WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 12, 878-893. Research Article ISSN 2277–7105

DEVELOPMENT AND CHARACTERIZATION OF TAPENTADOL NANOGEL BY MODIFIED EMULSIFICATION TECHNIQUE

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Article Received on
27 April 2024,

Revised on 17 May 2024,
Accepted on 07 June 2024

DOI: 10.20959/wjpr202412-32829

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ABSTRACT

This study focuses on creating a new kind of tapentadol, a strong pain reliever, using a modified emulsification diffusion technique. The tapentadol will be in the form of a nano gel, and its design, development, and properties will be thoroughly examined. The nano gel was developed using a blend of polymers, namely Eudragit RL-100, ethylcellulose, and Carbopol 934P, which were selected for their beneficial characteristics in drug delivery systems. The research used a modified emulsification diffusion technique to provide accurate control over the distribution of particle sizes. This approach improved the bioavailability and therapeutic effectiveness of tapentadol. The process involves emulsifying tapentadol in an appropriate organic solvent and then diffusing it into an aqueous phase containing the polymer mix while stirring under controlled conditions. The produced nano gel underwent extensive characterization testing. The physicochemical characterisation, which included analyzing particle size, measuring zeta potential, and examining shape using SEM, showed that tapentadol nanoparticles were evenly distributed inside the gel matrix. The rheological characteristics of the nano gel were assessed to determine its appropriateness for topical use. In addition, research on the kinetics of drug release showed that the nano gel formulation effectively and consistently released tapentadol, suggesting its ability to provide long-lasting pain relief. The stability investigations have proven that the formed nano gel is stable over a long period of time. Overall, the tapentadol nano gel created using the modified emulsification diffusion process using Eudragit RL-100, ethylcellulose, and Carbopol 934P

has great promise for improving drug delivery and might be used effectively in pain treatment. This work enhances the progress of nano drug delivery systems to provide better therapeutic results.

KEYWORDS: Tapentadol, Eudragit RL-100, ethylcellulose, and Carbopol 934P.

INTRODUCTION

Transdermal drug delivery system is available local as well as systemic effect of the drug. The entry of the drug through the deeper layers of the skin (intra cellular and Tran's cellular). Transdermal delivery is more convenient because it is a non-invasive. Further, problem of drug degradation by digestive enzymes after oral administration and discomfort associated with parenteral drug administration can be avoided.[1] It is the most preferred route for systemic delivery of drugs for several diseases. Hence, transdermal dosage form enhances patient compliant mode of drug delivery and bypasses hepatic first pass metabolism.[2] The principle of transdermal drug delivery system is that they could provide sustained drug delivery (and hence constant drug concentrations in plasma), over a prolonged period of time.[3]

Nano gels are water soluble carriers containing nano sized particles formed by physically or chemically cross linked polymer networks that swells in solvent. Nano gels are prepared from the nano dispersion. Nano dispersion containing aqueous phase and organic phase continuous stirring formation of nanodispersion by adding gelling agent forms nano gel. The resulting nano gel are more uniform in size, they are used to potential to deliver the drugs in controlled, sustained and targeted sites. Effective for the treatment as well as clinical trial progress. Nano gel approaches minimizes the problems associated with nanoparticles and nano suspensions by using dry, free flowing product, which is more stable during sterilization, storage and there is no formation of particles aggregation. Ease of transfer, distribution, measuring and storage make nano gels a versatile delivery system with potential for use with a wide range of active compounds.[4]

The main aim of current research was to Design development and characterization the Nano gel of Tapentadol by using Modified emulsification diffusion method by using polymers like eutragidRL-100, Ethylcellulose, carbapol934P for the improvement to bypass the first pass effect, to reduce dose frequency, to improve bioavailability and increased patient compliance.[5]

MATERIALS AND METHODS

Materials

Tapentadol (Natco Labs), Eudragit RS100, Ethyl cellulose (Merck Specialties Pvt. Ltd, Mumbai), Carbopol (SD fine chemicals, Mumbai) Ethanol (Changshu Hongsheng Fine chemical Co. Ltd, China).

