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Floating *In Situ* Gelling Drug Delivery System of Verapamil Hydrochloride

Bhushan S. Gulecha[1*], Sadhana Shahi [1], Swaroop R. Lahoti [2]

1. Government College of Pharmacy Aurangabad- 431001

2. Shri Bhagwan College of Pharmacy Aurangabad-431003

ABSTRACT

Gastro retentive drug delivery system has been widely used to prolong retention of dosage forms in stomach. Amongst the various approaches, the Raft formulation offers sustained drug release as well as prolonged gastric retention, along with the added advantage of liquid oral dosage form. The present study was an attempt to formulate and evaluate Raft forming floating drug delivery system for Verapamil Hydrochloride which undergoes pH dependent sol-gel transition at gastric pH; thereby prolonging the retention of the system in stomach. Gellan gum (Gelrite®) was employed as gelling agent whose gelation is triggered by source of Ca2+ ions in the form of Calcium Carbonate. The evaluation was carried out for *In Vitro* parameters and the results substantiated that the optimized formulation revealed excellent floating characteristics and gastric retention.

Keywords: Verapamil Hydrochloride, Raft, *In situ* gelation, gastroretentive.

*Corresponding Author Email: bhushangulecha@rediffmail.com

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INTRODUCTION

Drugs that are absorbed from the upper segments of the G.I.T are supposed to be characterized by Narrow Absorption Window. These drugs have a good solubility and thus absorbed to a significant extent from this region. Such drugs are therefore required to be formulated in dosage form that offers the release of drug in vicinity of such region [1, 2]. Verapamil hydrochloride is the first calcium channel blocker and used for the treatment of angina pectoris, hypertension and supraventricular tachyarrhythmia. Verapamil hydrochloride is approximately 90 % absorbed from gastrointestinal tract, but has low bioavailability of 22 ± 8 %. Biological half life of verapamil hydrochloride is 4.0 ± 1.5 h.[3, 4]

The main objectives of the present study were to prepare sol-gel system of Verapamil Hydrochloride using gellan gum and to study the effect of polymer and Ca^{2+} ion concentrations on the release and floating behavior of the gel formed in-situ. The sol is formulated as the solution of gellan gum(Gelrite®) which is an anionic polymer sensitive to presence of cations that triggers its gelation [5-7] Verapamil Hydrochloride is dispersed in this sol along with the cation source in the form of Calcium Carbonate. The resulting sol when comes in contact with the acidic environment, the cations (Ca^{2+}) released triggers gelation of gellan gum and the released CO_2 gets entrapped in the gel thereby forming a buoyant gel matrix which further controls the drug release[8]. The floating characteristics and the drug release are the function of polymer and cation concentration.

MATERIALS AND METHODS

Materials:

Verapamil Hydrochloride was obtained as gift sample from Shreya Life sciences Aurangabad, India. Gellan gum (Gelrite®) was obtained as gift sample from Applied Bioscience Consultants & Distributors Ltd, Mumbai, India. Calcium Carbonate and Calcium Chloride were from Merck Ltd. Mumbai, India. All other ingredients were of Analytical grades.

Preparation of Verapamil Hydrochloride insitu gelling solution (Sol):

Gellan Gum was dispersed in deionized water preheated to 90^0C with continuous stirring. To this Sodium Citrate and Calcium Chloride was added. This solution was cooled to below 40^0C followed by addition of Calcium Carbonate and Verapamil Hydrochloride (200mg/5ml of sol). Then resulting solution was subjected to stirring using magnetic stirrer for definite period of time until dispersion was uniformly formed [9,10]. The Gellan gum and Calcium Carbonate concentration were used in the concentration of (0.5-1%w/v) as per the 3^2 factorial deign.

Calcium Chloride was used in concentration of 0.016%w/v after studying the effect of various concentrations (mmoles) of Calcium Cloride solution on gelation of gellan solution. Composition of insitu geling solution was in accordance to Table: 1

***In-Vitro* Buoyancy study:**

In Vitro Buoyancy study is characterized by floating lag time and total floating duration. *In Vitro* Buoyancy study of the sol was carried out using USP dissolution apparatus Type II. The medium used was 900 ml of 0.1N HCl. The testing was carried out at 50 rpm. The temperature of the bath and medium was maintained at 37 ± 0.5^{o}C throughout the study. 10ml of the insitu gelling solution was transferred in a petriplate (Diameter 2") using a syringe. The plate was then placed on the surface of the medium and plunged in to the medium with the moving paddle. The time required for gelled mass to rise to the surface of the dissolution medium [Floating Lag time] and the duration of the time for which the gel constantly floated on the dissolution medium [Floating duration] was noted for each formulation trial[11-13].

