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Original Article

EVALUATION OF CELLULOSE POLYMERS FOR BUCCAL FILM FORMULATION OF RASAGILINE

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ABSTRACT

Objective: Rasagiline Mesylate is used to treat the signs and symptoms of Parkinsonism. It has an oral bioavailability of 36% due to first pass hepatic and intestinal metabolism. To improve the bioavailability; a buccal films formulation was planned.

Methods: Compatibility of the drug with the excipients was studied with the help of FTIR and DSC. 2^3 factorial design was planned using concentration of polyox, concentration of film former as numerical variables and type of film former as a categorical variable. Solvent casting method was used for the fabrication of films. Weight, thickness, surface pH, mucoadhesive strength, *in vitro* residence time, % swelling and % drug release were evaluated for the prepared film formulations.

Results:All the films were found havesurface pH close to neutral pHand werefound to have content uniformity. Mucoadhesive strength was found to increase with increase in concentration of polyox. Three polymers polyox, sodium CMC and HPMC were showing positive effect on swelling. Comparatively polyox has less influence than either of the cellulose polymers on swelling.Drug release is more controlled by the high swelling film formers than polyox. Among the film formers, though swelling is more, % drug release is also more from Na CMC films because of its ionic nature and more solubility.

Conclusion: Because of high mucoadhesive strength and more % drug release, combination of Polyox with Na CMC film formulations were selected over HPMCfilm formulation to improve the bioavailability of Rasagiline**.**

Keywords: Rasagiline, buccal film, Sodium carboxy methyl cellulose, factorial design

INTRODUCTION

Drug delivery by transmucosal routes i.e., through the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity offer distinct advantages over per oral administration for systemic drug delivery. The main advantages include possible avoidance of pre systemic elimination within the GI tract and bypasses first pass hepatic effect. Delivery of drugs through oral mucosa is classified into three categories: (i) buccal delivery, in which the drug administered through the mucosal membranes lining the cheeks (buccal mucosa), (ii) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes of the lining the floor of the mouth, and (iii) local delivery, in which the drug is delivered into the oral cavity.

Within the oral mucosal cavity, the buccal delivery offers an attractive route of administration for systemic drug delivery as the buccal mucosa has rich blood supply, easy accessibility and it is relatively permeable[1].

Buccal mucosa is most suited for local, as well as systemic delivery of drugs. Different dosage forms administered by buccal route, include tablet[2], gel[3], films[4] and bi-layered and multi-layered devices[5] etc. Among all, films have improved patient compliance due to their small size and reduced thickness, compared to lozenges and tablets. Films may be preferred over buccal tablet, in terms of flexibility and comfort[6][7]. In addition, films will have relatively long residence time on the mucosa compared to oral gels, which are easily washed away and removed by saliva. Buccal films also ensure more accurate dosing of drugs when compared to gels and ointments[8].

Rasagiline is a second generation, selective, irreversible inhibitor of mono amine oxidase type B. It is an anti-Parkinson's drug which acts by inhibiting the oxidative breakdown of dopamine (DA) in the striatum, and it can be used for both as mono therapy in the early stages of the disease, or as an adjunct to L-dopa, in the advanced stages. Neuro protective effect, an additional property of Rasagiline, was shown to be independent ofitsMAO-inhibitory effect in preclinical studies, and found to occur in patients treated with normal therapeutic doses of the drug at 0.5 or 1mg [9]. The absolute bioavailability of Rasagiline after a single oral dose is about 36%. First pass metabolism is responsible for the incomplete bioavailability.

Literature reveals alternate routes to improve the bioavailability of Rasagiline like transdermal[10], iontophoretic delivery[11], oro dispersible tablets[12].

The present study is planned to formulate a buccal film formulation using a factorial design with polyox and two cellulose polymers and evaluating its *in vitro* performance.

The advantages of formulating Rasagiline as buccal films are, 1). Improvement of the bioavailability of the drug by avoiding first pass hepatic and intestinal metabolism[13].

