

Formulation, Optimization and Characterization of Gastro-retentive Troxipide Microspheres

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Abstract

Troxipide -loaded gastro retentive floating microspheres using Ethylcellulose as matrix and methanol as mucoadhesive polymer were prepared for the purpose of improving sustain drug release for about 12h of troxipide to produce local action and reduce dose frequency. The morphological properties of the microspheres were studied by optical microscopy and scanning electron microscopy (SEM). Floating microspheres are gaining attention due to their wide applicability in the targeting of drugs to the stomach. These floating microspheres have the advantage they remain buoyant and distributed uniformly over the gastric fluid to avoid the vagaries of gastric emptying and release the drug for prolonged periods of time. Multi-particulates low-density particles can successfully prolong the gastric retention time of the drugs. This article can provide an overview of two important approaches utilized to prepare and improve the performance of floating microspheres.

Keywords: GRDFs, FDDS, Hollow Microspheres, Troxipide, Sustain release, Local actions.

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Introduction

Troxipide is a novel systemic non-antisecretory gastric cytoprotective agent with anti-ulcer, anti-inflammatory and mucus secreting properties. so the drug has its site of action in stomach to achieve this sustained release gastro retentive floating microspheres of Troxipide formulate to produce local action and reduce dose frequency. It has half-life of 7 – 8 hr. It is mostly absorbed from upper GIT.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery has historically been by oral ingestion.

Drugs that are easily absorbed from the GIT and having a short half-life are eliminated quickly from the blood circulation. To avoid these problems oral controlled drug delivery systems have been developed as they release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time.

However, incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bioavailability. Efforts to improve oral drug bioavailability have grown in parallel with the pharmaceutical industry. As the

number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics.

Not all drugs get uniformly absorbed throughout the GIT. Some drugs show absorption variability. Such drugs have an “absorption window” - region from where absorption primarily occurs. There can be various reasons for presence of such a window. Absorption window in stomach or upper small intestine IDEAL CANDIDATES. Thus, gastro retentive dosage forms (GRDDS) which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed.

Gastro-retentive Drug Delivery Systems/ Gastro-retentive Dosage Forms (GRDFS)

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time i.e. Gastro retentive Dosage Forms (GRDFs). These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.

Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drug exhibiting an ‘absorption window’ in the GI tract. The intimate contact of the DDS with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption.

These considerations have led to the development of oral controlled release (CR) dosage forms possessing gastric retention capabilities. Drug may not be absorbed

uniformly over the length of the gastrointestinal tract, because dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less absorbed and drug absorption from colon is usually erratic and inefficient. Moreover, certain drugs are absorbed only from the stomach or the upper part of small intestine.

GRDDS are preferred for drugs:

- Acting locally in the stomach.
- Primarily absorbed in the stomach or upper parts of the small intestine.
- Poorly soluble at an alkaline pH (pH dependent solubility).
- Narrow window of absorption.
- Unstable in colonic environment (pH dependent stability).
- Enzymatic degradation in intestine.

Advantages of GRDDS:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.

Basic gastrointestinal tract physiology

The stomach is anatomically divided into 3 parts:

1. Fundus. {acts as a reservoir for undigested material}
2. Body.
3. Antrum (mixing motions and acts as a pump for gastric emptying, through propelling actions)

During the fasting state, an interdigestive series of electrical events takes place, cycling through both stomach and intestine every two to three hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC).

4 phases

1. Basal phase – lack of secretory or electrical activity or contractile motions.
2. Pre-burst phase – intermittent contractions.
3. Burst phase – intense regular contractions, sweeps all undigested material out – housekeeper wave.
4. Transitional phase.

Gastric emptying rate depends on:

1. Nature and caloric content of meal.

2. Posture
3. Gender
4. Age
5. Osmolarity
6. pH of food
7. Mental stress
8. Disease state

Approaches to gastric retention^{10,11}

A number of approaches have been used to increase gastric retention time (GRT) of a dosage form in stomach by employing a variety of concepts. These includes in Fig.

