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Rheological Characterization of Bioadhesive Nasal Gels

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ABSTRACT

Bioadhesive gels improve both effectiveness and efficiency of the product due to intimate contact between a delivery device and the absorbing cell layer. The interaction at the functional group level often results in the formation of mixtures capable of exhibiting rheological synergy. Rheological synergy is the demonstration of greatly excess of viscosity and gel like properties when mixed with mucin than if the mucin and gels were examined separately. This rheological synergism between gels and mucin could be used as an *in vitro* parameter to determine the mucoadhesive properties. In this study a simple rheological method is used to quantitatively determine various parameters like viscosity enhancement ($\eta_{enhance}$), relative viscosity enhancement of the combination system (η_{rel}), force of mucoadhesion (F) and viscosity component of bioadhesion (η_b). This is used to quantitatively compare different bioadhesive nasal gels prepared using carbopol which contain cyclodextrin as absorption enhancer. Composition of a gel can strongly influence its rheological properties and even one different constituent can lead to significantly different rheological behavior. The influence of the presence of cyclodextrin and different methods of addition of cyclodextrin was studied. The pattern noticed in this study was that the gels without the cyclodextrin showed the highest force of bioadhesion which was followed by the gels with cyclodextrin as inclusion complex and then by the gels with cyclodextrin as a physical mixture. These gels were also subjected to Texture Profile Analysis.

Keywords: Bioadhesive gels, mucin, bioadhesive force, texture profile analysis.

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INTRODUCTION

The use of nasal cavity as a route for drug delivery has been an area of great interest to the pharmaceutical industry, especially for systemic acting drugs that are difficult to deliver via routes other than injection[1]. Different dosage forms can be considered for the nasal delivery which includes drops, sprays, powders and gels. In this study nasal gels were prepared using a bioadhesive polymer, carbopol along with cyclodextrin as absorption enhancer. A bioadhesive force is required between the drug device and the mucosal surface to successfully retain the device and retard the natural clearance process. Determination of bioadhesive bond is important in the development of bioadhesive drug delivery as it can compare different formulations.

Mucus is a weak viscoelastic gel that adheres to and covers all the internal tracts of the body. It is the major structure forming components of mucus, namely the mucin glycoproteins that are responsible for its rheological properties[2]. The mucin glycoproteins are capable of associating with each other by means of non-covalent interactions to form the gel matrix. Inter diffusion or interpenetration of mucoadhesive polymer chains and mucus glycoproteins chains would include chain interlocking, conformational changes and secondary chemical interactions[3]. Hence strong mucoadhesion would most likely produce changes in the rheological properties of the interfacial region, strengthening the weakest component of the adhesive joint. Thus rheological synergism between mucin-polymer mixtures can be used as an in vitro parameter to determine bioadhesive properties of a material[4,5].

It was generally accepted[6] that chain interlocking (physical entanglement), conformational change and chemical interactions (like hydrogen and Van der Waal bonds), which occurred between a bioadhesive polymer and mucin (or mucus) were likely to produce changes in the rheological behavior of the two macromolecules species. The interaction at the functional group level often resulted in the formation of mixtures capable of exhibiting rheological synergy that is, to demonstrate gel like properties when mixed, greatly in excess of when the mucin and polymer dispersions were examined separately. Several authors[7] had suggested that rheological synergism between polymer and mucin could be used as an *in vitro* parameter to determine the mucoadhesive properties of a material. Determination of mucoadhesive bond strength was also important in the development of mucoadhesive drug delivery systems as it could quantitatively compare different mucoadhesive formulations and allow for quality control testing.

In the present work the model drug chosen was progesterone. Progesterone itself undergoes rapid first pass metabolism and low oral bioavailability limited the administration of the natural hormone

to intramuscular injections in oil or to vaginal suppositories use[8]. Aserious need exists for the improved delivery of this hormone for greatly enhanced bioavailability as compared to oral administration while at the same time providing relative ease of administration when compared to intramuscular injection. Novel nasal gels were prepared for accomplishing the delivery of this natural female hormone and to avoid the disadvantages inherent in the use of potentially unsafe synthetic progestins. Progesterone is useful in the treatment of conditions such as menopause, menstrual disorder, habitual abortion, etc., which are known to respond to natural hormone. Progesterone is a poorly water-soluble drug, thereby complicating nasal absorption and hence hydroxypropyl β-cyclodextrin (HPβ-CD) was used as solubilizer and absorption enhancer. It was added to the nasal gels as a physical mixture or inclusion complex.

