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Research Article

Conception and *in vitro* evaluation of Salbutamol sulphate sustained release tablets using natural mucoadhesive materials

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ABSTRACT

The present objective of the work is to investigate the efficiency of freshly extracted natural mucoadhesive materials *Caesalpinia pulcherrima* (NMM01) and *Leucaena leucocephala (*NMM02) were compared with synthetic and semi synthetic mucoadhesive polymers like hydro propyl cellulose (HPC) and sodium alginate respectively. The tablets were prepared by wet granulation method and followed by evaluation of granules and tablets were carried out by possible methods like, angle of repose, bulk density, tapped density, compressibility index and hausner's ratios showed that the granules good to compress, gelling and mucoadhesive strength of natural materials were studied by swelling index and *ex vivo* methods, NMM01 was showed more adhesion, 0.1535 neutons at 30 minutes of time, greatest retardation of drug release was observed. *In vitro* drug release mechanism was found out by fitting the cumulative percentage drug release against time in hours to higuchi, Korsmeyer-Peppa's first and zero order. The drug release studies reveals that best formulation was follows non-fickian diffusion, due to erosion of the matrices. There is no significant difference in drug release between the marketed sustained release product and natural mucoadhesive materials incorporated best formulation.

Keywords: Salbutamol sulphate; natural mucoadhesive materials; release kinetics

INTRODUCTION

In the recent years, transmucosal delivery of therapeutic agents has gained significant attention owing to presystemic metabolism or instability in the acidic environment. Mucoadhesive materials from natural sources are gaining more advantage spatial placement of mucoadhesive dosage devices. The advantages of such materials include their availability, economic, biodegradability and capability of chemical modifications. Mucoadhesive drug delivery systems (MDDS) are very beneficial to controlled drug release over the time and to a specific site of the body. The prolonged residence time of the drug in the body is believed to prolong the duration of action. MDDS can be applied to any mucosal tissue in the body, including the gastrointestinal, ocular, respiratory, buccal, nasal, rectal, urethral and vaginal path.

This part of the work investigates the feasibility of using *Caesalpinia pulcherrima* (NMM01) and *Leucaena leucocephala (*NMM02) are as the natural mucoadhesive materials in the formulation of sustained release tablets. The NMM01 and NMM02 materials studied for mucoadhesive nature, swelling index, *in vitro* drug release studies were compared with synthetic (hydoxy propyl cellulose) and semi-synthetic polymers (sodium alginate) incorporated formulations.

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Materials and methods

Materials

Salbutamol sulphate was procured from Aurobindo Pharma Ltd (Hyd, India). Hydroxyl propyl cellulose used as a synthetic material, sodium alginate was used as a semi-synthetic material, were purchased from yarrow chemicals Pvt ltd, (Mumbai, India). Phosphate buffer pH 7.4, 0.1 N Hcl were used for dissolution and mucoadhesion studies. Ten station tablet compression machine was used to press the matrices (Cadmach, Mumbai, India), Monsanto hardness tester was used for determine the crushing strength of tablet, Roche friability tester is used to find the % abrasion on tablets, British standard sieve (BSS) no: 16# was used for screen the granules.

Pre-formulation studies

Drug – Polymer interaction study

The study of compatibility between drug and other excipients were evaluated by performing drug – polymer interaction studies. The interactions were deter-

Table 1: Compositions of different formulations

S.No	Ingredients (mg)	Formulation Code											
		SF01	SF02	SF03	SF04	SF05	SF06	SF07	SF08	SF09	SF10	SF11	SF12
1.	NMM-01	25	50	75	-	-	-	-	-	-	-	-	-
2.	NMM-02	-	-	-	25	50	75	-	-	-	-	-	-
3.	HPC	-	-	-	-	-	-	25	50	75	-	-	-
4.	Sodium Alginate	-	-	-	-	-	-	-	-	-	25	50	75
5.	Salbutamol sulphate	4	4	4	4	4	4	4	4	4	4	4	4
6.	Dibasic Calcium Phosphate	69	44	19	69	44	19	69	44	19	69	44	19
7.	Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1	1
8.	Talc	1	1	1	1	1	1	1	1	1	1	1	1

mined by using fourier transform infrared spectroscopy (FTIR) and differential scanning calorimeter (DSC). The FTIR spectra and DSC pattern of pure drug, polymer and drug-polymer mix were taken and compared for studying the presence or absence of incompatibility between drug and polymer.

