DEVELOPMENT OF DUAL LAYERS OF ORAL MUCOSAL DRUG DELIVERY OF SCOPOLAMINE FOR MOTION SICKNESS

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ABSTRACT:

The present study aimed to develop a dual-layer oral mucosal drug delivery system for scopolamine to effectively manage motion sickness. Scopolamine, a potent anticholinergic agent, is commonly used to alleviate motion sickness symptoms. However, its oral administration faces challenges such as low bioavailability and inconsistent absorption.

To overcome these limitations, a dual-layer oral mucosal drug delivery system was designed and optimized. The first layer comprised an immediate-release (IR) formulation of scopolamine, providing rapid symptom relief by addressing acute symptoms. The second layer incorporated a sustained-release (SR) formulation to maintain therapeutic drug levels for up to 12 hours, ensuring long-lasting efficacy.

Our approach focused on optimizing the characteristics of mucoadhesive buccal dosage forms, considering both human acceptability and proper drug release. The prepared system exhibited optimal properties for the development of such dosage forms. By employing this innovative strategy, we were able to deliver the treatment for motion sickness in two distinct phases. The initial dose provided immediate relief, addressing the acute symptoms, while the sustained drug release ensured prolonged efficacy, making it more convenient and desirable for patients.

The results of this investigation demonstrate the potential of the dual-layer oral mucosal drug delivery system as a promising alternative for motion sickness management. This advancement in drug delivery technology opens new opportunities for optimizing the therapeutic outcomes of scopolamine and enhancing the quality of life for individuals affected by motion sickness.

KEYWORDS:

Scopolamine, Dual-layer, Sodium Alginate, IR, DSC, Polyethylene glycol, Immediate-release,

Sustained-release, Motion sickness, Mucoadhesive buccal dosage forms

INTRODUCTION

The development of dual-layered oral mucosal drug delivery systems for scopolamine in the context of motion sickness aims to provide an effective and convenient way to administer the medication. Motion sickness is a common condition characterized by nausea, dizziness, and vomiting that occurs during travel or exposure to certain motion stimuli. Scopolamine, an anticholinergic drug, is commonly used to alleviate motion sickness symptoms.

The dual-layered oral mucosal drug delivery system involves a unique design that facilitates controlled release of scopolamine, ensuring optimal therapeutic effect while minimizing side effects. The system consists of two layers: a mucoadhesive layer and a drug reservoir layer.

MUCOADHESIVE LAYER

The mucoadhesive layer is designed to adhere to the oral mucosa, which enhances the contact time between the drug delivery system and the mucosal tissues. This layer typically contains mucoadhesive polymers or bioadhesive agents that promote the retention of the system at the site of administration, allowing for sustained drug release.

DRUG RESERVOIR LAYER

The drug reservoir layer contains scopolamine, either in the form of a solid dispersion, microspheres, or nanoparticles. This layer serves as a reservoir from which the drug is released gradually, ensuring a controlled and prolonged release profile. The selection of appropriate excipients and formulation techniques plays a crucial role in achieving the desired drug release kinetics.

The key components of in the development of dual layers of oral mucosal drug delivery systems for Scopolamine in the context of motion sickness can vary based on the specific formulation and research approach. Commonly used mucoadhesive polymers include hydroxypropyl methylcellulose (HPMC), Polyvinyl Alcohol (PVA), polyvinylpyrrolidone (PVP), and chitosan.

Buccal mucoadhesive films offer a promising approach to drug delivery with potential benefits in terms of enhanced bioavailability, patient compliance, and reduced side effects. However, like any other drug delivery system, their development and formulation require careful consideration of the drug's physicochemical properties and the selection of appropriate mucoadhesive polymers and excipients.

MATERIAL USED

Scopolamine is the pure drug procured from India Cadila Pharmaceutical Ltd., Dholka, India as gift sample. Hydroxyl propyl methylcellulose (HPMC E15C; K4M) got as gift sample from Alembic Pharmaceuticals, Vadodara, India. Poloxamer-407 procured from Signet chemicals, Mumbai,india.Di-calcium Phosphate (DCP), Polyethylene glycol, Polyvinyl Pyrrolidone K30, Hydroxy Propyl cellulose, Hydroxy Ethyl Cellulose, Polyvinyl alcohol, cellulose acetate Hydrochloric acid, Sodium chloride (NaCl) , Sodium Phosphate, Sodium deoxycholate, Sodium glycocholate, Myrrh B- cyclodextrin from S.D. Fine Chemicals, Mumbai, India.

