Research Article

Design and Development of Satranidazole Microspheres For Colon Targeted Drug Delivery

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ABSTRACT

The aim of this research was to develop and evaluate Multiparticulate system of Eudragit based Satranidazole microspheres exploiting pH sensitivity property and specific biodegradability for colon targeted delivery of Satranidazole. Eudragit S 100 based microspheres were prepared by oil-in-oil solvent evaporation method using different drug- polymer ratios (1:1 to 1:5), stirring speeds (1400 rpm) and emulsifier concentrations (0.5%-1.5% wt/vol). All formulations were evaluated for particle size and shape, swellability and percentage drug entrapment. The yield of preparation and the encapsulation efficiencies were high for all Eudragit microspheres. The in vitro drug release study of optimized formulation was also performed in simulated gastrointestinal fluids (SGF). The release profile of satranidazole from Eudragit microspheres was pH dependent. In acidic medium, the release rate was much slower; however, the drug was released quickly at pH 7.4. It is concluded from the present investigation that Eudragit microspheres are promising controlled release carriers for colon-targeted delivery of satranidazole.

Keywords: pH sensitive polymer, Eudragit S100, Colon specific drug delivery, Microspheres.

INTRODUCTION

Multiparticulate approaches tried for colonic delivery include includes formulations in the form of pellets, granules, microparticles and nanoparticles. The use of multiparticulate drug delivery systems in preference to single unit dosage forms for colon targeting purposes dates back to 1985 when Hardy and co-workers showed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time. Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GI tract easily, leading to less inter- and intra subject variability[1].

Microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged drug delivery, improve bioavailability or stability and target drug to specific sites. They have played a vital role in the development of controlled/sustained release drug delivery systems. Microspheres can be defined as solid, approximately spherical particles ranging from 1 to 1000µm, containing dispersed drug in either solution (or) microcrystalline form. These microspheres are suitable alternatives for conventional dosage forms[2].

Delivery of drugs to the colon via, the oral route is valuable in treating diseases of the colon (ulcerative colitis, amoebiasis, chron's disease, carcinomas & infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release higher up in the gastrointestinal tract or because of unnecessary systematic absorption[3].

There are several approaches, which is utilized in achieving colon targeting include use of pH-sensitive polymer, time-dependent formulation, bacterial degrading coating material, biodegradable polymer matrix and hydrogels and prodrug.[3] The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction[4].

There are several publications based on drug-containing microspheres using the Eudragit series of polymers as the encapsulating materials[3]. The Eudragits are a family of polymers based on acrylic and methacrylic acids suitable for use in orally administered drug delivery systems. These polymers are available in various grades possessing a range of physicochemical properties.

The aim of the peresent study is to develop controlled and colon targeted drug delivery system of satranidazole for the treatment of local colon disease by using Eudragit S 100 as a pH- sensitive polymer. The advantages of targeting drugs specifically to the chronic amoebisis disease of colon are reduced incidence of systemic side effects by directly targeting the drug to colon, the maximum concentration of drug reaches and increases the residence time of drug in colon.

MATERIALS AND METHOD

MATERIALS

Satranidazole was obtained as a gift sample from Alkem Laboratories Mumbai, India. Eudragit S-100 was procured as a gift sample from Degusssa Darmstadt, Germany. All other solvents and reagents used were of analytical grade.

METHOD

Prepration of Eudragit microsphere[5,6]

The Eudragit microspheres were prepared emulsion solvent evaporation method. Satranidazole and Eudragit S100 were dissolved in an ethanol: acetone (4:1) mixture, then emulsified in to liquid paraffin oil solution containing (0.5%-1.5% span-80 w/v) to form the oil in oil emulsion.

The system was maintained under agitation speed of 1400 rpm at room temperature for 4 hours to allow for the evaporation of solvent. Finally, the microspheres were filtered, washed with n-hexane, and air-dried overnight. Formulation variables are shown in Table 1.

All formulations were evaluated for particle size and shape, swellability and percentage drug entrapment. The particle size was examined by digital photomicroscope.

Scanning Electron Microscopy

The shape and surface morphology of Eudragit microspheres and were investigated using scanning electron microscopy (SEM). The samples for SEM study were prepared by lightly sprinkling the formulation on a double-adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of ~300 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with a scanning electron microscope[7].

Determination of Drug Content and Entrapment efficiency

Ten milligram of microspheres were weighed and dissolved in 10 ml of water. This solution was shaken with the help of wrist action shaking machine for 5 hrs and then kept for 24 hrs. Then it was filtered. The filtrate was assayed by spectrophotometer at 318 nm. The drug content and the encapsulation efficiency were determined.

