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Characterization and optimization of various polymers based on mucoadhesive strength and wash off period for mucoadesive drug delivery system

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ABSTRACT

The aim of the present study was to characterize various mucoadhesive polymer combinations, viz. Carbopol 934, Hydroxy Propyl Methyl Cellulose (HPMC)-E15, Sodium Alginate and optimize the best polymer combination based on the mucoadhesive strength and Wash off period using a factorial design for two factors at two levels. A series of formulations with varied ratios of the above polymers were prepared by keeping the total weight of tablets constant. The tablets were tested for mucoadhesive strength using modified digital balance apparatus. The wash off test was performed using modified USP tablet disintegration test apparatus at 37ºC. The force of detachment and the time of detachment were considered as main parameters. From the results obtained, formulation F10 was chosen as the best formulation with 3hr 53min detachment time. Formulation F10 was optimized using two level two factor factorial design, as a good model to predict the effect of various factors like the ratio of Carbopol to HPMC 'Factor A' and the ratio of HPMC to Sodium alginate 'Factor B'. From the design M2 formulation which has coded level of -1 and +1 for considered factors A and B with the maximum mucoadhesive strength of 40 gm and wash off period of 4hr 10min was optimized as the best formulation.

Key words: Mucoadhesive polymers, Mucoadhesive strength, wash- off test, factorial design

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INTRODUCTION

Bioadhesion can be defined as the process by which a natural or a synthetic polymer can adhere to a biological substrate. When the biological substrate is a mucosal layer then the phenomena is known as mucoadhesion. Mucoadhesion can be obtained by the building of non-specific interactions, which are driven by the physicochemical properties of the particles and the intestinal surfaces or specific interactions when a ligand attached to the particle is used for the recognition and attachment to a specific site at the mucosal surface[1-5]

Mucoadhesive controlled release systems can improve the effectiveness of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of a drug in the body fluids. Mucoadhesion increases the intimacy and duration of contact between a drug containing polymer and a mucous surface. The combined effect of direct drug absorption and decrease in excretion rate due to prolonged residence time allow for an increased bioavailability of drug with a smaller dosage and less frequent administration.

Mucoadhesive polymers are classified into two categories, i.e. Polymers that are water soluble, linear and random polymers and Water insoluble compounds that are swellable networks joined by cross-linking agents.

The factorial designs [6] are used in experiments where the effects of different factors or conditions on experimental results are to be elucidated, e.g. to determine the effect of various polymers and their concentrations on mucoadhesive behavior. The factorial design, therefore, helps in optimization of suitable polymer combination and concentration in designing suitable dosage form. In general, optimization process consists of preparing a series of formulations with varying concentration of polymers in a systematic manner.

MATERIALS AND METHODS

Materials

Carbopol 934 p was a gift sample from Dr. Reddy's, Hyderabad. HPMC - E15, Sodium Alginate, Lactose, Magnesium Stearate were purchased from National Scientific Products, Mumbai. All other materials used were of Pharmaceutical grade.

Methods:

Preparation of tablets

A total of 15 formulations with various polymer combinations were prepared. The polymers were mixed in geometric ratio using sieve number 20 to get a uniform mixture and finally lubricated using a suitable lubricant depending on the formula design.

The required weight of the blend was weighed and compressed on enteric coated core tablets using Elite – 10 station GMP model rotary press using round biconcave punches showing VIGNAN embossing as seen in **Figure No. 1**.

Evaluation of prepared mucoadhesive tablets:

Weight Variation [8, 10]:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by ± 7.5% as per the USP. The results were shown in Table No. 2

Hardness[8]:

Hardness was measured using Monsanto hardness tester. For each batch three tablets were tested.

