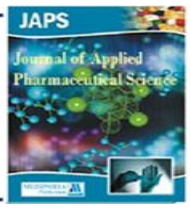
Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 16-07-2012
Revised on: 22-07-2012
Accepted on: 26-07-2012
DOI: 10.7324/JAPS.2012.2729

Formulation and Evaluation of Sustained Release Ondansetron Poloxamer Based Solid Suppositories

Zawar L R and Bhandari G S

Zawar L R
Dept.of Pharmaceutics,
H. R. Patel Institute of Pharmaceutical Education & Research, Shirpur, India.

Bhandari G S
Dept.of Pharmaceutics,
R.C.Patel Institute of Pharmacy, Shirpur, India.

For Correspondence
Mr. L. R. Zawar
Dept .of Pharmaceutics
H R Patel Institute of Pharmaceutical Education & Research
Shirpur (Dhule) MS, India.

ABSTRACT

The present investigation studies the effect of water swellable polymer hydroxylpropylmethyl cellulose (HPMC K4M, Methocel) on *in vitro* release of ondansetron from suppositories. Suppositories were prepared by using mixture of Poloxamer 407 and Poloxamer 188 hydrophilic bases. Suppositories containing 16 mg of ondansetron were prepared by fusion method. Weight variation, content uniformity, breaking (hardness), disintegration time, melting point and liquefaction time of the formulations were determined. *In vitro* release test was carried out according to USP XXII basket method. *In vitro* release data demonstrates ondansetron release from suppositories up to 12hrs and follows the zero order kinetics from poloxamer mixture based suppositories.

Keywords: Ondansetron, Poloxamer 407, poloxamer 188, HPMC, sustain release.

INTRODUCTION

Conventional suppository are made up of polyethylene glycol (PEG) base, which may softens or melts after considerable time in the rectum due to its relatively high melting point and thus cannot be rapidly adsorbed in rectal mucous membranes (Burstein *et al.,* 2000). Furthermore, such PEG based suppository, which may reach the end of the colon due to their higher melting point and results into the loss of drug due to first-pass effect (Kim *et al.,* 1998). To solve these problems of conventional suppository, it would be desirable to develop a novel solid suppository, which is solid in phase at room temperature but instantly melts at physiological temperature and retains for longer duration in rectum instead of colon. Such a suppository must have the suppository base with the suitable melting point (30-36ºC) & mucoadhesive property.

In this study, novel poloxamer-based suppository have been developed with a mixture of poloxamer 407 & poloxamer 188 with melting point of about 15 & 55º C respectively (Abhaham C., 1994). In addition to lower melting point of P124 & P188, they are known to have suitable mucoadhesive force (Choi *et al.*, 1998), low toxicity (Yun *et al.*, 1999), less skin irritation (Choi *et al.*, 1998), compatibility with other chemicals and good drug release characteristics.According to biopharmaceutical classification system, Ondansetron comes under class II with low solubility and high permeability. Ondansetron is chemically 1,2,3,9- tetrahydro – 9- methyl-3- [(2-methyl-1-H-imidazole-1-y1) methyl]- 4H carbazol – 4-one which is highly selective 5-HT3 receptor antagonist and numerous studies have demonstrated its superior anti-emetic efficacy over high dose metoclopramide in the prevention of nausea and vomiting (Fumoleau *et al.*, 1997). Ondansetron is currently available as a tablet (Zofran tablet), an intravenous formulation (Zofran injection). The intravenous form is not suitable for patients as it requires the ambulatory setting and has to be administered by nurse or doctor. The tablet form is not appropriate in patients with chemotherapy induced nausea and vomiting. Thus the aim of the present study is to develop a novel poloxamer- based mucoadhesive solid suppository system of ondansetron which will sustain the release of ondansetron, melts at physiological temperature and has prolonged retention time by adhering to rectal mucosa in patients with chemotherapy induced nausea and vomiting.

EXPERIMENTAL

Materials

Ondansetron (<150µm) (Cadila pharma, Gujarat), poloxamer 188 (BASF India Ltd.), poloxamer 407 (SD Fine chemical), hydroxypropylmethyl cellulose (HPMC K4M) (Colorcon, Mumbai), Sodium lauryl sulphate (SLS), castor oil (Loba chemie, Mumbai).

