ejpmr, 2017,4(12), 249-253

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

"FORMULATION AND EVALUATION OF INTRA NASAL *IN SITU* MUCOADHESIVE GEL OF DOMPERIDONE MALEATE"

Mathew George[1], Lincy Joseph[2] and Kavitha A. K.[3*]

[1]Professor, Department of Pharmacology, Department of Pharmaceutical Chemistry, Pushpagiri College of Pharmacy, Medicity Campus, Perumthuruthy P.O, Thiruvalla-689107 Kerala.

[2]Professor, Department of Pharmaceutical Chemistry, Pushpagiri College of Pharmacy, Medicity Campus, Perumthuruthy P.O, Thiruvalla-689107 Kerala.

[3]Assistant Professor, Department of Pharmaceutics Pushpagiri College of Pharmacy, Medicity Campus, Perumthuruthy P.O, Thiruvalla- 689107 Kerala.

***Corresponding Author: Kavitha A. K.**
Assistant Professor, Department of Pharmaceutics Pushpagiri College of Pharmacy, Medicity Campus, Perumthuruthy P.O, Thiruvalla- 689107 Kerala.

Article Received on 11/09/2017 **Article Revised on 21/10/2017** **Article Accepted on 01/11/2017**

ABSTRACT

The prolonged residence of drug formulation in the nasal cavity is of outmost important for intra nasal drug delivery. The objective the present study was to develop a mucoadhesive insitu nasal gel with reduced nasal mucocilliary clearance inorder to improve the bioavailability of the antiemetic drug, domperidone maleate. The insitu gelation upon contacted with nasal mucosa was conferred via the use of of the thermogelling ploxomar 407 where as mucoadhesive and drug release enhancement were modulated via the use of sodium alginate and PEG 6000 plymers respectively. The result revealed that the mucoadhesive polymers increased the gel viscosity but reduced its sol gel transition temperature and the drug release. The inclusion of PEG plymers counteracted the effect of mucoadhesive polymer were by it decreased the gel consistency and increased the sol gel transition as well as invitro drug diffusion. The invitro test performed for mucoadhesive strength and drug diffusion showed that nasal insitu gelling formulation prepared are good mucoadhesive strength with nearly 85% drug diffusion within 8 hours. So this study provides ease of administration, accuracy of dosing, prolonged residence time, improved nasal absorption and avoid typical side effects associated with oral administration of domperidone.

KEYWORDS: Insitu nasal gel, Domperidone Maleate, Gelling Temperatur.

INTRODUCTION

Domperidone is a peripherally selective dopamine D2 - receptor antogonists. The drug provide relief from nausea by blocking receptor at the chemoreceptor trigger zone of the medulla(area postrema) resulting in potent Antinausea and Antiemetic action. Dopamine is extremily well tolerated. Because it does not cross the blood brain barrier to a significant degree; neuropsychiatric and extrapyramidal effects are rare.[1]

Oral administration of domperidone is extensively metabolized in the liver and in the intestine. Due to the marked first pass effect via this rout, so the oral bioavailability of domperidone is low (13-17%). Oral forms of domperidone often get vomited out before systemic absorption. Conversely, its bioavailability is high via parenteral or rectal rout but it result in low patient complaiance. In this regard, the intranasal delivery seems to be an attractive alternative. The major disadvantage associated with nasal drug delivery is rapid mucociliary clearance that limits the time available for drug absorption from applied dosage form upto allowing amounts drug dosing.[2]

Low volume and high concentration is the essential condition required for nasal drug formulation to be administerd. Too large volume and too weak concentration may lead to failure because the drug cannote be absorbed in high enough quantity to be feffective. Ideal volume for nasal delivery is ¼ to ½ ml per nostril. Volume one ml per nostril is too large and may result in runoffout of the nostril. There fore nasal formulation must have a high drug loading in low volume.[3]

The temperature triggered system was employed in this article. The sustained drug release in this gelling system is triggered by altered in temperature. These gel solutions are fluid at room temperature (20-25^{o}c) and so through gelation while the gel in touch with body fluids (35-37^{o}c). The employment of biomaterial whose sol-gel formation is triggered by raise in temperature, is an effective method for in -situ gel formation.[4]

Poloxamer 407 is a thermo sensitive polymer with excellent water solubility, good drug release character and has compatability with other excipients. Aquoes

poloxamer dispersion (18-35%) are solution at low temperature and are converted into semisolid get at higher (or body temperature).

