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Design and characterization of floating microspheres for rheumatoid arthritis

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ABSTRACT

Gastroretentive systems can remain in the gastric region for several hours and significantly prolong the gastric residence of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, improve solubility of drugs that are less soluble in a high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine. The main objective of any drug therapy is to achieve a desire concentration of the drug in blood or tissue which is therapeutically effective and nontoxic for extended period of time, and this goal can be achieved by proper design of sustain release dosage regimen. Microspheres have been widely accepted as a mean to achieve oral and parenteral controlled release. The microspheres require a polymeric substance as a coating material or carrier. A number of different substances biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. The aim of this study is to prepare floating microspheres containing Sulfasalazineto achieve a controlled drug release profile suitable for peroral administration.

Keywords: Gastroretentive, Sulfasalazine, sustain release, Microspheres

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INTRODUCTION

Gastroretentive systems can remain in the gastric region for several hours and significantly prolong the gastric residence of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, improve solubility of drugs that are less soluble in a high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine.

The main objective of any drug therapy is to achieve a desire concentration of the drug in blood or tissue which is therapeutically effective and nontoxic for extended period of time, and this goal can be achieved by proper design of sustain release dosage regimen. Microspheres have been widely accepted as a mean to achieve oral and parenteral controlled release. The microspheres require a polymeric substance as a coating material or carrier. A number of different substances biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. The aim of this study is to prepare floating microspheres containing Sulfasalazine to achieve a controlled drug release profile suitable for peroral administration.[1-5]

MATERIALS AND METHODS

Materials

Sulfasalazine was generous gift sample from Valens molecules Pvt Ltd, Hyderabad. Polymers were obtained from Aurobindo Pharma Ltd, Hyderabad. All other chemicals and solvents are of analytical grade.

Methods

Preparation of Floating Microsphere of Sulfasalazine

Floating microspheres containing aceclofenac were prepared using emulsion- solvent diffusion technique. The drug to polymer ratio used to prepare the different formulations was as shown in table 1. The drug polymer mixture dissolved in a mixture of ethanol (8 mL) and dichloromethane (8 mL) was dropped in to 0.2% sodium lauryl sulfate solution (400 ml). The solution was stirred with a propeller-type agitator at room temperature for 1 h at 500 rpm. The formed floating microspheres were filtered, washed with water and dried at room temperature in a desicator. The various batches of floating microsphere were prepared as follows.[5,8-10]

Table 1: Formulations of the Floating Microspheres Prepared

Sr. No	Formulation Code	Sulfasalazine (mg)	EC (mg)	HPMC (mg)	PVA (mg)
1	**F1**	250	50	250	-
2	**F2**	250	100	250	-
3	**F3**	250	150	250	-
4	**F4**	250	200	250	-
5	**F5**	250	-	250	50
6	**F6**	250	-	250	100
7	**F7**	250	-	250	150
8	**F8**	250	-	250	200

Evaluation of Microspheres

Particle size analysis:

Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of floating microspheres were measured by using an optical microscope, and the mean particle size was calculated by measuring nearly 200 particles with the help of a calculated ocular micrometer.[6-8]

Floating behavior of Floating microsphere:

100 mg of the floating microsphere were placed in 0.1 N HCI. The mixture was stirred with paddle at 100rpm. The layer of buoyant microspheres was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in a desiccator over night.[7-10]The percentage of microspheres was calculated by the following equation:

$$\% \text{ floating microsphere} = \frac{\text{Wt of floating microsphere}}{\text{Initial Wt of floating microsphere}} \text{x } 100$$

Drug Entrapment

The various formulations of the floating microspheres were subjected for drug content. 50 mg of floating microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl and the absorbance was measured at 350.50 nm against blank.[6-9] The percentage drug entrapment was calculated as follows.

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

Percentage Yield

The prepared microspheres with a size range of 609-874 µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.[6-11]

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \text{x } 100$$

Shape and Surface Characterization of Floating Microspheres by Scanning Electron Microscopy:

From the formulated batches of floating microspheres, formulations (F4) which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope JEOL, JSM-670F Japan. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 3.0 KV during scanning. Microphotographs were taken on different magnification and higher magnification (500X) was used for surface morphology. [7-11]

***In-vitro* Release Studies**

The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37± 0.5°C and stirred at 100 rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples were treated with methyl orange and analyzed spectrophotometrically at 350.50 nm to determine the concentration of drug present in the dissolution medium.[5-10]

Drug Release Kinetic Data Analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsmeyer-Peppa's equation (Plotted as Log cumulative percentage of drug released vs Log time).

