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Formulation and Evaluation of Novel Sericin Nanoparticles for Buccal Delivery of Antihypertensive Drug

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Keywords: nanoparticles (NPs); verapamil Hcl; sericin; In vivo rat model studies; buccal administration;

Abstract:

The aim of this study is to prepare and evaluate sericin nanoparticles (NPs) of Verapamil Hcl which are finally formulated as buccal gel. It was envisaged to formulate the nanoparticles with gelatine, sericin and genipin. Nanoparticles incorporated gel was successfully prepared by using carbopol 934. Nanoparticles were prepared by dessolvation followed by crosslinking. Various parameters like drug content, viscosity, pH, spreadability and drug release were used to obtain the optimized formulation. The sericin nanoparticles incorporated gel shows better fast release as compare to API. The obtained results like drug content, % drug release, buccal permeation study confirmed the potential of nanoparticles as good carrier for buccal administration. The optimised sericin nanoparticles range between 100-400 nm with a zeta potential of 29.91mv showing good stability. Later, we proved our hypothesis through In vitro studies for pharmacokinetics, where we found that NPs had better bioavailability than API. NPs showed protective action and maintained normal tissue architecture. We concluded that nanoparticle form of verapamil had better bioavailability and good pharmacological actions, which might be beneficial for future formulation design perspective.

1. Introduction

Oral mucosal drug delivery is one of method of systemic drug delivery that offers several advantages over both injectable and enteral methods. The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein, and braciocephalic vein into the systemic circulation (Din S. Fakhr et al., 2012). Hypertension or high blood pressure is a chronic medical condition in which the blood pressure in the arteries is elevated. It is classified as either primary (essential) or secondary. About 90-95% of cases are termed "primary hypertension", which refers to high blood pressure for which no medical cause can be found (F. Hong et al., 2008). The remaining 5-10% of cases (Secondary hypertension) is caused by other conditions that affect the kidneys, arteries, heart, or endocrine system. VER is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Which exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells. It is an arterial vasodilator with some venodilator effect, which has been used in the management of angina pectoris, essential hypertension and antiarrhythmia (S. Wiesław et al., 2002; Gondaliya P et al., 2013). The oral absorption of the drug is 90% but its bioavailability approaches only 10–20%, due to extensive first-pass effect mainly in the liver. The buccal mucosa may be a more favorable site of absorption of VER than the digestive tract because it is non-keratinized and strongly supplied with blood, thus it constitutes a relatively large drug absorption area (T. Nagai et al., 1993; H. Junginger et al., 1991). Drug can thus reach the systemic circulation directly through capillary vessels, bypassing the first-pass metabolism in the intestine and liver or avoiding inactivation in the stomach,which in turn

contributes to higher bioavailability parameters after administration of a smaller dose of the drug than in conventional tablets (D. Harris et al., 1992).

2. Materials and methods

Verapamil hydrochloride was obtained as gift sample from M/s Dr. Reddy's Laboratories Ltd., Hyderabad. Sericin was isolated from cacoons. All other reagents used were of analytical grade.

2.1 Isolation of Sericin

Cocoons were cut into small pieces and washed thrice with distilled water. The washed cocoon pieces were mixed with 50ml of distilled water and kept in a reagent bottle and itsmouth was covered with cotton. It was placed in an autoclave at 120^{o} C and 15 pascal pressure for about 30 minutes. After this, the bottle was cooled to room temperature and the contents was transfered in a muslin cloth and pressed to extrude out the sericin and kept in a refrigerator for 24 hours and then lyophilized (Christ Alpha 1-4 lyophilizator, osterodo, Germanay) to get dry powder (Zhu L. et al., 1996; Bhat P.N et al., 2011).

2.2 Preparation of sericin nanoparticles

Nanoparticles were prepared by desolvation followed by crosslinking method. Sericin and gelatin were taken in 50:50 ratios and dissolved in tris-HCl buffer solution of different pH (H. Junginger et al., 1991; F. Hong et al., 2008; Zhu L.J et al., 1996). Sericin, gelatine solution was desolvated with ethanol through continous stirring. At the time of desolvation drug was added in formulation. Desolvated solution was sonicated (Prob sonicator, Labsonic^{R}M, 80 amplitude, 9 cycles) for different time i.e (10, 20 and 30min). After sonication crosslinker (genipin) was added and kept for 12 hr, 24 hr and 36hr for crosslinking. Further formulation was centrifuged (REMI CPR -24) for 10min at 10,000 rpm and pellets were re-dispersed in water and analysed for particle size determination. The sericin nanoparticles of desired particle size range were obtained. The liquid sample may be lyophilized to obtain a powdered product (Doaa A. H etal, 2012).

2.3 Incorporation of optimized nanoparticles into gel

After preparation of sericin nanoparticles, specified quantity of Carbopol 934 was allowed to swell in water. Prepared nanoparticles were incorporated in gel. Finally pH of gel was adjusted to 6.5 with triethanolamine (Shin S etal, 2000).

2.4 Characterization of Nanoparticles (Wantanasiri P etal, 2014)**:**

2.4.1 Particle size analysis

The particle size of nanoparticles was determined with the help of zeta sizer using uv grade cuvettes after treatment on an ultrasonic water bath to break aggregates present in the formulations. The particle size of nanoparticles was measured using zeta sizer (NanoPlus-3).

2.4.2 Determination of Zeta Potential of nanoparticles

The zeta potentials of nanoparticles was measured using zeta sizer (NanoPlus-3). All analysis was performed in triplicate manner.

