Indian Journal of Drugs, 2018, 6(4), 189-200 ISSN: 2348-1684

Research Article

DEVELOPMENT AND CHARACTERIZATION OF GASTRORETENTIVE FLOATING MICROSPHERE FOR CONTROLLED RELEASE OF METOCLOPRAMIDE HYDROCHLORIDE

Monika Kumbhar D.*, Pournima Morey H., Manisha Karpe S., Vilasroa Kadam J.

Department of Pharmaceutics, Bharati Vidyapeeth's College of Pharmacy, C.B.D. Belapur, Navi Mumbai– 400614, Maharashtra, India.

***For Correspondence:**
Department of Pharmaceutics, Bharati Vidyapeeth's College of Pharmacy, C.B.D. Belapur, Navi Mumbai–400614, Maharashtra, India.

Received: 03.05.2018
Accepted: 22.12.2018

Access this article online

Website:
www.drugresearch.in

Quick Response Code:

ABSTRACT

Background: The principle point of this work was to build up a gastroretentive drug delivery system for a drug which is inadequately absorbed from the lower gastrointestinal tract. Such a system may give an extended retention of drug in the upper gastrointestinal tract bringing about upgraded absorption and enhanced bioavailability.

Purpose: To design and evaluate sustain release of microsphere filled capsule for anti-emetic drug Metaclopramide Hydrochloride (METO).

Method: Microspheres were prepared by the non-aqueous emulsion solvent evaporation technique using Eudragit S100 (ES100), Eudragit L100 (EL100), Eudragit RS 100 (ERS100), Eudragit RL 100 (ERL100), Ethyl cellulose 18-22 cps (EC) polymers and physicochemical properties were characterized. Optimization was done on microsphere prepared by ethyl cellulose polymer using 32 full factorial design (Software used: Design Expert) to study the effect of independent variables viz. stirring rate and concentration of ethyl cellulose, which significantly influenced the entrapment efficiency and drug release from the microsphere. Microsphere were described by scanning electron microscopy, X-ray diffraction, Thermal analysis.

Result: Hollow microspheres were characterized using optical microscopy. Particle size was dependent on stirring rate whereas drug release was dependent on polymer concentration. The drug release mechanism of microspheres clarified with first order model which depicts concentration dependent drug release also followed Higuchi kinetic model which depicts diffusion-controlled drug release. The entrapment efficiency of this formulation was 95.56% with sustained drug release of 85.95% at the end of 24 hours and % buoyancy was 85%. Microspheres acquired with good flow properties. The main considerations impacting % entrapment efficiency and % drug release were observed to be polymer concentration and stirring speed, separately.

Conclusion: Thus, prepared floating hollow microspheres of Metaclopramide Hydrochloride may turn out to be potential candidate for the multiple-unit drug delivery device versatile for emetic condition.

KEY WORDS: Gastroretentive floating microsphere, controlled release, non-aqueous emulsion solvent evaporation technique, polymer concentration, stirring speed.

1. INTRODUCTION

Metoclopramide HCl (METO) is a one of the rapid and short acting anti-emetic prokinetic agent. It is available as a conventional tablet in market and there is no sustained release formulation available in market. *Address correspondence to this author at the Bharati