RESULTS AND DISCUSSION

Evaluation of sulfasalazine floating microspheres:

Particle size analysis:

Particle size was determined by Optical microscopy method. It plays important role in floating ability and release of drug from Microsphere. If size of Microspheres is less than 500 µm release rate of drug will be high and floating ability will reduce, white Microspheres ranging between 400µm - 600µm, the floating ability will be more and release rate will be in sustained manner. The mean particle size of Sulfasalazine microsphere was in range 479.2 – 589.8 µm as shown in Table 1.

Mean particle size of Different Batches of Sulfasalazine microsphere

Table 2: Mean particle size of Different Batches of Sulfasalazine microsphere

S. No	Formulation code	Mean particle size (µm)
1.	F1	479.2±15
2.	F2	495.8±45
3.	F3	490.2±32
4.	F4	498.5±23
5.	F5	512.2± 15
6.	F6	545.6±22
7.	F7	589.8±12
8.	F8	521.2±21

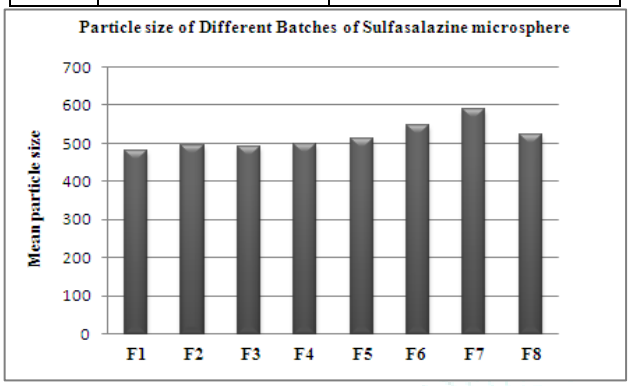

Figure 1: Mean particle size of Different Batches of Sulfasalazine microsphere

Mean Particle size of Optimized Batch F1

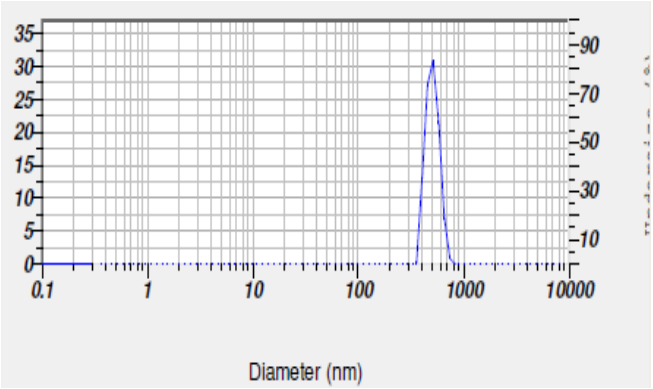

Figure 2: Mean Particle size of Optimized Batch

Floating behavior of microsphere:

Sulfasalazine Microsphere was dispersed in 0.1 HCl as simulate gastric fluid. Floating ability of different formulation was found to be differed according to EC and HPMC ratio. F_1-F_4 formulations showed best floating ability (91.47-72.97%) in 6 hours. F_5-F_8 formulation showed less floating ability (66.12-45.09%) as showed in Table-3.

Percentage buoyancy for different formulation

Table 3: Percentage Buoyancy for Different Formulation

Formulation	1 hour	2 hours	4 hours	6 hours
F1	98.41	97.08	93.23	91.47
F2	98.11	95.58	92.17	87.34
F3	98.54	95.64	85.34	78.45
F4	99.54	92.49	80.57	72.97
F5	98.72	91.95	73.49	66.12
F6	98.45	86.62	65.14	57.76
F7	88.34	75.41	56.04	45.09
F8	82.25	74.56	55.25	40.56

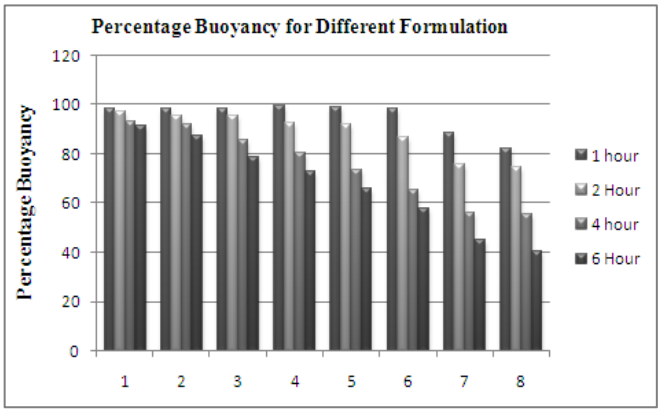

Figure 3: Percentage Buoyancy for Different Formulation

Drug Entrapment:

The drug entrapment efficacies of different formulations were in range of 48.47 - 76.19 % w/w as shown in Table No-4. Drug entrapment efficacy slightly decreases with increase EC content in Microspheres. This is due to the permeation characteristics of that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of Sulfasalazine microspheres.

