Formulation and Development of Mucoadhesive Dental Gel

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Abstract

Dental diseases are a major health problem in all parts of the world, common in all age groups, races and genders. The most familiar symptom of a tooth problem is toothache [(1)]. The severity of the pain depends on the level of which part of the tooth is affected and how deeply the decay extends. Periodontal disease is a term which includes a number of pathological conditions described by inflammation and degeneration of the gums (gingival)and the supporting structures of the teeth. The local anaesthetics are widely used in dentistry for dental pain control. Effective administration of a local anaesthetic without the need for injection would be a major advance in dental pain control, this research work was planned with the objectives to develop a mucoadhesive gelling system suitable for periodontal pocket administration, which would enable a patient to have painless treatment without distress of injection.. The local anaesthetic [(3)]agents used throughout the study is lidocaine.The aim of the work with these substances is to achieve systems which can be easily administered to the periodontal pocket, stay at the application site due to a viscosity increase, give a fast onset of anaesthesia lasting throughout the dental procedure and thereafter be easily rinsed out-with water causing a fast decline in anaesthetic effect. Poloxamer 407 is a triblock copolymer with a central hydrophobic chain of polyoxypropylene (PPO) and two identical lateral hydrophilic chains of polyoxyethylene (PEO). The polymer solution is a highly viscous gel at room temperature but becomes a liquid at refrigerator temperature The gel has thermoreversible gelification and it can be cooled and warmed many times without changing its properties . The main reasons for addition of mucoadhesive polymers in the system are the possibilities of prolongation of residence time in organ and increase of the contact time with absorbing mucosa, resulting in the enhancement of drug absorption Such formulation stays at application site due to increased viscosity and mucoadhesiveness, and gives a fast onset of anaesthesia.

The gel has thermoreversible gelification and it can be cooled and warmed many times without changing its properties . Poloxamer 407 is biocompatible and due to its stability is used in pharmaceutical preparations; low toxicity and weak immunogenic properties make it suitable as a vehicle for drug delivery.

Keywords: *Periodontal disease, Poloxamer 407, mucoadhesive gel, lidocaine,thermoreversible.*

INTRODUCTION

Pain and infection is always associated with these dental problems. Many a times eventhough the infection appears to be local it spreads into more deeper layers and even may become systemic. In such cases use of analgesics, antibiotics and antipyretics is common in the dental treatment.The local anaesthetics are widely used in dentistry for dental pain control. Effective administration of a local anaesthetic without the need for injection would be a major advance in dental pain control. Numbers of topical anaesthetics are used in dentistry, but the disadvantages with most of these formulations include their low degree of efficacy, tendency to spread in other areas causing numbness of lips and tongue, bitter taste, difficulty in administration and short duration of action Considering the above shortcomings, this research work was planned with the objectives to develop a mucoadhesive gelling system suitable for periodontal pocket administration, which would enable a patient to have painless treatment without distress of injection.and which will overcome the above drawbacks. Such formulation stays at application site due to increased viscosity and mucoadhesiveness, and gives a fast onset of anaesthesia. The gel can be easily rinsed out with water after the treatment causing a fast decline in anaesthetic effect.

This study deals with drug delivery systems undergoing transitions from a low to a high viscous state as a consequence of an increase in temperature or dilution with water (saliva). Such systems have gained significant interest among formulators within the pharmaceutical field as drug delivery vehicles for dermal, nasal, ocular, oral, buccal, vaginal, rectal and parenteral administration. Despite the interest in these systems, topical formulations for local anaesthesia of the periodontal pocket are scarce. In relieving local pains, local anesthetics such as lidocaine, procaine, tetracaine, have been extensively used. Even though their analgesic activities have been well demonstrated, traditional methods of spinal anesthesia have problems in the outpatient setting .Moreover, since they have short half-lives after parenteral injection, an alternative route, to achieve the substantially sustained analgesic effects while avoiding any side effects, needs to be considered · The main reasons for addition of mucoadhesive polymers in the system are the possibilities of prolongation of residence time in organ and increase of the contact time with absorbing mucosa, resulting in the enhancement of drug absorption.The local anaesthetic agents used throughout the thesis is lidocaine.The aim of the work with these substances is to achieve systems which can be easily administered to the periodontal pocket, stay at the application site due to a viscosity increase, give a fast onset of anaesthesia lasting throughout the dental procedure and thereafter be easily rinsed out-with water causing a fast decline in anaesthetic effect.There are a number of challenges when preparing these kind of systems since the phase behaviour of PEO-PPO-PEO block copolymers are affected by various factors such as temperature, copolymer composition, molecular weight, concentration, and presence of cosolutes such as surfactants, electrolytes, and hydrophobic substances ..Intimate contact of a delivery system with an absorbing membrane maximizes not only drug absorption, but also influences the rate of drug absorption Though several approaches such as particle density,particle size and the use of fibrous materials have been reported to prolong GI transit time, the use of bioadhesive polymers have been most investigated.

MATERIALS AND METHODS

Materials: Pluronic F 127 was obtained from BASF Corp (Ludwigshafen,Germany), Lidocaine hydrochloride was obtained as a gift sample from Nulife Pharmaceuticals.,Pune..Xanthan gum was purchased from MERCK. Polyvinyl alcohol was procured from Research lab fine chem.,industries(INDIA)

Preformulation characerisation of drug and excipient:

Lidocaine hydrochloride:

