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Research paper

EFFECT OF TABLET EXCIPIENTS ON MUCOADHESIVE PROPERTIES OF POLYOXYETHYLENE AND CARBOPOL 971P

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ABSTRACT

The aim of present study was to investigate the effect of tablet excipients on the observed in vitro mucoadhesion combination of two representative polymers Polyoxyethylene and Carbopol 971P to make inferences on the possible mechanisms of actions of the mucoadhesives and those materials which interact with them. In this study the effect commonly used tablet excipients on the observed mucoadhesion of combination of Carbopol 971P and Polyoxyethylene has been studied. It was found that tablet diluents, however, do appear to have a significant influence on the observed mucoadhesion in this system. The effect of a range of surfactants (non-ionic, cationic and anionic), on mucoadhesion was quantified, as is the influence of some salts and a chelating agent. It is concluded that the addition of additives to gastric mucoadhesive formulations can crucially influence the ability of the dosage form to bind to the goat stomach in this test system. Tablet diluents when used in concentration of 5%, reduces the adhesion of polymers to gastric mucosa whereas disintegrant like starch reduce the adhesion force of polymers. Binder, PVP K30 on the other hand increases the mucoadhesion of polymeric discs. Surfactants, Cyclodextrin, EDTA have not shown any significant effect on mucoadhesion between goat mucosa and polymers. From the above study it was concluded that addition of tablet excipient to Gastro-retentive mucoadhesive formulation significantly affects the mucoadhesion time of dosage form. This fact may be useful for development of Gastro-retentive dosage form of antimicrobial drugs like metronidazole, ofloxacin and acyclovir.

Keywords: mucoadhesion, excipient, gastric mucoadhesion, percent hydration

INTRODUCTION

It has been demonstrated that method dependent parameters can influence the observed mucoadhesion in a particular test system.[1] Further, the physical properties of the polymers used can be demonstrated to have a significant influence on the observed mucoadhesion of systems manufactured from them.[2]

To date, only some limited studies have been carried out on the optimization of mucoadhesive formulations, however, no systematic studies in this area have been published.[3-5] More recently it has been shown that the addition of small amounts of excipients in tablet formulation can effect in observed mucoadhesion in in-vitro test system, which suggests that formulation of these systems could be crucial in developing successful dosage forms.[6, 7]

EXPERIMENTAL METHODS

Materials

Polyoxyethylene and Carbopol 971P were obtained as a gift sample from Colorcon INDIA Ltd, Goa. Excipients used in study were obtained as a gift sample from Glenmark R & D Centre, Sinnar**.** All other reagents used were of analytical grade. USP type VI rotating cylinder apparatus (Disso-Lab India), 16 station rotary tablet compression machine (Rimek) were used for experiment work.

Methods

Mucoadhesive polymers were tested according to the method previously described.[1]

Preparation of polymeric discs

Different combinations of mucoadhesive polymers Polyoxyethylene, Carbopol 971P and excipients were made as shown in Table 2 and compressed using 16 station rotary tablet compression machine (RIMEK) using 15mm X 6.5mm punch. Average weight of each disc was kept 525mg as shown in Table 2. Hardness of all the discs was maintained 70 N. Previous validation indicated that this high force did not cause a diminution of the observed mucoadhesion of tablets in this system. [7-9]

Determination of adhesion time

Adhesion time of polymeric disc was determined by using USP type VI (rotating cylinder method) apparatus, DISSO 2000 LABINDIA at 37 ± 0.5^0 C at 100 rpm using 0.1N HCl as a medium. The goat gastric mucosa was adhered to the cylinder by using cynoacrylate glue. The disc was pressed on the mucosa gently with the finger for 1 minute. Time upto which disc remains adhered to goat gastric mucosa was measured and shown in Table 3.[10]

Determination of percent hydration (Swelling index)

Swelling study of individual polymers and combinations was carried out using USP type II dissolution apparatus (rotating paddle), DISSO 2000 LAB INDIA at 100 rpm and 0.1 N HCl was used as medium, temperature was

maintained at 37± 0.5^{o} C.[11,12] Weight of individual disc was taken prior to the swelling study (W1). The disc was pressed against goat gastric mucosa for 2 minutes which was attached to the paddle using cynoacrylate glue and the weight of each disc was noted after 12 hours (W2). Percent hydration (swelling index) was calculated as shown in Table 3 using following formula,[26]

% of hydration = (W2-W1) X 100 / W2

Where W1:- initial weight of disc, W2:- weight of disc after 12 hours.