Vidyapeeth's College of Pharmacy, C.B.D. Belapur, Navi Mumbai–400 614, Maharashtra, India; Tel: +91 7506263961; E-mail: monikakumbhar19@gmail.com. The daily dose of anti- emetic is 3-4 times a day, while in chemotherapeutic treatment the dose is up to 6 times a day causing non-compliance. Oral drug delivery has been known for decades as the most widely used route of administration among all the routes that have been explored for the systemic delivery. Oral route is the most convenient and extensively used route of drug administration. The conventional oral delivery systems have limited bioavailability because of fast gastric-emptying time among many other reasons involved [1, 2]. However, the recent technological development has resulted in many novel pharmaceutical products, mainly the controlled release drug delivery systems to overcome this problem. But all controlled release systems possess limited applications if the system cannot remain in the vicinity of the absorption site. Therefore, there is a need for system that retain in the stomach over a longer period of time and release the drug in a controlled manner. The absorption of METO is strongly dependent on the local physiology in the gastrointestinal tract. METO is mainly absorbed from the upper part of the gastrointestinal tract. So, sustain release formulation is necessary to reduce the dosing frequency as a result it increases patient compliance. This can be fulfil by designing and development of gastroretentive floating drug delivery system which would deliver the drug in the upper part of gastrointestinal tract in a sustained manner by floating over gastric fluid [1]. Nowadays, various sustained release formulations are being progressed to reduce dosing frequency while maintaining drug concentration for prolonged period, decrease fluctuation of drug concentration in blood plasma, enhance patient compliance and improve drug efficacy [2, 3]. Oral multi-unit microspheres are one of the sustain release drug delivery systems that have uniform gastrointestinal distribution, drug absorption and thus reduced patient-patient variability, avoidance of dose dumping, reduced side effects [4-6]. Microspheres have points of interest of sustained release, avoidance of dose dumping, reduced side effects [7, 8, 9]. Some inherent limitations of the conventional oral drug delivery systems have ignited the interest in new delivery system. Fast gastric emptying associated with conventional oral medications leads to a bioavailability issue for many drug molecules (e.g. pranlukast hydrate, metformin HCl, baclofen, etc.), of which the main principal site of absorption is the stomach or the upper part of the small intestine, or have the absorption issue in the distal part of the intestine [3–5]. Solubility can also be improved by prolonging the gastric retention of drugs that are less soluble in an elevated pH environment of the intestine [2]. There are many drugs (e.g. metronidazole, ranitidine HCl, etc.) that are prone to degradation in the colonic area [2, 6]. To attain required therapeutic activity, recurrent dosing is needed for the drugs with short half-lives as they have the tendency of getting eliminated quickly from the systemic circulation. However, an oral sustained-controlled release formulation with additional gastric retention property can avoid these limitations by releasing the drug slowly in the stomach along with maintaining an effective drug concentration for an extended period of time [7]. Therefore, gastro- retentive drug delivery system (GRDDS) is one which couples gastric retention time with the drug release for extended time has significantly improved patient compliance.This system may help in approaching the oral controlled delivery of drugs having "absorption window" thereby continuous releasing drug to the absorption site for prolonged period of time, thus improving bioavailability [10]. In this research work, floating microspheres filled capsules (multiple unit dosage forms) are prepared as it has many more advantageous than single-unit form [such as hydrodynamically balanced system (HBS)], since microspheres pass uniformly through the GIT to avoid the fluctuation of gastric emptying and provide an adaptable release, thereby, reducing the inter subject variability in absorption and risk of local irritation [13, 14, 15, 16]. Generally, for water insoluble drugs, microspheres are ideally prepared by non-aqueous emulsion solvent evaporation technique [17]. So as METO being water insoluble, non-aqueous emulsion solvent evaporation was selected for the preparation of floating microspheres [18]. Solvent evaporation method is the most suitable and easy-going to perform on lab scale for preparation of microspheres [19]. The critical process parameters for microspheres by this method involves solvent evaporation rate, temperature,

selection of solvent having solubility for polymer, drug and excipients in both emulsion phases [20-23], dispersion medium, dispersion stirring rate [24], viscosity, volume and volume ratio between inner and outer phases [25, 26], optimization of quantity and ratio of polymer and drug and lastly physico-chemical properties, as all these affect the quality of microspheres [27, 28].

2. MATERIALS AND METHODS

2.1. Materials and Chemicals

Metoclopramide hydrochloride was obtained as a gift sample (IPCA Laboratories). Ethyl cellulose, Span 80, Tween 80 from S.D. Fine Chemicals Limited Mumbai, Dichloromethane from Research Lab Fine Chem Industries, Ethanol Gogia & company, and poly vinyl alcohol (PVA) were procured from Central Drug House, Mumbai. Other chemicals used were of analytical grade.

2.2. Preparation of Floating microspheres:

Drug and polymers were added to the solvent mixture and dissolved by stirring on magnetic stirrer to form homogenous polymer solution. Require quantity of span 80/ tween80 was weighed and dissolved in 100ml of liquid paraffin and stirred for some time with the help of overhead stirrer with required stirring speed for proper dissolution of span80/ tween80. The drug-polymer solution was slowly poured into the liquid paraffin dispersion i.e. oil phase with the help of pipette by dipping into the dispersion medium. Then the emulsion formed was stirred for about 2-3 h and allowed the solvent to evaporate completely. The microspheres formed were collected by filtration, washed repeatedly with n-hexane to remove the traces of oil and then washed with distilled water to remove unentrapped drug. The collected microspheres were dried at room temperature. The microspheres were prepared according to the formulae given in Table **1.**

Table 1: Composition of GRDDS microsphere formulation

Formulation code	Drug:Polymer (mg)	Used Polymer (mg)	Surfactant (g)	Stirring rate (rpm)
Using different polymers:				
F1	1:5 (100:500)	ES100 (100:500)	Tween 80 (0.5)	800
F2	1:5 (100:500)	EL100 (100:500)	Tween 80 (0.5)	800
F3	1:5 (100:500)	EC (100:500)	Tween 80 (0.5)	800
F4	1:5 (100:500)	ERS100 (100:500)	Tween 80 (0.5)	800
F5	1:5 (100:500)	ERL100 (100:500)	Tween 80 (0.5)	800
Using higher polymer concentration and different surfactant:				
F6	1:7(100:700)	EC (700)	Span80 (0.5)	800
Using higher polymer concentration with higher surfactant concentration:				
F7	1:10 (100:1000)	EC (1000)	Span80 (1)	1000
Using various concentration of EC:				
F8	1:15 (100:1500)	EC (1500)	Span80 (1)	1000
F9	1:20 (100:2000)	EC (2000)	Span80 (1)	1000
Using different stirring speed:				
F10	1:10(100:1000)	EC (1000)	Span80 (1)	800
F11	1:10(100:1000)	EC (1000)	Span80 (1)	900
F12	1:10(100:1000)	EC (1000)	Span80 (1)	1000
F13	1:10(100:1000)	EC (1000)	Span80 (1)	1200

