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Preparation and Evaluation of Tapentadol Hydrochloride Solid Lipid Nanoparticles

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ABSTRACT

Tapentadol Hydrochloride is a centrally acting opioid analgesic used for the treatment of musculoskeletal pain. The aim of the present study is to release the drug at a controlled rate by formulating solid lipid nanoparticles using Hot Homogenization method. In the present study SLN's are prepared by using Glycerol Monostearate and Stearic acid as lipids and Poloxamer-188 as stabilizer in different ratios in order to get the optimized formulation. The solid lipids and drug were evaluated for drug interactions by using FTIR, DSC, and surface morphology by SEM in order to select the effective formulation. The prepared formulations (F1-F12) were evaluated for Particle size, Zeta potential, %Entrapment efficiency, *in vitro* drug release studies and stability studies. The FTIR spectra revealed that there is no significant interaction between the drug and lipids. SEM images revealed that the particles are spherical in shape with smooth surface. The particle size was found as 101.9 nm, Zeta potential was found as -18.1mV, % Entrapment Efficiency (%EE) was found as 88.7±0.36 and the % drug release was found as 97.8±0.60 in 10 hours following first order release kinetics and Higuchi model. The Tapentadol Hcl loaded SLN's of F3 formulation shows more effective when compared to all the other formulations. All the results shows that the Tapentadol Hcl SLN's can be effectively used for treating severe pain by controlling the rate of release at the targeted site.

Keywords: Tapentadol Hydrochloride, Glycerol Monostearate, Stearic acid, Poloxamer-188, Hot Homogenoisation method.

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INTRODUCTION

Nanoparticles are the colloidal carriers ranges in the size of 10-1000 nm prepared by using natural/ synthetic polymers in order to target the drug at the specific site and to release the drug at controlled rate. To overcome the toxicity and the high cost of the polymer solid lipids has been put forward to prepare solid lipid nanoparticles [1].

Solid lipid nanoparticles (SLN's) were introduced in 1991 which represent an alternate carrier system to the traditional colloidal carriers such as emulsions, liposomes, polymeric microspheres and polymeric nanoparticles. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system [2]. This system consists of spherical solid lipid particles which ranges in the size of nanometer, dispersed in aqueous surfactant solution. Generally, the solid lipids are made of hydrophobic core having a single layer of phospholipids coating. These solid lipid nanoparticles have potential of carrying both lipophilic drugs and hydrophilic drugs as they are amphipathic in nature [3].

Neuropathic pain (NP) has been defined as "pain caused by a lesion or disease of the somatosensory nervous system. NP is a common condition that results from various aetiologies and can be categorised into either peripheral or central NP syndromes. Central NP is the result of a central lesion or disease such as stroke, multiple sclerosis or spinal cord injury, whereas peripheral NP occurs from dysfunction or damage to peripheral nerves. [4]. Tapentadol Hydrochloride is a centrally acting opioid analgesic used for the treatment of neuropathic pain. It belongs to the class of benzenoids with dual mechanism of action as an agonist of the μ-opioid recptor and as a norepinephrine reuptake inhibitor. It's bioavailability is about 32% with an elimination half-life of about 4 hours [5]. In the present study solid lipid nanoparticles are prepared and loaded with tapentadol hydrochloride in order to release the drug at the targeted site at a controlled rate.

MATERIALS AND METHODS

Materials

Glycerol Monostearate and Stearic Acid was obtained from Qualikems fine chem. Pvt. Ltd., Vadodara, Gujarat, India and

NR chem.., Mumbai, India. Poloxamer-188 was obtained from Merck life sciences Pvt. Ltd., Mumbai, India. Tapentadol Hydrochloride was obtained as a gift sample from Halmark Pharmaceuticals Pvt. Ltd., India.