METHODOLOGY

Infrared (IR) Spectroscopic Analysis

Fourier–transform infrared (FTIR) spectra of moisture free powdered samples were obtained using a spectrophotometer (FTIR-8300, Shimadzu Co., Japan) by potassium bromide (KBr) pellet method (app. 5 mg sample in 200 mg KBr). The scanning range was 400–4000 cm-1 and the resolution was 1 cm-1.

Differential Scanning Calorimetry (DSC) Analysis

DSC scans of the powdered samples were recorded using DSC- Shimadzu 60 with TDA trend line software. All samples were weighed (8-10 mg) and heated at a scanning rate of 10°C/min under dry nitrogen flow (100 ml/min) between 50 and 300° C. Aluminium pans and lids were used for all samples. Pure water and indium were used to calibrate the DSC temperature scale and enthalpic response.

Preparation of calibration curve

The calibration curve of scopolamine in Phosphate buffer pH 6.6 was prepared by measuring the absorbance of the solution in the rage of 5-25 □g/ml. The absorbance of the solution measured at the wavelength of 235 nm. Scopolamine (10mg) was dissolved in 10 ml of Phosphate buffer and volume was made up to 100 ml in volumetric flask. This stock solution (0.1 mg/ml) was further diluted with phosphate buffer pH 6.6 to obtained solution of 5-25 µg/ml. Absorbance of each solution was measured at 235 nm using UV/Vis spectrophotometer with phosphate buffer pH 6.6 as a reference standard. The standard curve was generated for entire range of 5-25 µg/ml. The experiment was performed in triplicate and based on average absorbance; the equation for the best line fit was generated.

Table 1: Formula for immediate release (IR) drug delivery systems

Ingredients (%)	IR1	IR2	IR3	IR4	IR5	IR6
Drug	0.006	0.006	0.006	0.006	0.006	0.006
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

Table 2: Formula for sustained release (SR) drug delivery systems

Ingredients in (%)	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9	SR10	SR11	SR12
Drug	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Chitosan	3	3	3	3	3	3	3	3	3	3	3	3
Poly vinyl alcohol	0.5	1	-	-	-	-	-	-	-	-	-	-
Polyvinyl pyrrolidone	-	-	0.5	1	-	-	-	-	-	-	-	-
Hydroxy Propyl Cellulose	-	-	-	-	0.5	1	-	-	0.5	0.5	1	0.5
Eudragit S 100	-	-	-	-	-	-	0.5	1	0.5	0.25	0.5	1
Glycerol	5	5	5	5	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	0.5	0.5	0.5	0.5
Clove oil	1	1	1	1	1	1	1	1	1	1	1	1
Solvent systems:	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml

EVALUATION PARAMETERS

Physical appearance
The films were observed visually for their physical appearance such as colour andtransparency.

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 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 patches was determined using a modified USP tablet-disintegrating tester. The tester had fixed and movable jaws that mimicked a jaw's movement, with a rate of 28 strokes per minute. The distance between the jaws was 6 cm at the farthest point and 0.5 cm at the closest point. The 8 cm patch was clamped between the jaws, causing it to bend across the middle at the closest position and stretch at the farthest position. Each stroke of the movable jaw completed one bending and stretching cycle. The folding endurance was expressed as the number of strokes needed to either break or develop visible cracks on the patch. The test duration was 1 hour, totalling 1680 strokes.

Swelling studies
Three patches were tested for each formulation of sustained release. 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:

$$\% \text{ Swelling index} = [(W_2 - W_1) / W_1] \times 100$$

Where SI is the percent swelling obtained by the diameter method, W2 is the diameter of the swollen patch after time t, W1 is the original patch diameter at time zero. 93

Mucoretention time

The *in vitro* mucoretention time was determined by using a locally modified apparatus. A semi-circular sheet of 10cm length was kept at 30^{o} 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 thepatch from the mucosal surface was recorded (mean of triplicate determinations were recorded).

