Research Article

Formulation and Evaluation of Thermoreversible in-situ Nasal Gel of Rizatriptan Benzoate and Caffeine

Amit Jadhav[1*], Abhishek Sagade[1], Sudarshan Jagtap[1], Gaurav shinde[1], Dr.G.Chhabra[1], Mahesh Shinde[2].
[1]Sandip Institute of Pharmaceutical Sciences (SIPS), Savitribai Phule Pune University Trimbakeshwar Road, Nashik, M.S.India.
[2]Dept.Of Pharmaceutical Sciences, RTM Nagpur University, Nagpur, M.S.India.
***Corresponding author's E-mail:** jadhavamit026@gmail.com

Received: 10-02-2018; **Revised:** 02-03-2018; **Accepted:** 15-03-2018.

ABSTRACT

Rizatriptan benzoate undergo hepatic first pass metabolism. Aim of present research work is to overcome hepatic first pass metabolism by formulating in-situ nasal gel along with caffeine to get cumulative effect. Formulation was developed to decrease the mucociliary authorization by using thermo-reversible polymer in gel, thus increase the contact time with nasal mucosa and humanizing the absorption of drug. Gels were prepared by cold technique process and evaluate by Appearance, Viscosity, Gelation Temperature, Permeation Studies, Drug Content, Gel strength etc. The gelation temperature of all studied gel formulations were found in range. pH of gel was in the range and drug content was found between 90-98.86%. Gel strength was found in range of 60-120 sec.

Keywords: Rizatriptan benzoate, caffeine, Mucociliary, thermo-reversible, polymer.

INTRODUCTION

A Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe. Typically, the headaches affect one half of the head, are pulsating in nature, and last from two to 72 hours. Associated symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell. The bioavailability of drugs from nasal formulations depends on the physicochemical properties of drug and formulation that work together to yield optimal drug delivery across the membrane. There are certain criteria that the drug should satisfy to be distributed optimally from the nasal formulation. These are molecular weight, lipophilicity, solubility, partition coefficient and pKa. Extent of the absorption of the drug depends on molecular weight particularly for hydrophilic compounds. The absorption of molecules less than 300 Da may not be influenced by their physicochemical properties. Nasal route is suitable for efficient delivery of the drugs up to 1000 Da. Absorption reduces significantly if the molecular weight is greater than 1000 Da except with the use of penetration enhancers. Lipophilic drugs have been found to be relatively more permeable across the nasal epithelium. Drug solubility is a major factor in determining absorption of drug through biological membranes. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution.

The conventional drug delivery systems like solutions, suspensions, ointments, and emulsions are no longer sufficient to fulfill the present day requirements of providing a constant rate of delivery and prolonged time. One of the main reasons for that is first pass metabolism of drug in the liver before reaching to systemic circulation which results into poor bioavailability. To overcome these problems nasal gel is the dosage form to improve the residence time and increased the bioavailability. Gels are defined as a substantially dilute cross-linked system, which exhibits no flow when in the steady-state. Gel state exists between solid and liquid phase. It has properties ranging from soft and weak to hard and tough. Thermo-reversible gel refer to those that have the capacity to make ,break ,and modify the bonds responsible for holding the network together under varied conditions of temperature , P^H or ionic concentration. The application of mucoadhesive polymers in nasal drug delivery systems has gained to promote dosage form residence time in the nasal cavity as well as improving intimacy of contact with absorptive membranes of the biological system. Carbopol is high molecular weight, cross linked poly-acrylic acid derivative with a strong mucoadhesive property. Carbopol being a pH dependant polymer is present in solution form at acidic pH but at alkaline pH forms a low viscosity gel. Carbopol polymers have very good water sorption property7. They swell in water up to 1000 times their original volume and 10 times their original diameter to form a gel when exposed to a pH environment above 4.0-6.0 because the pKa of these polymers is 6.0 ± 0.5. Rizatriptan benzoate and caffeine is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45%, and mean peak plasma concentrations (Cmax) are reached in approximately 1-1.5 hours (Tmax). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of Rizatriptan benzoate and caffeine. Food has no significant effect on the bioavailability of Rizatriptan benzoate and caffeine but delays the time to reach peak concentration by an hour. In clinical trials, Rizatriptan benzoate and caffeine was administered without regard to food. The plasma half-life of Rizatriptan benzoate in males and females averages 2-