Formulation of nanogel of tapentadol

Nano gels were prepared by modified emulsification diffusion method. It includes in two steps. Step 1 includes preparation of nano dispersion and step 2 includes preparation of nano gel. Nano dispersion phase includes preparation of organic and aqueous phases. Organic phase is prepared by dissolving 175 mg of tapentadol, ethyl cellulose and Eudragit RS100 in 10 ml ethanol as per table 1. Aqueous phase contains 40 ml of distilled water and 10 ml of tween 80. Addition of aqueous phase to the organic phase at the rate of 0.5 ml/min by maintaining constant stirring for 5-6 min at 5000-10000 rpm using homogenizer. Add 10 ml of distilled water. Maintain continuous stirring for 1 hr which results in formation of Nano dispersion. In step 2 Nano dispersion which is prepared in step I is added with 1 grams Carbapol 934 P with constant stirring which results in formation of nano gel.[6,7]

Table 1: Composition of nano gels containing tapentadol.

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Tapentadol (mg)	175	175	175	175	175	175	175
2	Eudragit RS100 (mg)	600	-	300	500	100	300	-
3	Ethyl cellulose	-	600	300	100	500	-	300
4	Carbopol (gm)	1	1	1	1	1	1	1
5	Ethanol (ml)	10	10	10	10	10	10	10
6	Distilled water (ml)	40	40	40	40	40	40	40

Drug- excipient compatibility studies by FT-IR

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T). The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 4000 to 400cm^{-1}.[8]

Evaluation of Nano gel[9, 10]

1. Physical characterization of gel

Nano gel formulations were characterized for PH using PH meter, Spreadability and Homogenesity.

a) pH

Thep of the various gel formulations was determined by using digital pH meter.

b) Spreadability

It was determined by wooden block and glass slide apparatus. Weights of about 10 g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slide.

Spreadability was then calculated by using the formula:

S=M.L/T

Where

S= Spreadability

M=Weight tide to upper slide

L=Length of glass slide

T=Time taken to separate the slide completely from each other.

c) Homogenesity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. Preparations were tested for their appearance and presence of any aggregates.

2. Vesicle physical analysis

Optical microscopy

The vesicle formation was confirmed by optical microscopy in 45x resolution.thenano gel suspension placed over a glass slide and fixed over by drying at room tempature, the dry thin film of nano gel suspension observed for the formation of vesicles. The photo micrograph of the Tapentadol nano gel was obtained from the micro scope by using digital camera.

3. Encapsulation efficiency

To 0.2g of nano gel, weighed in a glass tube, was added10ml of PH 7.4 phosphate buffer. The acuate suspension of sonicated in the sonicated bath. the Tapentadol containing nano gel were separated from un trapped drug by centrifugation at 25000 rpm at 20ºc for 30 min. the supernatant was recovered and was analysed at 272 nm by UV/Vis spectrophotometer for Tapentadol content.

The percentage of drug encapsulation (EP (%)) was calculated by the following equation:

%EE= [(Ct-Cf)/Ct] X100

Where

Ct is the concentration of total Tapentadol and

Cf is the concentration of free Tapentadol

4. *In-vitro* drug released study

The permeation experiments were performed using Keshary-Chien diffusion cells.

Dissolution parameters

- Medium : PH 7.4
- Volume : 13.5ml
- RPM : 700 RPM
- Time intervals : 1 to 24 hours
- Temperature : 37.0 ± 0.5^{ºC}

0.45-µm cellulose acetate membrane at 37±0.1ºc using a thermostatic water pump. The effective diffusion area was 2.54cm² (18 mm diameter orifice), and the receptor compartments was filled with 13.5ml of phosphate buffer at a PH of 7.4. The receptor fluid was constantly stirred by externally driven Teflon coated star head magnetic bars. Nano gel equalent 10 mg drug was placed in the donor compartment. Samples (1ml) were withdrawn from the receptor fluid at pre determined time intervals for up to 24 h after the beginning. An equal volume of fresh phosphate buffer immediately replaced after each sampling. Samples with drawn were suitably diluted and analysed spectrophotometrically at 272nm. From the resulted absorbance determined concentration, amount of drug release was calculated by incorporating this concentration into the following formula:

$$Concentration = \frac{Absorbance}{Slope}$$

$$A.D.R(mg) = Concentration \times V.D.M \times D.F \times \frac{1}{1000}$$

Where

A.D.R = Amount of drug release

V.D.M = Volume of dissolution medium

D.F = Dilution factor

***In-Vitro* drug release pharmaco kinetic models**

The results of *In Vitro* release profiles obtained for all formulations were fitted into three kinetic models of data treatment as follows.