2).Though dietary amine restriction is not advised for Rasagiline at therapeutic doses, but certain foods like aged cheese are avoided as these contain very high amounts of tyramine. No such a restriction is required for buccal Rasagiline as the drug will not come in contact with peripheral MAO[14]. 3). Patients of parkinsonism will suffer from swallowing disorders[15]. Compliance of the patients can be improved by avoiding the swallowing of tablets and capsules.

Literature reveals the use of Polyox[16][17] and cellulose polymers[18]in mucoadhesive drug delivery systems.The present study is planned at evaluating two cellulose polymers namely sodium carboxy methyl cellulose(Na CMC) and hydroxy propyl methyl cellulose (HPMC) with polyethylene oxide (polyox) for the formulation Rasagiline buccal film. Polyox was used as a mucoadhesive polymer and Na CMC/HPMC were selected as film forming polymers.

MATERIALS AND METHODS

Rasagiline Mesylate is obtained as a gift sample from Apotex Research Private Ltd, Bangalore. Samples of PolyoxWSR N 10, Na

CMCmedium gradeviscosity and HPMC100cps were obtained from Colorcon,Rolex chemical industries and Central Drug House respectively**.**

Drug-excipient compatibility study

Pure Rasagiline Mesylate and its physical mixture with the polymers is prepared by mixing with spatula followed by mixing in polybag. The samples were packed in vials and charged at 40^{0}C and 75% RH for 15 days. After 15 days, the samples were examined for DSC and FTIR to find any interaction between the drug and excipients. For FTIR analysis the samples were blended with potassium bromide in 1:100 ratio and the blend was made into pellet under high pressure. The pellets were scanned over a wave number range of 4000–400 cm^{-1} using Shimadzu, FTIR instrument. For DSC study 2-5 mg sample was programmed to increase temperature at a rate of 5°C/min from 20°C–500°C using DSC-60 Differential Scanning Calorimeter, Shimadzu.

Experimental Design

The formulations were prepared as per 2^3 factorial design. Three independent factors were selected out of which two are numerical factors and one is a categorical factor. The two numerical factors are concentration of polyox and concentration of film former. Type of film former is the selected categorical factor which can be either Na CMC or HPMC. The levels studied were 10% and 20 % for Polyox and 1% and 3% for film formers. The prepared films were evaluated for weight, thickness, content uniformity, surface pH. In addition, mucoadhesive strength, *in vitro* residence time, %swelling and % drug release were selected as dependent variables and evaluated with help of regression equation. Design Expert software version 9.0.2 was used for evaluation. Table 1 gives the polymer composition of all formulations as per the factorial design.

Table 1: Composition of buccal formulations as per factorial design.

Formulation	Concentration of Polyox (%)	Type of film former	Concentration of film former (%)
F1	10.00	HPMC	1.00
F2	20.00	Na Cmc	1.00
F3	10.00	Na Cmc	1.00
F4	20.00	HPMC	1.00
F5	20.00	HPMC	3.00
F6	10.00	Na Cmc	3.00
F7	10.00	HPMC	3.00
F8	20.00	Na Cmc	3.00

Fabrication of buccal films

Solvent casting method was used for the fabrication of buccal films. As per the experimental design, the polymers required to make 40 ml of polymeric gels were accurately weighed, dissolved in water and allowed to swell till we get a clear, uniform gel. Both polymer solutions were mixed,added with glycerine at 10% of the total polymer weight as a plasticizer. Then calculated amount of drug was added so that 1 mg of the Rasagiline will be present in a film unit of 1cm diameter. This was casted on 7 cm ring, bottom of which is covered with aluminium foil and placed on a horizontal surface whose level is adjusted with the help of spirit level. The casted films were allowed to dry in a dryer a till constant weight film was formed. After drying the films were cut using 1 cm circular mould.Each 1cm circular film unit will be having 1.56 mg of Rasagiline Mesylate which is equivalent to 1 mg of Rasagiline. These film units were evaluated for the various parameters.