Table 1: Composition of in-situ gelling solution as per 3^2 factorial deign

Formulation code	Gellan Gum	Calcium Carbonate	Sodium citrate	Calcium Chloride	Methyl Paraben	Propyl Paraben
P1	0.5 %	0.5 %				
P4	0.5 %	0.75 %				
P7	0.5 %	1 %				
P2	0.75 %	0.5 %	0.25%	0.016%	0.18%	0.02%
P5	0.75 %	0.75 %				
P8	0.75 %	1 %				
P3	1 %	0.5 %				
P6	1 %	0.75 %				
P9	1 %	1 %				

***In Vitro* Dissolution study:**

In Vitro Dissolution study of the sol was carried out using USP dissolution apparatus Type II. The medium used was 900 ml of 0.1N HCl. The testing was carried out at 50 rpm. The temperature of the bath and medium was maintained at 37 ± 0.5^{o}C throughout the study. 10ml of the in-situ gelling solution was transferred in a petriplate (Diameter 2") using a syringe. The plate was then placed on the surface of the medium and plunged in to the medium with the moving paddle [14]. Aliquots of 5ml were withdrawn at hourly interval for duration of 8 hours. These aliquots were then further diluted and analyzed by UV spectrophotometer at λ_{max} 278nm (Shimadzu UV 1800).

Residual Verapamil Hydrochloride content in gel after dissolution studies:

The gelled mass formed after coming in contact with 0.1N HCl is a matrix structure. This gelled

mass is responsible for the sustained release of the drug from matrix structure as the wall of the gelled mass acts a diffusion controlling membrane. The inner core of the gel mass contains the drug in sol form that diffuses through this membrane. To estimate residual Verapamil Hydrochloride content in gel after dissolution studies the raft/gelled mass was transferred to 50ml of 0.1N HCl and crushed using a mechanical stirrer so as to get uniform dispersion. The resulting dispersion is then filtered using Whatman filter paper and analyzed using UV spectrophotometer at λ_{max} 278nm.

Measurement of gel Strength:

Gel strength is indicative of the tensile strength of the gelled mass. It signifies the ability of the gelled mass to withstand the peristaltic movement's in-vivo. The gel strength of the formulation is an important variable dependent on the concentration of the gelling agent as well as cation source.

The method as explained by Dettmar et al[5] was modified to measure the gel strength of the gelled mass. The gel strength apparatus was fabricated in house using a measuring cylinder of 1.2 cm radius and a bore of 0.1mm at its base. A needle 2cm in length was used to which a nylon threads was tied. [Figure: 1]. Sol (10 ml) was taken in the cylinder with temporarily sealed bore followed by addition of 50ml 0.1 N HCl for gelation. After gelation the HCl was drained off by opening bore seal leaving the gel mass formed with the needle was rested on to surface of the gel. At the free end of the thread a light weight pan was attached to which the weights were added. The gel strength was reported in terms of weight required to pass the needle probe through the formed gel mass.

Figure 1. Gel strength measuring apparatus.

Density measurement of gel:

The prime requirement of the raft formed is that it must have density lesser than gastric contents (~1.004 gcm^{-3}). The density was measured by forming gel of known volume (10ml) inside the measuring cylinder. The weight of this gel was noted and accordingly density was reported.

Viscosity and Rheology studies:

Viscosity determinations of the prepared *in situ* gelling solutions were carried out on Brookfield Viscometer (Model No.CAT200+) using spindle 62. Viscosity of *in situ* gelling solutions was measured at different angular velocities at a temperature of 37±1 °C. A typical run comprised changing of the angular velocity from 0.5 to 100 rpm with a run time of 30sec. After completing the cycle with a similar wait at each speed the hierarchy of angular velocity was reversed (100 rpm to 0.5 rpm) with a similar wait of 30sec. The absolute viscosity of formulations was reported at a fixed torque value of 60%. The averages of three readings were used to calculate the viscosity. The rheological behavior was explained by plotting viscosity against angular velocity [15, 16].

RESULTS AND DISCUSSION

The formulations prepared as per the Table-I were uniform dispersions and exhibited excellent sol to gel transition on coming in contact with the acidic environment. It had excellent properties in terms of flow properties and pourability

Table: 2 show the gelation and the floating lag time of the formulations. For a particular combination of ingredients as in case of batches P1, P4 & P7 the gelation time and lag time shows a characteristic pattern. The lag time is minimum for P7 and highest for P1. This is because P7 contains highest concentration of Calcium Carbonate. Similar is the case with formulation P8 & P2 and P9 & P3. This is because on increasing the Calcium Carbonate concentration, the floating lag time was reduced. The increase in the amount of Ca^{2+} ion and CO_2, content are responsible for the observed reduction in floating lag time. Similarly an increase in the polymer concentration resulted in decreased floating lag time of the prepared systems but there was no significant effect on the floating duration. This is evident in case of formulation from [P1, P2, P3], [P4, P5, P6] and [P7, P8, P9] which contains 0.5%w/v, 0.75%w/v and 1%w/v of $CaCO_3$ respectively. This is mainly because increase in polymer concentration results in increase in viscosity. Hence time taken by the sol to form a cohesive gel mass and to emerge on the surface of medium is lowered.

