Research Article [Kukde *et al.*, 6(12): Dec, 2015:4845-4850]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Comparative Study on Formulation and Development of Promethazine Hydrochloride Hydrogel and Organogel

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Abstract

Promethazine Hydrochloride (PMH) is a phenothiazine derivative that act as an anti-histaminic, it has sedative, anti-motion-sickness, anti-emetic, and anti-cholinergic effects. The most preferred dosage forms of PMH are oral tablets, injections, syrups, linctuses, suspension, elixirs, and suppositories, in order to overcome the disadvantages of these dosage forms there is a need of a new formulation in the form of topical hydrogel. The drug is formulated as topical hydrogel preparation by using Carbopol 934 that could be applied for site-specific drug delivery additional to this by using soya lecithin organogel was also formulated for comparative studies. Different studies were conducted and discussed to successfully formulate the dosage form. The results including drug content and drug release pattern and stability studies showed that the drug can be formulated both as hydrogel and organogel.

Key-Words: Promethazine Hydrochloride, Hydrogel, Soya lecithin, Carbopol 934, Organogel

Introduction

Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use.[1] gels are relatively newer classes of dosage forms created by entrapment of large amount of aqueous or hydroalcoholic liquid in a network of colloidal solid particles. Gel formulation generally provides faster drug release compared with ointments and creams.[2,3] Hydrogels are three-dimentional, water-swollen structures composed of mainly hydrophillic homopolymers or co-polymers. Hydrophilic gels called hydrogels are cross-linked materials absorbing large quantities of water without dissolving. Softness, smartness, and the capacity to store water make hydrogels unique materials.[4,5]

Organogel, a viscoelastic system, can be regarded as a semi-solid preparation, which has an immobilized external apolar phase. The apolar phase gets immobilized within spaces of the three-dimensional networked structure formed due to the physical interactions amongst the self assembled structures of compounds regarded as gelators. The three-dimensional networked structure, hence formed, prevents the flow of external apolar phase. Some common examples of gelators include sterol, sorbitan monostearate, and lecithin and cholesteryl anthraquinone derivates. [6]

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Promethazine Hydrochloride (PMH) is a phenothiazine derivative that competitively and potently blocks histamine H_1 receptors without blocking the secretion of histamine and act as an anti-histaminic, it has sedative, anti-motion-sickness, anti-emetic, and anti-cholinergic effects. The drug competitively and reversibly antagonize the effects of histamine at the H_1-receptor site on effector cells which are responsible for vasodilatation, increased capillary permeability, flare and itch reaction in the skin, and to some extent for contraction of smooth muscle in the bronchi and gastrointestinal tract.

Material and Methods

Promethazine Hydrochloride was received as a gift sample by Cyno Pharma, Indore. Preformulation study was done initially and results directed for the further course of formulation. Identification was done by UV, IR, melting point and chemical test.

Preparation method:

Experimental Design: The Hit and Trial method of experimental design was selected to investigate the effect of different parameters on the mean and variance of the process performance and to obtain an optimal, well-functioning process. It can be methodical in manipulating the variables in an attempt to sort through possibilities that may result in success. To find the best solution, one finds all solutions by the method just described and then comparatively evaluates them based upon some predefined set of criteria, the existence of

which is a condition for the possibility of finding an optimal quality best product.

The data analysis was done on the basis of parameters viz, appearance, gelling (rigidity), viscosity and drug release study. On the basis of these sequential analyses one optimized batch was selected for further formulation.

Method for hydrogel with drug

The required quantity of carbopol was taken in a beaker which was then mixed with water with continuous stirring. To the above mixture the weighed quantities of disodium EDTA, propyl paraben and methyl paraben were added sequentially. To the obtained viscous solution measured volume of propylene glycol and ethanol were added. Then required quantity of drug was mixed in water as drug solution, drug solution was added to the final homogeneous mixture and triethanolamine was added to adjust the pH between 6 and 7. [7]

Table No.1 Formulation of gel

S. No.	Ingredients (% weight)	Formulation code (%)					
		HG_1	HG_2	HG_3	HG_4	HG_5	HG_6
1	Carbopol-934	0.5	0.7	1	1.2	1.5	1.8
2	Propylene Glycol	15	15	15	15	15	15
3	Disodium EDTA	0.1	0.1	0.1	0.1	0.1	0.1
4	Propyl Paraben	0.01	0.01	0.01	0.01	0.01	0.01
5	Methyl Paraben	0.05	0.05	0.05	0.05	0.05	0.05
6	Ethanol	1	1	1	1	1	1
7	Promethazine HCl	1	1	1	1	1	1
8	Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
9	Distilled Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Method for organogel

