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FORMULATION CHARACTERIZATION AND *IN-VITRO* DIFFUSION STUDIES OF HERBAL EXTRACT LOADED MUCOADHESIVE BUCCAL PATCHES

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ABSTRACT: The present paper deals with a novel approach in formulating and characterizing mucoadhesive buccal patches with the incorporation of herbal extract. In the present arena of Novel Drug Delivery System, delivery of drugs through buccal mucosa serves an easier method for utilization of drugs leading to reduction of dose frequencies and thereby tends to sustain the drug release. Buccal patches were prepared with herbal (Neem) extract with two polymers such as Methyl Cellulose and Hydroxy Propyl Methyl Cellulose in a respective solvent such as Ethanol with Propylene glycol as the plasticizer. Buccal patches were successfully formulated by solvent casting technique with several concentrations of polymers and those prepared patches were characterized in terms of film thickness, film weight, colour, surface texture, folding endurance, surface pH, swelling behaviour and percentage of moisture loss. Percentage of drug content in all patches was also determined and all patches showed their significant properties upon characterization and there was uniformity in drug content for all patches. *In-vitro* drug diffusion studies were carried out using a dialysis membrane for four hours which signified satisfactory resuts.

INTRODUCTION: The term 'Mucoadhesion' signifies the adhesion between two materials with each other where one of the material is a mucosal surface. The mucoadhesive drug delivery system plays a pivotal role as an innovative drug delivery system of the modern era. In simple words, mucoadhesion can be stated as the attachment of drug along with a suitable carrier that attaches to the mucous membrane. Such formulations have a wide scope of application for both systemic and local effects of drug[1].

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Drug delivery through oral mucosa also helps in overcoming hepatic metabolism, controlled and sustained rate of drug release[2]. Two mechanisms underlying the mucoadhesive phenomenon are the intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon) and the penetration of the bioadhesive into the tissue or the surface of the mucous membrane [3, 4].

Apart from inhalable, injectables, transdermal routes, buccal route of drug delivery are at the most[5]. Normally, molecular weight, flexibility, hydrogen bonding, concentration, hydration etc are influenced by the polymers employed in the formulation.[6] Environmental factors such as saliva also plays a key role. Polymers which can be employed are like hydrophilic polymers such as Polyvinyl Pyrrolidone (PVP), Methyl Cellulose[6] etc. Non specific bioadhesive polymers include

Polyacrilic acid, Cyanocryllates. Anionic polymers such as CMC, cationic polymers such as Chitosan can be used. Non ionic polymers include PVP, HPMC and Hydrogels. Several plasticizers can be used for formulating buccal films/patch which includes alcohol, Glycerine, Dibutyl phthalate, Propylene glycol, Triethanolamine etc. Utilization of mucoadhesive buccal drug delivery system promotes prolong drug delivery, improved patient compliance and therapeutic efficacy. In terms of safety, flexibility and comfortness, buccal drug delivery can be the ultimate choice.

Neem (*Azadirachta indica*) is a fast-growing tree that can reach a height of 15–20 metres (49–66 ft). It is evergreen, but in severe drought it sheds most or nearly all of its leaves. The branches are wide and spreading. The neem tree is very similar in appearance to its relative, the Chinaberry (*Melia azedarach*). The growth of neem tree occurs in different types of soil, but it thrives best on well drained deep and sandy soils. It can tolerate high to very high temperatures and does not tolerate temperature below 4 °C (39 °F). Literature speaks about neem's antibacterial, sedative, antimicrobial, antiseptic and several properties. It is considered a major component in Ayurvedic and Unani medicine and is particularly prescribed for skin diseases.

Neem oil is also used for healthy hair, to improve liver function, blood purification and balance blood sugar levels. Apart from that it is used as traditional medicine as well as pest and disease control aid[7]. All such kinds of properties can be enhanced by a novel route of administration such as buccal route by which a minimum dose can be administered which will give a sustained release assuring maximum bioavailability finally leading to good therapeutic activity.

MATERIALS AND METHODS:

Materials and Equipments

Ethanolic extracts of Neem, Hydroxy Propyl Methyl Cellulose (HPMC), Methyl Cellulose, Propylene glycol, Ethanol, Sorbitol liquid were used and several equipments employed in the formulation of herbal patches were Magnetic stirrer, Petridish, Ultrasonic cleaner, Electronic balance, pH meter, UV-visible spectrophotometer, Tray drier and Hot air oven.