3 hours and plasma half- life of caffeine is 5-6 hours. Present study is to achieve brain targeted drug delivery of rizatriptan benzoate and caffeine for patients suffering from migraine. It is a general study that tries to cover a nose-to-brain pathway for drug rizatriptan benzoate and caffeine. Intranasal delivery which significantly increases brain accumulation of rizatriptan benzoate and caffeine and could be an effective alternative to parenteral and oral formulations.[8, 12]

MATERIALS AND METHOD

Table 1: List of Chemicals and Instruments

S.no.	Name of chemicals/ instrument	Use
1	Carbopol 941	Polymer
2	Pluronic F127	Polymer
3	Propylene Glycol	Humectant
4	Methyl hydroxybenzoate	Preservative
5	Rizatriptan	Anti-migraine
6	Caffeine	Anti-migraine
7	Ethanol	Solvent
8	Water	Solvent
9	Sonicator	Solubility
10	Weighing balance	Weighing
11	Freeze	Gelling
12	Brookfield viscometer	Viscosity

A) Formulation of Nasal Gel

Procedure

- The thermo-reversible *in-situ* nasal gel formulation was prepared by cold method.
- For preparation of PF127 solutions, the required amount of polymer was dispersed in distilled, deionized water with continuous stirring for 1 h.
- The partially dissolved pluronic solutions were stored in the refrigerator until the polymer was completely dissolved (approximately 24 h).
- The preparation of carbopol 941 P solution is the same as that of PF127. The carbopol 941/pluronic F127 solution was mixed together.
- Then add measured volume of propylene glycol, methyl hydroxyl benzoate to the formulation and add the measured amount of rizatriptan benzoate (2%) and caffeine (8%).
- The samples were then allowed to equilibrate at 4 °C overnight (24 h at least). The composition of nasal gel is given in (above table).[4,6]

Table 2: Factorial design of batches for Optimization

Composition (%(w/v))	Carbopol 941	Pluronic F127
F1	H	H
F2	H	M
F3	H	L
F4	M	H
F5	M	M
F6	M	L
F7	L	H
F8	L	M
F9	L	L

Table 3: different Concentration of Carbopol AND PLURONIC F127

S.no.	Short form	Long form	Carbopol	Pluronic F127
1	H	High	1	19
2	M	Medium	0.50	18
3	L	Low	0.25	17

Table 4: Name of active ingredients

Sr.no	Name of active ingredient	Quantity (%)
1	Rizatriptan Benzoate	2
2	Caffeine	8

A) Evaluation of Gels

Appearance

The developed formulations were inspected visually for clarity in sol and gel form.

The formulation F4 was found to be Transparent Gel.

Content uniformity

Formulations were tested for content uniformity. Bottles containing the formulation were properly shaken for 2.3 min. The formulation, 1.0 ml was transferred into a 100-ml volumetric flask and 50 ml of simulated nasal fluid was added. The formed gel was completely crushed with the help of a glass rod, followed by vigorous shaking until the formed gel got completely dispersed to give a clear solution. The volume was adjusted to 100 ml with simulated tear fluid. The solution was filtered through a 0.45-mm filter membrane and the drug concentration was determined with a UV-Visible spectrophotometer at 280 nm and 273 nm.

Gelation Temperature

It was previously proved that pluronic undergo thermal gelation or sol-gel transition at a temperature of about 25 to 37°C. Below the transition temperature Pluronic solutions allow a comfortable and precise delivery in the

nasal cavity where thermo-gelation occurs. Immediate gelling increases residence time and enhances bioavailability of drug. The gelation temperature of all batches is shown in table 8. In Pluronic gels, gelation studies in 20-24 %(w/w) concentration showed that gelation temperature decreases with increase in gel melting temperature as Pluronic concentration increases. Gelation of PF-127 was found dependent on aqueous solubility of the polymer.