1. Cumulative percentage drug release versus time (Zero order kinetic model)
2. Cumulative percentage drug release versus square root of time(Higuchi's model)
3. Log cumulative percentage drug released versus log time (Korsmeyer – Peppa's model)

Stability studies

From the prepared Nano gel the F3 show maximum percentage of drug release was selected for stability studies. The prepared formulation TBSF – VII were placed in borosilicate screw capped glass containers and stored at three different temperature (27±2°C, 65% RH), Oven temperature (40±2°C, 65% RH) and in freezing temperature (5 – 8°C, 65% RH) in stability chamber for a period of 90 days. The samples were evaluated for cumulative percentage drug release at regular intervals of two weeks.[11]

RESULTS

It was found that the estimation of Tapentadol by UV spectrophotometric method at λ_{max} 272 nm in pH 7.7 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 20- 100 µg/ml. The regression equation generated was y = 0.006x, R^2 = 0.998.

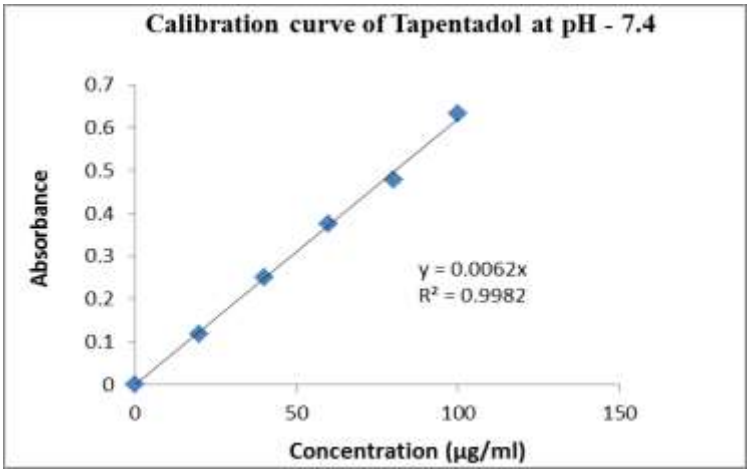

Figure 1: Standard graph of Tapentadol in pH 7.4 Phosphate buffer.

Drug- excipient compatibility studies by FT-IR

Table 2: FTIR Interpretation of tapentadol.

Functional group	Peak appear region
Aromatic C-H stretching	3234.62
Aromatic-OH	3169.04
Tertiary amine	2900.94
C-H aliphatic	2873.94

Pre formulation studies results

Table 3: Pre formulation studies results.

S. No.	Parameters	Values
1	Solubility	Freely soluble in ethanol
2	Melting point	175ºc
3	Partition co-efficient	2.37

Physical characterization of the gels

Table 4: Physical characterization of the gel.

Formulation code	PH	Homogeneity	Spread ability (g.cm/sec)
F1	7.27	Clear&Homogenous	13.1
F2	7.32	Clear&Homogenous	13.7
F3	7.42	Clear&Homogenous	14.2
F4	7.38	Clear&Homogenous	13.9
F5	7.42	Clear&Homogenous	14.1
F6	7.39	Clear&Homogenous	13.3
F7	7.14	Clear&Homogenous	13.8

Vesicle physical analysis

Optical microscopy

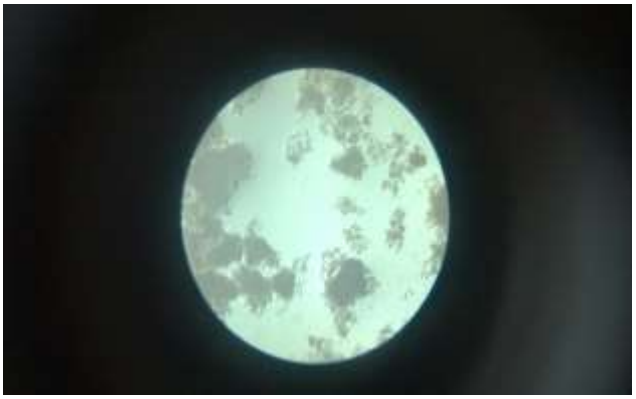

Figure 2: SEM Image of F1.

