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DESIGN AND EVALUATION OF AN *in situ* FORMING IMPLANT SYSTEM OF AN ANTI-INFLAMMATORY DRUG

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Abstract:

The objective of the research work was to design and evaluate an in situ implant system of an anti-inflammatory drug. Deflazacort was the selected drug for the study. In situ formation of the implant was achieved by temperatere trigger approach. Combination of poloxamer 188 and poloxamer 407 was the selected thermoresponsive polymers. Optimization of the formulations was done based on gelation temperature, gel melting temperature, gelling time, gel duration, % entrapment efficiency etc. The optimized batch of FTH-2 exhibited a gelation temperature of 34.6 ± 0.26℃, gel melting temperature of 52.1 ± 0.25℃, gelling time of 5.4 ± 0.02 sec, and gel duration 172 ± 2.1, % entrapment efficiency of 78.4%. Based on these results it was decided that Insitu formulations with a Concentration of thermoreversible polymers, poloxamer 188 at 10% and poloxamer 407 at 17%. The burst release was controlled with incorporation of rate controlling polymer HPMC K4M at 1%. The process parameters was subjected to optimization and the results revealed that at mixing RPM of 2000, mixing time of 24 hrs resulted in formulation with ideal characteristics. The in vitro release of Deflazacort from the optimized batch, FTH-2 showed a controlled burst release of 06.39 ± 0.29 in initial 6 hours and 14.57 ± 0.14% on day-1 and the release was extended up to 168 hour (7days). The drug release of this batch when subjected to pharmacokinetics studies using various models showed that the data best into zero order and Higuchi release kinetic model with a coefficient of determination (R^2) value of 0.9989 and 0.9330. Linearity to Higuchi kinetic model indicated a diffusion controlled drug release. The release component (n) from peppas model was found to be 0.87, which indicated non-fickian diffusion from which it can be assumed that the drug delivery system under study is a swellable device and drug release followed an erosion controlled mechanism.

Key words: *Deflazacort, in situ injectable implant, thermoreversible, Poloxamer 188, Poloxamer 407, burst release.*

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INTRODUCTION:

Parenteral injectable *in situ* forming implants (ISFI)

Novel parenteral controlled drug delivery systems has grown significantly in last few years mainly due to their potential advantages when compared with the traditional parenteral controlled release dosage forms[1]. In the area of novel parenteral controlled release formulations, *in situ* forming implants (ISFI) has been reported as an attractive alternative against the existing preformed implants[2]. ISFI avoid the use of invasive surgical procedure associated with administration and removal of implant device. Also their manufacturing methods are simple, reproducible and feasible for scale up. They are injected as solutions and upon reaching body, transform to a gel or solid implant[3]. Different triggers can be adopted to stimulate this transformation: (1) Temperature (2) pH (3 Crosslinking (4) Ion exchange etc. Although the principle of ISFI looks attractive in literature reviews, key issues remain to be attended. These includes (i) variability of the implant shape and structure, (ii) avoidance of burst release (iii) toxicity issues[4,5] Limited research has been reported to overcome these limitations. Hence in the present research study an attempt will be made to formulate, evaluate and optimize *in situ* forming implant of a novel anti-inflammatory drug. Deflazacort is a_glucocorticoid used as an anti-inflammatory and immunosuppressant and indicated in treatment of Rheumatoid arthritis, Ulcerative colitis, Juvenile chronic arthritis, Muscular Dystrophy, Nephrotic syndrome[6].

MATERIALS AND METHODS:

Materials

Deflazacort was obtained as a gift sample from German remedies, Goa. Poloxamer 188 and 407 were purchased from Fizmerk India chemicals, Hapur (U.P).

Methods

Formulation development of Deflazacort *in situ* implant system

The experiment was designed as per the cold technique suggested by Schmolka as per the composition given in Table No:1 Add required quantity of polymer slowly into cold water maintained at a temp of 4-8ºC. Stir this solution using a magnetic stirrer with temperature maintained at 4-8 ºC. After mixing the container is sealed kept overnight in the refrigerator at a temperature of 4-8 ºC to obtain a clear solution. Deflazacort was dissolved in DMSO with stirring. The drug solution is then added to polymer solution with stirring at 2000 rpm for 30 minutes. Prepared solution was packed and sealed into containers[6].

Table 1: Formulation of Deflazacort *in situ* implant systems

Formulation Code	Ingredients (% w/v)			
	Deflazacort	Poloxamer 188	Poloxamer 407	Purified water
FT-1	10.00	5.00	-	85.00
FT-2	10.00	10.00	-	80.00
FT-3	10.00	15.00	-	75.00
FT-4	10.00	20.00	-	70.00
FT-5	10.00	-	5.00	85.00
FT-6	10.00	-	10.00	20.00
FT-7	10.00	-	15.00	75.00
FT-8	10.00	-	16.00	74.00
FT-9	10.00	-	17.00	73.00
FT-10	10.00	-	18.00	72.00
FT-11	10.00	-	19.00	71.00
FT-12	10.00	-	20.00	70.00
FT-13	10.00	5.00	16.00	69.00
FT-14	10.00	10.00	16.00	64.00
FT-15	10.00	15.00	16.00	59.00
FT-16	10.00	20.00	16.00	54.00
FT-17	10.00	5.00	17.00	63.00
FT-18	10.00	10.00	17.00	63.00
FT-19	10.00	15.00	17.00	58.00
FT-20	10.00	20.00	17.00	53.00
FT-21	10.00	5.00	18.00	67.00
FT-22	10.00	10.00	18.00	62.00
FT-23	10.00	15.00	18.00	57.00
FT-24	10.00	20.00	18.00	52.00

Evaluation of Deflazacort *in situ* implant systems

Clarity

The clarity of in-situ gel was assed to detect the presence of any foreign substances. It is done by the visual inspection of gel held against light under a dark background.

pH of the gel

pH of the test formulations prepared was determined with a digital pH meter. 1 ml of the test formulation was diluted with distilled water to make up 25 ml. the pH of this solution is tested and reported.