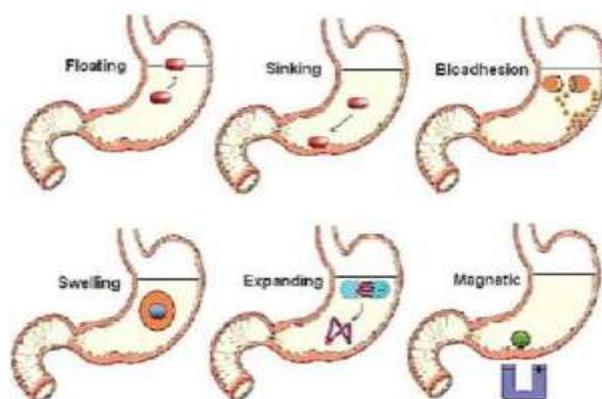


Fig. 1: Illustration of types of gastro-retentive drug delivery systems

- a. Floating Systems
- b. Bio/Muco-adhesive Systems
- c. Swelling and Expanding Systems
- d. High density systems
- e. Incorporation of passage delaying food agents
- f. Ion exchange resins
- g. Osmotic regulated systems
- h. Superporous hydrogels
- i. Magnetic system

Floating Drug Delivery Systems (FDDS)^{11,12}

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage forms (GRDFs).

Approaches to Design Floating Drug Delivery System

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

Classification of FDDS

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are,

A. Effervescent System

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) gas, thus reducing the density of the system and making it float on the gastric fluid. These effervescent systems further classified into two types:

1. Gas generating systems:

- a. Gastric single layer floating tablets or Hydrodynamically Balanced System (HBS)
- b. Intra gastric bilayered floating tablets.
- c. Multiple Unit type floating pills.

2. Volatile Liquid / Vacuum Containing Systems

- a. Intra gastric floating gastrointestinal drug delivery system
- b. Inflatable gastrointestinal delivery systems.
- c. Intra gastric osmotically controlled drug delivery system

B. Raft forming system

This system is used for delivery of antacids and drug delivery for treatment of gastrointestinal infections and disorders. The mechanism involved in this system includes the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells, forming a continuous layer called raft. This raft floats in gastric fluids because of the low bulk density created by the formation of CO₂. Usually the system contains a gel-forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and more apt to float on the gastric fluids.

C. Non effervescent systems

The Non effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. Single layer floating tablets
2. Bilayer floating tablets
3. Alginate beads

4. Hollow microspheres

Hollow Microspheres^{13,14}:

Hollow microspheres (microballons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 h in vitro.

Development of floating microspheres

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Advantages of floating microspheres:

1. Bioavailability enhances, despite first pass effect, because fluctuations in plasma drug concentration are avoided, and a desirable plasma drug concentration is maintained by continuous drug release.
2. Superior to single-unit floating dosage forms, as such microspheres release drugs uniformly and there is no risk of dose dumping.
3. Enhanced absorption of drugs that solubilise only in stomach.
4. Site-specific drug delivery to the stomach can be achieved.
5. Avoidance of gastric irritation, due to sustained release effect.
6. Better therapeutic effect of short half-life drugs can be achieved.

Reproducibility of the particle size of the formulation is the main problem associated with floating microspheres.

Mechanism of floating microspheres

When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the

rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments.

Materials and reagents used

Polymers used were Eudragit L 100 (EL100), Eudragit RS 100 (ERS 100), Eudragit RL 100 (ERL 100), Ethyl cellulose 18–22 cps (EC) and HPMC 4K, HPMC 15LV, HPMC100 K. Methanol and dichloromethane (DCM) as solvent were selected after a review of literature and formulation trials. PVA, SLS, Span 80 were used as surfactants to form a stable emulsion. Distilled water was dispersion medium used to form an emulsion.