Determination of Mucoadhesive Strength

Mucoadhesive Strengths of gel was determined by using the modified method reported by Agrawal et al (7). Nasal mucosal tissues, obtained from the local slaughterhouse, were carefully removed from the nasal cavity of goat and mounted on glass surface using adhesive tape while another mucosal section was fixed in inverted position to the cylinder. 50mg of gel was placed on mucosal surface. The glass mounted mucosal surface with gel formulation and mucosal surface attached to cylinder were held in contact with each other for 2min to ensure intimate contact between them. In second pan, the weights were kept rising until two mucosa get detached from each other. The nasal mucosa was changed for each measurement.

Viscosity Measurement

The viscosity measurements were carried out by using Brookfield DV1 Digital model with spindle No.62.The instrument was equipped with the temperature control unit and the sample were equilibrated for 10 min before the measurement. The viscosity was measured against increasing shear rate.

Measurement was taken at 4^0C and 37^0C respectively.[18,16]

Table 5: Gelation Temperture, Gel Strength, Bioadhesive Force and Viscosity

Sr.No	Gelation Temp.(^{0}C)	Gel strength (Sec)	Bioadhesive Force (Dynes/cm2)	Viscosity (CP) at 4^0C	Viscosity (CP) at 37^0C
F1	36^0c	133	8014.64±0.118	51	**1463**
F2	38^0c	127	7652.64±0.118	43	**1233**
F3	38^0c	126	7591.74±0.118	39	**1180**
F4	37.5^0c	129	7775.56±0.118	41	**1240**
F5	41^0c	124	7473.64±0.118	38	**1149**
F6	42^0c	120	7232.55±0.118	35	**1058**
F7	38.5^0c	118	7112.01±0.118	33.5	**1012**
F8	39^0c	114	6870.80±0.118	31	**951**
F9	36.5^0c	110	6629.84±0.118	30.5	**910**

In-vitro Release Studies

The drug release of the Rizatriptan Benzoate and caffeine in *situ* gel was measured using Franz diffusion cell. Assembly was set and the temperature was maintained at 37±0.5°C, then 2 ml of *in -situ* nasal gel of Rizatriptan Benzoate and caffeine was applied in the donor compartment, which was separated by the receptor compartment with the cellophane membrane. 3 ml aliquots of samples were withdrawn at regular time intervals and replaced with an equal volume of phosphate buffer as fresh receptor medium. The samples were appropriately diluted with Phosphate buffer and analyzed spectro-photometrically (Double beam UV-visible spectrophotometer) at 280 nm and 273 nm.[12, 20]

In order to understand the kinetic and mechanism of drug release, the result of *in vitro* drug release study of in-situ nasal gels were fitted with various mathematical models. Based on the R2-value or n-value, the best-fitted model was selected.

Drug content estimation

Each formulation (1 ml) was taken in a 100 ml volumetric flask diluted with distilled water and shaken to dissolve the drug. The solution was filtered through Whitman filter paper and 1ml of filtered solution was further diluted to 100 ml with distilled water. Drug content was estimated spectrophotometric ally by measuring the absorbance of the above solution at 280 nm and 273 nm.

Table 6: p^H, Gelling Capacity, Drug Contents

Sr.No	pH	Gelling Capacity	Drug Content
F1	4.2	+ +	96.01±0.13
F2	4.5	+ +	97.10±0.22
F3	5.0	+ + +	97.51±0.25
F4	5.7	+ + +	98.86±0.22
F5	5.5	+ +	98.24±0.28
F6	4.8	+ +	96.04±0.18
F7	4.3	+ +	97.28±0.23
F8	4.5	+	96.03±0.56
F9	4.7	+	96.84±0.64