Method

Preparation of Tapentadol Hydrochloride Solid Lipid Nanoparticles by Hot Homogenization method

Weighed quantities of Tapentadol hydrochloride and Polaxamer-188 were dissolved in hot distilled water at temperature of 70˚c .GMS was melted at temperature of 70˚c and added drop wise to the hot aqueous solution under stirring at 500 rpm for 30 mins by using a mechanical stirrer. This results in the formation of emulsion which was homogenised by using a homogenizer at 1000 rpm for 45mins. This results in the formation of Solid lipid nanoparticles which were stored in a refrigerator [6].

Evaluation of Tapentadol Hydrochloride Solid Lipid Nanoparticles

Fourier transform infrared spectroscopy (FTIR)

The samples of Tapentadol Hydrochloride and optimized formulation (F3) was triturated and mixed well with IR grade potassium bromide in 1:100 ratio. The mixture was introduced in the sample holder of FT-IR instrument and scanned in the range from 4000 to 400 cm-1 to obtain the spectrum. The obtained spectrum was compared with the spectrum obtained for Tapentadol Hcl and physical mixture of Tapentadol Hcl with a Glyceol monostearate and Stearic acid [7].

Table-1: FTIR Spectrum Interpretation

Functional Group	Freq. (cm^{-1}) range of Functional group	Freq. (cm^{-1}) range of Pure drug	Freq. (cm^{-1}) range of optimized formulation
Amine /Amide N-H	3400- 3100	`3414.12	3423.76
Alkene C=C	1580-1500	1546.96	1519.96
Alkane-C-H	1350-1480	1352.14	1383.01
-OH	1000-1200	1170.83	1163.11

Table-2: Composition of formulations from F1 to F12

Chemicals	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Glycerol monostearate(%)	1.2	1.2	0.6	0.6	0.85	0.85	-	-	-	-	-	-
Stearic acid(%)	-	-	-	-	-	-	1.2	1.2	0.6	0.6	0.85	0.85
Poloxamer-188(%)	0.25	0.8	0.25	0.8	0.25	0.8	0.25	0.8	0.25	0.8	0.25	0.8
Distilled water(ml)	100	100	100	100	100	100	100	100	100	100	100	100

Differential Scanning Colorimetry (DSC)

The samples of drug and optimized formulation (F3) were kept in desiccator for 24 h before thermal analysis. The accurately weighed sample, 5 mg was hermetically sealed in aluminum crucible and heated at a constant rate of 10°C/min over a temperature range of 25 to 200 °C. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 20 mL/min. An empty aluminum pan was used as a reference [8].

Scanning Electron Microscopy (SEM)

The surface morphology of lyophilized Tapentadol Hydrochloride SLN's was visualized using SEM (Zeiss SEM EVO-18, Carl Zeiss Microscopy). The water suspended nanoparticles were mounted on a glass slide as a thin smear and left to dry. The particles on dried glass slide were subjected to gold sputtering and the slide was attached on SEM holder using a double side carbon tape mounted on an aluminum stud. The SEM photomicrographs were captured by operating at an accelerating voltage of 20 kV electron beam at desired magnification [9].

Zeta Potential

The zeta potential parameter is used to characterize the charge on the surface of the nanoparticles that plays a vital role in determining the stability of the formed nanoparticles. Zetasizer Nano ZS 90 (Malvern Instruments, UK), which calculates the zeta potential by determining the electrophoretic mobility and then applying the henry equation was used to determine zeta potential of the formulations (F1-F12). The electrophoretic mobility is obtained by performing an electrophoresis experiment on the sample and measuring the velocity of particles using laser doppler velocimetry [10].

Percentage Entrapment Efficiency (%EE)

The method for determination of entrapment efficiency was based on the amount of Tapentadol Hcl recovered from supernatants. It was assumed that the rest of the Tapentadol Hcl used during preparation had been encapsulated. The blank used was the supernatant obtained after centrifugation of dummy nanoparticles (without drug) at 10,000 rpm for 30 minutes at 15°C. The supernatant obtained was diluted and analysed Spectrophotometrically at 272 nm. Following equation was used to calculate entrapment efficiency [11].

