

In Vitro and PRI-Evaluation of Implantable Drug Delivery System of FTIR, Dacarbazine by Using Hydrophilic Polymer”

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Abstract

➤ Object

The aim of this study was to formulate and evaluate Dacarbazine (5-(3, 3-dimethyltriaz-1-en-1-yl)-1H-imidazole-4-carboxamide implants using hydrophilic polymers. Dacarbazine implants were made using hydrophilic polymers. Nine formulas were prepared using Carbopol 931, Carbopol 934 and Carbopol 971.

➤ Method

Pre-formulation parameters for the dry mixture were performed. Total amounts of results are off limits. Implants were made using the extrusion method. The physical parameters of all aggregates were found to be within limits. All nine formulations had an in vitro cancellation test, of which the F7 formulation released 98.78% drug release within 12 hours, while others showed lower drug release. FTIR studies have shown that there is no chemical interaction between dacarbazine and polymer used in the study. Hopefully short-term stability studies of aggregates have indicated no significant changes in the appearance and content of the implants.

➤ Result

The hydrophilic polymer (Dacarbazine) In vitro & physical evaluation

Keyword:- Dacarbazine by using Hydrophilic Polymer, Carbopol 931, Carbopol 934 and Carbopol 971.

I. INTRODUCTION

The aim of this study was to formulate and evaluate Dacarbazine (5-(3,3-dimethyltriaz-1-en-1-yl)-1H-imidazole-4-carboxamide; CAS Reg. No. 4342-03-4) implants using hydrophilic polymers¹.

Now a day, in developed countries, cancer is the first cause of death and the second leading cause of death in developing countries. The disease caused 7.6 million deaths worldwide, as well as an annual report of 12.7 million new cancer cases. Breast cancer, colorectal, prostate and lung are the most common types of cancer, the last one, accounting for 1.6 million deaths. Radiotherapy and surgery are the most widely used methods of treating local

and non-metastatic cancer, while chemotherapy is a unique cancer treatment. Three treatments are often mixed².

Chemotherapy focuses on the use of anti-cancer drugs designed to prevent the rapid growth of cancer cells, but lack of selection can eventually destroy healthy tissues and cause serious side effects. Conversely, medications show lower half-life times in the blood stream and lower bioavailability due to the chemical structure. These two facts are related to the need for a higher dose of the drug, and the complications associated with undesirable side effects³.

One of the major challenges of cancer treatment is that anti-cancer drugs do not target cancer cells and "death" of healthy cells can occur during chemotherapy. Implementation of this concept can be seen as a powerful tool to reduce or overcome this most important problem⁴.

While scientists have done a great deal of research into the causes of cancer and the mortality rate is still high in diagnosis and treatment because the exact cure has not been found. Cancer treatment is one of the major challenges of modern science, as the delivery of drugs to the intestines is an obstacle to making more effective cancer treatments. Oral administered drugs in the abdominal cavity should be protected from denaturation and should be able to drain into the intestinal wall⁵.

Controlled drug delivery has now achieved zero long-term drug release. With advances in technology and techniques, various techniques such as osmotic pumps, the emergence of unchanged swelling or matrices, uniform drug loading profiles, multi-factor matrices, and pulsatile or stationary medical or protein formulas are used to create continuous release volume. In 1930, a subtle way of introducing a new drug release system was introduced⁶.

Plants are very useful in cancer treatment as they improve the delivery of drugs to the "right" place and can deliver the drug over a longer period. This fact prevents repeated drug administration, which increases patient compliance⁷.

In this case, the use of implanted materials will provide important "chemical reactions". In general, the implant enables controlled delivery of the active component (timing and release rate) and allows the concentration of the

drug in the body to be stored within an acceptable therapeutic window⁸.

Dacarbazine is a cell cycle repeat antineoplastic agent that acts as an alkylating agent after activation in the liver. This is used in the treatment of metastatic malignant melanoma. It is also given to patients with Hodgkin's disease, particularly doxorubicin, bleomycin and vinblin. Dacarbazine is used in the treatment of soft tissue sarcoma, along with other side effects, and may be given in neuroblastoma, kaposi sarcoma, and other tumors. Dacarbazine is a chemotherapeutic agent used to treat many types of cancer such as Hodgkin's disease, malignant melanomas, soft tissue tumors, and advanced neuroblastomas. Most patients are of childbearing age and express concern about the genetic risk of receiving treatment⁹.

Dacarbazine is an oral agent used as a first-line treatment for multiform glioblastoma and for the treatment of second-line astrocytoma in the treatment of brain cancer. Dacarbazine is in the imidazotetrazine class. These are organic polycyclic compounds with imidazole rings attached to the tetrazine ring. Dacarbazine is found in imidazotetrazine and antineoplasty¹⁰.

Increased entries include a matrix of drug materials and a polymeric excipient that may or may not have a functional level control membrane. The polymeric acceptor must be accompanied by two substances; however, bioresorbable may or may not be¹¹.

Within these results, some implants are made of medical-grade metal with osmotic pumps. Extended release of the product substance. The implants need to be sterile and are usually tube-shaped, although other forms may be used¹².

It should provide the tumor with an ideal delivery rate, that is, to be able to provide the target areas with effective concentrations of concentrations. Second, the system must be part of a comprehensive and effective care plan of flexible and practical care in a variety of real situations¹³.

