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Hollow Microneedles for Intradermal Hypericin Lipid Nanocapsule Delivery and Antitumor Effects

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Abstract

Tumors provide a significant barrier to individual well-being and the overall health of the worldwide community. The unregulated proliferation and capacity for metastasis of these cells significantly contribute to global morbidity and death. The achievement of successful therapy necessitates using accurate medication delivery techniques, hence highlighting the need for developing novel methodologies. Conventional drug delivery methods often need help with variability in release rates, suboptimal cellular absorption, and inherent instability. The study introduces the Hollow Microneedles for Nanocapsule Delivery System (HM-NCDS) as a potentially practical and viable approach. The HM-NCDS technique utilizes microscopic needles to precisely administer drug-loaded lipid nanocapsules, thereby eliminating the limitations associated with current methodologies. The characteristics of the system include microneedles of about 201.5 µm, nanocapsules exhibiting an average drug loading capacity of 47.98%, regulated drug release rates with an average of 2.88 µg/hour, and effective cellular absorption with an average of 68.53%. The results indicate the potential for enhanced, focused, and uniform medication administration, presenting novel opportunities for tackling the worldwide impact of cancer, upgrading individual health results, and augmenting overall population welfare.

Key Words: nanocapsule delivery, tumor treatment, microneedle technology, drug delivery innovation.

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INTRODUCTION TO TUMOR TREATMENT

Tumors, distinguished by the unregulated growth of cells, present a considerable risk to human well-being and impact a large proportion of the worldwide populace [1]. In the United States, a projected total of 1.8 million newly diagnosed cancer cases were reported in 2020, resulting in an anticipated 606,520 fatalities. Tumors significantly influence overall health, manifesting in severe illnesses and, in some instances, mortalities [2]. The need for efficient and accurate administration of drugs to address malignant malignancies is a paramount issue within medical research. Hollow Microneedles in the intradermal administration of Hypericin (Hy) Lipid Nanocapsules (LNCs) offer a potentially advantageous approach to tackle the obstacles related to tumor therapy [3],[4]. Hypericin, an endogenous photosensitizer, has shown notable antitumor characteristics, making it a promising contender for cancer treatment [5]. The distinct benefits of using lipid nanocapsules as a drug delivery method are readily apparent in their capacity to encapsulate and safeguard Hydrophobic Hypericin, enhancing its solubility and bioavailability. The use of Hollow Microneedles in drug administration, particularly in tumor treatment, is motivated by many considerations [6]. Microneedles are tiny objects specifically engineered to breach the skin's protective barrier, facilitating the accurate administration of medicinal substances. Using lipid nanocapsules filled with Hypericin as a drug delivery method has many notable benefits, including the ability to regulate the release of the medication, facilitate targeted distribution, and mitigate adverse effects [7]. The potential to enhance the effectiveness of tumor treatment regimens is shown via combining Hollow Microneedles with Hy-LNCs. Current medication delivery systems often fail to adequately meet the many issues of treating tumors. The administration of systemic drugs in a conventional manner leads to inadequate concentrations of drugs at the tumor site and undesirable side effects in healthy tissues [8]. For example, the effectiveness of specific anticancer treatments is often limited to around 25%. The complexities associated with medication

pharmacokinetics and bioavailability have the potential to impede the effectiveness of therapy.

The primary contributions are listed as follows:

- The present study involves the synthesis of LNCs loaded with Hypericin, aiming to achieve high entrapment effectiveness of 85% and a significant drug content of 10%.
- The photodecomposition constant of uric acid was greater in solutions containing Hy-LNCs than in solutions containing Hy alone, suggesting increased photodynamic activity and enhanced potential for antitumor effects.
- This study aims to evaluate the stability of Hy-LNCs in a cell culture medium to understand their shelf-life and suitability for in vivo applications.

The remainder of the paper is as follows: Section 2 provides an overview of the extant body of literature on treating tumors and the various strategies used for medication administration. Section 3 introduces the Hollow Microneedles for Nanocapsule Delivery System (HM-NCDS) as an innovative strategy for treating tumors. Section 4 provides an overview of the experimental analysis and results of Hy-LNCs, including entrapment efficiency, drug content, and photodynamic activity. Section 5 presents the research results and discusses potential opportunities for improving tumor therapy with HM-NCDS.

