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Research Article

FORMULATION AND EVALUATION OF MICROEMULSION GEL FOR TRANSDERMAL DELIVERY OF TRAMADOL

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ABSTRACT

Objective: The present work was carried out to design microemulsion gel system for transdermal delivery of the drug to minimize the side effects and to reduce the frequency of administration and for prolonging the duration of action.

Methods: Tramadol, an opioid analgesic drug, was mixed with various selected polymers such as sodium alginate (SA), acacia, hydroxypropyl methylcellulose (HPMC), and Eudragit in geometric mixing ratios. The drug, polymer, and other excipients were mixed thoroughly by trituration method and different formulations (F1-F8) were prepared the same quantity of all the ingredients excepting the polymers.

Results: The different formulations prepared, studied, and showed that the formulation using SA as polymeric carrier had a better effect on the evaluated parameters. The drug-SA formulation exhibited better drug-polymer compatibility, optimal viscosity (2750 cps), zeta potential (−26.1 Mv), and particle size distribution (262.8 d.nm) values. The *in vitro* release studies also indicated that the drug-SA formulation was of desirable release pattern, thus indicating that SA to be a better choice in formulating a transdermal delivery gel system.

Conclusion: Evaluated microemulsion gel formulation F2 of tramadol with polymeric carriers SA was much stable than other carriers used. Thus, it could be concluded that the gel formulation with SA can be taken as an ideal formulation.

Keywords: Tramadol, Microemulsion gel, Transdermal drug delivery system.

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INTRODUCTION

Microemulsion is defined as an oil-in-water or water-in-oil emulsion producing a transparent product [1]. Techniques for enhancement of transdermal permeation of drugs are the use of nanoemulsion and microemulsion vehicles [2]. Microemulsions have received great attention for various applications including dermal and transdermal drug delivery due to ease of preparation, thermodynamic stability, permeation enhancement activity of their components, and a high solubilizing capacity for various drugs over conventional topical formulation vehicles [3]. Microemulsions are known to enhance the bioavailability of drugs through topical and systemic routes. Microemulsion prepared and it's evaluated and this microemulsion incorporated in suitable gelling agent. Microemulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin [4].

The ingredients of microemulsion could facilitate the permeation rate of the drug by reducing the diffusion barrier of the stratum corneum. However, due to low viscosity of the microemulsions, their minimal retention in the affected part imposes a resistance in its widespread use in pharmaceutical industry. It is important to prevent the drug loss due to draining out from the onycholytic cavity or reaching the systemic circulation. To circumvent these problems, the colloidal drug delivery carrier should be loaded in a gel base [5,6] In recent years, microemulsions continued to be used as solubilization capacity enhancers and dissolution rate improvers for poorly soluble drugs. The works in this area focus on two aspects: First, the effect of different microemulsion structures on drug solubilization capacity and dissolution efficiency, and second, on the physicochemical characterization of drug-loaded microemulsions compared to drug-free systems [7].

Microemulsion-based gels possess the previously mentioned advantages of both emulsions and gels such as better stability, better loading capacity, incorporation of hydrophobic drugs, and avoidance of the first pass effect and also have good patient acceptability. Advantages associated with low-surfactant microemulsion gels were formulated and characterized to enhance topical delivery of poorly soluble drugs. It was found that the choice of viscosity imparting agent played an important role in governing drug release from microemulsion gel. Microemulsion-based gels now have been used for the treatment of various kinds of skin disorder [8]. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat the cutaneous disorders. Topical drug delivery system has several advantages such as ability to deliver drug more selectively to a specific site, avoidance of gastrointestinal incompatibility, and metabolic degradation associated with oral administration. Moreover, topical deliveries provide an increased bioavailability by avoiding the first pass metabolism by liver and a consistent delivery for extended period. In topical drug delivery system, drug diffuses out of the delivery system, reaches to the site of action, and gets absorbed by the skin [9].

The aim of this study was to develop suitable microemulsion gel system (without addition of gelling agent) after screening of oils, surfactants, and cosurfactants for transdermal delivery of tramadol to enhance its dissolution and to improve its skin permeability with enhanced safety.

MATERIALS AND METHODS

Materials

Tramadol was received as a gift sample from Zydus Cadila Healthcare Ltd., Ahmedabad, Gujarat. Sodium alginate (SA), *Acacia*, hydroxypropyl methylcellulose (HPMC), Eudragit, Tween-80, sodium lauryl sulfate,

castor oil, and methylparaben were used as gelling agents and additives. All reagents and solvents used were of analytical grade.

Methods

Preparation of microemulsion gel of tramadol

Tramadol was mixed with different polymers such as SA, *Acacia*, HPMC, and Eudragit by geometric mixing. Drug, polymer, and other excipients were mixed thoroughly by trituration method and eight different formulations were prepared in which the amount of all the ingredients (except polymers) was kept constant including drug. The detail of composition of each formulation is given in Table 1.

