Research Paper

Eudragit® Microparticles for the Release of Budesonide: A Comparative Study

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This study compares the behaviour of budesonide-containing microparticles made of Eudragit®RS or Eudragit®RS/Eudragit®RL 70:30 (w/w) prepared either by solvent evaporation or spray-drying technique. The loading efficiency of budesonide within microparticles was about 72% for microparticles prepared by solvent evaporation and around 78% for spray-dried microparticles. Thermal analyses were assessed to collect information about the structural stability of budesonide within the polymeric microspheres. The *in vitro* release was performed using simulating gastric (fasted state simulated gastric fluid) and intestinal (fasted state simulated intestinal fluid) fluids as the receiving solutions. After 3 h the drug release from Eudragit®RS/Eudragit®RL microparticles was about 6-fold higher than that obtained in the case of monopolymer microparticles. Using fasted state simulated intestinal fluid the drug was released between 4 and 30% in both types of preparations. Eudragit®RS microparticles showed a better protection of the drug from gastric acidity than those of Eudragit®RS/Eudragit®RL allowing us to propose Eudragit®RS microparticles as a hypothetical system of colon specific controlled delivery.

Key words: Budesonide, controlled release, Crohn's disease, microparticles

Inflammatory bowel diseases (IBD) are rare afflictions of unknown aetiology affecting the intestines and characterized by a chronic course and recurrent inflammation. IBD consist of Crohn's disease and ulcerative colitis, which have an onset of disease between 15 and 40 years. While ulcerative colitis causes inflammation only in the colon (colitis) and/or in the rectum (proctitis), Crohn's disease may cause inflammation in the colon, rectum, small intestine (jejunum and ileum), and occasionally even in the stomach, mouth and oesophagus[1].

In the treatment of IBD, sustained release devices like pellets, capsules or tablets have less efficiency due to diarrhoea that enhances their elimination and reduces the time of drug release. Particularly, drug carrier systems with a size larger than 200 μm would be subjected to speedy bowel evacuation due to diarrhoea[2]. Therefore, a particulate system in the micron size range could be useful to design a suitable dosage form for IBD.

According to the different pathologic steps of Crohn's disease[3], therapeutic studies have focused on different classes of drug[4]. Corticosteroids typify the current first line treatment option in moderate-severe Crohn's disease until resolution of symptoms[3-7]. A comparison between budesonide (BD) standard formulation and a controlled release one demonstrated that the later, released a major fraction of active in the ileum and throughout the colon[8]. In particular, this drug has been widely used in polymeric microsystems such as poly(lactic-co-glycolic acid)-microparticles (PLGA-microparticles)[9], Polylactic acid-microparticles (PLA-microparticles)[10] and chitosan coated Ca-alginate microparticles[11] to optimize the delivery to the inflamed colonic mucosa.

Most of the commercially available systems for colon-specific drug delivery utilize Eudragit® polymers (i.e., L100 and S100), soluble at pH 7, or cellulose acetate phthalate, dissolving at pH 6. In the present study, we employed Eudragit®RS (E-RS) 100 and Eudragit®RL (E-RL) 100 to produce micro-carriers for a specific colon release of BD. Among the different types of Eudragit®, RS100 and RL100 are copolymers based on acrylic and metacrylic acid esters, containing a low level of quaternary ammonium groups. E-RS has a lower content of charged groups (4.5-6.8%), and it is considered less permeable to water with respect

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to the more readily permeable E-RL (8.8-12% ammonium groups). These copolymers are insoluble at physiological pH values, are able to swell forming permeable films enabling sustained release formulation manufacture[12]. Eudragit® polymers have been proposed in various studies for colon targeting[13] because of their low content in ammonium groups allowing a low solubility in gastric fluids.

Summarizing, this study reports (a) the production by two different techniques of microparticles constituted of sole E-RS or of a mixture of E-RS and E-RL[12,13], (b) the influence of preparation procedure on microparticle characteristics (i.e. morphology and encapsulation yield) and (c) the analysis the *in vitro* drug release profiles.

