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FORMULATION AND EVALUATION OF SALBUTAMOL SULPHATE MUCOADHESIVE SUSTAINED RELEASE TABLETS USING NATURAL EXCIPIENTS

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ABSTRACT

Generally synthetic polymers are used for the preparation of oral mucoadhesive controlled release tablets. Since the biodegradability of synthetic polymers is questionable, various natural materials extracted from edible fruits like *Tamarindus indica* (Linn), seeds of *Tamarindus indica* (Linn), which showed good mucoadhesive property was effectively used in the formulation of mucoadhesive dosage forms. In this present study Salbutamol sulphate controlled release tablets were prepared by using various natural mucoadhesive materials. In vitro and in vivo mucoadhesive strength of materials was evaluated by *In Vitro* and *In Vivo* methods. Dissolution study and release kinetics of salbutamol sulphate was performed.

KEY WORDS: Mucoadhesive drug delivery, Salbutamol sulphate, Natural materials.

1. INTRODUCTION

1.1. Mucoadhesion: Bioadhesion is an interfacial phenomenon in which two materials at least one of which is of biological nature are held together by means of interfacial forces for extended period of time. When the biological substrate is mucosal coat of surface tissues then the phenomenon is called Mucoadhesion. Oral controlled release (CR) system continues to be the most popular ones among all the drug delivery systems. But mucoadhesive delivery systems offers several advantages over other oral CR systems by virtue of prolongation of residence time of drug in gastrointestinal (GI) tract, and targeting and localization of the dosages form at a specific site. Also, these mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting there by in high drug flux through the absorbing tissue.

1.2. Natural materials used as mucoadhesive materials: Synthetic polymers are used in mucoadhesive controlled dosage forms. Since the biodegradability of the synthetic polymers is questionable, various materials extracted from natural sources have been used as the natural mucoadhesive polymers. It was proved that mucoadhesive strength and viscosity of natural material were same or some times better than synthetic polymer (Das and Das,2003; Singh and Kwor,2000; Khar,2001; Singh,2006).

2. MATERIALS AND METHODS

2.1.Materials: Salbutamol sulphate was obtained as gift sample from Agape Drugs and Pharmaceuticals, Sikkim. The fruits of *Tamarindus indica,* (Tamarind), *Aegle marmelos* (Bale), and Tamarind seeds were purchased from local market. Sodium chloride, Sodium hydroxide, Hydrochloric acid, Dipotassium hydrogen ortho phosphate, Magnesium stearate and Talcum were purchased from S.D.Fine Chem, Mumbai. Potassium dihydrogen ortho phosphate was purchased from Qualigens. Acetone was purchased from Lab Reagent. Pepsin was purchased from Loba Chem., Mumbai. Methanol was purchased from Universal Lab, Mumbai. Ethanol was purchased from Sikkim Distilleries.

2.2.Extraction of natural mucoadhesive materials: The extraction procedure of natural mucoadhesive material was described by Rao. In this method, 250 gm of natural material obtained from edible fruits. Seeds were soaked in double distilled water and boiled for 5 hours in a water bath until slurry was formed. The slurry was cooled and kept in refrigerator overnight, so that most of the undissolved portion was settled out. The upper clear solution was decanted off and centrifuged at 500 rpm for 20 min. The supernatant was concentrated at 60^0C on a water bath until the volume reduced to one third of its original volume. Solution was cooled down to room temperature and was poured into thrice the volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried at 50^0C under vacuum. The dried material was powdered and kept in a desiccators (Rao and Srivastava,1973; Chanda and Roy,2010).

2.3.Determination of mucoadhesiveness by Wilhelmy plate method: In this method small glass plates were coated uniformly by natural bioadhesive material solution and dried at 60^0 C. The prepared coated plates were immersed in to U.S.P. simulated intestinal fluid (pH 6.0), or U.S.P. simulated gastric fluid (pH 1.2), for 5, 10, 15, and 20 min interval at room temperature. The force required to pull the plate out of the solution was determined under constant experimental conditions (Gandhi and Robinson,1988).

