International Journal of Drug Research and Technology
Available online at http://www.ijdrt.com
Original Research Paper

FORMULATION AND EVALUATION OF pH INDUCED *IN-SITU* NASAL GEL FOR BRAIN TARGETING OF LEVODOPA

Piyush Jangam* and Ambekar Abdul Wahid

Department of Pharmaceutics, P.D.V.V.P.F's College of Pharmacy, Vilad Ghat, MIDC, Ahemadnagar-414001, Maharashtra, India

ABSTRACT

Background: Levodopa is used in the treatment of Parkinson. It get absorbed from small intestine, but Levodopa get metabolized in peripheral tissues by L-aromatic amino acid decarboxylase (AAAD) enzyme, which degrades levodopa and thus serves as a significant barrier to the absorption of intact levodopa; only 30% of an orally administered dose reaches the circulation.

Methods: In situ nasal gel of levodopa was prepared to increase its bioavailability as well as rapid onset of action. Carbapol 934 was used as the gelling agent to form the gel in the nasal pH. To overcome the problem of mucociliary clearance we used here HPMC K4M as the mucoadhesive polymer. Thus different formulations were prepared by using different combination of the polymers judicially and evaluated them in respect of pH, gelation temperature, mucoadhesive force and permeation of levodopa.

Results: From the above study, we observed that the pH sensitive polymer and mucoadhesive polymer used here had distinct effects.

Keywords: Formulation, Development, Evaluation, Levodopa, Parkinson drugs, In situ nasal gel, Brain targeting treatment.

INTRODUCTION

The Delivery of especially CNS acting drugs through oral route is possible but the bioavailability of the drug through this route is very less as compared to nasal route. This is due to the First pass metabolism in the GIT. Nasal drug delivery system is the most effective way of drug delivery of Brain targeting therapies. The high permeability, high vasculature and low enzymatic environment of nasal cavity are well suitable for systemic delivery of drug molecules via nose increases its specificity and efficiency of the CNS acting drugs. Due to the CNS acting drugs used for the treatment of Brain diseases are not easily able to cross these barriers due to their physicochemical properties. There are various drug delivery and targeting strategies are currently being developed to enhance the transport and distribution of drugs into the brain which are highly specific to their target. Nasal drug delivery is an emerging technique and even better option to transport the drug directly to brain bypassing the metabolism.

Advantages of In Situ Gel

- Increased residence time of drug in nasal cavity.
- Decreased frequency of drug administration.
- Results in rapid absorption and onset of effect.
- Avoids degradation of drug in gastrointestinal tract resulting from acidic or Enzymatic degradation.
- Low dose required.
- Minimized local and systemic side effects.
- Improved bioavailability of drug.
- Direct transport into systemic circulation and CNS is possible.

- Offers lower risk of overdose of CNS acting drug.
- Improved patient compliance.

Properties of Nasal *In-Situ* Gel

- It should be low viscous.
- It should be free flowing to allow for reproducible administration to the nasal cavity, as droplet mist or as a spray.
- Nasal *in-situ* gel should have long residence time.
- The nasal *in-situ* gel follows phase transition mechanism and to stand with the shear forces in the nasal cavity wall.

MATERIALS AND METHODS

Levodopa was received as a gift sample from Lupin Pharma Pune. Carbapol 934 and HPMC K4M were purchased from Sigma Drug Laboratory Pvt. Ltd, Sodium metabisulphite, and Sodium chloride of analytical grade was purchased from Vishal Chemicals, Mumbai. Compatibility study was carried out with drug and the excipients in standard manner.

Selection of Polymers Concentration

The concentration of Carbapol 934 was selected so as to obtain gel at minimum possible concentration below 34°C and pH of 4.5. HPMC K4M was used as mucoadhesive polymer to increase the gel strength.

Selection of Excipients

Excipients such as 0.9% w/v NaCl was added as to maintain the isotonicity of the formulation, benzalkonium chloride was added as preservative and sodium metabisulphide was used as antioxidant to protect the formulation from microorganisms and oxidation. Distilled water was used as vehicle.

