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RESEARCH ARTICLE

Delayed Release Pharmaceutical Pellets having Duloxetine Hydrochloride Containing Core and Acid Resistant Acrylic Polymer Based Outer Layer Coat.

***Shahana Sharmin[1], Ishtiaq Ahmed[2]**

[1]Department of Pharmacy, BRAC University, Dhaka-1212, Bangladesh

[2]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh.

ABSTRACT

The aim of this investigation was to develop a delayed release pellets dosage form of duloxetine hydrochloride. Drug loaded nuclei was prepared using powder-layering technique in a conventional coating pan. The nuclei was coated with an acid resistant acrylic polymer (Eudragit L30 D55) in a wurster coater to different thickness equivalent to theoretical polymer load 25%, 30%, 35% and 40% (w/w) on dry basis. The *in vitro* dissolution studies were conducted in 0.1 N HCl (pH≈1.1) for 2 hours followed by phosphate buffer (pH≈6.8) for 1 hour with USP dissolution tester (Type-II). Enteric coated pellets with polymer load 25% and 30% failed to provide required acid resistant to the pellets but very insignificant amount of drug was leached from the coated pellets in acid phase with polymer load 35% and 40% in the acidic phase whereas almost the whole amount of drug was released in the buffer phase. The results generated in this study showed that proper selection of polymeric materials based on their physicochemical properties as well as polymer load is important in designing delayed release pellets dosage form with acceptable dissolution profile.

KEY WORDS: Eudragit L30 D 55, Duloxetine hydrochloride, enteric coating, pellets, powder layering.

INTRODUCTION:

An enteric coat is usually a special film coat designed to resist gastric fluids and to disrupt or dissolve in the small intestine. The enteric coat is used to protect a drug from degrading in the stomach or to minimize gastric distress caused by some drugs. Enteric-coated tablets must empty from the stomach before drug absorption can begin. The rate of appearance of drug in the blood after giving an enteric-coated tablet is therefore a function of gastric emptying. Differences in gastric emptying from one patient to another or in the same patient from one administration to another contribute to the large variability in drug absorption commonly found with this dosage form (Gibaldi, 1991). The enteric-coated tablet dosage form has been the object of well-deserved criticism in recent years. Many reports of clinical failure because of erratic and incomplete absorption can be found in the literature. Far fewer problems are found with newer products, but variability remains a substantial concern. One approach to minimize that appears to minimize variability is the use of individually enteric-coated granules (Green, 1966). These granules may be compressed into rapidly disintegrating tablets or administered in capsules. After disintegration of the dosage form in the stomach, gradual but continual emptying of the granules into the intestine is anticipated (Gibaldi, 1991). A theoretical analysis of blood level profiles resulting from enteric-coated granules has been published (Story, 1977). It concludes that: Enteric-coated tablets may require approximately 0.5 to more than 8 hours. to travel from the stomach to the duodenum but enteric-coated pellets are dispersed in the stomach and pass through the pyloric sphincter after a mean residence time in the stomach that is similar to a suspension dosage form. Investigators in Sweden have compared the absorption of aspirin from two different enteric-coated dosage forms, tablets and granules, in healthy subjects under fasting and nonfasting conditions. Under fasting conditions, the absorption of aspirin from both preparations was complete. When the dosage forms were taken after a meal, the enteric-coated tablets gave much lower concentrations of salicylate in plasma than under fasting conditions and absorption was incomplete in some subjects. Neither the rate nor extent of absorption from the enteric-coated granules was affected by food (Bogentoft, 1978). Duloxetine hydrochloride is pharmacologically classed as a selective serotonin and norepinephrine reuptake inhibitor (SSNRI). Chemically it is (+)-(S)-N-methyl-γ-(1-napthyloxy)-2-triophenepropylamine hydrochloride. Duloxetine hydrochloride is white to slightly brownish white solid which is slightly soluble in water (Martindale, 2002). Pellets can be prepared using several techniques. The compaction and drug-layering techniques are the most widely used among all techniques. The layering process involves successive layering of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds (Jackson *et al.* 1989). In powder layering, a binder solution is first sprayed on to the non