Drug entrapment for different formulation

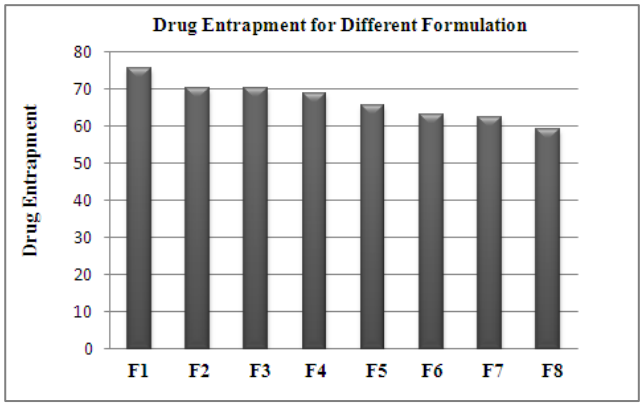

Figure 4: Drug Entrapment for Different Formulation

Table 4: Drug Entrapment for Different Formulation

Formulation	Drug entrapment (% w/w)
F1	75.56±0.21
F2	70.12±0.32
F3	70.21±0.54
F4	68.89±0.41
F5	65.56±0.25
F6	63.25±0.38
F7	62.25±0.25
F8	58.98±0.24

Percentage Yield:

Percentage yield of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 56.84 - 82.87% as shown in Table-5.

Table 5: Percentage Yield for Different Formulation

Formulation	Percent Yield (%)
F1	82.87
F2	78.53
F3	76.47
F4	71.56
F5	69.31
F6	66.03
F7	56.84
F8	52.25

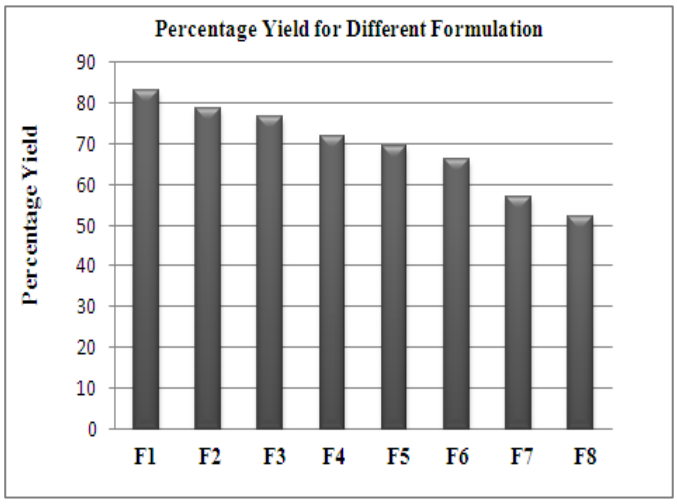

Figure 5: Percentage Yield for Different Formulation

Scanning Electronic Microscopy:

Shape and surface characteristic of Sulfasalazine microspheres examine by Scanning Electronic Microscopy analysis. Surface morphology of formulation examines at different magnification, which illustrate the smooth surface of floating Microspheres.

