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Article

Extended release promethazine HCl using acrylic polymers by freeze-drying and spray-drying techniques: formulation considerations

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The present study investigated a novel extended release system of promethazine hydrochloride (PHC) with acrylic polymers Eudragit RL100 and Eudragit S100 in different weight ratios (1:1 and 1: 5), and in combination (0.5+1.5), using freeze-drying and spray-drying techniques. Solid dispersions were characterized by Fourier-transformed infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), Powder X-ray diffractometry (PXRD), Nuclear magnetic resonance (NMR), Scanning electron microscopy (SEM), as well as solubility and in vitro dissolution studies in 0.1 N HCl (pH 1.2), double-distilled water and phosphate buffer (pH 7.4). Adsorption tests from drug solution to solid polymers were also performed. A selected solid dispersion system was developed into capsule dosage form and evaluated for in vitro dissolution studies. The progressive disappearance of drug peaks in thermotropic profiles of spray-dried dispersions were related to increasing amount of polymers, while SEM studies suggested homogenous dispersion of drug in polymer. Eudragit RL100 had a greater adsorptive capacity than Eudragit S100, and thus its combination in (0.5+1.5) for S100 and RL 100 exhibited a higher dissolution rate with 97.14% drug release for twelve hours. Among different formulations, capsules prepared by combination of acrylic polymers using spray-drying (1:0.5 + 1.5) displayed extended release of drug for twelve hours with 96.87% release followed by zero order kinetics (r^2= 0.9986).

Uniterms: Promethazine hydrochloride/extended release. Drugs/extended release. Eudragit RL100. Eudragit S100. Acrylic polymers. Spray drying/pharmacotechnics. Freeze drying/pharmacotechnics. Extended realease/pharmacotechnics. Pharmaceutical formulations/evaluation.

O presente trabalho compreendeu estudo de um novo sistema de liberação prolongada de cloridrato de prometazina (PHC) com polímeros acrílicos Eudragit RL100 e Eudragit S100 em diferentes proporções em massa (1:1 e 1:5) e em combinação (0,5+1,5), utilizando técnicas de liofilização e de secagem por aspersão As dispersões sólidas foram caracterizadas por espectrofotometria no infravermelho por transformada de Fourier (FT-IR), calorimetria diferencial de varredura (DSC), difratometria de raios X (PXRD), Ressonância Magnética Nuclear (RMN), microscopia eletrônica de varredura (SEM) e, também, por estudos de solubilidade e de dissolução *in vitro* em HCl 0,1 *N* (pH 1,2), água bidestilada e tampão fosfato (pH 7,4). Realizaram-se, também, testes de adsorção da solução do fármaco nos polímeros sólidos. Desenvolveu-se sistema de dispersão sólida exclusiva dentro das cápsulas, que foi avaliado por meio de estudos de dissolução *in vitro*. Relacionou-se o desaparecimento progressivo de picos do fármaco em perfis termotrópicos de dispersões secas por spray à quantidade aumentada de polímero, enquanto os estudos de SEM sugeriram dispersão homogênea do fármaco no polímero. O Eudragit RL100 apresentou maior capacidade de adsorção do que o Eudragit S100 e, dessa forma, a combinação de (0,5+1,5) para S100 e para RL100 mostrou taxa de dissolução maior, com liberação de 94,17% de fármaco em 12 horas. Entre as várias formulações, as cápsulas preparadas pela combinação de polímeros acrílicos utilizando secagem por aspersão (0,5+1,5) apresentou liberação prolongada do fármaco em 12 horas, com 96,78% de liberação, seguindo cinética de ordem zero (r^2 = 0,9986)

Unitermos: Cloridrato de prometazina/liberação prolongada. Fármacos/liberação prolongada. Eudragit RL100. Eudragit S100. Polímeros acrílicos. Secagem por aspersão/farmacotécnica. Liofilização/farmacotécnica. Formulações farmacêuticas/avaliação.

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INTRODUCTION

The solid dispersion approach is commonly used to improve the dissolution properties of poorly water-soluble drugs using hydrophilic polymeric carriers as dispersing agents. More recently, several studies on solid dispersions have been carried out using water-insoluble carriers to produce sustained release pharmaceutical forms of freely water soluble drugs (Zijlstra *et al.*, 2007; Drooge *et al.*, 2004; Nagarsenker *et al.*, 2000). For this goal, different types of polymethacrylates (Eudragit) have been considered. The most interesting among acrylic polymers are highly permeable Eudragit RL and low permeable Eudragit RS. Both are neutral copolymers of poly ethylacrylate (methyl methacrylate and trimethyl aminoethyl methacrylate chloride), and are insoluble in water and digestive juices, though both swell and are permeable. Extended-release systems are the methods that can achieve therapeutically effective concentrations of drugs in systemic circulation over an extended period of time. Several studies (Thybo *et al.*, 2008; El-badry *et al.*, 2006; Torrado *et al.*, 1996; Drooge *et al.*, 2005) and (Mangal *et al.*, 1997; Mooter *et al.*, 2001; Miyazaki *et al.*, 2006; Ammar *et al.*, 1997; Hirasawa *et al.*, 2003) used the solid dispersion method for this purpose. A combination of solid dispersion and extended-release is one of the attractive approaches since supersaturation of the drugs can be achieved by employing the solid dispersion technique (Ozeki *et al.*, 1995). In the present study, Eudragit RL100 and Eudragit S100 have been used as retardants to prepare a novel extended-release system of highly water soluble medicine promethazine hydrochloride using spray-drying and freeze-drying techniques in order to extend their dissolution rates. A selected solid-dispersion system was further subjected to capsule preparation in order to study the feasibility of incorporating solid-dispersion for formulation as a drug delivery system.

MATERIALS AND METHODS

Promethazine hydrochloride (PHC) was supplied by Seimens Laboratory, India. Eudragit S100 (S100) and Eudragit RL100 (RL100) were donated by Rohm Pharma, Germany. Lactose, sodium starch glycolate (Explotab), and silicon dioxide (Aerosil) were purchased from Merck India Limited, Mumbai. Other chemicals were of analytical grade. Double-distilled water was used throughout the study.

