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DESIGN, SIMULATION AND ANALYSIS OF MICRONEEDLES FOR TRANSDERMAL DRUG DELIVERY

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Abstract: The paper presents development of a device which could help the oral therapy of drug delivery to patients. The paper focuses on development of a patient friendly drug delivery device, which could automatically deliver the drug into the patient body without his notice. The proposed deice will definitely help the elderly people who very often forget taking their pills on time. In this work, we present the design, simulation and analysis of silicon-based microneedles with piezoelectrically actuated microfluidic device for transdermal drug delivery (TDD). In the work presented in the paper depicts the use of array of cantilever beams, containing a microfluidic chamber and array of needles for drug storage and delivery. Silicon microneedles are used to pears the superficial skin layer followed by the delivery of the drug. Microneedles deliver the drug into the epidermis without disruption of nerve endings, due to which the patient does not feel any pain during drug delivery using transdermal system. Microneedles are fabricated using MEMS technology employing silicon, metals, polymers. The development of microneedle arrays is an approach which allows drug delivery through skin by improving safety, efficiency, bioavailability. The device developed in this work can deliver drug as per patient requirement.

Index Terms **– MEMS, Microneedles, TDD, PMMA, Polymers.**

I. INTRODUCTION

MEMS is a process technology which integrates tiny devices that combine mechanical and electrical components. MEMS fabrication technology has been derived from the conventional IC fabrication technology. The scale of the MEMS devices range from few micrometers to millimeters. Sensing happens at micro level using micro sensing elements, followed by the conversion of sensed parameter into an electrical signal. The electrical signal generated will be amplified and so that the macro devices can read. The only major drawback MEMS technology faces is in interfacing with macro circuitry. MEMS technology has become very popular because of its versatility in its application range. MEMS is highly interdisciplinary technology and its micromachining techniques is very versatile, which has resulted in an unprecedented range of devices. MEMS provide the basis for the manufacture of products that cannot be made by other methods. These factors and features of MEMS technology make it a more pervasive technology than integrated circuit microchips. Since the inception of MEMS technology there were many challenges and technological obstacles associated with miniaturization, which have been addressed in the recent past leading to a very fast and overwhelming growth of many sensors and actuators. Sensors and actuators are the most commercial and primitive MEMS devices, which require very low power and possess extremely higher accuracy, sensitivity and selectivity. At microscopic levels design and dynamic mechanisms are achieved which are not possible at macroscales. Micro sensors sense external parameter and convert it into a proportional readable electrical signal. Microactuator is a device which makes something move in accordance with the input power supply or an external stimulus. Many transduction principles are found very commonly used in development of these microsensors and microactuator viz., Piezoresistivity, piezo mechanics, piezoresistivity, resonant, strain gauge principle, thermal principles, electrostatic principle and electromagnetic. Various To achieve embedded mechatronic systems MEMS can be readily integrated with microelectronics. Disadvantages of MEMS are that they are very complex in design procedure, prior knowledge is needed to integrate MEMS devices. testing equipment to characterise the quality and performance can also be expensive reliability issues, Due to their size it is physically impossible for MEMS to transfer any significant power. The MEMS devices cannot be loaded with larger load.

MEMS use largely use silicon as its basic building block, due to a very good electrical and mechanical properties of Silicon. MEMS has evolved as one of the most revolutionized technology in development of devices that address the needs of personal health care and a wide variety of biomedical systems. MEMS devices used in biological and medical fields are referred to as BioMEMS. Biomedical sensors, biomedical instrumentation and biosensors are typical application areas of BioMEMS. BioMEMS technology strive to enhance the quality of medical diagnosis and treatment which include: Measuring drug delivery rate for infusion systems, measure pressure gradients across heart valves accurately, diagnose and monitor congestive heart failure, measure cardiac output and compliance, monitoring intracranial and intraocular pressures, understand glucose level, improve gastrointestinal tract diagnostic capabilities and assist in diagnosis of urological disorders. MEMS is the ultimate technology for integration of physical, biochemical and biological phenomena that include motion, light, sound, chemistry, biochemistry, radio waves and computation. MEMS can sense pressure, detect motion, measure forces, identify bio-agents, pump and control fluids and perform other actions