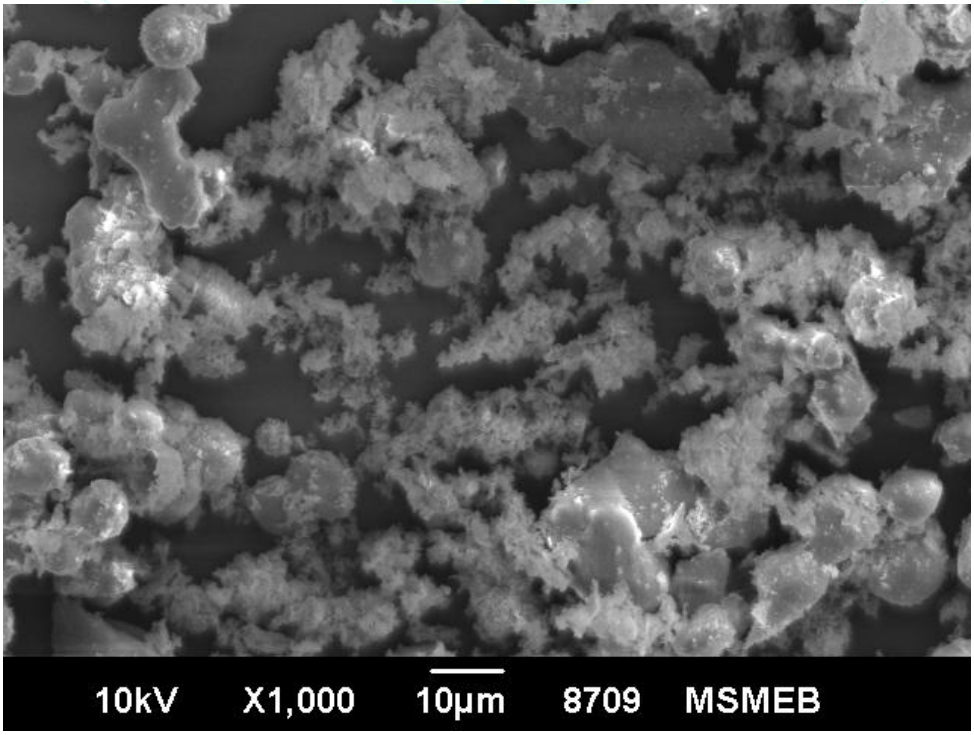

Figure 6: Scanning Electronic Microscopy Image of Optimized Formulation F-1

***In-Vitro* Drug release study:**

***In vitro* drug release study of Sulfasalazine loaded Floating Microsphere**

Comparative release study of all formulation

Table 6: Comparative Release Study data of formulation F1-F8

Time	% of Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	16.429	15.000	14.286	14.286	17.857	16.429	14.286	11.21
1.0	26.536	18.607	18.571	18.571	28.036	25.821	22.857	21.47
1.5	30.679	27.357	27.321	27.321	34.393	31.357	33.964	32.32
2.0	57.107	32.929	32.893	32.893	43.857	43.536	39.143	34.61
3.0	71.214	60.143	40.821	40.821	61.571	54.821	58.786	52.00
4.0	81.607	77.214	52.643	52.643	71.500	78.000	56.464	42.28
6.0	95.214	85.714	72.107	72.107	78.214	93.643	66.036	53.21
8.0	100.036	90.179	86.714	86.714	95.107	99.893	95.250	81.93