Friability[8, 9]:

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where, % F = friability in percentage
Wo = Initial weight of tablet
W = weight of tablets after revolution

Swelling Studies[11-14]

Swelling studies were performed to estimate molecular parameters of the swellable polymers such as Carbopol, HPMC and Sodium alginate using USP type II dissolution apparatus (DR 8000). The tablets were initially weighed using an electronic balance having sensitivity 10mg. the tablets were added to dissolution basket. After 5 minutes, the tablets were removed and placed on a butter paper and the tablets were re-weighed. The swelling ratio was caluculated from the following formula:

$$\text{Swelling Ratio} = \frac{\text{(Weight of tablet after swelling – weight of tablet before swelling)}}{\text{Weight of tablet before swelling}}$$

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Mucoadhesive Strength[15, 16]:
Mucoadhesive strength of the tablet was measured on the modified digital balance. The design used for measuring the mucoadhesive strength was shown in Fig. No.7. The apparatus consist of a modified electronic digital balance on which a rectangularly bent aluminum rod was affixed and at the bottom end of the rod an iron punch was fixed at the centre, to which the tablet was adhered as shown in the **figure 8**. The balance was tared to zero before performing the experiment. At the lower end, a beaker containing a block for placing the mucosal layer is arranged and the up and down moments of the beaker was fabricated by using syringes assembly as shown in the **figure 7**. The beaker was filled with Tyrodes solution for maintaining the consistency of the tissue. The other side (outer part of stomach) tissue was adhered to the support in the beaker.

Pig stomach mucosa was used as a model membrane since it has higher similarities with that of human stomach mucosal layer. The pork stomach mucosa was kept in Tyrodes buffer solution during transportation.

After the arrangement of the assembly was done, the one side of the tablet was fixed to the punch with the aid of Cyanoacrylate gum and the beaker containing mucosal layer was raised slowly until contact between the goat mucosa and the mucoadhesive tablet was established. A preload of 10 mg was placed on the punch for 5 min (preload time) to establish adhesion bonding between mucoadhesive tablet and pig stomach mucosa. The preload and preload time were kept constant for all formulations. After completion of preload time, preload was removed from the punch and the beaker assembly was lowered slowly. The weight at which the tablet was detached from the mucoadhesive layer was noted as mucoadhesive strength in grams. From the mucoadhesive strength following parameter was calculated.

Force of adhesion (N) = (Mucoadhesive strength × 9.81) / 1000

Bond strength (N/m2) = Force of adhesion (N) / Surface area of tablet (m2)

Wash off test[17, 18]:
The mucoadhesive properties of the tablets were evaluated by an *in vitro*, wash-off method using modified USP tablet disintegration apparatus shown in **figure 3 & 4**. Pieces of stomach mucosa of pig were mounted on the glass slides provided with suitable support. The slides were fixed to the arm of disintegration apparatus such that height from the bottom is 25mm at the down stroke and at the highest point the slide is 15 mm below the liquid surface. After fixing of 2 tablets to this glass slide, it was tied to the arm of USP tablet disintegration test apparatus and was run at 37^{o}C. Time of detachment of both tablets was noted down as wash- off period

Optimization of the best formulation using 2^2 factorial designs:
A 2^2 factorial designs was used to study two factors each at two levels, i.e. actual values and coded values. The ratio of Carbopol to HPMC was considered as 'Factor A' and the ratio of HPMC to Sodium alginate was considered as 'Factor B'. Actual and coded levels for the factors were shown in **table 6**. A total of four experiments were conducted according to the model and in order to see the curvature effect, if any, the centre points were added. The total number of experiments was five. $2^2 = 2 \times 2 = 4 + 1$ design at the centre as shown in **Table 7.**

Invitro Drug release studies:
Invitro drug release studies of optimized Montelukast Sodium mucoadhesive tablets M2 was performed using Lab India 8 basket model, USP Type I dissolution apparatus (basket type). The baskets were completely covered with aluminium foil to prevent photolytic degradation as shown in **fig 10**. The dissolution studies were performed for duration of 8 hr using change over medium method. Dissolution was performed in 0.1N HCl for 4hrs and was continued upto 8hrs in 7.4 pH Phosphate buffer containing 0.5% SLS as dissolution medium. Sink conditions was maintained. Required dilutions were made using 0.1N HCl and 7.4 pH Phosphate buffer containing 0.5% SLS and the absorbance of the samples were measured at 287.3nm using Systronics Double beam UV Visible Spectrophotometer.