Table 2: Floating Lag Time and Floating duration of Formulations

Sr No.	Formulation Code	Floating Lag Time (sec)	Floating Duration(h)
1	P1	177	>20
2	P4	156	>20
3	P7	125	>20
4	P2	112	>20
5	P5	93	>20
6	P8	73	>20
7	P3	82	>20
8	P6	78	>20
9	P9	65	>20

***In Vitro* Dissolution study**

The *In Vitro* release profile of Verapamil Hydrochloride from various combinations of gellan gum and calcium carbonate was studied so as to determine the effect of polymer concentration and Ca^{2+} ions in the raft on drug release. [Figure: 2] shows the release profile of formulation of sol containing 0.5%w/v of gelrite. P1 had lowest viscosity and when it was introduced in to the dissolution medium it formed slimy gel mass. Moreover it had highest lag time owing to low $CaCO_3$ content. Thus the drug dispersed in the sol shows a burst release as gel formation occurs gradually and by that time>90% drug is released in 2 hours. This is because the Ca^{2+} ions responsible for cross linking are too low to form intact raft. Incase of P7 which contains 1% of $CaCO_3$ the gelling and raft formation is faster than P1. Hence as gelling proceeds there gradual decline in the burst release pattern. But due to low polymer concentration about 90% of drug is released in about 3 hours.

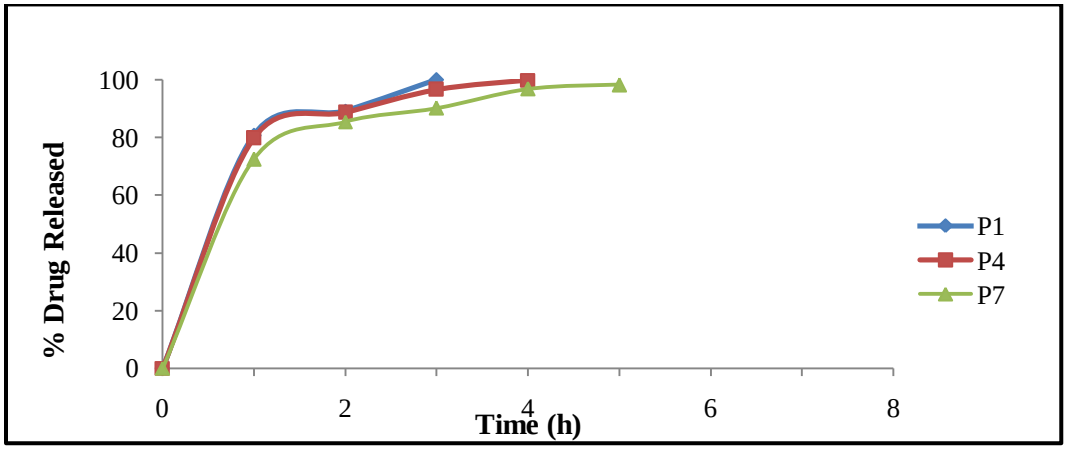

Figure: 2. Drug Release profile from gel containing 0.5%w/v of gelrite.

As evident from the release profile [Figure: 3] of P5 there is no burst release as compared to P1 & P4. P5 has sufficient viscosity and lag time owing to which this effect is minimized. It contains equal proportion of Gelrite and $CaCO_3$ hence forms a stable raft structure that controls

drug diffusion as the gelation proceeds, the remaining drug was released at a slower rate followed by a second phase of moderate release. The Ca^{2+} ions is highest in case of P8 hence the extent of polymer cross linking is higher and hence the consequent decline in drug release was seen with increase in $CaCO_3$ proportion.

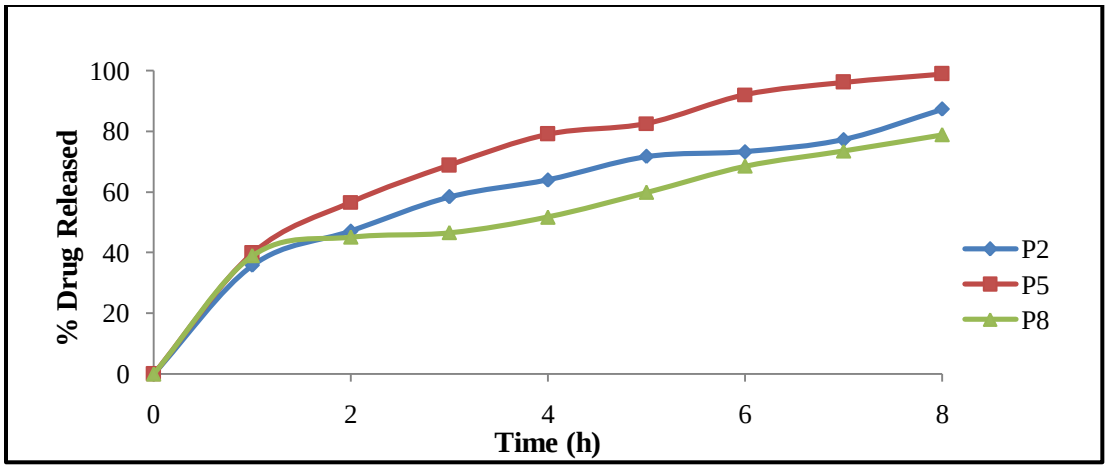

Figure: 3. Drug Release profile from gel containing 0.75%w/v of gelrite.

