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Design and evaluation of subcutaneous implantable drug delivery system of tramadol using natural biodegradable polymer

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Abstract

This present research study was carried out to develop and evaluate the subcutaneous implants of chitosan for the administration of tramadol. Tramadol is one of the centrally acting analgesics with opioid agonist properties and can be safely used in such condition without the side effects.

Rod shaped implants of 1 mm diameter and 2.7 mm in length were prepared by extrusion method, using a specially designed galaxy extruder. Implants were analyzed for drug content uniformity, thickness, weight variation, short term stability study. *In vitro* release study in phosphate buffer at 37 ± 1^{o}C, demonstrated that the rate of release of the tramadol from the implant matrix was a function of concentrations of the polymer. The implant formulations, having different concentrations of crosslinking, show varied drug release, can be extended for 17 days, compared to drug released from implants with no crosslinking. Thus, crosslinikng effectively control the amount of drug release. The release of drug from all implant formulations was uniform and was spread over a period of 17 days. The implant formulations were found sterile, uniform in weight, drug content and size. Short term stability studies of drug implants revealed that the implants formulations were stable, and there were no significant changes in the physical appearance and drug content of the implants formulations. Data obtained from the study suggest that the implants prepared from chitosan would be promising as an interesting biodegradable system for sustained delivery of tramadol for the pain management.

Key words: Chitosan, Crosslinking, Biodegradable polymer, Implants, Tramadol

Introduction

In the past, drugs were frequently administered orally, as liquids or in powder forms. To avoid problems incurred through the utilization of the oral route of drug administration, new dosage forms containing the drug(s) were introduced. As time progressed, there was a need for delivery systems that could maintain a steady release of drug to the specific site of action. Therefore, drug delivery systems were developed to optimize the therapeutic properties of drug products and render them more safe, effective, and reliable. Implantable drug delivery systems (IDDS) are an example of such systems available for therapeutic use (Alekha, 1998).

The veterinary field is an area, rich with opportunity for the application of controlled release technology. Because of the large number of food producing animals and the unique problems associated with the administration of drugs to these animals, the potential markets are large as are the potential benefits. The range of therapeutic areas which have need for

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controlled release technologies is limited to those diseases which lead to an economic loss to the grower and/or to applications in which cost effective growth of the animal is achieved. Thus, the major areas of application of controlled release technology include the delivery of therapeutic concentrations of antibiotic or antiparasitic agents, the long term administration of anthelmintic and/or antibacterial agents for growth promotion, the delivery of hormones to achieve accelerated growth or estrus synchronization, and the long term administration of trace nutrients (Denesly and Parkes, 1936).

Historically pellets or implants were sterile. Small, usually cylindrical shaped solid object intended to be implanted subcutaneously for the purpose of providing the continuous release of medicaments over a prolonged period of time. The pellets, which are to be implanted under the skin (usually of the thigh or abdomen) with a special injector or by surgical incisions. The drug may be dissolved, dispersed or embedded in a matrix of polymers that control release by dissolution, diffusion or both, bioerosion, biodegradation or an activation process such as osmosis or hydrolysis. The system is generally prepared as implantable flexible/rigid moulded or extruded rods, spherical pellets or compressed tablets. Polymers used are silicone elastomers, polymethacrylates, polycaprolactone, poylactide/glycolide. Drugs generally presented in such systems are steroids like contraceptives (megestrol acetate, norgestrone), morphine antagonists like naltrexone for opiod-dependent addicts. (Brahmanker, 1995).

Pharmaceutical applications of implants

Implants are used **(**Jarnette *et al.,* 2004**)** for ocular disease, contraception, dental applications, antibiotics, immunization, anticoagulation, cancer, narcotic, antagonists, insulin, and protein delivery ocular implants, pain management, implants for fracture fixation and other applications.

The thematic view is as follows:

(i) Design and development of subcutaneous implant formulation by extrusion technique, using chitosan as biodegradable polymer with tramadol as a model drug.

