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Leveraging the Centrifugal Spinning Production Boom for Gel-Like Spun Preparations of Vitamin C for Potential Acne Treatment: From Process-Formulation Optimization to Thermal and *in vitro* Release Characterization

Esra'a Albarahmieh
Assistant Professor
German Jordanian University
Jordan

Bayan Zakaria
Engineering graduate
German Jordanian University

Emad Alzubi
Lecturer
German Jordanian University
Jordan

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Athens Institute for Education and Research
8 Valaoritou Street, Kolonaki, 10671 Athens, Greece
Tel: + 30 210 3634210 Fax: + 30 210 3634209 Email: info@atiner.gr URL: www.atiner.gr
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Esra'a Albarahmieh
Bayan Zakaria
Emad Alzubi

Abstract

Centrifugal spinning plays an increasing role in providing affordable yet successful homogenous fibres for pharmaceutical applications. Therefore, we used our own-simplified spinneret-design to prepare stable gel-like dispersion of vitamin C for potential scar treatment, through incorporation of a cationic resin of Dowex 50X, which may aid in the vitamin-stability. Four formulations were developed for vitamin C encapsulation. Formulations coded as X1 and X2 contained the resin, diethyleneglycol (DEG) and disodium hydrogen orthophosphate 12-hydrate (DiHO) at two levels. Similarly, formulations coded as X3 and X4 contained DiHO at two levels with the use of the resin but with the addition of sorbitol. The spinning method produced uniform-droplets with gel-like nature and an average dimeter of circa ~800 μm from 1-mm diameter perforations. In general, the formulations did not show significant difference in encapsulating vitamin C, with an exception of the X3 formulation, which includes lower level of DiOH and sorbitol and showed superior encapsulation of ~30% of vitamin C.The DSC studies revealed the physical compatibility of the used ingredients and solubilisation role of DiOH or sorbitol on the drug in an amorphous dispersion or solution state, in addition to support the argument of stabilization-effect of the resin on vitamin C. Interestingly, the level of DiOH has shown a controlling-role in terms of drug release. Thus, only formulations with higher level of DiOH (X2 or X4) resulted in complete drug release within 24h. Finally, we demonstrated that sorbitol addition could relatively prolong *in vitro*-drug release. In conclusion, our spinner provides simple-mean to produce gel-like droplets containing vitamin C, in which variation of its ingredients, mainly DiHO and sorbitol can manipulate its encapsulation capacity in the Dowex resin, thus its potential stability, in addition to control the rate and the fraction of the drug to be released under *in vitro* conditions within 24h.

Keywords: Centrifugal spinning, Vitamin C gel, Ion exchange resin, *in vitro* drug release, DSC.

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Introduction

Acne vulgaris is one of the most common dermatological disorders, especially for young adults [1]. Although it may seem to be treatable with proper medication, accompanying scars are usually one of the most complicating problems to be managed [2]. However, there is considerable effort to find solutions for acne scarring, such as application of topical vitamin C.

L-ascorbic acid or vitamin C, is a water-soluble molecule that shows biological functionality and can be found in citrus fruits and some vegetables [3]. Vitamin C proves to have an excellent antioxidant activity, a great potential for wound healing, improvement of scars and anti-inflammatory effects [4-13]. Therefore, it has been recommended to treat acne scars and associated post-inflammatory erythema [14-15]. It is important to note that topically applied L-ascorbic acid has shown a better activity compared to oral administration and in this context, it should remain stable, especially from air and light induced oxidation [16-21]. Therefore, maintaining the stability of L-ascorbic acid is critical for its activity especially that the efficacy is limited up to a concentration of 20% [22].

In this work, cationic ion exchange resin of Dowex 50X was tested to determine whether it can load this vitamin and thus could offer a protection against its oxidative degradation. Dowex 50X is a strong cationic resin, which has been used for ion chromatography applications. As other resins, it has the ability to exchange its counter ions for other counter ions in the surrounding medium, and it can be used to surmount pharmaceutical problems, including poor stability and bitter taste [23-25]. Vitamin C is acidic in nature and it can be deprotonated in a neutral pH, thus it may show an affinity to this positively charged resin while maintaining a stability in the pH range of 3-8 [26].