The formulation P9 (Figure: 4) has the minimum floating lag time and shows instantaneous gelation. It has the highest raft strength and therefore shows complete absence of burst release effect. It contains the highest proportion of both $CaCO_3$ and gelrite [1%w/v] and hence forms a stable matrix that controls the drug diffusion.

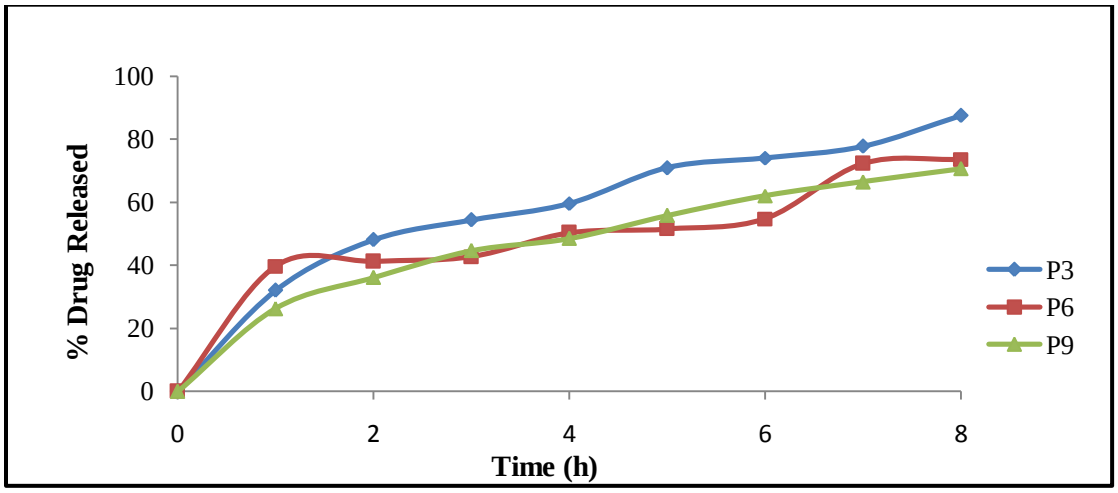

Figure: 4 Drug Release profile from gel containing 1 %w/v of gelrite.

From the dissolution profile of all the batches it can be concluded that concentration of gelrite and $CaCO_3$ both have an important role in drug release pattern. Among the nine formulations evaluated, P1 which contained lowest proportion of gelrite and $CaCO_3$ showed burst release and poor sustained release effect with >90% drug released in about 2 hours. On the other hand the formulation P9 which contained highest proportion of gelrite and $CaCO_3$ did not give burst

release but rather the release was gradual and sustained over period of 8hours. In case of formulation P5 the release was gradually increased upto 4hours and it was sustained thereafter. From the release profiles of formulation P4, P5 & P6 which composed of different proportions of gelrite at fixed amount of $CaCO_3$ [0.75%w/v] it can be concluded that the release decreases as the concentration of polymer is increased. Similarly from the release profiles of formulation P2, P5 & P8 which composed of different proportions of $CaCO_3$ at fixed amount of gelrite [0.75%w/v] it can be concluded that release decreases as the concentration of $CaCO_3$ is increased. Hence it can be concluded that a significant decrease in the rate and extent of drug release is observed with the increase in polymer concentration in in-situ gels and is attributed to increase in the density of the polymer matrix and also an increase in the diffusional path length which the drug molecules have to traverse. Also with increase in calcium carbonate concentration in formulations decreased percentage of drug release is observed. This is because the increase in calcium carbonate concentration increases the number of Ca^{2+} ions and their extent of cross linking with the polymeric chains thereby contributing to increase in the density of the polymer matrix and consequent increase in the diffusional path length [17-18].

Table 3: Raft residual Verapamil Hydrochloride content after dissolution studies

Sr No.	Batch Code	Verapamil Hydrochloride Content In Raft (%)*
1	P1	---
2	P2	14.2 ± 0.2642
3	P3	11.72 ± 0.7453
4	P4	---
5	P5	1.21 ± 0.0865
6	P6	28.04 ± 0.6142
7	P7	---
8	P8	20.16 ± 0.8789
9	P9	30.56 ± 1.0782

* n=3 ±S.D.

Residual Verapamil Hydrochloride content in gel after dissolution studies:

Incase of formulation P1, P4 & P7 the raft structure was poorly formed. P1 formed slimy gel mass and P4 &P7 formed fragmented gel mass. Hence it was not possible to determine the drug content. P5 showed minimum residual drug content as formed a stable raft structure that released >98% drug in 8hours. Incase of P8 & P9 harder gels were formed owing to higher proportions of polymer and calcium carbonate. Hence it produced highly crosslinked gel structure retaining 20.16% & 30.56% drug respectively at the end of 8hours (Table: 3).

Release kinetic studies

In order to understand the mechanism and kinetics of drug release, the results of the *In Vitro* drug

release were analyzed for various drug release models. These studies were performed by using PCP Disso V3 software (Table-4).

