A STUDY ON ULTRASOUND BASED TRANSDERMAL DRUG DELIVERY SYSTEM

Thesis submitted in partial fulfillment of the requirements for the degree

of

Master of Technology

in

Biomedical Engineering

by

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Roll No: 211BM1214

Department of Biotechnology & Medical Engineering
National Institute of Technology
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Under the guidance of

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NATIONAL INSTITUTE OF TECHNOLOGY, ROURKELA

CERTIFICATE

This is to certify that the thesis entitled, "**A STUDY ON ULTRASOUND BASED TRANSDERMAL DRUG DELIVERY SYSTEM**" submitted by Mr. SANJEET KUMAR MADDHESHIYA in partial fulfillment of the requirements for the award of degree of Master of Technology degree in Biotechnology & Medical Engineering with specialization in "Biomedical Engineering" at National Institute of Technology, Rourkela is an authentic work carried out by him under my supervision and guidance.

To the best of my knowledge, the matter embodied in the thesis has not been submitted to any other university/institute for the award of any Degree or Diploma.

Date: 04/06/2013

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I am especially indebted to my parents for their love, sacrifice, and support. My full dedication to the work would have not been possible without their blessings and moral support. This thesis is a dedication to them.

Date: 04.06.2013

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ABSTRACT

The development of an ultrasound based Transdermal drug delivery device (or sonophoresis) has received increased attention over the past few years. Meaningful enhanced carrying of model drugs such as mannitol and insulin has been determined using commercial sonicators. However, its practical use is hampered by its large size and weight of the common ultrasound transducer devices. In this project work, a remote controlled drug delivery system (sonophoresis device) with a flat flextensional ultrasound transducer was proposed. It is clearly known that low frequency ultrasound can be used to enhance transdermal drug penetration which is known as sonophoresis. Scientifically, acoustic cavitations outcome in the creation of defects in the stratum corneum allows accelerated absorption of currently applied molecules. The aim of this study was to develop a low cast optimized remotely controlled sonophoresis device with variable resonant frequency for studying Transdermal drug delivery in vitro. Following acoustic validation, 21.75 kHz ultrasound was applied for different durations (range: 5 s to1 min) using three different modes (10%, 33% or 100% duty cycles). The simulation result of first resonance frequency was found to be comparable to that of the experimental result. In comparison with the other types of sonophoresis device, it has a simple structure and its fabrication process is easy and inexpensive.

Keywords: Sonophoresis, Drug delivery, Remote Controlled, Microcontroller (AT89C51), Optimized, Sonophoresis device, Ultrasound, Transdermal drug delivery system.

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ACRONYMS

LED.....Light Emitting Diode
SC .....Stratum Corneum
TDD .....Transdermal Drug Delivery
LCD .....Liquid Crystal Display
RF .....Radio Frequency
RISC .....Reduced Instruction Set Computing
GA.....Glutaraldehyde
CMOS .....Complementary Metal-Oxide Semiconductor
PEROM.....Programmable Erasable Read Only Memory
RISC .....Reduced Instruction Set Computing
CPU.....Central Processing Unit
IC .....Integrated Circuit
CRO ..... Cathode-Ray Oscilloscope

Chapter 1
Introduction

1.1 Introduction

The project entitled "A STUDY ON ULTRASOUND BASED TRANSDERMAL DRUG DELIVERY SYSTEM" is based on the Transdermal Drug Delivery (TDD) using sonophoresis. TDD offers an alternative to the oral drug delivery and provides an attractive alternative to the hypodermal injection too. TDD is basically a painless drug delivery method which offers several advantages over the conventional drug delivery methods. Although TDD is limited by the low permeability of the upper guarding layer of the skin, i.e. Stratum Corneum (SC; the upper 5^{th} layer of the epidermis) which is filled with flat, dead cells and some filaments of keratin. Stratum Corneum provides a barrier to safe the underlying layers of the epidermis from the temperature, infection, chemicals and mechanical stress.

Several methods exist to overcome this barrier and for developing transdermal drug delivery such as chemical enhancers and physical mechanisms such as electroporation (use of a high voltage current), iontophoresis (use of low value current), and ultrasound (also called phonophoresis or sonophoresis, use of ultrasound) [1-4]. This remote controlled drug delivery system was based on the theory of low frequency ultrasound. Ultrasound has also been proposed as a physical enhancer, a method referred to as sonophoresis. Since the mid-1990s that low frequency ultrasound (20 to 150 kHz) has been considered as an effective means of improving transdermal drug delivery. Application of low frequency ultrasound for medical purposes is known as sonophoresis [6-7]. Sonophoresis is widely used in hospitals to deliver drugs through the skin.

1.1.1 How is ultrasound generated?

Ultrasonic signals are basically sound waves which are generated beyond the human audible range. Only few birds like bats and few animals like dogs can hear that sounds. The sounds having the frequency of more than 16 kHz can be considered as ultrasound but only 20 to 50 kHz ultrasound is used for the medical purposes. Ultrasounds are generated by device called a piezoelectric transducer; this piezoelectric transducer has a crystal driver which converts electrical energy in sounds waves. The shape of a crystal can be changed by electrical

simulation and by changing the shape of a crystal one can produce electrical signal. This effect is known as piezoelectric effect.

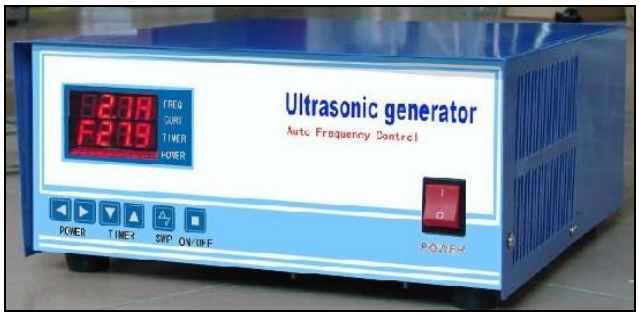

Figure 1.1: Ultrasonic Generator

1.2 Objective

The objective of the thesis was to design a Sonophoresis device in which a low frequency ultrasound (nearby 20 KHz) had been used for the transdermal drug delivery. A temperature Sensor (LM35) was used for the measurement of human body temperature and the temperature had been displayed in a Liquid Crystal Display (LCD).

1.2.1 Data transfer between Transmitter and Receiver using RF signal.

When anyone switches of remote control (switch 1, 2, 3, or 4) had been pressed, the data were decoded by a decoder (HT12D), and then those decoded data had been transmitted using a RF Transmitter. The transmitted data had been received by a RF Receiver and then it had been encoded by an encoder (HT12E). The encoded data was send to the microcontroller (AT89C51) for the generation of signal which had driven the piezoelectric transducer to generate a low frequency ultrasound for different duty cycles.

1.3 Proposed Work

In this work, a commercially available RF Transmitter and RF Receiver along with an AT89C51 microcontroller had been used. A temperature sensor (LM35), for the measurement of human body temperature and Liquid Crystal Display (LCD), for the temperature display had been used.

1.3.1 Thesis overview

This thesis has basically two major part, 1st is Ultrasonic drug delivery & 2nd is remotely controlled drug delivery. The overview of this thesis is as follows:

Chapter 2- Review of Literature: It explains about the anatomy of stratum corneum, background of ultrasound, mechanism of ultrasound and ultrasonic transducer.

Chapter 3- Materials and Method: It explains about different types of hydrogel preparation, different combinations, effect of sonication in vitro and different electronics and electrical components used in this project.

Chapter 4- Results and Discussions: Describes the results and output of the remote controlled drug delivery device.

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Chapter 5- Conclusion and Future work: This concludes about the remote controlled drug delivery system and tells about the future work.

Chapter 2
Review of Literature

Review of Literature

2.1 Anatomy and Physiology of Stratum Corneum

Structurally, the skin is made up of two layers of tissue that have different histological and function characteristics. The first upper thin layer is called epidermis while the lower thick layer is called dermis. Beneath the dermis lies a third layer, consisting largely of adipose tissue. Although this is not part of the skin itself, this layer serves to bind the skin to underlying tissues and supplies it with nerves and blood vessels. This layer is called the hypodermis.

Structurally, the epidermis is well adapted to its key function of preventing fluid loss and providing an effective physical barrier against environmental hazards.

As figure 2.1 shows, the epidermis consists of five distinct layers of cells. Starting from the surface and working toward the deepest layer, these are:

1. Stratum corneum
2. Stratum lucidum
3. Stratum granulosum
4. Stratum spinosum
5. Stratum basale (basal layer).

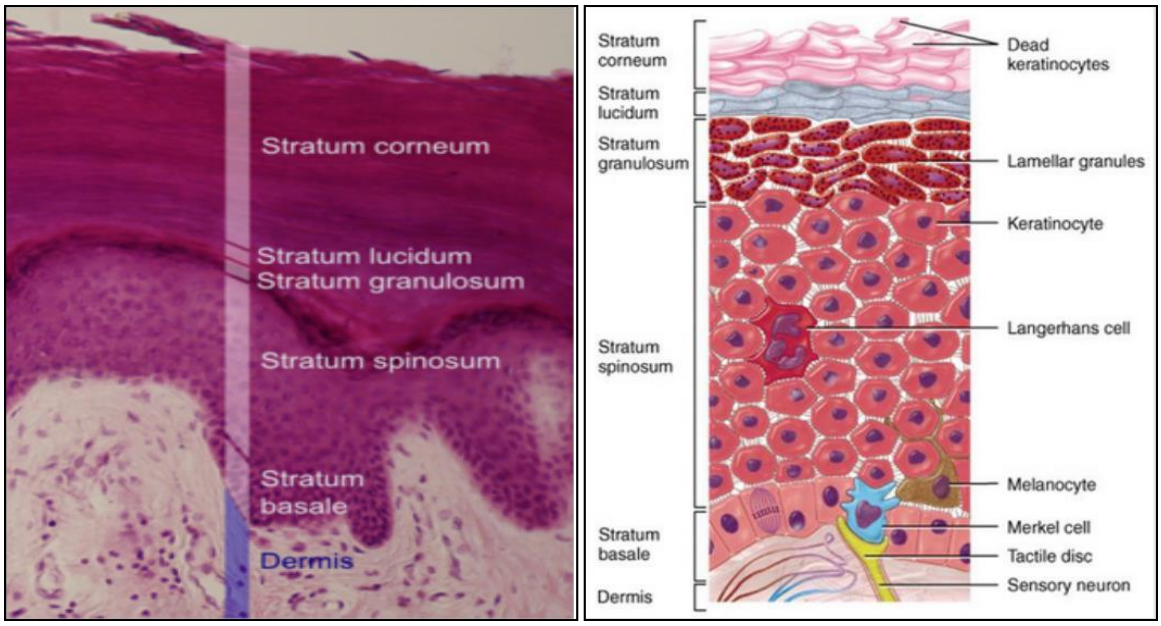


Figure 2.1: Histologic Image of Human Epidermis

The stratum corneum (SC) is the outermost of the 5 layers of the epidermis, consisting of dead cells (corneocytes) that deficiency nuclei and organelles. Cells in the stratum corneum are known as 'horny cells'. They are completely filled with keratin and the spaces between them are filled with lipids, which binds the cells together to form a continuous membrane. The objective of the stratum corneum is to form a barrier to safe underlying tissue from dehydration, chemicals, infection and mechanical stress. To understand the structure and function of the stratum corneum is vital because it is the key to healthy skin and its associated attractive appearance.

2.2 Background on ultrasound delivery and biological effects

There are so many works and paper for the interaction between biological tissue and ultrasonic wave [11]. The ultrasound used for the diagnostic imaging is different from the therapeutic ultrasound. Therapeutic ultrasound gives the results as a controlled sound so that it can interact with the biological tissue and giving the benefit to the health. There are some meaningful application of this technology was developed by Francis and William Fry in the 1950s [13]. They applied their work to make more advance their ultrasonic devices for the surgical treatment of neurological disorders.

