}{L_0} \times 100$$

Where, L₀ = Original length.

L = length after force was applied.

In-vitro drug release

The drug release from mucoadhesive films was determined using the USP dissolution apparatus 1 basket method. The test film 2x2 cm was stuck to the basket shaft end with few drops of SVF. Allowed to dry. SVF 900 mL was used as dissolution medium and the study was continued up to 12 h. Stirring rate was maintained at 100 rpm and temperature at 37 ± 0.5°C. Aliquots (4 mL) were withdrawn at predeter

Table 1: Formulae of curcumin film.

Content Batch	Curcumin (mg)	HPMC (mg)	K15 M	Xanthan gum (mg)	PEG 400 (mg)	Acetone (mL)	Water (mL)
CF1	135	450		225	60	7	13
CF2	135	450		112	30	7	13
CF3	135	450		96	60	7	13
CF4	135	560		225	60	7	13
CF5	135	560		112	30	7	13
CF6	135	560		96	60	7	13
CF7	135	580		225	30	7	13
CF8	135	580		112	30	7	13
CF9	135	580		96	60	7	13

Table 2: Formulation of curcumin tablet.

Batch	Content Curcumin (mg)	HPMC	HPMC K 15 M (mg)	Xanthan gum(mg)	Magnesium stearate(mg)	Talc (mg)
CT1	100	50	100	150	10	90
CT2	100	45	105	150	10	90
CT3	100	40	110	150	10	90
CT4	100	105	100	95	10	90
CT5	100	100	105	95	10	90
CT6	100	95	110	95	10	90
CT7	100	110	100	90	10	90
CT8	100	105	105	90	10	90
CT9	100	100	110	90	10	90

Table 3: Solubility of Curcumin in different media.

Media	Solubility(mg/mL)
Methanol	10
Distilled water	0.1
Stimulated vaginal fluid	0.500

mined time points and replenished with same volume of SVF. The samples were analyzed for drug content using UV spectrophotometer at 417 nm^{5,6}.

Mucoadhesive strength

The mucoadhesion study was performed by using goat vaginal mucosa. It was performed by texture analyzer method. The patch of shape and size of the tablet face (dia 12 mm, area 1.13 cm²) was attached to the sample holder and at the other holder mucosa was attached. The attachments were with suitable glue. The film was wetted with SVF and allowed to come in contact with the wet mucosa and get adhered. The upper probe of the texture analyser moved at a speed of 0.1 mm/s. This resulted in application of a pull force to detach the film from the mucosa. This detachment of the sample from the mucosal substrate was indicative of the mucoadhesion.

Evaluation of Mucoadhesive Tablets

Weight variation

The weight variation test was carried out as per the guidelines of Indian Pharmacopoeia. Tablets from each batch were weighed in a balance (Sartorius digital balance) and the average weight and individual deviations were calculated^{8,10}.

Thickness

The thickness of ten samples was determined using the digital vernier calliper. Average thickness and deviations were determined¹⁰.

Hardness

Hardness of the tablet is an indication of its mechanical strength. It was tested by measuring the force required to break the tablet across the diameter. The force was measured in kg/cm² and the hardness of about 4 kg/cm² was considered to be satisfactory. Tablet requires a certain amount of mechanical strength to withstand the shock of handling during its manufacture, packaging, shipping and dispensing. Hardness of the tablet was determined using a hardness tester (Erweka hardness tester, Germany)^{7,8,10}.

Friability

Friability is the measure of a tablet's ability to withstand both shock and abrasion without crumbling during manufacturing, packing, and shipping of tablets. Weighed tablets were exposed to a Roche friabilator. The sample was removed after 100 revolutions, dedusted and reweighed. Tablets that lose less than 0.5 to 1 percent in weight are generally considered acceptable^{8,10}.

% Friability

$$= \frac{\text{Initial wt of 10 tab.} - \text{Final wt. of 10 tab.}}{\text{Initial wt. of 10 tab.}} \times 100$$

Drug content

The Drug content of curcumin in the tablets was determined through UV spectrophotometry. Tablets were finely powdered, quantity of the powder equivalent to 10 mg of curcumin was transferred to a 100 mL volumetric flask. Methanol was added, mixed thoroughly and volume was made up with methanol and filtered. A 10 mL portion was diluted to 100 mL with methanol and the absorbance was measured at 417^{3,7,8,10}.