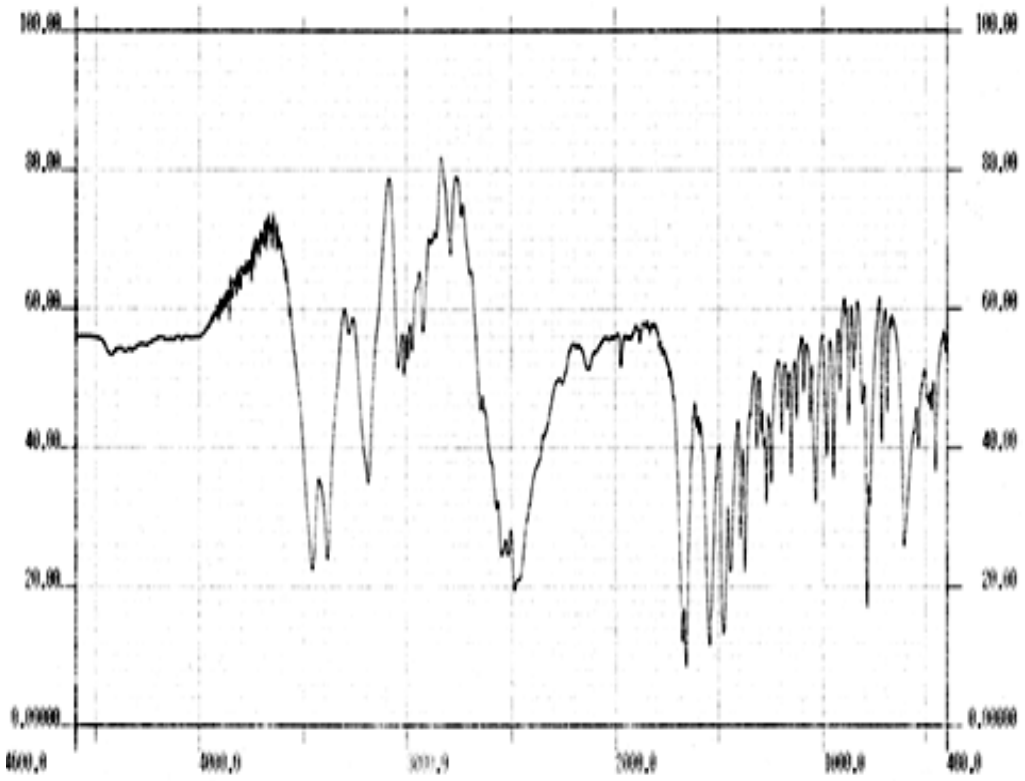


Fig1. :FTIR of lidocaine hydrochloride: **Polyvinyl alcohol:**

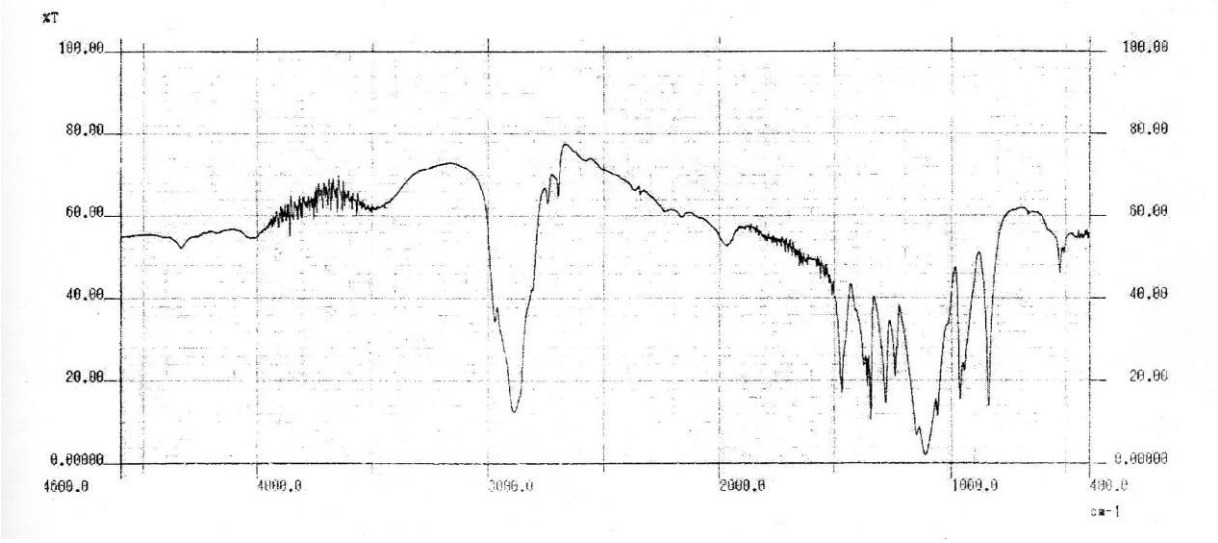


Fig 2: FTIR of Polyvinyl alcohol **Pluronic F 127:**

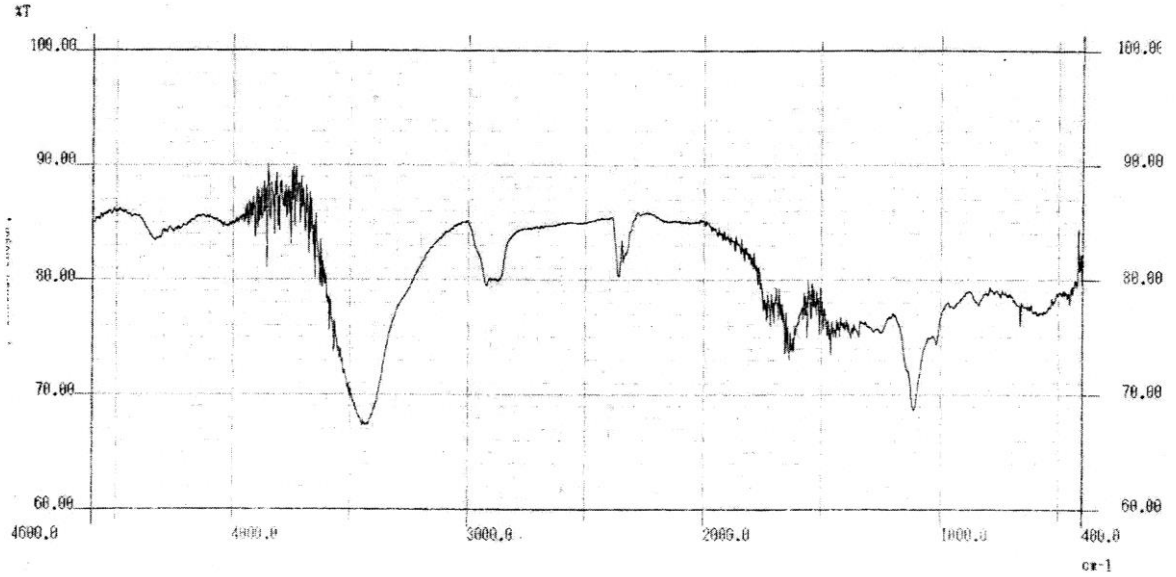


Fig: 3 **FTIR of Pluronic F 1273.3.1. Preparation of Lidocaine gel formulation**

Lidocaine was selectedas a model drug because, although widely used in the treatment of pain, its use is limited by short duration of its effects. The use of P407 gels prolongs the residence time of the lidocaine at the injection site, sustains drug release and increases therapeutic efficacy.Gel was prepared on a weight basis using the cold method. An amount of Pluronic F-127 sufficient to yield 20% gel was slowly added to cold water (5˚C); constant stirring was maintained. Prepared dispersion was refrigerated until a clear solution was formed (24hours)[(76)] .

Table 1. : Formula for Lidocaine Hydrocloride Gel

FORMULATION	LIDOCAINE HCL%	PF-127 %	XANTHAN GUM%	PVA%
F1	1	20	0.5	0.2
F2	1	20	0.25	0.1
F3	1	20	0.25	0.2
F4	1	20	0.5	0.1
F5	1	20	0.5	--
F6	1	20	0.25	--
F7	1	20	--	0.2
F8	1	20	--	0.1

(PF127- Pluronic F 127, PVA- Poly Vinyl Alcohol)

Characterization of formulations : Various formulations prepared were characterized for the following properties;

Determination of pH : The pH of the gel was determined using a calibrated pH meter (ROLEX). The readings were taken in triplicate for each sample ,and results were presented as average±SD..

The gelation temperature: Gelling temperature of the formulations were determined as follows; A 20 ml transparent vial containing a magnetic bar in 5 ml of Pluronic_F127 gel was placed in a water bath. A thermometer was immersed into the gel, which was heated at a rate of 2°C/min with constant (150 rpm) stirring. *In vitro* Release Studies *In vitro* drug release study was performed as drug dissolution studies. The dissolution test was performed in Dissolution apparatus (ELECTROLAB)), type II (paddle) using pH 6.8 buffer solution [(81)] Weighed amount of lidocaine hydrochloride gel(around 1 to 2 g) were packed in dialysis membrane bags. Dialysis membranes are semi permeable in nature made from cellulosic polymeric materials such as cellulose acetate phthalate etc. The bags were then tied to the paddles of the apparatus with the help of string. Around 900 ml of buffer was taken in each vessel and the paddles were set to rotate at 100 rpm. The study was performed for 4 hrs. Aliquots were taken at each hour, replaced by same volume of buffer at the same time to maintain the sink condition. The aliquots were analyzed at its analytical wavelength against the blank. For the blank, gel devoid of the drug were taken, treated in the same manner that of the drug loaded gels. The absorbance was converted to drug concentration using a calibration curve and then cumulative %drug released was calculated with the help of dilution factor.

Viscosity measurement: The viscosities of different gelling solutions were carried out by Brookfield Viscometer LV II +Pro (model-ML VT115) using spindle number S 18 at 10 rpm and S
96 at 3 rpm for gelling and gel respectively. Viscosity of optimized formulations was carried out at temperature of 4 ^{0}C and elevated temperature (37 ^{0}C.)