So one can divide therapeutic ultrasound in two different types which use "low intensity" and "high intensity" though this division is not purely accurate. Ultrasound having low intensity is an appealing means of noninvasive concentration of deep tissues using external sources where as low intensity ultrasound can be used to deliver the drug inside the body and it can be clinically used in physical therapy to stimulate a normal biological response. Many recent reviews have shown that sonophoresis transdermal drug delivery offers assuring potential for noninvasive drug application [15-17].

2.3 Mechanism of ultrasound

Although ultrasound is known to upgrade transdermal drug delivery, the mechanisms of which have not been fully distinguish. Bioeffects from ultrasound includes the thermal or

mechanical (cavitation) mechanism. The effective principle of sonophoresis (or phonophoresis), is not entirely understood. It is a hypothesis that ultrasound generates an acoustic waves. This acoustic waves cause the result of creating micro bubbles (micro cavitation) in the drug molecules and tissue. Since the ultrasound is transmitted in the fluid media, the high amount of negative pressure causes destructive collapse in bubbles. This bubble creates the pathway in the skin. The other bilipid layers of the skin are temporarily disrupted by this acoustic wave and is cause to create a rearrangement in the SC and thus to pass the drug molecules inside the skin. During transient cavitation, the fast, destructive collapse of bubbles is associated with high acoustic pressures and temperatures of the order of 1000–2000 K [18]. Transient cavities are created in response to high acoustic pressures and/or lower frequencies.

The range of enhancement is calculated by four principal acoustic variables - intensity, frequency, duty cycle, and duration. In common, enhancement of drugs increases with decreasing ultrasound frequency and this is due to the fact that ultrasound causes to happen proportionally more cavitational activity at lower frequencies. Extending the duration of application or using a larger duty cycle in the case of pulsed ultrasound will similarly tend to increase enhancement.

2.4 Ultrasonic Transducer

Ultrasonic transducers play a very important character in nondestructive testing systems, ultrasonic welding instruments, ultrasonic machining technology, and ultrasonic imaging and diagnostic systems. Recently, ultrasound appreciated transdermal drug delivery (TDD) technology (sonophoresis) has taken increasing attention.

To design and fabricate a sonophoresis device, different types of transducer can be used. These are mainly horn-type and the disk-type [22-24]. When the piezoelectric transducer operates on its fundamental resonant frequency its produces the maximum acoustic waves, that’s why in most of the drug delivery system the transducer is performed on it fundamental frequency. This is the major drawback for the sonophoretic drug delivery system that it is associated by large physical size.

2.5 Related Work and Motivation

2.5.1 Related Work

The related works has been mentioned [25]. This paper introduces about design and fabrication of a sonophoresis device with different types of transducer for transdermal drug delivery. In this proposed sonophoresis device, a ring-shaped piezoelectric material and a piece of vibration metal plate were bonded together. The flat flextensional transducer was usually supported at the periphery and vibrates at its first flexure vibration mode. The paper [26] proposes a application protocol for sonophoretic transdermal delivery of a model hydrophilic drug. In this caffeine was selected as a model hydrophilic drug while porcine skin was used as a model barrier. Following acoustic validation, 20 kHz ultrasound was applied for different durations (range: 5 s to 10 min) using three different modes (10%, 33% or 100% duty cycles) and two distinct sonication procedures (either before or concurrent with drug deposition). The paper [27] explains about Effect of sonication parameters on transdermal delivery of insulin to hairless rats.

2.5.2 Motivation

Referring to the Literature survey in Paper [25, 26, 27], our work is extended to design microcontroller based a Remote Controlled Sonophoresis System for Transdermal Drug Delivery.

Chapter 3
Materials and Methods

Materials & Methods

The project entitiled with "A STUDY ON ULTRASOUND BASED TRANSDERMAL DRUG DELIVERY SYSTEM" has two major part, 1st is Drug Dlivery part and 2nd is Electronics part that is Remote Control. Here 1st Drug Dlivery part is in concern.

3.1 Materials Required for Hydrogels Preparation

3.1.1 Gelatin Based Hydrogels as A Matrix for Controlled Delivery

3.1.1.1 Materials

Gelatin was procured from Himedia, Mumbai, India. Ethanol was obtained from Honyon International Inc., Hong Yang Chemical Corpn., China. Glutaraldehyde (25%, for synthesis; GA) and hydrochloric acid (35% pure) was obtained from Merck Specialties Private Limited Mumbai, India. Double distilled water was used throughout the study. Pilot Sl Hi-Tech Ink was purchased from a local student shop.

3.1.1.2 Required Instruments

- Sonicator- apl digital ultrasonic cleaner
- Cooling centrifuge-REMD (C-24BL)
- Magnetic stirrer
- Double beam UV Spectrometer

3.1.1.3 Standard solution for Gaur gum (1% w/v)

0.6 gm. gaur gum was mixed with 60 ml of distilled water at magnetic stirrer, as it takes 6-7 hours to dissolve in water completely.

3.1.1.4 Standard solution for Glutaraldehyde (0.25% v/v)

120 µl of 25% Glutaraldehyde was mixed with 120 ml of distilled water.

3.1.1.5 Standard solution for Ink (0.1% v/v)

500 µl of ink from Hi-tech point ink was mixed with 5 ml of distilled water; hence it is 10 times diluted. Again 50 µl of this diluted ink was mixed with 5 ml of distilled water, that's why the concentration of ink was then 0.1 %v/v.

3.1.2. Preparation of Hydrogel

Twenty grams of gelatin was dissolved in 200 ml of water, whose temperature was maintained at 50^{o}C and kept on stirring at 400 rpm, so as to obtain a clear homogeneous sol. This resulted in the formation of a 10 % (w/v) gelatin sol (GS). Hydrogel were prepared by hot homogenizing (at 50^{o}C) GS and Gaur gum in various proportions (GS:GG ratio being 1:1, 3:1 and pure gelatin) at 800 rpm for 15 min. To this homogenized hydrogel, 1.1 ml of GA reagent (0.5 ml GA+ 0.5 ml ethanol + 0.1 ml HCl) was added and was further stirred for 30 sec. The mixture was then immediately poured into 100 ml beaker and was allowed to form gels. The hydrogelss, so obtained, were washed thoroughly to wash off any unreacted GA and hydrochloric acid.

3.2 Materials Required for Hardware Circuit

3.2.1 AT89C51 Microcontroller

The AT89C51 is an 8-bit microcomputer from ATMEL. It has 128 bytes RAM, 4 k bytes flash programmable and erasable read only memory (PEROM), 2 timers and 6 interrupts. The high-density nonvolatile memory technology of AT89C51 makes it perfect for the family of MCS-51 instruction set and pin out.

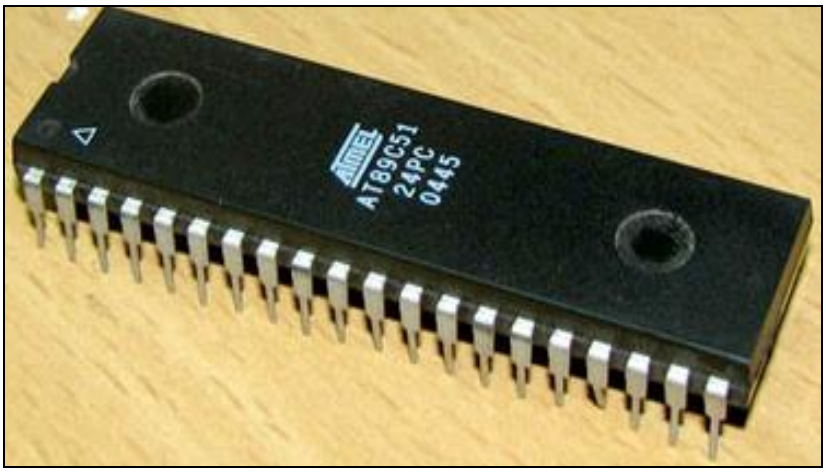


Figure 3.2.1: AT89C51 Microcontroller

3.2.1.2 Features of AT89C51 Microcontroller

- Compatible with MCS-51™ Products
- 4 K Bytes of In-System Reprogrammable Flash Memory
- Fully Static Operation: 0 Hz to 24 MHz
- Three-level Program Memory Lock
- 128 x 8-bit Internal RAM
- 32 Programmable I/O Lines
- Two 16-bit Timer/Counters
- Six Interrupt Sources
- Programmable Serial Channel
- Low-power Idle and Power-down Modes.

3.2.1.3 Architecture and Pin Configuration of AT89C51

The following figure 3.2.2 is the architecture given by the manufacturer:

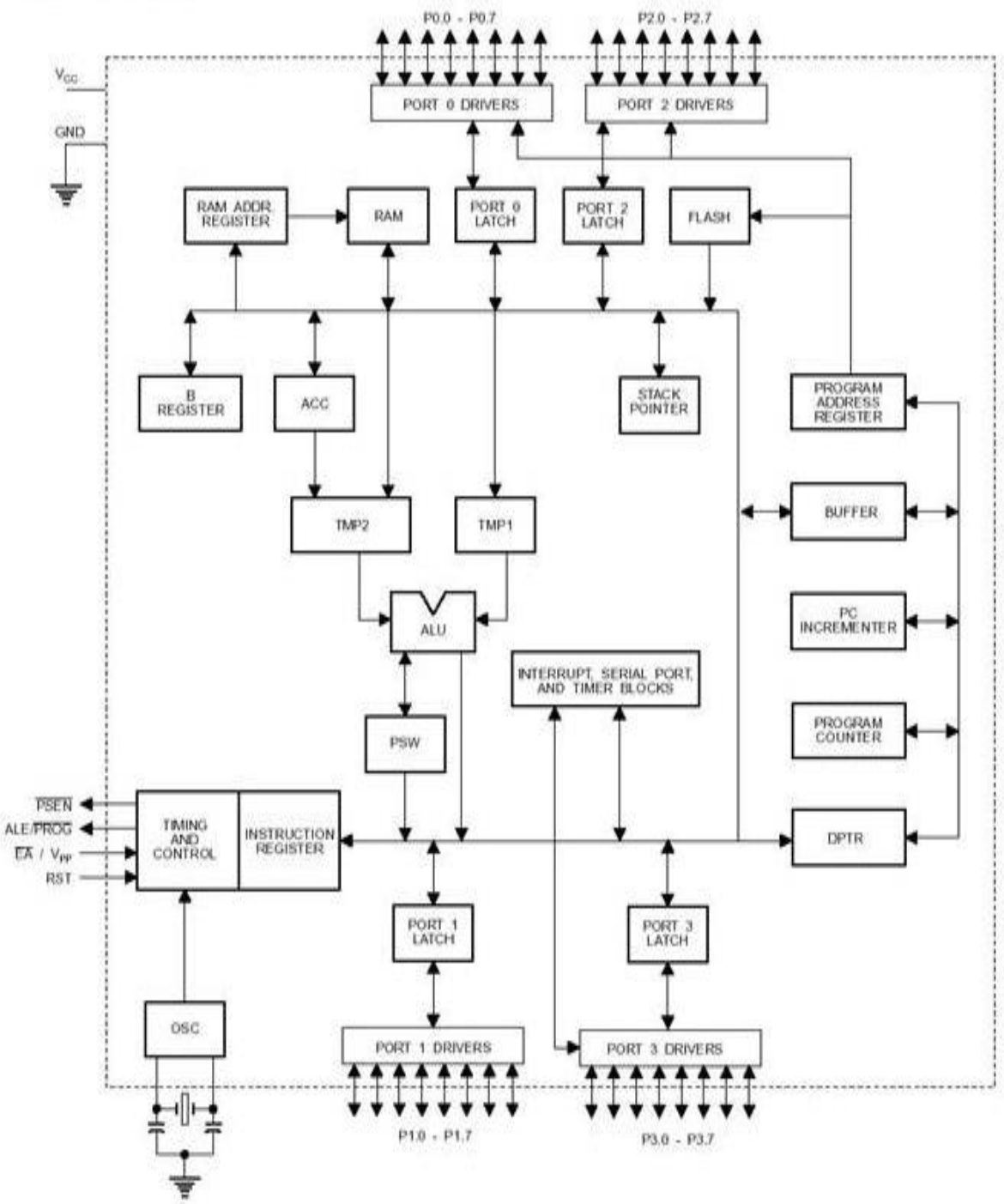


Figure 3.2.2: Architecture of AT89C51

The following figure 3.2.3 illustrates the Pin Configuration of AT89C51:

