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Research Article
Prolonged and Floating Drug Delivery System of Gabapentin for Effective Management of Pain in Spinal Cord Injury

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Abstract
Gabapentin is an effective drug in post-traumatic spinal injury induced neuropathic pain. But it requires high dosage and frequency in the management of neuropathic pain. As it is typically absorbed from the upper intestine its floating microspheres were prepared in order to improve the drug release with prolonged drug delivery. The floating microspheres of gabapentin were prepared using two polymers polyvinyl alcohol and carbopol 934 and characterized for drug loading, particle size, floating time, *in vitro* drug release, *in vivo* analgesic activity and clinical analgesic study. The physicochemical characterization of floating microspheres showed high percentage drug loading ranging from 81.20±0.04-91.08±0.86%. The particle size was found to be 415.50±18.12-524.68±10.09 μm in optical microscopy. The floating time *in vitro* was 5.88±0.25-9.02±0.12 h. The microspheres showed prolonged drug release extending to more than 12 h in the *in vitro* study. The percentage drug release was found to be 79.24, 84.28, 92.24 and 90.12% at the end of 12 h. The formulation MG4 showed best *in vivo* analgesic activity in rats (by hot plate method). In human MG4 showed better mean pain score at Visual Analogue Scale (VAS) at each time point of observation in 4 week study. The MG4 showed mean pain score of 4.96±0.45 as compared to that of conventional tablet treatment (5.99±1.01). The significant improvement in neuropathic pain by the prepared floating microspheres was obtained. It was concluded that the floating microspheres of gabapentin may serve as a potential alternative of conventional dosage forms which require high dosage frequency and still result in effective pain management.

Key words: Gabapentin, analgesic, neuropathic pain, floating, spinal injury

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The traumatic injury to spinal cord causes primary (immediate damage to nerve tissues) and secondary (series of adverse events like apoptosis, inflammation etc. triggered by the primary damage) type of spinal injury which results in the neuropathic pain and inflammation (Chang *et al*., 2013; Turner and Cardenas, 1999; Eide, 1998; Warms *et al*., 2002). Neuropathic pain many times remains either unrecognized or inadequately treated. The typical signs and symptoms of neuropathic pain vary from person to person with tingling or burning like sensation. The medications traditionally used for neuropathic pain include opioid analgesics, nonsteroidal anti-inflammatory drugs and tricyclic antidepressants (TCAs). Out of these TCAs are considered as first-line agents for neuropathic pain. But the use of TCAs is limited by unwanted side effects and a risk of cardiovascular mortality (Siddall *et al*., 1997; Thuret *et al*., 2006; Demirel *et al*., 1998; Celik *et al*., 2012; New *et al*., 1997).

Gabapentin [1-(aminomethyl) cyclohexaneacetic acid] is a white to off-white crystalline solid an antiepileptic drug but now it is used to treat neuropathic pain induced by spinal injuries. For treating the peripheral and neuropathic pain caused by traumatic spinal njuries, it is used upto 3.6 g day^{-1} (in tablet, capsule and/or oral solution) (Backonja *et al*., 1998; Rowbotham *et al*., 1998; To *et al*., 2002; Tai *et al*., 2002). It is freely soluble in water (4491 mg L^{-1} at 25°C), basic and acidic aqueous solutions with dissociation constants pKa of 3.68 and 10.7, respectively. An absolute bioavailability of approximately 50% makes gabapentin a good candidate for improvement of oral bioavailability (Meimandi *et al*., 2005). Due to short biological half life (5-7 h) frequent dosing (at least three times daily) is required for maintaining the desired drug level for the whole day. But this leads to significant fluctuations in the plasma concentration of gabapentin. Moreover, gabapentin is associated with the absorption window phenomenon because it is absorbed through a large neutral amino acid transporter (with limited transport capacity) located in the upper small intestine (Finnerup *et al*., 2001; Levendoglu *et al*., 2004; Mellegers *et al*., 2001; Hagen and Rekand, 2015; Hama *et al*., 2014; Kukkar *et al*., 2013). Due to limited capacity nature of transporter the higher doses of gabapentin cannot give the higher plasma levels. Therefore, to overcome the above limitations the Floating Drug Delivery Systems (FDDS) or Hydrodynamically Balanced Systems (HBS) of gabapentin have been investigated to increase the gastric residence and hence, the increased drug delivery in its absorption window. The FDDS were prepared for providing continuous delivery at the optimal site of absorption (absorption window) over 8-10 h leading to higher bioavailability. Floating microspheres of gabapentin were developed and evaluated for various physiochemical parameters as well as *in vitro* and *in vivo* tests in various previous studies (Sang *et al*., 2013; Gupta and Li, 2013; Chen *et al*., 2013).

