DESIGN AND EVALUATION OF GARLIC SUSTAINED RELEASE MATRIX TABLETS.

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ABSTRACT

Herbal Supplements are vital part of today's comprehensive health maintenance because of their safety, efficacy and lesser side effects. One of such herb having medicinal importance is Garlic (*Allium sativum L.*, family Liliaceae) which has been used to prevent cardiovascular disorders. Different forms of garlic preparations (powders, oils, Aged Garlic Extract etc.) differ in chemical composition. Present study deals with the formulation of enteric coated oral sustained release garlic tablet which will be most effective on all circulatory disorders as it is a very important system affected in every form of disease. Tablets were formulated by non-aqueous wet granulation method using HPMC, Carbopol, Ethyl cellulose, Xanthan gum as release retarding polymers. The influence of polymer type and concentration on dissolution of tablets and release mechanisms were explained. 2^3 full factorial design was applied to systematically optimize the drug release profile using amount of polymer, binder and diluent as independent variables and release after 12h was selected as dependent variables. The tablets were found to release 85.66% of active constituents in 12h. Drug release mechanism was found to be diffusion controlled. Suitable combination of polymer, binder and diluent provided fairly good regulated release profile. The optimum formulation was chosen and its predicted result found to be in close agreement with experimental findings. A decrease in release kinetics of the drug was observed by increasing the polymer concentration. Sustained release garlic tablets can provide maximum health benefits of fresh, wholesome garlic to the cardiovascular and immune systems all day long without the garlic odor.

Keywords: garlic SR tablets, allin, 2^3 factorial, Xanthan gum, mathematical modeling.

INTRODUCTION

Circulatory system is a very important system affected in every form of disease. Hence such herbal medicine is needed to be developed which is most effective on all circulatory disorders. Garlic (*Allium sativum L.*, family Liliaceae) is one of the most famous of medicinal plants in human history. Medical research has been underway to assess whether the traditional uses of garlic have scientific validity. While the science is not definitive at this point, much of the research is showing real promise and many clinicians continue to report improvements in the areas of infection and heart-related risk factors for their individual patients. Researchers have proved that, for its promising effect, daily intake of at least 7-8 garlic cloves (3-4 grams) is necessary[1]. Garlic contains powerful, natural components identified through scientific research as providing significant benefits to the cardiovascular and immune systems. Taken internally, these compounds can even help to maintain cholesterol levels already within a normal range[2]. Garlic and its preparations have been widely recognized as agents for prevention and treatment of cardiovascular and other metabolic diseases, atherosclerosis, hyperlipidemia, thrombosis, hypertension and diabetes. Effectiveness of garlic in cardiovascular diseases was more encouraging in experimental studies, which prompted several clinical trials. To date, many favorable experimental and clinical effects of garlic preparations, including aged garlic extract, Garlic Essential Oil, Garlic Powder/ tablets, Oil Macerate (soft gelatin garlic capsule) have been reported. These biological responses have been largely attributed to i) reduction of risk factors for cardiovascular diseases and cancer, ii) stimulation of immune function, iii) enhanced detoxification of foreign compound, iv) hepatoprotection, v) antimicrobial effect and vi) antioxidant effect[3]. Numerous reviews on medicinal effects and new studies are continuously being published[4-7]. It is a great challenge for scientists all over the world to make a proper use of garlic and enjoy its maximum beneficial effect as it is the cheapest way to prevent cardiovascular disease. Blood thinners are most frequently prescribed for people who have had a history of clotting problems and/or strokes. In the current model of atherosclerotic disease, such as heart attack or stroke, "thick" blood running through cholesterol-narrowed arteries forms a clot. Enhancement in oxidized LDL cholesterol appears to be the main causative mechanism in atherosclerosis. Hence, the risk of atherosclerotic disease can be reduced either by "thinning" the blood or by preventing the narrowing of the arterial passage. Garlic apparently does both, i.e. it reduces clotting and lowers the cholesterol which builds the deposits that narrow the walls, by reducing the production of cholesterol in liver. It also inhibits the production of fatty acids there[8-9]. Most doctors recommend that people who are prone to develop heart attacks take aspirin as a blood-thinner. Aspirin does the job, but it can cause gastrointestinal bleeding and peptic ulcers with long-term use. Garlic, by combining blood-pressure-lowering, cholesterol-lowering, atherosclerosis-prevention and blood-thinning, combines the properties of at least three major allopathic drugs, without any of their side effects. Furthermore, several studies have shown that the use of cholesterol-lowering drugs, although leading to lower deaths from atherosclerotic disease, actually increase the overall death rate. If this is true then garlic is certainly preferable to these drugs.

