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Formulation and In-vitro Evaluation of Tramadol Hydrochloride Gel

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ABSTRACT

Tramadol is an opioid analgesic. The most common side effects with opioid analgesics are nausea and vomiting (particularly at the start of treatment), constipation, and dry mouth. Opioids can also cause drowsiness and confusion. Due to the adverse drug reactions associated with oral formulations opioid analgesics can be administered by topical route. Gelling agents like xanthan gum, carbopol are used in the formulation of Tramadol hydrochloride gel. In vitro permeability studies using a semipermeable membrane was carried out to find the optimized formulation

Keywords: Tramadol hydrochloride, Gel, Xanthan gum, carbopol, Permeabilty study

I. INTRODUCTION

Gels contain more amount of liquid and selection of suitable gelling agents play a key role in maintaining the consistency of gel. Gelling agents that are generally used in the formulation of gels are polymers and gums. Gelling agents should be safe, biocompatible and inert with other ingredients. Rheological properties, Syneresis and Swelling properties of the gelling agent should be good. Carbomers, cellulose derivatives, and semi synthetic cellulose derivatives are few examples which can be used as gelling agents.

Gels are prepared from the liquid phase which is thickened by other components. Gels contain liquid phase which allows free diffusion of molecules through the polymer and the release rate of drug is almost equivalent to that of simple solution.

Gels contain a covalent polymer network, e.g., a network formed by cross linking polymer chains or by nonlinear polymerization, a polymer network formed through the physical aggregation of polymer chains, caused by hydrogen bonds, crystallization, helix formation, complexation, etc., that results in regions of local order acting as the network junction points. The resulting swollen network may be termed a "thermoreversible gel" if the regions of local order are thermally reversible, a polymer network formed through glassy junction points, e.g., one based on block copolymers. If the junction points are thermally reversible glassy domains, the resulting swollen network may also be termed a thermoreversible gel, lamellar structures including mesophases e.g., soap gels, phospholipids, and clays, particulate disordered structures, e.g., a flocculent precipitate usually consisting of particles with large geometrical anisotropy.

These gels can be classified as
Hydrogels- Hydrogels (V. R. Patel 1996) may also show a swelling behavior dependent on the external environment the factors affecting the swelling behaviour of physiologically-responsive hydrogels include pH, ionic strength, temperature and electromagnetic radiation (Peppas 1991).

Organogels-These are solid material composed of a liquid organic phase entrapped in a three dimensionally cross-linked network.

Xerogels-Xerogel is a solid formed from a gel by drying phenomenon.These are highly porous and low density material.

II. METHODS AND MATERIAL

Materials that were used in the preparation of Tramadaol hydrochloride gel are Tramadol hydrochloride, Propylene glycol, Xanthan gum, Methyl Paraben, Triethanolamine (TEA), Carbomer (Carbopol 940).

A. **Estimation of Tramadol hydrochloride using UV Spectrophotometry**

1) Preparation of Stock Solution: Suitable amount of Tramadol hydrochloride was weighed and dissolved in little amount of distilled water. Finally using distilled water it is made upto the required volume.

2) Preparation of standard solutions: Serial dilutions such as 20, 40, 60, 80, 100µg/ml are prepared from the stock solution. Then the absorbance was measured at 271 nm using UV-spectrophotometry.

B. **Formulation of Tramadol hydrochloride Gel**

1) Formulation of Tramadol hydrochloride gel using Xanthan gum: Tramadol hydrochloride (1g) was dissolved in 95% methanol (30g) while stirring. On the other hand, propylene glycol (10g), 2%, 3% and 4% aqueous solution (37 g) of Xanthan gum and distilled water (20g) were mixed uniformly by stirring; Triethanolamine (1.5g) was added to the mixture while continuing the stirring. To the gel the alcoholic solution of Tramadol hydrochloride previously prepared was added and the whole was adjusted to 100g by further adding distilled water. Gels prepared using 2%, 3% and 4% Xanthan gum were named as F1, F2 and F3 respectively.