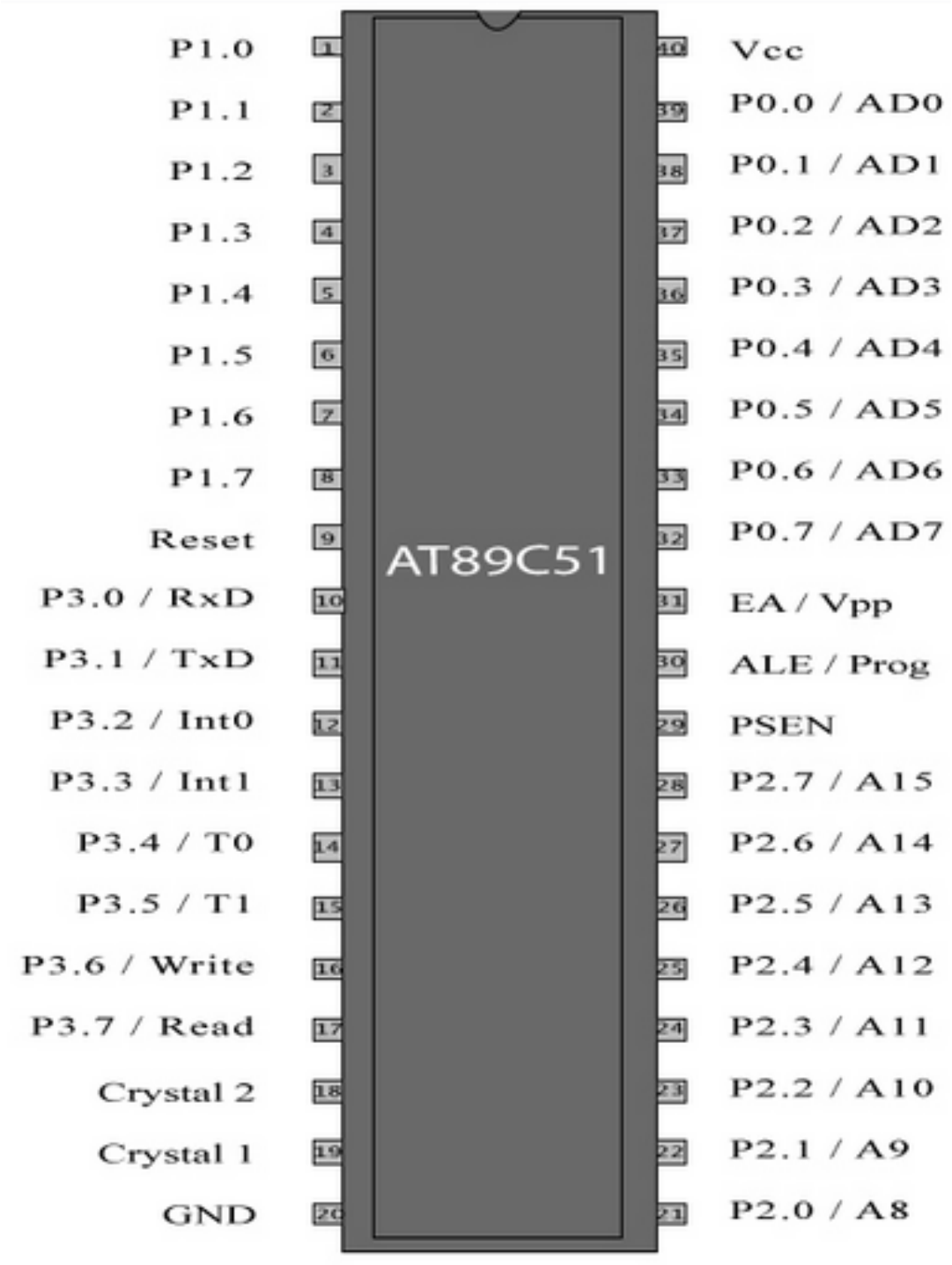


Figure 3.2.3: Pin configuration

3.2.2 7805 Voltage Regulator

A voltage regulator is for to supply a constant voltage level. The 78xx family comprises of commonly used voltage regulators which provide a positive regulated power supply and they are less expensive. The voltage regular 7805 is a regulated power supply which will generate constant 5 V. It is 3 pin self-contained fixed linear voltage regulator integrated circuit. Similarly 79xx family comprises of commonly used voltage regulators which provide a negative regulated power supply. The xx is replaced with two digits, indicating the output voltage.

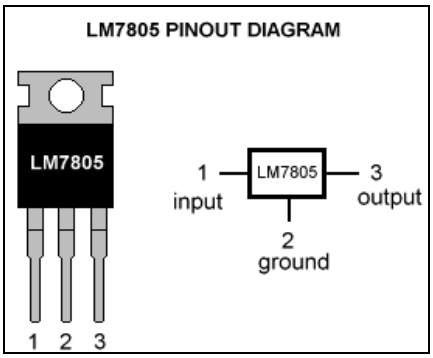


Figure 3.2.4: 7805 Voltage Regulator

3.2.3 Temperature Sensor LM35

The LM35 series are accurate IC temperature sensors. The output of LM35 is linearly proportional to the Celsius (Centigrade) temperature. For 1ºC it will give 10 mV output. The LM 35 does not require any external calibration or correction to provide typical accuracies of ±1⁄4˚C at room temperature and ±3⁄4˚C over a full −55 to +150˚C temperature range.

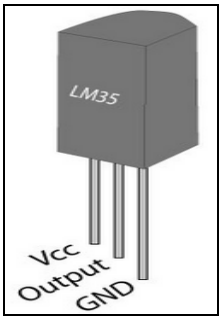


Figure 3.2.5: LM 35 Temperature Sensor

3.2.4 Encoder/Decoder

The encoder/decoder is used before and after transmitter and receiver. The encoder is used for encoding parallel data to serial data for serial transmission. The received data from the RF receiver is decoded to parallel data using decoder. In this project work HT12E encoder and HT12D decoder had been used. These are basically 18 pin Integrated Circuits.

Figure 3.2.6: Encoder HT12E & Decoder HT12D

3.2.4.1 Pin Assignment Of Encoder And Decoder

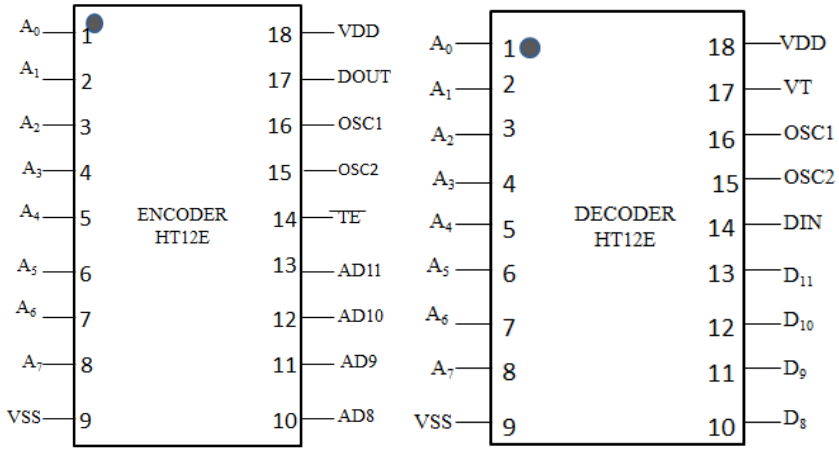


Figure 3.2.7: Pin Assignment Of Encoder And Decoder

3.2.5 LM358

LM358 is an 8-pin Integrated Circuit. It contains two low power operational amplifiers. The LM358 is generally used as amplifiers, all types of filters and analog adders. The main advantage of using this LM358 in place of OP741 is that it can operate with a single static

power supply. This power supply can be varying between a minimum of 3 V to a maximum of 32 V. While using single power supply the LM358 can be connected to the positive power only while the negative supply is replaced by the mass.

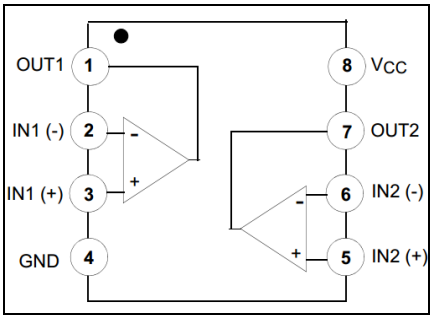


Figure 3.2.8: LM358

3.2.6 RF Module

Radio Frequency (RF) Modules are most widely used wireless transfer data. This makes them most suitable for remote control applications. The RF module which is used in this project is operated on 433 MHz.

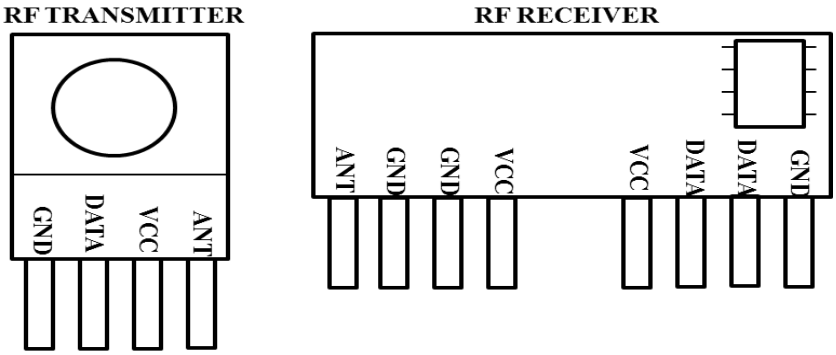


Fig: 3.2.9 RF MODULE PAI PIN CONFIGURATION

3.2.6.1 Features of RF Module

- Range in open space (Standard Condition) : 100 Meters
- TX supply voltage : 3V – 6V
- Low Power Consumption
- RX Receiver Frequency : 433 MHz
- RX Typical Sensitivity: 105 dBm.

3.2.6 ADC0804

The ADC080X fanily of the ADC0800 series from National Semiconductor. The ADC0804 is an 8 bit parallel Integrated Circuit. This IC requires +5 V power supply for operation and it has resolution of 8 bit, hence the number of steps will be 256. Thus for +5 V power supply (if pin. 9 is not connected) the step size will be 19.53 mV. ADC0804 has two clocks, one is external and another one is internal clock. The conversion time i.e. to the time for analog to digital conversion, depends upon the clocking signals. The conversion time cannot be faster than 110µs. if the resolution is high, it will provide a smaller step size, where step size is the smallest change that can be detected by an ADC. Conversion time is defined as the time it takes the ADC to convert the analog input to a digital number and is dependent the value of the resistance and capacitor fixed with the pin number 4.

