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Novel dextran/β-cyclodextrin and dextran macroporous cryogels for topical delivery of curcumin in the treatment of cutaneous T-cell lymphoma

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Cutaneous T-cell lymphoma (CTCL) is a rare disease affecting middle-aged as well as paediatric patients. The early stages might be successfully treated with local medications. As a phytochemical with pleiotropic pharmacological activity including anti-inflammatory and anti-cancer activity curcumin presents a safe alternative to the current state for the early therapy of CTCL, albeit its low water solubility and chemical instability. In this study, original sponge-like cryogels based on dextran/β-cyclodextrin mixture and pure dextran were prepared and assessed as platforms for topical controlled delivery of curcumin. Cryogel carriers with macroporous structure were synthesized by photochemical crosslinking in frozen state and subsequent thawing. Curcumin was successfully loaded into the cryogels by physical adsorption and satisfactory encapsulation efficiency was achieved, especially in the case of dextran/β-cyclodextrin systems (57.8 %). The *in vitro* dissolution tests showed sustained release of the API within 72 h and when dextran/β-cyclodextrin was used as a carrier no burst effect was noticed. In addition, cytotoxicity assessment on both tumour and non-malignant cells was performed whereby comparable activity and selectivity with the free drug were evident. The proposed novel macroporous cryogel systems with curcumin show aptitude for application as controlled dermal drug delivery systems for the treatment of CTCL.

Keywords: Curcumin; CTCL local therapy; cryogel; macroporous sponges; dextran; β-cyclodextrin.

INTRODUCTION

The primary lymphoproliferative disorders are divided into the groups of B-cell and T-cell lymphomas. Although the T-cell lymphomas are not very common a tendency is observed regarding the increase of new patients per year [1]. Cutaneous T-cell lymphomas (CTCL) in particular are characterized with heterogeneous manifestations, mycosis fungoides and Sézary syndrome being the two main forms. They predominantly affect middle-aged or older people (average onset 50-60 years of age) but also children in the first decade of their life can be affected [2]. The disease is considered a rare one according to the European Medicine Agency (EMA) criteria, the prevalence varies between 3 and 6 cases per million [3] and is a life-threatening condition. The early stage CTCL are mainly topically treated while in advanced stages the topical therapy is adjuvant [4] but there are no established protocols neither for adults nor for paediatric patients [2]. The main issues related to the disease are its early and correct diagnosis, as well as the complex and usually chronic therapy [2].

Curcumin is a natural yellow pigment isolated from the plant Curcuma longa. It is practically a polyphenol not soluble in water (about 11 ng/ml) with pleiotropic pharmacological activities including anti-inflammatory, anti-cancer, antioxidant, hypoglycaemic and other effects [5, 6]. Curcumin's mechanism of action is based mainly on the inhibition of the NF-kB signalling pathway related to both inflammation and tumour biology [7]. Other pharmacological targets of this phytochemical include growth factors, protein kinases and other enzymes such as cyclooxygenase 2 and 5 lipoxygenase [8]. The oral application of curcumin, albeit very attractive, has major drawbacks as it is characterized by chemical instability, low water solubility, low intestinal absorption, rapid metabolism and rapid elimination of the drug, leading together to a disappointingly low bioavailability [9]. Considering these issues and the cutaneous manifestation of CTCL, curcumin can be successfully applied topically, thus bypassing the pharmacokinetic barriers and attaining pharmacologically active levels at the targeted neoplastic lesions. Moreover, an anticipated advantage of topical curcumin *versus* the available conventional local treatments in CTCL, such as retinoids, corticosteroids, photosensitizers and especially cytotoxic agents such as mechloretamine is the excellent safety profile of this natural compound.

The literature survey shows several approaches for topical delivery of curcumin employing hydrogels [10], foams [11], sponges [12, 13] nanosized delivery systems [14] and others in which

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it is used as wound healing [11, 12, 14], antipsoriatic [15], anti-inflammatory [10] or anticancer agent [13]. In particular, the macroporous sponges represent a promising system for tissue engineering, wound dressings and local drug delivery [16]. Controlling the release of the API by loading macroporous sponges can result in an enhanced bioavailability and better efficacy of hydrophobic drugs such as curcumin [13].

The present study aims at developing original sponge-like cryogels based on the natural polymer dextran and β-cyclodextrin and to assess their applicability as controlled drug delivery system for curcumin intended to be used in the treatment of CTCL.