Formulation of *In-Situ* Gel

The Formulation of *in situ* gel consists of pH sensitive polymers such as Carbapol 934 was slowly added to distilled water with continuous dispersion was kept on magnetic stirrer until clear solution was formed (12hrs). After clear solution is formed drug of yield 0.25% were then dissolve to this clear solution and stirred on magnetic stirrer. Then mucoadhesive polymer HPMC K4M

was slowly added to this solution with continuous agitation. The remaining excipients i.e. Benzalkonium chloride, sodium chloride, sodium metabisulfite was added with continues stirring on magnetic stirrer to form a clear solution. Adjust the pH of formulation to 4.5 by 0.5 M sodium hydroxide.

Standard Calibration Curve of Levodopa

A simple and sensitive UV spectrophotometric method was developed and validated for the determination of levodopa in bulk & pharmaceutical formulations. A stock solution of PGB (50 μg/ml) was prepared by dissolving 5 mg PGB in 100 ml volumetric flasks with double distilled water. The stock solution (50 μg/ml) was used to prepare the working solutions by suitable dilutions with distilled water. The solutions were stable at least 10 days in room temperature.

Evaluation Parameters of *In-Situ* Nasal Gel Clarity

It is one of the most important characteristics features of gel formulation. All developed formulations were evaluated for clarity by visual observation against black and white background.

pH

The pH of each batch was measured using digital pH meter which was calibrated using buffers of pH 4 and pH 7 before the measurements.

Drug Content

Uniform distribution of active ingredient is important to get dose uniformity. 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.

Viscosity Determination

Viscosity of formulation is an important factor in determining the intactness and residence time of formulation in nasal cavity. The rheological

studies were carried using the Brookfield's DV – II + model viscometer. The gel formulations under study were placed in the sample holder and the suitable spindle selected was lowered perpendicular in to the sample. The Viscosity was measured at 10 rpm for 30 sec for solution as well as gel. The apparent single viscosity values of formulation were measured at constant temperature 37±1°C. Viscosity is determined for all 6 formulations.

Gelation Study

These formulation are solution at pH 4.5 and when exposed to pH above 5.5 it undergoes gelation which is at nasal pH. Take a test tube fill it with formulation in solution form to it add 2 ml of 0.5 M sodium hydroxide whose pH is endogenous to nasal pH which forms gel upon the visual examination we can observe the gelation.

Gel Strength Measurement

A sample of 50 gm of formulation was placed in 100 ml graduated cylinder and gelled by neutralizing by 0.5 M NaOH. A weight of 35 gm was placed onto gel, The gel strength which is the indication for viscosity of nasal *in-situ* gel at physiological condition was determined by time in seconds the weight took to penetrate 5 cm down through the gel.

In-Vitro Diffusion Study

Tissue samples are inserted in Franz diffusion cells displaying a permeation area of 0.785 cm, 2. 20 ml phosphate buffer saline (PBS) pH 6.8 at 34°C was added in the acceptor chamber. The temperature within the chambers is maintained at 34°C. Formulation equivalent to 25 mg was placed in the donor chamber. At predetermined time points, 1ml sample was withdrawn from the acceptor compartment, replacing the sampled volume with PBS pH 6.8 after each sampling for four hours. Samples withdrawn were filtered and analyzed spectrophotometrically. Blank samples can be run simultaneously throughout the experiment to check for any interference. The amount of permeated drug was determined using UV visible spectrophotometer at 2.

DISCUSSION

The absorbance of levodopa in distilled water at 281 nm. The standard calibration curve of levodopa is shown in table below. The formulation can be formulated along with carbapol 934 and HPMC k4m where carbapol 934 is a pH sensitive polymer and HPMC k4m gives mucoadhesive strength to the formulation. All the formulations are clear solutions in appearance having Ph in the range of 5.78 to 6.48. The viscosities of the formulations are shown in table below. All formulations have drug content in between Table. The gelation studies shows in Table below. The gel strength is between 25-50 seconds which shows that the gel formed is having sufficient mucoadhesive strength and the greater gel strength may cause choking or incompliance to the patient it can be adjusted with the concentration of HPMC k4m with the carbapol 934.The cumulative drug release shown in table below.

