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Development of Dual layers Drug Delivery for Motion Sickness

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Abstract: We have developed the mucoadhesive buccal films for delivery of scopolamine using various polymers for immediate and sustained release formulation with Chitosan as basic polymer and polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP) hydroxy propyl cellulose (HPC) and Eudragit. Radial swelling and mucoretention characteristics were determined for both plain and medicated patches. Various physical parameters were evaluated for compatibilities for oral mucosal drug delivery. The surface pH of all formulations was within 6.2 to 6.7 ±0.5 units of the neutral pH so no mucosal irritation was expected. A decrease in the residence time was observed for PVA and eudragit containing formulae. The immediate release formulation has shown a total release with in 30 minutes. And sustained release formulation has shown a delayed release up to 12 hrs. Prolong drug release was obtained from HPC. A considerable drop in release was observed for chitosan formulae after the addition of water-soluble additives, polyvinyl pyrrolidone (PVP). The mucoretention was carried out up to the end of studies which makes the system suitable and compatible for buccal delivery

Keywords: Buccal patches, Motion sickness, Scopolamine, Mucoretention, Polymers

Introduction:

The buccal route, as an alternative to other traditional methods of systemic drug administration, is a subject of growing interest because of its numerous advantages[1]. It is well known that the absorption of therapeutic compounds from the oral mucosa provides a direct entry of the drug into the systemic circulation, therefore, avoiding the first pass hepatic metabolism and gastrointestinal drug degradation, which is associated with oral administration. The oral cavity is easily accessible for self medication and, hence is well accepted by patients, and is safe, since device can be easily administered and even removed from the site of application, stopping the input of drug whenever desired.

From a technological point of view, an ideal buccal dosage form must have three properties; It must maintains its position in the mouth for a few hours, release the drug in a controlled fashion and provide drug release in a unidirectional way towards the mucosa. In the present study; we chose the polymer to develop the release of drug in immediate and sustained manner. This will achieve the better treatment for motion sickness in terms of suitability and acceptance. [2]

Materials and Methods:

Preparation of Patches:

Chitosan was dissolved in sufficient quantity of solvent systems under constant stirring using a magnetic stirrer for 1 h. The resultant viscous solution was filtered through gauze. The filtrate was left to stand until all air bubbles disappeared. In all cases, 5% (w/w of polymer) glycerol was added as plasticizer. The solution was poured into a clean, dry, glass Petri dish (5 cm in diameter) and left to dry at room temperature. Hydrophilic additives were first dissolved in a small volume of vehicle, and then added to the chitosan solution prepared as described above. The drug solution was added to the polymeric solution under stirring. Sodium benzoate (0.5%) as preservative and Clove oil (1%) as flavouring agent were added in the systems.

The dried films (plain patches) were carefully removed from the Petri dish, checked for any imperfections or air bubbles and cut into 0.75 x 0.50 inch patch size so that each patch contained 1 mg of the drug.,. The samples were packed in aluminum foil and stored in a glass container maintained at room temperature and 58% relative humidity (7); this condition maintained the integrity and elasticity of the patches. [3]

Same methods were adopted for the preparation of immediate release patches were glycerol (2% w/w of polymer) was added as plasticizer and water was used as solvent systems.

Evaluation Parameters:

Physical appearance: The films were observed visually for their physical appearance such as colour and transparency.

Table: 1 Formula for sustained release (SR) drug delivery systems.

Ingredients in (%)	**SR_1**	**SR_2**	**SR_3**	**SR_4**	**SR_5**	**SR_6**	**SR_7**	**SR_8**
Drug	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33
Chitosan	3	3	3	3	3	3	3	3
Poly vinyl alcohol	0.5	1	-	-	-	-	-	-
Polyvinyl pyrollidone	-	-	0.5	1	-	-	-	-
Hydroxy propyl cellulose	-	-	-	-	0.5	1	-	-
Eudragit S 100	-	-	-	-	-	-	0.5	1
Glycerol	5	5	5	5	5	5	5	5
Sodium benzoate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Clove oil	1	1	1	1	1	1	1	1
Solvent systems: (chloroform+ methanol + dichloromethane)-2:1:2 q.s. to	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml

Table: 2 Formula for immediate release (IR) drug delivery systems.

