Research Article [Thadanki *et al.*, 6(1): Jan., 2015:4195-4201]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Development and Characterisation of Omeprazole controlled release Microspheres

Madhurilatha Thadanki[1*], A. Kishore Babu[2] and A. Seetha Devi[3]
1, Avanthi Institute of Pharmaceutical Sciences, Gunthapalli, Rangareddy - India
2, G.B.N College of Pharmacy, Edulabad, Ghatkesar, Rangareddy – India
3, Department of Pharmaceutics, Hindu College of Pharmacy, Guntur, (Andhra Pradesh) - India

Abstract

The objective of the present study was development and characterization of controlled release microspheres of omeprazole. Generally administration of microspheres will provide the localization of active substance at the site of action for prolonged period of the time. The microspheres of omeprazole was prepared by solvent evaporation technique by using different polymers with varying concentrations.The formulations were evaluated for particle size distribution analysis,flow properties like Angle of repose,bulk density,tapped density,true density, Hausner's Ratio,Carr's index, microencapsulation efficiency,Scanning electron microscopy(SEM) and *in vitro* releasestudies. The optimized formulation showed good *in vitro* controlled release activity of the drug omeprazole.

Key-Words: Omeprazole, Eudragit-L-100(E-L-100), Celluose acetate phalate (CAP), Hydroxy Propyl Methyl Cellulose-55(HPMCP-55), Controlled release microspheres

Introduction

Omeprazole belongs to the group of medicines called proton pump inhibitors.It works on the body by blocking the H+/K+ ATPase,It is used to block the production of stomach acid[1,11,13].The pharmacokinetic profile and cellular metabolism of omeprazole provides a strong rationale for development of controlled release formulation[2,3,19].A microsphere based drug delivery system of omeprazole was planned for development and characterization for *invitro* performance**s.** Microspheres containing omeprazole was prepared by solvent evaporation method using variouspolymers[4].It has short biological half life of 0.5-3hrs.This necessitates multiple daily dosing for maintenance of its plasma concentration within the therapeutic index, hence there is impetus for developing sustained release dosage form that maintains therapeutic plasma drug concentration for long period compared to conventional dosage forms 4-5hrs. Among these systems microspheres have emerged as an attractive dosage forms due to the advantages it offers like effective taste masking, improvement of flow, safe handling and good controlling drug release properties.

*** Corresponding Author**
E.Mail: madhurithadanki31@gmail.com, akishorebabu@gmail.com

Much interest is also being shown these days to the formulations based on its biocompatibility, biodegradability, non toxicity, and ease in availability. As the current study also deals with the same available polymers[5,6].

Material and Method

Omeprazole was obtained as gift sample from aurobindo Pharma Pvt. Ltd., Eudragit –L-100(E-L-100) was obtained from orchid pharma private limited, Hyderabad,Cellulose acetate phthalate (CAP)was obtained from Accord labs, Hydroxyl propyl methyl cellulose phthalate-55 (HPMCP-55) was obtained fromMeenaxy pharma Pvt.Ltd,Qutbullapur,Hyderabad, Ethyl cellulose,Cellulose acetate,Dichloro methane,Poly vinyl alcohol was obtained fromQualigens Fine Chemicals, Mumbai.

PREPARATION OF MICROSPHERES

Solvent evaporation technique[7]

In this technique required amount of polymer was dissolved in solvent containing (Dichloromethane, Acetone: Ethanol (1:1)) and make them in to fine dispersion using organic phase. Then the drug was dissolved in the polymer solution.Then add one drop of plasticizer and wetting agent.The resulting solution was added to 0.5%PVA solution in drop wise manner and mixture was agitated using a mechanical stirrer with rotation speed 500 rpm. The dispersed drug and polymers were transformed into fine droplets, which

subsequently solidified into rigid microspheres due to solvent evaporation. The particles were collected by filtration, washed with demineralised water and petroleum ether, and dried at room temperature for 24 hours.

