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PREPARATION AND EVALUATION OF PARACETOMOL MUCOADHESIVE BUCCAL PATCHES USING TAMARIND SEED POLYSACCHARIDE AS A NATURAL BINDER

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ABSTRACT: Mucoadhesive buccal patches provide a wide variant of therapeutic effect via mucosa and buccal region of the mouth. They provide zero first pass metabolism and high bioavailability providing patient compliance. In the present study, buccal patches of paracetamol were developed to improve the bioavailability and half life of the drug. In the process of its preparation binder plays a greater role in holding the drug. One of such is Tamarind seed polysaccharide (TSP) isolated from the kernels of *Tamarindus indica* seeds was used as a binder in the preparation of paracetamol mucoadhesive buccal patches. Here, solvent casting method was employed and performed various evaluation parameters. Mucilage extracts at 0.5,1, 1.5, 2, 2.5% concentrations were used. All the patches were shown smooth surface and elegant texture. The weights of (10 mm) patches were in the range of 21.6 to 26.8 mg. The results indicate that the formulation with 2% mucilage extract shows maximum drug release. Among the five formulations (F1 to F5), F4 formulation showed maximum percentage of drug release.

INTRODUCTION: Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for systemic drug delivery of drugs via various pharmaceutical products of different dosage forms. [1] Pharmaceutical products designed for oral delivery are mostly the immediate-release type, which are designed for immediate drug absorption. Recently, a new generation of pharmaceutical products called controlled-release drug delivery systems received regulatory approval for marketing and their pharmaceutical superiority and clinical benefits over the sustained-release and immediate release pharmaceutical products [2].

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Buccal patches: Buccal route of drug delivery is a good alternative, amongst the various routes of drug delivery [3]. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery and offer distinct advantages over oral administration for systemic drug delivery such as possible bypass of first pass effect, avoidance of pre-systemic elimination within the GI tract, these factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery. Buccal mucosa has rich blood supply and it is relatively permeable [4].

In this project, it is proposed to use tamarind as a natural gum. Tamarind *(Tamarindus Indica* L.) is amongst the most common and commercially important, large evergreen tree that grows abundantly in dry tracks of central and south Indian states, also in other south East Asian countries. The pulpy portion of fruit is mainly used as acidulant in Indian recipes [5].

Tamarind seed polysaccharide: Polysaccharide present in tamarind kernel powder is called as tamarind seed polysaccharide. Tamarind seed polysaccharide is having molecular weight 52350 units and monomer of glucose, galactose and xylose in molar ratio of 3:1:2 [6]. Various methods have been reported for the isolation of tamarind seed polysaccharide from tamarind kernel powder. It is insoluble in organic solvents and dispersible in hot water to form a highly viscous gel such as mucilaginous solutions with a broad pH tolerance and adhesivity. In addition, it is non-toxic and non-irritant with haemostatic activity. Recently tamarind seed polysaccharide is widely used for pharmaceutical applications [7-8].

MATERIALS AND METHODS: Tamarind seed polysaccharide (TSP), Distilled water, Acetone, Propylene glycol (plasticizer), polyvinyl pyrrolidine, hydroxyl propyl methyl cellulose, paracetomol, mucilage (binder) were used for the study. Solvent casting method was employed for the preparation of buccal patches.

Mucilage extraction: Tamarind seeds are collected and dried in sunlight. The kernels are crushed into fine powder. 20g of fine kernel powder is added to cold distilled water to prepare slurry. The slurry thus obtained must be poured into 800 ml of boiling distilled water and boiled for 20 minutes on a water bath to obtain a clear solution which is kept aside overnight. The thin clear solution was then centrifuged at 5000 rpm for 20 minutes to separate all the foreign matter. Supernatant liquid was separated and poured into excess of acetone with continuous stirring. Precipitate obtained was collected by suitable method. It was washed with 200ml of acetone and dried at 50^0 C for 10 hrs. The polymer was stored in a dessicator [9].

Preparation of mucoadhesive buccal patches: For the preparation of patches, 250mg of drug (Paracetamol), 50mg of polyvinyl pyrrolidine (polymer), and 3% of hydroxyl propyl methyl cellulose (polymer) were accurately weighed and mixed by trituration in a glass pestle and mortar. The mixture was then added gradually to mechanical stir solvent system containing the plasticizer (propylene glycol) and binder (tamarind seed polysaccharide). Stirring was continued until a clear solution was obtained. The solution was then transferred quantitatively to petri-dish (glass) diameter 6cm. The petri-dishes were covered with inverted funnels to allow controlled evaporation of the solvents. These were left undisturbed upon temperature (20-25^0C) for one to two days depending upon the solvent system used. Small patches of size 15mm and 20mm diameter, 0.2 to 0.3 mm thick were carefully pulled out from the petri-dishes [10].

