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ORIGINAL ARTICLE

Formulation And Evaluation of Microbeads Loaded with Lovastatin Using Ionic Gelation Technique

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ABSTRACT
Novel drug delivery system has been reported to upgrade the solubility, efficacy, bioavailability profile to elicit enhanced pharmacological effect. The ongoing work intends to assess the ionic gelation strategy for incorporating microbeads utilizing alginate polymer with the objective to work on the dissolving and solvency characteristics of lovastatin, which is less soluble. The gelation technique was utilized, including sodium alginate filling in as an anionic specialist and calcium chloride ($CaCl_2$) filling in as a cationic specialist. 0.5% w/v polyvinyl alcohol (PVA) was added to 3.0% w/v sodium alginate and 2% w/v polyvinyl pyrrolidine (PVP) was added to 1% w/v calcium chloride ($CaCl_2$). Drug polymer interaction (FTIR), shape and surface structure (SEM), drug content and drug incorporation, and in-vitro drug release were all investigated in the produced microbeads. The use of PVP and PVA resulted in significant improvements in enveloping efficiency, drug-loading, and release characteristics, as demonstrated by the results.
KEYWORDS: Lovastatin, Ionic gelation method, PVP, PVA, Sodium alginate

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INTRODUCTION

Drug delivery is growing zone of the research that is evolving the most. Beads are among the multiparticulate delivery system and are prepared to secure prolonged or sustained drug delivery. It seems to be advantageous in reducing fluctuations in therapeutic range, improve drug stability, prevent or diminish drug degradation and metabolism, decrease dosage frequency and uplift patient compliance. IN fast moving world, a novel dosage form has evolved as move to tackle formulation problems linked with drugs that are sparingly soluble in lipids and water [1-2].

WHO (World Health Organization) also estimated that over 23.6 million people will die by 2030, due to cardiovascular disease [CVD] (WHO, 2012). Hypercholesterolemia is a major contributor to the development of CVD, where the cholesterol deposition takes places in the blood vessel. Lovastatin is a fungal polyketide, which consist of naphthalene ring and lactone ring where lactone ring attaches to 3-hydroxy-3-methylglutaryl-coenzyme to mevalonate through enzyme (HMG-CoA) reductase and hence inhibit development of cholesterol. It belongs to the class of Statins which inhibits the function of HMG-CoA reductase, a rate limiting step in biochemical synthesis of cholesterol. Lovastatin (Mevinolin) was the 1st statin to be approved by USFDA in the year 1987 and synthesized in 1979 [3]. Lovastatin belongs to Bio pharmaceutics Classification System (BCS) class II. The plasma concentration reaches maximum in 4hr, it has t1/2 of 3hr and a bioavailability of only 5%. Lovastatin is approached as the drug of choice (DOC) for primary hyperlipidaemias characterized by elevated LDL levels, also for secondary conditions like hypercholesterolemia and diabetes [4-5].

In order to achieve maximum absorption and increased bioavailability of drugs, researchers need to investigate effective and feasible techniques to uplift the dissolution rate and solubility of drug samples. The utilization of polymeric dosage form showed a significant contribution towards the enhancement of innovative methods for pharmaceutical applications [6].

Sodium alginate was taken into consideration in case of bioavailability for the drug delivery application. Sodium alginate is a naturally occurring non-toxic polysaccharide that is derived from brown algae. It is an anionic salt of alginic acid that consists of homopolymer blocks with an alternating sequence of α-L-guluronic and β-D-mannuronic acids [7]. The gelation occurs when an uronic acid crosslink with divalent cations. This phenomenon was utilized to formulate drug-delivering beads. The calcium-alginate beads were made by dropping the drug holding sodium alginate dispersion into divalent cation bath, such as Ca^{+2} [8].

The drug release pattern of the microbead is parallel to the diffusion from gel matrix. In previous works, it has been observed that complexation of natural polymer such as alginate-chitosan lovastatin composites can enhance the release profile of the trapped compound by utilizing the solid dispersion technique [10]. The previous studies also explored improved release characteristics by chondroitin sulfate, a hydrophilic polymer of natural origin, both individually and when in combination with alginate [11-12].