FORMULATION OF MICROEMULSION BASED GELS

Solubility studies : The solubility of drug in various oils, co-solvent and surfactants were carried out in order to screen the components to be used for formulation development. The solubility of drug in various components (oils, surfactants, and co-surfactants) was determined as follows. Two ml of each of the selected vehicles was added to screw capped vial containing an excess of drug (100 mg). After tightening the cap, the mixture was heated at 40 ºC in a water bath to facilitate the solubilisation. Mixing of the systems was performed using ultra sonicator for 2 hours with 10 minute intervals at every 15 minutes of sonication. Vials were again shaken with water bath shaker a 25 ºC for 48 hours. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 20 minutes, and excess insoluble drug in supernatant was discarded by filtration using a Whatmann filter paper (#35). Aliquot of sample was taken and diluted with methanol to specific volume to give specific point concentration in calibration curve. Analysis of the drug was carried out on UV-Visible spectrophotometer at respective wavelength.

Phase diagram studies : The physicochemical properties of micellar solutions like droplet size, turbidity, viscosity and drug release, are really contingent to different phases present in solutions. So in any practical use of surfactants, it is mandatory to have control over the phase structure. The regions of existence of different phases and the equilibrium between different phases are described by phase diagrams.

Preparation of lidocaine-loaded microemulsion : Based on the solubility studies and the ternary phase diagram studies, series of microemulsiom systems consisting of lidocaine were prepared by keeping proportion of surfactant and co-surfactant at constant value. The oil was chosen according to solubility studies.1% w/w of lidocaine was added to the mixtures of oil, surfactant, and co-surfactant with varying component ratio as described in Table 2

TABLE 2 Formulae for preparation of lidocaine microemulsion

Batch no.	Oleic acid	Chremophor RH 40	PEG 600	Water	Lidocaine HCL
M1	5.0 %	28 %	14 %	53 %	1%
M2	10%	26 %	13 %	61 %	1%
M3	15%	24%	12 %	64 %	1%
M4	20 %	22%	11%	47 %	1%
M5	25 %	20%	10 %	45 %	1%

IN- VITRO DRUG RELEASE COMPARISON : In vitro drug release study was performed as drug dissolution studies. The dissolution test was performed in Dissolution apparatus , type II (paddle) using pH 6.8 buffer solution.

Compatibility studies: FT-IR spectrum of pure drug and mixture of drug and polymer is shown in Fig 4.2 .From the spectral study it was observed that there was no significant change in the peaks of pure drug and drug polymer mixture. Hence no specific interaction was observed between the drug and the polymers used in the formulations.

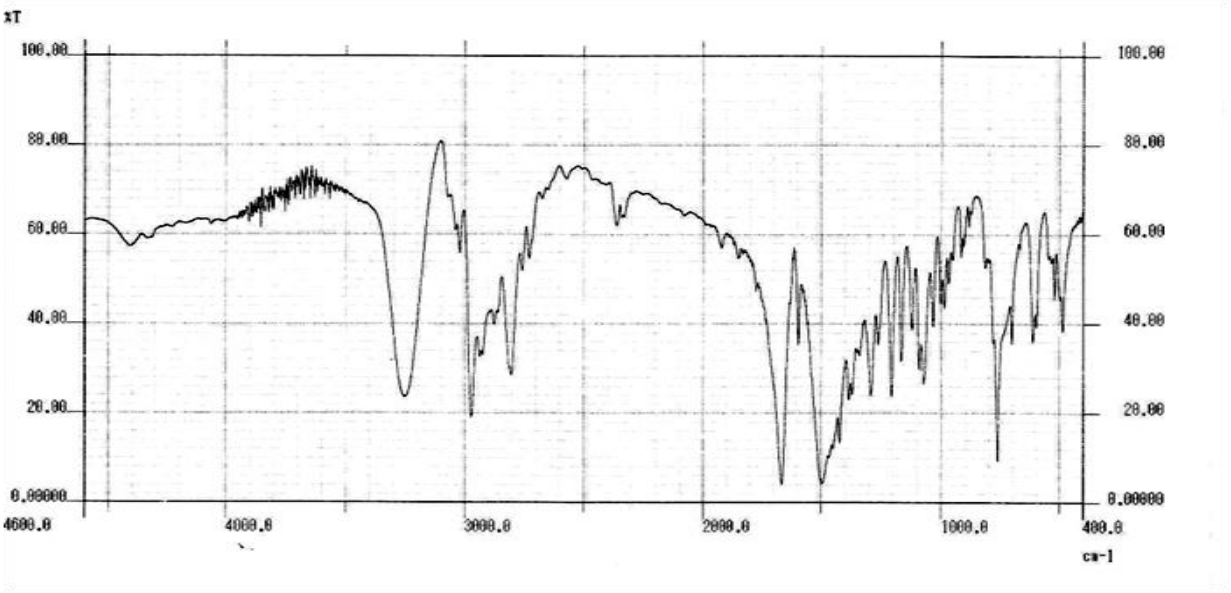


Fig 4. FTIR of drug polymer physical mixture

Determination of pH, gelation temperature,and spreadability:

Table 3 Characterisation of Lidocaine hydrochloride gels for various physico-chemical properties

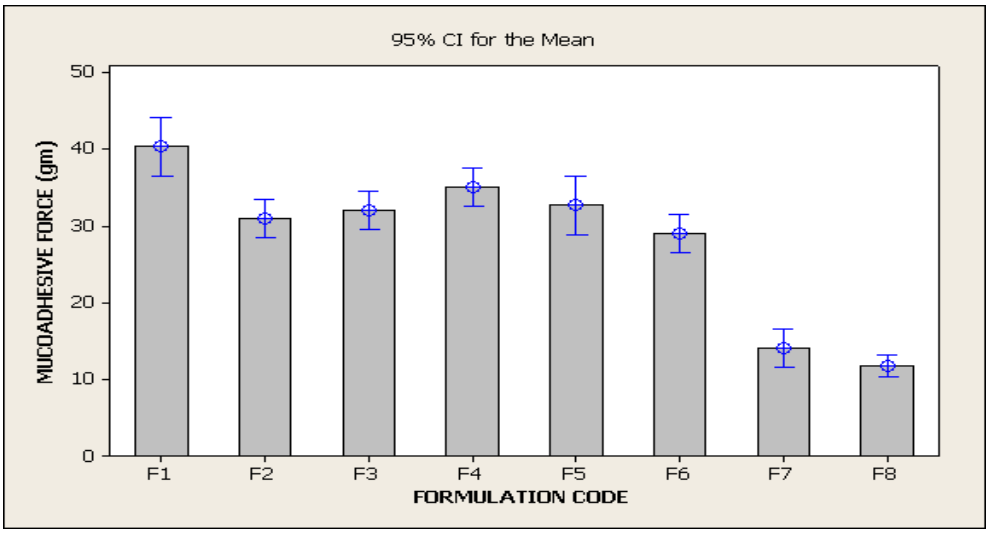
Formulation code	Viscosity Mean ±SD at 4^0C	Viscosity Mean ±SD at 37^0C	pH Mean ±SD	Spreadability (gm/sec) Mean ±SD	gelation temperature °C Mean ±SD
F1	5850±4	48130±18	6.4±0.57	15±2.6	32.33±0.29
F2	5821±2.5	41221±22	6.4±0.43	18±1	31.87±0.23
F3	5283±2.1	40218±15.1	6.5±0.81	18.33±0.57	31±0.2
F4	5751±2.8	44138±20	6.5±0.57	16.33±0.57	27±0.1
F5	5926±3.2	42260±15	6.4±0.57	17.. 67±0.57	28.37±0.55
F6	5012±1.4	34126±12.5	6.4±0.57	22. 67±0.57	31.73±0.83
F7	4228±0.5	32508±22.1	6.4±0.43	32±1	34±0.5
F8	4014±1.3	31290±12.4	6.4±0.45	31±1	34.2±0.53

Viscosity measurements: The viscosity of the formulations at 4^0C was in the range of 4000-5930 cps.and the viscosity of the gels at 37^0C was in the range of 31270-48000 cps. The concentration of polaxamer in all the formulations was kept constant. The viscosity of the formulation (F1) containing xanthan gum (0.5%) and PVA (0.2%) was found to be optimum for periodontal application.PVA does not have much effect on viscosity of the formulation at the concentration of 0.1to 0.2%. The pH of all the formulations was found in the range of 6.4-6.5 which is the average pH of human saliva.