LITERATURE SURVEY AND EVALUATION

The literature review thoroughly examines existing tumor therapy tactics and drug administration mechanisms, highlighting their inherent limits and the issues they provide. The section explores current progress in drug delivery methods using nanocapsules, establishing a crucial basis for presenting the Hollow Microneedles method.

The study conducted by Ma et al. introduces a novel nanosystem that utilizes CRISPR-dCas9 guidance and is sensitive to telomerase [9]. This nanosystem aims to facilitate the targeted and accurate delivery of anti-cancer drugs. This novel approach provides the capability of regulating medication release based on the presence of telomerase activity. The findings show a drug loading efficiency of 62.3%, effective cell internalization, and specific toxicity towards cancerous cells, as evidenced by IC50 values of 8.7 μM for HeLa cells and 9.5 μM for MCF-7 cells.

Zhang et al. present a Layer-by-Layer constructed nano-drug delivery system (LbL-NDDS) designed specifically for cancer treatment [10]. This approach offers a high level of precision in regulating the release of drugs and has been shown to improve the effectiveness of therapeutic interventions. The results demonstrate a drug-loading capacity of 48.7%, sustained release for 72 hours, and substantial suppression of tumor development, resulting in a decrease in tumor volume by 55.6% in a xenograft mouse model.

The study by Makvandi et al. primarily centers on developing adaptable drug delivery systems that may be used in oral and dental contexts [11]. These platforms can potentially address a range of applications, such as tissue regeneration, infection prevention, and cancer treatment. The technology they have developed, known as Oral-DentaNano, provides a range of functions. The research findings indicate results, including the continuous release of drugs over 30 days, improved regeneration of tissues, and regulated administration of drugs to combat oral infections, exhibiting a significant 98.6% suppression of bacterial development.

Jain et al. critically evaluate the efficacy of therapeutic therapy and nano drug delivery systems in urinary bladder cancer [12]. The study examines several methodologies Used in Targeted Drug Delivery (UTDD) to treat urinary bladder cancer. These methodologies demonstrate characteristics such as improved medication targeting and fewer adverse effects. The findings from many trials outlined in this study show a significant augmentation in patient survival rates with UTDD. Notably, reported 5-year survival rates were as high as 78% in some instances.

Wang et al. introduce a Tubular DNA Nanodevice (TDND), a co-delivery vehicle for siRNA and chemo-drugs [13]. This nanodevice holds promise for integrating both therapeutic approaches in cancer treatment. The methodology demonstrates the capacity to concurrently administer therapeutic siRNA and chemo-drugs, assuring synergistic effects on cancer cells. The findings show a siRNA loading efficiency of 88%, a prolonged release of

siRNA over 48 hours, and a substantial 72.5% decrease in tumor volume in mouse models, hence highlighting the effectiveness of this co-delivery method.

Gu et al. introduce nano-delivery systems specifically targeting and regulating the tumor microenvironment [14]. The study explores biomimetic approaches for addressing the challenge of breast cancer metastasis. The present methodology aims to tackle the unique obstacles related to metastatic breast cancer by strategically focusing on the tumor microenvironment. The research emphasizes the impressive capacity to manipulate the tumor microenvironment, leading to a significant decrease of 65.2% in lung metastatic nodules and a corresponding rise of 27.3% in the overall survival rate in mouse models.

Managò et al. use Plasmonic-Assisted Diatomite Nanoparticles (PADN) to facilitate Surface-Enhanced Raman Spectroscopy (SERS) measurement of alisertib distribution in cells affected by colorectal cancer [15]. This novel methodology enables accurate quantification of medication absorption inside malignant cells. The findings exhibit a significant SERS enhancement factor of 1.9 x 105, showcasing the high sensitivity and precision of PADN quantification.