(ii) Crosslinking of chitosan implants using glutaraldehyde.

(iii) Effect of polymer concentration on release of tramadol and effect of crosslinking in controlling release of drug from polymeric matrix.

(iv) Evaluation of the developed subcutaneous implants.

- Diameter and length
- Weight variation
- Drug content uniformity
- Test for sterility
- Swelling index
- *In vitro* drug release study in saline phosphate buffer (pH 7.4)

(v) Short-term stability studies for the selected formulation

(vi) Drug excipients interaction studies

Materials and Methods

Materials

The procurement details of the materials is as follows: Tramadol (European Pharmacopoeia 5.0) gifted sample from Satwick Pharmaceutical Ltd. Chitosan, Dimethyl phthalate and Methanol purchased from Signet Chemical Corp., Mumbai. Other like Sodium dihydrogen phosphate, Sodium chloride, Glacial Acetic acid purchased from S.D. Fine Chem. Ltd. Glutaraldehyde purchased from Loba Chemie, Mumbai.

Galaxy extruder: It is used to prepare implants. Galaxy extruder **(**Rao *et al.,* 2005**)** is fabricated with 316L Grade stainless steel, which is non corrosive with most of the materials. The extruder consist of a cylinder which has an inner diameter of 15 mm and outer diameter 17 mm with a nozzle at the bottom, having a diameter of 3 mm. The cylinder is supported by two bent roads mounted on a frame. A plunger with screw and a handle to rotate (to provide pressures needed for extrusion) is mounted on the frame which has a hole with inner threads. Plunger has a diameter of 14.8 mm and a handle, is rotated and goes into the cylinder and extrudes the material present in the cylinder through nozzle into long threads. The Galaxy extruder used was found suitable to produce long rod shaped implants.

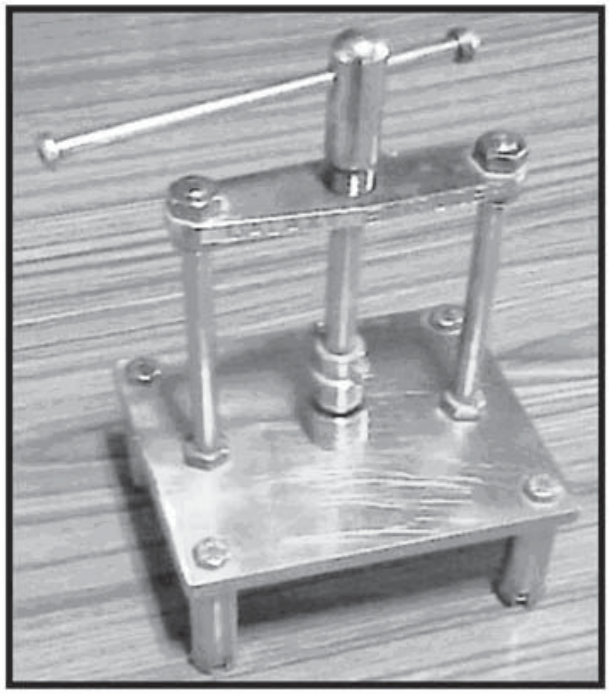

Figure 1: Galaxy extruder

Table 1: Formulations of tramadol HCl implants prepared using chitosan

Ingredients (mg)	Formula-I	Formula-II
Tramadol	250	200
Chitosan	750	800
5% Acetic acid	5ml	5ml
25% Glutaraldehyde solution	QS	QS
Drug: Polymer	1:3	1:4

Methods

Preparation of implants using extrusion method

Preparation of tramadol implants

Procedure: Implants of tramadol were prepared with chitosan as per the formula given in Table 1.

The drug was dissolved in 5% acetic acid solution. After that chitosan powder was added slowly which is allowed to soak for 10-15 minutes, the swollen mass so formed was mixed uniformly in a glass mortar and mixed thoroughly until it becomes a sticky dough mass. The dough mass was fed into the cylinder of the extruder and was extruded in the form of long rods through the nozzle. The rods were kept for overnight drying on a glass plate and cut into 27mm sized implants. The implants were than dried at 40 ^{o}C.