Evaluation of formulated buccal films

Weight and thickness of films:

The weight of the film units was determined using a digital balance and thickness at different places of the film were measured with a digital vernier calipers (Mitutoyo, Japan).Weight and thickness were determined for five units.(n=5)

Folding endurance[5]

Folding endurance of the films was determined by repeatedly folding the film at the same place till it broke or folded up to 200 times manually, which was considered satisfactory to reveal good film properties. The number of times a film could be folded at the same place without breaking was considered as the value of the folding endurance. This test was done on five films. (n=5)

Surface pH[19]

One mL of distilled water was added on to the film surface, pH was measured by allowing the electrode of a pH meter to come in contact with the film for 1 minute to equilibrate**.**(n=3)

Drug content uniformity

Each film unit was dissolved in water by soaking it for 12 hours followed by stirring. The absorbance of the resulting solution was measured at 271.6 nm using blank film solution prepared similarly using as reference sample. Average of five film units was considered.(n=5)

Swelling percentage [5]

Buccal film units were weighed individually, W1, and placed separately on 2% agar gel plates and incubated at 37^0 C±1^{0}C. At every 30 minutes regular intervals, the films were removed from the gel and adhering gel was removed carefully with tissue paper. The weight of the swollen film was W2. Percentage swelling was calculated using the formula (W2-W1)/W1 *100.Mean of three determinations was considered. (n=3)

Muco adhesive strength

Muco adhesive strength was measured by modified physical balance which is modification of the apparatus applied by Gupta *et al*[20]. Average of triplicate readings was considered.(n=3)

***In vitro* residence time**[21][22][23]

The *in-vitro* residence time was determined using a locally modified USP disintegration apparatus. The average of triplicate readings is considered for the each formulation. (n=3)

***In vitro* drug release studies**[2][24]

Drug release from the buccal films was studied using diffusion cell. A buccal film unit of 1 cm diameter was fixed on the aluminium foil by using acrylate glue and it is placed between the donor and receptor compartment such that the film faces the receptor compartment. Small magnetic bead was placed and the receptor compartment was filled with distilled water and this whole assembly was kept on the water bath, which is placed on the magnetic stirrer and the temperature of the water bath was maintained at 37±0.5ºC. Periodically samples were withdrawn and same volume of water was replaced. The samples were analysed spectrophotometrically at 271.6 nm. For each formulation, average release of three film units was calculated. (n=3)

RESULTS

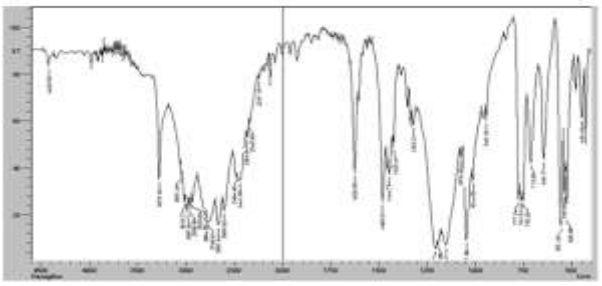

Fig 1: "FTIR spectra of Rasagiline Mesylate"