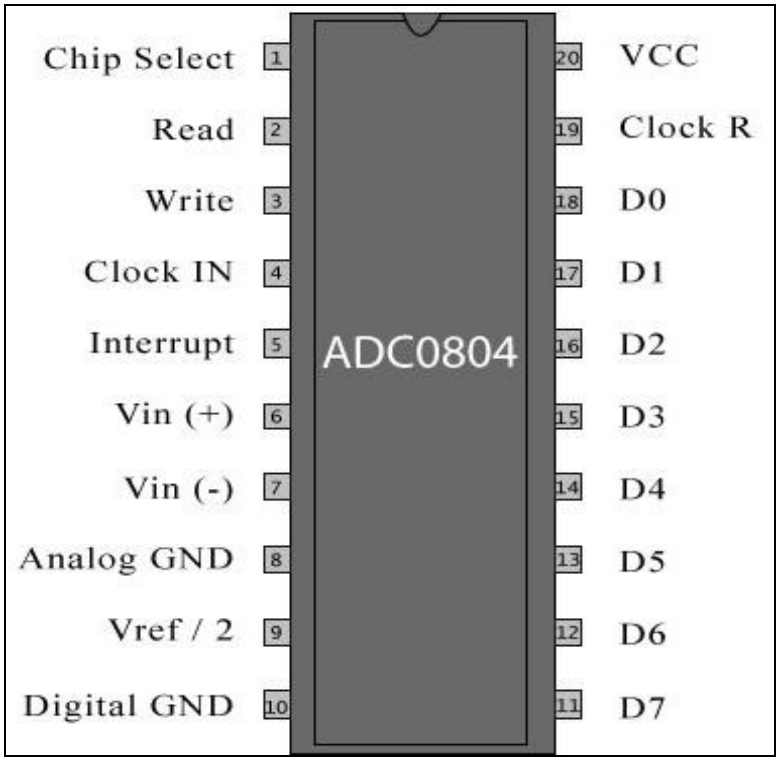


Figure 3.2.10: ADC 0804

Chapter 4
Results and Discussions

Results and Discussions

4.1 Standard Absorbance Curve for Ink

500 µl of ink from Hi-tech point ink was mixed with 5 ml of distilled water; hence it was 10 times diluted. Again 50 µl of that diluted ink was mixed with 5 ml of distilled water, that's why the concentration of ink was then 0.1 %v/v.

In test tube 1st, took 1 ml of 0.1 %v/v and 4 ml of water, so the concentration of the ink in the test tube 1st was then 0.04 %v/v. Similarly in test tube 2nd 2 ml of ink and 3 ml of water, in test tube 3rd 3 ml of ink and 2 ml of water, in test tube 4th 4 ml of ink and 1 ml of water and in test tube 5th 5 ml of ink (fig. 4.1). The concentration of the ink in the respective test tubes and their optical density taken at 585.5 nm is given in the table below:

Table 4.1: Standard Absorbance Curve for Ink

S. No.	Conc. Of Ink (µl/ml)	Absorbance(585.5nm)
1	0.02	0.0903
2	0.04	0.1743
3	0.06	0.2903
4	0.08	0.3414
5	0.10	0.4204

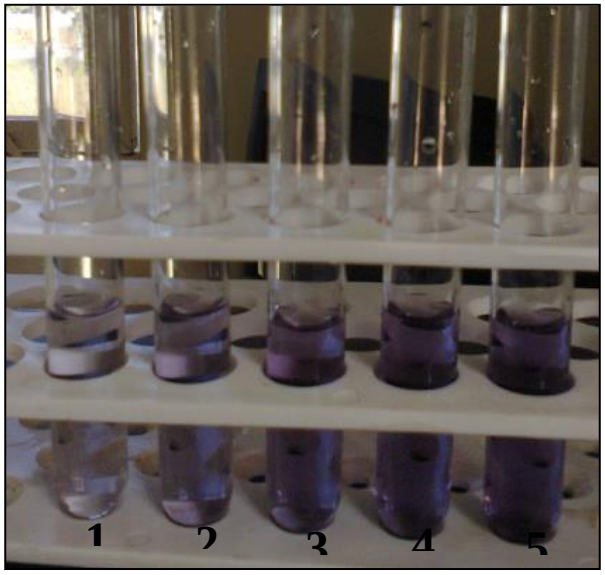


Figure 4.1: Sample of inks for the standard graph

On the basis of the above table, plot the curve in **Origin Pro 8** software.

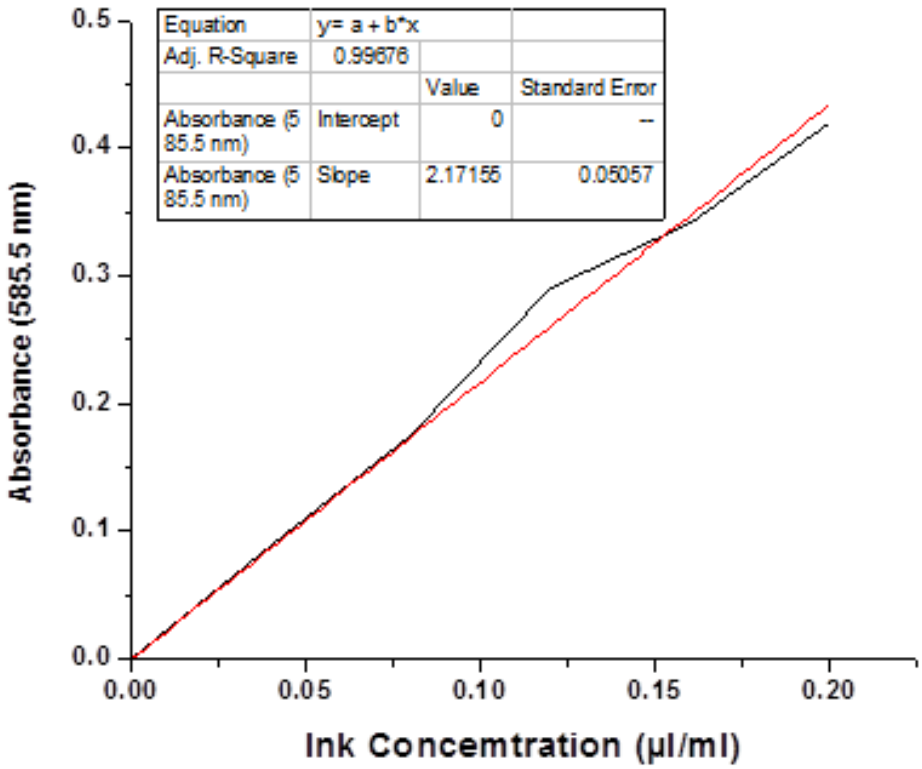


Figure 4.2: Standard Absorbance Curve for Ink

Result: The curve is a straight line as expected.

4.2 Preparation of Hydrogels

The various compositions of the hydrogel have been tabulated in table 4.2.

Table 4.2: Composition of Hydrogels

S. No.	Gelatin	Gaur gum	V/V Ratio	W/V Ratio
1.	20 ml	-	-	-
2.	10 ml	10 ml	1:1	10:1
3.	15 ml	05 ml	3:1	30:1

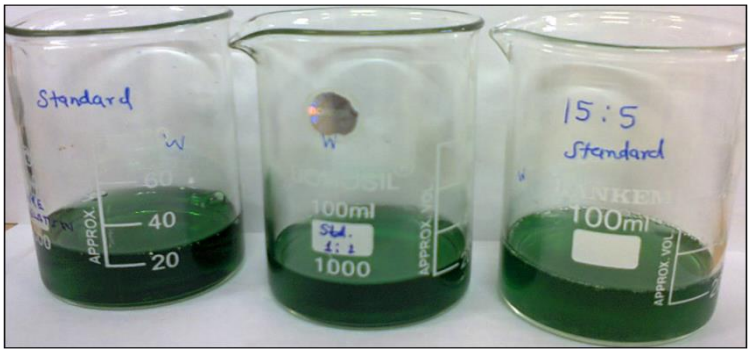


Figure 4.3: Standard Solution

In this 20 ml solution of gelatin and gaur gum, mixed 300 µl of standard ink 3.33% and 1.1 ml of GA reagent (0.5 ml GA+ 0.5 ml ethanol + 0.1 ml HCl) was added and was further stirred for 30 sec and after that keep this solution for 3-4 hours for the gel formation.

4.3 Sonication of Hydrogels

After the gel formation, put 10 ml distilled water in all the beakers and take out the water after sonication for the ink absorption using optical density measurement.

So we had made the 4 different samples for different duty cycles of sonication (fig. 4.4). Standard solution will be used as without sonication, solution 1 will be used for 10% duty cycle of sonication, 2nd will be used for 33% duty cycle of sonication and 3rd will be used for 100% duty cycle of sonication (fig. 4.5).