Crosslinking of implants

25 ml of 25% of glutaraldehyde solution was kept in 100 ml beaker and kept in an empty desciccator **(**Pradip *et al.*, 2004). On the top of beaker, a wire mesh containing the implants was kept and immediately the desiccator was closed.

The implants were made to react with glutaraldehyde vapours for different time intervals (6h, 12h and 24h). Then they were removed and air dried for 72 hours. So that complete reaction between the chitosan and glutaraldehyde should take place. After words, the implants were kept in an open atmosphere for a week to make the residual glutaraldehyde gets evaporated. The crosslinking was carried out at low temperature. The residual glutaraldehyde can also remove by using an aqueous sodium metabisulfite solution (2%) and then immediately removed and placed in absolute alcohol bath. If the excess of glutaraldehyde was not removed from the surface, it may cause irritation.

Diameter of implants

The length and diameter of implants from every batch was measured with the help of vernier caliper and were subjected to previously mention in statistical analysis where three samples were taken for study from each batch.

Weight variation

Samples of implants **(**Jameela *et al.*, 1998**)** from each batch (n = 3) were selected randomly and weighed individually on electronic balance. The average weight and percent deviation were calculated.

Procedure for drug content uniformity test

Drug content of implants **(**Jameela *et al.*, 1998**)** from every batch was estimated. The implant was cut into small pieces and were taken into 50 ml volumetric flask and 45ml of glacial acetic acid was added and shaken thoroughly to dissolve the drug and the volume was made up to 50 ml with glacial acetic acid. This solution was suitably diluted with glacial acetic acid and assayed for tramadol content by measuring the absorbance at 270 nm. Tramadol contents were calculated, using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

The drug content data were subjected to statistical analysis to test whether the drug content was uniformly distributed in the implants and the reproducibility of the method was possible. Mean ($\bar{x}$) and standard deviations (s) were calculated.

Swelling index

In order to study swelling index **(**Martínez *et al.*, 2009**),** the implant formulations were immersed into swelling solution phosphate buffer pH 7. The implants were placed in swelling solution and weight of implant was measured after one hour and the excess of solution was removed gently by tapping the surface with dry piece of filter paper. The degree swelling for each implant formulation at given time was calculated using the following equation:

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

where W_t and W_o are the sample's weight at any given time, and in the dry state, respectively.

Procedure for in vitro drug release study

The *in vitro* drug release studies **(**Brahmanker and Jaiswal, 1995**)** were conducted by immersing one implant in each vial containing 10 ml of phosphate buffer pH7.4. The vials were sealed with rubber closures and kept in shaker incubator thermostated at 37 ^{o}C. The dissolution fluid was changed for every 24 hours, throughout the experimental period with fresh 10 ml phosphate buffer pH7.4. The drug concentration in every dissolution fluid was analyzed spectrophotometrically at 270 nm after suitable dilution with phosphate buffer pH7.4.

Drug polymer interaction study

The IR spectra of tramadol and its formulations were obtained by KBr Pellet method using Perking Elmer FTIR series model

1615 spectrometer. The subdermal implants of tramadol prepared with chitosan were tested for compatibility of the drug with the excipients by I.R. study.

Stability study

The purpose of stability testing **(**International Conference on Harmonization, 2004**)** is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, retest periods and shelflives.

The International Conference on Harmonization (ICH) guidelines stability studies were carried out at 40^0C / 75 % RH for the selected formulation for the period of 3 months.

The selected formulations were wrapped in butter paper and were then stored at 40^oC / 75 % RH for 3 months and evaluated for their physical appearance and drug content at specified intervals of time.

Results

Diameters of implants

The diameter determined for formulated implants are tabulated in Table 2. Implants mean diameters were almost uniform in all the batches of implants formulations and were found to be in the range of 1.05 mm to 1.70 mm.