RESULTS AND DISCUSSION

Formulation:
All the 15 Mucoadhesive formulation tablets were evaluated for Swelling Index, Mucoadhesive Strength, Force of Adhesion, Bond strength and Wash-off test.

Swelling Index was found to be in the range of 14.08 – 52.22%. Results showed that there is increase in the swelling ratio with increase in the polymer concentration upto some extent. Further increase in the polymer concentration showed decrease in the swelling ratio due to obstruction caused by the polymers for the movement of water molecules. Mucoadhesive Strength was found to be in the range of 18 – 38.6 gm, Force of Adhesion was found to be in the range of 0.17 - 0.378 N, Bond Strength was found to be in the range of 390.6 – 837.75 N/m^2. Results showed that there is an increase in the mucoadhesive strength upon increase in the viscosity. There is a marked increase in the viscosity of the polymer and bonding forces when the polymers were used in combination rather than when used alone. Combination of HPMC E15, Carbopol 934p and Sodium alginate showed greater bioadhesive properties due to increased number of hydroxyl and carboxy groups. Wash-off test was found to be in the range of 40 sec to 3hr 53min. Based on the results Formulation **F10** with Swelling Index of 52.22 %, Force of Adhesion of 0.378 N, Mucoadhesive Strength of 38.6 gm, Bond strength of 837.75 N/m^2 and Wash-off period of 3hr 53min was **selected for optimization**.

Optimization:

Formulation F10 with good bio-adhesive properties was further optimized using 2^2 Factorial design. Four formulations were prepared considering two factors at 2 levels. i.e. high level(+) and low level(-) fifth formulation was designed by considering midpoint. The optimized formulations were evaluated for specific mucoadhesive tests like Swelling Index, Mucoadhesive Strength, Force of Adhesion, Bond strength and Wash-off test. Swelling Index was found to be in the range of 51.12 – 59.43 %, Force of adhesion was found to in the range of 0.276 – 0.384 N, Mucoadhesive strength ranges from 29.48 – 40 gm, Bond strength was found to be in the range 390.66 – 842.58 N/m^2.

The results concluded that M2 with Swelling Index 59.43%, Mucoadhesive Strength of 40 gm, Force of Adhesion of 0.384 N, Bond Strength of 842.58 N/m^2 and Wash-off period of 4hr 10min was the best formulation.

TABLE 1: Formula of various polymer combinations and their quantities

Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Carbopol	100	75	50	-	-	-	-	-	-	100	50	25	50	100	25
HPMC E15	-	-	-	100	75	50	-	-	-	50	100	50	25	25	100
Sodium alginate	-	-	-	-	-	-	100	75	50	25	25	100	100	50	50
Lactose	395	420	445	395	420	445	395	420	445	320	320	320	320	320	320
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500

Table 2: Various parameters of mucoadhesive formulations

Tests	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Weight Variation (mg)	500 ± 9.2	500 ±00	500 ± 0.1	500 ± 8.3	500 ± 7.6	500 ± 8.4	500 ± 9.2	500 ± 7.9	500 ± 5.4	500 ± 6.3	500 ± 7.1	500 ± 8.6	500 ± 9.0	500 ± 6.2	500 ± 4.3
Hardness	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5	3±0.5
Friability	0.34	0.25	0.23	0.91	0.87	0.83	0.23	0.25	0.21	0.32	0.21	0.23	0.32	0.24	0.21

Table 3: Swelling ratio of various formulations

Formulation	Swelling ratio
F1	14.08451
F2	13.88889
F3	14.08451
F4	Disintegrated
F5	Disintegrated
F6	Disintegrated
F7	53.52113
F8	46.47887
F9	48.61111
F10	22.22222
F11	22.53521
F12	39.43662
F13	31.94444
F14	23.61111
F15	28.16901