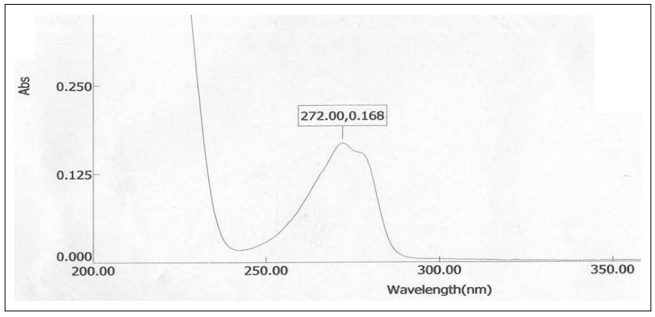

Fig. 1: Ultraviolet spectrum of pure tramadol

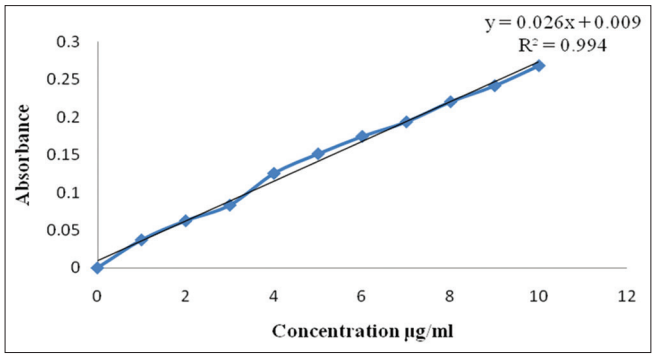

Fig. 2: Standard calibration curve of tramadol

Evaluation of tramadol microemulsion gel

Evaluated parameters for the gel formulations were appearance, pH, viscosity, spreadability, extrudability, zeta potential, *in-vitro* drug diffusion study.

pH [10]

The pH value conventionally represents the acidity or alkalinity of solution in the pharmacopoeia, standard and limit of pH have been provided for those pharmacopoeial substances in which pH as a measure of the hydrogen ion activity is important from the standpoint of stability.

The pH of gel was checked using a digital pH meter at constant temperature. Before this, the pH meter was calibrated using phosphate buffer solution of pH 3.99, 7.0, and 9.2, and then, the electrode was washed with dematerialized water. The electrode was then directly dipped into gel formulation and constant reading was noted. The results are mentioned in Table 2.

Viscosity [10,11]

Viscosity of the formulated microemulsion gel was determined using Brookfield viscometer at 25°C. The results are mentioned in Table 3.

Spreadability [10]

Spreadability of the formulations was determined by texture analyzer apparatus suitably modified for the study. The spreadability was calculated using the formula.

S=ML/T

Where,
S=Spreadability
M=Weight tied to upper glass slide
L=Length of glass slide
T=Time taken in seconds.

The results are mentioned in Table 3 and Fig. 13.

Table 1: Composition of tramadol microemulsion gel with different polymer concentrations

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Tramadol (mg)	1000	1000	1000	1000	1000	1000	1000	1000
2	SA (mg)	1000	2000	-	-	-	-	-	-
3	Acacia (mg)	-	-	1000	2000	-	-	-	-
4	HPMC (mg)	-	-	-	-	1000	2000	-	-
5	Eudragit (mg)	-	-	-	-	-	-	1000	2000
6	Tween 80 (mg)	1100	1100	1100	1100	1100	1100	1100	1100
7	Sodium lauryl sulfate (mg)	150	150	150	150	150	150	150	150
8	Castor oil (mg)	1900	1900	1900	1900	1900	1900	1900	1900
9	Methylparaben (mg)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
10	Distilled water (qs) (ml)	100	100	100	100	100	100	100	100

SA: Sodium alginate, HPMC: Hydroxypropyl methylcellulose

Table 2: Physical evaluations of gel formulations

Formulations	Appearance	Feel on application	Gelling	pH
F1	Off white color	Smooth	+ + +	6.99
F2	Off white color	Smooth	+ + + +	7.42
F3	Off white color	Smooth	+ +	6.83
F4	Off white color	Smooth	+ + +	6.91
F5	Off white color	Smooth	+ +	6.89
F6	Off white color	Smooth	+ + +	6.95
F7	Off white color	Smooth	+ +	6.80
F8	Off white color	Smooth	+ + +	6.92

Grades were allotted as + + + + Excellent, + + + Good, + + Fair, and +Poor

Assay [10-14]

An amount of the formulated gel equivalent to 5 mg tramadol was weighed and immersed in a 100 ml volumetric flask containing 80 ml of phosphate buffer (pH 7.4). The flask was stoppered and placed in a mechanical shaking water bath set at 37°C for 2 h to allow for complete dissolution of the drug and made up to volume with phosphate buffer. 20 ml aliquot of this solution was withdrawn and placed in 100 ml volumetric flask and the volume made up using distilled water. The ultraviolet (UV) absorbance of the solution was read at 272 nm using phosphate buffer (pH 7.4) as the blank. The tramadol content, in µg/ml, was determined from the absorbance value obtained and read against a standard calibration curve. This content was then calculated as a percentage of the expected concentration of tramadol. The results are mentioned in Table 4.

Table 3: Viscosity and spreadability determination

Formulations	Viscosity (cps)	Spreadability (g)
F2	2750	124.699
F4	2420	120.187
F6	2690	122.670
F8	2540	121.142

Zeta potential

Zeta potential was measured using Zetasizer Nano ZS (Malvern Instruments, Worcestershire, UK). The measurement was performed at 25°C. The results are mentioned in Table 4 and Fig. 14.

In vitro drug diffusion study [10-14]

Arrangement of assembly

- The *in vitro* release of tramadol gel from the prepared formulation through using double end open cylinder and is ready to diffuse from the cellophane membrane.
- The release medium used was phosphate buffer pH 7.4. Cellulose acetate paper was soaked for 2 h in phosphate buffer.