Methods

Preparation of Ethanolic extract of Neem leaves:

Fresh Neem leaves were collected and they were washed thoroughly with normal water to remove dust particles from the surface of leaves. Then they were again washed with distilled water and they were shed dried. After drying, leaves were grinded until coarse powder is obtained. Then significant amount of the powdered leaves (200gm) were weighed and they were macerated in 1000ml of ethanol for 7 days. Solvent containing the extract was decanted and was concentrated using a rotary evaporator to get the crude extract. The concentrated extract was then dried under room temperature and it was used further for preparing mucoadhesive patches[8]. The net yield of the crude extract was found to be 2gm.

Preperation of buccal patches:

The technique employed for preparing mucoadhesive buccal patches was solvent casting technique[9]. They were prepared by dissolving several concentrations of polymers such as 150mg, 300mg and 600mg in 5ml of ethanol and calculated amount of the extract (40mg) was dissolved in another 5ml of ethanol and this mixture was added to the polymer mixture followed by the addition of 0.5ml of sweetening agent. Then 0.5ml of the plasticizer was added to all formulations and were further sonicated to remove all entrapped air bubbles.

HYDROXY PROPYL METHYL CELLULOSE PATCH

METHYL CELLULOSE PATCH

FIG 1: FORMULATED BUCCAL PATCHES

Then they were transferred to a petridish and allowed to dry under room temperature by placing a funnel in an inverted position over the petridish for 24 hours. After that all the patches were studied for further characterizations. Composition of all patches is shown in **Table 1**. Formulated patches with polymers Hydroxy Propyl Methyl Cellulose and Methyl Cellulose are depicted in the **Fig 1**.

TABLE 1: COMPOSITION OF MUCOADHESIVE BUCCAL PATCHES

S.no	Ingredients	F1	F2	F3	F4	F5	F6
1	Neem extract	40mg	40mg	40mg	40mg	40mg	40mg
2	Methyl Cellulose	600mg	300mg	150mg	-	-	-
3	Hydroxy Propyl Methyl Cellulose (HPMC)	-	-	-	600mg	300mg	150mg
4	Ethanol	10ml	10ml	10ml	10ml	10ml	10ml
5	Propylene glycol	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml
6	Sorbitol liquid	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml

CHARACTERIZATIONS OF FORMULATED MUCOADHESIVE BUCCAL PATCHES [Table 2(a), 2(b)]

Patch weight, Patch thickness and Surface texture:

All patches were weighed on a digital weighing balance and their weights were noted. Film thickness was measured using Vernier Callipers from all sides at different position and the average value was noted. Surface texture of all the patches were noted by touching the surface of the films [9,10].

Colour:

Colour of all the formulated patches was noted visually and they were reported finally.

Folding endurance:

Folding endurance of buccal patches was determined by folding each patches at the same place repeatedly until it breaks. Number of times the patches can be folded until it breaks gives the value of folding endurance and the average value was noted[11].

Surface pH:

Patches of $1cm^2$ each were allowed to swell in 2% agar solution in a clean, dry petridish for two hours consecutively. Surface pH of patches was determined by placing pH paper on the surface of patches[12].

Swelling behavior:

Each patches of size (1cmx1cm) was cut and their initial weight was noted. Then they were allowed to swell for 5min in 20ml of distilled water. Patches were than taken out, dried and weighed. Percentage of swelling was noted using the following formula:

Swelling Index (SI) = Final weight - Initial weight/Initial weight x 100

Percentage Moisture Loss (PML):

All patches of size 1cmx1cm was initially weighed. They were placed in a dessicator containing Calcium chloride and the internal humidity was maintained. After 72 hours, all patches were collected back and reweighed. Average value was noted using the following formula**:**

Percentage Moisture Absorption (PML) = Initial weight - Final weight/Initial weight x 100

Percentage drug content estimation:

For estimating percentage of drug content in all the patches, three patches of 1cmx1cm was cut and dissolved in 5ml of ethanol and was diluted to 100ml with phosphate buffer of pH 6.8. From this stock solution, 10ml of the solution was withdrawn using a pippette and diluted to 100ml with phosphate buffer of pH 6.8 to get a primary solution. 10ml of solution was again withdrawn from this primary solution and diluted to 100ml with the same buffer solution to get 10µg/ml solution[11]. Drug content was estimated using UV spectrophotometer at 510nm. Percentage drug content estimation is shown in **Table 3**, **Fig 2**.