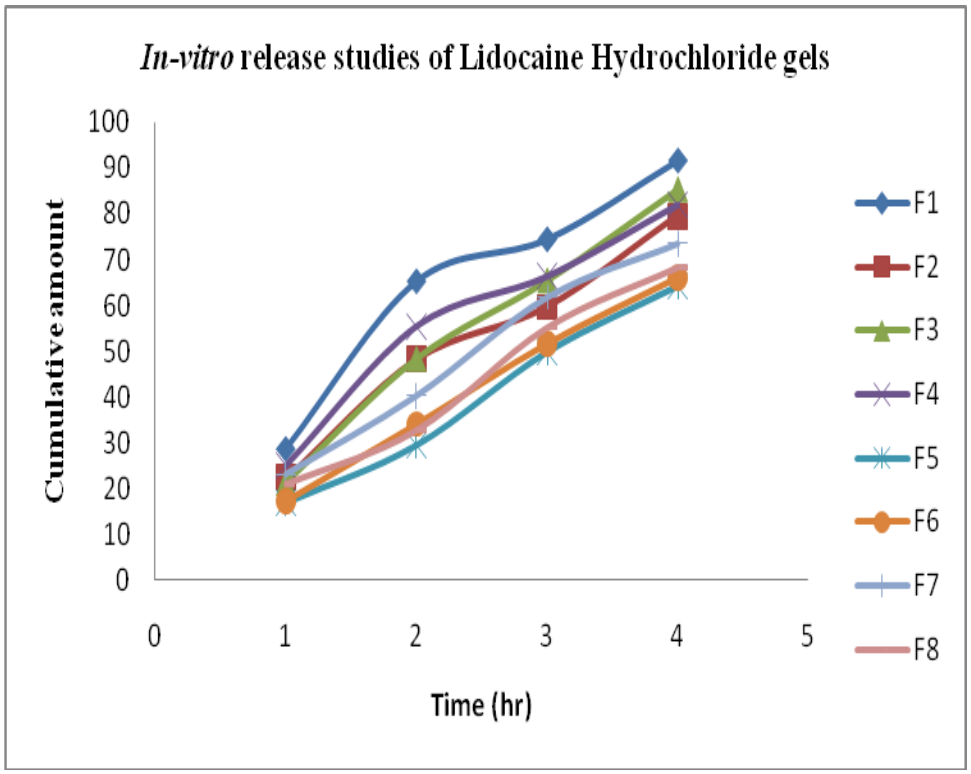
Gelation temperature: The presence of the lidocaine in the gel did not change the transition temperature .The addition of lidocaine did not affect the process of gelation and sol–gel transition temperature. Poloxamer 407 has thermo reversible gelation and in aqueous solution, with in creasing temperature, it aggregates in micelles to minimize the free energy of solution. In the low temperature region, Poloxamer 407 exists as monomers in solution.

Mucoadhesive strength: The mucoadhesive force is an important physicochemical parameter for local anesthetic used for surface anesthesia**.** The mucoadhesive strength of various formulations were determined and it was found that the

formulation F1 had maximum mucoadhesive strength which is desirable for periodontal application to remain at the site till the dental surgery.The formulations F7 and F8 had minimum mucoadhesive strength due to the absence of mucoadhesive polymer ,xanthan gum.The mucoadhesive strength of various formulations are depicted in fig 5.



Mucoadhesive strength of various lidocaine hydrochloride gels.

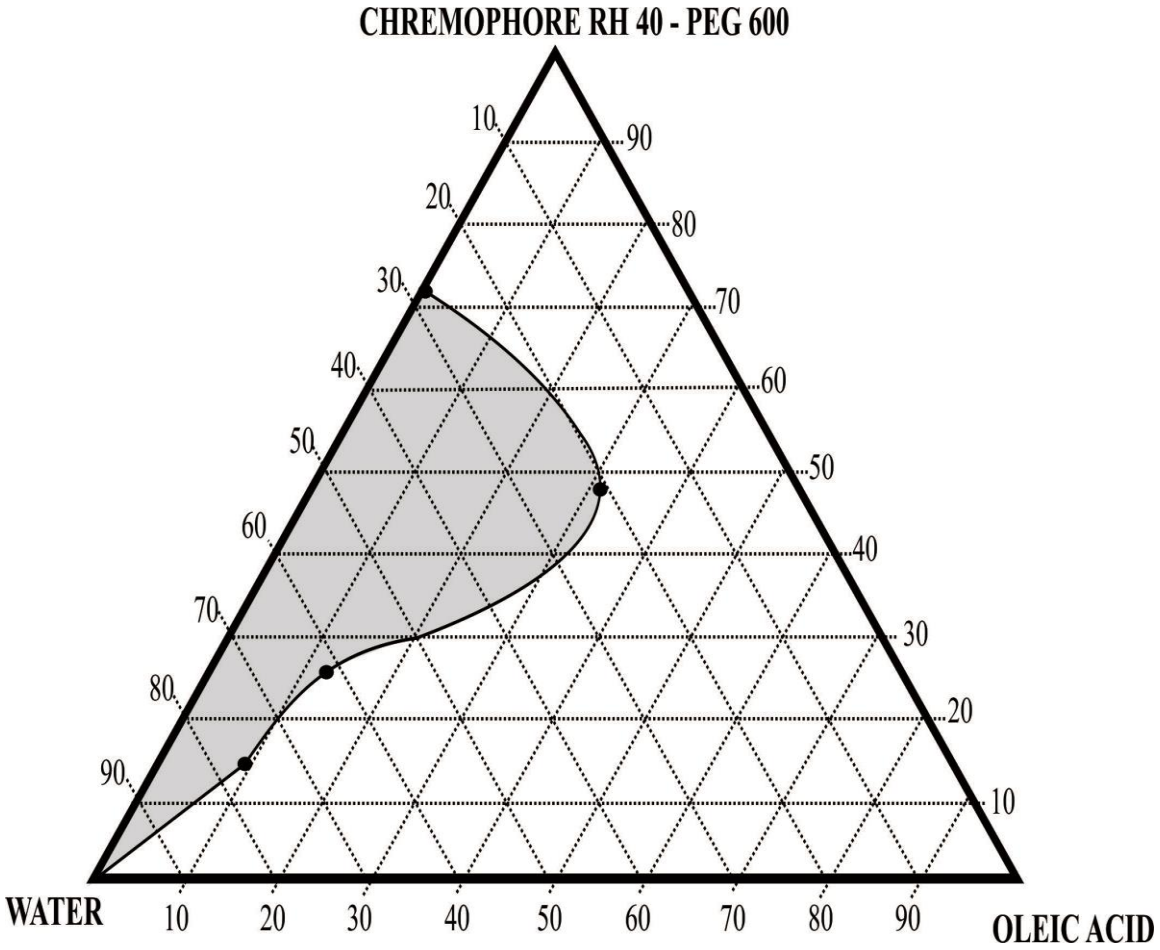


Cumulative% drug released from lidocaine hydrochloride gels. : The cumulative percentage of lidocaine hydrochloride released as a function of time is shown in Fig 4.4 . PVA is instrumental in releasing the drug. F5 and F6 formulation is without PVA , show much less release as compared to other formulations which may be because of specific nature of PVA inspite of its hydrophilic properties .Formulations F7 and F8 showed drug release faster, gelling temperature optimum, but mucoadhesive strength was very less. Formulations F2 F3,and F4 show satisfactory mucoadhesive strength but less drug release as compared to other formulations. The drug released from formulation F1 was found to be optimum.. It was observed that F1 formulation with xanthan gum (0.5%) and PVA (0.2%) showed good mucoadhesive strength and gelation near to body temperature with 91.7% drug release and hence was considered as optimized formulation as compared to others.