To achieve these goals, the success of these implants must be maximized. The methods of each good implant must be considered in order to increase the distance from drug distribution. The success of chemotherapeutic implants for cancer treatment based on their inclusion in a comprehensive tumor therapeutic strategy¹⁴.

In addition, the implant should be delivered to the surrounding tissue at an affordable rate. The implants must provide the right drug release profile to deliver their drug product to the tumor, the ability to deliver large amounts of delivery, rapidly achieving therapeutic concentration and long-term therapeutic concentration¹⁵.

Polymers, both natural and synthetic, are commonly used in the production of implants because of their flexibility and properties. Hydropolymers have high

biocompatibility and biodegradability and easily modify functional groups. Additionally, synthetic polymers can be manufactured with Taylor-Made aggregates and their properties can be easily adjusted to fit a specific application¹⁶.

In particular, bioabsorbable synthetic polymers have particular relevance in the context of implant since they (or their degradation products) can be metabolized in the biological environment¹⁷.

Synthetic biodegradable polymers have appeared in health care applications since the 1960s and are very important in tissue engineering. They are widely used and have many capabilities. Synthetic polymers can be easily adapted to provide a wide range of properties. In addition, they are clean, easy to process and their surface can be modified. The US Food and Drug Administration has approved some synthetic polymers for use in certain biomedical applications, such as polylactic acid (PLA), polyglycolic acid (PGA), and polylactic-co-glycolic acid (PLGA), commonly used in tissues. Used in engineering scaffolding¹⁸.

Among the various synthetic polymers, PLA has high biocompatibility and biodegradability and synthetic polymers are commonly used in scaffolding. There are two enantiomeric forms of PLA, the left-hand (L-lactide) form and the right-hand (D-lactide) form. L-lactide is commonly used because of its high bioavailability. Both forms have different biodegradation rates. L-lactide has a glass transition temperature of 60-65 °C with a melting point of 175-68 °C and is a hydrophobic and semivolatile polymer. It exhibits low extension and high modulus and tensile strength, making it suitable for biomedical applications¹⁹.

II. MATERIALS AND METHODS

A. Preparation of implants using extrusion method

Dacarbazine Sigma (CAS No. 4342-03-4), Carbopol 931 was obtained from SIGMA Chemical Corporation, Mumbai, Maharashtra, India, acetic acid was extracted from Aceta, Mumbai, Loba Chemie, and glycerinaldehydes solution was purchased from S.D. Fine Chem. Ltd, Mumbai, Maharashtra, India.

Nine dacarbazine implants were made with different grade carbopol according to the formula specified in Table I. The darbhazine was dissolved and a solution of 5% acetic acid was formulated with the corresponding formulas. Then the carbopol powder is slowly mixed into the solution and soaked for 15-20 minutes. The mixture of feed residue and 5% acetic acid promotes the symmetry of the feed material by slowly turning and mixing the powder. The swollen mass formed in this process is uniformly mixed in a mortar and the remaining mass is collected with the help of a spatula, which becomes a viscous starchy mass. During each extrusion run, sufficient polymer-drug mixes were fed through the extruder and the extruder's room was filled before the Dakarbazin roads were collected. The starch-like mass of the implant is then fed into the cylinder of the

extruder and the cylinders are extracted from the nozzle of the cylinder.

The feed rate of the uniform mass of flour in the extrusion is maintained at 0.2g / min and the production rate of the implant rods. Pressure inside the extruder to maintain and prevent overloading was maintained below 4000 psi; At this pressure the feed rate is constant and uniform.

Rods were collected from the nose and allowed to dry in the desiccator overnight to avoid direct exposure to the open environment. Then the rods were cut into 27mm size implants. The sticks were kept to dry overnight at 40°C±1.

B. Cross linking of implants

25 mL of 25% glutaraldehyde was taken into a 100 mL beaker and placed in an empty desiccator. The implant rods were placed in a desiccator with a wire mesh and closed immediately. Pre-treatment was performed with glutaraldehyde vapor at different time intervals (6 hours, 12 hours and 24 hours).²⁰

The implant was then removed from the desiccator and allowed to dry for 72 hours, and this process allowed complete reaction between the carbopol. And glutaraldehyde. After 72 hours later, the implant was placed in an open environment for 7 days to evaporate the residual glutaraldehyde. Again, implants were kept at low temperature and rinsed with distilled water to allow cross-linkings and remove residues of glutaraldehyde left during the process.

In the final step, the implant was washed with phosphate buffer saline (PBS) at pH 7.4 to ensure the absence of residues of glutaraldehyde.

C. Evaluation of pre-compression parameters of the powder blend

The formulation of powder was prepared according to the formula and tested accordingly as per the standard procedure for determining the angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner's ratio²¹.

❖ Evaluation parameters for implant

➤ Uniformity of weight

The uniformity of the weight test was performed to maintain the uniformity of the weight of each implant. The 3 implants were randomly weighted to calculate the mean weight. No more than two individual weights exceed one percent from the average weight, and none is more than twice the percentage. The mean and standard deviation were determined and reported²². (Table-2).

➤ Bulk density and Tapped density (g/mL)

• Bulk density

The mass of a powder sample that does not use a high density of a powder is proportional to its volume. Interparticulate zero volume contribution. Therefore, the bulk density depends on both the density of the dry particles and the spatial arrangement of the particles in the dry bed. The gross density is expressed in grams per gram (g / mL), whereas the international unit is kilograms per kilogram (1g/ mL = 1000 kg / m³), because measurements are made using cylinders. It is also expressed in grams per cubic centimetre (g /cm³).