Thermosensitivity Evaluation[7,8]

Gelation temperature and gel melting temperature[7,8]

Gelation temperature is the temperature at which the drug solution gets converted to gel. Gelation temperature is determined by test tube inversion method suggested by Miller and Donovan. In this method, 2 ml of the test formulation is taken in a test tube. Immerse the tube in a water bath assisted with a thermostat. Increase the temperature slowly at increments of 1ºC.At every temperature set, the formulation is left to equilibrate for 5 minute during which gelation is observed. For this the test tube is tilted at an angle of 90 degree. The temperature at which the meniscus remains stagnant without movement is taken as gelation temperature. After this the gel is again heat further until the gel reverses back to a solution. This temperature is called gel melting temperature. At gel melting temperature the meniscus starts moving upon tilting the test tube at 90 degree.

Measurement of gelation time[7,8]:

Determination of gelation time is done at 37 ±0.5 ºC by tube inversion method as above. 2 ml of the formulation is taken in a test tube and kept in a water bath maintained at 37 ± 0.5 ºC. Observe the time taken for the solution to convert into a gel. For determining the gelling time the test tube is occasionally tilted at 90 degree and flow/non flow criteria of meniscus is observed.

Gel duration[7]:

Gel duration is the time until which the gel consistency can be maintained by formulation at 37 ±0.5ºC. For this 2 ml of the test formulation is taken in a test tube and kept in a water bath maintained at 37 ±0.5ºC. Observe the time taken for the solution to convert into a gel. This time is noted. The experimental temperature is maintained at the 37 ±0.5°C and observed for the time at which the gel loses its integrity. The duration for which the gel remains intact is calculated and reported as gel duration for the formulations.

Viscosity[7,8]

The viscosity of the formulations was calculated using Brookfield viscometer. The in-situ gel formulations were placed in the sampler tube. The samples were analyzed both at room temperature (27 ±2°C) and at 37±0.5°C (achieved by a thermostat equipped circulating bath connected to the viscometer adaptor). Viscosity is measured at 100 rpm with Spindle no S-62 for samples at 27 ±2°C and spindle No: 64 for sample at 37±0.5°C.

Syringeability test[9]

The test was done using a 5 ml syringe. The syringe was slightly modified to keep a weight of 500 g over the piston by syringe. An 18G needle was fixed on syringe. The gel was filled into the syringe and weight kept over the piston. The time taken for gel to be expelled from the syringe was taken as syringeability time. This time was compared with that of a market sample.

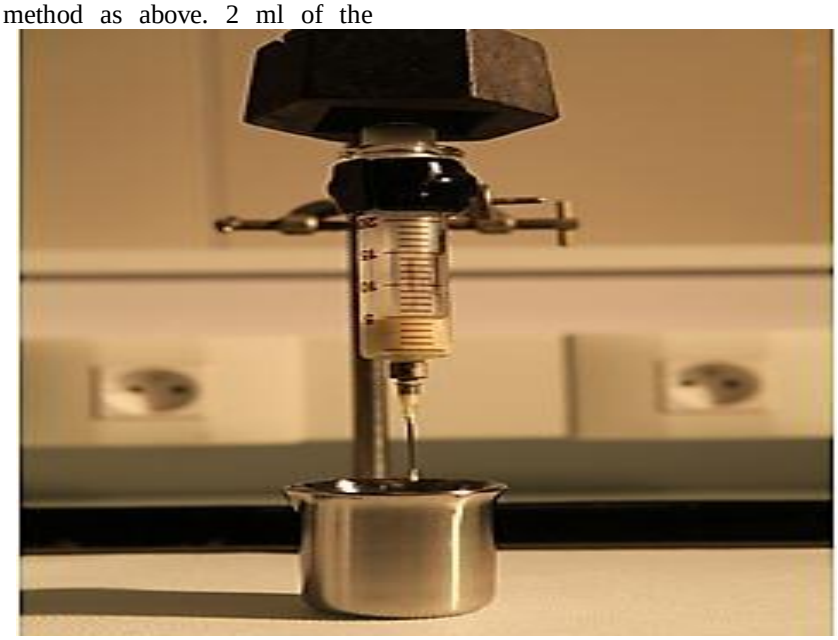

Fig1: Syringeability test apparatus

Drug entrapment efficiency Drug Content Estimation[8]

Deflazacort *in situ* implant formulation containing 180 mg of Deflazacort is injected into a 100 ml phosphate buffer pH 6.4 maintained at 37 ±0.5°C. The implant formed is taken and washed with buffer. This implant is further dissolved into 100ml of ethanol with vigorous stirring. 10 ml of the above formulation is diluted suitably and absorbance of the diluted test solution was measured at 246 nm by using UV-visible spectrophotometer.

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Drug content estimation

To estimate the drug content, test formulation containing Deflazacort equivalent to 100 mg of was taken. 10 ml of the above solution is taken and diluted suitably with ethanol and absorbance of the diluted test solution was measured at 246 nm by using UV-visible spectrophotometer.

In vitro drug release studies[10,12]

The in-vitro studies were carried out using a semi permeable membrane. The test is conducted with a semipermeable visking dialysis membrane of 14 mm diameter x 1 meter, which is having a capacity of 200 ml/meter volume

Treatment of dialysis bag[12]

Dialysis bag was treated as per directions on the leaflet of the package

1. Wear gloves.
2. Calculate the length of the dialysis tubing required for holding test gel formulation volume that contains 180 mg of drug. Cut off a length of required length.
3. Wet the dialysis tubing with distilled water.
4. Once the tube gets wet, place it under the running water.
5. Rinse the inner side properly to remove the glycerol.
6. Washing is done for 5 - 10 minutes.
7. A knot is tied near one end of the tubing.