Formulation of microemulsion based gels: Solubility studies: The drug used in the formulation of microemulsion system should have high solubility in the components of the system used for formulation of microemulsion. The solubility of lidocaine hydrochloride was checked in various oils, surfactants and co-surfactants and the components having highest solubility was selected for microemusion.

Oleic acid	Chremophor RH 40	PEG 600	Water
28.5mg/ml	34.19mg/ml	31.18mg/ml	5mg/ml

Phase diagram studies: The relationship between the phase behaviour of a mixture and its composition can be captured with the aid of a phase diagram



Pseudo ternary phase diagram for S:Cos:2:1

Eventhough the release of drug from the gel formulation containing xanthan gum 0.5% ,pluronic F 127 20%,and PVA 0.2% was observed to be good in comparison with the other gel formulations and it also gave good formulation characteristics ,it was thought worthwhile to prepare the microemulsions of the drug to solubilised it in the gels.The microemulsions were prepared and the optimized microemulsion was then incorporated in optimed gel formulation. The lidocaine loaded microemulsion containing oleic acid(5%), chremophor RH 40(28%),PEG 600(14%) and water(53%) was showing the highest solubilisation region which was selected for the optimized microemulsion from the various combinations.The drug released from lidocaine microemulsion was found to be 71.19%.

In-vitro release of microemulsion based gel: The lidocaine loaded microemulsion was incorporated in gel base and further their release were compared . The microemulsion based gel appeared transparent to translucent ,free of lumps and yellowish in colour. Moreover the viscosity of the formulation decreased with the addition of microemulsion. The release studies carried out in dissolution apparatus revealed that the drug release was more as compared to plain microemulsion. The cumulative % of drug released from lidocaine microemulsion based gel was found to be 96.78%.

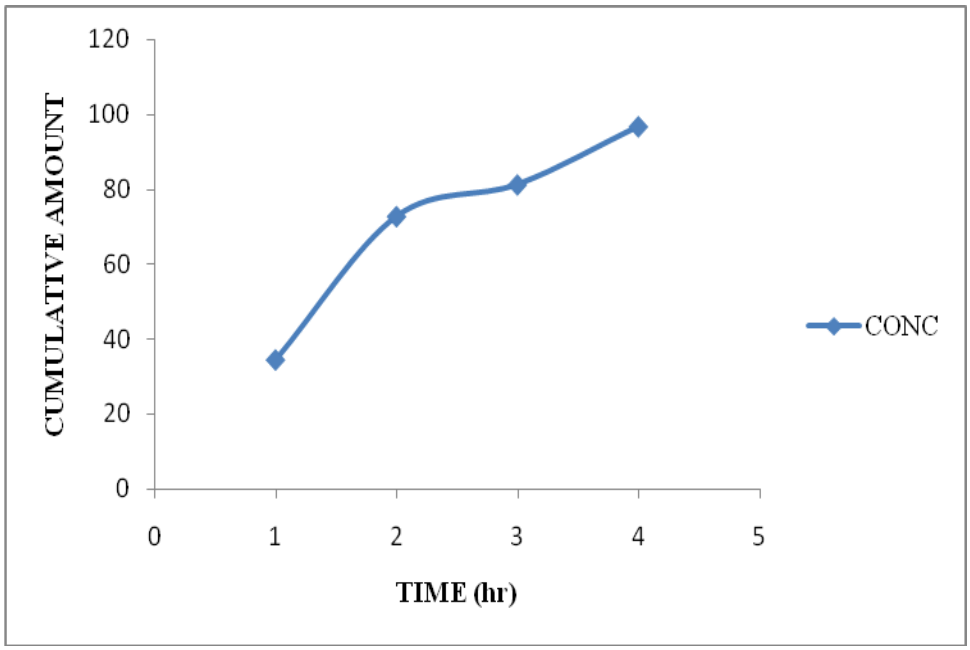


Fig 6:-Cumulative % drug release from microemulsion based gel.

Comparative study of microemulsion based gel with simple gel: The choice of proper apparatus was necessary for the above study. Many studies, reported in the literature, involve dissolution testing of microemulsion based gels using United States Pharmacopeia apparatus. Thus, USP dissolution test apparatus (Type II, paddle type) was finalised for the study. This apparatus had a thermostat, it was possible to maintain the temperature of 37 ± 0.2°C that of body temperature**..** The microemulsion based gel containing lidocaine hydrochloride was then compared with optimized gel containing drug.The result revealed that the drug release from microemulsion based gel was more than the optimized gel, may be due to the increase in the solubilization capacity of lidocaine in the microemulsion .

RESULTS AND DISCUSSION

The calibration curve of lidocaine hydrochloride in pH 6.8 buffer

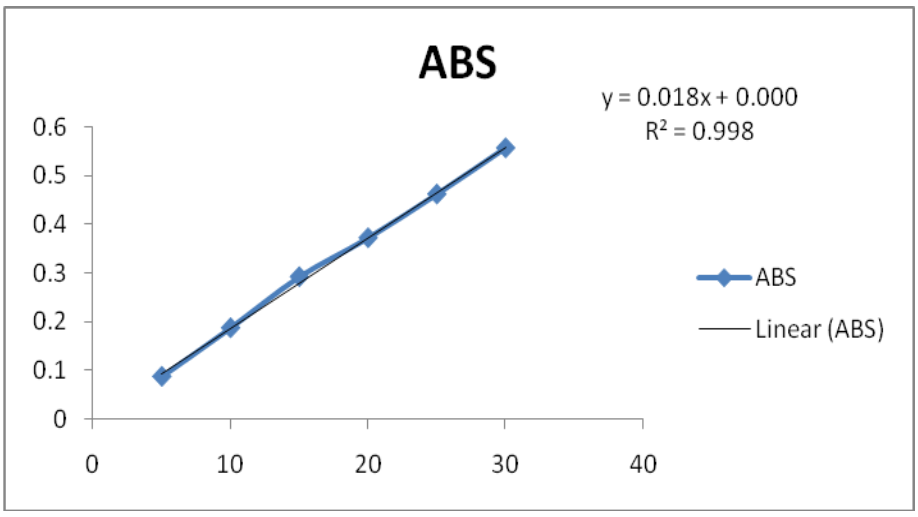


Fig. 6 Calibration curve of lidocaine Hcl in pH 6.8 buffer

The calibration curve of lidocaine Hcl in pH 6.8 were found to obey the Beer-Lambert's law within the concentration range of 5-25µg/ml .The R^2 values was found to be 0.998 in pH 6.8 buffer.The calculation of in vitro drug release was based on this calibration curve.

