Journal of Pharmaceutical Research Vol. 12, No. 2, April-June 2013 : 43-47.

NOVEL MODIFIED RELEASE HYDROGEL PARTICLES OF LOVASTATIN-DEVELOPMENT AND EVALUATION STUDIES

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Received on : 20.05.2013 Revised : 12.06.13 Accepted : 12.06.13

ABSTRACT
Novel Xanthan gum-soluplus-acrylamide based hydrogel particles using methylene bis acrylamide as cross linking agent and potassium persulfate as a reaction initiator were developed and further characterized by Scanning Electron Microscopy for the surface morphology, Swelling studies, *in vitro* dissolution and stability studies. The surface morphology of the hydrogels exhibited a rough network like surface. Hydrogel particles exhibited pH dependant swelling. The *in vitro* dissolution studies performed for 12 hours showed that the release of the drug varied with the concentrations of Xanthan gum and acryl amide. Hydrogel particles formulations without soluplus showed a remarkable reduction in the drug release. Formulation F9 showed a release rate of 88.90%. Further the release rates were found to decrease with increase in the concentration of cross linking agent. The mathematical modeling followed zero order kinetics by fickian diffusion following super case-II transport mechanism. The stability studies revealed that the hydrogel formulations prepared using Xanthan gum offers good stability to the drug. Hence the hydrogel formulation can be recommended as suitable modified release dosage forms using Xanthan gum and novel polymeric solubilizer soluplus for better industrial applications.

Keywords: *Hydrogels; soluplus; acryl amide; Xanthan gum; modified release.*

INTRODUCTION

An aptly designed drug delivery system can be a major advance towards solving the problems of spatial placement and temporal delivery of the drug. Modified release drug delivery systems have potential advantages to avoid systemic and local accumulative side effects, patient compliance problems and provide an efficient route to deliver the large molecular weight drugs like proteins and peptides etc. without altering the bioactives[1]. Hydrogels are the recent technologies for the modified release of drugs. They are defined as 3-dimensional, hydrophilic polymeric networks composed of homo or co-polymers which are capable of imbibing large amounts of water or biological fluids[2-5]. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymer backbone while their resistance to dissolution arises from cross-links between network chains. Water inside the hydrogel allows free diffusion of some solute molecules, while the polymer serves as a matrix to hold water together.

Dyslipidaemia or hyperlipidaemia is a major prevalent indicator and risk factor of Cardio vascular disease which is characterized by hypercholesteremia. The clinically important lipids in the blood (unesterified and esterified cholesterol and triglycerides) are not readily soluble in plasma and are rendered miscible by the incorporation into lipoproteins. They are classified into Chylomicrons, Chylomicron remnants, Very low-density lipoproteins (VLDL-C), Intermediate-density lipoproteins (IDL-C), Low-density lipoproteins (LDL-C) and High-density lipoproteins (HDL-C). LDL-C is the major cholesterol carrier in plasma. It provides cholesterol, an essential component of cell membranes, bile acid and a precursor of steroid hormones and is also involved in atherogenesis. VLDL-C and LDL-C are considered 'bad lipoproteins'. HDL-C is formed from the unesterified cholesterol and phospholipid removed from peripheral tissues and the surface of the triglyceride-rich proteins. It is considered to be the 'good' atherogenic lipoprotein. About 65% of the total cholesterol is carried in LDL-C and 25% in HDL-C. Elevation of Triglycerides may be the independent risk factor of a primary disorder of lipid metabolism[6]. The discovery of Statins that inhibit HMG-CoA reductase has a significant advancement in the treatment of dyslipidaemia. They primarily inhibit HMG CoA reductase in the liver and subsequently the mevalonic acid, the rate-limiting step in the biosynthesis of cholesterol.

Lovastatin is an antihyperlipidemic agent- HMG-CoA Reductase inhibitor indicated to reduce risk of

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Myocardial Infarction, unstable angina, and coronary revascularization procedures in patients without symptomatic cardiovascular disease. Its oral bioavailability is (< 5%). 30% of an administered oral dose is absorbed, but less than 5% reaches the systemic circulation as active drug (beta- hydroxyacid form). The human cholesterol synthesis reaches a peak around midnight and if a single dose which can deliver the drug effectively throughout the day for 24 hrs or more would be more effective in the reduction of the cholesterol levels. Lovastatin is well accepted and tolerated by the patients and has a substantial effective result in the coronary event rates[7-9].