Table 1: Composition of TROX loaded microsphere

Sr. No	Name of material/reagent	Supplied/gifted by
1.	Troxipide	Zuventus Healthcare Ltd., India
2.	Dicholomethane	Research Lab Fine Chem Industries
3.	Ethanol	Gogia & company
4.	Ethyl cellulose	S.D. Fine Chemicals Limited Mumbai
5.	Methanol	Research Lab Fine Chem Industries

Methods of preparation of floating microspheres

Table 3: Parameters used in the formulation

Drug: Troxipide
Polymer: Ethylcellulose
Solvents (ml): Methanol
Inlet & Outlet temperature
Aspiration
Feed Pump
Nozzle size
Pressure

Process variables affecting physicochemical properties of hollow microspheres

1. **Stirring rate:** The effects of the stirring rate on microsphere particle size. To observe the effect of agitation speed on the size of the resulting microspheres, formulations were prepared at varying agitation speeds; 300 rpm, 500 rpm, 1000 rpm. The size of the resulting microspheres

For formulating floating microspheres following methods were used,

1. Solvent evaporation method
2. Spray drying method

1. **Solvent evaporation method:** Floating multiparticulate dosage form was prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring⁶, the solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties.

Table 2: Parameters used in the formulation

Drug : Troxipide
Polymers : Ethylcellulose
Solvents (ml) : Methanol
Stirring speed (rpm)
Surfactant (%)
Volume of aqueous dispersion medium.
Temperature (°C)

2. Spray drying method:

Procedure for spray drying method:

- Exact amount of solvents were measured
- Drug and polymers were added to the solvent and dissolved by stirring on magnetic stirrer to form homogenous polymer solution.
- Polymer solution was sprayed.

decreased with increasing agitation, but the increase was not statistically significant. It may be inferred that the agitation speed in the study range was not able to break up the bulk of the polymer into finer droplets.

2. **Temperature of preparation:** Optimum preparation temperature with respect to microsphere cavity formation. The solution drug and polymer were poured into an aqueous solution of polyvinyl alcohol at various temperatures, i.e., 20, 30, 40 and 50°C. They concluded that preparation at 20 or 30°C provided porous microspheres having higher porosity with a surface so rough as to crumble upon touching. Although the respective apparent particle densities of the resulting hollow microspheres were low, both buoyancies were low, probably due to easy penetration of the dissolution medium through the

porous surface. The roundness of hollow microspheres prepared at 40°C was close to 1; moreover, surfaces were less rough than those of hollow microspheres prepared at 20 or 30°C. Hollow microspheres prepared at 50°C exhibited no hollow nature; however, a single large depression occurred on the surface. The hollow microspheres possessed high apparent particle density and low buoyancy due to the absence of a cavity. Few traces of evaporation were observed on the surface, which was attributable to the rapid evaporation of dichloromethane at temperatures beyond the boiling point (40.2°C). At 40°C, polymers and the drug were coprecipitated, and the shell was formed by the diffusion of ethanol into the aqueous solution and simultaneous evaporation of dichloromethane. In contrast, hollow microspheres prepared at 50°C demonstrated a single large depression on the surface, which was a consequence of the rapid evaporation of dichloromethane.

- 3. Plasticizers:** The effect of plasticizer concentration on the surface of microspheres and on the release of the drug. They have found that the addition of plasticizer made the wall of material more elastic and flexible, so that it never got brittle or ruptured under pressure. It was also observed that the release of the drug increased significantly with the increase of plasticizer concentration.
- 4. Volume of aqueous phase:** Volumes of aqueous phase used were 200, 300, 400 and 500 ml they observed that the potential advantage of using large volumes of the external aqueous phase was the reduction of the required stirring times. The solubility of dichloromethane in water is 1% w/v. Using a larger volume (400 to 500 ml), the diffusion of dichloromethane into the aqueous phase, and hence the solidification of particles, occurred faster, when compared to a volume of 200 ml.
- 5. Solvent ratio:** The bridging liquid plays a key role in microsphere preparation. When a good solvent diffuses into the poor solvent, which causes the precipitation of the drug and the polymer, a bridge liquid must be present in order to maintain the spherical shape of the microsphere. Too small a volume of the bridging liquid can lead to irregularly shaped microspheres while too large a volume of bridging liquid could prevent the emulsion droplets from solidifying. Therefore, the amount of dichloromethane needs to be carefully controlled. The ratio of dichloromethane with ethanol also affected the morphology of the microspheres and the best results with spherical shape were obtained when the ratio of ethanol to dichloromethane was 2:1.
- 6. Amount of polymer and viscosity:** Increased density of the polymer matrix at higher

