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Formulation and Characterization of Tramadol Emulgel

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Abstract: Topical drug delivery system (TDDS) facilitates the passage of therapeutic quantities of drug substance through the skin and into the general circulation for their systemic effects. Although having plenty of advantages over other routes of administration topical drug delivery system is having certain limitations including hydrophilic drugs cannot easily penetrate across skin, to overcome this problem drug made into sufficient lipophilic or lipophilic drugs are sued along with certain penetration enhancers which help to achieve desired results. Tramadol is a narcotic analgesic proposed for moderate to severe pain. It may be habituating. Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. On this contest, emulgel was formulated using carbopol 934 and HPMC K15M, liquid paraffin as oil phase, emulsifying agents like tween 20 and span 20 and propylene glycol as permeation enhancers. On basis of quality of emulgel produces total eight formulations F1 to F8 were selected. They were evaluated for physical appearance, pH, rheological study, drug content and in-vitro drug permeation study, FTIR and globule size determination. The skin irritation test was performed on rabbit's skin using best formulation F7. Thus, the formulated emulgel had a distinct advantage over existing conventional dosage form in that the drug permeation was found to be rapid across the skin and hence the increased therapeutic response by bypassing 1st pass metabolism and with no gastro intestinal bleeding and also patient compliance.
Keywords: Emulsion, Gel, Transdemal Drug Delivery Systems, Tramadol, *In-Vitro* Drug Permeation Study.

INTRODUCTION

Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied lotions, creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption of the drugs through the skin, which lead to the idea of TDDS. In a broad sense, the term transdermal delivery system includes all topically administered drug formulations intended to deliver the active ingredient into the general circulation. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation [1, 2].

Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. The novel Transdermal drug delivery is defined as self-contained, discrete dosage forms which when applied to the intact skin, deliver the drug through the skin at controlled rate to the systemic circulation [3, 4].

EMULGEL

When gels and emulsions are used in combined form the dosage forms are referred as emulgels. In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase [5, 6]. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance [7, 8].

Rationale of Emulgel as a Topical Drug Delivery System

Numbers of medicated products are applied to the skin or mucous membrane that either enhance or restore a fundamental function of skin or pharmacologically alter an action in the underlined tissues. Such products are referred as topical or dermatological products. Many widely used topical agents like ointments, creams lotions have many disadvantages. They have very sticky causing uneasiness to the patient when applied [9-15]. Moreover they also have lesser spreading coefficient and need to apply with rubbing. And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelating substance present. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels [16-20].

Advantages of Emulgel as a drug delivery System

1. Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions: Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

2. Better stability: Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base [20-23].

3. Better loading capacity: Other novel approaches like niosomes and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.

4. Production feasibility and low preparation cost: Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.

5. No intensive sonication: Production of vesicular molecules need intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.

6. Controlled release: Emulgels can be used to prolong the effect of drugs having shorter t1/2 [23-28].

MARTERIALS AND METHODS

Tramadol API is the gifted sample from KP labs, HPMC K15M, Carbopol 934 ,Light liquid paraffin, Span 20, Propylene glycol, Ethanol, Methyl paraben, Propyl paraben , Glutaraldehyde, Tween 20 are procured from sree srinivasa scientifics.

Formulation of Tramadol Emulgel

1) Gel preparation

- ✓ The composition of Tramadol emulgel 10% w/w was shown in the formulation code table. The carbopol gel was prepared by dispersing 1.25g of carbopol 934 in purified water with constant stirring at a moderate speed and soaked overnight. The gel was obtained by neutralizing the dispersion with tri ethanol amine and pH is adjusted to 6.5 and purified water was added to adjust the weight to 50g.
- ✓ In case of HPMC K15M gel was prepared by dispersing HPMC K15M in hot purified water (80^0C) and the dispersion was cooled, then weight was adjusted to 50g with purified water.