***IN VITRO* EVALUATION OF MICROSPHERES[8,9]**

The evalution of microspheres can be done by determining its particle size distribution, bulk density, true density, Carr's index, Hausner's ratio, Angle of repose, entrapment efficiency, drug content andpercentage yield were tabulated.

Scanning Electron Microscopy (SEM)[10,12]

The samples for the SEM analysis were prepared by sprinkling the microspheres on one side of the double adhesive stub. The stub was then coated with fine gold dust. The microspheres were then observed with the scanning electron microscope (Leica Electron Optics, Cambridge, USA) at 15 kv.

***In Vitro* Release Studies[14]**

The *in vitro* release studies of drug-loaded microspheres were carried out at 37±0.5°C and 50 rpm using 0.1N Hcl (900 ml) for 2 hrs and followed by phosphate buffer pH 6.8 (900 ml) in a USP dissolution apparatus type Π (Lab India) under sink conditions[15]. Accurately weighed samples of microspheres (containing approximately 20 mg of drug) were filled in gelatin capsule and placed in a dissolution medium and at present time intervals aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. After suitable dilution, the samples were analyzed spectrophotometrically at 276 nm. The concentration of omeprazole in test samples was corrected and calculated using a regression equation of the calibration curve[16].

Analysis of release data

In order to elucidate the mode and mechanism of drug release, the *in vitro* drug release data was transformed and interpreted at graphical interface constructed using various kinetic models[17].The *in vitro* release data obtained from microspheres formulation in 6.8 pH phosphate buffer was fitted to various kinetic models.The results were shown in table no 1&2 and fig 1-6.The kinetic and the release mechanisms were estimated by Regression plots for Zero order. First order, Higuchi model, Erosion model and Kores Meyer Peppa's model.when the R^2 values of regression plots for First order and Zero order were considered, it is evident that the drug release from all omeprazole microspheres formulations, follow Zero order release kinetics[18.19,20].

By incorporating release data in Higuchi and Erosion models,the R^2 value of F4 and F6 is greater for Erosion model.To further confirm the exact mechanism of drug release, the data was incorporated in to KoresMeyer Peppas model and the mechanism of drug release was indicated according to value of release exponent 'n'.The release exponent value 'n' for F2,F5, and F8 was found to be 0.982,0.899 and 0.904 respectively, and remaining formulations from F1-F12 (except F2,F5 & F8) to be with in the range of 1.1-2.0.Since the release exponent 'n' value of F2,F5 & F8 were around 0.9.It indicates that the formulation undergoes Non-Fickian Diffusion or Anamolous Diffusion.The remaining formulations will undergoes Supercase-Π Transport[22,23].

Results and Discussion

The omeprazole loaded microspheres prepared by solvent evaporation technique are found to be discrete, spherical, free flowing and particle size in the range of 50-386µm(fig.1-6).All the prepared microsphere formulations were subjected to many evaluation parameters such as particle size evaluation,Angle of repose,Bulk density,Tapped density,Carr's index, Hausner's ratio,Drug content and Encapsulation efficiency.The encapsulation efficiency of all microspheres was from 65-91%.(Table no.1).It indicates that all the formulations are showing good encapsulation efficiency.The percentage yield of all microspheres formulation was from 65-83%.(Table no.1).It indicates good yield.Further the microspheres were subjected to various evaluation parameters like Angle of repose,Bulk density,Tapped density,Carr's index ,Hausner's ratio.The values of Angle of repose ranged from 20-25°.The values of bulk density ranged from 0.29-0.55g/c.c and the values of tapped density ranged from 2.14-8.89g/c.c(Table no.1).The flow properties of the microspheres were further confirmed by determining Carr's index and Hausner's ratio.The Carr's indexvalues and Hausner's ratiovalues ranged from12.52-15.89 and 0.91-1.51 respectively (Table no.1) indicating all the values were within the limits as per U.S.P.

The cumulative percentage drug release for formulations containing different polymers were shown in (Table no.2) and (Fig.7).The formulations(F1-F6) released 88.74±0.56 in 12 hrs, 86.74±0.80 in 11 hrs, 84.71±0.22 in 11 hrs, 85.49± 0.26 in 10 hrs,95.21±0.56 in 12 hrs, 91.84±0.23 in 12 hrs respectively.