Liquid paraffin (ml) = 100, Temperature (°C) = 25, Ethanol:DCM (ml) = 10:20 (1:2)

2.3. Design of Experiment (DOE)

Therefore, after illuminating the results for different trials; batch F7 that possessed good appearance, % entrapment efficiency and in vitro % drug release was optimized by 32 full factorial design using design expert software. Stirring rate and concentration of polymer were kept as independent variables, which were varied at three levels, and their effects were noticed over % entrapment efficiency and % drug release as a dependent variable from the microsphere.

2.4. Characterization of METO-loaded microspheres

2.4.1. Particle size

The particle size distribution measured using an optical microscope with the help of a calibrated stage and ocular micrometer and the mean particle size was calculated.

2.4.2. Bulk density

Microspheres were placed into measuring cylinder. Volume occupied by the microspheres was noted without disturbing the cylinder and bulk density was calculated.

2.4.3. Tap density

Microspheres were placed into measuring cylinder. The cylinder was then subjected to a fixed number of taps (approximately 100). The final volume was noted and tapped density was calculated.

2.4.4. Flow properties

The flow properties were characterized in terms of angle of repose, flow rate, % compressibility also termed as Carr's index (C) and Hausner ratio.

2.4.5. % Recovery yield

This parameter was helpful in choosing the preparation method of microspheres giving minimum losses and highest yield. Percent recovery yield of microspheres was calculated by the formula,

$$\% \text{ Recovery yield} = \frac{\text{Total weight of microspheres}}{\text{Total weight of excipients added}} \times 100$$

2.4.6. % Entrapment efficiency

The drug content of drug loaded microspheres was determined by dispersing microspheres in 0.1 N HCl, after that agitation with a magnetic stirrer to extract the drug. After filtration through a whatman filter paper, the drug concentration was determined by taking the absorbance of this solution spectrophotometrically with suitable dilution. Polymers did not interfere under these conditions. The concentration of drug in a solution was calculated from the formula,

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

2.4.7. In vitro buoyancy of microspheres (% Floating or % Buoyancy)

The floatation study was carried out to determine the floating behaviour of the microspheres. Floating behaviour of hollow microspheres was studied using a USP XIII dissolution apparatus type II (paddle type) by spreading the microspheres (100 mg) on 900 ml of 0.1 N HCl containing 0.02 % v/v tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37 ±0.5 °C for 24 h. Both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. The percentage of floating microspheres was calculated using the following formula,

$$\% \text{ Buoyancy} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100$$

2.4.8. Morphology

The external and internal morphology of the microspheres were studied by Scanning electron microscope. SEM was performed using ZEISS EVO LS10 instrument (Software - SmartSem) at Tata Institute of Fundamental Research (TIFR).

2.4.9. Thermal Analysis of Microspheres

Thermal Analysis was carried using SII Nanotechnology (SEIKO) and DSC 6220 differential scanning calorimetry (DSC). Accurately weighed samples were sealed in flat aluminium pans and heated from temperature range of 30°C - 300°C at heating rate of 10°C /min in a nitrogen atmosphere (flow rate, 50-60 mi/min).

2.4.10. *In vitro* drug release study

The *in vitro* drug release was studied by conducting dissolution test for capsule. Dissolution was carried out using USP XIII dissolution apparatus type II (paddle type). Nine hundred milliliters of 0.1 N HCl, which was maintained at 37°C, was used as dissolution medium. The speed of paddle was maintained at 100 rpm. Five milliliters samples were withdrawn at the time intervals of 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, and 24h and replaced with equal volume of fresh dissolution medium each time to maintain the sink condition, maintained at same temperature. The samples were filtered and suitably diluted. Absorbances of these solutions were recorded at wavelength 276 nm using UV spectrophotometer. All the
studies were carried out in triplicate. Linear regression was used to analyse the *in-vitro* release mechanism.

2.4.11. X-ray diffraction studies

X-ray diffraction studies of the METO, polymer, METO microspheres were performed by a diffractometer at TIFR to observe the physical state of METO in the microspheres. The instrument details are as follows,
Manufacturer: Panalytical
Model: Xpert PRO MPD
Anode: Copper K-alpha
Wavelength: 1.5405 Angstorm
Power: 45KV and 40mA
Detector: Xcelerator with Diffracted Beam Monochromator

2.5. Evaluation of the METO-loaded microsphere capsule:

2.5.1. Weight variation of capsules

20 capsules were taken at random and average weight was calculated. Individual weight was taken and % relative standard deviation was calculated.

2.5.2. Assay

Content of 5 capsules were mixed and powered. Drug was extracted using ethanol and filtered. The filtrate was analysed by UV/ visible spectrophotometer at 276nm.

