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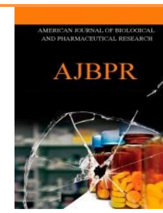

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FABRICATION AND EVALUATION OF ORAL TABLETS USING NATURAL MUCOADHESIVE AGENT FROM *ADINA CORDIFOLIA*

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ABSTRACT

Mucoadhesive polymer owing to its binding capacity with gastric mucin prolongs the gastric residence time and thereby increases the drug bioavailability. In the present study, oral controlled release mucoadhesive matrix tablets have been developed for Salbutamol Sulphate as model drug using natural mucoadhesive agent from the plant *Adina cordifolia*. The tablets were formulated with the natural polymer in different concentration (25%, 50 %, &75% w/w) employing wet granulation method. The mucoadhesive characters of the isolated substance were identified by a comparative study with hydroxyl propyl cellulose and sodium alginate, by various in vitro methods, such as, Shear stress measurement, Wilhelmy's method, and Falling sphere method. The mucoadhesive strength was in the range from20.4± 0.21 to 30.5±0.28 with the increase in natural polymer concentration from 25 to 75 % (F1 to F3). Swelling index of natural polymer was testified towards proliferation by together increasing gum concentration and the time period and was in the range of 2.6081±0.15 to 4.51±0.19. Formulation and evaluation of mucoadhesive oral tablets of salbutamol sulfate (100 mg), using isolated natural materials in different proportions, and in vitro release studies, were carried out for three different formulations according to the U.S.P apparatus two (paddle method). Each 100 mg tablet was taken in 900 ml of acid buffer 1.2 and maintained at 37˚C. After two hours the filtrate was collected and replaced in buffer 7.4. In- vitro release of three different formulations for nine hours were studied, which showed the sustained action of drug release with increasing the concentration of the isolated natural mucoadhesive agent in the formulations. These research outcomes clearly specify the potential of *Adina cordifolia* can be used as binder, release retardant and mucoadhesive natural material in tablet formulations.

INTRODUCTION

Sustained release drug delivery system significantly improve therapeutic efficacy of the drug. Drug release retarding polymers are the key performer in such systems. Much of the development in SR drug delivery systems is focusing in the preparation and use of polymers with specificity designed macroscopic and microscopic structural and chemical features. Numbers of natural, semi-synthetic and synthetic polymeric materials are used in the controlled delivery of drugs. Recent trend towards the use of vegetable and nontoxic products demands the replacement of synthetic additives with natural one. The natural materials have been extensively used in the field of drug delivery for their easy availability cost effectiveness, ecofriendliness, capable of multitude of

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chemical modifications, potentially degradable and compatible due to natural origin.

Mucoadhesion or the attachment of a natural or synthetic polymer to a biological substrate is a practical method of drug immobility or localization and an important new aspect of controlled drug delivery. The concept of mucoadhesion was introduced into controlled drug delivery in the early 1980's. Mucoadhesive is a topic of current interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or adsorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drug. There are two broad classes of mucoadhesive polymers: hydrophilic polymers and hydro gels. In the large classes of hydrophilic polymers those containing carboxylic group exhibit the best mucoadhesive properties.

Different types of bioadhesive synthetic polymers such as acrylic based hydro gels including carbopol 934, carbopol 937, a hydroxy propyl methyl cellulose are used to prepare oral mucoadhesive tablets [1]. Since the biodegradability of the synthetic polymers is questionable, some natural mucoadhesive materials extracted from plants having good mucoadhesive properties are used for this purpose.

The concept is that insitu; they will form disulphide links not only among the polymers themselves, thus inhibiting over hydration and formation of slippery mucilage, but also with the mucin layer, mucosa, thus strengthening the adhesive joint and loading to an improved adhesive performance.

The plant agents may have a linear or branched structure. They may have acidic, basic or natural characteristics, among them the hydrocolloids, with basic characteristics, have limited commercial importance, whereas acidic and natural polymers have wide pharmaceutical applications.

Hence in the present study, a natural mucoadhesive agent from the plant *Adina cordifolia* has been used as a release modifying agent for the development of the oral drug delivery of Salbutamol sulfate in the form Oral mucoadhesive tablets.

METHODS

Isolation of Natural Mucoadhesive Agent

The mucoadhesive agent from *Adina cordifolia* was prepared following method by Rao *et al* [2, 3] in 3 batches on a laboratory scale. To 20g of aqueous extract of *Adina cordifolia*, 200 ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 min under stirring condition in a water bath. The resulting thin clear solution was kept overnight. The solution was then centrifuged at 500 rpm for 20 min. The supernatant was separated and poured into twice the volume of acetone by continous stirring. The precipitate was filtered and washed with acetone and then dried at 50-60º C. The dried material was ground sieved and then stored in a desicator.