Preparation of Freeze-dried solid dispersions

PHC and Eudragit polymers were dissolved separately in absolute ethanol. The mixture formed by adding polymer solution to the PHC solution, was frozen overnight in a petri dish at -45 °C and lyophilized in a freeze-dryer (model Lyph-Lock 12L) at -45 °C for forty-eight hours. Secondary drying was carried out at room temperature. The freeze-drying process was run until a dry, solid dispersion of drug was obtained. The obtained dispersion was then screened through a 40-mesh standard sieve and stored in desiccators (Govindrajan *et al.,* 2004).

Preparation of spray-dried solid dispersions

Polymers were dissolved in a sufficient amount of ethanol: water 50% (v/v) solution and PHC was added under continuous stirring. The resulting mixture was

TABLE I - Formulation of PHC and Eudragit solid dispersion systems

Method of Preparation	Type of Polymer	Weight Ratio (Drug: Polymer)	Formulation code
Physical mixing	RL100	1:1	PM1RL
Freeze drying	RL100	1:1	FD1RL
Spray drying	RL100	1:1	SD1RL
Physical mixing	RL100	1:5	PM5RL
Freeze drying	RL100	1:5	FD5RL
Spray drying	RL100	1:5	SD5RL
Physical mixing	S100	1:1	PM1S
Freeze drying	S100	1:1	FD1S
Spray drying	S100	1:1	SD1S
Physical mixing	S100	1:5	PM5S
Freeze drying	S100	1:5	FD5S
Spray drying	S100	1:5	SD5S
Physical mixing	S100+RL100 (0.5+1.5)	1:2	PM2SRL
Freeze drying	S100+RL100 (0.5+1.5)	1:2	FD2SRL
Spray drying	S100+RL100 (0.5+1.5)	1:2	SD2SRL

stirred for twenty-four hours at room temperature and the obtained solution was subsequently spray-dried (LabPlant SD-05), under the following conditions: air flow rate – 50 m^3/h; atomizing air pressure – 1×10^5 Pa; inlet temperature of 160° C, outlet temperature of 85 °C; flow rate of the solution at 400 ml/h. The obtained product was sieved through a 40-mesh standard sieve and stored in desiccators. Physical mixtures (PMs) with corresponding weight ratios were prepared by triturating the drug and polymer in a glass mortar (Table I). The powders were then sifted (150 mm sieve) and stored in desiccators.

Determination of Drug Content

Ten milligrams of the solid dispersion was accurately weighed and diluted up to 10 mL with double distilled water. From this, a 1ml of sample was withdrawn and diluted up to 10 mL with double-distilled water and assayed spectrophotometrically for promethazine HCl at 249 nm using a suitably constructed calibration curve in double-distilled water. The studies were conducted in triplicate (Pignatello *et al.,* 2002).

Solubility Measurements and Adsorption Studies

The solubility of solid dispersions was studied in 0.1 N HCl (pH 1.2), double-distilled water and phosphate buffer (pH 7.4). The samples were subsequently allowed to equilibrate at 37 ± 0.1 °C in a mechanical shaker (HICON, India) for twenty-four hours. The samples were filtered, suitably diluted and analyzed spectrophotometrically (Shimadzu 1700, Japan) (Cui *et al.*, 2003). For adsorption studies, the drug was dissolved in phosphate buffer pH 7.4 (50 mL). A ten-fold weight of ground S100 or RL100 was added to the solution, and the mixture was magnetically stirred at room temperature for fifteen days. Samples were periodically drawn, filtered, diluted and assayed spectrophotometrically (Shimadzu, Pharmaspec 1700, Japan) at 249 nm (Esclusa-Diaz *et al.*, 2003).

Preparation of Capsules

A SD2SRL solid dispersion was developed into capsule dosage forms according to the formulations listed in Table II. Lactose was used as the capsule diluent, while various concentrations of a disintegrant, Explotab (2%, 5% and 8%), were used in capsule formulations. Silicon dioxide (Aerosil) was used as a glidant in the capsules. A control capsule containing 0% Explotab was also prepared.

TABLE II - Composition of solid dispersion capsules

Formulation	F1	F2	F3	F4
SD2SRL (mg)	124.08	124.08	124.08	124.08
Lactose (mg)	287.52	280.32	270.22	261.12
Explotab® (%)	-	2	5	8
Aerosil® (%)	0.5	0.5	0.5	0.5

Observation of Dissolution Behavior of PHC from Solid Dispersions and Capsules

The dissolution behavior of PHC from pure PHC powder or its FDs, SDs and PMs was performed using a USP XXVII Apparatus I in 900 mL of 0.1 N HCl (pH 1.2) , double-distilled water, and phosphate buffer (pH 7.4) at an agitation rate of 100 rpm (USP, 2005). The temperature of the medium was maintained at 37 ± 0.5 °C. Seventy-five milligrams of drug, or its equivalent, of the prepared dispersions were packed in transparent gelatin capsules and analyzed for dissolution. Capsules prepared with the selected solid-dispersion system were also analyzed for dissolution. A 5.0 mL sample was withdrawn at specific hourly time points (beginning at zero) over a twelve hour period and replaced immediately with an equal volume of fresh dissolution medium to maintain a constant volume. The aliquot samples were filtered and the drug concentrations were determined spectrophotometrically at 249 nm. The drug release kinetics were investigated by fitting the dissolution data to PCP Disso V 2.0 software (Pune, India).

Disintegration studies

Disintegration studies of the PHC-controlled release solid-dispersion capsules were performed by a USP-type disintegrator (K.S.L. Engineering Co., Ltd., USP type, Thailand) according to USP XXIII, using distilled water as medium. Average disintegration time of a capsule formulation was obtained from six capsules.

FTIR spectroscopy

IR spectra of pure drug and polymers, and of freeze-dried solid dispersion, spray-dried solid dispersions and physical mixtures, were obtained with an FTIR spectrophotometer, (Shimadzu 8201 PC) using KBr disks (about 10 mg sample for 100 mg drug KBr). The scanning range used was 4000 to 400 cm^{-1} at a scan period of one minute (Huang *et al.,* 2008).