In vitro diffusion study

In-vitro diffusion studies were carried out in Franz diffusion cell with an internal diameter of 15 mm and a diffusion area of 1.8 cm^{2} through sigma dialysis membrane.The sigma dialysis membrane was hydrated by addition of distilled water and fixed to the one end which acts as a donor compartment. The assembly was filled with 50 ml of phosphate buffer of pH 6.6. The teflon coated magnetic bead was placed in the beaker and rotated at 50 rpm using magnetic stirrer and the temperature was maintained at $37\pm1\ ^{0}$ C. Samples of 1 ml were withdrawn at regular intervals and replace the volume with same buffer and maintained sink condition through the studies. Averages of duplicate readings were taken.

The amount of drug permeated was determined by removing samples (5 ml aliquots),from the receptor compartment using a micro syringe at appropriate time intervals followed by their HPLC analysis. The volume withdrawn was replenished with an equal quantity of pre-warmed receptor solution. The samples were analysed by HPLC(Shimadzu, Japan) at 214 nm according to the procedure mentioned in USP-24 using 25 cm x 4.5 mm, L1 packing (5µm) Rp-18 Column and phosphate buffer pH 2.3: acetonitrile (74:26) as the mobile phase.

Ex-vivo diffusion study

Ex-vivo drug release studies were carried out for the selected formulation by using goat cheek pouch membrane. In this method goat cheek pouch was attached to one end of donor compartment of the area of 1.5 cm^{2} was selected and the above procedure was repeated.

Kinetic modeling and Mechanism of drug release

Data obtained form in vitro drug release studies were fitted to various kinetic equations. The kinetic models used are zero order, first order and Higuchi equation. The following plots were made for appropriate model.

- Q Vs t (zero order kinetic model)
- Log (Qo - Qt) Vs t (first order kinetic model)

- Qt Vs √t (Higuchi model)
- Korsmeyer-Peppas. $\frac{M_t}{M_\infty} = kt^n$

RESULTS AND DISCUSSION

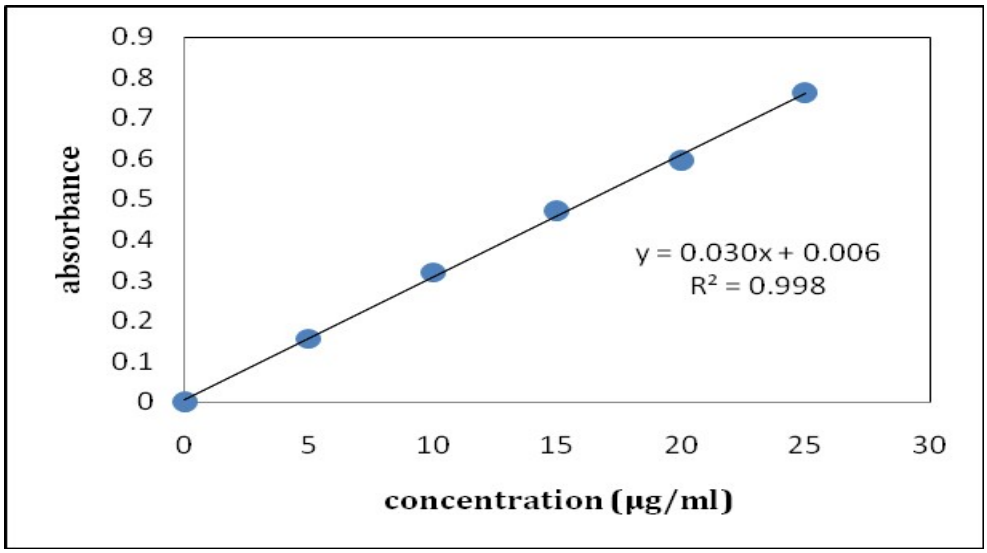

Figure 1: Calibration curve of scopolamine in phosphate buffer pH 6.6 Preparation of dual layer drug delivery systems.