2) Emulsion preparation

- ✓ The oil phase of emulsion was prepared by dissolving span 20 in light liquid paraffin and heated upto 70^0-80^0C.
- ✓ Aqueous phase was prepared by dissolving tween 20 and drug in 5ml ethanol and heated upto 70^0-80^0C.
- ✓ Methylparaben, propylparaben were mixed in propylene glycol and glutaraldehyde and this added this mixture was dissolved in aqueous phase.
- ✓ Then oil phase was mixed slowly with aqueous phase and final volume is made with purified water.

3) Emulgel preparation

- ✓ The obtained emulsion was mixed with the gel and weight was adjusted to 50g with water and subjected to homogenization for 45 minutes to get Tramadol emulgel 10% w/w.

Formulation design of tramadol emulgel preparation

Table 1: Final formulation code

Ingredients (% w/w)	F1	F2	F3	F4	F5	F6	F7	F8
Tramadol	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
HPMC K15M	0.5	0.5	0.5	0.5	-	-	-	-
Carbopol 934	-	-	-	-	0.25	0.25	0.25	0.25
Light liquid paraffin	2.5	3.75	2.5	3.75	2.5	3.75	2.5	3.75
Tween 20	0.3	0.3	0.5	0.5	0.3	0.3	0.5	0.5
Span 20	0.45	0.45	0.75	0.75	0.45	0.45	0.75	0.75
Propylene glycol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethanol	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Methylparaben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Propylparaben	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
glutaraldehyde	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Purified water (q.s)	50	50	50	50	50	50	50	50

Pre-formulation studies

FTIR spectroscopy

Preformulation studies were carried out to study the compatibility of pure drug Tramadol with polymers Carbopol 934 and HPMC K15M prior to the preparation of Emulgel. The individual IR spectra of pure drug and polymers as well as the combination spectra of drug and polymers were shown in the fig.5, 6 and compared. It indicates that there was no change in the peak values of the drug in the physical mixture thus providing that drug and polymer were compatible with each other.

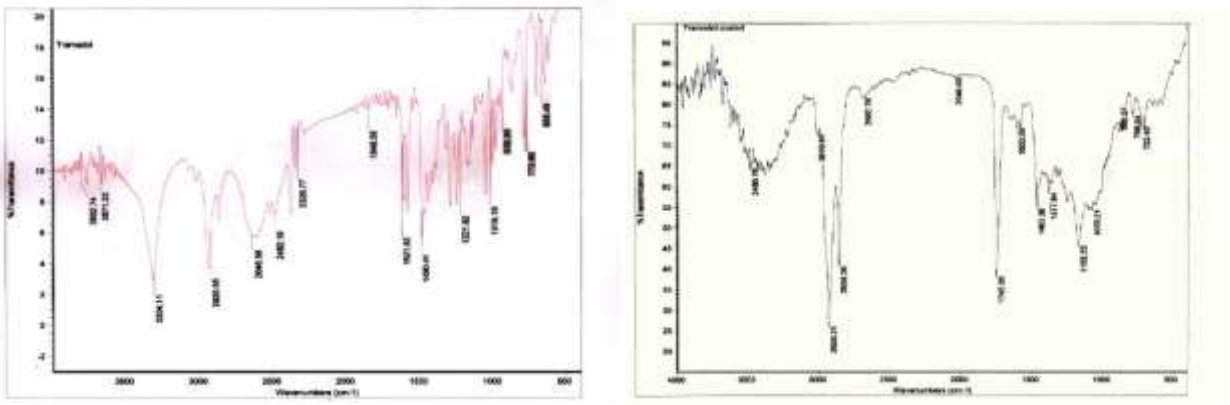

Fig-1 : FTIR Image of Pure Tramadol HCl and FTIR Image of Formulation F7

Evaluation parameters

Physical appearance: All the formulations were evaluated for color, homogeneity and consistency. The physical appearance of all the formulations was found to be, creamy white, homogenous and consistent.