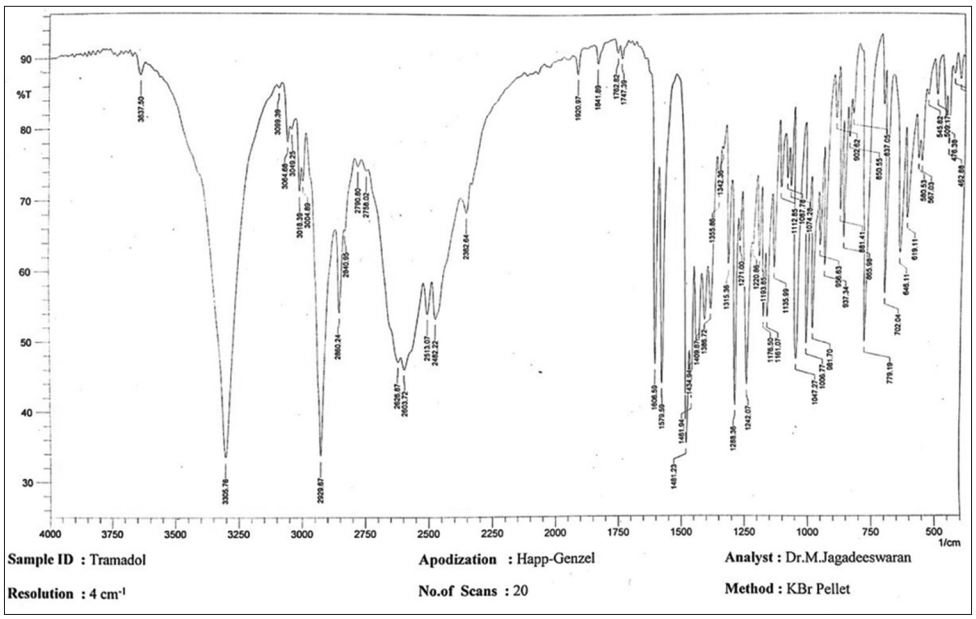

Fig. 3: Infrared spectrum of tramadol

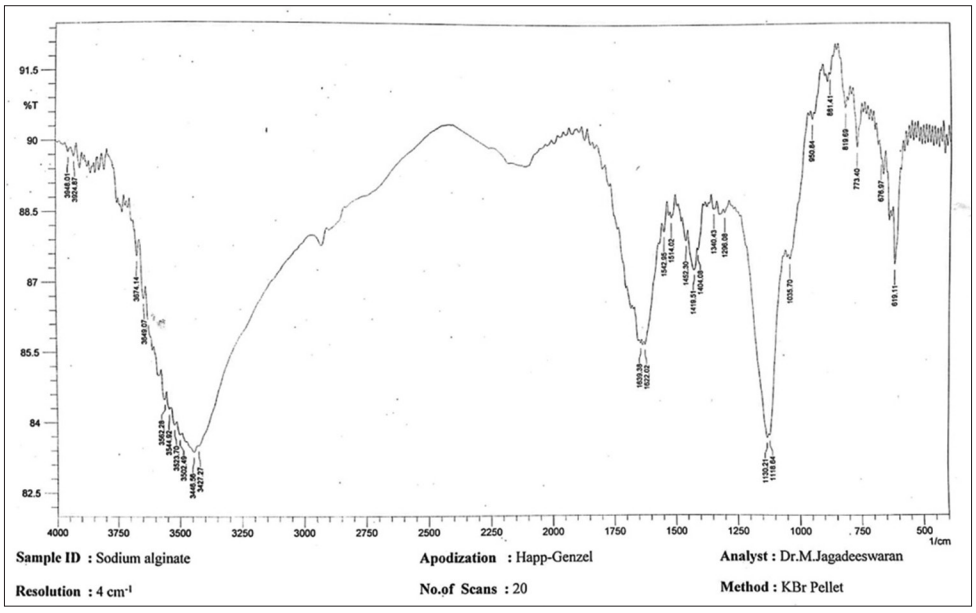

Fig. 4: Infrared spectrum of sodium alginate

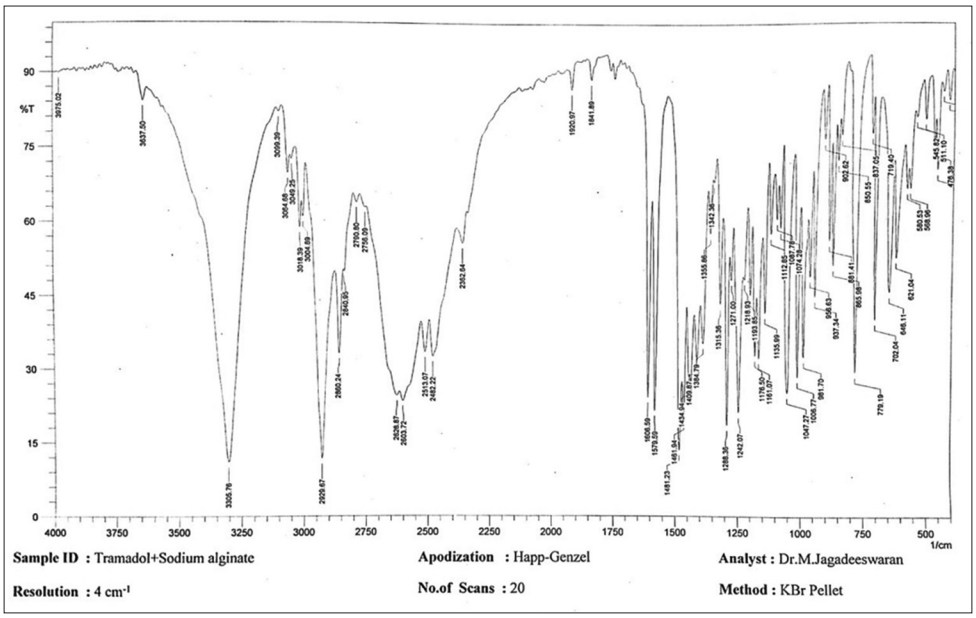

Fig. 5: Infrared spectrum of tramadol + sodium alginate

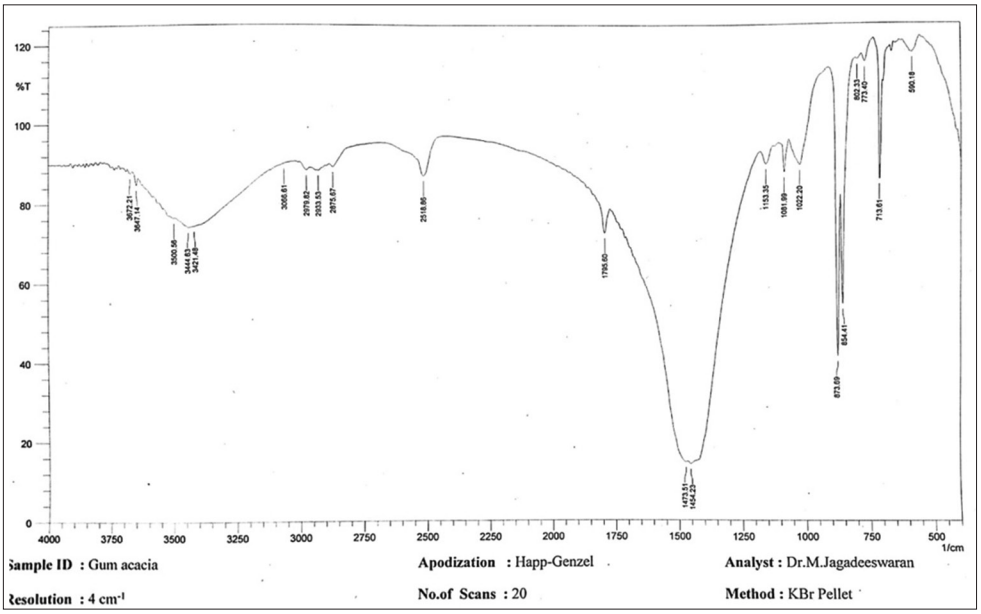

Fig. 6: Infrared spectrum of gum acacia

Table 4: Physicochemical evaluation of optimized gel formulation (F2)

S. No.	Evaluation parameters	Results
1	Extrudability	268.464 g
2	Assay	99.7%
3	Zeta potential	−26.1 Mv
4	Size distribution	262.8 (d.nm)

- 2.5 g of the formulated gel (equivalent to 200 mg tramadol) were weighed onto separate open end glass tube.
- The glass tube was then suspended in 250 ml phosphate buffer pH 7.4 solution maintained at 37±0.5°C. The paddles were rotated at 75 rpm and aliquots of 1 ml withdrawn at 10, 20, 30, 40, and 50 min and 1, 2, and 4 h.
- Aliquots were replaced by equal volumes of the phosphate buffer solution. The absorbance of the aliquots was measured at 272 nm.

Table 5: *In vitro* diffusion study of tramadol gel

Time	F2	F4	F6	F8
10 min	16.74	11.24	12.36	9.29
20 min	25.26	20.82	23.12	19.43
30 min	36.28	28.12	37.28	31.38
40 min	47.86	38.48	41.22	43.92
50 min	53.18	49.16	63.12	52.84
1 h	64.26	63.28	75.64	65.46
2 h	78.97	74.81	81.27	73.89
4 h	89.17	79.72	84.13	80.74

- The cumulative percentage drug release was calculated based on the concentrations obtained for the various gels overtime as a function of the loading doses (equivalent weight of tramadol in 1 g samples of the gel).

The results are mentioned in Table 5.