that have great value to the medical and biological fields. BioMEMS is the term used to describe the chips designed specifically for these applications. In the work presented in this paper, address the Transdermal drug delivery (TDD) systems which deals with the movement of pharmaceutical compound through the skin to reach the systemic circulation for subsequent distribution in the human body. The transdermal drug delivery system is a technique that provides drug absorption via the skin. The system has many advantages over conventional administration routes such as intravenous or oral administration for systemic and local drug delivery with simple administration. TDD is a painless method of delivering drugs by applying a drug formulation onto intact and healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer [2, 5]. Although this method is painless but it causes cell damage at the point of contact and cannot be automated. In patients suffering from chronic illness specially diabatic patients need the delivery of drugs on timely basis, hence there is need to automatically inject the drug into patients body on predefined times. MEMS researchers are developing tiny needle-based devices which can deliver the drug without damaging he cells and as these devices are very small these can be easily mounted onto patients body and can automate the drug delivery process. A MEMS based microneedle is a needle with diameter and length in micrometers. A microneedle is different from standard hypodermic needles used in medical applications as generally the length of the MEMS based microneedles is less than 1 mm. Thus, microneedles are significantly smaller in length than ordinary needles. In the work, a piezoelectrically actuated array of cantilever consisting of array of microneedles is presented. The fluid is stored in the microchannel placed right above he cantilevers. The micro chamber is made up of a polymer material. When the cantilever is actuated the drug through the chamber moves into array of needles and then into the patients body. The block diagram of the process flow for the proposed drug delivery system is shown in Fig. 1.

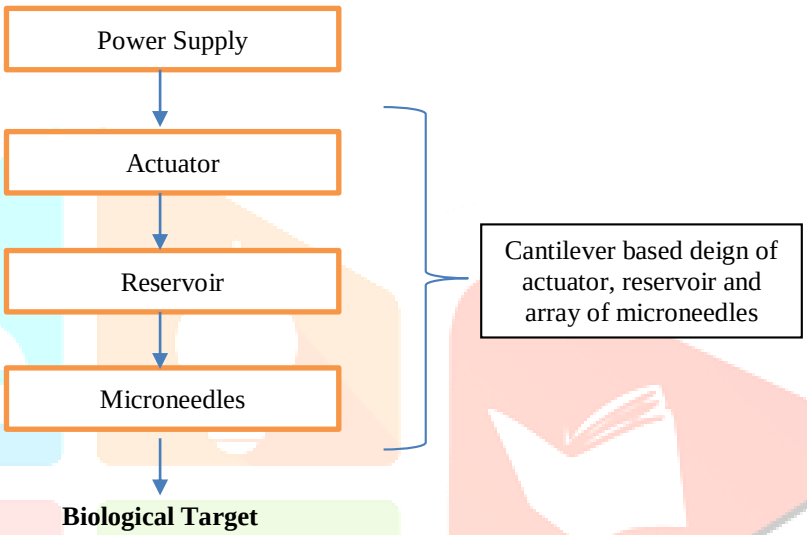

Fig. 1. Block diagram of the proposed TDD model

The model developed for the TDD is shown in Fig. 2. The model is developed using COMSOL Multiphysics software.

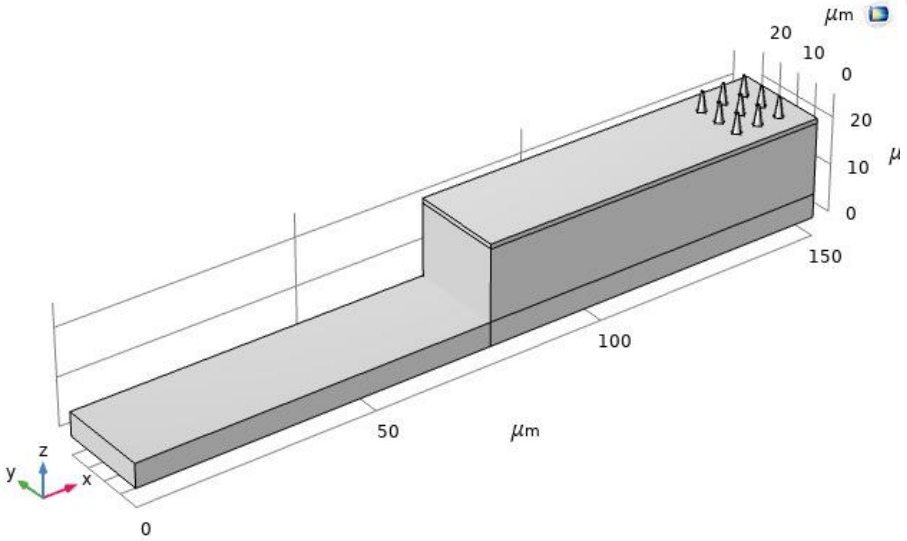

Fig. 2. Model showing a single cantilever for TDD

The model was further extended to array of cantilever consisting of array of microneedles. This was done to enhance the reservoir storage capability. The reservoir with the array of cantilevers shown in Fig. 2. Can store 6.5 ml of drug. The Fig. 2 presents the model of array of cantilevers used for TTD.