Comparative Mucoadhesive Characterization of Natural Agent with Existing Polymers

Shear stress measurement

Different concentration of the mucoadhesive agent solution such as 3%,6%,9% using sodium alginate carbopol 940, HPMC- E5LV(premium), PVP-K30 and Natural isolated mucoadhesive mucilage of *Adina cordifolia* were prepared using water as a solvent [4]. A fixed amount (1drop) of polymer solution was kept on the centre of the first block with a pipette and then the second block was placed on the first block and pressed by applying 100g of weight such that the drop of polymer spreads as a uniform film in between the two blocks after keeping it for fixed time intervals of 5, 10, 15 and 30 min. The weights were added into the pan. The weights just sufficient to pull the upper block to make it slide down from the base block will represent the adhesion strength, the shear stress is required.

Shear Strength

The shear stress measures the forces that cause the bioadhesive to slide with respect to the mucus layer in a direction parallel to their plane to contact. An e.g is the Whihelmy Plate Method [5]. The glass plates were coated by dipping them into a 1%w/v solution of test materials and dried at 60ºC for 3 hours. One end of a glass rod was tied to pan in which a beaker was placed. The polymer coated glass plate was suspended from one end of the rod and made to penetrate the mucus, which was kept in a 50 ml vial. Next this assembly was kept undisturbed. After keeping it for a time interval of 5, 10, 15 and 30 min, the water required to pull out the glass plate from the mucus represented the force required to break the mucus polymer contact against adhesion.

Falling Sphere Method

The method used was the method developed by Teng & Ho with slight modification. 5 gm of mustard grain were weighed and coated with 3% w/v of mucilage of Adina Cord folia. The coating continued until the entire grain was covered with the mucilage. The exact spherical grains were selected and used for this study. A clean burette was taken and filled with 10% v/v of mucus solution and fixed in a stainless steel stand. A polymer coated mustard grain was taken and slowly placed at the top of the mucus layer. The time taken by the grain to cover 50 divisions in the burette was noted and values were tabulated [6].

Tensile Strength

These methods usually measure the force required to break the adhesive bond between a model membrane and test polymers. The instruments usually employed are modified balances. A typical example is the method employed by Robinson *et al* [7]. In this method, the force required to separate the bioadhesive sample from freshly excised goat intestine tissue was determined using a modified tensiometer. A section of the tissue, having the mucus side exposed was secured on a weighed glass vial placed in a beaker containing USP stimulated gastric fluid. Another section of the same tissue was placed over a rubber stopper again with a vial cap and a small quantity of polymer was placed between the two mucosal tissues. The force used to detach the polymer from the tissue was then recorded.

Preparation of Granules of Oral Tablets using Isolated Natural Agent

For the preparation of granules, the wet granulation method was used. Accurately weighed quantities of the ingradients were mixed in a glass mortar and the required quantity of warm water was added to the powder mass and mixed thoroughly. The granules were prepared by passing the wet mass through standard sieve number .16. The wet granules were dried in a hot air oven for 30min at 60ºc and passed through sieve no: 22. Finally the granules were collected to do the evaluation. Each tablet weight was calculated and finally the required quantity of ingredients was used to prepare the mass, for the granules to formulate sufficient tablets.

Evaluation of Blend Characteristics of Salbutamol Sulphate

Micromeritic characteristic properties such as flow property, bulk density, tapped density; compressilbility index and Hausels ratio were analyzed for the prepared blend [8, 9].

Evaluation of oral tablets of Salbutamol Sulphate

The thickness and diameter of the tablet were determined using digital vernier calipers. The hardness of the tablets was determined by using Monsanto hardness tester. The friability of the tablets was determined using Roche friabilator. Weight variation test of the tablets were carried out as per the official method. Determination of surface pH, water absorption studies, and muco adhesive strength measurement were evaluated [10, 11].

In vitro release studies

The in vitro release study of salbutamol sulphate oral mucoadhesive tablets were carried out using USP dissolution test apparatus type II. The temperature of dissolution medium (0.1 N HCl, 900ml) was maintained at 37 ºC +_ 1º C with a stirring rate of 50 rpm. After 2 hrs dissolution medium was replaced with phosphate buffer pH 7.8. At predetermined intervals 5ml sample was withdrawn & equal volume of medium was replaced immediately. The withdrawn sample were then filtered & suitably diluted. The amount of drug present was determined by using UV spectroscopy at a wavelength of 279 nm [12-14].