Methods

Preparation of suppositories

Conventional and sustained release suppositories were prepared by fusion method. Calculated amount of poloxamer 188 and poloxamer 407 were melted individually at 40^0C and mixed, ondansetron was dispersed homogeneously into melted base. Finally, these mixtures were poured into moulds (1 g capacity) and the moulds were left in ice bath at 4^0C. The obtained suppositories were sealed in aluminum packaging coated inside with polyethylene and stored at 10^0C. (Composition shown in Table I.). Sustained release suppositories were prepared using same method used for preparation of conventional suppository with addition of HPMC in different concentration as shown in composition Table I.

Table. 1: Formulation Composition of Suppositories.

INGREDIENTS	Formulation Code			
(mg /suppository)	P1	P2	P3	P4
Ondansetron	16	16	16	16
Poloxamer 188:407(2:5)	730	714	698	682
HPMC K4M	-	16	32	48

DSC Study

The possibility of any interaction between ondansetron and excipients used in formulations was assessed by carrying out the thermal analysis on pure drug and formulation using differential scanning calorimeter. The thermograms of samples were obtained at a scanning rate of 10^0 C / min conducted over range of 50-300^{0}C.

Uniformity of weight

Twenty suppositories were selected randomly from each batch and weighed individually and also the average weight and the percentage deviation values were calculated (babar *et al.*, 1999).

Hardness (breaking) test

The hardness of three suppositories from each batch was determined by cutting the middle portion of suppository. It was measured in its diametric direction using Monsanto hardness tester.

Melting point

Melting point of suppository was measured by capillary method using melting point apparatus (SCIENTIFIC).

Disintegration test

Randomly six suppositories were selected from each batch for disintegration test. Disintegration test was performed without disc in phosphate buffer pH 7.2 using USP disintegration apparatus (Electrolab ED-2L) (Stanislav *et al.*, 2001).

Content uniformity

Content uniformity of suppositories was determined by spectrophotometric method. The suppositories were individually melted and dissolved in 100 ml phosphate buffer.

After dilution, the absorbance was measured spectrophotometrically at 267 nm (Shimadzu, UV-1700, Japan) (Hanaee *et al.*, 2004).

Liquefaction time

It measures the time necessary for suppository to liquefy under pressure similar to those found in rectum in presence of water at body temperature. Liquefaction time measured by using modified apparatus (Fig. 3).

A condenser was taken having broad opening at one end and narrow opening at another end. Dialysis membrane tubing passed through condenser tied at both ends of condenser. The sample suppository was introduced from the top of condenser through broad end and carefully pushed up to some extent. Water (at 37 ^{0}C) was circulated through condenser. When temperature of dialysis membrane tubing was stabilized at 37 ^{0}C, suppository moved downwards and dropped into beaker. The time required for suppository to move from broad end to narrow end was measured (Larry *et al.*, 1991).