Herein, we also studied the utilization of a well-known rapid, simple and facile approach of centrifugal spinning [27-28] that we have customized towards creating the basis for a topical gel preparation of vitamin C and Dowex 50X combination, through adjusting its speed and dwelling time with variation of the solubilizers used of diethylene glycol and/or sorbitol. Then we analyzed the compatibility of the developed blends using differential scanning calorimetry thermal characterization coupled with spectrophotochemical investigations of vitamin C encapsulation efficiency in the used resin and its *in vitro* release behaviour from these blends.

Materials and Methodology

Materials

Dowex-50-X 8 100-200 mesh cation exchange resin was purchased from Sigma-Aldrich (USA), L- Ascorbic acid (vitamin C) and diethylene glycol were purchased from Carlo Elba Reagents (France). Disodium hydrogen orthophosphate 12-hydrate and sorbitol were purchased from VWR International Ltd (England).

The rest reagents were analytical grade. Distilled water was used entirely in this work.

Methodology

Preparation and Centrifugal Spinning of Vitamin C Dispersions

A dispersion of vitamin C, added as 15% (w/v) of L-ascorbic acid in distilled water kept at 5◦C, was obtained through mechanical stirring for one hour with Dowex 50X resin and disodium hydrogen orthophosphate 12-hydrate (DiOH) in the specified weight ratio, dissolved in diethylene glycol or diethylene glycol and sorbitol (1:1) mixture. The resulting dispersions were prepared under dark conditions and housed immediately in the used spinneret system. The formulations and processing parameters are presented in Table 1.By incorporating different quantities of DiOH and changing the solvent components, the speed of the spinning system and the dwelling time was varied to empty the filled volume of the spinneret cup and to collect the product on wax paper. A Teflon spinneret, designed as a cylindrical cup (3-cm diameter) with perforations of 1-mm distributed evenly in four sides, was used by fitting onto a chuck of G3P-8 programmable spin coater (Specialty Coating Systems, USA). The resulting bead-like gel droplets were collected on wax paper, which has been used to coat the surrounding pan of this Teflon cup. Square patches of 1cmx1cm dimensions were cut from two layers of sandwiched wax paper containing these droplets and stored at room conditions (~20◦C and 60% RH) for further evaluation. The pH of the preparations were between 6 to 7.5. Placebo formulations (without vitamin C) were obtained using the same respective composition ratios and spinning parameters as shown in Table 1, and were used for comparative purposes.

Table 1. *Vitamin C Tested Formulations and the Used Processing Parameters of Centrifugal Spinning for 50% Solvent(S) in Wt.% Concentrations and Ratios of Solids in 50% by Weigh of the Used Formulations*

Formula Code	Ratios of solids in 50 wt.%			Solvents ratio in 50 wt.%			Speed (rpm)	Time (Sec.)
	Dowex50X	DiOH+	Vitamin C	DEG++	Sorbitol	Distilled water(DW)		
X1	6	1.5	1	35	-	15	750	75
X2	6	3	1	35	-	15	750	90
X3	6	1.5	1	17.5	17.5	15	650	75
X4	6	3	1	17.5	17.5	15	650	90

+Disodium hydrogen orthophosphate 12-hydrate
++Diethylene glycol

Encapsulation of Vitamin C (L-Ascorbic Acid) by the Used Resin (Dowex 50X)

The vitamin C dispersions were also prepared to determine efficiency of the Dowex 50X resin encapsulation of L-ascorbic acid (the drug). Aliquot amounts of these dispersions were filtered through a Buchner funnel. Then the precipitate was washed with 0.2M HcL (3 times the volume of the precipitate)

for not less than 5 minutes and the washing solution was assayed for vitamin C content using and analyzed using UV–Vis Shimadzu UV-1800 spectrophotometer (Shimadzu Corporation, Kyoto, Japan) at 247 nm. All the liquid samples were stored at ~5◦C for one day under dark condition and retested on the next day to confirm the obtained results has not been confused with any instability that would results from photodegrdation of vitamin C from UV irradiation. The encapsulation efficiency was expressed as entrapment percentage of the fraction of the drug detected relative to the initial amount of the drug in the original dispersion.