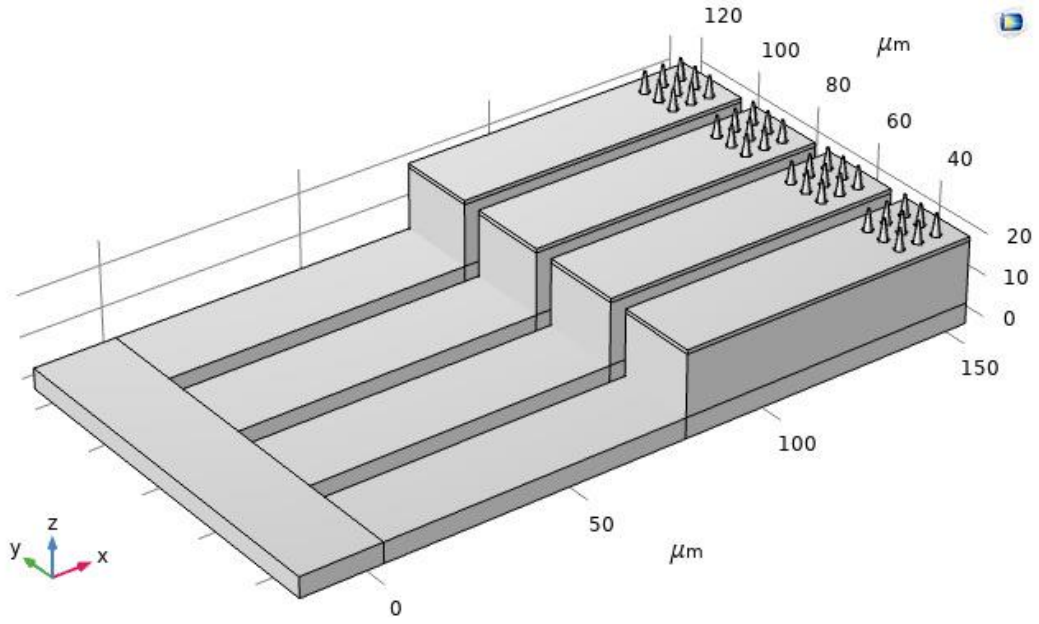

Fig. 2. Model showing the array of cantilever for TTD

Section II., describes the TDD and its related theory. In section III the proposed work for TDD is described. Simulation procedure followed is presented in section IV. Section V, discusses the results and calculations. Conclusion is provided in Section VI.

II. TRANSDERMAL DRUG DELIVERY

TDD is a minimally invasive and a painless approach. TDD is more beneficial compared to the ODD (Oral Drug Delivery) method. TDD is systemic way of delivering the drug formulation onto intact and healthy skin. The most common and conventional route of drug delivery is oral path. The oral delivery has an advantage of pre-determined doses, portability and patient self-administration. However, most therapeutic peptides or proteins are not delivered by the oral route, due to rapid degradation in the stomach and size-limited transport across the epithelium [7]. To avoid this, injection method is used which is not without limitations, as it is invasive leading to and lower acceptance by patients. Also, it requires administration by a trained administrator. TDDS potentially overcomes these limitations.

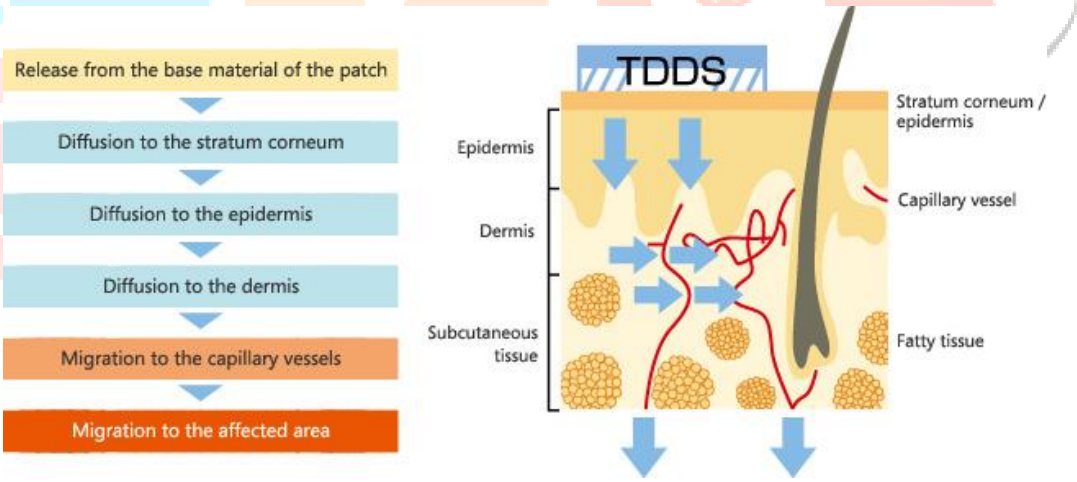

Fig. 3. TDDS process [6]

