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Design and evaluation of mucoadhesive buccal patch of Aminophylline

Vishal Nirgude

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ABSTRACT

Theophylline and ethylenediamine are present in a 2:1 ratio in the medication combination known as aminophylline. Aminophylline is indicated for the treatment of lung diseases such as respiratory difficulties brought on by bronchitis, emphysema, or asthma, include wheezing and shortness of breath. hence was used in formulating and developing of muccoadhesive buccal patch for the treatment of bronchitis.To promote local action and to increase patient compliance.Nine formulations were prepared using three distinct polymers in different ratios and went through the physicochemical parameter screening process. Like Thickness uniformity, Weight uniformity, Swelling-index, Folding endurance, percentage of elongation at break, tensile strength, bioadhesion, homogeneity of drug content, In vitro release studies.With formulation CH8, which included 50% by weight of polymer as propylene glycol as a plasticizer and chitosan and hydroxypropyl methylcellulose (1:1), promising results were seen. The improved film demonstrated acceptable bioadhesive strength and tensile strength, as well as a five-hour greater than 90% in vitro drug release.

Keywords: Aminophylline, theophylline, ethylenediamine, bronchitis, polyvinyl pyrolidine (PVP), chitosan, HPMC.

I. INTRODUCTION

Numerous studies on buccal medication delivery have been conducted in the past several decades systems[1-3]. Buccal medication delivery is the process of delivering medication through the buccal mucosa to the bloodstream.[4]There is a larger contact area due to the buccal mucosa's big, smooth, and generally stationary surface. Which aids in the extensive and quick absorption of drugs.[5]Compared to other drug delivery methods, buccal drug delivery has shown to be especially helpful in recent years. Byboosting patient compliance by enhancing the bioavailability of medications taken orally that would otherwise undergo hepatic first-pass metabolism because injection pain is eliminated, administering drugs to patients who are unconscious, sustained drug delivery, ease of administering dosages, and the ability to quickly stop the drug's delivery by taking out the dose container. 6. Several buccal patches of various medications have been used in recent yearshave been investigated by several study teams.[7-10]Buccal patches are dose forms with modulated release that consistcomprising a thin matrix that includes drugs, excipients, and one or more polymers.[8] Aminophylline a drug used to treat the acute symptoms of asthma, bronchitis, emphysema and other lung diseases[11]. Since the buccal route bypasses the first pass effect, a lower dosage of aminophylline is needed than with the oral route, even if the medication is efficiently taken up from the digestive system, although has a poor bioavailability due to severe first pass metabolism. Aminophylline's physio-chemical characteristics, low molecular weight (420.4), and appropriate half-life (7-8 hours) make it a good choice for buccal administration. The current study is on creating and assessing an aminophylline buccal patch. In this work, The solvent casting method was employed to produce novel mucoadhesive films. Several polymers that form films, such as PVP, HPMC, and chitosan, were employed for this purpose. a backing membrane made of 4% w/v ethyl cellulose that is drug-free. The backing layer was Ethyl cellulose at 4% w/v.

II. MATERIALS AND METHODS

Aminophylline was purchased from yarrow chem products, mumbai Chitosan (65 cps) was kindly donated by the Central Institute of Fisheries Technology, Cochin, and Vikhroli, respectively.SD Fine Chemicals, Boisar, Maharashtra, India is the source of the polymers propylene glycol, ethylcellulose (EC), polyvinyl pyrrolidone (PVPK-30), and hydroxypropyl methylcellulose (HPMC15cps).