Mucoadhesion

Freshly excised goat vaginal mucosa was washed with saline solution and kept in SVF prior to use. A square piece

IR Spectrum.

Study of IR spectra of Drug and Excipients.

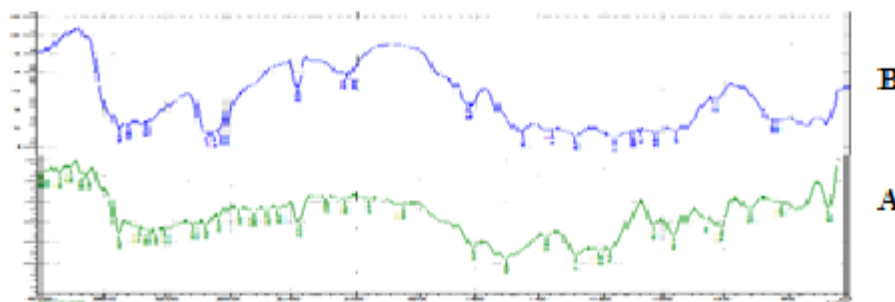


Figure 1: IR Spectra of (A) Drug sample, (B) Mixture of Drug and Polymer.

DSC Study

DSC study was performed for identity & compatibility stability study.

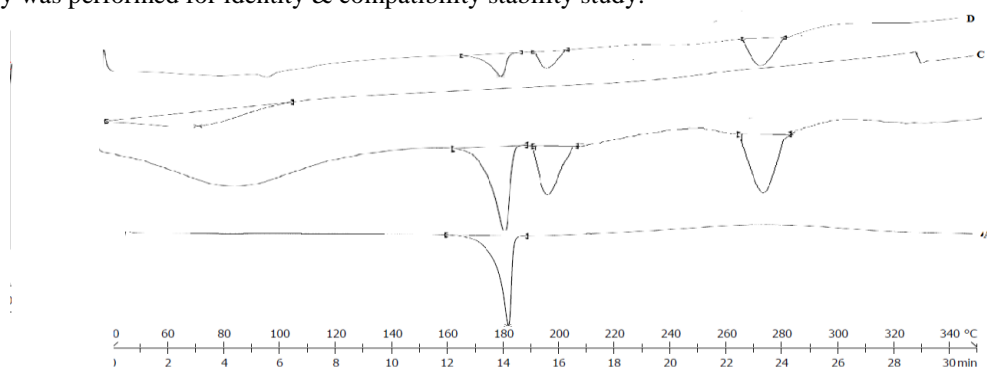


Figure 2: DSC of (A) Plane drug, (B) Physical mix. of drug and excipients, (C) Film, (D) Tablet.

XRD Study

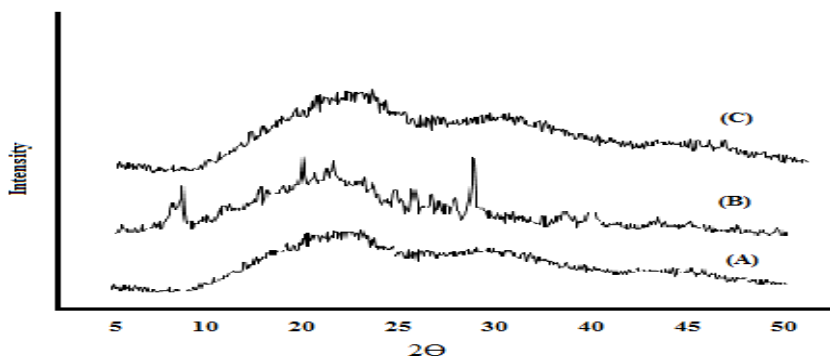


Figure 3: XRD study of (A) Tablet, (B) Curcumin, (C) Film.

(surface area 1 cm²) of the mucosa was glued to an upper probe of the same size. The vaginal mucosa was moistened using SVF. The tablet was glued similarly to the lower probe. Mucosal membrane was kept in contact with the tablet for 2 min to allow the formation of an adhesive bond. The upper probe of the texture analyzer moved at a speed of 0.1 mm/s. The force required to detach the tablet from the tissue surface was available as mucoadhesive strength¹⁰.

