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Formulation and assessment of clay - polymer hydrogel based on Georgian bentonite

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Abstract

Bentonite clays are broadly employed in the design of varied drug delivery systems due to their characteristic feature such as adsorption, swelling ability and biocompatibility. Combination polymers with clay particles considerably improve mechanical and physical properties, drug - encapsulation efficiency and controlled release behavior of hybrids comparing with the starting components. One of the priority research areas at the I. Kutateladze Institute of Pharmacochemistry is extension the usage potential of Georgian bentonite clay in pharmacy, medicine, veterinary and cosmetics. Numerous semisolid dosage forms and dry ointments were proposed by the Institute on the bases of preparation Tikha Ascane, obtained from the clay of Askana Deposit (Ozurgeti region of Georgia).

The aim of this study was to examine the suitability of Tikha Ascane as a substrate for the obtaining hybrid material with Sodium alginate (SA) and develop and characterize drug loaded clay/ polymer hydrogel

Optimized formulation for Tikha Ascane/SA hybrids was selected and Nitrofurazone (NFZ) as a model drug was incorporated. The samples were characterized by examining FTIR spectra, morphology, viscosity, pH, homogeneity and appearance. Content of NFZ in hydrogel was determined by HPLC.

FTIR analysis revealed that Tikha Ascane and SA act as a simply physical mixture. Infrared spectra showed that NFZ did not bind strongly to the hybrid material. Microscopic analyses allowed verification of homogeneity of samples. Optimal clay / polymer composites contained Tikha Ascane - SA at the ration of 1:3 (w/w) and 0.2 % w/w incorporated NFZ.

From this work it is cleared that Georgian bentonite clay preparation - Tikha Ascane can be successfully used as a substrate for clay / polymer hybrid material; formulated complex exhibits promising characteristics that allows considering it as a potential drug delivery system. Further studies are on-going for the preparation of TA hybrid material with different polymers.

Keywords: Bentonite clay, Tikha Ascane, SA, clay / polymer hybrid.

Introduction

Clay minerals are extensively used in the preparation of numerous drug delivery systems because of their distinctive properties like biocompatibility, swelling and adsorption ability /1/. Combination clay particles with polymers considerably meliorate characteristics of each single component: for clay mineral - stability of the dispersions and ion exchange behavior, and for the polymer material - mechanical and rheological properties, swelling capacity abilities are modified /2,3/.

One of the priority research areas at the I. Kutateladze Institute of Pharmacochemistry is extension the usage potential of Georgian bentonite clay in pharmacy, medicine, veterinary and cosmetics. Preparation Tikha Ascane, obtained from Askana Deposit (Ozurgeti region, Georgia) clay, is permitted for the medicinal and pharmaceutical application by Georgian healthcare authorities /4/. Several semisolids and dry ointments were proposed on the bases of this preparation /5/.

Alginate is a natural linear copolymer largely utilized in topical drug delivery systems with successful outcomes. Alginate-based gels show attractive adhesive properties and a very good compatibility profile /6/.

In this study we examined the applicability of Tikha Ascane as a substrate for obtaining combined material with Sodium alginate (SA) and formulated and characterized drug loaded clay/ polymer hydrogel.

Material and Methods

Tikha Ascane - Bentonite Clay, was available in the Direction of Pharmaceutical Technology (I. Kutateladze Institute of Pharmacochemistry, TSMU). SA (CAS: 9005-38-3, P Code: 102233388) was purchased from Sigma-Aldrich. All the other chemicals or solvents used were commercially available and of reagent grade. Nitrofurazone (NFZ) (CAS: 59-87-0) was used as a model drug in experiments.

Preparation of the hybrid materials

Samples of clay/alginate hybrids were composed with varied ratios of Tikha Ascane to alginate solution. Specified quantity of bentonite clay was dispersed in ultrapure water and magnetically stirred for 6 h, then certain amount of an alginate aqueous solution (2% w/v) was added. The mixture was stirred at 1000 rpm to ensure homogenous dispersion and allowed to stand in a water bath at 37°C for 24 h. Drug loaded (0.2%) material was prepared by mixing NFZ aqueous solution with the swelled clay; incorporation efficiency and release profile of model drug was analyzed by high-performance liquid chromatography /7/.