Procedure for *in vitro* drug release studies

The dialysis bag method is used to perform the *In-vitro* release studies. Tube was tied at one end. A volume of test gel formulation containing 180 mg of Deflazacort was taken for the study. Add 10 ml of phosphate buffer solution (PH-6.4) into the dialysis tubing that is tied at one end. This is followed by injection of formulation containing 180 mg of Deflazacort into the bag. The membrane is then tied and placed into the release medium. Phosphate buffer solution of pH 6.4 was used as the release medium. It was stirred with a magnetic stirrer and is maintained at 37 $\pm 0.5^0$C using a thermostat. Maintain the stirrer speed in such a way that the dialysis bag will slowly float at the top of the solution. At the same time ensure that the bag is not moving too quickly resulting in an erratic release. 1 ml of the sample was withdrawn at time intervals of 0, 6, 12, 24, 48, 72, 96, 120, 144, 168 and 192 hours. The withdrawn samples were analyzed using UV spectrometry at 246 nm. Samples were replaced with equal volume of release medium at every sampling point.

Optimization of rate controlling polymer

To modify the burst release it was decided to incorporate a rate controlling polymer into the formulation. Formulations with HPMC K4M as rate controlling polymer were prepared as per the method given earlier. Trials with HPMC ratio of 0.5, 1.0 and 1.5 % were tried out as per the table No: 2

Evaluation of Deflazacort *in situ* implant systems incorporated with rate controlling polymer

The Deflazacort *in situ* implant systems upon incorporation with HPMC K4M as rate controlling polymer were further evaluated for pH, viscosity, gel temperature, gel melting temperature, gel duration, syringeability time, drug content, drug entrapment efficiency and drug release studies to determine the effect of HPMC K4M on formulation parameters.

Table No. 2: optimization of rate controlling polymer

Formulation Code	Ingredients (% w/v)				
	Deflazacort	Poloxamer 188	Poloxamer 407	HPMC K4M	DMSO
FTH-1	10.00	10.00	17.00	0.50	62.50
FTH-2	10.00	10.00	17.00	1.00	62.00
FTH-3	10.00	10.00	17.00	1.50	61.50

RESULT AND DISCUSSION:

Evaluation result for *in situ* gel of Deflazacort

Clarity

All the gels formulated were transparent and clear. They were free from polymeric clumps, any visible foreign and undissolved particles.

pH of the gel

The ideal pH of the formulations should be between 6 to 7.5 so as to avoid irritation at the injection site. All formulations were checked for pH and is determined by using digital pH meter. The results are tabulated in Table No. 3 as given below. The pH of all the formulations was found to be within the range of 6.7 to 7.0 and was found to be satisfactory.

Table 3: optimization of rate controlling polymer

Formulation code	pH*
FT-1	7.1 ± 0.06
FT-2	7.0 ± 0.02
FT-3	7.0 ± 0.02
FT-4	7.1 ± 0.05
FT-5	6.7 ± 0.02
FT-6	6.8 ± 0.03
FT-7	7.1 ± 0.01
FT-8	7.2 ± 0.03
FT-9	7.2 ± 0.03
FT-10	7.1 ± 0.03
FT-11	7.1 ± 0.02
FT-12	7.1 ± 0.01
FT-13	7.2 ± 0.02
FT-14	7.1 ± 0.02
FT-15	7.2 ± 0.03
FT-16	7.2 ± 0.03
FT-17	7.1 ± 0.02
FT-18	7.2 ± 0.02
FT-19	7.1 ± 0.03
FT-20	7.2 ± 0.01
FT-21	7.0 ± 0.02
FT-22	7.0±0.03
FT-23	7.2±0.02
FT-24	7.1±0.01

* Average of three readings

Thermosensitivity Evaluations:
Thermosensitivity evaluations for prepared in-situ gels were done to determine the ability of the system to form a gel upon influence of temperature. Gelation temperature, gel melting temperature and gelling time was determined in triplicates for optimizing the formulation variables.

Gelation temperature and gel melting temperature
In case of pluronic gels, the physical character depends on the length of co polymer block chains i.e. PEO-PPO-PEO ratio. The gelation temperature is the temperature at which the solution gets converted to gel form. The gelation time and temperature of formulated systems are found to be dependent on concentration of poloxamers. As the concentration of polymer increased the system became more thermo responsive. With poloxamer-188 the gelation temperature varied between 69.1 to 54.5°C. From the results, it can be concluded that the gelation time of pluronic 188 alone is high above the body temperature and hence poloxamer 188 formulations (FT-1 to FT-4) are discarded and not included for further studies. Trials were continued with PF-407(FT-5 – FT-13), where it was observed that gelation occurred at temperature varying from 27 to 49°C. Poloxamer 407 having a concentration of 5, 10 and 15 (FT-5, FT-6, and FT-7) are discarded as their gelation temperature was above 37°C. Poloxamer-407 at concentration16,17and 18% (FT-8,FT-9,FT-10) had gelation temperature varying from 33 to 36°C which was found to be within the desired range. Poloxamer 407 at concentration of 19 %w/v and 20 %w/v (FT-11 and FT-12) was also discarded as gel was formed at room temperature itself. Further trials were taken with a combination of PF-188 and PF-407 (FT-13 to FT-24) which gave gelation temperature varying between 21 to 41°C. In case of test formulations FT-13, FT-14, FT-15 and FT-16 where the gelation temperature above 37°C it was decided to discard from further study. Gelation temperature for batches no FT-17 ,FT-18, FT-19, FT-21and FT-22 ranges from 31°C to 38 °C which was found to be in a an optimal range and was selected for further studies. Batches FT-20, FT- 23 and FT-24 were also discarded due to gel formation occurs at room temperature. Hence the formulations FT-8, FT-9, FT-10, FT-1, FT-18, FT-19, FT-21 and FT-22 had a gelation temperature ranging from 30.2 to 36.5°C and was subjected to further studies. Gel melting temperatures were also determined and was found to vary between 45.2 to 82.2°C. Hence from this data we can confirm that the implants formed will not be melted at body temperature and can remain intact. Results for gelation and gel melting temperature were shown in table No: 4.