MATERIALS AND METHODS

Materials

Dextran (DEX) from Leuconostoc spp. with molar mass ~ 2 000 000 g/mol, β-cyclodextrin (β-CD), acryloyl chloride, trimethylamine (TEA), (4-benzoylbenzyl) trimethylammonium chloride (BBTMAC), N,N'-methylenebisacrylamide (BAAm), acetic acid (analytical grade), sodium acetate, acetone, N,N-dimethylformamide (DMF, anhydrous, 99.8 %), ethanol 95 % (analytical grade), L-glutamine, RPMI-1640 cell medium and foetal calf serum (FCS) were purchased from Sigma–Aldrich (USA).

Methods

Synthesis of β-CD-acrylate

β-CD (4.0 g, 3.52 mmol) was added to 10 mL of toluene and dried by azeotropic distillation. Then, the dry β-CD was dissolved in 30 mL of freshly distilled DMF and TEA (2 mL, 24.64 mmol) was added via syringe. The solution was cooled down to 0 °C by dint of an ice bath and acryloyl chloride (3.43 mL, 24.64 mmol) was added dropwise. The reaction mixture was stirred at 700 rpm for 20 h at 20 °C. Thereafter, the reaction mixture was filtered off to remove the insoluble white salt. The residual solution of β-CD-acrylate (β-CD-Ac) in DMF was concentrated by rotary evaporation prior to precipitation into a 10-fold excess of cold acetone (-20 °C) and recovered by filtration. Yield 60%.

Synthesis of cryogels

Dextran (1 g) was dissolved in deionized water (8 mL) under stirring to obtain a homogeneous solution. Then, the photoinitiator BBTMAC (0.05 g, 5 wt.% with respect to dextran) and crosslinking agent, β-CD-Ac (0.25 g) or BAAm (0.05 g, 5 wt.% with respect to dextran), dissolved in 2 mL water were added under stirring at room temperature. The solution was poured into 8 Teflon dishes (2 cm diameter) forming layers with a thickness of 2.5 mm. Then, the solution was frozen at -20 °C for 2 h. After that the frozen system was irradiated with full spectrum UV-vis light with "Dymax 5000-EC" UV equipment with 400 W metal halide flood lamp for 5 min (dose rate = 5.7 J/cm^2.min).

Calculation of gel fraction yield and swelling degree

Gel fraction (GF) yield and swelling degree (SD) of cryogels were determined gravimetrically. Prior to calculation all samples were extracted in distilled water for 6 days at room temperature, freeze-dried and weighed. GF yield was calculated by the relationship:

$$GF\ (\%) = \frac{weight\ of\ freeze-dried\ sample}{initial\ weight\ of\ polymer\ and\ crosslinking\ agent} * 100$$

SD was determined as follow:

$$SD = \frac{weight\ of\ swollen\ sample}{weight\ of\ freeze-dried\ sample}$$

The experimental errors of GF yields and SD calculations are in the range of 2 – 3 %.

Drug loading and encapsulation efficiency

Curcumin was loaded onto the prepared cryogels by physical adsorption. The cryogels based on dextran and dextran/ β-cyclodextrin were immersed into a solution of curcumin (0.5 mg/ml in anhydrous ethanol:water 7:3 v/v mixture) and left in the dark at 36 °C for 6 h to allow loading of the API. Afterwards, ethanol was removed by immersing the cryogels in water for 15 min. Finally, the cryogels loaded with curcumin were lyophilized.

The encapsulation efficiency of the model systems based on dextran and dextran/β-cyclodextrin was calculated according to the equation:

$$EE\% = \frac{Curcumin\ (mg) in\ polymer\ disk}{Total\ Curcumin\ (mg)\ in\ loading\ solution} * 100$$

The amount of curcumin loaded into the systems was determined spectrophotometrically at 427 nm

after incubation of the cryogel disks for 24 h in 95% ethanol at 36 °C.

Release profiles

The curcumin release from DEX and DEX/β-CD macroporous cryogels was investigated as a function of time at 35 °C. As a dissolution medium 50 ml acetate buffer (pH 5.5) with 10 % anhydrous ethanol under constant stirring at 50 rpm was used. Samples from the acceptor phase were withdrawn at predetermined time intervals and the amount of released curcumin was evaluated spectrophotometrically at 427 nm on the UV-vis

spectrophotometer Evolution EVOT063002 (Thermo Fisher Scientific, Germany). All samples were measured in triplicate and the mean cumulative percentage of drug release was calculated based on a calibration curve of curcumin in the dissolution medium in the concentration range from 0,0005 to 0,01 mg/ml (y=69.826x-0.0033; R^2=0.994).