Thermal Characterization Using Conventional Differential Scanning Calorimetry (cDSC)

Differential scanning calorimetry (DSC) was used to evaluate the compatibility of used ingredients shown in Table 1 and to characterize potential protective effect of the used resin (Dowex 50X) on the oxidative decomposition of vitamin C. Temperature calibration was performed using indium, benzoic acid and n-octadecane. Samples were equilibrated at-70◦C for 5 minutes followed by heating at 10◦C/min. DSC of Q series (20) equipped with a refrigerated cooling system (TA Instruments, USA) was used to obtain data. Nitrogen was used as the purge gas through the DSC cell at a flow rate of 50 mL/min. TA instruments standard pans were used for all calorimetric studies; the mass of each empty sample pan was matched to the mass of the empty reference pan within ±0.05 mg and all the measurements were performed in triplicate. Vitamin C was tested as a powder sample for general characterization. The placebo formulations were compared to their respective medicated formulations loaded with vitamin C, using the product of the spinning process of the gel droplets removed from the wax paper. Data were analysed using TA Universal Analysis Advantage Software v5.5.3.

In Vitro Release Study

In vitro release studies of the resulted gel were performed using six-jacketed vertical Franz diffusion cells (Perme Gear, USA) fitted with cellulose acetate membranes (diffusion area of ~0.7854 cm^2) and sheltered with aluminum foil to avoid light exposure of the gel formulations. The cellulose membranes were moistened with the receptor phase. The receptor phase used was 5 mL of distilled water (pH =6.8±0.2), maintained at 37◦C. The gel beads, which have been freshly prepared and sandwiched in the wax paper of 1cmx1cm dimensions square patch, were removed and mounted on the used membranes in the donor phase. They have been weighed out before and after removal from the waxpaper to ensure uniformity of the tested weights from similar medicated formulation samples of vitamin C on the used cells (3 cells per each formulation). Placebo formulations were tested using the same protocol and no interference was detected at the selected wavelength for vitamin C quantification (3 cells per each formulation tested on the same time of the respective medicated one). Samples (1 mL) were withdrawn at specified time intervals for 24 hours and analyzed using UV–Vis

Shimadzu UV-1800 spectrophotometer (Shimadzu Corporation, Kyoto, Japan) at 265.5nm. All the liquid samples were stored at ~5◦C for one day after the end of the experiment, under dark condition and then retested using UV spectrophotometer to confirm that the obtained results have not been confused with any instability that would results from photodegrdation of vitamin C from UV irradiation.

Results and Discussion

Influence of Formulae Composition on the Used Centrifugal Spinning Parameters

Four formulations were developed for Vitamin C encapsulation. These formulations as illustrated earlier in Table 1 were spun at different parameters. It was noted that manipulating the DiOH content or the solvent used, could affect the ease of the ejection of the dispersion from the Teflon spinneret into gel-like beads with an average diameter of ~800 μm (see Figure 1). Relatively higher DiOH content as in formulations coded as X2 and X4 or inclusion of sorbitol to the solvent system used required a longer spinning time or a slower speed, respectively, thus indicating an increase in the viscosity of the gel.

