Research Article
CODEN (USA): IJPLCP

[Sony & Jain, 4(4): April, 2013]
ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Formulation & evaluation of floating microspheres of flupirtine maleate

Arjun Sony[1*] and Sonam Jain[2]
1, Production Chemist, Gwalior, (MP) - India
2, Central India Institute of Pharmacy, Indore, (MP) - India

Abstract

Flupirtine is an amino pyridine that functions as a centrally acting non-opioid, non-steroidal analgesic. It is a selective neuronal potassium channel opener that also has NMDA receptor antagonist properties. Its muscle relaxant properties make it popular for back pain and other orthopedics uses and it is also used for migraines, in oncology, postoperative care, and gynecology, and its neuro-protective properties make it for possible use in Creutzfeldt-Jakob disease, Alzheimer's disease, and multiple sclerosis. It has also been proposed as a possible treatment for Batten disease. Controlled release dosage forms of flupirtine maleate were prepared so as to release drug moiety in delayed action around 0.001 to 20 parts for each parts by weight and the release rate is to be 5 to 300 mg / hr. Floating microspheres were prepared with the help of Ethyl Cellulose, Hydroxypropyl methyl cellulose polymer & Tween 80 as a surfactant with ethanol, dicholromethane as solvents. Different formulations were characterized in terms of Buoyancy study, Particle size, SEM, Entrapment efficiency, Release kinetic.

Key-Words: Flupirtine, Floating microspheres, Evaluation

Introduction

The basic rationale of controlled drug delivery system is to optimize the biopharmaceutical, pharmacokinetics and pharmacodynamic properties of drug in such a way that its utility is maximized through reduction in the side effects and cure or control of condition in the shortest possible time by using smaller quantity of drug administered by the most suitable route [1]. Oral controlled release (CR) dosage forms have been developed for the past 3 decades due to their considerable therapeutic advantages. However, this approach has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the gastrointestinal tract i.e. stomach and small intestine due to short transit time, resulting lesser bioavailability. Many orally-administered drugs display poor bioavailability (30% or less) when administered in conventional dosage form, i.e., the rate and extent to which the drugs are absorbed is less than desirable indicating requirement of a very large dose. Unab-sorbed drug may also have undesirable side effect within the gastrointestinal tract. This problem maybe overcome by modified release drug delivery system with prolonged residence time in the stomach.

*** Corresponding Author**
Email: arj_arj@rediffmail.com

Systems that prolong the gastric residence time can also be used as sustained release devices with a reduced frequency of administration by density-controlled delivery systems that either float or sink in gastric fluids [2]. Sustained release floating dosage forms offer various potential advantages such as prolong retention in gastric region, improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment and site-specific drug delivery [3]. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDF). A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease [4].

Micro-encapsulation is one of the most intriguing areas in the field of new drug delivery systems to achieve sustained drug release in the body. The rate of drug release from a dosage form and its subsequent absorption following a variety of mechanisms is

controlled by dispersing the drug in a polymeric system or using a polymer coat.

The range of techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration. This approach facilitates the accurate delivery of small quantity of the potent drugs ,reduced drug concentration at the site other than the target site and the protection of the labile compound before and after the administration and prior to appearance at the site of action. The behaviour of the drugs *in vivo* can be manipulated by coupling the drug to a carrier particle. The clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug are strongly influenced by the behaviour of the carrier. The exploitation of these changes in pharmacodynamics behaviour may lead to enhanced therapeutic effect. However ,an intelligent approach to therapeutics employing drug carriers technology requires a detailed understanding of the carrier interaction with critical cellular and organ systems and of the limitations of the systems with respect to the formulation procedures and stability. A variety of agents have been used as drug carrier, including immune globulins serum proteins, liposomes, microspheres, nanoparticles microcapsules and even cells such as erythrocytes. The characteristics of microspheres containing drug should be correlated with the required therapeutic action and are dictated by the materials and the methods employed in the manufacture of delivery system [5].

There are various approaches in delivering a therapeutics substance to the target site in a controlled fashion. One such approach is polymeric microspheres as drug carriers. Microspheres of biodegradable and non-biodegradable polymers have been investigated for sustained release dosage forms depending on their final application. The mechanism of drug release is either controlled dissolution or diffusion of drug and the formulation is either as an encapsulated form (microcapsules) or a matrix form (microspheres). [6]

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 μm. Microspheres are sometimes referred to as micro particles.