Table 4: Release kinetics of Factorial Batches

Batches	Regression- Value					Best Fit	Parameters For Peppas Equation	
	Zero Order	First Order	Matrix	Peppas	Hixon Crowell		*n*	K
P1	--	--	--		--	--	-2.407	188.6278
P2	0.7867	0.9659	0.9895	0.9953	0.9319	Peppas	0.4030	36.0593
P3	0.8359	0.9762	0.9944	0.9928	0.9541	Matrix	0.4437	33.0547
P4	--	--	--		--	--	-2.081	241.863
P5	0.8202	--	0.9943	0.9958	0.9536	Matrix	0.4413	40.9473
P6	0.7298	0.9018	0.9511	0.8836	0.8645	Matrix	0.2885	35.1261
P7	--	--	--		--	--	-1.615	224.65
P8	0.7712	0.9466	0.9763	0.9510	0.9081	Matrix	0.3310	35.375
P9	0.8822	0.9787	0.9984	0.9978	0.9577	Matrix	0.49	25.6510

The results were as per the following equations.

1. Zero order $Q_t = Q_0 + K_0 t$
2. First order $\ln Q_t = \ln Q_0 + K_1 t$
3. Second order $Q_t / Q_\infty (Q_\infty - Q_t) K_2 t$
4. Hixson–Crowell $Q_0^{1/3} - Q_t^{1/3} = K_s t$
5. Korsmeyer–Peppas $Q_t / Q_\infty = K_k t^n$

Where; Q_t = Amount of drug released in time t.

Q_0 = Initial amount of drug.

K = Release rate constant.

n = Release exponent indicative of drug release mechanism.

As mentioned in the earlier section, the Batches P1, P4 & P7 form weak raft structure due to formation slimy or softer gel structure. Hence the burst release is most prominent in this case as >90% drug is released in 2hours. From the release kinetics, it can be concluded that the release pattern does not fit in any of the models.

On the other hand the batches P2, P3, P5, P6, P8 & P9. All of which forms a stable raft structure and thereby gradually controls the drug release, show some what similar release kinetics. They follow the matrix release model except the batch P2 which follows the Peppas model. The values of 'n' are less than 0.5 which further supports the principle of diffusion controlled release (Higuchi model).

Measurement of gel Strength:

Gel strength is indicative of the tensile strength of the gelled mass. It signifies the ability of the

gelled mass to withstand the peristaltic movement in-vivo. Table: 5 reveal the gel strength of the various combinations of Gelrite and calcium carbonate. Formulation containing low amount of gellan formed very weak slimy gel. But with increase in $CaCO_3$ content there was slight increase in gel strength. This is evident in case of P1, P4 & P7. The gels with 0.75% w/v of gelrite formed gels with moderate gel strength whereas in gel with 1%w/v of Gelrite and $CaCO_3$ (formulation P8 & P9) the gel strength is highest forming a rigid raft.

The degree of rigidness of the gel can thus be attributed to the concentration of the polymer and Ca^{2+} ions. The degree of rigidness of the gel is related to the degree of cross linking of divalent ions with polymer chains, thus complying with the findings reported by Juming[16].

Table 5: Measured gel strength

Sr No.	Batch Code	Gel strength (g/cm^2)*
1	P1	18.53 ± 0.5121
2	P2	45.28 ± 1.5275
3	P3	64.57 ± 0.2650
4	P4	20.78 ± 0.1050
5	P5	52.56 ±0.514
6	P6	68.49 ± 0.1357
7	P7	25.51 ± 0.2891
8	P8	70.61 ±0.1844
9	P9	82.26 ±0.2645

* n=3 ±S.D.

Density measurement of gel:

Density is important parameter as far as the floating properties of the gastro retentive dosage form is concerned. Ideally the density of the dosage form, to float on the gastric content must have density less than or equal to gastric contents (~1.004 gcm-3). The density of all the formulations was recorded and found to lesser than above specified value. (Table: 6). All the formulations contain entrapped CO2 and thus have excellent buoyancy especially those containing higher proportion of polymer and $CaCO_3$.

Table 6: Measured Density of Gel Formulations

Sr No.	Batch code	Density (g/cm^2)
1	P1	0.605 ± 0.0204
2	P2	0.558 ± 0.0113
3	P3	0.627 ± 0.0055
4	P4	0.634 ± 0.0028
5	P5	0.654 ± 0.0135
6	P6	0.657 ± 0.0306
7	P7	0.623 ± 0.0166
8	P8	0.686 ± 0.0035
9	P9	0.669 ± 0.0121

* n=3 ±S.D.

Viscosity and Rheology studies:

The rheological properties of the solutions are of importance in view of their proposed oral administration. The two main pre-requisites of *in situ* gelling systems are optimum viscosity and gelling capacity (speed and extent of gelation). The formulation should have an optimum viscosity that will allow easy swallowing as a liquid, which then undergoes a rapid sol–gel transition due to ionic interaction.