MATERIALS AND METHODS

E-RS and E-RL were from Rohm GmbH (Darmstadt, Germany). BD and all other materials and solvents were from Sigma-Aldrich, Germany.

Solvent evaporation method for microparticles:
500 mg of polymer (eventually added with 5 mg of BD) were dissolved in 5 ml of CH_2Cl_2. The mixture was emulsified with 100 ml of an aqueous phase containing 1% (w/v) of 88% hydrolyzed polyvinyl alcohol as dispersing agent. The emulsion was continuously magnetic stirred at 750 rpm for 3-5 h. Microparticles were isolated by filtration and left to completely desiccate in Petri dishes[14].

Spray drying method for microparticles:
Microparticles were produced using a Mini Spray Dryer Model 190 (Büchi, Laboratoriums Technik AG, Germany). Briefly, 100 ml of E-RS aqueous suspension (eventually containing 2 mg of BD) were withdrawn through a peristaltic pump at 10 ml/min and sprayed with a 0.7 mm nozzle by mean of a flow of compressed air (600l/h), in the drying chamber of the apparatus. The desiccating air was 130°[15].

Size and morphology analysis:
Size and size distribution of microspheres were determined using an average of 300-400 measured microparticles, visualized by an optical microscope with a digital camera (Nikon Diaphot inverted microscope, Tokyo, Japan). The morphology of microspheres was evaluated by scanning electron microscopy observation using a SEM Zeiss EVO 40 (Carl Zeiss NTS GmbH, Oberkochen, Germany).

FTIR spectroscopy, thermal analysis and X-ray diffraction:
IR spectra of pure drugs, polymers, microparticles and physical mixtures were obtained with a Perkin-Elmer 1600 spectrophotometer (Monza, Italy) using potassium bromide disks containing about 10 mg of sample. The scanning range used was 4000-500 cm^{-1} at a scan period of 1 min.

Temperature and enthalpy measurements of raw materials and samples were performed by means of a Netzsch model 409STA (Netzsch-Gerätebau GmbH, Germany) equipped with a platinum furnace and platinum/rhodium sample carrier. All experiments were conducted at heating rates of 10°/min from 25 to 280°. Instrument calibration was performed with standard indium and zinc samples (purity>99.99%). Analyses were made in duplicate.

X-ray diffractograms of BD, empty and drug loaded microparticles and physical mixtures between polymers and drug substance were recorded using Philips PW 1820, Netherlands. Samples were irradiated with monochromatized Cu-Kα radiation and analysed between 2 and 60°. The range and the chart speed were 2×10^4 cps and 10 mm/2θ, respectively.

Drug content of microparticles:
About 5-7 mg of microparticles were dissolved in 5 ml of mobile phase. Then, 20 µl of the solution were injected on a Platinum C18 A100 column (15×0.46 cm, 5 µm) in an HPLC system (Jasco, Japan). The mobile phase used for the elution was acetonitrile/phosphate buffer (0.025M, pH 3.2) (60:40 *v/v*) at a flow rate of 0.8 ml/min. Under these conditions BD showed a limit of quantization of 10 ng/ml and a retention time of 4.2 min. The calibration curve was linear in the concentration range 10-5000 ng/ml, r=0.9982.

***In vitro* release of BD:**
The *in vitro* release of BD from microparticles was performed using the horizontal shaker method. Seven milligrams of BD-containing microparticles were poured in 20 ml of a receiving phase simulating the gastric juice (fasted state simulated gastric fluid, FaSSGF) or intestinal fluid (fasted state simulated intestinal fluid, FaSSIF)[16]. Experiments were performed at 37° in FaSSGF for 2 h and in FaSSIF for 22 h. 500 µl of the receiving buffer were withdrawn at different time intervals and the drug content was analysed by HPLC.

Data analysis and statistics:
Statistical analysis was performed by the analysis of variance (ANOVA), followed by SPSS 11.5. The level of significance was taken at P values<0.05.