Garlic therapy requires large doses of garlic and that too for long duration. Hence the normal dose using conventional tablets would be 2-3 tablets/day. Frequent administration of such a high dose of dried garlic powder can also cause reddening of the mucosa, loss of epithelial cells at the top of crypts in the ileum[10]. As a result, preparation of sustained release garlic tablet is essential as it will reduce the frequency of administration. However, for better patient compliance (especially as the therapy would be long-term) and to maintain plasma drug levels, a once a day dosage regimen, using a sustained release form will be preferable.

Present work involves the preparation of Garlic SR tablets and a comparative study of release retarding polymers like HPMC K-15[11], Carbopol 71NF G[12-14], Ethyl cellulose N-22[15], Xanthan gum[16].

MATERIALS AND METHODS

Garlic was procured from local market and the whole sample of garlic plant was authentified by Piramal Healthcare, Mumbai. HPMC K-15, Carbopol 71NF G, Ethyl cellulose N-22, Xanthan gum were obtained from Leben Laboratories, Akola. All other chemicals used in the study were of analytical grade.

Dry powder preparation and its analysis: Garlic cloves were peeled and kept in hot air oven, temperature maintained between 58^0 and 59^0 C, each clove weighing not more than 1g. Moisture loss of garlic cloves is determined by percent weight loss per day. Out of the many varieties of garlic, one clove garlic (*Allium porrum*) and multiple clove garlic (*Allium sativum*) are widely used to prevent circulatory disorders. Thus, both the varieties are tested for their allicin (an important thiosulfinate) content.

Allicin reacts with free thiol groups via a thiol-disulfide exchange reaction. Therefore, using a free thiol containing compound 2-Mercaptobenzothiazole (2-MBT) would quantify the content of allicin or the total thiosulfinates. Due to the 1:1 interaction of allicin and 2-MBT, a product is formed, which shows increase in optical density at 311nm. On the basis of this principle, a novel UV method had developed for quantification of allicin in garlic powder.

The molar solution of allicin was prepared by weighing the calculated quantity and transferring it to 100ml volumetric flask and to it 20ml cold (4^0 C) phosphate buffer pH 6.8 was added, shaken for 5 min. Volume made up to 100ml and kept at room temperature (25^0 C) for 30 min. Then filtered through whatman filter paper no. 1 and the filtrate collected were used for further dilutions.

The molar solution of 2-MBT was prepared by weighing the calculated quantity and transferring it to 100ml volumetric flask, to it 20 ml of methanol was added, allowed to dissolve and volume made up with methanol. This solution was used for further dilutions.

10ml of each solution added to 25ml volumetric flask and the reaction for 30min was allowed to take place at room temperature (25^0 C). UV absorbance has taken at 311nm.

Determination of allicin content with increase in drying time: 10 samples of 540 mg garlic samples were weighed and kept in hot air oven with temperature between 58^0 and 59^0C. Every day one sample is withdrawn and analysed by above mentioned method.

Similarly 0.4 millimolar (mM) solution prepared and reacted with 0.4 mM 2-MBT. Absorbance was taken at 311nm. It was then kept for incubation, at room temperature, for 30 minutes. (1ml to 10ml dilution done at the time of taking absorbance)

Both the varieties are dried at temperature between 58 and 59^0 C for 10 days and then powdered. The 1mM allicin solution of both the varieties were prepared by weighing the calculated quantity and transferring it to 100ml volumetric flask and to it 20ml cold (4^0 C) phosphate buffer pH 7.2 was added, shaken for 5 min. It is then kept at room temperature (25^0 C) for 30 min. Then filtered through whatman filter paper no. 1 and the filtrate collected were used to make 0.4mM allicin solutions.