PEG is a nontoxic, nonimmunogenetic and non antigenic polymer. It has high solubility in water and rapid invivo clearance. It also has the ability to form hydrogen bonds with sugar moieties on glycosylated protiens. This causes PEG to form strong bonds with mucus leading to increased mucoadhesion.[5]

Sodium alginate is a natural anionic polysaccharide, where through binding with water it form a viscus gum. It is highly viscus and is often used as a gelling agent.[6]

The purpose of the present work was to develop insitu-nasal mucoadhesive gel. This drug delivery system indorses the ease and convenience of administration, delivery of accurate dose and prolonged residence time of the drug in the nasal mucosa, it bypass the hepatic first pass metabolisam provides rapid onset of action and relativelty high bioavailability.

MATERIALS AND METHODS

Domperidonen was obtained sample from shagunPharmaceuticals, Indore, India. Poloxamer 407 was obtained as a gift sample from BASF corporation Mumbai, India. Sodium alginate and PEG 6000 were collected from kota college of pharmacy, Kota.

PREPARATION OF MUCOADHESIVE THERMOREVERSIBLE NASL GEL

In-situ nasal gel of domperidone was prepared by cold technique. Mucoadhesive polymer, PEG 6000 and methylparaben was dissoleved in double distilled water, this solution was added to the solution of Domperidone in methanol by agitation at room temperature. After cooling the solution to 4^0c. Poloxamer 407 was added slowly with agitation. The resulting dispersion was then kept overnight at 4ºc untile clear and viscus transparent solution was formed. Finally volume was adjusted by using cold distilled water.[7]

Table 1: Composition of various thermoreversible mucoadhesive nasal gel formulations.

Composition	F1	F2	F3	F4
Domperidone maleate	10	10	10	10
Poloxomer407	18	18	18	18
Sodium alginate	0.1	0.2	0.3	0.4
PEG 6000	-	0.2	0.4	0.6
Methyl paraben	0.33	0.33	0.33	0.33
Distilled water	q.s	q.s	q.s	q.s

*All concentrations in percentage: batch size 20ml

APPEARENCE

The clarity was determined by visual inspection under black and white background

pH

Formulation equivalent to 10 mg of drug was transferred and diluted with methanol. pH of resulting solution was determined using pH meter.

DRUG CONTENT

The drug content was determined by dissolving 100 µl of formulation in 50ml methanol and volume was made up to 100ml with demineralized water in a 100ml volumetric flask. Then was estimated spectrophotometrically using double beam uv-visible spectrophotometer at 284nm against reagent blank.

GELATION TEMPERATURE

Formulation equivalent to 10 mg was transferred to a test tube and immersed in a water bath. The temperature of water bath was increased slowly and left to equilibrate for 5 min at each new setting. The sample was then examined for gelation, which was said to have occurred when the meniscus would no longer move upon tilting through 90°C.

MUCOADHESIVE STRENGTH[8]

Mucoadhesive potential of each formulation was determined by measuring a force required to detach the formulation from membrane. It was measured by modified balance. Egg membrane was used for the study. It was mounted on lower side of glass surface using adhesive tape while another membrane was fixed on upper side of glass slide, kept on inverted cylinder. Gel equivalent to the 10 mg was placed on membrane surface. Empty beaker was attached to another side of the balance. Membrane surface with gel formulation and upper membrane surface were held in contact with each other for 2 min to ensure intimate contact. Water was added to the beaker until detachment takes place. The mucoadhesive force was expressed as the detachment stress in dynes/cm^2 as shown in

$$\text{Mucoadhesive Strength (dynes/cm}^2\text{)} = mg/A$$

Where m is weight required for detachment in gram, g is acceleration due to gravity (980 cm/s^2), and A is area of mucosa exposed.