Table 4: Evaluation of poloxamer formulations for gelation and gel melting temperature

Formulation code	Gelation temperature* °C	Gel melting temperature* °C
FT-1	69.1 ± 0.42	82.2 ± 0.10
FT-2	64.8 ± 0.46	81.2 ± 0.22
FT-3	58.0 ± 0.52	73.4 ± 0.15
FT-4	54.5 ± 0.51	72.3 ± 0.46
FT-5	49.5 ± 0.42	63.1 ±0.46
FT-6	43.2 ± 0.32	61.5 ± 0.22
FT-7	40.2 ± 0.48	60.4 ± 0.32
FT-8	36.5 ± 0.43	59.4 ± 0.39
FT-9	33.3 ± 0.23	58.1 ± 0.47
FT-10	30.4 ± 0.26	57.1 ± 0.54
FT-11	28.2 ± 0.54	54 .3 ± 0.55
FT-12	27.5 ± 0.24	53.0 ± 0.43
FT-13	41.0 ± 0.28	74.2 ± 0.44
FT-14	42.1 ± 0.56	78.3 ± 0.31
FT-15	40.1 ± 0.22	76.5 ± 0.34
FT-16	38.2 ± 0.43	62.4 ± 0.45
FT-17	33.4 ± 0.25	60.3 ± 0.23
FT-18	35.1 ± 0.22	48.5 ± 0.13
FT-19	32.3 ± 0.34	49.4± 0.15
FT-20	28.5 ± 0.21	48.1± 0.16
FT-21	30.2 ± 0.35	47.3 ± 0.25
FT-22	31.1 ± 0.41	47.4 ±0.56
FT-23	29.4 ±0.15	45.3 ±0.13
FT-24	21.2± 0.25	45.2±0.35

* Average of three readings

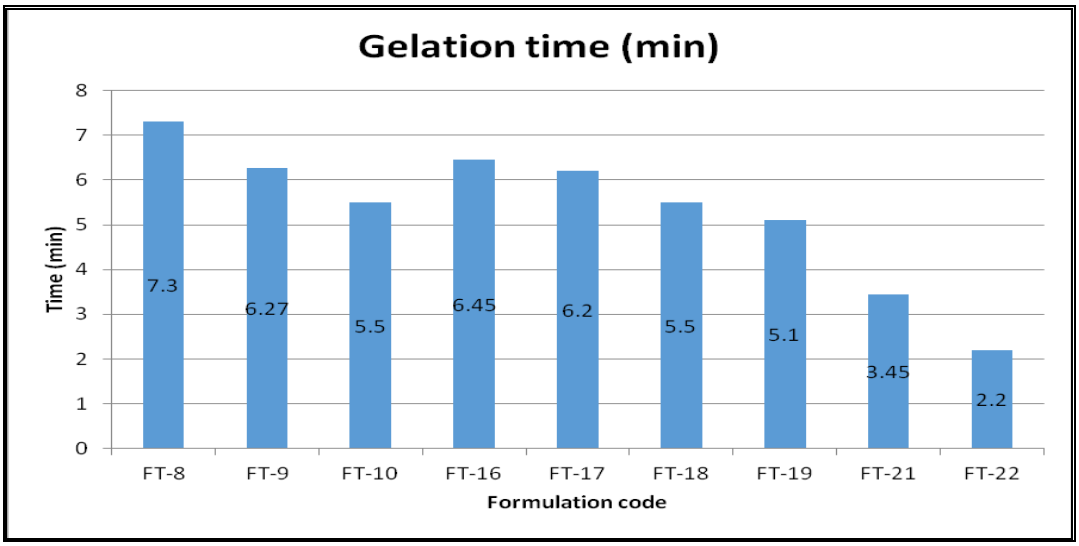

Fig 2: gelation time for formulations F1 to F15

Gelation time

The time required for an in-situ system for transition from solution form to a gel state at its gelation temperature is called as gelling time. An ideal system should gel immediately on exposure to gelation temperature. The gelling time for various formulations varied from 7.3 to 2.2 min. Formulations FT-8, with 16% of poloxamer 407, showed longest gelation time (7.3minutes) and formulation FT-22 with polymer combination of poloxamer188 (10%) and poloxamer 407 (18%) showed the shorter duration for gelling time i.e. 2.2 minutes. The gelling time for various formulations are in Fig No.: 2

Gel duration

Gel duration corresponds to the time to which the formed gel remains intact in the simulated physiological body fluid. This shows the integrity of the formed implant matrix to provide a sustained release the desired period of time. As per the results obtained the formulations exhibited a gel duration time varying from 172 to 288 hrs except for F8 and F9 which showed lesser gel duration of only 20 and 22 hrs. After this period the integrity of the formulations were lost. Hence it can be expected that the implants developed based on F8 and F9 will not be able to extend the release even upto 24 hrs. Hence these two batches were excluded from further studies. The results are given in Fig.No. 3