Figure 1. *Representative Photograph showing Gel-Like Beads Collected from Spun-Formula*

Influence of the Composition on the Physical Compatibility with Vitamin C and its Encapsulation Efficiency

Dowex-50-X 8 100-200 mesh cation exchange resin was investigated for its encapsulation efficiency of the L-ascorbic acid (vitamin C). The entrapment percentage of this drug was achieved up to circa 20% (w/w) in all the formulations except X3 coded formula. This formula which contain relatively the low level of DiOH and sorbitol: DEG mixture, showed the best encapsulation efficiency with an almost 30% (w/w), with no marked difference of the measured pH (~7.6) compared to the X4 formula (pH ~7.5), which has the same composition yet a higher level of DiOH. Therefore, it could be speculated that DiOH in these formulations (X3 or X4) may orchestrate its hosting ability of vitamin C at a

molecular level. In that context, differential scanning calorimetry can be used as a way of Figureuring out how these materials behaved together to generate these beads. In order to do so, two simultaneous measurements were performed for each formulation, I) the formulation before the addition of vitamin C (placebo) and II) the formulation containing vitamin C (medicated as shown in Table 1), thereby evaluation of the physical compatibility can be investigated as a function of different formulation components as shown in Figure 1 through to Figure 5.

It is shown in Figure 2 that studied vitamin C is characterized with a sharp melting temperature, confirming crystalline nature. This melting has been observed around 195.20±0.03◦C (n=3) determined as the peak temperature (Tp). Vitamin C was also associated with an exothermic transition around Tp (230.1◦C±0.35; n=3), which implied a decomposition, most likely due to oxidation.

The main issue to detect drug fate in a multicomponent system is the deconvolution of its thermal events due to overlapped transitions from other components. This is the context in which placebo formulations were spun and thermally characterized as shown in Figure 3 and Figure 5. Therefore, their analysis could be predictive for any other component integration in the region of interest (ROI) of the drug (~195-230◦C) of endothermic or exothermic transitions. In addition, these placebo formulae could be used to identify the effect of changing the level of DiOH or addition of sorbitol in the homogeneity or compatibility of the studied compositions.

In Figure 3, spun formulations that used different levels of DiOH and (DEG: DW) solvent system were compared without the drug (placebo). X1 and X2 formulae have shown none overlapping to similar events detected in the ROI of vitamin C (Figure 2). On the other hand, the relatively lower content of DiOH at X1 composition resulted in multi-melting peaks over the studied temperature range. These peaks started to broaden and to fuse together, especially in the region below 150◦C, when the DiOH content was increased at X2 composition. Thereby, it can be inferred that higher level of the used DiOH may enable better compatibility, implied by broadening of the melting endotherms (lower enthalpy of fusion) and thus possible miscibility. At the same time, Figure 4 illustrated these compositions but with the drug (vitamin C). These medicated formulations did not show the melting endotherm of the drug or its decomposition exotherm. From this, vitamin C was concluded to have an amorphous solid dispersion in these spun-medicated formulations.

Figure 2. *Heat Flow Signal of Vitamin C Heated at 10◦C Min^{-1} in Standard Aluminium Pans*