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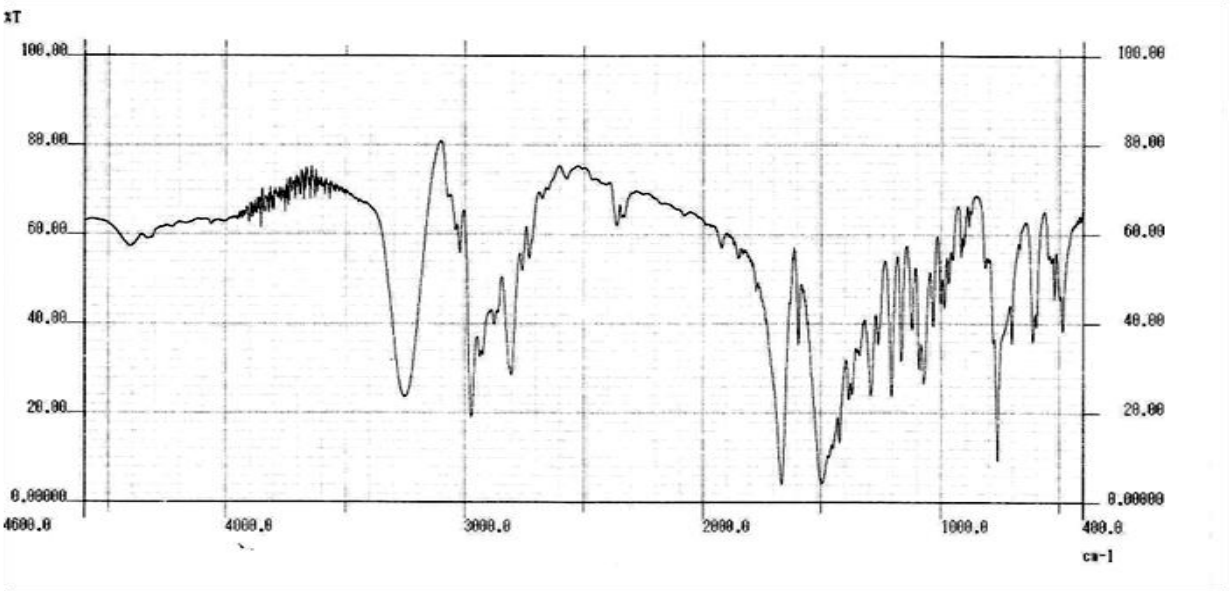

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The concentration of polaxamer affects the gelation temperature. At a concentration of 18-20% it forms a gel at room temperature. The increase of the polaxamer concentration in the solution decreases the sol–gel transition temperature.

At high concentrations the preparations would be gels already at room temperature. Xanthan gum which is used as a mucoadhesive polymer increases the viscosity at the same gelling temperature.

Spreadability: This was an important parameter since it gave an idea for ease of spreading the gel to the affected area. Spreadability was determined using wooden block and glass slide apparatus. As the concentration of xanthan gum was increased ,the spreadability of the lidocaine hydrochloride gel went on decreasing. The spreadability of the optimized lidocaine hydrochloride gel went on increasing with the addition of microemulsion .Since spreadability is a function of viscosity, as the viscosity of the gel increased the spreadability decreased and vice-versa.The results are represented in table 4.1.

Mucoadhesive strength: The mucoadhesive force is an important physicochemical parameter for local anesthetic used for surface anesthesia **.** The mucoadhesive strength of various formulations were determined and it was found that the formulation F1 had maximum mucoadhesive strength which is desirable for periodontal application to remain at the site till the dental surgery.The formulations F7 and F8 had minimum mucoadhesive strength due to the absence of mucoadhesive polymer ,xanthan gum.The mucoadhesive strength of various formulations are depicted in fig 8.

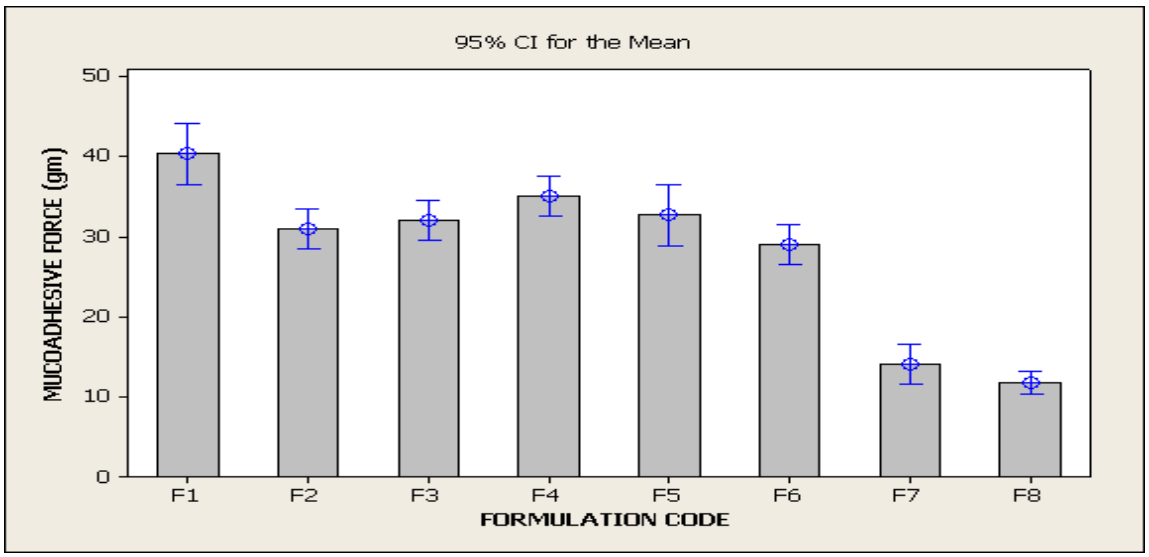

Fig 8 Mucoadhesive strength of various lidocaine hydrochloride gels.

***In-vitro* release studies of lidocaine hydrochloride gels**

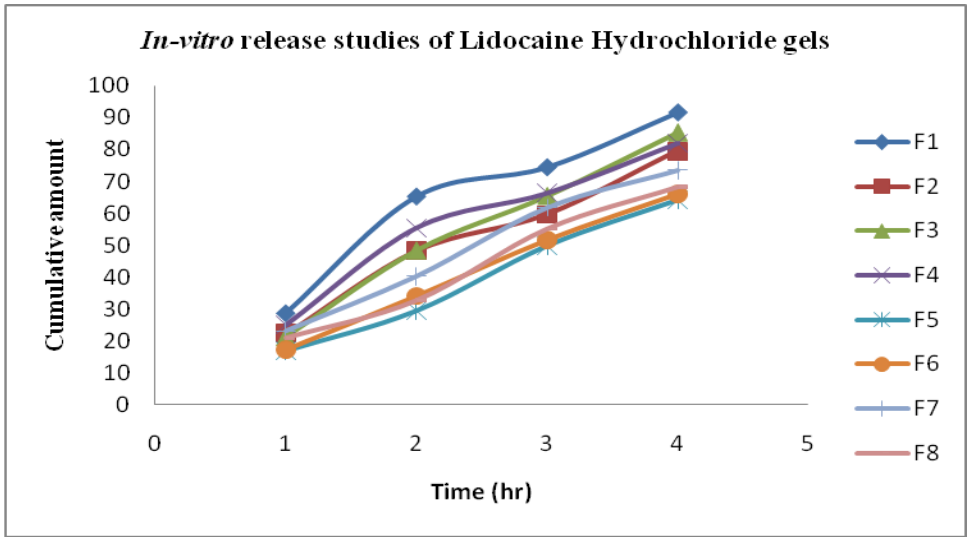

Fig: 9 Cumulative% drug released from lidocaine hydrochloride gels.

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Oleic acid	Chremophor RH 40	PEG 600	Water
28.5mg/ml	34.19mg/ml	31.18mg/ml	5mg/ml

Phase diagram studies: The relationship between the phase behaviour of a mixture and its composition can be captured with the aid of a phase diagram. A pseudo ternary phase diagram of the investigated quaternary system water/Oleic acid/ ChremophorRH 40/PEG600 are presented in following figures. Formation of microemulsion system (the shaded area) was observed at room temperature. Phase behavior investigation of this system demonstrated the suitable approach for determining the water phase, oil phase, surfactant concentration, and cosurfactant concentration with which the transparent, one phase low-viscous microemulsion system was formed. The region of microemulsion was found to increase with increasing ratio of surfactant to co-surfactant. The phase study revealed that the region of microemulsion was maximum when the surfactant to co-surfactant ratio was 2:1.

