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DEVELOPMENT AND CHARACTERIZATION OF CEFIXIME IN SITU GEL FOR BACTERIAL MENINGITIS

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ABSTRACT

Among all the routes, parenteral route of drug administration exhibits rapid effect, efficient drug delivery, avoidance of gastric irritation, prevention of first pass metabolism and easy administration to unconscious patients. In most of the cases frequent administration is unsuitable as it causes more risk of infection. tDevelopment of in situ biodegradable injectables solve this problem as it consists of polymers and it is administered in liquid form and converted into gel on coming across a stimulus. The aim of this research work was to develop in situ gelling system of cefixime based on biodegradable polymers. Cefixime is used in urinary tract infection as 20% of drug excreted by kidney in active form so preferred in UTIs. Therapy is for 7 days and conventional parenteral solution of cefixime need frequent administration that is painful and expensive. Hence, parenteral in-situ gel of cefixime was designed. The developed formulation contains temperature dependent polymer poloxamer P407 and pH dependent polymer Carbopol 934 which showed solution to gel transition from room temperature to body temperature and pH from 6.0 to physiological pH of body respectively. The formulation was evaluated for physical parameters: found clear in appearance, pH was within the tolerable range of body and show remarkable gelling capacity. Formulation also exhibited pseudo plastic behaviour on rheological studies. FTIR and DSC studies were performed for purity and compatibility studies of formulation. In vitro release studies showed that the formulation with required concentration of polymers prolonged the release for eleven days and followed first order kinetics. The prepared formulation was effective, stable and prolonged release for eleven days.

Keywords: *In situ biodegradable injection, gastric irritation, first pass metabolism, pseudo plastic behaviour.*

1. INTRODUCTION

Application of novel drug delivery system to the parenteral preparations led to the development of liposomes, microspheres, nanoparticles and implants. Implants are larger in size and need surgical insertion and removal. Microspheres are smaller and can be injected using conventional needles but they are difficult to form and batch to batch variations occured. Moreover, they have limited drug loading capacity. [1].

Though implants and microspheres were successful in reducing the dosage frequency yet the physicians and the patients were interested in non-invasive techniques that could achieve therapeutic levels and should be non-expensive as well as maintain plasma fluctuations while preventing the side effects. [2]. Biodegradable injectable *in-situ* was a promising alternative of liposomes, microspheres and implants. They were made up of such polymers that are liquid when administered and once into the body are converted to gels on coming across appropriate stimulus. The drug incorporated in the solution gets entrapped in the polymer degrade over the period of time.

Approaches of *in-situ* gel drug delivery system were physiological stimuli which include temperature and pH changes. Biomaterials whose sol-gel transition occur at ambient temperature are gaining importance in the pharmaceutical industries. These polymers were gel at body temperature and no external heat source is required. Examples include poly nisopropyl (PNIPAAM), pluronis (poly ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPO-PEO) triblock copolymers. [3]. pH dependent polymers contain acidic and basic groups that either donate or accept protons in response to changes in pH. Examples include cabopol and carbomer etc.

Chemical reactions include ionic cross linking, enzymatic reaction and photo-initiated reactions. Ionic cross-linked polymers undergo phase transition in the presence of ions e.g., K-caragenan forms gel in the presence of Ca^{+2}, Mg^{+2} and monovalent ions like sodium and potassium ions [4]. Some polymers in the presence of certain enzymes were converted into gels. It has the advantage over the other systems that it does not require external chemicals and ions. [5]. Photopolymerization polymers were injected into the body and electromagnetic radiation was applied to form gel. Acrylates were converted to gels in the presence of photo initiators. Cefixime, an antibiotic, is a third-generation cephalosporin like ceftriaxone and cefotaxime. Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillin and some cephalosporins due to the presence of beta-lactamases, may be susceptible to cefixime. The antibacterial effect of cefixime results from inhibition of mucopeptide synthesis in the bacterial cell wall. Cefixime is used in urinary tract infections as 20% of drug excreted by kidney as active drug so preferred in UTIs for 7-10 days depending on severity of the condition. Conventional parenteral dosage form required frequent administration which was painful. Hence, parenteral *in situ* gel of cefixime was designed for the treatment of UTIs in adults.

The surfactant property of poloxamer makes its use in detergents, dispersions, stabilizers and emulsification. Poloxamer P407 was used for the sustained release topical formulation of lidocaine. Results showed that poloxamer *in situ* gel provided sustained release than the conventional dosage forms. Poloxamer P407 was used to make parenteral *in situ* gel of cefixime which release drug slowly with change in temperature. [6].

Carbopol is flocculated powder with particles having diameter of 2-7 microns. All the carbopol grades have the ability to swell up in water thousand times than their original volume. Glass transition temperature of carbopol is 105℃. Results showed that gel had elastic solid behaviour and the elasticity depended on the concentration of carbopol used. [7].