2.4.Determination of mucoadhesiveness by Falling ball method: The synthetic polymer or natural mucoadhesive material coated mustard seeds were passed through U.S.P. simulated intestinal fluid (pH 6.0) at a specific distance (21 inches). The time required to pass this distance for the coated seeds were noted. All experiments were performed at room temperature. The mustard seeds were coated with 0.75% w/v synthetic polymer or natural mucoadhesive material solution in a small laboratory type coating pan (Chanada and Bandopahaya, 2001).

2.5.X-Ray Diffraction study: To detect crystalline or amorphous nature of two best acting natural mucoadhesive material x ray diffraction study has performed. The study has performed in powder crystallographic machine model name and number (Scifert XDAL 3000) and test was performed in wave length 1.540598nm.(Kar Asutosh,2005; Rao and Vani,1998).

2.6.*In Vivo* Study of natural mucoadhesion material: *In vivo* method is very much useful than in vitro method because it presumably provide a more realistic picture of the expected behavior. Three formulations containing Barium sulphate were prepared.

1. Control Barium sulphate tablets.
2. Barium sulphate tablet using natural polymer of *Tamarindus indica* , (seed, TS)
3. Barium sulphate tablet using natural polymer of *Tamarindus indicia,* (fruit, T)

Nine healthy rabbits of same age and weight were taken as subject. They were overnight fasted and on the next day morning the tablets were administered to them followed by giving 25 ml of water. At different time intervals of 1, 3, 5 and 8 hours the rabbits were x-ray photographed and observed for the nature and the position of the tablets (Mishra and Mishra,1999).

2.7.Preparation of Mucoadhesive Salbutamol sulphate tablets: The tablets were prepared by wet granulation method, using natural mucoadhesive materials extracted from tamarind seeds and tamarind fruits. Matrix tablets of Salbutamol sulphate were prepared by conventional wet granulation method as per the formula given in the table 6. The required quantity of medicament and matrix materials was mixed thoroughly in a motor by following geometric dilution technique. The binder solution (mixture of alcohol and purified water at 3:7ratio) was added and mixed thoroughly to form a dough mass. The mass was passed through mesh number 14 to obtain wet granules. The wet granules were dried at 60ºc for 4 hours. The dried granules were passed through mesh no.14 to break the aggregates. Talc and Magnesium Stearate were mixed with dry granules after passing through mesh number 100 and blended in a closed polythene bag. The granules were compressed into tablets on a rotary multi station tableting machine to a hardness of 7kg/sq. cm. using 9mm round and flat punches (Chowdary and Sundari,2003; I.P.,1996).

3. RESULTS AND DISCUSSION

The results obtained from Wilhelmy plate method and from Falling ball method were represented in table 1 and 2 respectively. From the results obtained we can conclude that tamarind and tamarind seeds have mucoadhesive property. X- ray diffraction study of both materials has done. The result obtained from the X-ray diffraction study in figure 2shows tamarind seed is amorphous in nature. The *in vivo* test of natural mucoadhesive materials in rabit body (figure 3) shows control Barium sulphate tablets disintegrates within 3 hours but tamarind and tamarind seed containing Barium sulphate tablets adhere up to 5 and 7 hours. The mucoadhesive property of selected materials showed very good results in both *In Vitro* and *In Vivo*.

Dissolution study of different formulations has shown in table 3 and 4, and Tamarind Fruit T2 (1:2–Drug:Polymer ratio) which has shown 96% release up to 12 hrs and Tamarind seed – TS2 (1:2–Drug : Polymer ratio) has been found to show 95% release within 12hrs. An appropriate kinetic model study was conducted by plotting the slopes for various appropriate formulations and their R^2 values (Regression constant) were also calculated (table 5). T2 and TS2 formulations exhibited zero order release kinetics followed by first order kinetics.

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4.CONCLUSION

In the present study, the adhesiveness and other physicochemical properties of natural material were performed by *in vitro* method and from the results tamarind seeds had shown good results. The Salbutamol sulfate mucoadhesive tablets were prepared by using tamarind seed as well as tamrind fruit containing polysaccharide .in various drug: polymer ratios. By using the *In vitro* drug release data, kinetic studies were performed and R^2 value was calculated. From the R^2 values it was found that the drug release of the natural materials containing tamarind and tamarind seed shows zero order followed by first order release kinetics. Among various drug polymer ratio tamarind fruit T2 (Drug: Polymer = 1: 2) and tamarind seed TS2 (Drug: Polymer = 1: 2) showed better results for sustained property of anti-asthmatic drug of Salbutamol sulfate in the present study.