The FDDSs are the delivery systems which float over the gastric fluids (due to lower density than the gastric fluid) for prolonged period of time and thereby increasing the gastric residence time of the drug delivery system. This allows the drug to get released slowly in the desired absorption site (upper GIT) with a better control of the fluctuations in plasma drug concentration. It is one of the most feasible approaches for achieving a prolonged, predictable and systemic drug delivery profiles (Prinderre *et al*., 2011; Jiang *et al*., 2015; Semalty and Semwal, 2014).

In this study, the floating microspheres of gabapentin were prepared using carbopol 934 and polyvinyl alcohol in order to improve the drug release with prolonged drug delivery. The prepared microspheres were evaluated for preclinical and clinical analgesic activity.

MATERIALS AND METHODS

Materials: Gabapentin, carbopol 934 and polyvinyl alcohol (cold) were purchased from Sigma Aldrich Japan. Rest of the chemicals were of analytical grade.

Preparation of floating microspheres of gabapentin: The microspheres were prepared by emulsion solvent evaporation technique (Table 1). Oil phase was prepared by dissolving the carbopol 934 to a chloroform solution of the drug. The PVA in 0.2% w/v was used as the aqueous phase and then the polymeric solution with drug was added to it with stirring (200 rpm) till the solvent gets evaporated off completely. The floating microspheres were obtained by filtration, washed (with deionized water) and then air dried in shade for 12 h.

Drug loading: Microspheres equivalent to 100 mg of gabapentin were transferred to 100 mL volumetric flask containing 20 mL of 0.1 N HCl. The flask was shaken well and then volume was made up to 100 mL with 0.1 N HCl. The flask

Table 1: Composition of microspheres of gabapentin

Formulation code	Drug (%w/v)	Polyvinyl alcohol (%w/v)	Carbopol 934 (%w/v)
MG1	1	2	2
MG2	1	2	4
MG3	1	3	2
MG4	1	3	4

was stirred for 2 h on magnetic stirrer at 37°C till all the solid microparticles get dissolved. The sample was withdrawn and analysed spectrophotometrically at 210 nm after suitable dilution using 0.1 N HCl as a blank.

Particle-size analysis: The size of the microspheres were determined using an optical microscope (Olympus, Tokyo, Japan) fited with an ocular micrometer. The ocular micrometer was calibrated with a stage micrometer. A total of 100 microspheres of each formulation were evaluated and the mean diameter was reported.

***In vitro* drug release study:** *In vitro* drug release study was performed by using USPXXIV (Type 2) dissolution test apparatus for 12 h. Operating conditions were: Dissolution medium 900 mL 0.1 N HCl, agitation speed 50 rpm and temperature 37±0.5°C. Samples (5 mL each) were withdrawn at definite time intervals, suitably diluted and then analyzed spectrophotometrically at 210 nm using 0.1 N HCl as a blank. At the time of each withdrawal of samples same volume of prewarmed (37±0.5°C) fresh media was replaced to compensate the withdrawn fluid.

***In vivo* study**

Animals: Healthy male Wistar rats (200-270 g) were used for the study. The rats were kept in standard environmental conditions of light and temperature. The rats were allowed free access to drinking water and standard diet. Rats were used after a resting period of 2 days post procurement. The animal and clinical study protocols were approved by the Animal Ethical Committee of Xinxiang Medical University, Weihui (2015/0023a).

***In vivo* analgesic activity by hot plate assay:** The rats were divided in three groups (2 test, control and standard) with 6 animals in each group. Test was performed on an electronically controlled hot plate heated to 55°C (±0.2°C). Baseline measurements for each mouse were taken by placing them unrestrained on the hot plate just before administration of saline or drug. Samples were given (50 mg kg^{-1}) or saline (control). Latency to licking a hind paw or jumping from the apparatus was measured after 30 and 60 min of drug administration.

Clinical analgesic performance of gabapentin microspheres: From the hospital records the patients of spinal injuries being prescribed gabapentin were identified. Those were a total of 32 patients (with mean age of 49 years, with a range of 21-69 years. There were 21 males and 11 females. The patients were randomized to receive gabapentin 300 mg (t.i.d.) and gabapentin microspheres (equivalent to 600 mg, o.d.) for 1 month in a randomized crossover design with a 2-week washout period. Pain was assessed prior to treatment (baseline) and at 1, 2 and 4 weeks during treatment with a 10 cm visual analogue scale (ranging from 0 `no pain' to 10 `worst pain imaginable').

Statistical analysis: Results were expressed as Mean±Standard Deviations and the significance of the difference observed was analyzed by the student's t-test.

RESULTS

The floating microspheres of gabapentin were prepared for the improved performance in spinal injury induced neuropathic pain.