Evaluation of muco adhesive buccal patches [11-12]

Thickness: The thickness of three randomly selected buccal patches from every batch was determined using a standard screw gauge.

Weight uniformity: Weight uniformity of patch determined by taking weight of ten patches of sizes 10mm diameter from every batch and weigh individually on electronic balance.

Surface pH: The patches was allowed to swell then in contact with 0.5 ml of distilled water (pH 6.5±0.5) for one hour at room temperature and pH was noted down by bringing electrode in contact the surface the pH , allowing it equilibrate for 1 minute [13].

Swelling Index of patches: Swelling of excipients of mucoadhesive dosage form involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the mucoadhesive dosage form.

For the determination of swelling index, the pre weighed (W1) three patches 10mm diameter from each formulation was placed in Petri dishes (containing 20 ml of water). After 5, 10, up to 30 min intervals, the patches were removed and the excess water on their surface was carefully removed using filter paper. The swollen patches were weighed (W2) accurately.

The percentage of swelling index calculated by,

$$\% \text{ Swelling Index} = (W2-W1) \div W1 \times 100$$

Folding endurance: Folding endurance of the patches was determined (Khanna et al., 1997) by repeatedly folding one patch at 180^0 angle the same place till it broke or folded up to 300 times manually without breaking, which was considered satisfactory to reveal good patch properties [14].

***In vitro* release study:** The rotating paddle method was used to study the drug release from buccal patches. The dissolution medium consisted of 400 ml of isotonic phosphate buffer pH 6.6. The release was performed at 37 ± 0.5 °C, at a rotation speed of 50 rpm. One side of the buccal patch was attached to a glass disk with instant adhesive. The disk was put in the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Samples (1 ml) were withdrawn by using calibrated pipette at pre-determined time (1 hour) intervals and replaced with fresh medium. The samples were filtered through 0.45µm Whatman filter paper with appropriate dilutions with phosphate buffer pH 6.6 and were assayed spectrophotometrically at 278 nm [15].

RESULTS AND DISCUSSION: All the patch formulations containing HPMC as the mucoadhesive polymer with propylene glycol as plasticizer, paracetamol as the drug and tamarind seed polysaccharide as the natural binder were readily prepared by solvent casting method by using 50mg drug per 1*1 cm2 patch. Patch formulations with higher percentage of polymer were shown to be easily removed from the petridishes and are shown to be more prominent. The Composition of mucoadhesive buccal patches was shown in **Table 1**.

In the present study, buccal patches were developed to improve the bioavailability and half life of the drug. All the patches shown smooth surface and elegant texture. The weights of (10 mm) patches were in the range of 21.6 to 26.8 mg. The patches were found uniform in weight. All the patches have uniform thickness throughout and patch thickness in the range of 0.90 to 0.96 mm. The folding endurance was measured manually, patches were folded repeatedly till it broke, and it was considered as the end point. Folding endurance was found to be in the range of 220 to 255. The folding endurance was found to be more for F4 and the lowest for F1 formulation.

The surface pH of all patches was 6-7. It indicates that the surface pH of all formulations was neutral pH and hence no mucosal irritation is expected. From the results, formulation F4 was found to be prominent over all formulation. The results of all the above mentioned tests are shown in **Table 2**. Drug release study was performed for various mucoadhesive patch formulations **(Fig. 1**). All formulation showed more than 75% of drug release after. Among them, F4 formulation shows maximum % release. The results were shown in **Table 3**.