Interaction study by FTIR and DSC

FTIR spectroscopy studies were carried out by using Perkin Elmer model 2000 at Laila Impex Research Centre, India, and KBr pellet method was used. Materials were compressed under 10 tones pressure in a hydraulic press to form a homogeneous sample /KBr pellet. The pellet was scanned over the frequency range from 4000 to 400 cm^{-1}.

DSC thermo grams of pure drug, polymer and blends were recorded in a DSC analyzer Model DSC-50 Shimadzu, Sipra labs, Hyderabad, India at a heating rate of 20°C/min from 0 to 600°C in a nitrogen atmosphere.

Formulation of sustained release tablets

The granules were prepared by wet granulation method (Subramaniyam et al., 2003, Lachman et al., 1987, Gambhire M N et al., 2007). Accurately weighed quantities of the ingredients were mixed and the sufficient quantity of warm water was added to form damp mass. The damp mass was screened through BSS sieve no. 16. The granules were dried in a hot air oven at 45° C for 30minutes.

The granules were lubricated with magnesium stearate compressed into tablets by using 8/32 biconcave punch in Chamunda ten station rotary tablet punching machine to force of 5 ton. A total 12 formulations were prepared as mentioned in table 1. The evaluation of the granules includes bulk density, angle of repose, Carr Index and Hausner ratio. On the other hand evaluation of the tablets included the official methods like hardness , friability, and weight variations.

Determination of surface pH

The tablets were placed in small beaker with 4 mL of buffer solution (pH 7.4 ± 0.50) and the pH was measured at time interval of 2hrs by pH meter (ei-samaligy et al., 2004, marvola. M. et al., 1982). The average pH of three determinations was recorded.

Assay

The twenty tablets of were crushed in a mortar to fine powder. Then the powder was dissolved in 100 mL of buffer pH 7.4 in a volumetric flask. The flask was shaken for 12hr using a metabolic shaker. After shaking, the solution was filtered and from the filtrate, appropriate dilutions were made and the absorbance was measured at a 276nm, using UV/Visible spectrophotometer. The amount of drug was estimated from the absorbance values by using calibration curve.

Determination of Swelling Index

Swelling index of all the batches of sustained-release tablets was determined. An individual tablet was weighed accurately (W_1) and placed in a Petri dish containing 4 mL of buffer solution (pH 7.4). At the end of 30 minutes, the tablet was removed from the Petri dish, and excess surface water was removed carefully using filter paper. The weight of the swollen tablet was reweighed (W_2) (Ferdous et al., 2008). The same procedure was repeated for time intervals (60, 120, 180 and 240minutes).

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

Determination of Mucoadhesive strength

The mucoadhesive capacity of all formulations was determined by the method by Martti Marvola[18]. The apparatus used for this study consist of two glass slides; one modified physical balance, weights, thread, goat intestine, tyrode solution, distilled water and a beaker to hold the water (Agarwal D et al., 1997).

Freshly excised intestine of a goat was collected from local slaughter, preserved in tyrode solution until for the experimental use. Selected portion of the intestine is stretched on a glass plate placed on right arm of the

balance. The mucoadhesive tablet kept on the stretched part. The glass plate hanging on the right arm is allowed to contact the tablet on the skin and is moistened with some drops of water. The left arm is to equilibrate by the weight of detachment force to mucous part of intestine. The same procedure was repeated at different time intervals of 10, 15 and 30minutes by using fresh tablets. The experiment was repeated for different mucoadhesive materials. The force in Newton's was characterized by below formula,

$$F = 0.00981\ W/2$$

Where, W is the amount of water.