Characterization

The formulations were visually observed directly for color, homogeneity, stability and viscosity at preparation.

Swelling potential of Tikha Ascane was analyzed by the standard method according to ASTM D5890 /8/.

All pH measurements were performed at room temperature using a pH meter (MW150, Milwaukee, Romania).

Fourier transform infrared (FT-IR) spectral analyses of samples was conducted to identify the presence of functional groups existing in starting materials. The spectrum was recorded over the wavenumber range of 4000–350 cm−1 using a Jasco 600 FT-IR spectrometer, equipped with a deuterated triglycine sulphate detector (DTGS) with KBr beam splitter.

The structure of the optimized composites was examination under Light microscopy (ZEISS Jeneval Microscope CF250; 3,2 x/0,06 GF planachromat 40x/0,65 GF Planachromat).

The rheological characteristics of the formulations were evaluated by Visco QC 300 Anton Paar rotational viscometer.

The in vitro release assay was performed by a dialysis method with a molecular porous membrane /9/.

NFZ was analyzed by HPLC method (Agilent technologies 1260) using an Eclipse Plus C18 column (5 µm, 4.6 mm x250 mm; 100˚A) for the separation /7/. The mobile phase consisted of pure water (A) and acetonitrile (B). The gradient elution profile had the following components: initial condition 15% B; gradient 15–25% B over 6 min; 25–70% B over 2 min and increased to 90% B and held for 7 min. The flow-rate was 1.0 mL/min and the injection volume was 5 µL. The eluant was monitored by DAD and chromatograms were recorded at the wavelengths 365 and 375 nm. All determinations were performed at 25°C. The samples were dissolved in methanol (HPLC grade) and filtered through a 0.45-µm pore size membrane filter prior to use.

All measurements were conducted in triplicate. Mean values and standard deviations were calculated using Microsoft Excel 2016 (Microsoft Corp.) software.

Results and Discussion

Characterization of raw materials

Swelling is an important characteristic of bentonite clays and depends on several factors such as type (sodium, calcium), solvents, temperature, time, pH. The swelling behavior of Tikha Ascane in ultrapure water and in aqueous solution of NFZ (0.2 %) was compared at room temperature. The swelling kinetics were recorded as a function of time. The swell index was calculated using the formula

$$\text{Swell index} = (V2-V1)/V1 * 100$$

Were - V1 – the volume of 2g sample before swelling;

V2 - the volume of sample after swelling

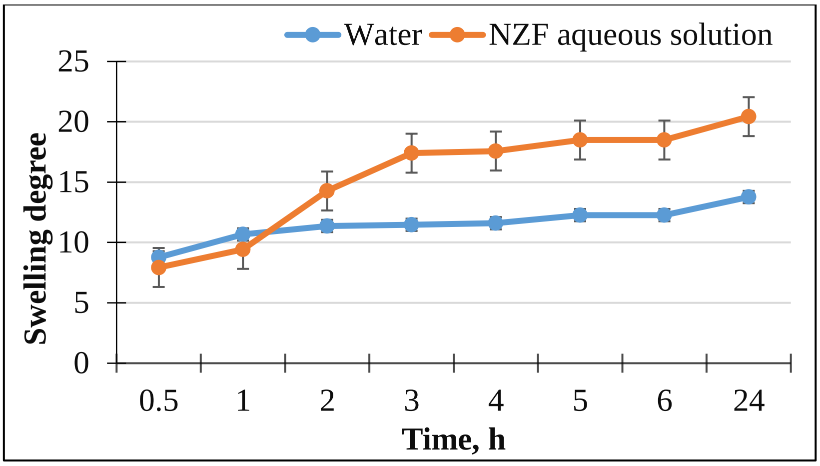

Figure 1. Swelling kinetics of Tikha Ascane in water and NZF aqueous solution

As presented in Fig. 1 Tikha Ascane is characterized by a pronounced time-dependent swelling ability; however increased swelling behavior was detected in NFZ aqueous solution. The average swell index in NFZ solution was 1.52 times higher compared to pure water; this could be explained by intercalation of drug molecules into clay layers.