Uniformity of weight

The weight variations for all formulations are shown in Table 2. All the implants passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the implants formulations were found to be in the range of 50±5 to 70±17.32mg.

Drug content uniformity

The drug content of the formulations was determined according to procedure described in methods. The values are shown in Table 2. The percentage of drug content was found to be between 98.50±0.50 and 100.47±1.46% of tramadol, which was within acceptable limits.

Swelling index

The swelling indexes of formulations are shown in Table 2. All the implants formulations have swelling index within pharmacopeial limits. The swelling index, was found as 3.69 to 1.99.

***In vitro* dissolution studies**

The *in vitro* drug release study of drug implants from each batch (F_1 to F_8) was carried out in pH 7.4 phosphate buffer solution for 20 days, using the procedure as mentioned earlier. The cumulative % drug release of tramadol from implants is shown in Tables 3 and 4 and in Figures 2 and 3.

Drug excipients interaction study (By FTIR)

The I.R. spectrum of tramadol with excipients is similar to that of pure drug (Tramadol). All the characteristic bands of drug are retained in the I.R. spectrum of tramadol implant formulations, indicating that the drug is compatible with excipients, present in the formulations. The spectra for all formulations are shown in Figures 4 and 5.

Stability studies

The stability studies were carried out on selected formulations stored at 40^0C, 75% RH for 3 months. Implants were analyzed for their physical parameters and drug content at 15 days interval. The residual drug contents of formulations were found to be within the permissible limits. The results were shown in the Table 5 which confirms the stability of drug delivery device.

Discussion

The work was undertaken with an objective of designing rod shaped, matrix type implants for use in livestock. Controlled delivery of progesterone and its synthetics analogs through implantable devices for estrus control and synchronization is relatively new and require investigation to develop implantable therapeutic system. Attempts were made in the present work to design rod shaped implants containing progesterone. For this purpose, an extruder named as galaxy extruder was used. The extruder was found suitable for making rod shaped implants of polymeric substance in the laboratory for investigation purposes.

From the *in vitro* dissolution data, it was found that 62.54%, 60.63%, 58.36%, and 54.18% drug is released within a day from implants, prepared using drug and polymer ratios 1:3 and 1:4, (F_1 to F_4), respectively. Later on, the release is slowed and sustained up to 7 days. The maximum amounts of drug released from these formulations were found to be 96.23%, 94.12%, 92.78%, and 91.24%, respectively in 7 days.

The implant formulations prepared, using same drug: polymer and crosslinked with glutaraldehyde for 6h, 12h and 24h (F_5 to F_8) released 40.460%, 38.740%, 36.68%, and 34.45% tramadol within a day and than sustained the release for a period up to 17 days. The complete drug released from formulations F_5 to F_8 were found to be 86.74%, 82.68%, 79.23%, respectively after 17 days.

In all the implants formulations, it was observed that drug release was effectively modified by polymer concentration and duration of crosslinking concentrations. On increasing the concentration of polymer, the amount of drug release was decreased and increasing the crossliking time also decreases drug release. In all the implants formulations, the release of drug was constant and sustained over a period of 8 days in this case which are not crosslinked whereas

formulations which are crosslinked for 24 hours drug release was spread over 17 days.

Conclusion

In the present work, implants of tramadol were prepared by extrusion method, using specially designed extruder with biodegradable naturally occurring polymer chitosan, Tramadol hydrochloride (TRH). From the findings obtained, it can be concluded as:

- The extruder used is suitable for making rod shaped implants.
- The method employed was reproducible with regard to the dimensions and weight of implants.
- The low values of standard deviation for average weight and drug content of the prepared implants indicate weight and drug content uniformity within the batches prepared.
- Due to hydrophilic in nature, the natural polymer chitosan expected to absorb the water. To verify this swelling index, test was carried out. The result indicate that the swelling index decrease by increasing crosslinking time.

