ejpmr, 2018,5(03), 343-348

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

IDENTIFICATION OF POLYMER SYNERGY WITH HELP OF DOE

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Article Received on 01/01/2018 **Article Revised on 23/01/2018** **Article Accepted on 11/02/2018**

ABSTRACT

Ophthalmic solutions undergo rapid clearance from eye due to instant tear drainage, lower volume of cul-de-sac and lesser contact time with eye. All these drawbacks of ophthalmic solutions results in less efficacious product or requires repeated dosing. Repeated dosing of formulation could lead to lesser patient compliance and possible adverse effects. There are numerous approved polymeric ingredients available for ophthalmic use; however less information is available on their synergies. Hence there was a need to identify synergies among various polymeric ingredients with increased adhesiveness for sustained release ophthalmic formulations. Formulation adhesiveness is the function of viscosity being directly proportional; it plays a major role to sustain the drug release by increasing the contact time in eye with help of muco-adhesive forces or by polymer inter-penetrated network (IPN). Choice of selection of polymeric ingredients were based on their individual viscosities. Significant synergies were considered for those combinations which have higher viscosities compared to their individual viscosities at lower concentrations. The identified synergistic combination was also studied for stress study with the impact of pH, buffers and temperature during steam sterilization process.

KEYWORDS: Ophthalmic, Polymer, Synergy, Viscosity.

INTRODUCTION

Generally it is assumed that drug applied topical in eye would be available completely for eliciting it's therapeutically action. However it is not the case due to rapid tear drainage, blinking of eye, lower residence time of ophthalmic formulation in eye and lower cul-de sac volume.[1,2] There are different routes of administration of drug in to eye are available however topical route remains the most preferred choice. One way to increase the ocular bioavailability is by prolonging drug residence time in eye. Residence time in eye can be increased by increasing the viscosity of formulation with use of various viscosity enhancing agents such as polymers. There are different kinds of polymers such as natural, semisynthetic and synthetic polymers.[3] Various polymers are available which can be utilized for formulation of long acting ophthalmic formulation.

Rationale of work was to identify a suitable polymer based platform system which is derived from the polymer concentration approved in inactive ingredients guide approved by USFDA[4] or based on toxicity study data of polymers. This kind of polymer platform would serve as ready tool which can be incorporated in various ophthalmic formulations which requires frequent dosing. These systems would be resulting more viscous solution which remains in the eye for a longer period of time and thus enhances the sustained release of the medicament.[5]

Systematic approach of quality by design was used to identify the synergistic polymer platform system. By use of quality by design interaction amongst various polymers can be studied in more effective way with less number of experiments.

As these polymer platform systems are to be used in ophthalmic formulation which needs to be sterile hence many times sterilization process, buffers or pH adversely or synergistically impact these polymers. Hence the impact of all sterilization process & pH or buffers data becomes useful for further formulation development activity.

MATERIAL AND METHODS

Gift sample of polymers sodium alginate, locust bean gum, carrageenan, hydroxy ethyl cellulose were provided by Signet. Polycarbophil was procured from lubrizol. Pullulan sample was provided by DKSH Corporation. Povidone K- 30 was provided by BASF. Polyvinyl sample was provided by Merck.

EXPERIMENT METHODOLOGY

Selection of polymer

Polymers generally used in ophthalmic formulations were selected to identify the synergy. Polymers were studied at concentration 1.0%.

Table No. 1: Viscosity of single polymer (1.0%).

Polymer	Viscosity (cps)
Hydroxy ethyl cellulose (Natrosol 250 G pharm)	20.3
Carragenan (Gelcarin PH-812)	697.4
Polycarbophil	4439
Polyvinyl alcohol 26-88	2.31
Povidone K 30	1.8
Sodium Alginate (Manukol LKX)	107.7
Sodium Alginate(Protanal LFR 5/60)	4.03
Locust bean gum (Viscogum	184.2
Pullulan	2.12

Preparation of polymer solution

1.0 % aqueous solution was prepared by dissolving polymer in purified water under stirring. Viscosity of these aqueous solutions was measured by using appropriate spindle and rpm.

Screening of polymers

Polymer short listing was done based on viscosity studies. Polymer of more than 100 cps viscosity was selected for further interaction study.

Carragenan, Sodium Alginate (Manukol LKX), Polycarbophil, Locust Bean Gum were selected.

Experimental design

For identification of synergistic polymer combination

The design of experiment was employed systematically to identify the synergistic polymeric combination.