The shaded microemulsion region is presented in the phase diagrams. The rest of the region on the phase diagram represents the turbid and conventional emulsions based on visual observation. Outside the microemulsion region, particularly for compositions close to the oil-water binary axis, there is insufficient surfactant to facilitate the formation of single microemulsion phase. In this case multiple phases may exist, the complexity of which increases with the number of components in the mixture. It was observed that increasing the surfactant ratio resulted in a loss of flowability due to increase in viscosity

From pseudo ternary phase diagrams, the S/Cos mix of 2:1 was selected for the microemulsion formulation

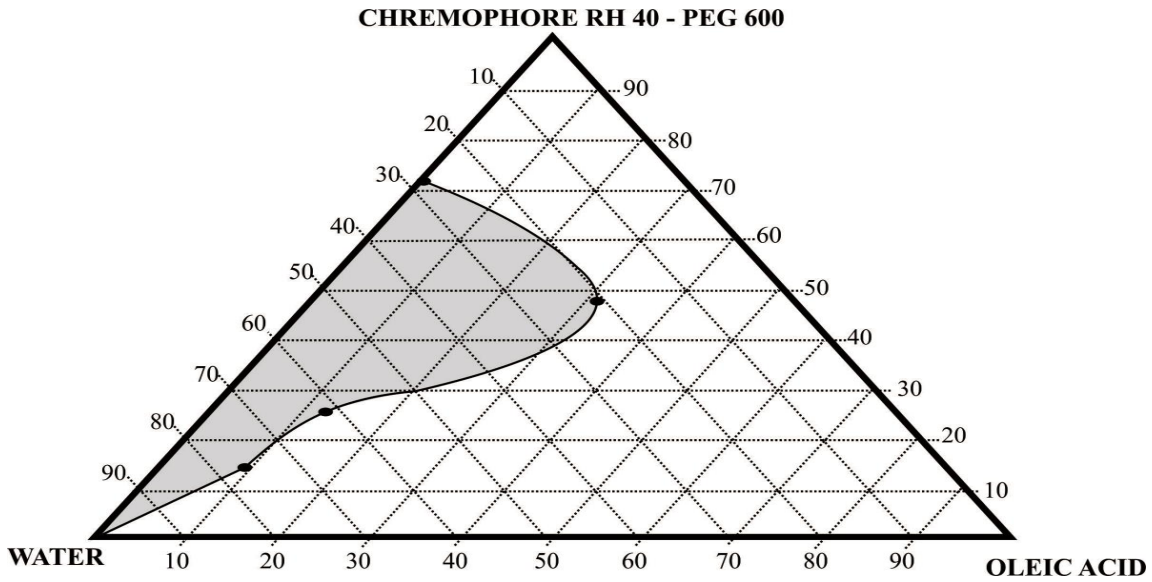

Fig. 8.:- Pseudo ternary phase diagram for S:Cos:1:1 Results and Discussion

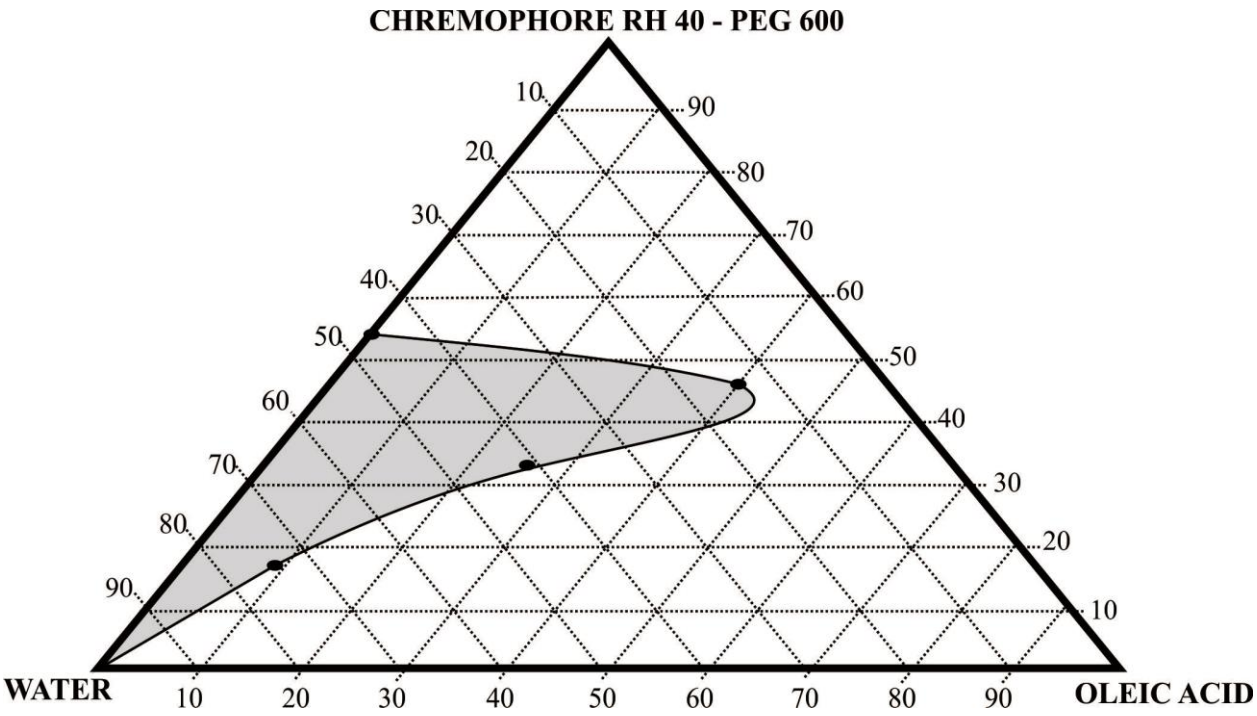

Fig.9.:-Pseudo ternary phase diagram for S:Cos:3:1

4.4.3 *In-vitro* release studies of lidocaine loaded microemulsion

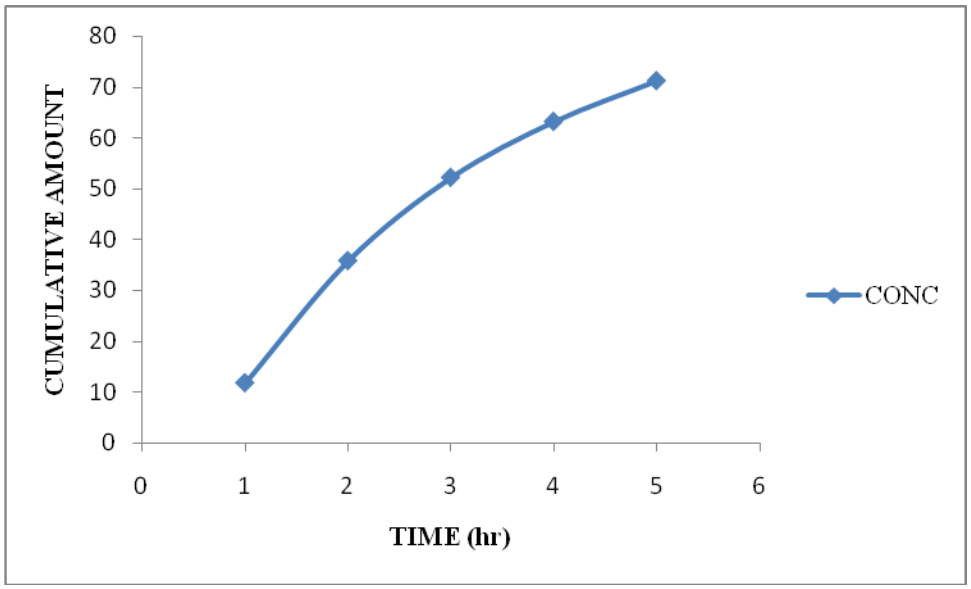

Fig 10:- Cumulative% drug release from lidocaine loaded microemulsion.