Allicin content is determined by abovementioned analytical method using 2-MBT. Absorbance was taken at wavelength 311nm.

Preformulation study: Dried garlic samples are ground in grinder. Particle size is approximately 450 microns. The prepared garlic powder has undergone through various preformulation studies as reported in USP 25. The values obtained for the various tests were in specified pharmacopoeial range[17].

IR spectrum of the garlic powder confirmed the presence of allin (thiosulfinate).

Ultraviolet spectrum of total thiosulfinates in garlic powder: The ultraviolet spectra of the thiosulfinates containing only allyl or methyl groups are characterized by a prominent shoulder at 240 nm in water or 245 nm in methanol, while those containing a 1-propenyl group have a shoulder at 260-262 nm. A garlic powder solution of 1000ppm concentration is prepared in phosphate buffer of pH 6.8 and scanned under UV spectrometer (JASCO). It showed shoulder at 262nm. Thus the standard curve of garlic powder solution was prepared at 262nm.

Drug-excipient compatibility was checked by DSC study which showed that garlic powder does not interact with any other excipients used in formulation.

Formulation development: All the ingredients were weighed accurately. The garlic powder was mixed with diluent. The addition was done in geometric proportion to ensure uniform distribution. Then the polymer and other excipients were added along with 50% of weighed Aerosil 200 and mixed in geometric proportion to ensure uniform distribution. The granules were prepared by wet granulation method. Polyvinyl pyrrolidine (PVP) in

isopropyl alcohol was used as binding agent. Granulated mass was passed through sieve #16. Granules were dried below 55^0 C. Dry granulation was done through sieve #36. The dry granules lubricated with magnesium stearate along with remaining amount of Aerosil 200. The granules were compressed, using concave punches of length 21.06 mm and 11.6 mm in width, in room where the humidity was controlled using dehumidifier. Tablet weight and hardness were checked at regular intervals during punching.

Factorial design: A 2^3 factorial design was constructed where concentration of Xanthan gum, diluent (DCP) and binder (PVP) were selected as the factors. Two levels (high and low) for each factor were selected. All the other formulations and processing variables were kept invariant throughout the study. Table 6 summarizes the experimental runs and their factor combinations.

Table 1: Formulation development of garlic SR tablet.

Batch no.	Garlic powder (%)	Polymer (%)				Diluent (%)	Binder (%)	% Drug release after 12h
		HPMC K-15	Carbopol 71G NF	Ethyl Cellulose N-20	Xanthan Gum			
A1	63	10	-	-	-	18	2	95.88
A2	63	20	-	-	-	6	2	92.11
B1	63	-	10	-	-	18	2	94.73
B2	63	-	20	-	-	6	2	92.81
C1	63	-	-	10	-	18	2	95.35
C2	63	-	-	20	-	6	2	91.23
D1	63	-	-	-	10	18	2	92.56
D2	63	-	-	-	20	6	2	85.66

Table 2: Evaluation of granules of the tablets containing polymer.

Tablet	Angle of repose (^{0})	Loose Bulk Density (g/mL)	Tapped bulk density (g/mL)	Hausner ratio	Flow rate	Compressibility Index (%)	Drug Content (%)
A1	35.32	0.4545	0.5	1.1001	3.64	9.09	100.67
A2	38.07	0.4166	0.4545	1.0909	2.403	13.04	95.97
B1	34.11	0.4	0.4347	1.0867	3.144	8	98.76
B2	35.05	0.4545	0.4761	1.0475	1.6	4.545	99.03
C1	33.81	0.5	0.5555	1.1111	2.29	10	97.94
C2	38.1	0.5263	0.5555	1.0554	2.008	5.2631	99.05
D1	34.18	0.5263	0.5882	1.1176	1.51	10.52	98.91
D2	35.39	0.4761	0.5263	1.1054	2.202	9.52	99.03

Tablet coating: Enteric coating is applied to the tablets using HPMCP (Hydroxypropyl methylcellulose phthalate) [16].