3. RESULTS

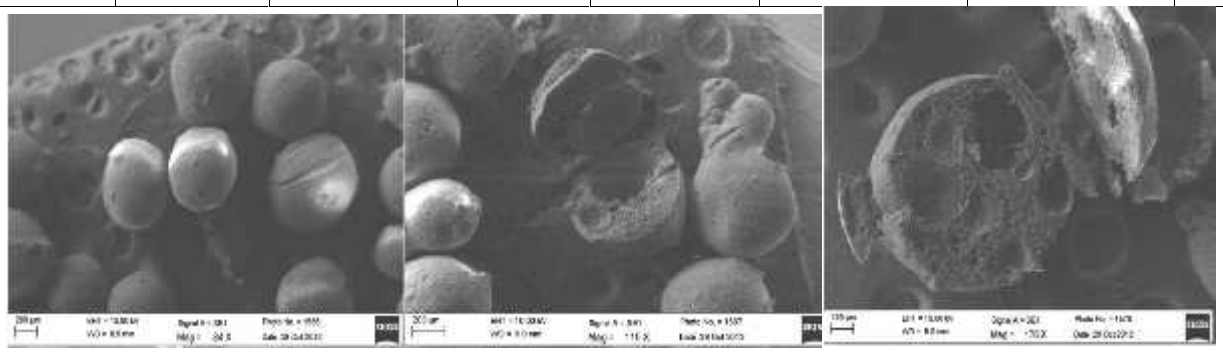
3.1. Characterization of Microsphere

Results of recovery yield, % entrapment efficiency, % buoyancy, shape and particle size of microsphere, dissolution studies obtained in 12 hr for microsphere formation are described in (Table **2**). The scanning electron micrographs of METO microsphere are illustrated in Fig. **1**. METO microspheres were found to be spherical in shape with smooth surface, uniform size and not aggregated (Fig. **1(a)**). Scanning electron microscopy (SEM) was employed to observe surface and inner part of the microspheres (Fig. **1(b)**). It indicates that there is no precipitated drug on the surface of microspheres and drug was completely embedded in the shell. Also microsphere had shown hollow cavity which indicates that pores were predicted to be formed during the solvent evaporation process which might form passages that help to release the drug from microspheres. Fig. (**1(c)**) reveals the dense and inner core of the microsphere. DSC (Fig. **2**) thermogram represents the change in thermal behaviour as a result of interaction during preparation between excipients. For plain METO, a sharp melting peak at 96.3°C was noticed. The DSC of METO -loaded microspheres did not show any significant different melting peaks which indicated complete entrapment of METO in the polymer

matrix and possible reduction of drug crystallinity in polymer matrix. As showed in Fig. **3**, the XRD pattern of microsphere was different with that of pure METO and EC. From XRD patterns, it was observable that the pure drug exhibited crystalline characteristics peaks of pure drug and formulations did not showed crystalline peaks of pure METO; instead of formulation showed different pattern of XRD. It might be due to dilution effect and decrease in crystallinity of the drug. It could be suggested that METO was dispersed in polymer matrix.The floating behaviour of microspheres of METO in Fig. **4** describes that the densities of floating microspheres are less than the gastric fluid, therefore they tend to float over gastric fluid.

Table 2: Physical evaluation of floating microspheres of Metaclopramide Hydrocloride

Formulation code	% Recovery Yield (%)	% Entrapment efficiency (%)	*In vitro* % drug release at end of 24h (%)	% Buoyancy (%)	Shape of microsphere	Particle size of Microsphere (µm)	Angle of repose (degree)
F1	Small fine sticky microsphere						
F2	Sticky mass						
F3	85	60.005	-	-	Small, spherical	-	-
F4	Sticky, needle shaped aggregates						
F5	Lumpy mass						
F6	60	55	28.84	+	Spherical, discrete	-	-
F7	89.00	95.48	92.03	83	Spherical	-	-
F8	94.00	92.00	21.83	86	Spherical	-	-
F9	88.00	88.00	57.43	88	Spherical	-	-
F10	96	91.15	88.51	79	Spherical, discrete	574.52	26.45°
F11	97	95.48	92.03	82	Spherical, discrete	518.41	23.78°
F12	94	95.25	90.18	86	Spherical, discrete	395.4	29.63°
F13	92	89.50	91.47	84	Spherical, elongated, discrete.	364.64	25.51°