Fig. 3. Describe the process of TDDS (Transdermal Drug Delivery System). The drug initially penetrates through the stratum corneum and then diffuses through the epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption through dermal microcirculation. Further, it migrates to the capillary vessels and then to the affected area. The kinetics of the TDD is well presented in [7]. TDD has many advantages over other conventional oral and injection mode of drug delivery. It can provide a non-invasive method of drug delivery by transdermal absorption. Furthermore, the pharmacokinetic profiles of drugs are more uniform with fewer peaks, thus minimizing the risk of toxic side effects [7]. It helps those who rely on self-administration. Human skin known to be with dendritic cells in both the epidermal and dermal layers which play a very important role in immune responses. Hence, TDD is a very god method for drug delivery and vaccination. The requirement for an inexpensive and non-invasive means of vaccination has given rise to substantial research focused on the development of simple systems such as TDD for drug delivery and vaccination. Some drugs, such as hormones, may be more effective when released in a manner like the way it would be produced naturally. This type of dosing would be possible with MEMS devices. Implantable devices can be actuated such that the drug is released continuously, periodically, or selectively by the doctor or patient. The drawbacks of the TDD are that, when working on the micro scale, the mechanics of the system are different compared to the macro scale. Also, the amount of drug that can be stored and delivered will be limited. Biocompatibility issues arise when using MEMS devices. Any device intended to be implanted in the body for an extended period should not induce toxicity or damage local tissue. Also, the functionality of the device should not be compromised by its surroundings. Microneedles potentially provide a painless means to penetrate the stratum corneum and create channels to directly administer drugs. Arrays of micrometer-scale needles could enable minimally invasive transdermal delivery of therapeutic agents. Microfabrication techniques have been developed for silicon, metal, and biodegradable polymer microneedle arrays. Needles can be produced with solid or hollow bores, tapered or beveled tips, and feature

sizes from 1 to 1000 mm. Microneedle offers painless/easy drug delivery. When the drug is injected using the microneedle, it only aims the targeted tissue leaving the other tissue unaffected, thus the side effect is reduced. It is reliable that there is no need of skilled professionals to use the microneedle. Microprobes were fabricated using an integrated circuit method to achieve more precision and reproducibility. There are many methods suggested by researchers for TDDS viz., Thermal ablation, Electrical and mechanical methods (microneedles), jet injectors, ultrasound methods, chemical enhancers and eutectic systems. Amongst all, microneedle technology is found to be easier and effective method for TDD. The microprobes designed were used in the recording of biopotentials generated by nerve cells. In mid-1990s the technique of using microneedles were applied to improve cell uptake of genes and molecules. Later microneedles were proposed by several researchers for application in TDD. Researchers have demonstrated that inserting microneedles into the skin enhanced the permeation of substances through the skin. After this, many works have been followed by a wide range of studies on microneedles to explore the possibilities of their applications in drug delivery. Today, the possible benefits of their applications range from providing a more controllable insulin delivery system that better mimics the body's natural hemostatic to delivering vaccines to people faster than the disease can spread.

III. PROPOSED TDD MODEL

In the proposed TDDS, two models are developed: 1. single cantilever microneedle, 2. array of cantilever microneedle system. Piezoelectric based actuation mechanism is used to delivery drug into human body using the two models. The block diagram of drug delivery system is shown in Fig. 1. The main components of the proposed TTDS are: 1. Cantilever, 2. actuator, 3. reservoir and 4. microneedles. Drug delivery device consists of piezoelectric actuator and a reservoir integrated with microneedle array. Actuator provides actuation mechanism to the reservoir integrated with microneedle array providing drug storage and crossing point between the drug delivery system and the patient's body for releasing the drug. A microcantilever is developed in the model which carries a small micro reservoir on it. A Microcantilever is a device that can be used as physical, chemical or biological sensor by detecting the changes in cantilever bending or vibrational frequency. Reservoir is storage slot for storing the required drug in required proportion based on dosage insisted by physicians. In the proposed TDDS a micro reservoir is developed ontop of the microcantilever as shown in Fi. 5. It is made up of PMMA which has a property of undergoing compression when force is applied to it. The PMMA reservoir is micro hollow block placed on top of the microcantilever. On top of PMMA hollow block, microneedles are developed which interface with the human body for the drug delivery. For designing the microneedle, the dimension plays a very vital role. In the work, length of the Microneedle is 5 µm. The height of the conical portion of Micro Needle is 5 µm. The hole is bored from the top portion of the microneedle for delivery of drug into skin. Diameter of the conical section is 1 µm. The drawback with the single cantilever design is the limitation in the amount\quantity\volume of drug it can store and deliver, hence the single cantilever model was extended further to an array of cantilever, reservoir and microneedles system. This model can store sufficient amount of drug in the reservoir and hence can deliver the required amount of drug into human body. The volume of the drug which can be stored is discussed in the next section. Material used for designing of microneedle is Silicon and the material used for designing reservoir is PMMA. Microcantilever is developed using silicon as silicon mechanical properties are very good to be a structural material. Fig. 5 and Fig. 6 show the TTDS models. The material properties and dimensions used for the proposed models is described in Table 1. Table 2 and Table 3., respectively.