2.4.3 Scanning electron microscopy (SEM) analysis

Surface morphology of sample was performed by using SEM (Scanning Electron Microscopy) model JSM-6490LV (Jeol, Japan).The prepared nanoparticles were sprinkled on upper side of double sided conductive carbon tape on a metal discs coated with 80 nm of gold/palladium. Analysis of surface was performed at 500x, 1000x and 2000x magnifications.

2.4.4 Entrapment Efficiency

Entrapment efficiency was determined by centrifugation method. 10 ml of formulation mixture was centrifuged (REMI CPR -24) for 15min at 10,000 rpm at 25^{0}C to separate free drug in supernatant. Supernatant was then separated and concentration of free drug (Verapamil HCl) in the supernatant was measured by scanning on UV-visible spectrophotometer at 275nm.

$$\text{E.E \%} = \frac{W_{\text{initial drug}} - W_{\text{free drug}} \times 100}{W_{\text{initial drug}}}$$

2.4.5 X-ray Diffraction (XRD) analysis

The X-ray diffraction patterns of VER, sericin, gelatin and sericin nanoparticles were recorded on a diffractometer.

2.4.6 In-vitro Drug release

In vitro release studies was performed using diffusion membrane . Diffusion membrane was activated with pH 6.8 phosphate buffer for 12 hrs. Dissolution media was freshly prepared by using sodium hydroxide pellets and potassium dihydrogen phosphate. pH was maintained by using pH-meter (NIG-333).

The dissolution apparatus (Veego) was used for *in-vitro* release study. The cylinder were filled with 250ml of phosphate buffer of pH 6.8 and maintained at 37± 2^{0}C temperature. 1ml of formulation was placed in the bag of diffusion membrane, the sac was tied with paddle and was touched the dissolution medium surface. Medium was stirred with 50 rpm and drug release was carried out up to 24 hrs and 5ml sample was withdrawn at time interval of 0, 15 min, 30 min, 1hr, 2hr, 4hr, 8hr, 16hr and 24hr. Samples were analyzed by UV-visible spectrophotometer at a wavelength of 275nm.

2.4.7 Drug Content

1ml of formulation was taken in volumetric flask and 10 ml of 6.8 pH buffer was added in the flask to dissolve the formulation. The solution was kept for stirring for 15

min and after that it was scanned in UV-visible spectrophotometer (Labtronics LT-2910).

2.4.8 Differential scanning calorimetry (DSC)

DSC was performed to conclude the degree of crystallinity of the VER and Sericin in the crystallized dispersions with the help of thermal analysis i.e. melting point and enthalpy.

2.5 Evaluation of gel (Scmolka IV etal, 1972; Jones DS etal, 1997; Karavana SY etal, 2009)

2.5.1 Physical appearance

Physical appearance of the formulations was visually observed which included the colour, homogeneity, consistency and phase separation. The prepared gel formulations were inspected visually for physical properties.

2.5.2 Determination of pH

The pH of gel was determined with the help of digital pH meter (NIG333 New Delhi). 1 g weight of gel was dissolved in 100ml of distilled water and stored for 2 hrs. Then pH was recorded by inserting the probe in gel solution.

2.5.3 Determination of viscosity

The viscosity of gel was determined using digital viscometer (Labsonic LT-730) by using probe (4) at different angular velocity (6, 12, 30, and 60) for 1 minute interval.

2.5.4 Drug content

For determination of drug content of gel, 20mg of gel was dissolved in the 10ml of distilled water. The solution was shaken for 24 hrs on a shaker mixture. After 24 hours the absorbance was taken through UV-visible spectrophotometer (Labtronics Model LT-2910) at 275nm.

2.5.5 In-vitro drug release studies

The release studies of buccal gel was performed with the help of franz diffusion cell (diameter 1.5cm and volume 60ml) through diffusion membrane. The phosphate buffer having pH 6.8 was filled in receptor compartment along with magnetic bead. The fixed amount of gel was put into the donar compartment of modified franz diffusion cell assembly. The buffer was stirred with magnetic stirrer (50 rpm) and inlet and outlet of water supply were properly arranged to maintain the temperature. The samples were withdrawn through the receptor compartment at fixed time intervals upto 12 hours and fixed quantity of fluid was replaced with the phosphate buffer after every withdrawal of sample. Finally the samples were examined through the UV-Visible Spectrophotometer (Labtronics Model LT-2910) at a wavelength of 275nm to determine release of drug (Verapamil HCl) through gel formulation.

2.5.6 Bioadhesive Strength

Bioadhesive strength of the buccal gel was measured on the modified physical balance. The design used for measuring the bioadhesive strength was shown in Figure 3.4. The apparatus consisted of a modified double beam physical balance in which the right pan was replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. This was kept in a beaker filled with phosphate buffer pH 6.8, and then placed below the right side of the balance (Luana Periolia etal, 2004; Yves Jacques etal, 2007**)**.

Goat buccal mucosa was used as a model membrane and phosphate buffer pH 6.8 was used as moistening fluid. The goat buccal mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The underlying mucous membrane was separated using surgical blade and washed thoroughly with buffer media phosphate buffer pH 6.8. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in glass beaker. The beaker was filled with phosphate buffer pH 6.8 up to the upper surface of the goat buccal mucosa to maintain buccal mucosa viability during the experiment (JD Smart etal, 1984; Gu JM etal, 1988**)**.

The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and buccoadhesive gel was establish. A preload of 10 mg was placed on the slide for 5 min (preload time) to established adhesion bonding between buccoadhesive tablet and goat buccal mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added to the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when buccoadhesive gel was detached from the goat buccal mucosa. The weight of water required to detach buccoadhesive gel from buccal mucosa was noted as bioadhesive strength in grams (Park H etal, 1985; Anlar S etal, 1993**).**

2.5.7 Ex-vivo buccal permeation study

The *ex-vivo* buccal permeation study of drug through the goat buccal mucosa was performed using a Franz diffusion cell. Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments. The gel was placed on the mucosa and the compartments were clamped together. The receptor compartment (60 mL capacity) was filled with pH 6.8 and the receptor compartment were kept in shaker water bath. The permeation was performed at 37ºC ± 0.2ºC, and shaker water bath speed of 50 rpm. At predetermined time intervals, 2 mL sample was withdrawn and analyzed using a UV spectrophotometer (Labtronics-LT2010) at 275 nm.