In-vitro drug release

Drug release was evaluated using a modified standard basket apparatus. The basket was removed and only the rod was made available. One phase of the test tablet was

wetted with few drops of SVF and fixed to the bottom end of the stirring rod. After 2 min of drying, USP apparatus 1 basket assembly was employed. The test tablet was placed in the basket. The vessel was filled with 900 mL SVF at 37°C and stirred at 100 rpm. Samples (5 mL) were collected at predetermined time intervals, diluted up to 10 mL and replaced with an equal volume of the medium. Curcumin concentration in each sample was determined at 417 nm using the UV Visible spectrometer^{7,8,10}.

In-vitro antifungal study

Sabouraud Dextrose agar was prepared in 100 mL water. Media and all instruments were sterilized at 15 lb pressure for 20 min in an autoclave. Under aseptic condition

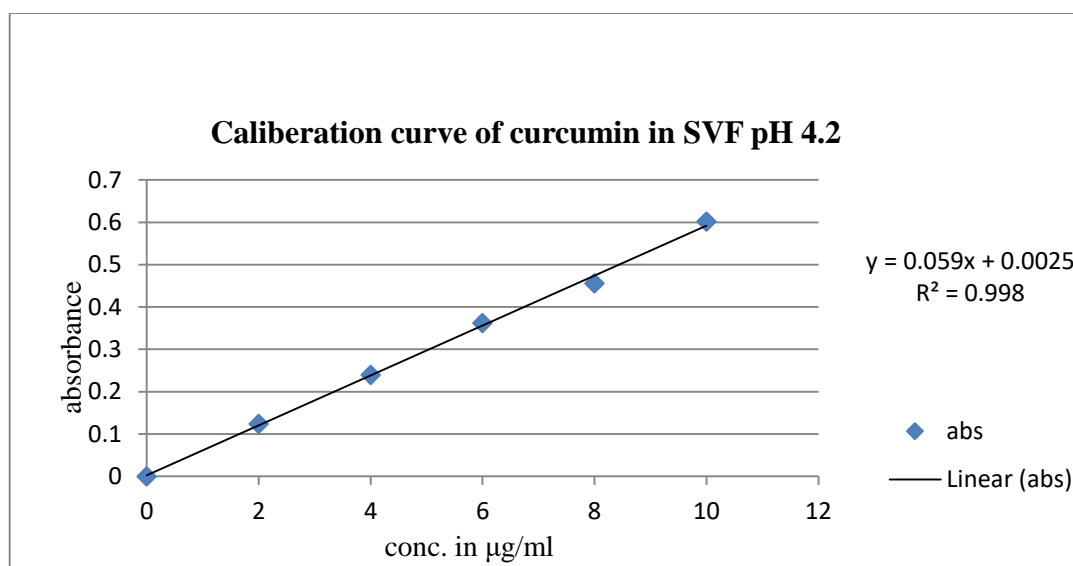


Figure 4: Calibration curve of Curcumin in SVF.

Table 4: Physical evaluation of optimized batches.

Batches	Appearance	Thickness (mm)	Surface pH	Moisture Loss (%)	Moisture uptake (%) At	
					58% RH	79% RH
CF1	Thin, tough, Opaque	0.26±0.015	3-4	1.36	4.4	4.3
CF2	Thin, tough, Opaque	0.27±0.019	3-4	2.41	5.2	6.3
CF3	Thin, tough, opaque	0.31±0.019	3-4	3.54	3.8	6.2
CF4	Thin, flexible, Opaque	0.28±0.020	3-4	3.67	2.8	5.4
CF5	Thin, flexible, transparent	0.22±0.03	3-4	5.20	6.4	7.9
CF6	Thin, flexible, transparent	0.25±0.2	3-4	4.26	4.5	5.1
CF7	Thin, flexible, transparent	0.22±0.3	3-4	4.35	3.2	6.4
CF8	Thin, flexible, transparent	0.24±0.2	3-4	4.98	4.7	5.1
CF9	Thin, flexible, transparent	0.12±0.3	3-4	4.55	7.3	8.8

Table 5: Mechanical Evaluation Optimized Batches.