VISCOSITY

Viscosity was determined using Brookfield viscometer.

INVITRO DRUG RELEASE STUDY

(1) **In Vitro Diffusion Study**: Cellophane Membrane. Franz diffusion cell was used for permeation study with cellophane membrane (mol.wt. 12,000–14,000) having pore size of 2.4 nm. Cellophane membrane was placed in between the donor and the receptor compartment. Gel containing drug equivalent to 10 mg(100µl) was applied on surface of membrane. It was in contact with receptor compartment containing 25 mL of 50% v/v methanolic buffer (acetate buffer of pH 5.5 + methanol). The cell was agitated by a magnetic stirrer at 50 rpm and maintained at 37°C. Aliquots were withdrawn at intervals till 420min and were replaced

with equal volume of fresh methanolic buffer pH5.5. Absorbance was measured at 284 nm.

(2) **Ex Vivo Diffusion Study (Nasal Mucosa).** Ex vivo drug permeation study was carried out for best formulations. Fresh nasal tissue was removed from nasal cavity of sheep obtained from local slaughter house. Mucosa was stored in saline water at frozen condition. It was placed in between the donor and the receptor compartment. Same procedure as given in the above section.

HISTOPATHOLOGICAL STUDY

In histopathological evaluation, fresh nasal tissue was removed from the nasal cavity of sheep. The tissue was inserted in the diffusion cell. Methanolic buffer soluton pH 5.5 was then added to the receptor chamber. Gel was applied to the mucosa and left for 24 hr. After 24 hrs each piece of mucosa was carefully removed from the diffusion chamber and rinsed with methanolic buffer solution. Sections were examined under a light microscope, to detect any damage to the tissue.[8]

RESULT AND DISCUSION

APPEARANCE

The appearance of all formulations were found to be clear.

pH

It is known that the normal physiological pH of nasal mucosa is 4.5–6.5. However, the nasal mucosa can tolerate solutions within pH range of 3–10. pH for all formulation was found in range of 4.7–6.4.

DRUG CONTENT

Drug contents were found in the range of 84.42–99.7%. It was observed that f4 showed less drug content, that is, 84.42%, and f3 showed high drug content, that is, 99.7%

GELATION TEMPERATURE

Gelation temperature range suitable for nasal gel is 32–35°C. Gelation temperature for all formulations was found in the range of 28–34°C. Various excipients like mucoadhesive polymer as well as PEG 6000 had shown to have effect on the gelation temperature. Mucoadhesive polymer reduced the gelation temperature while PEG 6000 increased the $T_{sol\text{-}gel}$ of the corresponding mucoadhesive nasal insitu gelling formulations in a concentration dependent manner.

Table 2: Gelation temperature of mucoadhesive nasal insitu gelling formulations.

Formulation	Gelation Temperature (°C) Mean ± S.D. n= 3
F1	28.76±0.12
F2	31.32±0.39
F3	32.03±0.18
F4	34.92±0.21

MUCOADHESIVE SRENGTH

Mucoadhesive strength was determined by measuring the force required to detach the formulation from membrane, that is, detachment force. It was observed that sodiumalginate had shown effect on mucoadhesive strength. As the concentration for mucoadhesive polymer increases, mucoadhesive strength was also found to be increased. f1 had shown least mucoadhesive strength, that is, 1125.42, and f4 had showed the highest mucoadhesive strength, that is, 2183.12.

Table 3: Mucoadhesive strength of batch f1–f4.

