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Research Article

Formulation Development and Evaluation of Gastroresistant Microparticles of Diosmin for the Treatment of Chronic Venous Insufficiency (CVI)

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Abstract
Diosmin exhibits antioxidant and anti-inflammatory activities, improves venous tone and is used for the treatment of chronic venous insufficiency. In this research, Gastroresistant microparticles of diosmin were prepared by a spray-drying process using cellulose acetate phthalate (CAP) as enteric polymer and a series of enhancers of dissolution rate, such as sodium carboxymethylcellulose (NaCMC), sodium lauryl sulphate and Tween 80. The raw materials were characterized by DSC. The prepared microparticles were analyzed by DSC and scanning electron microscopy. *In-vitro* dissolution tests were carried out using a pH-change method to find out the influence of formulative parameters on the drug release from microparticles. The presence of a combination of CAP and enhancers in the formulations produced microparticles with good resistance at low pH of the gastric fluid and complete flavanoid release in the simulated intestinal environment. The spray-drying technique and the process conditions selected for microparticles were able to give satisfactory encapsulation efficiency, production yield, microparticles morphology and a complete drug release in the intestine.

Keywords: - : dissolution enhancers, gastroresistant spray-dried microparticles, Diosmin: morphological and physicochemical characterization**.**

Introduction
Diosmin is a naturally occurring flavanoid glycoside that can be isolated from various plant sources or derived from the flavanoid hesperidine. Diosmin was first isolated in 1925 from Scrophularia nodosa (1), and first introduced as a therapeutic agent in 1969. Diosmin is considered to be a vascular-protecting agent used to treat chronic venous insufficiency, haemorrhoids, lymphedema, and varicose veins. As a flavanoid, diosmin also exhibits anti-inflammatory, free-radical scavenging, and antimutagenic properties (1,2).As a drawback diosmin undergoes hydrolysis into aglycone diosmetin and enzymatic degradation in the drastic environment of stomach (3,4). In fact, it has very slightly water solubility which leads to low dissolution rate. Thus to encapsulate Dsm in gastroresistant polymer, which by carrying them directly to the intestine, may improve their bioavailability after oral administration. Since the design and development of gastroresistant microparticles containing low-solubility drugs such as Dsm requires a compromise between the enhancement of the dissolution rate in the intestinal fluid and protection in the gastric coating of enteric polymer, cellulose acetate phthalate (CAP), and a series of enhancers of the dissolution rate were used in the formulation. Among the preparation methods of microparticles, spray-drying is widely used in the pharmaceutical field due to large availability of equipments. It is also a mild "one-step" processing operation to move from a liquid feed into a powder product. The influence of formulation parameters on drug dissolution/release properties as well as on yield, morphology of the prepared gastroresistant microparticles was studied.

Materials and Methods
Diosmin was supplied by Xylie Pharmaceuticals, Cellulose acetate phthalate (CAP) from Medicamen Biotech, NaCMC from Ranbaxy, Tween 80 from Ranbaxy. All other chemicals used were of reagent

Solubility

The Solubility of Diosmin was evaluated according to USP 31 (USP 31, 2008) by UV spectrometry at room temperature (25ºC in distilled water and in simulated biological fluids without enzymes (Gastric fluid, GF, pH 1.2, and Intestinal fluid, IF, pH 7.5). Each analysis was made in triplicate and results expressed as average values in terms of mg/ml. An excess amount of each flavanoid was introduced into glass vials containing 50 ml of solvents; samples were shaken and then stored at room temperature. After 2 days, liquid phases were centrifuged for 15 minutes 3000 rpm, and supernatants filtered with 0.45 µm filters and analyzed by UV.

Microparticles Preparation

Gastroresistant CAP/Dsm Microparticles

Preparation of Feed mixture

The composition of different batches of spray-dried microparticles is given in Table 1. Initially CAP (1% and 2%) was dissolved in aqueous buffer at pH 7.5 (simulated intestinal fluid, IF, pH 7.5, according to USP 31 without enzymes).

