RESEARCH ARTICLE

Novel eatable silk fibroin gels containing salbutamol sulphate for dysphagic and geriatric patients

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The purpose of this research work is to prepare novel eatable gel formulations with suitable rheological characteristics, which provide a means of administering salbutamol sulphate to dysphagic and geriatric patients. Gels prepared using a natural polymer silk fibroin of different concentrations was subjected for *in vitro* characterization. The effect of concentration of the solution on gelation time, viscosity, and drug release was studied. FTIR and DSC spectra reveal that the drug was found compatible with silk fibroin. TGA curves showed weight loss as the temperature increased. Formulations F3, F4, F6, and F9 had thin, nectar like, honey like, and spoon thick viscosity range respectively, which is considered suitable for dysphagia patients as given by National Dysphagia Diet Task Force. Formulations showed shear thinning pseudoplastic behavior. Based on the concentration and viscosity of the polymer, formulation F9 was found to sustain the release of drug up to 90 min (99.4 ± 0.5%), whereas F3 showed release within 5 min (99.2 ± 2.0%). Mechanism of drug release was found to be anomalous transport. All formulations were found stable after 6 months when kept at refrigerated temperature (4°C – 8°C) and room temperature. It can be concluded that the salbutamol sulphate gels prepared are suitable as vehicles for dysphagic patients.

Key words: *Dysphagia, gels, oral swallowing, silk fibroin*

INTRODUCTION

Oral administration is the most popular route due to ease of ingestion, pain avoidance, no requirement of sterile conditions, less expensive to manufacture and patient compliance. However, tablets, capsules, and liquids, which are used orally are difficult to swallow in case of dysphagia patients. Patients with advanced age cannot easily take tablets or capsules. The irritation or pain resulting from contact of the solid preparation with the oral cavity or with the larynx and pharynx, or a physical injury caused upon rubbing of the solid preparation against mucous membrane can give discomfort to a patient.[1] However, certain modifications are undesirable, such as crushing of the enteric-coated or sustained-release tablet which can lead to adverse events.[2] Crushed tablets are the most frequent cause of obstruction of feeding tubes, which results in increased morbidity and trauma to the patient besides the cost of replacing the tube. This may require surgical intervention.

Dysphagia is a clinical syndrome resulting from a biomechanical disorder defined as "an inability to swallow, or a sensation that solids or liquids do not pass easily from the mouth to the stomach". Swallowing disorders (dysphagia) occur in all age groups, preterm babies to the elderly. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water.[3-5]

Salbutamol Sulphate (SS) is a sympathomimetic amine, which is used as a bronchodilator in the treatment of asthma. Its usual dose is 2 - 4 mg, 3 - 4 times a day.

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Salbutamol sulphate available as tablets and syrups are found difficult for swallowing for dysphagic patients. Regular use of inhalers has been linked to a tendency for candidiasis of throat. Injections cause pain at the site of injection and also needs a trained person to administer.

Thickened liquids play a vital role in reducing risk of aspiration for dysphagia patients. Previous studies have indicated the importance of viscosity as a bolus variable during the swallowing process.[6-7] Dietary professionals work closely with the speech-language pathologist (SLP) to determine the appropriate consistencies of fluid for each patient. A videofluoroscopyswallow study (VFSS) is carried out to look closely at the swallowing process. The VFSS will test your ability to drink safely and comfortably. If you have trouble swallowing, you may be at risk for aspiration. Aspiration occurs when food or drink enters the windpipe, potentially going into the lungs. Aspiration may put you at risk for developing an infection of the lungs, called aspiration pneumonia. Even swallowing problems may also put you at risk for not getting enough liquids or food (dehydration or malnutrition). So based on information from the study, the SLP, and doctor will tell how thick liquids (consistency) should be for you to swallow safely.[8-10]

In 2002, the American Dietetic Association established the National Dysphagia Diet (NDD) guidelines for thickened dietary supplements. This Task Force proposed viscosity ranges for thin, nectar-thick, and honey-thick and spoon thick liquids [Table 1].[11] To ensure safety during oral administration, patients with dysphagia require an appropriate oral dosage form or modification of the dosage form. The objective of this work is to prepare and evaluate eatable dosage form for the treatment of asthma in dysphagia patients using silk fibroin (SF) as polymer.