Microspheres are multiparticulate drug delivery systems which are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. They are made of polymeric, waxy or other protective materials that are biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly-lactic acid and poly-glycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations. Microspheres are small and have large surface-to-volume ratio. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often indicating their activity. [7, 8]

Material and Methods

Preparation of Microspheres

The microspheres were prepared by solvent evaporation technique. The polymer ethyl cellulose and hydroxyl propyl methyl cellulose in various ratio was dissolved in the mixture of ethanol and dichloromethane having ratio (1:1). The drug was dispersed in above solution of polymers for 10 minutes under stirring at 200 rpm. The resulting dispersion was poured slowly under stirring into distilled water (dispersion medium) containing 0.01% of tween 80. The stirring speed was maintained at 500 rpm and temperature was maintained at 30^0C. Stirring was continued for 1 hours and allow evaporating dichloromethane and ethanol completely. After evaporation of dichloromethane and ethanol, the microspheres formed were collected by filtration using filter paper, then washed 3 to 4 times with distilled water and dried at room temperature for 24 hrs. After that subsequently stored in a desiccator.[9]

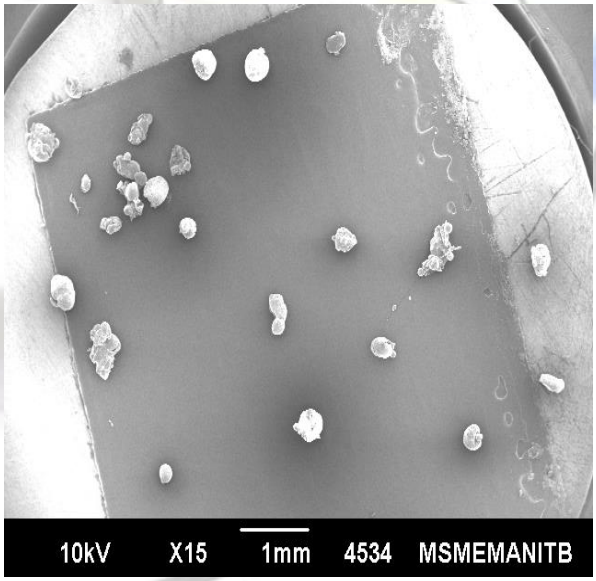

Fig. 1: SEM photograph of Flupirtine maleate microspheres (F1)

Table 1: Different type of formulations

INGREDIENTS	FORMULATIONS				
	F1	F2	F3	F4	F5
Flupirtine Maleate	50 mg	50 mg	50 mg	50 mg	50 mg
Hydroxy propyl methyl cellulose	50 mg	100 mg	150 mg	300mg	250 mg
Ethyl cellulose	450 mg	400 mg	350 mg	200 mg	250 mg
Ethanol	10 ml	10 ml	10 ml	10 ml	10 ml
Dichloromethane	10 ml	10 ml	10 ml	10 ml	10 ml
Tween 80	0.25µl	0.25 µl	0.25 µl	0.25µl	0.25µl
Distilled water	250 ml	250 ml	250ml	250 ml	250 ml

Evaluation of Microspheres

Percentage yield

The prepared microspheres were collected and weighed from different formulations. The measured weight was divided by the total amount of drug and polymers which were used for the preparation of the microspheres to obtained percentage yield.

$$\text{Percentage Yield} = \frac{\text{Weight of floating microspheres}}{\text{Weight of drug + weight of polymer}} \times 100$$

Drug entrapment efficiency[10]

To determine entrapment efficiency, 10.0 mg accurately weighted microspheres were crushed and dissolved in 100.0 mL 0.1 N HCl. The microspheres were kept to soak for overnight. After that the solution was filtered through 0.45 µ membrane filter. After appropriate dilution with 0.1 N HCl the drug content was determined spectrophotometrically at 328 (nm).

$$\text{\% Drug entrapment efficiency} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Percentage Buoyancy[11]

Microspheres was spread over a surface of a USP XXII dissolution apparatus type II filled with 900ml 0.1 mol/lit Hcl containing 0.02% tween 80. The medium is to be agitated with a paddle rotating at 50 rpm for 12 hrs. The floating and the settled portion of microsphere will be recovered separately. The microsphere was dried and weigh. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remain floating and the total mass of the microsphere.

$$\text{Buoyancy } (\%) = \frac{Wf}{(Wf + Ws)} X\ 100$$

Where, Wf and Ws are the weights of the floating and settled microparticles, respectively.

Scanning electron microscopy[12]

The shape and surface morphology of the microspheres were examined using scanning electron microscopy (JSM-6390, Japan). Microspheres were dusted onto double-sided carbon dust, which was placed onto a sample carrier in the shape of cylinder. After fixing the samples on the stubs, capture a photomicrograph.