^{1}H-NMR analysis of β-CD-Ac

The ^{1}H-NMR spectrum of β-CD-Ac was recorded in D_2O using a 600 MHz Bruker AC-spectrometer.

Scanning electron microscopy (SEM)

The morphology of the fractured surface of cryogels was examined on a scanning electron microscope (JSM-5510, JEOL, Japan) operating at 10 kV. The samples were coated with gold for 30 s using a sputter-coater (JSC 1200, JEOL, Japan) in an inert argon atmosphere prior to imaging.

Differential scanning calorimetry (DSC)

DSC was performed on a DSC apparatus Q200, TA instruments, USA. The temperature calibration was performed with a sapphire disc supplied by TA instruments in Standard aluminium pans (TA instruments) in the desired temperature interval. Samples with room humidity were tested in the same type of pans from 20 to 250 ˚C with 10 ˚C/min heating rate under nitrogen flow (50 ml/min).

Cell lines and culture conditions

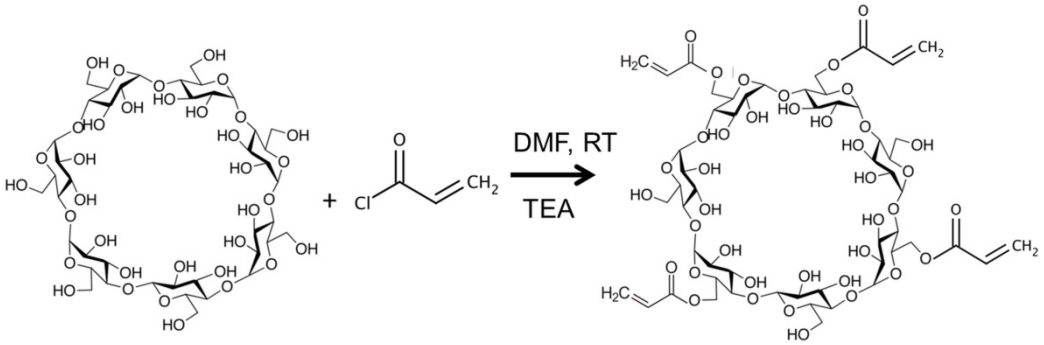
The cytotoxic activity of free drug and curcumin loaded on macroporous cryogels was assessed against the skin T-cell lymphoma derived cell line Hut-78 and non-malignant human embryonal kidney cells (HEK-293). The cell lines were purchased from the German Collection of Microorganisms and Cell Cultures (DSMZ GmbH, Braunschweig, Germany). The cells were grown in controlled environment – cell culture flasks at 37 ºC in an incubator 'BB 16-Function Line' Heraeus (Kendro, Hanau, Germany) with humidified atmosphere and 5 % CO_2. The growth medium was 90 % RPMI-1640 + 10 % FBS.

Cytotoxicity assessment (MTT-dye reduction assay)

The cellular viability after exposure to free curcumin or its formulations was assessed using the standard MTT-dye reduction assay as previously described [17] with slight modifications [18]. The method is based on the reduction of the yellow tetrazolium salt MTT to a violet MTT-formazan via the mitochondrial succinate dehydrogenase in viable cells. In brief, exponentially proliferating cells were seeded in 6-well flat-bottomed microplates (3 ml/well) at a density of 1×10^5 cells per ml and after 24 h incubation at 37 °C, they were exposed to various concentrations of the tested curcumin formulations (see below) or free drug, used as a reference antineoplastic agent for 72 h. For each concentration a set of 3 wells was used. After the exposure period, 100 µl MTT solution (10 mg/ml in PBS) aliquots were added to each well. Thereafter, the microplates were incubated for 4 h at 37 °C and the MTT-formazan crystals formed were dissolved through addition of 100 µl per well of 5 % formic acid-acidified 2-propanol. The MTT-formazan absorption was recorded using a LabeximLMR-1 microplate reader at 580 nm. Cell survival fractions were calculated as a percentage of the untreated control. In addition, IC_{50} values were derived from the concentration-response curves using non-linear regression analysis (GraphPad Prizm Software for PC).