Then variable amount of Dsm (polymer:drug weight rations 1:1, 3:1 and 5:1) were suspended in the polymer solution under magnetic stirring. CAP/Dsm (batches 1, 2 and 3) microparticles were obtained by spray-drying of these feed solutions. After that gastroresistant microparticles of Dsm were obtained with different enhancers. The weighed amount of drug in polymer/drug ratio 3:1 was suspended in the prepared polymeric solution under magnetic stirring. Then different enhancers of dissolution rate were added in the prepared drug-polymer solution. Na CMC 0.4% W/V, SLS and Tween 80 are spray-dried to obtain CAP/Dsm/CMC (B4), CAP/Dsm/SLS (B5), CAP/Dsm/Tween (B6) gastroresistant microparticles.

For the preparation of batch B4, Dsm and CMC were previously blended using a Galena top mixer in the presence of micronizing spheres until uniformity, and the resultant mixture was suspended into the polymeric- CAP liquid feed.

For the preparation of both CAP/Dsm/SLS (B5) and CAP/Dsm/Tween 80 (B6), Dsm was previously dampened with SLS or Tween 80 and then suspended in the polymeric CAP liquid feed.

Table 1 Composition and characterization of all the Microsystems prepared

Batches	Feed composition	Drug concentration (% w/v)	Enhancer concentration (%w/v)	CAP concentration (%w/v)
B1	CAP/Dsm	0.67	-	2
B2	CAP/Dsm	2.0	-	2
B3	CAP/Dsm	0.4	-	2
B4	CAP/Dsm/CMC	0.67	0.4	2
B5	CAP/Dsm/SLS	0.67	0.5	2
B6	CAP/Dsm/Tween	0.67	0.5	2
B7	CAP blank	-	-	2
B8	Dsm sd	0.67	-	-
B9	Dsm/CMC	0.67	0.4	-
B10	Dsm/SLS	0.67	0.5	-
B11	Dsm/Tween	0.67	0.5	-

Table 2 Characterization of all Microsystems prepared

Batches	Yield (%)	Particle size	TDC	PDC	E.E
B1	77.25 ± 1.92	2.89 ± 0.153	12.54	9.79	78.12± 1.0
B2	62.49 ± 2.61	2.56 ± 0.190	25	17.28	69.12± 1.05
B3	84.12 ± 2.98	3.74 ± 0.131	8.33	6.02	72.3 ± 1.0
B4	73.83 ± 1.52	3.93 ± 0.528	10.56	7.51	71.2 ± 1.32
B5	75 ± 3.50	2.69 ± 0.248	10.91	6.84	62.7 ± 1.30
B6	80.18 ± 2.42	2.00 ± 0.234	10.56	8.57	81.2 ± 0.907
B7	90.8± 3.12	2.32 ± 0.135	-	-	-
B8	65.14± 1.50	4.01 ± 0.07	50	50	-
B9	60.81± 1.30	4.75 ± 0.289	31.3	11	35.17 ± 0.95
B10	80.6 ± 1.27	2.79 ± 0.296	28.63	15.03	52.5 ± 1.32
B11	60.6 ± 3.03	3.23 ± 0.11	28.03	12.50	43.6 ± 1.24

Values are mean ± S.D, where n=3

Spray-drying

The feeds were spray-dried in a Buchi B-191 Mini Spray Dryer (Buchi Laboratoriums-Teecnik, Flawil, Switzerland), using a total amount of 6-8 g of raw materials in 200 ml of total feed volume sprayed. Each liquid feed prepared for spray-drying was made under continuous magnetic stirring and sonication for 10 minutes.The drier conditions were: inlet temp. 125 ºC, outlet temperature 75-80ºC, spray flow feed rate 5ml/min, nozzle diameter 0.5 mm, drying air flow 500 l/h, air pressure 6 atm, aspirator 100 %.

Each preparation was carried out in triplicate. All the spray-dried microparticles were collected and stored under vacuum for 48 h at room temperature.The production yield, theoretical drug content, practical drug content, encapsulation efficiency and mean size of gastroresistant and CAP free microparticles were determined.