In view of the pharmacological importance of Xanthan gum in the drug delivery systems, if suitably tailored, it can be used to prepare as hydrogel drug delivery systems that can act as a potential candidate for the controlled drug delivery. The potential of the polymers with the utilization of soluplus a polymeric solubilizer in the entrapment of poorly soluble drugs in the hydrogel matrix networks has not been explored yet. Hence an attempt was made to develop novel grafted hydrogels based on Xanthan gum and acrylamide with a novel solubilizing matrix polymer, soluplus using methylene bis acrylamide as a cross linking agent and potassium persulphate as a reaction initiator to achieve modified release dosage forms.

MATERIALS AND METHODS

Materials

Lovastatin was kindly provided by Dr. Reddy's Laboratories, Bachupally, Hyderabad. Soluplus was generously provided by BASF, The Chemical Company, Germany. Xanthan gum, Acrylamide and methylene bis acrylamide were procured from Sigma-Aldrich Pvt ltd. All other reagents and chemicals were of analytical grade or HPLC grade.

Preparation of Lovastatin Hydrogel particles

An accurately weighed quantity of xanthan gum and soluplus was dissolved in about 15 ml of double distilled water by mixing vigorously at a speed of 800-900rpm to which acrylamide was added, and homogenized at 1500-2000 rpm for 20 mins, using ultrasonic homogenizer. Methylene bis acryl amide and potassium per sulfate were dissolved separately in 5 ml of demonized water and added to the above mixture. Stirring was continued for 20 mins and 10 ml of 0.1N Na OH was added and kept aside for 1 Hr. It was then immersed in 100 ml of ethanol. The formed gel was filtered using membrane filter paper under vacuum at the end of 48 hours and dried at 50° C for further use. Various hydrogel formulations were prepared using different ratios of Xanthan gum, soluplus and the cross linking agent and their effects on the release rate were studied. The hydrogels were formulated as shown in the Table 1.

Table 1: *Formulation of Lovastatin Hydrogels*

Formulation code	LST (mg)	SLP (mg)	XG (mg)	Aam (mg)	PPS (%w/v)	MBS (%w/v)
F1	40	100	50	100	0.1	0.02
F2	40	100	100	50	0.1	0.02
F3	40	100	50	50	0.1	0.02
F4	40	100	100	100	0.1	0.02
F5	40	----	100	100	0.1	0.02
F6	40	25	100	100	0.1	0.02
F7	40	50	100	100	0.1	0.02
F8	40	75	100	100	0.1	0.02
F9	40	100	100	100	0.1	0.02
F10	40	100	100	100	0.1	0.025
F11	40	100	100	100	0.1	0.03
F12	40	100	100	100	0.1	0.035
F13	40	100	100	100	0.1	0.05
F14	40	100	100	100	0.1	0.06

LST- Lovastatin; SLP-Soluplus; XG-Xanthan gum; Aam-Acrylamide; PPS- Potassium Persulfate; MBS: Methylene bis acrylamide.

Characterization of Hydrogel Particles

Scanning Electron Microscopy (SEM)

The hydrogel particles were further characterized using Jeol JSM- 840 (Japan) Scanning Electron Microscope.

Swelling behavior of the hydrogel particles

Hydrogel particles were placed in 10 ml of buffer solutions of different pH i.e., in 0.1N HCl, double distilled water and pH 6.8 buffer. The Hydrogel particles were removed from their respective swelling media, blotted to remove excess water and their weight obtained on analytical balance. The equilibrium weight swelling ratio (ESR) of hydrogel particles was calculated using the following equation:

$$ESR = \frac{W_2 - W_1}{W_1}$$

W_2 represents the swollen Hydrogel at time't' and W_1 is the weight of the hydrogel before swelling. This process was continued until the sample appeared to be dissolved.

In vitro drug release studies

The study was carried out in triplicate using USP type I (Basket) apparatus (Electro Lab TDT-O8L, Mumbai) , in 900 mL of 0.1 N HCl, at 37°C ± 0.5°C at 50 rpm for the first 2 hours and then replaced by phosphate buffer pH 6.8 containing 0.5% sodium dodecyl sulphate.. Aliquots of 5 ml samples were withdrawn at appropriate time intervals for 24 hours, and were replaced with fresh dissolution medium after every withdrawal. They were filtered through a 0.45-ìm membrane filter and absorbance of these solutions were measured at 238 nm using a Shimadzu UV- 1601 UV/Visible double-beam spectrophotometer (Shimadzu Corp, Kyoto, Japan) after appropriate dilution. Cumulative percentage drug release was calculated using the calibration curve.