Formulation	Mucoadhesive strength (dyne/cm^2)
F1	1125.42 ± 34.58
F2	1414.90 ± 89.25
F3	1845.39 ± 92.14
F4	2183.12±54.12

VISCOSITY MEASUREMENT

From the results it was observed that sodium alginate had viscosity enhancing effect. The viscosity was in range of 125.13±.27cps to 182.32±.56 cps. With increase in concentration of sodium alginate, viscosity was found to be increasing with retarding % drug release. Residence time got enhanced with higher viscosity, but drug absorption was found to be diminished. Profile of viscosity followed shear thickening pattern indicating sol to gel conversion.

INVITRO DIFFUSION STUDY

(1) Cellophane Membrane. From Figure 1, it was observed that polymer concentration affects drug release. As the concentration of sodium alginate increases, it retarded % drug release. % drug release of batche f3 was found to be 85.31±23 after 8hrs.

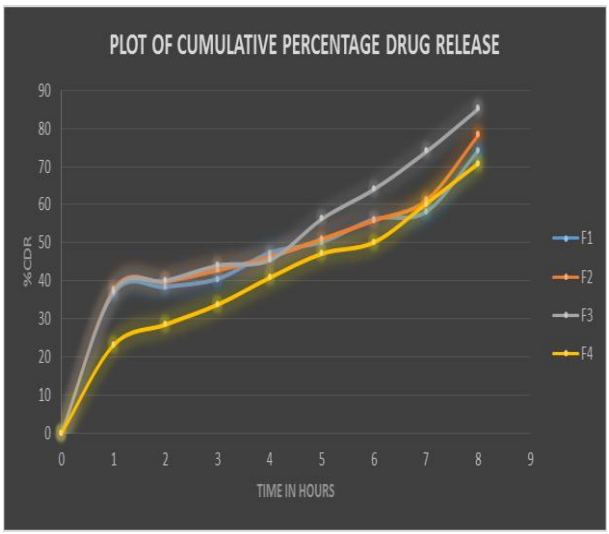

Figure 1: % cumulative drug release for formulations f1-f4.

Ex VIVO DRUG PERMEATION STUDY

From Figure 2 it was observed that, as compared to cellophane membrane nasal mucosa gave less % drug

release. The reason may be attributed to high thickness of mucosa. f3 had shown % cumulative drug release, 74.04±.23.

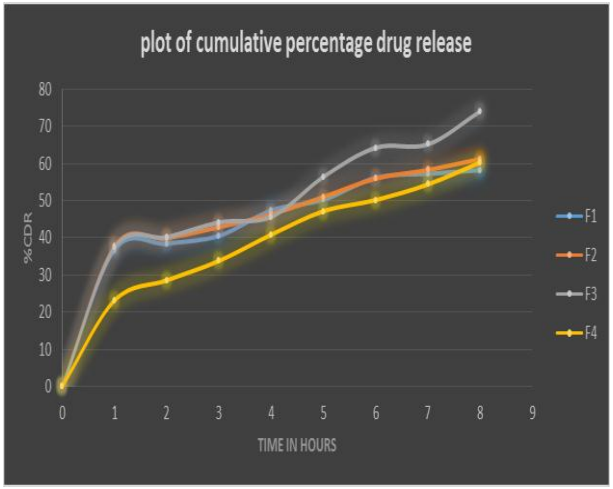

Figure 2: Ex vivo % drug release of formulations F1, F2, F3, F4.

HISTOPATHOLOGICAL STUDIES

In histopathological study it was found that there are no changes to the nasal mucosa after the study. The microscopic observation indicated that optimized formulation f3 has no effect on the nasal mucosa. The epithelial layer was intact and showed no damage to the mucosa. Thus, gel formulations seem to be safe with respect to nasal administration.

