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Design Of Drug Implants Of Meloxicam For Breast Cancer Patients

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ABSTRACT: In the present work, it was planned to prepare sub dermal implants for the treatment post operative surgical care in breast cancer patients. Meloxicam the anti-inflammatory agent was chosen as a model drug due to its wide spectrum of activity, low toxicity and high efficiency against inflammation. Bio degradable Gelatin based Implants comprised plasticizer, glycerin was formulated. The implants were evaluated for drug content uniformity, thickness, weight variation, IR, microbial degradation studies. Invitro release of implants was studied in phosphate buffer pH 7.4 and stability studies were done at ambient temperatures for 3 months. In-vivo studies in rabbits were carried out for polymer-tissue compatibility at sub dermal region. The prepared Meloxicam sub dermal implants were found to contain uniform drug content, weight, thickness and invitro release of Meloxicam sub dermal implants which are treated with formaldehyde for 12 hours was found to be sustaining release of drug for a period of 6 days. In-vivo studies in rabbits for polymer tissue compatibility, in animals showed encouraging results depicting no changes in tissue configuration histopathologically and compatible with the surrounding tissue of sub dermal region.

Key words: Meloxicam, breast cancer, sub dermal implants.

INTRODUCTION & OBJECTIVES:

Breast cancer primarily effects women with abnormal, uncontrolled cell growth arising in the breast tissue The breasts are made of fat, glands, and connective (fibrous) tissue .The breast has several lobes, which are divided into lobules and end in the milk glands .Tiny ducts run from the many tiny glands, connect together, and end in the nipple . Although breast cancer can occur at any age the risk factor increases the older one gets{Campiglio.2003 }The average woman at age 30 has 1 chance in 280 of developing breast cancer in the next 10 years .This chance increases to 1 in 70 for a woman aged 40 .By age 50 the chances are1 in 40.A 60-year-old woman has a 1 in 30 chance of developing breast cancer in the next 10 years. The Study is designed for Post operative surgical care is very much necessary for Speedy recovery breast cancer patients Love RR., 2002}. The Present study is aimed at to design, prepare and characterize gelatin based biodegradable NSAID sub dermal implants (Goodman & Gilman 1996). Subcutaneous tissue is a sheet of areolar connective tissue lying underneath the skin (sub dermal region), rich in fat but poor in nerve network and haemoperfusion which is ideal location for drug implantation (Tortora 1996).Histopathological observations at sub dermal region helps if there is any tissue incompatibility or lapses in formulation design of drug implants (Howard C. et. al., 1991). To study the prepared gelatin based biodegradable sub dermal implants for tissue-polymer compatibility studies studied in rabbits on implantation at thigh and neck regions. Meloxicam has been taken as model drug in the present study.

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MATERIALS AND METHODS:

Meloxicam -Unichem Labs, Mumbai (M.S.) Gelatin, Glycerin – Ranbaxy Labs Ltd., SAS Nagar, Punjab. Formaldehyde - Loba Chemicals, Mumbai. All the other chemicals used were of analytical grade. Heating and congealing technique was followed to prepare the Gelatin based implants. (Anita, 2002) Weighed quantities of Gelatin were hydrated for 30 minutes in water (Table-1).

Table-1: Formula of Implants Prepared

Sl. No.	Ingredients	Formulations
1.	Meloxicam	1 gram
2.	Gelatin	15 grams
3.	Glycerin	10 grams
4.	Water Q.S. to	50 grams

Glycerin and ethanolic drug solution was added and heated the contents on a water bath to 60°C with continuous stirring until gelatin was completely dissolved in water. This solution was transferred poured in to a glass petridish to a 3mm height and allowed to gel for 30 minutes on ice pack and dried for 72 hours at room temperature (Table-1).

The implants were then cut into rod shaped discs weighing each 125mg. containing 10mg. of drug. (Figure-1 and Table-2).

Figure-1: Models of Prepared Meloxicam 10mg. Implants

Table-2: Characterization of prepared Meloxicam implants hardened for 12 hrs. With formaldehyde

Sl. No.	Hardening time (hrs.)	Weight of implants (mg.)	Thickness of implants (mm)	Drug Content each implant (mg.)
1.	0	125±1.32	3.05±0.54	10.05±0.06
2.	3	126±0.73	3.24±0.74	10.15±0.05
3.	6	126±0.90	3.33±0.13	10.16±0.15
4.	12	125±0.33	3.55±0.33	10.07±0.47
5.	24	125±0.75	3.22±0.12	10.37±0.16

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* Each reading is a mean of 10 replicates.
* Each Implant weighs 125mg and contains 10mg of drug.