Biodegradable injectable *in situ* was a promising alternative of liposomes, microspheres and implants. They were made up of such polymers that are liquid when administered once into the body were converted to gels on coming across a proper stimulus. The drug incorporated in the solution gets entrapped in the polymer degrade over the period of time. [8]. The developed formulation has increase bioavailability of cefixime, improve patient compliance by single dose administration, reduce dosage frequency and prolong residence time, provide less invasive technique and economical manufacturing and prevent plasma fluctuations of drug concentration due to missed dose or late dose.

2. MATERIAL AND METHODS

2.1 Equipments Stability chamber (QYM TDKO302), Brookfield Viscometer (LVDVE 230), FTIR (Agilent Technologies Cary 630), Franz cell apparatus (EMFDC 06), UV-Visible spectrophotometer (Ultra-3660, Rigol), Freeze dryer (BK-FDIOP BIOBASE)

2.2 Chemicals

Poloxamer P407 (Sigma Aldrich), Carbopol 934 (Chief scientific), HPMC K15M (Sigma Aldrich), PVA (Sigma Aldrich), Sodium bicarbonate (Chief scientific store), Lactic acid (Science world), Sodium hydroxide
(Sigma Aldrich), Potassium dihydrogen phosphate (Sigma Aldrich). Active ingredient was received as gift
sample from Lotus pharmaceuticals Islamabad.

2.3 Lyophillization of API and Prepapration of in situ gel

Lyophilization of API was done in lyophilizer at temperature -50℃ and pressure range from 1000 pascal to 5 pascals. [9]. Melting point of cefixime was measured by using capillary tube method. [10]. Weighed amount of HPMC K15M, Carbopol 934, PVA, poloxamer P407 was dissolved in phosphate buffer solution separately with proper stirring and left for overnight at 2-8°C. Then polymers were mixed and weighed amount of drug was dissolved in phosphate buffer solution and added to the polymer solution with continuous stirring to form final formulation. Solution of opaque white color was obtained and stored for further evaluation.

2.4 Optimization of the formulation

Formulation was optimized using different polymers and different concentration of polymers. Various grades of polymers were used and check compatibility with active shown in Table 1. Then gelation behaviour of formulation was observed with different concentration of compatible polymers.

TABLE 1. DIFFERENT CONCENTRATION OF FORMULATIONS FORMED

Ingredients	Concentration %age	Quantity used (ml)			
		F1	F2	F3T	F4T
PVA	1.5	1.0	1.0	2.0	0.5
Carbopol 934	1.0	0.5	1.0	1.0	0.5
	1.5	0.5	1.0	1.0	0.5
Carbopol 940	1.0	0.5	1.0	1.0	0.5
	1.5	0.5	1.0	1.0	0.5
HPMC K15M	5	0.5	0.5	0.5	1.0
	10	0.5	0.5l	0.5	1.0
	15	0.5	0.5	0.5	1.0
	20	0.5	0.5	0.5	1.0

P407	15	2.0	1.5	0.5	0.5
	20	2.0	1.5	0.5	0.5
F127	15	2.0	1.5	0.5	0.5
	20	2.0	1.5	0.5	0.5
P188	15	2.0	1.5	0.5	2.0
	20	2.0	1.5	0.5	2.0
NaHCO3/Lactic acid	0.1	0.1	0.1	0.1	0.1

2.5 EVALUATION OF FORMULATION

Following tests were performed for the evaluation of the parenteral *in situ* gel of cefixime:

2.5.1 Physical Evaluation

Formulation was inspected visually for the color, homogeneity, appearance and presence of any aggregates, separation of ingredients, presence of any particles or grits. [11]. The clarity test of formulation was done by visual observation against white and black background alternatively. The formulation was observed both in solution gel form against white and black background. [12]. The pH of formulation was measured with pH meter. The pH of formulation was measured by dipping electrode of pH meter in formulation and pH meter readings were noted. [13].

2.5.2 Rheological Studies

Gel strength was measured in terms of time required by 35g weight for penetration of 5cm distance through the gel. The test was performed by placing 50gof gel in 100mL measuring cylinder. Then 35g weight placed onto the gel and the gel strength measured by noting time required to move weight 5cm down the gel. [14]. Viscosity of gel was directly dependent on polymer content of the formulation. Spindle number of 62 was selected and lowered perpendicularly into the fixed volume of gel which was measured at speed of 100 rpm. [15].

2.5.3 Fourier Transform Infrared Spectroscopy

FTIR was also used to characterize the presence of specific chemical groups in polymer i.e. HPMC, Poloxamer, Carbopol, Cefixime and hybrid network reflecting effectiveness of developed procedure for producing different Nano-structured material. FTIR of drug and excipients were recorded on FTIR spectrometer. [16].