Graph of release study of formulation F1-F8

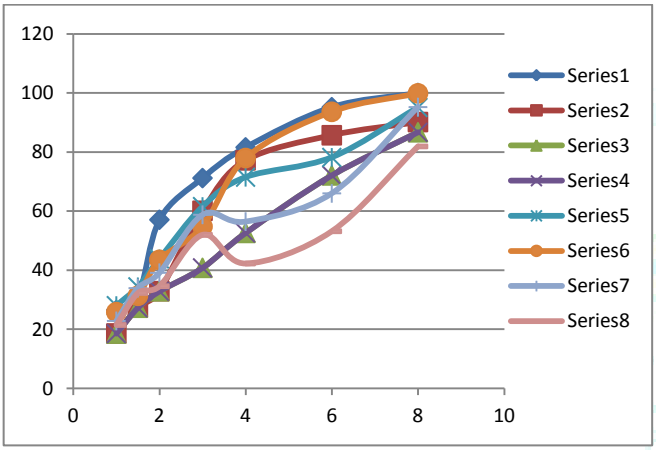

Figure 8: Graph of release study of formulation F1-F8

Release Kinetics of Optimized Formulation F-1

Graph of Zero order release kinetics of F-1

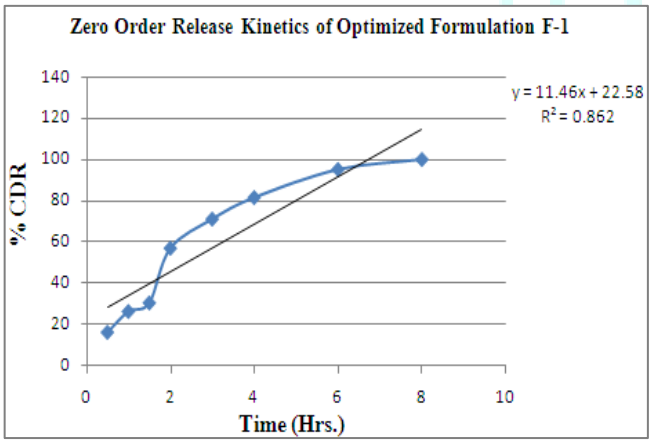

Figure 9: Graph of Zero order release kinetics of F-1

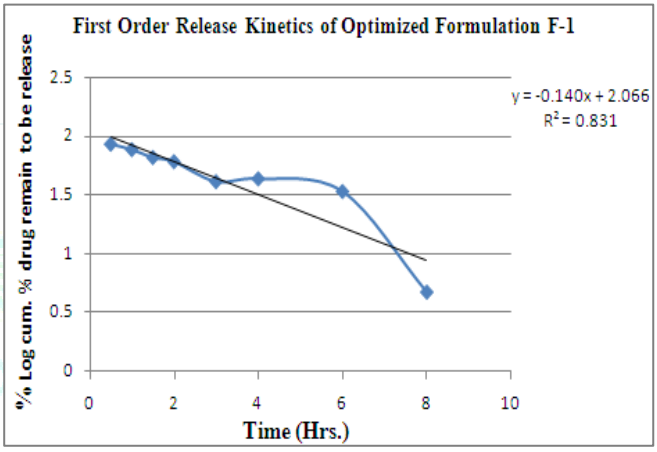

Figure 10: Graph of First order release kinetics of F-1

Graph of Higuchi release Kinetics

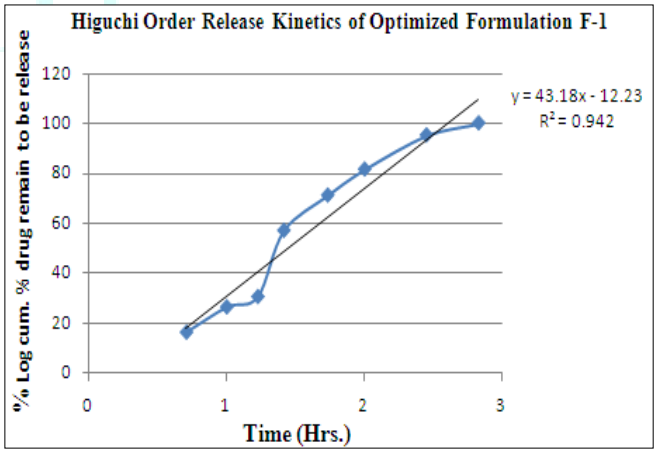

Figure 11: Graph of Higuchi release Kinetics

Graph of Korsemayer – Papas Kinetics

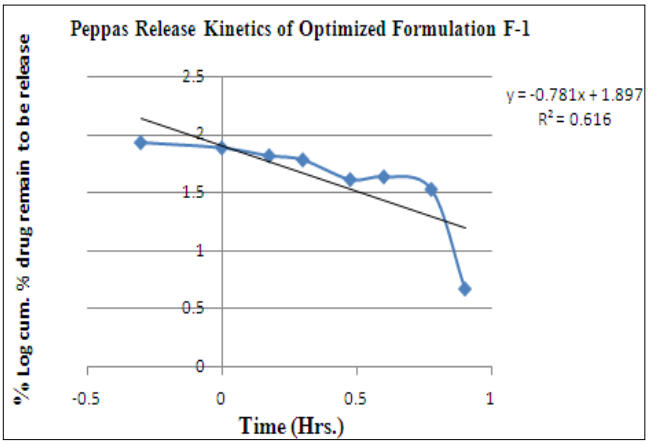

Figure 12: Graph of Korsemayer – Papas Kinetics

Table 7: Comparative study of regression coefficient for selection of optimize Formulation F-7

Zero order		First order	Higuchi	Korsmayer
r2	0.862	0.831	0.942	0.616

The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of **Higuchi** was maximum i.e 0.942 hence indicating drug release from formulations was found to follow **Higuchi** kinetics.

CONCLUSION

Floating microspheres of Sulfasalazine were prepared by the solvent evaporation technique. Sulfasalazineis a slightly water soluble drug which has good absorption in gastric pH. Sulfasalazine suffers from poor oral bioavailability since it is less soluble in water and shows poor absorption in lower GIT. Hence, such a drug requires a novel gastroretentive drug delivery system which can provide an extended period of time in stomach and improve oral bioavailability. Microspheres are the suitable drug delivery system for the drugs that have poor absorption from lower GIT. Microspheres were studied for characterization, compatibility study, particle size and shape, *in vitro* drug release, entrapment efficiency, and buoyancy time. The formulation using Ethyl cellulose and HPMC showed a constant rate of release. Thus, prepared floating microspheres of Sulfasalazine may prove to be potential candidates for a drug delivery.

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