For prolongation of drug release the implants were subjected for cross linking with formaldehyde vapors to varied time intervals (3, 6, 12, and 24 hours) and air dried for another 72 hours to be free from formaldehyde vapors. The formulated implants were evaluated for drug content uniformity, thickness, weight variation, IR and test for sterility etc. In-vitro drug release studies from implants were studied in 7.4 PH Phosphate buffer media for a period of 192 hours. (Tayade, 2004 and Shivkumar 2002) . In-vitro drug release studies carried out using vial method taking one vial of 10ml sample of dissolution media at predetermined time intervals and the drug concentration was measured. (Allababidi 2003 and Manvi F.V. 1997) (Table-3).

Table-3: In Vitro Release of Meloxicam from prepared implants hardened with formaldehyde in pH 7.4

Sl. No.	Time (hrs.)	Percent drug released with S.D.				
		0 Hrs	3 hours hardening	6 hours hardening	12 hours hardening	24 hours hardening
1	0	0	0	0	0	0
2	12	44.4±1.38	36.84±0.15	23.34±1.36	27.16±1.64	25.26±1.02
3	24	65.34±1.17	47.13±1.34	48.13±20.81	39.05±0.86	36.83±1.36
4	48	74.83±0.76	55.36±2.36	47.74±0.42	48.97±1.33	34.16±0.24
5	72	94.15±0.35	66.15±1.73	66.15±0.36	52.26±20.45	46.43±0.93
6	96	-	84.46±0.75	65.86±0.19	57.27 ±0.44	57.35±1.32
7	120	-	97.07±1.16	75.13±1.22	64.15±1.75	67.14±0.35
8	144	-	-	78.36±1.42	87.86±0.74	64.15±0.32
9	168	-	-	94.97±0.46	86.37±1.15	73.34±0.16
10	192	-	-	-	95.28±0.66	93.92±1.37

* Each reading is a mean of three replicates.
* Each Implant weighs 125mg and contains 10mg of drug.
* "0" hour means without hardening.

The drug concentration in dissolution period measured at 364mm in Shimadzu UV-Visible spectrophotometer. Stability studies were carried out at ambient temperatures for 3 months (Lachman 1987). In-vivo studies at neck region in rabbits (2 male + 1 female) animal models were carried out for polymer-tissue compatibility at sub dermal region (Culling F.A. 1974, John D. 1984).

RESULTS AND DISCUSSIONS:

Results showed that all the implantable formulations were found to be uniform thickness, weight and drug content (Table-2). Formaldehyde was found to be superior cross linking agent for prolongation of drug release from implants. The I.R. reports of drug implants hardened with formaldehyde and basic drug confirmed the undisturbed drug in formulation (Figure-3).

Figure-3: FTIR Spectrum of Meloxicam as pure drug and in prepared gelatin based implants hardened for 12 hours with formaldehyde

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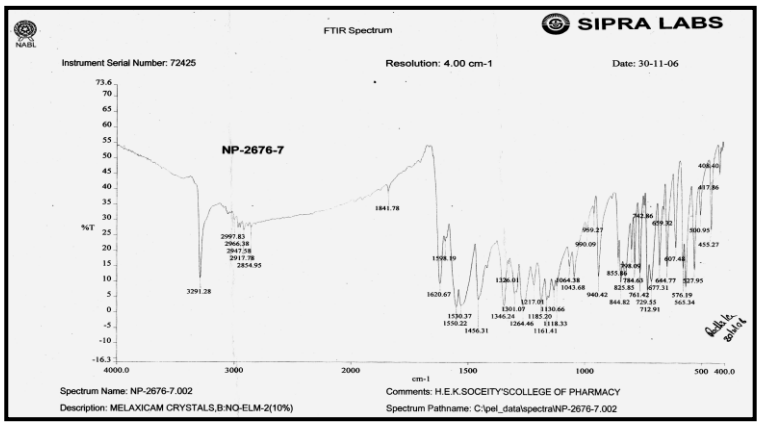
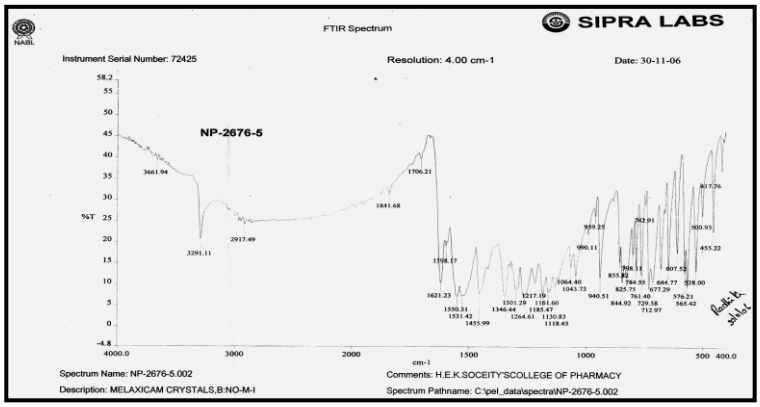