Batches	Tensile Strength (dynes/cm ²)	Elongation (%)	Weight Variation (mg)	Folding Endurance (folds)	Drug content (%)
CF1	7.83x10 ⁶ ±21.7	50.42±0.8	105	190	94.21
CF2	7.23x10 ⁶ ±1.7	54.37±0.8	108	170	94.70
CF3	6.99x10 ⁶ ±1.7	55.97±0.8	110	220	95.01
CF4	10.46.8x10 ⁶ ±2.0	61.29±1.8	106	200	95.32
CF5	9.64x10 ⁶ ±2.0	67.56±1.8	109	210	96.65
CF6	9.15x10 ⁶ ±2.0	71±1.8	112	190	96.20
CF7	10.31x10 ⁶ ±1.5	59.84±1.8	111	200	95.11
CF8	9.86x10 ⁶ ±1.5	60.61±1.8	114	200	96.98
CF9	9.30x10 ⁶ ±1.5	68.64±1.8	115	210	98.50

prepared medium cool up to 30^oc then add 15 mL of microbial suspension of *C.albicans* transferred in it stirred to mix well with glass rod. Saburud agar media was transferred into 3 sterile petri plates. After solidification 0.5 mL of Wells were prepared by using a sterile borer of

diameter 10 mm. The optimized batch of film 2cm² area cut and dissolved in DMSO and sample were added in a well. Also optimized batch of tablet crush and weighed 10 mg powder and dissolved in 10 ml DMSO then sample were added in well. The plates were incubated at 37^oc for 24 hours. The zone of inhibition was measured.

Mucoadhesive strength.

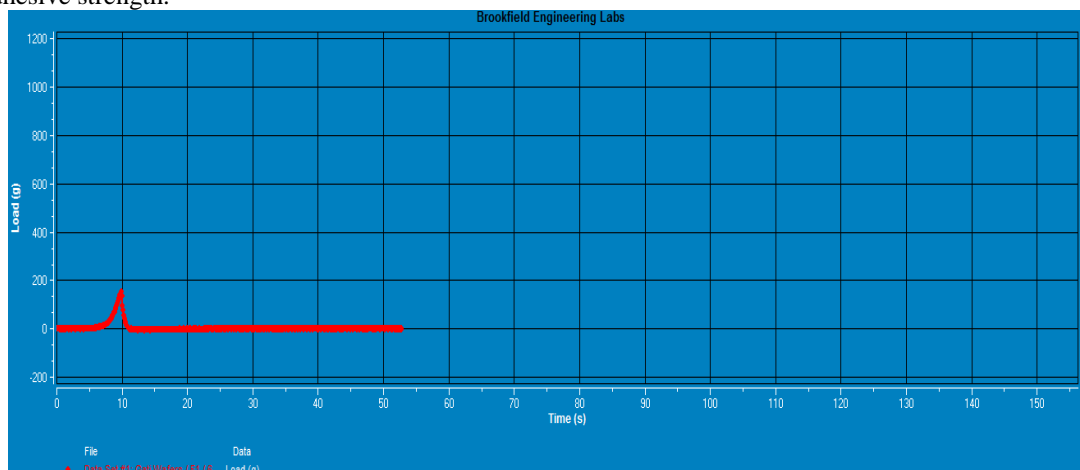


Figure 5: Texture analysis of CF9.

Drug Release

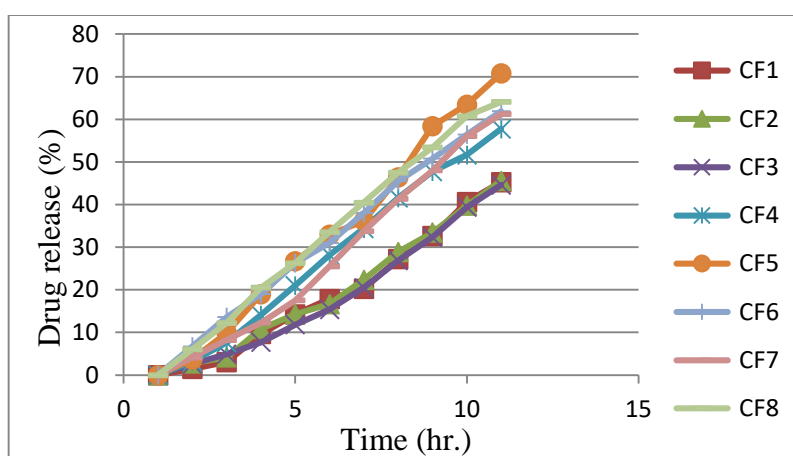


Figure 6: Drug Release from optimized batches of film.