***in vitro* dissolution test**

The optimized formulations of ES2 were selected for the dissolution test. In vitro release study of microspheres was performed in pH progression medium at 37ºC ± 0.5ºC. The drug dissolution test of microspheres was performed by the paddle method (model DT-06, Erweka, Darmstadt, Germany) specified in USP XXIII. Microspheres (100 mg) were weighed accurately and gently spread over the surface of 900 mL of dissolution medium. The content was rotated at 100 rpm. The simulation of GI transit condition was achieved by altering the pH of dissolution medium at different time intervals. The pH of the dissolution medium was kept 1.2 for 2 hours using 0.1N HCl. After 2 hours, the pH of the dissolution medium was adjusted to 7.4 with 0.1 N NaOH and maintained up to 10 hours. The samples were withdrawn from the dissolution medium at various time intervals using a pipette fitted with a

microfilter. The rate of drug release was analyzed using UV spectrophotometer (Shimadzu 1700, Japan). The receptor volume was maintained constant by replacing equivalent amount of SGF[8].

Kinetic treatment of dissolution data[9,10]

In order to describe the kinetics of the release process of drug in the different formulations, zero- order (Qt = Q0 + K0t), first- order (ln Qt =ln Q0 + K1t), Higuchi (Qt =KHt1/2) and Korsmeyer- Peppas (Qt/Q8= Ktn) models were fitted to the dissolution data of optimized formulations ES2i using linear regression analysis. A value of n = 0.5 indicates case I (Fickian) diffusion or square root of time kinetics, 0.5<n<1 anomalous (non- Fickian) diffusion, n=1 Case –II transport and n>1 Super Case II transport.

Accelerated stability studies:

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on optimized formulation ES2i by keeping at 40°C, in airtight high-density polyethylene bottles for three months, at RH 75±5%. Physical evaluation and *in vitro* drug release was carried out each month for three months.

RESULTS AND DISCUSSION

Eudragit microspheres of satranidazole were successfully prepared by Solvent evaporation technique. The result shown in Table no 1 indicates that there were five formulation prepared at higher stirring speed 1400 rpm and the formulations selected on the basis size, shape and entrapment efficiency which shown in table 2-5 . ES2 Formulation was selected for study of effect of polymer concentration and surfactant concentration which results of physical properties shown in table 6.

Uniform and almost spherical microspheres were obtained at higher stirring speed (1400 rpm) as shown in scanning electron photomicrographs of batch no. ES2i (Fig. 1).

The mean diameter of Eudragit microspheres(ES2) varied from 55.81±0.02 to 56.94±0.09µm with varying polymer concentration.

A higher concentration of polymer produced a more viscous dispersion, which formed larger droplets and consequently larger microspheres as reported by Pongpaibul et al.[11] The result also indicate that batches prepared at low surfactant concentration (0.5%w/v), the emulsifier may not be sufficient to cover the droplet resulting in coalescence, however at high concentration (1.0%w/v) free flowing spherical microspheres are obtained. Increased surfactant concentration led to the formation of particles with a lower mean geometric diameter. Increasing Span 80 concentration from 0.05% to 1.5% wt/vol led to stabilization of the emulsion droplets avoiding their coalescence, resulting in smaller microspheres.[12]

The comparative study of in vitro release of drug showed the effect of polymer and surfactant on the drug release in Fig.2. The cumulative percentage drug release from Eudragit -S based microspheres showed the desired rate, as there was no measurable drug release observed up to 2 hours in SGF (pH 1.2) and no drug release occurred below the pH of polymer solubility while at pH 7.4, the significant drug release was observed. On the basis of drug release, the formulation ES2i was found suitable for colonic delivery of Satranidazole, because it showed more precise controlled release amongst other formulations.

Table 7 showed data analysis of release profile of optimized and selected formulation ES2i according to different kinetic models. The kinetic treatment reflected that release data of ES2i showed r^2 value of 0.9561 which is close to 1, indicating that release of drug follows zero order kinetics followed by higuchi's and first order model. Zero-order kinetics indicated that the concentration was nearly independent of drug release. Further Korsmeyer and Peppas equation resulted into the value of n= 0.9704, which appears to indicate anomalous (non-Fickian) diffusion.

The results of stability study of optimized formulation of Satranidazole microspheres (EF6) revealed that there was no significant change in size, shape drug content, entrapment efficiency and

dissolution profile. Thus, formulation was stable at different conditions of temperature and humidity.

CONCLUSION

From the results of present study, it can be concluded that Eudragit S 100 based satranidazole microspheres provides high degree of protection from premature drug release in simulated upper GIT conditions and deliver most of the drug load in the colon and allow drug release at the desired site. Hence Eudragit S100 based satranidazole microspheres are a potential system for colon delivery in case of amoebic infection.