2.6 Stability studies

The optimized formulation of nanoparticles incorporated gel was stored at room temperature and 45^{0}C for a period of 1 month. The sample was assayed for drug content at regular interval of 5 days.

3. Results

3.1 Preparation of calibration curve: (in pH 6.8)

The calibration curve was prepared in 6.8 phosphate buffer using lowry method. The data was regressed to obtain a straight line. The R^2 = 0.987 indicating excellent linearity. The calibration curve was found to obey Beer Lambert `s law in the concentration range studied.

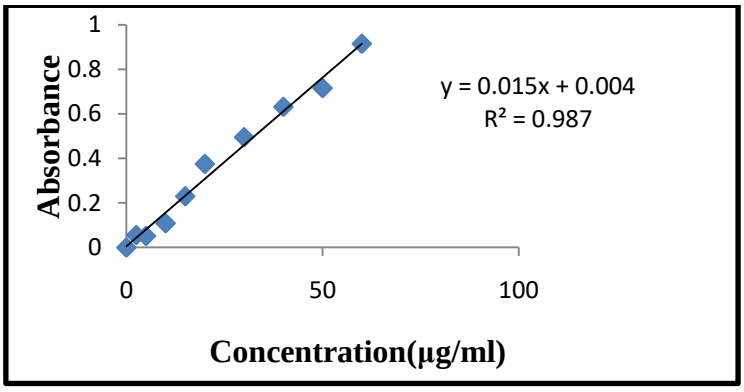


Figure 1: Calibration curve of optimized sample

3.2 Particle size distribution and zeta potential of sericin nanoparticles

The mean particle size and polydispersity index of sericin nanoparticles were of nanoscalar size range indicating successful generation of bio-polymer based nanoparticles via desolvation method. The best suited pH for generation of nanoparticles was found to be neutral pH 7. It may be concluded that the peptide chains of sericin unfold at basic pH and forms smaller particles **Figure1(a).** The zeta potential of the optimised formulation was found to be 29.91 mv **Figure 1(b)** which suggests excellent stability of the nanoparticles.

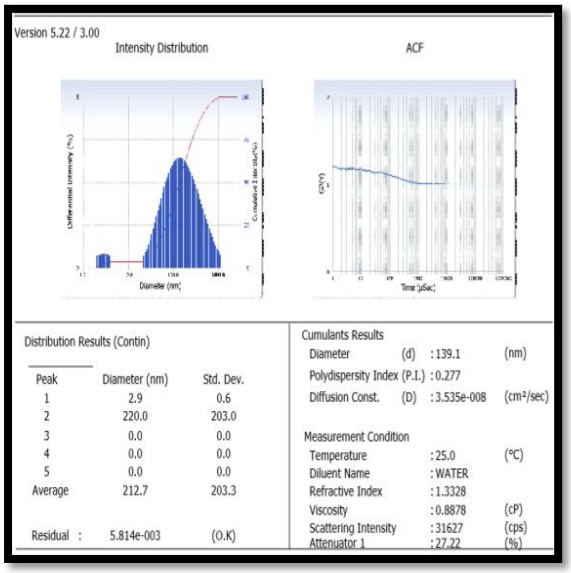


Figure 1(a): Particle size distribution of sericin nanoparticles

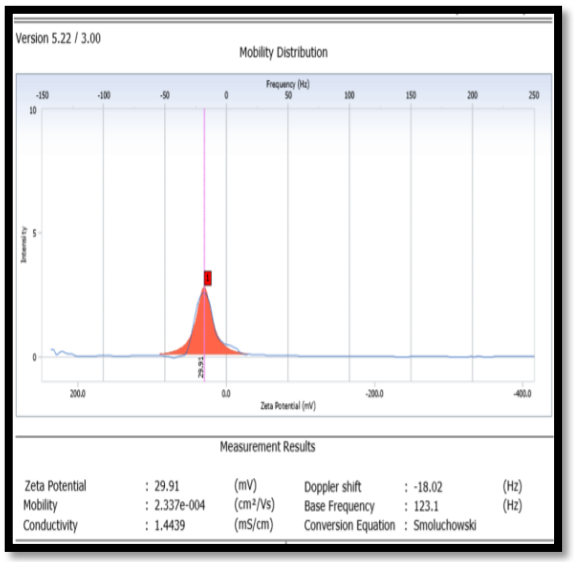
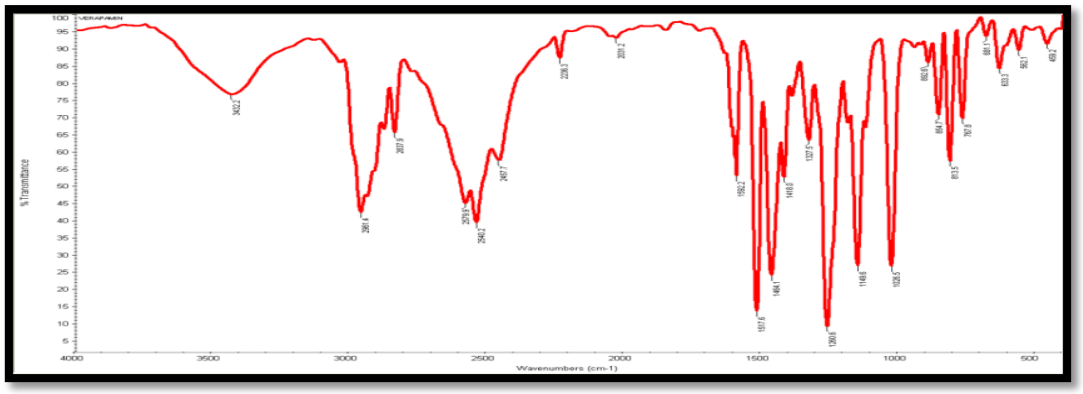