Differential scanning calorimetry

Thermal analysis was performed on the drug, freeze-dried solid dispersion, spray-dried solid dispersions, physical mixtures and Eudragit polymers using a PERKIN – ELMER DSC-7. Samples (10-15 mg) were weighed and sealed into 40μL aluminium pans. DSC runs were conducted over a temperature range of 70 °C to 250 °C at a rate of 10 °C/minute in a nitrogen atmosphere (Law *et al.,* 2001).

X-ray powder diffractometry

Diffraction patterns of physical mixtures, drug, freeze-dried solid dispersion, spray-dried solid dispersions and Eudragit polymers were recorded with a PW 3040/60 X' Pert PRO (Netherland). A voltage of 40kV and a current of 30 mA for the generator were used, with Cu as the tube anode material. The solids were exposed to Cu-K_α radiation (α1=1.54060 Å and α2=1.54439 Å, with a α1/α2 ratio of 0.5), over a range of 2θ angles from 10 °C to 30 °C, at an angular speed of 1° (2θ) per minute (Law *et al.,* 2001).

^{1}H NMR spectroscopy

To determine the nature of proton or protonated groups in the PHC and polymeric dispersions of PHC, the ^{1}H NMR spectrum in $CDCl_3$ were recorded on a Bruker Avance 400, FT-NMR spectrometer, 300 MHz, using TMS as an internal standard, and the chemical shift (δ) was recorded in ppm (Zajc *et al.*, 2005).

Scanning electron microscopy

The morphology of solid dispersion particles was characterized by scanning electron microscopy using LEO 435 VP, UK. Solid dispersions were fixed on supports with carbon glue and coated with gold using a gold sputter model in a high vacuum evaporator. Samples were then observed with scanning electron microscopy (WU *et al.,* 2008).

Stability studies

A three-month accelerating condition stability test was carried out after preparation by which solid dispersion capsules were kept in an oven at a temperature of 40 ± 1 °C and a relative humidity of 75%. The release profiles and drug content of the capsules were determined at the end of one, two and three months, respectively, and then compared with that of freshly prepared solid dispersion capsules (Mura *et al.*, 1999).

RESULTS AND DISCUSSION

Determination of Drug Content

The actual drug content of solid dispersion systems were estimated in the range of 13.06 ± 0.001% to 47.98 ± 0.001% (Table III). The drug content was found to be uniform in all solid dispersions and was in good agreement with theoretical drug content.

TABLE III - Drug Content and Model-Independent Parameters of PHC Solid Dispersions

S. No.	Formulations	Drug Content* (%)	$t_{50\%*}$ (h)	$t_{plateau}$	$\%DE_{(0\text{-}12\ h)}$
1.	PM1S	47.98± 0.001	1.0	6.0	58.12
2.	SD1S	45.45 ± 0.001	2.0	4.0	53.44
3.	FD1S	47.17 ± 0.002	2.0	5.0	30.21
4.	PM5S	15.56± 0.002	3.0	10.0	63.85
5.	SD5S	13.06 ± 0.001	3.0	9.0	56.21
6.	FD5S	13.22 ± 0.001	3.5	6.0	49.74
7.	PM1RL	50.00 ± 0.001	2.0	6.0	63.22
8.	SD1RL	41.73± 0.001	2.5	9.0	66.78
9.	FD1RL	47.16 ± 0.002	2.0	7.0	55.89
10.	PM5RL	15.80 ± 0.002	4.50	12.0	65.42
11.	SD5RL	13.33 ± 0.001	5.0	12.0	76.22
12.	FD5RL	13.06 ± 0.001	4.75	12.0	60.88
13.	PM2SRL	30.21±0.014	5.25	12.0	69.56
14.	SD2SRL	29.88±0.011	6.0	12.0	81.02
15.	FD2SRL	27.23±0.52	5.75	12.0	66.23

*Zero order kinetics used for t50% measurement; Values of ED are different because this depends on % of released PHC after 12 hours; *Average of three determinations

Solubility Measurements and Adsorption Studies

The solubility of PHC in 0.1 N HCl (pH 1.2), double-distilled water and phosphate buffer (pH 7.4) was found to be 590.0 mg/mL, 557.7 mg/mL and 554.3 mg/mL respectively. The results revealed that the magnitude of the drug's aqueous solubility can be decreased using methacrylate copolymers (Fig. 1). It was interesting to note that the magnitude of decreased solubility in physical mixtures was quite similar to that of solid dispersions, indicating that preparation conditions used to obtain solid dispersions did not ultimately induce either polymorphic changes or amorphization of drug molecules. However, increasing the drug to polymer ratio from 1:1 to 1:5 exhibited an approximately two-fold decrease in magnitude of drug solubility in each medium irrespective of the preparation method. The behavior of physical mixtures thus indicated that a dilution effect of drug microcrystal within the polymer network is mainly responsible for changes observed during solubility studies. Among all solid dispersions, SD2SRL had a greater capacity to retard the solubility of PHC, *i.e.,* 3.19 mg/mL, 3.01 mg/mL and 2.41 mg/mL in 0.1 N HCl (pH 1.2), double-distilled water and phosphate buffer (pH 7.4) respectively. The rank order of decrease in solubility was as follows: 0.1 N HCl (pH 1.2), double-distilled water, phosphate buffer (pH 7.4) (Figure 1). This was due to the fact that PHC possesses a basic group that becomes protonated at acidic pH, making the drug readily soluble. To further evaluate the affinity between the tested molecules and polymers, adsorption of the drug onto S100 and RL100 was calculated quantitatively. The ability of Eudragit polymers to adsorb basic drug from a solution was characterized at pH 7.4. In adsorption studies, RL100 had greater adsorptive capacity than S100 (Figure 2) because of its greater number of quaternary ammonium functions, which act as the activity sites for electrostatic interactions in solution (Dollo *et al.*, 1996; Saenger *et al.*, 1998).