Table 1. composition and concentration of tramadol hydrochloride gel prepared using xanthan gum

Formulation code	F1	F2	F3
Tramadol hcl(g)	1	1	1
Methanol (g)	30	30	30
Xanthan gum (g)	2	3	4
Xanthan gum gel (g)	37	37	37
Propylene glycol (g)	10	10	10
TEA (g)	1.5	1.5	1.5
Distilled water (g)	Q.S to 100 g	Q.S to 100 g	Q.S to 100 g

2) Formulation of Tramadol hydrochloride gel using Carbopol 940: Tramadol Hcl (1g) was dissolved in 95% methanol (30g) while stirring. On the other hand, propylene glycol (10g), 2%, 3% and 4% aqueous solution (37 g) of carbomers (carbopol 940) and distilled water (20g) were mixed uniformly by stirring; Triethanolamine (1.5g) was added to the mixture while continuing the stirring. To the gel thus prepared, the alcoholic solution of Tramadol Hcl previously prepared was added and the whole was adjusted to 100g by further adding distilled water. Gels prepared using 2%, 3% and 4% carbopol were named as F4, F5, and F6 respectively.

Table 2. Composition and concentration of Tramadol hydrochloride gel prepared using carbopol 940

Formulation code	F4	F5	F6
Tramadol hcl(g)	1	1	1
Methanol (g)	30	30	30
Carbopol 940 (g)	2	3	4
Carbopol 940 gel (g)	37	37	37

Propylene glycol (g)	10	10	10
TEA (g)	1.5	1.5	1.5
Distilled water (g)	Q.S to 100 g	Q.S to 100 g	Q.S to 100 g

C. **Evaluation of gel containing Tramadol hcl**

1) pH: The pH of the various gel formulations was determined by using digital pH meter.

2) Appearance: The prepared gel bases were inspected visually for clarity, colour and presence of any particles.

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

4) *In Vitro* Permeability studies of Tramadol gels: Distilled water was used as a receptor medium for *in vitro* release study. The gel sample was applied on the cellophane membrane (semi permeable membrane) and then tied to a funnel. Inner surface of the semi permeable membrane contains 1 gram of gel and the outer surface is in continuous contact with the receptor compartment for diffusion of drug. The receptor compartment containing 400ml of distilled water was stirred using magnetic stirrer. The samples at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The fluids withdrawn were spectrophotometrically estimated at 271 nm against their respective blank.

III. RESULTS AND DISCUSSION

A. Estimation of Tramadol Hcl using UV Spectrophotometer

Tramadol Hcl was estimated using distilled water and measured at 271nm using UV Spectrophotometer. It obeyed Beer's law in the range of 20-100 µg/ml. Slope was found to be 0.0051 and the correlation coefficient was found to be 0.999 and the results were given in table 3.

Table 3. Estimation of Tramadol Hcl UV Spectrophotometer

S.No	Concentration (µg/ml)	Absorbance at 271nm
1	0	0.000
2	20	0.095
3	40	0.205
4	60	0.302
5	80	0.402
6	100	0.510

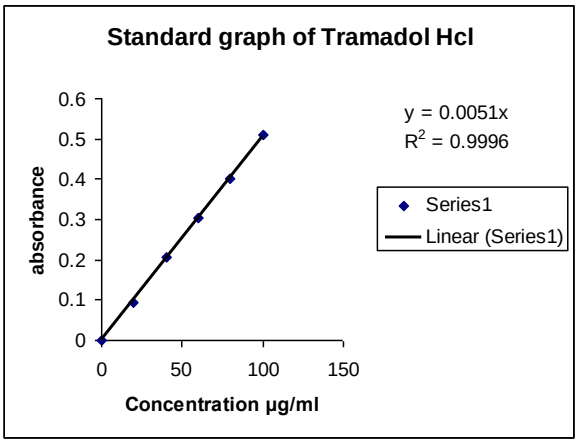

Figure 1. Estimation of Tramadol Hcl, measured at 271 nm using UV Spectrophotometer

B. In Vitro Permeability studies of Tramadol hcl gel

In Vitro Permeability studies of formulated Tramadol gels were carried out using cellophane sheet as a semi permeable membrane. Samples withdrawn at predetermined intervals were estimated at 271nm and the drug release from the prepared gels is estimated. Results for the percentage of drug released from the gels made of Xanthan gum and carbopol 940 were given in table 4 and table 5 respectively and time *vs* percentage release was plotted and given in figure 2 and figure3 respectively.