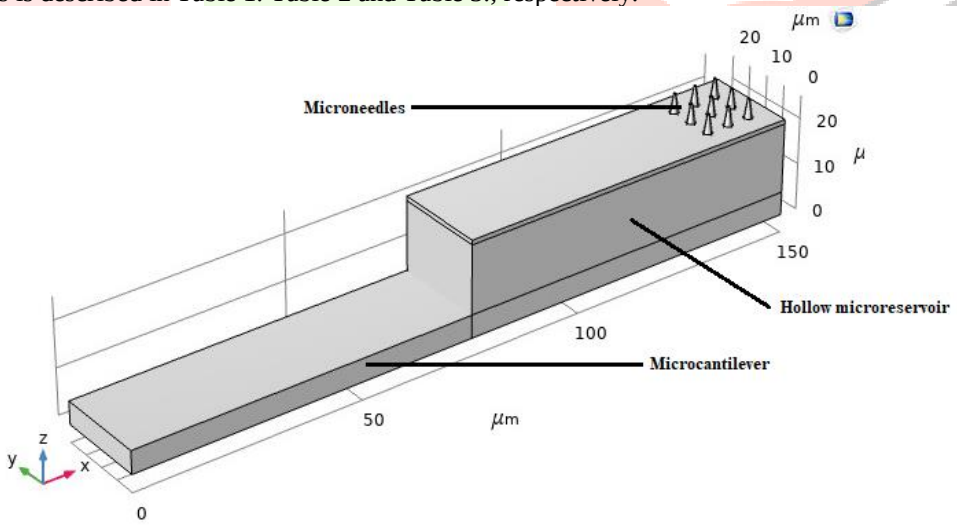

Fig. 5. Proposed TDDS model of single microcantilever with reservoir and microneedles

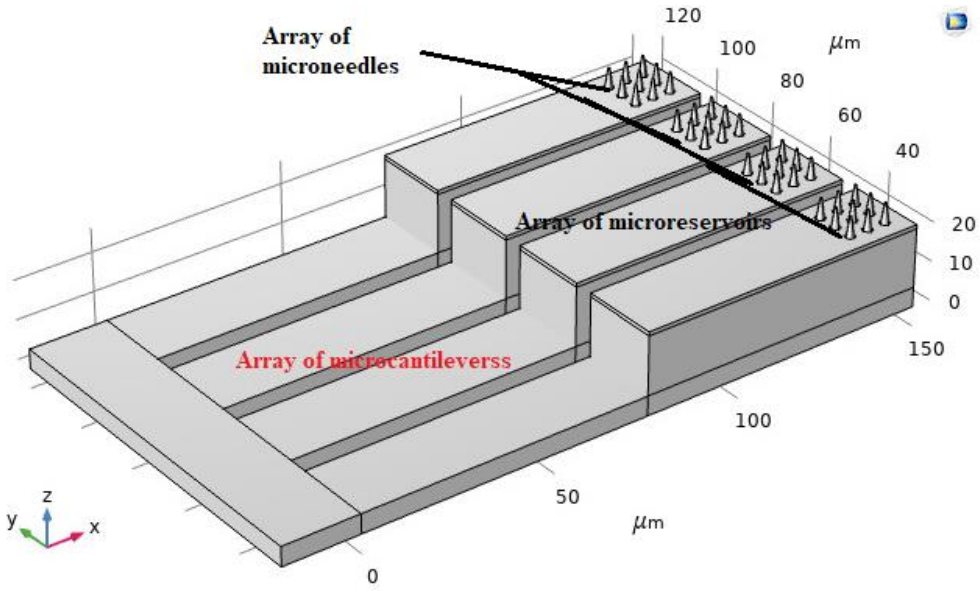

Fig. 6. TDDS model showing array of microcantilevers, micro reservoirs and microneedles.

The model shown in Fig. 6 can be used to multipurpose application. If a variety\combination of the drugs has to be delivered into human body, each drug can be stored in different micro reservoirs and can be delivered into human body at the same time. Models in both Fig. 5 & Fig. 6 are actuated by using piezoelectric actuation. A piezoelectric crystal is placed below the cantilevers and is subjected to external potential. When external potential is applied to the piezoelectric crystal, it starts vibrating which will in turn create mechanical motion in the microcantilevers and flowed by the reservoirs and microneedles.