Table 2: Physical appearance data

Formulation code	Color	Homogeneity	Consistency	Phase separation
F1	Creamy white	Homogenous	Smooth	-
F2	Creamy white	Homogenous	Smooth	-
F3	Creamy white	Homogenous	Smooth	-
F4	Creamy white	Homogenous	Smooth	-
F5	Creamy white	Homogenous	Smooth	-
F6	Creamy white	Homogenous	Smooth	-
F7	Creamy white	Homogenous	Smooth	-
F8	Creamy white	Homogenous	Smooth	-

pH determination: pH evaluation of the topical formulation is more important as it may cause irritation to the skin if varied from normal skin pH conditions. Furthermore the polymer like carbopol gives consistency if the pH is between 5-6 so all the formulations were evaluated for the pH and pH was found to between 5-6 for all the formulations.

Rheological studies: The viscosities of all the formulations were measured using Brookfield viscometer at 10 rpm and values were represented in table 3and fig 2, it was found that all the formulations were followed shear thinning effect with thixotropic property. It was observed that the viscosity of the formulation increases with increase in emulsion-gel ratio.

Drug content determination: Drug content of all the formulations were carried out as per procedure stated in the methodology section. Drug content of all the formulations was found to be in the range 68.96%±3.1 - 83.12%±2.3 as indicates in the table 3.

Table 3: pH determination, rheological studies, drug content

S.no	Formulation code	pH	Viscosity (cp)	Drug content
1	F1	5.31	3600	71.74±3.9
2	F2	5.22	3300	70.27±2.3
3	F3	5.47	3900	71.50±3.2
4	F4	5.50	3650	69.50±1.9
5	F5	5.48	4300	79.43±2.1
6	F6	5.32	3100	72.51±1.9
7	F7	5.61	4800	83.12±2.3
8	F8	5.56	3100	68.96±3.1

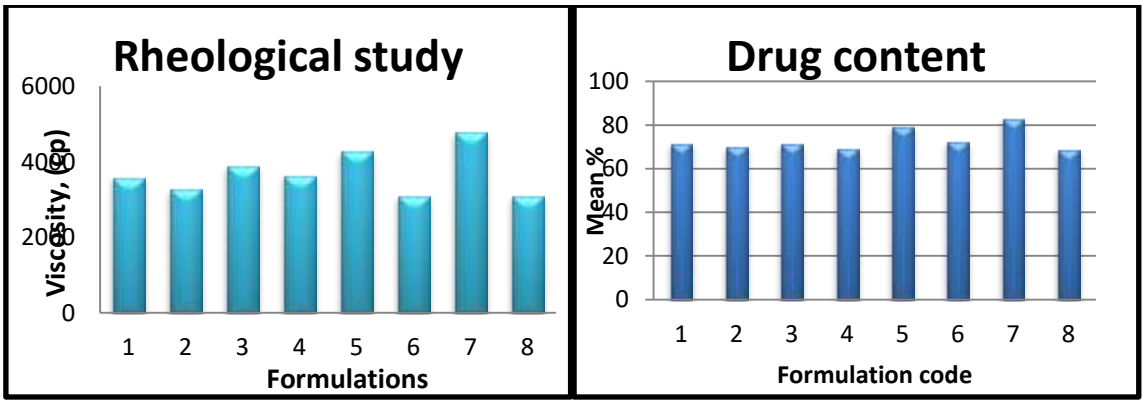

Fig-2: Rheogram for formulations F1 to F8 and Graph for drug content (F1 to F8)

***In-Vitro* Drug permeation data**

The in-vitro permeation studies of all the formulations were carried out using Franz diffusion cell as described in the methodology section using egg membrane as a permeation membrane for the study. The comparative cumulative percentage drug permeation data of all the formulations F1 to F8 were shown in the table 4 and plots in the fig. 3 respectively.

The optimized formulation F7 containing maximum concentration of span 20 and tween 20 showed highest % drug permeation at the end of 12 hrs and hence this formulation was selected as optimized formulation for further study. It was revealed that span 20 and tween 20 concentrations were having positive effect on the drug permeation through the membrane.