Figure 1(b): Zeta potential of sericin nanoparticles

3.3 FT-IR spectrum of Verapamil hydrochloride drug

The FTIR Spectrum of Verapamil hydrochloride along with carrier (Sericin, gelatin) and selected formulations was taken and the characteristic peaks were compared with the FTIR spectrum of the selected samples. The FTIR peak did not show presence of any additional groups, indicating no chemical reaction between drug and used polymers. IR spectrum showed all prominent peaks of Verapamil which was comparable with standard IR graph. The major IR peak observed in verapamil were (3030&2860) C-H stretching of methyl and methylene groups, (2838) C-H stretching vibration of the methoxy

group, (2800-2300) N-H stretching vibration of the protonated amine, (2227) C=N stetching vibration of the saturated alkyl nitrile, (1597,1518,1462) C-H stretch of benzene ring, (1258) strong C-O stretching vibration of the aromatic ethers **Figure 2(a).**



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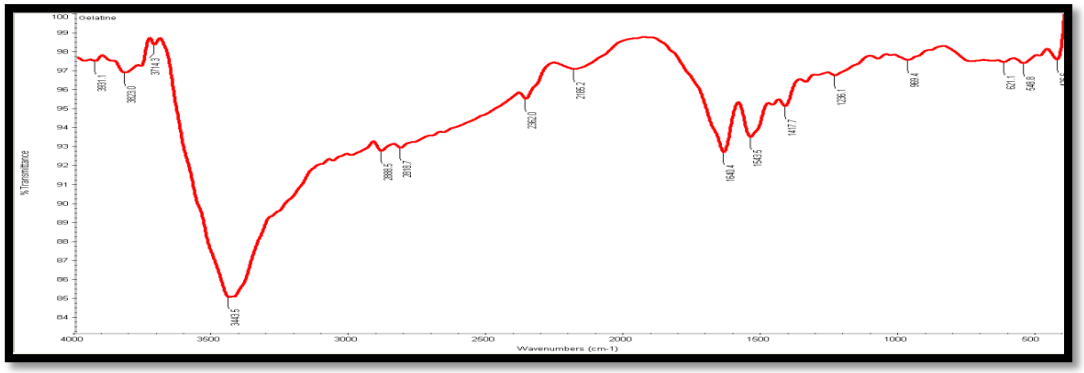

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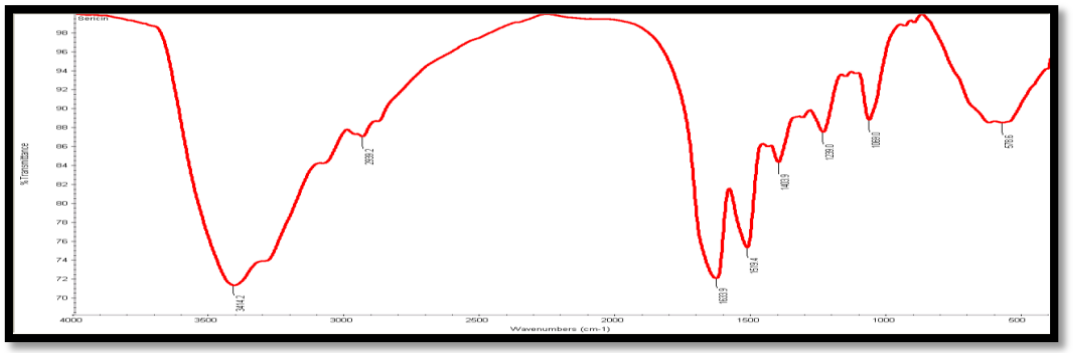

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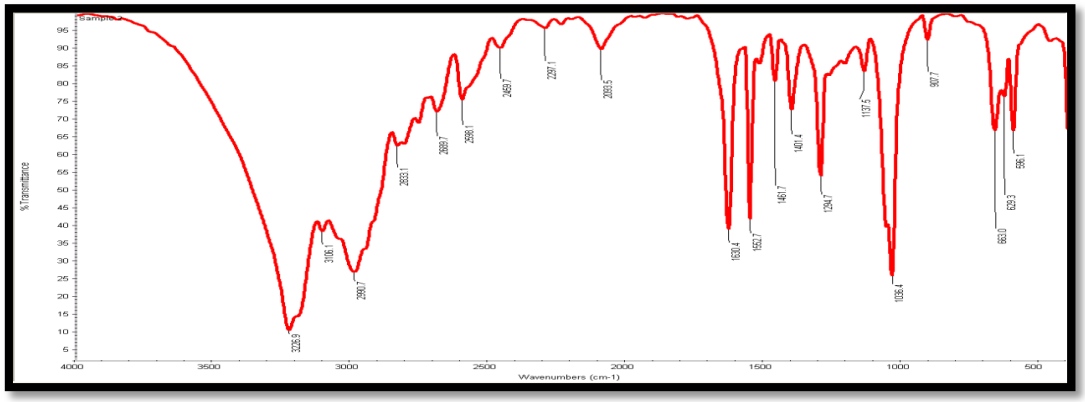


(d)

