Research Article

Design and Characterization of *In Situ* Gel of Ebastine

Dibyalochan Mohanty[1], Nandini Simharaju[1], Bakshi Vasudha[1], B.Nirosha[1], Chinmaya Keshari Sahoo[2], Shivani Kalavantha[3]

[1]Department of Pharmaceutics, School of Pharmacy, Anurag Group of Institutions, Ghatkesar, Telangana, India.

[2]Department of Pharmaceutics, College of Pharmaceutical Sciences (affiliated to BPUT), Puri-Konark Marine Drive Road, Baliguali, Puri, Odisha, India.

[3]Department of Pharmaceutics, Guru Nanak Institute of technical campus, School of Pharmacy, Ibrahimpatnam, Telangana, India.

***Corresponding author's E-mail:** sahoo.chinmaya83@gmail.com

Received: 18-07-2019; **Revised:** 26-08-2019; **Accepted:** 05-09-2019.

ABSTRACT

The objective of the present study was to obtain an optimized formula of Ebastine *in situ* gel. Ebastine *in situ* gel was prepared using poloxamer 407 and HPMCK100 as polymers, by cold method. Parameters such as gel strength, pH, drug content, *in vitro* drug release, were assessed for evaluation of *in situ* gel. The release pattern shown by these formulations was diffusion cell through egg membrane. Optimized formulation showed 93.15% drug release at the end of 8 h. The results of short term stability studies for optimized formulation indicated insignificant changes in pH, drug content, gel strength and appearance.

Keywords: Gel, Ebastine, design, characterization.

INTRODUCTION

The development of in situ gel systems has received considerable attention over the past few years. In the past few years, increasing number of *in situ* gel[1] forming systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported. In situ gelation is a process of gel formation at the site of action after the formulation has been applied at the site. In situ gel phenomenon based upon liquid solution of drug formulation and converted into semi-solid mucoadhesive key depot. This interest has been sparked by the advantages shown by *in situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. *In situ* gel formulations offers an interesting alternative for achieving systemic drug effects of parenteral routes, which can been convenient or oral route, which can result in unacceptably low bioavailability and passes the hepatic first-pass metabolism, in particular of proteins and peptides. This novel drug delivery system promotes the importantly ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with mucosa, that problems generally encountered in semi-solid dosage forms. *In situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition[2], once administered. From the early 1970's natural and synthetic polymers began to be investigated for controlled release formulations. The advantages of using biodegradable polymers in clinical applications are apparent. Various natural and synthetic polymers are used for formulation development of *in situ* forming drug delivery systems.

Ebastine is an effective anti-allergic medicine used to relieve the symptoms caused by allergic reactions such as hay fever or urticaria (hives). The symptoms may include sneezing, runny nose, itchy eyes, skin rashes, redness of the eyes, etc. Ebastine has a rapid onset of action and it can be administered once-daily, with or without food. Dose modifications are not needed in elderly patients, or in those with renal or mild to moderate hepatic impairment. Ebastine is generally well-tolerated[3], and clinical studies showed that at usual therapeutic doses of 10 and 20 mg once-daily, it had no clinically relevant adverse effects on cognitive function and psychomotor performance or on cardiovascular function.

MATERIALS AND METHODS

MATERIALS

Ebastine was obtained from Aspire Life sciences Pvt Ltd, Mumbai, India. Poloxamer407, HPMC K100 and Maltodextrin were purchased from Sigma Chemical Company, (USA). Ethanol, Tween 80, methyl paraben was purchased from El-Nasr Chemical Company, (Egypt). All other chemicals used were of analytical grade.

METHODS

Drug - excipients compatibility studies

Fourier transform infrared (FTIR) spectroscopy studies[4]

FTIR has been used to study the physical and chemical interactions between drug and the excipients used. KBr pellet is used to know drug-excipient interactions. The samples were scanned over a range of 400-4000 cm^{-1} using FTIR instrument (Alpha, Brucker pvt ltd, Japan).