%EE=Wt. of drug used in formulation-Wt of unbound drug in supernatant/Wt. of drug used in formulation x 100

***In-vitro* drug release studies**

Franz diffusion cell was employed for *in-vitro* characterization of transdermal formulations. This is a reliable method for the prediction of drug transport across skin from topical formulations. The receptor compartment of the diffusion cell was filled with 20 mL of phosphate buffered saline pH 7.4 and *invitro* drug release studies were carried out using synthetic cellophane membrane. The prepared solid lipid nanoparticles were placed in the donor compartment. The assembly was constantly maintained at 32.0 ± 0.5 °C at 100 rpm. Samples (1.0 mL aliquots) were then withdrawn at suitable time intervals (0, 1, 2, 4, 6, 8, 10

hrs) and replenished with an amount of medium to maintain the receptor phase volume to 20 mL. The samples were analyzed spectrophotometrically at 272 nm [12].

In order to understand the mechanism and kinetics of drug release, the drug release data of the *in-vitro* drug release was analyzed with various kinetic models like zero order, first order, Higuchi, Korsmeyer peppas model and correlation co efficient values were calculated for the linear curves.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy (FTIR)

The IR Spectrum of Tapentadol hydrochloride (Pure drug) shoes peaks at 3414.12 cm^{-1}, 1519.96 cm^{-1}, 1383.01 cm^{-1}, 1163.11 cm^{-1}. The physical mxture on the other hand shows peaks at 3423.76 cm^{-1}, 1519.96 cm^{-1}, 1383.01 cm^{-1}, 1163.11 cm^{-1}. Thus it is concluded that the physical mixture of the drug (Tapentadol Hydrochloride) does not show any major interactions with the formulation components like lipid (Glycerol monostearate) and surfactant (Poloxamer-188). This indicates that drug was compatible with the excipients which were represented in the figure 1 and figure 2.