Figure 2: FTIR of (a)Verapamil HCl, (b)Sericin, (c)Gelatin, (d)Formulation

Table 1: Observation of formulation

NPS	Particle size	PDI	Drug content	Entrapment efficiency	% release (in 24 hr)
NP1	388.6	0.281	61.35	95.16	76.12
NP2	429.7	0.339	54.27	80.1	76.2
NP3	167.3	0.128	48.85	72.26	89.2
NP4	417.3	0.331	55.83	80.13	78.39
NP5	404.8	0.247	62.50	95.06	83.21
NP6	269.7	0.233	69.89	76.86	86.22
NP7	419.5	0.308	44.37	79.9	82.5
NP8	248.3	0.321	65.52	95.23	80.7
NP9	508.5	0.289	81.35	75.93	75.8
NP10	70.9	0.175	69.68	69.93	85.66
NP11	245.8	0.328	63.43	95.16	70.41
NP12	508.5	0.289	81.35	75.93	75.8
NP13	321.6	0.307	86.25	79.86	91.6
NP14	139.1	0.277	80.41	95.33	89.62
NP15	439.2	0.278	51.45	75.73	83.80

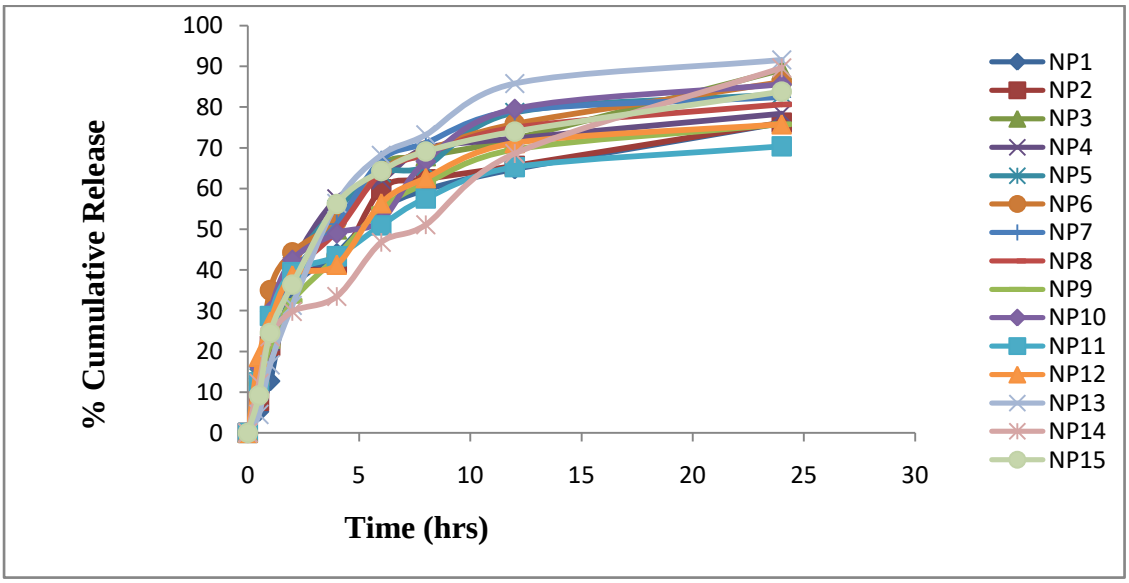


Figure 3: *In-vitro* release profile of Sericin nanoparticle containing Verapamil

3.4 Differential scanning calorimetry(DSC)

DSC thermograms showed that the endothermic melting peak of Sericin nanoparticle was long and shifted when compared to that of the verapamil HCl drug. These results indicated possibility of an alteration of drug to other crystalline forms or to amorphous stage and presence of sericin & gelatin bound to the surface of nanoparticles. Long shifting of melting peak indicated that formulation goes to the molecular level. Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic and exothermic phase transformations). The thermograms for pure VER, sericin, gelatin and nanoparticles are presented in **Figure 3**. The VER showed a melting endotherm at 150.66°C **Figure 3(c)** whereas pure sericin showed a melting endotherm at 134ºC **Figure 3(b).** Thermograms of nanoparticles showed the absence of a verapamil peak **Figure 3(d),** suggesting that sericin & gelatine was completely bound to the surface of drug.

3.5 Shape and Surface morphology

The morphological micrographs of Sericin nanoparticles were examined by SEM as demonstrated in **Figure 4**. It was observed that the Sericin nanoparticles were spongy spherical in shape with smooth surface. Intermolecular attraction and hydrophilic interaction might have played a role in the formation of structure.

3.6 Release kinetics study

The release pattern was fit into Higuchi model and r^2 value was found to be 0.988.

3.7 Characterization of nanoparticle loaded gel

As per the data mentioned in **Table 2** it can be estimated that 1% w/v gel was superior to than 1.5% w/v gel. As it had good adhesiveness strength & spreadability on comparison to 1.5% gel. Its % drug release and drug content better than 1.5% w/v gel.

3.8 Permeation study of optimized gel and API

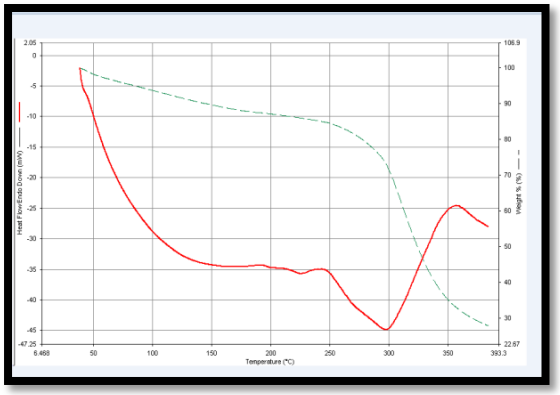
The release study was conducted for 6 hrs to estimate the difference and prove that nanoparticle incorporated gel follow a fast release pattern when compared to API.