MATERIALS AND METHODS

Materials

Silk cocoons (CSRTI, Mysore), citric acid monohydrate (Lobachemie, Mumbai), salbutamol sulphate (Cipla India Ltd.), sucralose (J.K. Suralose Ind. Ltd., Delhi), methyl paraben (s d Fine-chem. Ltd., Bombay), propyl paraben (s d Fine-chem. Ltd., Bombay). All other chemicals and reagents used were of analytical grade.

Table 1: Proposed terms and viscosity ranges for DDF

Proposed terms and viscosity ranges for DDF*		
Liquid	**Viscosity range**	
	Pas	**cps**
Thin	0.001-0.05	1-50
Nectar-like	0.051-0.350	51-350
Honey-like	0.351-1.75	351-1,750
Spoon-thick	>1.751	>1,750

*From the national dysphagia diet task force, done at shear rate of 50 s^{-1} at 25°C

Methods

Extraction of fibroin powder from silk cocoons

Before preparation of films, the fibroin used as natural polymer to prepare gels was extracted from raw silk by the following procedure. Fibroin solution was obtained by removing sericin, a gummy binding protein coating the silk fibroin filaments, through the degumming process. Silk cocoons of *Bombyx mori* were cut into small pieces and were boiled in 0.5 wt% Na_2CO_3 solutions at 85°C for three times (30 min each). SF fiber solution without sericin were washed with copious amount of deionized water and allowed to air dry at room temperature. Dried degummed silk were then dissolved in 15 times (v/w) of Ajisawa's reagent ($CaCl_2$/ethanol/water, 1:2:8 mole ratio). The mixture was stirred at 85°C until complete dissolution. The solution was filtered by cotton gauze to remove foreign materials and dialyzed (molecular weight cut-off value of 12000) against running deionized water. The dialysis was ended as the dialysate tested negative for chloride ion by performing silver chloride precipitation test using $AgNO_3$. This solution was then lyophilized with a freeze drier (IIshin Lab. Co. Ltd., korea) to get SF powder, which was kept in desiccator till further use.[12-14]

Preparation of eatable gels from fibroin powder

Different concentrations of gels were prepared by dissolving fibroin powder in distilled water [Table 2]. The pH of the solution was adjusted to 3.2 using 1M citric acid solution drop wise under constant stirring. The solutions were kept undisturbed in glass bottle tightly capped for gelation at 25°C, 55% RH. The obtained gel was stored at refrigerated temperature (4 - 8°C) to prevent putrefaction of protein.[15]

Evaluation of the eatable gels

Determination of gelation time

Gelation time, the time required for the formation of gel from the solution was determined by placing the gel in a 20 ml flat bottomed cylindrical vial. Gelation time was determined when the sample seemed opaque straw yellow and was difficult to fall from the inverted vial.[15]

Appearance and texture evaluation of the gel

Appearance of the gel in terms of transparent and semitransparent was checked by visually observing the gels. Texture of the gel was evaluated in terms of stickiness and grittiness by mildly rubbing the gel between two fingers.[16] Grittiness was also evaluated microscopically (Trinocular microscope, Coslab, Model HL-10) for the presence of particulate matter.[17]

pH of the eatable gel

pH of the solution has influence in the formation of strong gels. Hence, the pH of eatable gel was measured using digital pH meter by dipping the electrodes into the gel at room temperature (25 ± 0.5°C).[18,19]

Table 2: Composition of SF gel formulations

Ingredients (g%)	Formulations prepared at pH 3.2								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
SF	0.4	0.6	0.8	1.0	1.2	1.4	1.8	2.0	2.2
SS	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008
Sucralose	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Strawberry flavor	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004
Methyl paraben	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Propyl paraben	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Citric acid	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

