Atul S. Sayare et al /J. Pharm. Sci. & Res. Vol. 11(8), 2019, 2872-2877

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Formulation and Evaluation of Gabapentin Loaded Chitosan Transdermal Films

Atul S. Sayare*, AniketR. Pithe, Prashant D.Ghode, K. R.Khandelwal
JSPM's RajarshiShahu College of Pharmacy and Research, Pune, Maharashtra, India-411033

Abstract

Aim: Gabapentin, an anticonvulsant drug also indicated for neuropathic pain has short half-life and saturable absorption which increases the frequency of dosing. Hence, to achieve extended release the drug has been formulated as sustained dosage form using chitosan.

Method: Chitosan films loaded with drug gabapentin were formulated at four different concentrations (0.5%, 1%, 1.5% and 2% of chitosan) using 3% v/v acetic acid solution by the solvent casting method. The formulated film has been characterized for its physicochemical properties such as thickness, % swelling, folding endurance, texture. FTIR-ATR, differential scanning calorimetry (DSC) and drug content by UV-Vis spectrophotometry. The in-vitro drug release from the film was evaluated using the Franz-type diffusion cell.

***Results*:** 1% chitosan film loaded with gabapentin was found have uniform thickness in the range of 0.47 mm to 0.64 mm, optimum folding endurance (more than 260) and swelling in the range of 76%-87%. Drug content was found to be in the range of 91% to 95% Also the result for in-vitro drug diffusion was found to be 93.76% after 24hrs, indicating the sustained release of the drug.

***Conclusion*:** Hence, formulating gabapentin as a sustained release formulation helps in improving its absorption avoiding saturation of drug and extending its half –life.

Keywords: Gabapentin, Chitosan, Transdermal film, Solvent casting

1. INTRODUCTION

Gabapentin,an anticonvulsant, analgesic, anxiolytic, having IUPAC name 2-[1-(aminomethyl)cyclohexyl]acetic acid (Fig. 1) is also used to mitigate chronic pain disorders. Hence, is indicated to patients having neuropathic pain but are not responding to non-steroidal anti-inflammatory drugs (NSAIDs) or opiates [1]. It structurally mimics the GABA neurotransmitter which has a cyclohexane ring incorporated [2].gabapentinis believed to inhibit excitatory neuron activity. This molecule also shows analgesic properties [3]. Its mechanism of action comprises inhibition of the alpha 2-δ-subunit of voltage-gated calcium channels being an antiepileptic agent [4]. It has also ascertained and approved to be effective in the management of neuropathic pain [5]. It is a water-soluble, bitter-tasting, white crystalline substance and a saturable mechanism of absorption. It also has been reported that gabapentin has high water solubility, low permeability, has no protein binding and not metabolized by the liver [6]. To overcome the problems of its short half-life (4 to 6 h) and saturable absorption new formulations need to be established [7].

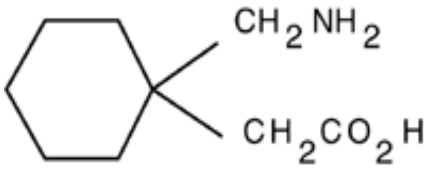

Figure 1: Chemical structure of Gabapentin

Topical formulations are another choice for formulating a dosage form to combine and transport drug into and across biological barriers, like the skin [8]. Consequently, there are several different types like topical cream, ointment and gel formulations. Also, gabapentin sustained release topical film is not available. Thus, an attempt to develop sustained dosage form in form of a film was performed.

Chitosan, (1,4)-2 amino-2-deoxy β-D glucan is analogous to glucosaminoglycans due to its similar structural characteristics. Chitosan is tough, biodegradable, inert, and non-toxic polymer. Also chitosan is majorly used for formulating sustained released dosage forms. It has good compatibility with the drugs when dispersed into it for formulation [9]. Hence, it proves to be an ideal polymer for formulating chitosan films loaded with drug.