Table 3: Calibration curve of scopolamine in phosphate buffer pH 6.6

Concentration (□g/ml)	Absorbance
0	0.000
5	0.156 (0.004)
10	0.320 (0.003)
15	0.471 (0.007)
20	0.596 (0.004)
25	0.763 (0.002)
Correlation coefficient = 0.998 Absorbance = 0.030 × concentration + 0.006	
Values in parenthesis indicates standard deviation (n = 3)	

Infrared (IR) Spectroscopic Analysis:

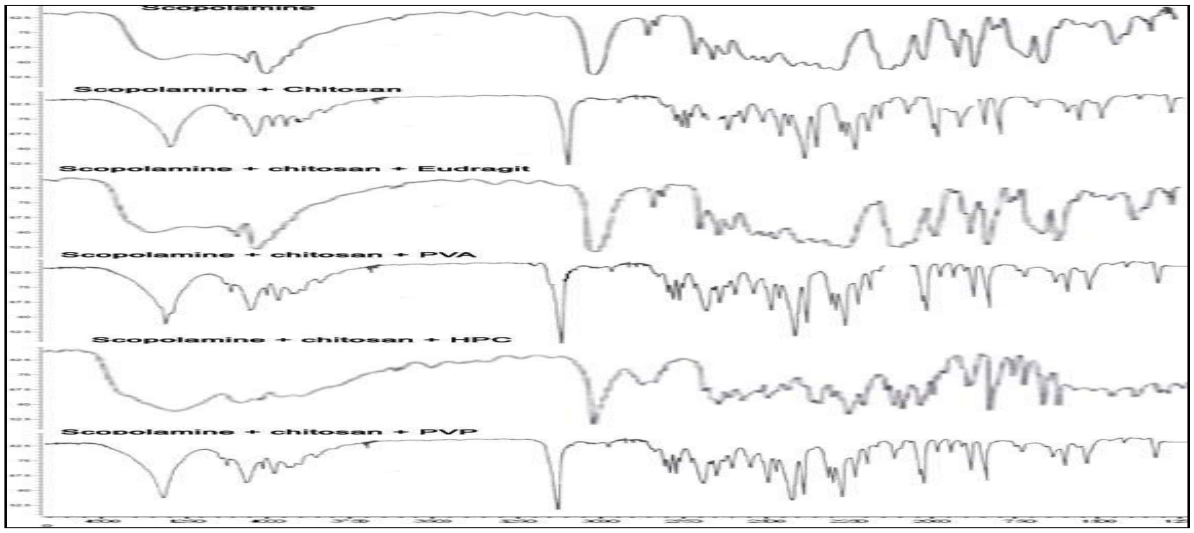

Figure .2:-Infrared (FTIR) Spectra of pure drug with different material

Differential Scanning Calorimetry (DSC) Analysis:

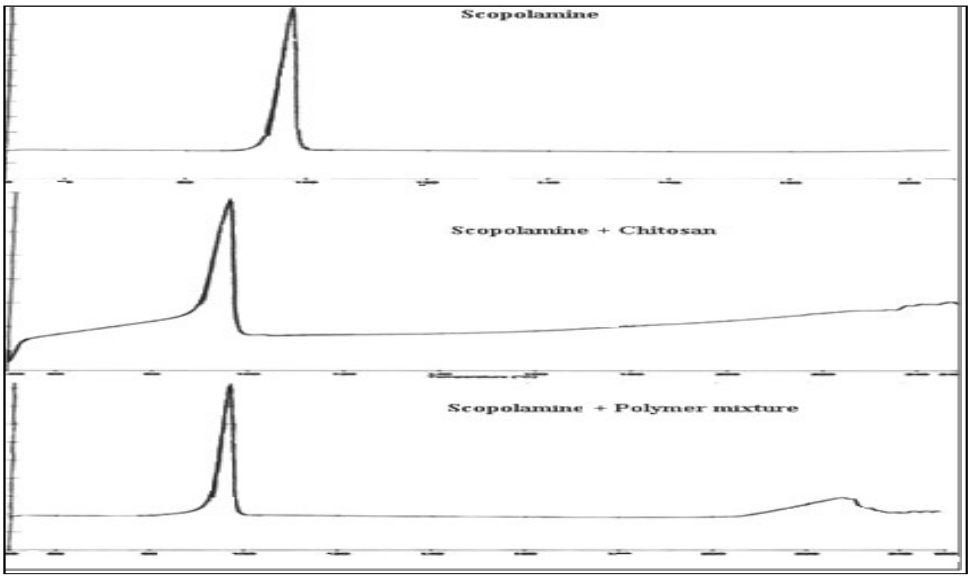

Figure.3:-DSC thermograms of pure drug with different materials

Table 4: Physical characteristics of IR buccal films

Formulation Code	Appearance	Surface texture	**Average weight (mg SD)	**Thickness(m)	*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