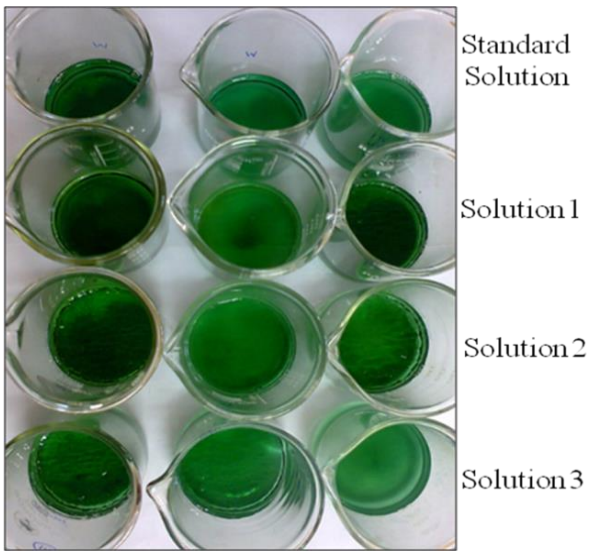


Figure 4.4: Set of Solutions

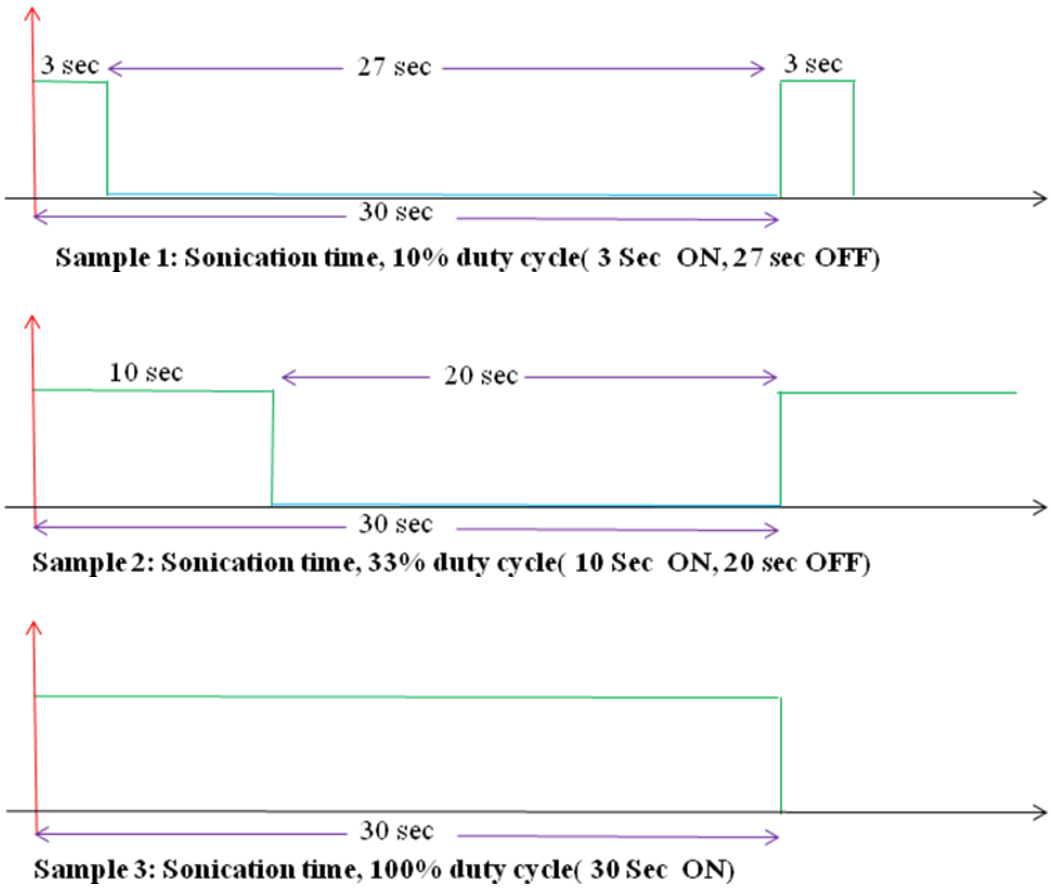


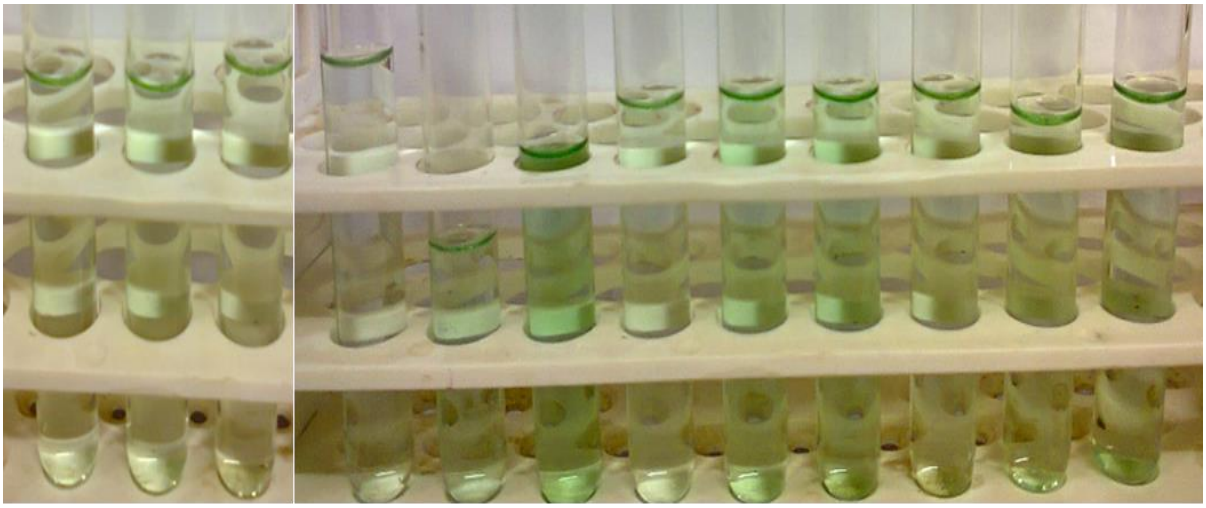
Figure 4.5: Sonication Time (duty Cycles)

4.4 Spectrometer Reading of Different Samples (hydrogels)

After sonication of all the samples, take the spectrometer reading for the absorption of the ink in the distilled water. The spectrometer reading is shown below in table 4.3.

Table 4.3: Spectrometer Reading of Different Samples (hydrogels)

S. No.	Sample	Pure Gelatin	Gelatin: GG(1:1)	Gelatin: GG(15:5)
1	Standard Sol.	0.0130	0.0150	0.0115
2	1	0.0107	0.0306	0.0608
3	2	0.0156	0.0322	0.0357
4	3	0.0248	0.0320	0.0451



Standard solution Solution 1 Solution 2 Solution 3

Fig. 4.6 Ink absorption after sonication with different duty cycles

4.4.1 Calculation Table

On the basis of the spectrometer reading the calculation has been done and the calculation table is shown below in the table:

Table 4.4: Calculation Table

S. No.	Optical Density	µg/ml	µg/10 ml	% of Release of ink
1.	0.0130	0.00598	0.0598	0.598
2.	0.0150	0.0069	0.069	0.69
3.	0.0115	0.0053	0.053	0.53
4.	0.0107	0.00493	0.0493	0.493
5.	0.0306	0.00141	0.0141	0.141
6.	0.0608	0.0280	0.280	2.80
7.	0.0156	0.0072	0.072	0.72
8.	0.0322	0.01483	0.1483	1.483
9.	0.0357	0.01644	0.1644	1.644
10.	0.0248	0.01142	0.1142	1.142
11.	0.0320	0.014736	0.14736	1.4736
12.	0.0451	0.021	0.21	2.1

4.5 Graphs for the concentration of ink released

On the basis of the calculation table, the % absorption of ink in the distilled water has been plotted using **Origin Pro 8** software. The graph for the concentration of ink released is shown below in the figure 4.7.

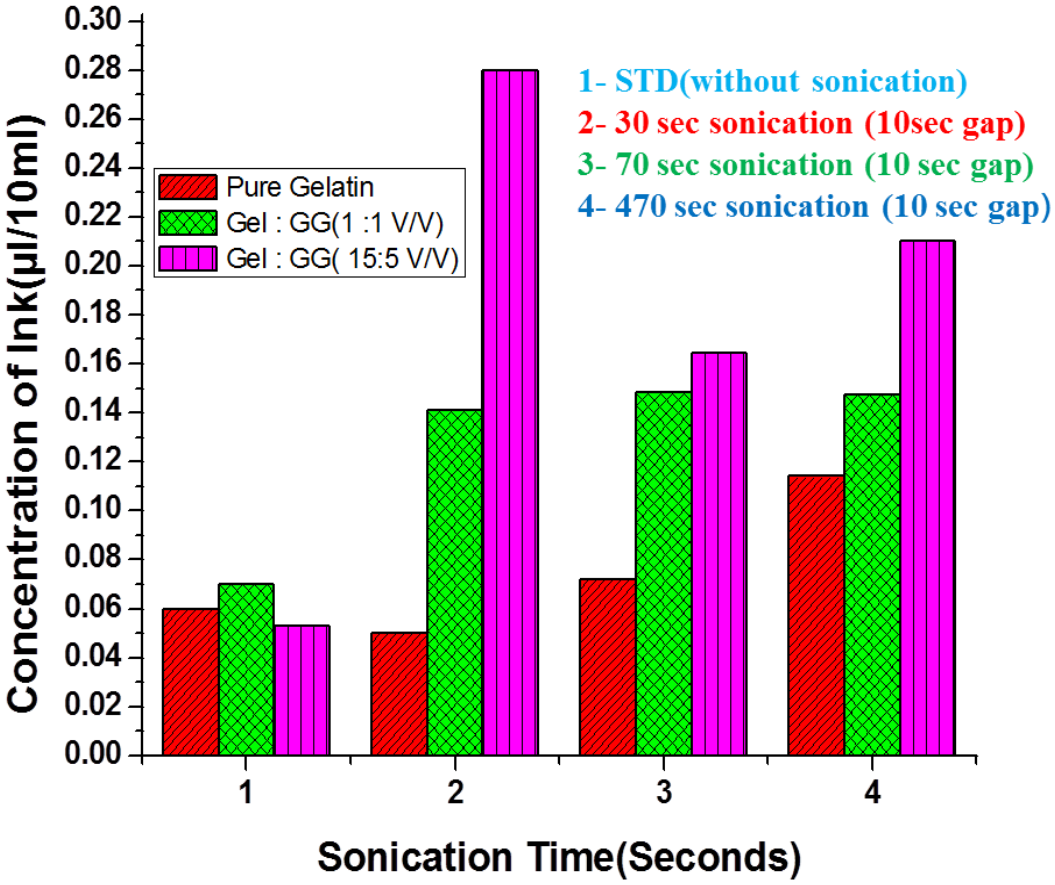


Figure 4.7: Graphs for the concentration of ink released

4.6 Resonant Frequency of Piezoelectric Transducer

The piezoelectric transducer can be considering as a series RLC circuit. The resonance of a series RLC circuit occurs when the inductive and capacitive reactance are equal in magnitude but cancel in each other because they are 180^0 apart in phase. The RLC circuit has a minimum of impedances Z=R at the resonant frequency and the phase angle is equal to zero at resonance.

4.6.1 Block diagram

The block diagram of resonant frequency circuit is shown below. In this circuit a function generator is used for the supply of alternative voltage with variable frequency from 200 Hz to 25 MHz. A CRO is used for the measurement of output voltage from the load resistance of 100 ohms.

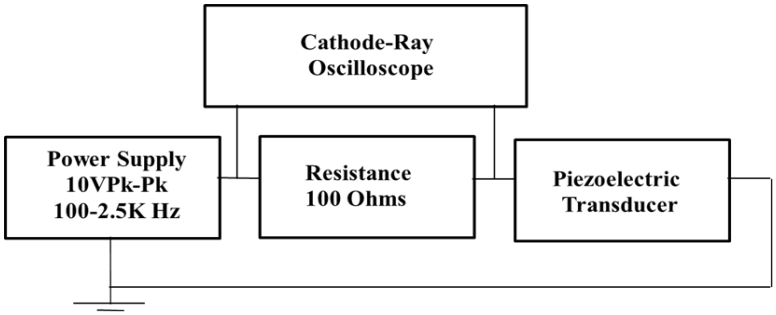


Figure 4.8: Block diagram of frequency measurement circuit

4.6.2 Circuit Diagram

The circuit diagram is shown below;

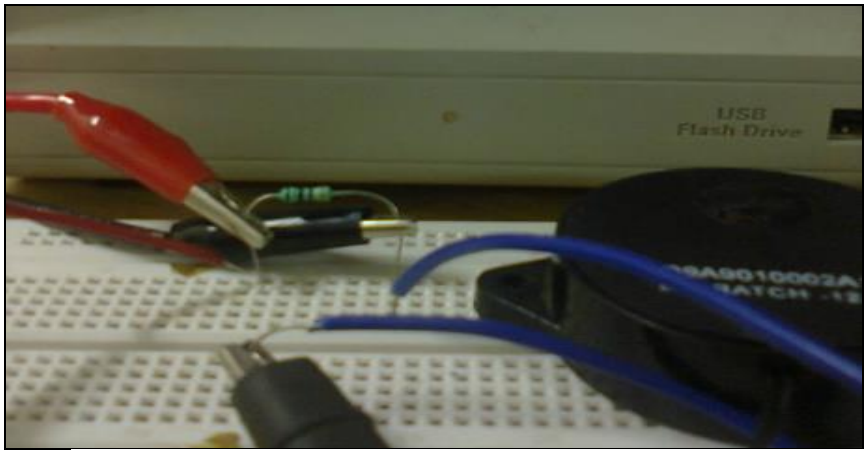


Figure 4.9: Circuit Diagram of Resonant Frequency Measurement

4.6.3 Output voltage across the load resistance

The table between frequency variation and output voltage in CRO is given below. As well as the frequency of the input signal is increasing the output voltage across load resistance is also increasing. The whole circuit is behaving like a low pass filter.

The supply voltage is 10 $V_{Pk\text{-}Pk}$ and the value of the load resistance is 100 Ohms.

Table 4.5: Measurement Table

S. No.	Frequency (Hz)	$V_{PK\text{-}PK}$ Range(Volt)	$V_{PK\text{-}PK}$ (Volt)
1.	500	7.76 - 7.84	7.80
2.	700	8.32 - 8.40	8.36
3.	900	8.70 - 8.80	8.75
4.	1000	8.96 - 9.04	9.00
5.	1100	9.20 – 9.28	9.24
6.	1200	9.36 – 9.44	9.40
7.	1300	9.44 – 9.52	9.48
8.	1400	9.60 – 9.68	9.64
9.	1500	9.68 – 9.76	9.72
10.	1600	9.76 – 9.84	9.80
11.	1700	9.84 – 9.92	9.84
12.	1800	9.92 – 10.10	10.01
13.	1900	9.92 – 10.10	10.01
14.	2000	10.00 – 10.10	10.05
15.	2100	10.00 – 10.10	10.05
16.	2200	10.00 – 10.10	10.05
17.	2300	10.00 – 10.10	10.05

4.6.4 Graph for the Calculation of Resonant Frequency of Piezoelectric Transducer

On the basis of the measurement table the graph has been plotted using Origin Pro 8 software. The graph for the Calculation of Resonant Frequency of Piezoelectric Transducer is shown below in the figure 4.7.