*SF: Silk Fibroin, SS: Salbutamol Sulphate, Q.S: Quantity Sufficient

Syneresis

Syneresis means contraction of the gel upon standing and separation of the water from the gel. Syneresis is more pronounced in the gel where very low concentration of gelling agent is used. Gels were kept under scrutiny for sign of syneresis (25°C, 55% RH and 4°C for 90 days). The eatable gels showing syneresis where rejected and not considered for further studies.[18-20]

Fourier transform infrared spectroscopy (FTIR) studies

Solid pellet technique was used to predict any significant difference in the spectra of SF and salbutamol with SF. Samples was mixed with potassium bromide separately in the ratio 1:100, triturated, and compressed to prepare the pellet. Twenty scans were acquired in the 4000 – 600 cm^{-1} range with a resolution of 4 cm^{-1} using FT-IR spectroscopy (Shimadzu, 8400S, Japan). FT-IR spectrum of SF was compared with FT-IR spectra of silk fibroin-Salbutamol sulphate combination spectra.[21]

Differential scanning calorimeter (DSC) studies

DSC allows the faster evaluation of possible incompatibilities, because it shows changes in appearance, shift of melting endotherms and exotherms, and variation in the corresponding enthalpies of the reaction. 5 mg sample was sealed in aluminum pans under a nitrogen atmosphere at a flow rate of 50 mL/min and DSC (DSC-60, Shimadzu Co., Japan) was performed from ambient temperature to 330°C at the heating rate of 10 C°/min.

Thermal gravimetric analysis (TGA)

The objective of TGA is to measure the change in mass of a sample, as the sample is heated. TGA was performed by using a Shimadzu TGA-50 (Japan) analyzer at a heating rate of 10°C/min in the temperature range of ambient temperature to 1000°C under nitrogen atmosphere (50 mL/min). Known quantity of the sample was taken for the analysis.

Rheological measurements

Gels were prepared according to the viscosity guidelines given by national dysphagia diet task force given in Table 1. Solutions of gelling agents are typically pseudoplastic, exhibiting non-Newtonian flow behavior characterized by decreasing viscosity with increasing shear rate. The influence of polymer content on gel strength was measured using stress controlled rheometer (Anton Paar) MCR 300. Cone-plate geometry (cone diameter 50 mm, cone angle 2°) was used and the experiment was carried out using a shear rate of 50 s^{-1} at room temperature 25°C. Each data points were obtained over duration of 20 s.[22,23]

Drug content and uniformity

Known quantity of gel (5 ml) was dissolved in 50 ml of 0.1N HCl, stirred and allowed to stand for about 1 hr. The solution was diluted (if necessary), filtered through 0.45-μm membrane filter, and analyzed on a double beam UV Spectrometer at 276 nm. A blank solution containing equivalent amount of excipients (without drug) was treated in similar manner as that of the sample. The drug content was calculated using a standard calibration curve. Recovery studies were performed to demonstrate the suitability of the method. Salbutamol sulphate content of all the gels was estimated by withdrawing samples at random from three different sampling points in a single batch of the gel. Three batches were estimated in similar manner. The gels comply with the content uniformity, if not more than one of the values obtained is outside the limits of 85-115% of the average value and none is outside the limits 75-125%.[1]

In vitro release studies

Measurement of the *In vitro* dissolution study from Salbutamol SF gel was carried using USP XXIV dissolution apparatus type II at 37 ± 0.5°C and at 100 rpm. Simulated gastric (pH 1.2) fluid was used as the release medium using 500 ml of pH 1.2 dissolution media. Gels prepared from 10 ml of the polymer solution containing drug was taken in 50 ml disposable syringe. Fixed amount of the gel (5 ml) was pressed out through the syringe into the release test fluid. A 5.0 mL portion of the fluid was removed at suitable intervals and the volume was kept constant by adding the same amount of release medium at the same temperature. The concentration of drug in the samples was determined by UV spectrophotometer at 276 nm. The determination was performed in triplicate and average value was considered.