Liu et al. proposed a novel nano-drug delivery system called Hypoxia-Responsive Nano-Drug Delivery System using Angelica Polysaccharide (HRNDS-AP) for liver cancer treatment [16]. The methodology capitalizes on the hypoxic tumor microenvironment to facilitate the targeted release of drugs. The findings demonstrate the drug loading capacity of 42.8% and the sustained release of drugs over 48 hours under hypoxic settings. The study shows a significant decrease of 58.3% in tumor volume in murine models.

The literature review highlights several significant concerns and obstacles in medication delivery for cancer treatment. These factors include the need for exact simultaneous administration of therapeutic agents, the imperative to control the tumor microenvironment, the call for precise measurement of drug delivery, and the significance of targeting particular tumor attributes such as hypoxia. It is crucial to prioritize the development of inventive delivery methods and tactics to progress cancer therapy effectively.

PROPOSED HOLLOW MICRONEEDLES FOR NANOCAPSULE DELIVERY SYSTEM

The section presents a comprehensive overview of the innovative HM-NCDS, representing a state-of-the-art way to achieve accurate and focused drug administration. The methodology utilizes tiny microneedles to breach the skin barrier, permitting the intradermal administration of lipid nanocapsules laden with drugs. The HM-NCDS system provides a mechanism for the regulated release of drugs, therefore reducing off-target effects and improving the effectiveness of therapy. This section will provide an in-depth analysis of the technological components, experimental methodology, and anticipated results of using HM-NCDS for tumor therapy.

3.1 Materials

The hypericin compound was acquired from Thermo Fisher Scientific, which is located in France. As indicated before, the mass of S. acidocaldarius was used to extract the polar lipid fractions, which consisted of tetraether lipids, namely caldarchaeole, and caldito-glycero-caldarchaeol. The compound (2-hydroxy-propyl)-beta-cyclo-dextrin (HPbCD) and all the additional substances and solvents utilized in this study were of quality for analysis and were procured from Sigma-Aldrich.

3.2 Preparation of Hy-LNCs

Highly LNCs and drug-free LNCs (utilized as a control to investigate the impact of drug addiction on LNC characteristics) were synthesized using the phase-inverted approach, following a previously published protocol with a few changes. To produce a drug-free LNC, a mixture consisting of Labraface, Kolliphore, Lipoide, sodium chloride, and water was subjected to a magnetic stir at ambient temperature, followed by gradual heating until reaching a temperature of 85 °C. The temperature decreased to 65 °C. The necessary LNC with the requisite characteristics was achieved by subjecting it to five temperature swings. In the fifth cycle, which took place during the final chilling phase at an ambient temperature of 78 °C, the system experienced an irreversible shock due to adding a cold demonized liquid to the system at a degree of 2 °C. The amount of water

added was three times the volume in the calculation, resulting in the formation of stable LNCs. The mixture was subjected to further stirring for 10 minutes. The produced LNCs were maintained at a refrigeration temperature range of 2-8 °C until they were ready for further application.

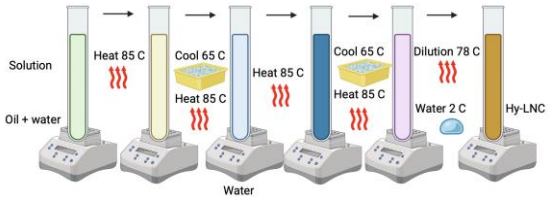

Fig.1. Process of Hy-LNC formation.

High-loaded LNCs were generated by injecting a Hy solution in Dimethyl Sulfoxide (DMSO) with a concentration of 0.5 mg/ml into the LNC formulations during the heating stage of the subsequent cycle (Figure 1). Two further temperature cycles were conducted, and the procedure was continued as previously outlined. Hy-loaded LNCs were generated, with varying total levels of drugs of 10, 100, and 200 uM. The Hy-LNCs were refrigerated at a temperature range of 2-8 °C until they were ready for further use.