RESULTS AND DISCUSSION

As previously reported, the present study describes the behaviour of two different poly(methacrylate) microparticle formulations designed for oral administration of BD obtained either by solvent evaporation (SE) and spray drying (SD). Particularly, BD-containing microparticles were prepared using E-RS or a mixture of E-RS/E-RL 70:30 (w/w).

In the first approach, microparticles were produced by SE method[14]. As reported in Table 1, the percentage of recovery by weight of both types of BD-containing microspheres was about 92%.

Dimensional analysis was performed by mean of both optical and scanning electron microscopy. This shows that BD-containing microparticles have similar mean diameters and homogeneous size distribution, being 32.34±9.07 μm for E-RS and 27.26±4.98 μm for E-RS/E-RL (Table 2). As shown in fig. 1, microparticles produced by SE are characterized by spherical shape and generally with porous surface.

BD-containing microparticles were also produced through SD technique[15]. Microparticles obtained by SD are usually organic solvent free with respect to other preparation methods often resulting in particles possibly contaminated by toxic organic solvents[16,17]. From data reported in fig. 1, Tables 1 and 2 it is evident that microparticles are spherically shaped with smooth surface and are characterized by smaller mean diameters with respect to microparticles produced by SE, being 4.60±2.65 μm for E-RS and 3.75±2.12 μm for E-RS/E-RL. From SEM micrographs, it was observed that both processes yielded porous surface and spherical microspheres with uniform particle size distribution. Microparticles obtained by SE showed a higher porous structure as compared to that of microparticles obtained by SD technique. The presence of a porous structure could be interesting for the release of the entrapped drug for the treatment of Crohn's disease making this new formulation to be a good candidate for an application in colon delivery. However, the recovery efficiency of BD-containing microspheres produced by SD was lower as compared to that of microparticle produced

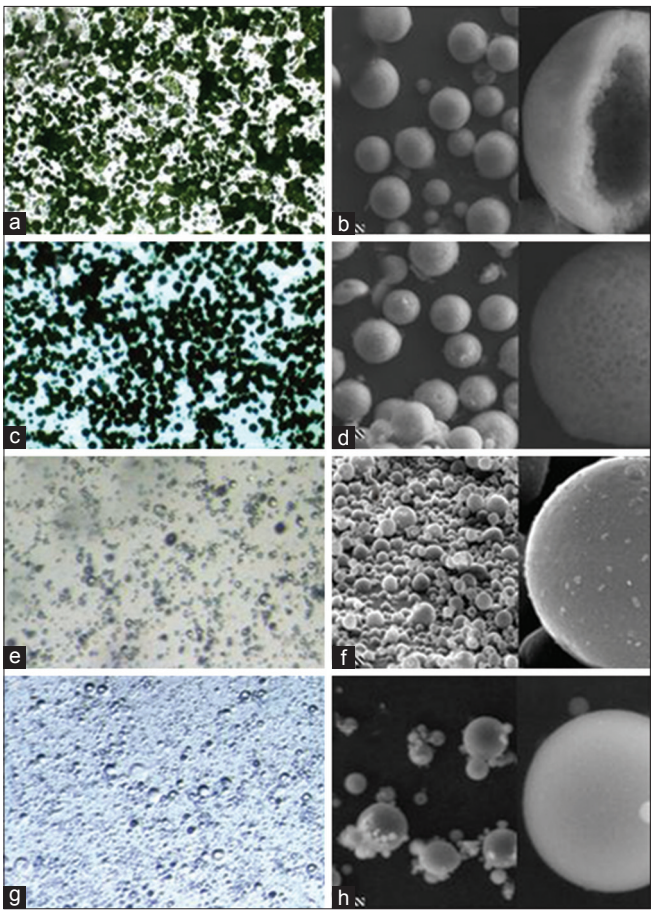

Fig. 1: Optical and scanning electron micrographs.
Optical and scanning electron micrographs of budesonide-containing microspheres obtained by solvent evaporation (a-d) or spray-drying (e-h). Microparticles were composed of E-RS (a, b, e, f) or E-RS/E-RL (c, d, g, h). Bar corresponds to 20 mm (panels b, d) or to 15 mm (panels f, h).