3.9 Histopathological studies

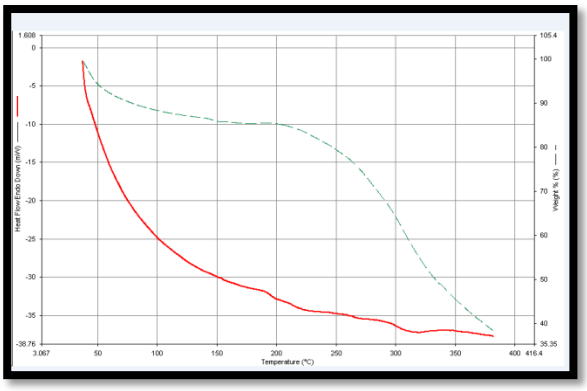
The buccal tissues samples of treated and control (API) were collected and put into 10% formalin solution and progressively dehydrated in different concentration of ethanol solution (70, 80, 95 and 100%) then embedded with paraffin wax under vacuum. The histopathological study showed in **Figure 7(b)** showed no significant effect of optimized formulation on the mucosal tissue. There is no alternation on epithelial layer, thus the formulation assumed to be safe.

3.10 Stability study

The optimized batch G1 was stored in storage vials at 25^0C and 45^0C **Figure 8(a), (b).** The stability study was performed for the period of 30 days. The optimized formulation G1 was analysed for physical appearance, there was no change in physical appearance of optimized formulation. Drug content and drug release was slightly decreased with time at temperature (25^0C) but decreased with high rate at temperature (45^0C).The result of stability study suggests the Verapamil buccal gel can be used for long time and can be kept at room temperature and ambient condition.



(a)



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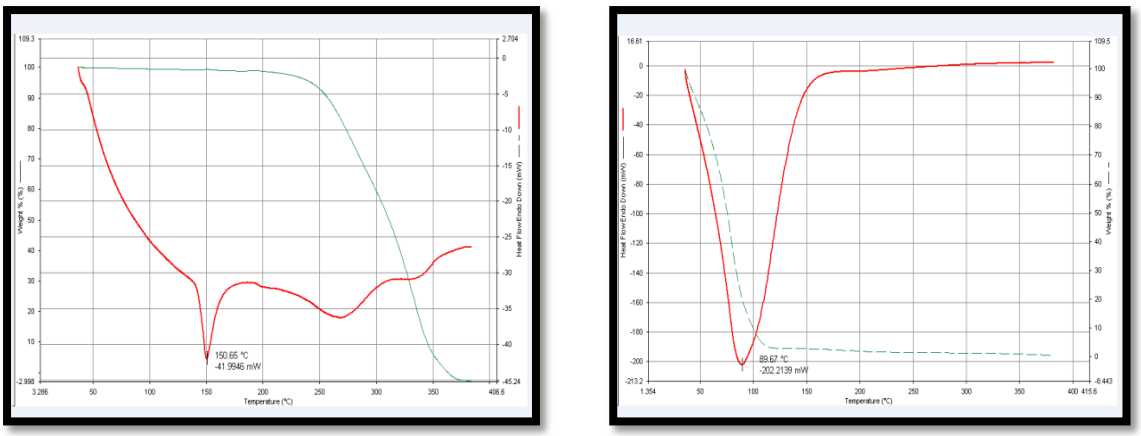

(c) (d)

Figure 3: DSC thermogram of (a)Gelatin, (b)Sericin, (c)Verapamil HCl, (d)Formulation