(a) **(b)** **(c)**

Fig. (1). Scanning electron micrographs of METO microspheres

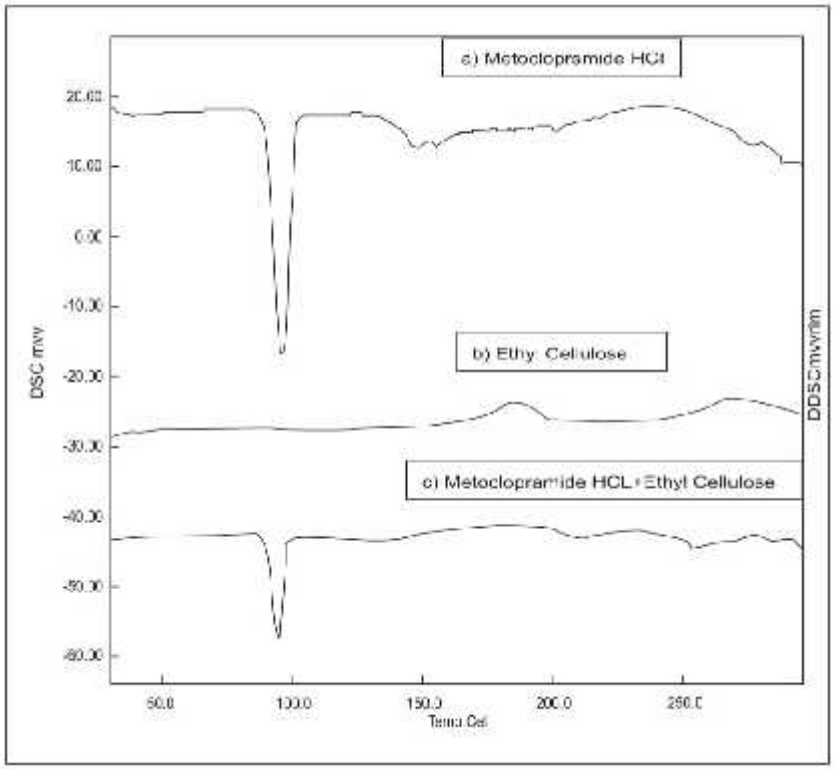


Fig. (2). DSC of METO, ethyl cellulose and drug loaded microsphere

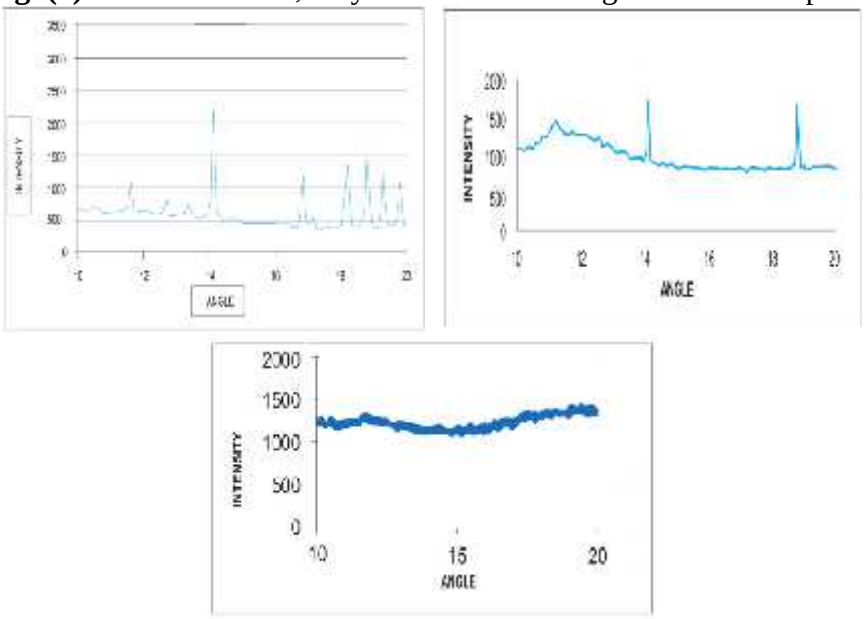
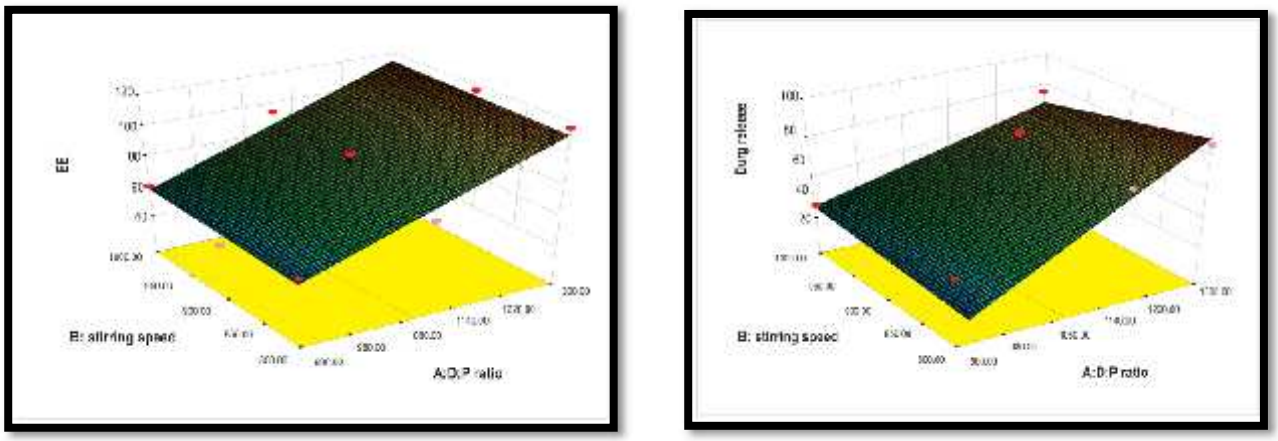