2.5.4 Differential Scanning Calorimeter

DSC was frequently used thermal analysis technique. DSC measured enthalpy changes in the sample due to changes occur in their physical and chemical properties as a function of temperature or time. It was a thermal analysis technique that looks at how material's heat capacity Cp was changed by temperature. [17]. Thermal analysis of formulation was performed using DSC analyser. A sample of 5 mg was sealed in aluminium pan and heated under nitrogen atmosphere at a heating rate of 10°C/ minute over temperature range of 10 –30°C.

2.6 *In vitro* Studies

Franz diffusion cell with 20mm diameter orifice (3.14 cm^2 area) was used for the drug release study of parenteral *in situ* gel. [18]. The samples were withdrawn from the recipient compartment at 0, 6, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240 and 264 hrs and subjected to UV analysis for determination of release rate.

Model dependent methods use different mathematical functions which describe the dissolution profile of dosage forms. In this study First order, Higuchi models, Hixon Crowel Erosion model and Korsmeyer-Peppas model were used for the determination of dissolution profile of formulation. Evaluation of diffusional release mechanisms from polymeric films was done. [19].

2.7 Stability Studies

Stability of a pharmaceutical product was defined as 'Ability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications'. The formulation was stored for period of 6 months for accelerated studies under following conditions at 37 ± 1°C, 40 ± 1°Cand 50 ± 1°C at RH 65% ± 5% and 75% ± 5%. The formulation was analysed for all the characters such as visual defects, color changes, precipitate formation etc. [20].

3. RESULTS

3.1 OPTIMIZATION OF FORMULATION

Different grades of polymers were tested at different concentration in trials which were compatible with drug. They also have syringiblility in solution form at room temperature and gave strong gel at body temperature and pH. Different concentrations of polymers were tested in trial with different grades. In trials, different grades of poloxamer were used as temperature dependent polymers. They were solutions at room temperature and formed gel upon increase in temperature and concentration, Carbopol was used as pH dependent polymer, HPMC and PVA was used as viscosity enhancer and right concentration was found by trials. [21]. Then gelation behaviour of formulations was observed. Detail of gelation behaviour of formulation while optimizing are given in Table 2. F6T show strong gelation upon change in temperature and pH as it has poloxamer P407 as temperature dependent polymer and Carbopol 934 as pH dependent polymer.

TABLE 2: GELATION BEHAVIOR WHILE OPTIMIZING

Formulation code	Poloxamer	HPMC	Carbopol	PVA	LA/NaHCO3	Drug 2g/5ml	Results
F1T	P127 (15%)	K15M (15%)	934 (0.5%)	10%	Few drops	1 ml	No gelation
F2T	P127 (20%)	K15M (20%)	934 (1.0%)	15%	Few drops	1 5ml	No gelation
F3T	P188 (15%)	K15M (15%)	934 (0.5%)	10%	Few drops	1 ml	No gelation
F4T	P188 (20%)	K15M (20%)	934 (1.0%)	15%	Few drops	1 ml	No gelation
F5T	P407 (15%)	K15M (15%)	934 (0.5%)	10%	Few drops	1 ml	Slight gelation
F6T	P407 (20%)	K15M (20%)	934 (1.0%)	15%	Few drops	1 ml	Strong gelation

3.2 PHYSICAL EVALUATION

Melting point of cefixime was found to be within the range of 218-225°C which is according to standard that was 210°C. Change in melting point from standard occur due to the presence of impurities. [22]. The appearance of formulation was inspected visually for colour, homogeneity, presence of aggregates, presence of any particles or grits etc. All formulation showed no colour change and were of opaque white in colour due to cefixime even after autoclaving. [23]. No particles, grits were present and formulation was

clear. The clarity test of formulation was done by visual observation against white and black background to detect presence of any particle. It was clear, there was no precipitation and there was no particle both in solution form of formulation and in gel form of the formulation. pH was a critical variable and an important factor in the formulation of pharmaceutical products. It served as a measure of acidity/ alkalinity of substances. The pH of a pharmaceutical product has greater influence on its solubility and stability. [24]. pH of formulation was within the range of 6.00-6.3 as terminal sterilization has no significant effect on the pH. Results are shown in Table 3.