RESULTS AND DISCUSSION

Macroporous dextran cryogels with incorporated β-CD moieties (DEX/β-CD) were synthesized by photochemical crosslinking of high molar mass dextran and β-CD-Ac in frozen aqueous solution and subsequent thawing. Firstly, β-CD-Ac was synthesized by reacting β-CD with acryloyl chloride in DMF in the presence of triethylamine (Scheme 1).



Scheme 1. Synthesis of crosslinking agent based on β-CD.

An excess of acryloyl chloride (7 mol eq. with respect to β-CD) was used to achieve attachment of several acryloyl groups to one β-CD molecule. The reaction product was purified, isolated and analysed by ^{1}H-NMR (Fig. 1).

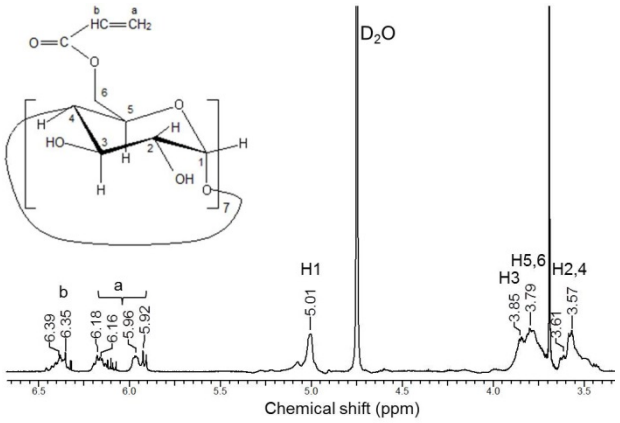
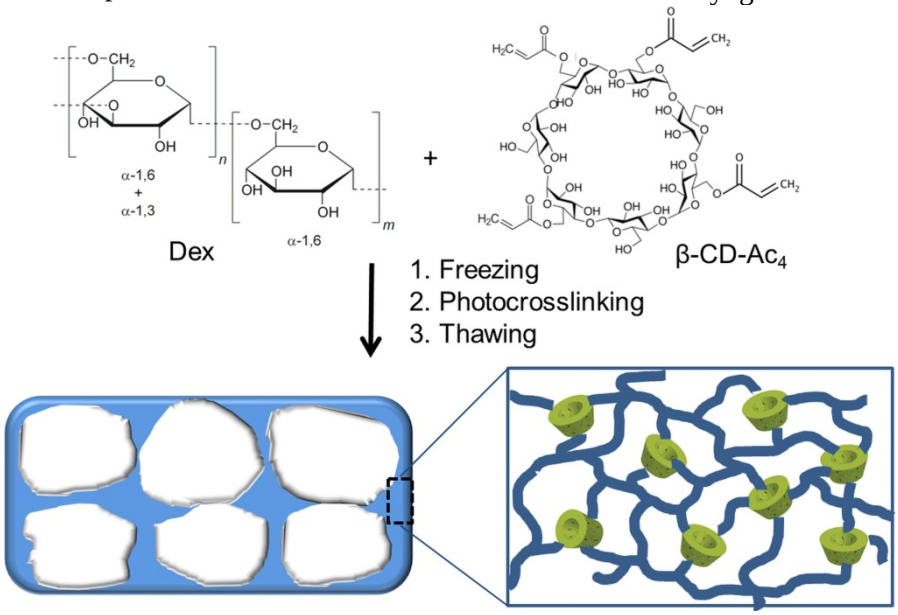


Fig. 1. Proton-NMR spectrum of β-CD-Ac in D_2O.

Based on peak integrals assigned to the β-CD protons at 5.01 ppm to the vinyl protons at 5.8 – 6.4 ppm a degree of substitution equal to four was calculated. Thus, a crosslinking agent (denoted as β-CD-Ac$_4$), containing four reactive vinyl groups per molecule, was synthesized and used for preparation of cryogels. Macroporous dextran cryogels with incorporated β-CD moieties were prepared by freezing an aqueous solution of reagents at – 20 °C for 2 h, irradiation with UV light for 5 min with an irradiation dose rate of 5.7 J/cm^2.min and subsequent thawing to room temperature (Scheme 2). These experimental conditions have been established in our previous studies as optimal conditions for preparation of cryogels from high molar mass polysaccharides with fairly high gel fraction yield and good mechanical properties [19, 20].