TABLE 1: CHARACTERISTICS OF BUDESONIDE-CONTAINING EUDRAGIT® MICROPARTICLES PRODUCED BY SOLVENT EVAPORATION (SE) OR SPRAY-DRYING (SD)

Polymer type (method of production)	Polymer composition (%)	Microspheres recovery*±SD (%)	Budesonide loading (%w/w)±SD	Mean size±SD (μm)
E-RS (solvent evaporation)	100	92.60±3.27	72.57±0.47	32.34±9.07
E-RS (spray drying)	100	44.76±3.68	79.33±0.84	4.60±2.65
E-RS/E-RL (solvent evaporation)	70/30	92.18±2.57	71.72±0.78	27.26±4.98
E-RS/E-RL (spray drying)	70/30	26.65±6.84	78.31±1.22	3.75±2.12

E-RS=Eudragit®RS, E-RL=Eudragit®RL. Data are the mean of five independent experiments±SD. P<0.05,*Percentage of recovery with respect to the total amount of polymer used for the preparation

TABLE 2: SIZE DISTRIBUTION ANALYSIS OF BUDESONIDE-CONTAINING MICROPARTICLES PRODUCED BY SOLVENT EVAPORATION (SE) OR SPRAY-DRYING (SD)

Parameter	E-RS SE	E-RS/E-RL SE	E-RS SD	E-RS/E-RL SD
Number of microparticles	364	338	399	328
Size max. (μm)	81.0	40.7	16.19	10.52
Size min. (μm)	8.9	13.0	0.95	0.57
Mean	32.34	27.26	4.60	3.75
Median	30.5	27.2	3.81	3.58
Range	35.25	27.71	5.31	4.22
Standard deviation	9.07	4.98	2.65	2.12
Variance	198.03	24.81	7.01	4.44
Standard error	1.109	0.352	0.133	0.140
Skewness	0.475	−0.106	1.125	0.927
Kurtosis	−0.235	0.264	0.965	0.566

E-RS=Eudragit®RS, E-RL=Eudragit®RL, SE=Solvent evaporation, SD=Spray-drying. Data are the mean of three independent analyses. $P<0.05$

TABLE 3: ONSET TEMPERATURE OF EXOTHERMIC PEAKS OF THERMOGRAMS REPORTED IN FIGURE 2*

Samples	E-RS(°)	E-RS/E-RL 70:30(°)
BD	215	215
Empty polymeric microspheres	197	197
BD-containing polymeric microspheres	232	193
Polymer/BD physical mixture	188	192

BD=Budesonide, E-RS=Eudragit®RS, E-RL=Eudragit®RL.*Analyses were made in duplicate

