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SURFACE TENSION BASED MICROCAPSULES AND MICRODISCS FOR COLON SPECIFIC DELIVERY OF SULFASALAZINE

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ABSTRACT

Microcapsules and microdiscs of poorly water-soluble drug sulfasalazine were prepared to enhance its dissolution rate and bioavailability. Sulfasalazine microcapsules and microdiscs were prepared by encapsulation technology using advantage of surface tension phenomenon. Sulfasalazine is used in the treatment of Inflammatory Bowel Disease (IBD) .Sulfasalazine is an anti-inflammatory drug, which acts on the inflamed colon to provide relief. Often sulfasalazine is targeted in colon to minimize side effects. The present study was also designed to achieve colonic release of sulfasalazine by formulating microcapsules. In the present study, a time and pH dependent colon targeted system was developed and evaluated. The drug was dispersed in various colon specific polymeric solutions. Various combination of polymers were tried like eudragit S 100, eudragit L100 and ethyl cellulose, which prevented the microcapsule/microdiscs disintegration in stomach and small intestine and targeted it to the colon. The design of formulation hence ensured colon targeted delivery of drug, preventing premature drug release in stomach or small intestine and enhanced availability of the drug at stable absorption site potentiating probable enhancement in bioavailability. Microcapsules were evaluated for various physicochemical and drug content and drug release parameters. Multimedia *in-vitro* release studies were carried out in 0.1 N HCL pH1.2, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4 mimicking *in- vivo* conditions for dissolution. The combinations showed sustained release up until 19-21 hours in various combinations of the synthetic polymers. This approach is therefore a promising approach to target the colon for the delivery of sulfasalazine in the form of sustained release formulation.

INTRODUCTION:

Sulfasalazine is a BCS Class IV drug. It has low solubility and low permeability. Sulfasalazine is poorly absorbed from the small intestine (up to 30%) and subsequently gets absorbed after reaching colon followed by biliary excretion[1,2,3]Around 90 % of a dose of sulfasalazine reaches the colon, where most of it is metabolized by bacteria into sulfapyridine and mesalazine (5-ASA) .Both

metabolites are active; most of the sulfapyridine is absorbed and then further metabolized, but most mesalazineis not, and remain in the colon. The objective of this research was to formulate sulfasalazine sustained release microcapsules for colon targeting.Colonic-targeted approach is often found to be effected in minimizing side effects, which are uncertain. Colon poses an advantage for having a near neutral pH, a much longer transit time, relatively low proteolytic enzymatic activity and offers a much great responsiveness to absorption enhancers. Colon specific delivery systems should prevent the release of drug in upper part of GIT and require a triggering mechanism to release the drug on reaching the colon.The microencapsulation technique is often used in order to increase the surface area and better absorption to the colon.Microcapsules are dosage forms, which contain the drug along with a polymeric coat in order to protect the drug from unnecessary pH regions and show the activity at the required site of action. However, the efficiency remains on proper encapsulation of drug, size and shape of microcapsules, which in turn is dependent upon nature and amount of solvent, phase volume ratio, rate of addition, speed ofmixing,and time for curing.A major factor which plays role over here is surface tension which decides the shape of microcapsules, whether spherical oblong or any other. In this research we have tried to correlate the same property for preparation of microcapsules (Relativelydense, Spherical or oblong) and micro discs(flat and spherical) by using traditional polymers for colon targeting in suitable solvent system.This physical phenomenon was never explored before which results in formation of uniform flat microdiscs giving suitable packing density and active area for dissolution.

Materials and Methods

Sulfasalzine was received as a gift sample from Wallace Pharmaceuticals. The Eudragit polymers used were manufactured by Evonik India Pvt Ltd. Ethyl Cellulose was received from S.D. Fine Chemicals Ltd., Mumbai. All the solvents and reagents used were of analytical grade.The preformulation testing of the drug was carried out in order to check identity, purity and nature of drug.

The various identification tests were carried out were-

1. **Appearance.**

The appearance of the drug was observed visually.

2. **IR spectroscopy.**

IR study was carried out using KBr pellet method.

3. **Melting point determination.**

Melting point was determined using theil's tube.

4. **DSC and XRD studies.**

DSC and XRD studies of the drug sample were carried out at Asian Labs, Mumbai. The DSC peak was then subsequently compared with the observed melting point.