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METHOD OF PREPARATION OF BUCCAL PATCHES

Using solvent casting, create buccal patches that included drug reservoirs.[12]As a plasticiser, 30% to 50% of the weight of the polymer is propylene glycol was used and PVP (16.7% of the polymer weight) as a mucoadhesive polymer. The quantity of HPMC that was weighed was evenly distributed in 25 milliliters of an aqueous acetic acid solution at 1% v/v. A measured amount of chitosan was added to the solution mentioned above. After a 24-hour period, The mixture was strained using #80 mesh fine muslin fabric to eliminate any remaining chitin. PVP was weighed precisely and then added to the filtered solution to dissolve it. Propylene glycol, the necessary plasticizer, and aspartame (2% of the polymer weight) were added. The medication was continuously stirred while being evenly distributed throughout the thick fluid. The final concoction was put into 5 x 5 cm glass molds that had been carefully made and coated with aluminum foil. For a whole day, the drying process was done at room temperature. By Placing an inverted glass funnel allowed the drying rate to be adjusted. Additionally, this configuration managed the air current's impact on the films. The molds were left in a 45±1° hot-air oven for a further 12 hours to ensure full drying. The films were taken out of the glass molds once they had completely dried. Using a sharp pen knife, little patches (1 cm × 1 cm) with 25 mg of aminophylline were cut. Additionally, Using the polymer EC (4% w/v), a rate-controlling membrane was cast onto a glass mould and a solvent mixture of 1:1:4, with 10% of the polymer's weight made up of glycerol as a plasticizer. For unidirectional drug release, A 1 × 1 cm membrane was cut, and it was used to seal one side of the drug reservoir.

Table 1: Composition of buccal patches

Formulation code	Drug	Chitosan Ratio	Chitosan-(mg) (65cps)	HPMC (mg) 15cpc	Propyleneglycol*(mg)*	Pvp (pvpk-30)	Aspartane	Acetic acid
CH_1	25mg	1:2	250	500	225	125	18	28
CH_2	25mg	1:1	375	375	225	125	18	28
CH_3	25mg	2:1	500	250	225	125	18	28
CH_4	25mg	1:2	250	500	300	125	18	28
CH_5	25mg	1:1	375	375	300	125	18	28
CH_6	25mg	2:1	500	250	300	125	18	28
CH_7	25mg	1:2	250	500	375	125	18	28
CH_8	25mg	1:1	375	375	375	125	18	28
CH_9	25mg	2:1	500	250	375	125	18	28

EVALUATION

Numerous physio-chemical attributes, including physical appearance, surface texture, patch thickness, weight variation, the produced buccal patches were evaluated for folding durability, surface pH, swelling index, drug content homogeneity, mucoadhesive strength, percent elongation break, and in vitro drug release.

Appearance

The created buccal patches were examined visually for transparency and color.[13]

Surface texture

The buccal patch's surface texture after preparation can be assessed just by touching it.

Thickness of the patch

Using a Vernier Calliper, the thickness of each manufactured aminophylline buccal patch was measured five times. The five sites were used to calculate the average thickness.[14]

Weight variation

The At room temperature, the patches were let to air dry in vacuum desiccators.An area measuring 2 cms by 2 cms was cut in order to measure the weight homogeneity of the patches. On a digital balance, Each formulation's three patches were weighed independently before the average weight was determined.[15-16]

Folding endurance

A mechanical test called folding endurance is used to determine the elasticity and strength of patches. The created buccal patch's folding endurance was assessed manually by folding it

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repeatedly in till it shattered, in the same location. How many times might the patch be folded in the same way before cracking or breaking? was used to calculate the folding endurance value.[17]

Surface pH

pH 6.8 hot phosphate buffer was used to dissolve 2% w/v agar while stirring to create the agar plate. The slurry was subsequently moved to a Petri dish to harden for two hours at room temperature. An electrode was positioned against the surface and given permission to equilibrate for one minute to determine the pH. This allowed the buccal patches to swell on the agar plate's surface.