Here we have added PVA in the administration of drug solely for its attributes such as non-toxicity and non-carcinogenicity. PVA is hydrophilic but shows poor stability with water. To overcome the challenge, crosslinking, grafting and copolymerisation is done to insolubilize the PVA. Therefore, blending of polymer can be useful for the preparation of beads with PVA [1].

PVP was used owing to the proved result in safe and better patient compliance in use as drug delivery application. It was seen to impact the drug content, flow property, plasma circulation period and drug size distribution [9-13-14-15].

The aim of this investigation was to formulate microbeads of lovastatin with the intention of enhancing drug release kinetics and minimizing drug leaching. The impact of incorporating PVP into the sodium alginate solution and PVA into the calcium chloride solution, both individually and together, on the drug loading and in-vitro release properties was investigated as formulation variables.

MATERIAL AND METHODS

Sodium alginate (SA) was purchased from Loba Chemie PVTLTD (Mumbai, India). Lovastatin U.S.P was received as a gift sample from M/s Lupin (Maharashtra), polyvinyl pyrrolidine (PVP) and polyvinyl alcohol (PVA) were obtained from Sigma Aldrich chemie GmbH, (Sigma Aldrich, Germany). Calcium chloride ($CaCl_2$) was received from Rankem laboratories (Mumbai, India).

Preparation of Lovastatin-alginate beads

Lovastatin loaded microbeads (LOV-Beads) are made using ionic gelation method **[13].** A 3% w/v sodium alginate solution was prepared by dissolving 750mg of SA in 25 mL of distilled water under mild agitation with heating. 20 mg of Lovastatin was mixed with this sodium alginate blend and agitated using an overhead stirrer (Remi instruments, Mumbai) for 5-10 min at 1000 rpm to achieve homogenous mixture. The mixture was allowed to settle until complete disappearance of air bubbles and subsequently, it was extruded dropwise through a 0.45mm needle into 100 mL of 1% calcium chloride solution (P-1 beads). Similarly ,the P-2 beads were produced by infusing 0.5% w/v PVA (preheated at 90°C for 1h to avoid clogging) to the drug-alginate mixture and extruding it drop wise into 100 mL of 1% $CaCl_2$ solution. To prepare P-3 beads, the drug-alginate mixture was extruded drop wise into a 100 mL solution of 1% $CaCl_2$ and 2% w/v PVP. P-4 beads were procured by adding 0.5% w/v PVA and the drug-alginate mixture to 100 mL of a 1% $CaCl_2$ solution comprising of 2% w/v PVP. In Table -1, the various formulations were tabulated for easy comparison. The gel beads were cured in gelation solution for one hour, filtered and washed multiple times with distilled water. Subsequently, the beads were air-dried in room temperature for 24 hours, followed by drying at 40°C for two hours in a hot air oven.

Fourier transforms infrared measurements (FTIR)

Infrared spectroscopy was engaged for the investigation of the interactions between the polymer and the drug. JASCO FTIR 4100 DOUBLE BEAM SPECTROPHOTOMETER was employed for capturing the IR spectra for pure lovastatin and lovastatin-loaded alginate beads in the mid-infrared range of wavelength 400–4000 cm^{-1}.

Scanning electron microscope (SEM)

To examine the morphology and surface structure of the microbeads, SEM photographs were taken using a JEOL JSM-5610LV instrument. The beads were mounted on metal stubs and coated with a layer of gold prior to imaging.

Determination of microbeads drug content

A number of bead containing a hypothetical load of 20mg of lovastatin was precisely burdened and broken utilizing mortar and pestle and moved into a measuring glass containing 100 mL phosphate buffer with pH of 6.8 and blended involving above stirrer for the total expanding and blasting of the microbeads, then, at that point, the arrangement was sifted through 0.45 μm layer channel and after legitimate

weakening, drug focus in the arrangement was resolved utilizing phosphate buffer with pH of 6.8, utilizing JASCO FTIR 4100 DOUBLE BEAM SPECTROPHOTOMETER at 238 nm. The Percentage drug loading and incorporation efficiency were computed using the following equations [16].