Percentage drug content = Test absorbance /Standard absorbance x 100

IN-VITRO DRUG DIFFUSION STUDY:

The *in-vitro* drug diffusion study was carried out using open ended cylinder method with the use of a membrane that is semi permeable. The dialysis membrane was activated by immersing it into the water. The membrane of appropriate size was tied to one end of the open ended cylinder which acted as the donor compatment.

Then the cylinder was dipped into the diffusion medium which acted as the receptor compartment. Phosphate buffer of pH 6.8 was used as the diffusion medium. Patches of appropriate sizes were than placed in the donor compartment and they were kept seperated from the receptor compartment using the dialysis membrane. Temperature was maintained at 37°C at 50 rpm. 10 ml of the sample was withdrawn after every half an hour for 4 consecutive hours and simultaneously the receptor compartment that is the diffusion medium was replaced with the fresh buffer[13]. The absorbance was determined using UV spectrophotometer at 510nm. Percentage of drug diffusion is depicted in **Table 4, Fig 3**.

RESULTS AND DISCUSSION:

Patch weight, Patch thickness and Surface texture:

Overall patches weights were found in the range of 0.21-0.59g, patch thickness were found in the range of 0.101-0.112mm and surface texture were found to be smooth for all the patches.

Colour:

Colour of all the patches were uniformly found to be green.

Folding endurance:

Folding endurance of all the patches were found to be flexible exceptionally for F3, F4 and F6 but F1, F2, F5 were found to be very flexible.

Surface pH:

Surface pH of all the patches were found almost neutral i.e 7-8.

Swelling behaviour:

Overall swelling index of all the patches were found in the range of 25-130% except F3 and F6, which were found to be negligible.

Percentage Moisture Loss (PML):

Percentage of moisture loss were found to be negligible for all the patches.

TABLE 2(A): CHARACTERIZATIONS OF MUCOADHESIVE BUCCAL PATCHES

S. No.	Formulations	Patch weight	Patch thickness	Surface texture	Colour
1	F1	0.59g	0.110mm	Smooth	Green
2	F2	0.39g	0.112mm	Smooth	Green
3	F3	0.21g	0.104mm	Smooth	Green
4	F4	0.51g	0.112mm	Smooth	Green
5	F5	0.23g	0.101mm	Smooth	Green
6	F6	0.25g	0.110mm	Smooth	Green

TABLE 2(B): CHARACTERIZATIONS OF MUCOADHESIVE BUCCAL PATCHES

S. No.	Formulations	Folding endurance	Surface pH	Swelling behavior	Percentage Moisture Loss
1	F1	**	8	25%	Negligible
2	F2	**	8	55%	Negligible
3	F3	*	8	Negligible	Negligible
4	F4	*	7	40%	Negligible
5	F5	**	7	130%	Negligible
6	F6	*	8	Negligible	Negligible

*Flexible **Very flexible

Percentage drug content estimation: Percentage of drug content in all the patches were found in the range of 89.71% - 96%.

TABLE 3: PERCENTAGE DRUG CONTENT ESTIMATION

S. no.	Formulations	Test absorbance	Percentage drug content
1	F1	0.0165	94.28
2	F2	0.0166	94.85
3	F3	0.0157	89.71
4	F4	0.0168	96
5	F5	0.0167	95.42
6	F6	0.0160	91.42