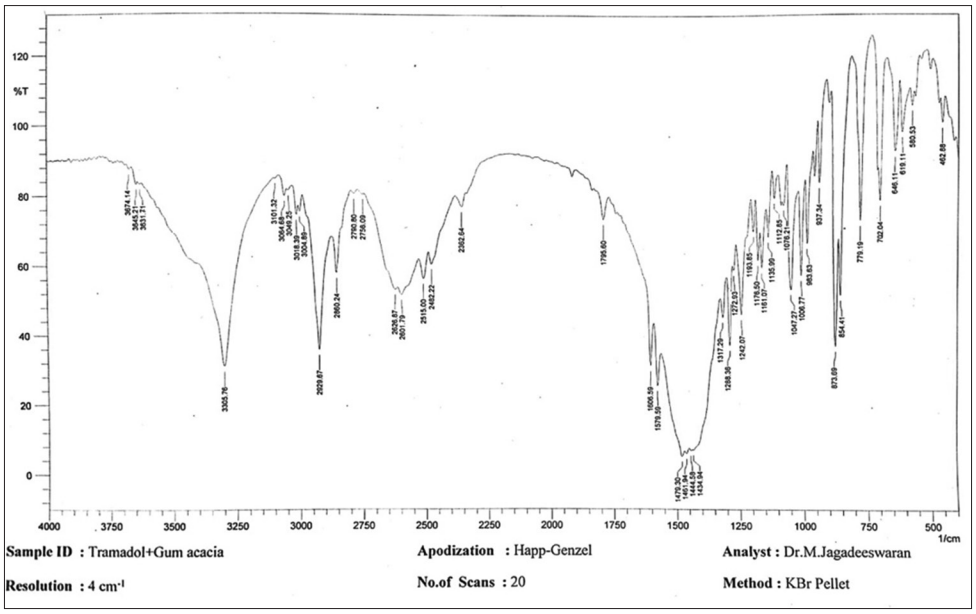

Fig. 7: Infrared spectrum of tramadol + gum acacia

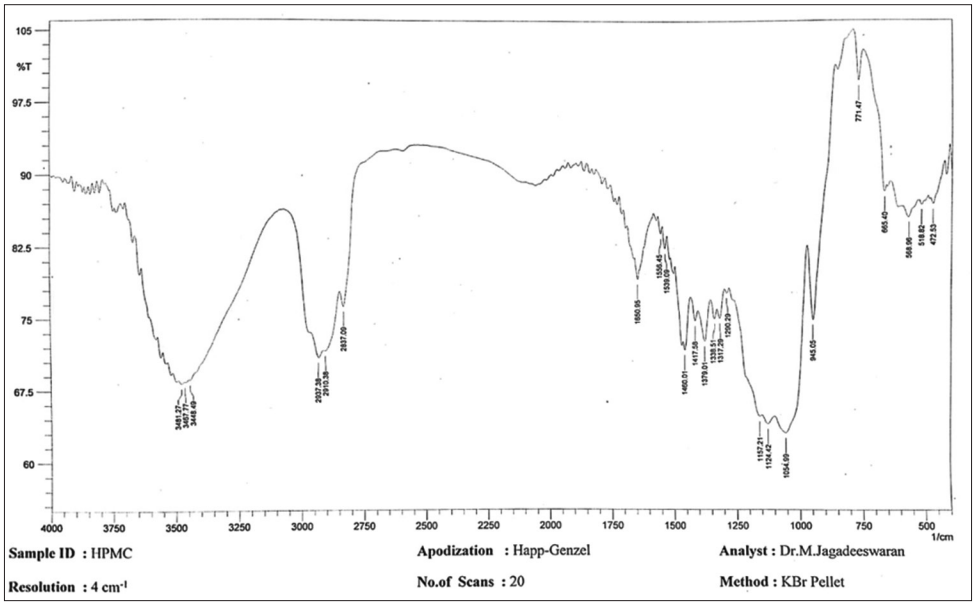

Fig. 8: Infrared spectrum of hydroxypropyl methylcellulose

Table 6: Stability parameter of selected formulation F2

Parameters	Initial	After 1 month 40/75 (°C/RH)
Appearance	Off white color	Off white color
Feel on application	Smooth	Smooth
pH	7.42	7.29
Viscosity	2750 cps	2712 cps
Spreadability	124. 699 g	123.579 g
Extrudability	268. 464 g	270.347 g

Table 7: Standard calibration curve of tramadol

Concentration (μg/ml)	Absorbance
1	0.0371
2	0.0624
3	0.0831
4	0.1252
5	0.1511
6	0.1742
7	0.1935
8	0.2201
9	0.2414
10	0.2679

Stability studies [15-17]

Stability testing of the optimized formulation was performed to predict the quality of drug substance or drug product variation with time under the influence of changing environmental factors such as temperature, humidity and light, enabling recommended storage condition, retest periods, and shelf lives. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The results are mentioned in Table 6.