Table 1. Material properties used in the development of both the TDDS models

Sl. No.	Material	Property	Value
1.	Silicon	Coefficient of thermal expansion	$2.6e^{-6}$ [1/K]
		Relative Permittivity	11.7
		Density	2329 [kg/m^3]
		Young's modulus	$170e^{9}$ [Pa]
		Poisson's ratio	0.28
2.	PMMA	Coefficient of thermal expansion	$70e^{-6}$[1/K]
		Relative Permittivity	3.0
		Density	1190[kg/m^3]
		Young's modulus	$3e^{9}$[Pa]
		Poisson's ratio	0.40
3.	Aluminum Nitrate	Density	3300[kg/m^3]
		Relative Permittivity	9

Table2. Dimension used for the proposed TDDS

Sl. No.	Structure	Dimensions (in μm)
1.	Microcantilever	150 X 20 X 5 (length X width X height)
2.	Microreservior	70 X 15 X 15 (length X width X height)
3.	Microneedles	Length 5, height 5 and diameter 1

The models described are subjected to FEM analysis-based simulation. The models are simulated using COMSOL Multiphysics. The simulated and heroical results are presented in next section. Also, the volume of drug that this model can hold is presented in next section.

IV. Results and Discussions

The single cantilever microneedle consists of a reservoir of 70*15*15 μm, and the reservoir is made of PMMA materials due to its properties which helps specially in medical field. When the pressure is applied at the end of microcantilever beam, it gets displaced. The displacement will be in proportion to the applied pressure. The Array of cantilever microneedle system is developed basically to increase the dosage capacity. Depending of patient's requirement, the number of arrays of cantilever can be varied. When pressure is applied, pressure will be equally distributed to each of the cantilever. The reservoir compression also depends on pressure applied to the end of cantilever. **Calculation:**

Volume of reservoir:

70 μm × 15 μm × 15 μm = 15750 μm^3

1 litre = 3.345×10^{25} molecules

1 m^3 = 3.345×10^{25} molecules

For the proposed system the total number of molecules occupancy is 5.2683×10^{14} molecules.

1 ml = 3.3×10^{22} molecules

Therefore, for 5.2683×10^{14} molecules = 1.5964 ml.

Hence, one cantilever system can hold up to **1.594 ml.**

For the whole system with 4 cantilever system **6.3856 ml**.

Deflection:

The models were subjected to external pressure. Stoney's equation, which relates cantilever end deflection, "**δ**" to applied stress, "**σ**" and it indicates that the end deflection of cantilever beam is directly proportional to the applied stress. Where, "**ϑ**" is Poisson's ratio, "**E**"is the young's modulus, "**L**" is the beam length and "**t**" is the cantilever thickness.