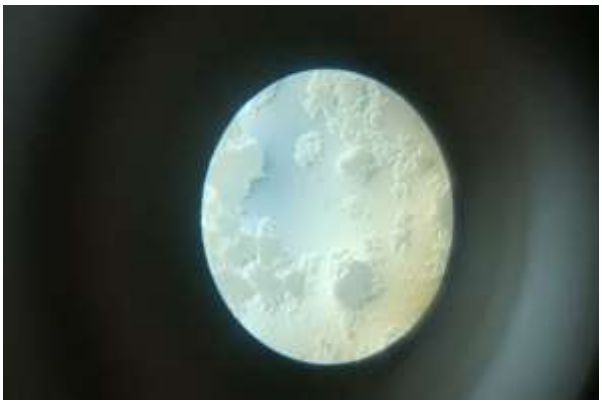

Figure 3: SEM Image of F2.

Figure 4: SEM Image of F3.

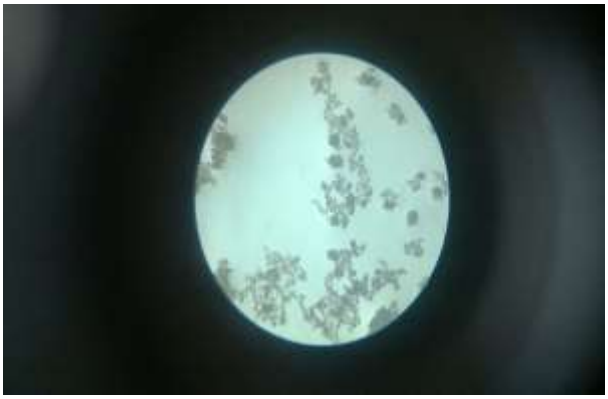

Figure 5: SEM Image of F4.

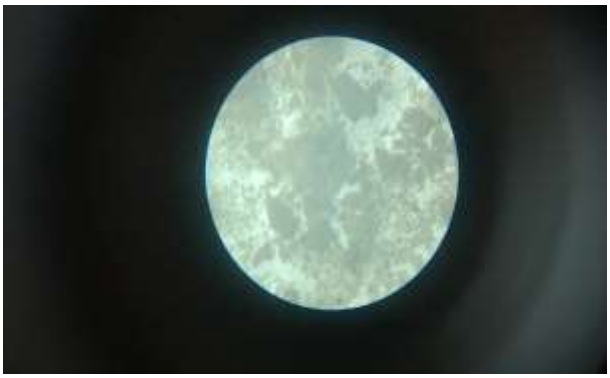

Figure 6: SEM Image of F5.

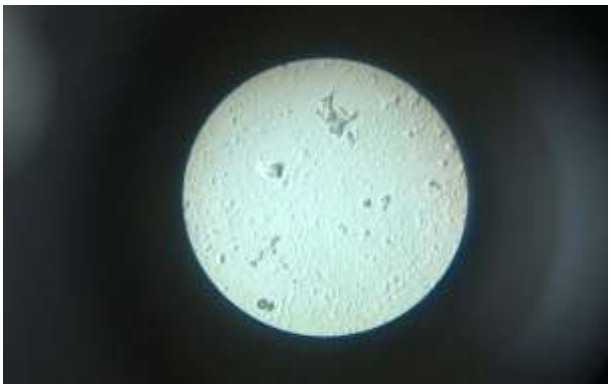

Figure 7: SEM Image of F6.

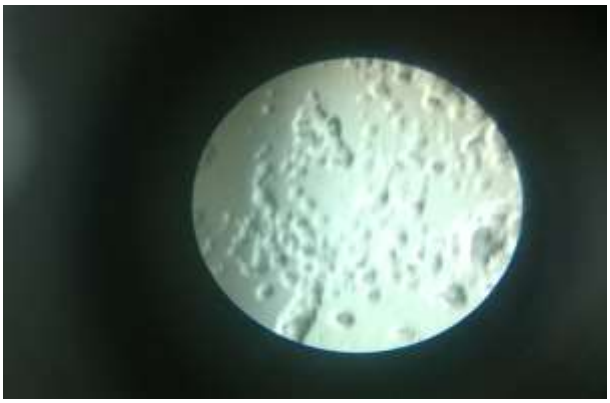

Figure 8: SEM Image of F7.

Encapsulation efficiency

Table 5: Encapsulation efficiency of nano gel formulations.