Selection of optimal composition of Tikha Ascane and SA for the drug delivery system.

Based on our preliminary experiments, in the present study three samples of clay/alginate (1:3; 1:1 and 3:1 w/w) hybrids were selected and characterized. Infrared spectroscopy (IR) is a one of the simplest methods for qualitative analysis of materials in complex matrices. By comparison the IR spectra of the starting compounds with the final product, it is possible to determine if the modification was integrated.

The FTIR spectra of Tikha Ascane, SA and prepared samples are shown in Fig. 2. The bands at 3467 and 3620 cm^{-1} in Tikha Ascane correspond to the stretching vibrations of the hydroxyl group in molecular water and Si –OH, Al–OH bonds correspondingly. The spectrum showed the band at 1640 cm^{-1} (OH vibration in water), 1044, 620 and 528 cm^{-1} due to Si–O stretching in $[SiO_4]^{4-}$ tetrahedra. 912 cm^{-1} corresponds to Al-Al-OH bending vibration and 791 cm^{-1} is for Si-O vibration in SiO_2. The bond at 461 cm^{-1} is due Si–O–Si and Na-AlOH vibrations /6 /.

SA showed asymmetric stretching vibrations at 1627.14 cm^{-1}, due to the carboxyl anion and at 1036 cm^{-1} for oxygen stretching in cyclic ether bridge, the band at 2902 cm^{-1} is assigned to the –CH stretching /10/.

The FTIR spectra of sample containing Tikha Ascane and SA at the ratio of 3:1 (W/W) shows all the characteristic bands of each components and did not illustrate any changes, confirming that Tikha Ascane and SA act as a simply physical mixture.