Table1&2: *In Vitro* mucoadhesive nature of tamarind and tamarind seed polymers

(Wilhelmy plate method)

Name of the material	Time (min)	Weight required (gm)
Tamarind Seed *(Tamarindus indica)*	5	0.77
	10	0.89
	15	1.09
	20	0.59
Tamarind fruit *(Tamarindus indica)*	5	0.49
	10	0.62
	15	0.77
	20	0.56

(Falling ball method)

Name	Time(sec)
TS1	30.71
T1	36.687
Blank	1.286

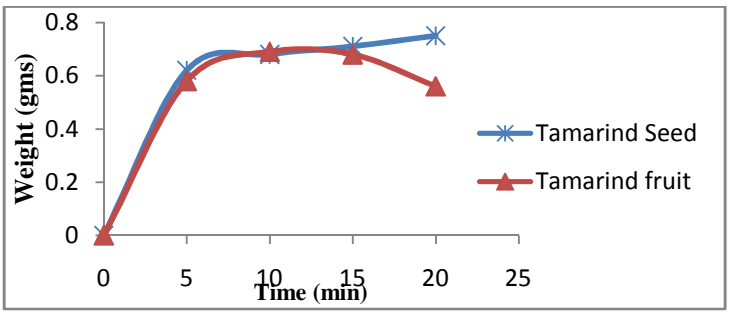

Figure1. Comparison of mucoadhesive nature of tamarind and tamarind fruit and tamarind seed polymers (Wilhelmy plate method)

*The avarage weight of each material are taken at room temp(30^0c).