Microparticles Characterization

Particle size analyses

Particle size analyses of prepared spray-dried microparticles were carried out by Malvern particle size analyzer. The dried powder sample was suspended in water and sonicated for1 min with an ultrasound probe before measurement. The particle size was determined by laser diffraction technique.

Morphology

The morphology of the prepared microparticles was assessed by EV040 scanning electron microscope. For scanning electron microscopy samples were prepared by lightly sprinkling microparticles on a double adhesive plate, which stuck to an aluminium stub. The stubs were then coated with gold using a fine coat ion sputter. The microparticles were then examined under scanning electron microscope.

Drug content evaluation

Samples 50 mg of each batch of microparticles were dissolved in 0.05 M NaOH and the drug content was determined spectrophotometrically at λmax 267.5 nm. The analysis was made in triplicate and the results expressed as average values.

Encapsulation efficiency evaluation

The encapsulation efficiency (EE%) was calculated as the ratio of practical (PDC) to theoretical drug content (TDC) in drug microparticles.

Differential Scanning Colorimetry

Differential scanning calorimetry was performed on an indium-calibrated Mettler Toledo DSC 822e (Mettler Toledo, OH, USA) in order to study the thermal behavior on samples of raw materials, drug-free-, CAP-free-, and drug-loaded microparticles. DSC thermograms were recorded by placing accurately weighed quantities (8–10 mg weighed with a microbalance MTS Mettler Toledo, OH, USA) of each sample in a 40-µl aluminum pan which was sealed and pierced. The samples were exposed to two thermal cycles. For the dehydration cycle, the samples were heated up to 130°C with a heating rate of 20°C/min and the temperature was maintained at 130°C for 15 min in order to remove the residual solvent. Afterwards, the samples were cooled at 25°C and heated up to 350°C with a heating rate of 10°/min. From this second thermal cycle, the glass transition temperature (Tg), the melting temperature (Tm), and the heat of fusion (ΔHm) were measured for all samples and compared with each other. The analyses were carried out in triplicate.

Stability studies

The stability test was performed according with conventional method (long- term studies- 12 months) reproted by ICH (International Conference on Harmonization) guidelines. The formulations were stored at 25ºC ± 2ºC/ 60% RH in a climatic chamber for the period of 12 months. The samples were analyzed for physical changes and drug content after an interval of 0, 3, 6 and 12 months.

In vitro Dissolution/Release Test

In-vitro dissolution studies were carried out on the microparticles at 37 (± 0.5) at 100 rpm with USP Dissolution Apparatus II (Type II, Veego DA, 6DR Japan).For the acid stage, accurately weighed sample of microparticles was suspended in the dissolution media consisting of 750 ml of 0.1 N (pH 1) hydrochloric acid without enzymes and dissolution was done for 2 h. At the end of the 2 h, 250 ml of 0.2 M tribasic sodium phosphate was added to dissolution vessel, the pH was adjusted to 6.8 (± 0.2) and the dissolution was continued until the microparticles were depleted of drug or for 6 h. Aliquots of dissolution fluid were withdrawn at specified time intervals to assay the released drug spectrophotometrically at 267.5 nm in both stages of dissolution. Corrections were made for the removal of samples.

Results and Discussions

In a preliminary set of experiments, Dsm was spray dried using CAP (1% and 2%) as coating polymer in different polymer/drug ratios (1:1, 3:1, 5:1) in order to achieve gastroresistant microparticle systems able to avoid the flavanoid exposure to harsh gastric conditions .Only using 2 % polymeric solution, satisfactory yields of the process and drug encapsulation efficiency were obtained.