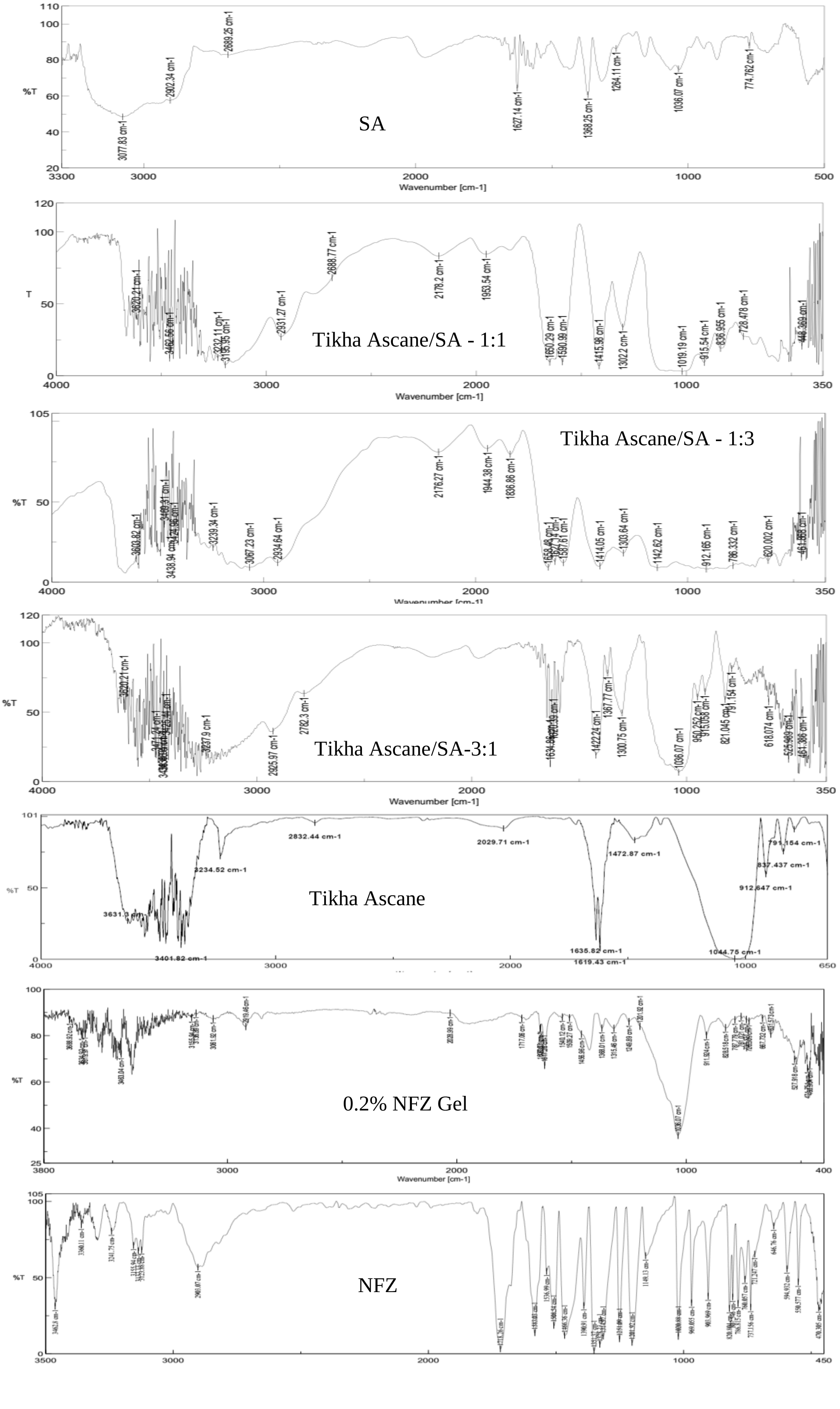

Figure 2. FT/IR spectra of tested samples

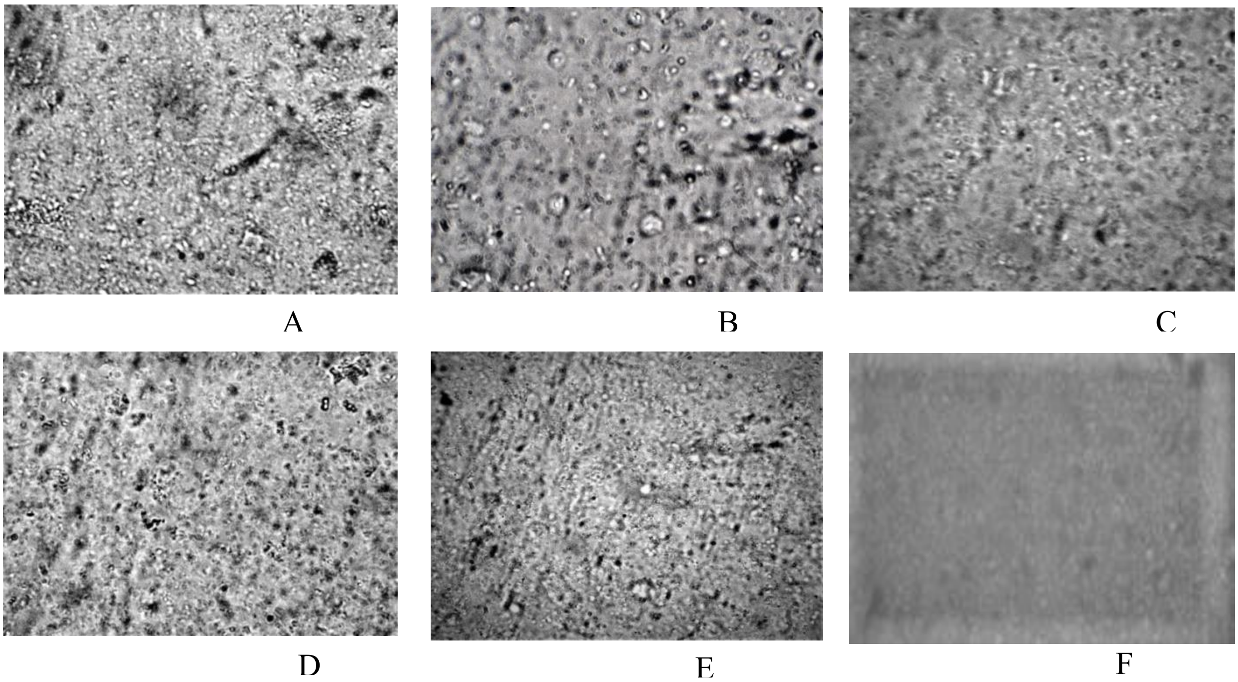

Figure 3. Light microphotographs of tested samples. A – Tikha Ascane; B - SA; C – Tikha Ascane/SA - 1:1; D – Tikha Ascane/SA - 3:1; E- Tikha Ascane/SA - 1:3; F- 0.02% NFZ hydrogel (Tikha Ascane/SA - 3:1)