Table 4: Wash off period for various formulations

Formulation	Wash off period
F1	2hr 45min
F2	3hr 4min
F3	1hr 10min
F4	40 sec
F5	2min 41sec
F6	4min 25sec
F7	2hrs
F8	22min
F9	1hr 38min
F10	3hr 53min
F11	2hr
F12	2hr 55min
F13	2hr 38min
F14	2hr 51min
F15	1hr 12min

Table 5: Mucoadhesive Strength of various formulations

Formulation	Mucoadhesive Strength (gm)	Force of Adhesion (N)	Bond strength (N/m^2)
F1	21 ± 0.5	0.20601	455.7743
F2	25 ± 1.2	0.24525	542.5885
F3	35 ± 0.82	0.34335	759.6239
F4	18 ± 0.65	0.17658	390.6637
F5	21 ± 0.73	0.20601	455.7743
F6	20 ± 1.13	0.1962	434.0708
F7	23 ± 0.53	0.22563	499.1814
F8	22.4 ± 0.92	0.219744	486.1593
F9	24 ± 0.395	0.23544	520.885
F10	38.6 ± 0.756	0.378666	837.7566
F11	19.23 ± 0.99	0.188646	417.3591
F12	23 ± 0.874	0.22563	499.1814
F13	36 ± 0.182	0.35316	781.3274
F14	22 ± 0.872	0.21582	477.4779
F15	19 ± 0.765	0.18639	412.3673

Table 6: Actual and Coded levels for the factors

Formula	Actual Values		Coded Values	
	A	B	A	B
M1	1:0.5	1:0.5	-1	-1
M2	1:0.5	1:1	-1	+1
M3	1:1	1:0.5	+1	-1
M4	1:1	1:1	+1	+1
M5	1:0.75	1:0.75	0	0

Table 7: Formulae for preparation of tablets using 2^2 Factorial designs

Ingredients(wt in mg)	M1	M2	M3	M4	M5
Carbopol934p	100	100	100	100	100
HPMC E15	50	50	100	100	75
Sodium Alginate	25	50	50	100	37.5
Lactose	320	295	245	195	282.5
Magnesium Stearate	5	5	5	5	5
Total Weight	500	500	500	500	500

Fig 1 Mucoadhesive tablets (F10 formulation) with VIGNAN embossing

Fig 2 representing differentiation between swelled and normal tablet

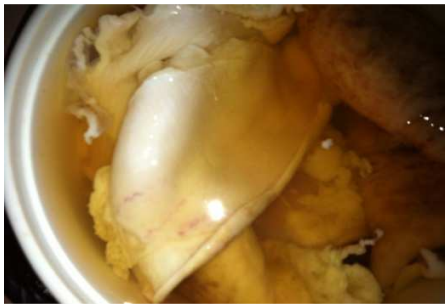

Figure 3: Freshly collected pig stomach stored in ringer solution

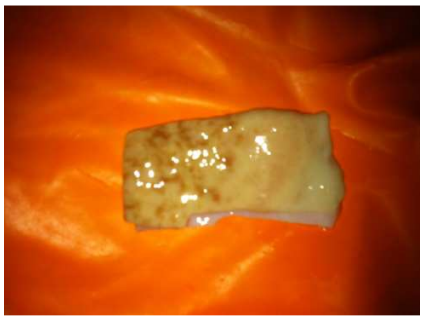

Fig 4: Sliced Portion of pig stomach for wash off test

Fig 5 and 6: modified Disintegration Apparatus for Wash off Test

Fig 7: Modified electronic Balance with Hydraulic syringe system for measuring Mucoadhesive strength of tablets

Fig 8 and 9 representing mucoadhesive strength testing of formulations

Fig 10 represents the LabIndia model USP type I dissolution apparatus covered with aluminium foil to prevent degradation of Montelukast sodium from light

CONCLUSION

The application of 2^2 factorial designs was a significant model to obtain the effect of mucoadhesive polymers at various factors and from optimization; it was clear that formulation M2 showed maximum desired mucoadhesive nature.

From the results of optimization, it was clear that not only the polymer combination but also the ratio of polymer combination with each other highly influenced mucoadhesive nature.

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