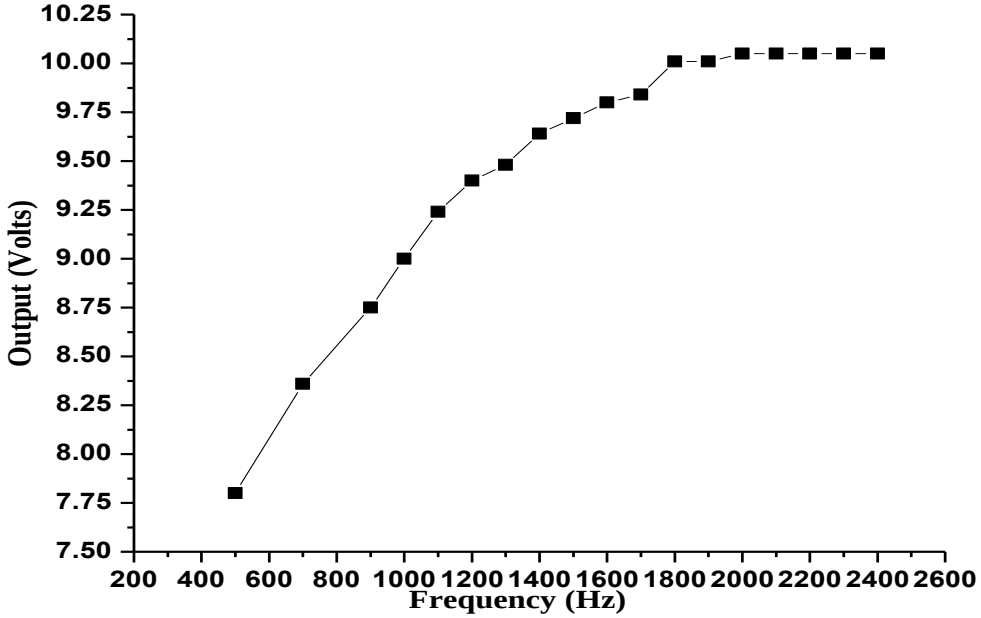


Figure 4.10: Graph for resonant frequency of Piezoelectric Transducer

4.6.5 Result

From the graph it is very clear that the piezoelectric transducer is behaving like a low pass filter and the cut off frequency (Resonant Frequency for the RLC circuit) is 1.999 KHz.

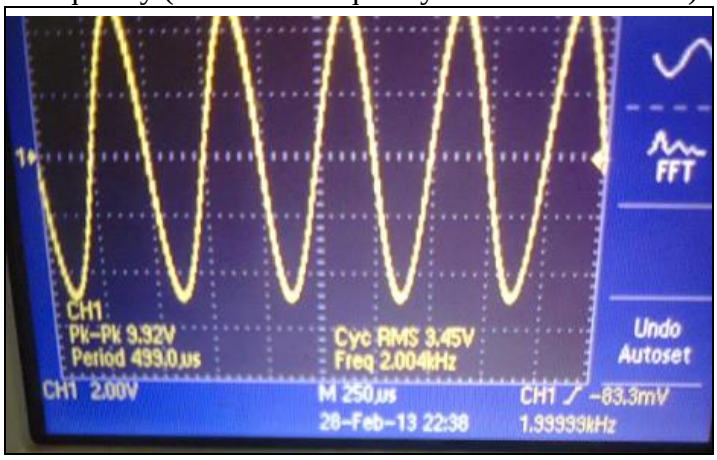


Figure 4.11: CRO Output for Resonant Frequency Measurement

4.7 Generation of 20 KHz Frequency of sine wave using ICL8038 IC

The sine wave signal generator was developed using a monolithic ICL8038. The designed circuit has been shown in figure 4.12. The circuit was designed to generate sinusoidal signal of variable frequency in the range of 100 Hz to 25 KHz. The frequency of the generated signal may be controlled by varying the R1 and C1 components. A potentiometer of 10 KΩ was used as R1 while 0.1 µF and 0.001 µF capacitors were used for generating frequency in the range of 100 Hz-1 KHz and 1 KHz-25 KHz, respectively. The amplitude of the sinusoidal signal may be altered by varying R2, R3 and R4 resistors. When R2, R3 and R4 was chosen as 15 KΩ, 1 KΩ and 15 KΩ, respectively, the amplitude of the sinusoidal waveform was found to be 4.6 Vpp. The stability of the signal generator was determined by determining the Vpp and Vrms across the frequency range. The results have been shown in table 4.6. The results suggested that the output of the signal generator was stable in the desired frequency range of 100 Hz to 25 KHz. The output of the signal generator was fed into a unity gain voltage buffer working in the non-inverting mode (figure 4.2). This was done to ensure that the signal generator is not affected due to the loading effect. The signal generator followed by the voltage buffer was regarded as the sinusoidal waveform generator (SWG).

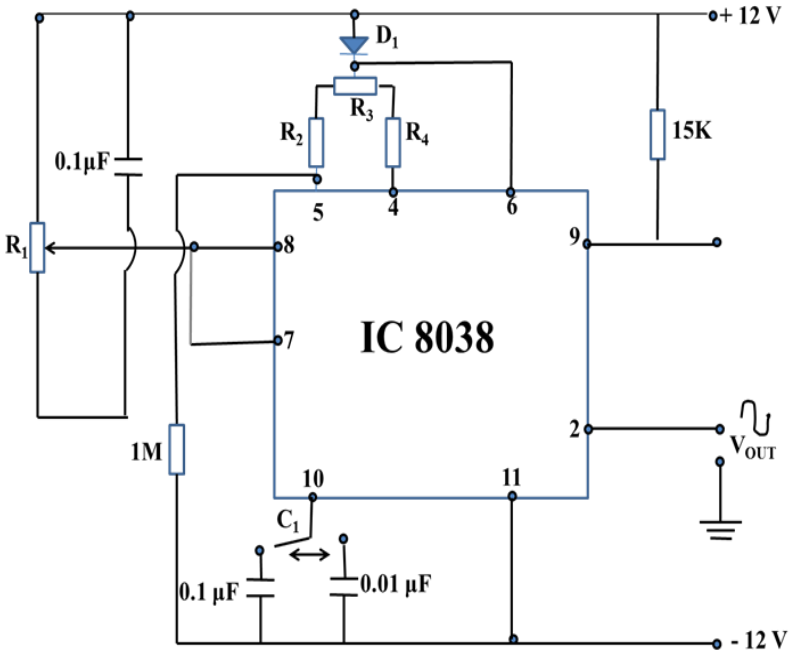


Figure 4.12: Circuit diagram of sine wave signal generator

Table 4.6: The output stability of IC 8038

S. No.	Frequency (Hz)	V_{PK-PK} (Volt)	V_{RMS} (Volt)
1.	100	4.60	1.626
2.	300	4.60	1.626
3.	500	4.60	1.626
4.	700	4.60	1.626
5.	900	4.53	1.601
6.	1000	4.53	1.601
7.	2000	4.53	1.601
8.	3000	4.53	1.601
9.	4000	4.53	1.601
10.	5000	4.53	1.601

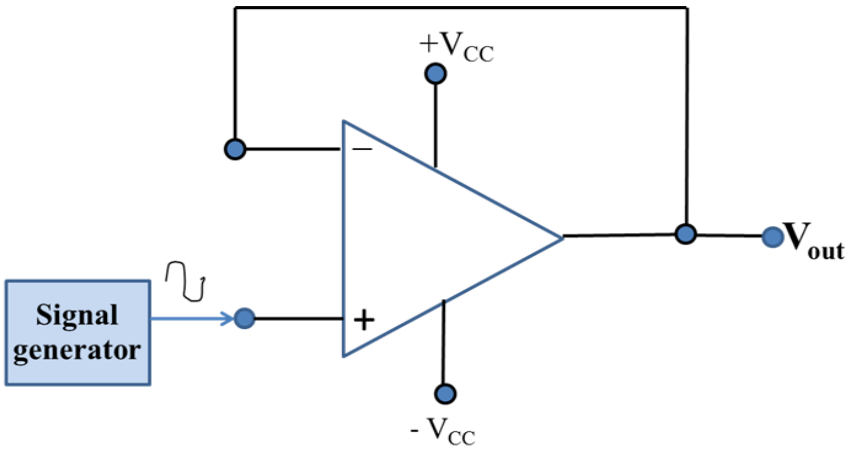


Figure 4.13: Schematic representation of sinusoidal waveform generator.

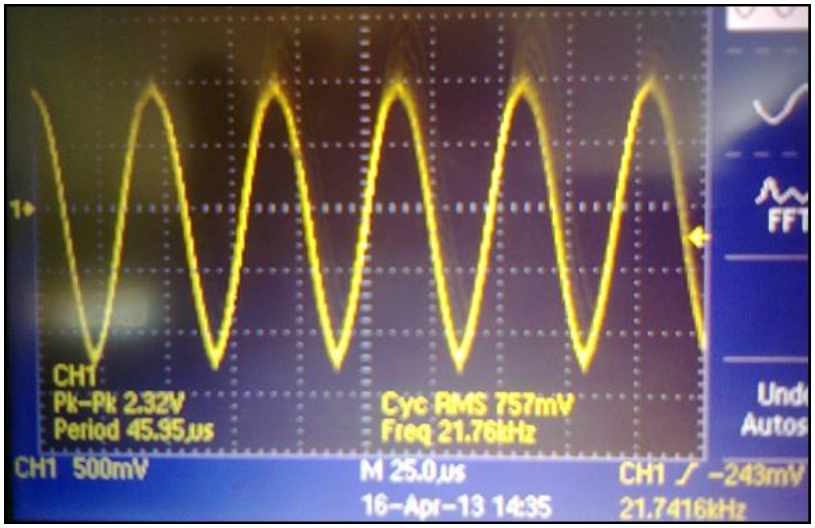


Figure 4.14: Generation of 21 KHz Frequency of sine wave using ICL8038 IC

4.8 Design and Fabrication of a Remote Controlled Drug Delivery System

The development of an ultrasound based transdermal drug delivery device had received increasing attention over the recent years. In this project we had designed a low cast optimized sonophoresis device with variable resonant frequency for studying transdermal drug delivery in vitro.

4.8.1 Simulation of Circuit Diagram in Proteus ISIS

The simulation of circuit diagram in Proteus ISIS for LED blinking program using microcontroller AT89C51 with temperature sensor LM35 is shown below (figure 4.15).