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Table 1: Formulation Development of Microspheres Based on Eudragit-S

Batch. no	D:P Ratio	Polymeric solution concentration (%w/v)	Name of surfactant	Surfactant concentration (%w/v)	Stirring speed (rpm)
ES1	1: 1	10	Span-80	0.5	1400
ES2	1: 2	10	Span-80	0.5	1400
ES3	1: 3	10	Span-80	0.5	1400
ES4	1: 4	10	Span-80	0.5	1400
ES5	1:5	10	Span-80	0.5	1400
ES2a	1:2	05	Span-80	0.5	1400
ES2b	1:2	10	Span-80	0.5	1400
ES2c	1:2	15	Span-80	0.5	1400
ES2d	1:2	20	Span-80	0.5	1400
ES2e	1:2	05	Span-80	1.0	1400
ES2f	1:2	05	Span-80	1.5	1400
ES2g	1:2	10	Span-80	1.0	1400
ES2h	1:2	10	Span-80	1.5	1400
ES2i	1:2	15	Span-80	1.0	1400
ES2j	1:2	15	Span-80	1.5	1400
ES2k	1:2	20	Span-80	1.0	1400
ES2l	1:2	20	Span-80	1.5	1400

Table: 2 Size & Shape of Eud-S based microspheres

S.No.	Code	Mean diameter (µm)±S.D. (n=20)	Shape
1	ES1	54.55±0.08	Irregular and aggregated
2	ES2	56.55±0.07	Spherical and less aggregated
3	ES3	57.35±0.06	Irregular and less aggregated
4	ES4	54.34±0.07	Spherical and aggregated
5	ES5	56.54±0.08	Spherical and aggregated

Table 3: Selected Batch on The Basis of Spherical Shape of Eud-S based microspheres

Batch. No	D:P Ratio	Polymeric solution concentration (%w/v)	Name of surfactant	Surfactant concentration (%w/v)	Stirring speed (rpm)
ES 2	1:2	10	Span-80	0.5	1400
ES 4	1: 4	10	Span-80	0.5	1400
ES 5	1:5	10	Span-80	0.5	1400

Table 4: Entrapment Efficiency and Drug Content of Selected Eud-S based microspheres

Batch code	D:P Ratio	Entrapment efficiency (%)	Drug content (%)
ES2	1: 2	85.65	91.35
ES4	1:3	71.78	82.15
ES5	1: 5	67.65	78.46

Table 5: Selected Batch on The Basis of Size and Entrapment Efficiency of Eud-S based microspheres

Batch. No	D:P Ratio	Polymeric solution concentration (%w/v)	Name of surfactant	Surfactant concentration (%w/v)	Stirring speed (rpm)
ES2	1: 2	10	Span-80	0.5	1400

Table 6: Physical properties of Satranidazole microspheres of optimized formulation ES2

S.No.	Formulation Code	Mean diameter (µm)±S.D. (n=20)	Shape	Entrapment efficiency (%)	Drug content (%)
1	ES2a	56.72±0.07	Spherical & aggregation	79.45	83.78
2	ES2b	55.79±0.06	Spherical & aggregation	81.24	86.12
3	ES2c	56.14±0.03	Spherical & aggregation	75.12	80.75
4	ES2d	56.77±0.08	Spherical & aggregation	78.45	84.69
5	ES2e	55.88±0.07	Spherical & no aggregation	79.45	85.37
6	ES2f	56.32±0.05	Spherical & less aggregation	81.45	87.12
7	ES2g	56.83±0.16	Spherical & no aggregation	82.96	89.76
8	ES2h	56.39±0.12	Spherical & less aggregation	80.12	88.45
9	ES2i	55.81±0.02	Spherical & no aggregation	85.95	92.47
10	ES2j	56.94±0.09	Spherical & less aggregation	79.96	84.25
11	ES2k	56.04±0.05	Spherical & no aggregation	77.98	83.21
12	ES2l	56.33±0.04	Spherical & less aggregation	81.87	86.27

Table 7: Kinetic treatment of dissolution data of Optimized formulations

Formulation	Zero- order (r^2)	First- order (r^2)	Higuchi (r^2)	Korsmeyer- Peppas (n)
ES2i	0.9561	0.7312	0.9162	0.9704