Table 6: Physical Evaluation of optimize batches.

Batches	Weight (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Content uniformity(%)
CT1	502±1.23	3.3±0.3	5±0.2	0.2	98
CT2	500±2.12	3.2±0.2	5±0.3	0.3	98
CT3	500±1.24	3.4±0.1	6±0.1	0.5	99
CT4	502±2.18	3.3±0.2	6±0.3	0.2	99
CT5	503±2.26	3.3±0.3	6±0.3	0.2	98
CT6	500±1.32	3.2±0.2	7±0.1	0.3	98
CT7	502±1.26	3.2±0.3	7±0.1	0.2	98
CT8	500±2.17	3.3±0.3	7±0.2	0.3	99
CT9	500±2.26	3.3±0.2	7±0.3	0.3	99

RESULTS

Solubility

Solubility of the drug was determined in 5 different media as given in Table 3.

XRD study was performed for determination of the morphological nature of Drug under various conditions viz., as drug alone, in film and in tablet.

Calibration curve in simulated vaginal fluid

Evaluation of Film

Evaluation of Tablet

Evaluation of flow properties of drug and excipients

Flow properties of drug, excipients and its composition were checked. Micrometrics results of drug curcumin showed that it had fair flow property (angle of repose: 30.45) and had compressibility index around 25 and it suggested that it has poor compression property. Hausner's ratio of drug was 1.33. The bulk density and tapped density were found to be 0.585 and 0.780 respectively. The drug-powder blend evaluated for all this parameters viz. angle of repose, Carr's index were found to be in range 18-19 and 19-20 respectively.

DISCUSSIONS

Mucoadhesive strength

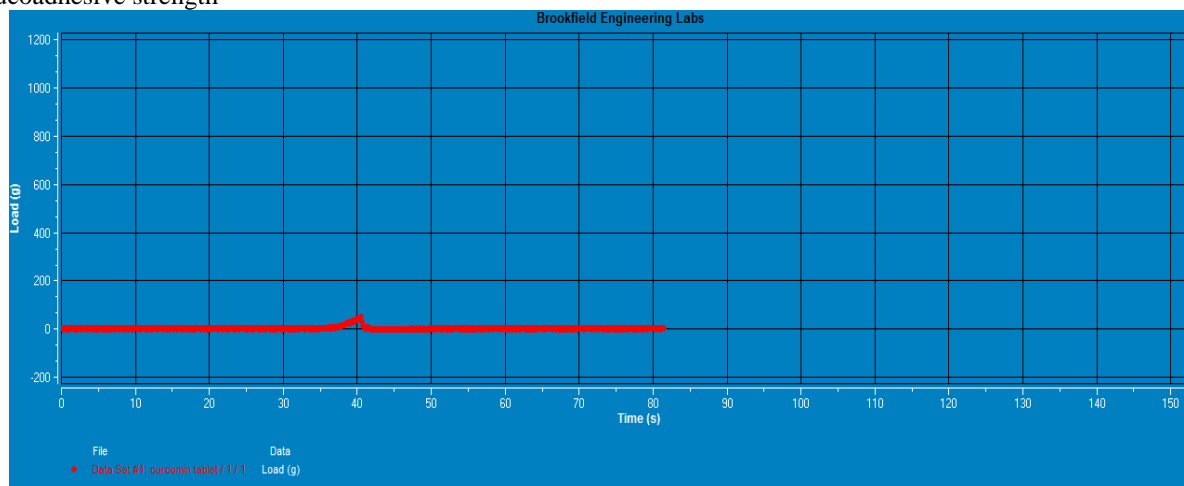


Figure 7: Texture analysis of CT7.