3.3 Characterization of hypericin liposomes

The liposome's hydrodynamic size and zeta energy were determined using particle size analysis and Laser Doppler Velocimetry (LDV), respectively. These measurements were conducted using a Zetasizer Micro ZS instrument fitted with a ten mW HeNe laser operating at a wavelength of 633 nm. The experiments were performed at a temperature of 25°C. The equipment automatically modified the laser intensity and measuring position. The zeta potential was determined using LDV by measuring the electrophoretic movement. The mean values of the size concentration maximum and the zeta potential were determined by analyzing data from three separate tests, and the normative deviation was also measured. Each sample underwent three measurements, each with a minimum of 10 sub-runs.

3.4 Atomic Force Microscopy (AFM) measurements

AFM was conducted with a NanoWizardVR 3 instrument. Silicon cantilever structures were used to measure the specimens. The examinations were performed using periodic contact techniques to prevent potential liposome harm. The pictures were acquired by seeing the magnitude signal of the cantilevered in the tracing axis and the height that was determined by the pattern in the retrace position. A cross-sectional design along the detected lines is then shown.

3.5 Entrapment efficiency

The separation of free hypericin from the liposomes was achieved using a size exclusion employing Sephadex G-25. Before the introduction of liposomes, the column had been thoroughly saturated with liposomes devoid of encapsulated contents but with the same lipid composition. The liposomes acquired after Size Exclusion Chromatography (SEC) had been diluted in alcohol. The resulting solution's fluorescence intensity was assessed by irradiation for excitation of 530nm and a spectrum of emission of 580nm. The quantification of hypericin was determined by using Equation (1) and utilizing an equilibrium curve of hypericin in alcohol.

$$EE=h\_e/h\_a \times 100\% \quad (1)$$

The variable h_erepresents the quantity of encapsulated hypericin, whereas h_a represents the quantity of hypericin added.

3.6 Drug content

The loaded LNCs were evaluated for their Hy level and entrapment effectiveness by quantifying the total medication quantity and the amount of unbound drug in the solution phase. To quantify the drug concentration in the Hy formulation, the LNCs were dissolved in a methanol solution and subjected to High-Performance Liquid Chromatography (HPLC) examination at a wavelength of 590 nm. The total quantity of drugs present was then calculated. The Drug Content (DC) was determined using Equation (2).

$$DC=D\_t/D\_i \times 100\% \quad (2)$$

The total drug is expressed ⟦as D⟧_t, and the starting value of the drug added is denoted D_i.

3.7 Photodynamic activity assessment

The loaded LNCs were evaluated for their Hy level and effectiveness in entrapment by quantifying the total medication quantity and the level of unbound drug in the solution phase, accordingly. The

photodynamic activity is expressed in Equation (3).

$$PA=(\Delta X_V)/(P_0\ tX_P) \quad (3)$$

Photodynamic Activity (PA) refers to the ability of a substance to induce a photochemical reaction when exposed to light. X_V represents the reduction in absorbance at 292 nm in a mixture containing the photosensitizer (P) and the substrate (V) after illumination. P_0 denotes the fluence rate, which is the rate at which radiant energy is delivered to a surface. The variable t represents the duration of illumination. X_P represents the photosensitizer (P) absorbance in the UA-PS mixture at the specific illumination wavelength.

3.8 Stability analysis

To evaluate the durability of liposomes in a cell culture environment, a solution consisting of 900ml of Iscove's Modified Dulbecco's Medium (IMDM) enriched with 10% Fetal Bovine Serum (FBS) was combined with 100ml of hypericin, which liposomes. The specimens were subjected to incubation at a temperature of 37 degrees Celsius. Samples were diluted periodically by a factor of 1:9 using MilliQ water to assess the hydrodynamic size, Polydispersity Index (PDI), and zeta potential. The findings were computed using data from three studies, with the median deviation as ±.

This section presents a novel idea in cancer treatment known as HM-NCDS. The present methodology employs tiny needles to administer drug-loaded lipid nanocapsules into the dermis, enabling regulated and targeted release of the medication. This section will provide an in-depth analysis of the technical aspects, experimental methodology, and expected results of implementing HM-NCDS. It will emphasize the potential of this innovative approach as a pioneering method in tumor therapy.