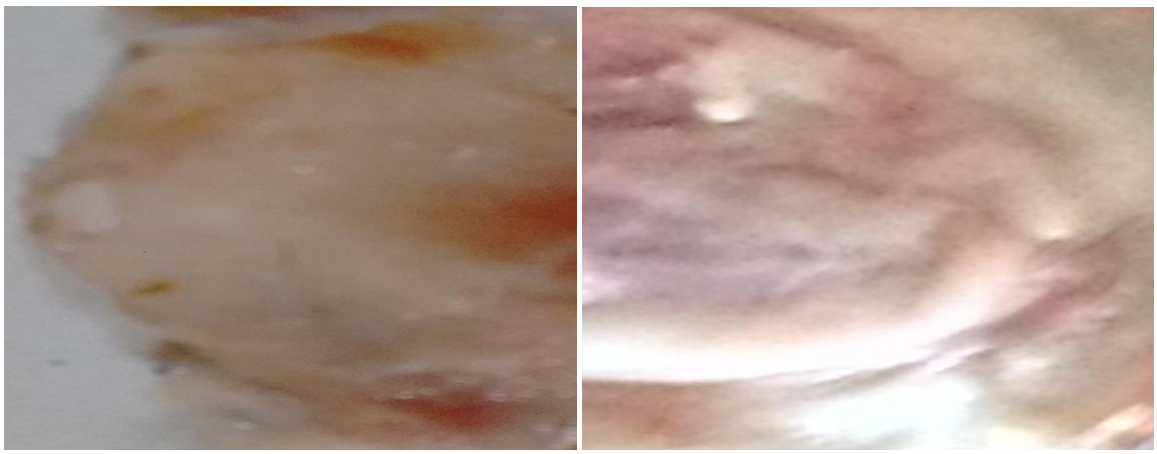

Figure (a) **Figure: b**

Figure 3: (a) controlled mucosa treated with methanolic buffer pH 5.5 (b) mucosa treated with formulation F3.

CONCLUSION

Sodium alginate and PEG 6000 were used as independent variables, F3 gave significant and good results with respect to gelation temperature, mucoadhesive strength, and release study. F3 revealed the highest drug release through the cellophane membrane, that is, 85.31 ± 23%.The histopathological observations indicate that F3 had no significant effect on the nasal mucosa. In conclusion, it can be said that a stable, effective in situ nasal gel of domperidone maleate was formulated which will bypass the first-pass effect, improve the bioavailability, and give a controlled release for the drug at the site which gave possibility of lowering the dosing frequency

REFERENCE

1. Bertran G. Ketzung, SusanB, Anthony J, Trever Basic and clinical pharmacology 12th edition page no: 1092.
2. Paresh Mohan, Parth Gandhi etal. Formulation and Evaluation of insitu mucoadhesive nasal gel of metochlorpropamide hydrochloride, Internation journal of Advanced in Pharmaceutical Analysis, 2012; 2(4): 88-90.
3. Archana Agarwal, Maheshwari R.K. Formulation and Evaluation of insitu nasal gel of poorly water soluble drug using mixed solvency concept,Asian journal of pharmaceutics, july-september, 2011: 131.
4. Baban A. more, Harshad R, Mene, Rohit. K. Pawar, Nitin S. Mishel, Sagar S. Pathak, Kapil J. Shirsharan, A reviews on insitu nasal gel drug delivery system, International journal of pharmaceutical science.Rev. Res., July-August 2015; 33(1): 199-207.
5. Prasant s. khairnar, Prasant s. walke, M.R. Narkhede, J.Y. Nehete Formulation and Evaluation of Thermoreversible Riza Triptan Benzoate nasal gel. International journal of pharmacy and pharmaceutical sciences, 2011; 3(4).

6. RaoM, Agrawal DK, Shirsath C, Thermoreversible mucoadhesive in situ nasal gel for treatment of Parkinson' desease. Drug Dev. Ind. Pharm., Jan, 2017: 43(1): 142-150.
7. Mandar J. Bhandwalkar and Amelia M, Avachat Thermoreversible nasal in situ gel of Venlafoxine Hydrochloride; Formulation, Characterization and Pharmacodynamic Evaluation, March 2013; 14: 1.
8. Reena M.P. Singh, Anilkumar and Kamla Pathak Thermally Triggered Mucoadhesive in situ gel of Lorantadine: β-Cyclodextrin Complex for nasal delivery.