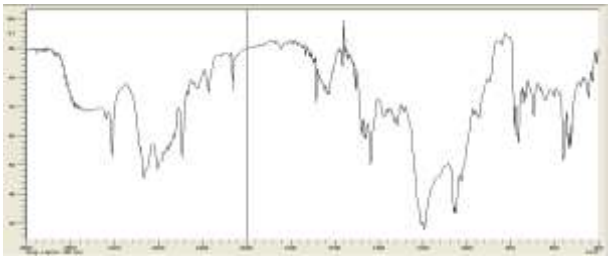

Fig 2: FTIR spectra of physical mixture of Rasagiline with HPMC

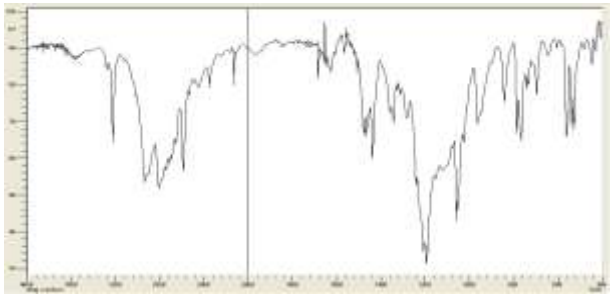

Fig 3: FTIR spectra of physical mixture of Rasagiline with Polyox

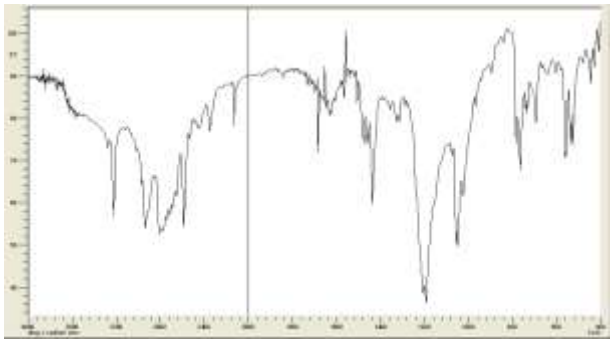

Fig 4: FTIR spectra of physical mixture of Rasagiline with Na CMC

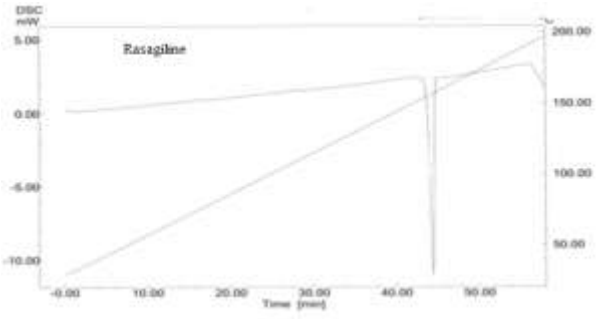

Fig 5: DSC thermogram of Rasagiline Mesylate

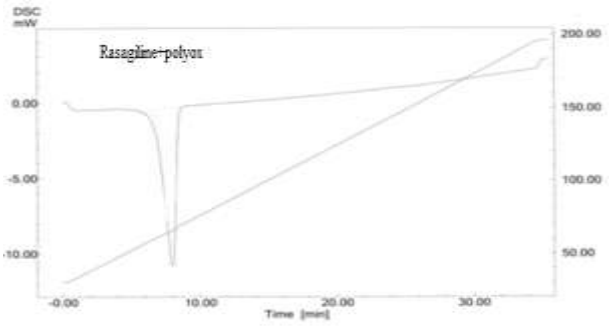

Fig 6: DSC thermogram of Rasagiline Mesylate and its physical mixture with polyox

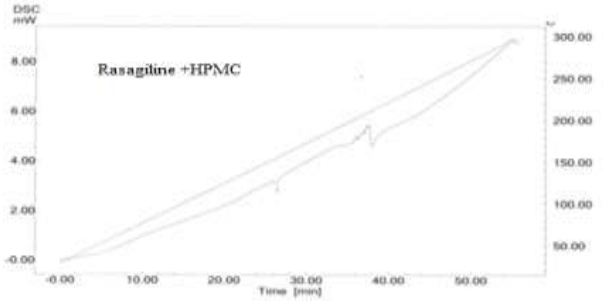

Fig 7: DSC thermogram of Rasagiline Mesylate and its physical mixture with HPMC

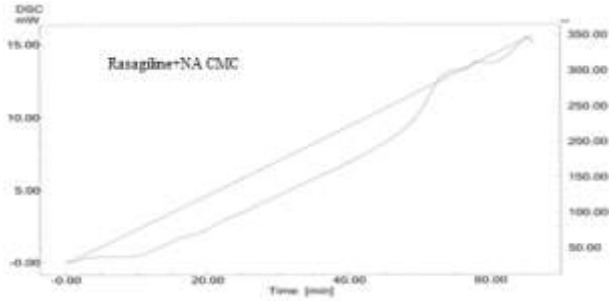

Fig 8: DSC thermogram of Rasagiline Mesylate and its physical mixture with Na CMC

Table 2: Evaluated parameters of prepared buccal films of Rasagiline

Formulation	Mucoadhesive strength (gm)	Invitro residence time (min)	% drug release at 1 hour	% swelling
F1	18.77	28	94.66	58.66
F2	23.06	17	97.18	91
F3	21.95	22	100.0	63
F4	20.11	33	78.21	74.66
F5	15	60	52.41	108
F6	19	40	96.59	84
F7	13	84	66.86	69.33
F8	24	38	75.419	118.33

All theabove values are average values of 3 determinations

DISCUSSION

Drug-excipient compatibility study

To asses any interaction between the drug and the polymer, FTIR and DSC studies were carried out and the spectra were shown in Fig 1-8.