The untapped sample of pure drug (W) was weighed and poured separately into a graduated measuring cylinder. The initial level (bulk) volume (VB) was noted for every time to identify the density of powder particle and spatial arrangement of particle in powder bed²³.

• Tapped Density

Increased bulk density, which is obtained after mechanically pressing a dry container Sample. Tapping density is obtained by pressing a mechanically measuring cylinder or vessel with a dry sample. After viewing the amount or weight of the initial powder, measure the cylinder or vessel volume or weight readings are taken until mechanically tapping and switching to more volume or weight. The mechanical tapping allows the cylinder or ship to lift up and fall under its own weight according to the distance specified in one of the three ways. When pressing a cylinder or ship rotating device may be preferred to reduce mass separation.

The measuring cylinder is placed on the tapped density tester USP and is subject to continuous tapping at 200 drop / minute until the difference between the initial and final volume is less than 2%. It was recorded as the final (tapped) volume (VT) and the various flow characteristics are calculated with the following formulas²⁴.

Bulk density- $pB=W/VB$

Tapped density- $pT=W/VT$

➤ Compressibility Index

Compressibility Index Measuring the propensity of a powder. It therefore measures the disposal efficiency of the powder and allows it to evaluate the relative importance of interparticulate interactions. Relative to compressibility index and flexibility. In the free-flowing layer, such interactions are of less significant, and are related to the tapped density value. For poorly flowing materials, interparticle interactions are frequent and large differences between bulk and tapped concentrations were observed.

It was calculated by using the following formula Carr's Index or Compressibility Index (CI) = The CI value below 15% indicates good flow of the powder and above 30% indicates poor flow property of the powder²⁵.

Compressibility Index = $1-pB/pT \times 100$

pB= Bulk density, pT=Tapped density

➤ *Hausner's Ratio*

Both the Hausner's ratio and the carrs index are calculated from compressibility data. The test powder is gently loaded in a 100 ml cylinder through a funnel and weighed to calculate its bulk density. Next, the cylinder is tapped into a single platform tapped density meter, in this case 1500 times until the volume changes. The Hausner's ratio is calculated from the equation and from the car index equation, where BD is the dry bulk density and the TD powder tape density.

It is calculated by the following formula; Hausner's Ratio= The Hausner's ratio below 1.25 indicates good flow property and above 1.25 indicates poor flow property of the powder²⁶.

Hausner's Ratio= pT/pB

pB= Bulk density, pT=Tapped density

➤ *Drug content uniformity test*

Content uniformity of matter refers to a dose analysis technique that is used to ensure that each dose contains an equal amount of active drug fraction or amount, but that the test is qualitatively or quantitatively targeted. Appearance refers to the investigative process for measuring volume or functional activity of unit.

For each individual implant were subjected to assess the dug content uniformity test. Measurements of the content were done by the HPLC. The mean and SD of drug content, formulation weight and concentration of active ingredient (w/w %) were calculated for each implant²⁷.

Implants were individually tested for weight and its active content. The concentration of the active substance is calculated by dividing the form content by the formulation weight.

The content of the conversion from each batch is estimated. The implant was cut into small pieces of 50 ml volumetric flask, mixed with 45 ml of glacial acetic acid and stirred to dissolve the material. The volume was made up to 50 ml with glacial acetic acid. The solution was diluted with glacial acetic acid and tested for dacarbazine content by measuring the absorbance at 330 nm.²⁸.

Dacarbazine contents were calculated, using the standard calibration curve (Table-3).

➤ *Diameter of implants*

A minimum of three implants were measured for length and diameter with the help of Vernier calipers. Three samples were taken for the study from each batch, and mean value was calculated for the same²⁹. Mean of the implant is mentioned in Table-4.

➤ *Swelling index*

Implants were placed in a glass beaker containing 50 ml of phosphate buffered saline (PBS, pH 7.4) and the beakers were placed in a shaking incubator at 37 °C and 100 rpm. The implants were weighed periodically throughout the experiment. The weight of implant was measured after 1 hr, and the excess of solution was removed gently by tapping the surface with a dry piece of filter paper. The swelling studies were carried out in triplicate. The degree of swelling for each implant formulation at given time was evaluated using the following equation³⁰:

$$H = \frac{W_t - W_0}{W_0} \times 100$$

Where, W_t and W_0 are the weight of the sample at any given time and in the dry state, respectively.

➤ *In vitro dissolution studies*

USP XXIV (Model DISSO, M / s. Lab India, Chennai) Dissolution test was performed using the rotating paddle method. 900 mL of 0.1N hydrochloric acid was used as a dissolving medium and the stirring rate was maintained at 50 rpm and the temperature at $37^\circ\text{C} \pm 0.5^\circ\text{C}$. 5 ml samples were withdrawn at a predetermined time interval; the filter and fresh dissolution medium was replaced with 5 ml³¹. The collected samples were diluted with dissolution fluid and analysed for dacarbazine using a double-beam ultraviolet spectrophotometer (Shimadzu-2000) at 330 nm. The same amount (about 10 μl) of dissolved media is injected separately into the chromatograph, empty, standard preparation and sample preparation, and the chromatogram is recorded and analysed to measure the maximum field responses to the peak. Each cancellation study was recorded thrice and mean values³².