***In-vitro* drug release profile** [13]

A USP basket apparatus was used to study *in-vitro* drug release from microspheres. *In-vitro* drug release studies were carried out for all batches in USP type I dissolution test apparatus at 100 rpm and the dissolution medium was 900 mL of 0.1 N HCl solution. Microspheres containing 100.0 mg of drug was used for dissolution study. One mL of the aliquot was withdrawn at predetermined intervals. Required dilutions were made with 0.1 N HCl solution and filter the solution and analyzed for the drug content spetrophotometrically (UV 1800, Shimadzu, Japan) at 328 nm nm against suitable blank. Equal volume of the dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition.

Excipients and Active Compatibility Studies by FT-IR Spectroscopy

Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients.

Results and Discussion

The percentage yield of different formulation was in range 69.09 to 27.09 % as shown in Table.no.2

Table 2: Percentage Yield

S/No.	Formulations	Percent Yield (%)
1	F1	69.09
2	F2	46.36
3	F3	44.90
4	F4	30.18
5	F5	27.09

The drug entrapment efficacies of different formulations were in range of 30-86.00 % w/w as shown in Table no.3.

Table 3: Drug Entrapment

S/No.	Formulation	Drug entrapment (%w/w)
1	F1	85.87
2	F2	76.03
3	F3	68.46
4	F4	41.26
5	F5	31.07

The percentage yields of different formulations were in range of 97.5-68.5 % as shown in Table 4.

Table 4: Percentage Buoyancy

S/No.	Formulation	% Buoyancy
1	F1	97.5
2	F2	91.0
3	F3	85.5
4	F4	73.0
5	F5	68.5

Scanning electron microscopy

The shape and surface morphology of the microspheres were studied by SEM. The microspheres were spherical in shape with no visible irregularities as shown in Figure.2 To observed surface morphology, photographs were taken at higher magnification (10,000 X) and it was found that small pores were observed at the surface which may be due to evaporation of solvent during drying process.

***In-vitro* dissolution release profile**

In-vitro study was performed by using USP dissolution apparatus type I. The release was found in the range of to 80.87 to31.67 % at the end of 10 hrs. The formulation F1 showed 80.87 % release at the end of 10 hrs.

Form.→ Time [hrs] ↓	F-1	F-2	F-3	F-4	F-5
1	14.96	13.97	10.95	10.34	8.34
2	23.20	22.28	15.72	13.87	11.13
3	34.81	36.51	21.01	18.20	15.06
4	46.85	43.79	28.76	21.01	18.04
5	57.48	48.14	35.02	26.46	21.78
6	67.31	52.43	41.65	29.03	23.89
7	73.43	57.69	48.36	31.51	25.33
8	76.17	62.50	55.06	34.48	27.25
9	78.47	71.21	61.62	39.29	29.46
10	80.87	75.17	68.25	41.54	31.67

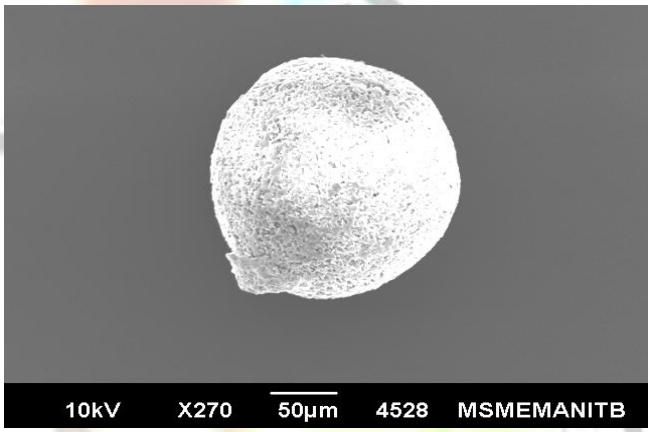

Fig. 2: SEM photograph of Flupirtine maleate microspheres (F1)

Kinetics modeling

The drug release data was fitted to various kinetic equations such as Zero order, First order and Higuchi and Korsmeyer Peppas model. The Zero-order rate describes the systems where the drug release rate is independent of its concentration. The First order rate describes the release from systems where the release rate is concentration dependent. Higuchi's model describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. Data suggested that drug release followed diffusion mechanism. Here these formulations shows regression value nearer to First & zero order.