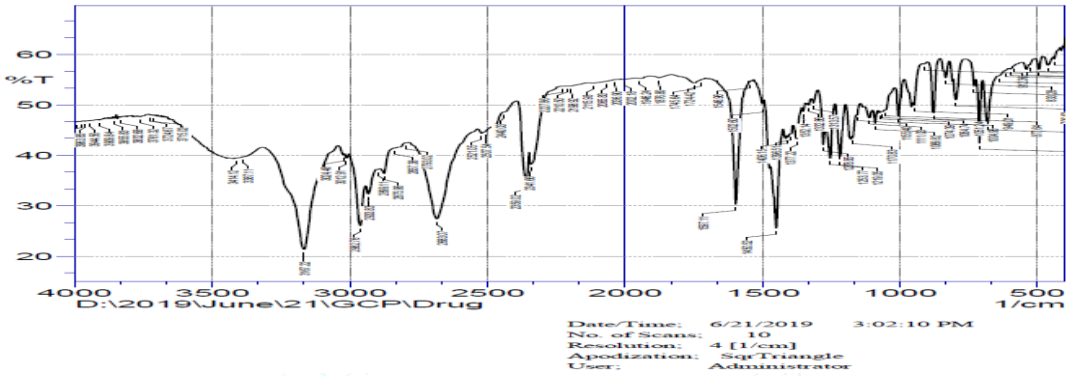


Figure-1: FTIR Spectra of Tapentadol hydrochloride

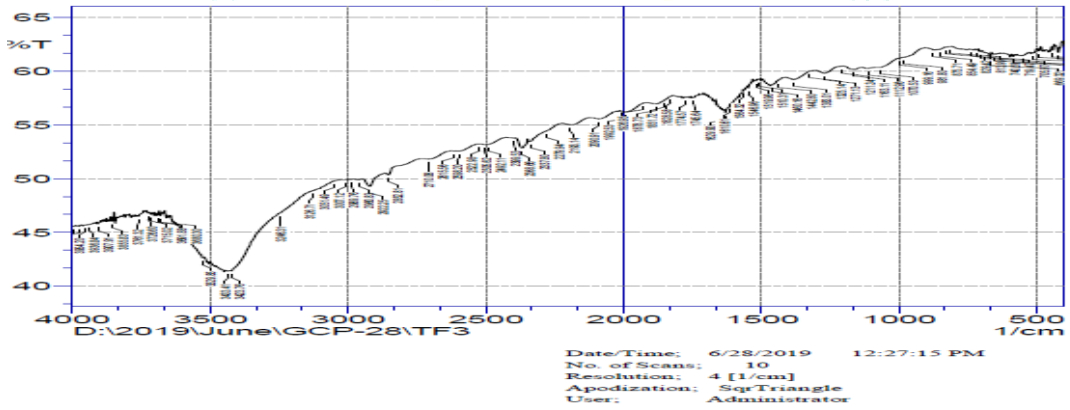


Figure-2: FTIR spectra of Optimized Formulation

Differential Scanning Colorimetry (DSC)

The best and optimized formulation of Tapentadol hydrochloride solid lipid nanaoparticles were evaluated for DSC. The pure Tapentadol hydrochloride shows a sharp endothermic peak at 212.23˚C and some of the similar changes occured in endothermic peak were observed at similar temperatue in prepared formulation at 209.68˚C. Thus it is concluded that,no interaction between the drug and the excipients which were represented in the figure 3 and figure 4.

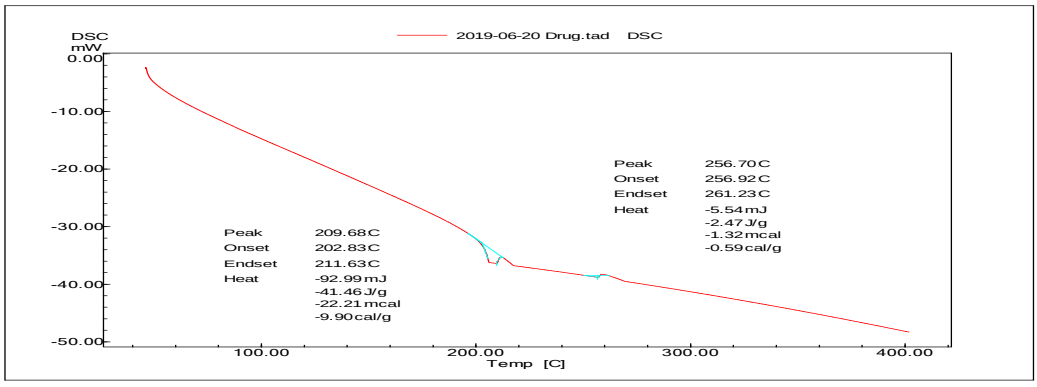


Figure-3: DSC of Tapentadol hydrochloride

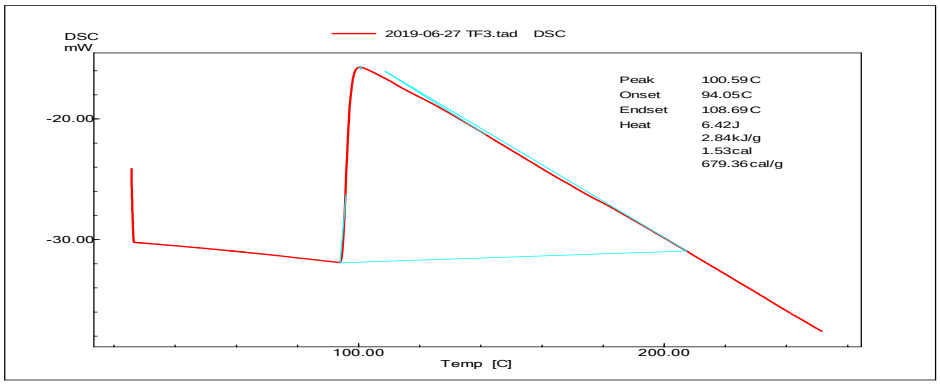


Figure-4: DSC of Optimized Formulation

Scanning Electron Microscopy (SEM)

The SEM photomicrographs of sample solution (F3 formulation) were obtained and as shown in figure 5. The photomicrographs revealed that the surface was smooth and uniform with appearance of spherical shape.