Drug release kinetics

The drug release profile was fitted into several mathematical models like zero order, first order kinetics, Higuchi and Peppas model to get an insight of release mechanism of the drug from the dosage form.

Stability studies

The prepared gel formulations were stored away from light in high-density polyethylene bottles at 40 ± 2°C / 75 ± 5% RH, room temperature and refrigerated temperature (4 - 8°C) for 6 months. The sampling was done in a 15 day gap up to 6 months and was evaluated for their physical appearance, pH, rheological behavior, and drug release.

RESULTS AND DISCUSSION

Determination of gelation time

The pH of the fibroin solution was adjusted to acidic side to prepare fibroin gel. The adjustment of the pH to the isoelectric point (*PI* = 3.8 – 3.9) accelerated the gelation process and thus the gel was formed within a short period. [24] pH 3.2 was selected for the preparation of gels, as the gel formed near pH 3.2 had a high strength. It can be found that the amount of net electric charges near pH 3.2 is appropriate for the formation of a network structure.[24] It was found that formulations F1 and F2 took more than 5 days for gelation than rest of the formulations [Table 3].

Appearance and texture evaluation of the gel

All the formulated gels were transparent in appearance, non-sticky, and non-gritty in nature as determined visually and by mildly rubbing in between two fingers. The gels taken from different points (15 points) were visualized using microscope [Figure 1]. (A) and (B) in Figure 1 shows presence of particulate matter whereas (C) and (D) shows no presence of particulate matter. A and B were represented here for differentiation purpose; however, those with particulate matter were discarded and gels were re-prepared until there is no presence of particulate matter.

pH and syneresis of the eatable gel

pH and syneresis are interconnected to each other. pH has an influence on syneresis. When pH changes, syneresis was seen. Hence, adjustment of pH plays an important role to prevent syneresis.[1] The pH of the SF gels was found to be 3.2 ± 0.1°C. Syneresis is one of the major problems associated with gels where very low concentration of gelling agent is used. It was found that formulation F1 and F2 showed sign of syneresis [Table 3] which may due to very low concentration of polymer. Hence, F1 and F2 were not considered for further evaluations.

Fourier transform infrared spectroscopy (FTIR) studies

The FTIR spectra are presented in [Figure 2]. The peaks were found at wavelength of 1624.89 (amide I), 1518.02 cm^{-1} (amide II), 1249.01 cm^{-1} (amide III). Amide I (1,700-1,600 cm^{-1}) is mainly related to C=O stretching, amide II (1,540- 1,520 cm^{-1}) is related to N-H bending and C-H stretching vibration, and amide III (1,300-1,220 cm^{-1}) results from in-phase combination of C-N stretching and C=O bending vibration.[14]

Ayub *et al.*,[24] reported Infra-red spectra typical for the gels freeze-dried from 3.5% fibroin solution at various pH. The peak appeared at 1625 cm^{-1} in amide I region for pH 3.8. This peak corresponds to the intermolecular β -structure. The peak obtained in our study, i.e., at pH 3.2 was similar as reported by Ayub *et al.*,[24] hence, it can be said that peak corresponds to intermolecular β-structure.

Differential scanning calorimeter (DSC) studies

DSC thermograms [Figure 3] present two endothermic peaks, one just below 100°C, due to the loss of unbound water and another at 290.5°C attributed to melting/ decomposition of SF chains. Well-oriented silk fibers normally exhibit a decomposition peak located at above 300°C. The decomposition behavior was similar to one observed in Freddi *et al*.[25] Non-oriented silk materials with β-sheet structure usually decompose in the range of 290-295°C and amorphous SF occurs at a lower temperature, normally less than 290°C.[25] A peak at 199.95°C indicates drug peak[26] (Shady *et al*., 2010).