Physical evaluation: All the batches were evaluated for weight variation, hardness, friability, thickness and drug content as per USP XXV monograph. The weight variation was determined by taking 20 tablets using an electronic balance. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 20 tablets in a friability tester for 4 minutes at 25 RPM[17].

Swelling Behavior of Matrix Tablets: The release behavior of tablet was studied in relation to their erosion and swelling to investigate the relationship between their drug release profiles. The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behavior of all the formulations was studied. Five tablets from each formulation were kept in Petri dish containing phosphate buffer pH 6.8. At the end of 2, 4, 6, 8, 10 and 12hrs tablets were withdrawn, soaked on tissue paper and weighed, and then percentage weight gain by the tablet was calculated using formula.[18-19]

$$SI = \frac{M_t - M_o}{M_o} \times 100$$

Where, SI = Swelling index, Mt= Weight of tablet at time 't', Mo = Weight of tablet at time '0'. % weight gain by the tablet containing various polymers is graphically represented.

Dissolution study: Dissolution study is carried out as per USP 25 under the heading *'Delayed –Release (Enteric coated) Articles – General Drug Release Standards-Method A'*, in USP Apparatus 2 (Model Electrolab, India)

Mathematical modeling: The release profile of the drug obtained was analysed using different kinetic models such as zero order, first order, Higuchi, Hixson- Crowell and

Korsemeyer-Peppas model in order to evaluate the release mechanism from the matrices[20-22].

Stability study: The formulated garlic SR tablets, batch X2, were kept for short term accelerated stability study in high density polyethylene sealed cover at refrigeration, 25^0C- 60% RH, 40^0C- 75% RH as per protocol. Samples were withdrawn for every month of storage and evaluated for appearance, hardness and drug content.

RESULT AND DISCUSSION

Analytical method: Allicin content in both the species is almost similar (Table 3). Therefore, the cheaper species i.e *Allium sativum* is selected for formulating the tablet. Alliin content, thus allicin content is highest in fresh garlic. It decreases with increase in drying time. The UV spectrum of garlic powder extract in buffer pH 6.8 showed a shoulder at 262 nm, showing the presence of thiosulfinates having 1-propenyl group (70% of it is allicin). Thus the quantification of total thiosulfinates in present garlic formulation was done at 262 nm.

Table 3: Comparison of allicin content in two different Allium species

Time (Days)	Absorbance (311nm)	
	Multiple clove garlic	One clove garlic
0	0.983	0.992
1	0.961	0.976
2	0.891	0.883
3	0.872	0.862
4	0.846	0.85
5	0.801	0.794
6	0.799	0.781
7	0.78	0.789
8	0.78	0.778
9	0.775	0.771
10	0.715	0.706

Physical characterization: The formulated matrix tablets met the pharmacopoieal requirement of uniformity of weight. All the tablets conformed to the requirement of assay, hardness, % friability and thickness. Results are provided in table 4.

Assay and *In vitro* dissolution study: All formulations showed no drug release in 0.1 N HCl. Sustained drug release was displayed by all formulations in phosphate buffer (pH 6.8) (Fig. 1-5). The % weight gain of tablet was calculated with respect to time (Table 5). It has been observed that the cumulative percent drug release decreases with increasing concentration of gum. The response surfaces and contour plots for each response parameter are presented for further interpretation of the results (Fig.6). The plots show that as the concentration of binder, diluent and polymer increases, drug release decreases. The optimum formulations were chosen and their predicted results found to be in close agreement with experimental findings. The assay of tablets revealed that the total thiosulfinates content of the tablet was found to be 98.68% and found to release 85.66% of active constituents in 12 hours.

All formulations showed no drug release in 0.1 N HCl. Sustained drug release was displayed by all formulations in phosphate buffer (pH 6.8) (Fig. 1-5).

Table 5: Percent weight gain study.

Time (hr)	% Weight gain		
	A2	B2	X2
1	96.08	121.063	63.13
2	101.08	145.235	101.59
4	194.15	200.2	179.82
6	254.85	233.701	249.45
8	256.732	186.258	368.03
24	196.831	206.01	600

Table 6: Comparison of experimental and predicted values, of the optimized batch, obtained by Design Expert 6.7.1 software.