Mixture design was selected as this design is used when the response changes as function of the relative proportion of the component.

Optimal mixture design with quadratic model was used to study interaction. Total 19 experimental runs were conducted with 2 center point and 2 replicate. Total concentration for mixture was kept 1.0%.

Aqueous solutions were prepared by dissolving polymer in purified water under stirring. Viscosity of these aqueous solutions was measured by using appropriate spindle and rpm.

Table No. 2: Mixture design for 4 polymer mixture.

Run	Polycarbophil	Sodium alginate (Manukol LKX)	Locust bean gum (Viscogum)	Carrageenan (Gelacrin PH-812)	Viscosity
1	0.000	0.500	0.000	0.500	6903
2	1.000	0.000	0.000	0.000	1587
3	0.000	0.000	1.000	0.000	9.02
4	0.000	0.500	0.500	0.000	30.1
5	0.250	0.250	0.250	0.250	1500
6	0.125	0.125	0.625	0.125	623.9
7	0.000	0.000	0.500	0.500	418.9
8	0.125	0.125	0.125	0.625	16834
9	0.000	0.500	0.000	0.500	8408
10	0.333	0.000	0.333	0.333	2754
11	0.500	0.500	0.000	0.000	405.9
12	0.500	0.000	0.000	0.500	623.9
13	0.625	0.125	0.125	0.125	200.4
14	0.000	1.000	0.000	0.000	77.7
15	0.000	0.500	0.500	0.000	88.6
16	0.000	0.000	0.000	1.000	925.8
17	0.500	0.000	0.500	0.000	483.5
18	0.250	0.250	0.250	0.250	346.4
19	0.125	0.625	0.125	0.125	129.9

Response surface and contour plot

The regression analysis of the data obtained from the experimental runs generated the following polynomial equations in which the model F ratio was statistically significant at $\alpha < 0.05$ with a statistically non-significant lack of fit at $\alpha > 0.05$.

+ 3.21 x A + 1.78 x B + 1.10 x C + 2.98 x D + 0.16 x AB + 2.34 x AC -1.24 x AD +1.98 x BC + 4.54 x BD + 2.56 x CD. Where A, B, C and D are concentration of polycarbophil, sodium alginate, locust bean gum and carrageenan respectively.

Table No. 3: Statistical analysis of experimental design.

Response	Model p value	Adequate precision	Lack of fit test p value
Viscosity (cps)	0.0109	10.277	*0.0600*

Table no 3 suggest that model is significant. The p value for lack of fit was not significant, indicating that this model equation fitted the data well. Adequate precision of 10.277 indicates adequate model discrimination. Therefore quadratic model could adequately describe the data and could be employed to arrive at synergy.

A positive sign represents a synergistic effect, while a negative sign indicates antagonistic effect. The negative coefficient of A and D in the model refers to decrease in viscosity, for Polycarbophil and Carrageenan combination. Highest positive coefficient of 4.54 between B and D showed the highest viscosity which in turn means maximum synergy between sodium alginate and carrageenan.

3-D surface and contour plots were plotted in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots. The Contour plots and 3 D graphs are presented in fig 1 and 2.