The aim of the present work is to determine mucoadhesive bond strength which is important in the development of mucoadhesive drug delivery systems and to quantitatively compare different nasal gel formulations and allow for quality control testing. This study uses simple rheological method to calculate the absolute force of bioadhesion. The advantages of this method are that it is a simple procedure and does not require specialized equipment. Here the force of bioadhesion is calculated by monitoring the viscoelastic changes in a system of mucin and gel.

MATERIAL AND METHODS

Progesterone and carpobol were received as a gift samples from AIN Medicare (I) Pvt.Ltd, Chennai and NoveonInc respectively. HPβ-CD was purchased from Rolex Laboratories; propylene glycol and benzalkonium chloride were obtained from S.D.Fine Chemicals.

Preparation of nasal gels

Three nasal gels of progesterone F1, F2 and F3 were prepared using Cabopol 974 as the gelling agent and HPβ-CD as the absorption enhancer. (Table 1).

Table 1: Composition of the nasal gels

Ingredients	F1	F2	F3
Progesterone (mg)	250	250	-
Progesterone -HPβ-CD complex equivalent to drug (mg)	-	-	250
HPβ-CD (mg)	-	1183	-
Propylene glycol (ml)	1.5	1.5	1.5
Carbopol 974 (mg)	100	100	100
BKC 100 mg/100 ml (ml)	1.0	1.0	1.0
Water q.s (g)	10	10	10

In case of formulations F1, progesterone was dispersed in propylene glycol and sonicated (Vibra Cell VCX 500, Sonics & Materials Ins.,) for 5 min. Required quantity of carbopol 974 was wet

blended thoroughly. This was then suspended in water and allowed to swell. The polymeric dispersions was stirred in a magnetic stirrer for 60 min to which benzalkonium chloride (BKC) solution and the drug was incorporated in a drop wise manner and the pH was then adjusted to 7.0 by addition of triethanolamine.

In case of formulations F2, progesterone along with HPβ-CD was dispersed in propylene glycol and water mixture and sonicated (Vibra Cell VCX 500, Sonics & Materials Ins.,) for 5 min. required quantity of carbopol 974 was wet blended thoroughly. This was then suspended in water and allowed to swell. The polymeric dispersions were stirred in a magnetic stirrer for 60 min to which BKC solution and drug dispersion was incorporated in a drop wise manner and the pH was then adjusted to 7.0 by addition of triethanolamine.

Formulation F3 contains inclusion complex of progesterone with HPβ-CD. Progesterone- HPβ-CD inclusion complexes were prepared by freeze drying technique[9,10]. Accurately weighed HPβ-CD was first dissolved in distilled water. Progesterone was added to these solutions in carefully predetermined molar ratio of 1:1. The entire solutions were stirred with a magnetic stirrer for 7 days at room temperature. The resulting solutions were filtered through 0.22 m filter. The filtrates were frozen at -40^{o}C for 10 h in a Telstar L-3 freeze drier and then a vacuum was applied to obtain a pressure of 0.05 mbar. Temperature was increased from -40^{o}C to 0^{o}C in a 37 h cycle and after 2 h at this temperature it was increased to 30^{o}C over 6 h. Vials containing the freeze dried products were plugged immediately after removal from the freeze dryer.

In case of formulations F3, progesterone-inclusion complex with HPβ-CD was dispersed in propylene glycol and water and sonicated (Vibra Cell VCX 500, Sonics & Materials Inc.,) for 5 min. Required quantity of carbopol 974 was wet blended thoroughly. This was then suspended in water and allowed to swell. The polymeric dispersions were stirred in a magnetic stirrer for 60 min to which BKC solution and the drug complex dispersion was incorporated in a drop wise manner and the pH was then adjusted to 7.0 by addition of triethanolamine.