5. **Surface tension determination.**

The surface tension studies of the various polymers used was carried out using a Stalagmometer and as according to the standard procedure given in Indian Pharmacopeia[4,5] and the surface tension was calculated using the equation:-

$$\gamma_2 = \frac{\gamma_1 n_1 \rho_2}{n_2 \rho_2}$$

Where:-

γ=surface tension

n=number of drops

ρ=density

$\gamma_1 n_1 \rho_1$=water

$\gamma_2 n_2 \rho_2$= unknown

Analytical methods were developed for evaluation of drug content and drug release of Sulfasalazine.The sulfasalazine microcapsules and microdiscs were

formulated using the microencapsulation technology. The various polymers were weighed as shown in table 1 and dissolved in methanol. 500 mg drug was eventually dispersed in the above prepared solution. The dispersion was injected onto distilled water using a hypodermic needle. The polymers were used individually and in combination and the optimized formulation was chosen.

Characterization of sulfasalazine microcapsules.

a. Appearance

The colour and appearance of the microcapsules was observed.

b. Dimensions of the microcapsules

The length and thickness of the microcapsules were measured using a Vernier calliper and a comparative study between the dimensions of the microcapsules and microdiscs was carried out and the properties were studied.

c. Drug Content

The prepared microcapsules and microdiscs equivalent to unit dose of drug (500mg) were weighed accurately and dissolved in 100 ml of methanol. The stock solutions were diluted with methanol and analyzed by UV- spectrophotometer at 359 nm and drug content was calculated accordingly**.**

d. *In - vitro* Drug Release

In vitro drug release of sulfasalazine from the microcapsules and microdiscs was carried out in 0.1N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 using USP (type I) dissolution apparatus in 900 ml dissolution medium at 37±0.5°C. The rotation speed was maintained at 50 rpm. The samples were withdrawn at intervals of 1 h in 0.1 N HCl pH in first 2 hours, phosphate buffer pH 6.8 in the next 4 hours and subsequently in phosphate buffer pH 7.4 until 100% release was observed. Samples withdrawn was subjected to analysis by Shimadzu UV-1800 spectrophotometer for determination of drug release.

Table1: Formulation of sulfasalazine microcapsules.

Formulation	Eudragit L100	Eudragit S100	Ethyl Cellulose
F1	500 mg	-	-
F2	-	500 mg	-
F3	-	-	500 mg
F4	500 mg	500 mg	-
F5	-	500 mg	500 mg
F6	500 mg	-	500 mg
F7	200 mg	400 mg	100 mg

Table 2: Surface tension studies

S. No.	Liquid	Density g/cm^3 (ρ)	No. of drops(n)	Surface tension dynes/cm(γ)
1.	Water	2	227	72
2	Ethyl cellulose	1.15	192	50.456
3.	Eudragit L100	1.02	166	51.762
4.	Eudragit S100	1.02	254	33.829