Table 1. Shear stress measurement values of different polymers

Polymer name	Concentration (%w/w)	Wt. required (g) at time intervals (n=3)		
		10min	20min	30min
Sodium alginate	3	14.67±0.58	31.33 ±1.53	36± 2
	6	30.67±1.15	42.67 ±2.3	50 ±2.1
	9	58.67±1.15	96.34 ±1.52	128 ±2.4
Carbopol 940	3	30.67±2.25	89.83 ±2.57	141 ±10.54
	6	87.67±2.5	160 ±2.2	202.34± 3.5
	9	132.34±2.5	242.34 ±2.51	342.67± 3
HPMC-E5LV	3	95.67±5.03	158.67± 7.77	327.67 ±7.1
	6	135 ±5.1	201 ±3.6	297.34 ±6.4
	9	165.6 ±4.04	322.67 ±6.42	452 ±2.51
PVP-K30	3	73 ±2.1	145.33 ±5.69	192.33± 7.51
	6	105.3± 4.16	188.34 ±7.63	230 ±9.16
	9	134.34± 4.04	233.3 ±4.16	316± 4
Natural mucoadhesive agent	3	65.34 ±1.52	110.67± 2.08	133 ±1.73
	6	75.67 ±2.08	121 ±1.1	142.34± 1.52
	9	113 ±1.1	141± 3.2	156.34 ±8.05

Table 2. Wilhelmy's method

S.No.	Name of polymer	Wt. required to detach (g) at time intervals
1	Sodium alginate	17.67 ±1.15
2	Carbopol 940	23.33 ±1.73
3	HPMC-E5LV	21.33 ±0.58
4	PVP-K30	16.33± 1.53
5	Mucilage of *Adina cordifolia*	23 ±1.21

Table 3. Falling sphere method

Name of Sample	Concentration	Average time taken (seconds)
Sodium alginate	3%	16.67 ±1.53
Carbopol 940	3%	27.1 ±2.2
HPMC-E5LV	3%	12.33 ±1.15
PVP-K30	3%	12.34 ±0.58
Mucilage of *Adina cordifolia*	3%	25 ±1

Table 4. Tensile strength of different polymers

S.No.	Polymers (3%)	Wt. required (g)
1	Sodium alginate	16.33 ±0.58
2	Carbopol 940	20.67± 0.58
3	HPMC-E5LV	18.67 ±1.15
4	PVP-K30	15.33 ±1.53
5	Mucilage of *Adina cordifolia*	20.67 ±0.58

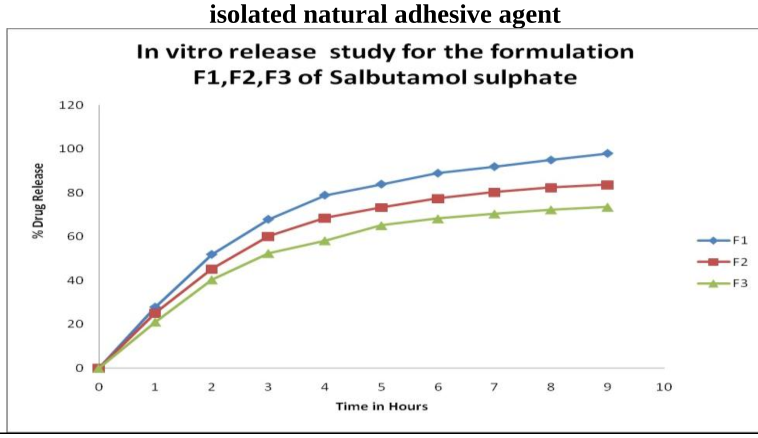
Table 5. Evaluation of Oral Tablets of Salbutamol Sulphate

S. No.	Thickness	Hardness	% friability	% wt variation	%drug content	Swelling index	Mucoadhesive strength
F1	2.10 ±0.128	4.8± 0.4	2.23± 0.15	2.28± 0.25	97.1± 1.46	2.6081± 0.15	20.4± 0.21
F2	2.22 ±0.2015	5.3± 0.5	4.10± 0.15	3.2± 0.24	98.7± 1.25	3.564 ±0.23	25.4± 0.38
F3	2.40 ±0.203	5.4± 0.5	3.50± 0.13	3.67± 0.25	99.3 ±1.50	4.51± 0.19	30.5± 0.28

Table 6. Formulation of Salbutamol sulfate tablets using natural mucoadhesive agent

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)
Salbutamol Sulphate	4	4	4
Di Calcium Phosphate	68	43	18
Natural mucoadhesive polymer	25	50	75
Magnesium stearate	2	2	2
Talc	1	1	1

Fig 1. In vitro release comparative study for three different formulation of Salbutamol sulphate tablet using isolated natural adhesive agent



RESULTS AND DISCUSSION

Adina cordifolia leaves & barks yielded 5% of natural mucoadhesive agent. The isolated mucoadhesive agent was tested by chemical test for identification of various phytoconstituents mainly in the extract of petroleum ether, chloroform, acetone, alcohol & aqueous extract. The result showed present of carbohydrate only.