CONCLUSION

From the results we conclude that the *In-situ* nasal liquid formulation was successfully formulated and it converts into gel when administered into nasal tract due to change in pH as it contains carbapol 934 and HPMC k4m which are the pH sensitive polymers which increases the drug residence time prevents draining of drug and also release of the drug for extended period of time. Hence it increases bioavailability with less dose and prevents first pass effect and acts as the targeted drug delivery system which targets drug to the brain through nasal mucosa and bypasses blood brain barrier which are its superiority over the conventional dosage forms.

Table 1: Formulation table

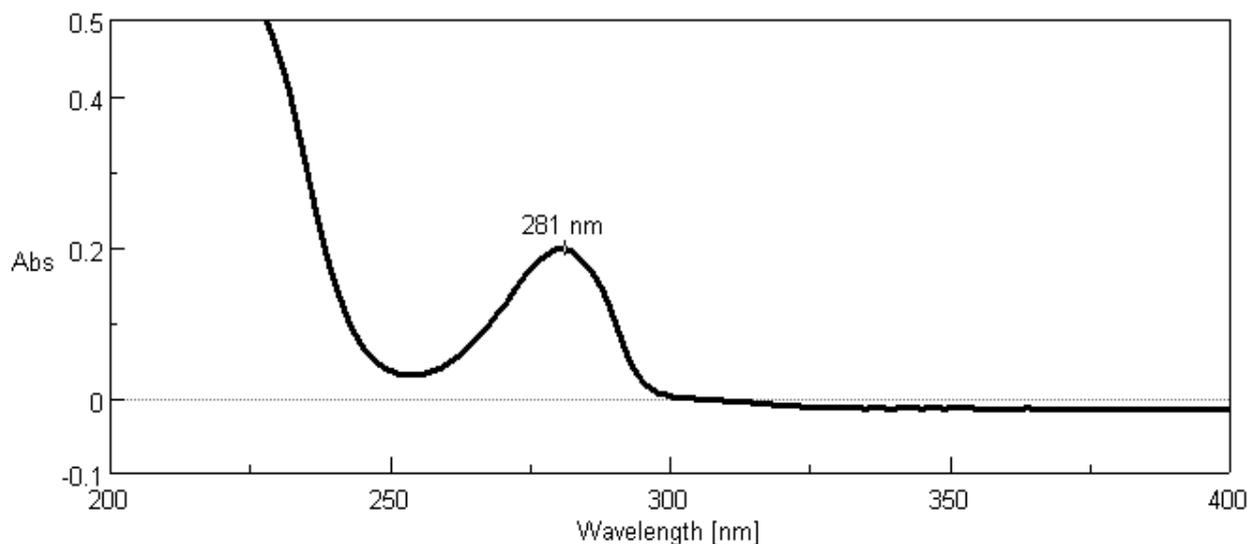| Ingredients	F1	F2	F3	F4	F5	F6
Levodopa	0.25	0.25	0.25	0.25	0.25	0.25
Carbapol 934(%w/v)	0.1	0.2	0.3	0.4	0.5	0.6
HPMC K4M(%w/v)	0.1	0.1	0.1	0.2	0.3	0.4
Nacl (%w/v)	0.9	0.9	0.9	0.9	0.9	0.9
Benzalkonium chloride (%w/v)	0.02	0.02	0.02	0.02	0.02	0.02
Sodium metabisuphate(%w/v)	0.1	0.1	0.1	0.1	0.1	0.1
Distilled water (ml)	q.s	q.s	q.s	q.s	q.s	q.s