➤ *Stability study*

Stability testing is a process performed for pharmaceutical products and is used at various stages of product development. In the early stages, quick stability tests (at relatively high temperatures and / or humidity) are used to determine the type of degradation products that can be found after prolonged storage.

The stability protocol was based on the International Conference on Harmonisation (ICH) 'Q1A (R2) guidelines. The stability test provides evidence on the quality of a drug substance or drug product variations with time under the influence of a variety of environmental factors such as temperature, humidity, and light, enabling recommended storage conditions, retest periods, and shelf lives³³. The ICH guidelines stability studies were carried out at $25^\circ\text{C}/75\% \text{RH}$ for the selected formulation for 3 months. The selected formulations were wrapped in butter paper, were then stored at $37^\circ\text{C}/75\% \text{RH}$ for 3 months, and evaluated for their physical appearance and drug content at specified intervals of time³⁴.

III. RESULTS AND DISCUSSION

A. Pre-compression evaluation parameters of Dacarbazine formulation blend

The Powder blend were made from a mixture of different ingredients and used to characterize the different flow characteristics of the powder. Concentrations of all formulations were found to be in the range of 0.46 ± 0.01 to 0.56 ± 0.03 (g/cm³), which showed that the powder had good flow characteristics. The tapped density of all aggregates was found to be in the range of 0.59 ± 0.02 to 0.68 ± 0.08 . The compression index of all aggregates was found to be between 15.19 ± 0.04 and 17.67 ± 0.03 . All composition showed Hausner ratios between 0.84 ± 0.04 and 1.25 ± 0.05 and 0.84 ± 0.04 and 1.25 ± 0.05 , indicating that the dry has good flow characteristics (Table 5, 6, 7 and 8).

❖ Evaluation parameters of Dacarbazine implants

➤ Physical characteristics

The physical characteristics of Dacarbazine implants (F1-F9) such as weight variation and drug content were determined, and results of the formulations (F1-F9) were found to be within the limits specified in official data books.

➤ Drug content

All the implant formulations showed desirable uniformity in drug content and contained 98.9-102.03% of Dacarbazine which is well within the specified limit (Table-2).

➤ c.% swelling index

The % swelling index of the prepared implants was recorded and was found to range from 90-176 % (Table-3).

➤ Diameters of implants

The thickness of the implants was measured with vernier calipers by taking three samples of implants for a specific representation and time of exposure. The diameters of the implants were determined and recorded (Table 4). The average diameter of the implants was found to be the same in the implant aggregates in all batches and was found to be in the range of 1.12–1.70 mm.

➤ Uniformity of weight

The weight differences for the all the formulations were recorded (Table 1). The weight of all implants was within the pharmacopoeal limit. The weight of all the implant formulations was found to be in the range of 50.5 mg.

• In vitro drug release

Dissolution test was performed using USP XXIV (Model Disco, M / s Lab India, Hyderabad) paddle method as a dissolving medium with 900 mL 0.1 N hydrochloric acid at 50 rpm. Each dissolution study was conducted three times, and the mean was averaged. In vitro dissolution studies of the setting of dacarbazine were performed in simulated gastric fluid 0.1N HCl for 12 hours. Formulations F1 - F3 were prepared with carbopol 931. The implants were unable to maintain their shape and integrity beyond 4 hours. Therefore, they were not considered. Carbopol 934 aggregates are formulated with retarded drug release. F4 and F5 formulations released complete medication at 5 and 6 h. The F4 and F5 formulations did not slow the release time until the desired time. The F6 formulation release has slowed the release of the release for 12 hours and showed a maximum of 89.87 at 12 hours.

Formulations F7 - F9 were prepared with carbopol 971. Formulas F7, F8 and F9 retarded the release for more than 12 hours. F7 was shown at 98.78% in 12 days, while F8 and F9 formulations showed 84% and 78% release in 12 hours, respectively. As the ration of the polymer increases, the amount of residue is also slowed down. Initially, low-density and low-viscosity formulations release 50–100% drug content within 4–6 hours. High-viscosity and high-density aggregates were able to release the release state for more than 12 hours. Therefore, based on the dissolution study, formulation F7 is considered the best representation (Table 4 and Fig. 1-3).

• Stability studies

Stability studies were performed at 25°C / 75% RH and 37°C / 75% RH for the selected formulation for 3 months. Selected formulations are wrapped in butter paper and then evaluated for a period of time for their physical appearance and content. By looking at stability studies, it has been concluded that the optimized formulation is stable over a period of 3 months and that the release profile is also intact over time (Table 10).

• Compatibility studies by FTIR

FTIR and Excipient Compatibility Studies was performed by FTIR. The study showed peaks for the respective functional groups in Dakarbazin. When studied with dacarbazine and polymer, there were no major changes in the peaks. From looking at the FTIR spectrum above, there is no difference between the internal models at the molecular level and the confirmation of these models. There was no interaction between the used and the residue and the polymer.