This paper mainly focuses on the novel idea to formulate the transdermal dosage form for gabapentin drug indicated for analgesic and anti-inflammatory activity. Hence, an attempt has been made to formulate and evaluate chitosan transdermal films loaded with gabapentin.

2. MATERIALS AND METHODS

2.1 Materials

Gabapentin (purity 99.2%) was procured from Glenmark Pharmaceuticals, Mumbai, India. Glacial acetic acid, glycerine and dimethyl sulphoxide (DMSO) were procured from Thermosil Fine Chemical Industries, Pune, India. Chitosan was obtained from Hi-media Chemicals, Mumbai, India.Distilled water was used throughout the experiments. Allother chemicals and reagents used were of AR grade.

2.2 Preparation of films [10, 11]

Drug-loaded transdermal films of gabapentin were prepared by using solvent casting method. A petri dish with a total area of 44.50 cm^2 was used. Chitosan was accurately weighed and dissolved in 50mL of 3% aqueous acetic acid and the mixture was stirred overnight to remove air entrapped in the solution to form clear solution. Drug was dissolved in the above solution and mixed until clear solution was obtained. Glycerine (2% w/w of total

weight of chitosan) was used as plasticizer and DMSO (5% w/w of total weight of chitosan) was used as permeation enhancer. The resulted uniform solution was casted on the petri dish, which was lubricated with glycerin and dried at room temperature for 24 h. An inverted funnel was placed over the petri dish to prevent fast evaporation of the solvent. After 24 h, the dried films were taken out and stored in a desiccator for further studies. The films were casted as described above so as to obtain 450 mg of gabapentin in 4 $cm^2$of each film.

3. Evaluation Parameters Of Transdermal Films.

3.1 Folding endurance [12]

A strip of specific area (2 cm × 2 cm)was cut evenly and repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance.

3.2 Thickness [12]

Film thickness was measured using digital micrometer screw gauge at three different places, and the mean value was calculated.

3.3 Tensile strength [13]

The tensile strength of the film was determined by using a CT3 Texture Analyser (Brookfield, USA) with Texture Pro CT software. The film was attached between two clamps of TA-DGA probe having 2 cm distance. The lower clamp was stationary and moving upper clamp stretched the film with speed test of 0.5 mm/s until breaking of the film. The instrument was equipped with 4.5 kg load cell. The process was repeated three times for each film. The average of readings of three films was taken as tensile strength. The weight required to break the film was noted.

3.4 Swelling study [13]

The prepared blank and drug loaded chitosan films of size 2 cm × 2 cm was cut and immersed into water for 24h to determine the water uptake property. Dry and wet weight of film was measured and % swelling was calculated by the following formula.

% Swelling = $(W_w–W_d)/W_d \times 100$

Where, $W_d$andW_w is the dry and wet weight of the film respectively.

3.5 Drug content [14]

A specified area of film (2 cm× 2 cm) was dissolved in 100mL water and shaken continuously for24 h. Then the whole solution was ultra sonicated for 15min.After filtration, the drug was estimated spectrophotometrically at wavelength of 568 nm using ninhydrin solution as a chromogenic agent and determined the drug content from the calibration curve of standard gabapentin as follows. Solution of 0.1 mg/mL gabapentin was prepared in water. Ninhydrin reagent was 2 mg/mL in methanol prepared fresh. Different aliquots of drug solution were transfered into test tubes. To each test tube 2 mL of ninhydrin reagent in methanol was added and 10 mL of de-ionized water was added, then test tubes were heated on a water-bath at 70°C for 15 min. These solutions were transferred to volumetric flasks after cooling and the volume was made up to the mark with de-ionized water to provide final concentration range of 30-250µg/ml. The absorbance of the solution was measured against a reagent blank at 568 nm. The calibration graph was prepared by plotting absorbance vs concentration of gabapentin.

3.6. FTIR study[15]

The gabapentin and polymer interaction was determined by recording the FT-IR spectrum (Bruker Alpha ATR Spectrophotometer) of the pure gabapentin and mixture of gabapentin and excipients in powder form.