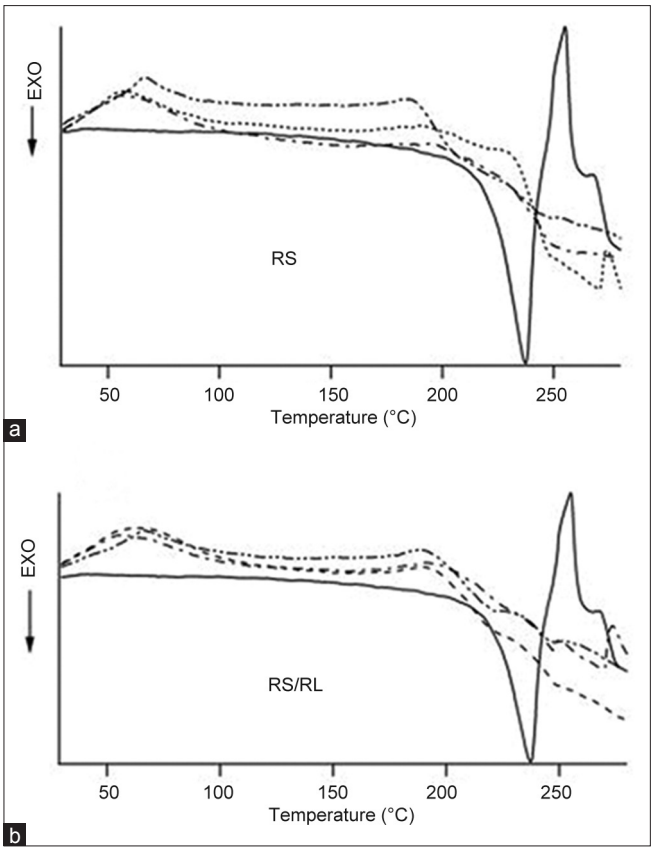

Fig. 2: DSC thermograms.
DSC thermograms of budesonide (BD) (— —), empty polymeric microspheres (---), BD-containing microparticles (— — —) obtained by solvent evaporation and physical mixture of polymer plus BD (— — —). Panel a: E-RS. Panel b: E-RS/RL.

by SE being 44.76±3.68% for E-RS and 26.65±6.84% for E-RS/E-RL (Table 1). This drawback can be possibly attributed to the polymer that tends to adhere to the desiccating chamber, minimizing the recovery of microspheres. In addition, while no differences in terms of morphology are evident between empty and drug-loaded microparticles, the mean diameter of microspheres is affected by the presence of BD possibly due to an increase of the precursor emulsion droplet size during microparticle production[18,19].

Concerning the drug loading capacity it was found that in all cases BD encapsulation was around 72% for microparticles prepared by SE and around 80% for microparticles obtained by SD (Table 1)[20,21].

The physical state of BD within polymer matrices was studied by mean of FTIR and differential scanning calorimetry, IR spectrum of BD shows a C=C stretching band at 1666 cm^{-1} and the O-H stretching peak at 3490 cm^{-1}. These two peaks were still visible in the physical mixtures of BD with either E-RS or E-RS/E-RL, whilst totally disappeared in the IR spectra of BD-containing microspheres obtained by both preparation methods (data not shown). The thermal curves of BD and Eudragit® microparticles obtained by SE are shown in fig. 2, the onset temperature of exothermic peaks is reported in Table 3. The sharp endothermic peak of pure drug was observed at 250° characteristic for the melting behaviour of BD. On the other hand, the thermograms of both types of BD-containing microparticles resulted in a complete suppression of the endothermic peak of the drug, suggesting a homogeneous dissolution of the drug within the polymers. The same behaviour was obtained for physical mixture between BD and Eudragit® polymers. These results were further confirmed by X-ray diffraction studies. The diffraction patterns of both types of BD loaded Eudragit microparticles did not contain any peaks associated with the crystalline molecule of the drug substance. In addition, no differences in terms of calorimetric peaks were appreciable for SD BD-containing microparticles made of either E-RS or E-RS/E-RL (data not shown).

Thermal studies confirmed that there was no interaction between drug and polymer as endotherms of drug and polymers were separate in formulation prepared by SD or SE. However, from the analysis of onset temperature of exothermic peak (Table 3) it seems that E-RS and BD are characterized by a higher intimate interaction as compared to that of E-RS/E-RL polymer composition and BD. IR spectra of BD and BD-containing E-RS or E-RS/E-RL microparticles both in water and in phosphate buffer (pH 3.2-0.025 M). Particularly, the experiments were carried out both on microparticles obtained by SE and by SD. As reported in the fig. 3, the presence of acidic conditions does not influence the signal of the characteristic peak at 1635 nm of BD either alone or included in both type of SE microparticles. The same results were obtained for SD. Taken together these results it should be supposed that the slower release of BD in the acidic conditions could be possibly ascribed to the inner morphology (fig. 1) and