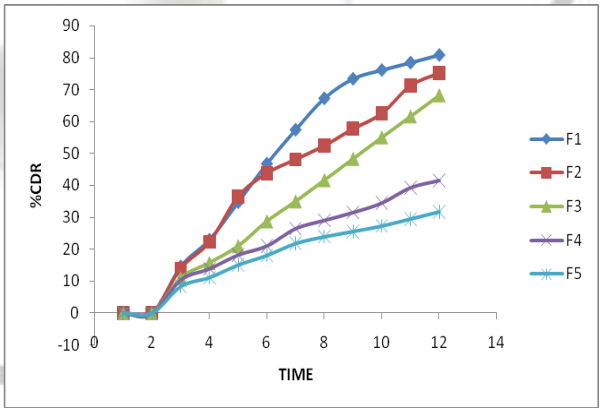

Fig. 3: Zero order plot for drug release kinetics for formulation F1-F5

[Sony & Jain, 4(4): April, 2013]
ISSN: 0976-7126

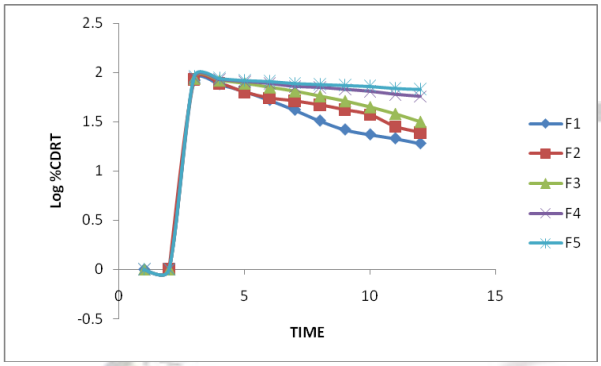

Fig. 4: First order plot for drug release kinetics for formulation F1-F5

Interpretation of FT-IR graphs

In following interpretations of drug and polymers none of the either drug or polymers exhibits similar peaks at various stretching or deformation. Thus, it was concluded that no polymers interact with drug or itself. Hence formulation with these drugs in combination with these polymers should be possible and maintain stability and also not resulting in any kind of toxicity due to interaction, if it exits.

Table 6: FT-IR peaks exhibit by the drug, polymers and formulation

Type of stretching /bending	Drug	Ethyl Cellulose	HPMC	F_1
O-H str Interm/Intra Molecular	3483.56/ 3338.18	3423.28	3475.52/ 3461.20	3423.92
C-H str.	2864	2925.21	2887.72	2943.61
O-H str 1^0 (OH)	1279.84	1031.88	1342.56	1306.87
C=O str	-------	1742.68	----------	--------
C-O str	1409.10		1433.23	1250.64
C-O-C str	1118.12	1180.53	1106.27	1119.27
C=C str	2232.74	1417.14	1608.34	1624.98
C-C str/def	1280.42	----------	1504.91	1591.74
C-H def	1437.82	1430.26	1445.98	1434.55

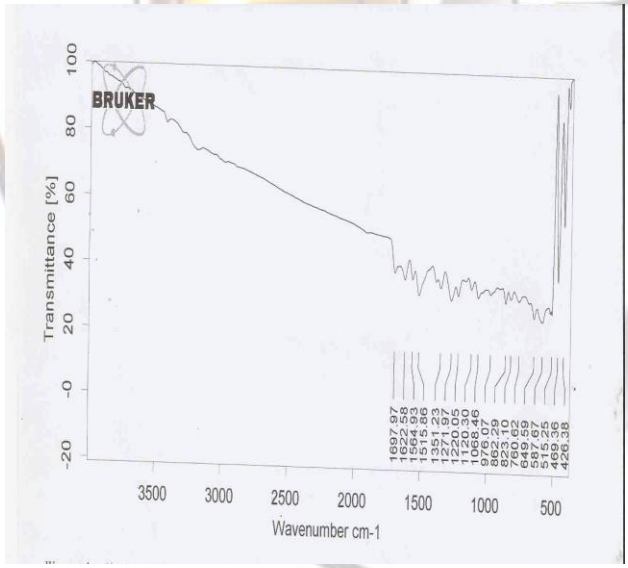

Fig. 5: IR spectra of pure drug Flupirtine maleate (Sample)