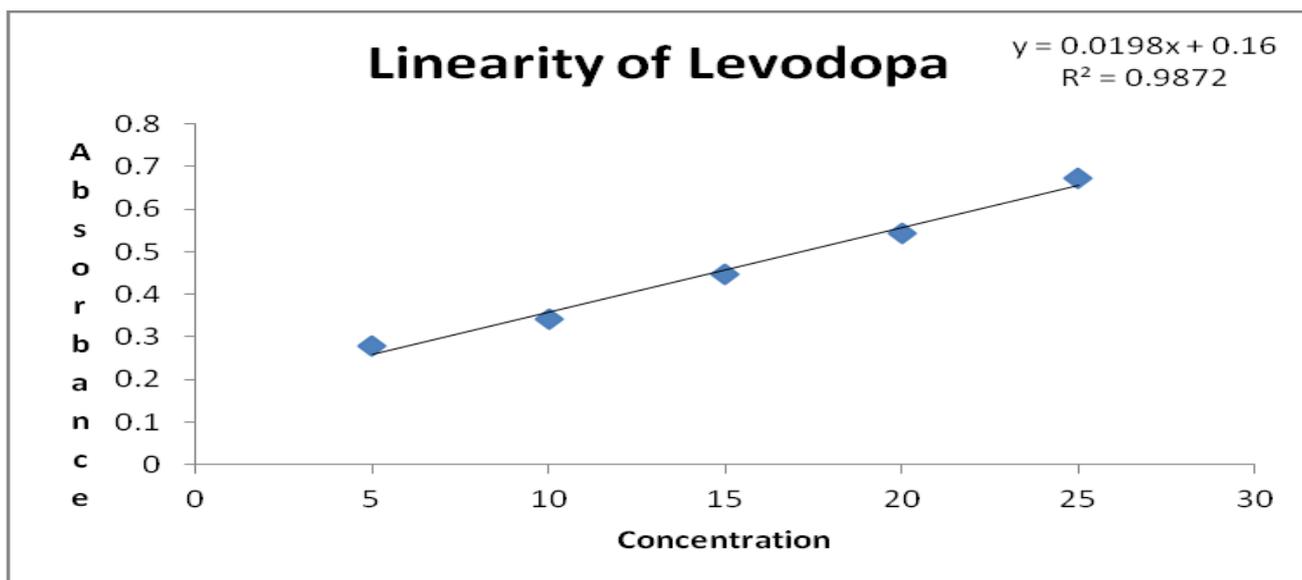
Figure 1: UV spectrum of levodopa

Figure 2: Calibration curve of levodopa (Wavelength maxima at 210 nm of Levodopa)

Table 2: pH and gelling capacities of Formulations

Formulation	Appearance	Fragrance efficiency	pH	Gelling capacity
F1	Colourless	Pleasant Odour	6.5	+ + + +
F2	Colourless	Pleasant Odour	6.2	+ + +
F3	Colourless	Pleasant Odour	6.1	+ + +
F4	Colourless	Pleasant Odour	6.4	+ +
F5	Colourless	Pleasant Odour	6.2	+ + +

Table 3: Drug content, Viscosity and Gel strength of prepared formulations

Formulation	Drug content (%w/w)	Viscosity of liquid Formulation (Pa.S)	Viscosity of Gel (Pa.S)	Gel strength (Seconds)
F1	94.00%	1.440	36.120	28.00
F2	92.93%	1.500	33.600	25.33
F3	96.83%	1.560	34.080	27.00
F4	93.21%	3.708	36.380	29.66
F5	95.75%	3.812	38.230	39.66

Table 4: Cumulative % release and levodopa through goat nasal membrane for all formulations