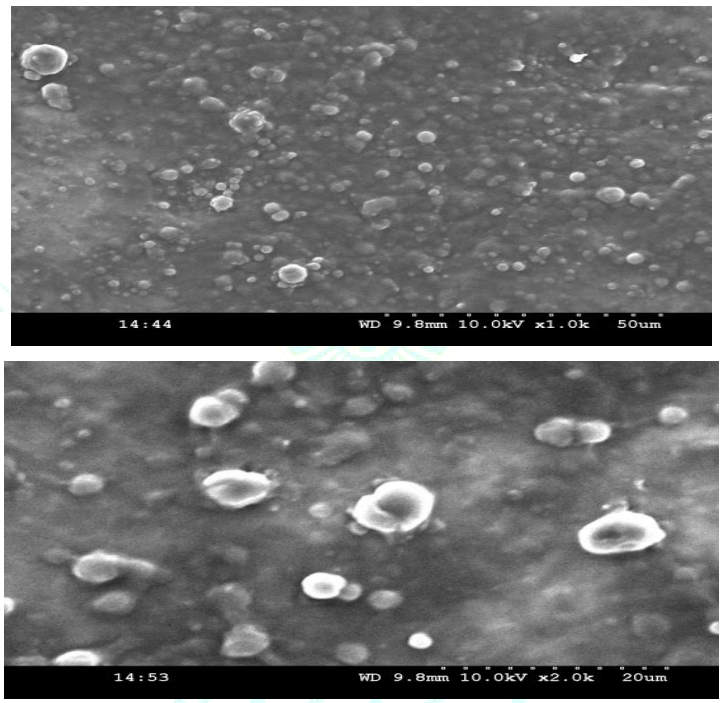


Figure-5: SEM images of F3 formulation

Percent Entrapment Efficiency (%EE)

Percent drug entrapment efficiency was used to determine the amount of drug entrapped into the prepared solid lipid nanoparticles.The % Entrapment Efficiency of all the formulations ranges between 60.9±0.65 to 8.7±0.36. This indicates that increase in drug loading increase the percentage of drug entramen efficiency. The %Entrapment efficiency values of all the Formulations were given in table 3 and graph representing the % Entrapment efficiency was given in Figure 6.

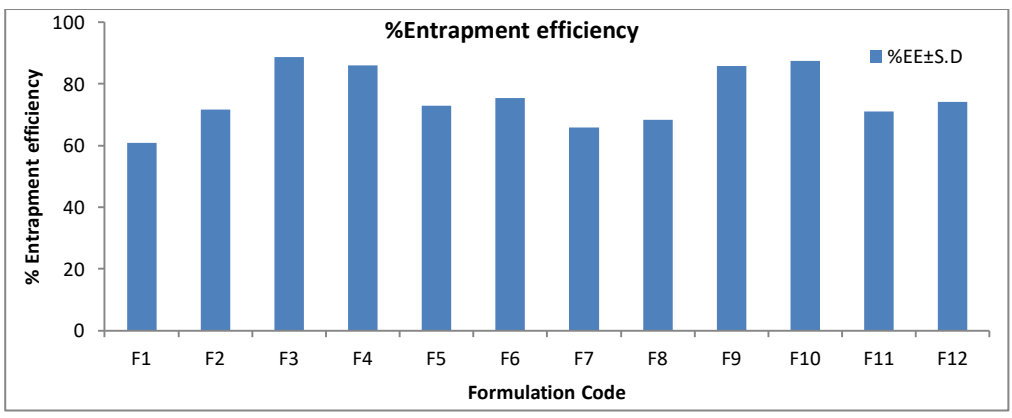


Figure-6: Graph representing the % EE of Formulations

Table-3: %EE values of the formulations

S.N0	Formulation Code	%EE±S.D
1	F1	60.9±0.65
2	F2	71.6±0.23
3	F3	88.7±0.36
4	F4	86.0±0.69
5	F5	72.9±0.53
6	F6	75.3±0.80
7	F7	65.8±0.23
8	F8	68.3±0.12
9	F9	85.7±0.63
10	F10	87.5±0.56
11	F11	71.0±0.31
12	F12	74.2±0.11