TABLE 3: PHYSICAL PROPERTIES OF THE FORMULATION

Sr. No.	Sample time	Appearance	Particle presence	Clarity	pH	Melting Point
1	0 hr	Opaque white	No	Clear	6.00	218
2	15 days	Opaque white	No	Clear	6.01	220
3	1 month	Opaque white	No	Clear	6.00	220
4	3 months	Opaque white	No	Clear	6.03	220
5	3 months	Opaque white	No	Clear	6.01	218

3.3 RHEOLOGICAL STUDIES

In the development of parenteral *in situ* gelling system, the gel strength was important in finding conditions which allows easy administration. The syringe ability of solution form is important and its conversion to strong gel that release drug slowly over required period of time. Optimal *in situ* gel must have suitable strength so has to be administered easily and can be retained in body. The gel strength values between 25-50 s were considered sufficient. The gel strength less than 25 s may not retain its integrity and may erode rapidly while gels having strength greater than 50 s are too stiff and may cause discomfort. The formulation showed gel strength values in the range of 35-40 s which are acceptable. [25]. In parenteral solutions, inclusion of polymers increases viscosity of formulation which may result in difficulty in administration. Concentration of polymers and other ingredients should be such that the formulation must flow through the narrow pore of needle. It should be in solution form at room temperature and converted into strong gel at body temperature and pH. Literature review show that viscosity of 50-200 milli Pascals was optimum as it is syringe able. [26]. Rheological behaviour of formulation was studied by measuring viscosity with Brookfield viscometer.

Viscosity determination was performed in temperature range between 25^{0}C-40°C. Graph showed viscosity of developed formulation from solution to gel transition. The results revealed that viscosity increased with increasing temperature and pH (fig 1 & fig 2). [27].

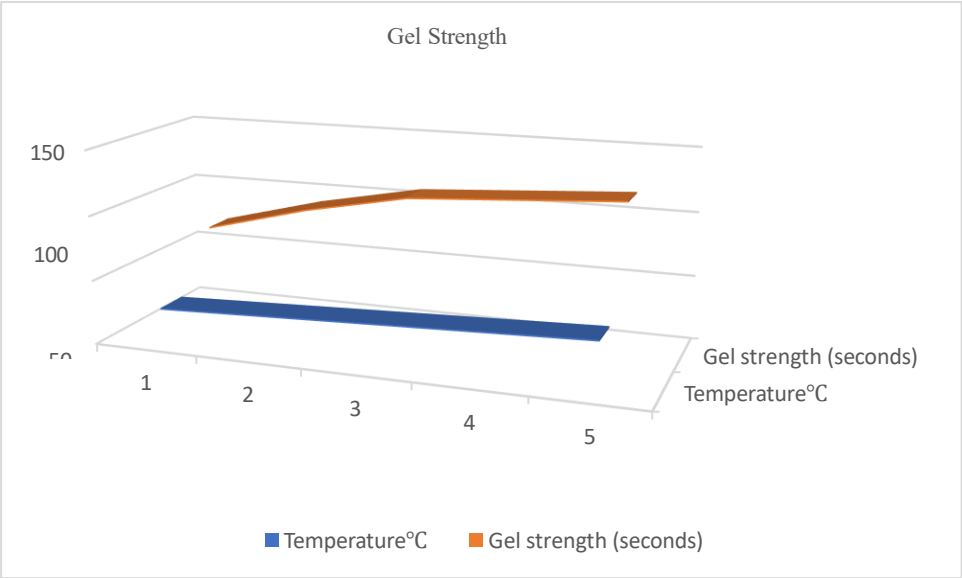

FIG. 1: GEL STRENGTH OF CEFIXIME *IN SITU* GEL

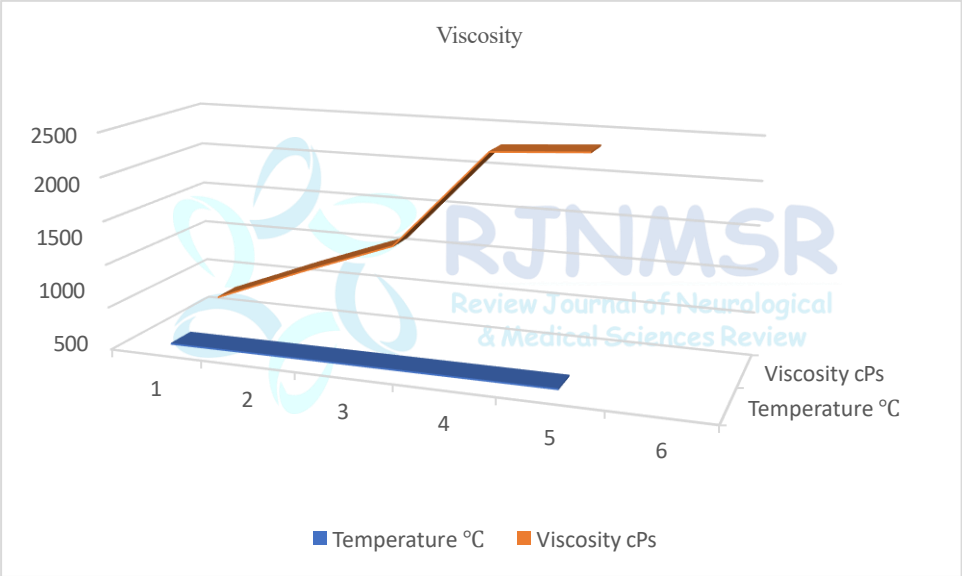

FIG. 2: RHEOLOGICAL BEHAVIOUR OF CEFIXIME *IN SITU* GEL TRANSITION

3.4 FOURIER TRANSFORMED INFRARED SPECTROSCOPY

FTIR is an important and emerging tool for analysing of ingredients to depict quality parameters. This technique was rapid and sensitive. It worked on the basis of functional groups and provide information in form of peaks. FTIR was performed at a range of 4000-650cm-1 to determine the compatibility and purity of cefixime, PVA and polymers HPMC K15M, Poloxamer P407, Carbopol 934.