Swelling index

By immersing the buccoadhesive patches in PBS(Phosphate buffer saline)At 37 ± 0.5 ◦C, pH 6.8, the swelling index of the patches was measured.For every batch, three patches were weighed after being chopped; the average starting weight is W1. After being immersed in PBS, the patches were removed five, ten, fifteen, twenty, twenty-five, and thirty minutes apart or until their weight increased to its maximum. Any remaining Filter paper was used to thoroughly drain the surface water, and swollen areas were weighed again. Three duplicates of the experiment were conducted. The weight W2 average was computed.[18], and The swelling index was calculated using the following formula:

(W2 − W1)/W1 = 100 times (swelling index)

Were, W2-swollen patch weight, W1-initial patch weight

Drug content estimation

By soaking the patch in phosphate buffer (pH 6.8) for 100 millilitres. four hours while periodically shaking it, The uniformity of the medication content was established. Following removing 1 ml of the solution and diluting it with 10 ml of isotonic Whatman filter paper was used to filter the mixture through phosphate buffer (pH 6.8). A UV spectrophotometer is used to The drug content at 275 nm was then ascertained following the proper dilution.

Muco-adhesive strength

The patch's mucoadhesive strength was assessed using a modified physical balance. Within two hours of the goats' slaughter, the fresh A local abattoir provided the buccal mucosa, which was utilised. Slice into a 3-centimeter piece and rinse with a Phosphate buffer, pH 6.8. The buccal mucosa was partially attached to the 50 ml beaker that was inverted and positioned in the middle of the 250 ml phosphate buffer beaker (pH 6.8). The patch was adhered using cyanoacrylate adhesive to the glass vial's lower surface. Five grams of weight were placed on the right-hand pan to balance two of the balance's pans. The right-hand pan and the patch covering the mucosa were lowered when a 5-gram weight was taken out of it. The equilibrium was maintained in this posture for a duration of five minutes. The right-side pan was filled with water gradually by hand (100 drops per minute) until the patch separated from the mucosal surface. Muco-adhesive strength was determined by weighing the patch in grams until it detached from the mucosal surfaces. The gauge of muco-adhesive Weight is strength. expressed needed in grammes to extract the patch from the mucosal surface (goat buccal mucosa).

Percent elongation break

The greatest amount of distortion a film may undergo before disintegrating is determined by its elongation at break. This formula is used to calculate it.At break,

%Elongation = L2-L1/L1×100

Were, L2Extended duration of the break, L1The first length of the film

***In vitro* drug release study**

The A Franz diffusion cell was used to perform drug release in vitro research of aminophylline buccal patch via the cellophane membrane at 37.0±0.5°C. The cellophane membrane divided the donor as well as receptor compartments. The sections were clamped together once the patch was positioned on top of the cellophane membrane. One milliliter of A The donor compartment was filled with 6.8% pH phosphate buffer. 200 cc of pH 6.8 phosphate buffer were added to the receptor compartment while being stirred at 50 rpm with a magnetic bead was used to maintain the hydrodynamics therein. One milliliter of the The sample was removed, and new medium was added at prearranged intervals. The samples' absorbance was then measured at 275 nm to ascertain the cumulative percentage release. The trials were carried out.for each formulated batch.