Preparation of Ebastine *in situ* Gel

In situ gel was prepared by the cold method. A weighed amount of poloxamer 407 was slowly added to 15 mL water (at 42^0 C) in a beaker with continuous stirring using a magnetic stirrer at a speed of 500 rpm for 2 h. The temperature of water was maintained at 42° C throughout the preparation. This solution was kept overnight in refrigerator. HPMC K-100 (0.5% W/V) and the preservatives (methyl and propyl paraben 0.1 % and 0.01 %, W/V resp.) were added to poloxamer dispersion with continuous stirring. The preservative solution was prepared by solubilizing it in hot water. It was mixed with above dispersion after cooling. The weighed amount of drug (2% W/V) was dissolved in the mixture of tween 80 and ethanol (1:2) or glycerin. The drug solution was then mixed in the above described poloxamer dispersion. The final volume was made up and pH of the poloxamer dispersion was adjusted to 7 using triethanolamine.

Table 1: Formulation Chart of in Ebastine situ gel composition

Formulations	Ebastine (mg)	Tween and ethanol (ml)	Poloxamer 407 (mg)	Poloxamer 188 (mg)	HPMC k100 (mg)	Methyl Paraben	Distilled water
F1	10	6	4	2	0.10	0.03	30
F2	10	6	3	2	0.35	0.03	30
F3	10	6	4	2	0.35	0.03	30
F4	10	6	4	2	0.60	0.03	30
F5	10	6	2	2	0.10	0.03	30
F6	10	6	2	2	0.35	0.03	30
F7	10	6	2	2	0.60	0.03	30
F8	10	6	3	2	0.60	0.03	30
F9	10	6	3	2	0.10	0.03	30

Evaluation of Gel

Organoleptic properties

Organoleptic property is an important characteristic in gel formulations as it increases the patient acceptability. Organoleptic properties like taste, odor and color were evaluated.

***Gel strength*[5]**

A sample of 50 g of the gel was put in a 50 ml graduated cylinder. A weight of 14.33 g was placed on the gel surface. The gel strength, which is an indication for the ophthalmic gel at physiological temperature, was determined by the time in seconds required by the weight to penetrate 5 cm into the gel.

pH of the in-situ gels

The pH of the *in-situ* gel was measured using Labindia SAB 5000 digital pH meter at room temperature.

***Drug content of gel*[6]**

The drug content was determined by taking 1 ml of the formulation and diluting it to 100 ml with distilled water. Aliquot of 5 ml was withdrawn and further diluted to 25 ml with distilled water. Ebastine concentration was determined at 287 nm by using UV-Visible spectrophotometer.

***In vitro drug release study*[7]**

In vitro release study of the formulated in-situ gel was carried out by using diffusion cell through egg membrane as a biological membrane. Diffusion cell with inner diameter 24 mm was used for the study. 10 ml formulation was placed in donor compartment and freshly prepared 100 ml phosphate buffer pH 6.8 was placed in receptor compartment. The position of the donor compartment was adjusted so that egg membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 5 ml of sample was withdrawn from receiver compartment in respective intervals, 1, 2, 3, 4, 5, 6, 7 & 8 h and same volume of fresh medium was replaced. The withdrawn samples were diluted with phosphate buffer pH 6.8 and analysed by UV spectrophotometer at 287 nm.

Stability studies of in-situ gel

A physically stable *in-situ* gel retains its, appearance, pH and drug content, odor throughout its shelf life. Stability studies were carried out on eye sol-to-gel systems according to ICH guidelines. A sufficient quantity of sol-to-gel system in amber colored bottles was stored in a desiccator containing a saturated solution of sodium chloride, which gives a relative humidity of 75%. The desiccator was placed in a hot air oven maintained at a temperature of 40 ± 0.5^0C, and samples were withdrawn after one month. The samples were evaluated for parameters viz. pH, appearance, drug content, viscosity.

RESULTS AND DISCUSSION

FTIR Studies

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2mg of Ebastine polymer and physical mixtures of samples were weighed and mixed properly to a uniform mixture. It was observed that there was no interaction with drug and Excipients.

Organoleptic property

Organoleptic properties of developed gel were evaluated and depicted in table 2.

Table 2: Organoleptic properties of Ebastine

Properties	Results
Taste	Tasteless
Odour	Odourless
Colour	White

Gel strength

All the formulations were evaluated for gel strength. All the formulations were found to be in acceptable range. It is shown in table 3.

pH of the *in-situ* gels

All the formulations were evaluated for pH using pH meter. All the formulation's pH were found to be in acceptable range. It is shown in table 3.

Drug content of gel

All the formulations were evaluated for drug content. All the formulation's drug content were found to be in acceptable range. It is shown in table 3.