concentrations results in increased diffusional path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release. When viscosity is increased, the yield of hollow microspheres is decreased, and mean diameter and drug loading amount are increased. The effect of the drug-to-polymer ratio on the properties of drug the drug dissolution profile could be slowed down by increasing polymer amount in the formulations, and that particle size, surface characteristics of microspheres, and dissolution rate modified through the variation of drug-to-polymer ratio.

- 7. Effect of solvents:** Various organic solvents on the formation of microspheres by the solvent evaporation method. Dichloromethane was employed as polar internal organic solvent phase for preparation of microspheres because it is a good solvent for most of polymers and drugs. However, it was observed that the microspheres obtained were not at all spherical in shape. To solve this problem, methanol was used, along with dichloromethane, in the preparation of microspheres. The microspheres so obtained were spherical, but lacked smooth texture.
- 8. Emulsifier concentration:** Effect of emulsifier concentration on particle size. They found that the particle size and size distribution were increased when the surfactant concentration was reduced from 1% to 0.25% (w/w). The role of the surfactant is to decrease the interfacial tension between the dispersed droplets and the continuous phase, as well as to protect the droplets from collision and coalescence. Low emulsifier concentrations may be insufficient to shield the entire droplet surface; droplets are more susceptible to collision and fusion. Also, at higher concentration of emulsifier, lower encapsulation efficiency and larger particle size were obtained, which suggests that the critical micelle concentration had been exceeded, which directly affected emulsion stability. Hence, the optimum concentration of the emulsifier should be identified.

Evaluation of microsphere

Floating microspheres are characterized by their micromeritic properties such as particle size, tapped density, compressibility index, true density and flow properties. Particle size is measured using an optical microscopy and mean particle size was calculated by measuring 200 to 300 particles with the help of calibrated ocular micrometer. True density is determined by liquid displacement method; tapped density and compressibility index are calculated by measuring the change in volume using a bulk density

apparatus; angle of repose is determined by fixed funnel method, also flow rate, % compressibility also termed as Carr's index (C) and Hausner ratio determined¹.

% recovery yield was calculated by formula,

$$\% \text{ Recovery yield}^2 = \frac{\text{Total weight of microspheres}}{\text{Total weight of polymer and drug added}} \times 100$$

% Entrapment efficiency

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

In vitro buoyancy of microspheres (% Floating or % Buoyancy):

Floating behaviour of hollow microspheres was studied using a USP dissolution test apparatus 1 (Basket Apparatus) by spreading the microspheres (150 mg) on 900 ml of 0.1 N HCl. The medium was agitated with a basket rotating at 100 rpm and maintained at 37°C±0.5°C for 12 h. Both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. The % of floating microspheres was calculated using the following formula,

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

In vitro % Drug release:

The drug release rate from microspheres was determined using USP dissolution test Apparatus 1 (Basket apparatus) and analysed spectrophotometrically at 257 nm to determine the concentration of drug present in the dissolution medium. The dissolution study was conducted for 12 h.

Surface morphology:

The external and internal morphology of the microspheres were studied by SEM. The samples for SEM were prepared by lightly sprinkling microspheres on a double sided adhesive tape stuck to an aluminium

grooved edge stub. The stubs were then coated with gold 93. The coated samples were then randomly scanned and photographs were taken with a scanning electron microscope. SEM was performed using Central Institute for Research on Cotton Technology instrument.

X-ray diffraction studies³:

X-ray diffractometry of the TROX, polymer and TROX microspheres were performed by a diffractometer at TIFR to observe the physical state of TROX in the microspheres 94. The instrument details are as follows,

Manufacturer: Panalytical

Model: Xpert PRO MPD

Anode: Copper K-alpha

Wavelength: 1.5405 angstrom

Power: 45KV and 40mA

Detector: Xcelerator with diffracted beam monochromator.