Gastroresistant CAP/Dsm Microparticles

Microparticles Production

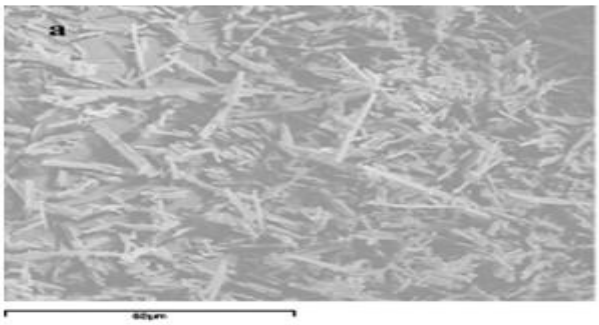
The actual and theoretical drug contents of each batch, production yield, and encapsulation efficiency were reported in Table 2. The results showed that encapsulation efficiency ranging from 69.12 ± 1.05 to 78.12 ± 1.0 % for all batches B1, B2 and B3. The highest actual drug content and encapsulation efficiency was observed for batch B1 (polymer/drug ratio 3:1). As reported in previous work (7), a very slightly soluble drugs such as flavanoids due to the phase separation, can undergo deposition in the chamber during the spray-drying process giving a reduction of encapsulation efficiency. CAP seems to be able to limit this loss process giving acceptable results.

Microparticles Characterization

Particle size analyses and Morphology

Raw materials

Dsm is commercially available in a crystalline state with a needle shape (d50 9.86 ± 0.03) characterized by a very slight water solubility. Dsm processed by spray-drying and analyzed by SEM does not show changes in its solid crystalline state as shown in Fig. 1(a) and (b) but only a mean diameter reduction (d50 4.01 ± 0.07) with respect to the raw material was observed.



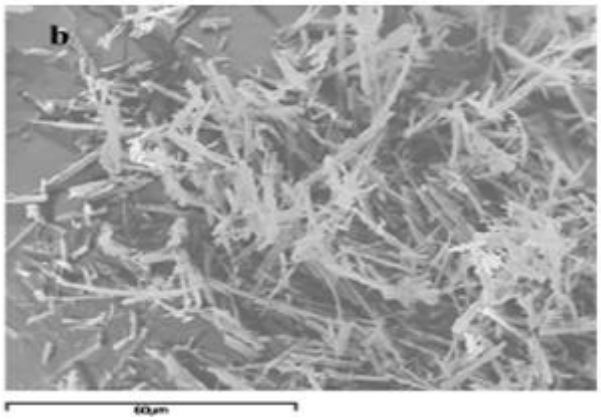


Fig. 1 Scanning electron microscopy micrographs of (a) Dsm raw material and (b) Dsm spray-dried

The SEM picture of CAP raw material show the presence of flakes Fig.2(a) while spray-dried CAP Fig.2(b) showed microparticles with spherical trend, some wrinkled and with a variable particle size lower than 8 µm.

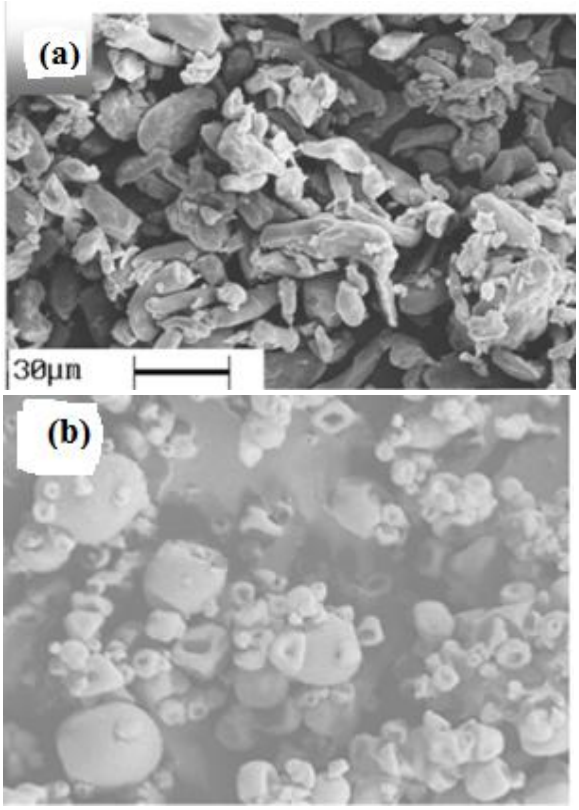


Fig. 2 Scanning electron microscopy micrographs of (a) CAP raw material and (b) CAP spray-dried

Differential Scanning Colorimetry

The DSC analyses indicated the same crystallinity nature for both pure and spray-dries Dsm shown by superimposable DSC profile. However, in the DSC curves, the melting point of spray-dried Dsm showed a small shift to lower value in comparison with pure Dsm due to the size reduction of Dsm crystals during spray-drying.