The formulation batches P1, P4, & P7 contains 0.5%w/v of geltrite and 0.5% 0.75% and 1%w/v of calcium carbonate respectively. As evident from (Figure: 5) all formulations shows slight decrease in viscosity with increase in RPM. The viscosity of these three combinations is low as compared to other formulations. The flow of these formulations changes slightly with increase in RPM. These formulations show better flow and good sol properties. But the formulation P4, P7 due to low viscosity shows formation of slimy and scattered gel formation on contact with 0.1N HCl.

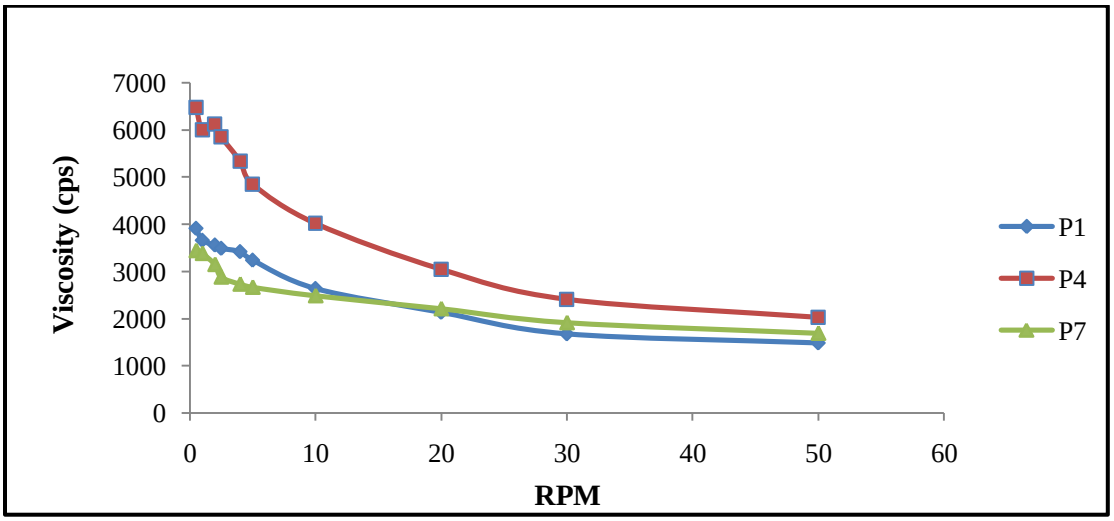

Figure: 5 .Rheological properties of in-situ gelling solution (sol) containing 0.5%w/v Gelrite.

The formulation batches P2, P5, & P8 contains 0.75%w/v of geltrite and 0.5% 0.75% and 1%w/v of calcium carbonate respectively. As evident from (Figure: 6) all formulations shows decrease in viscosity with increase in RPM. This decline in viscosity is quite prominent and this may be due to the extension of the polymeric chains on increase in the shear. This decline in the viscosity with increase in RPM signifies the shear thinning behavior. This decline in viscosity uniform in case of P5 and it shows good dispersibility of the contents and formation of stable raft structure on contact with 0.1N HCl.

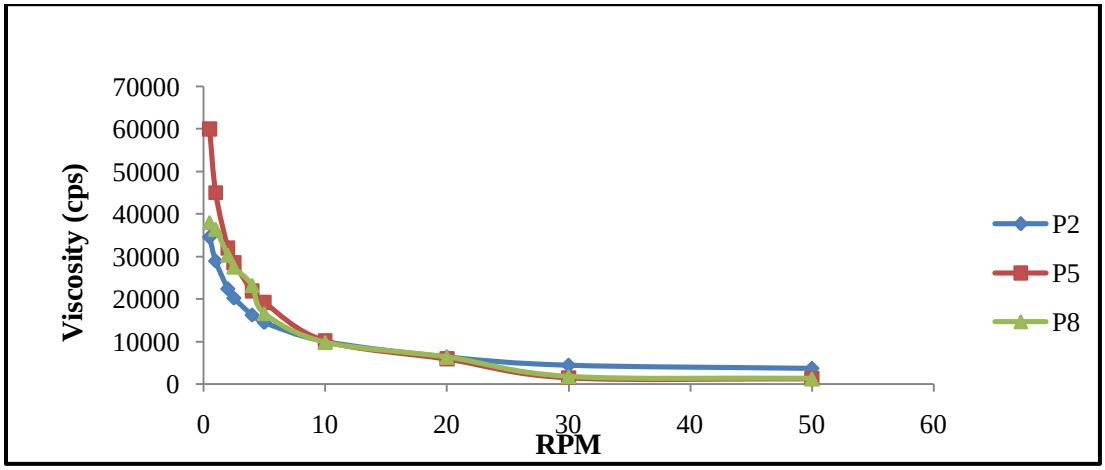

Figure: 6.Rheological properties of in-situ gelling solution (sol) containing 0.75%w/v Gelrite.

The formulation P3, P6, & P9 contains 1%w/v of geltrite and 0.5% 0.75% and 1%w/v of calcium carbonate respectively. These are the batch that contains the highest concentration of Gelrite and hence have higher viscosity amongst all other formulations. Though there was a shear thinning pattern observed, there was a fair resistance to flow as far as pourability of the sol was concerned. This is mainly attributed to high polymer concentration. Moreover in case of P8 & P9 the solid content was quite high with 0.75% & 1% of $CaCO_3$. But formation of raft was instantaneous with minimal lag time for P8 & P9 (Figure 7).