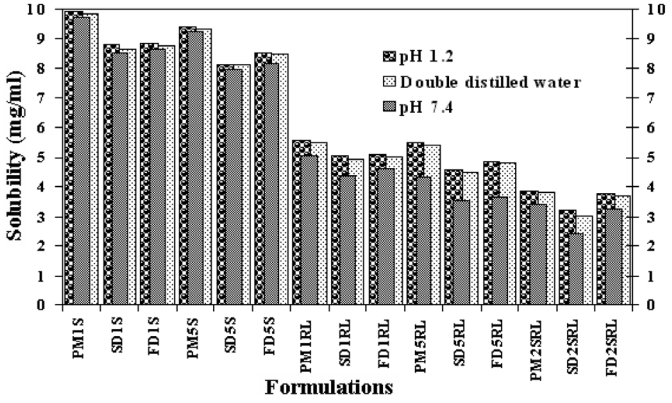

FIGURE 1 - Equilibrium solubility study of PHC and its solid dispersions in 0.1 N HCl (pH 1.2), Double distilled water, Phosphate buffer (pH 7.4)

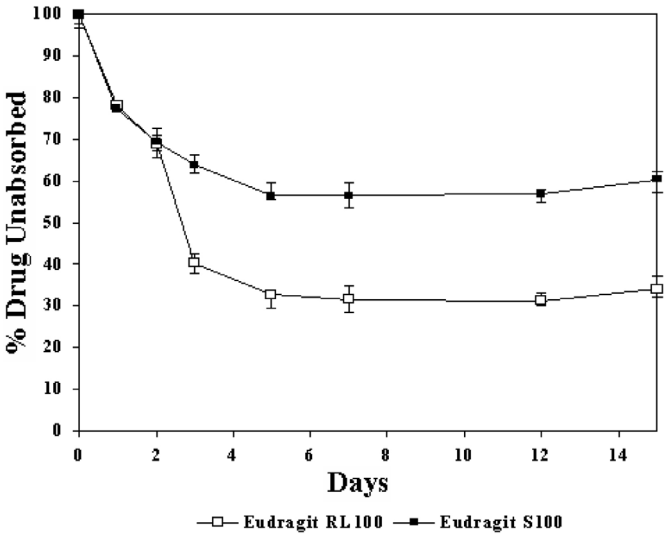

FIGURE 2 - Adsorption pattern of PHC onto RL100 and S100 Particles from pH 7.4 Phosphate buffer

Release mechanism of Single carrier solid dispersions

The dissolution profiles of PHC and solid dispersions are presented in Figure 3. The dispersions of drug in polymer matrices strongly influenced their dissolution rate, which appeared slower and more gradual than that of pure drug. At pH 7.4, solid dispersions were found to extend drug release up to twelve hours because of a decrease in solubility as compared to other media. The presence of the polymer also reduced the massive initial drug dissolution observed with pure PHC. On the contrary, the drug dissolution rate was markedly retarded from both the freeze-dried and spray-dried solid dispersions. Retarding effect on PHC dissolution was dramatically more evident for the spray-dried system. After eight hours, the percentage of dissolved drug from the spray-dried solid dispersions was only about 60% in contrast to the freeze-dried solid dispersions which was nearly 80%. In addition, it was clearly observed that the drug release profile of the spray-dried solid dispersions consisted of a very slow release in the first stage (up to one hour) and a faster release in the second phase. In the first stage, the PHC seems to be released according to zero-order kinetics. It was also clear from the results that the dissolution rate of SD5S was much lower than that of SD5RL. These results might be attributed to the higher swelling and permeation characteristics of RL100 at pH 1.2- 7.4, and due to its permeability, diffusion occurs. At the same time, Eudragit S100 is soluble in a buffer solution above pH 7.0 and remains intact throughout the dissolution period. Thus the release rate of the drug from

Eudragit S100 spray-dried solid dispersions is less than that from Eudragit RL100 spray-dried solid dispersions. Increasing the drug-to-polymer ratio (from 1:1 and 1:5) dramatically increased the release time ($t_{50\%}$ values from 1-3.5 hours to 2-5.0 hours) as well as the percentage of released PHC. However, $t_{50\%}$ values also seemed to be dependent on the type of polymer, as evidenced by the fact that SD1S and SD1RL showed $t_{50\%}$ values of two and two and a half hours whereas SD5S and SD5RL showed $t_{50\%}$ values of three and five hours respectively. This indicated that the polymer properties affected the drug release behavior more prominently when used at higher ratios in the solid dispersions. As DE takes into account the entire dissolution profile as a whole, as opposed to $t_{50\%}$ values, this approach employed a more realistic and meaningful method of comparison as well as interpretation of *in vitro* dissolution data for various formulations (Chowdary *et al.*, 2006). The dissolution efficiency throughout the entire dissolution period ($DE_{0—12\,h}$) showed that dissolution of the drug from its spray-dried solid dispersions with RL100 was evidently higher than from systems containing S100 (Table III). Freeze-dried solid dispersions containing S100 at higher drug to polymer ratio (FD5S) was also able to slow down the diffusion rate of drug (Figure 3). The dissolution data showed that the difference in release profiles was mainly influenced by the type and amount of polymer used. However, when the type and amount of polymer was similar, the difference in release profile (as in the release pattern of SD5RL and FD5RL) can be better explained based on the different morphological states of drug within the polymer matrix. When PHC was freeze-dried, drug–polymer multi-dispersion was possible. This is characterized by embedding the drug particles within the polymer matrices, wherein the exact uniform distribution of the drug within the polymer matrices is difficult with a consequent aggregation of drug and polymer in discrete domains resulting in undesirable release profiles. After twelve hours of dissolution, none of the solid dispersions prepared with 1: 1 ratios were able to retard the drug release significantly. However, at 1:5 ratios, the spray-dried solid dispersions displayed more sustained and gradual dissolution as compared to other solid dispersions with S100 and RL100. Such behavior might be due to the fact that the dissolved drug was re-adsorbed back onto the polymer particles resulting in subsequent saturation of the binding sites on the polymer backbone, and evidenced by a shorter time to reach plateau ($t_{plateau}$) in the dissolution curves. The phenomenon is proportionally related to the amount of polymer present in solid dispersions.