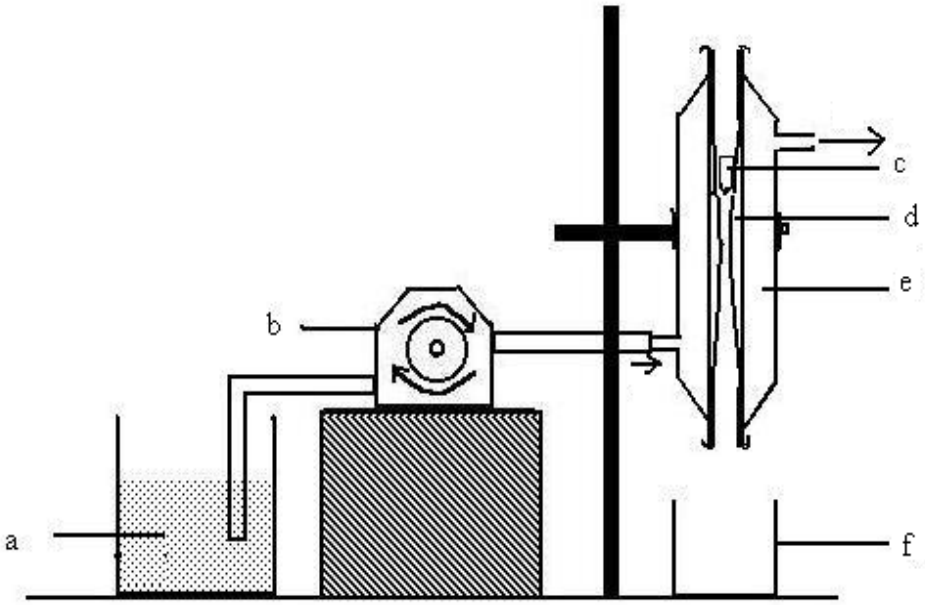


Fig. 3: Schematic diagram of the model used to test the liquefaction time of Suppositories (a) Water at $37^0C \pm 5^0C$ (b) Peristaltic pump (c) Suppository (d) Dialysis membrane tubing (e) Condenser (f) Collector.

Table. 2: Physicochemical characteristics of sustained release suppositories.

Batch code	Uniformity of Weight* (mg) n = 20	Hardness† (kg/cm^2) n = 6	Melting Point‡ (^0C) n = 3	Disintegration* (minutes) n = 6	Content Uniformity† (%) n = 3	Liquefaction Time‡ (minutes) n = 3
P1	0.7325 ± 0.02	1.20 ± 0.4	32.0-33.5	8.00 ± 0.02	99.45 ± 1.20	7.20 ± 0.02
P2	0.7325 ± 0.02	3.20 ± 0.40	32.0-33.5	22.00 ± 0.02	99.45 ± 1.20	9.05 ± 0.04
P3	0.6873 ± 0.02	4.01 ± 0.25	32.5-33.0	22.20 ±0.03	99.25 ± 1.40	10.15 ± 0.02
P4	0.6652 ± 0.02	4.38 ± 0.32	32.5-33.0	24.00 ± 0.01	98.30 ± 2.36	10.20 ± 0.03

*All values with mean ± SD, (n = 20), † All values with mean ± SD, (n =6), ‡ All values with mean, (n = 3)

In vitro Release Test

In vitro release test was carried out according to the USP XXII basket method. The USP rotating basket dissolution apparatus was used for the determination of release rates of Ondansetron from the various suppository bases. Each suppository was placed in basket and lowered into a flask containing 900 ml of phosphate buffer solution (pH 7.2) with 0.5% sodium lauryl sulphate. The basket was rotated at 50 rpm at a constant temperature $37^0C \pm 0.5^0C$. Aliquots of 5 ml were withdrawn at appropriate time intervals and immediately replaced by 5 ml fresh phosphate buffer. Drug concentration was measured spectrophotometrically at 267 nm. (Shimadzu, UV-1700, Japan). This test was performed on 6 suppositories and mean ± SD was calculated.

RESULTS AND DISCUSSION

During the manufacturing of suppositories, some difficulties are experienced in achieving the exact dosage. This is because the volume of suppositories from particular mold is uniform, but its weight may vary because the density of drug usually differs from density of base with which the mold is calibrated. Therefore, displacement values of Ondansetron from bases were determined and were found to be 0.02 for poloxamer mixture.

Physicochemical characteristics

The physicochemical characteristics of suppositories were measured according to the methods described. The results are listed in Table II. The results show that all prepared suppositories were acceptable in terms of weight variation, content uniformity, hardness, disintegration time, melting point and liquefaction time. Weight variation is in conformity with BP *(British pharmacopoeia)* with standard deviation less than 5%[17]. The drug content was within the limit of 75% to 125%.The hardness of conventional suppository is less than sustained release suppositories, this may be due to increase in concentration of HPMC. According to BP the disintegration time of each suppository should be less than 60 min for hydrophilic suppository which was found to be within limit. The appropriate melting point of a suppository ensures its handling and release of drug after administration in the rectum (Yahagi *et al.*, 1999). Poloxamer 407 and poloxamer 188 have melting points 15^0C and 55^0C respectively but in case of mixture melting point was found to be $32 – 33.5^0C$ (Chul Soon *et al.,* 2005).