Zeta Potential

The zeta potential of the Tapentadol Hcl Solid lipid nanoparticles is important to determine the stability and uptake mechanism of the particles inside the body. The zeta potential values of formulations are shown in table 4 and zeta potential values of optimized formulation (F3) are shown in figure 7.

Table-4: Zeta Potential values of the formulations

S.No.	Formulations Code	Particle size (nm)	Zeta Potential (mV)
1	F1	252.1	-28.6
2	F2	280.3	-24.6
3	F3	101.9	-18.1
4	F4	89.0	-20.8
5	F5	132.9	-21.6
6	F6	159.0	-24.6
7	F7	307.8	-27.8
8	F8	348.2	-25.0
9	F9	198.6	-20.6
10	F10	172.4	-21.8
11	F11	125.6	-10.9
12	F12	121.7	-9.8

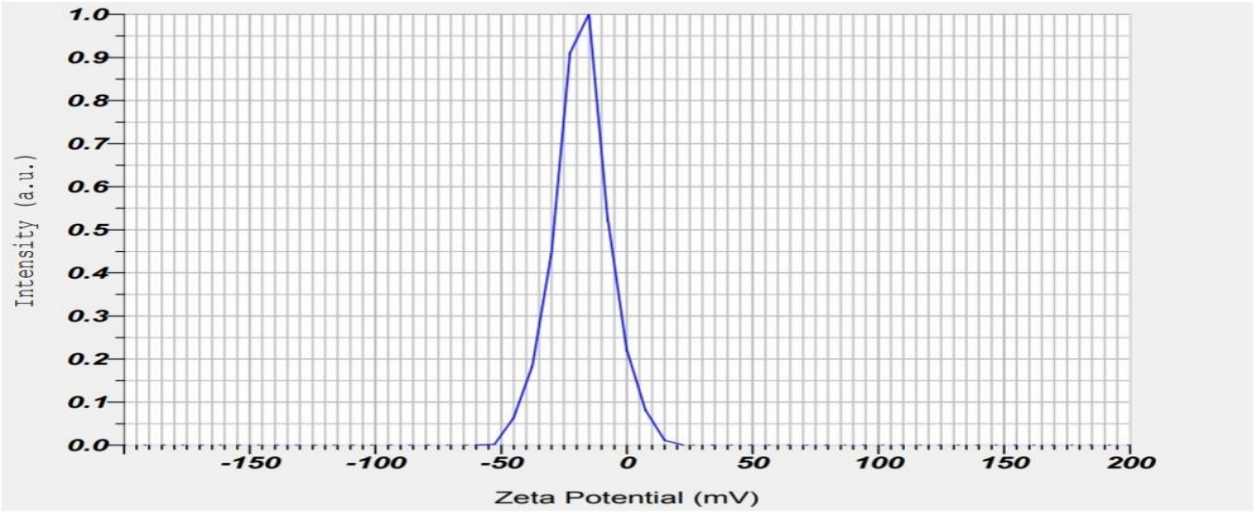


Figure-7: Graph representing the Zeta potential of Optimized formulation

***In vitro* drug release studies**

In vitro drug release studies were carried out by using Franzz diffusion cell using phosphate buffer (pH 7.4) as a dissolution medium which is carried out for about 10 hrs. The drug release from all the formulations were found to be higher than the pure drug which were given in table 5 and table 6 and graphical representations were represented in Figures 8,9,10,11The drug release from the optimized formulation (F3) was found to be 97.8±0.60 in 10 hours following first order release kinetics and Higuchi model.