Percent drug loading = (amount of drug in beads/amount of beads) × 100

Percent incorporation efficiency = (%drug loading / %theoretical loading) × 100

In-vitro drug release

The *in-vitro* drug release out of beads is viewed were buffer with pH of 6.8, by the application of a vibrating incubator. In each formulation, a predetermined amount of beads (100 mg) was added to conical flasks consisting of 100 mL of buffer solution and were agitated at 50 rpm and 37°C. At precise time intervals, 5 mL aliquots of the samples were removed, and an equal volume of buffer medium was included in the conical flasks to ensure that the sink condition was maintained throughout the experiment. The filtered aliquots were then analysed for drug content using UV spectrophotometry at 238 nm, after appropriate dilution with corresponding buffer solutions [8].

RESULTS AND DISCUSSION

FTIR studies

The IR study was analysed to examine the interaction between polymer and the drug. FTIR spectral data of pure lovastatin and LOV-beads (P-4) are shown in Figure 1 and Figure 2.The principle absorption peak of LOV showed, C=O stretching of α pyrone ring at 1698 cm-1, C-O stretching of lactone ring at 1223 cm-1, O-H stretching at 3315 cm-1, -OCH2 stretching of cyclic ether at 2966cm-1, -C=C- stretching of unsaturated cyclic diene at 1458 cm-1. The spectra of LOV and LOV-beads showed no discernible alterations, showing that polymers were not engaged in molecular interactions.

SEM analysis

A SEM photograph of formulation (P-4), capturing a single bead at a magnification of 60x, was shown in Figure 3. As seen from the figure, the beads were almost of spherical in shape and have a rough surface.

Drug-loading and incorporation efficiency

The drug-loading and incorporation efficiency of different formulations were displayed in Table 1. Among the various formulations tested, the one containing PVA (0.5% w/v) and PVP (2% w/v) (P-4) exhibited superior drug-loading efficiency.

Effect on drug-loading with PVA and incorporation efficiency

Incorporating PVA into the drug-alginate mixture solution (P-2) led to a significant augmentation in loading of drug and incorporation within the alginate beads, probably because of an elevation in the viscidity of the bead preparation solution. This led to an enhanced capacity of the alginate beads to entrap drug molecules, resulting in a higher loading and incorporation efficiency in contrast to drug-alginate mixture without PVA.

Effect of PVP on drug-loading and incorporation efficiency

Incorporating PVP into the network-linking solution (P-3) yielded in a noteworthy rise in drug-loading and incorporation efficiency, potentially as an outcome of the elevated viscidity of the cross-linking solution caused by PVP. This could obstruct the pores of the alginate beads, thereby impeding the drug leaching into the networking forming solution.

In-vitro drug release

At 37°C, the release patterns of alginate bead was examined in buffer solutions with a pH of 6.8. Figures 4 exhibited the drug discharge in phosphate buffer solutions using multiple formulations. At pH 6.8, there was a significant variance in release data, with the P-4 formulation obtaining the best extended drug release related to other formulations.

40-90% increase in release rate was noted after 8 hours at pH 6.8, as the deprotonation of alginic acid directed to the disintegration of the bead systems and almost completes release of lovastatin as a soluble molecular form. Incorporating PVA into the drug-alginate mixture (P-2) yields in a lowering the pace of lovastatin release, as exhibited in Figure 4. Alginate is a natural water-soluble polymer that contains hydroxyl and carboxyl groups, which make the molecule hydrophilic. In comparison, alginate has a larger hydrated volume than PVA and is a non-linear polymer. Thus, the molecular chains in the mix beads are less minimalistically organized. As an outcome, fluid particles pervade all the more promptly by means of drug alginate beads looked at through drug-alginate globules containing PVA. Accordingly, drug dispersion between the drug alginate globules containing PVA to the outer media is difficult [1].