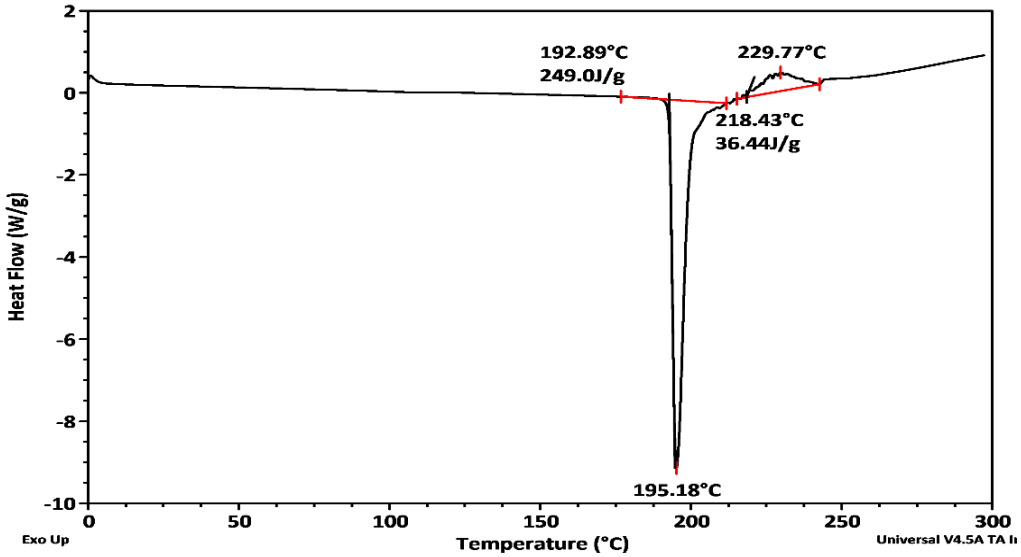


Figure 3. *Heat Flow Signals of Spun Beads without Vitamin C at a Similar Composition found in Table 1 for X1 and X2 Formulations (Termed Here as Placebo) Heated at 10◦C Min^{-1} in Standard Aluminium Pans. X1-Placebo Has a Relatively Lower Content of Dioh compared to X2-Placebo, Both with a Solvent System of DEG: Distilled Water*

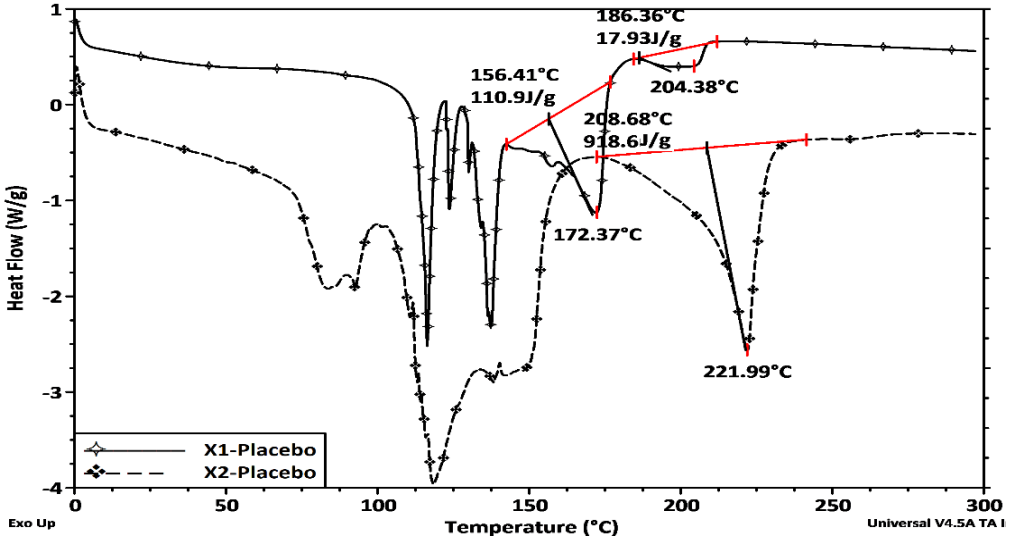
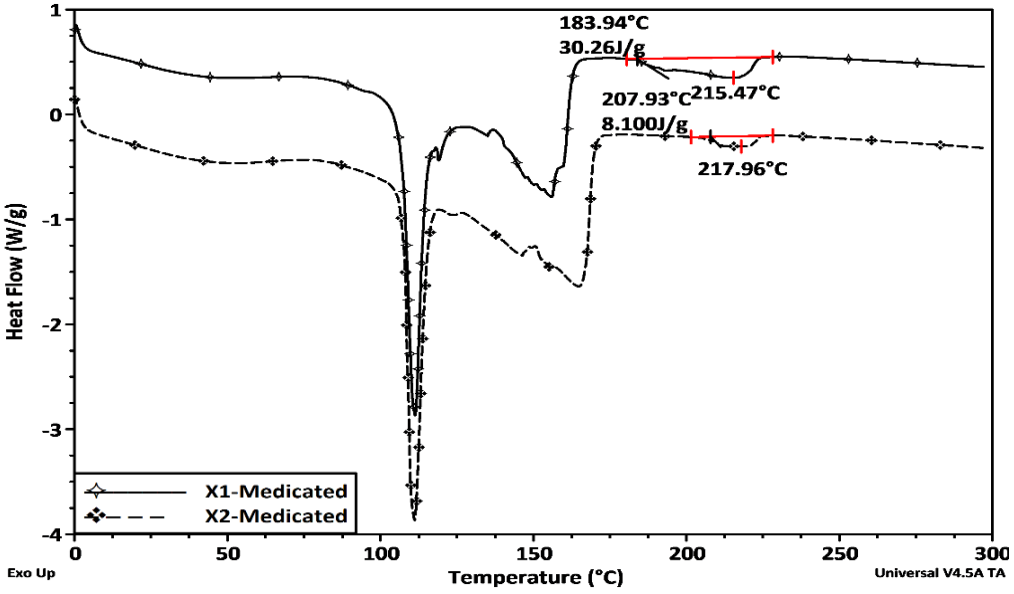