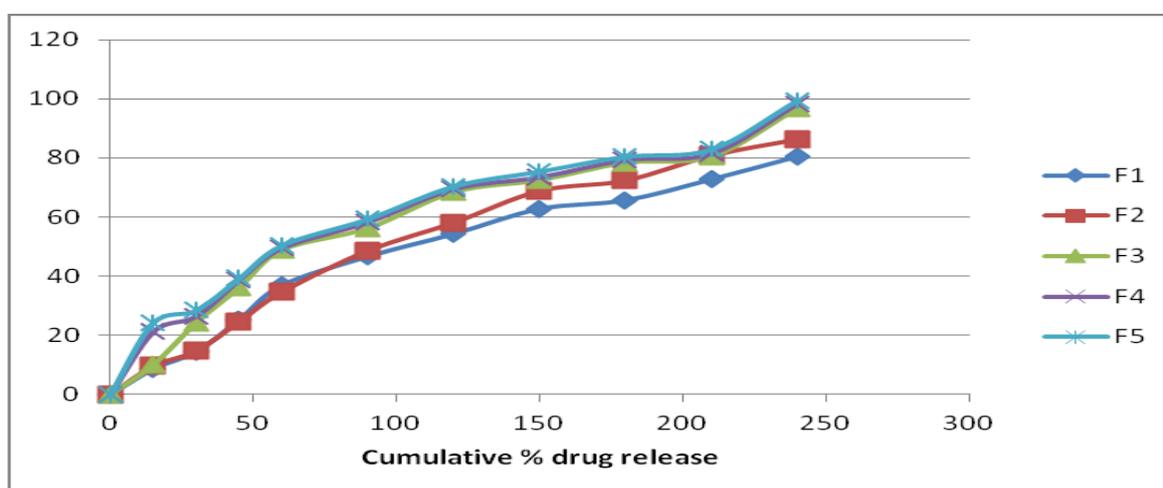| Time (min)	F1	F2	F3	F4	F5
15	8.72	9.70	10.14	11.24	12.48
30	14.56	14.72	24.36	26.36	28.67
45	25.29	34.76	36.24	38.45	39.65
60	36.92	34.76	48.24	49.95	50.45
90	46.62	48.62	56.26	57.83	59.35
12	54.25	58.12	68.46	69.47	70.46
150	62.68	68.84	72.48	73.48	75.45
180	65.57	72.34	78.36	79.57	80.94
210	72.67	80.76	80.46	81.25	84.88
240	80.34	86.24	96.75	98.48	99.45

Figure 3: Comparative effect on drug release of various formulation

REFERENCES

1. Hermans, PH(2004), "***Colloid Science, Kruty H.R.(Ed)***", Elsevier, Amsterdam, 2, 483-651.

2. Honrao, MS and Pabari, R (2004), "***The Indian Pharmacist***", India, 16-21.

3. Shah, H and Patel, M (2012), "In Situ Gelling System: An Insight", ***Inventi Impact***, (3),143-170.

4. Kute, JU; Darekar, AB and Saudagar, RB (2013), "In Situ Gel-Novel Approach for Nasal Delivery", ***World Journal of Pharmacy and Pharmaceutical Sciences***, 3(1), 187-203.

5. Peppas, N and Langer, R (1994), "***New Challenges in Biomaterials Science***", 263, 171-520.

6. Nerkar, TS; Gujarathi, N; Rane, BR; Bakliwal, SR and Pawar, SP, (2013),"In situ gel: Novel Approach in Sustained and Controlled Drug Delivery System", ***International Journal of Pharmaceutical Sciences***, 4(4), 1-18.

7. Upadhyay, S; Parikh, A; Joshi, P; Upadhyay, UM and Chotai, NP (2011), "Intranasal Drug Delivery System- A glimpse to become maestro", ***Journal of Applied Pharmaceutical Science***, 01 (03), 34-44.

8. Chhajed, S; Sangale, S and Barhate, SD (2011), "Advantageous Nasal Drug Delivery System: A Review", ***International Journal of Pharmaceutical Sciences and Research***, 2(6), 1322-1336.

9. Findlay, SM (2008), "Drug Delivery Markets-An Outlook, Industry Analyst, Pharmaceutical & Biotechnology, Healthcare", ***EIA***, 1-2.

10. Cauna, N (1982), "***Blood and Nerve Supply of the Nasal Lining***", in: D, FProctor; IB, Andersen (Eds.), Chapter in The Nose: Upper Airway Physiology and the Atmospheric Environment, Elsevier Biomedical Press, Amsterdam, 45-69.