PVP contains a carbonyl gathering and a sub-atomic load of around a million Da, which is remembered to obstruct PVP dispersion inside the bead. The PVP in the definition causes drug efflux from the 'pseudo-gel layer' covering the bead to change, which balances the release rate [9-15].

TABLE 1: Formulation sketch for Lovastatin-alginate bead

Formulation	Sodium alginate (%)	Drug(mg)	$CaCl_2$	PVA (%)	PVP (%)	Needle (mm)	**Incorporation efficiency %**
P-1	**3.0**	**20.0**	**1.0**			**0.45**	78
P-2	**3.0**	**20.0**	**1.0**		**0.5**	**0.45**	80
P-3	**3.0**	**20.0**	**1.0**	**2.0**		**0.45**	79.9
P-4	**3.0**	**20.0**	**1.0**	**2.0**	**0.5**	**0.45**	85

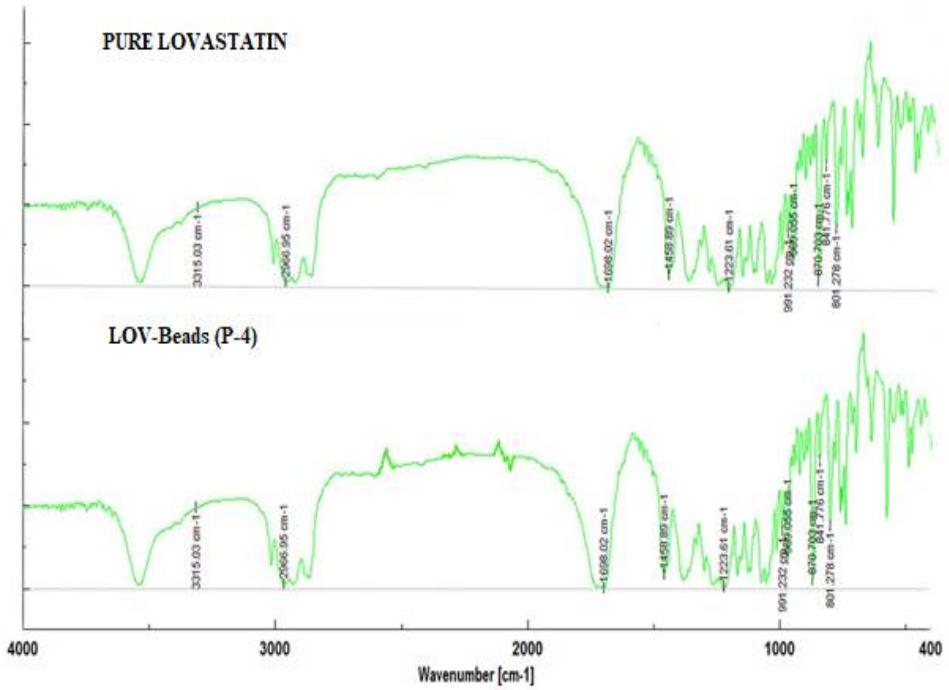

Fig 1 IR spectra of Lovastatin and IR spectra of LOV-Bead (P-4)