Drug Release

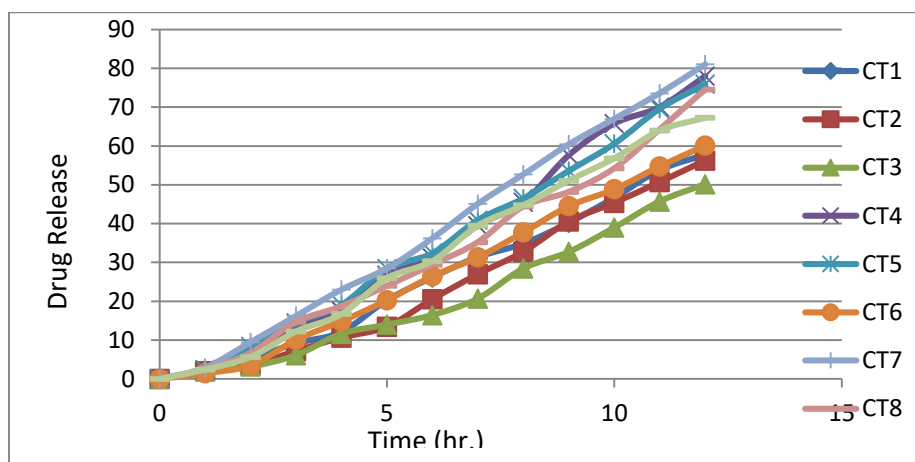


Figure 8: Dissolution from optimized batches.

Solubility

The drug was found to be sufficiently soluble in methanol, acetone and DMSO. It was insufficiently soluble in water & SVF. Solubility in water was important in formulation as well as to construct calibration curve. As the solubility in water was found to be very less, solubility in probable co-solvents like acetone & methanol was investigated. Regarding SVF, the solubility though appeared to be low but it would be sufficient for dissolution study where sink condition would prevail. Solubility in DMSO had a role in anti-microbial zone of inhibition study and was found to be adequate.

IR Spectra

IR spectra were recorded on the FTIR spectrophotometer. The scanning range was $4000-400\text{cm}^{-1}$. Figure 1 (A) shows IR spectrum of drug sample which indicated that given sample got identified as curcumin. And (B) shows IR spectrum of mixture of drug and polymer which indicated that small hydrogen bonding interaction could be there between -OH group of the Curcumin aromatic ring with Xanthan gum and HPMC. Generally it might be said that drug and polymer were compatible with each other.

DSC Study

From figure 2 (A) endotherm of pure Curcumin was found at 180°C . Which represented the melting point of the sample. (B) gave the DSC graph of physical mixture of drug and polymer. The graph showed the compatibility of the drug and polymer as there was no change occurred in melting point of drug which was retained at 183°C . (C) gave the DSC of formulated film. It did not show drug peak, which meant drug might have got changed in another form i.e. amorphous. (D) gave the DSC graph of the tablet. In this fig there was no change in melting point of drug and excipients. This might have indicated the retention of the morphologies. This might hint towards a better performance of the film design in dissolution. This observation could be correlated with the drug release and zone of inhibition outcomes shown elsewhere.

XRD Study

Figure 2. Shows the XRD study of (A) gave graph of tablet which showed amorphous nature, (B) gave graph of drug alone showing crystalline nature, (C) gave graph of film that showed amorphous nature. This would indicate similar dissolution performance of the two dosages. But the DSC and drug release result indicated better status of the film. This meant, in the XRD there might be minor differences between the graphs of tab and film. There might be slight

Comparisons of the designed film and tablet.
Microbial Study of Film and Tablet.

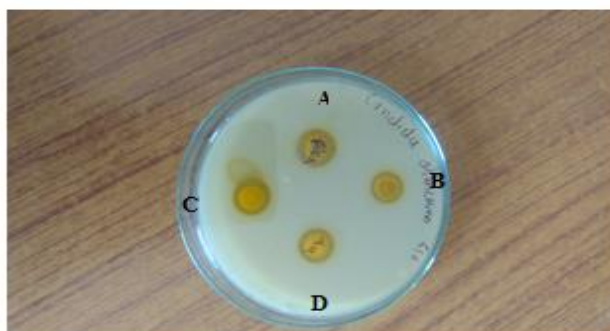


Figure 9: Zone of inhibition (A)& (B) Film CF9; (C) & (D) Tablet CT7.

Drug release from film and tablet.