RESULTS AND DISCUSSION

Diluents like Pharmatose, Perlitol, Mannitol, Prosolv, have not shown any significant effect on mucoadhesion when added at concentration of 5% whereas Avicel pH 112 was found to decrease mucoadhesion of polymers at 5% concentration because of its porous nature. PVP K30 was found to increase mucoadhesion of polymer by binding strongly to gastric mucosa.[11] Pregelatinised starch on the other hand found to decrease mucoadhesion of polymeric discs at 5% concentration. Primogel and Polyplasdone-XL-10, both reduce the mucoadhesion of polymer by acting as a disintegrant, preventing swelling of Carbopol 971P. β-cyclodextrin has not shown any significant effect on mucoadhesion of polymers because concentration of β-cyclodextrin was too small to form inclusion complex with polymeric combination.[17] As a result there was no hydrogen bonding found between polymer and β-cyclodextrin, hence there was no significant effect on mucoadhesion.[18-20] Surfactants (5%) which were initially thought to affect mucoadhesion have not shown any increase or decrease in mucoadhesion. Chelating agent EDTA (5%) has not shown any effect on mucoadhesion may indicate that the calcium ions in mucus do not have any significant role in mucoadhesion. But the study was carried out at pH 1 which is very low as compared to the pH 11 at which EDTA displays its best chelating ability. In case of Calcium chloride (5%) Ca^{++} ions acts as counter ions and hinder the formation of hydrogen bond between polymer and mucosal Ca^{++} ions[15,16], as a result reduce mucoadhesion time. One way ANOVA test is applied to the adhesion time of formulations as shown in Table 3, which indicates significant reduction in adhesion time of Formulation D, E, F, L and O as shown in Figure 1.

Table 1 : Excipients used in Tablet Formulation

Sr.no.	Excipient	Company
1	Mannitol	Biocon
2	Polyvinyl Pyrrolidone k 30	DMF, Germany
3	Pharmatose 200M (Lactose)	Biocon
4	Primogel (Sodium starch glycolate)	Colorcon, India
5	Polyplasdone XL-10 (cross povidone XL-10)	Dow chemicals
6	Prosolv (silicified microcrystalline cellulose)	Dow chemicals
7	Ac-di-sol (Cross carmellose sodium)	Dow chemicals
8	Avicel pH 112 (microcrystalline cellulose)	Dow chemicals
9	Starch	Colorcon, India
10	β-cyclodextrin	Colorcon, India
11	Sodium dodecyl sulphate	SD Fine Chemicals
12	Tween 80	SD Fine Chemicals
13	Cetrimide	SD Fine Chemicals
14	EDTA	SD Fine Chemicals
15	Calcium chloride ($CaCl_2$)	SD Fine Chemicals