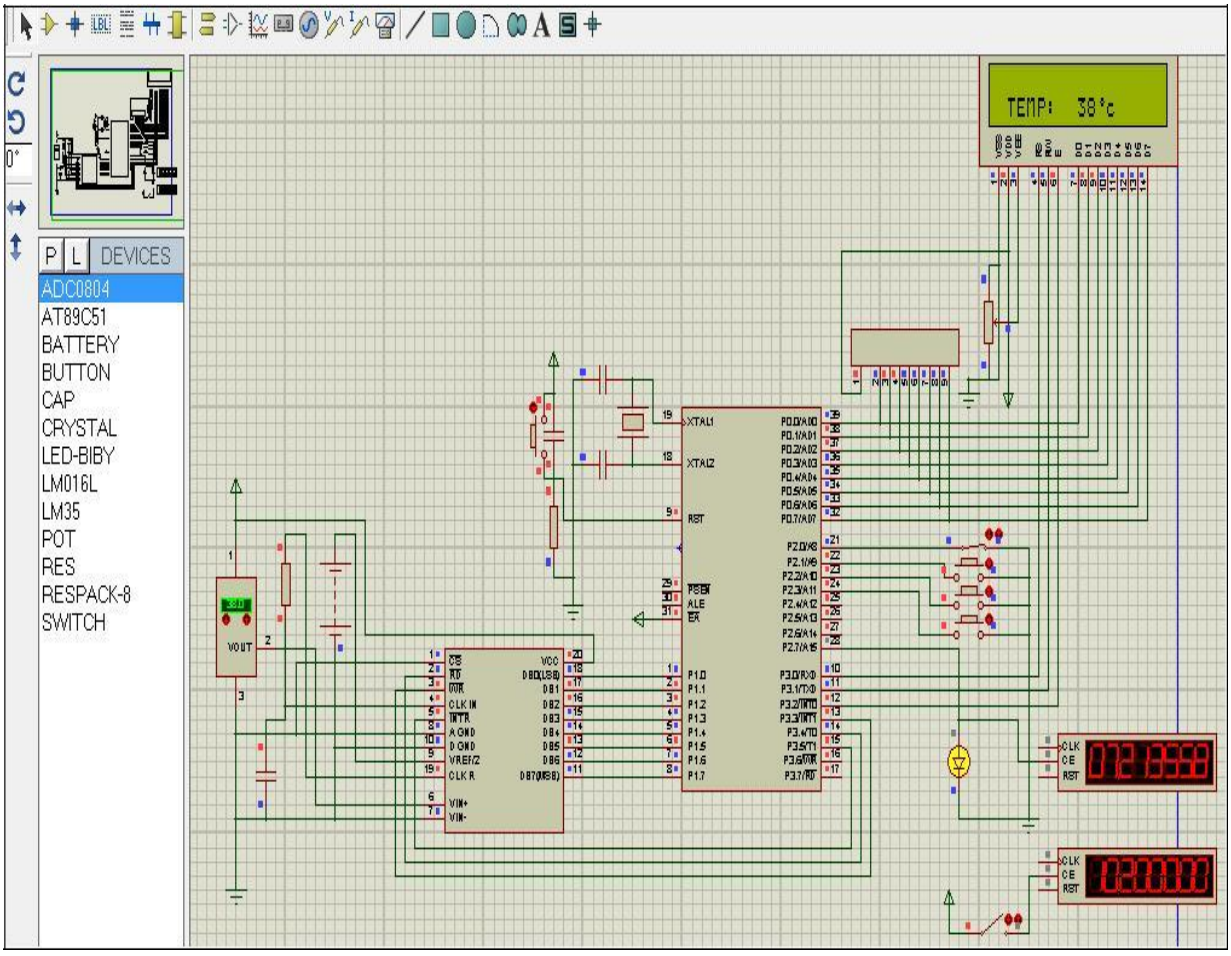


Figure 4.15: Simulation of Led Blinking Program Using Microcontroller "AT89C51" With Temperature Sensor "LM35"

4.8.2 Use of LED Blinking Output

This was the main output, which was used for the supplying of the power supply voltage for the sine wave signal generator ICL8038 to generate a sine wave of 21 KHz frequency. This sine wave was used as an alternative voltage source for the operating of piezoelectric transducer to generate ultrasound for transdermal drug delivery. In the simulation software the LED was blinking for different duty cycle. The programming was done in this manner, like if switch 1^{st} from the remote control section was pressed; the LED was glowing continuously until the switch 1^{st} is unpressed. When the switch 2^{nd} was pressed once; the LED was glowing exactly for 3 sec and after that it was off for exactly 27 sec. Again it was on for 3 sec and off for 27 sec. The whole process was repeated for three times. Similarly when the 3^{rd} switch was pressed once; the LED was glowing exactly for 10 sec and after that it was off for exactly 20 sec. Again it was on for 10 sec and off for 20 sec. The whole process was repeated for three times. Similarly when the 4^{th} switch was pressed once, the LED was on for 30 sec continuously and after that it was off automatically.

4.8.3 Remote Control Section of Drug Delivery Device

The remote control of the drug delivery device is shown below.

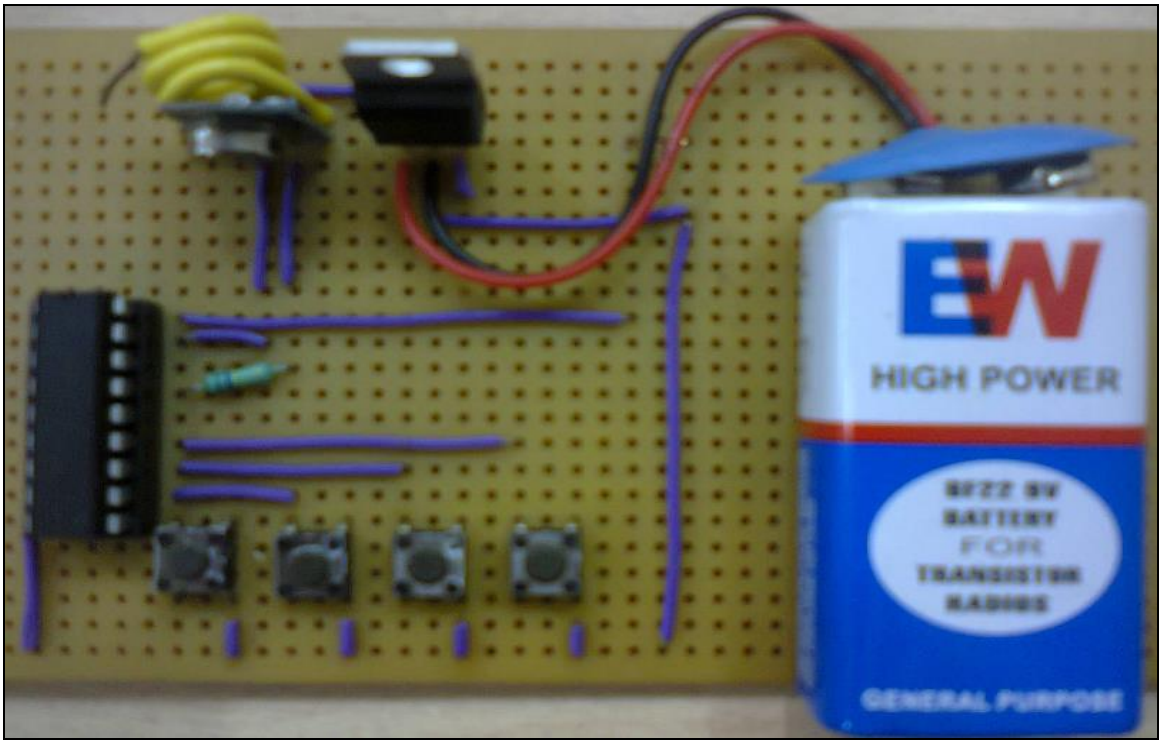


Figure 4.16: Remote Control Section of Remote Controlled Drug delivery Device

4.8.4 Temperature Output of Remote Controlled Drug Delivery Device

The receiver part of the drug delivery device is shown below in which temperature sensor LM35 was inbuilt to measure the body temperature. The circuit uses IC LM35 as the temperature sensor. The output of LM 35 is given to the IC ADC0804 which converts the analog output of the LM35 to digital output. Again this digital output is given to the microcontroller AT89C51 to process and display the temperature in LCD display.

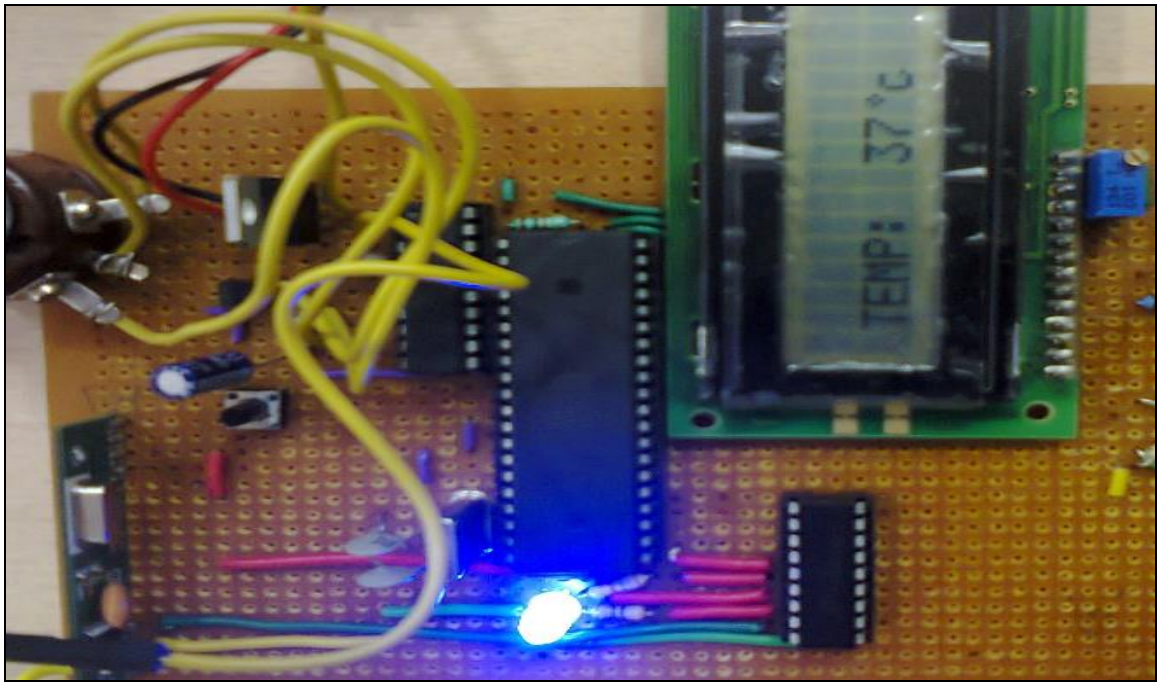


Figure 4.17: Temperature Output of Remote Controlled Drug Delivery Device

4.9 Generating 21 KHz frequency from the circuit remotely

Here with the help of designed circuit, a sine wave of 21 KHz frequency was generated to operate the piezoelectric transducer to produce low frequency ultrasound (20 KHz) for the transdermal drug delivery. In this circuit microcontroller was used for the generating of a pulse having different duty cycles (10%, 33% & 100%). The output of the microcontroller was used as the power supply for the signal generator IC 8038, which was the main IC for the generation of sine wave having 21 KHz frequency. The output frequency is shown in a CRO. The output of the designed circuit is shown below in the figure 4.18.