Required quantity of lecithin was dissolved in glyceryl monostearate as a solvent obtained by previous heating. Lecithin was dissolved in the solvent at continuous stirring until homogeneity. To this tween 80 and propylene glycol were added. 1% drug solution in water (aqueous base) was added drop wise with the help of microsyringe to form organogel. To this triethanolamine was added for adjustment of pH between 6 and 7.[7,8]

Table No. 2 Formulation of organogel

S. No.	Ingredients (% weight)	Formulation Code		
		OG_1	OG_2	OG_3
1	Soya lecithin	7	10	15
2	Glyceryl monostearate	10	10	10
3	Propylene glycol	15	15	15

4	Disodium EDTA	0.1	0.1	0.1
5	Propyl paraben	0.01	0.01	0.01
6	Methyl paraben	0.05	0.05	0.05
7	Tween-80	1	1	1
8	Triethanolamine	q.s.	q.s.	q.s.
9	Distilled water	q.s	q.s	q.s

Evaluation Parameters for Optimization

All gel formulations were subjected to analysis on the basis of appearance, viscosity, consistency and drug release studies. From these studies an optimized formulation batch was selected. The parameters analyzed are as follows: [9,10]

Appearance

The gels were analyzed on physical basis. They were checked for their color, gelling (rigidity), and overall elegancy

Viscosity determination

Viscosity of different formulation was measured using Brookfield Viscometer [DV-E (RV), USA]. Viscosity was determined by using spindle number-06; viscometer was set at 10 RPM. The viscosity of different formulation was measured.

Drug diffusion studies

The drug diffusion studies of prepared gel were carried out in Franz diffusion cell using through a dialysis membrane. Phosphate buffer 6.8 solution was used as bathing solution in the receptor compartment. The cellophane membrane was mounted between the donor and receiver compartments of the diffusion cell. The donor cell was filled with 1 g of gel. The receiver medium is continuously agitated with a magnetic stirrer at a temperature of 37^0C ± 2^0C maintained thermostatically. Samples 1ml in each case was withdrawn at regular intervals and fresh receptor fluid was added to maintain a constant volume of receptor fluid. The sample withdrawn from the receptor compartment was then analyzed spectrophotometrically at 250 nm and the drug content was determined from the calibration curve .

Table No.3 Drug release studies of hydrogel formulations

S. No.	Time (hrs)	Cumulative % drug release					
		HG_1	HG_2	HG_3	HG_4	HG_5	HG_6
1	1	16.44±0.20	14.98±1.36	12.28±0.66	11.28±0.78	10.21±0.43	10.09±1.44
2	2	21.91±0.44	22.89±2.28	21.29±0.96	18.52±0.95	16.35±1.22	15.88±1.44
3	3	28.68±0.37	31.01±2.10	30.16±0.38	26.15±1.68	24.55±0.69	23.26±1.19
4	4	46.40±1.88	43.80±1.31	42.95±1.00	38.19±1.81	35.68±1.74	32.11±1.13
5	5	57.05±1.72	52.44±1.54	49.58±0.69	48.06±1.60	46.21±1.82	45.59±1.42
6	6	65.58±1.32	60.89±0.99	60.19±0.80	58.59±1.06	54.52±0.94	52.67±0.47
All values are mean ± S.D for n=3; HG=Hydrogel formulation							

Table No.4 Drug release studies of organogel formulation

S. No.	Time (hrs)	Cumulative % drug release		
		OG_1	OG_2	OG_3
1	1	18.45±0.81	15.81±1.43	13.53±0.51
2	2	28.61±1.58	21.82±1.76	20.58±1.36
3	3	36.18±1.69	38.11±1.62	35.61±1.85
4	4	46.21±2.15	44.32±2.14	43.26±1.39
5	5	59.25±1.84	58.28±1.36	55.61±1.15
6	6	69.81±1.38	64.92±2.24	60.82±1.71
All values are mean ± S.D for n=3 OG=Organogel formulation				

The optimization of hydrogel and organogel was done on the basis of experimental design. On the basis of combined data of appearance, gelling, elegancy, viscosity and % drug release HG_3 formulation was selected as the optimized formulation and final formulation was prepared with respective concentrations for further evaluations.