In vitro release test

In vitro release study was carried out using USP XXII basket method, the drug was released directly to the aqueous medium from the surface of suppository. The result shows all conventional suppositories release the drug within 90 minutes. The

drug release was found to be 98.10%. *In vitro* drug release profile of conventional suppository is shown in Fig. 1.

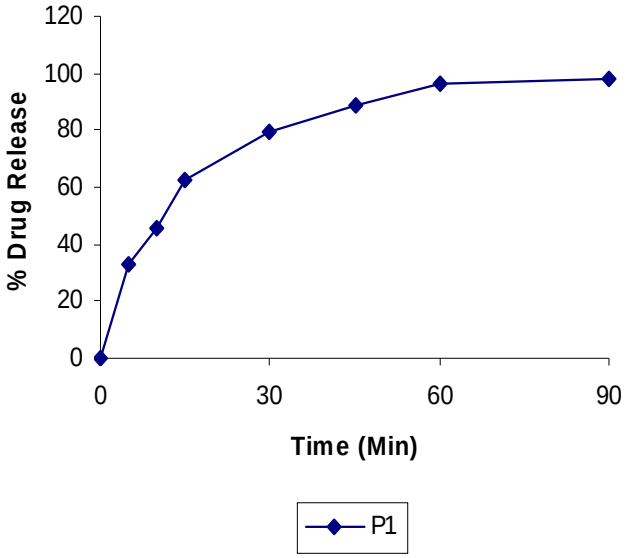


Fig. 1: *In vitro* drug release study of conventional suppository of ondansetron**.**

Formulations P2, P3 and P4 suppositories containing poloxamer mixture base with HPMC showed sustained release up to 12 hours, this is because HPMC has an inert matrix structure and hence forms cage on the surface and the suppositories, thus preventing release of drug from the suppository to the aqueous medium (Masuda *et al*., 2004). Increasing concentration of HPMC shows release up to 83.77%, 93.10% in 7 and 9 hours respectively. Formulation P4 containing drug: HPMC in ratio 1:3 releases drug up to 97.47%. *In vitro* release profile is shown in **Fig. 2.**

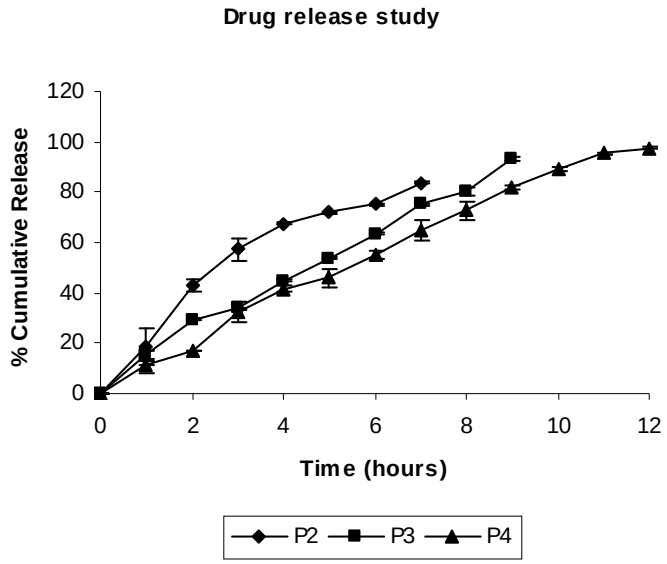


Fig.2: *In vitro* drug release study of poloxamer mixture based sustained release suppositories of ondansetron.

Among the poloxamer based suppositories tested, the suppositories formulated only with P 188 had significantly lowest dissolution rates for drug (Yong *et al.*, 2001) this may be due to the fact that P 188 remained in solid phase and could not turned into gel in the dissolution medium due to relatively high melting point of P188 (Chul Soon *et al.*, 2005) . So, in this study a combination of two different poloxamer grades was used which resulted in enhancement of dissolution of ondansetron (Choi *et al.*, 1998). To know the mechanism of drug release from these formulations, the data were treated according to zero-order (cumulative amount of drug released versus time), first-order (log cumulative percentage of drug remaining versus time), Highuchi's (cumulative percentage of drug released versus square root of time) model and Peppas-Korsmeyer (log cumulative percentage of drug released versus log time) equations. Poloxamer mixture based suppositories follows zero order release i.e. dissolution rate dependent upon drug concentration with r value in between 0.95 to 0.99.