Table 5: Physical characteristics of SR buccal films

Code	Appearance	Surface texture	**Average weight (mg SD)	**Thickness(m)	*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 ± 0.03	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 ± 0.02	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 ± 0.03	98.07 ±0.3
SR7	+	smooth	224.18 ±0.53	85.13 ± 0.57	> 350	6.6 ± 0.04	98.27 ±0.2
SR8	+	smooth	290.78 ±0.49	121.1 ±0.57	> 350	6.3 ± 0.05	98.43 ±0.4

SR9	+	Very smooth	291.31 ± 0.52	126.2 ±0.41	> 350	6.5 ± 0.05	99.46 ±0.5
SR10	–	Very smooth	250.27 ± 0.49	110.1 ± 0.60	> 350	6.4 ± 0.02	98.65 ±0.3
SR11	+	smooth	284.18 ± 0.53	156.3 ±0.57	> 350	6.6 ± 0.05	99.21 ±0.1
SR12	+	smooth	288.78 ±0.49	151.1 ±0.57	> 350	6.3 ± 0.05	98.43 ±0.3
+: Transparent - : Opaque, * Average value of three determinations, ** Average value of four determinations							

Table 6: In vitro diffusion study for IR formulation

Time (Minutes)	IR1	IR2	IR3	IR4	IR5	IR6
0	0	0	0	0	0	0
2	21.26	16.87	13.21	15.82	13.41	10.34
4	37.98	27.23	21.02	18.91	21.67	18.23
6	54.09	42.22	35.62	33.55	31	24.1
8	66.12	54.81	48.41	42.43	35.79	30.28
10	85.27	66.29	59.15	54.16	41.12	36.61
12	99.47	82.35	71.88	61.8	48.65	46.61
14	99.53	98.11	89.28	72.47	55.62	60.11
16		98.12	98.73	83.29	72.54	69.23
18			98.77	92.14	81.10	71.20
20				99.21	91.22	83.43
22					99.02	99.65

Table 7: In vitro diffusion study for SR formulation

Time (hrs)	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9	SR10	SR11	SR12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	21.26	16.87	13.21	15.82	13.41	10.34	25.02	15.17	17.32	13.24	14.24	20.82
2	37.98	27.23	21.02	18.91	21.67	18.23	41.24	28.41	26.54	22.81	21.86	31.21
3	54.09	42.22	35.62	33.55	31	24.1	63.82	42.35	33.4	30.1	29.31	40.46
4	66.12	54.81	48.41	42.43	35.79	30.28	81.48	58.67	45.38	39.67	36.84	49.94
5	85.27	66.29	59.15	54.16	41.12	36.61	96.62	71.36	57.86	48.22	42.18	60.54
6	97.47	82.35	71.88	61.8	48.65	46.61	96.22	82.84	71.12	55.67	50.52	72.81
7	97.33	98.11	89.28	72.47	55.62	60.11		99.76	82.94	63.74	57.13	86.14
8		98.10	98.73	83.29	72.54	69.23		99.19	94.83	72.86	62.94	97.24
9			98.34	91.13	83.61	77.29			97.28	84.67	70.84	97.14
10				98.73	99.19	85.21			97.10	99.82	78.24	
11				98.93	99.06	93.07				99.48	86.28	
12						97.61					96.24	