Figure 4. *Heat Flow Signals of Spun Beads with Vitamin C at a Similar Composition Found in Table 1 for X1 And X2 Formulations (Termed Here as Medicated) Heated at 10◦C Min^{-1} in Standard Aluminium Pans. X1-Mediacted Has a Relatively Lower Content of Dioh Compared to X2-Medicated, Both with a Solvent System of DEG: Distilled Water*



In the same manner, X3 and X4 formulations were investigated. In short, X3 and X4 mainly vary in the DiOH content; however, both prepared by the same solvent system of DEG, distilled water and sorbitol. X3 and X4 placebo compositions did not overlap with the ROI anticipated for vitamin C; as illustrated in Figure 5. Before loading the drug (placebo), the formulation of higher level of DiOH (i.e. X4) showed almost a complete miscibility between studied components, implied by general disappearance of melting peaks and detection of only a flattened small endothermic peak (low enthalpy of fusion) around 99◦C (Figure 5). This is consistent with the behaviour observed for X2 formulation in terms of the trend of increasing homogeneity between the studied components at higher content of DiOH. However, it seems that sorbitol addition in this mix furtherly aided in compatibility between the studied components. In addition, X3-placebo formula with a lower level of DiOH, showed major melting endotherms below 150◦C (Figure 5), consistent with studied X1 formulae (Figure 3); though observed less intensively (lower enthalpy of fusion) due to incorporation of sorbitol .

On the other hand, as shown in Figure 6, upon addition of vitamin C at X4 composition, the components showed a certain extent of separation. This was detected in form of a broad multi-dentate melting peak below 150 ◦C. Interestingly, lower level of DiOH at X3 composition mixed well with the vitamin C to form most likely an amorphous solid solution with a representative glass transition temperature (Tg) determined as the mid-point around 267.01±0.2◦C (n=3). However, in both formulations the drug did not show its melting endotherm

nor its decomposition exotherm, thus indicating potential miscibility and oxidative stability; respectively.

Figure 5. *Heat Flow Signals of Spun Beads without Vitamin C at a Similar Composition Found in Table 1 for X3 And X4 Formulations (Termed Here as Placebo) Heated at 10◦C Min^{-1} in Standard Aluminium Pans. X3-Placebo Has a Relatively Lower Content of Dioh compared to X4-Placebo, Both with a Solvent System of DEG: Distilled Water: Sorbitol*