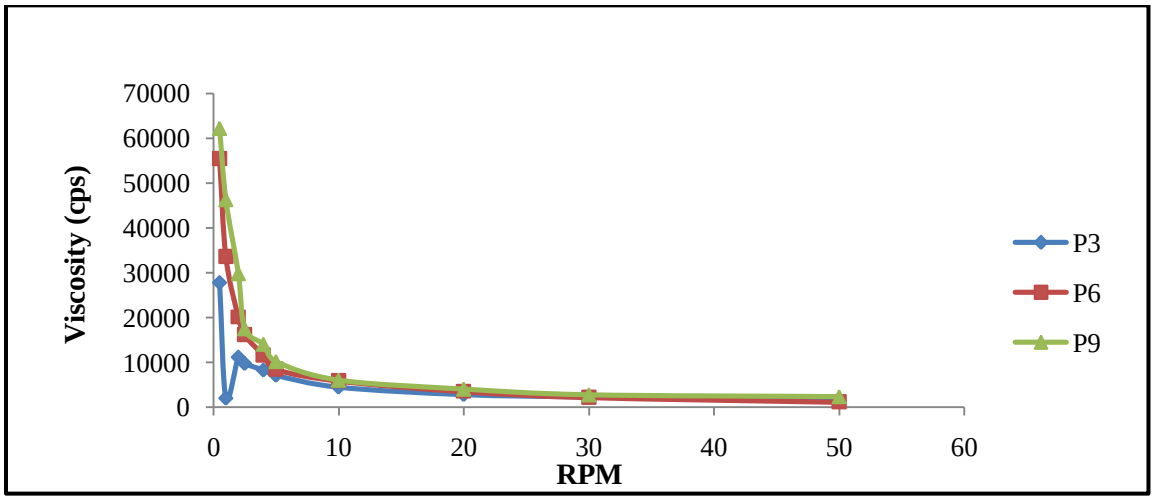

Figure: 7 Rheological properties of in-situ gelling solution containing 1%w/v Gelrite.

Thus the rheological properties of sol of gellan at various levels of calcium carbonate were studied. From the observations it can be concluded that the observed increase in viscosity with increase in concentration of gellan can be attributed to a consequence of increasing chain interaction with polymer concentration. Increasing the calcium carbonate content in the formulation simultaneously increased the viscosity at all polymer concentrations studied. Since

the calcium carbonate is present in the formulations as insoluble dispersion, an increase in its concentration proportionally increased the number of particles dispersed, thus contributing to the increased viscosity.

Multiple regression analysis for 3^2 factorial designs:

From the results, it was clearly evident that evaluation parameters were dependent on the composition of the independent variables i.e. concentration of the Gellan gum and the Calcium carbonate. The responses i.e. floating lag time, Gel strength and time required for the release 50% of loaded drug were reported and were analyzed by multiple regression analysis.

The statistical analysis of the data obtained was carried out by using PCP Disso V3 software (Table 7 and 8).

Table 7: Factorial batches with their responses

Responses	Factorial Batches								
	P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
Floating Lag time (Y_1)	177	112	82	156	93	78	125	73	65
Gel strength(Y_2)	18.53	45.28	64.57	20.78	52.56	68.49	25.51	70.61	82.26
$T_{50\%}{}^{*}$(Y_3)	1.5	4.57	4.57	2.0	4.04	5.43	2.54	5.07	5.65

*$T_{50\%}$ -- Time required for release of 50% of loaded drug dose.

Table 8: Summary of results of regression analysis

Responses	Coefficients					
	b_0	b_1	b_2	b_{12}	b_{11}	R^2
Floating Lag time (Y_1)	92.667	-40.1905	-18	8.1429	19.811	0.9972
Gel strength(Y_2)	49.843	25.0833	8.33	--	--	0.9331
$T_{50\%}{}^{*}$(Y_3)	4.56	1.6017	--	--	0.945	0.9088

*$T_{50\%}$ -- Time required for release of 50% of loaded drug dose.

The factorial equations for the three responses as per the coefficient obtained were as follows:

$Y_1 = 92.667 - 40.1905X_1 - 18X_2 + 8.1429X_1X_2 + 19.811X_1^2$

$Y_2 = 49.843 + 25.0833X_1 + 8.33X_2$

$Y_3 = 4.56 + 1.6017X_1 - 0.9450X_1^2$

Where Y_1 = Floating Lag time.

Y_2 = Gel strength.

Y_3 = Time required for release of 50% of loaded drug dose.