Batch no.	XG	DCP	PVP	% Drug release after 12h	
				Experimental	Predicted
X1	10	5	2	96.92	95.87
X2	20	5	2	85.66	85.22
X3	10	5	1	96.83	96.79
X4	20	15	1	86.27	86.23
X5	20	15	2	86.38	86.43
X6	10	15	2	91.63	91.59
X7	20	5	1	85.18	85.61
X8	10	15	1	91.58	91.62

[a]The results are average of three determinations.

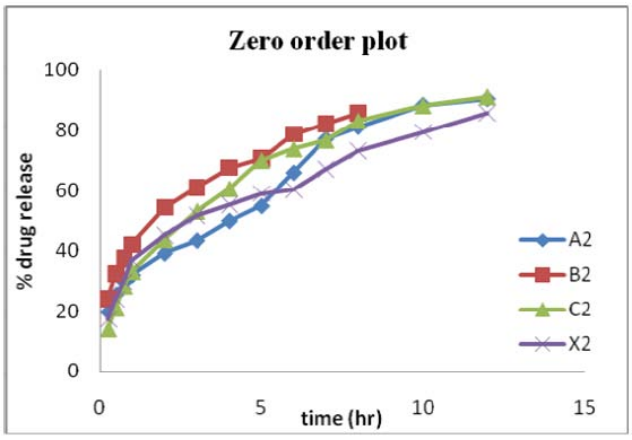

Figure 1: Zero order plot for different polymer batches

Swelling study (% water uptake): The reason attributed to this fact is slow erosion of the gelled layer from the

tablets containing higher amount of xanthan gum. Slow drug release is because of the formation of thick gel structure that delays drug release from the tablet matrix, where hydration of individual xanthan gum particles result in extensive swelling. As a result of rheology of hydrated product, the swollen particles coalesce. This results in continuous viscoelastic matrix that fills the interstices, maintaining the integrity of the tablet, and retarding further penetration of the dissolution medium.