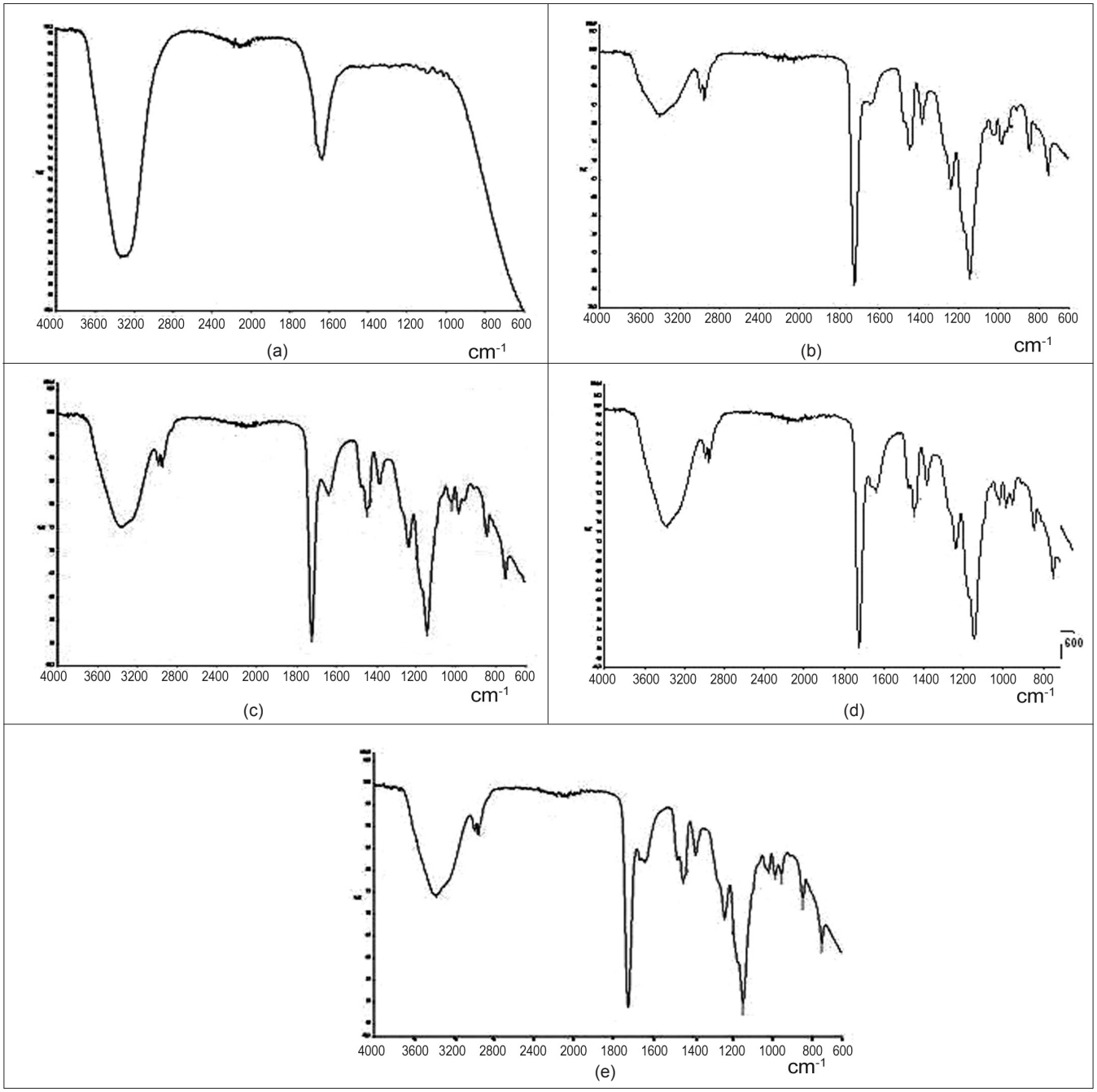

Fig. 3: IR specta of Budesonide and formulations.
IR spectra of pure budesonide (BD) (a) and BD-containing microparticles of Eudragit®RS (b, c) or Eudragit® RS/RL (d, e) produced by solvent evaporation. Spectra were performed in water (b, d) or in phosphate buffer (pH 3.2-0.025M) (c, e).

to the mean size of microparticles that influences their surface specific area.