Fig. (3). XRD patterns of: (a) METO (b) EC and (c) METO-loaded microspheres

Fig. (4). Floating behaviour of microsphere

3.2. Optimization of process parameters

The surface response plot (Fig. **5 (a)**) exhibited that with an increase in stirring speed no significant increase in % entrapment efficiency but the opposite effect was seen with increase in polymer concentration because as polymer concentration increases may cause higher the drug surrounded by polymer at high amount of polymer. The surface response plot (Fig. **5(b)**) revealed that a with an increase in the stirring speed, the particle size goes on decreasing, This was due to the higher shearing force contributed by the stirrer which allowed the organic polymer solution to broken into small droplets in micrometer range to form emulsion. It was also reveale that corresponding decrease in drug release of microspheres observed with an increase in stirring speed. As stirring speed increases high shear force breaks down the large droplets to smaller one which provides the large surface area to small particles thereby increases dissolution rate of drug. It was also seen that as increase in concentration of polymer, drug release was decreased. This may be attributed to polymer at high concentration retarded the release of drug from microspheres.



(a) (b)

Fig. (5). Response surface plot for (a) % entrapment efficiency (b) % drug release.

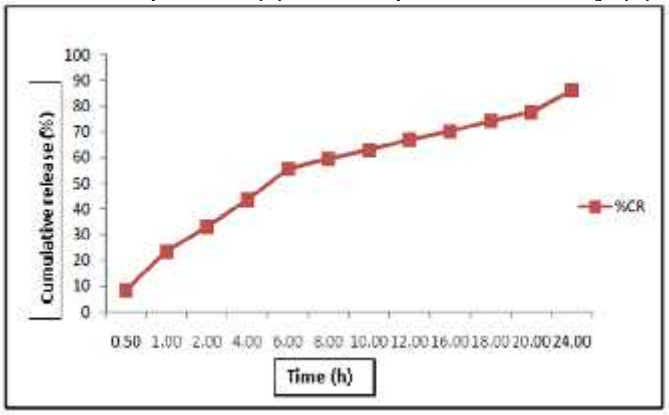


Fig. (6). In vitro drug release over 24 hrs.

3.3. Evaluation of METO-loaded microspheres filled capsule

The weight uniformity, content uniformity, flow properties (bulk density, tapped density, % compressibility, hausner ratio, angle of repose, flow rate) of prepared capsules were found to be satisfactory (Table **3**). The in vitro drug release profiles were checked on various kinetic models (such as zero-order, first-order, Hixson–Crowell, Weibull, Higuchi, Baker–Lonsdale, Korsmeyer–Peppas, and Hopfenberg models) in order to locate the drug release mechanism. The best fit with the highest correlation coefficient was showed first order model along with Higuchi model (r2 = 0.955) which

relates the diffusion controlled drug release from microspheres. The values of in-vitro drug dissolution were in the range of 80- 85% which revealed that microspheres can retard the release of drug.

Table 3: Micromeritic properties of floating microsphere

Parameters	Results
Bulk density	0.2794 ±0.025
Tapped density	0.2899 ±0.024
% Compressibility	5.2333 ±0.493
Hausner ratio	1.0366 ±0.026
Angle of repose	28.8566 ±0.636
Flow rate	1.0000 ±0
Weight variation	401.0238 ±1.3449
Content uniformity	97.47%

4. DISCUSSION

The Floating microspheres of METO were prepared by non-aqueous emulsion solvent evaporation method using different polymers. So, polymer was selected to formulate quality microspheres with good entrapment efficiency and to achievesustained drug release. Different formulation trials were carried out to decide the desirable parameters like drug:polymer ratio, higher polymer concentration, different surfactant, higher surfactant concentration which will affect different microspheres properties and also processing parameter like stirring speed. The prepared floating microspheres were evaluated for different physicochemical tests such as particle size, morphology, bulk density, tap density, true density, flow properties, % recovery yield, % entrapment efficiency, drug content, in vitro floatability and in vitro drug release studies. Polymers ES 100, EL 100, ERS100, ERL100 and EC were screened by keeping the same drug to polymer ratio of 1:5 and another parameters constant. Batch F1, F2, F4, F5 gave spherical and sticky microspheres. Batch F3 which contained EC polymer showed 85% of recovery yield, 60% entrapment with spherical, elongated shape but not uniform in size. From these trials it is observed that EC give good entrapment efficiency, % recovery yield and % drug release and microspheres obtained were comparatively good in size, shape, colour, discrete and free flowing. So, batches were carried for next trial with higher polymer ratio. Also, in these trials' microspheres were little sticky and white sticky material was observed at the bottom of the beaker which may be tween 80 as it is less soluble in oil phase. Therefore, from the above observation surfactant tween 80 was replaced by span 80 at concentration of 0.5% and batches with higher polymer ratio taken which would form better polymer matrix and good quality microsphere. So, in batch F6, the microspheres obtained were hard, free flowing and non-sticky. This may be due to span 80 as it is oil soluble it gets completely dissolved in liquid paraffin giving a very clear dispersion medium even after addition of internal phase solvents. The drug was completely dispersed in external phase medium. From these trials surfactant span 80 was finalized for further use. But, the entrapment efficiency and % drug release both were not satisfactory this may be due to lower polymer concentration. Hence same batch was tried at further higher concentration of polymer with increase in concentration of surfactant in next trials.