FTIR spectra of cefixime obtained which showed standard peaks of NH stretching at 3300cm^{-1} CN stretching peaks at 1100cm^{-1}, stretching peaks at 1637cm^{-1} for CO groups of amides of asymmetric and symmetric vibrations. Carbopol 934 showed sharp peak of vibrational stretching of C=O group at 1700cm^{-1} while 2900cm^{-1} band which was due to the presence of CH stretching vibration. Bands in the range of 1100cm^{-1} showed C-O-C stretching for carbopol 934. [28].

FTIR spectra of HPMC K15M obtained which showed that bands were seen at 3600cm^{-1} and 3100cm^{-1} with max at 3400cm^{-1} was attributed to OH group vibrations. The two peaks at 2900cm^{-1} and 2850cm^{-1} was due to asymmetric and symmetric stretching of CH2 groups. The small peaks at 1600cm^{-1} showed propyl stretching vibrations. The sharp peak at 1250cm^{-1} to 1450cm^{-1} showed bending vibrations for CH groups. Asymmetric C-O-C for cyclic ethers showed stretching peaks at 1118cm^{-1} and COH

stretching was observed at 1000cm^{-1} [29].

FTIR spectra of poloxamer P407 obtained that showed CH stretching peak at 2900cm^{-1}. OH, bending peaks were observed at 1100cm^{-1}. CO stretching peaks were observed at 1250cm^{-1} for poloxamer P407 (Pore et al., 2009). FTIR spectra of PVA showed a broad stretching band at 2800cm^{-1} to 3000cm^{-1} for alkyl stretching, 3600cm^{-1} to 3700cm^{-1} small peaks for OH bond stretching and 3250cm^{-1} to 3500cm^{-1} broad peaks for hydrogen bonding. The peaks at 1700cm^{-1} to 1735cm^{-1} were observed due to the stretching of C=O and C-O from acetone group (fig 3). [30].

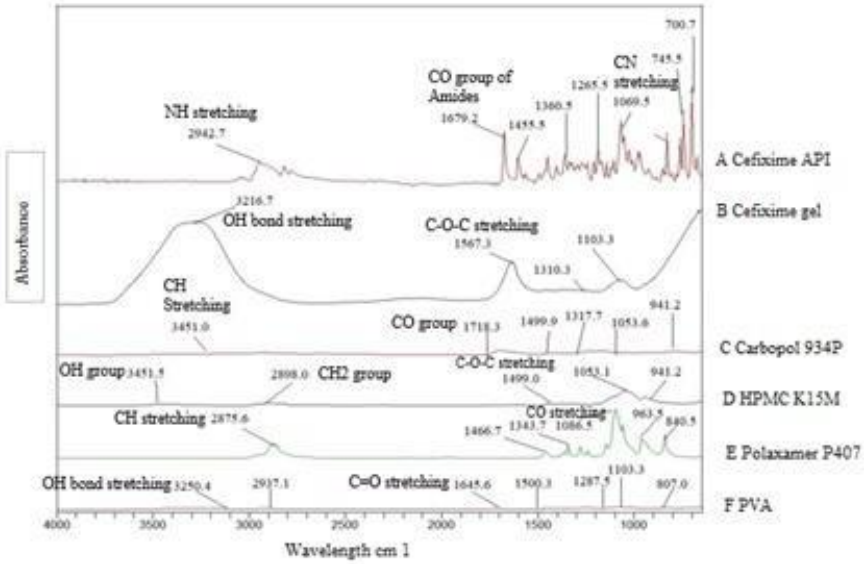

FIG. 3: FTIR OF CEFIXIME PARENTERAL IN SITU GELLING SYSTEM

3.5 DIFFERENTIAL SCANNING CALORIMETRY

DSC was frequently used thermal analysis technique. DSC measured enthalpy changes in the sample. Difference in heat flow arise when a sample absorbs or release heat due to thermal effects such as melting, crystallization, chemical reactions, polymorphic transitions, vaporization and many other processes. Specific heat capacities and changes in heat capacity e.g. during glass transition can be determined from difference in heat flow. It was a fundamental tool in thermal analysis. The information generated by this instrument was used to understand amorphous and crystalline behaviour, polymorph and eutectic transitions and many other properties used to design, manufacture and test products. [31].