Formulation code	Encapsulation efficiency (%)
F1	88.22
F2	84.54
F3	96.14
F4	90.02
F5	92.63
F6	91.02
F7	89.48

Table 6: *In-Vitro* drug release kinetic values of all formulations.

Formulation Code	Correlation Coefficient Values(R^2)		Diffusion Exponent value(n)
	Zero Order	Higuchi's model	Peppa's Model
F1	0.914	0.942	0.627
F2	0.909	0.948	0.689
F3	0.974	0.870	0.680
F4	0.958	0.856	0.691
F5	0.959	0.835	0.751
F6	0.949	0.901	0.615
F7	0.966	0.808	0.741

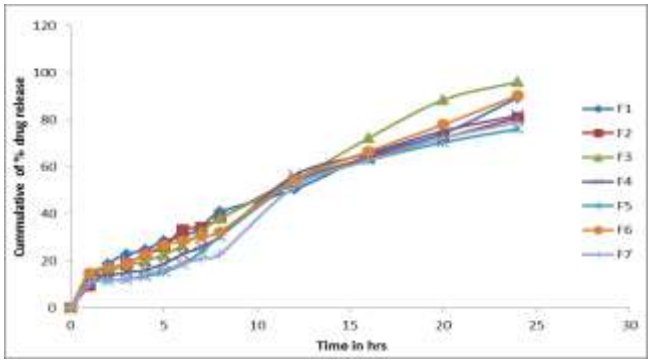

Figure 9: Comparative in-*vitro* drug release plot of F1 – F7 formulations.

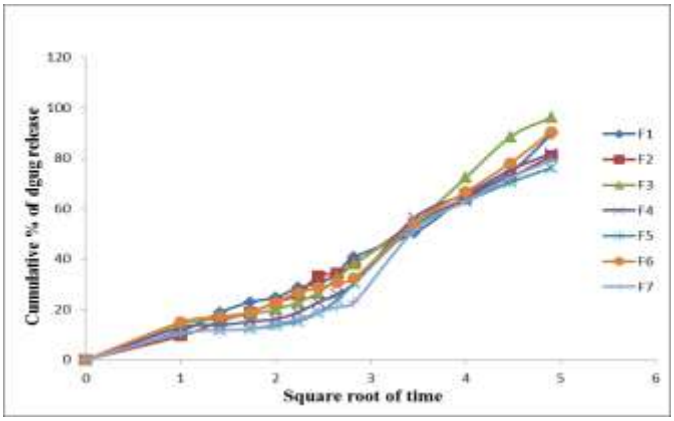

Figure 10: Comparative Higuchi's drug release plot of F1-F7 formulation.

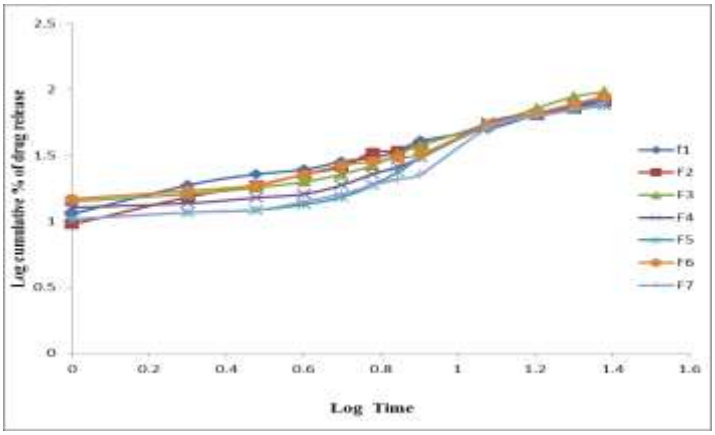

Figure 11: Comparative Peppa's drug release plot of F1-F7 formulation.

Stability studies

Table 7: Data showing the stability studies of formulation (F3) at three different temperatures.

Time (days)	Drug Release (%) At 5°c	Drug Release(%)At 25°c	Drug Release (%) At 40°c
0	96.19	96.19	96.19
15	96.12	96.00	93.20
30	95.75	95.74	88.18
60	95.36	95.36	86.12
90	94.67	93.14	78.17

DISCUSSION

Seven formulations of Tapentadol Nano gel were formulated using different excipients and composition of which is shown in formulation table. The formulations are subjected to evaluation parameters such as entrapment efficiency, vesicle morphology, and analysis of physical parameters of gel, *in-vitro* drug release studies, and stability studies.