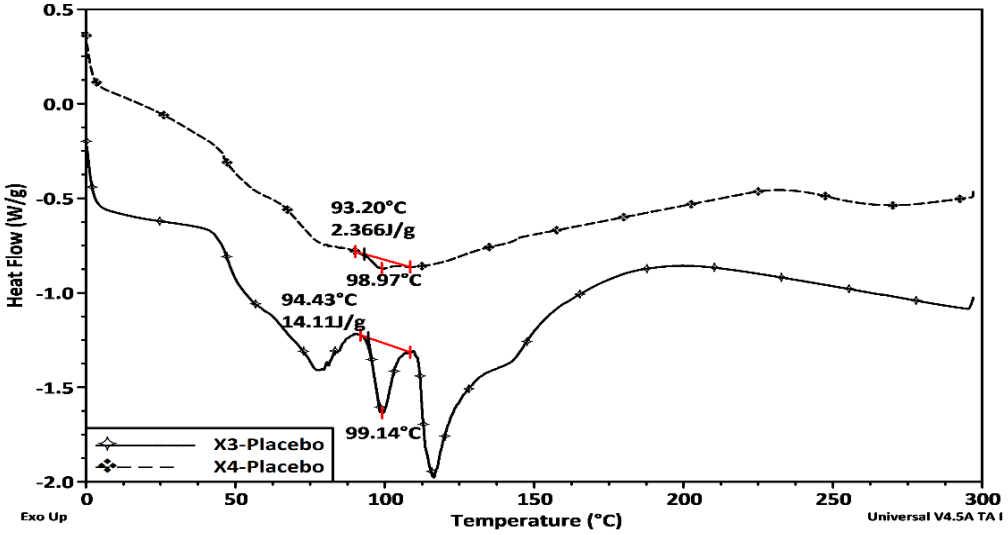
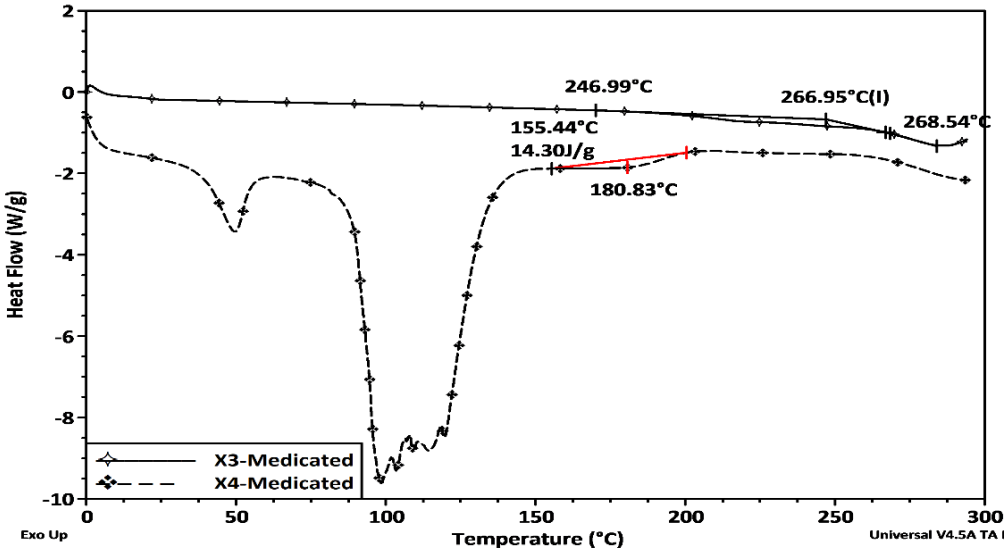


Figure 6. *Heat Flow Signals of Spun Beads with Vitamin C at a Similar Composition Found in Table 1 for X3 and X4 Formulations (Termed Here as Medicated) Heated at 10◦C Min^{-1} in Standard Aluminium Pans. X3- Medicated Has a Relatively Lower Content of Dioh Compared to X4- Medicated, Both with a Solvent System of DEG: Distilled Water: Sorbitol*