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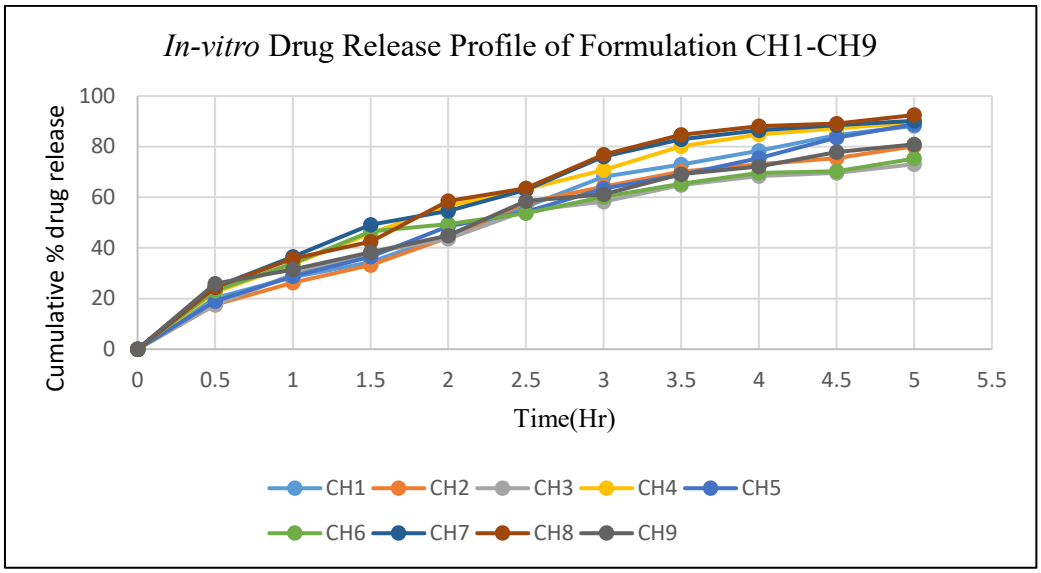

Fig 1: In vitro drug release profiles of formulations CH1to CH9

Table 2: Evaluation of buccal patch

Film Code	Mean Thicknes s* (mm)	Mean Weight* (mg)	Folding endurance*	Swelling Index*	Tensile Strength* (dy nes/cm^{2}x10^7)	Elongation At break* (%)	*Invitro* Biadhesion Strength* (g m)	Mean DrugContent %
CH_1	0.21 ±(0.01)	9.78 ±(0.36)	92.65 ±(4.50)	45.61 ±(0.36)	1.80 ±(0.03)	5.02 ±(0.078)	3.94 ±(0.15)	97.95 ±(2.28)
CH_2	0.31 ±(0.02)	10.28 ±(0.36)	74.00 ±(4.72)	38.12 ±(0.36)	1.63 ±(0.08)	4.31 ±(0.051)	3.81 ±(0.20)	96.37 ±(1.64)
CH_3	0.21 ±(0.01)	10.25 ±(0.35)	52.65 ±(4.72)	36.91 ±(0.35)	1.85 ±(0.09)	5.76 ±(0.070)	4.44 ±(0.21)	96.41 ±(0.76)
CH_4	0.22 ±(0.01)	9.80 ±(0.28)	117.67 ±(2.51)	49.41 ±(0.28)	1.53 ±(0.06)	3.18 ±(0.075)	3.24 ±(0.13)	98.17 ±(1.42)
CH_5	0.28 ±(0.03)	11.71 ±(0.38)	83.34 ±(3.51)	40.61 ±(0.38)	1.91 ±(0.03)	5.03 ±(0.41)	3.91 ±(0.23)	96.24 ±(0.52)
CH_6	0.24 ±(0.02)	10.67 ±(0.40)	60.00 ±(4.58)	38.24 ±(0.40)	2.09 ±(0.10)	6.58 ±(0.231)	4.32 ±(0.15)	96.34 ±(0.72)
CH_7	0.25 ±(0.02)	9.90 ±(0.33)	135.65 ±(4.50)	47.16 ±(0.40)	1.77 ±(0.02)	6.08 ±(0.133)	3.95 ±(0.16)	96.91 ±(1.89)
CH_8	0.35 ±(0.03)	11.74 ±(0.40)	99.39 ±(5.13)	43.61 ±(0.33)	2.05 ±(0.04)	7.19 ±(0.032)	4.15 ±(0.09)	99.21 ±(0.55)
CH9	0.21 ±(0.02)	9.85 ±(0.22)	79.34 ±(6.50)	33.81 ±(0.22)	2.14 ±(0.07)	7.30 ±(0.096)	5.57 ±(0.16)	96.80 ±(0.51)

III. Results

Nine mucoadhesive aminophylline patches in total were made and assessed for mechanical, physical, and biological characteristics. The patch's look, Weight fluctuation, folding endurance, swelling index, tensile strength, elongation at break, surface roughness, thickness, homogeneity of drug content, in vitro drug release, and short-term

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stability-excipient interaction were all assessed in accordance with the work plan.