The cumulative percentage drug release for formulations containing different polymers were shown in (Table no.2) and (Fig.8).The formulations (F7-F12) released , 97.94±0.99 in 12 hrs, 91.59 ± 0.92 in 12 hrs,96.66±0.35 in 12 hrs, 95.67±0.39 in 12 hrs, 91.75±0.82 in 12 hrs, 93.06 ± 0.12 in 12 hrs respectively.

The invitro release data obtained from microspheres formulation in 6.8 pH phosphate buffer was fitted to various kinetic models. The kinetic and the release mechanisms were estimated by Regression plots for Zero order. First order, Higuchi model, Erosion model and Kores Meyer Peppas model.when the R^2 values of regression plots for First order and Zero order were considered, it is evident that the drug release from all omeprazole microspheres formulations, follow Zero order release kinetics.

By incorporating release data in Higuchi and Erosion models,the R^2 value of F4 and F6 is greater for Erosion model.To further confirm the exact mechanism of drug release, the data was incorporated in to KoresMeyer Peppas model and the mechanism of drug release was indicated according to value of release exponent 'n'.The release exponent value 'n' for F2,F5, and F8 was found to be 0.982,0.899 and 0.904 respectively, and remaining formulations from F1-F12 (except F2,F5 & F8) to be with in the range of 1.1-2.0.Since the release exponent 'n' value of F2,F5 & F8 were around 0.9.It indicates that the formulation followed Non-Fickian Diffusion or Anamolous Diffusion.The remaining formulations followed Supercase-Π Transport.

Conclusion

Omeprazole loaded microspheres were prepared successfully using solvent evaporation technique. Both cellulose acetate phthalate (CAP) and hydroxyl propyl methyl cellulose pthalate-55(HPMCP-55) microspheres showed better sustain release properties. From the twelve formulations of microspheres, cellulose acetate phthalate (CAP) micropsheres show better controlled release property. The assessment of the release kinetics revealed that drug release from microspheres follows Peppa's model. It was suggested that mechanism of drug release from microspheres was diffusion coupled with erosion non fickian anamolous and super case Π transport mechanism.The order of drug release was found to be as follows,

F7>F9>F10>F5>F12>F6>F11>F8>F1>F2>F4>F3.

The formula which showed better release among the six formulations is F-VII is of 97.94% at 12hours of dissolution study. Controlled release without initial peak level achieved with these formulations may reduce frequency and side effects as well as improve patient compliance.

Acknowledgement

We sincerely thank our Management, Hindu College of Pharmacy for providing all the facilities for successful completion of this work.