The FTIR spectra of combination of drug with the polymer did not show any changes in the characteristic peaks of the Rasagiline Mesylate. The specific peaks at wave number1479.45 cm^{-1} due to -CH_2- bending, **at** 646.17 cm^{-1} due to S- O bending, at 3279.10 cm^{-1}due to ≡ C-H stretching, at 2125.63 cm^{-1} due to C ≡ C stretching, 1626.05, 1604.83, 1560.46 cm^{-1}due to N-H bending (secondary amines) remain unchanged indicating that the drug had not interacted with the polymer.

The DSC thermogram revealed sharp distinct endothermic peak at 156.1°C which remained unchanged when the drug was combined with the polymer. The DSC analysis of the physical mixture of the drug and the polymer revealed a negligible change in the melting point of Rasagiline Mesylate

Evaluation of formulated buccal films

Weight and thickness of films

Weight of the films was ranging from 51 mg to 109.5 mg. The thicknesses of all the films were between 0.85-1.25 mm. As the

amount of polyox was changed, weight and thickness of formulationsalso changed.

Drug content uniformity

The content uniformity was found to be between 91% to 101%. As the dose of the drug is low, ut most care is needed in casting the solution to eliminate the variation in thickness, which in turn changes the weight of the film which further has an impact on content. Uniform thickness was maintained by adjusting the surface level horizontal using a spirit level while casting the polymer solution. Content uniformity can also be improved by casting the films in the individual casting wells for each dosage unit, but this approach has a limitation on scaling up the process [7].

Folding endurance and surface pH

All the films were found to be brittle and not flexible, and folding endurance was less than 50 in all the films.The pH of the films was ±0.5 of the neutral pH which indicates that patient compliance can be improved as no irritation occurs because of change in pH.

Evaluation of parameters using regression analysis

As two polymers are considered for comparison of the dependent factors, only main effects are selected to get the regression equation which helps in easy analysis of each categorical factor. A better correlation coefficient can be obtained if interaction terms are also considered. The design was evaluated by a linear model, which bears the form of the equation:

$Y=b_0 +b_1 X_1 +b_2 X_2$ Where Y is the response variable, b_0 the constant, and b_1, b_2 are the regression coefficients of X_1 and X_2,which stand for two independent factors. Here the equations were generated with different (b_0) constant values and same regression coefficients ($b_1$and b_2). When interaction terms are considered,the constant (b_0) and regression coefficients ($b_1$and b_2) will change, though we get a better adjusted correlation coefficient,differencebetween the two film formers in terms of dependent factors will not be easily observed.

Mucoadhesive strength

Mucoadhesive strength varies between 13-24 gm. When the concentration of polyox is increasing, mucoadhesive strength is increasing. Na CMC or HPMC has got negative effect on mucoadhesive strength when compared to polyox.Mucoadhesive strength value is observed to be more with Sodium CMCfilms than with HPMC films[25]. Literature[26]also reveals that non-ionic polymer undergo lesser degree of mucoadhesion when compared to anionic polymers. HPMC is a non-ionic polymer and will not contain proton donating carboxyl groups[27] whereas Sodium CMC is an anionic polymer and contains carboxyl groups; this could be the reason for the high mucoadhesive strength of Sodium CMC films.

The regression equation for mucoadhesive strength was as follows (R square value of 0.8566)

When the type of film former is Na CMC

Mucoadhesive strength= + 21.6812 + 0.23625 * polyox – 1.61125* concentration of film former

When the type of film former is HPMC

Mucoadhesive strength= + 16.3987+ 0.23625 * polyox – 1.61125* concentration of film former

% swelling and % drug release

% Swelling values range between 58-118%. Three polymers polyox, sodium CMC andHPMC were showing positive effect on swelling. Comparatively polyox has less influence than either of the cellulose polymers.This could be due to less viscosity of the polyox grade[28].Literature also infers that sodium CMC films show greater % swelling compared to HPMC films[29][27].