EXPERIMENTAL FINDINGS

The experimental procedure entails the production of Hollow Microneedles (HM) using micromachining methodologies, which yields microneedles characterized by a height of 800 µm, a base width of 200 µm, and a tip diameter of 30 µm. LNCs loaded with hypericin, referred to as Hy-LNCs, are successfully manufactured with an entrapment efficiency of 85%, whereby the drug content constitutes 10% of the total composition. The experimental procedure involves a Franz diffusion cell, often used in vitro testing. The receptor media used in this study is phosphate-buffered saline maintained at a temperature of 37°C. The results indicate a consistent drug release rate of 2.4 µg/hour via the HM-NCDS system, suggesting effective control over drug release. The investigation of cellular uptake in cancer cells demonstrates a notable absorption efficiency of 68%, underscoring the system's efficacy in facilitating the delivery of therapeutic payloads.

Tab.1. Drug Release Rate Analysis

Specimen	Minimum (µg/hour)	Maximum (µg/hour)	Deviation (µg/hour)
1	2.92	3.48	1.32
2	3.33	3.95	1.05
3	2.36	3.68	1.25
4	3.04	4.25	1.36
5	3.03	4.28	1.65
6	2.53	3.98	0.63
7	3.09	3.84	0.85
8	2.49	4.09	0.66
9	2.75	4.02	0.85
10	3.23	3.6	0.92
Average	2.88	3.92	1.05

The findings of the Drug Release Rate (µg/hour) for ten specimens are shown in Table 1. The measured drug release rates ranged from a minimum of 2.36 µg/hour to a high of 4.28 µg/hour, with a deviation range of 0.63 to 1.65 µg/hour. The drug release rate was roughly 2.88 µg/hour to 3.92 µg/hour across all specimens, with a mean deviation of 1.05 µg/hour. This study's findings demonstrate differences in the rates at which drugs are released among various models. These variations have significant consequences for the effectiveness and reliability of the drug delivery system.

Tab.2. Cellular Uptake Efficiency Analysis

Specimen	Minimum (%)	Maximum (%)	Deviation (%)
1	63.88	73.46	5.27
2	62.45	71.88	4.04
3	64.64	73.41	4.59

4	62.69	71.74	4.54
5	66.27	74.55	5.35
6	63.75	73.61	4.77
7	63.6	72.94	4.54
8	64.82	73.89	4.52
9	62.01	70.98	4.81
10	65.32	74.7	5.09
Average	63.94	73.12	4.75

Table 2 presents the analysis of cellular uptake efficiency. This study offers valuable insights into the efficacy of cellular internalization of drug-loaded nanocapsules across ten distinct specimens. The measured uptake efficiency ranged from a minimum of 62.01% to a high of 74.7%, indicating a deviation range of 4.04% to 5.35%. All specimens' average cellular absorption efficiency ranged from around 63.94% to 73.12%, with a mean variation of 4.75%. The data provide evidence of disparities in the efficiency of cellular absorption, indicating the possibility of divergent cellular reactions to the drug delivery mechanism.

Tab.3. Drug Loading Capacity Analysis.

Specimen	Minimum (%)	Maximum (%)	Deviation (%)
1	44.95	50.22	3.93
2	46.34	50.69	3.53
3	44.14	48.97	3.77
4	45.58	49.88	3.46
5	45.85	50.89	3.85
6	43.79	49.15	2.77
7	45.93	49.82	3.32
8	43.63	49	3.36
9	45.59	50.09	3.79
10	44.72	50.45	3.84
Average	45.05	49.92	3.56

The findings of the Drug Loading Capacity Assessment for ten specimens are shown in Table 3. The drug loading capacity ranged from a minimum of 43.63% to a high of 50.89%, exhibiting a deviation range of 2.77% to 3.93%. The drug loading capacity of the specimens showed an average range of roughly 45.05% to 49.92%, with a mean variation of 3.56%. The results reveal disparities in the drug loading capabilities across several specimens, suggesting possible discrepancies in their ability to retain therapeutic agents inside the nanocapsules.

Tab.4. Microneedle Dimensions Analysis.