3.7. Differential scanning calorimetry(DSC) analysis [15]

To investigate the drug excipient compatibility the melting temperature (T_m) of the drug, excipients, physical mixture of drug and excipients was determined by DSC, Mettle, Toledo, Switzerland, DSC1 model was used for the study. Samples were sealed hermetically in flat bottomed aluminium cells or pans. Then the samples were heated over a temperature of 30-450ºC in an atmosphere of nitrogen (30 ml/min) at a constant rate of 10ºC per min using alumina as reference standard.

3.8 In-vitro drug release [16]

In Vitro drug releasestudies were performed by using a Franz diffusion cell with receptor compartment capacity of 50 mL. The cellulose acetate membrane was used for the determination of drug from the prepared transdermal films. The cellulose acetate membrane having a pore size 0.45 μ was mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal film was placed on the cellulose acetate membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was continuously stirred using magnetic beads, and the temperature was maintained at 32±0.5℃, because the normal skin temperature of human is 32℃. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

4. Result And Discussion

4.1 Preliminary study

The thickness of films of different concentration of chitosan is shown in Table 2. All the films have uniform thickness throughout film. The thickness of all films was between 0.47- 0.64mm.There was no significant difference in thickness of the films.

The folding endurance values of all the films were found satisfactory which indicates that the films prepared using glycerin (2% of chitosan concentration) as plasticizer were having optimum flexibility and were not brittle. It indicates that drug loading has no influence on folding endurance of film.

4.2 Mechanical properties

High tensile strength is favourable that prevents the breaking of film during application storage and transportation.It was observed that with the increase of chitosan concentrations, the tensile strength of the films gradually increased.

Table 1: Composition of gabapentin film

Ingredients (%w/v)	Formula code					
	F1	F2	F3	F4	F5	F6
Gabapentin	5	5	5	5	5	5
Chitosan(%w/v of acetic acid)	0.5	1.0	1.5	2.0	1.0	1.0
DMSO (% of Chitosan)	-	-	-	-	2.5	5.0
Glycerin(% of Chitosan)	2.0	2.0	2.0	2.0	2.0	2.0
Water (to Make) ml	50	50	50	50	50	50

Table no.2characteristics of drug loaded film

Batches (drug loaded)	Thickness (mm) (mean±S.D.)	Folding endurance (mean±S.D.)	Swelling capacity(%) (mean±S.D.)	Tensile strength(N) (mean±S.D.)	Drug content(%) (mean±S.D.)
F1	0.47±0.05	260±1.20	76±0.3%	9±0.05	91.2%
F2	0.54±0.01	267±1.53	79±1.7%	11±0.03	93.5%
F3	0.59±0.03	277±3.25	84±0.25%	12±0.07	89.7%
F4	0.64±0.06	285±2.24	87±0.55%	13±0.04	92.5%
F5	0.58±0.04	263±1.80	74±1.4%	11±0.08	93.8%
F6	0.62±0.2	268±2.77	81±2.43	13±0.05	95.7%