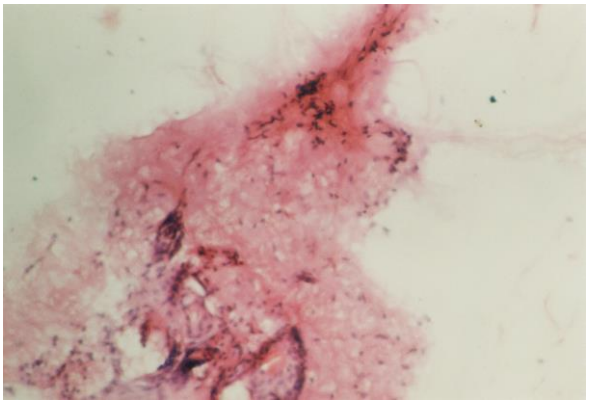
Meloxicam as Pure Drug



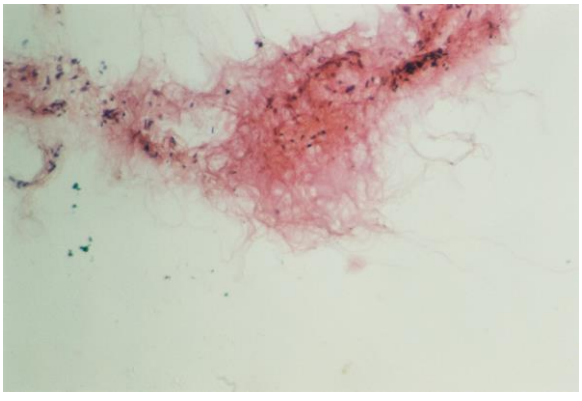
Meloxicam in Gelatin based implants

In-vitro release kinetics of implants hardened with formaldehyde for different time intervals 3, 6, 12 and 24 hours showed 97.07% in 12o hrs, 94.97% in 168 hrs, 95.28% 192 hrs and 93.92% in 192 hrs respectively. However without hardening of drug implants the drug release was 94.15% in 72hrs . In sterility test no evidence of micro-organisms found in the samples. In free formaldehyde test, no traces of formaldehyde noticed. Stability studies for a period of 90 days revealed that the implantable dosage forms were stable during period of study. In-vivo studies of the prepared implants in rabbits for polymer compatibility results depicted no changes in tissue configuration, no inflammation, no foreign body granuloma and no necrosis / hemorrhage observed in the tissue samples collected, hence confirms polymer compatibility with tissues of sub dermal region. (Figure 4 & 5)