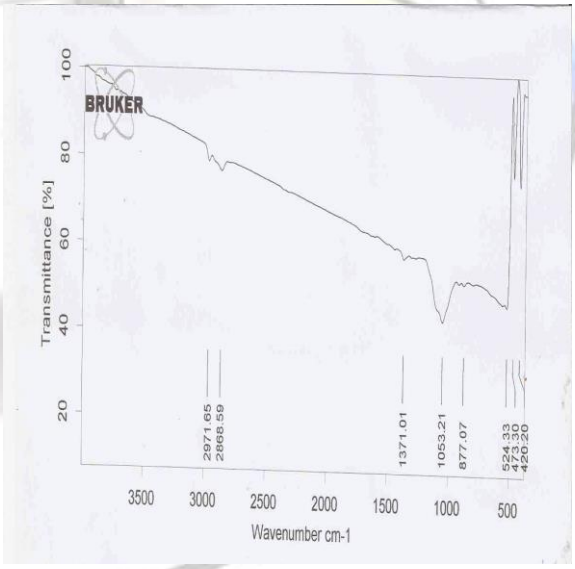

Fig. 6: IR spectra of Flupirtine Formulation

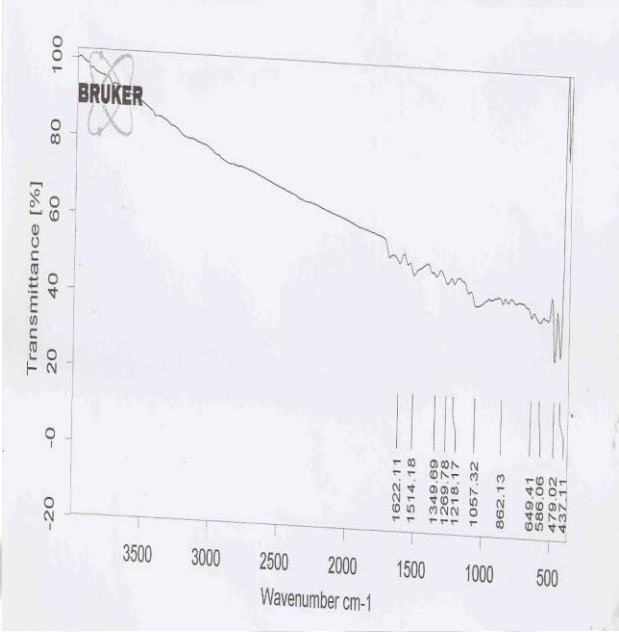

Fig. 7: IR spectra of Flupirtine Maleate + EC + HPMC

Acknowledgement

We are heartly thankful to Mr. R .V. Sheorey, Principal, Central India Institute of Pharmacy, Indore for providing facilities and precious guidance in carrying out my study. I express my sincere thanks to my eminently esteemed teacher and guide Mr. Rakesh K. Jatav (HOD), for his valuable guidance, keen interest, inspiration, unflinching encouragement and moral support throughout my dissertation work.

References

1. Bramhmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics – A Treatise. Ist ed. New Delhi; Vallabh Prakashan. 2005; 335-338.
2. Timmermans J, Moes AJ. How well floating dosage form float. Int J Pharm 1990; 62:207-16.
3. Hwang SJ, Park K. Gastric Retentive Drug Delivery Sys-tem. Crit Rev Therap Drug Carrier System 1998; 15:243-84.
4. Patel A, Ray S, Thakur RS. In vitro evaluation and optimi-zation of controlled release floating drug delivery system of metformin hydrochloride. Daru 2006; 14:57-64.
5. Chaturvedi G. A review on microspheres technology and its application. Encyclopedia Pharm tech -2328-37.
6. Najuddin M, Shelar S, Ali A, Patel V, khan T. Formulation and in vitro evaluation of floating microspheres of Ketoprofen prepared by emulsion solvent diffusion method. Inter J applied Pharmaceutics 2010; 2(1):13-17.
7. Lachman LA, Liberman HA, Kanig JL.The Theory and Practice of IndustrialPharmacy. Mumbai, India: Varghese Publishng House; 3: 414-415.
8. Ramington GA. The Science and Practicevof Pharmacy. Delhi, India: BIvpublication;2006, 21st Edition, Volume-I :924.
9. Nixon, J.R., and Meleka, M.R. 1984. The preparation and characterization of ethyl cellulose-walled theophylline microcapsules. *J. Microcapsul.* 1, 53-64.
10. Arya RKK, Juyal V, Singh RD.Development and Evaluation of Gastro resistant Microsphere of Pantoprazole. Int J Pharm and Pharm Sci 2010; 2(3): 112-16.
11. Jain SK, Agrawal GP, Jain NK. Evaluation of Porous Car-rier-based Floating Orlistat Microspheres for Gastric Deli-very. AAPS Pharm Sci Tech 2006;7(4):E1-E9.
12. Senthilkumar SK, Jaykar B, Kavimani S. Formulation, Characterization & *In-vitro* Evaluation of Floating Microsphere Containing Rabeprazole Sodium. J Inn Tre Pharm Sci 2010; 1 (6): 274-82.
13. Vueba ML, Carvalho LB, Veiga F, Sousa JJ, Pina ME. Influence of cellulose ether polymers on ketoprofen release from hydrophilic matrix tablets. Eur J Pharm and Biopharm 2004; 58: 51-59.