The results of DSC of cefixime parenteral *in situ* gel showed that drug and polymers were compatible with each other. There was no extra peak as elimination of any peak and presence of extra peak indicates incompatibilities. The peaks obtained by DSC of cefixime parenteral *in situ* gel showed that all ingredients are compatibility. DSC of cefixime showed peak at 210℃ that was comparable to its melting point 218-225℃. This showed that there was no major peak shift in chemical complex. A broad peak at 125℃ showed that cefixime exist in amorphous form. The peaks for poloxamer P407 and Carbopol 934 were seen at 75℃ and 60℃ shown in graph. There was no endothermic peak of Carbopol because of its amorphous nature. [32]. There was no appearance or elimination of any endothermic peak which indicates that drug and polymers are compatible with each other. (fig 4)

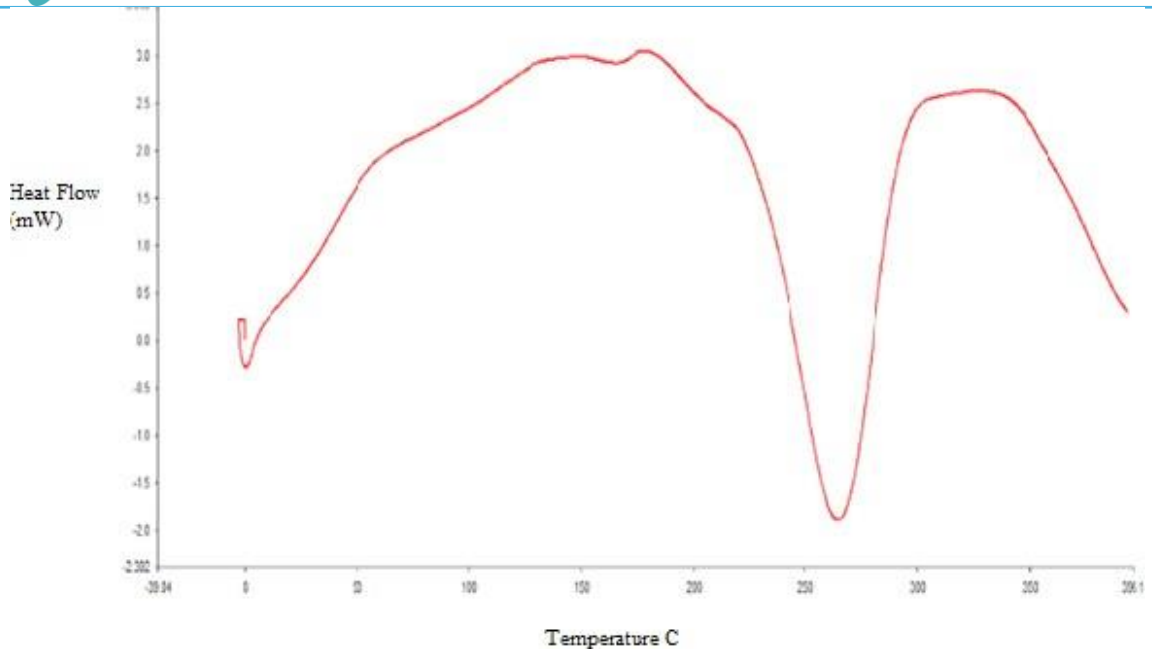

FIG. 4: DSC OF CEFIXIME PARENTERAL IN SITU GELLING SYSTEM

3.6 *IN VITRO* STUDIES

The *in vitro* release profile of any drug gave valuable approach that how developed delivery system will behave in vivo conditions. Franz cell studies was conducted to assess *in vitro* release pattern of drug. Franz diffusion cell was used for *in vitro* studies. The samples were withdrawn from Franz diffusion and was analysed with UV-spectrophotometer at 254nm after dilution. [33]. For evaluation of drug release different models were applied (zero order, first order, Higuchi, korsmeyer peppas and Hixson Crowel). Values obtained from these models tell us about the release mechanism of the drug. If we look at the value of regression coefficient, it became clear that first order model best fitted to our formulation. According to first order release kinetics the drug release was constant with respect to time and it was released constantly over eleven days (fig 5). [34].