The complete release profile of BD from microspheres was determined by dialysis method. The profile and kinetics of drug release are important to correlate the *in vitro* and *in vivo* drug responses by comparing results of pharmacokinetics and dissolution profile patterns[22-24]. Fig. 4 reports the release kinetics of BD from microparticles obtained either by SE or SD.

As clearly appreciable, both types of microparticles showed a controlled release as compared to the free drug. In particular microparticles produced by SE (fig. 4a) showed within the 24 h for the mixture E-RS/E-RL a release of BD reaching the 30% of total drug content higher with respect to E-RS microparticles that showed a release of the 24% of the drug. In the case of microparticles produced by spray-drying the release of BD was surprisingly different (fig. 4b). Spray dried E-RS and E-RS/E-RL microparticles obtained showed BD release kinetics almost superimposable reaching a pseudo-plateau after 24 h with a maximum of drug released of 25 and 32%, respectively. Concerning microparticles obtained by SD the release kinetics of BD from E-RS shows after 24 h a release around 32-35% without presenting a pseudo-plateau. On the other hand, BD release from E-RS/E-RL reaches a pseudo-plateau after 8 h showing a maximum of drug released of 15%. However, both types of preparation methods lead to microparticles characterized, within the first 2 h of release (when FASSGF was used), by a slower release of BD in the case of E-RS as compared to that of E-RS/E-RL due to the different polymer permeability in simulated gastric fluid. These results could be explained considering the chemical structure of Eudragit®. E-RL and E-RS are synthetized from acrylic and methacrylic esters with high and low content of quaternary ammonium groups (8.8-12 and 4.5-6.8%, respectively) and results in different permeability behaviours. Due to the content of the quaternary ammonium groups, E-RS is only slightly permeable; hence drug release is relatively retarded, whereas E-RL is freely permeable, so that the release is less retarded. The combination of E-RS and E-RL increase the permeability of the obtained microparticles and determine a minor drug protection from the gastric ambient.

The release of a drug from microparticles can be described using some mathematical models