Evaluation of Release Kinetics

The mechanism of the drug release of the hydrogels of Valsartan and Lovastatin was investigated by fitting the *in vitro* release data using zero order, first order, Higuchi model, Hixon-Crowell model, Korsemeyer – Peppas equation [1, 10] and Erosion models as shown in the Table 2.

Table 2 : *Mathematical models for the drug release kinetics*

Model	Equation
Zero order	$Q = Q_o + K_o t$
First order	$\text{Log } Q_t = \text{Log } Q_0 + Kt/2.303$
Higuchi	$Q_t = Q_o + K_H t^{1/2}$
Korsmeyer-Peppas	$Q_t = K_{KP} t^n$
Hixon-Crowell	$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = K_{HC.} t$

Stability studies

The optimized best Hydrogel formulations of Lovastatin prepared was taken separately in High density Poly Ethylene screw capped bottles, labelled and subjected to accelerated stability studies to 40 ± 2 °C and 75 ± 5% RH and at ambient conditions of 25° ± 2° C and 60 ± 5% RH (as per ICH guidelines). Samples were withdrawn at predetermined time points i.e., at the end of 1, 2, 3 and 6 months at accelerated conditions. Similarly at the end of 3rd and 6th months at ambient conditions and evaluated for drug content, physical appearance, dissolution profile and any changes in the same are reported.

RESULTS

Scanning Electron Microscopy (SEM)

The surface morphology of the hydrogel particles was observed as shown in the figure 1.

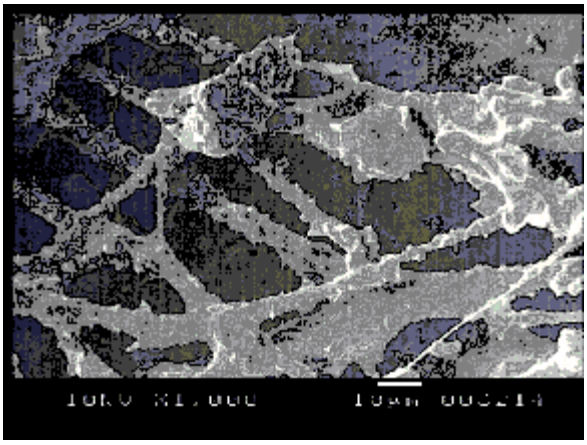

Fig. 1: Scanning Electron Microscopy of Lovastatin Hydrogel systems.

Swelling behavior of the hydrogel p articles

The swelling behavior of the prepared hydrogel particles in various media was shown in the figure 2.

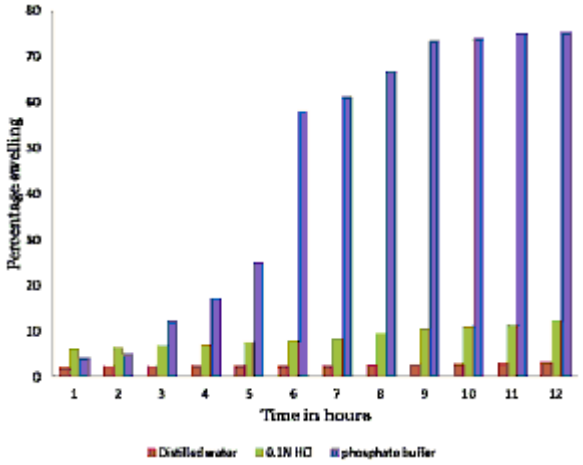

Fig. 2 : *Swelling kinetics of Lovastatin Hydrogel particles in distilled water, 0.1 N HCl and PBS pH6.8*

In vitro drug release

The *in vitro* studies were conducted and the effects of Xanthan gum, soluplus and crosslinking agent were studied.The cumulative percentage drug release is shown in the Figure 3.