Eventhough the release of drug from the gel formulation containing xanthan gum 0.5% ,pluronic F 127 20%,and PVA 0.2% was observed to be good in comparison with the other gel formulations and it also gave good formulation characteristics ,it was thought worthwhile to prepare the microemulsions of the drug to solubilised it in the gels.The microemulsions were prepared and the optimized microemulsion was then incorporated in optimed gel formulation. The lidocaine loaded microemulsion containing oleic acid(5%), chremophor RH 40(28%),PEG 600(14%) and water(53%) was showing the highest solubilisation region which was selected for the optimized microemulsion from the various combinations.The drug released from lidocaine microemulsion was found to be 71.19%.

In-vitro release of microemulsion based gel: The lidocaine loaded microemulsion was incorporated in gel base and further their release were compared . The microemulsion based gel appeared transparent to translucent ,free of lumps and yellowish in colour. Moreover the viscosity of the formulation decreased with the addition of microemulsion. The release studies carried out in dissolution apparatus revealed that the drug release was more as compared to plain microemulsion. The cumulative % of drug released from lidocaine microemulsion based gel was found to be 96.78%.

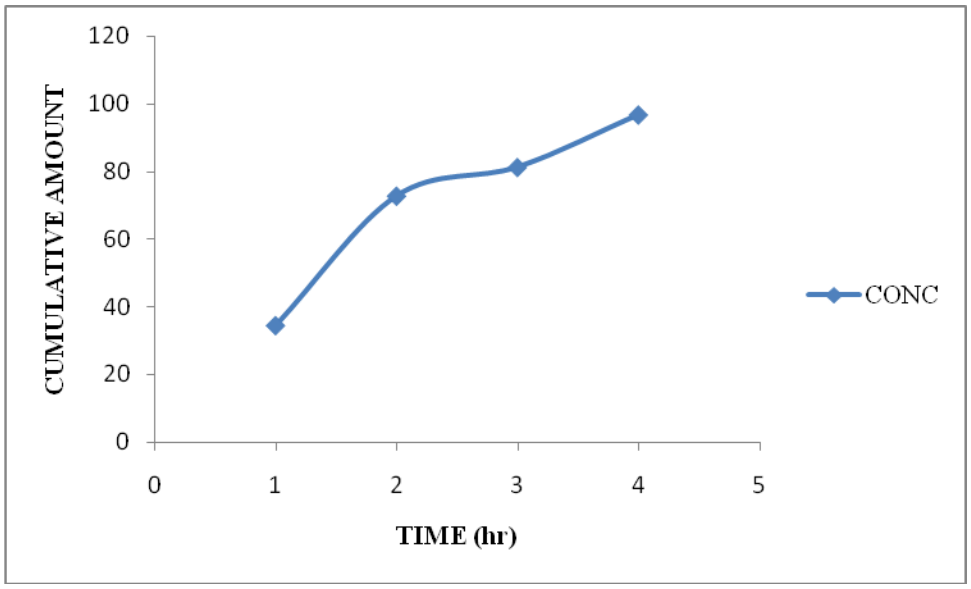

Fig 10:-Cumulative % drug release from microemulsion based gel.

Comparative study of microemulsion based gel with simple gel: The choice of proper apparatus was necessary for the above study. Many studies, reported in the literature, involve dissolution testing of microemulsion based gels using United States Pharmacopeia apparatus. Thus, USP dissolution test apparatus (Type II, paddle type) was finalised for the study. This apparatus had a thermostat, it was possible to maintain the temperature of 37 ± 0.2°C that of body temperature**..** The microemulsion based gel containing lidocaine hydrochloride was then compared with optimized gel containing drug.The result revealed that the drug release from microemulsion based gel was more than the optimized gel, may be due to the increase in the solubilization capacity of lidocaine in the microemulsion .

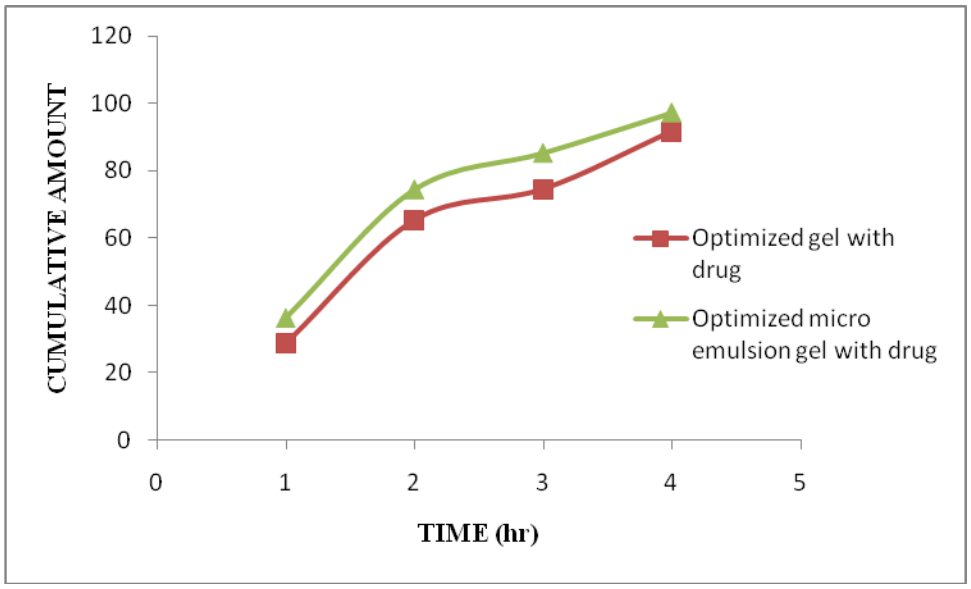

Fig. 11 : Comparative release of microemulsion based gel and simple lidocaine gel.

CONCLUSION

According to F TIR studies there is no interaction between drug and polymers. There is a good compatibility between Poloxamer 407 and lidocaine hydrochloride. Eight different formulations were prepared using various proportions of Pluronic F 127,Xanthan gum, and Polyvinyl alcohol. The various Lidocaine hydrochloride gels were prepared and their release were compared.The F1 formulation containing Pluronic F 127(20%), xanthan gum (0.5%) ,and polyvinyl alcohol (0.2%) can be considered as optimized formulation as it shows gelation at 32^0C onwards and the desired viscosity at 37^0C. Release rate:When the release was compared ,F1 formulation gave the optimum release. Hence F1 formulation was Eventhough the release of drug from the gel formulation containing Pluronic F 127, xanthan gum, and polyvinyl alcohol was observed to be good in comparision with the other gel formulation and it also gave good formulation characteristics ,it was thought worthwhile to prepare the microemulsions of the drug to solubilise it in gels.The microemulsions were prepared and the optimized microemulsion was then incorporated in optimized gel formulation and then they were compared.When it was evenly distributed in the gels, the release was fast. The mucoadhesive strength were found out and the optimized formulation showed a very good mucoadhesive strength which is most desirable characteristics for a periodontal formulation. The microemulsion based gel was developed to efficiently deliver lidocaine with objective of enhanced bioavailability in the periodontal treatment. Solubility and phase diagram protocols were found productive and accurate to assist further development of system. The surfactant ,co-surfactant mixture of ratio 2:1 was finalized for the formulation of microemulsion.A lidocaine loaded microemulsion having the composition oleic acid(5%) ,Chremophor RH 40 (28%) ,PEG 600(14%), and water (53%) was showing the highest solubilisation region which was selected for the optimized microemulsion from the various combinations. In –vitro release of microemulsion based gel was also found to be comparatively more than the optimized gel. So the microemulsion based gel can be used for the dental formulation which is having good mucoadhesive strength and optimum release.

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