$$\delta = \frac{3\sigma(1-\vartheta)}{E}\left[\frac{L}{t}\right]^2$$

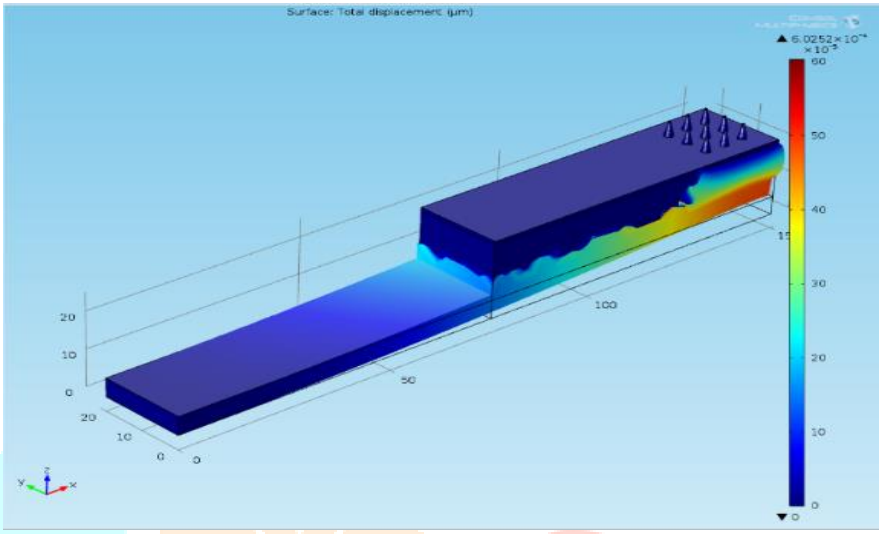

Fig. 7 Displacement plot of single cantilever beam with microneedles

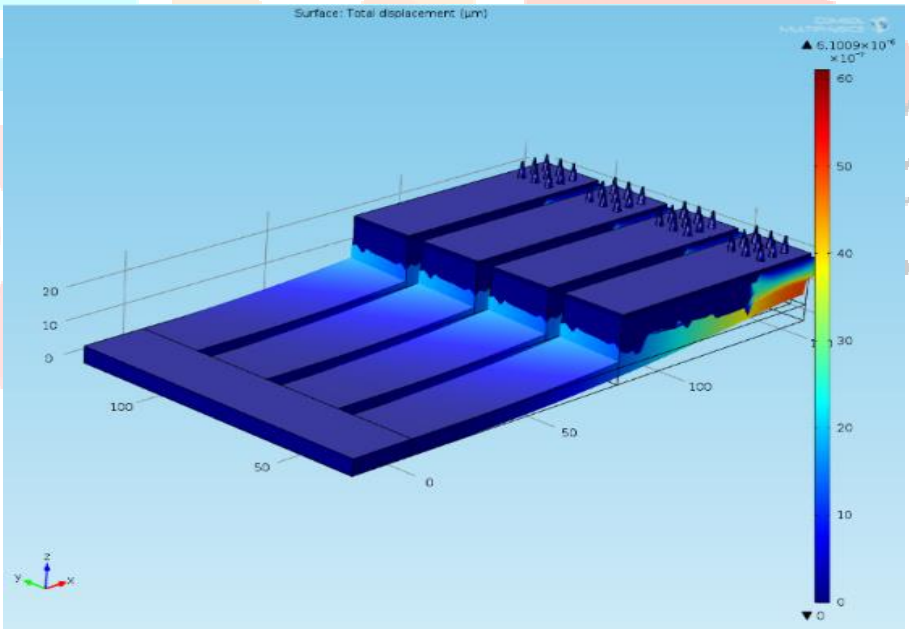

Fig. 8 displacement plot of array of microcantilever for the proposed TTDS

Fig. 7 presents the plot of displacement of the single cantilever based TDDS. Fig. 8 describes the displacement plot of array of microcantilever for the proposed TTDS. The plot in Fig. 10 illustrates comparison between simulation deflection and values of theoretical deflection of array of cantilever microneedle system. This graph depicts pressure in N/m^2 v/s displacement in µm. The above graph illustrates comparison between simulation deflection and values of theoretical deflection of single cantilever microneedle system and array of cantilever microneedle system. This graph depicts pressure in N/m^2 v/s displacement in µm.