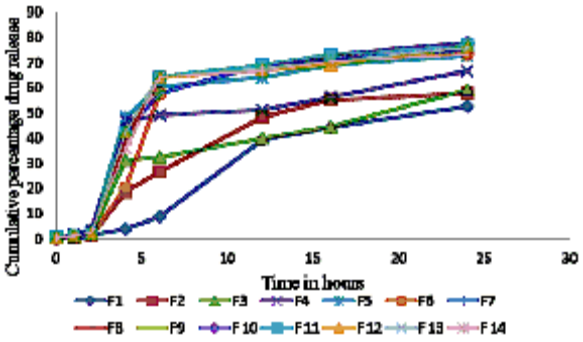

Fig. 3 : *Comparative dissolution profiles of Lovastatin Xanthan gum Hydrogel Formulations*

Evaluation of Release Kinetics

The release mechanism of the drug from the hydrogels is shown in Table 3.

Table 3 : *Mechanism of drug release from the hydrogels*.

Formulation Code	Zero order plot	First order plot	Higuchi plot	Hixon - crowell plot	Korsemeyer -peppas plot		
	R^2	R^2	R^2	R^2	R^2	n value	Transport mechanism
F1	0.9337	0.8502	0.8095	0.692	0.6328	1.30	Supercase-II
F2	0.6886	0.6381	0.9116	0.745	0.7319	1.42	Supercase-II
F3	0.8339	0.5942	0.9012	0.662	0.7319	1.36	Supercase-II
F4	0.8845	0.5418	0.8187	0.588	0.7935	1.44	Supercase-II
F5	0.6709	0.5377	0.9311	0.588	0.7097	1.51	Supercase-II
F6	0.7606	0.8464	0.9240	0.679	0.8168	1.54	Supercase-II
F7	0.7236	0.5595	0.9895	0.608	0.9087	1.35	Supercase-II
F8	0.7181	0.6427	0.9822	0.609	0.8687	1.24	Supercase-II
F9	0.7131	0.5654	0.9574	0.582	0.7274	1.43	Supercase-II
F10	0.7147	0.8502	0.9424	0.582	0.7247	1.44	Supercase-II
F11	0.7062	0.6381	0.9286	0.609	0.7537	1.37	Supercase-II
F12	0.7016	0.5574	0.9221	0.580	0.7013	1.33	Supercase-II
F13	0.6984	0.5464	0.9238	0.401	0.7253	1.35	Supercase-II
F14	0.6996	0.5548	0.9029	0.603	0.6986	1.37	Supercase-II

Stability studies

The Stability studies of Lovastatin-Xanthan gum Hydrogels at 40 ± 2º C and 75 ± 5% RH and the results were shown in the Table 4.

Table 4: *Stability studies of Lovastatin-Xanthan gum Hydrogels at 40 ± 2º C and 75 ± 5% RH.*

SNO	Test		Specification	Time in Months				
				0	1	2	3	6
1	Morphology		White in color, rough texture	No change in the morpHology				
2	Assay (% w/w)		90-110	100± 0.00	96.18±0.1	95.67±0.1	94.18±0.1	94.1±0.1
3	Dissolution profile							
	Time (hrs)	Limits	Time in months					
			0	1	2	3	6	
	0	O	0	0	0	0	0	
	1	NMT 10%	7.44±0.01	7.44±0.1	7.44±0.1	6.91±0.1	6.85.1±0.1	
	2	10-25%	10.25±0.01	9.05±0.1	9.25±0.1	9.25±0.1	9.25±0.1	
	4	30-50%	49.45±0.1	47.45±0.1	49.5±0.1	49.45±0.1	49.45±0.1	
	8	55-85%	67.11±0.1	67.11±0.1	66.1±0.1	67.11±0.1	67.11±0.1	
	12	NLT 85%	78.11±0.1	78.11±0.1	78.2±0.1	76.11±0.1	75.11±0.1	

DISCUSSION

The surface of the hydrogels observed under Scanning Electron Microscope exhibited a rough network like surface due to the presence of acrylamide, Xanthan gum and crosslinking agent. Swelling is mainly due to the presence of xanthan gum a complex extra cellular polysaccharide. The rate of swelling mainly depends upon the cross linking nature of the hydrogel. The hydrodynamic free volume is high if the gel network is less which in turn lowers the cross linking density. The higher swelling is due to the accommodation of more of the solvent molecules. The swelling rate was found to be different basing on the concentrations of xanthan gum and acryl amide. Due to polymer-polymer interactions and solvent-polymer interactions a mixed phase is observed where a hydrogel gains its maximum of hydrophilicity and swells. It was observed that rate of swelling depends on PH of the medium i.e. high in the phosphate buffer saline compared to distilled water and 0.1 N HCl.