Ingredients in (%)	**IR_1**	**IR_2**	**IR_3**	**IR_4**	**IR_5**	**IR_6**
Drug	0.5	0.5	0.5	0.5	0.5	0.5
HPMC E-15	10	15	20	25	30	35
Dextrose	2.5	2.5	2.5	2.5	2.5	2.5
Glycerol	2	2	2	2	2	2
Sodium benzoate	0.5	0.5	0.5	0.5	0.5	0.5
Clove oil	1	1	1	1	1	1
Water q. s.	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml

***Surface texture**:* The surface textures of the films were evaluated by pressing the film with finger.

Weight variation: Four films of each formulation were taken weighed by using single pan balance and average weight films were calculated and standard deviations were computed.

***Thickness and size**:* Four Films of each formulation were taken and the thickness of the film was measured using screw gauge at different places. The average film thickness and standard deviation were computed.

***Surface pH**:* Buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (m/v) agar in warmed phosphate buffer of pH 6.6 under stirring and then pouring the solution into a Petri dish till gelling at room temperature. The surface pH was measured by means of a pH meter by bringing the glass electrode on the surface of the swollen patch. The mean of two readings was recorded.

***Folding endurance test**:* The folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Swelling: Three patches were tested for each formulation of sustained release (SR). After determination of the original patch diameter, the sample was allowed to swell on the surface of an agar plate kept in an incubator maintained at 37 °C. Measurement of the diameter of the swollen patch was done at one-hour intervals for 12 h. Radial swelling was calculated from the following equation:

$SD\ (\%) = (Dt - Do)/Do \times 100$

Where *S*D (%) is the percent swelling obtained by the diameter method, *D*t is the diameter of the swollen patch after time *t*, *D*o is the original patch diameter at time zero.[4]

Mucoretention time: The *in vitro* mucoretention time was determined using a locally modified apparatus. A semi circular sheet of 10 cm length was kept at 30° angle. The Rabbit intestinal mucosa was adhered to the center portion of the disc and the film was placed over it. The flow of phosphate buffer was maintained at 0.5 ml/min by using peristaltic pump. The time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded (mean of triplicate determinations).[5]

Figure: 1 Modified instrument for in vitro mucoretention studies

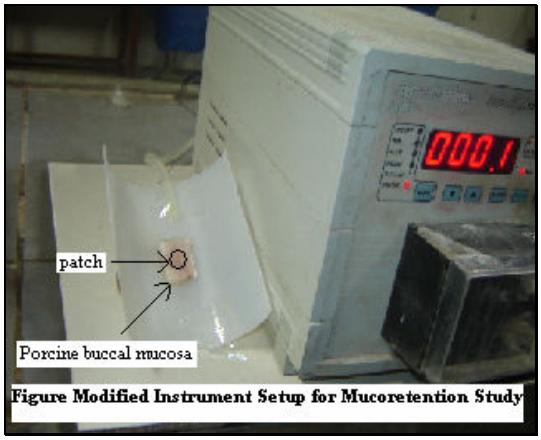


Figure Modified Instrument Setup for Mucoretention Study

In vivo residence study: Four healthy subjects (25–50 years old) agreed to participate in the *in vivo* study. The experiment was carried out with plain patches only. The bioadhesive patch was placed on the buccal mucosa between the cheek and gingiva in the region of the upper canine and gently pressed onto the mucosa for about 30s. The patch and the inner upper lip were carefully moistened with saliva to prevent patch from sticking to the lip. The subjects were not allowed to eat or drink during the study (12 h). They were asked to monitor the ease with which the system was retained on the mucosa and note any tendency to detachment. The adhesion time was indicated by either complete erosion of the patch or failure of the adhesive bond. Any complaints and bad feelings were also recorded. Repeated application of the bioadhesive patches by the same volunteer was allowed after a two-day period.[6]

In vitro diffusion study: *In-vitro* diffusion studies were carried out in fabricated diffusion tube of surface area 1.5 cm^2 through sigma dialysis membrane. The sigma dialysis membrane was hydrated by addition of distilled water and fixed to the one end of the tube which acts as a donor compartment. The assembly was placed in the beaker contained 50 ml of phosphate buffer of pH 6.6. The teflon coated magnetic bead was placed in the beaker and rotated at 100 rpm using magnetic stirrer and the temperature was maintained at 37 ± 1 ^{0} C. Samples of 1 ml were withdrawn at regular intervals and replace the volume with same buffer and maintained sink condition through the studies. The absorbance was measured at 235 nm for the entire sample. The same study was conducted for drug devoid film. Averages of triplicate readings were taken.