Optimization⁴:

The word, optimize is defined as, to make as perfect, effective or functional as possible and optimization may be interpreted as the way to find those values of the dependent variable.

Design-Expert® software has been used for data analysis of optimization experiments.

Optimization experimental^{5,6,7}:

After interpreting the results obtained for the trial batches, it was observed that batch showed good appearance, % entrapment efficiency, % recovery yield and *in vitro* % drug release. Therefore, this formula was further optimized using 32 randomized full factorial design. Final formula of batch to be optimized is given,

Table 4: Optimized batch of TROX

Ingredients	Quantity	Parameters	
TROX(mg)	100	Inlet & Outlet temperature	1200c & 600c
Ethyl cellulose (mg)	300	Aspiration	1200 rpm
Methanol (ml)	40	Feed Pump	30 rpm
		Nozzle	1.5 mm
		Pressure	1 kg/cm ²

Factors used were drug to polymer ratio and the Aspiration for three levels viz. low (-1), medium (0) and high (+1).

% entrapment efficiency and *in vitro* % drug release were considered as dependent variables and various plots were obtained using Statease Design-Expert®9.0.3.1 software for the desired optimum range of 80 – 90% for entrapment efficiency and 80–90% for % drug release. The data was analyzed using ANOVA.

Optimization results

A 32 randomized full factorial design was constructed to study the effect of drug to polymer ratio and Aspiration on the % entrapment efficiency and % drug release of microspheres and evaluate the response.

Various trials were taken as per the 32 factorial design along with their responses and after analyzing the data, the formulation which had drug to polymer ratio of 100:300 and Aspiration 1300 rpm was found to be optimum with regards to % entrapment efficiency and *in vitro* % drug release. This batch was further subjected to stability studies.

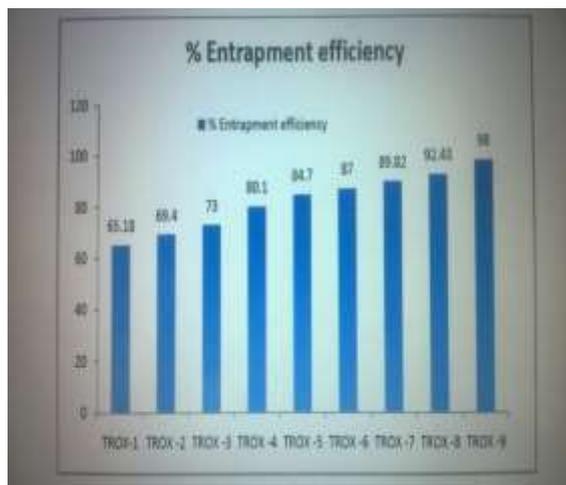


Fig. 2: Surface response plot for % entrapment efficiency

The surface response plot revealed that increase in the % entrapment efficiency was seen with increase in aspiration and same effect was also seen with increase in polymer concentration.

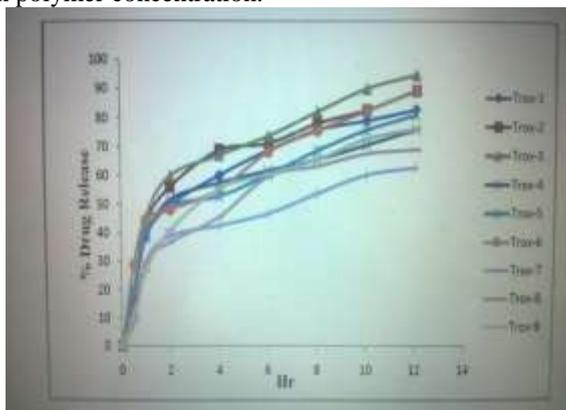


Fig. 3: Surface response plot for % drug release

The surface response plot revealed that a corresponding increase in drug release of microspheres observed with an increase in aspiration. It was also seen that with increase in polymer concentration, drug release was decreased.