The physicochemical characterization of floating microspheres showed high percentage drug loading ranging from 81.20±0.04-91.08±0.86% (Table 2). The particle size was found to be 415.50±18.12-524.68±10.09 μm in optical microscopy. The floating time *in vitro* was 5.88±0.25-9.02±0.12 h. It was observed that the surface of the microspheres were irregular and rough.

The microspheres showed prolonged drug release in the *in vitro* study extending the release to more than 12 h. The percentage drug release was found to be 79.24, 84.28, 92.24 and 90.12% at the end of 12 h.

The *in vivo* study was performed for assessing the analgesic activity of prepared microspheres. The hot plate method was used to assess the analgesic activity. The formulation MG3 and MG4 were selected for the study. Gabapentin microspheres were used at doses of 50 mg kg^{-1} and all the formulations significantly increased hot plate latency (Table 3). It was observed that gabapentin microspheres delayed the reaction time on the hot plate with the best activity shown by MG4.

The MG4 (600 mg, o.d.) was further assessed in the patients suffering from neuropathic pain due to spinal injuries as compared to oral gabapentin conventional tablet (300 mg, t.i.d) (Table 4). It was observed that MG showed better mean pain score on VAS at each time point of observation in 4 week study. The MG4 showed mean

Table 2: Physicochemical evaluation of gabapentin microspheres

Microspheres	Drug loading (%)	Particle size (μm)	Floating time (h)
MG1	89.80±0.62	415.50±18.12	6.47±3.08
MG2	88.46±0.24	458.30±12.20	5.88±0.25
MG3	91.08±0.86	524.68±10.09	6.60±0.94
MG4	81.20±0.04	504.84±10.75	9.02 ±0.12

Table 3: *In vivo* analgesic activity of floating microspheres of gabapentin

	Latencies (sec) for nociceptive reaction after time (h)*		
Formulation	0	0.5	1.0
Control	10.1±0.66	11.01±0.61	111.4±1.0
MG3	10.2±0.65	12.9±1.2[a]	14.50±1.1[a]
MG4	11.1±0.90	16.5±1.20 [b]	18.54±1.2[b]

*SEM (n = 6). Significant increase in nociceptive latencies [a]p<0.05,[b]p<0.01 compared to the baseline level of nociceptive reaction (Student's t test)

Table 4: Pain score on visual analogue scale in spinal injury patients

	Mean pain score in VAS*	
Time point of observation	Gabapentin tablet (300 mg, t.i.d.)	Gabapentin microspheres (600 mg, o.d.)
Baseline	8.98±0.99	8.87±0.89
1 week	8.01±1.21	7.69±1.02
2 week	6.45±1.09	5.86±1.22
4 week	5.99±1.01	4.96±0.45

*VAS : Visual analogue scale

VAS of 4.96±0.45 as compared to that of conventional tablet treatment (5.99±1.01).

DISCUSSION

Various studies have investigated the gastroretentive modified release dosage forms of gabapentin for the management of neuropathic pain (Arora *et al*., 2005; Jain *et al*., 2008).

The gastroretention is one of the most practical and the most successful approach for delivering the high levels of drugs without adverse effects. Moreover, the gastroretention approach reduces the required dose and the dosage frequency of the drug. Among the various gastroretentive drug delivery systems the microspheres being multiple unit dosage forms have received much attention floating drug delivery systems. These floating microspheres show various advantages over the single unit dosage forms like tablets. These systems are devoid of any adverse effects like dose dumping which is a quite common adverse effect with controlled release single unit dosage forms. Moreover, these systems provide more uniform drug absorption and distribution which in turn lead to the reduction in patient to patient variability (Kotreka and Adeyeye, 2011; Bhadouriya *et al*., 2012; Soppimath *et al*., 2001; Semalty *et al*., 2010).

In the present study, the gastroretention was planned through the delivering the drugs in the polymeric matrix which was having good buoyancy over the gastro intestinal fluid. The particle size, percent drug loading, floating time and the *in vitro* drug release was very satisfactory for the formulations. The formulation of gabapentin microspheres delayed the reaction time on the hot plate with the best activity shown by MG4 (containing drug: PVA: CP in 1:3:4). The same formulation showed better mean pain score on VAS in randomized trial on the patients. The significant improvement in neuropathic pain by the prepared floating microspheres was well supported by the previous studies (Gaur *et al*., 2014; North *et al*., 2015; Kaye *et al*., 2014; Freeman *et al*., 2015).

CONCLUSION

It can be concluded that the gastroretentive floating microspheres of gabapentin might serve as a potential alternative of conventional dosage forms (which require high dosage frequency and still result in ineffective pain management). It was concluded that the neuropathic pain can be well managed with the floating microspheres loaded with gabapentin.

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