The coefficient b_0 is the arithmetic mean of the 9 responses and b_1 is estimated coefficient for the factor X_1 and similarly b_2, b_{11} and b_{12} for the respective terms X_2, X_1^2 and X_1X_2. The main effects (X_1 and X_2) represents average results of changing one factor at a time from low to high value. The term X_1^2 indicates curvilinear relationship. The interaction X_1X_2 shows how dependent variable changes when two or more factors are simultaneously changed. Thus, for

response Y_1 we get a linear decline as X_2 increases indicating the effect of Calcium carbonate with increase in value of which results in decline of lag time. Moreover, it also has the term $X_1 X_2$ which explains the contributing effect of both the variables as evident from the curvilinear plot. Similar is the response for Y_3. In case of Y_2 the distinct coefficients for term X_1 and X_2 indicates that both variables have contributing effect on gel strength independent of the other. Graphically these responses can be depicted as; (Figure: 8, 9, 10)

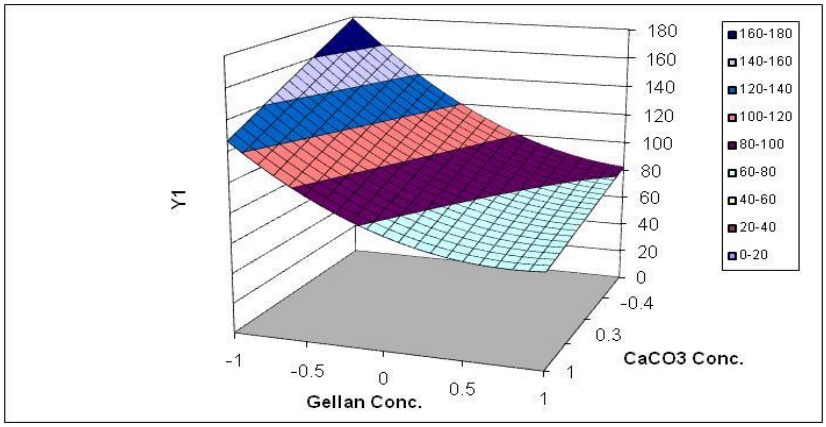

Figure: 8 Surface response plot for variable Y_1(Floating Lag time).

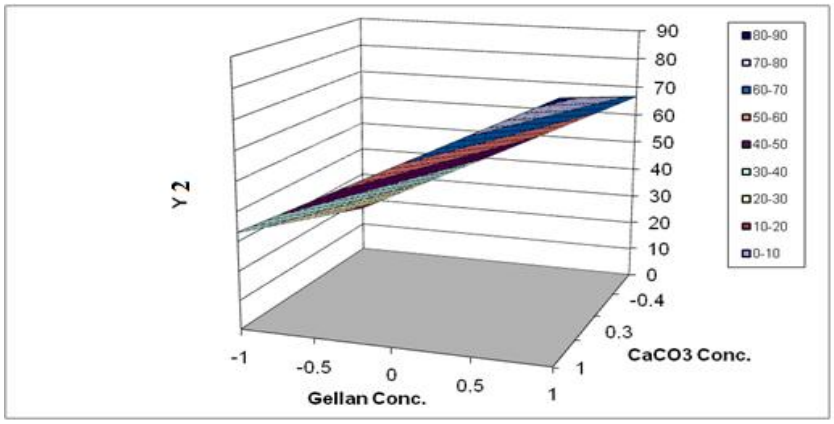

Figure 9: Surface response plot for variable Y_2 (Gel Strength).

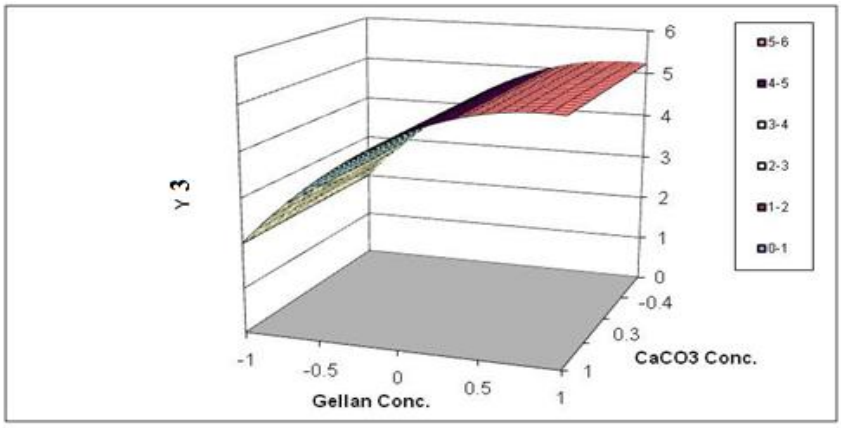

Figure: 10 Surface response plot for variable Y_3($T_{50\%}$).

CONCLUSION

From the present study carried out on pH dependent sol gel system of Verapamil Hydrochloride using Gellan gum (Gelrite®) Calcium Carbonate sol-gel system, it can be concluded that a lesser floating lag time and prolonged floating duration could be achieved by varying the combination of Gelrite® and Calcium Carbonate. Both Gelrite® and Calcium Carbonate have contributing effect on the floating performance and the *In Vitro* drug release pattern. The raft structure formed *In Vivo* elicits excellent gastric retention as proposed in observations based on *In Vitro* evaluation. Gellan gum is a very excellent excipient which can be utilized for the development of sustained release gastroretentive formulation.

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