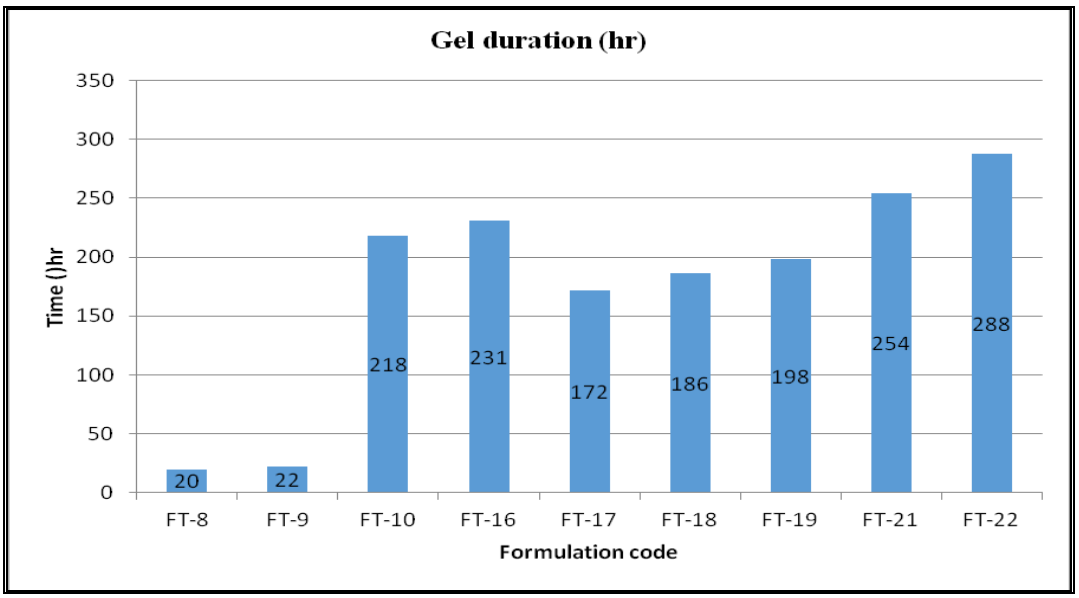

Fig 3: gel duration time for poloxamer formulations

Table 5: Evaluation of poloxamer formulations for Viscosity at room temperature and 37°C

Formulation code	Viscosity (cps)	
	Room temperature*	37±0.5°C*
FT-10	4975± 1.2	68964 ± 8.2
FT-16	5114 ± 3.3	73281 ± 5.2
FT-17	1926 ± 3.1	49268 ± 6.4
FT-18	2281 ± 2.3	52456 ± 4.6
FT-19	2376 ± 2.9	59963 ± 3.1
FT-21	5048 ± 3.1	79541 ± 5.4
FT-22	5351 ± 2.5	81113 ±5.3

*average of 3 readings

Viscosity measurements

Viscosity is an important parameter of in-situ gelling systems which impart ideal rheological properties. Viscosity of test formulations was measured at 27 ± 2°C and 37 ± 0.5°C representing the viscosity at storage conditions and at the body temperature. Studies of formulation exhibited a temperature dependent increase in viscosity. The viscosity for the solution of poloxamer 407 at 27 ± 2°C ranged from 2176 – 5351 cps. When the viscosity of these same formulations were measured at 37±0.5°C there was a significant increase in viscosity as the solutions are converted to their gel form and the values change from 59963 to 81113cps. This could be due to sol-gel conversion and formation of an implant. It was also observed that as the concentrations of the polymer increased the viscosity also increased. The viscosity should not be increased beyond an optimum level as it may affect the syringeability. The viscosity for the formulations was recorded in Table No. : 5

Syringeability

The time required to inject the formulation from a syringe by the application of a constant force is called syringeability time. Syringeability plays a significant role in clinical application while administering the gel into the body. For the evaluation an 18 G needle is used. Syringeability of the test formulations are compared with a market injectable formulation. The results revealed that for the market sample the syringeability time was 4 seconds. The time required for syringeability of test formulations ranged between 4 to 46.3 seconds. Three formulations F10, F16, F21 and F22 showed difficulty in getting injected and the same was reflected in the results with syringeability time of 35, 40, 42 and 46 seconds respectively. This difficulty in syringeability can be attributed to their increased viscosity. Thus study revealed that as the viscosity increased, syringeability time also correspondingly increased. So batches F10, F16, F21 and F22 were not considered for further formulation development. All other formulation tested had a syringeability time varied between 4 to 6 seconds and was comparable with marketed injectable sample obtained from syringeability data. The results for the formulations were recorded in Table No. : 6

Table 6: Evaluation of Syringeability Time for poloxamer formulations

Formulation code	Syringeability Time* (seconds)
Market formulation	4.3 ± 0.2
FT-10	35.2 ±0.1
FT-16	40.2 ± 0.4
FT-17	4.2 ± 0.3
FT-18	5.1.± 0.4
FT-19	5.5 ±0 .2
FT-21	39.5 ± 0.1
FT-22	46.3 ± 0.3