In vitro drug release study

The *in vitro* drug release characteristics were studied in 8 hrs in phosphate buffer pH 6.8 using diffusion cell. The cumulative percentage drug release for F1, F2, F3, F4, F5, F6, F7, F8 and F9 were 88.93, 90.82, 91.28, 83.67, 89.18, 91.16, 93.15, 90.58 and 89.99 % respectively of Ebastine at the end of 8 hrs. Out of nine formulations F7 formulation was found to be best. It is shown in table 4.

Table 3: Evaluation of *in situ* gel formulation

Batches	Gel Strength (gm/cm)	Drug content (%)	pH
F1	12.36	97.90	7.02
F2	14.25	96.23	7.03
F3	13.26	98.21	7.06
F4	16.25	98.53	7.05
F5	14.11	97.56	7.01
F6	16.46	98.29	7.03
F7	15.33	99.56	7.08
F8	14.25	98.63	7.02
F9	16.38	98.21	7.05

Table 4: *In vitro* drug release study of batches F1-F9

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.03	13.95	13.88	11.25	14.25	13.86	15.96	13.91	11.83
2	25.96	23.86	26.87	21.83	20.17	23.45	25.17	24.56	26.89
3	32.15	30.45	32.95	30.45	32.94	33.82	34.91	32.19	34.58
4	43.96	42.85	43.72	42.85	40.27	42.18	43.75	40.30	41.75
5	52.18	54.94	56.90	55.16	53.86	53.49	55.48	52.48	54.82
6	60.79	63.89	67.82	66.12	61.15	63.48	69.41	70.15	69.18
7	75.16	78.90	81.95	79.18	77.58	79.27	80.18	79.18	81.45
8	88.93	90.82	91.28	83.67	89.18	91.16	93.15	90.58	89.99

Stability studies of *in-situ* gel

The results of short term stability studies for optimized formulation indicated insignificant changes in pH, drug content, gel strength and appearance in the formulation with time. Precipitation of drug in the *in-situ* gels was not observed. Hence F7 formulation was found to be stable

CONCLUSION

Ebastine was chosen was as a model drug with an aim to develop a sustained release system for 8 hrs. FTIR study of pure Ebastine and formulation showed that they are in no drug polymer interaction. Various evaluation parameters were studied for the formulation like pH, drug content, gel strength, *in vitro* drug release studies. By addition or increase in the concentration of hydrophilic polymer, the gelling capacity, gel strength, viscosity was increased

whereas spreadability was decreased. Drug release study of all the formulations showed sustained release properties and the optimized formulation was found to be F7. Delivery of drug through oral mucosa by *in situ* gel formulation avoids the first pass effect. So it is a logical choice for local and systemic delivery of drug, which eventually improves the bioavailability of drug. This approach can be used to treat oral herpes infection locally by improving the patient compliance.

REFERENCES

1. Chand P, Pratibha, Gnanarajan G, Kothiyal P. In situ gel: A Review. Indian J. Pharm. Biol. Res. 4(2), 2016, 11-19

2.Mohanty D, Bakshi V, Simharaju N, Haque MA, Sahoo CK.A Review on *in situ* Gel: A Novel Drug Delivery System. Int. J. Pharm. Sci. Rev. Res., 50(1), 2018, 175-181.

3. Sastre J. Ebastine in allergic rhinitis and chronic idiopathic urticaria. Allergy. 63 Suppl., 2008, 1-20.

4. Wen-Di Ma, Hui Xu, Chao Wang, Shu-Fang Nie, Wei-San Pan, Pluronic F127-gpoly(acrylic acid) copolymers as in situ gelling vehicle for ophthalmic drug delivery system. Int. J. of Pharmaceutics, 350, 2008, 247-256

5. Cohen S, Lobel E, Trevgoda A, Peled Y. A novel in situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J. Control. Release, 44, 1997, 201–208.

6. Reddy AV, Panda KC, Das B, Panda N, Sahoo CK, Pratap RK. Formulation and Evaluation of Pluronic F127-Sodium CMC Based In Situ Gel of Ophthalmic Drug Delivery of Acetazolamide. Journal of Pharmacy and Chemistry 6(3), 2012, 3-10.

7. Srividya B, Cardoza RM, Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J. Control Release. 73, 2001, 205–211.

Source of Support: Nil, **Conflict of Interest:** None.