pH of the gels

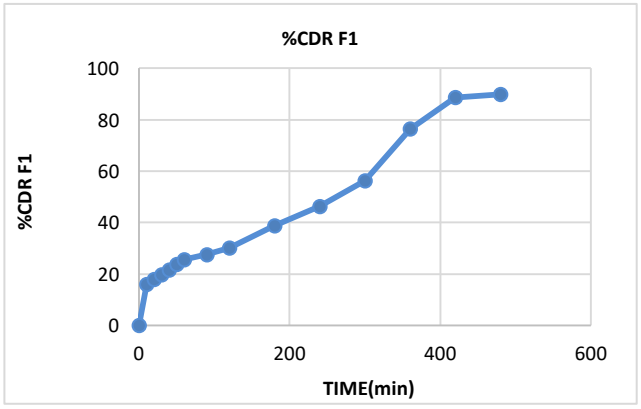
The pH of the formulations was found to be satisfactory and was in the range of 4.3-5.7. The p^H of optimized formulation (F4) was found to be 4.7.

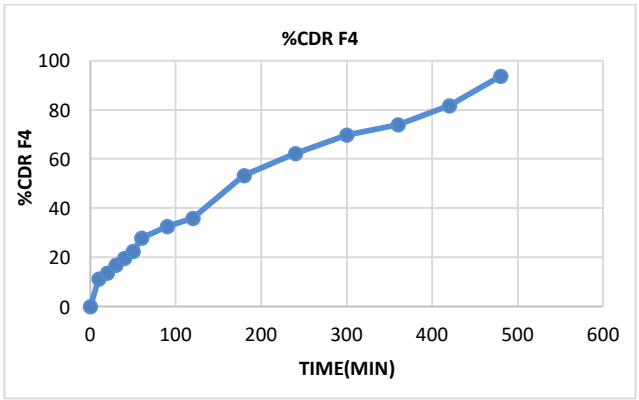
% Drug Release

Diffusion studies were carrying out using franz diffusion cell, F4 showed the persistent drug release. F1 showed drug release intermittent. Drug release in following table.

Table 7: % Drug Release:

Time(min)	%CDRF1	%CDRF4
0	0	0
10	15.942	11.254
20	17.899	13.641
30	19.699	16.842
40	21.566	19.647
50	23.744	22.456
60	25.566	27.874
90	27.496	32.581
120	30.121	35.897
180	38.755	53.264
240	46.259	62.215
300	56.263	69.754
360	76.457	73.934
420	88.694	81.631
480	89.874	93.653





RESULTS AND DISCUSSION

Thermo-reversible *in-situ* nasal gel was prepared and evaluated. Thermo-reversible *in-situ* nasal gel was evaluated in terms of appearance and it was found to be clear transparent gel. P^H of gel was checked and it was found to be in the range of 5.5 to 6.5. the formula was optimized by using 3^2 factorial design. the different gel formulation ranging from F1 to F9 was prepared by using different concentration of polymer and all nine formulations were evaluated in terms of appearance, p^H, gelation temperature, mucoadhesive strength, drug content, in-vitro drug release, drug release kinetic, content uniformity, gel strength, viscosity, gelation studies. Formulation F4 provide a good result in terms of drug release, PH, appearance, mucoadhesive strength, drug release kinetic and all other evaluation parameter within range. the formula F4 was optimized one for formulation of thermo- reversible in-situ nasal gel of rizatriptan and caffeine. The combined in-situ nasal gel formulation of rizatriptan and caffeine was more effective than rizatriptan in-situ nasal gel and dose of rizatriptan is reduced than oral and nasal formulation because of cumulative effect of rizatriptan and caffeine and it also avoid the first pass metabolism of rizatriptan thus increase bioavailability of rizatriptan.

Acknowledgement: The author's thanks to Dr.Anil jadhav principal of SIPS College Nasik, Dr.N.A.Gujarathi, Prashant Salunke, Ramhari Sagar for providing all the support and encouragements to do this work. The author's also thanks to Vikas Choure,Tushar gangurde, Mahesh choudhari and Gaurav more .etc.