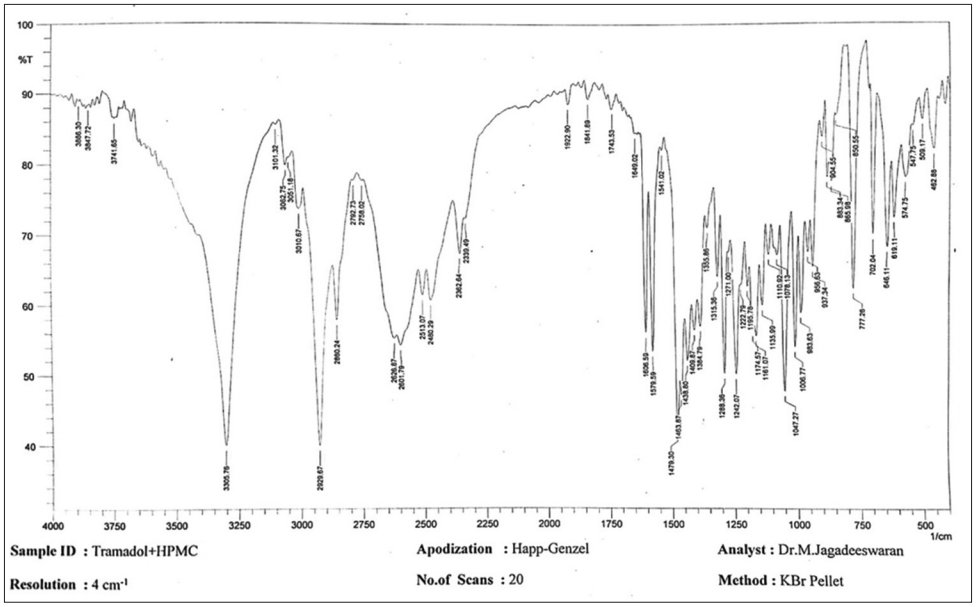

Fig. 9: Infrared spectrum of tramadol + hydroxypropyl methylcellulose

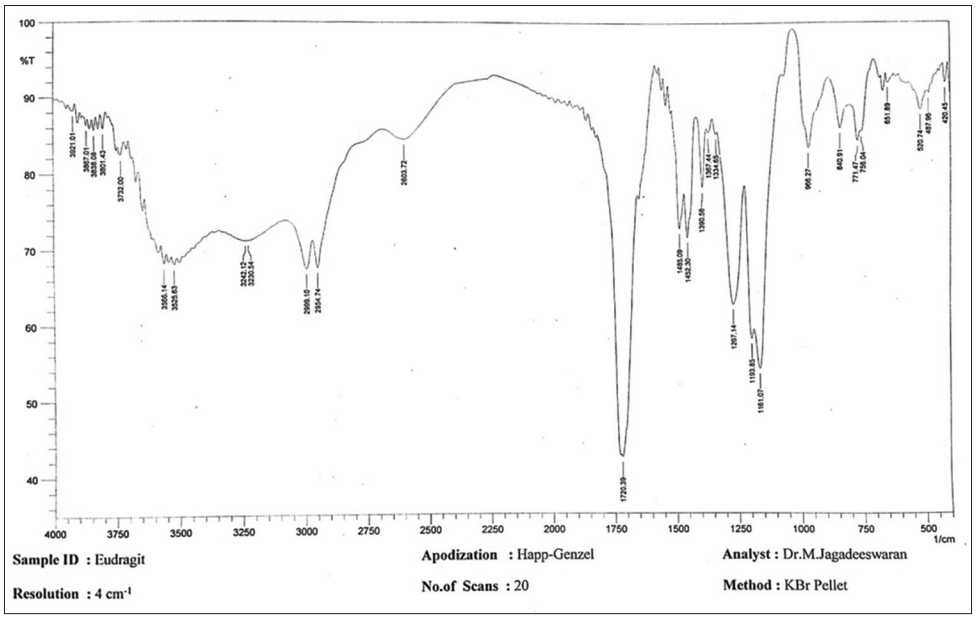

Fig. 10: Infrared spectrum of Eudragit

RESULTS AND DISCUSSION

The present study was carried out to develop gel tramadol to enhance absorption and bioavailability of the drug.

Physicochemical properties

Tramadol is a white crystalline powder with bitter taste, sparingly soluble in water (1151 mg/L at 25°C) and freely soluble in alcohol and acid. Tramadol exhibits crystal polymorphism. Tramadol melting point was determined to be 180–181°C which was in compliance with the official value.

UV spectroscopic study

Tramadol in 0.1 N phosphate buffer solutions showed maximum absorbance (λ_{max}) of 272 nm and calibration curve exhibiting good linearity that obeys Beer–Lambert's law. The Beer–Lambert's concentration range was studied with a concentration range of 1–10 µg/ml at 272 nm showed coefficient of correlation value of 0.994. The slope and intercept values were 0.026 and 0.009, respectively. The data are shown in Table 7 and Figs. 1 and 2.

Drug and excipient interaction studies

Drug-excipient interaction of tramadol and the polymers (SA, *Acacia*, Eudragit, and HPMC) studied in drug-excipient physical mixture showed no significant changes in the peak (at 163.88, 163.01, and 163.33°C, respectively) of the drug in these mixtures, which refers that there was no interaction. The results are mentioned in Figs. 3-12.

The nitroglycerin (NTG)-magnesium stearate mixture was subjected to infrared (IR) studies and its spectrum was compared with the IR spectra of NTG. Characteristic bands of NTG were observed at 1647 cm^{-1} (–C=O), 1713 cm^{-1} (–COOH), 2862–3096 cm^{-1} (–CH2-cycloalkane), and 3296 cm^{-1} (–NH stretching). However, the IR spectrum of the NTG-magnesium stearate mixture showed the respective characteristic bands of NTG at 1647, 1712, 2850–2953 (–CH2-cycloalkane), and 3300