***In vitro* drug release study**

Dissolution studies were conducted by using EDT-08Lx 8-station Electro lab dissolution tester compliance with USP (24) type II (paddle) apparatus. A 900mL of 0.1 N Hcl, pH 1.2 was used for first two hours and followed by phosphate buffer 7.4 at 37˚C ± 0.5˚C. Paddle was set at the speed of 50rpm. The 2.5mL was withdrawn and further diluted to 25mL in volumetric flask and filtered through 0.45µ membrane filter. Samples were analyzed spectrophotometrically at 276nm. The content of drug was calculated by using following expression.

$$\text{Cumulative percentage drug release} = \frac{\text{Amount of drug released}}{\text{Amount of drug loaded}} X100$$

Treatment of dissolution data with different kinetic model

The quantity of drug released from the SR tablets was analyzed as a function of the square root of time, *In vitro* data was fitted to following kinetic studies in order to study the drug release mechanisms from swellable matrices (Jala I et al., 1989, Nakano M et al., 1983, USFDA, Pillay et al., 1998).

$Q = K_0\ t$, $\text{Log}\ Q_t = \text{Log}\ Q_0 + Kt/2.303$, $Q = K_H\ t^{½}$, $F = (M_t/M) = K_m\ t^n$, Zero order release, First order release, Higuchi's, Korsmeyer-Peppa's resepectively.

Where, Q = amount of drug release at time, Q_0 = initial amount of drug, Q_t = cumulative amount of drug release at time, M_t = drug release at time, M = total amount of drug in dosage form, F = fraction of drug release at time, K_0 = zero order release rate constant, K = first order release rate constant, K_H = Higuchi's square root of time release rate constant, K_m = constant depend on geometry of dosage form, t = time in hours and n = diffusion exponent value.

Similarity for Marketed product with best formulation

The similarity factor *f*2 as defined by (food and drug administration) FDA and (European Medical Agency) EMA, logarithmic reciprocal square root transformation of one plus the mean squared (the average sum square) difference of drug percent dissolved between the test and reference products. It is given by following equation:

$$f_2 = 50 \times \text{Log}\left\{\left[\sum_{n=1}^{\infty} W_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where, n is the number of pull points, W_t is an optional weight factor, R_t is the profile at time point t and T_t is the reference profile at the same time point.

For dissolution profile is to be considered similar, the value of *f*2 is between 50 and 100 (Gohel MC et al., 2000, 2002), indicates that the test and reference profiles were identical and as the value becomes smaller, the dissimilarity between release profiles increases. The similarity factor (standard deviation) SD was given as

$$S_d = \sum_{t=1}^{n=1}\left[\text{Log}\left((\ AUC_{R_t}\ )/(AUC_{T_t})\right)\right]/n - 1$$

Where, 'n' is the number of data points collected during the *in vitro* dissolution test and

AUC_{Rt} and AUC_{Tt} are the areas under curves of the reference and test formulation, respectively, at't' time. For the test and reference formulations to be identical, the SD value should be zero (Sutariya et al., 2006).

RESULTS AND DISCUSSION

Drug –polymer interaction studies

FTIR spectral study

FTIR spectra of pure drug, mucoadhesive materials (NMM01, NMM02, HPC, Sodium alginate) and blends were studied. The salbutamol sulphate was characterized by identifying the peaks were found at 2827 cm^{-1} (C-H stretching at 2931 cm^{-1}), at 1622 cm^{-1} (C=C stretching) at wave number in the pure spectra and in blend, due to and out of plane C- H were shown in pure spectra of salbutamol sulphate as well as in the spectra of the blend with NMM01. There is no incompatibility between NMM01 and salbutamol sulphate.

The characteristic peaks of salbutamol sulphate at wave number 3551 cm^{-1} due to O-H (stretching), wave number at 3402 due to N-H (stretching), wave number 2931 cm^{-1} due to C-H (stretching) were identified in pure and blend form with NMM02. There is no incompatibility between salbutamol sulphate and NMM02.

The FTIR studies revealed the absence of any onward incompatibility between the drugs and polymers taken for the study.