Light microscopy was employed to examine the surface morphology of the samples. According to the data (Fig. 3A-F), the larger pores is observed in the hybrid material of Tikha Ascane/SA at the ratio of 3:1. These pores likely provide additional area for incorporation by the active substances. The expanding drug loading and also facilitated faster water penetration as a consequence affect the release of the active compounds after application /11/.

Evaluation of hydrogel.

Amount of NFZ (0.2%) was chosen based on the published data /12, 13/. The model drug was incorporated into the selected composite as described in Materials and Methods.

The formulated hydrogel was yellowish, homogenous mass with no signs of phase separation and had a smooth feeling on application. NFZ gel showed a neutral pH of 6.02 ± 0.31.

By comparing the infrared spectra of the hybrid material - Tikha Ascane/SA at 3:1 ratio with or without model drug, it can be noted that there is no displacement of the main peaks (Fig.2). This may suggest that NFZ has not established a strong connection with the components of hydrogel.

The presence and distribution uniformity of NFZ in the formulations were evaluated by light microscopy. The microphotographs of the samples provided in Fig.3 indicate the homogenous and uniform distribution of model drug in gel formulation.

The rheological behavior of the gel was also determined at varying shear stresses using a Brookfield viscometer, being analyzing shear thinning since the apparent viscosity gradually reduces with rising shear stress. The obtained results (Fig. 4) were characteristic of pseudoplastic fluid. It is definitely to note that as the speed increase, the viscosity of the samples decreased. Also, hybrid material

(Tikha Ascane/SA at 3:1) exhibited a lower viscosity than NFZ hydrogel. The incorporation of model drug affects on the structural viscosity of the system and increases this value for drug-loaded formulation.

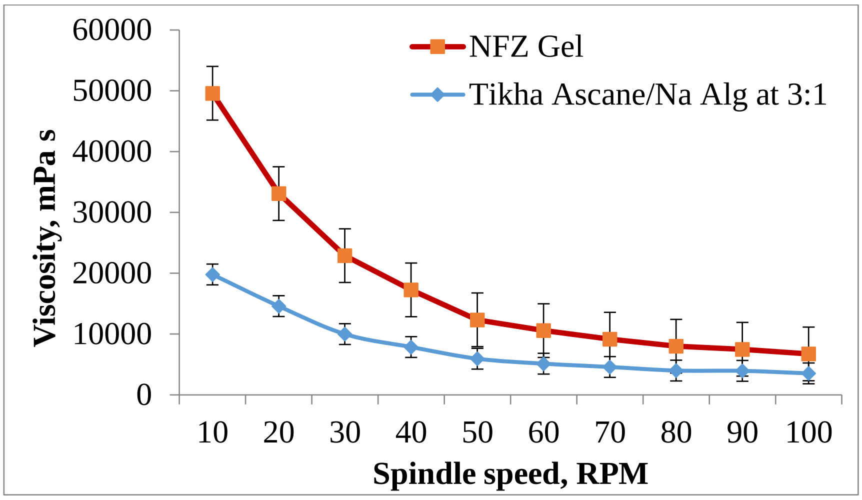

Figure 4. Viscosity data versus RPM of tested formulations with and without NFZ.

NFZ content in the hydrogel was assayed by HPLC method and detected in the range of 0.19-0.21 % /7/.

The release of the active substance from hydrogel was studied by in vitro method using semipermeable membrane. The gel (1 g, exact weight) placed in the dialysis membrane (pore size 12 – 12 kDa) was incubated in purified water at 37° C with stirring at 20 ± 2 rpm. Dialysates were collected after 0, 0.5, 2, 4 and 6 hours and the area was filled with the same volume of water. The active substance was determined by a HPLC method. According to the results obtained, 69.2% of the active substance is released within 6 h.