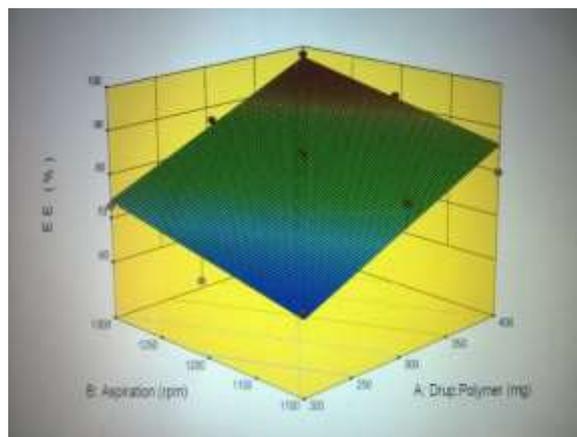


Fig. 4: Surface response plot for % entrapment efficiency

The surface response plot revealed that increase in the % entrapment efficiency was seen with increase in aspiration and same effect was also seen with increase in polymer concentration.

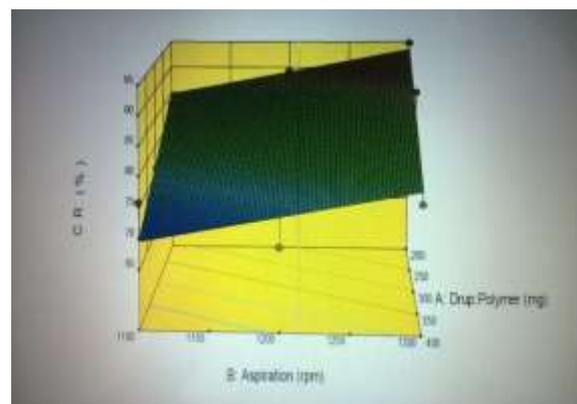


Fig. 5: Surface response plot for % drug release

The surface response plot revealed that a corresponding increase in drug release of microspheres observed with an increase in aspiration.

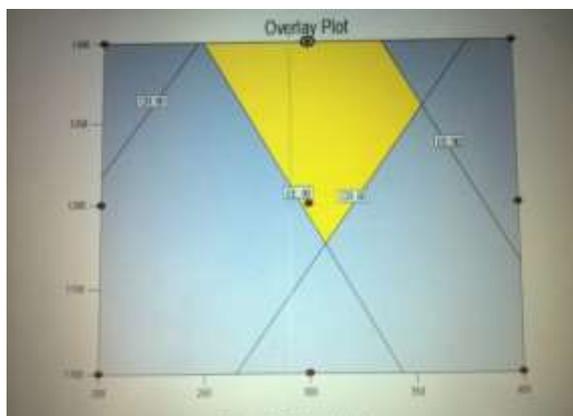


Fig. 6: Overlay plot

From the overlay plot it was concluded that to get desired microspheres having % entrapment efficiency of 80-90% and *in vitro* % drug release 80–90%, the overlay plot gives a range of aspiration and the concentration of ethyl cellulose that can be used to obtain a desired formulation.

Evaluation of optimized batch

The micromeritics properties of microspheres of optimized batch TROX-6OP is,

Table 5: Evaluation parameters of TROX

Parameters	Results (Average±SD)
Average particle size	8.58 μ m
Shape of microspheres	Spherical, discrete
Bulk density (g/ml)	0.3798±0.008
Tapped density (g/ml)	0.3953±0.008
% Compressibility	3.916±0.114
Hausner ratio	1.04±0.001
Angle of repose (°)	29±0.67
Flow rate (g/sec)	1±0

Optimized batch gave % recovery yield of 72 with % entrapment efficiency of 85.87%. % Buoyancy of batch was found to be 80%. The *in vitro* % drug release of batch was found 85.93% at the end of 12 hr.

The photographs of microspheres and *in vitro* floating behaviour of batch TROX-6OP.



Fig. 7: Floating behavior of Hollow microspheres

Morphology of floating microspheres

The photographs of SEM analysis of optimized batch (TROX– 6OP) were shown in Fig.