CONCLUSION

From above studies it can be concluded that suppositories of Ondansetron prepared with different grades of poloxamer as base in combination with HPMC holds potential in patients with chemotherapy induced nausea and vomiting. The prepared poloxamer- based mucoadhesive solid suppositories of ondansetron sustains the release of ondansetron, melts at physiological temperature and has prolonged retention time by adhering to rectal mucosa.

ACKNOWLEDGEMENT

The authors are very grateful to Cadila pharma, for generous supply of ondansetron. The authors are also grateful to Gattefosse for supply of Suppocire AM base.

REFERENCES

Abhaham C. Poloxamer gel systems with gelling temperatures higher than room temperature. Canadian Patent. 1994, 1, 413.

Babar A. Bellet T. and Plakogiannis F.M. Ketoprofen suppository dosage forms: *in vitro* release and *in vivo* absorption studies in rabbits. Drug Dev. Ind. Pharm, 1999; 25(2): 241-245.

British Pharmacopeia. The department of health, social services and public safety, London, 5th ed. Vol IV. Appendix XIIB: A270

Burstein A.H., Fisher K.M., Roby C.A. Absorption of phenytoin from rectal suppositories formulated with a polyethylene glycol base. Pharmacotherapy 2000, 20, 562-567.

Choi H.G., Oh Y.K., Kim C.K. In- situ gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability. Int. J. Pharm. 1998, 165, 23-32.

Chul Soon Y., Yu-Kyoung O. Yong K., Chong Kook K. Physicochemical characterization and in vivo evaluation of Poloxamer based solid suppository containing diclofenac sodium in rats. 2005; 301:54-61.

Fumoleau P., Giovannini M. and French Ondansetron study group. Ondansetron Suppository: an effective treatment for the prevention of emetic disorders induced by cisplatin based chemotherapy. Oral oncology, 1997; 33(5): 354-358.

Hanaee J., Javadzadeh Y., Taftachi S., Farid. A.Nokhodechi. The role of various surfactants on release of salbutamol from suppositories. II Farmaco 2004; 59: 903-906.

Kim C.K., Lee S.W., Choi H.G., Park K.M. Trials of in situ gelling and mucoadhesive acetaminophen liquid suppository in human subjects. Int. J. Pharm. 1998, 174, 201-207.

Larry J. and Lieberman H A. Theory and practice of industrial pharmacy, 3 rd, Edited by Lachman L Lieberman H A, Verghese publishing house, Bombay 1991; 564-588.

Masuda K., Ashraful S. M Parvin A., Mohiuddin A., Md. Selim R. Controlled Release of Naproxen Sodium from Eudragit RS 100 Transdermal Film. Dhaka University Journal of Pharmaceutical Sciences.2004; 3(1, 2):52-56.

Stanislav J., Malgorzata S.and Weronika Z. Evaluation of paracetamol suppositories by pharmacopoeial dissolution test-comments on methodology. Eur.J.Pharm.Biopharm.2001; 52:249-254.

Yahagi R., Onishi H., Machida Y. Preparation and evaluation of double-phased mucoadhesive rectal suppositories of lidocaine utilizing Carbapol and White Beeswax. J. Controlled Release. 1999; 61:1-8

Yong C.S., Choi H.G., Jung J.H., Kim C.K. Rhee J.D., Kim K.M. Effect of sodium chloride on the gelation temperature, gel strength and bioadhesive force of Poloxamer gels containing diclofenac sodium. Int. J. Pharm. 2001; 226: 195-205.

Yun M.O., Choi H.G., Kim C.K. Development of thermoreversible insulin liquid suppository with sodium salicylate. Int. J. Pharm. 1999, 189, 137-145.