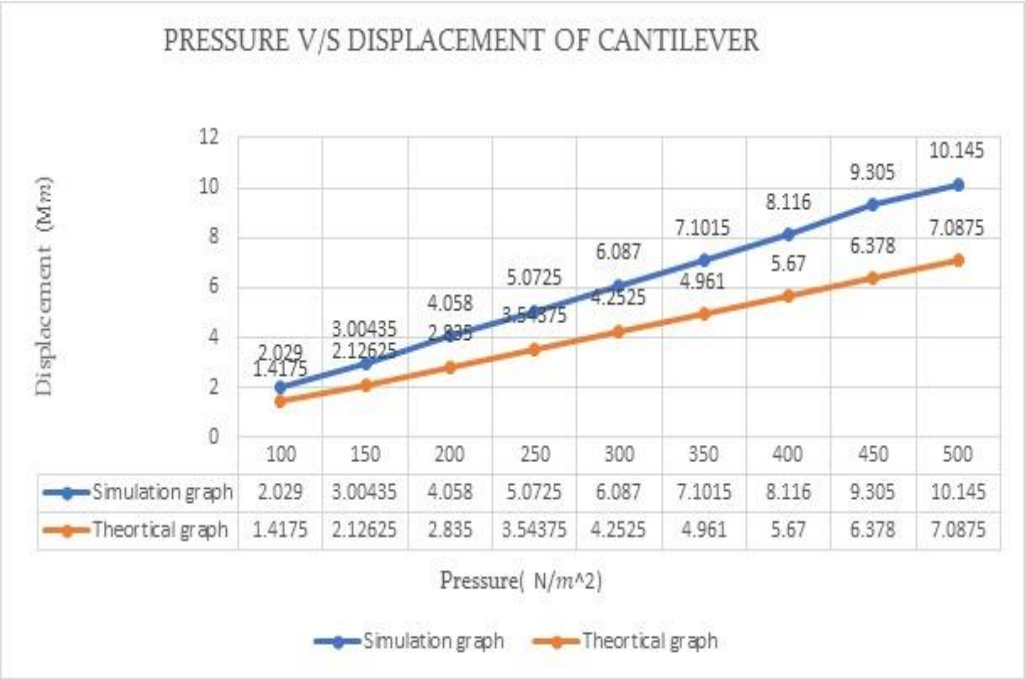

Fig. 10 Plot of pressure v/s displacement

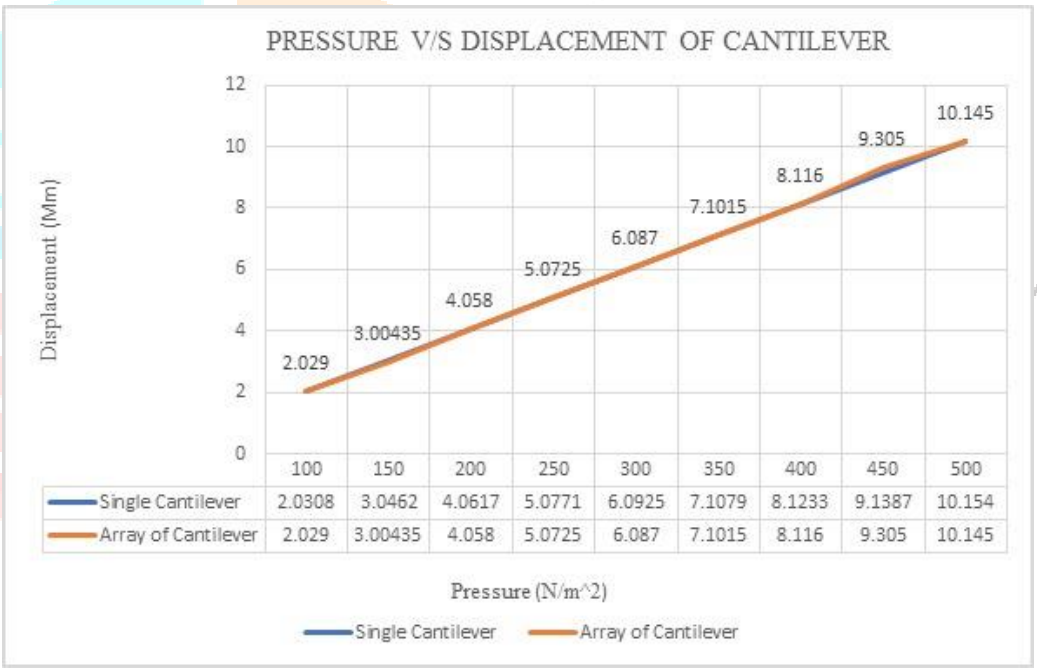

Fig. 11 Plot of pressure v/s displacement

The plot if Fig. 11 illustrates comparison between simulation deflection and values of theoretical deflection of single cantilever microneedle system and array of cantilever microneedle system. This graph depicts pressure in N/m^2 v/s displacement in µm. The above plots and graphs represent deflection and potential plot of the TDDS when external pressure is applied. In order to make the device autonomous a piezoelectric material (aluminum Nitride) is attached at the bottom of the cantilever. When potential is applied to the TDDS the device deflects and in this way the drug can be injected into human body autonomously. The piezoelectric TDDS is shown in Fig. 12. The thickness of the piezoelectric material is taken as 5 µm.

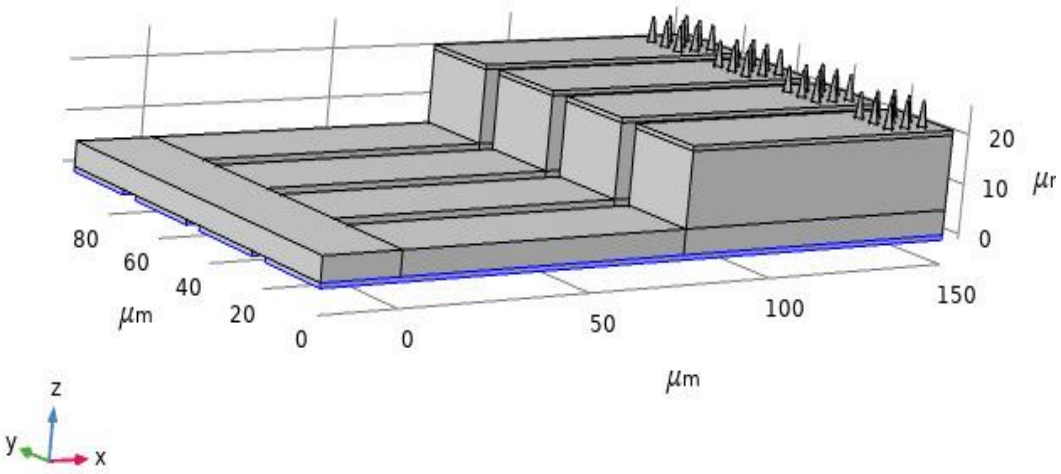

Fig. 12. Piezoelectrically actuated TDDS model

The above model was simulated by applying different potentials. When a potential of 10 V was applied the proposed TDDS model displaced by 10 µm. This TDDS could be placed onto the human body with a small battery embedded to it and a required amount of drug can be delivered autonomously into the human body.

V. CONCLUSION

Compared to the traditional drug delivery system, microneedles have been demonstrated to be safe and successful enough to deliver various drugs. By the model of microneedle array, it is clear that even spacing between microneedles provides the efficient output with the least deformation in the structure. The first model, single cantilever with array of microneedles is effective when the prescribed dosage of drug is limited to the above calculated value **1.594ml**. Whereas the second model, array of cantilever with array of microneedles is designed to meet the higher dosage of drugs according to the patient requirement. Number of cantilevers can be further increased to meet higher dosages. The second model in proposed work can deliver **6.3856ml.** The proposed TDDS model was developed using a piezoelectric actuation, which makes it an autonomous drug delivery system. The actuation voltage can be optimized and the battery needed for the TDDS can be inbuilt on a same chip.

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