The freezing of the aqueous solution led to formation of a solid phase (ice crystals) and a liquid microphase, where non-frozen water, dextran, photoinitiator and cross-linking agent were located. The reaction of crosslinking took place in the liquid microphase by recombination of (macro)radicals generated in dextran and β-CD-Ac molecules by UV light. In fact, the liquid microphase acted as a template for the formation of cryogel walls, while ice crystals acted as a porogen. As expected, the combination of cryogenic treatment and photochemical crosslinking resulted in formation of sponge-like cryogels comprising large interconnected pores surrounded by thin walls (Fig. 2a).

In addition, dextran cryogels without β-CD were synthesized following the same synthesis procedure by using BAAm as a crosslinking agent instead of β-CD-Ac$_4$. The use of a small amount of BAAm was essential to obtain gels of good strength since dextran cryogels synthesized without crosslinking agent were weak and fell to pieces on handling. Importantly, DEX/β-CD cryogels exhibited similar morphology and swelling properties as compared to DEX cryogels. Actually, the calculated GF yield (73 ± 3 %) and SD (34 ± 3) of DEX/β-CD cryogels were comparable to the GF yield (82 ± 3 %) and SD (28 ± 3) of pure dextran cryogels. This fact allowed us to compare the two cryogels as carriers of curcumin and to emphasize the role of β-CD on the release of curcumin from the cryogel matrix.



Scheme 2. Preparation of sponge-like cryogels by photochemical crosslinking of DEX and β-CD-Ac$_4$ in a frozen aqueous solution and thawing.

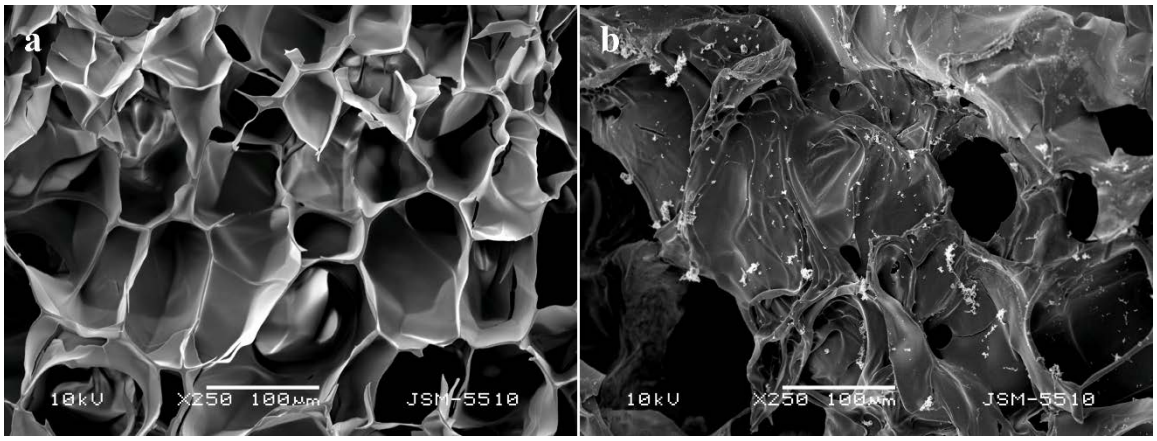


Fig. 2. SEM micrograph of freeze dried DEX/β-CD cryogel (a) and curcumin loaded DEX/β-CD cryogel (b).