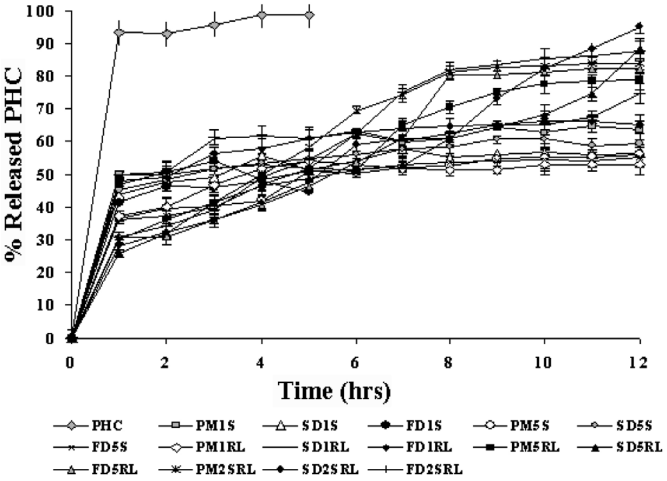

FIGURE 3 - Comparative Dissolution Profiles of PHC and Solid Dispersions in Phosphate buffer pH 7.4.

Release mechanism of solid dispersions with combined carriers

Incorporation of the drug with a mixture of anionic polymer Eudragit S100 and the zwitterionic polymer Eudragit RL100 (SD2SRL) in herit? to the drug dissolution rate, which is clearly lower than that of the drug, but still higher than that of SD5RL and SD5S (Figure 3). This is also obvious from the data of the dissolution efficiency of these systems calculated from the amount of drug dissolved through the entire dissolution run. Studies revealed that $t_{50\%}$ values of PM2SRL, SD2SRL and FD2SRL were 5.25, 6.0 and 5.75 hours respectively (Table III). This indicated that when used in combination, Eudragit polymers customize the release profile of drug.

In order to identify the interactive effect, the dissolution data for the prepared solid dispersions of PHC were subjected to multiple regressions, using a statistical computer program. The dissolution profile of prepared PM2SRL, FD2SRL and SD2SRL solid dispersions were analyzed by linear regression. The kinetics treatment of SD2SRL showed that the release of drug followed zero order kinetics ($r^2 = 0.9812$). Korsemeyer and Peppa's equation gave value of $n = 0.5050$, indicating that the drug was released by Fickian diffusion.

Development of PHC-controlled release capsules

The prepared SD2SRL solid dispersion was developed into a capsule dosage form. A water-soluble diluent lactose was selected because of its hydrophilicity, which would impart little dissolution-retarding effect to the solid dispersion with packing into capsules. The SD2SRL solid dispersion was chosen as a model of solid dispersion to be

developed into a capsule formulation because its dissolution profile lay above the profiles of SD5RL and FD5RL solid dispersions. The effect of disintegrant Explotab was studied by varying its concentration (0%, 2%, 5%, and 8%) in the capsule formulations. The goal of the study was to develop a solid dispersion capsule having the closest dissolution to a solid dispersion powder being encapsulated. Therefore, a dissolution parameter indicating characteristics of the dissolution profile had to be established.

Figure 4 illustrates dissolution profiles of the PHC-controlled release, solid dispersion capsules as compared to that of the solid dispersion powder. Table IV shows the r^2 values (Correlation coefficients) of zero order, first order and Korsemeyer Peppas equation for SD2SRL solid dispersion and capsules from two to twelve hours. First order and Peppas model were found to yield a smaller r^2 than the zero order model. Therefore, the dissolutions of solid dispersion powder and capsules were found to follow zero order kinetics, rather than the first order or peppas models. As shown in Figure 4, the capsules containing 5% Explotab exhibited a similar dissolution profile to solid dispersion powder. The dissolution profiles of the capsules with 0% and 2% Explotab were comparable, and the dissolution profiles of the capsules of 5% and 8% Explotab were similar. Since the capsule of 8% Explotab showed the fastest dissolution, followed by the capsules of 5%, 2% and 0% Explotab, respectively, it was the prime target of capsule formulation development. Thus, increasing the Explotab concentration resulted in faster capsule dissolution. The capsules of 0% Explotab provided less drug dissolution than did the solid dispersion powder. Consequently, the incorporation of solid dispersion powder into capsules using lactose as diluent, resulted in less drug dissolution. The use of the disintegrant Explotab in the capsule was proven to help in restoring drug dissolution; however, an adequate concentration of the disintegrant was needed.

Disintegration times (DTs) of PHC-controlled release solid dispersion capsules are shown in Table 4, and ranged from 1.91 to 3.54 minutes. Since lactose was a water-soluble

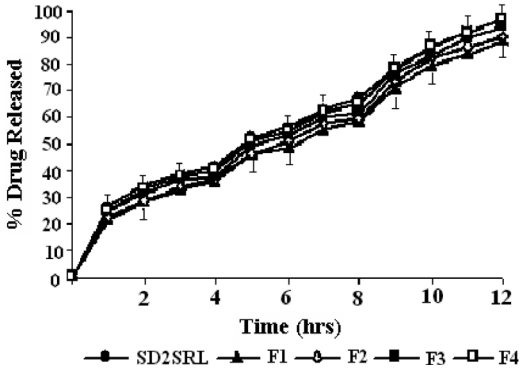

FIGURE 4 - Dissolution Profiles of the SD2SRL Extended Release Solid Dispersion Capsules as Compared to the Profile of the Solid Dispersion Powder

diluent, it provided no disintegration-retardation effect. All of the capsule formulations provided similar dissolution profiles during their initial stages of drug dissolutions and the capsule disintegration times were therefore not responsible for the differences in capsule dissolutions. As the capsules disintegrated, they yielded small coarse powder agglomerates, which could pass through the 10-mesh sieve of the disintegrator within a short period of time. The coarse agglomerates then disintegrated further into fine powders. The effect of Explotab as a disintegrant was not significant in the initial stage of capsule disintegration. However, its influence was more significant in the latter stage of powder agglomerate disintegration. Faster disintegration of the powder agglomerate resulted in faster drug dissolution owing to a greater surface area available for the dissolution process. This was responsible for the faster capsule dissolution at higher Explotab concentration in the capsule.