Based on *in vitro* dissolutions profile, it was observed that the release from implants prepared from chitosan which are not exposed to gluteraladehyde (F_1-F_4) can sustain release over a period of only 8 days, while the implants which are exposed to glutaladehyde for different time interval can sustain the release up to 17 days, depending upon time, duration of exposure, the implants exposed to 6 hours (F_5-F_8) sustain release up to 17 days.

- The difference in rate of drug release is explained by fact that crosslinking process usually harden chitosan matrix and prevent the penetration of release medium into the implants. The drug release mechanism for all implant formulations was found to be matrix diffusion controlled.
- The release tramadol can be controlled by varying concentration of chitosan as well as exposure time.
- The implants which are not exposed crosslinking agent show rapid release and completed within 8 days.
- FT-IR studies revealed that there were no chemical interactions between tramadol and the polymers used in the study.
- Short-term stability studies of promising formulations indicated that there were no significant changes in appearance and drug content of implants.

Since the release of tramadol from chitosan was spread over a period of 8 to 17 days by varying the concentration of polymer and crosslinking time, these implants could be used for pain management such as carcinomas, post operative surgery, osteoarthritis by suitable modification in the formulae, or in the drug release from implants.

Although, the present drug delivery system was not completely optimized to deliver the drug over prolonged period, the *in vitro* and other data obtained in the study points out the possibility of constructing such a system using chitosan as naturally occurring biodegradable polymer.

Table 2: Post formulation parameters

Formulations code	Diameter of implants	Weight of the implants in (mg)	Drug content of the implants in (mg)	Drug content of implant formulations	Selling index of implants
F_1	1.05±0.01	50±5.00	248.67±1.70	99.47±0.83	1.99
F_2	1.14±0.01	50±9.57	198.33±1.25	99.17±0.76	2.99
F_3	1.13±0.01	60±9.57	165.67±1.70	99.00±1.38	3.19
F_4	1.34±0.43	50±9.57	142.67±2.49	99.77±2.14	2.29
F_5	1.13±0.00	50±9.57	249.00±2.16	99.60±1.06	2.28
F_6	1.03±0.00	50±5.00	199.00±0.82	99.50±0.50	2.38
F_7	1.63±0.00	50±5.77	165.00±1.63	98.80±1.20	2.98
F_8	1.57±0.01	50±10.00	143.67±1.70	100.47±1.46	2.58

Each reading is an average of three determinations

Table 3: *In vitro* (Cumulative % Drug release) tramadol release from implant

Time in days	[F_1] Drug: Polymer 1:3 without crosslinking	[F_2] Drug: Polymer 1:3 with 6 hours crosslinking	[F_3]Drug: Polymer 1:3 with 12 hours crosslinking	[F_4]Drug: Polymer 1:3 with 24 hours crosslinking
1	62.54	60.63	58.36	54.18
2	72.42	70.78	68.54	64.34
3	80.25	78.32	76.32	72.28
4	84.56	82.60	84.56	76.39
5	88.36	86.26	88.38	82.81
6	92.20	90.32	90.52	86.72
7	94.56	92.65	91.89	90.46
8	96.23	94.12	92.78	91.24

Each reading is an average of three determinations

Table 4: *In vitro* (Cumulative % Drug release) tramadol release from implant

Time in days	[F_5] Drug: Polymer 1:4 without crosslinking	[F_6] Drug: Polymer 1:4 with 6 hours crosslinking	[F_7]Drug: Polymer 1:4 with 12 hours crosslinking	[F_8] Drug: Polymer 1:4 with 24 hours crosslinking
1	40.46	38.74	36.68	34.45
2	48.45	46.95	44.98	42.65
3	54.14	50.15	48.78	50.72
4	58.84	54.62	52.64	54.82
5	62.43	58.18	56.45	58.45
6	64.76	60.43	60.43	60.93
7	68.04	62.19	62.43	62.52
8	70.65	64.23	64.31	64.86
9	72.64	66.45	66.48	68.34
10	74.98	68.43	68.23	70.32
11	78.72	70.12	70.56	72.43
12	80.28	72.23	72.23	74.23
13	82.70	74.37	74.42	75.35
14	83.38	76.33	76.65	76.54
15	84.63	78.28	78.82	77.82
16	85.58	80.65	80.63	78.62
17	86.74	82.68	82.86	79.23