On the basis of combined results of appearance, gelling, elegancy, viscosity and % drug release OG_2 was selected as the optimized batch for further evaluation parameters.

COMPARATIVE STUDY OF HYDROGEL WITH ORGANOGEL

Hydrogel system differs with that of organogel system in various ways as both system prepared with different components and methods. Hydrogel is fully water based system in which the hydrogel polymers play an important role in formation of hydrogel based gel in contrast to these hydrogel system organogel is two phase system- one is organic phase and other is aqueous phase in which gelling is induced by addition of water as aqueous. From all the studies of these systems we had much parameter on the basis of which we can compare hydrogel with that of organogel formulations.

On The Basis of evaluation parameters

Both the gel formulations that are hydrogel and organogel were first compared for their physical parameters such as color, appearance, ease of application, viscosity and spreadibility. For the comparison optimal values were selected from the evaluation parameters. All these are mentioned in the table (Table No.5).

Table No.5 Comparative study of gels on the basis of evaluation parameters

S. No.	Evaluation parameters	Formulations code	
		HG_3	OG_2
1	Color	Transparent	Creamy yellow
2	Greasiness	Non-greasy	Greasy
3	Viscosity (cps)	18274±675.62	20519 ±837.95
4	Speadibility (gm.cm/sec)	20.33 ± 0.41	16.87 ± 0.60
All values are mean ± S.D for n=3 HG,OG=Gel formulation			

On The Basis of Flux

The mean cumulative amount of drug diffused per unit surface area of the membrane was plotted versus time. The slope of the linear portion of the plot was calculated as flux *J*ss (µg/cm^2/hr) (Table no. 6).

Table No. 6 Comparative study of gels on the basis of flux

S. No.	Formulation Code	Flux (µg/cm^2/hr)
1	HG_3	9.818±0.59
2	OG_2	11.58±0.78
HG,OG=Gel formulation		

On The Basis of Stability Studies

On the basis of stability studies, this was done as accelerated stability testing according to ICH guideline previously, both the gel formulations were subjected to stability studies and the values and observations recorded were used as the basis of comparison in between hydrogel and organogel formulations. The comparative studies are tabulated (Table No 7.)

Table No. 7 Comparative Study of Gels by Stability Study

S. No.	Evaluation parameters	HG_3		OG_2	
		Before(0 Day)	**After**(60 Day)	**Before**(0 Day)	**After**(60 Day)
1	Viscosity (cps)	18274±675.62	18542±307.51	20519±837.95	16982±586.48
2	pH	6.82±0.03	6.78±0.03	6.81±0.05	6.32±0.07
3	Homogeneity	+++	++	+++	+
4	Drug Content	98.65%±0.54	97.89%±0.69	97.48%±1.07	93.41%±1.07

Where, all values are mean ± S.D for n =3; (+)- Poor, (++)- Good, (+++)- Excellent (Stability study was conducted at 40^0C ± 2^0C/75% ± 5% relative humidity)

Results and Discussion

Various observations and calculations were done for optimized formulations on different evaluation parameters such as viscosity, spreadibility, pH, homogeneity, grittiness, drug content, and drug diffusion. Homogeneity was observed with the help of visual basis which showed good homogeneity in both the gel formulations that is HG_3, OG_2. Both the gels were found to be free from any lumps or any aggregates and were elegant.

Formulations were evaluated microscopically and also by feel on application. For the presence of particles if any, no appreciable particulate matter was seen under light microscope. No foreign particulate particles were observed and were smoothly applicable. Hence gel preparations fulfill the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

pH was determined by Digital pH meter. Hydrogel formulation (HG_3) showed pH range of 6.79 and that of organogel formulation (OG_2) was 6.71. These pH ranges were within the acceptable limit for topical formulations therefore both the gel formulations were acceptable for pH values.

The viscosity range of the gel formulations was determined; the viscosity of hydrogel formulation (HG_3) was 18274 cps, and that of organogel formulation (OG_2) was 20519 cps. Viscosity values were within acceptable range.

The spreadibilty was measured on the basis of slip and drag approach. The spreadibility of hydrogel formulation (HG_3) was 20.33 gm.cm/sec, and that of organogel formulation (OG_2) was 16.87 gm.cm/sec. More the value of spreadibility more easily and quickly the gel can be applied.