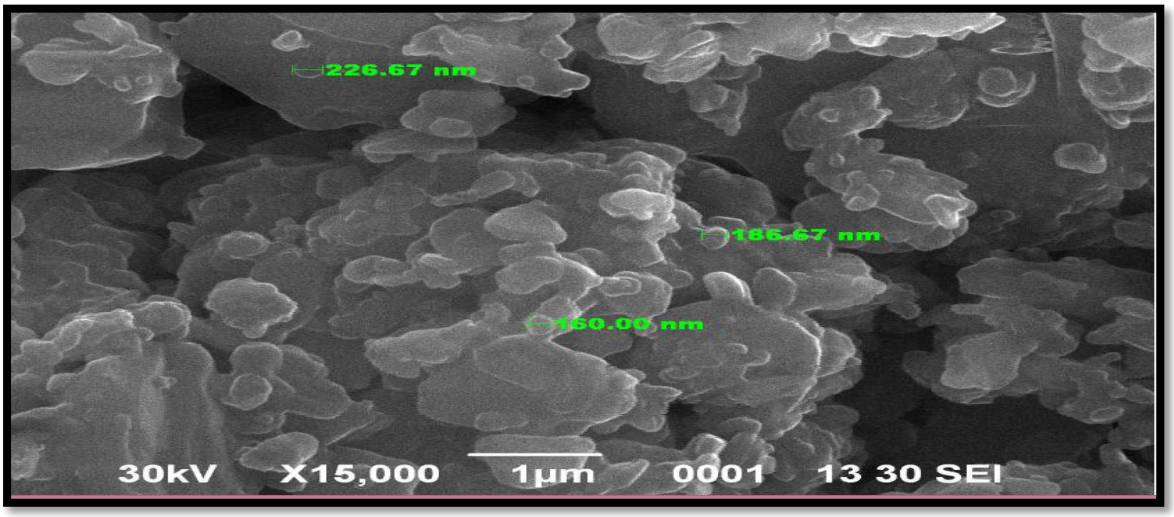

Figure 4: SEM image of Nanoparticles

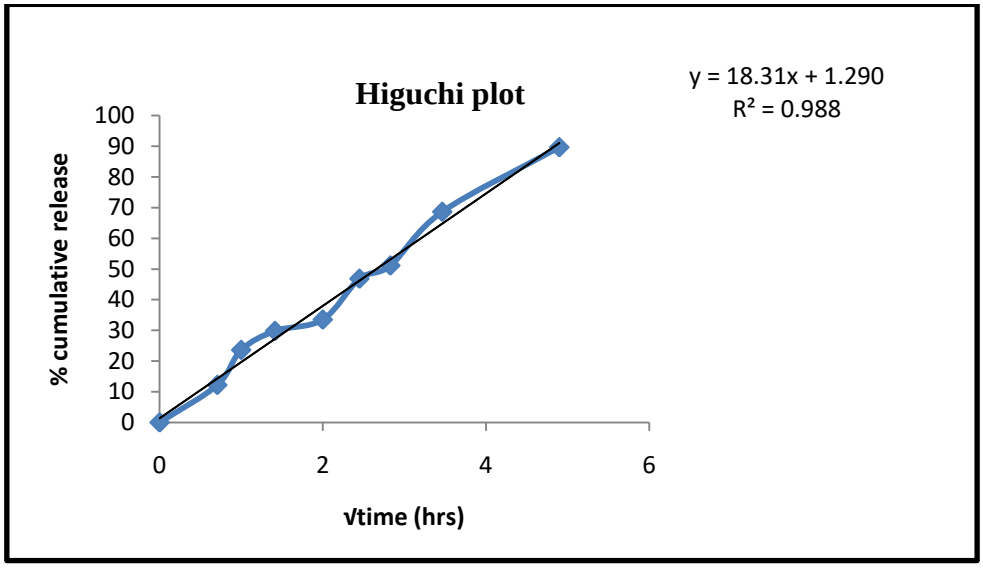

Figure 5- Highuchi plot of optimized formulation

Table 2: Characterization of nanoparticle loaded gel

Parameters	1% (w/v) gel(G1)	1.5%(w/v) gel(G2)
Appearance	Light bluish	Light bluish
pH	6.5	6.7
Extrudability	151.2 mJ	161.8 mJ
Adhesivness	37.66 mJ	32.4 mJ
Hardness	58g	68 g
Viscosity 6rpm	443.5	613.6
Spreadability	3.2 mJ	3.7 mJ
Drug content	79.6 %	77.84 %
% Release	69.17 %	64.26 %

Table 3: Permeation study of optimized gel (G1) and API

Parameters	Formulation (1%w/v gel)	API
Flux	0.4975	0.4255
Permeation coefficient	0.0565	0.04633
% Release(in 6 hrs)	71.13	62.35