Each reading is an average of three determinations

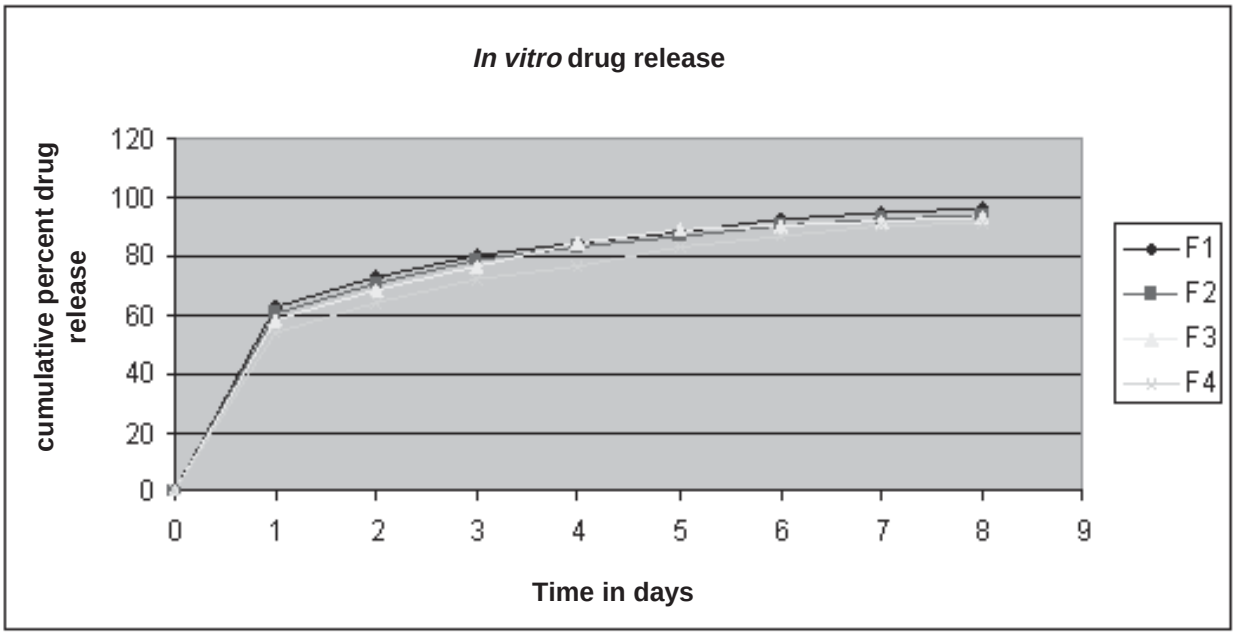

Figure 2: First order release plots for formulations F_1-F_4

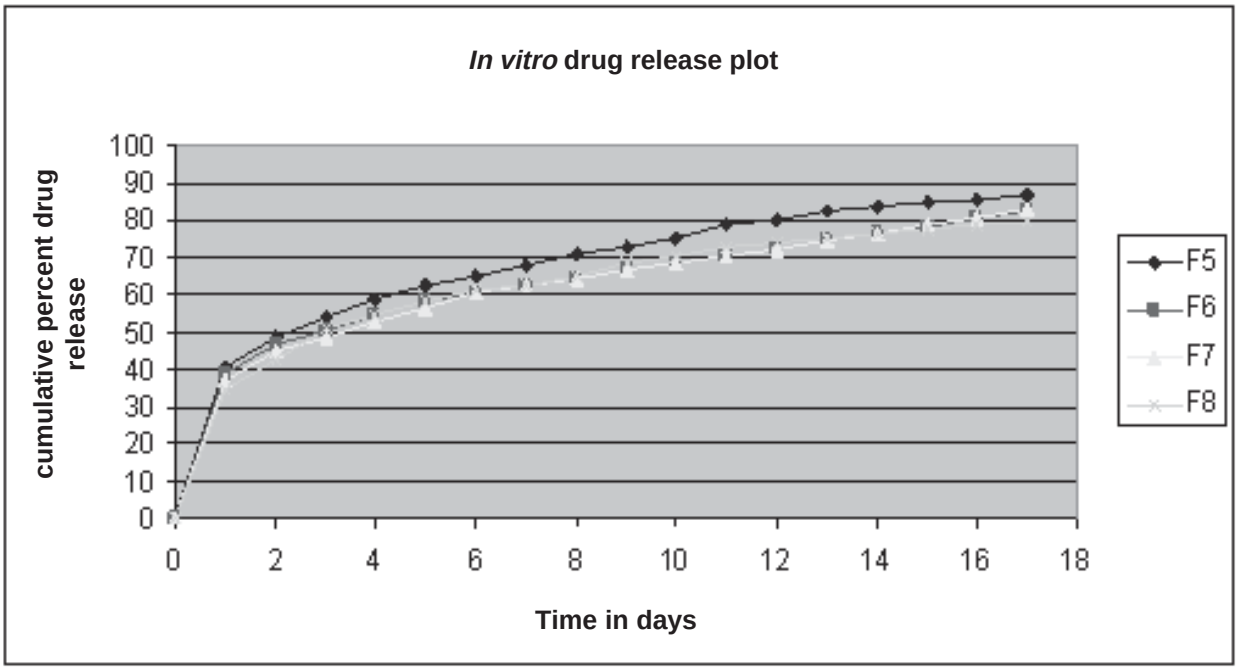

Figure 3: First order release plots for formulations F_5-F_8

Table 5: Stability data of selected implant formulations stored at 40 ^{0}C / 75% RH

Time in months	Formulations F_5		Formulations F_8	
	Physical appearance	% Drug content	Physical appearance	% Drug content
1	+++	97.24	+++	98.46
2	+++	97.32	+++	98.24
3	+++	97.28	++	98.12