Note- mg-milligram, mL- millilitre, Qs- quantity sufficient, %- Percentage

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Temozolomide (mg)	20	20	20	20	20	20	20	20	20
Carbopol 931 (mg)	200	400	600	-	-	-	-	-	-
Carbopol 934 (mg)	-	-	-	200	400	600	-	-	-
Carbopol 971 (mg)	-	-	-	-	-	-	200	400	600
5% acetic acid (ml)	5	5	5	5	5	5	5	5	5
25% glutaraldehyde solution	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Table 1:- Formulation composition for implant

Implants Code	Mean Weight (mg) (\pm SD)
IMP1	60 \pm 0.01
IMP2	59 \pm 0.01
IMP3	51 \pm 0.03
IMP4	58 \pm 0.04
IMP5	60 \pm 0.01
IMP6	56 \pm 0.03
IMP7	57 \pm 0.03
IMP8	58 \pm 0.05
IMP9	51 \pm 0.09

Note: IMP- Implant, SD- Standard Deviation, mg- Milligram

Table 2:- Uniformity of weight

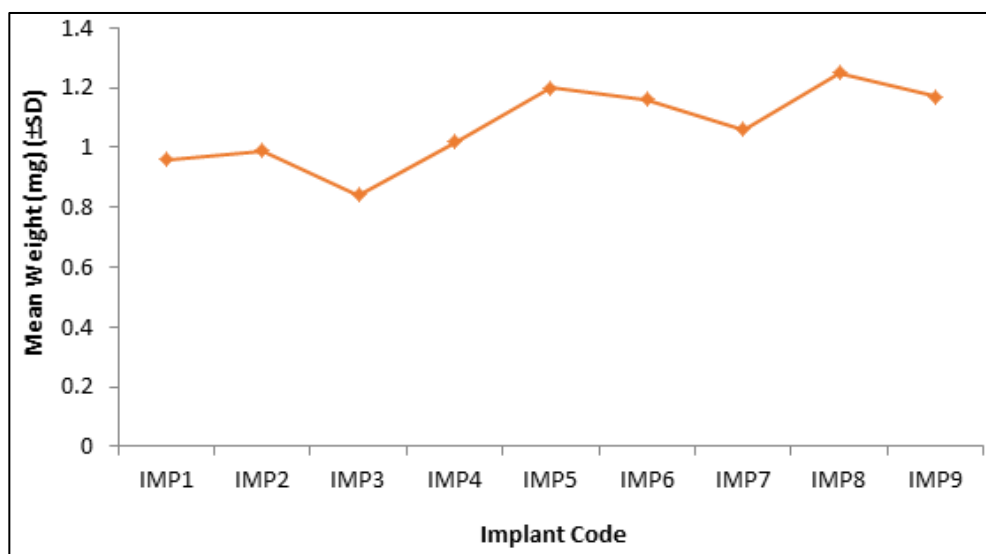


Fig 1:- Weight Variation

Implants Code	Drug Content %
IMP1	101.9 \pm 0.02
IMP2	98.9 \pm 0.03
IMP3	100.1 \pm 0.09
IMP4	102.03 \pm 0.05
IMP5	101.07 \pm 0.03
IMP6	99.6 \pm 0.04
IMP7	99.9 \pm 0.02
IMP8	101.2 \pm 0.02
IMP9	99.9 \pm 0.04

Table 3:- Drug Content %

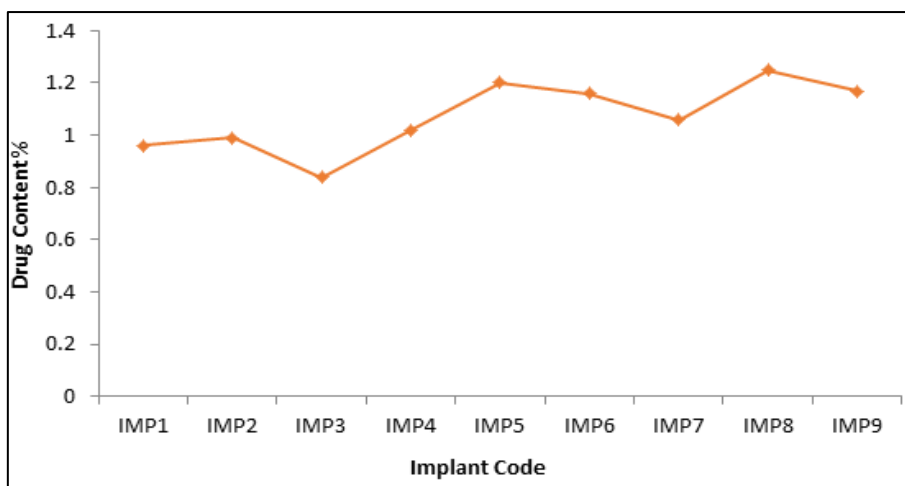


Fig 2:- Drug Content %

Implants Code	% Swelling index
IMP1	91
IMP2	102
IMP3	114
IMP4	114
IMP5	103
IMP6	115
IMP7	90
IMP8	109
IMP9	176