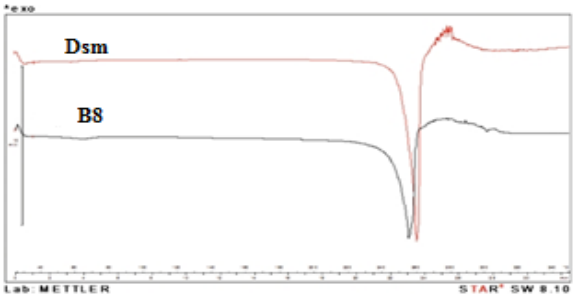


Fig.3 Differential Scanning Colorimetry thermogram of Dsm pure and Dsm spray-dried

Dissolution/Release studies

Firstly, to evaluate the dissolution/release profile of Dsm from the microparticles, its solubility in each dissolution medium was determined as mentioned in previous section. The solubility values of Dsm was 53.1 mg/l in water, 45.2 mg/l in simulated gastric fluid, 62.3 mg/l in simulated intestinal fluid. Then on the basis of solubility, dissolution studies were done.

The release profile of CAP/Dsm gastroresistant microparticles obtained with 3:1, 1:1, and 5:1 polymer/drug weight ratio is shown in Fig.4 with respect to the profile of pure Dsm.

The dissolution profiles of all CAP/Dsm microparticles (batches B1, B2, B3) were almost superimposable at pH 1.0 (Fig 4). Thus CAP was able to protect Dsm in the simulated gastric fluid. The amount of Dsm released/dissolved from these three batches in 2 h was about1.7 ± 1.13 to 2.12 ± 1.24 %, while about 21.40 ± 1.32 % of Dsm was dissolved at the same time.

At pH 6.8, the drug release profiles from all CAP/Dsm microparticles (batches B1, B2 and B3) were almost superimposable with the dissolution profile of pure Dsm with slight difference due to microparticles composition. About 25.96 ± 1.09 and 23.67 ± 1.17 % of drug was dissolved/released from batches B1 abd B2 respectively, and about 28.62 ± 1.17 % from B3at pH change, in comparison with about 25.94 ± 2.23 % of pure Dsm that dissolved at the same time. Thus, CAP was able to protect Dsm in gastric environment, but the release of flavanoid was incomplete in the intestinal fluid from all CAP/Dsm gastroresistant formulations.

Thus the polymer/drug weight ratio of 3:1 was selected for formulation of microparticles in the presence of enhancer on the basis of production yield, actual drug content and encapsulation efficiency.

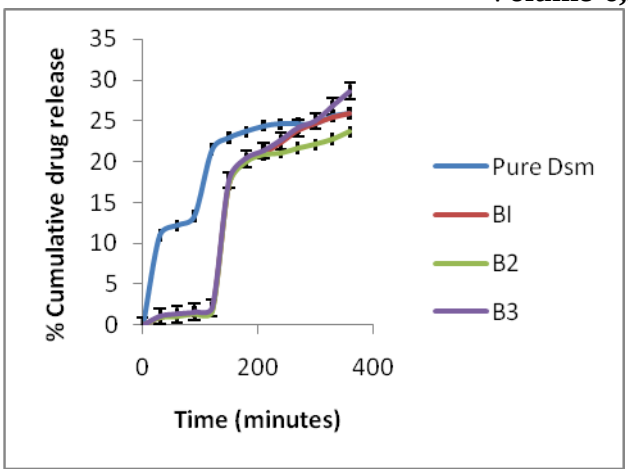


Fig. 4 Dissolution profile of CAP microparticles loaded with 50 (B), 25(B), 16.6 %(B) of diosmin prepared by spray-drying in comparison with dissolution profile of pure Dsm