Figure 1: Formulation F1

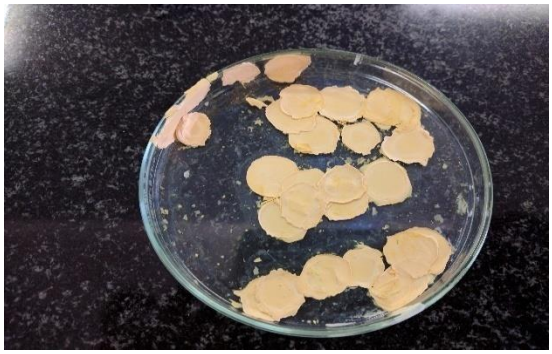


Figure 2: Formulation F2

Figure 3: Formulation F3

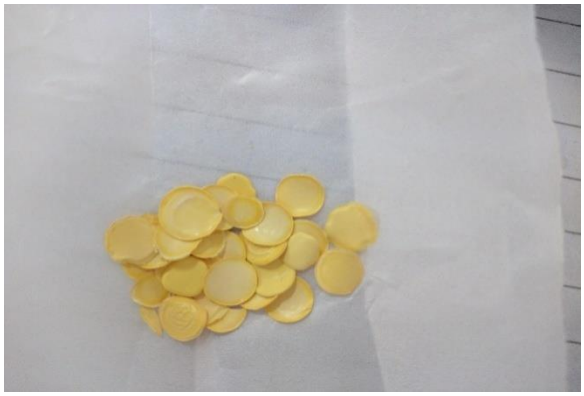


Figure 4: Formulation F4

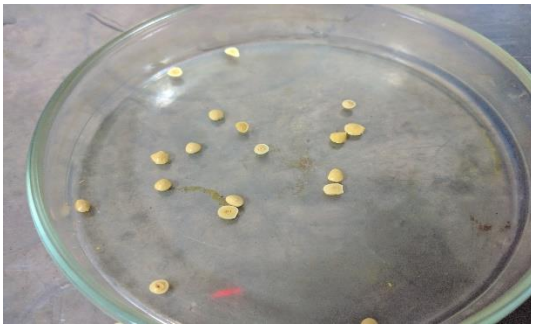


Figure 5: Formulation F5

Figure 6: Formulation F6

Figure 7: Formulation F7

Table 3: Length of Microcapsules and micro discs

Formulation	Length in mm	Average	Standard Deviation	%RSD
1.	12,11,10,12,11	11.2	0.837	7.473
2.	10,10,9,10,10	9.8	0.447	4.561
3.	13,15,15,14,13	14	1	7.143
4.	10,10,11,9,10	10	0.707	7.07
5.	5,4,4,4,5	4.4	0.548	12.455
6.	4,6,6,5,6	5.4	0.894	16.556
7.	3,2,3,2,2	2.4	0.548	22.833

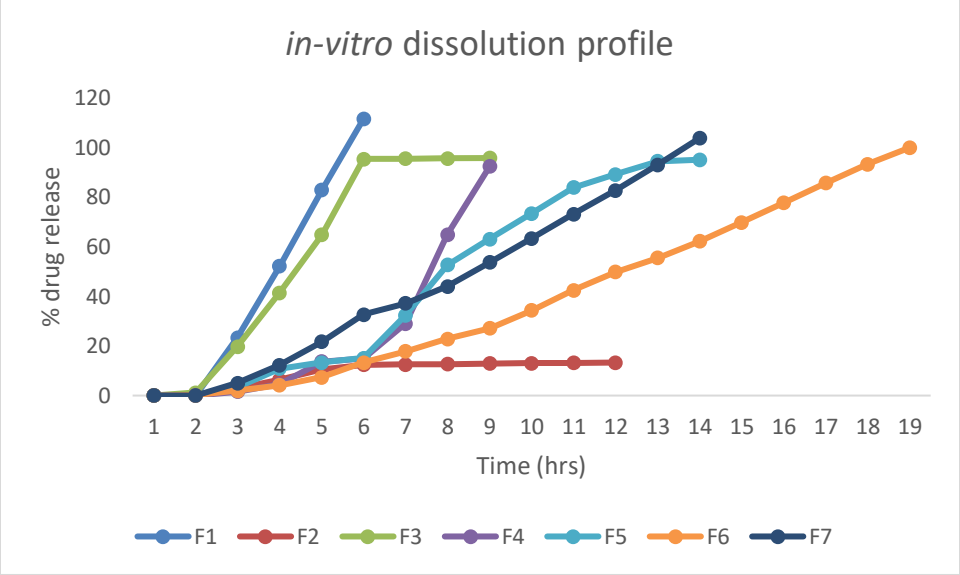
Table 4: Thickness of microcapsules and micro-discs

Formulation	Thickness in mm	Average	Standard Deviation	%RSD
1.	0.5,0.5,0.5,0.5,0.5	0.5	0	0
2.	0.5,0.5,0.5,0.5,0.5	0.5	0	0
3.	0.5,0.5,0.5,0.5,0.5	0.5	0	0
4.	0.7,0.7,0.7,0.7,0.7	0.7	0	0
5.	1,1,1,1,1	1	0	0
6.	1,1,1,1,1	1	0	0
7.	1,1,1,1,1	1	0	0

Table 5:Drug Content

Formulation	Drug Content
F1	0.2 mg
F2	1.32 mg
F3	1.36 mg
F4	0.24 mg
F5	0.12 mg
F6	2.67 mg
F7	3.75 mg

Figure 8:*In-vitro* dissolution profile.



Results

Preformulation Studies of Pure Drug

Identification

1. **Appearance :**

Yellow coloured amorphous powder.