The dissolution studies performed for 12 hours showed that the release of the drug from the hydrogel was found to be complete in 12 hours and proved to have no much difference with the concentrations of Xanthan gum and acryl amide on the release rate. Formulations F1 to F4 showed an acceptable release rate of the drug confirming the optimized concentration of Xanthan gum and acryl amide to be 100 mg. Formulations F5 to F8 showed a varied rate of release of the drug. Formulation F5 showed a release of less than 50% at the end of 12 hours. This can be explained due to the insoluble nature of the drug and nonexistence of soluplus. The gradual increase in the release was found with an increase in the concentration of soluplus from F6 to F8. Formulation F9 containing 100mg of soluplus has no comparable increase in the release of the drug may be due to the entrapment of the drug in the micelles of the soluplus which can be explained as by its amphiphilic nature.

Further the release rates were found to be reduced with the increase in the concentration of cross linker from F 9 t0 F 14. Therefore a lower concentration of the crosslinker would be preferred for the hydrogel formulation. Soluplus also played a pivotal role in the enhancement of solubility of the drug and entrapment in the crosslink networks. Hence F8 might be concluded to be the optimized formula for the preparation of hydrogels. The mechanism of drug release was found to follow zero order kinetics by fickian diffusion mechanism following super case-II transport. The stability studies showed that the hydrogel formulations prepared using Xanthan gum offers good stability to the drug.

CONCLUSION

The hydrogel formulations can be recommended as suitable modified release dosage forms using natural gums like Xanthan gum and novel polymeric solubilizer soluplus for the better industrial applications. With increasing efforts devoted to the controlled molecule release, the applications of hydrogel technology will continue to grow in future.

ACKNOWLEDGEMENTS

The authors are thankful to BASF, the Chemical Company, Germany and Dr. Reddy's Laboratories, Bachupally, Hyderabad, India for providing the gift samples and Prof. Dr. Roopa Karki for extending co-operation during the work.

REFERENCES

1. Peppas NA and Mikos AG. Preparation methods and structure of Hydrogels, "Hydrogels in Medicine and Pharmacy, CRC Press, Boca Raton, FL. 1986; Vol. 1: 1-27
2. Luke M. Greever, Ciaran C. Cooney et al., Characterization and controlled drug release from novel-drug loaded hydrogels. Eur J Pharm. And Biopharm. 2008; 69: 1147-1159.
3. Palapparambil Sunny Gils, Debajyoti Ray and Prafulla Kumar Sahoo, Characteristics of Xanthan gum-based biodegradable superporous hydrogel. Int.J.Biol.Macromolecules. 2009;45: 364-371
4. Shantha KL and Harding DR. Synthesis, Characterization and evaluation of poly lactose acrylate –*N*- vinyl 1, 2-pyrrolidone hydrogels for drug delivery. Eur. Polym. J. 2003; 3963-3970
5. Coviello T, Grassi M, Lapasin R, Marino A and Alhaique F. Scleroglucan/borax: characterization of a novel hydrogel system suitable for drug delivery. Biomaterials 2003; 24:16: 2789-2798.
6. *Michael Lamson, Gale PHillips, Jason Shen et al. Pharmacokinetics of lovastatin extended-release dosage form (Lovastatin XL) in healthy volunteers. Biopharm Drug Disp. 2002; 23:4.143-149.*
7. *Yamamura, T; Sudo, H.; Ishikawa, K.; Yamamoto, A. Familial type I hyperlipoproteinemia caused*

by apolipoprotein C-II deficiency. Atherosclerosis. 1979; 34: 1. 53–65.

8. John C. LaRosa, Jian He, Suma Vupputuri. Effect of Statins on Risk of Coronary Disease: A Meta-analysis of Randomized Controlled Trials. J. American Med. Assoc. 1999; 282: 24: 22-29.

9. JA. Tobert, New developments in lipid-lowering therapy: the role of inhibitors of hydroxy-methylglutaryl-coenzyme A reductase, Circulation. 1987; 76 :3:534-538.

10. Suvakanta dash, Padala Narasimha murthy, Lilakanta nath, Prasanta chowdhury, Kinetic modeling on drug release from Controlled drug delivery systems. Acta Poloniae PHarmaceutica-Dr. Res. 2010; 67:3:217-223.

11. Hoffman, A.S, Hydrogels for biomedical applications. Adv.Drug Delivery Rev. 2002, 43, 3-12.