Differential scanning calorimetric study

Salbutamol sulphate showed endothermic peak at 271^o C. The natural mucoadhesive polymers NMM01 and NMM02 showed endothermic peaks at 338^o C and 330^o C respectively. DSC spectra of the blend containing NMM01 and salbutamol sulphate demonstrated endothermic peak at 158.2^o C evident to salbutamol sulphate is still in the crystal form in the formulation. The

thermographs showed with NMM02 at 157.8° C. with HPC at 157.2° C. There was no incompatibility between the drug and the mucoadhesive materials taken for this study. The relative graphs can find in fig.1, 2 and 3.

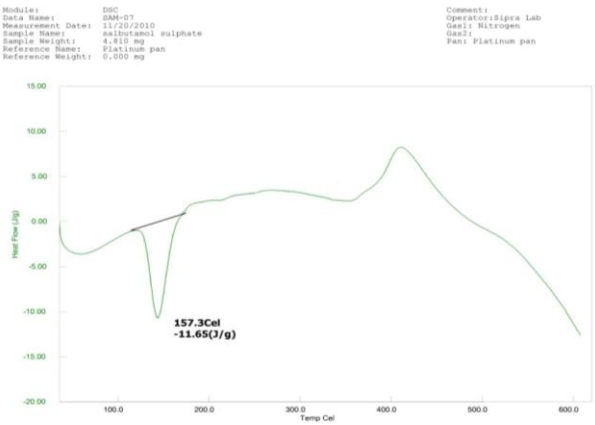

Figure 1: DSC Spectra of Salbutamol sulphate

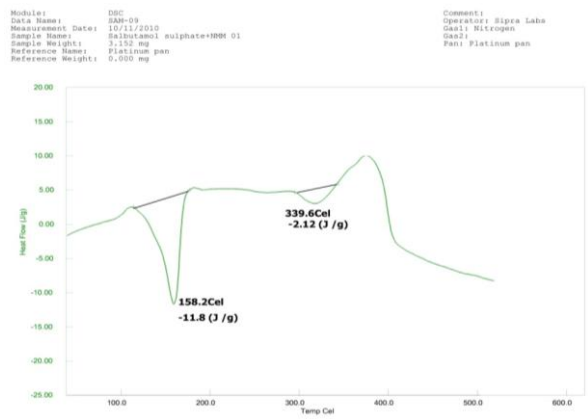

Figure 2: DSC Spectra of blend NMM 01and Salbutamol sulphate

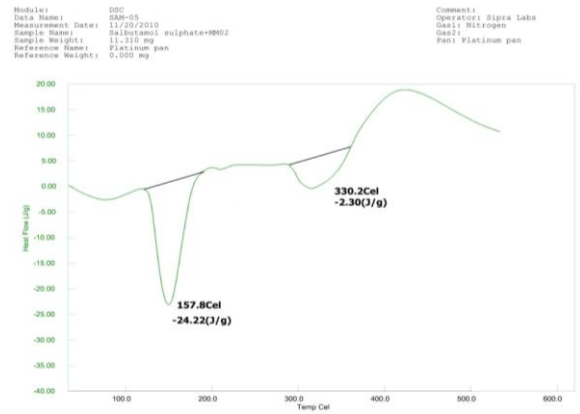

Figure 3: DSC Spectra of blend NMM 02 and Salbutamol sulphate

Evaluation of granules

The experimental values obtained for the determination of derived properties such as Bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio for granules containing salbutamol sulphate. The bulk densities were found to be in the range of 0.42 -0.45 gm/cc. The tapped density was found to be in the range of 0.44- 0.50 gm/cc. The granules had excellent flow property having angle of repose within 25°–30°. The compressibility index were well below 10% and the Hausner's ratio values were found between 1.04 -1.10. The overall physical properties of the granules of salbutamol sulphate were good and suitable for compression into tablets.