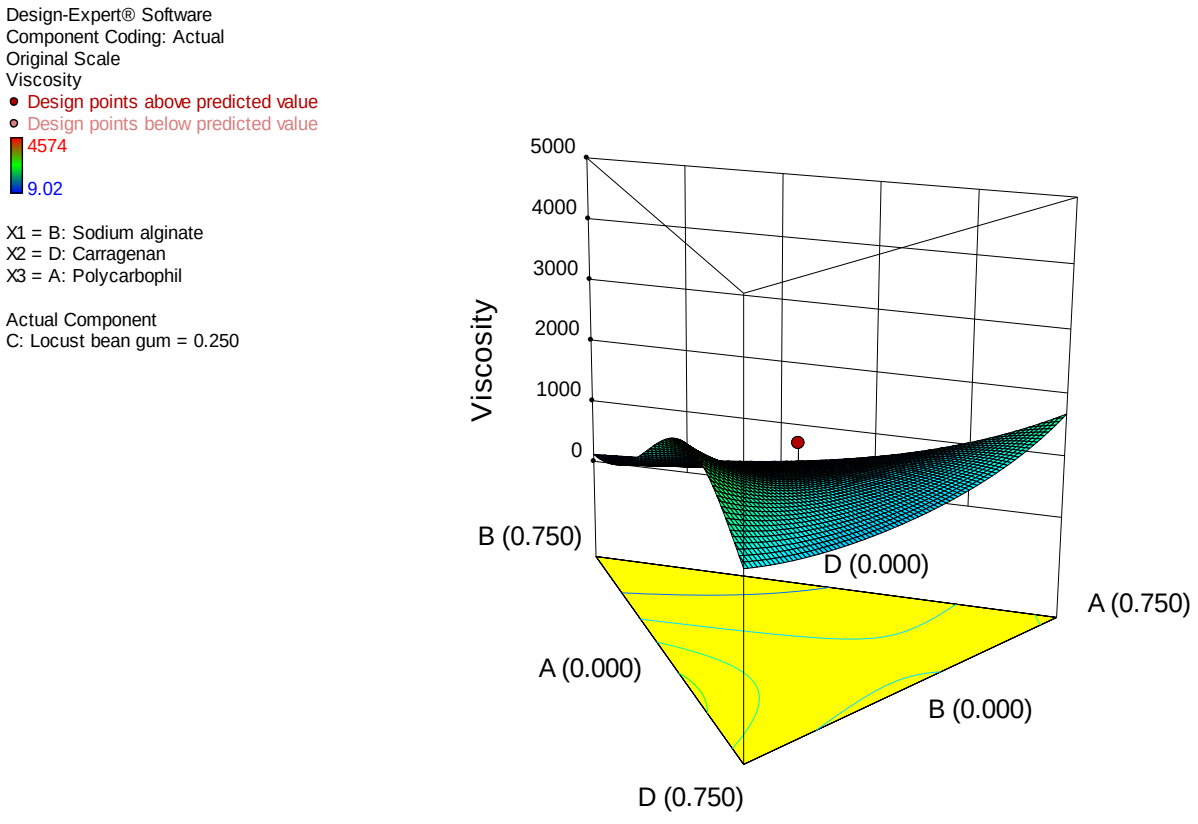

Figure 1: Contour Plot for 4 polymer mixture.

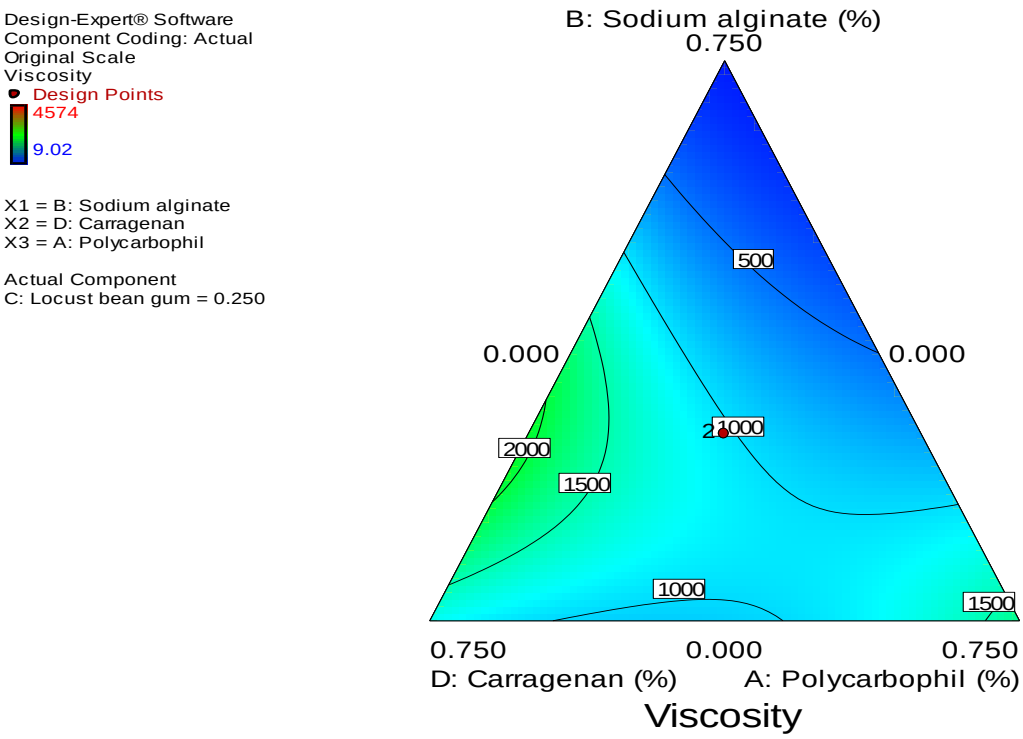

Figure 2: 3 D Graph for 4 polymer mixture design.