Table-5: %Drug release of formulations F1 to F6

Time (hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	14.5±0.10	14.6±0.13	15.1±0.20	15.8±0.02	16.1±0.23	17.4±0.43
2	22.6±0.25	21.2±0.24	25.3±0.13	26.1±0.81	28.0±0.34	24.6±0.65
3	35.2±0.36	28.7±0.37	31.4±0.32	37.8±1.33	39.3±0.46	36.0±0.87
4	39.8±0.21	32.5±0.45	37.8±0.83	42.5±1.26	44.3±1.23	47.9±0.76
5	43.6±0.58	39.7±1.2	42.4±1.40	45.6±0.41	49.19±1.37	54.9±0.45
6	52.7±0.12	46.5±1.9	49.7±0.90	53.6±0.76	57.8±0.67	65.6±1.34
7	59.4±0.32	51.9±0.7	58.7±0.15	65.9±1.54	66.8±0.25	71.4±1.98
8	64.7±0.52	67.8±0.5	75.3±0.12	78.7±0.35	69.1±1.23	84.0±0.57
9	76.9±0.01	72.8±0.4	83.4±1.40	87.4±0.67	74.9±1.42	95.4±0.34
10	88.6±0.40	85.0±1.2	97.8±0.60	95.6±1.02	82.7±0.43	97.8±1.24

Table-6: % Drug release of formulations F7 to F12

Time (hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	18.2±0.23	16.1±0.20	14.5±0.32	15.9±0.32	17.2±0.45	13.2±0.23
2	26.2±0.25	21.2±0.36	22.6±0.50	28.3±0.65	25.2±0.58	21.3±0.85
3	35.2±0.60	32.6±0.51	35.2±0.75	36.9±0.54	36.5±0.14	36.5±0.56
4	46.3±0.52	44.5±0.66	39.8±0.89	46.5±0.42	43.2±0.23	47.2±0.76
5	52.6±0.32	59.2±0.52	43.6±0.97	58.9±0.35	58.1±0.54	56.1±0.42
6	65.2±0.69	66.1±0.32	52.7±1.3	66.4±0.12	65.2±0.36	70.4±0.31
7	78.5±0.54	75.6±0.21	59.4±1.8	74.2±0.65	75.5±0.87	76.5±0.14
8	85.6±0.84	86.1±0.32	64.7±2.1	84.5±0.85	78.2±0.56	82.2±0.51
9	89.5±0.54	89.1±0.11	76.9±0.2	88.9±0.65	81.2±0.32	88.3±0.32
10	90.2±0.25	91.0±0.28	88.6±1.5	91.6±0.32	90.1±0.25	91.5±0.95