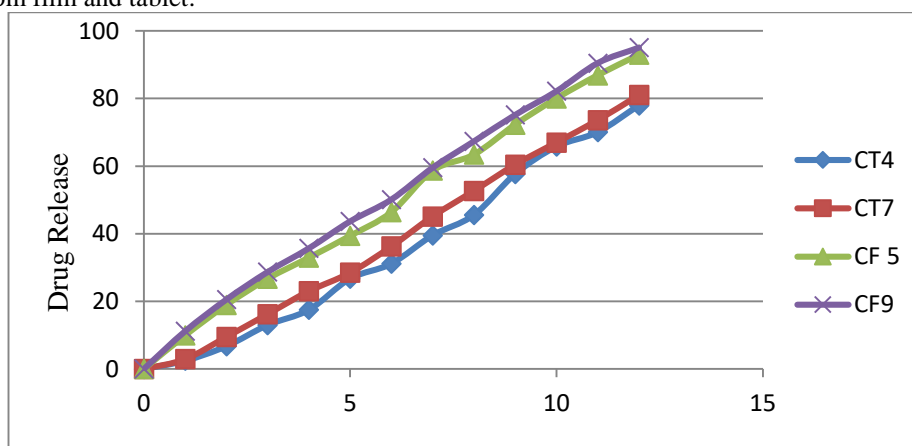


Figure 10: Drug release of film and tablet.

changes in tablet during compression due to some momentarily temp rise, friction, fusion etc. which might have given minor drop in the crystallinity of the drug, but not as much as in the film. In any case it was confirmed that the crystallinity did get reduced in the delivery systems.

Evaluation of film

Physical Evaluation

Table 4 shows physical evaluation of film. The curcumin film was studied using polymers in different ratios. Higher concentration of xanthan gum in batches from CF1-CF4 might have lead to large number of bubbles, gave tough films which might have eventually affected drug release. CF6 and CF9 contained the maximum level of HPMC K15M giving thin, flexible and transparent film with max elongation. The pH of all the patches was found in the range of 4-6, weak acidic nature. Moisture uptake is dependent on quality & quantity of polymer. Both polymers used in formulation are hydrophilic in nature. But water uptake capacity of HPMC K 15 M is known to be higher than the Xanthan gum. Therefore, as concentration of HPMC K15 M increased, moisture uptake also increased. Same rule was found to be followed for the Moisture loss also. Batches CF5 and CF9 showed better moisture uptake and loss. Moisture uptake is useful for mucoadhesion and drug release. And ability to lose less

moisture during storage would reflect retention of plasticity and physical integrity during storage.

Mechanical Evaluation

Table 5 shows Mechanical evaluation of batches of film. Batches CF1-CF3 gave minimum percent elongation. The batches from CF5 and CF9 gave the percent elongation which is 67 and 68% because of higher concentration of PEG. Tensile strength was found to be changing in tune with the polymer concentration.

Mucoadhesion Study

Figure 5 shows Mucoadhesion of optimized CF9 batch that was evaluated by using Texture analyzer by applying varying loads. From the Fig.7.11 it was deduced that 5.60 g was the applied force proportional to 0.37mJ adhesion.

Drug Release

Figure 5 shows drug release data of optimized batches of films. The dissolution of all batches was evaluated and the batch CF5 and CF9 showed higher drug release as compared with CF1-CF4 batches. Batch CF1-CF2 showed poor release probably because of presence of air bubbles in the film. It was also found that as concentration of Xanthan gum increased, drug release was decreases. Xanthan gum reduces initial burst. Also as it has high swelling and gelling capacity this affected the drug release. Batch CF1-CF2 had Xanthan gum and HPMC in 3:1 ratio, large amount of xanthan gum increased the viscosity of

polymer dispersion due to that bubbles occurred in film and also due gelling capacity of xanthan gum drug might be stuck with it & due to that drug release retarded. Therefore, batch CF1-CF2 showed 50-54% release. Batches other CF5 and CF9 gave up to 90-95% drug release which was considered better. In CT5 and CT9 HPMC: Xanthan gum was as 1:6 and 1:7 respectively. In this case concentration of xanthan gum was very less due to that it did not affect initial burst effect of HPMC. Also, swelling and gelling was optimum, so drug release was found to be higher in the batch CT5 and CT9.

Evaluation of Tablet

Preformulation micromeritics

The results hinted acceptable flow & compression properties of the blend. Thus the blend could be recommended for direct compression.