Figure-3: Histopathological Observations of Polymer Tissue Compatibility



(A) Before Implantation



(A) After one month of Implantation

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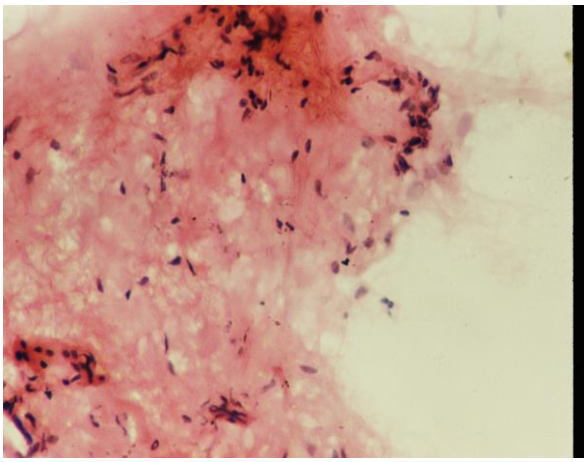
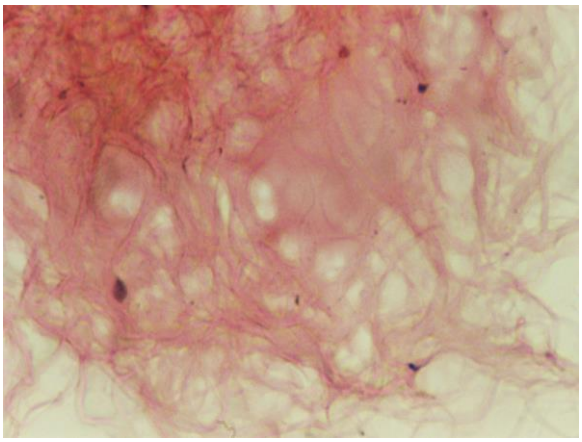
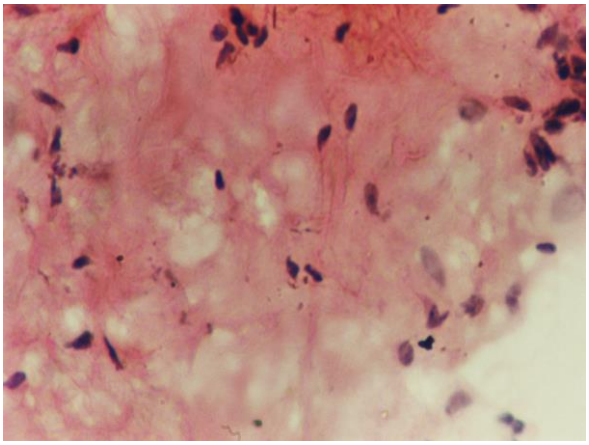