Thermal gravimetric analysis (TGA)

The mass of a sample / weight (%) as a function of temperature is measured [Figure 4]. The initial weight loss at around 80 - 100°C is due to the loss of water, while the second weight loss in a temperature range of 255 – 355°C is associated with the breakdown of side chain groups of amino acid residues, as well the cleavage of peptide bonds.[13]

Rheological measurements

The formulations subjected for rheological measurement at a particular shear rate as given by NDD were tabulated in Table 4. Normal oral swallowing occurs at a shear rate of 50 s^{-1} at room temperature (perhaps the upper end of the shear rate of swallowing).[27] To date, estimation of lingual shear rates for swallowing have been proposed on the basis of perceptual viscosity discrimination studies and there is little consensus, with estimates ranging from 5 to 1000 s^{-1} and a value of 50 s^{-1} most frequently cited.[28]

All samples were found to be shear thinning (they exhibit a reduction in viscosity with increasing shear rate). The viscosity of the formulations is given in the following order: F3 < F4 < F5 < F6 < F7 < F8 < F9. It was found that formulation F3 showed viscosity similar to consistency of

Table 3: Gelation time and syneresis of SF gels

Formulations		F1	F2	F3	F4	F5	F6	F7	F8	F9
Gelation time (hrs)		156	120	96	72	60	48	48	36	24
Syneresis	@ 25°C	Yes	Yes	No	No	No	No	No	No	No
	@ 4°C	Yes	Yes	No	No	No	No	No	No	No

'thin-type'. Formulation F4 and F5 showed viscosity similar to consistency of 'nectar-like' and formulation F6 to F8 showed viscosity similar to consistency of 'honey-like'. Lastly, formulation F9 showed viscosity similar to consistency of 'spoon-thick' as specified by NDD guidelines [Table 1].[11] Optimized formulations showing consistency as specified in NDD guidelines were graphically represented in Figure 5.

Drug content and uniformity

The content of drug in all the gel formulations was found to be 98.7 ± 0.3%. The gels comply with the content uniformity as none of the samples taken from the formulations shown values outside the limits.

In vitro release rtudies

Optimized formulations were evaluated for drug release [Figure 6]. The release of drug from the formulations depends on the concentration and the viscosity of the formulation.

Based on the concentration and viscosity of the polymer, formulation F9 was found to sustain the release of drug, whereas F3 showed immediate release. It is evident from the Figure 6 that as the concentration of the polymer is increased, the viscosity increased there by the release of drug is retarded and vice versa. Except for formulation F3, there was burst release initially seen for all the formulations, later they sustained for short time with release getting faster in later phase; this shows that as long as polymer integrity is retained, the release would be in sustained phase, later the drug starts releases at faster rate.

Drug release kinetics

The drug release profile was fitted into several mathematical models like zero order, first order kinetics, higuchi and peppas model to get an insight of release mechanism of the drug from the dosage form. All the formulations showed good fit for first-order release kinetics with correlation coefficient of 0.992 - 0.998. For all the formulations, the values of diffusional exponent *'n'* obtained from the slopes of the fitted Korsemeyer–Peppas model was found between 0.5918 - 0.7204, suggesting that combination of passive diffusion (Fickian diffusion) and erosion was the drug release controlling mechanism. When $n \leq 0.45$ indicates fickian (case I) release; >0.45 but <0.89 indicates non-fickian (anomalous) release; and >0.89 indicates super case II type of release. Anomalous transport (non-fickian) refers to combination of both diffusion and erosion.[29] Hence, diffusion coupled with erosion may be the mechanism for the drug release from salbutamol sulphate SF gels.

Stability studies

All the prepared gel formulations were found to be stable upon storage for 6 months. No significant change was observed in their physical appearance, pH, rheological properties, drug content, and drug release when stored at refrigerated temperature (4 - 8°C) and room temperature. However, at 40 ± 2°C / 75 ± 5% formulated gels were not stable as its rheological properties, drug content, and release changed drastically.