Table 4:- % Swelling Index

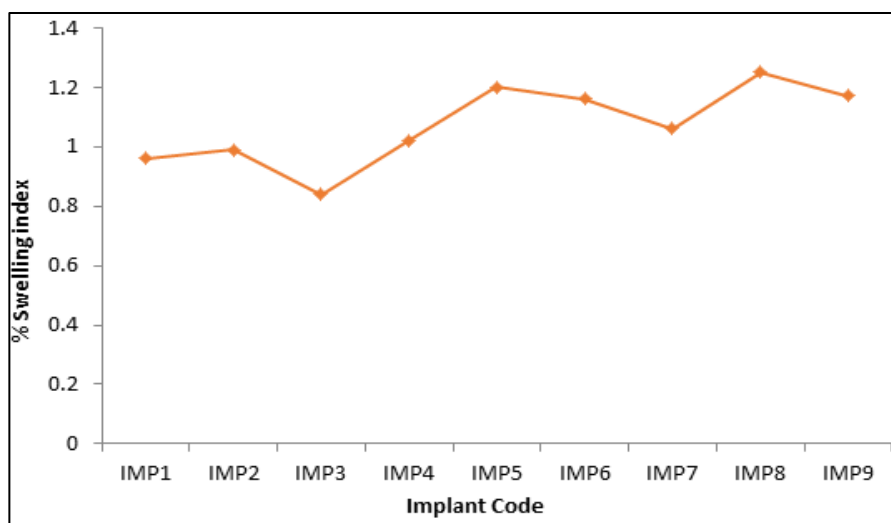


Fig 3:- % swelling index

Implants Code	Diameter of implants
IMP1	1.12
IMP2	1.21
IMP3	1.34
IMP4	1.54
IMP5	1.34
IMP6	1.54
IMP7	1.56
IMP8	1.70
IMP9	1.41

Table 5:- Diameter of Implants

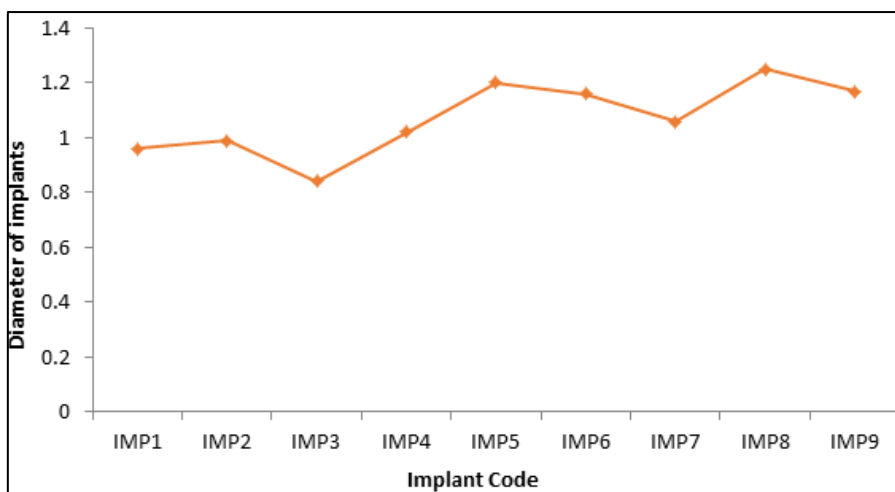


Fig 4:- Diameter of implants

Implants Code	Bulkdensity
IMP1	0.50±0.02
IMP2	0.46±0.01
IMP3	0.50±0.03
IMP4	0.51±0.02
IMP5	0.50±0.03
IMP6	0.55±0.02
IMP7	0.56±0.03
IMP8	0.50±0.04
IMP9	0.49±0.05

Table 6:-Bulk Density

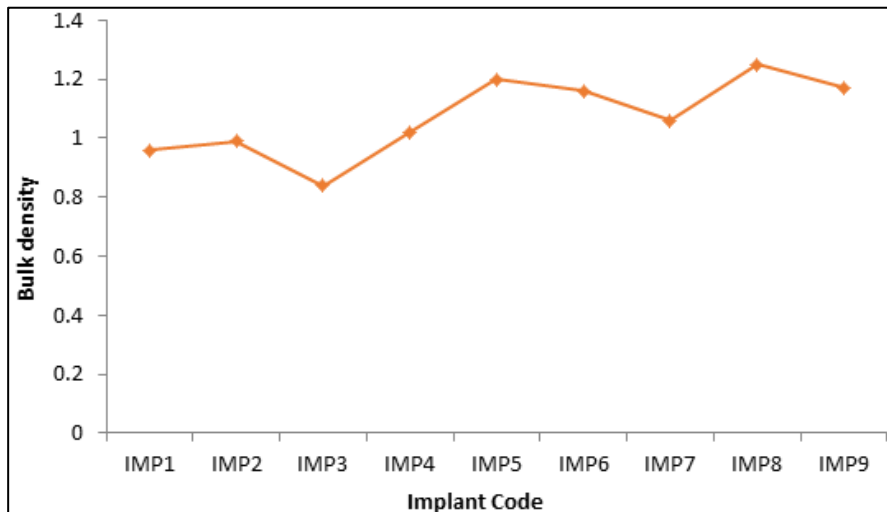


Fig 5:- Diameter of Bulk density

Implants Code	Tappeddensity
IMP1	0.60±0.03
IMP2	0.59±0.02
IMP3	0.62±0.05
IMP4	0.63±0.07
IMP5	0.66±0.04
IMP6	0.68±0.05
IMP7	0.68±0.08
IMP8	0.60±0.05
IMP9	0.59±0.06