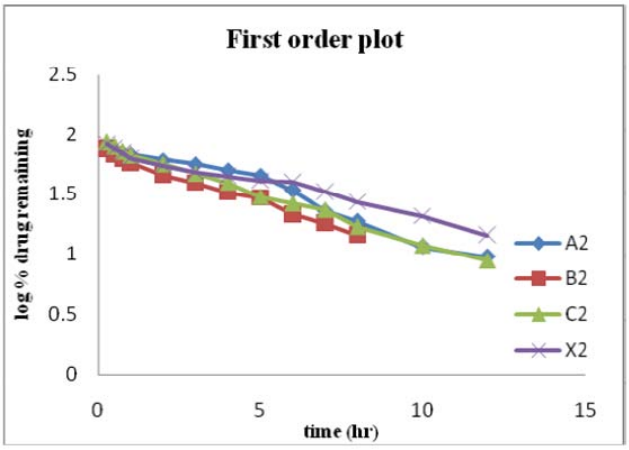

Figure 2: First order plot for different polymer batches

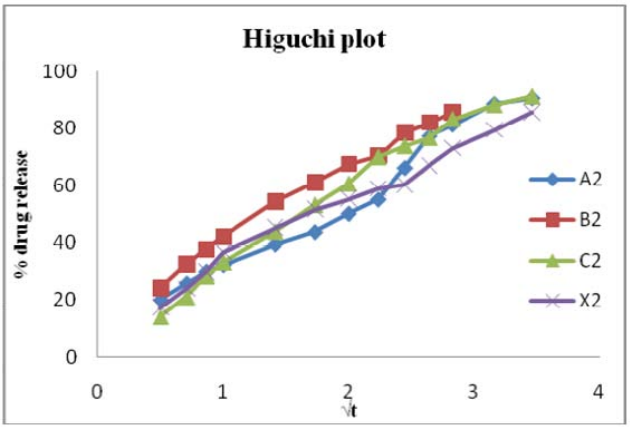

Figure 3: Higuchi plot for different polymer batches

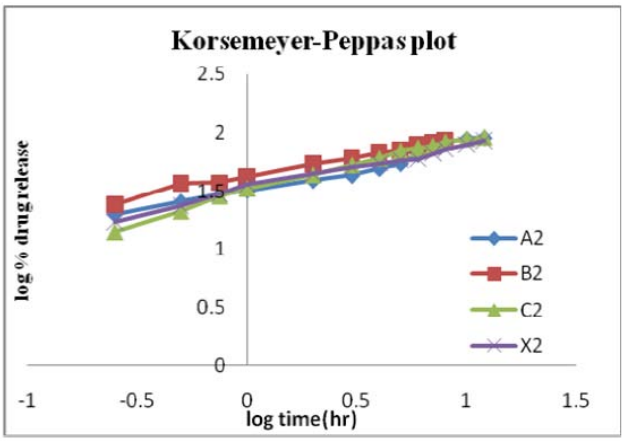

Figure 4: Korsemeyer- Peppas plot for different polymer batches

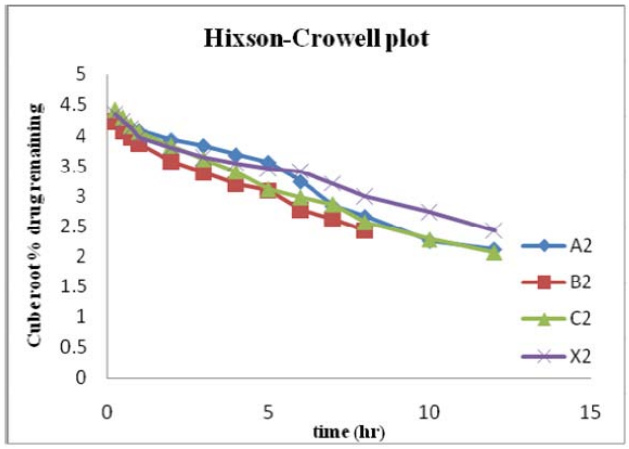

Figure 5: Hixson Crowell plot for different polymer batches

Drug release mechanism: In order to investigate the release mechanism the data were fitted to different models as mentioned earlier. From the table, it is concluded that the optimized batch X2 followed Higuchi release kinetics as it showed the highest linearity (R^2 = 0.985) (Table 8). A decrease in release kinetics of the drug was observed by increasing the polymer concentration. Further, to understand the drug release mechanism, the data were fitted to Korsermeyer-Peppas exponential equation. For all the batches, the value of n ranged between 0.340 and 0.480 (Table 7) which revealed the drug release mechanism to be Fickian diffusion controlled.

All the dissolution study and mathematical modeling plots are starting from 0 hr. this 0^{th} hour is starting in intestine and not in stomach. As tablet is enteric coated and did not show any release in gastric pH that period is not considered.

Table 7: Mathematical modeling and drug release mechanisms of garlic sustained release tablets

Batches	n	R^2	Mechanism
A2	0.397	0.97	Fickian diffusion
B2	0.342	0.986	Fickian diffusion
C2	0.48	0.99	Fickian diffusion
X2	0.389	0.986	Fickian diffusion

[a]NOTE: Based on Korsmeyer-Peppas equation, $M_t/M\infty = Kt^n$
[b]R^2= Regression coefficient
[c]n= diffusional release exponent, k= kinetic constant

Stability study: The accelerated stability studies were performed on Batch X2 as per the protocol. Drug content and hardness were tested at periodic time intervals. The batch was found to be stable for the tested period under the accelerated storage conditions.