Gastroresistant CAP/Dsm/Enhancers microparticles

The liquid feeds were prepared by dispersing Dsm in a 2 % CAP buffer solution (3:1 polymer/drug weight ratio) and in the presence of two different surfactants such as SLS, Tween 80 and a superdisintegrant such as CMC. These feeds were spray-dried to give batches B4 (CAP/Dsm/CMC), B5 (CAP/Dsm/SLS), and B6 (CAP/Dsm/Tween).

SLS was selected as anionic surfactant, used to enhance the dissolution rate of other drugs such as propanolol and theophylline (8), Tween 80 (an esterified and polyethoxylated derivative of sorbitan) as non-ionic surfactant used in pharmaceutical systems for its compatibility, stability, and minimal binding to proteins (9), Carboxymethylcellulose sodium (NaCMC) is an insoluble, hydrophilic, highly absorbent material reported to possess excellent water-swelling capacities with an enhancement of the drug dissolution rate due to its fibrous nature (10).

As control, CAP-free (B9, B10 and B11) microparticles were also prepared.

Microparticles Production

The practical and theoretical drug contents of each batch, production yields and encapsulation efficiency are shown in Table 2. The production yields were higher for CAP/Dsm/SLS (B5) than for CAP/Dsm/Tween (B6) or CAP/Dsm/CMC (B4).

Microparticles morphology

Malvern analysis indicated micronized SLS and Tween microparticles with very narrow size distribution (Table 2). Mean diameter of 2.69 ± 0.248 and 2.00 ± 0.234 for Dsm (B5 and B6, respectively) microparticles. Similar sizes were observed for CAP-free Microsystems, mean diameter ranges of 2.79 ± 0.296 and 3.23 ± 0.11 for Dsm microparticles (B10 and B11). On the contrary, CMC microparticles had much larger particle sizes both for CAP- containing (B4) and for CAP-free microparticles (B9). The small and comparable dimensions exhibited by SLS and Tween microparticles may be due to arrangement of both surfactants and flavanoid in micelles of colloidal size in which the drug is homogenously distributed. In addition, the SLS microparticles (B5), showed few uncoated flavanoid .Crystals embedded on the surface, whereas, images of Tween microparticles (B6) displayed the complete absence of crystals and aggregates. The results confirmed the major interaction and solubilisation of flavanoids in the non-ionic surfactant (Tween) micelles with respect to the anionic surfactant (SLS).