2. **Melting point determination:**

The melting point of sulfasalazine was found to be 236ºC. The reported melting point is 240ºC thus indicating purity of the sample.

3. **FT-IR Spectroscopy:**

The pellets of the drug samples were prepared by KBr pellet method. The FT-IR spectrum of the obtained drug samples were compared with the reference standard FT-IR spectrum of Sulfasalazine. The characteristics peaks for Sulfasalazine were obtained at 3134.33cm^{-1}, 3061.03 cm^{-1}, 3028.24cm^{-1}, 1676.14cm^{-1} and 1357.89cm^{-1},

1263.42cm.The resultant spectra showed all reported characteristics peaks. Hence, the drug carried forward for the purpose of research.

4. DSC studies:

A sharp endothermic peak was observed at 236.16°c that nearly matched with the melting point of the drug.

5. XRD:

The XRD spectrum of drug shows existence of prominent peaks indicating crystalline nature of the drug. This shows that the drug is in the pure form.

6. Surface tension studies of polymers:

The surface tension of the various polymers used was studied using Stalagmometer and it was reported in Table 2.

Evaluation of microcapsules

1) Appearance

The appearance of all seven formulations is shown in the figure 1-7

Formulation F1-F4 were of insignificant rigidity as compared to formulations F5-F7. Formulations F1, F2 and F3 resembled disc shape while formulation F4 resembled pellet shape. The formulations F5-F7 resembled consistent spherical shaped discs.

2) Dimensions of the microcapsules

The length and thickness of the microcapsule were measured using a Vernier calliper. The percent relative standard deviation was determined as shown in table 3-16.

A comparative study of the dimensions and the rigidity of the microcapsules was carried out and it was seen that formulation F1-F4 were very less rigid as compared to formulation F5-F7. This can pose as a setback for colon targeted drug delivery of the microcapsules. Formulation F5 and F6, had better rigidity and thickness. However, they did not fit into the ideal microcapsule size limit (50nm to 2mm). Further size reduction can be carried out in order to reduce its particle size. Formulation F7 had much better rigidity and dimensions compared to the other formulations.

3) Drug Content

The drug content per microcapsule was recorded as shown in Table 3:

4) **Drug Release**

The *in-vitro* dissolution profile was found out as shown in figure 8.

Discussion

Here from the results it is quite clear that surface tension plays a very important role in deciding the shape of microsystem with polymer along with solubility of drug. Even if we are using anti solvent for the preparation of microcapsules, which shape it will acquire will be dependent upon solubility and concentration of polymer, which in turn will influence the surface tension.Here, formulation F1-F3 were containing single polymer in almost same amount as shown in table 1. It was seen that polymeric solution was having surface tension. Hence, after addition in water, it automatically acquired a shape, which was having greater surface area and in turn resulted in production of microdiscs. These microdiscs were so uniformly prepared that after addition of each

drop, the length and thickness of microdiscs was almost the same as shown in table 3 and 4.On the contrary, in the combination of polymers was done as in case of formulation F5-F7, the surface tension of the system was increased resulting in production of spherical shaped microcapsules, which had comparatively lesser surface area.[]The microcapsules were having smaller size and the effective surface area for dissolution was more. Micro discs were having comparable packing density as that of microcapsules. Because of the compact disc structure, it can be modified into tablet shaped capsule with many discs delivered together with novel aesthetic appearance.Each micro disc or microcapsule can further be coated to modify the rate and site of release.Hence, it can be concluded that micro discs and microcapsule will be efficient in modifying the release of the drug with comparatively less efforts of uniformity in particle size in the forthcoming revolutions in the drug delivery systems.Speaking about the in-vitro dissolution profile, almost all the formulations shows sustained release. Formulation F1 shows 111.6% in the 6th hour itself i.e. it completes its release in phosphate buffer pH 6.8. Formulation F2 only show 13.3% release even in the 12th hour. However, when these polymers were combined with other polymers they showed good amount of release in the colonic pH with only some amount in the phosphate buffer pH 6.8. The combination of two polymers and also three formulations (formulation F4-F7) shows 100% release up till 10th, 15th, 19th and 14thhour respectively. Thus, the formulated micro discs and micro capsules seem to look like a promising novel drug delivery system. Further research can be can carried out on this in the near future.

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