CONCLUSION

SF gels were prepared using fibroin as a polymer extracted from silk. The gels were transparent in appearance, non-sticky, and non-gritty in nature. The pH of the SF gels was found to be 3.2 ± 0.1°C. FTIR and DSC spectra reveal that the drug was found compatible with silk fibroin. TGA curve showed initial weight loss at around 80 - 100°C, which is due to the loss of

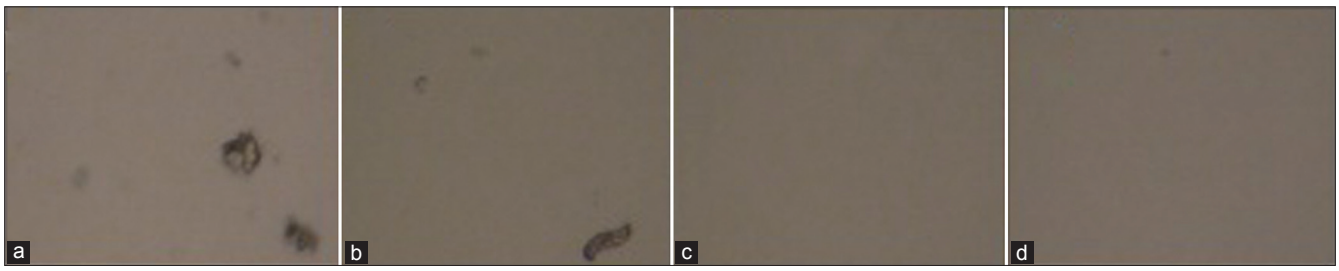

Figure 1: Microscopic representation of the gels showing (a) and (b) with presence of particulate matter (grittiness) and (c) and (d) without presence of particulate matter

Table 4: Viscosity and shear stress of SF gels at 50 s^{-1} shear rate

Parameters	Formulations						
	F3	F4	F5	F6	F7	F8	F9
Shear Stress (Pa)*	2.286 ± 0.010	11.6 ± 0.06	23.85 ± 0.08	39.566 ± 0.011	58.77 ± 0.014	75.73 ± 0.05	89.863 ± 0.09
Viscosity (Pa·s)*	0.0457 ± 0.0005	0.2326 ± 0.0003	0.4776 ± 0.0010	0.7943 ± 0.0015	1.1806 ± 0.0014	1.5180 ± 0.0020	1.8013 ± 0.0018
Speed (1/min)	16.7	16.7	16.7	16.7	16.7	16.7	16.7
Shear rate (1/s)	50	50	50	50	50	50	50

* Mean ± S.D., *n* = 3

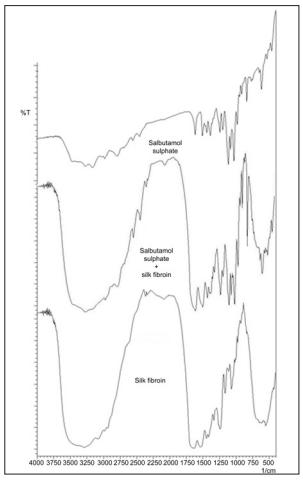

Figure 2: The FTIR spectra of salbutamol, SF gel, with and without salbutamol

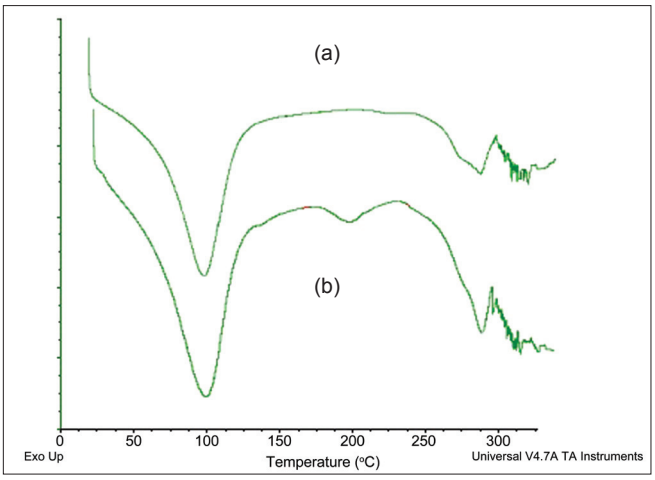

Figure 3: DSC thermograms of SF powder (a) and SF powder with salbutamol (b)