Table 8: In vitro diffusion study for factorial design formulation

Time (hrs)	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
0	0	0	0	0	0	0	0	0	0
1	17.32	20.82	26.4	14.24	18.24	24.84	12.24	16.54	15.54
2	26.54	31.21	38.51	21.86	28.44	36.42	17.58	23.56	28.54
3	33.4	40.46	60.7	29.31	39.89	44.96	22.34	31.86	36.58
4	45.38	49.94	79.42	36.84	50.56	52.72	28.27	39.52	41.17
5	57.86	60.54	92.84	42.18	59.26	60.54	34.44	48.52	47.24
6	71.12	72.81	98.82	50.52	68.52	72.81	42.51	54.72	53.22
7	82.94	86.14	98.65	57.13	75.84	86.14	47.94	62.84	58.24
8	94.83	99.24		62.94	81.36	97.24	54.17	70.51	63.72
9	97.28	97.12		70.84	89.76	97.16	60.62	76.82	69.3
10	97.39			78.24	98.24		68.74	81.62	76.71
11				86.28	98.12		76.82	88.94	82.92
12				92.24			84.72	98.54	90.53
13							90.15	98.33	98.19
14							98.12		

Table 9: Multiple regression analysis for dependent variables:

Coefficient ofregression parameters	**t50**	**t80**
b0	4.52709	7.779039
b1	1.298793	2.260476
b2	-0.87552	-1.25433
b11	0.15976	0.169543
b22	0.304458	0.410908
b12	0.088217	0.309375

Table 10: Results of dependent variables for factorial design batches

Batch code	*t50*	*t80*	*Ex vivo* Mucoadhesion strength (gm)
PF1	4.26	6.97	25.23
PF2	3.91	6.53	28.94
PF3	2.60	4.39	32.86
PF4	6.03	10.06	42.85
PF5	4.41	7.63	43.96
PF6	3.74	6.46	46.96
PF7	7.15	11.64	57.96
PF8	5.58	9.52	59.63
PF9	5.84	10.29	62.95

Figure 4: Scanning electron micrograph for optimised formulation

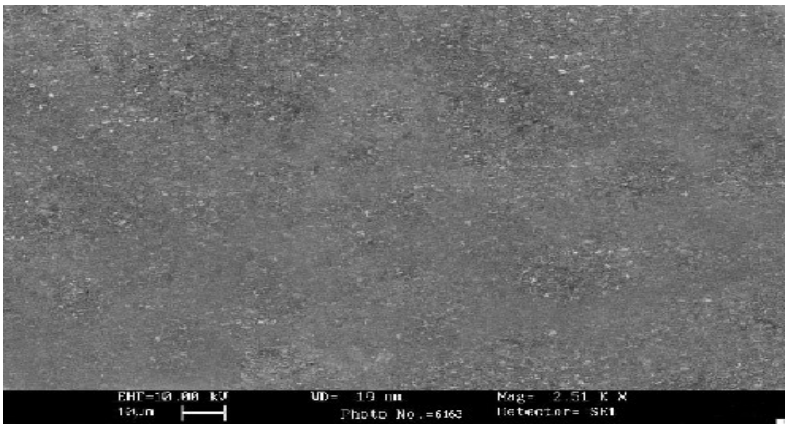

Table 12: Result of model fitting of factorial batch

batches	Zero order		First Order		Higuchi		Korsmeyer's peppas	
	K	r^2	K	r^2	K	r^2	N	r^2
PF1	9.36	0.974	0.033	0.952	0.740	0.983	0.638	0.987
PF2	8.23	0.991	0.021	0.872	0.843	0.992	0.659	0.991
PF3	8.64	0.980	0.034	0.781	0.891	0.985	0.648	0.994
PF4	7.95	0.990	0.028	0.818	0.895	0.990	0.604	0.973
PF5	6.79	0.973	0.022	0.673	0.914	0.976	0.691	0.994
PF6	7.63	0.980	0.026	0.779	0.913	0.993	0.638	0.991
PF7	7.54	0.994	0.028	0.889	0.956	0.958	0.759	0.976
PF8	8.83	0.993	0.016	0.839	0.994	0.956	0.879	0.991
PF9	6.20	0.991	0.030	0.983	1.180	0.964	0.718	0.972

CONCLUSION:

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. By considering the human acceptability and proper drug release the present studies has shown the optimum characteristics for the development of mucoadhesive buccal dosage forms. The prepared system allows the treatment of motion sickness in two different phases by delivering immediate dose and sustaining the drug release, which makes it convenient and desirable for the patient. This type of approaches will remove the barrier of oral mucosal drug delivery systems.

SCOPE OF FUTURE WORK:

The future work aims to carry out full-scale studies to obtain the functional status of this promising scopolamine formulation in many functions.

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