The regression equation for % swelling with an R square value of 0.9535 is as follows

When the type of film former is Na CMC

% swelling = +22.12514 + 2.9249 *polyox + 11.5416 * concentration of film former

When the type of film former is HPMC

% swelling = +10.7085 + 2.9249 *polyox + 11.5416 * concentration of film former

It was observed that polyox films with Sodium CMC showed higher percent swelling than HPMC containing films at the same concentration. Due to presence of more hydroxyl groups in the Sodium CMC molecules which hold more amount of water in their network and shows greater swelling.As polyox has less swelling, drug release is comparatively more than film forming polymers.At the same time the drug release from the Sodium CMC films was more because of ionic nature which causes the films hydrate at faster rate, dissolve and erode at a higher rate than HPMC. The percentage drugrelease at 1 hour varies between 52.4-100%. Higher swelling and erosion of Sodium CMC was observed by Singh et al [30].

The regression equation for % drug release with an R square value of 0.9079 is

When the type of film former is Na CMC

% drug release at 1 hour = + 132.5757 -1.3724 * polyox – 9.8465 * concentration of film former

When the type of film former is HPMC

% drug release at 1 hour = + 113.3181 - 1.3724 * polyox – 9.8465 * concentration of film former

***In vitro* residence time**

The films got detached from the mucosal surface before they were completely eroded. Time of detachment was considered for *invitro* residence time. It varied between 17-88 minutes. Polyox exihibits a negative coefficient and cellulose polymers were having a positive coefficient. The lubricity of polyox when it was wet[28]could be reason for the detachment and negative influence on *invitro* residence time and this could be playing a major role as polyox is present in high proportion in the film matrix. The regression equation for *in vitro* residence time with an R square value of 0.8604 is

When the type of film former is Na CMC

Invitro residence time = + 8.5000 –0.6500 * polyox +15.2500* concentration of film former

When the type of film former is HPMC

In vitro residence time = + 30.500– 0.6500 * polyox + 15.2500* concentration of film former

Lesser *invitro* residence time of sodium CMC films could be because of its greater solubility, which makes the film to erode and dissolve during the test. Similar results were observed in the literature[29].

Anhydro glucose unit is the basic monomer of cellulose. It contains substitutable H or OH groups. In HPMC, these were substituted with methyl and hydroxy propyl groups and in Na CMC, ionic sodium carboxy methyl group was substituted. The differences in these substitutions will lead to differences in the properties of celluloses.

The solubility of polymers is compared by solubility parameters instead of the saturation solubility in each individual solvent. As per the literature[31]the solubility parameters were found to be 28.9 and 23.2 for Na CMC and HPMC respectively. So the order of hydrophilicity also follows Na CMC > HPMC.

The greater hydrophilicity could be the reason for more swelling, more % drug release of Na CMC containing film formulations when compared to HPMC films. Because of ionic nature it is exhibiting high mucoadhesive strength, so among the two cellulose polymers Na CMC is selected asthe bestpolymer, as it is having both film forming and mucoadhesive properties.

CONCLUSIONS

An attempt to improve the bioavailability Rasagiline was planned using 2^3 Factorial design to statistically evaluate the effect of combination of polyox and cellulose polymers on dependent parameters. Na CMC and HPMC were studied at two concentration levels and polyox at two different concentration levels. Sodium CMC was found to be superior to HPMC in terms of mucoadhesive strength, % drug release and %swelling. Because of ionic nature and greater solubility of NaCMC, it was selected as the polymer for the development of mucoadhesive drug delivery systems. By formulating a buccal film of Rasagiline, we can improve the bioavailability. Patient compliance can also be improved as delayed gastric emptying and swallowing disordersof patients of Parkinsonismand diet restriction (cheese reaction) can be overcome by formulating Rasagiline buccal films.

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