Effect of mucin on viscosity enhancement (synergy) and calculation of force of bioadhesion

To study the polymer-mucin interaction, mucin solutions were prepared in deionised water (DI). Dried mucin was gently hydrated in DI by gentle stirring for 10 min to yield a concentration of 10 % w/w solution. 100 mg of the mucin solution was mixed with 100 mg of each of the prepared gels to give a final concentration of mucin at 5%. The viscosity of the mucin solution (5%), prepared gels (f1, F2 and F3) and the above mixture of gels and mucin were measured using R.E.L Cone and Plate Viscometer (Research Equipment London Ltd.,). Type of cone used was 'C' at an angle of 0.5^{o} with diameter of 19.4 mm and volume of plate was 13 µL. Samples of each of the

formulations were added to the plate and allowed to equilibrate for at least 2 min prior to test. The viscosity measurements were made at shear rates of 5 s^{-1}. The expected viscosity (η_{exp}), viscosity enhancement ($\eta_{enhance}$) and relative viscosity enhancement of the combination system (η_{rel}) were calculated from equation given below[11]

$$\eta_{exp} = \eta_p + \eta_m$$

$$\eta_{enhance} = \eta_{obs} - \eta_{exp}$$

$$\eta_{rel} = \eta_{obs}/\eta_{exp}$$

The η_p and η_m were the viscosities of the formulation and mucin alone, respectively. It could be seen that all the observed viscosity values were higher than the expected viscosity and the viscosity enhancement was calculated using the equation given above. The viscosity enhancement was equivalent to the viscosity component of bioadhesion (η_b) as given in the equation

$$\eta_t = \eta_m + \eta_p + \eta_b$$

where, η_t is the viscosity of the system. Consequently the force of mucoadhesion (F) represents the additional intermolecular frictional force per unit area and is determined by the equation $F = \eta_b \sigma$ where σ is the shear rate (s^{-1}). The two parameters, force of mucoadhesion (F) and viscosity component of bioadhesion (η_b) gave a direct estimate of the gel-mucin interaction occurring in mucoadhesion.

Texture profile analysis

This is a technique[12,13] used to characterize the mechanical properties of gels and other semi solids. The mechanical properties of gel formulations mixed with mucin were determined using a texture analyzer (QTS 25 Texture Analyser, Brookefield). Each gel sample was packed to a fixed height in a universal bottle. A stainless steel probe was compressed into the formulation at a defined rate of 4 mm/s to a depth of 1 cm. Two parameters of hardness and adhesiveness were used to characterize the gel.

RESULTS AND DISCUSSION

Viscosity component of bioadhesion

Effect of mucin on viscosity enhancement (synergy) and the calculated force of bioadhesion values are shown in Table 2. It was apparent from the table that viscosity of the system was greater than the sum of individual viscosities. This suggested that all the gels were able to interact strongly with mucin. The carbopol gels interact[15] with mucin by forming physical entanglements followed by hydrogen bonds with sugar residues on the oligosaccharide chains, which resulted in the formation of a strengthened mucus gel network. The presence of cyclodextrins decreased the $\eta_{enhance}$ values.

The HPβ-CD gels F2 and F3 showed viscosity enhancement of 584.3 and 601.2 m Pa s respectively as compared to 752.2 m Pa s for F1.

Table 2: Effect of mucin on viscosity enhancement (synergy) and force of bioadhesion

Sample	η_p (m Pa s)	η_m (m Pa s)	η_{exp} (m Pa s)	η_{obs} (m Pa s)	$\eta_{enhance}$ (m Pa s)	η rel	F(m Pa)
F1	285.2	56.7	341.9	1094.1	752.2	3.2	3761.1
F2	240.0	56.7	296.7	881.0	584.3	2.9	2921.5
F3	242.2	56.7	298.9	900.1	601.2	3.0	3006.0

The next factor to consider was the magnitude of the rheological synergism by consideration of the relative viscosity enhancement η_{rel}. This allowed the viscosity enhancement effect to be expressed as a proportion of the unmixed materials viscosities. A η_{rel} = 1 meant[16] that there was no interaction between polymer and mucin. A higher value of η_{rel} showed rheological synergism between polymer and mucin and was indicative of potentially mucoadhesive association between them. It was evident that presence of HPβ-CD had a detrimental effect on the rheological synergism which caused a decrease in the η_{rel}values.The presence of HPβ-CD either as physical mixture or inclusion complex did not have a significant effect on the η_{rel}values (P>0.05).