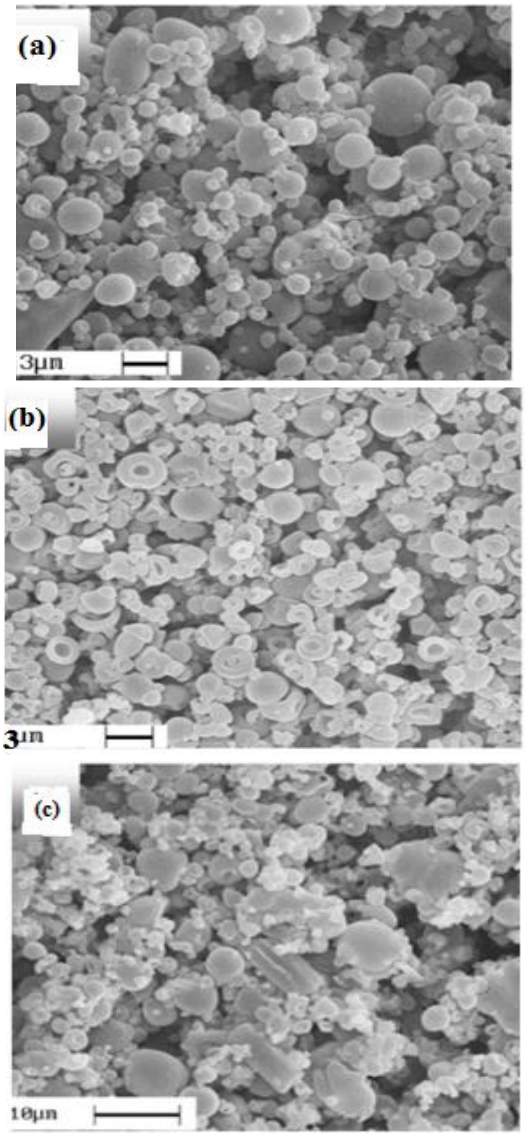


Fig. 5 Scanning electron microscopy images of (a) CAP/Dsm/SLS (B5) (b) CAP/Dsm/Tween (B6) (c) CAP/Dsm/CMC (B4) microparticles

Differential Scanning Colorimetry

The absence of Dsm melting point in the thermal profile of batches B4 and B5 suggested that the flavonoid was well encapsulated . Only for batch B6, a small peak in correspondence of the Hd melt value, ascribable to few drug crystals not completely encapsulated, was observed. In addition, the DSC profiles of batches B5 and B6, showed the thermal trend of CAP shifted to lower temperature; the shift may be due to the physical interaction between the polymer and the surfactants (Fig. 6(a) and (b)). These results do not exclude the presence of drug in residual crystalline state, because, sometimes, the DSC technique could not detect any residual crystalline structure, due to the ability of low-melting-point polymers to act as solvent for a drug (9) . In fact, by increasing the temperature, CAP which melts at lower temperature than flavonoids starts to melt and dissolve drug crystals.

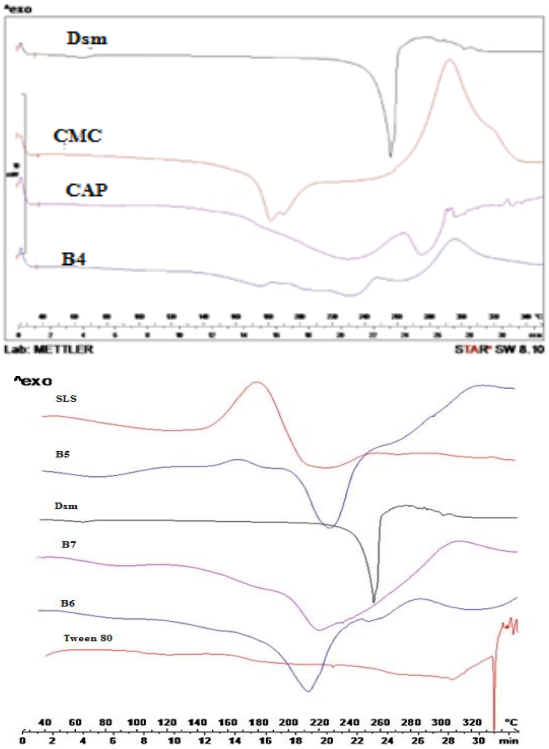


Fig.6(a) Differential Scanning Colorimetry thermograms of raw materials Dsm, CMC, CAP and CAP/Dsm/CMC microparticles (B4) and

(b) Differential Scanning Colorimetry thermograms of raw materials SLS, Dsm and Tween 80, CAP blank (B7), CAP/Dsm/SLS (B5) and CAP/Dsm/Tween (B6)

Dissolution/Release studies

The dissolution/release profile of Dsm from B4 (CAP/Dsm/CMC), B5(CAP/Dsm/SLS) and B6 (CAP/Dsm/Tween) is shown in Fig. in comparison with dissolution/release profiles of pure Dsm.

The dissolution profiles of batches B4 and B6 were almost superimposable at pH 1.0 (Fig. 7); in fact, the amount of Dsm released/dissolved from these two batches was about 1.93 ± 1.29, 1.97 ± 1.27% respectively. At the same time, about 1.84 ± 1.20 % of Dsm was released from B5 microparticles in comparison with 21.49 ± 1.32 % of pure Dsm. As expected, a very high amount of flavanoids was released from the non-gastroresistant microparticles (B9,B10 and B11) into the gastric fluid (Fig.8). In particular, the highest Dsm release from CAP-free microparticles was observed in the presence of Tween (B11) with respect to B10 and B9. Also, after pH change, the release of Dsm increased from all these three non-gastroresistant batches with repect to pure Dsm is due to the action of enhancers.