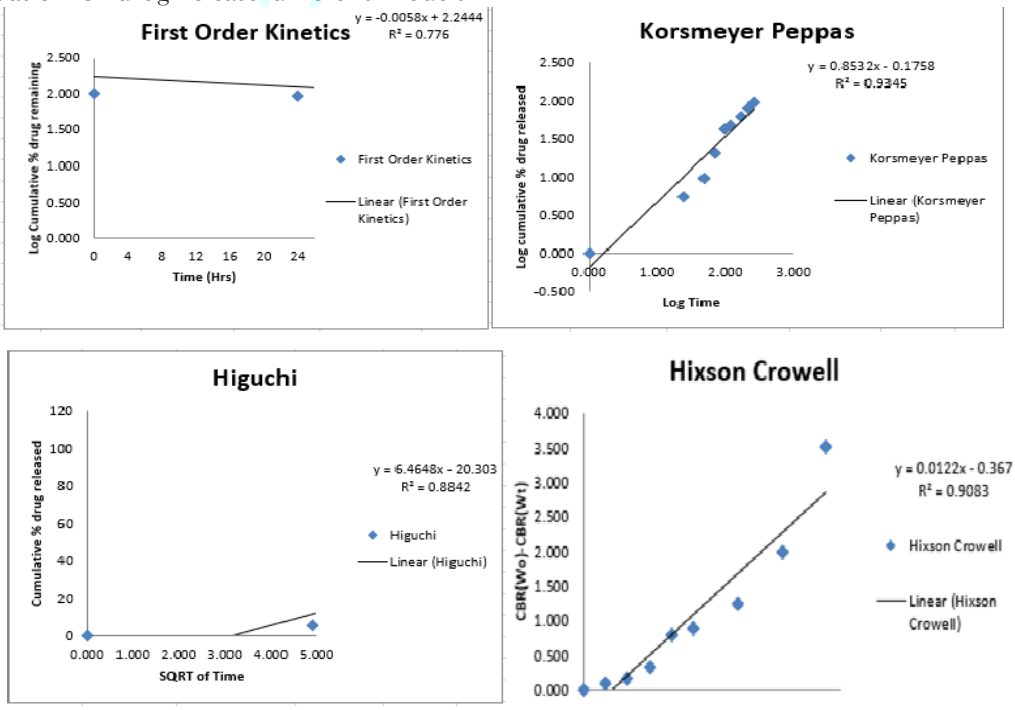

FIG. 5: IN VITRO RELEASE PROFILE OF CEFIXIME

3.7 STABILITY STUDIES

The purpose of stability studies was to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of variety of environmental factors such as temperature, humidity, light enabling recommended storage conditions, re-test periods and shelf lives. Generally, the observation of rate at which product degrades under normal room temperature requires a long time to avoid undesirable delay. The principles of accelerated studies were adopted. The ICH guidelines titled 'stability testing of new drug substance and product' described the ICH specified length of study and storage conditions. In Table 4 parameters are present showing results of stability studies.

TABLE 4: PARAMETERS SHOWING RESULTS OF STABILITY STUDIES OF FORMULATION

Storage conditions	Initial results	Results After 15 days	Results After 1 month	Results After 3 months	Results After 6 months
25°C RH 65%	Opaque white in color	Opaque white in color	Opaque white in color	Opaque white in color	Opaque white in color
40°C RH 75%	Opaque white in color	Opaque white in color	Opaque white in color	Opaque white in color	Slight change in color
50°C RH 75%	Opaque white in color	Opaque white in color	Opaque white in color	Slight change in color	Color changed

4. DISCUSSION

The conventional parenteral dosage forms cause many problems which urged the scientists to develop new mechanisms of drug delivery. Most manufacturing industries were focusing on novel parenteral preparations. Development of biodegradable injectable *in situ* solve this problem as it was made up of biodegradable polymers and it was administered in liquid form which converted into gel on coming across a stimulus. The drug incorporated in solution gets entrapped in polymer matrix on solidification and provide sustain release effects. The aim of this research work was to designed parenteral *in situ* gelling system of cefixime based on biodegradable polymers. Cefixime is third generation cephalosporin and is used in urinary tract infection as 20% of drug excreted by kidney in active form so preferred in UTIs.

In this project temperature dependent and pH dependent parenteral *in-situ* gel of cefixime was prepared with combination of polymers. At room temperature the formulation was in solution form which converted to gel at body temperature due to change in pH and temperature. [35]. Quality and purity of API and polymers was checked. Melting point of cefixime was measured with capillary tube method. The results of melting point lied within the range of 218 - 225°C which was according to standard i.e. 210°C. Lyophilization or freeze drying was a process in which frozen material was directly converted to vapor without liquid water formation.

This process of sublimation involved vaporization of ice by absorption of heat from the frozen sample and vacuum pump was used for water vapor removal from the surface. Then transfer of water vapor to a collector and the removal of heat by the collector occurred to condense the water vapours. Freeze drying was the process of balancing between the heat removed from the collector to convert the water vapor into ice and the heat absorbed by the sample to vaporize the ice. This process was mostly used for water removal from sensitive products, specially of biological origin products, without damaging them. Hence, they can be permanently preserved in storable state and reconstituted easily by addition of water. The material can be easily reconstituted to its original form for injection later on, stored and shipped when its water was removed and it was sealed in vial. The significance of lyophilized cefixime included easy processing of liquid, which simplified aseptic handling, increased stability of a dry powder, water removal become easier without use of excessive heat of the product, increases shelf life, rapid and easy dissolution of reconstituted product, it can be stored at room temperature indefinitely. [36].