Table 4. Permeability study of Tramadol Hcl gel prepared using Xanthan gum

S.No	Time interval(minutes)	Percentage of Drug Released		
		F1	F2	F3
1	10	37.3	30.7	32.8
2	20	60.7	36.9	41.3
3	30	68.2	43.7	50.4
4	40	73.6	48.5	60.1
5	50	77.8	55.3	67.9
6	60	84.7	67.6	75.3
7	70	91.7	87.4	83.5
8	80	99	92.2	90.8

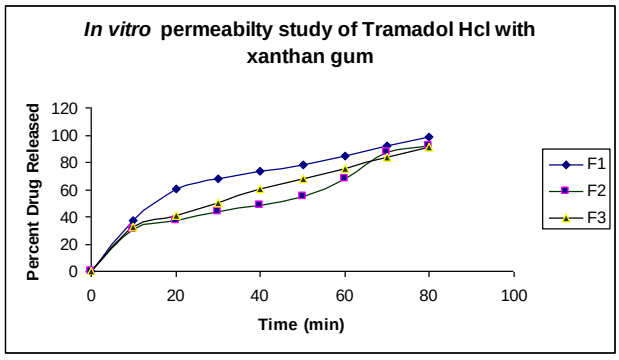

Figure 2. Permeability study of Tramadol Hcl gel prepared using Xanthan gum

Table 5. Permeability study of Tramadol Hcl gel prepared using carbopol 940

S.No	Time interval(minutes)	Percentage of Drug Released		
		F4	F5	F6
1	10	18.22	34.4	35.6
2	20	36.18	62.2	51.2
3	30	69.07	75.3	56.4
4	40	98.8	84.3	81.4

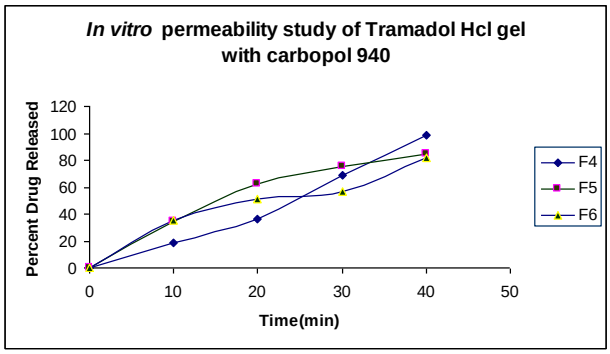

Figure 3. Permeability study of Tramadol Hcl gel prepared using Carbopol 940

Tramadol Hcl was very soluble in methanol, soluble in ethanol, and water. All the Tramadol Hcl gels formulations showed no clogging and lumps which indicate good texture of system. The pH of gels was around in the range of 5.5-7.5. The data obtained from drug content, pH, spreadability test, *in vitro* drug diffusion of various formulations was compared which gave satisfactory results. All the developed gels showed good homogeneity with absence of lumps. *In vitro* permeability studies show that permeation studies of F4 formulation have good permeability when compared with other formulations. Release of Tramadol Hcl was faster from F4 formulation and it also showed good homogeneity. The gel has wider prospects to be used as a topical drug delivery system.

IV. CONCLUSION

Tramadol Hcl gels prepared using Carbopol 940 produced better consistency as compared to gels prepared using Xanthan gum. Gels prepared using carbopol 940 have faster release of drug when compared with other formulations. Formulation F4 can be selected as optimized formulation. The optimized batch produces the gel with good

homogeneity, appearance and fast release of drug; hence it can be further developed for scale-up to industrial production. Development of gels which delivers the drug quickly would be of great use to human race. This work can be extended for the preparation of gels using smart polymers (M. Amiji, 1997) which are sensitive to pH (A. M. Lowman, 1999), temperature etc and make them to deliver the drug quickly and wisely.

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