Buccal patches have a consistent, smooth surface texture. As we increase the chitosan content between 33.3 and 66.7% w/w of the concentration of the whole polymer, the patches' color shifts from white to yellowish white.

The low standard deviation figures suggest that the films' Weight and thickness were determined to be consistent.

In order to find the ideal ratio of polymers, plasticizers, and solvents needed to create formulations that would work, blank films were first made. The formulations that displayed a A surface that was completely uniform, smooth, flexible, and non-sticky was

then chosen for additional research and assessed according to the previously listed parameters. The findings showed that the polymer ratio and plasticizer (PG) concentration affect the drug's release. The films' remarkable flexibility was demonstrated by the folding endurance assessment (Table 2). When we raise the concentration of propylene glycol or HPMC, the folding endurance of films continues to increase. Formulation CH 7 indicates a maximum folding endurance of about 135times. Tensile strength and polymer composition shown a strong association. The film's tensile strength rises with increasing chitosan content, but plasticizer concentration has little bearing.Testing all the films with different polymer ratios revealed that the amount of chitosan in the film enhances the mucoadhesivity *(in vitro* bioadhesion strength). This could be because mucus or a negatively charged mucous membrane are strongly electrostatically attracted to positive charges on the surface of chitosan. The average amount of The films' drug content (Table 2) was found to be between 96.24 and 99.21 percent. The low standard deviation values suggest that the medication was distributed uniformly across the manufactured films.It was discovered that the polymer ratio and plasticizer concentration had a significant impact on drug release from the films, and that this dependence increased as HPMC and plasticiser concentrations increased.The different formulations exhibit *in vitro* release parameters, ranging from 0hrs to 5hrs,after every 30min respectively. Plotting the data Linear linear plots Having 'r' values between 0.980 and 0.997. were generated using log cumulative % of medicine surviving as a function of time, indicating kinetics of initial order were followed by the release. To ascertain the drug release mechanism and the polymer matrix's swellability, Higuchi and Peppa's models were adapted to the in vitro drug release data. When Higuchi's equation—which plots the When the data was analysed, the square root of time vs the cumulative percentage of drugs released revealed that the drug is released. from films via a diffusion mechanism. The 'r' values in the linear plots ranged from 0.988 to 0.997. It was discovered that all formulations had 'n' values of 0.5. Formulation CH8, which contains 50% plasticiser by weight of polymer and chitosan and HPMC in a 1:1 ratio, has demonstrated encouraging results. It discharged over 90% of the medication in 5 hours, respectively.Its tensile strength and mucoadhesive properties are also passably strong. By employing a Perkin-Elmer IR spectrophotometer and the potassium bromide pellet technique, IR spectroscopic experiments (Fig.2) were able to eliminate interactions between drugs and excipients. Studies on the short-term stability of the promising formulation CH8 over a period of 90 days showed no significant variations in drug content between 30±2º at room temperature and 40±2º/75% RH.