Physical evaluation of the formulation was done which include appearance, clarity, pH. Other evaluation includes rheological studies, FTIR, DSC, kinetic release of drug from dosage form, and stability studies. The solution of parenteral *in situ* gel was obtained perfectly clear and opaque white in colour. The formulation was screened visually using standard procedure to detect presence of any particle, any turbidity etc. The result of solution which was stored at room temperature and elevated temperature confirm that there was no evidence of colour change and physical change found. [37].

pH is an important parameter which is very important as gel is directly injected into the body so pH is very important. As carbopol is a pH dependent polymer which got converted into gel form at slightly change in pH, pH meter was used to measure pH of the formulation which was found to be 6.0 and after injecting into the body it got converted into gel at body pH.

Gel strength of parenteral *in situ* gel was measured to observe how much strong gel or it is strong enough to stay in body and release slowly the active ingredient over extended period of time (Mahajan and Gattani, 2010). Viscosity test was performed by using Brookfield viscometer by increasing temperature from solution to gel transition. Results indicates that solution was converted to gel at body temperature and gel was strong enough that it can be retained in body for specific period of time to release drug over specific period of time. Rheological studies revealed that formulation exhibited pseudoplastic flow.

FTIR data showed that cefixime was compatible with the polymers and ingredients in physical mixture. The presence of specific chemical groups in the ingredients were characterized by Fourier Transformed Infrared spectroscopy. FTIR of drug and excipients were recorded on FTIR spectrometer to check quality and purity of polymers and drugs. Results of peaks of drug and polymers indicates that drug and polymers were pure. [38].

DSC was done for thermal analysis of formulation and it was used to measured enthalpy changes due to change in properties of melting, crystallization, transition and vaporization in formulation. Melting temperature, heat of fusion, latent heat of melting, reaction energy and temperature, glass transition temperature, precipitation energy and temperature, crystalline phase transition temperature and energy, denaturization temperatures, oxidation induction times, and specific heat or heat capacity were measured through DSC analysis. [39]. During heating and cooling of sample, amount of energy absorbed or released provide quantitative and qualitative data on endothermic (heat absorption) and exothermic (heat evolution) processes. These processes were measured through DSC analysis and it was used to determine the thermal stability of a formulation. Results of formulation showed no extra peak of transition which indicates that formulation was thermally stable. Results of DSC showed no extra peak which ensures absence of transition in peaks of formulation. [40].

The release of the active pharmaceutical ingredient (API) from the drug product matrix in controlled environment by *in vitro* drug release test, was a process of evaluation of drug development and quality control. In this process the dosage form was subjected to a set of conditions that will induce drug release and quantitating the amount of drug released under those conditions. Franz diffusion cell was used for *in vitro* testing of formulation and sample was detected by UV-spectrophotometer after dilution.

Result showed that it follows first order kinetic of release mechanism and drug release constantly with time over eleven days. [41]. Release studies showed that the formulation with required concentration of polymers sustained the release of cefixime for 11 days and follow first order kinetics. Stability studies revealed that formulation was stable at room temperature (25°C).

Hence, this research work proved to develop parenteral *in-situ* gelling system for cefixime with temperature and pH dependent polymer to optimize its effect, to improve patient compliance by giving relief from frequent administration of injection and improve bioavailability by constantly release drug over eleven days.

For the storage the drug will be lyophilized and packed in a glass syringe and covered with aluminium foil. The polymers in solution form will be packed in another glass syringe covered with aluminium foil as well. Before injection the contents will be mixed in a separate syringe and injected. [42].

CONCLUSION

It is concluded from the experimental work that parenteral *in situ* gel had been successfully developed using poloxamer P407 and HPMC K15M as temperature dependent polymer, carbopol as pH dependent polymer, PVA as viscosity enhancing agent which can significantly retard the release of drug from the polymeric system. This research work was conducted to develop parenteral *in situ* gelling system for cefixime with temperature and pH dependent polymer to optimize its effect and to improve patient compliance. Cefixime is used in urinary tract infections as 20% of drug excreted by kidney as active drug so preferred in UTIs for 7- 10 days depending on severity of the condition. Conventional parenteral dosage form required frequent administration which was painful. Hence, parenteral *in situ* gel of cefixime was designed for the treatment of UTIs in adults.

The developed formulation has increase bioavailability of cefixime, improve patient compliance by single dose administration, reduce dosage frequency and prolong residence time, provide less invasive technique and economical manufacturing and prevent plasma fluctuations of drug concentration due to missed dose or late dose.

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