Table 7:-Tapped Density

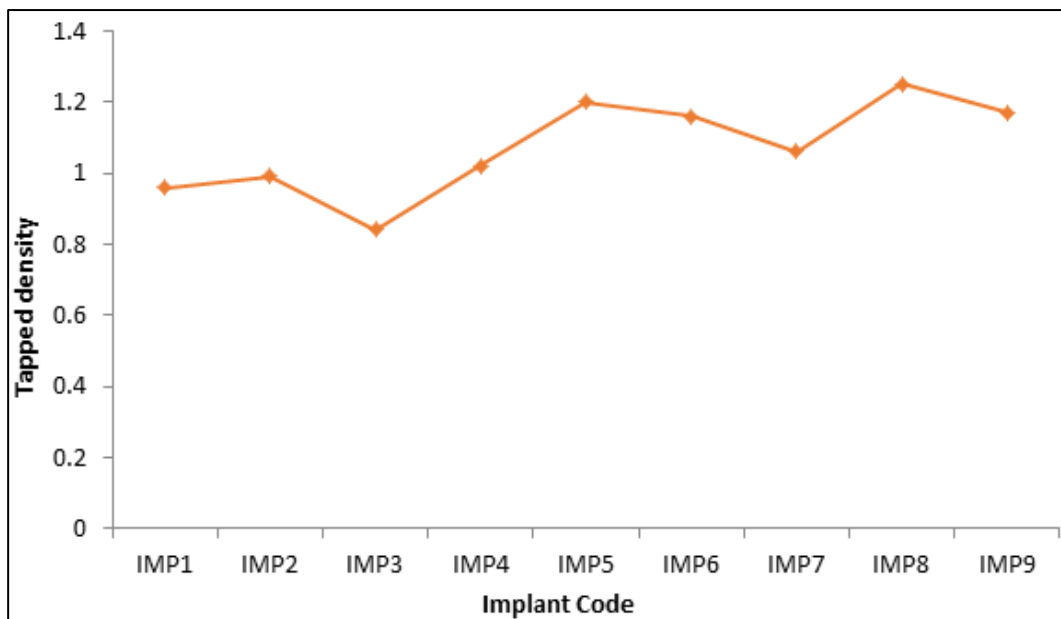


Fig 6:- Tappeddensity

Implants Code	Compressibilityindex
IMP1	15.19±0.04
IMP2	17.67±0.03
IMP3	16.19±0.02
IMP4	15.20±0.06
IMP5	16.02±0.04
IMP6	17.15±0.08
IMP7	17.02±0.04
IMP8	17.13±0.04
IMP9	16.44±0.02

Table 8:- Compressibility Index

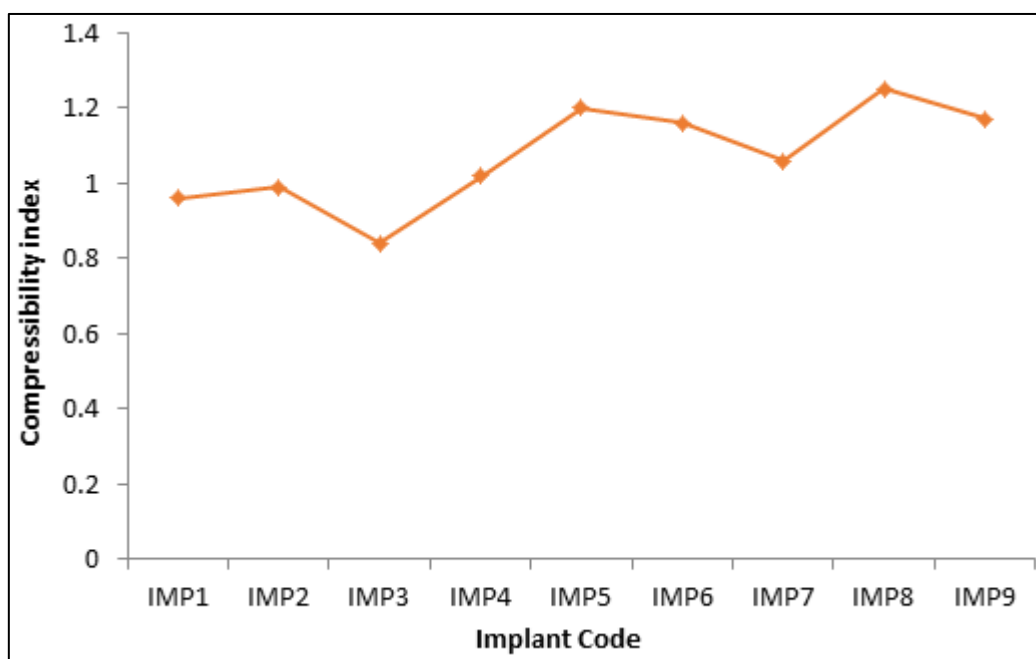


Fig 7:- Compressibilityindex

Implants Code	Hausner's ratio
IMP1	0.96±0.09
IMP2	0.99±0.02
IMP3	0.84±0.04
IMP4	1.02±0.03
IMP5	1.20±0.03
IMP6	1.16±0.04
IMP7	1.06±0.02
IMP8	1.25±0.05
IMP9	1.17±0.04