Pre formulation studies

A. Description

Tapentadol were light brown solid, which may reveal that the samples were pure and not adulterated.

B. Solubility

The Tapentadol solubility studies reveal that it was freely soluble in ethanol, in soluble in water, and very slightly soluble in dichloromethane.

C. Melting point

The melting point of Tapentadol was found to be 145^0c and which may reveal that the samples were pure and not adulterated.

D. Partition coefficient

Partition coefficient of Tapentadol in octanol/water system was found to be-2.37 which is favourable for transdermal drug delivery system.

E. Drug polymer compatibility studies of tapentadol

The FTIR spectra's of Tapentadol, Eudragit RS100, Ethyl cellulose and carbapol 934P were shown in fig 10.1 to 10.4 these graphs were Shown there is no significance interaction between drug and polymer. Graph 10.4 over lay spectrum was used for IR interpretation. The Tapentadol Functional groups Aromatic C=H Stretching appears at 3234 Cm^{-1}, Aromatic =OH appears at 3169 Cm^{-1}, Amide Teritionary amine appears at 2900 Cm^{-1} and C=H aliphatic Stretching appears at 2873 Cm^{-1}. The FTIR graphs of drug with individual and mixture of polymers were obtained as similar and also the all the graphs shows the functional groups of Tapentadol there by these studies reveal that there was no interaction between Tapentadol and polymers.

F. Standard calibration curve of tapentadol

The curve was found to be linear in the range of 20 -100µg/ml at 272 nm. The *In-Vitro* release and stability studies were performed based on this calibration curve. The calibration Graph shows a representative standard calibration curve at pH 7.4 with slope, regression coefficient 0.006 and 0.998 respectively.

Formulation of nano gel

The nano gel of Tapentadol was prepared by using Modified emulsification diffusion method. Total seven formulations were prepared and subjected to various evaluation parameters.

Evaluation parameters

Physical characterization of nano gel

The results of physical characterization of gel are reported in Table:

a) PH

Skin compatibility is the primary requirement for a good topical formulation it was found that the PH of all formulations was in the range of 7.14-7.42 that suits for skin PH, indicating skin compatibility.

b) Spread ability

The value spread ability of all nano gel formulations ranged from 13.1 to 14.2(g.cm/sec). The value of spread ability indicates that the gel is easily spreadable with minimal of shear.

c) Homogeneity

All developed gel showed good homogeneity with absence of lumps. All developed preparations were clear and translucent.

Vesicle physical analysis

Optical microscopy

The morphology of nano gel was studied using Optical microscope at 45X. The results are shown in the photo. It reveals that the nano gel formed were uniform and homogenous.

Percentage encapsulation efficiency

Encapsulation efficiency of nano gel formulations ranged from 84.54 to 96.94. The drug encapsulation efficiency of all seven formulations is shown in Table:

As shown in results, nano gel formed from Eudragit RS100, Tween-80 exhibited good encapsulation efficiency. This could be explained on the basis that the highly lipophilic portion of the drug is expected to be housed almost completely within the lipid bilayer of the nano gel. Most of the polymers and surfactant used to make non ionic surfactant vesicles have a low aqueous solubility. However, freely soluble non ionic surfactants such as Tween-80 and polymer Eudragit RS100.Eudragit RS100 formulations in the present study were also able to entrap Tapentadol efficiently. However, the encapsulation efficiency was relatively low as compared to those composed of Ethyl cellulose.

***In-Vitro* drug release studies**

The percentage cumulative drug release nano gel profiles values were tabulated in table no.10.15, 10.16 and 10.17 and graphs were shown in 10.12, 10.13, and 10.14 respectively. The release of Tapentadol from the investigated stable formulations followed Zero order kinetics with an immediate release of the drug (no lag time). The amount of drug release from

the different nano gel formulations was found in the order of F3>F6>F1>F4>F2>F7>F5, whose the percentage of drug release was found to be96.19%, 90.47%, 89.52%, 81.90%, 80.90%, 79.04%, 76.19% respectively.