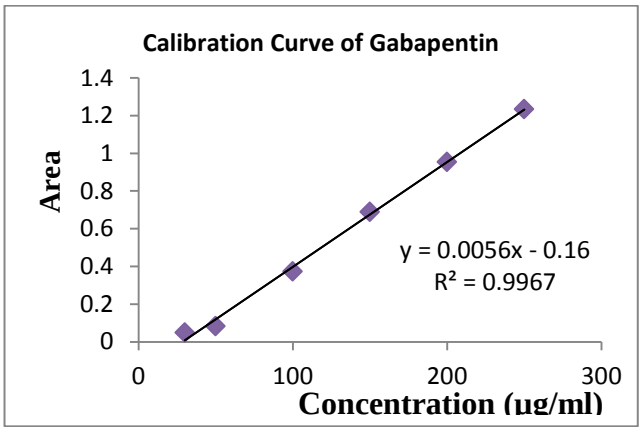

Figure 2: Calibration Curve Graph of Gabapentin

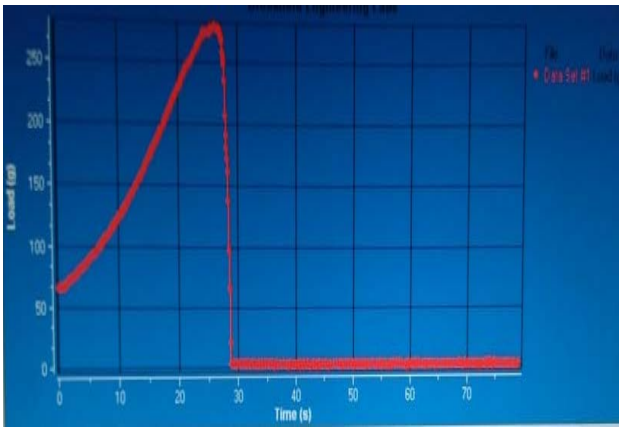

Figure 3: Texture analysis Graph

4.3 Swelling Study

Swelling study was performed to understand the absorbing capacity of individual films. Swelling represents the capacity of film to absorb water. The swelling behaviour of the chitosan films was analysed for the optimized batch F6 containing 1% chitosan at a different time interval, which shows that the film had 81% swelling.

4.4 Drug content

The absorbance of the gabapentinwas measured spectrophotometricaly at 568 nm by using nihydrin as a chromogenic agent as gabapentin lacks significant UV absorption. A calibration curve was constructed by plotting concentration vs absorption and was found to be linear in the range of 30-250µg/ml with correlation coefficient (r^2) of 0.99 (Fig. 2).The % drug content of gabapentinin the chitosan film was determined from calibration was found to be in the range of 91% to 95 % w/w, as shown in Table 2.

4.5 FTIR Study

The initial IR spectra of the drug and the polymers are satisfactory with their characteristics peaks (Figure (4a and 4b) similarly, the physical mixture (Figure 4c) also indicate the presence of characteristic peaks of the drug and the polymers. It is clear that he drug and the excipients are free from any significant chemical interactions.

4.6 Differential scanning calorimetry (DSC) analysis

The thermogram shown in Fig. 5(a), shows a sharp endothermic event at 175°C which corresponds to the melting point of gabapentin, as shown in Fig. 5(b). Also similar endothermic peak patterns have been observed for plain gabapentin drug and mixture of chitosan and gabapentin. No decomposition of gabapentin with chitosan was visible after melting, as there was no other exothermic event after 175°C, thus, indicating the compatibility of gabapentin and chitosan. While Fig 5(c), thermogram of gabapentin loaded chitosan film shows a broad endothermic peak starting from 70°C to 180°C. This indicates that gabapentin has cross-linked with chitosan and has interfered into its melting point. Thus, a broad endothermic peak was observed.