Conclusion

These results demonstrate that Georgian bentonite clay - preparation Tikha Ascane can be successfully used as a substrate for development clay/polymer hybrid material; formulated complex exhibits promising characteristics that allow consider it as a potential drug delivery system. Further studies are on-going for the preparation of Tikha Ascane hybrid material with different polymers.

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საქართველოს ბენტონიტური თიხისა და პოლიმერის ჰიბრიდის ფუძეზე ჰიდროგელის შემუშავება და შეფასება

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ბენტონიტური თიხები ფართოდ გამოიყენება წამლის მიწოდების სისტემების დიზაინში მათთვის დამახასიათებელი ისეთი უნიკალური თვისებების გამო, როგორიცაა ადსორბირებისა და გაჯირჯვების უნარი, ბიოთავსებადობა. პოლიმერების კომბინაცია თიხის ნაწილაკებთან საგრძნობლად აუმჯობესებს მათ მექანიკურ და ფიზიკურ თვისებებს, წამლის ინკაფსულაციის ხარისხს და კონტროლირებადი გამოთავისუფლების უნარს. ი. ქუთათელაძის ფარმაკოქიმიის ინსტიტუტის კვლევის ერთ-ერთი პრიორიტეტული მიმართულებაა ქართული ბენტონიტური თიხის გამოყენების პოტენციალის გაფართოება ფარმაციაში, მედიცინაში, ვეტერინარიასა და კოსმეტოლოგიაში. ასკანას საბადოს თიხისგან (ოზურგეთის რაიონი, საქართველო) მიღებულ პრეპარატ თიხა ასკანეს საფუძველზე ინსტიტუტის მიერ მოწოდებულია რბილი წამლის ფორმები და მშრალი მალამოები.

წარმოდგენილი კვლევის მიზანი იყო თიხა ასკანის, როგორც სუბსტრატის გამოყენების შესაძლებლობის შესწავლა ნატრიუმის ალგინატთან (ნა) ჰიბრიდული მასალის მისაღებად და მის საფუძველზე ჰიდროგელის შემუშავება და დახასიათება.

შეირჩა თიხა ასკანე / ნა ჰიბრიდის ოპტიმალური რეცეპტურა და მასში ინკორორირებული იქნა ნიტროფურაზონი, როგორც მოდელური წამალი. ნიმუშები ხასიათდებოდა FTIR სპექტრების, მორფოლოგიის, სიბლანტის, pH-ის, ჰომოგენურობის შესწავლით. ნიტროფურაზონის შემცველობა ისაზღვრებოდა. დადგინდა, რომ თიხა-ასკანეს და ნა-ს ინფრაწითელი სპექტრები ჰიბრიდულ მასალაში თითქმის იდენტურია რაც იმის მაჩვენებელია, რომ კომპონენტები ერთმანეთთან ქიმიურად არ არის დაკავშირებული და წარმოადგენს მხოლოდ ფიზიკურ ნარევს. ნიმუშების ერთგვაროვნების შეფასება ჩატარდა მიკროსკოპული ანალიზით. დადგინდა, რომ ჰიბრიდულ მასალაში თიხა ასკანეს და ნა -ის ოპტიმალური თანაფარდობა იყო 3:1 (w/w).

მიღებული შედეგების თანახმად საქართველოს ბენტონიტური თიხა - პრეპარატი თიხა ასკანე შეიძლება წარმატებით გამოყენებული იყოს თიხა/პოლიმერის შემცველი ჰიბრიდული მასალის მისაღებად, რომლის საფუძველზეც შესაძლებელია შემუშავდეს წამლის მიწოდების თანამედროვე სისტემები. მიმდინარეობს შემდგომი კვლევები თიხა ასკანესა და სხვადასხვა პოლიმერების კომბინირებით ჰიბრიდული მასალის შემუშავებისთვის.

საკვანძო სიტყვები: ბენტონიტური თიხა, თიხა-ასკანე, ნატრიუმის ალგინატი, თიხა-პოლიმერული ჰიბრიდი.