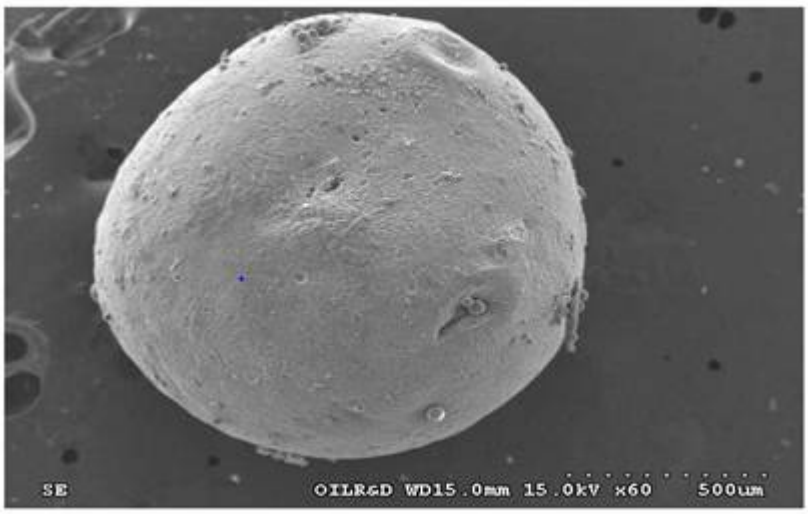

Fig 3 SEM photograph of LOV-beads (P-4) at 60x

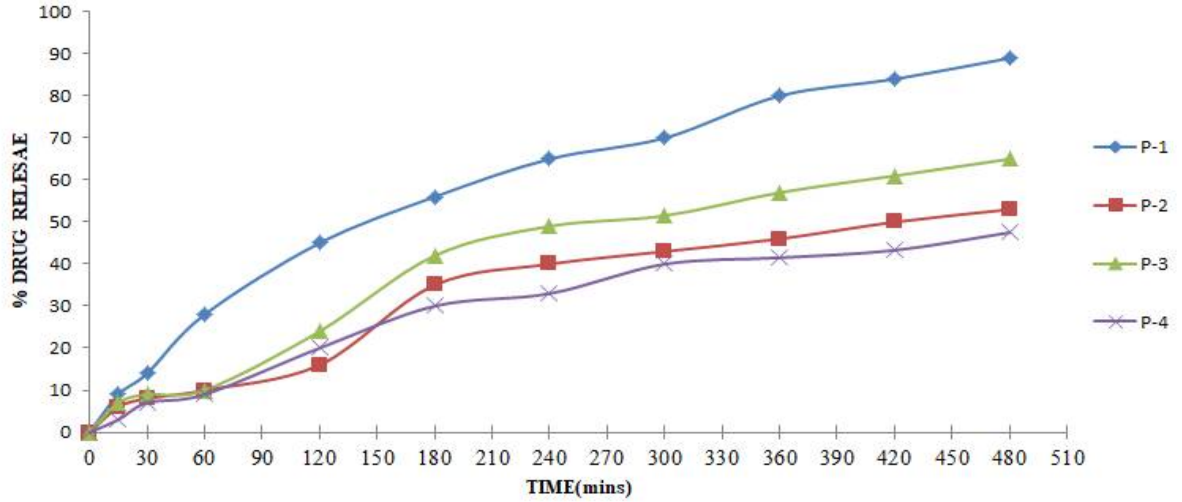

Fig 4 In-vitro drug release at pH 6.8 in formulation P1, P2 , P3 and P4

CONCLUSION

The gelation technique was used to create beads that were loaded with lovastatin. The drug-alginate mixture was supplemented with PVA and the network-forming solution was supplemented by PVP and different formulation variables were examined. The P4 formulation yielded high enveloping efficiency, drug-loading and prolonged drug release. To amplify the in-vitro properties of lovastatin microbeads, PVP and PVA could be approached in the dosage form.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. There are no studies by any of the authors in the article that involved using either human or animal subjects.

ABBREVIATIONS

$CaCl_2$: Calcium chloride; PVP: Polyvinyl pyrrolidine; PVA: Polyvinyl alcohol; SA: Sodium alginate; BCS: Bio pharmaceutics Classification System; CVD: Cardiovascular disease; HMG-CoA :3-hydroxy-3-methylglutaryl-coenzyme A; LOV-beads: Lovastatin loaded sodium alginate beads.