FTIR Spectroscopy

The above-mentioned results show a strong interaction between the drug and acrylic polymers, suggesting the formation of a real solid dispersion by the spray-drying method. FTIR spectroscopy was used in order to confirm

TABLE IV - Model fitting parameters and Disintegration Time of solid dispersion powder and capsules

Preparation	Explotab® (%)	r^2			DT ± SD (min.)
		Zero order	First order	Diffusion control	
SD2SRL	-	0.9812	0.9230	0.9337	-
F1	0	0.9941	0.8622	0.8875	3.54 ± 0.26
F2	2	0.9688	0.8633	0.8711	2.94 ± 0.11
F3	5	0.9898	0.8152	0.8823	2.12 ± 0.14
F4	8	0.9986	0.8895	0.8941	1.91± 0.22

Level of significance (p) of correlations = 5%.

this assumption. For PHC, the IR stretching band of tertiary amine around 1020 to 1250cm^{-1} (Figure 5) was still visible in physical mixtures, suggesting that there was no interaction between PHC/S100+RL100 in physical mixtures, while it completely disappeared in corresponding spray dried solid dispersions. This resulted in a broad band as well as altered stretching and bending vibrations. This result suggested the possibility of intermolecular hydrogen bonding between PHC and Eudragit polymers in spray-dried solid dispersions. These interactions were made while the molecules were in solution; when the distances between the molecules were so small that association between the functional groups is possible. Since in freeze-dried solid dispersion, FTIR spectrum showed no significant band modifications, we were able to confirm the hypothesis that this method does not give a true dispersion of PHC.

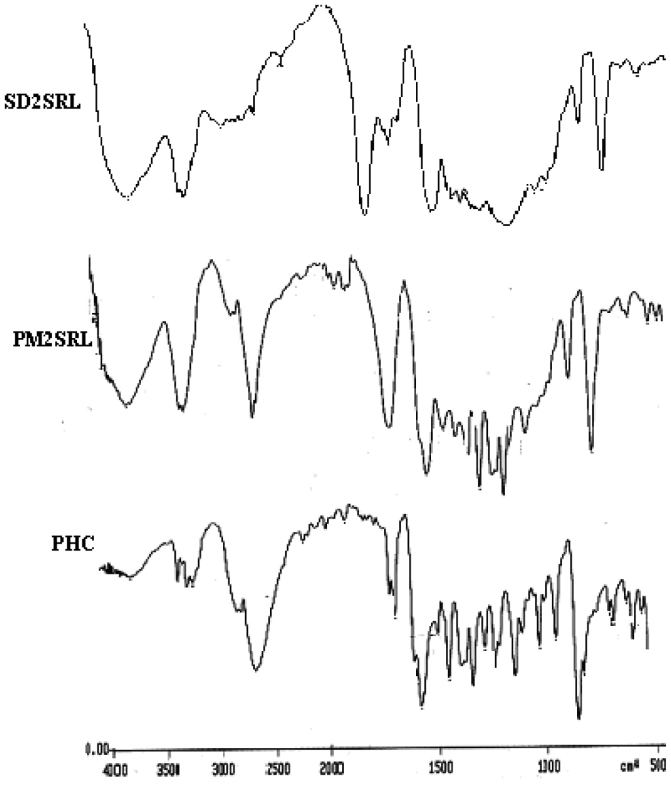

FIGURE 5 - FT-IR Spectra of PHC, PM2SRL and SD2SRL.

Differential scanning calorimetry

The solid dispersion systems were analyzed by means of DSC to detect possible altered thermal properties with regard to the pure substances. When guest molecules are incorporated in polymer matrix at 1:0.5 + 1.0 (Drug: S100+RL100) weight ratios, their melting points generally shift to a different temperature or disappear within the temperature range of pure drug. The DSC curves of PHC, a combination of Eudragit polymers (0.5+1.0, S100+RL100), and the respective drug carrier combinations are shown in Figure 6. The thermal curve of PHC indicated its crystalline anhydrous state with a characteristic endothermic fusion peak at 239 °C. The Eudragits thermogram displayed a very broad endothermic peak at 210 °C due to the fusion process. The appearance of two endothermic peaks corresponding to the fusion of both components, and to the dehydration of polymers, was also evident in the thermogram of the physical mixture - as if this DSC curve was the superposition of those of the components analyzed separately. The shape and area of the PHC melting peak was unaffected by the blending with Eudragit polymers, therefore, the drug maintained its original crystallinity in the physical mixture. Considering the freeze-dried system, the two characteristic endothermic peaks of PHC were also observed (not completely suppressed). However, the thermal profile of the freeze-dried product was slightly different from that obtained for the physical mixture, which was characterized by a sharp and definite endothermic effect in the region of the PHC melting endotherm. Some reduction of area, broadening and small downshift of the peak temperature of PHC melting endotherm (239 °C) was observed in the freeze-dried product. Since the freeze-dried product contains the same quantities of PHC and Eudragit polymers present in the physical mixture, the reduction of the drug melting peak is not a result of a dilution effect. That behavior may be explained by better dispersion of the PHC microcrystals in the Eudragit polymers, or could be ascribed to some drug-polymer interactions. Although the PHC endothermic peak was partially reduced, the presence of this peak indicates that a true dispersion was not achieved by this preparation method. Almost complete disappearance of the drug endothermic peak was found in the spray-dried preparation. The absence of the PHC fusion peak indicated the existence of interactions between the drug and Eudragit polymers in the solid state, and may be considered a strong indicator of the formation of real dispersions. The dispersion of PHC in matrix of Eudragit polymers S100 + RL100 (0.5 + 1.0) at 1: 2 weight ratios resulted in complete suppression of the drug fusion peak, suggesting possible solid solution of drug in polymer.