The drug content of the formulations that is hydrogel (HG_3) and organogel (OG_2) was determined as 98.65% and 97.48% respectively. The drug content was within the limits in both the formulations.

Drug diffusion studies were done by using an egg membrane for a period of 6 hrs which was calculated as cumulative percent drug release that showed

56.860% for hydrogel (HG_3) and 65.088% organogel (OG_2). The drug release pattern and values of both the gels concluded that the release rate from that of organogel is more as compared to that of hydrogel.

Stability studies were done to check the stability of dosage form for its drug potency, any changes at the physical and chemical basis. By following WHO-ICH guidelines both gel formulations were kept in accelerated stability conditions at 40ºC ± 2ºC/ 75% RH± 5% for a period of 60 days and studied for appearance, pH, viscosity and drug content. In case of hydrogel formulations (HG_3) the viscosity determined was 18542 cps, pH was 6.78, appearance was acceptable and good and the drug content was 97.89%. This result showed that the hydrogel formulation was stable at accelerated stability conditions as there were very slight changes in the observations. While in case of organogel formulation (OG_2) the viscosity shifted from the initial value to 16982 cps, pH was 6.31, appearance and gelling was poor and drug content decreased to 93.41%. This suggested that organogel formulation was not stable at accelerated stability conditions.

Conclusion

On the basis of all these studies it can be concluded that topical hydrogel formulation of PMH can be successfully prepared with the help of polymer carbopol-934. Its organogel can also be prepared successfully with lecithin as an organogelator. As organogel was prepared for the comparative studies of both the preparations it could be concluded that hydrogel are more stable in accelerated stability conditions at 40ºC ± 2ºC/ 75% RH ± 5%. From the drug release profile it is also concluded that hydrogel preparation could be used for local or site specific delivery of drug. Thus hydrogel of PMH could be better formulated and used commercially with various advantages over other dosage form. It could be used topically for site-specific drug delivery for any conditions of pruritus, insect bite induced urticaria or allergic conditions. PMH hydrogel preparation was found to be acceptable, elegant and more patient compliance than other dosage form of this drug.

References

1. Surver C, Davis FA. Bioavailability and bioequivalence, in walter ka dermatological and transdermal formulation edition. Marcel Dekker, Inc. Newyork. 2002: 323,326, 327, 403.
2. Kaur PL, Garg R, Gupta GD. Topical gels: a review. Res J Pharm and Tech. 2010; 3(1): 17-24.
3. Kumar L, Verma R. *In-vitro* evaluation of topical gel prepared using natural polymer. Int J Drug Dev. 2010; 2: 58-63.
4. Ratner DB. Biomaterials science. Second Edition. John Wiley & Sons. 1999: 397-406.
5. Chandira RM, Pradeep, Pasupathi A, Bhowmik D, Chiranjib, Jayakar B, Tripathi KK, Sampath Kumar KP. Design, developmant and formulation of antiacne dermatological gel. J Chem Pharm Res. 2010; 2(1): 401-414.
6. Tanaka T. Gels. Sci Am. 1981; 244: 110-123.
7. Patil DK, Bakliwal RS, Pawar PS. Organogel: topical and transdermal drug delivery system. Int J Pharm Res and Dev. 2011; 3(6): 58-66.
8. Shaikh IM, Jadhav SL, Jadhav KR, Kadam VJ, Pisal SS. Aceclofenac organogel: *in-vitro* and *in-vivo* characterization. Cur Drug Dev. 2009; 6: 1-7.
9. Ansel HC, Loy AV, Popovich NG. Pharmaceutical dosage forms and drug delivery systems. Eight edition. Lippincott Williams and Wilkins publication. 2004: 418.
10. Capkova Z, Vitkova Z, Subova M. Formulation of loratidine into hydrogel. Acta Facultatis Pharmaceuticae Universitatis Comenianae. 2005; 52: 73-78.

How to cite this article
Kukde D., Mishra D., Sahu K. and Sharma V. (2015). Comparative Study on Formulation and Development of Promethazine Hydrochloride Hydrogel and Organogel. *Int. J. Pharm. Life Sci.*, 6(12):4845-4850.
Source of Support: Nil; Conflict of Interest: None declared

Received: 01.11.15; Revised: 01.12.15; Accepted: 05.12.15