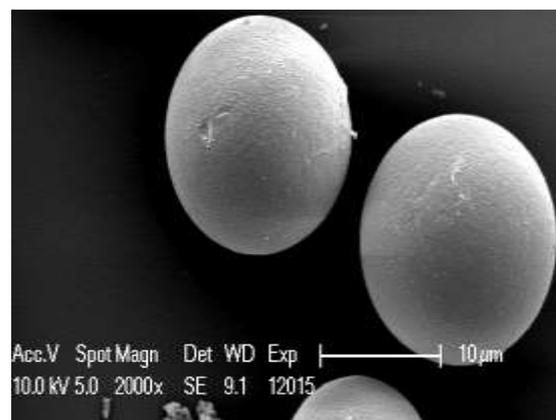
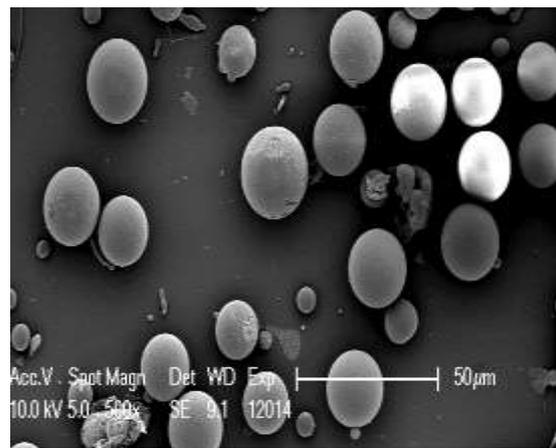


Fig. 8: SEM analysis of optimized batch

X-RD studies

The X-RD studies of pure TROX, EC and TROX–6OP microspheres were carried out. X-RD was carried out to investigate the effect of microencapsulation process on crystallinity of drug.

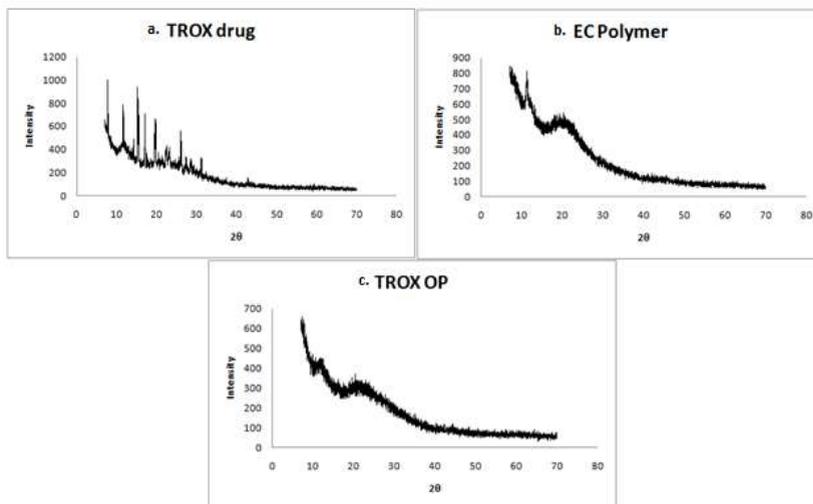


Fig. 9: XRD study of TROX

Fig. 6: Illustrates the comparative X-RD pattern of TROX, EC and TROX loaded EC microspheres. From X-RD patterns it was obvious that the pure drug exhibited characteristic crystalline peaks, formulations did not show crystalline peaks of pure drug instead it exhibited different pattern. It may be due to dilution effect and a decrease in crystallinity of the drug. It could be concluded that TROX was dispersed in polymer matrix.

In vitro % drug release

The drug release profile indicates that the release of TROX from microspheres was sustained over the period of 12 h with 85% drug release at 12h. The release of drug was effectively sustained in microspheres.