REFERENCES

1. A.K.Gupta and et.al "Introduction to Pharmaceutics-II" 4th edition 2000 and reprint 2016, published by CBS publishers and distributors pvt.ltd, New Delhi, page no.207-211.
2. Allen L.V. and et.al "Ansel's pharmaceutical dosage forms and drug delivery system", 8th edition, 2nd Indian reprint 2007, Lippincott Williams and Wilkins, published by Wolters Kluwer India pvt,ltd; New Delhi , page no.277-282.
3. Allen C, 2001. Rizatriptan: clinical update. In: The triptans: novel drugs for migraine. Humphrey, P., Ferrari, M., Olesen, J., (eds). New York: Oxford University Press; 1, 2001, 199-205.
4. Choi H.K., Jung J.H., Ryu J.m., Yoon S.J., Oh Y.K., And Kim C.K., Development of in situ gelling and mucoadhesive acetaminophen liquid suppository. Int. J. Pharm. 165, 1998, 33- 44.
5. Rheological characterization of Poloxamer 407 lidocaine hydrochloride gels. Eur J Pharm Sci 17, 2002, 161-167.
6. Dr.Pawar A.p. "Modern dispensing pharmacy", 4th edition, reprint, August 2016, career publications, Nashik, page no.243-245.
7. Dr.P.V.Kasture and et.al "Pharmaceutics-II", Fifteenth edition April 2016, Published by Nirali prakashan shivaji nagar, pune, page no.70-74.

8. Gupta A.K. " Pharmaceutics -2nd practical notebook" ,2nd edition 1994, reprint 2016, , CBS publishers and distributors pvt .ltd New Delhi, page no. 122-163.
9. Kokate C.K. and et.al, "Pharmacognosy", 1st edition 2008, published by Nirali prakashan pune, page no.11.51, 11.136.
10. Mahajan HS and Gattani SG. Gellan Gum Based Microparticles of Metoclopromide hydrochloride .for Intranasal Delivery: Development and .Evaluation. Chem. Pharm. Bull. 57(4), 2009, 388-392.
11. Majithiya RJ, Ghosh, PK and Umrethia, ML, Thermoreversible mucoadhesive gel for nasal delivery of sumatriptan, AAPS PharmSciTech, 7, 2006, E1-E7.
12. Mehta R.M "pharmaceutics 2nd, 'semi solid dosage forms' 3rd edition 2010, reprint 2013, vallabh prakashan, Delhi, page no.166-167.
13. Pisal SP, Paradkar AR, Mahadik KR, Kadam SS. Pluronic gels for nasal delivery of Vitamin B12. Part I: Preformulation study. Int J Pharma 270, 2004, 37-45.
14. Rangari V.D "Pharmacognosy and photochemistry" volume 2nd edition December 2009; career publication page no .134
15. RSR.Murthy and et.al "Pharmaceutical technology" volume-I, 1st edition 2013, published by New Age International pvt.ltd, New Delhi, page no.72-73.
16. Shinde JV, Mali KK, Dias RJ, Havaldar VDand Mahajan NS. In-situ Mucoadhesive Nasal Gels of Metoclopramide hydrochloride: Preformulation and Formulation Studies. Journal of Pharmacy Research. 1(1), 2008, 88-96.
17. Yong CS, Cho JS, Quan QZ, Rhee JD, Kim CK et al. Effect of sodium chloride on Gelation temperature temperature, gel strength and bioadhesive force of Carbopol 941 gels containing diclofenac sodium", Int. J. Pharm., 226, 2001, 195-205.
18. https://en.wikipedia.org/wiki/Caffeine(time:-16.15,Date:-11/02/2018)
19. https://en.wikipedia.org/wiki/Rizatriptan(time:-16.15,11/2/2018)
20. http://www.ijddr.in/drug-development/formulation-and-evaluation-of-rizatriptan-benzoate- orallydisintegrating-tablets.php?aid=5012(time:-16.25,11/02/2018)
21. https://www.rxlist.com/maxalt-drug.html(time:-16.3011/2/2018)

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