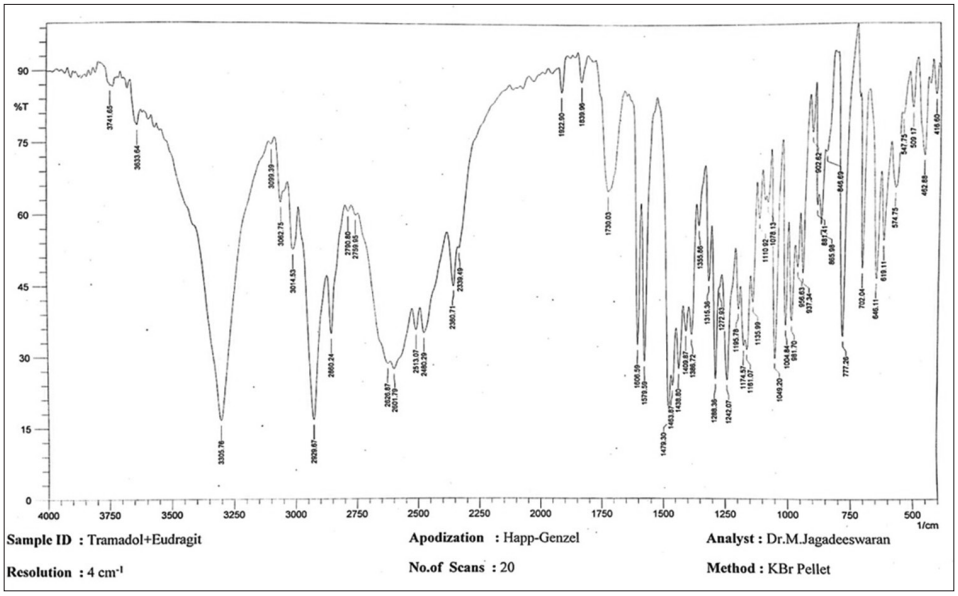

Fig. 11: Infrared spectrum of tramadol + Eudragit

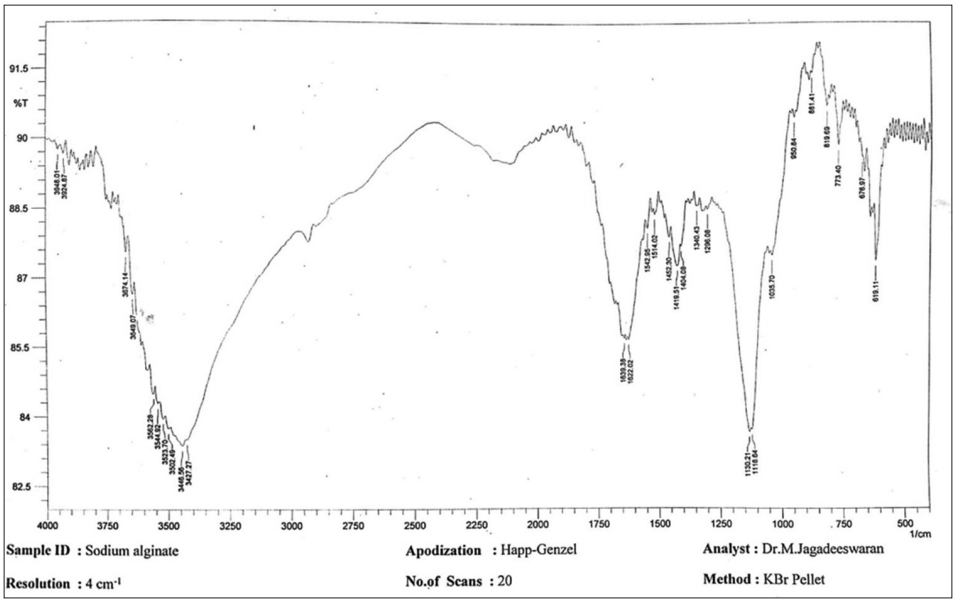

Fig. 12: Infrared spectrum of optimized formulation of F2

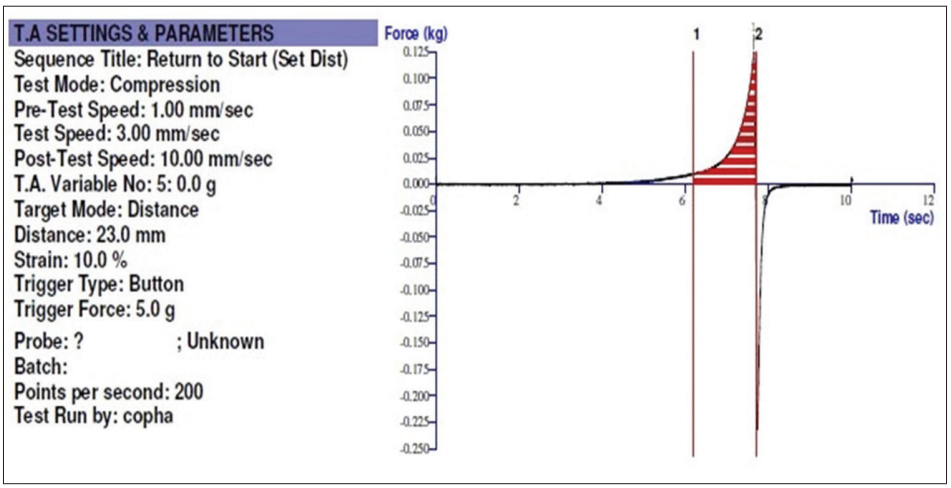

Fig. 13: Graph of spreadability

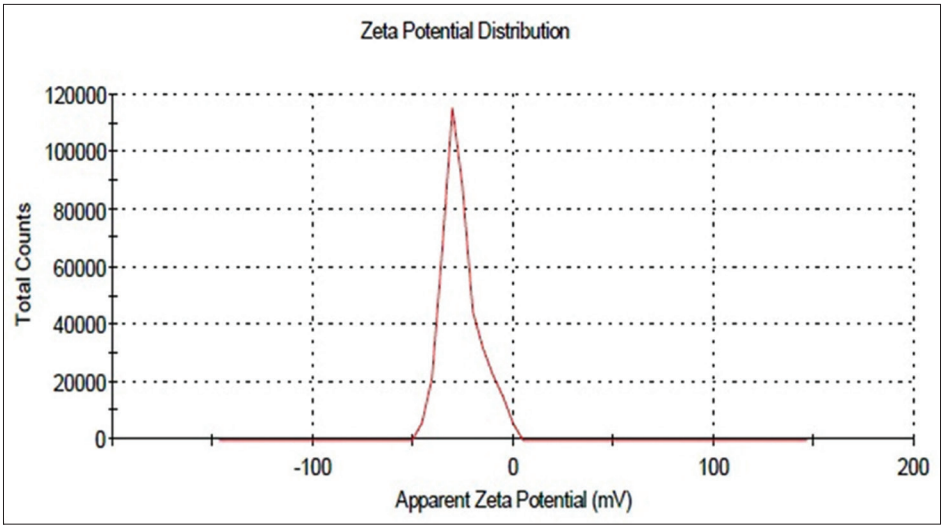

Fig. 14: Graph of zeta potential

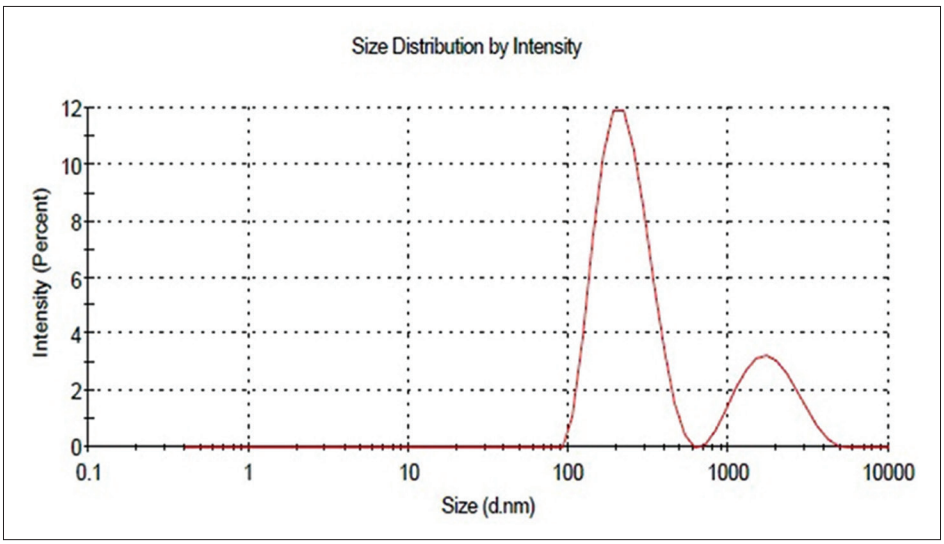

Fig. 15: Graph of size distribution

cm^{-1}. The results confirmed that there was no chemical interaction between NTG and magnesium stearate.

Evaluation of microemulsion gel formulations F1-F8

Different methods were selected for the preparation of gel. These depend on the nature of polymer used (Discussed in methodology). Different concentrations of polymers were tried for the formulation of tramadol gel. The concentration of SA, *Acacia*, HPMC, and Eudragit was taken 1 g and 2 g.

Physical evaluation of gel formulations

Evaluations such as physical appearance, texture of the gel, uniformity of the gel, and pH values studied results are mentioned in Table 2 and Fig. 15.

Physicochemical evaluation

Evaluations of the physicochemical properties for the selected formulation (F2, F4, F6, and F8) and optimized formulation (F2) are given in Tables 3 and 4.

Cumulative percentage drug release of microemulsion gel formulations

The cumulative percentage drug release from the selected formulations (F2, F4, F6, and F8) was studied exhibited the results as given in Table 5.

Stability study

Stability study was carried out for the optimized formulation according to ICH guidelines at 40°C/75% RH for 1 month. The results showed that there was no significant change in physical and chemical parameter of the gel; hence, the formulation (F2) was found to be stable (Table 6).

CONCLUSION