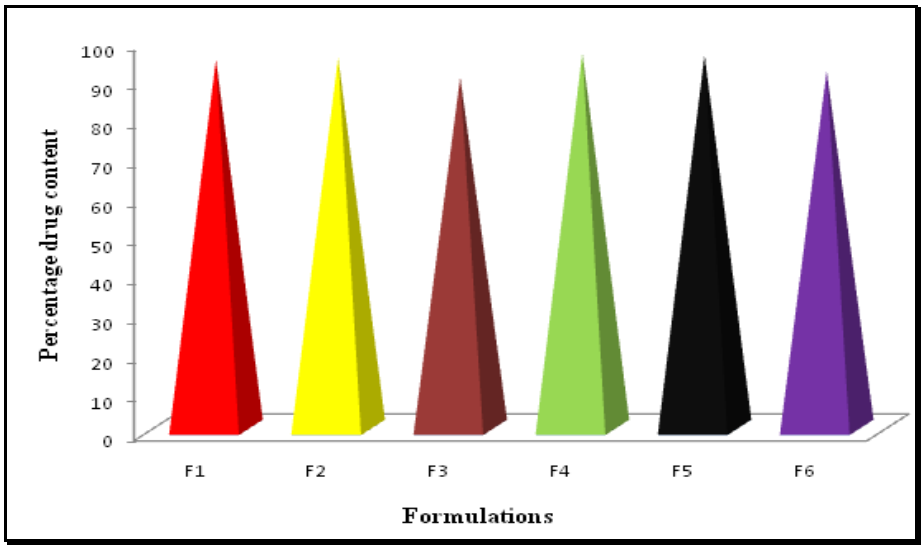

FIG 2: PERCENTAGE OF DRUG CONTENT

***IN-VITRO* PERCENTAGE DRUG DIFFUSION PROFILE:**

From the drug diffusion profile from all the patches, it is observed that patches with the high polymer concentration, that is F1 and F4 which contains 600mg of respected polymers gave a sustained drug diffusion pattern with 55.43% and 54.28% after a study period of 4 hours when compared to the other consecutive formulations with polymer concentrations of 300mg and 150mg and has significant amount of drug content which is revealed upon their characterizations. Hydroxy Propyl Methyl Cellulose showed a better result in sustaining the drug diffusion. Hence, it is proved that higher polymer concentration tends to release the drug from the formulation slowly and in a sustained manner.

TABLE 4: PERCENTAGE OF DRUG DIFFUSION

Formulations	0min	30min	60min	90min	120min	150min	180min	210min	240min
F1	0	27.08	42.3	45.49	48.78	49.6	53.21	54.3	55.43
F2	0	28.41	31.64	33.56	50.34	52.33	53	54.67	56.78
F3	0	33.33	35.45	43	46.6	49.34	52.33	56.33	58.92
F4	0	34.02	37.41	39.44	46.82	47.53	52.77	53	54.28
F5	0	33.68	42.7	46.58	48.77	53.22	54.54	56.77	57.1
F6	0	35.21	37.43	43.11	49.36	52.81	53.43	55.34	57.88

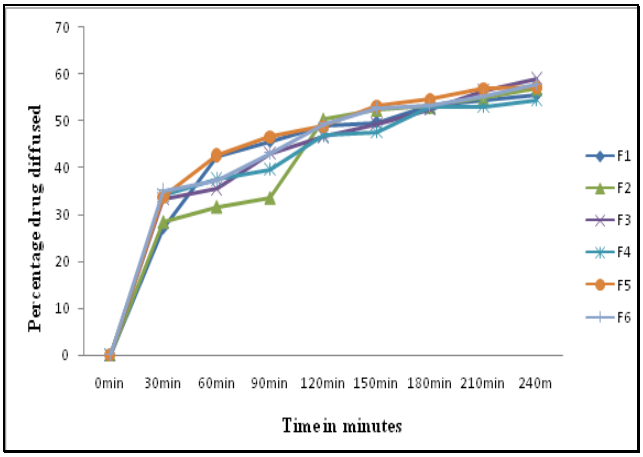

FIG 3: *IN-VITRO* PERCENTAGE DRUG DIFFUSION PROFILE

CONCLUSIONS: Herbal extract loaded mucoadhesive buccal patches were succesfully formulated by several concentrations of Methyl Cellulose and Hydroxy Propyl Methyl Cellulose (HPMC) polymers and with Propylene glycol plasticizer and with an organic solvent ethanol and were characterized. From this novel approach, it can be concluded that herbal drugs in the form of extracts can also be employed in formulating mucoadhesive patches in contrast with the usage of allopathic drugs in accordance with their appropriate concentrations and doses.

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