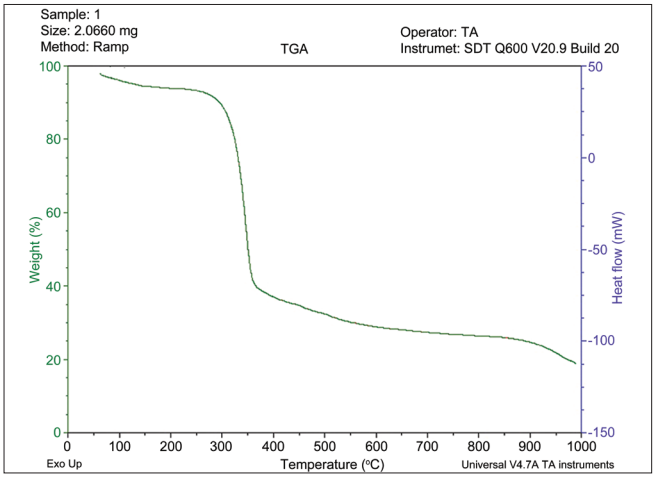

Figure 4: Thermogravimetric curves for SF powder

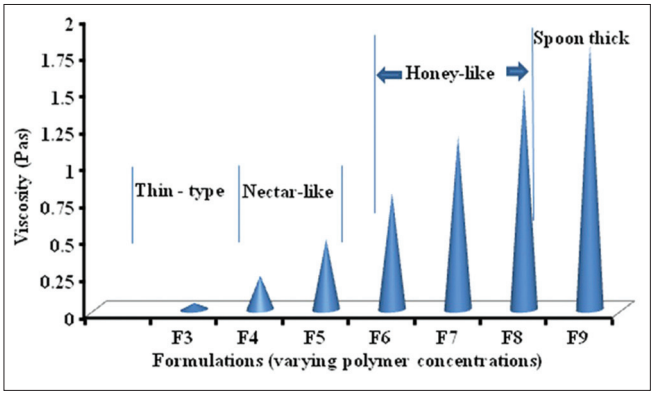

Figure 5: Viscosity chart of optimized formulations showing consistency as specified in NDD guidelines

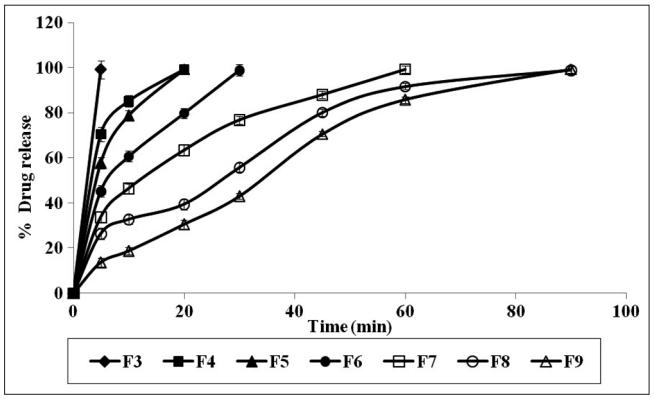

Figure 6: Cumulative % drug release of formulations F1 – F9, *Mean ± S.D., *n* = 3

water, while the second weight loss in a temperature range of 255 – 355°C due to cleavage of peptide bonds. Formulations showed shear thinning pseudoplastic behavior and viscosity consistencies as specified by NDD guidelines. Based on the concentration and viscosity of the polymer, formulation F9 was found to sustain the release of drug (99.4 ± 0.5% up to 90 min), whereas F3 showed immediate release (99.2 ± 2.0% within 5 min). Diffusion coupled with erosion may be the mechanism for the drug release from salbutamol sulphate SF gels. All the prepared gel formulations were found to be stable upon storage for 6 months when stored at refrigerated temperature (4 - 8°C) and room temperature. The results of this study suggest that the SF gels prepared form silk have potential to improve compliance for elderly and dysphagic patients.

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