Therefore, the drug: polymer ratio was taken 1:10 whereas surfactant concentration was increased to 1%. In batch F7, it was observed that the entrapment efficiency, % recovery yield, % drug release was increased and the microspheres were spherical, discrete, free flowing and uniform in size and shape. From these trials it can be predicted that as the polymer concentration increases, the surfactant concentration must be increased to get good results. From above trails it was concluded that EC was optimum polymer for this study as it gave good results for entrapment efficiency, % recovery yield, % drug release. So, EC was screened for various concentrations keeping rest of the parameters

same. In batches F8 and F9, the % recovery yield and entrapment efficiency were increased but % drug release was decreased. This may be due to higher concentration of EC that was 1:15, 1:20, as EC was release retardant. But in batch F7, it was observed that EC with concentration 1:10 gives maximum entrapment efficiency, % recovery yield, % drug release and microspheres which are spherical, discrete, free flowing, uniform in size and shape. So, batches with low drug to polymer ratio (i.e higher polymer concentration) showed increased entrapment as compared to batches that had high drug to polymer ratio. This was happened because; the entrapment of drug increases significantly at increased level of polymer concentration. But further increase in polymer concentration did not lead to further increase in entrapment efficiency. % Drug release was found to be lesser in batches with more amount of polymer than with less amount of polymer, this was presumably due to retardant property of the polymer. The higher amount of drug surrounded by the polymer with the higher the polymer content, which behaved as barrier to prevent diffusion of drug molecules into the external phase. Therefore, diffusional path length increased at higher polymer concentrations which leads to an increased density of the polymer matrix. This might decrease the overall drug release from the polymer matrix. Also with increasing polymer concentration, particle size of batches increased. This may be due to the increased viscosity of the internal phase. With the increasing amount of polymer, more amount of energy required to break the drug-polymer droplets into smaller particles, which resulted in large particle size. But decrease in particle size could be overwhelm by increasing stirring rate of an internal volume.Hence further trials were taken with EC in concentration of 1:10 with varying stirring speed and keeping rest of parameters same. So, it was observed that as the speed increases particle size decreases. But at speed of 1400, 1600, 1800 … the shape of microsphere was changed and the surface of microspheres shows small holes and depressions due to which there was decrease in entrapment efficiency and % drug release. At speed of 800 and 900 rpm there was no significant variation in results, the entrapment efficiency, % drug release and % recovery yield was good. But as the speed was increase to 1000 rpm the entrapment efficiency was not affected but release was comparatively less as in F8. In batch F13, it was observed that at speed of 1200 rpm there was decrease in both entrapment efficiency and % drug release. From all the above results it was concluded that batch F12 was the best formulation trial batch which shows comparatively good results.

Therefore, batch F7 took for optimization by a 32 full factorial design used to illustrate the impact of independent variables (concentration of polymer and stirring speed) on dependent variables (drug entrapment efficiency and % drug release). The effect of concentration of EC (A) and stirring speed (B) on dependent variables was represented in response surface plot in Figs. 5(a) and 5(b). Optimized batch was recognized in the experimental design with constraints on dependent variables. Stirring rate of 800 rpm and 1:12 ratio of drug: polymer was selected to formulate optimized batch of microsphere. Formulation containing 1:12 ratio of drug: polymer i.e. METO to ethyl cellulose showed % recovery yield of 91.86%, % entrapment efficiency of 95.56% and sustained drug release of 85.95% at the end of 24 hours with % buoyancy of 85%.

5. CONCLUSION

The study was found that gastro retentive of METO floating microspheres were prepared to overcome disadvantages of single unit dosage form. It was concluded that, floating microspheres administered in the form of capsule would be optimistic drug delivery for oral administration of drug METO, as in vitro studies suggest that microspheres for METO are ensuring that the improved bioavailability and retard the release in comparison with conventional dosage forms. Two process parameters namely, stirring speed and polymer concentration were found to be important for producing desirable microspheres.

There would be maximum advantages of microspheres, one of which is reducing dosing frequency by taking one dose only due to a slow and controlled release fashion of drug from

microspheres, which proves its potential in commercial application. Laboratory scale batches could be easily scaled up with the exactly same in vitro release pattern of microspheres that of laboratory batches. Therefore, to acquire highest market value compared to existing conventional formulations, still there is need of extensive research in his field.