*average of 3 readings

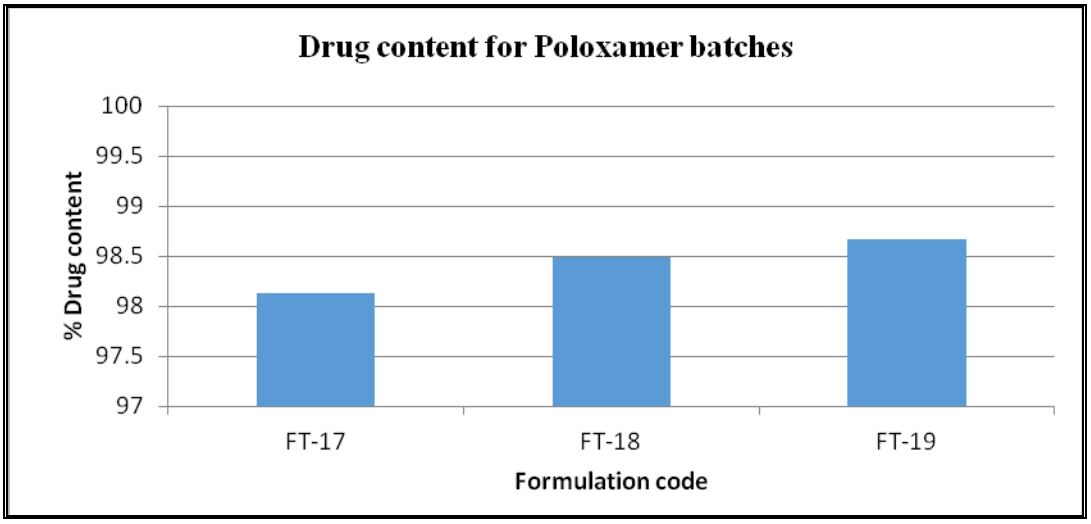

Fig 4: Drug content for FT-17, FT-18 and FT-19 formulations

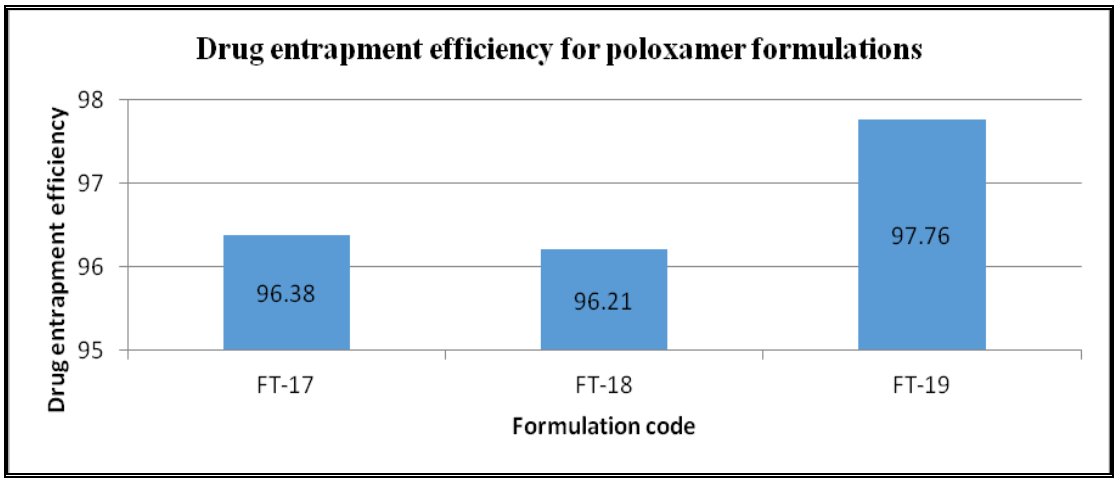

Fig 5: Drug content estimation for poloxamer formulations

Drug Content

Drug content estimation was done for FT-17, FT-18 and FT-19 formulations. The drug content found to be between 98.13 ±0.14 to 98.67 ± 0.4. The results for drug content estimations are shown in Figure No.: 4

Drug entrapment efficiency

The drug content of the implants determines the drug release and extent of burst release. Certain amount of drug present in the solution will not be entrapped upon gelation into the *in situ* formed implant. This drug will remain adsorbed over the surface of the implant. This non-entrapped drug will be responsible for the burst release. Percentage of drug entrapped is hence very significant as it may affect the desired release profile. The drug entrapment efficiency of each batch is determined and given in Figure No: 5. The entrapment efficiency of batches FT-17 and FT-18 ranged from 70.38 ± 0.28 to 79.76 ± 0.52%. From this we can conclude that as the concentration of polymer increased the entrapment efficiency increased.

***In-vitro* drug release study**

In vitro dissolution studies were carried out using visking dialysis membrane with phosphate buffer pH 6.4 as the release media. Three formulations FT-17, FT-18 and FT-19 were subjected to drug release studies, which contained 5%, 10% and 15% of poloxamer188 and 17% of poloxamer 407 respectively. Release data showed that irrespective of polymer concentration used, all prepared formulation exhibited a burst release. The results are tabulated in Table No:7 and figure No.:6. In FT-17, FT-18 and FT-19 there was a burst release of 45.87 ± 0.82, 42.34 ± 0.46 and 40.98 ± 0.65 % respectively in the initial six hours. Such a high burst release with more than 40% drug released within six hours showed the limitation of poloxamer system to retard the burst release. It was observed that formulation FT-17 exhibited a complete drug release of 98.10 ±0.23 % at 120 hrs. In case of FT-18 and FT-19 showed a complete drug release of 98.1 ± 0.67 % and 97.88 ± 0.19 % respectively at 168 hours. The release data revealed the following;

- Poloxamer formulations could sustain the drug release only up to 168 hrs. The drug release was dependent on poloxamer concentration. As the poloxamer 188 concentration increased from 5 to 10%w/v, drug release was sustained from 120 hrs to 168 hrs. But further increase in poloxamer concentration to 15% w/v could not further sustain the drug release.
- The burst release could not be controlled with poloxamer system since more than 40% drug released within 6 hrs. burst release was independent of poloxamer concentration

Hence it was concluded based on the drug release studies that a rate controlling polymer is needed to be incorporated to control the drug release.