11. Dey, S; Mahanti, B; Mazumder, B; Malgope, A and Dasgupta, S (2011), "Nasal drug delivery: An approach of drug delivery through nasal route", ***Der Pharmaciasinica***, 2(3), 94-106.

12. Anoop, KR; Nair, SC and John, MS (2014), "In situ Gel: An Innovative Approach for Safe and Sustained Nasal Drug Delivery", ***International Journal of Pharmaceutical Sciences Review and Research***, 24(1), 1-7.

13. Pagar, SA; Shinkar, DM and Saudagar, RB (2013), "A Review on Intranasal Drug Delivery System", ***Journal of Advanced Pharmacy Education & Research***, 3(4), 333-346.

14. Pires, A; Fortuna, A; Gilberto, A and Amilcar, F (2009), "Intranasal Drug Delivery: How, Why and What for?", ***Journal Pharmaceutical Science***, 12(3), 288-311.

15. Bajpai, V(2014), "In situ Gel Nasal Drug Delivery System – A Review", ***International Journal of Pharma Sciences***, 4, 2014,

16. Chavan, P; Dhole, S and Yadav, M (2014), "nasal drug delivery system: a review", ***World Journal of Pharmacy and Pharmaceutical Sciences***, 3(12), 598-617.

17. Ramya, DD; Abhirami, M; Brindha, R; Gomathi, S and Vedhahari, BN (2013) "*In-Situ* Gelling System – Potential Tool For Improving Therapeutic Effects Of Drugs", ***International Journal of Pharmacy And Pharmaceutical Sciences***, 5(3), 27-30.

18. Swamy, NGN and Zaheer, A (2012), "Mucoadhesive In situ Gels as Nasal Drug Delivery Systems: An Overview", ***Asian Journal of Pharmaceutical Sciences***, 7(3), 168-180.

19. Patil, PR; Salve, VK; Puranik, PK; Khadbadi, SS (2013), "Modern Encroachment and Provocation in Nasal Drug DeliverySystem", ***International Journal of Pharmaceutical Sciences and Research***, 4(7), 2569-2575.

20. Kute, JU; Darekar, AB and Saudagar, RB(2013), "In situ Gel-NovelApproach for Nasal Delivery", ***World Journal of PharmacyAnd Pharmaceutical Sciences***, 3(1), 187203.

21. Tyagi, S; Sharma, N; Sharma, PK (2012), "A Review on Applicationof Natural Bioadhesive Polysaccharides for Intranasal DrugDelivery", ***International Journal of Applied Pharmaceuticalsciences and Biomedical Sciences***, 1(2), 80-94.

22. Kamble, MS; Bhalerao, KK; Bhosale, AV; Chaudhari, PD(2013),"A Review on Nose-To-Brain Drug Delivery," ***International Journal of Pharmaceutical and Chemical Sciences***, 2(1),, 516-525.

23. Nirmal, HB; Bakliwal, SR and Pawar, SP (2010), "*In-Situ* Gel: Newtrends in controlled and Sustained Drug Delivery System", *International Journal of Pharmatech Research*, 2(2),1398-1408.

24. Panchal, DR; Patel, UL; Bhimani, BV; Daslaniya, DJ and Patel, GV (2012), "Nasal *In-Situ* Gel: A Novel Drug Delivery System",International Journal for Pharmaceutical Research Scholars, 1(2), 457-473.

25. Devmore, PS; Chothe, BT; Kambale. RP;Waghchoure, PS, Raut and SV, Waghmode RR (2014), "A Review on In Vitro Methodsand Factors Affecting Nasal Drug Absorption", *American Journal of Pharmatech Research*, 4(1), 283-307.

Correspondence Author:

Piyush Jangam＊

Department of Pharmaceutics, P.D.V.V.P.F's College of Pharmacy, Vilad Ghat, MIDC, Ahemadnagar-414001, Maharashtra, India

Cite This Article: Piyush, Jangam and Ambekar, AW (2016), "formulation development and evaluation of *in-situ* nasal gel of levodopa for brain targeting treatment of antiparkinson drugs", *International Journal of Drug Research and Technology*, Vol. 6 (3), 175-181.