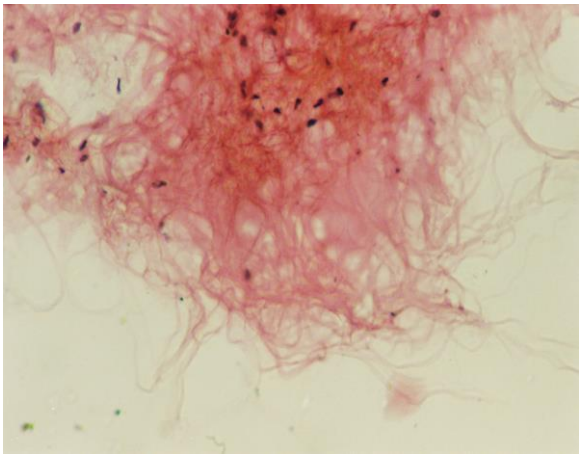
(B) Before Implantation



(B) After one month of Implantation



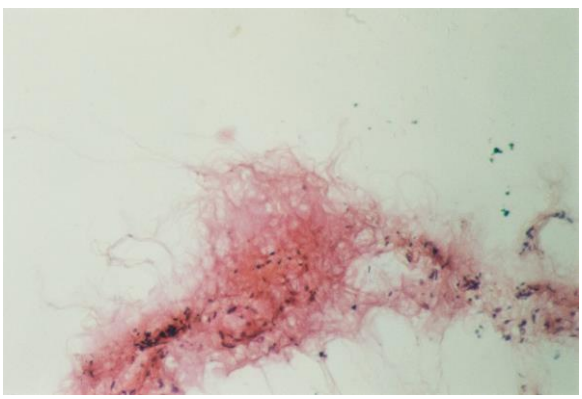
(C) Before Implantation



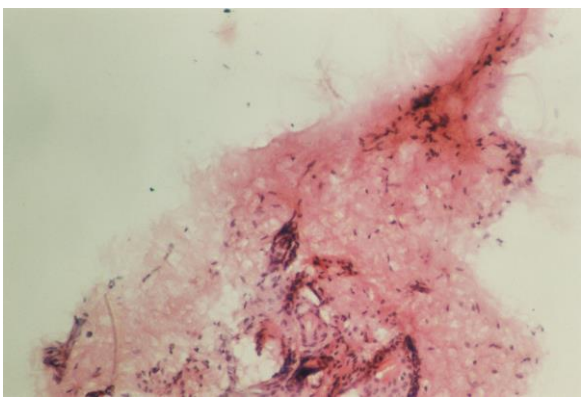
(C) After one month of Implantation

Magnification: A = 100x B = 200x C = 400x **Animal:** Rabbit
Site: Thigh Region

Figure-4: Histopathological Observations of Polymer Tissue Compatibility



(A) Before Implantation



(A) After one month of Implantation

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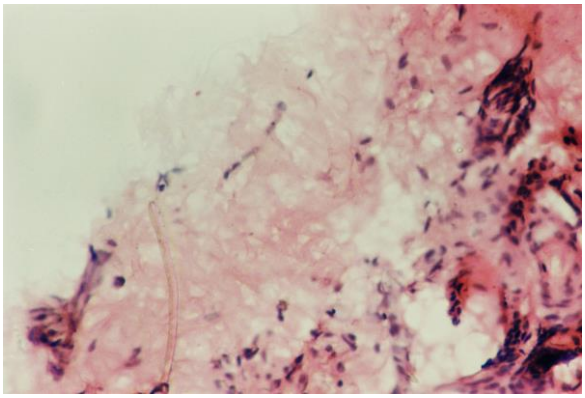
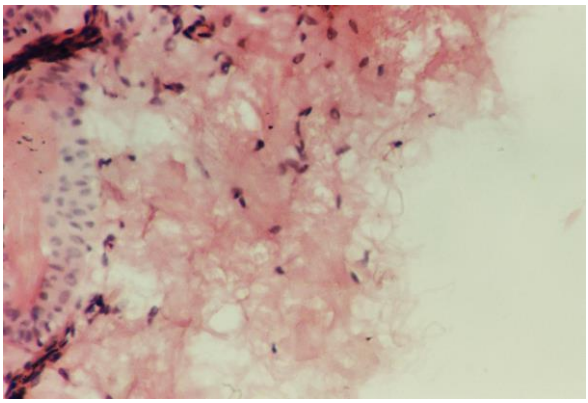
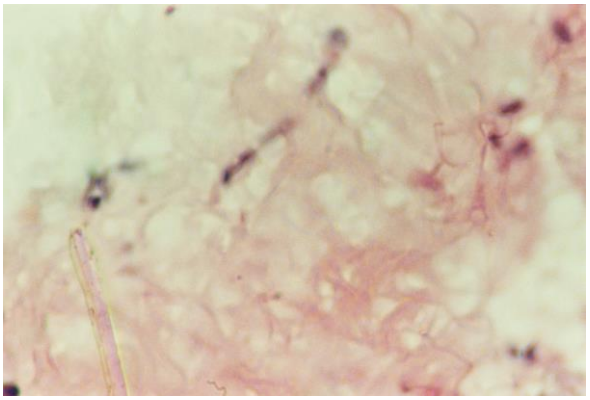


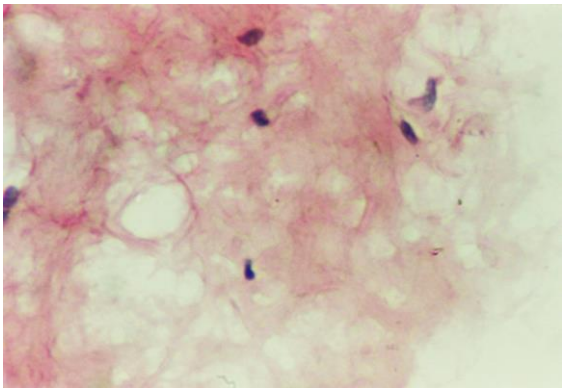
(B) Before Implantation



(B) After one month of Implantation



(C) Before Implantation



(C) After one month of Implantation

Magnification: A = 100x B = 200x C = 400x **Animal:** Rabbit
Site: Neck Region

CONCLUSIONS:

Use of biodegradable polymers in implantable dosage forms always an added advantage for prolonged therapeutic activity. In the present investigation Gelatin powder was used for implantable drug designing and to sustain the drug release for prolonged periods by cross linking with formaldehyde vapors. Usage of Gelatin as drug carrier will be economical and non-toxic, bio-compatible with body tissues. The results of I.R. reports revealed that there was no drug polymer excipient interaction. Drug implants formulated were found to be stable, sterile and free from formaldehyde vapors. The in-vitro results revealed that the drug release was observed for a period of 8 days. For any implantable dosage form, tissue-polymer compatibility plays important role and in our study in rabbit, it was proved that use of Gelatin base as drug carrier is safe for depot formulations.

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