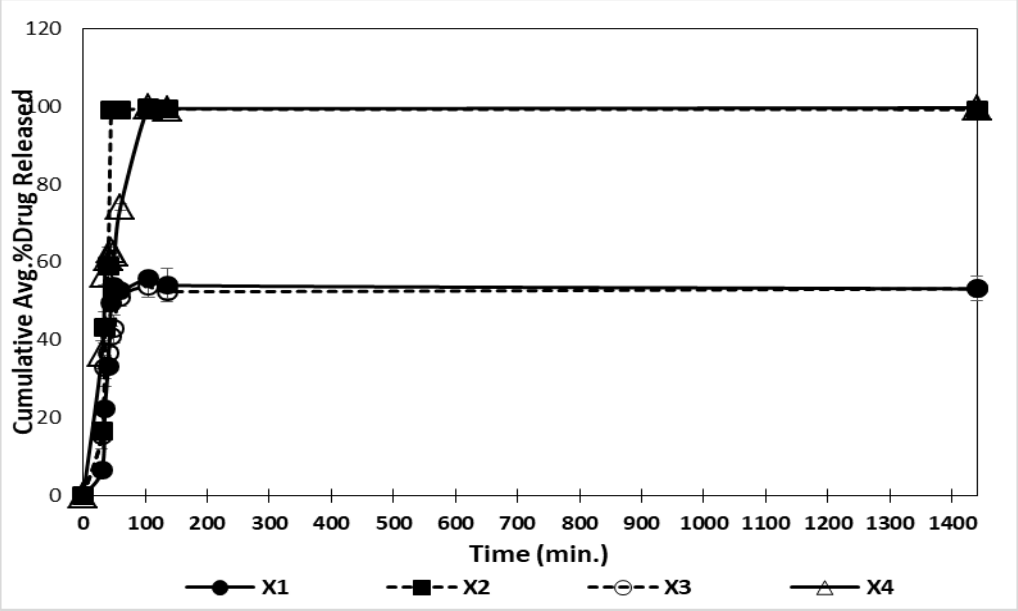
In Vitro Release Study

Through evaluation of compatibility of vitamin C in the spun formulations using differential scanning calorimetry, one would expect a miscibility in the range of 10-11.8 wt.% within the studied compositions. *In vitro* release study of vitamin C may lead to a better understanding of the interplay that could exist between studied potential thermally investigated compatibility and the ability of these formulations to release their drug cargo within a certain period.

As shown in Figure 7, formulations of X1 and X3 resulted in only 50% drug release over one day compared to X2 and X4 formulations, which alternatively resulted in complete drug release within the same period. Therefore, it could be generally argued that formulations in this study with lower level of DiOH, even with variable solvent system used, would not be able to liberate its content of vitamin C within 24 h. On the other hand, using the higher level of DiOH, which was associated with better compatibility between the used placebo components, would result in complete release of vitamin C within one day.

On the other hand, the change of the solvent system through the addition of sorbitol to the DEG and DW at X3 and X4 compositions affected the release rate. While X1 and X2 formulae needed an almost 45 minutes to release ~50% and ~100% of vitamin C; respectively, X3 formula achieved ~50% drug release after one hour and X4 formula needed an almost 105 minutes for complete drug release (~100%). The addition of sorbitol to these spun formulations is thereby having a positive contribution in relative prolongation of vitamin C release.

Figure 7. *Comparative Percent Cumulative Average Release of Vitamin C of Spun-formulations Coded as X1, X2, X3 and X4 (see Table 1 for composition) released across Cellulosic Filter Membranes into Distilled Water (pH =6.8±0.2) at 37±1°C. Each Data Point Represents the mean±S.D. of No Less than Three Measurements*



Conclusions

This work was based on two main premises. We have explored the utilization of centrifugal simple spinning to produce gel-like preparation suitable for topical application of vitamin C. This has been related to the inclusion of a cationic exchange resin to encapsulate vitamin C for enhanced stability. Increased amount of disodium hydrogen orthophosphate 12-hydrate (DiHO) and/or addition of sorbitol affected processing parameters, physical compatibility and performance in terms of vitamin C in vitro release. Our results demonstrated the applicability of the use of simple centrifugal spinning to produce gel of vitamin C through formulation approach. All investigated formulations have shown a potential for increased vitamin C stability from oxidative degradation. In general, increasing in the viscosity, homogeneity of the used ingredients and promoting complete drug release were all possible as a function of increased level of DiOH. This opens new perspective in view of application of these platforms for other drugs and future investigation for vitamin C delivery across the skin. In addition, to underline the importance of resin-encapsulation of vitamin C over extended stability program, that has been best achieved at lower level of DiOH and addition of sorbitol to DEG and DW solvent system. These will be the subsequent phase of this work, where other models of compatibility and possible components' interactions will be also evaluated.

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