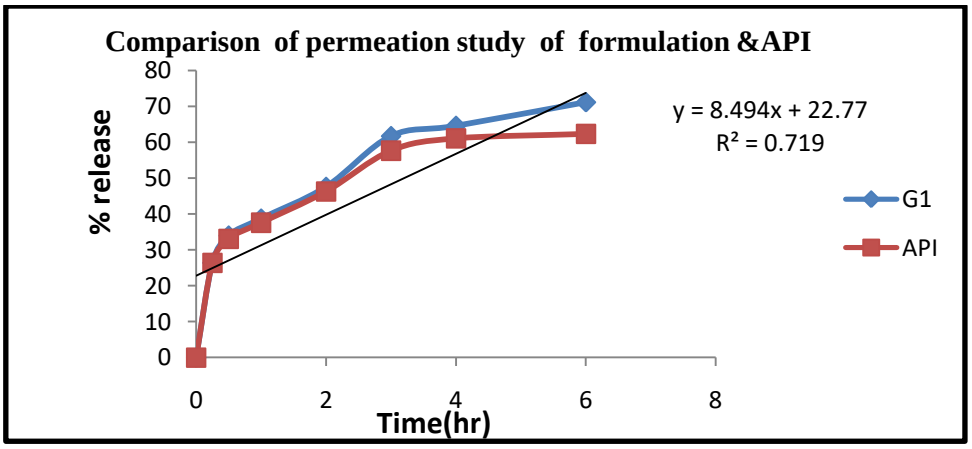

Figure 6: Comparison of permeation study of API and Formulation

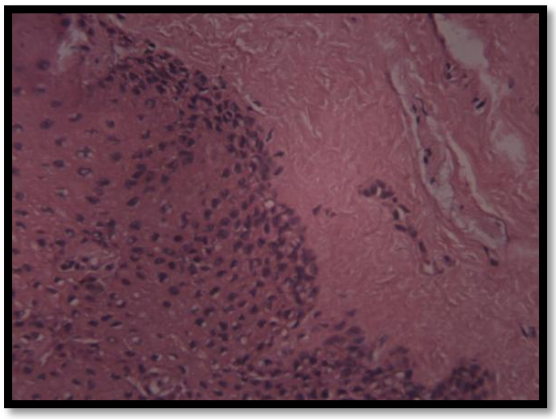

Figure 7(a): Control

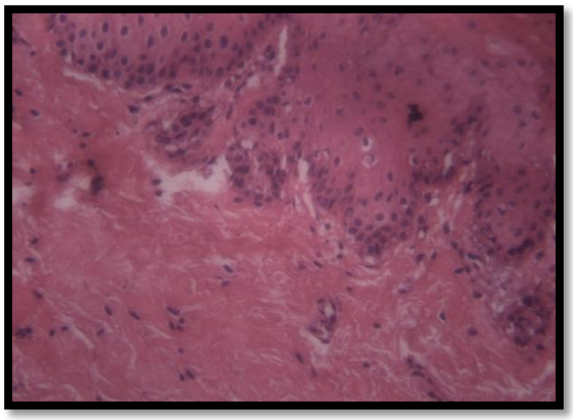

Figure 7(b): Formulation treated

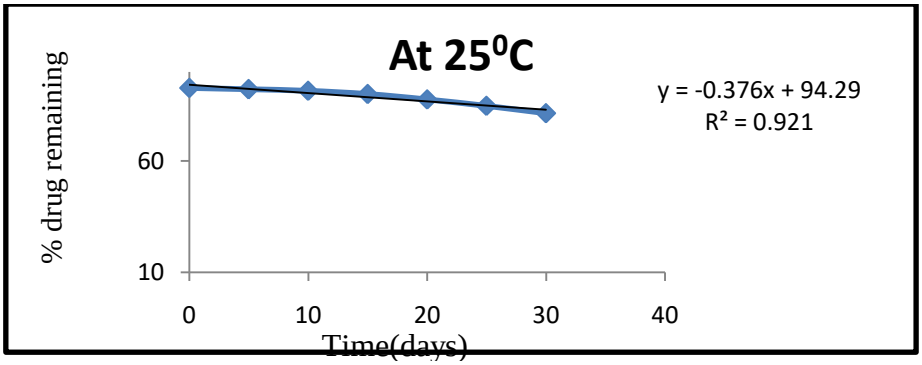

Figure 8(a): Stability studies for optimized batch at 25°C

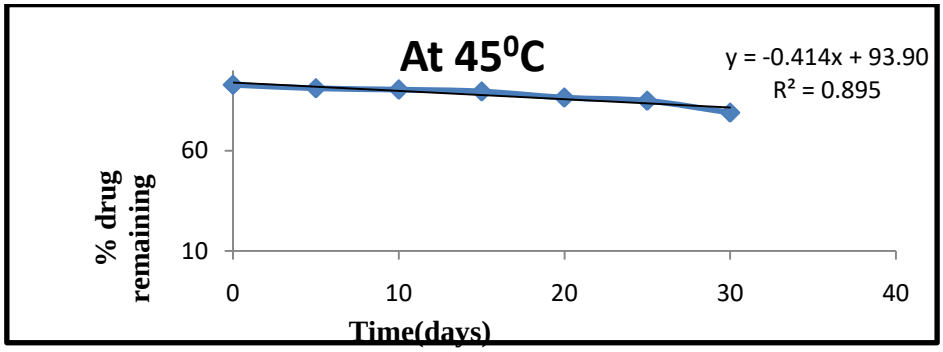

Figure 8(b): Stability studies for optimized batch at 45°C

4. Discussion

The drug was analyzed and identified by the various identification tests given in various literatures. The drug purity was characterized by UV spectroscopy. The solubility of drug was performed and the drug was found soluble in water. The drug was found to follow Beer's Lambert law in the range of 5-60µg/ml and the lambda max value was found to be 275nm in pH 6.8 buffers. Correlation coefficient of calibration curve was found to be 0.987 in pH 6.8 buffer indicating good linearity.

Nanoparticles incorporated gel was successfully prepared by using carbopol 934.The optimized formulation was G1 (1% w/v carbopol 934) obtain **Table 2**.

Various parameters like drug content, viscosity, pH, spreadability and release were used to obtain the optimized formulation. The formulation containing carbopol 934 (1% w/v) was selected as the optimized formulation. The said formulation exhibited the viscosity of 443.5 m.Pa.s (at 6 rpm), pH of 6.5, drug content of 79.6%, and in-vitro release of 69.17% **Table 2**. The drug content of the prepared formulation was within the acceptable range and ensures dose uniformity. Formulation show fast drug release for a period of 6 hours. The clarity of the prepared formulation was found satisfactory. The pH of all formulations was found to be satisfactory in the range of 6.2 to 6.9 **Table 2**, hence the formulation was non-irritating to the buccal mucosa.

It was observed that the best fit kinetic model for the formulation was the Highuchi kinetic model **Figure 5** followed by Korsmeyer and peppas model. The results of stability studies suggest that nanoparticles incorporated gel can be used for long time and has to be kept at room temperature and ambient humidity **Figure 8**.

The sericin nanoparticles incorporated gel shows better fast release as compare to API **Figure 6**. Flux and permeability co-efficient of optimized gel and API was found to be 0.4975, 0.0565 and 0.4255, 0.04633 respectively **Table.3**.

The obtained results like drug content, % drug release, buccal permeation study confirmed the potential of nanoparticles as good carrier for buccal administration.

NPs showed protective action and maintained normal tissue architecture on histopathological studies **Figure 7**.

Finally, we concluded that nanoparticles form of verapamil had better bioavailability and good pharmacological actions, which might be beneficial for future formulation design perspective.

5. Conclusion

Silk sericin (SS) is a glue-like protein from silkworm cocoon, *Bombyx mori*. It can be separated from insoluble protein called "fibroin" in degumming process. With the properties such as antioxidant and moisturizer, it also has been used as antihypertensive substance. Verapamil HCl also used in angina, anti-arrhythmia and in vasodilation.

Sericin acts as anti-oxidant and offers protection against oxidative stress and restores cell viability.

Nanoparticles incorporated gel was successfully prepared by using carbopol 934.The optimized formulation was G1 (1% w/v carbopol 934) which was obtained.

It was observed that the best fit kinetic model for the formulation was the Highuchi kinetic model. The obtained results like drug content, % drug release, buccal permeation study confirmed the potential of nanoparticles as good carrier for buccal administration.

Finally, we concluded that nanoparticles form of verapamil HCl incorporated in gel had better bioavailability and good pharmacological actions, which might be beneficial for future formulation design perspective.

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Conflict of interest
None declared

6. References

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