Ageing: Optimized medicated patches were subjected to accelerated stability testing. Patches were packed in glass Petri dishes lined with aluminum foil and kept in an incubator maintained at 37±0.5^{0}C and 75 ±5% RH for 6 months. Changes in the appearance, residence time, release behavior and drug content of the stored bioadhesive patches were investigated after 1, 2, 3, 4, 5, and 6 months. The data presented were the mean of three determinations. Fresh and aged medicated patches, after 6 months storage, were investigated using a Jeol, JSM-5300 scanning electron microscope (Jeol, Japan). The patches were coated with gold using the direct current sputter technique.[7]

Result and Discussion:

To develop the initial treatment for motion sickness, IR formulation of scopolamine for starting effect was designed and for sustained effect of drug up to 12 h, SR formulation was developed.Different Physical characteristics of the Sustained and immediate release patches containing polymers are evaluated. The patches were in uniform size of 0.75 inch x0.50 inch in length and having a thickness of 86 ± 2 µm and 124 ± 2 for 3.5% and 4% patch respectively. The surface pH of all formulations was within 6.2 to 6.7 ±0.5 units of the neutral pH so no mucosal irritation was expected. The measured folding endurance of the patches was > 350 time; this makes the system acceptable for movement of mouth. The results are shown in table: 3 and 4.

The swelling behavior was done by measuring radial swelling which shown a swelling at different concentration. The radial swelling of plain and drug containing patches shows an increase in patch swelling by the addition of the drug was noted. The presence of a water-soluble drug might improve the surface wetting of the matrix. In our study the formulation containing HPC shows almost 50 % of swelling compare to the initial one and slowest swelling was observed with hydrophobic

Table: 3 Physical characteristics SR buccal films of Scopolamine methyl bromide

Formulation Code	Appearance	Surface texture	**Average weight (mg± SD)	**Thickness (μm)	*Folding endurance	*Surface pH	*Drug content
SR1	+	Very smooth	222.18 ± 0.66	86.09 ± 0.35	> 350	6.5 ± 0.05	98.09±0.3
SR2	+	Very smooth	290.08 ± 0.61	122.9 ± 0.32	> 350	6.7 ± 0.05	98.29±0.2
SR3	–	smooth	223.11± 0.64	88.12 ± 0.59	> 350	6.2 ± 0.05	98.84±0.4
SR4	+	smooth	290.28 ± 0.57	124.9 ± 0.50	> 350	6.5 ± 0.05	98.57±0.2
SR5	+	Very smooth	221.31 ± 0.52	86.21± 0.48	> 350	6.2 ± 0.05	98.06±0.3
SR6	_	Very smooth	290.27 ± 0.49	126.1 ± 0.60	> 350	6.4 ± 0.05	98.07±0.3
SR7	+	smooth	224.18 ± 0.53	85.13 ± 0.57	> 350	6.6 ± 0.05	98.27±0.2
SR8	+	smooth	290.78 ± 0.49	121.1 ± 0.57	> 350	6.3 ± 0.05	98.43±0.4

+: Transparent -: Opaque
* Average value of three determinations
** Average value of four determinations

Table: 4 Physical characteristics IR buccal films of Scopolamine methyl bromide

Formulation Code	Appearance	Surface texture	**Average weight (mg± SD)	**Thickness (μm)	*Folding endurance	*Surface pH	*Drug content
IR1	+	Very smooth	211.34 ± 0.66	76.09 ± 0.33	> 450	6.5 ± 0.05	98.09±0.3
IR2	+	Very smooth	217.32 ± 0.61	80.39 ± 0.34	> 450	6.7 ± 0.05	99.29±0.2
IR3	+	Very smooth	223.15± 0.64	84.15 ± 0.52	> 450	6.2 ± 0.05	98.84±0.4
IR4	+	Very smooth	228.23 ± 0.57	88.9 ± 0.58	> 450	6.5 ± 0.05	99.57±0.2
IR5	+	Very smooth	233.61 ± 0.52	89.21± 0.65	> 450	6.2 ± 0.05	99.06±0.3
IR6	+	Very smooth	239.87 ± 0.49	94.1 ± 0.63	> 450	6.4 ± 0.05	98.07±0.3

+: Transparent -: Opaque
* Average value of three determinations
** Average value of four determinations

containing formulation SR7&8 due to poor water solubility which is depicted in figure 2.