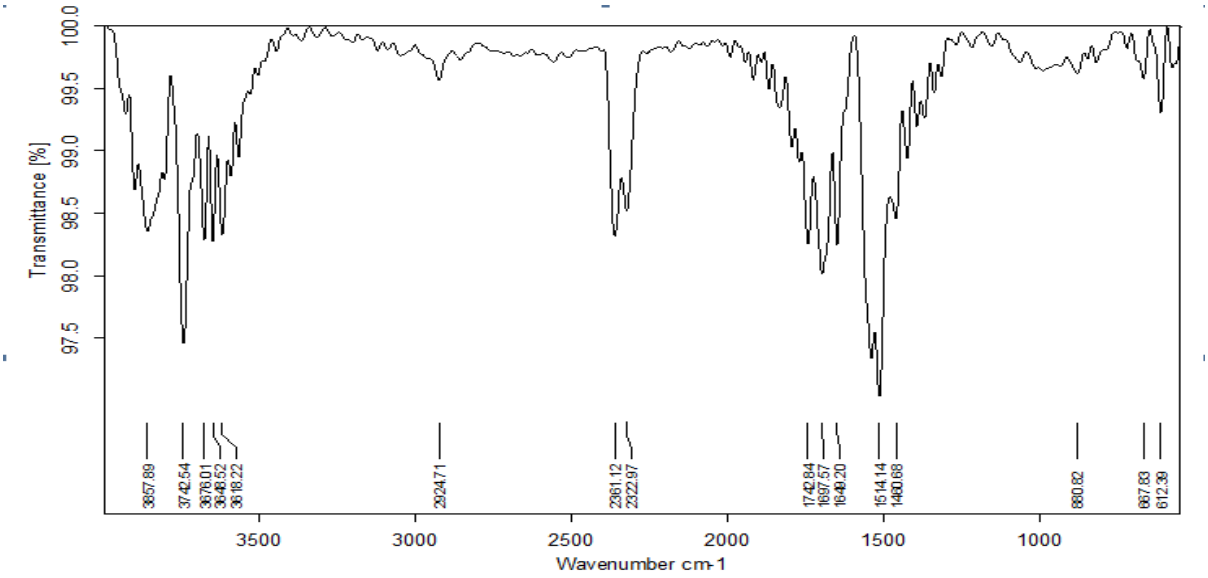

Figure 4(a): FTIR-ATR Spectra of Chitosan.

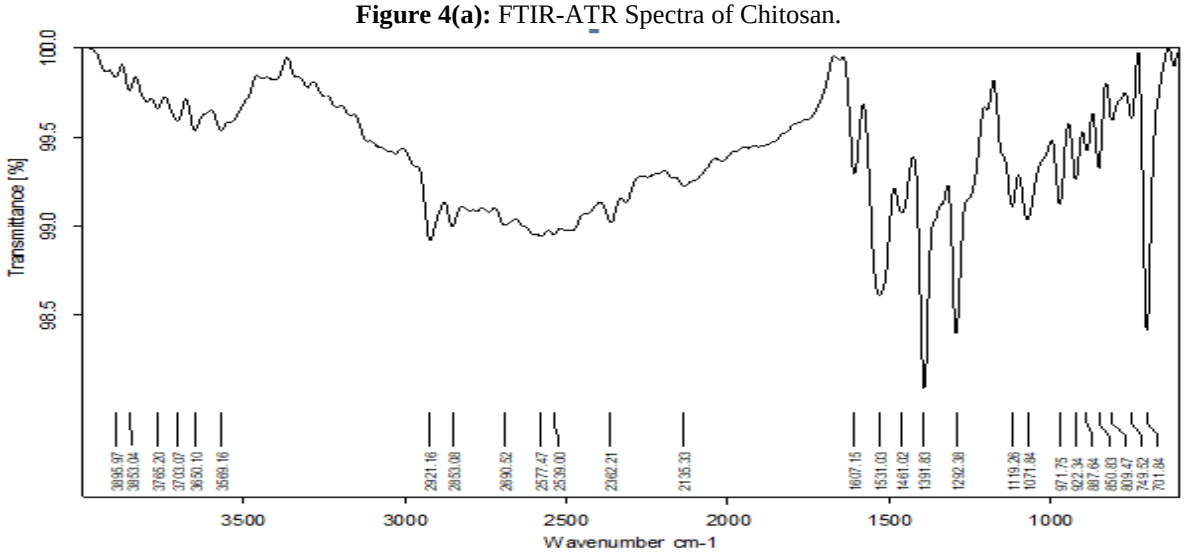

Figure 4(b): FTIR-ATR Spectra of Gabapentin.