Physiochemical evaluation of sustained release tablets

The SR tablets containing salbutamol sulphate was prepared and evaluated for its thickness, hardness, friability, uniformity of weight, uniformity of drug content, and surface pH. The average thickness of the tablets was found between 2.1–2.4 mm. The hardness of the tablets ranges from 5.2 kg to 6.8 kg. The % friability was 0.1% to 0.8%. The average weights of the tablets were between 99.85 mg to 100.11 mg. The drug content in each tablet was found to be within acceptable range 99.13 -100.46%. The surface pH of the mucoadhesive tablets was in the range of 7.0 -7.4.

The surface pH of all formulations was around neutral significantly similar to that of saliva and hence no mucosal irritation was expected thus improving patient compliance.

Swelling index

The swelling index values of various SR formulations containing salbutamol sulphate was depicted in table 2. At the end of 240 minutes Formulation SF03 swelling index was 0.89 and SF06 showed 1.04, which are similar to the swelling index produced by SF09 was 0.89 and SF12 was 1.06. These results illustrated the fact that the Natural mucoadhesive polymers showed swelling index equivalent to the standardized mucoadhesive polymer namely Hydroxy propyl cellulose and sodium alginate.

Mucoadhesive strength

Mucoadhesive strength of SR formulations containing salbutamol sulphate was represented in table 3. The force of adhesion of the formulations containing NMM01 found to increase on increasing the concentration of the polymer. At the end of 30 minutes the formulation SF03 containing highest concentration of the polymer NMM01 (75 mg) showed mucoadhesive strength of 0.1535N compared to SF06 with NMM02 polymer showed 0.146N. The Mucoadhesive strength or force of adhesion was comparable to the SR tablets formulated using HPC and sodium alginate.

In vitro drug release kinetics

As shown in fig. 4, after the end of 12 h dissolution study the formulation SF01 showed the drug release of 93%. On increasing the concentration, SF03 was gradually decreased to 83%. It may be due to the fact that NMM 01 upon contact with aqueous medium, forms a gel layer. This layer increases in thickness as time passes creating a considerable barrier for both pene-

Table 2: Swelling index of Sustained release tablets of Salbutamol sulphate

Formulation Code	Swelling index (Newton's)				
	30 min	60 min	120 min	180 min	240 min
SF01	0.14±0.02	0.27±0.02	0.56±0.02	0.61±0.03	0.65±0.03
SF02	0.20±0.02	0.37±0.02	0.72±0.02	0.77±0.01	0.79±0.01
SF03	0.25±0.01	0.41±0.01	0.81±0.01	0.86±0.00	0.89±0.02
SF04	0.10±0.02	0.22±0.02	0.45±0.01	0.52±0.03	0.57±0.03
SF05	0.15±0.01	0.31±0.02	0.61±0.02	0.69±0.01	0.72±0.02
SF06	0.22±0.02	0.49±0.02	0.92±0.03	1.00±0.03	1.04±0.03
SF07	0.07±0.01	0.20±0.01	0.40±0.01	0.49±0.00	0.54±0.02
SF08	0.12±0.01	0.29±0.01	0.62±0.01	0.67±0.01	0.71±0.02
SF09	0.19±0.02	0.35±0.01	0.72±0.02	0.77±0.03	0.81±0.04
SF10	0.20±0.03	0.36±0.02	0.71±0.02	0.80±0.02	0.86±0.02
SF11	0.24±0.02	0.48±0.01	0.96±0.02	0.99±0.00	1.01±0.02
SF12	0.32±0.03	0.60±0.02	1.01±0.03	1.04±0.03	1.06±0.04

Each value represents the mean ± standard deviation (n=3)

Table 3: Mucoadhesive strength of Salbutamol sulphate formulations

Formulation Code	Mucoadhesive strength (Newton's)			
	5 min	10 min	15 min	30 min
SF01	0.0432	0.0491	0.0853	0.1001
SF02	0.0441	0.0687	0.1295	0.1432
SF03	0.0500	0.0736	0.1462	0.1535
SF04	0.0407	0.0476	0.0839	0.1010
SF05	0.0461	0.0682	0.1246	0.1457
SF06	0.0486	0.0726	0.1476	0.1476
SF07	0.0378	0.0446	0.0750	0.0907
SF08	0.0402	0.0594	0.1148	0.1182
SF09	0.0441	0.0667	0.1187	0.1319
SF10	0.0437	0.0500	0.0858	0.1035
SF11	0.0451	0.0701	0.1300	0.1452
SF12	0.0540	0.0741	0.1467	0.1550