REFERENCES

1. Sanli, O., Nuran, A.Y., Nuran, I. (2007). Release characteristics of diclofenac sodium from poly (vinyl alcohol)/sodium alginate and poly (vinyl alcohol) - grafted poly (acrylamide)/ sodium alginate blend beads. Eur. J. Pharm.Biopharm., 65: pp. 204-214.
2. Majeti, N.V., Kumar, R. (2000). Nano and microparticles as controlled drug delivery devices. J. Pharm Sci.:3(2): pp. 234-258.
3. Zolkiflee, N.F., Redzuan, M., Majeed, A.B.A. (2017). Lovastatin: history, physiochemistry, pharmacokinetics and enhanced solubility. In.J.Pharmc.Sci.Res. vol. 8, no. 1, pp. 90–102.
4. Raja, R.K., Abbulu, K., Malla, S., Manasa, V. (2012). Studies on dissolution enhancement of lovastatin using soluplus by solid dispersion technique. Int. J. Pharm. Sci.; 4: pp.124-128.
5. Neduri, K., Bontha, V.K., Vammula, S.K. (2013). Different techniques to enhance the dissolution rate of lovastatin. formulation and evaluation. Asian J Pharm Clin Res; 6: pp. 56-60.
6. Patel, D.J., Patel, J.K., Pandya, V.M., Patel, R.D. (2010). Effect of formulation variables on nanosuspension containing famotidine prepared by solvent evaporation technique. In. J. Pharm. Sci. Nanotechnol. ; 2: pp. 707-713.
7. Draget, K.I., Philips, G.O., Williams, P.I. (2000). Handbook of Hydrocolloids. Woodhead Publishing, Cambridge: pp. 379-395.
8. Sarangi, B., Mishra, K., Mohanta, G., Manna, P.K. (2019). In vitro-in vivo correlation (IVIVC) of solid lipid nanoparticles loaded with poorly water-soluble drug lovastatin. Eur. Polym. J. 122. 109366.
9. Chan, L.W., Heng, P.W. (1998). Effects of polyvinylpyrrolidone and ethyl cellulose on alginate microspheres prepared by emulsification. J Microencapsul. Jul-Aug;15(4):409-20.

10. Thai H., Chinh, N., Thach, L.T., Mai, T.T., Mai, H.D., Trang, N.T.T, Giang, L.D., Can, M.V., Lam, T.D., Bach, L.G., Ramdass, K., Sathish, C.I., Van, Q.L. (2020). Characterization of chitosan/alginate/lovastatin nanoparticles and investigation of their toxic effects in vitro and in vivo. Sci Rep. Jan 22;10(1): pp. 909.
11. Murata, Y., Miyamoto. E., Kawashima, S. (1996). Additive effect of chondroitin sulfate and chitosan on drug release from calcium-induced alginate gel beads. J. Control. Rel. 38: pp. 108-110.
12. Thingreila, M., Prasanna H., Boruah, D., Pal, M. (2019). Current advances on polysaccharide-based nanoconjugates for efficient and targeted drug delivery in cancer treatment. Polysaccharide Carriers for Drug Delivery, Woodhead Publishing, pp. 413-441.
13. Mannur, V.S., Majik, K.K., Mastiholimath, V., Furtado, D. (2015). Formulation and comparative studies of lovastatin loaded polymeric nanoparticles prepared by ionic gelation and solvent evaporation technique. Int. J. Pharm. Sci. Res. 0975-8232.6(11).4796-03.
14. Ding, G., Adriane, K., Chen, X., Jie, C., Yinfeng, L. (2006). PVP magnetic nanospheres: Biocompatibility, in-vitro and in-vivo bleomycin release. Int. J. Pharm.328: pp. 78-85.
15. Hardy, I.J., Windberg, B.A., Neri, C., Byway, P.V., Booth, S.W., Fitzpatrick, S. (2007). Modulation of drug release kinetics from hydroxypropyl methyl cellulose matrix tablets using polyvinyl pyrrolidone. Int. J. Pharm. 337: pp. 246-253.
16. Al-Kassas, R.S., Al-gohary, O.M., Al-faadhel, M.M. (2007). Controlling of systemic absorption of gliclazide through incorporation into alginate beads. Int. J. Pharm.341; pp. 230–237.