Table 2 : Formulation of polymeric discs

Sr. no.	Ingredient (in mg)	Formulation															
		Plain	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	Polyoxyethylene	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
2	Carbopol 971P	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
3	Mannitol	-	25	_	_	_	_	_	_	_	_	_	_	_	_	_	_
4	Polyvinyl Pyrrolidone k 30	-	_	25	_	_	_	_	_	_	_	_	_	_	_	_	_
5	Pharmatose 200M	-	_	_	25	_	_	_	_	_	_	_	_	_	_	_	_
6	Primogel	-	_	_	_	25	_	_	_	_	_	_	_	_	_	_	_
7	Polyplasdone XL-10	-	_	_	_	_	25	_	_	_	_	_	_	_	_	_	_
8	Starch 1500	-	_	_	_	_	_	25	_	_	_	_	_	_	_	_	_
9	β-cyclodextrin	-	_	_	_	_	_	_	25	_	_	_	_	_	_	_	_
10	Sodium dodecyl sulphate	-	_	_	_	_	_	_	_	25	_	_	_	_	_	_	_
11	Tween 80	-	_	_	_	_	_	_	_	_	25	_	_	_	_	_	_
12	Cetrimide	-	_	_	_	_	_	_	_	_	_	25	_	_	_	_	_
13	EDTA	-	_	_	_	_	_	_	_	_	_	_	25	_	_	_	_
14	$CaCl_2$	-	_	_	_	_	_	_	_	_	_	_	_	25	_	_	_
15	Prosolv	-	_	_	_	_	_	_	_	_	_	_	_	_	25	_	_
16	Ac-di-sol	-	_	_	_	_	_	_	_	_	_	_	_	_	_	25	_
17	Avicel pH 112	-	_	_	_	_	_	_	_	_	_	_	_	_	_	_	25
Total weight (in mg)		**500**	**525**	**525**	**525**	**525**	**525**	**525**	**525**	**525**	**525**	**525**	**525**	**525**	**525**	**525**	**525**

Swelling index of polymers was found to be reduced by calcium chloride as it acts binds strongly with polymer which prevents entry of 0.1 N HCl into disc. Prosolv was found to aid the entry of water in polymeric structure as result showed considerable swelling. EDTA, Polyvinyl Pyrrolidone K30 significantly reduce swelling of polymeric disc as evident from Table 4. Surfactants, diluents, β-cyclodextrin, do not affect swelling index of polymers singificantly. Application of one way ANOVA test to the percent hydration of formulations has clearly shown that there is a significant effect of excipient on percent hydration of polymers in case of Formulation B, K, and L as shown in Figure 2.

Table 3 : Adhesion time of polymeric discs

Sr. no	Formulation	N (number of observation)	Adhesion time in hours ± S.D	Statistical significance (one ANOVA test)
1	A	3	27±1.65	NS
2	B	3	32±4.78	NS
3	C	3	26±4.1	NS
4	D	3	14±3.78	P<0.05
5	E	3	15±1.53	P<0.05
6	F	3	13±7.90	P<0.05
7	G	3	26±4.97	NS
8	H	3	25±3.79	NS
9	I	3	27±1.87	NS
10	J	3	29±5.90	NS
11	K	3	28±4.56	NS
12	L	3	15±1.20	P<0.05
13	M	3	27±9.78	NS
14	N	3	28±8.45	NS
15	O	3	15±7.23	P<0.05
16	P (Plain polymer disc)	3	28 ± 2.3	NS

Table 4 : Percent hydration of polymer disc

Sr. no	Formulation	N (number of observation)	Percent hydration (%)	Statistical significance (one ANOVA test)
1	A	3	72.57±3.4	NS
2	B	3	49.56±4.6	P<0.001
3	C	3	80.21±5.2	NS
4	D	3	79.56±8.7	NS
5	E	3	75.12±3.2	NS
6	F	3	72.21±4.6	NS
7	G	3	75.78±3.2	NS
8	H	3	74.55±1.7	NS
9	I	3	75.71±4.6	NS
10	J	3	79.45±1.3	NS
11	K	3	34.97±7.4	P<0.001
12	L	3	54.73±6.9	P<0.001
13	M	3	82.02±5.1	NS
14	N	3	75.61±3.7	NS
15	O	3	73.68±2.4	NS
16	P (Plain polymer disc)	3	83.65±1.7	NS

One way ANOVA table by comparing Plain tablet of polymers with tablet excipient and application of Dunnets test.