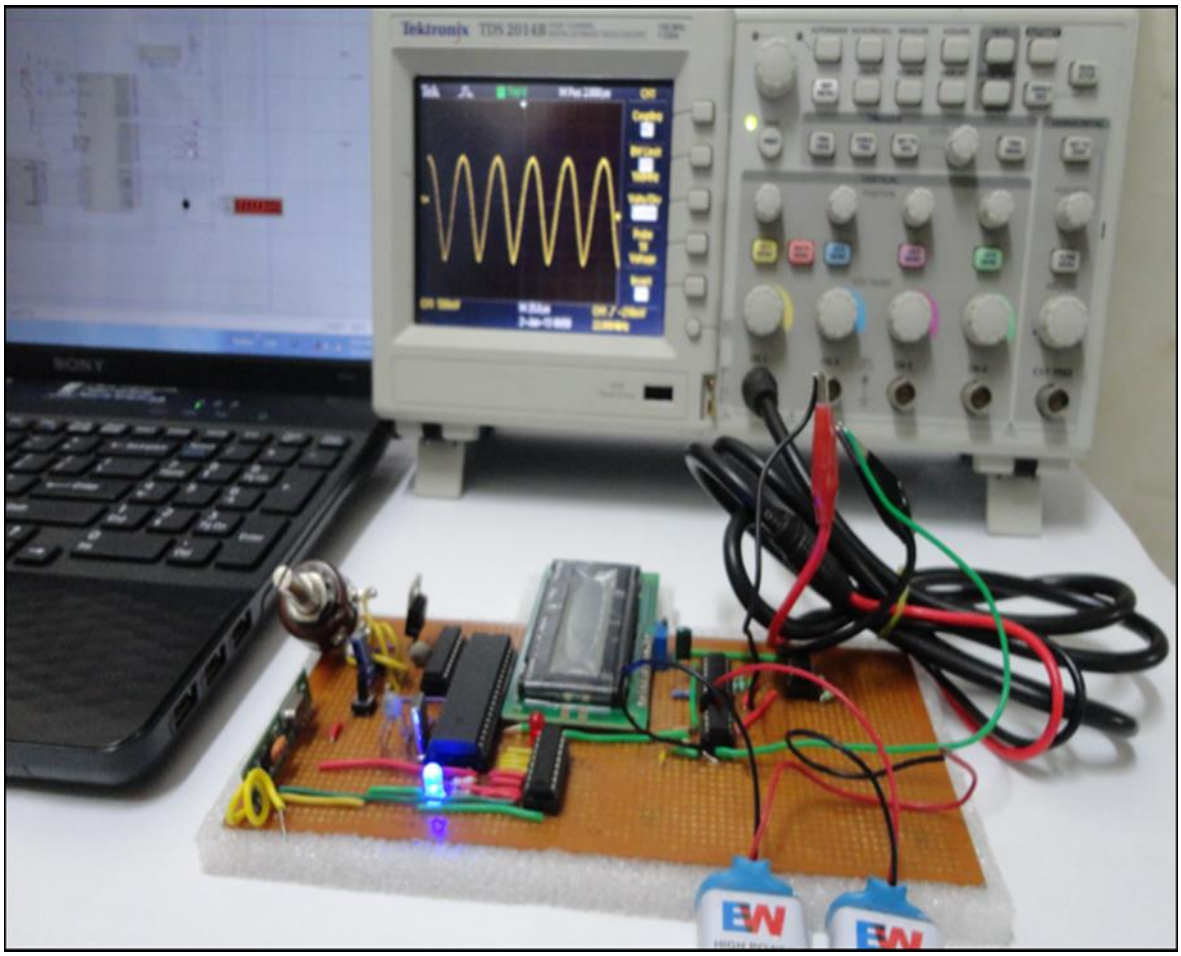


Figure 4.18: 21 KHz Frequency Generating From the Circuit

4.10 Remote Controlled Drug Delivery System

4.10.1 When none switch is pressed

When the circuit (or device) was in relaxing condition, it means that there was no command from the remote, that's why the device was only showing environmental temperature.

In the receiver section there were two indicating element that showed that any one of switch from remote section had been pressed. 1st indicating element was LED and 2nd was a buzzer. In the figure shown below neither led was glowing nor buzzer was ringing; which showed that none switch is pressed from remote section (fig. 4.19).

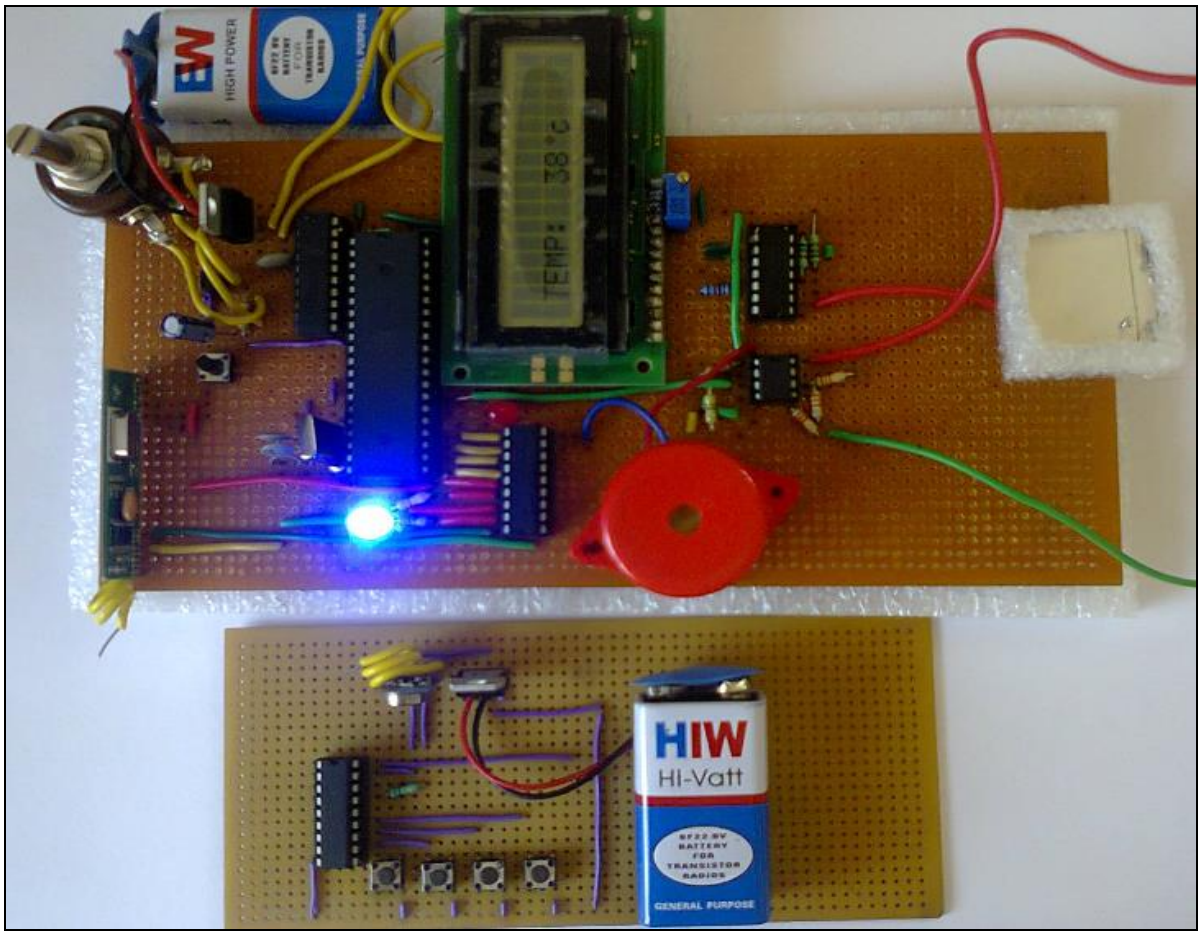


Figure 4.19: Remote controlled drug delivery device when none switch is pressed

4.10.2 When switch 1st is pressed

When switch 1st was pressed, the indicating LED was glowing and at the same time the buzzer was ringing and the piezoelectric transducer was generating the low frequency ultrasound. This low frequency ultrasound was used for the delivery of drug. The LCD was displaying the temperature simultaneously, but when the switch 2nd was pressed, the indicating LED was glowing and the piezoelectric transducer was generating the low frequency ultrasound for exactly 3 second and they were off for exactly 27 seconds. The whole process was repeated for 3 times. During the process of generating low frequency ultrasound the temperature was constant and after finishing the process the LCD was displaying the modified temperature. Thus the temperature difference had been calculated.

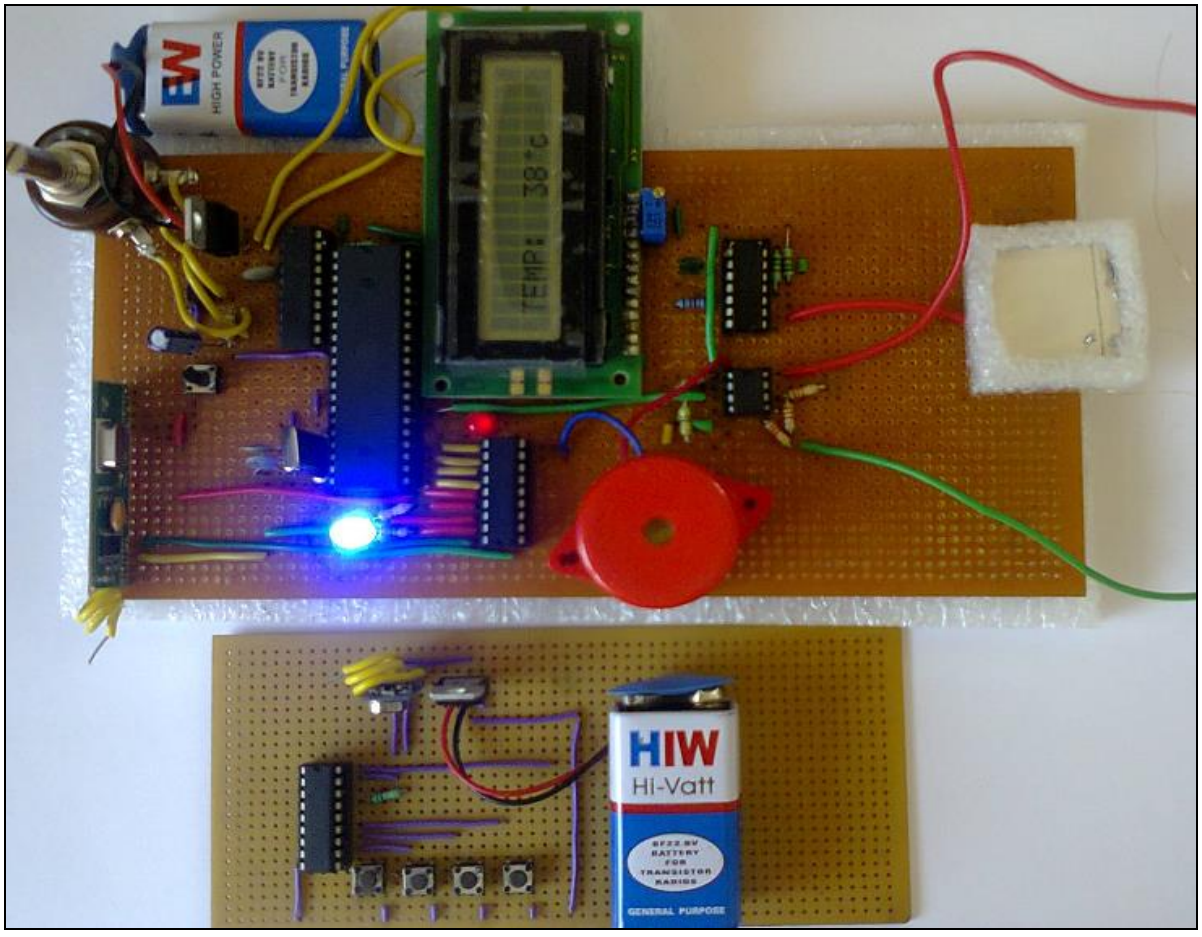


Figure 4.20: Remote Controlled Drug Delivery Device When Switch 1st Is Pressed

Chapter 5
Conclusion and Future Work

Conclusion and Future Work

5.1 Conclusion

The current study dealt with the design of a remote controlled drug delivery system which can work efficiently in the frequency range of 20 KHz to 40 KHz. The circuit was found to be stable in the operating frequency range. The developed system was tested to generate the low frequency ultrasound. Here in this system one can change the frequency of the ultrasound as well as the time for the sonication. This study showed that the most practical regimen for sonophoretic drug delivery was a concurrent 5 min, pulsed (10% duty cycle) beam. It can be easily calculated the increment of the temperature due to the sonication.

5.2 Future Work

The use of transdermal drug delivery methods has the most practical clinical application for medications that need to be injected multiple times either daily or weekly. The future works are as follows:

- Since in this project, intensity of the ultrasound had not been considered, that is also a very important component for the appropriate delivery of drug in transdermal drug delivery.
- Since in this project, the reset button of the microcontroller is not remotely controlled. It will be better to control remotely the reset button also.
- Since in this project, the frequency of the ultrasound is varying manually. It also can be controlled remotely.

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