Same physical characteristics were observed in case of IR formulation only a high folding endurance (>500) was observed compared to SR formulation. The IR formulation has shown an immediate dissolution in the system. The IR formulations get disappeared with in 5 minutes during mucoretention studies and it has shown a maximum drug release with in 30 minutes.

The release profile of scopolamine from chitosan-containing formulae is shown in figure: 3

Formulation SR6 containing chitosan and hydroxy propyl cellulose provided the prolong release profile with sustained and complete release within 12 h, a complex may be formed between drug and/or the cationic polymer, which may lead to a decrease in the release rate of the drug. At pH 6.6, chitosan shows partly positively charged inducing an electrostatic repulsion, which enhanced the drug release rate in case of chitosan alone formulation.

Figure: 2 Swelling studies for SR buccal films of Scopolamine methyl bromide

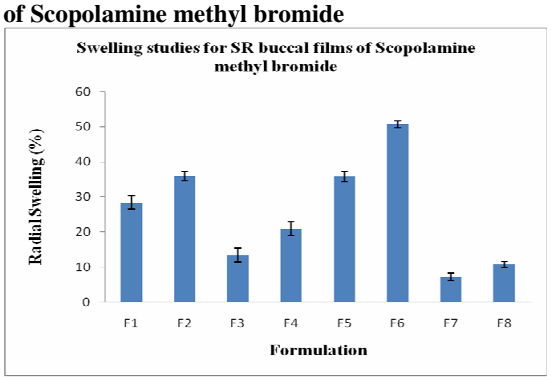
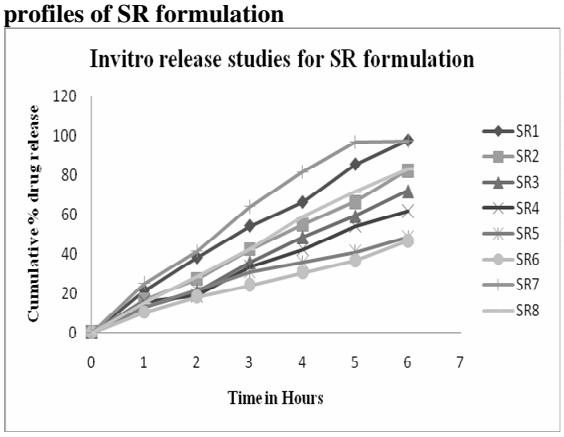


Figure : 3 Comparision of invitro release profiles of SR formulation



In this study, the relative rates at which the swelling and eroding fronts moved relative to each other were synchronized and a constant diffusional path length was obtained. For HPC containing patch, n is 0.796 indicating a non-fickian release behavior. When swelling is predominant, drug diffusion probably occurs through the solvent pathways of the patch. Erosion of the matrix can also influence the drug release from this polymer matrix. A relative contribution of erosion and diffusion to the overall release mechanism is suggested. In vivo residence study was conducted for the compatibility and acceptability of patient and result were depicted in the table 5.

The developed dosage form is well accepted by patient to make it convenient for oral mucosal drug delivery systems.

The SEM study of selected dosage form was also conducted to variefy the release from the prepared dosage form and their inertness structure. This indicates the uniformity in storage of dosage form.

Table 5 Response of human volunteers for various parameters

Criteria	Volunteer response
Irritation None	
Slight	100
Moderate	
Severe	
Taste Normal	
Slightly Unpleasant	
Very pleasant	5
Pleasant	95
Comfort	30
Very comfortable	40
Slightly Comfortable	30
Comfortable	
Uncomfortable	
Dryness of mouth	
None	90
Slight	10
Moderate	
Severe	
Salivary secretion	
None	20
Slight	70
Moderate	10
Severe	
Heaviness of patch at the site	60
	35
None	5
Slight	
Moderate	
Severe	

Conclusion:

The prepared system allows the treatment of motion sickness in two different phase which makes it convenient and desired on for the patient. This type of approaches will remove the barrier for implantation of oral mucosal drug delivery systems.

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