All the formulations exhibit Zero order drug release pattern up to 24 hours. Comparing the release profile of formulation F3 with other formulations; higher release rate and efficiency were observed, revealing that this particular nano gel structure improved the drug release properties. The formulation F3 selected as most efficient and most stable formulation, was can be proposed as optimized formulation for subjecting to further investigations. Higher drug release from nano gel prepared with Eudragit RS100 (300mg) than other formulations. This could be due to the high permeability, low phase transition temperature and emulsification effect of Eudragit after the hydration of the nano gel by the dissolution medium. The formulation F1 containing Eudragit RS100 releases 89.52% of drug release within 24 hours, formulation F2 containing Ethyl cellulose releases 80.90% of drug release within 24 hours, The formulation F3 containing Eudragit RS100, Ethyl cellulose in the ratio of 1:1 releases 96.19% of drug release within 24 hours, formulation F4 containing Eudragit RS100 and Ethyl cellulose in the ratio of 5:1 releases 81.90% of drug release within 24 hours, formulation F5 containing Eudragit RS100 and Ethyl cellulose in the ratio of 1:5 releases 76.19% of drug release within 24 hours, The formulation F6 containing Eudragit RS100 releases 90.47% of drug release within 24 hours, formulation F7 containing Ethyl cellulose in releases 79.04% of drug release within 24 hours.

Release kinetics

The dissolution data of every formulation with various drug release equations namely Zero order: $Q=K_0t$, which describes the system where the release rate is independent of the concentration of the dissolved drug. The first order equation describes the system where the release rate is dependent on the concentration of the dissolving drug. Higuchi's model: $Q=K_Ht^{1/2}$ equation describes the release from the system where solid drug is dispersed in insoluble matrix, and the rate of drug release is related to the rate of release. peppas: $F=K_mt$. K_m is used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved. The results are shown in the table. The constant incorporating structural and geometric characteristics of the nano gels, above the equations K_0 is zero order kinetic release drug constant, F is fraction release drug at time t, n is the exponent diffusion indicative of the

release mechanism. "The *in-vitro* drug deliver all the formulations (F1 to F7) shows Zero order release, where release rate is independent of the concentration of the drug. Higuchi's plot releaved that the rate of drug release from the system is related to diffusion release. Peppa's plot revealed release co-efficient (n) values showed that release is non-fickian type".

Stability studies

The stability studies were done by storing the optimized formulation F3 nano gel in Screw capped container in stability chamber at three different temperatures 5ºc±3ºc, 25 º c±2 º c temperatures with 60% RH±5% and 40ºc with 75%RH±5% for 3 months. Table shows the data for, *in-vitro* drug release after every one month till three months. Results showed that there were no significant changes observed in the *in-vitro* drug release of formulation at 5±3ºc and 25±2º shown in the Table and photo. It confirms that formulation F3 was stable at end of 90 days. On the other hand, significant changes observed in the *in-vitro* drug release after 3 months at 40^0c ± 2ºc temperatures release after 3 months at 40±2ºc temperatures. The results of drug release studies showed higher drug leakage at high temperature. This may be due to the higher fluidity of lipid bilayer at higher temperature, resulting in higher drug leakage. Loss of drug from vesicles stored at elevated temperature may be attributed to the effect of temperature on the gel to liquid transition of lipid bilayers together with possible chemical degradation of the polymers leading to defects in membrane packing. Acceleration in drug leakage at higher temperatures, as observed in storage stability studies, suggested keeping the nano gel in the refrigeration and room temperature.

CONCLUSION

Nano gel for transdermal delivery of Tapentadol were successfully formulated by using different excipients and non ionic surfactant. Linearity of Tapentadol standard curve was checked in the dissolution medium i.e., 7.4 pH phosphate buffer. It was found to be linear in the range between20 µg/ml to 100µg/ml. The FTIR studies revealed that there is no chemical interaction between Tapentadol and excipient mixture. So it can be concluded with drug and other excipients were compatible with each other. All the Formulations were evaluated for physicochemical parameters, In-*Vitro* dissolution studies and stability studies. From the presented study, it is clear that the nano gel formulations F3 provides both the highest entrapment efficiency and stability among other nano gel formulations. Hence the present work meets the mentioned objectives like physically and chemically stable transdermal drug delivery system, bypass the hepatic metabolism, reduced the side effects of drug, increase the

skin permeation & improved the patient compliance. Nano gel may become a useful dosage form for Tapentadol, specifically due to their simple, production procedure and ability to modulate drug transfer across skin.

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