From the viscosity study data it can be concluded that four polymer combination system and sodium alginate & Carrageenan (0.500: 0.500) system gave the best synergy. The viscosity of synergistic combination even at lower concentration (0.500:0.500) was higher than the viscosity of individual polymer at higher concentration (1.00). Further to identify the best ratio of binary polymer combination (sodium alginate & carrageenan), again mixture design was applied.

Identification for optimal synergistic ratio

Mixture I- optimal design, Quartic model was used for this study. 9 experimental runs were conducted. Total concentration for mixture was kept 1.0%.

Table No. 4: Experimental run along with viscosity data.

Run	Sodium alginate	Carrageenan	Viscosity
1	0.742	0.258	64
2	0.500	0.500	1377
3	0.000	1.000	1212
4	1.000	0.000	1188
5	1.000	0.000	82.4
6	0.249	0.751	6194
7	1.000	0.000	81.3
8	0.000	1.000	951.8
9	0.500	0.500	1215

The regression analysis of the data obtained from the experimental runs generated the following polynomial equations in which the model F ratio was statistically significant at $\alpha < 0.05$ with Adj – R^2 value in the range close to 1

+1.91 x A + 3.08 x B -7.67 x AB (A-B) – 3.56 x AB (A-B) ^ 2

Where A and B are concentration of sodium alginate and carrageenan respectively.

Table No. 5: Statistical analysis of experimental design.

Response	Model p value	Adequate precision
Viscosity (cps)	< 0.0001	107.83

Table no 5 suggest that model is significant. Adequate precision ratio of 107.83 indicates adequate model discrimination. Therefore quartic model could adequately describe the data and could be employed to arrive at synergy.A positive sign represents a synergistic effect, while a negative sign indicates antagonistic effect. Maximum synergy observed in 0.25 to 0.750 ratio of sodium alginate to carrageenan respectively.

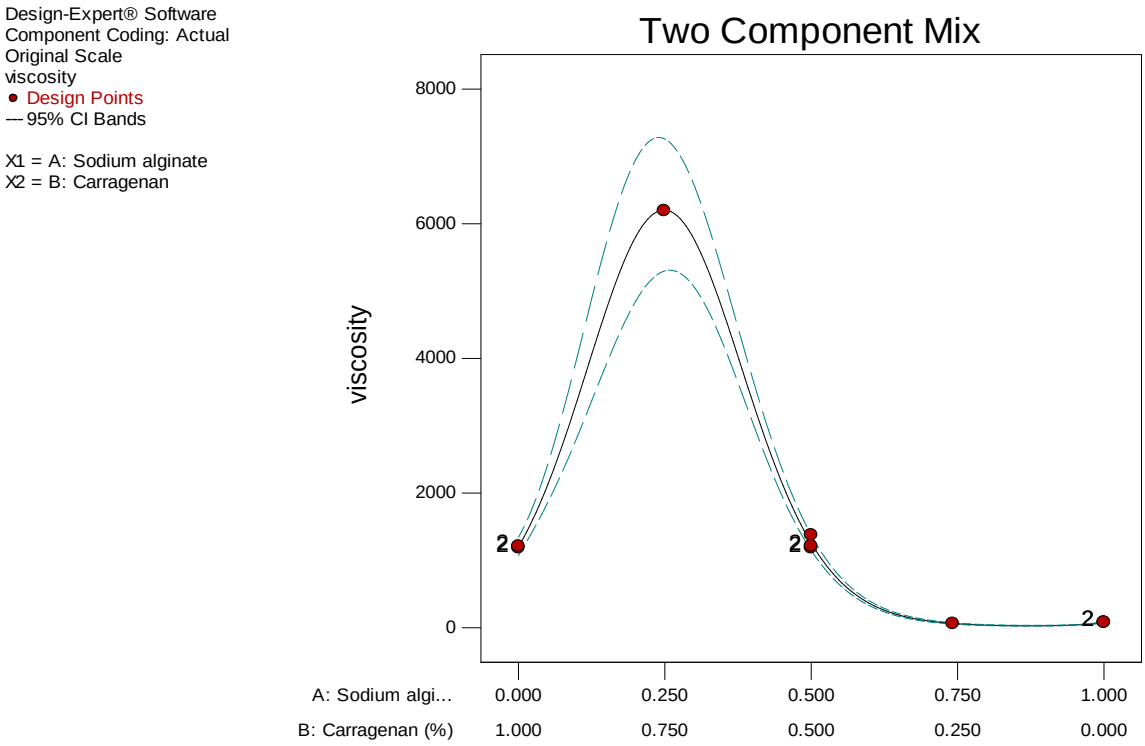

Figure 3: Graph of two component mixture.