TABLE 1: THE COMPOSITION OF MUCOADHESIVE BUCCAL PATCHES

Composition of formulation	Drug	Mucilage	PVP	Propylene glycol	HPMC
F1	250mg	0.5%	50mg	5%	3%
F2	250mg	1%	50mg	5%	3%
F3	250mg	1.5%	50mg	5%	3%
F4	250mg	2%	50mg	5%	3%
F5	250mg	2.5%	50mg	5%	3%

TABLE 2: EVALUATION TESTS OF MUCOADHESIVE BUCCAL PATCHES

S. No	Parameter	Referred value	F1	F2	F3	F4	F5
1	Weight variation	Average ± 25mg	21.6mg	23.9mg	25.4mg	28.2mg	26.8mg
2	Patch thickness	uniform	0.90mm	0.91mm	0.93m	0.94mm	0.96mm
3	Surface pH	6.2 – 7.0	7	6.8	6.4	6.1	6
4	Folding endurance	Not less than 250	224	238	248	255	242
5	% drug release	Above 75%	80	86	90	95	89
6	Swelling index	15.40±3.09	15.23±2.30	15.35±3.30	15.55±2.1	15.66±2.96	15.34±2.5

TABLE 3: *IN-VITRO* DRUG RELEASE OF FORMULATIONS FROM F1 TO F5 (N=3)

Time in (min)	Cumulative % of drug released (Mean ± SD)*				
	F1	F2	F3	F4	F5
10	17.16±2.25	22.26±6.75	26.71±0.22	26.98±2.06	26.48±3.12
15	25.54±3.65	34.48±7.24	33.73±1.71	38.20±2.45	37.11±3.26
30	46.57±6.21	46.98±8.12	41.10±1.68	48.65±3.15	49.11±7.20
45	58.62±2.67	59..24±6.25	52.27±1.27	63.83±3.26	60.72±5.68
60	73.56±3.76	70.88±6.64	62.84±1.47	70.01±1.46	72.21±4.16
90	82.16±2.62	76.42±4.38	77.65±1.29	82.18±2.48	79.81±2.18
120	84.36±3.32	88.65±2.36	90.34±1.57	90.13±0.49	84.73±2.56
150	85.45±2.46	92.17±0.66	92.32±0.68	95.15±1.28	86.38±1.46
180	86.68±1.75	93.11±0.92	93.34±1.18	95.46±1.38	87.61±1.34

* Indicates average of three determinations

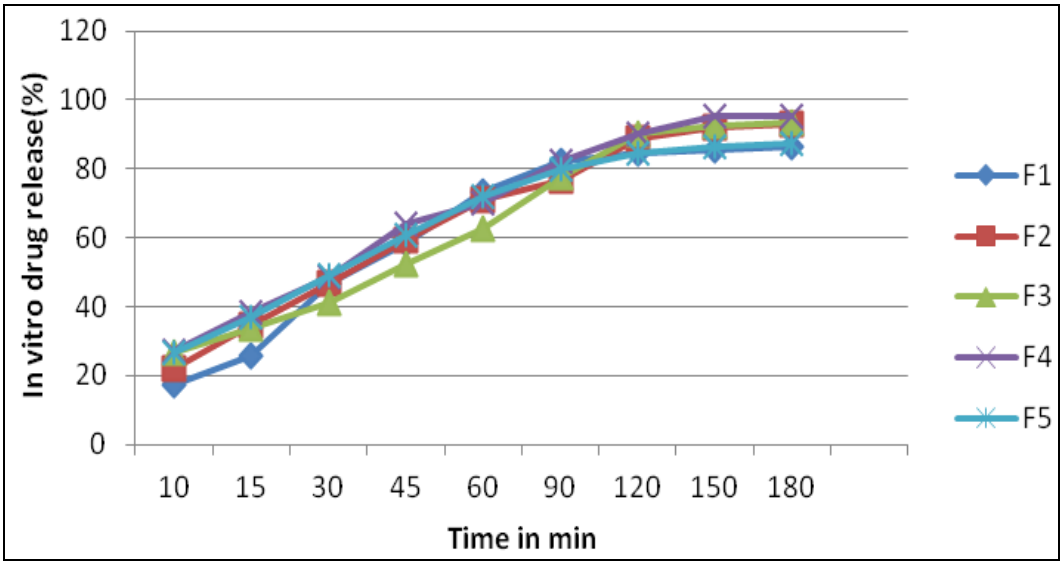

FIG. 1: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATIONS F1 TO F5

CONCLUSION: Polysaccharides are the choice of materials among the hydrophilic polymers. A novel polysaccharide named Tamarind Seed Polysaccharide is now being used as an excipient in the hydrophilic drug delivery system because of its properties which include non-carcinogenicity, mucoadhesivity etc. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein-drug molecules.

Buccal patches were developed using paracetamol as drug, PVP as plasticizer and tamarind as a natural binder. Tamarind seed Polysaccharide was found to be an adaptable excipient for novel drug delivery systems. However, the need for safe and effective buccal permeation or absorption enhancers is a crucial component for a prospective of future in the area of buccal drug delivery.

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