References

1. Brahmankar DM and Jaiswal SB. Biopharmaceutics and Pharmacokinetics- A Treatise. *Vallabh Prakashan*. 1995; 1: 345-47.
2. Lehmann, K.; Dreher, D. Pharm. Ind. 1972, 34, 894–903.
3. Banker, G.S. Pharm. Technol. 1981, 5, 54–62.
4. Lehmann, K. Microcapsules and Nanoparticles in Medicine and Pharmacy; Donbrow, M., Ed.; CRC Press: London, 1991; 73–97.
5. Wurster, D.E. US Patent 2,648,609, 1949.
6. Nixon, J.R.; Nouh, A. J. Pharm. Pharmacol. 1978, 30, 533–537.
7. Madan, P.L. Drug Dev. Ind. Pharm. 1978, 4 (95).
8. S.P.Vyas, Roop .K.Khar, Controlled drug relivery concepts and advances, 203-209.
9. N.K.Jain, Controlled and Novel Drug Delivery, 52-81, 1998.
10. Remington, The Science and Practise of Pharmacy, 21th edition, vol-Π, 1435-1438. Urmeda, T.; Matsuzawa, A.; Yokoyama, T.; Kuroda, K.; Kuroda, T. Chem., Pharm. Bull. 1983, 31, 2793–2798.
11. British Pharmacopoeia, 1998; IthEd, 33-34.
12. British Pharmacopoeia, 2005; IthEd, 38-42.
13. United states Pharmacopoeia, 2005, IthEd 345-387.
14. www.rxlist.com.
15. www.drugbank.com.
16. www.wikipedia.org.
17. Barar, F.S.K., Essential of Pharmacotherapeutics, 2000; 117-119.
18. The Merck Manual, 16th Ed., 1992; 1025-27.
19. Hand book of pharmaceutical excipients,2000, Raymond c.Rowe,Paul J Sheskey , 5th edition,140,135,112,452,785,897,762.
20. Hand book of pharmaceutical excipients,2000, Raymond c.Rowe,Paul J Sheskey , 6th edition,1350,135,162,452,785,877,782.
21. Essentials of pharmacology by K.D. Tripathi,3rd edition,423-456.
22. Text book of pharmacology by Rang and Dale,6th edition,134-156.
23. Bungenberg de Jong, H.G. Reversible systems. In Colloid Science; Kruyt, H.G., Ed.; Elsevier: New York, 1949; Vol. II, 335–432. de Sabata, V. Microencapsulation; Nixon, J.R., Ed.; Marcel Dekker, Inc.: New York, 1976; 143–162.
24. Jizomoto, H. J. Pharm. Sci. 1984, 73, 879–882.
25. Rha, C.K.; Rodrigues-Sanches, D. US Patent 4,749,620, 1980.
26. Kwok, K.K.; Groves, M.J.; Burgess, D.J. Pharm. Res. 1991, 8, 341–344.

27. Bodmeier, R.; Chen, H. J. Pharm. Pharmacol. 1988, 40, 754–757.

Table 1: Evaluation of different formulations

F. code	Average particle size	Encapsulation efficiency	Percentage yield	Angle of repose	Bulk density (g/c.c)	True density (g/c.c)	Hausner's ratio	Carr's index
F1	69.58±0.02	71.70±0.76	82.66±0.23	25.63±0.80	0.29±0.52	3.39±0.12	0.93±0.30	3.35±0.78
F2	229.01±0.03	72.70±0.12	77.33±0.33	21.74±0.90	0.38±0.78	4.13±0.21	0.91±0.78	3.45±0.32
F3	320.59±0.05	69.70±0.56	80.33±0.87	20.49±0.81	0.45±0.76	6.51±0.65	1.20±0.73	5.51±0.53
F4	140.79±0.12	67.00±0.78	76.31±0.44	19.74±0.42	0.53±0.23	7.34±0.76	1.34±0.78	6.62±0.23
F5	200.15±0.54	66.00±0.76	72.72±0.12	18.98±0.42	0.34±0.12	5.38±0.54	1.42±0.89	7.12±0.67
F6	387.73±0.98	67.00±0.14	79.25±0.65	24.26± 0.52	0.54±0.87	2.35±0.75	1.11±0.12	8.62±0.88
F7	50.08±0.46	91.00±0.87	84.70±0.72	24.49±0.87	0.53±0.71	2.14±0.70	1.21±0.12	6.12±0.98
F8	229.00±0.42	65.30±0.76	77.00±0.32	22.91±0.43	0.44±0.67	5.46±0.45	1.00±0.89	7.81±0.21
F9	173.14±0.74	67.00±0.34	65.70±0.10	21.50±0.12	0.52±0.89	6.90±0.12	1.02±0.76	7.98±0.87
F10	144.67±0.87	73.60±0.13	65.70±0.51	20.15±0.42	0.49±0.52	8.89±0.67	1.21±0.68	8.52±0.70
F11	153.33±0.67	64.00±0.43	82.50±0.87	22.49± 0.53	0.45±0.12	7.56±0.43	1.41±0.43	7.51±0.75
F12	115.81±0.77	70.00±0.70	83.00±0.67	23.91±0.31	0.55±0.18	7.89±0.12	1.51±0.65	6.89±0.21

All values represent mean standard deviation (SD), n=3

SEM AND Digital microscopic photographs of Omeprazole Microspheres formulated by employing solvent evaporation technique[24,25,26]