TS =Seedof tamarind(Tamarindus indica)*,*T=Tamarind *(Tamarindus indica)*

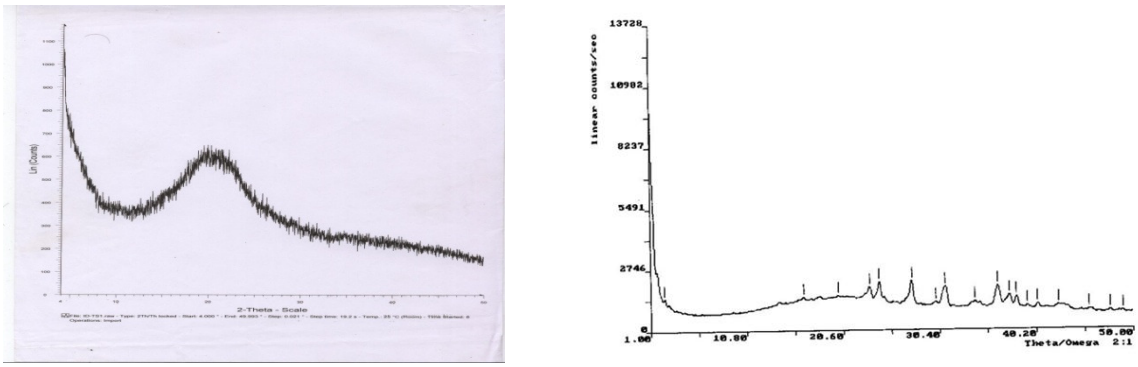

Figure2.a. and 2.b: X-ray diffraction study of tamarind fruit and seed

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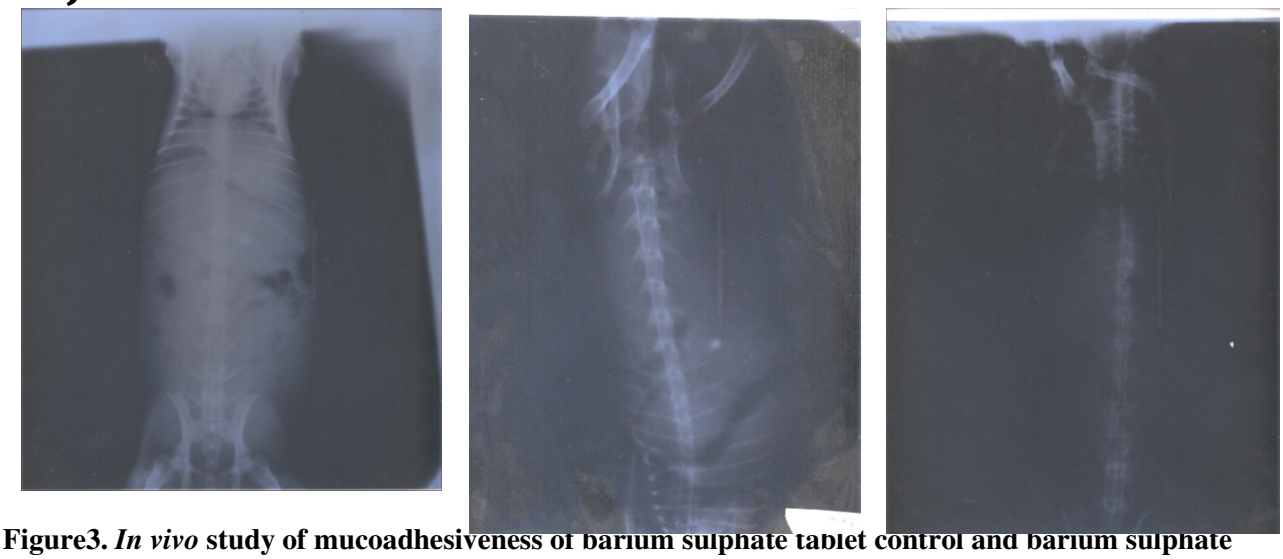

Figure3. *In vivo* study of mucoadhesiveness of barium sulphate tablet control and barium sulphate tablet containing tamarind and tamarind seed polysaccharide

Table3. *In vitro* percentage drug release of drug from tablets formulated with tamarind fruit polysaccharide

Time(hr)	T1	T2	T3	T4	Time(hr)	T1	T2	T3	T4
0.5	14.292	12.485	10.656	6.267	7	93.198	68.935	57.353	47.233
1	22.483	22.726	20.166	11.753	8	96.002	77.958	65.278	51.135
2	43.453	32.846	29.554	14.680	9	95.637	86.248	72.715	57.840
3	58.816	43.575	35.041	20.166	10	95.515	90.150	77.714	63.693
4	69.423	49.550	40.771	25.531	11	95.515	96.612	81.493	70.886
5	77.592	55.524	46.258	31.993	12	95.393	96.246	87.224	74.056
6	85.517	61.864	51.135	38.211					

Table4. *In vitro* percentage drug release of drug from tablets formulated with tamarind seed polysaccharide

Time(hr)	TS1	TS2	TS3	TS4	Time(hr)	TS1	TS2	TS3	TS4
0.5	24.521	21.907	17.511	13.335	7	85.584	71.803	66.932	56.376
1	32.361	28.441	24.521	23.449	8	95.563	76.318	72.397	62.608
2	38.895	36.044	32.005	30.857	9	95.445	88.317	83.683	69.782
3	55.409	41.747	37.470	36.267	10	95.088	95.563	90.811	76.602
4	62.299	48.637	45.667	41.206	11	95.207	95.445	95.088	84.011
5	72.160	58.616	48.756	46.733	12	95.088	95.563	94.851	92.125
6	80.119	63.606	60.280	49.320					

Table5. Kinetic studies of In vitro drug release from Natural polymer containing tablets

Formulation	R^2 for Zero order	R^2 for 1st order
T2	0.996	0.956
TS2	0.973	0.894

Table6. Master formula of Salbutamol tablets

Ingredients	Tamarind fruit				Tamarind seed			
	T1	T2	T3	T4	TS1	TS2	TS3	TS4
Salbutamol Sulphate	8	8	8	8	8	8	8	8
Tamarind fruit	8	16	24	32	-	-	-	-
Tamarind seed	-	-	-	-	8	16	24	32
Lactose	183	175	167	159	183	175	167	159
Magnesium stearate	1	1	1	1	1	1	1	1

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