Table 7: Evaluation of FT-17, FT-18 and FT-19 batches for in-vitro drug release profile

Time (hr)	cumulative % drug released		
	FT-17	FT-18	FT-19
0	0	0	0
6	45.87 ±0.82	42.34±0.46	40.98±0.65
12	53.46±0.64	49.45 ±0.37	47.46±0.36
24	71.45 ± 0.65	59.45 ±0.23	57.45±0.36
48	78.27 ± 0.25	66.45 ±0.27	68.34±0.67
72	86.47 ±0.34	72.45 ±0.45	74.30±0.16
96	95.38 ±0.75	78.29 ±0.36	80.25±0.45
120	98.10 ±0.23	87.54±0.76	84.56±0.17
144	97.67 ±0.11	94.93 ±0.34	94.45±0.16
168	-----	98.60 ± 0.67	97.88±0.19
192	-----	97.80 ± 0.22	96.31 ±0.1

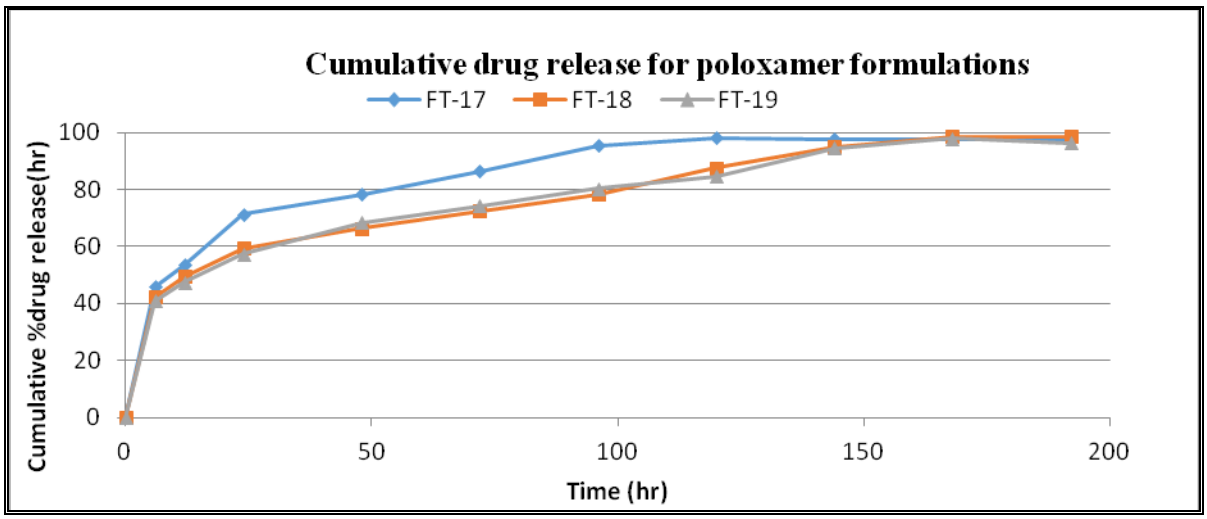

Fig 6: Cumulative drug release for FT-17, FT-18 and FT-19 batches

Optimization of concentration of rate controlling polymer.

To control the burst release and to further sustain the drug release, it was decided to incorporate a rate controlling polymer HPMC K4M into the formulations. HPMC K4M was tried out in concentrations of 0.5% w/v, 1% w/v and 1.5%w/v in formulations FPH-1, FPH-2 and FPH-3 respectively. The drug release rate was reported in Table No:8 and Figure No: 7. The study revealed that incorporation of HPMC K4M at 0.5% into formulation decreased the burst release with only 20.37 ± 0.21% releasing within 6 hrs in FT-19. But still the drug release within 24 hrs was found to be 30.26 ± 0.85%, which calls for further improvement. Drug release was found to be completed within 168 hrs with 98.12 ± 0.54% of release. Hence in the next trial HPMC concentration was increased to 1% which exhibited better control than over burst release with only 06.39 ± 0.29% was released in 6 hr and 14.57 ± 0.14% release in 24 hrs. But even with incorporation of rete controlling polymer the drug release could be sustained only up to 168 hrs (almost complete release of 98.28 ± 0.24% was observed at the end of 168 hrs).To study the effect of HPMC K4M in sustaining the drug release, another formulation FTH-3 was prepared with 1.5% of HPMC. It was observed that there was no significant improvement in burst release or sustaining the drug release beyond 168 hrs. Hence the study concluded that, HPMC K4M at a concentration of 1.5% w/v could control the burst release of drug and sustain and control the drug release for a period up to 7 days.

Table 8 : Drug release profile of FTH-1, FTH-2 and FTH-3 batches.

Time (hr.)	Cumulative percentage drug released*		
	FTH-1	FTH-2	FTH-3
0	0	0	0
6	20.37 ± 0.21	06.39 ± 0.29	06.38 ± 0.29
12	25.14 ± 0.25	10.09 ± 0.30	09.30 ± 0.49
24	30.26 ± 0.85	14.57 ± 0.14	14.26 ± 0.26
48	42.51 ± 0.46	27.45 ± 0.23	24.37 ± 0.47
72	52.23 ± 0.14	41.47 ± 0.15	39.30 ± 0.36
96	63.15 ± 0.84	56.29 ± 0.34	48.84 ± 0.39
120	82.64 ± 0.38	70.74 ± 0.47	62.16 ± 0.47
144	91.14 ± 0.23	84.23 ± 0.14	79.19 ± 0.56
168	98.12 ± 0.54	98.28 ± 0.24	97.92 ± 0.29
192	97.11 ±0.13	97.65 ± 0.53	97.20 ± 0.28