X-Ray Diffractometry

X-Ray diffraction studies were performed to examine the crystallinity and provide further evidence of dispersion formation. The analysis of the X-ray powder

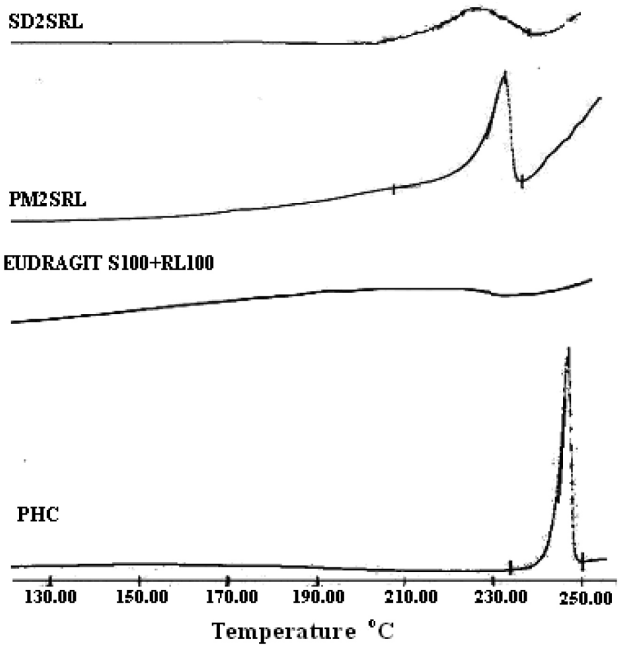

FIGURE 6 - Comparative DSC Thermograms of Pure drug, polymers, PM2SRL and SD2SRL.

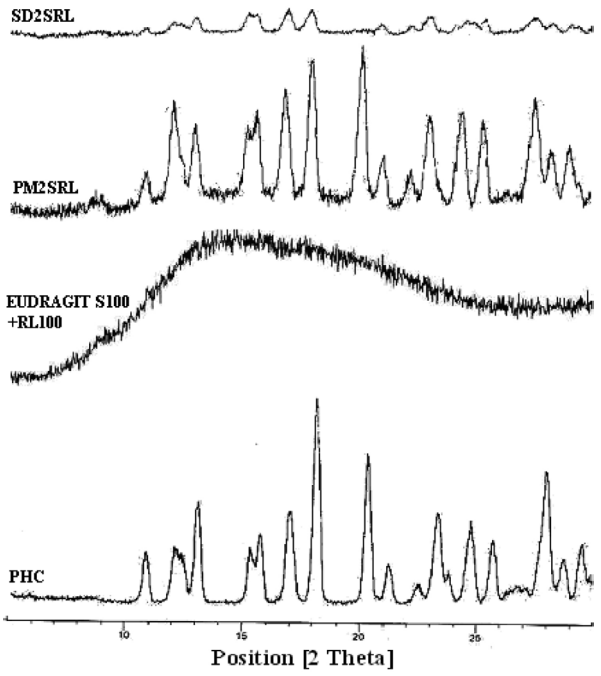

FIGURE 7 - Powder X-Ray Diffraction Patterns of Pure drug, polymers, PM2SRL and SD2SRL.

diffraction patterns of Eudragit solid dispersion systems is a powerful and very thoroughly assessed method for the characterization of solid dispersions in the solid state. Significantly different X-ray diffraction patterns are to be expected if solid dispersion is formed, since crystal structure will change. The X-ray diffraction patterns of PHC, Eudragit polymers and the corresponding solid dispersion systems are represented in Figure 7. The diffractograms of PHC exhibited a series of sharp and intense diffraction peaks, which are indicative of their crystallinity. The diffraction pattern of the physical mixture was found to correspond exactly to the simple sum of the raw materials' diffractograms, indicating the presence of PHC in the crystalline state. The freeze-dried systems showed, with respect to the diffraction patterns of the starting materials, the broadening and the disappearance or intensity diminution of some PHC diffraction peaks. These findings suggest the presence of a new solid phase with a lower degree of crystallinity, which could be created by the molecular interaction of the host Eudragit polymers and the guest PHC. The spray-dried compound presented a completely diffused diffraction pattern, with the disappearance of the characteristic peaks of PHC, reflecting the amorphous nature of this solid dispersion system. This is direct proof of the formation of a new solid phase, and can be considered a very probable indication of the dispersion formation between PHC and Eudragit S100 + RL100 in the solid state.

^{1}H NMR spectroscopy

FTNMR (1H-NMR) spectrum of PHC (Figure 8) showed chemical shift of 2.582 ppm (N $(CH_3)_2$) while in SD2SRL solid dispersion chemical shift was 2.697 to 2.745 ppm (N–$(CH_3)_2$). This supported the possible hydrogen bonding between drug and polymer. There seemed to be a possible interaction between functional groups of drug and polymer due to hydrogen bonding based on FT-IR and FT-NMR but this effect was considered to be superficial since the drug kept its chemical structure and potency. Nonetheless, issues such as effect of type and concentrations of polymer on matrix structure of solid dispersions were of great significance from the dissolution viewpoint. The physical state of the drug in the polymer matrices, as well as electrostatic interaction between drug and ammonium groups present in the polymer backbone, contributed to possible saturation of binding sites, consequently leading to modification of release profiles. However, the results again emphasized that a low drug-to-polymer ratio is not sufficient for preparing useful delivery systems since strong interactions between them do not allow a significant release of drug, either in acidic or mid alkaline dissolution media.