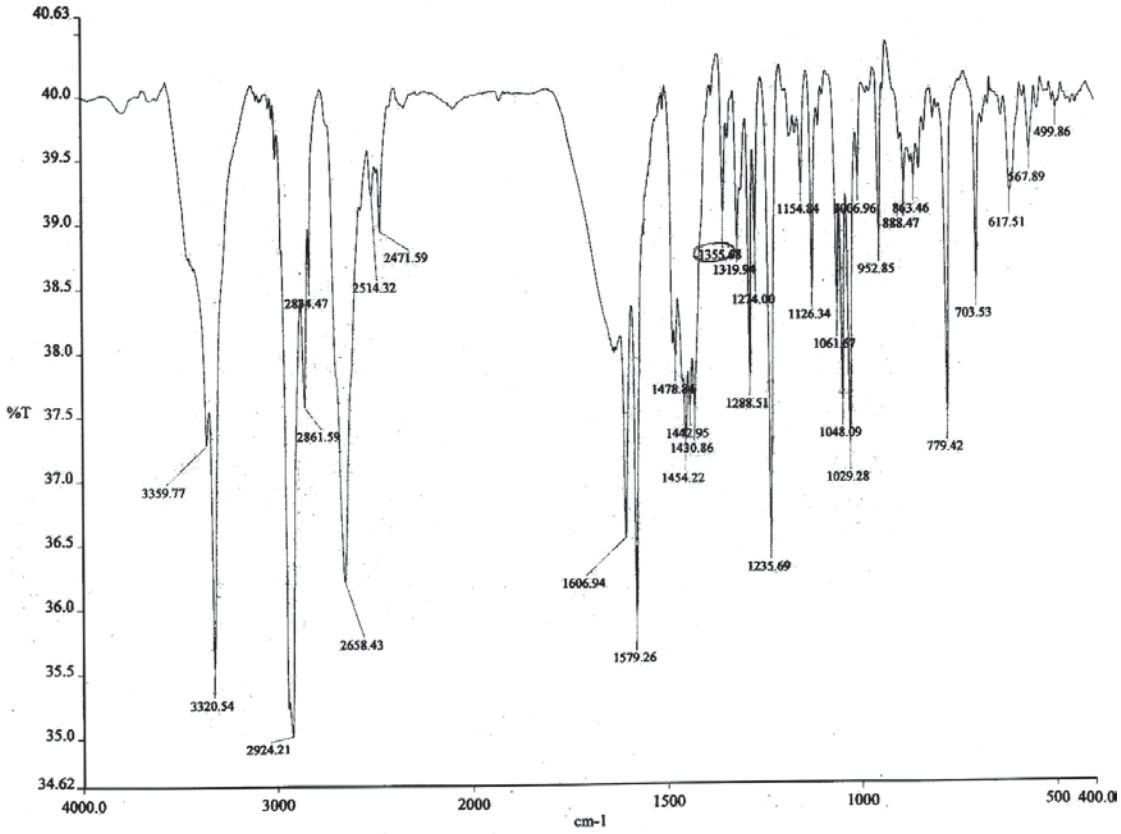

Figure 4: IR spectrum of tramadol

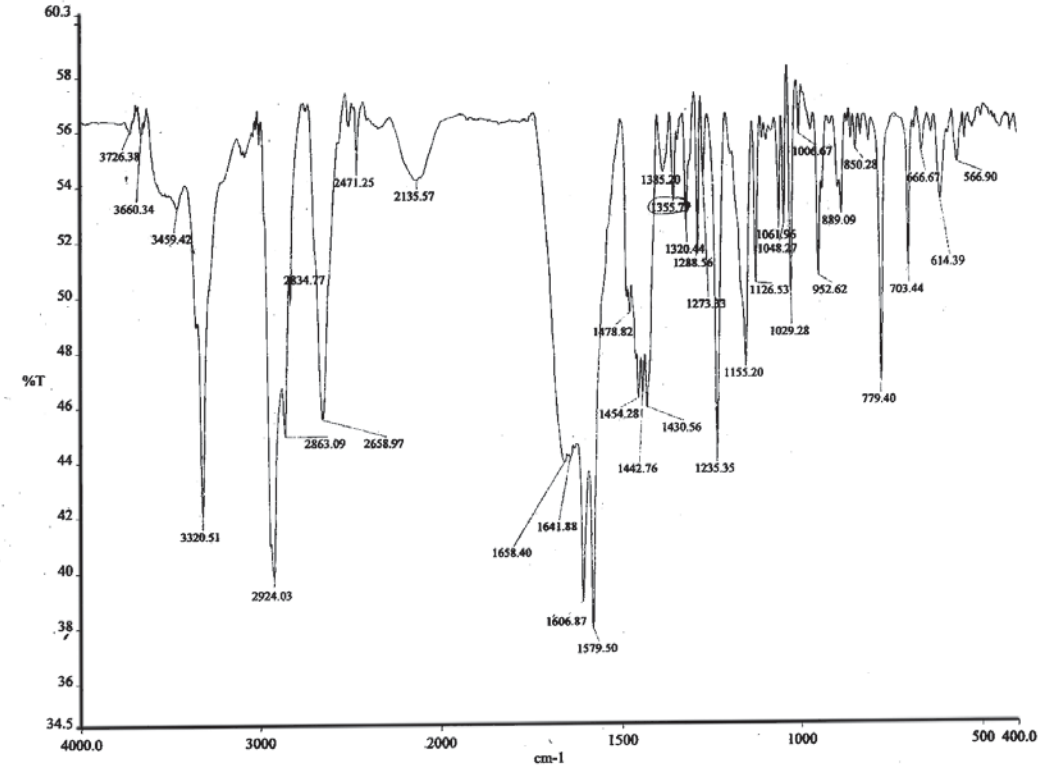

Figure 5: IR spectrum of formulation of tramadol

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