Fig no 1

Fig no 2

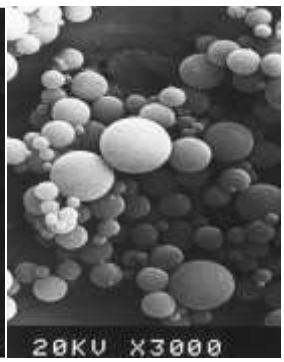

Fig no 3

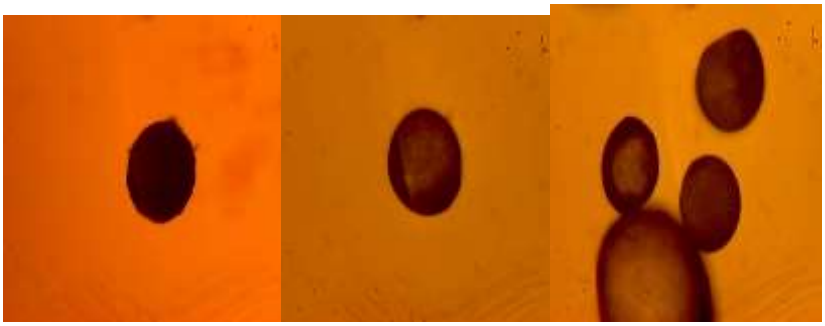

Fig no 4 **Fig no 5** **Fig no 6**

Table 3: Release kinetics studies of the formulation[27]

FORMULATION CODE	ZERO ORDER (R^2)	FIRST ORDER (R^2)	HIGUCHI MODEL (R^2)	EROSION MODEL (R^2)	PEPPAS MODEL (n)
F1	0.968	0.943	0.829	0.823	2.216
F2	0.993	0.962	0.999	0.906	0.982
F3	0.974	0.957	0.850	0.809	1.611
F4	0.973	0.953	0.853	0.860	1.496
F5	0.984	0.960	0.888	0.841	0.899
F6	0.987	0.916	0.877	0.887	1.905
F7	0.972	0.948	0.835	0.833	1.822
F8	0.975	0.985	0.922	0.901	0.904
F9	0.990	0.967	0.881	0.857	1.840
F10	0.960	0.894	0.793	0.769	1.621
F11	0.978	0.953	0.828	0.754	1.500
F12	0.957	0.887	0.780	0.758	2.091