It can be concluded that sodium alginate & carrageenan in ratio of 0.250: 0.750 showed the best synergy. This ratio was further selected to understand the impact of pH, temperature, buffers.

Impact of pH

Sodium alginate & carrageenan was dissolved in purified water in ratio of 0.250:0.750 under stirring. pH impact study was studied from pH 4.0 to 8.0. pH was adjusted with either 0.1N hydrochloric acid or 1 N Sodium hydroxide.

Impact of steam sterilization (autoclave): Being ophthalmic product it needs to be sterilized. In ophthalmic formulation sterilization process plays important role. Sodium alginate & carrageenan was dissolved in purified water in ratio of 0.250:0.750 under stirring. Solution was autoclaved at 121 degree centigrade for 15 minutes & viscosity was checked again.

Impact of buffers

Various buffers are used in ophthalmic formulation. These buffers again could modify the viscosity.

In purified water respective buffers were added one after, to dissolve each ingredient. Sodium alginate was added under stirring to buffer solution to get clear solution followed by Carrageenan addition. Viscosity of these aqueous solutions was measured by using appropriate spindle and rpm.

Table No. 6: Various buffer studied.

Citrate buffer	% w/v	Borate buffer	% w/v	Acetate buffer	% w/v	Phosphate buffer	% w/v
Sodium alginate	0.250	Sodium alginate	0.250	Sodium alginate	0.250	Sodium alginate	0.250
Carrageenan	0.750	Carrageenan	0.750	Carrageenan	0.750	Carrageenan	0.750
Citric acid monohydrate	0.20	Boric acid	1.8	Acetic acid	0.2	Monobasic sodium phosphate monohydrate	1.3
Trisodium citrate dihydrate	0.45	Borax	1.1	Sodium acetate trihydrate	1.28	Dibasic sodium phosphate dihydrate	1.2
Purified water	q.s	Purified water	q.s	Purified water	q.s	Purified water	q.s

RESULT AND DISCUSSION

Impact of pH on viscosity

With increase in pH there was not much significant change in viscosity.

Table No. 7: Impact of pH on viscosity.

pH	Viscosity (cps)
pH 4.0	3323
pH 6.0	3572
pH 8.0	3929

Impact of autoclaving on viscosity

Viscosity of sample was slightly increased after autoclaving. This could be due to viscoelastic behavior of both the polymers.

Table No. 8: Impact of Autoclaving.

Study	Viscosity (cps)
Viscosity before autoclaving	3203
Viscosity after autoclaving	3929

Impact of buffers on viscosity

Viscosity was changed in presence of various buffers, in case of citrate buffers it was decreased significantly.

Table No. 9: Viscosity with various buffers.

Sample	Viscosity (cps)
Unbuffered system	6194
Citrate buffer	778
Borate buffer	4019
Acetate buffer	3905
Phosphate buffer	1446

CONCLUSION

Design of experiment tool was used to identify polymeric synergy. Shortlisting of polymers were done based on individual polymer viscosity data. Four polymers viz. polycarbophil, sodium alginate, locust bean gum and carrageenan were shortlisted. Design of experimental study data showed sodium alginate in combination with carrageenan (0.500:0.500) gave best synergy. Optimal ratio for Sodium alginate and Carrageenan was identified (0.250:0.750) with help of mixture design.

With increase in pH there was not much significant change in viscosity. There was slight increase in viscosity observed for binary mixture after autoclaving which could be due to viscoelastic behavior of both the polymers.

There was significant impact of buffer system observed on viscosity hence selection of buffer while formulating finished product plays crucial role.

From all the studies conducted it can be concluded that a synergistic polymer platform system was identified by use of systematic approach with help of design of experiment. This platform system can be used for formulation of various ophthalmic formulation which would give sustain or modified release action.

ACKNOWLEGMENTS

I would like to acknowledge Indoco remedies for providing laboratory facility to conduct the experiments.

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