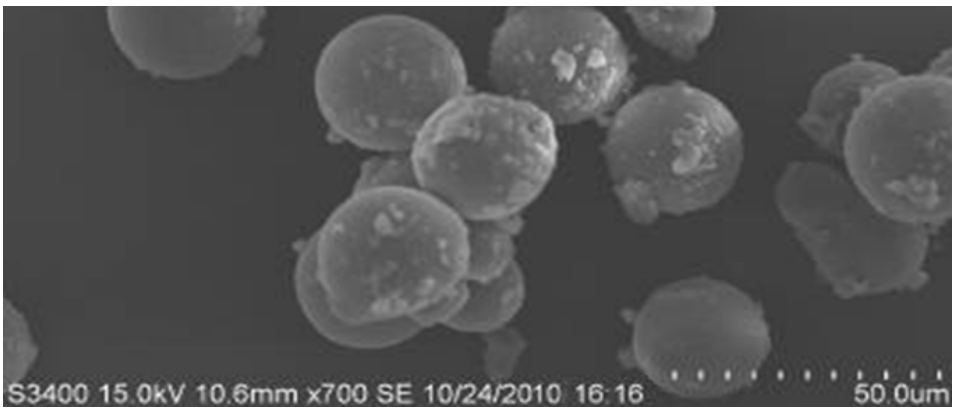

Fig. 1: Scanning electron microscopic photograph of Eudragit S 100 based satranidazole microspheres (ES2i)

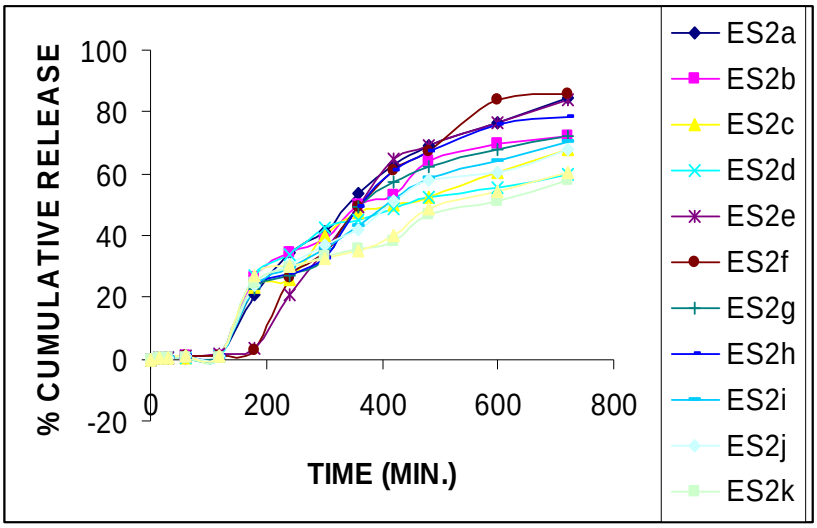

Fig. 2: Comparative study of *in vitro* dissolution profile of optimized formulations (ES2)

REFERENCES

1. Hardy JG, Evans DF, Zaki I, Clark AG, Tonnesen HH and Gamst ON. Evaluation of an enteric coated naproxen tablet using gamma scintigraphy and pH monitoring. Int J Pharm. 1987, 37:245-250.
2. Marwa H Abdallah, Omaima A Sammour, Hanaa A El-ghamry, Hanan M El-nahas and Waleed Barakat. Development and Characterization of Controlled Release Ketoprofen Microspheres, Journal of Applied Pharmaceutical Science, 2012, 02 (03): 60-67.
3. . Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Pharmaceutical Sci. 2003;6(1):33-66.
4. Ibekwe C Valentine, Fdda M Hala, Persons E Gary and Basi W Abdul. A Comparative in vitro Assessment of the drug release performance of pH – responsive polymers for Ileo-colonic delivery. Int J Pharm . 2005;55-62.
5. Ashford M, Fell JT, Attwood D and Woodhead PJ. An in vitro investigation into the suitability of pH-dependent polymers for colon targeting. Int J Pharm. 1993;91:241-243.
6. Evans DF, P ye G, Bramley R, Clark AG, Dyson TJ and Hardcastle J D. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut. 1988;29:1035-1041.
7. Paharia Amol. Eudragit-coated Pectin Microspheres of 5-Fluorouracil for Colon Targeting, AAPS PharmSciTech 2007;8(1);E1-E7
8. Jamakandi VG, Mulla JS, Vinay BL and Shivakumar HN. Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug, Asian J Pharm. 2009;59-65.
9. Raslan HK and Maswadeh H. in vitro dissolution kinetic study of theophylline from mixed controlled release matrix tablets containing hydroxypropylmethyl cellulose and glycerylbehenate. Ind J PharmSci. 2006;68 (3):308-312.

10. Clara I Vargas and Evone S Ghaly. Kinetic release of theophylline from hydrophilic swellable matrices. Drug Dev Ind Pharm. 1999;25(9):1045-1050.
11. Pongpaibul Y, Price JC and Whitworth CW. Preparation and evaluation of controlled release indomethacin microspheres. Drug Dev Ind Pharm. 1984;410:1597-1616.
12. Maia JL, Santana MHA and Re MI. The effect of some processing conditions on the characteristics of biodegradable microspheres obtained by an emulsion solvent evaporation process. Braz J Chem Eng. 2004;21:1-12.