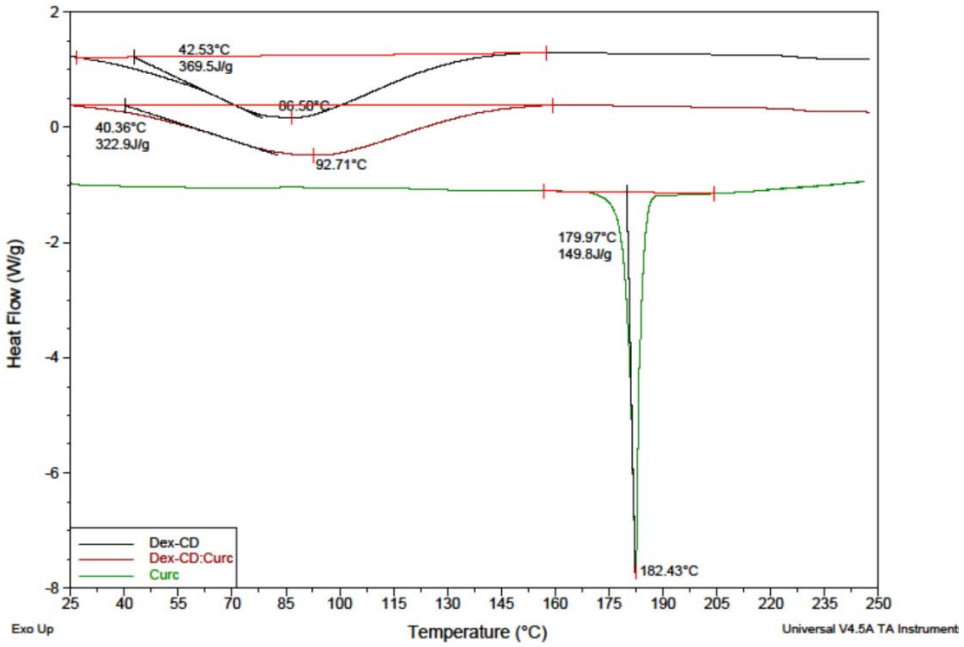


Fig. 3. DSC thermograms of Dex/β-CD cryogel, curcumin loaded Dex/β-CD cryogel and pure curcumin.

Both cryogels were loaded with curcumin by the physical adsorption method. Freeze dried disks were immersed in a solution of curcumin in ethanol/water (7:3 v/v) and allowed to absorb the drug for 6 h at 36 °C. Since curcumin is a hydrophobic substance, one may expect that in the case of DEX/β-CD cryogels a portion of the drug will be located into the cavity of β-CD molecules. In the next step, the curcumin solution filling the cryogel pores (free volume) was replaced by pure water to minimize the content of drug molecules which are not embedded into polymer matrix. Finally, the carriers were freeze dried and utilized for further experiments.

The calculated encapsulation efficiencies of DEX and DEX/β-CD cryogels were 36.2 % and 57.8 %, respectively. This significant difference could be attributed to the presence of cyclic oligosaccharides in the polymer matrix. Being very hydrophobic (log P= 2.3) [21] curcumin has higher affinity towards the hydrophobic cavities of β-CD and, therefore, larger amount of the drug were loaded into the DEX/β-CD systems.

DEX/β-CD cryogels loaded with curcumin were further analysed by SEM (Fig. 2b). In this case, unlike the smooth surface of pure DEX/β-CD cryogels (Fig. 2a), small particles regularly distributed on the inner cryogel surface were observed. Undoubtedly, this result confirms that curcumin is loaded into the cryogel carrier. However, the surface analysis by SEM cannot provide information whether and what amount of curcumin is embedded inside the polymer matrix. Additional information about the phase state of curcumin loaded in the polymer carriers was obtained from DSC analysis. DCS curves of pure curcumin and DEX/β-CD cryogel with and without curcumin are shown in Fig. 3.

Curcumin is a crystalline solid and DSC analysis of pure powder showed a narrow melting peak at 182 °C. However, the melting peak ascribed to curcumin

disappeared in the drug-loaded DEX/β-CD cryogel. This fact implies that curcumin is in amorphous state probably due to some specific interaction with the polymer carrier. The broad exothermic peaks in the 40 – 120 °C temperature range are attributed to some remaining bound water in the cryogel matrix. At first glance DSC results seem contradictory to SEM observation. Here, one should point out that DSC is a quantitative analysis unlike SEM. On this ground, one may suggest that the main portion of curcumin is homogeneously entrapped into the polymer matrix where the formation of typical crystalline structure of curcumin (Fig. 4) inside the polymer network is hindered. Most probably, the drug particles observed by SEM on the cryogel inner surface are crystalline, however, their portion is very small and cannot be detected by DSC.

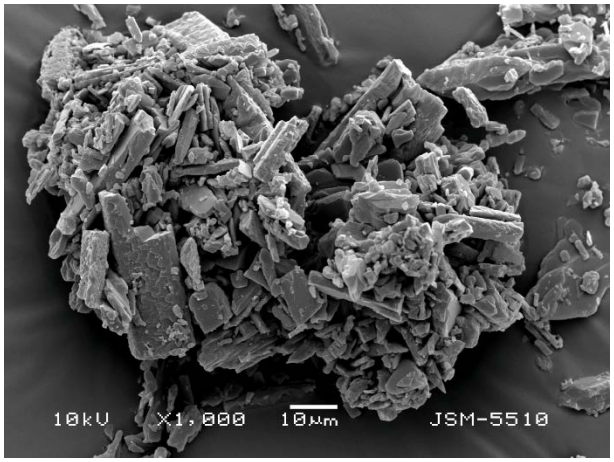


Fig. 4. SEM micrograph of pure curcumin.