The present study was aimed to formulate and evaluate the microemulsion gel formulations of tramadol using various polymeric carriers. Based on the preformulation studies, further course of formulation and evaluation of optimized formulation of the drug were carried out with using different polymers and selected excipients.

The microemulsion gels were evaluated for physical characterizations (pH, appearance, spreadability, extrudability, and viscosity) and *in vitro* diffusion and optimized formulation suitable for better delivery of the drug was identified and studied further. The initial evaluation studies were indicative that the F2 formulation exhibited optimal results for the study parameters evaluated and showed to comply with the pharmacopoeial standard references. Further, the data from physical, physiochemical, and *in vitro* diffusion studies for the microemulsion gel formulation F2 directed in concluding that the F2 formulation has a better delivery capacity and can also be a promising dosage form

for topical route of administration of the tramadol. Stability study was conducted of F2 stored at 40°C/75% RH for 1 month. Gels were evaluated for appearance, feel on application, pH, viscosity, assay, and *in vitro* diffusion profile after 1 month. It concluded that formulation F2 was stable. From the above results, it concluded that tramadol gel formulation containing SA 3% can be taken as an ideal formulation.

AUTHORS' CONTRIBUTIONS

M Prabakaran, C Pasupathi, LR Peely, and B. Pooja contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. Dr. V Muruganantham contributed to the final version of the manuscript and supervised the project.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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