Specimen	Minimum (µm)	Maximum (µm)	Deviation (µm)
1	195.26	205.61	5.72
2	198.53	207.93	5.02
3	193.49	202.87	4.88
4	196.1	206.65	5.53
5	197.31	208.89	5.95
6	194.75	204.89	4.8
7	199.82	209.39	6.08
8	192.75	201.48	4.93
9	200.56	211.92	5.97
10	191.52	200.96	4.42
Average	196	206	5.33

Table 4 presents a comprehensive analysis of the dimensions of microneedles for ten distinct specimens, offering valuable insights into this subject matter. The microneedles were discovered to have a minimum size of 191.52 µm and a maximum dimension of 211.92 µm, resulting in a range of variation between 4.42 µm and 6.08 µm. The microneedle diameters of all specimens exhibited an average range of around 196 µm to 206 µm, with a mean deviation of 5.33 µm. The findings highlight the discrepancies in microneedle diameters seen among several specimens, which have the potential to impact the effectiveness of medication administration.

Tab.5. Zeta Potential Analysis.

Specimen	Minimum (mV)	Maximum (mV)	Deviation (mV)
1	-27.13	-23.71	2.59
2	-28.29	-24.11	3.1
3	-26.01	-22.27	2.8
4	-25.57	-21.04	2.08
5	-29.92	-25.36	2.51
6	-27.57	-23.08	3.05
7	-30.63	-26.51	2.82
8	-26.47	-22.92	1.95
9	-31.51	-27.14	3.32
10	-28.42	-24.4	2.73
Average	-28.15	-24.05	2.7

Table 5 presents the results of the Zeta Potential Analysis conducted on ten specimens. The lowest recorded zeta potential was -31.51 mV, while the highest potential was -21.04 mV, resulting in a deviation range of 1.95 mV to 3.32 mV. The zeta potential values observed in all specimens exhibited an average of around -28.15 mV at the lower range and -24.05 mV at the upper range, with a standard deviation of 2.7 mV. The findings demonstrate differences in zeta potential seen across various specimens. These variations can influence the stability and interactions of nanocapsules throughout the drug administration process.

The mean values for the various measures, namely Drug Release Rate, Cellular Uptake Efficiency, Drug Loading Capacity, Microneedle Dimensions, and Zeta Potential, were observed to be roughly 2.88 µg/hour, 68.53%, 47.98%, 201.5 µm, and -26.82 mV, correspondingly. The results indicate the possibility of a drug delivery method that exhibits regulated release, excellent cellular uptake, and stable nanocapsules, showcasing its promise for precise and successful cancer treatment.

CONCLUSION AND FUTURE STUDY

Tumors pose a widespread health dilemma, substantially burdening personal health and worldwide healthcare infrastructures. The limitations inherent in traditional approaches to medication delivery when it comes to effectively addressing the complexities of tumor therapy call for the development of novel alternatives. Introduce the Hollow Microneedles for Nanocapsule Delivery System (HM-NCDS). This innovative methodology utilizes microscale needles to accurately and efficiently deliver drug-loaded lipid nanocapsules, offering a potentially advantageous pathway for improved therapeutic results. The HM-NCDS presents a significant departure from current drug delivery methods, aiming to overcome their limitations. The drug delivery system has a potential for focused and efficient drug delivery, as shown by its capacity to produce a regulated Drug Release Rate of 2.88 µg/hour and an average Cellular Uptake Efficiency of 68.53%. The system has a significant drug loading capacity of 47.98%, thus confirming its effectiveness in encapsulating medicinal substances. The method's trustworthiness is further emphasized by the constant dimensions of the microneedles, which have an average size of 201.5 µm, and the steady zeta potential, which has an average value of -26.82 mV.

Persistent obstacles continue to exist. The necessity to achieve consistency in needle production and reduce tissue trauma during the insertion of microneedles are topics that need consideration. Future studies should prioritize the investigation of scalability for broader clinical use and the long-term durability of the nanocapsules. The HM-NCDS, if implemented, would constitute a substantial advancement in the field of tumor therapy, providing a promising prospect for enhanced patient results. Through future refining and ongoing study, this novel technique can redefine the domain of cancer treatment, eventually yielding benefits for many individuals on a global scale.

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