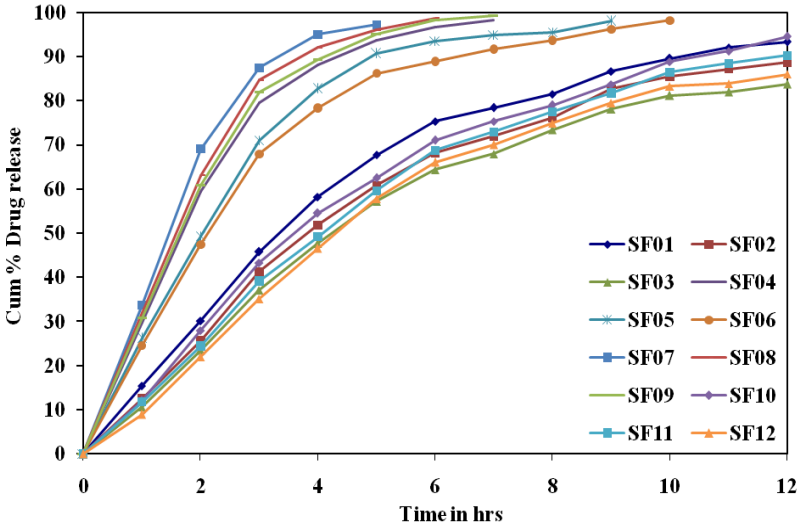

Figure 4: Comparison of drug release pattern of all SR tablets of Salbutamol sulphate with rank order

tration of solvent into the tablet and drug release from it. The release of salbutamol sulphate from the formulations containing NMM 02 slowed on increasing the concentration. The formulation SF 04 released 98.3% of its content within 7 h. On increasing the concentration NMM 02 to 50 mg showed release 98% in 9 h, where the formulation SF 06 showed release of 98.2% in 10 h. It was observed that NMM 02 showed less retardant effect when compared with NMM 01.

In order to determine the exact mechanism of drug release from the formulations, the in vitro drug release data was analyzed according to zero order kinetics, first order kinetics, Higuchi and Korsmeyer-Peppa's equation. The criterion for selecting the most appro-

priate model was on the basis of goodness of best fit. The formulations containing NMM01 showed first order drug release for salbutamol sulphate with r^2 value >0.9. The release exponent value of 0.8 determined from Korsmeyer-Peppa's plot indicate non-fickian drug release that means drug release occurred by diffusion and erosion of the polymer.Based on the *in vitro* drug release data, the best formulation was selected and compare with the market product for their release nature.

Similarity factor

Comparison of dissolution data of formulation SF03, the corresponding Marketed tablets, the similarity factor and Standard deviation (SD) were calculated by using DD Solver (MS Excel® add-In) software. The obtained similarity factor values for *f*2 of 93.95 and (SD) value of 0.008 indicates that the release profile of SF03, their corresponding marketed tablets were comparable and in a good agreement with each other.

CONCLUSION

The extracted natural mucoadhesive materials NMM01 and NMM02 were been used to formulation of sustained release tablets of salbutamol sulphate. The prepared tablets were been evaluated for various studies such as thickness, friability, Hardness, weight variation and for uniformity of the active ingredients. The results were meeting the standards of Indian pharmacopeia.

The prepared tablets were subjected to in vitro drug release kinetic studies. The formulation containing NMM01 as showed more retarded release of the drug than the formulation of NMM02. The kinetic study also reveals that the NMM01 exhibit better drug retardant characteristics compared with the polymer NMM02, HPC and sodium alginate. The *in vitro* release profile of the formulations with NMM01 was compared with the commercially marketed product of the same drug. The results showed that the formulations of NMM01 and Marketed product were having significant comparable release profiles.

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