*average of 3 readings

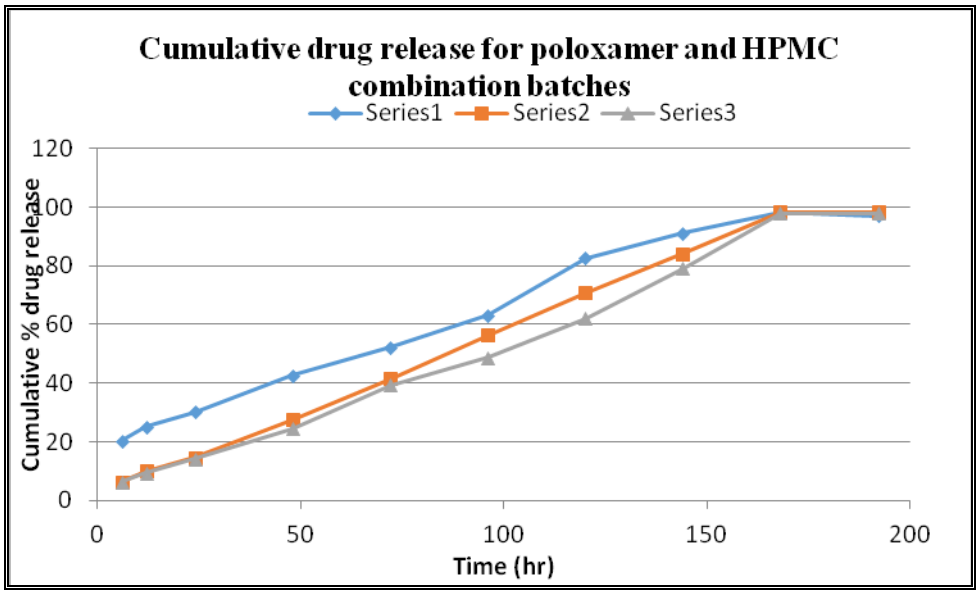

Fig 7: Formulation parameters for FPH-1, FPH-2 and FPH-3

Table 9: Evaluation of Deflazacort *in situ* implant systems incorporated with rate controlling polymer

Formulation Code		FTH- 1	FTH-2	FTH-3
pH*		7.2 ± 0.03	7.2 ± 0.02	7.2 ± 0.02
Gelation Temperature*(°C)		33.2 ± 0.43	34.6 ± 0.26	35.1 ± 0.43
Gel melting temperature*(°C)		50.2 ± 0.23	52.1 ± 0.25	54.2 ± 0.44
Gelling time*(Seconds)		5.2 ± 0.02	5.4 ± 0.02	5.4 ± 0.05
Gel duration* (hr.)		170 ± 1.1	172 ±2.1	188 ± 2.3
Viscosity* (cps)	Room temperature (°C)	2441 ± 3.2	2543 ± 2.3	2623 ± 4.2
	At 37±0.5°C	58621 ± 2.2	58722 ± 2.5	58824 ± 4.2
Syringeability Time* (sec)		6.3 ± 0.2	6.5 ± 0.3	6.5 ± 0.3
Drug Entrapment Efficiency*(%)		78.1 ±0.4	90.87± 0.2	91.1 ± 0.2
Drug content*(%)		99.1 ± 0.3	99.7± 0.2	98.3 ± 0.3

*average of 3 readings

Evaluation of *in sItu* implants incorporated with rate controlling polymer

The *in situ* implant formulations incorporated with rate controlling polymer, HPMC K4M was further evaluated for its effect on the various formulation characteristics. The results revealed that there were no significant difference in results as when compared to the optimal characteristics observed earlier. The results are tabulated in Table No. : 9

CONCLUSION:

Deflazacort parenteral injectable *in situ* implant may provide long-term management of inflammatory conditions with an improved patient compliance. The feasibility to achieve a controlled release from this delivery system can result in a better therapeutic index. The study established the potential of thermosensitive polymer like poloxamer 188 and poloxamer 407 to provide a controlled release delivery system.

REFERENCES:

1.Tejashree AG, Sagar D, Chavare DR, Ajit K, Shruti KE. A review on parenteral implants. International Journal of Research and Reviews in Pharmacy and Applied science. 2014; 4(2):1056-1072.

2.Shi, Y. and L. C. Li. 2005. Current advances in sustained-release systems for parenteral drug delivery. Expert Opin Drug Deliv. 2(6): 1039-1058.

3.Iyer SS, Barr WH, Karnes HT. Profiling in vitro drug release from subcutaneous implants: A review of current status and potential implications on drug product development. Biopharm Drug Dispos.2009; **27**: 157-170.

4.Nitsch MJ, Banakar UV. Implant drug delivery. J Biomater Appl. 1994; 8: 247-284.

5.Zhang L, Parsons DL, Navarre C, Kompella UB. Development and in-vitro evaluation of sustained release Poloxamer 407 (P407) gel formulations of ceftiofur. Journal of Controlled Release. 2002; 85(1–3):73-81.

6.Assandri A, Buniva G, Martinelli E, Perazzi A, Zerelli L. Pharmacokinetics and metabolism of deflazacort in the rat, dog, monkey and mean. Adv Exp Med Biol. 1984; 71:9–23.

7.Baloglu E, Karavana, Senyigit YS, Hilmioglu-Polat A, Metin S, Jones DS. In-situ gel formulations of econazole nitrate preparation and in-vitro and in-vivo evaluation. J Pharm Pharmacol. 2011; 63(10):1274-82.

8.Lalloo A, Chao P, Hu PS. Pharmacodynamic evaluation of a novel insitu poly (ethylene glycol)-based hydrogel for controlled delivery of camptothecins. Journal of controlled release 2006;112(3):333-42

9.Qiu B, Stefanos S, Ma J, Lalloo A, Perry BA, Leibowitz MJ. A hydrogel prepared by in situ cross-linking of a thiol containing poly (ethylene glycol)-beaded copolymer: a new biomaterial for protein drug delivery. Biomaterials. 2003; 24(1):11-8.

10.Pandit NK, Wang D. Salt effects on the diffusion and release rate of proponolol from poloxamer 407 gels. International journal of pharmaceutics 1998; 167(1-2):183-9.

11.Zhang L, Parsons DL, Navarre C, Kompella UB. Development and invitro evaluation of sustained release poloxmer 407 gel formulations of ceftiofur. Journal of controlled release2002; 85(1-3):73-81.

12.Choi HG, Jung JH, Ryu JM, Yoon SJ, Oh YK, Kim CK. Development of insitu gelling and mucoadhesive acetaminophen liquid suppository. International journal of pharmaceutics1998; 165(1):33-44.