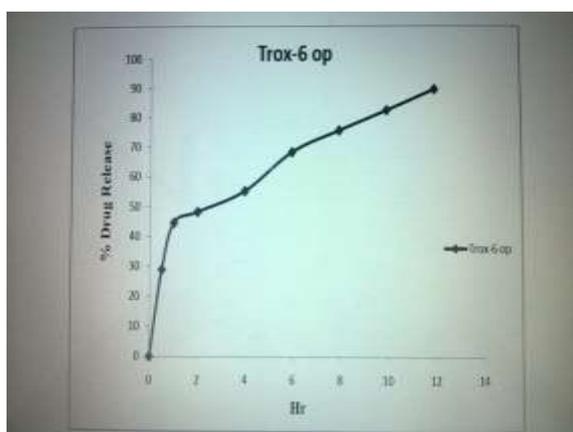


Fig. 10: In vitro % drug release of optimized batch

Physicochemical characteristics

Sr. no.	Parameter	Result (Average ± SD)
1	Average Particle size	8.58 μm
2	Shape of microsphere	Spherical, Hollow, Discrete

% Drug release of Troxipide 100 mg marketed tablet compared with formulated 150 mg sustained release Microsphere.

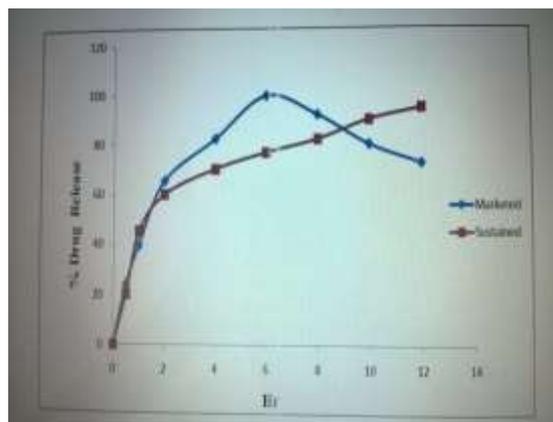


Fig. 11: Marketed Tablet and Formulated Sustained Release Graph

Stability Study⁸

Stability is a critical quality attribute of pharmaceutical products; therefore stability testing plays a crucial role in the drug development process.

The routes by which pharmaceuticals degrade may be chemical or physical. Although the decomposition of active ingredients in pharmaceutical dosage forms occurs through several chemical mechanisms, such as hydrolysis, oxidation-reduction, racemisation, decarboxylation, ring cleavage and photolysis those

most frequently encountered mechanisms are hydrolysis and oxidation-reduction. In physical routes, degradation carried out by the vaporisation, aging, adsorption, physical instability, etc.

Evaluation of batch TROX – 06 OP subjected to stability studies⁹:

The optimized batch of formulation was subjected to stability study. Time span for the stability study: 90 days. Storage conditions: 1. 30°C±2°C/65% RH±5% RH 2. 40°C±2°C/75% RH±5% RH. Sampling points: 0th day, 30th day, 60th day, 90th day.

The results of the all parameters evaluated after 0, 30th, 60th and 90th day and all the parameters were in the acceptable limits.

The formulated floating microspheres of Trox were found to be stable during the study period of stability testing. There were no significant changes in the physical parameters observed during study period. The optimized formulation did not show any significant change in the drug release profile. It also showed that the drug was stable in presence of excipients kept at elevated temperature and humidity conditions.

Conclusion

The present study reported the development of TROX loaded floating microspheres with polymer EC using spray drying method. From the experimental results it can be concluded that,

- Good % entrapment efficiency, % recovery yield and % buoyancy were obtained with the polymer.
- The optimized formulation showed % recovery yield of 72.54% with % entrapment efficiency of 85.87% and % buoyancy 80% with particle size of 1–50 µm.
- *In vitro* % drug release of optimized batch was 85.93% at the end of 12 h and microspheres followed diffusion controlled drug release mechanism.
- The SEM analysis showed microspheres formed were not aggregated and had hollow cavity.

The physical state of microspheres in the floating microspheres was studied by X-ray diffraction studies, which concluded there was decrease crystallinity of TROX in microspheres.

Therefore, it may be concluded that floating TROX microspheres tablet can be made and it would be a promising drug delivery system for oral administration of TROX to sustain the drug release for about 12h.

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