The evaluation of the dissolution test shows sustained release from both model formulations (Fig. 5). After 72 h the amount of API released from DEX cryogels was about 36.9 % while the released amount from DEX/β-CD was almost twice as low (14.98 %).

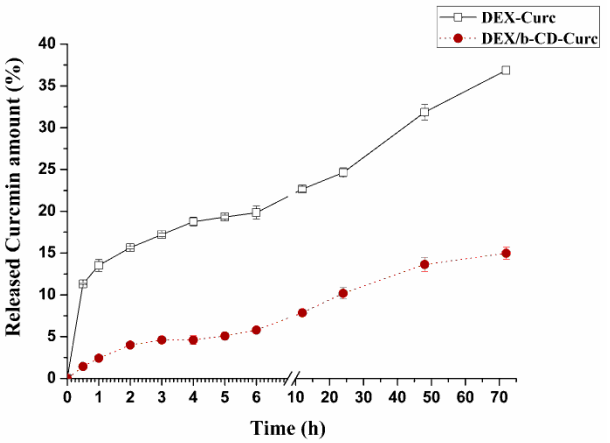


Fig. 5. Cumulative dissolution profiles of curcumin from the model formulations in acetate buffer (pH 5.5) and 10% ethanol; mean ± SD, n=3.

DEX cryogels showed burst release in the first hour of the dissolution. This fact can be due to the presence of some amount of curcumin on the inner surface of the sponge, resulting in fast diffusion and release into the dissolution medium in the beginning of the process. In the case of DEX/β-CD systems no burst effect was registered. Here, more pronounced sustained release was observed. Although the difference of the released curcumin in % is almost double the actual amount released from DEX cryogels is 0.331 ± 0.007 mg/ml, while in the case of DEX/β-CD it is 0.217 ± 0.004. The difference in the release behaviour is most probably due to the location of some portion of hydrophobic curcumin into the β-CD cavities as an inclusion complex, which slows down the release of the drug to the polar dissolution medium.

An integral element of the presented study was the comparative bioassay of cell growth-inhibitory effects of DEX and DEX/β-CD based systems vs. free drug (DMSO solution). The pharmacological study was conducted using the MTT-dye reduction assay in the skin T-cell lymphoma derived cell line Hut-78 and non-malignant human embryonal kidney cells (HEK-293).

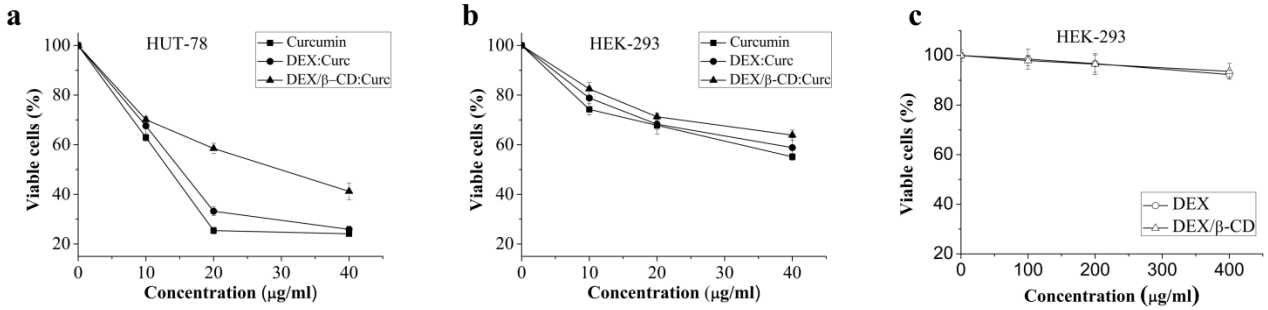


Fig. 6. Growth inhibitory concentration-response curves of loaded cryogels and free drug (a, b) and cytotoxicity of non-loaded systems (c) determined by the MTT-dye reduction assay after 72 h of continuous exposure. Each bar represents cell survival fractions (as percentage of the untreated control) from 3 independent experiments.