Table 4: Evaluation of granules of tablets containing different concentrations of xanthan gum

Tablet	Angle of repose (^{0})	Bulk Density (g/mL)	Tapped density (g/mL)	Hauser ratio	Flow rate	Compressibility Index (%)	Drug Content (%)	% Drug release
X1	34.11	0.4	0.4347	1.0867	3.144	8	92.11	97.87
X2	37.3	0.4347	0.5	1.1502	1.59	13.04	91.35	89.56
X3	38.07	0.4166	0.4545	1.0909	2.403	13.04	89.84	98.77
X4	32.53	0.4166	0.4761	1.1428	3.26	12.5	93.53	88.39
X5	32.7	0.7	0.87	1.24	3.33	19.54	92.46	87.27
X6	33.21	0.709	0.812	1.14	2.59	12.68	89.66	93.94
X7	32.5	0.722	0.852	1.18	3	15.25	87.76	88.42
X8	31.21	0.712	0.82	1.14	3.01	13.17	94.21	95.35

Table 8: Release rate constants and R2 values for different release kinetics of Garlic SR tablet

Formulation	Zero order		First order		Higuchi		Hixson-Crowell	
	K_0	R^2	K_1	R^2	K_h	R^2	K_{hc}	R^2
A2	14.55	0.963	-0.186	0.968	57.55	0.972	-0.449	0.979
B2	17.06	0.937	-0.202	0.992	59.09	0.992	-0.506	0.984
C2	15.07	0.901	-0.193	0.996	62.01	0.985	-0.462	0.98
X2	12.29	0.925	-0.133	0.981	49.9	0.985	-0.345	0.977

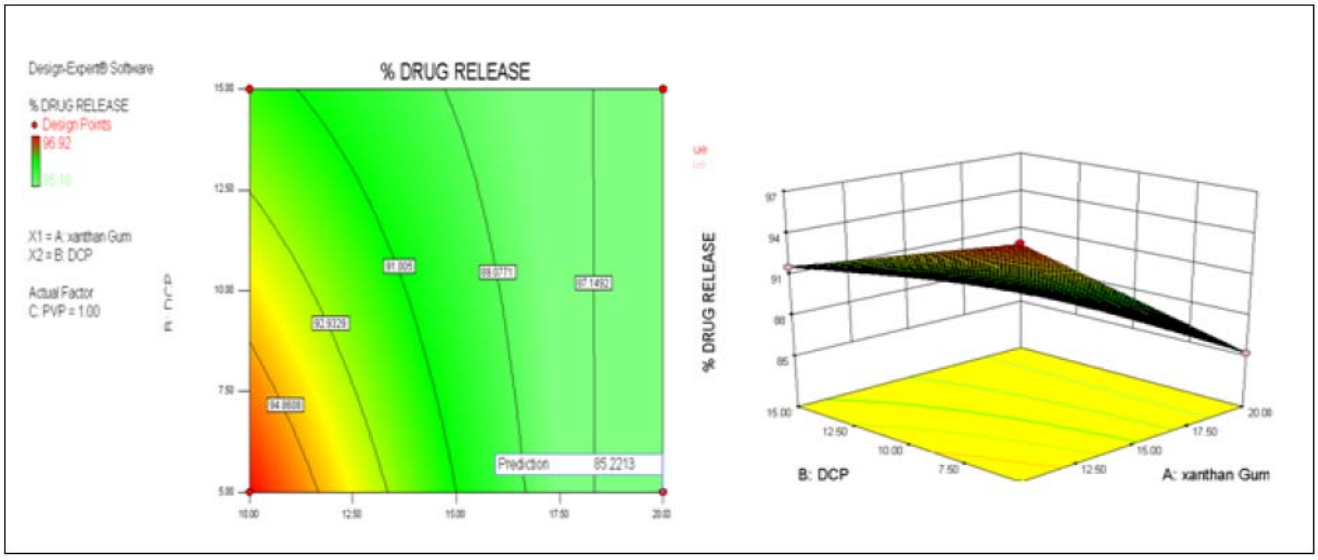

Figure 6: Response surface and contour plots showing influence of Xanthan Gum and DCP on percentage release in 12 hr for sustained release formulation of garlic tablet.

CONCLUSION

From the study it was concluded that the best sustained release tablet could be produced using Xanthan gum along with hydrophobic diluents and binder. Sustained release garlic tablets can provide maximum health benefits to the cardiovascular and immune systems. The prepared tablets will provide the natural health benefits of fresh, wholesome garlic all day long without the garlic odor. Directions: As a dietary supplement, take one (1) garlic tablet daily.

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