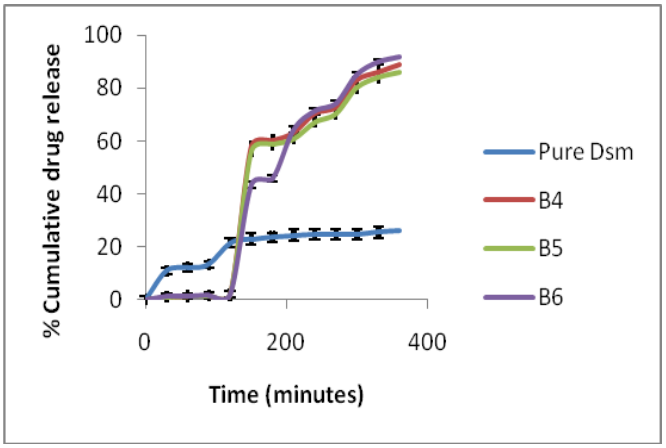


Fig. 7 Release profile of all CAP/Dsm gastroresistant microparticles (B4, B5,and B6) in comparison with pure Dsm

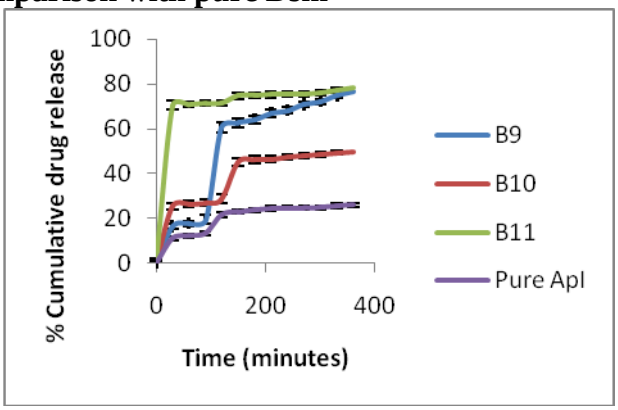


Fig. 8 Release profile of non-gastroresistant (CAP-free) microparticles (B9, B10 and B11) in comparison with pure Dsm

After pH change, in improvement of Dsm dissolution rate was observed from gastroresistant microparticles formulated with all different enhancers of the dissolution rate (Fig.7). At pH 6.8….. This behavior may be explained by an increase of the drug-water interaction due to the presence of enhancers of the dissolution rate that improved wettability and solubility of Dsm. Moreover, the enhancement of the drug dissolutuoion rate in IF was higher for all gastroresistant microparticles than that observed for microparticles prepared without CAP (B9, B10, B11, 49.86 ± 1.01 to 78.23 ± 1.13 %). This result may be due to the action of the enhancers of the dissolution rate of CAP itself.

Stability studies

Long term stability studies were performed on all microsystems to examine the effect of spray-drying process, surfactants and swelling materials on the stability and quality of the produced microparticles. The formulations were analyzed for Diosmin content over 12 months, including four time points (0,3,6, and 12 months) by UV method. No decrease in Dsm content and degradation product were recorded.

Conclusion

Slightly water-soluble flavanoid Dsm was microencapsulated by spray-drying using a combination of gastroresistant polymer CAP and a series of enhancers of the dissolution rate. The aim of the present work was to produce microparticles with enhanced dissolution rate in intestinal fluid able to improve the absorption and bioavailability of flavanoids after oral administration. The spray-drying technique and process conditions selected were effective in microencapsulating and stabilizing the Dsm. The best results were obtained with Tween-containing microparticles showing high encapsulation efficiency, low and homogenous dimensional distribution, spherical shape and absence of uncoated flavanoid crystals. Thus this approach is suitable for improving its bioavailability from oral solid dosage forms.

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