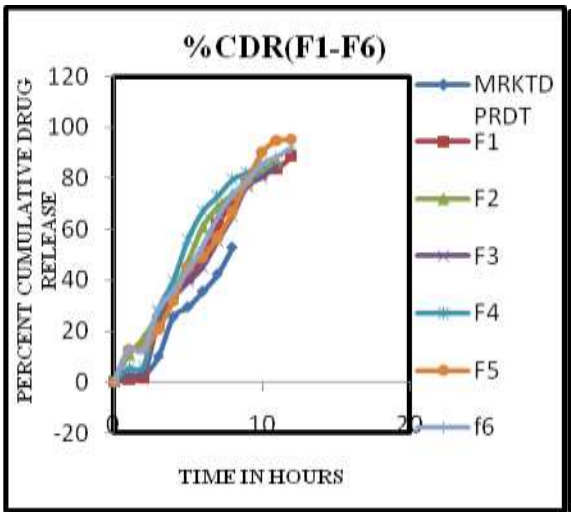

Fig no7

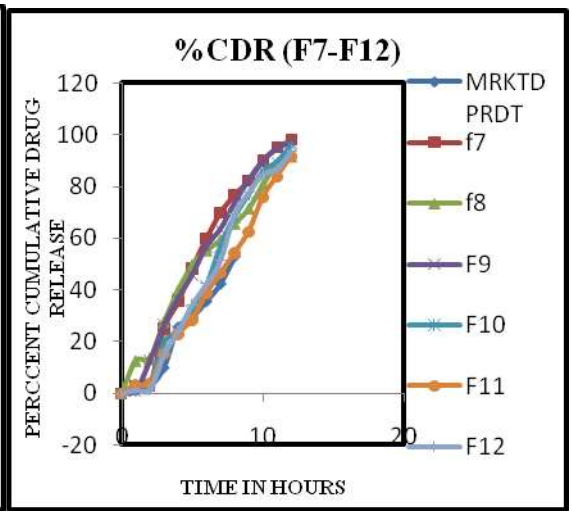

Fig no 8

Table 2: Drug Release

Time (Hrs.)	CUMMULATIVE PERCENTAGE OF OMEPRAZOLE RELEASED											
	F-I	F-II	F-III	F-IV	F- V	F- VI	F- VII	F- VIII	F- IX	F- X	F- XI	F- XII
0	0	0	0	0	0	0	0	0	0	0	0	0
1	1.04±0.71	10.30±0.78	3.12±0.65	5.04±0.76	12.59±0.89	12.64±0.45	2.83±0.25	12.59±0.12	1.25±0.35	3.11±0.72	3.19±0.92	1.44±0.30
2	1.76 ± 0.56	17.60±0.98	3.91±0.87	6.06±0.87	12.86±0.52	12.68±0.85	3.05±0.36	13.49±0.24	12.64±0.82	3.56±0.82	4.05±0.62	1.45±0.33
3	23.81± 0.76	26.64±0.56	22.82±0.98	28.17±0.74	20.83±0.56	28.62±0.96	24.88±0.92	27.58±0.22	26.46±0.62	19.53±0.32	15.19±0.22	15.03±0.62
4	34.52± 0.78	35.34±0.78	32.81±0.67	39.57±0.23	31.72±0.76	35.42±0.24	35.43±0.82	39.81±0.62	36.81±0.92	24.08±0.12	23.09±0.12	24.08±0.65
5	37.67±0.21	47.04±0.98	39.18±0.45	55.87±0.23	45.04±0.36	43.92±0.65	48.28±0.32	49.76±0.92	45.79±0.92	31.68±0.22	28.49±0.32	34.38±0.38
6	42.08±0.12	60.84±0.12	45.12±0.53	66.84±0.45	49.08±0.96	53.24±0.35	59.87±0.92	55.26±0.35	56.83±0.98	41.49±0.62	38.65±0.82	42.03±0.38
7	61.74±0.65	68.69±0.22	55.22±0.68	72.87±0.76	56.72±0.79	64.74±0.45	69.79±0.23	59.31±0.32	63.47±0.29	56.74±0.85	46.48±0.92	51.54±0.352
8	70.74±0.76	73.89±0.46	64.93±0.65	79.37±0.65	66.73±0.52	73.17±0.76	76.74±0.98	65.66±0.36	73.48±0.39	68.22±0.39	54.30±0.62	69.21±0.52
9	1.54±0.45	78.24±0.65	76.88±0.12	82.12±0.23	79.12±0.89	79.02±0.66	82.24±0.34	71.46±0.35	82.37±0.33	76.77±0.31	62.66±0.22	77.76±0.62
10	81.99±0.76	83.09±0.87	80.47±0.32	85.49±0.26	90.18±0.22	85.34±0.96	89.92±0.22	80.68±0.82	89.68±0.32	85.69±0.36	75.84±0.42	84.06±0.22
11	83.79±0.98	86.74±0.80	84.71±0.22	-	94.89±0.34	88.24±0.55	94.94±0.21	88.67±0.62	94.52±0.42	89.37±0.49	83.93±0.98	86.08±0.24
12	88.74±0.56	-	-	-	95.21±0.56	91.84±0.23	97.94±0.99	91.59± 0.92	96.66±0.35	95.67±0.39	91.75±0.82	93.06±0.12

How to cite this article
Thadanki M., Babu A.K. and Devi A.S. (2015). Development and Characterisation of Omeprazole controlled release Microspheres . *Int. J. Pharm. Life Sci.*, 6(1):4195-4201.
Source of Support: Nil; Conflict of Interest: None declared
Received: 01.12.14; Revised: 31.12.14; Accepted:07.01.15