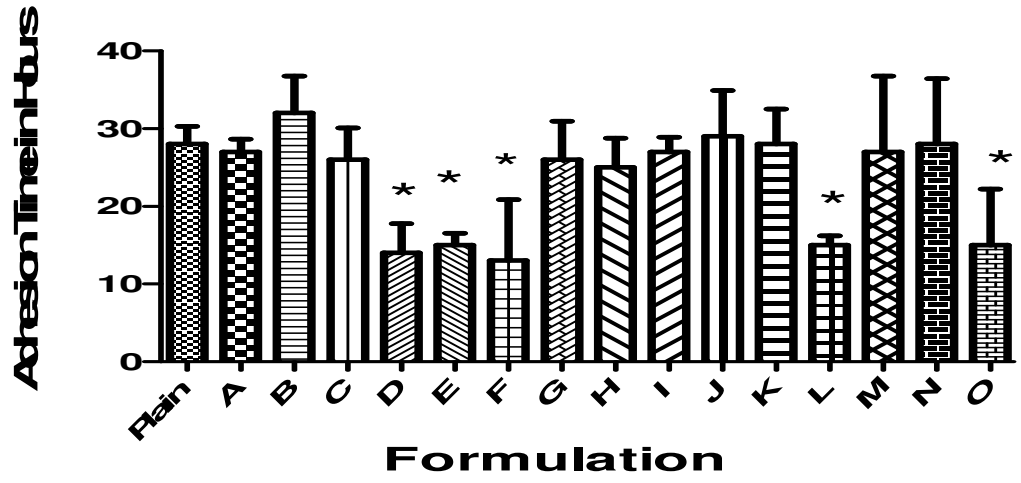

Fig. 1 : Effect of excipients on mucoadhesion time carbopol 971P and polyoxyethylene.

(* indicates $p < 0.05$ which means there is significant effect of excipient on adhesion time of polymer in case of Formulation F, E, D, L, O.)

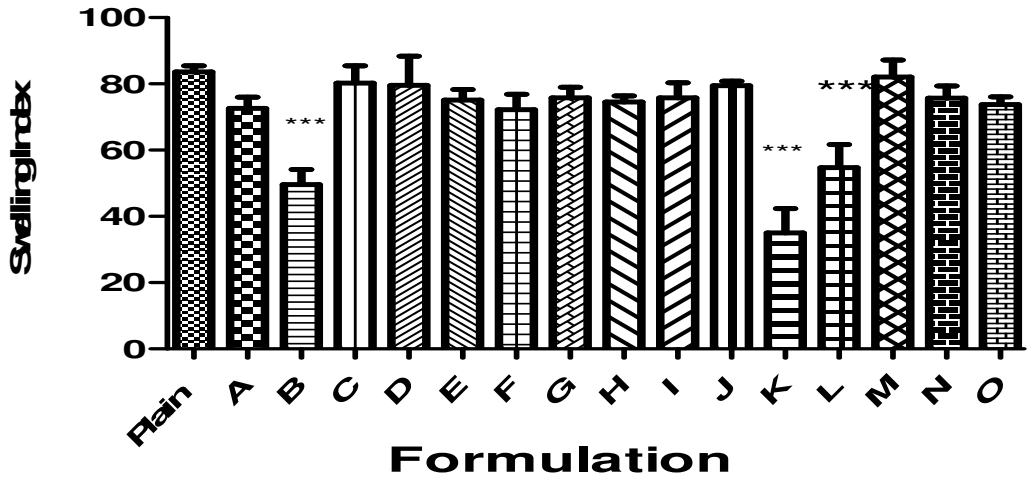

Fig. 2 : Effect of excipients on Swelling Index of carbopol 971P and polyoxyethylene.

(*** indicates $p < 0.001$ which means there is significant effect of excipient on percent hydration of polymer in case of Formulation B, K, L.)

CONCLUSION

A series of experiments have been carried out which indicated that the presence of excipients in tablets can affect the in vitro mucoadhesion and swelling index of polymers. Higher the swelling of polymers more the residence time of dosage form in stomach. This may be of importance in the formulation of Gastro-retentive tablets for in vivo use containing drugs like metronidazole, ofloxacin, and acyclovir.

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