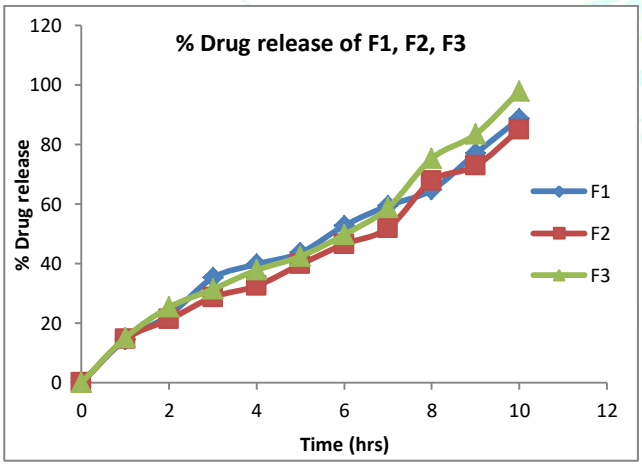


Figure-8: % Drug release of F1, F2, F3 Formulations

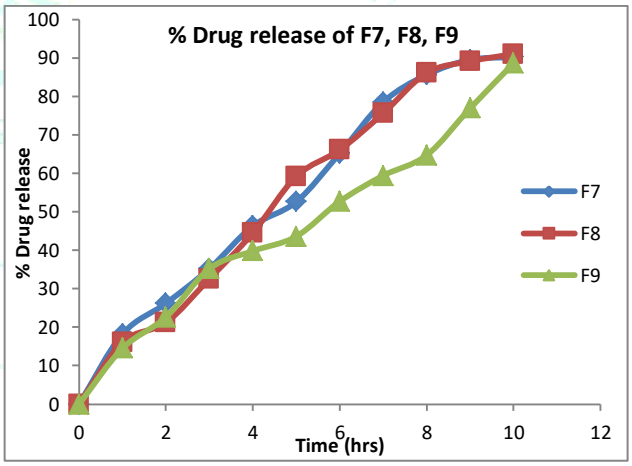


Figure-10: % Drug release of F7, F8, F9 Formulations

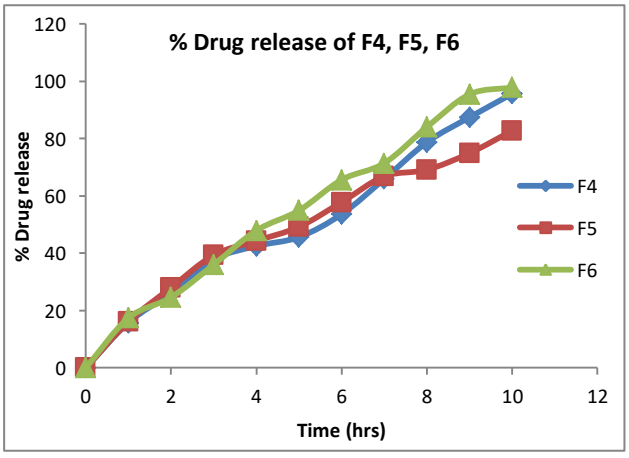


Figure-9: % Drug release of F4, F5, F6 Formulations

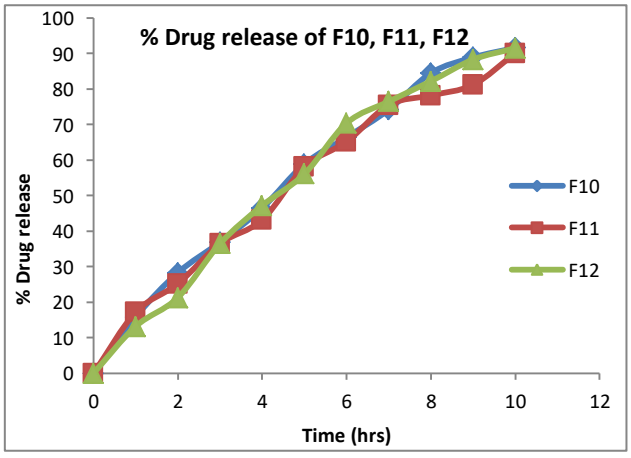


Figure-11: % Drug release of F10, F11, F12 Formulations

CONCLUSION

Tapentadol hydrochloride is a drug for the treating of severe pain and used as analgesic. Tapentadol Hcl loaded Solid Lipid Nanoparticles were prepared with the aim to release the drug at a controlled and prolonged rate at the targeted site. The Tapentadol hydrochloride Solid Lipid Nanoparticles was successfully prepared by using glycerol monostearate and Stearic acid as lipids and Poloxamer-188 as a Surfactant by Hot Homogenization method. The F1 to F12 Formulations were prepared by using different ratios of lipids and surfactant. The prepare formulations was evaluated for various parameters.

Tapentadol hydroichloride solid Lipid Nanoparticles prepared by using 0.6% of Glycerol monostearate and 0.25 % of Poloxamer-188 is effective when compared to other formulations. SEM study of prepared SLN's was within the range of (1-1000 nm). There is no drug- excipients interaction in FTIR and DSC. The % Entrapment Efficiency was found as 88.7±0.36. the Zeta potential was found as -18.1mV.The % drug release was found as 97.8±0.60 in 10 hrs following first order release kinetics and Higuchi model. Stability studies were done for 3 months and the formulation was stable without any physical changes and degradation.

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