Table 9:- Hausner's Ratio

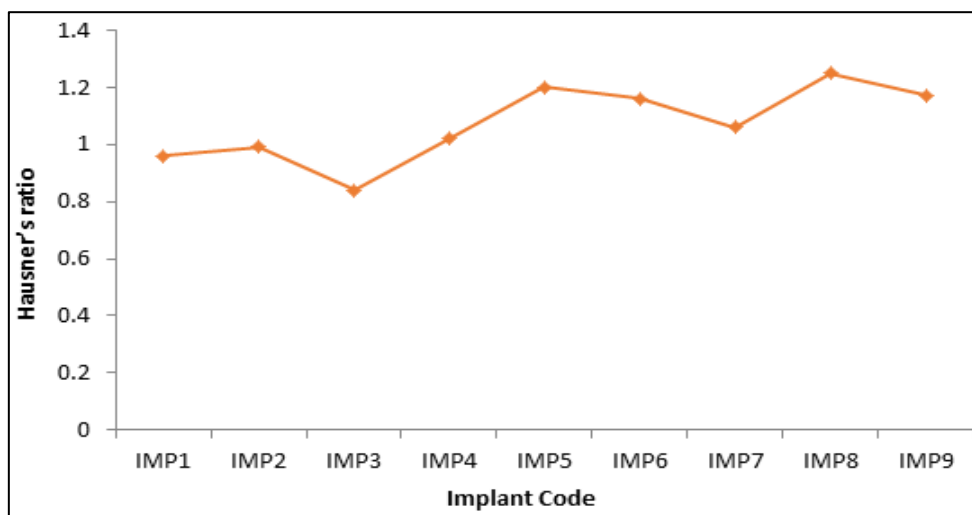


Fig 8:- Hausner's ratio

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	22.22±0.03	21.33±0.02	15.80±0.04	21.24±0.02	15.78±0.07	11.69±0.01	15.17±0.03	11.78±0.01	7.69±0.07
1	51.62±0.02	45.77±0.04	24.14±0.02	32.76±0.05	26.17±0.05	15.29±0.04	19.23±0.06	12.69±0.06	11.80±0.01
2	94.59±0.03	80.04±0.01	49.01±0.02	44.70±0.09	42.30±0.05	20.59±0.03	27.01±0.02	20.88±0.05	13.76±0.06
3	-	100.85±0.06	76.79±0.03	70.85±0.03	59.02±0.03	22.02±0.01	34.14±0.03	22.69±0.02	18.50±0.03
4	-	-	90.83±0.02	75.40±0.02	73.42±0.09	23.92±0.01	44.15±0.07	42.54±0.06	25.48±0.03
5	-	-	-	102.20±0.02	82.71±0.02	24.38±0.01	55.11±0.04	43.34±0.01	30.34±0.01
6	-	-	-	-	90.77±0.01	25.29±0.03	67.08±0.01	42.61±0.02	34.04±0.03
7	-	-	-	-	91.91±0.04	26.67±0.03	69.49±0.01	57.18±0.02	51.76±0.07
8	-	-	-	-	-	36.34±0.07	71.09±0.08	60.13±0.03	59.26±0.09
9	-	-	-	-	-	41.40±0.01	78.71±0.04	65.96±0.08	60.75±0.02
10	-	-	-	-	-	57.31±0.04	84.14±0.02	71.72±0.07	64.97±0.03
11	-	-	-	-	-	71.41±0.04	89.54±0.09	82.24±0.03	70.98±0.07
12	-	-	-	-	-	81.87±0.14	98.78±0.09	81.58±0.03	79.45±0.06

Table 10:- Drug release profile of Dacarbazine implants

S.No.	Optimized formulation (F3) Duration (months)	25°C (75% RH)	37°C (75% RH)
1	1	97.85	97.92
2	2	97.35	97.8
3	3	97.1	97.75

Table 11:- Stability studies for optimized formulation (F7)

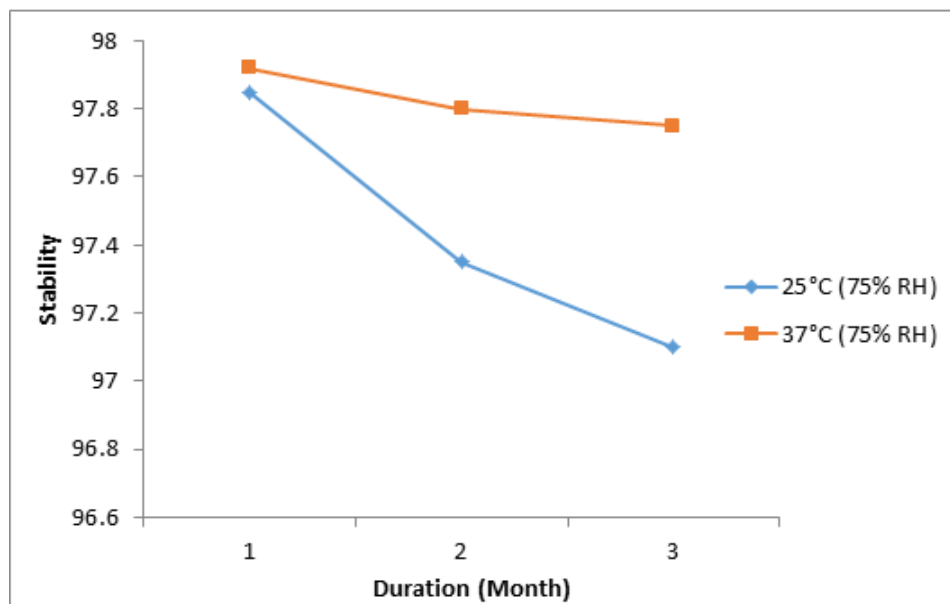


Fig 9:- Stability studies for optimized formulation

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