Table 4: % cumulative drug release data for F1 to F8

Time (hrs)	% Cumulative drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	**0**	0
1	6.17	5.56	4.10	5.18	7.01	3.94	**7.80**	4.76
2	10.82	8.61	7.25	7.93	13.42	6.15	**16.51**	7.51
3	17.54	13.25	10.93	12.45	25.08	9.37	**29.72**	11.05
4	25.26	19.13	12.28	17.62	32.75	11.20	**38.64**	16.54
5	32.47	26.58	23.68	26.01	38.62	22.46	**47.38**	25.93
6	40.31	34.40	28.41	32.85	45.27	25.34	**55.13**	30.24
7	49.07	42.79	33.06	42.56	56.91	29.81	**63.02**	38.85
8	58.46	49.83	37.12	46.42	62.84	34.65	**70.61**	40.69
9	62.02	52.32	42.62	49.83	68.56	40.65	**77.54**	45.65
10	68.32	59.82	49.53	52.64	76.85	46.74	**82.25**	52.25
11	73.65	63.25	53.62	57.45	80.25	51.05	**86.45**	55.48
12	75.86	69.53	59.31	61.26	84.32	57.29	**88.47**	60.12

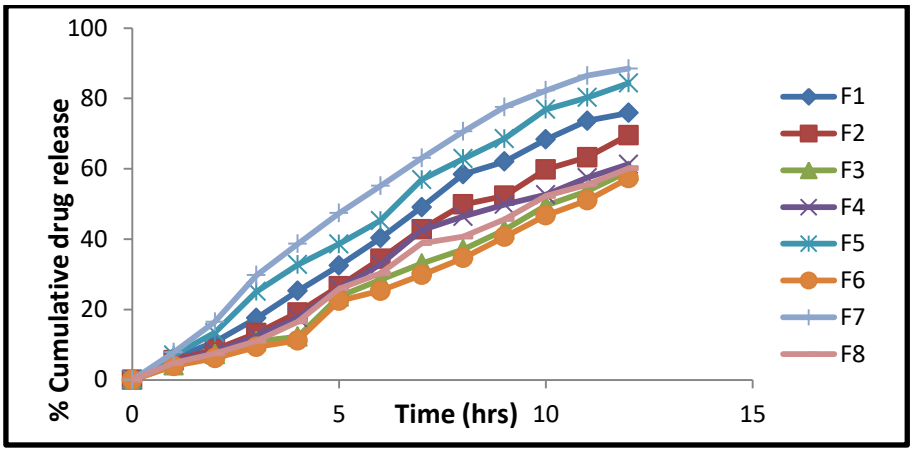

Fig-3: In vitro drug permeation graph (F1 to F8)

Drug release kinetics: The drug release kinetics was studied with invitro drug permeation data for all the formulations F1 to F8 and results were stated in the table 13, the best fit model for selected formulation F7 were found to be Zero order and Peppas with non-fickian diffusion with highest $\mathbf{r^2}$ **0.990** with **n** value **0.081** respectively.

Table 5: Drug release kinetics data

Formulation code	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	N
F7	0.971	0.369	0.920	0.991	0.081

Globule size determination: The globule size of the emulsion in the gel matrix was found to be 64.24±23.69 µm for formulation F7.

Fig-4: Globule size for best formulation (F7)

Table 6: globule size data

No. of globules	Globule size (µm)
	F7
1	33.13±6.92
3	64.24±23.69
1	32.44±6.19
3	33.43±11.02
2	47.20±9.73
2	42.66±13.04
2	32.68±8.02
4	35.41±11.51
2	29.40±8.43
2	32.90±8.40
2	28.23±7.14
1	33.53±8.45

Fig- 5: Final product of Emulgel (formulation F7)

Skin Irritation Test: The skin irritation test was performed using best formulation F7 in order to observe the sensitivity for 24hrs and there was no erythma and edema seen on rabbit skin