Scanning electron microscopy

The shape and surface morphology of PHC, Eudragit polymers and the solid dispersion systems are presented in

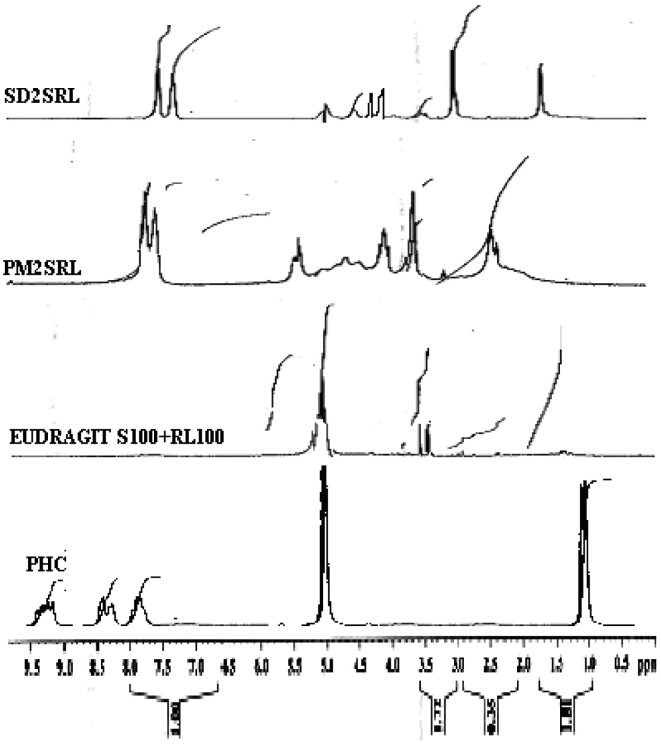

FIGURE 8 - ^{1}H-NMR Spectra of Pure drug, polymers, PM2SRL and SD2SRL.

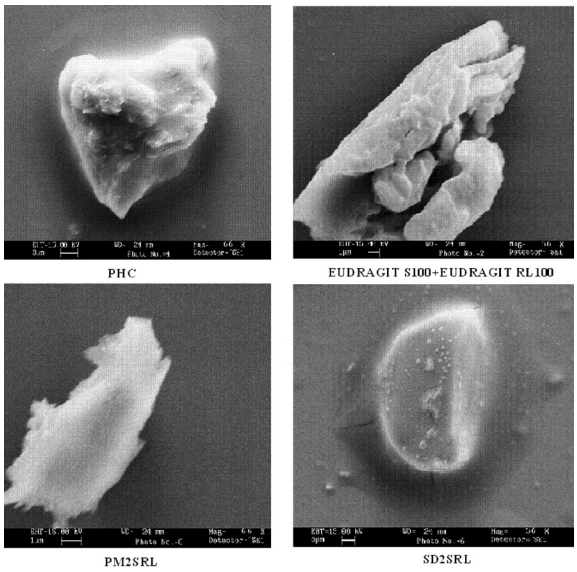

FIGURE 9 - SEM Images of Pure drug, polymers, PM2SRL and SD2SRL.

Figure 9. PHC and Eudragit polymers have quite different morphological characteristics. PHC appeared as irregular and three-dimensional crystals with smooth surfaces and homogeneous size. The combination of Eudragit S100 + RL100 (0.5 + 1.0), SEM analysis revealed the presence of rhomboidal shape crystals with different dimensions. The physically-mixed and the freeze-dried systems were characterized by the presence of unmodified particles of Eudragit polymers, which were mechanically covered by few crystals of drug. This phenomenon was more evident in the freeze-dried system, where it was more difficult to detect the features of the crystals of both components, appearing as only one type of granule. This behavior could be explained by the partial solubilization of Eudragit polymers, which improves the adhesion of PHC crystals to its surface. A remarkable change in the morphology of the materials was shown in the spray-dried system. The spray-drying technique yielded products of amorphous appearance, with the presence of particles, partially broken, of a typical spherical shape and a smooth surface with some fissures in the coating layer. The formation of aggregates of these spherical particles was also observed. In fact, the physical appearance, morphology and size of the spray-dried product were completely different from those of the mother products, and it was not possible to differentiate the distinctive crystals of PHC and Eudragit polymers. These observations, although scarcely conclusive, lead us to predict the existence of a single phase in the spray-dried preparation and, consequently, the formation of a dispersion system.

Stability studies

The stability data of extended release spray-dried solid dispersion capsules (SD2SRL capsules) are presented in Table 5. The results obtained in the stability test showed that the drug content and release rate of PHC from SD2SRL capsule formulation, stored at a temperature of 40 °C ± 1 °C and a relative humidity of 75%, was unchanged during three months of accelerating condition storage. It was indicated that solid dispersion incorporated in capsule formulation was stable, probably due to the fact that the stable excipients such as, Lactose, Explotab® and Aerosil® were employed in the preparation process of capsules; another reason was that the excipients contributed towards protecting the dispersion state of the drug.

CONCLUSION

The solubility of PHC was markedly decreased after formation of polymeric dispersions. RL100 had greater capacity to adsorb drug as compared to S100 in phosphate buffer pH 7.4. The analysis by FT-IR, FT-NMR suggested the possibility of hydrogen bonding, whereas the results of DSC, PXRD and SEM studies revealed the reduction in crystallinity of pure drug in solid dispersions associated with diluting effect of polymer. The results also revealed

TABLE V - Stability of extended release F4 (capsule containing 8% Explotab®) under accelerating conditions.

Time (month)	% drug * Content	% drug released*				
		1 h	2h	4h	8h	12h
0	98.82±0.005	37.58±0.005	42.43±0.005	56.06±0.002	83.02±0.006	96.87±0.005
1	90.36±0.009	30.09±0.002	38.20±0.007	52.04±0.009	81.21±0.009	90.53±0.004
2	89.55±0.008	28.28±0.008	33.99±0.006	47.83±0.008	78.50±0.003	89.12±0.002
3	87.97±0.007	28.58±0.009	33.09±0.004	46.33±0.004	76.69±0.001	89.03±0.003

* Study was performed on three replicates.

that the preparation conditions did not create significant polymorphic changes or amorphization of drug within the polymer network. The release of highly water-soluble PHC can not be controlled at lower polymer ratios, but was markedly sustained in spray-dried solid dispersions using RL100 at a higher ratio following better fit-to-zero order release kinetics. Eudragit polymers customize release profiles when used in combination, and could be successfully incorporated to formulate extended release capsules. The study provides better forecasting and understanding of the particulate systems to be incorporated to develop delivery systems.

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