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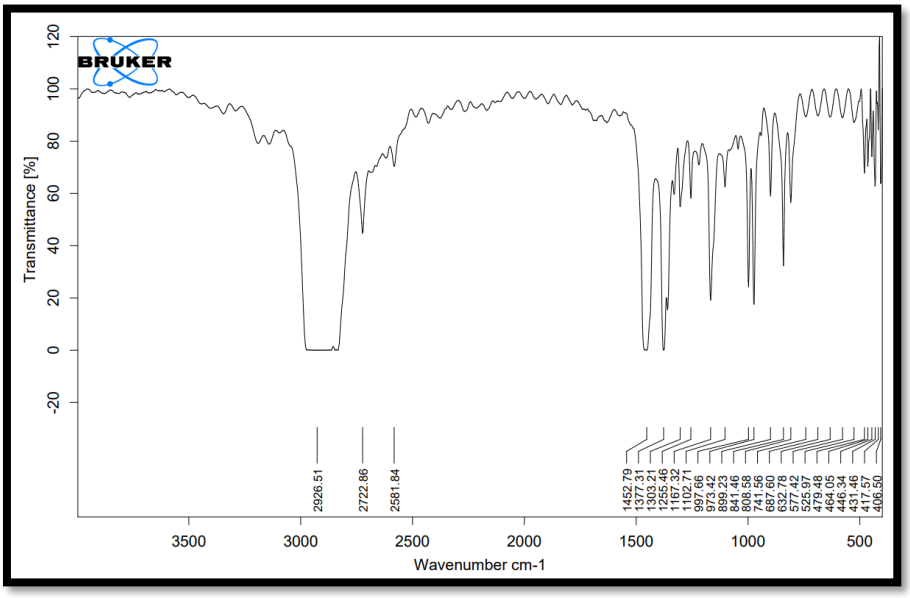
(A)



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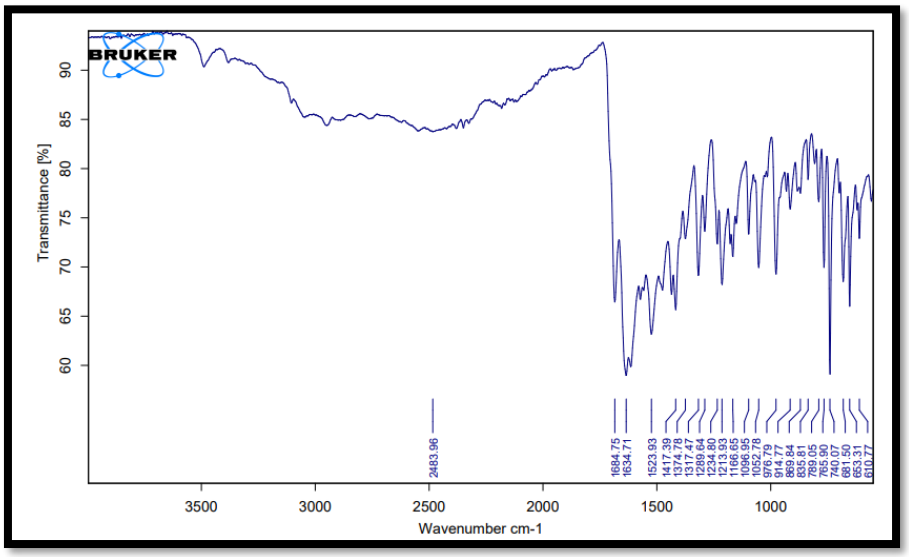

Fig 2: FT-IR Of (A) Aminophylline (B) Drug Excipient intraction

IV. Discussion

Aminophylline unidirectional mucoadhesive The spots in the buccal region were created to increase avoiding first-pass metabolism to increase bioavailability in the liver. The produced novel unidirectional mucoadhesive buccal patches of aminophylline would work well as a medication delivery method for systemic delivery of aminophylline, according to the release profile in vitro, which showed that the maximum amount of aminophylline is released from the prepared patches within the specified mucoadhesion period. However, in vivo research will need to be done in the future to verify this.

V. Conclusion

The current study's findings showed that chitosan and HPMC (15cps) can be used to successfully create buccal patches containing the medication Aminophylline. The formulation CH8, which has the polymers in a as a buccal drug administration method for aminophylline, a 1:1 ratio and a plasticiser concentration of 50% by weight of polymer have demonstrated potential. It released

over 90% of the drug in 5 hours respectively. It also had mucoadhesive and reasonably good tensile strength.

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