6. ACKNOWLEDGEMENT

The authors express thanks to M/s IPCA Laboratories Pvt. Ltd. and EVONIK laboratories Pvt. Ltd. for offering the necessary drugs for carrying out the experiments. We are thankful to Tata Institute of Fundamental Research (TIFR), for providing me with the required facilities.

7. REFRENCES

1. Drug bank: Open Data Drug and Drug Target Database. Metoclopramide HCl [internet] Available from: http://www.drugbank.ca/drugs/DB01233
2. Robinson JR et al. (1987). Influence of drug properties and routes of drug administration on the design of sustained and controlled release system. In: Robinson JR, Lee VHL, editors. Controlled drug delivery fundamentals and applications. 2nd Ed. New York: Marcel Dekker Inc; 4-94.
3. Sood A and Pachagnula R. (1998). Drug release evaluation of diltiazem CR preparations. Int J Pharm; 175, 95-107.
4. Celik M. (1987). Compaction of multiparticulate oral dosage forms. In: Ghebre-Sellassie I, Ed. Multiparticulate Oral Drug Delivery New York: Marcel Dekker Inc; 181-215
5. Kim CK and Kim MJ. (1994). Preparation and evaluation of sustained release microspheres of terbutalinesulfate. Int J Pharm; 106, 213-9.
6. Bhalerao SS et al. (2001). Study of processing parameters influencing the properties of diltiazem hydrochloride microspheres. J Microencapsul; 18, 299-307.
7. Vilivalam VD and Adeyeye Cm. (1994). Development and evaluation of controlled-release diclofenac microspheres and tabletted microspheres. J Microencapsul; 11, 455-70.
8. Lachman L et al. (1991). Theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 296-302.
9. Sveinsson S et al. (1993). The effect of tableting on the release characteristics of naproxen and ibuprofen microcapsule Int J Pharm.; 92, 29-34.
10. Singh BN. and Kim KH. (2000). Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Release;63, 235–59.
11. Streubel A et al. (2003). Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur. J. Pharm. Sci.; 18, 37–45.
12. Eytan AK et al. (2003). Novel gastroretentive dosage forms: evaluation of gastroretentivity and its effect on levodopa absorption in humans. Pharm. Res.; 20, 1466-73.
13. Kawashima Y et al. (1991). Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (I vivo). J. Controll. Release; 16, 279-290.
14. Vyas SP. and Khar RK. (2002). Targeted and controlled drug delivery- Novel carrier systems.I Edition,CBS Publications and Distributors; 417-425.
15. Yeole PG t al. (2005). Floating drug delivery system: Need and Development. Indian J Pharm Sci.;67, 265–72.
16. Aspde TJ et al. (1997). Chitosan as a nasal delivery system: The effect of chitosan solutions on *in vitro* and *in vivo* mucociliary transport rates in human turbinates and volunteers. J Pharm Sci.;86, 509–13.

17. Mundargi RC et al. (2008). Formulation and in-vitro evaluation of novel starch- based tableted microspheres for controlled release of ampicillin. Carbohydrat Polym; 71(1), 42-53.
18. Pe'reza MH et al. (2000). The preparation and evaluation of poly (e-caprolactone) microparticles containing both lipophilic and a hydrophilic drug. J Control Release; 65, 429-38.
19. AppaRao B et al. (2010). Design and evaluation of sustained release microcapsules containing diclofenac sodium. Int J Pharm Biomed Res; 1(3), 90-3.
20. Malik K et al. (2011). Taste Masked Microspheres of Oflaxacin: Sci Pharm; 79, 653-72.
21. Chung TW et al. (2001). Effect of rate of solvent evaporation on the characteristics of drug loaded PLLA and PDLLA microspheres. Int J Pharm; 212, 161-9.
22. Bogataj M et al. (1991). Eudragit microspheres containing bacampicillin: preparation by solvent removal method. J Microencapsul; 8, 401-6.
23. Wang J. and Schwendeman SP. (1999). Mechanism of solvent evaporation encapsulation processes: prediction of solvent evaporation rate. J Pharm Sci; 88, 1090-9.
24. Gabor F et al (1999). Ketoprofen poly (D, L Lactic-coglycolic acid) microspheres: influencing of manufacturing parameters and type of polymer on the release characteristics. J Microencapsul; 16, 1-12.
25. Joseph I. and Xiao YW. (1999) Bimodal Release of Thyophylline from "Seed-Matrix" Beads Made of Acrylic Polymers. Pharmaceutical development and technology; 4(2), 257-67.
26. Mateovic T et al (2002). The influence of stirring rate on biopharmaceutical properties of eudragit RS microspheres. J Microencapsul; 19, 29-36.
27. Bodmeier R. and McGinity JW. (1988). Solvent selection in the presence of poly (D,L-lactide) microspheres prepared by the sovent evaporation method. Int J Pharm; 43, 179-86.
28. Lin WJ. and Wu TL. (1999). Effect of manufacturing conditions on the formation of double walled polymer microspheres. J Microcapsul., 165, 153-67.