Force of bioadhesion

A bioadhesive force is required between the drug device and the mucosal surface to successfully retain the device and retard the natural clearance processes. A single shear rate of 5 $s^{-1}$was selected to determine the viscosity. The strongest force of adhesion was demonstrated by F1 at 3761 m Pa. It was 32921.5 m Pa and 3006.0 m Pa for F2 and F3. The pattern noticed in this study was that the gels without the HPβ-CD showed the highest force of bioadhesion which was followed by the gels with HPβ-CD as inclusion complex and then by the gels with CD as a physical mixture.

Texture profile analysis (TPA)

Texture profile analysis (TPA) has been used as an interesting technique to characterize the mechanical properties of pharmaceutical gels and semisolid systems. This simple and rapid technique can provide information related to the gel mechanical parameters, such as hardness and adhesiveness. The mechanical properties of the gels are shown in Table 3.

Table 3: Mechanical properties of gels

Sample	Hardness (g) Cycle 1			Hardness (g) Cycle 2			*Mean ± S.D	Adhesiveness (gs)			Mean ±S.D
F1	89	90	90	92	90	97	91.3 ± 2.9	15.2	15.4	15.3	15.3 ± 0.4
F2	30	40	39	30	42	43	37.3 ± 5.9	13.2	8.9	12.1	11.4 ± 2.2
F3	79	81	83	80	83	85	81.8 ± 2.2	16.5	17.0	12.0	15.1 ± 2.8

Hardness

It was seen that the addition of HPβ-CD significantly altered the gel hardness as compared to plain gel (P<0.0001). The gel F2 with HPβ-CD as physical mixture showed the lowest value of hardness as compared with the gel with no cyclodextrins. The hardness for F1 was 91.3 g while it was 37.3 g for F2 and 81.8 g for F3. There was significant difference in the hardness of the gels with different methods of addition of HPβ-CD (P<0.0001). The gel which had inclusion complex had a higher hardness as compared with gels which had drug and HPβ-CD as physical mixture. The addition of HPβ-CD considerably changed the hardness. The greatest effect on the decreasing hardness was observed with physical mixture of HPβ-CD with drug. The value of hardness follows the order: F1>F3>F2.

Adhesiveness

The adhesiveness was found to be 15.3 gs, 11.4 gs and 15.1 gs for F1, F2 and F3 respectively. The adhesiveness of gel formulation F1 (gel without HPβ-CD) was statistically different from F2 (gel with drug and HPβ-CD as physical mixture) (P<0.05). The TPA analysis showed that there was no significant difference between the F1 and F3 gel (P = 0.39). The adhesives of F1 and F3 were similar, and therefore presence of inclusion complex does not affect the adhesiveness as opposed to F2. The gel F3 also had best compromise between hardness and adhesiveness for nasal application.

The hardness values and adhesiveness decreased significantly when various constituents were incorporated especially in the presence of modified cyclodextrins. Hydrophobic interaction could occur between the polymer chains and the HPβ-CD resulting in a reduction of the polymer chains unfolding. Consequently it may modify the polymer affinity for the hydration medium, decreasing its firmness and swelling[17]. Qi *et al*[18] demonstrated that the addition of HPβ-CD in a pluronic gel increased the length of gelling but drastically reduced the gel strength and adhesiveness.

CONCLUSION

In conclusion, gel containing drug/ HPβ-CD inclusion complex showed a value of adhesiveness and hardness close to the gel without HPβ-CD suggesting that a gel with suitable properties was obtained by addition of inclusion complex. The results of the rheological method for determining the force of bioadhesion are in agreement with texture profile analysis. Hence this simple rheological method using a viscometer can be used in place of other methods requiring sophisticated instruments to compare different bioadhesive formulations. The ease of the method and exact quantification of the force of bioadhesion are important tools to optimize bioadhesive gels.

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