Physical Evaluation of tablets

The physical properties of the tablets are summarized in Table 6. Mean tablet weight for all the batches was in the range of 500 - 503 mg. Thus, they all complied with the mean weight variation requirement of the Indian Pharmacopoeia, as no batch varied by more than 5 % from the tablet weight. This indicated consistency in tablet formulation and production. Mean hardness of the tablets (5-7 kg/cm²) indicated satisfactory tablet strength especially as friability was also less than 1%, which complied with the requirements of USP. Mean drug content was 98.8 ± 0.6 % thus showing drug content uniformity of the tablets. These outcomes validated the formulation and process reliability. The tablets prepared would have adequate quality and the performance would show reliability.

Mucoadhesive strength

Fig 6 shows graphical outcome of mucoadhesion test of CT7 that was assessed by using the texture analyzer by applying varying load. The information was computed 5.10 g applied force proportional to 0.24mJ adhesion. The tablets showed the adhesion lesser than the film (Fig4).

Drug Release Study of Tablet

From the Fig 7, CT4 and CT7 gave maximum drug release in 12 h. CT1-CT3 showed minimum release in the same duration i.e. only 50-54%, could be because of maximum concentration of xanthan gum and HPMC K 15 M. As concentration of xanthan gum and HPMC K15 M decreased drug release increased. Use of HPMC in a matrix tablet as the only polymer could result in a very slow release of drug due to the build-up of an excessively viscous gel which would be very resistant to water penetration and erosion. HPMC based systems also has an initial burst effect. In order to overcome these problems, xanthan gum was mixed with the HPMC. A constant amount of Xanthan gum was used in the formulation from CT1-CT3 and the concentration of xanthan gum and HPMC K 15 M was a significant factor in the rate of drug release. In batch CT1 & CT3 concentration of xanthan gum was higher and HPMC K 15 M was lower. Both are hydrophilic polymers. But there was no initial burst effect in the batches CT1 -CT3 which might be due to rapid hydration and gelation of the xanthan gum in the tablets which gave a slower drug release. Unlike that, batches CT4

and CT7 had lower concentration of xanthan gum and higher concentration of HPMC K15M which showed optimum swelling and gelling capacity, also initial burst which favoured higher drug release. Thus, through logical experimentation a meaningful ratio and conc of the polymer blend could be determined.

Comparison of Film and Tablet of Curcumin

Comparison of Microbial results

Fig.8. shows zone of inhibition of *Candida albicans* by using Curcumin loaded film and tablet. The zone was recorded at same concentration of both formulations. Zone of inhibition were found to be 5 mm for film and 3 mm for tablet. Such zones are indicative of retention of the drug in the therapeutic nature, its release, its diffusion and the extent of inhibition of the microbial growth. This would correlate with an *in-vivo* study when performed. The film appeared to have an edge over the tablet, mainly due to the release.

Comparison of Mucoadhesion study of optimized batches of Curcumin Film and Tablet

Mucoadhesion study was performed by using the Texture analyzer. The surface area of film and the tablet were kept similar. Force required for the detachments of tablet and film was 5.10 and 5.60 g respectively. And adhesion found to be 0.24 mJ for tablet and 0.34 mJ for film. Film showed better mucoadhesion than the tablet. This could be due various reasons. Being matrix like, in films the Mucoadhesive polymers were directly and immediately available to the mucin strands for bonding. Also the quicker pulling of water from the mucus membrane could show a better result.

Comparison of drug release of film and tablet

Figure 10 depicted comparison of release profile of Film and tablet. Curcumin tablets and films were prepared using hydrophilic polymer combination. Film showed 90-95% of drug release and tablet showed 70-80% in 12 h. Explanation for this might be, film have larger surface area and might be more easily accessed by the VSF. The nature of all profile was near to linear. Thus, though release behaviour was similar, the films released relatively faster. Also xanthan gum concentration in tablet was higher than film and this gum might have retarded the release rate by its swelling and gelling capacity. Different concentration of HPMC might have altered initial burst rate as could be faintly seen in the graphs. Might be it could be said, with formulation modification it would be possible to obtain favourable release profile in both the cases.

CONCLUSION

From the obtained results, it could be concluded that, Curcumin mucoadhesive film and tablet could be conveniently formulated. It could be established that there was no interaction among the drug & excipients. For film casting Teflon was found to be a suitable substrate. Dissolution and Antimicrobial study supported the formulation validity. Film performed better than the Tablet. Formulations would have scalability. It appeared that, there would not be regulatory hurdles. With further support of *in-vivo* and clinical programs it might be possible to take the proposed film to the level of patients.

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