Evident from the concentration-response curves depicted in Figure 6 (a), the free drug in DMSO solution caused strong, concentration-dependent inhibition of malignant cell (HUT-78) growth ($IC_{50=}$13.35 μg/ml), which was practically paralleled by the cytotoxicity pattern of curcumin, loaded in the dextran-based system (IC_{50}=15.11 μg/ml.). The slower and less steeper release pattern of curcumin from the DEX/β-CD-system as compared to the dextran carrier was consistent with the less pronounced tumour cell growth inhibition at all data points, which is undoubtedly conditioned by the less intensive exposure to the free antineoplastic natural compound. The IC_{50} of DEX/β-CD-loaded curcumin was 29.71 μg/ml. Compared to the malignant cells the tested formulations showed far less cytotoxicity against non-malignant cell line (HEK-293) (Fig. 6 b), whereby they failed to induce 50 % inhibition of cellular viability. This finding could be explained with the pronounced selectivity of curcumin against tumour cells.

In order to determine whether the cytotoxic effect of the prepared formulation is caused only by the cytotoxic potential of curcumin rather than the toxic effect of the cryogel carriers, we sought to determine the intrinsic inhibitory potential of the non-loaded DEX and DEX/β-CD sponges. As is evident from the results presented the non-loaded cryogels are practically devoid from cytotoxic activity against the cell line under investigation. Even at the highest tested concentrations on empty sponges (200 μg/ml) the cell viability was only slightly affected and over 90 % of treated cells retained their vitality as compared to the untreated control (Fig. 6c).

CONCLUSIONS

Novel dextran/β-cyclodextrin and dextran macroporous cryogels were synthesized as potential platforms for dermal controlled delivery of curcumin for topical treatment of CTCL. The elaborated sponges were characterized with high drug loading efficiency (up to 57.8 %). DSC analysis showed that the encapsulation of curcumin into macroporous sponges is associated with transition from crystalline to amorphous state of the drug. This is a prerequisite for improved aqueous solubility of curcumin. Both model formulations demonstrated sustained release profiles of API within 72 h and in the case of DEX/β-CD no burst effect was evident. The cytotoxicity assessment of curcumin loaded DEX and DEX/β-CD showed comparable activity with the free drug while maintaining pronounced selectivity against tumour cells. Consequently, the novel macroporous cryogel systems based on dextran/β-cyclodextrin can be considered as an advantageous alternative to the current CTCL local treatment options.

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НОВИ МАКРОПОРЕСТИ КРИОГЕЛОВЕ ОТ ДЕКСТРАН/β-ЦИКЛОДЕКСТРИН И ДЕКСТРАН ЗА ДЕРМАЛНО ДОСТАВЯНЕ НА КУРКУМИН ПРИ ЛЕЧЕНИЕ НА КОЖЕН Т-КЛЕТЪЧЕН ЛИМФОМ

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(Резюме)

Кожната форма на Т-клетъчен лимфом (CTCL) представлява рядко заболяване, което засяга както пациенти на средна възраст, така и деца. Началните стадии могат успешно да бъдат лекувани с локална лекарствена терапия. Куркуминът – природно, фитохимично вещество с доказана плейотропна противовъзпалителна и противотуморна активност, предоставя безопасна алтернатива на настоящата терапия, независимо от ниската си водна разтворимост и химична нестабилност. В настоящото изследване оригинални криогелове на основата на смес от декстран и β-цикодекстрин и чист декстран бяха получени и оценени като платформи за дермално доставяне на куркумин. Криогелове с макропореста структура бяха синтезирани чрез фотохимично омрежване в замразено състояние с последващо размразяване. Куркумин беше натоварен чрез физична адсорбция при задоволителна ефикасност на енкапсулиране, особено в случая на криогелове от декстран/β-цикодекстрин (57.8%). *In vitro* тестовете за освобождаване показаха забавено лекарствено освобождаване в рамките на 72 ч, като за носителите от декстран/β-цикодекстрин, освобождаването на куркумин е плавно без първоначален ефект на бързо освобождаване. Цитотоксичният потенциал на натоварен в макропорестите носители куркумин бе оценен в сравнителен аспект със свободното вещество върху туморни клетки с произход от Т-клетъчен лимфом и върху немалгинени клетки. Получените резултати показаха съизмерима цитотоксична активност и селективност със свободното лекарствено вещество. Предложените нови макропорести криогелове показват потенциал за приложение като системи за контролирано дермално доставяне на куркумин при лечение на CTCL.