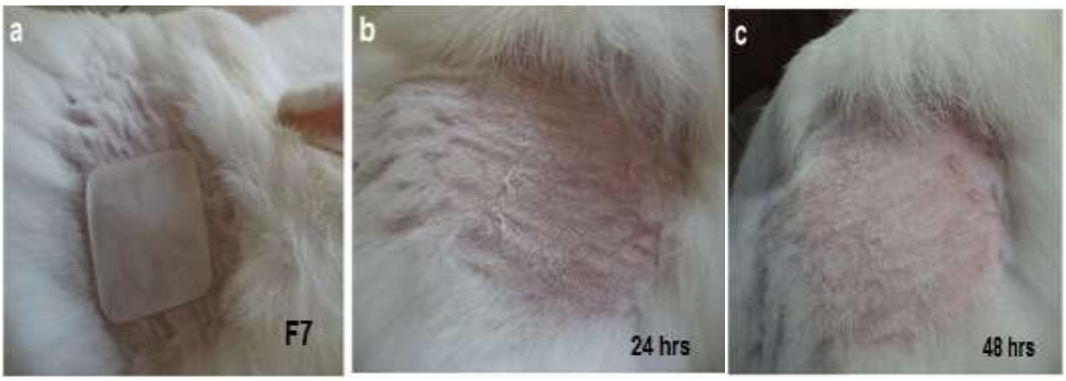

Fig-6: Rabbit (a), Rabbit (b), 24hrs, Rabbit (c), 48hrs (optimized formulation)

Table 7: Sensitivity test data

Rabbit	Erythma		Edema	
	24 hrs	48 hrs	24 hrs	48 hrs
a	0	0	0	0
b	0	0	0	0
c	0	0	0	0

Stability studies: Stability studies are conducted for optimized formulation at 5^0 ,25^0,60% RH,30^0C /65% RH for a period of three months . samples were withdrawn at 15 days time intervals and evaluated for physical appearance, PH , Rheological properties and drug content, drug release. Stability studies shown no changes in the product after 3 months, it is considered as a stable product.

Table 8: Stability studies

S.No	Observations	Before Stability Testing	After 3 Months
1	Appearance	White cream	White cream
2	PH	5.61	5.61
3	Viscosity (at 10 rpm)	4800	4800
4	Drug content	83.12	83.12
5	*In vitro* studies	88.47%	88.47%

CONCLUSIONS

- A narcotic analgesic proposed for moderate to severe pain. It may be habituating.
- Tramadol maximum wavelength is determined by UV-Visible spectrophotometer using 6.8 pH phosphate buffer and was detected to be 271nm
- FTIR studies of HPMC K15M, Carbopol 934, Tramadol drug and final formulastion was seen and peaks found to be within the range with no significant deviation. Hence can be concluded that there are no interactions between drug and polymers.

- ❖ Tramadol emulgel was formulated using light liquid paraffin as oil phase and emulsifying agent's tween 20 and span 20 for emulsion and incorporated into gel using HPMC K15M and carbopol 934 polymers in different ratios.
- ❖ The optimized formulation F7 showed a shear thinning with thixotropic property with better spreadability, viscosity and in-vitro permeability compared to other formulations.
- ❖ In the study it was observed that the concentrations of tween20, span 20 and light liquid paraffin has shown effect on extrudability, viscosity, spreadability and in-vitro drug permeability. Increased amount of liquid paraffin showed suppress activity of tween 20 and span 20.
- ❖ The steady state in-vitro drug permeation was found to be better with optimized formulation and follows zero order release and follows peppas non-fickian diffusion kinetics.
- ❖ The surface morphology of the optimized formulation was observed by Scanning Electron Microscopic study
- ❖ The skin irritation test of the optimized formulation was seen on rabbits for 24hrs and no reaction was found.
- ❖ Thus Tramadol emulgel which could increase the drug permeability across the skin and fast release of the drug could be successfully achieved.

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