The pH was found to be 6.5 , showing that the selected natural mucoadhesive agent might not irritate the epithelium & mucous membrane of oral route and was found to be suitable for oral dosage forms. The high water absorption capacity showed that the polymer could form a good bond with oral mucosa in a short duration; if pH increased the water absorption was reduced. The viscosity studies on 1% w/v solution of isolated natural mucoadhesive agent showed a decrease in viscosity with increase in temperature and the melting point range was also reported. The results obtained from shear stress measurement reveals that the natural and synthetic substances (in different concentration) when subjected to physical evaluation possess adhesive characteristics. Among these the natural mucoadhesive agent from the leaves and barks of *Adina cordifolia* also possess considerable adhesiveness.

The natural mucoadhesive agent from the leaves and barks of *Adina cordifolia* is found to contain more mucoadhesiveness than sodium alginate. In the shear strength measurement of different polymers with a concentration of 3%, (Table.1) it has been found that 23g of weight was required to detach a coated plate from the mucous gel of concentration 10%v/v. (Table.2)

While we compare this polymer (3%) for the mucoadhesive character, the isolated mucoadhesive agent shows nearly high adhesiveness towards the mucus gel. In the falling sphere method, the natural mucoadhesive agent from the leaves and barks of *Adina cordifolia* was found to contain more considerable adhesiveness than other polymers. Between the synthetic polymers, carbopol 940 was found to possess good adhesiveness. The adhesiveness increases with the increase in time and concentration (Table 3)

In case of tensile strength of different polymers, the force required to detach the polymer from tissue was found to contain more and almost similar as Carbopol 940. (Table 4)

The angle of repose of all formulations blends F1 to F3 were in the range of 31º50'±0.480 to 34°56'±0.560. The bulk density, tapped density, compressibility index and Hauser ratio were found in the range of 0.3846 to 0.4132g/cc, 0.4364-0.4629g/cc, 12.00-12.50 and 1.1260-1.1390 respectively. It reveals that all the formulation blends were having well flow characteristics and flow rates. The thickness of all the formulations from F1 to F3 was in the range of 2.15±0.127 to 2.42±0.203mm. The hardness of all formulations F1 to F3 was in the range of 4.9±0.4 to 5.5±0.5 kg/sq.cm. The percentage of friability of all formulation was in the range of 2.23 to 4.10%. The percentage weight variation for all formulation F1 to F3 was in the range of 2.25 to 3.65%. The percentage drug content for all formulations F1 to F3 was in the range of 97.5±1.46 to 99.65±1.52%. Surface pH of all the formulations was in the range of 7.2±0.3 to 7.8±0.4. Swelling index was high for formulation F3 (14.51±0.19) after 4 hours and low for formulation F1 (2.6581±0.15) (Table.5)

Based on the quantity of natural mucoadhesive agent in the formulation and at the different time intervals, the swelling index might increase, to control the drug release from the dosage form. The mucoadhesive strength of all the formulations F1 to F3 was found to be in the range of 20.05±0.3g to 32.3±0.25g. Due to a higher concentration of the isolated natural mucoadhesive agent in $F_{3,}$ it showed more mucoadhesive strength than $F_1$and F_2.The *in-vitro* release profile of all the formulations was studied for 8 hours. The tablets prepared with higher concentrations of mucoadhesive materials showed sustained release with the drug release percentage as F_1 (98.20±1.26%), F_2 (85.3±1.50%) and F_3 (75.4 ±1.68). The comparative release of all formulations showed the improvement in sustaining the property of drug release of Salbutamol sulfate using the extracted natural adhesive material.

CONCLUSION

In conclusion, the results of the present study indicated that the salbutamol sulfate tablets which were prepared from the mucoadhesive materials extracted from the leaves and barks of *Adina cordifolia* can be used as one of the excipients in controlling the drug release. The sustained action of drug release was seen in formulation F3. Where there is an increase in the concentration of the mucoadhesive agent. Thus the advantage of natural plant based excipients can be included on the basis of low cost, natural origin, fairly free from side effects and improve the national economy by providing inexpensive formulations to people, by using locally available material.

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