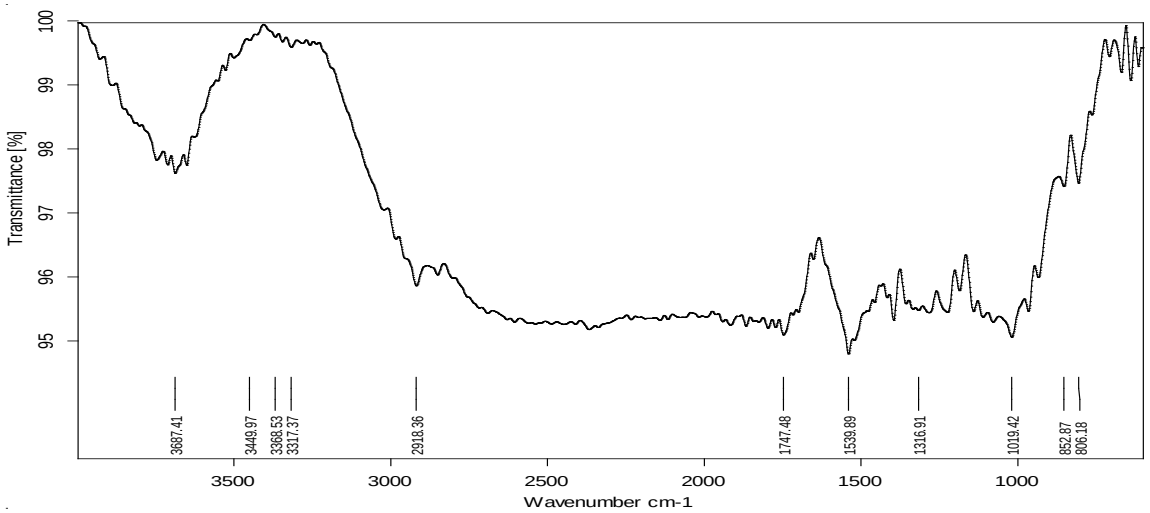

Figure 4(c): FTIR-ATR Spectra of gabapentin and excipient

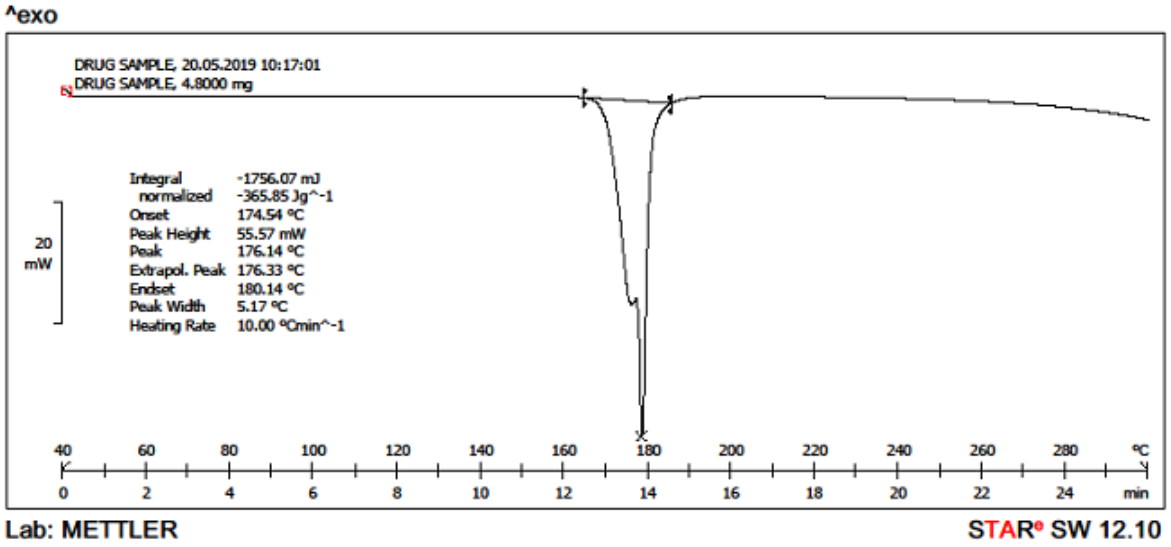

Figure 5(a): DSC graph of plain Gabapentin drug

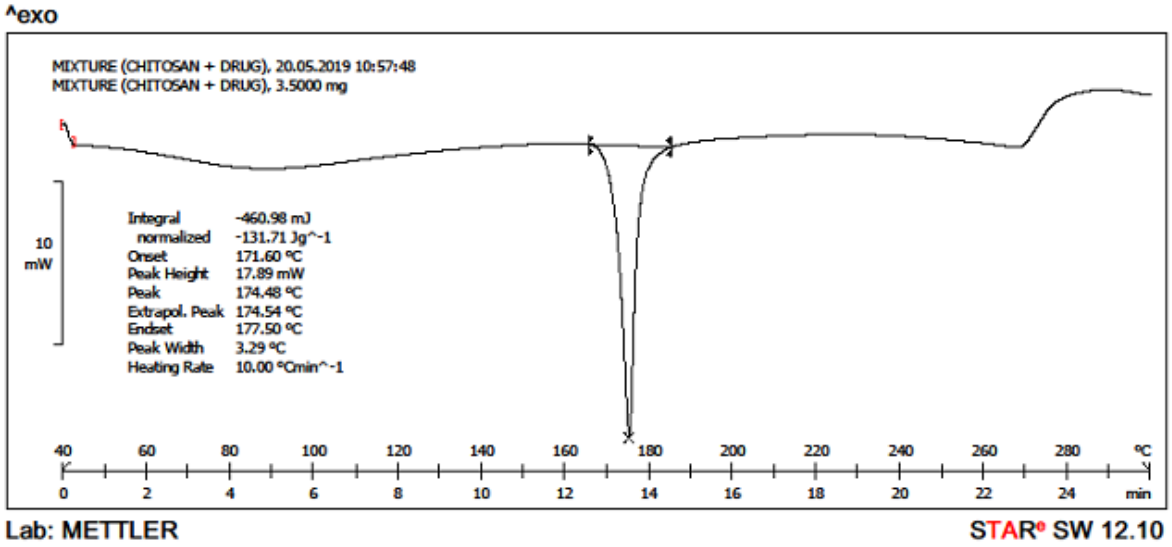

Figure 5(b): DSC graph of Chitosan and Gabapentin drug

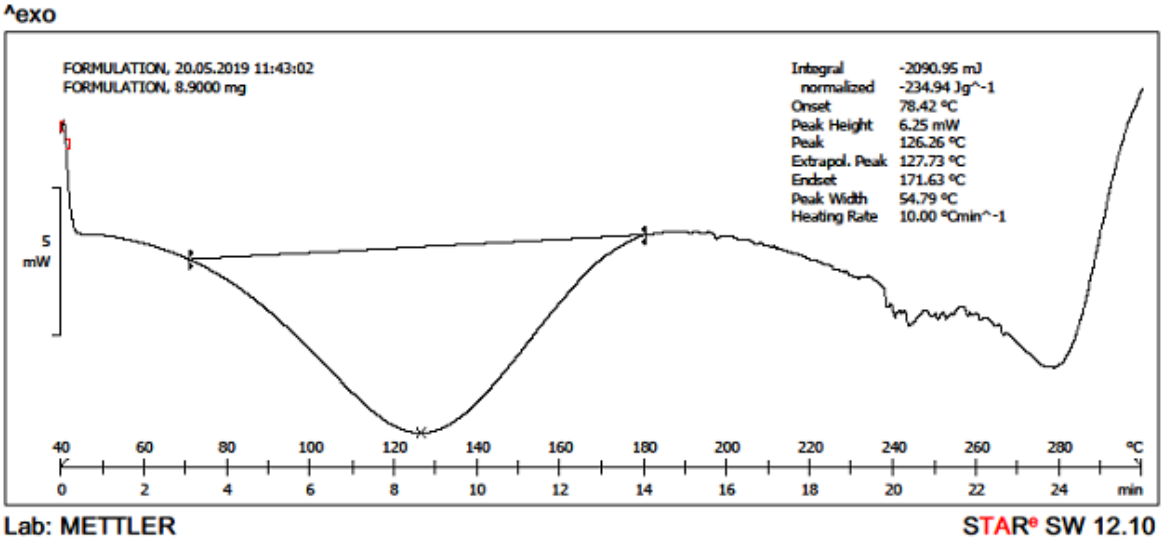

Figure 5(c): DSC graph of Gabapentin loaded chitosan film

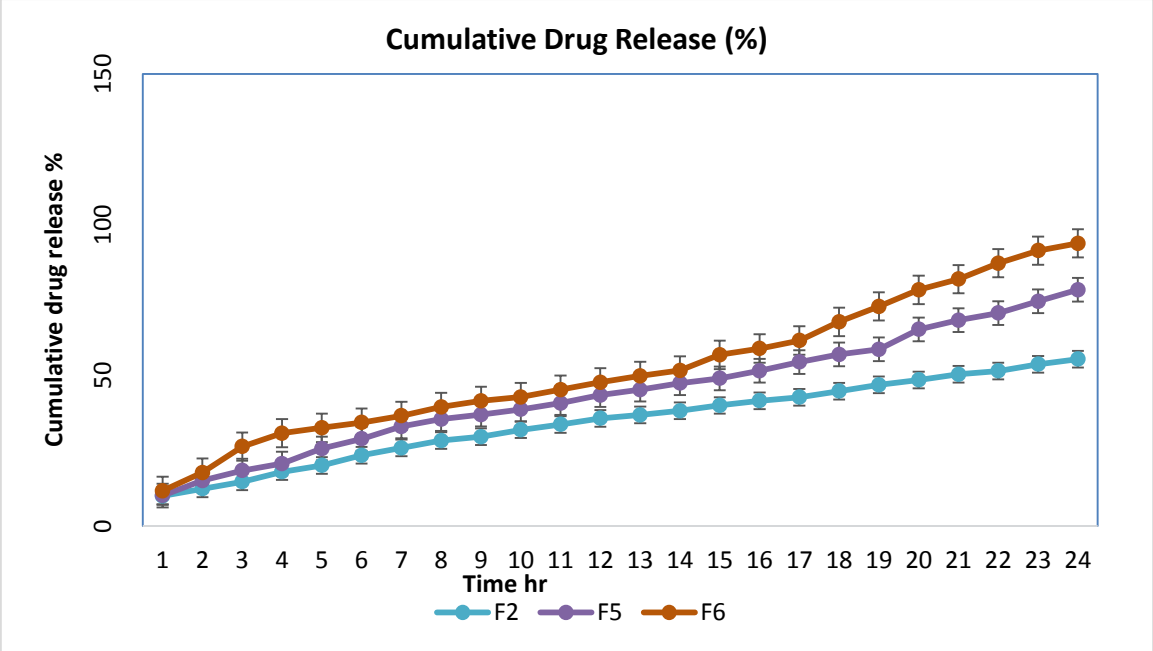

Figure 6: In-vitro drug release of Gabapentin loaded chitosan film for 24 Hrs.

4.7 In-vitrodrug release

The in-vitro drug release study was carried using a Franz-type diffusion cell for 24 hrs. The result for % release reveals a release of drug gabapentin for 24 h.The % release of film (F2) was found to be 55.32%, DMSO added films (F5, F6) reveals a release of drug was found to be 78.33%, 93.76% as shown in Fig. 6. The in vitro study reveals that the increase of the concentration of DMSO up to certain limit shows high penetration of drug through the membrane.

5. Conclusion

Topical delivery of gabapentin could provide an alternative treatment to oral delivery of the active drug for neuropathic pain conditions, with associated reduced systemic side effects. Gabapentin loaded chitosan transdermal film prepared by solvent casting method using glycerine and DMSO as plasticiser and penetration enhancer. Drug loaded transdermal films were evaluated for physicochemical parameters like physical appearance, thickness, folding endurance, swelling, tensile strength and drug content. FT-IR and DSC study was performed to study the drug-excipient interaction which reveals that there is no chemical interaction between the drug and the excipient. Drug release from the formulations was studied by *in- vitro* diffusion studies by Franz-type diffusion cell for 24 hrs. DMSO act as penetration enhancer and it improved the permeation of drug. The study concluded that the transdermal drug delivery of gabapentin film can be employed for the patient to obtain a steady state drug concentration, which would improve the patient compliance.

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