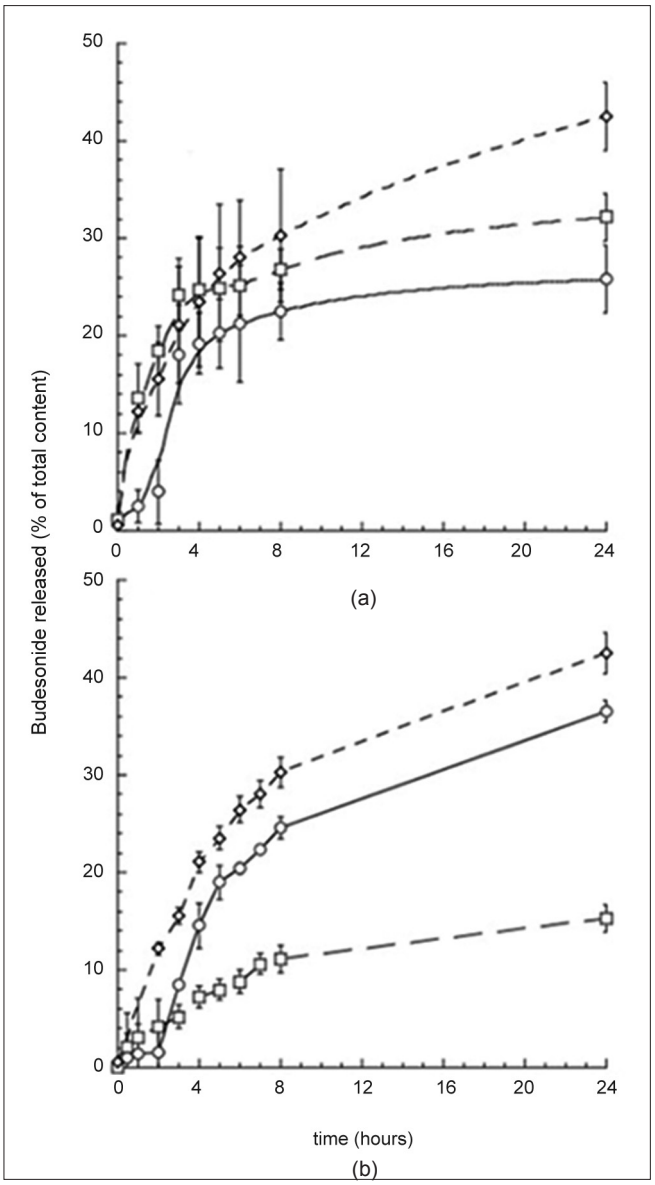

Fig. 4: *In vitro* release profiles of budesonide from microparticles.
***In vitro* release profiles of budesonide (BD) from E-RS (□) and E-RL/RS (○) microparticles obtained by solvent evaporation (a) and spray-drying (b). As reference the release of BD free solution is also reported (◊). The release was performed at 37° in fasted state simulated gastric fluid for 2 h and 18 h in fasted state simulated intestinal fluid. Data represent the average of three independent experiments±SD.**

describing Fickian diffusive and dissolutive release mechanisms[22,25,26] and nonFickian release (Korsmeyer-Peppas equation)[27,28]. The obtained data are reported in Table 4.

When the *n* value is >0.5, the release mechanism follows Fickian diffusion while for values comprised between 0.5 and 1 the release mechanism follows a nonFickian model. Correlation coefficients (R and R^2) were used to evaluate the accuracy of the fit.

TABLE 4: RELEASE KINETIC PARAMETERS OF DRUG RELEASE FROM EUDRAGIT® BUDESONIDE-CONTAINING MICROPARTICLES

Equation	K	c, c', n	*R*	R^2
$(1-Mt/M¥)=e^{-Kdiss^t}+c$				
E-RS (SE)	−0.35648	4.5829	0.90050	0.81090
E-RS (SD)	−0.071383	4.6254	0.94164	0.88669
E-RS/E-RL (SE)	−0.03250	4.4969	0.84483	0.71374
E-RS/E-RL (SD)	−0.006103	4.5918	0.82904	0.74769
$Mt/M¥=Kdifft^{0.5}+c'$				
E-RS (SE)	1.2046	2.2989	0.90249	0.81449
E-RS (SD)	2.0396	6.4528	0.96469	0.93063
E-RS/E-RL (SE)	1.1977	4.0073	0.95560	0.91317
E-RS/E-RL (SD)	0.3787	1.3604	0.93211	0.86883
$Mt/M¥=Kt^n$				
E-RS (SE)	1.0612	0.61421	0.71222	0.50726
E-RS (SD)	3.3255	0.74791	0.84510	0.71419
E-RS/E-RL (SE)	2.6242	0.20627	0.93184	0.86833
E-RS/E-RL (SD)	3.3044	0.88753	0.79820	0.63712

E-RS= Eudragit®RS, E-RL=Eudragit®RL, K and c=Mathematical coefficients obtained by plotting the linear forms of the indicated equations, *R*=*R*egression coefficient, R^2=Squared regression coefficient, SE=Solvent evaporation, SD=Spray-drying

On the basis of the value of R it appears that the release of BD from the prepared microspheres is more consistently diffusive rather than dissolutive[25,28]. These results are in agreement with the physicochemical characteristics of E-RS and E-RL.

Taking into consideration the above reported results the microparticles produced with E-RS showed a better protection of the drug from gastric acidity than E-RS/E-RL microparticles and a hypothetical system of colon specific controlled delivery.

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