* ***Corresponding author:*** Shahana Sharmin **/** ***Email:*** sharmin@bracuniversity.ac.bd

pareil seeds, followed by addition of powder (Ghebre-Sellassie 1985 and 1989, Niskanen 1990, Mohammed *et al.* 1991, Nastruzzi *et al.* 2000). Eudragit L 30 D-55 is supplied commercially as a milky-white colored dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate where polymer dry weight content is 30%. The copolymer corresponds to USP methacrylic acid copolymer, Type C. The ratio of ester groups to free carboxyl groups is 1:1. Eudragit L 30 D-55 films dissolve above pH 5.5 forming salts with alkalis, thus resulting coatings which are insoluble in gastric media, but soluble in the alkaline media of small intestine (Kibbe, 2000). In this study Duloxetine hydrochloride was taken to develop delayed release pellets dosage form using powder-layering technique followed by film coating with aqueous acrylic polymer dispersion to resist the release of drug the acidic environment of the stomach so that degradation of drug can be minimized.

MATERIALS AND METHODS:

Duloxetine Hydrochloride (Shodhana Lab Ltd, India), Disodium Hydrogen Phosphate (Merck, Germany), Mannitol (Getec, Germany), HPMC 5 cps (Cornileus Pharmaceuticals Pvt. Ltd., India), Sodium Hydroxide Pellets (Merck, Germany), Non Pareil Seeds (NPS) (Eskayef BD Ltd, Bangladesh), PEG-6000 (Clariant, Germany), Titanium Dioxide, Eudragit L30 D 55 (Rohm Pharma, Germany), Talc (Asian Mineral, Thailand), Triethyl Citrate (Clariant, Germany). Other materials used in this study were of reagent grade.

PREPARATION OF DULOXETINE HYDROCHLORIDE ENTERIC COATED PELLETS:

Duloxetine hydrochloride powder, mannitol and disodium hydrogen phosphate were blended and sieved through 250 micron screen mesh to prepare dusting powder. disodium hydrogen phosphate and sodium hydroxide pellets were dissolved in the purified water. HPMC 5cps was then dispersed using a stirrer to prepare the binding solution. NPS (710 micron-1.00 mm) was taken in the conventional coating pan and dusting powder was applied on to it. The pan was rotated at 40 rpm. Simultaneously binding solution was sprayed onto the NPS. After completion of drug loading the nuclei was dried in an oven at 600C for 5 hours. The dried nuclei were sieved through 1.18 mm screen mesh followed by 850 micron screen mesh to get desired size of nuclei (850 micron-1.18 mm) and to discard under and over sized nuclei. Seal coating suspension was prepared containing HPMC 5 cps, PEG-6000, titanium dioxide, sodium hydroxide pellets and purified water with the use of a Silverson Stirrer (UK). Dried uncoated nuclei were taken in the fluid bed coater (Umang Pharmatech Ltd, India) and the seal coating suspension was sprayed on to it. The seal coated pellets were dried at 60^0C for 3 hours. Dried seal coated pellets were sieved through 1.18 mm and 850 micron mesh to get 850 micron-1.18 mm size seal coated pellets and to discard under and over sized nuclei. Enteric coating suspension was prepared using Eudragit L30 D55 (Ammonio methacrylate copolymer dispersion, Type C), Talc, Titanium dioxide, triethyl citrate, sodium hydroxide pellets and purified water with the use of a Silverson Stirrer (UK). The seal coated pellets were coated lot wise using labcoater (Umang Pharmatech, India) with Eudragit L30 D55 containing coating suspension to different thickness equivalent to theoretical polymer load 25%, 30%, 35% and 40% w/w on dry basis. The enteric coated pellets were dried in the fluid bed coater at 60^0C for 5 hours and then sieved through 1.40 mm and 850 micron mesh to get 850 micron – 1.40 mm size enteric coated pellets and to discard the under and over sized pellets. In this way all lots of pellets were coated according to the formula for F-1 to F-4 (Table 2). The composition of nuclei, seal coated pellets and enteric-coated pellets are shown in Table 1 and Table 2. Machine parameters during fluid bed coating are shown in Table 3.

Nuclei	Quantity	Seal Coating	Quantity
Duloxetine hydrochloride	256.246	Nuclei	800.000
Disodium.hydrogen phosphate	5.531	HPMC-5 cps	50.428
HPMC-5cps (Methocel E-5)	38.305	PEG-6000	6.824
Mannitol	21.561	Sodium Hydroxide Pellets	0.060
Sodium hydroxide pellets	0.452	Titanium dioxide	10.484
NPS (16/22)	677.905	Weight of seal coated pellets	836.000
Weight of nuclei	920.000	Potency of seal coated nuclei (%)	23.015
Potency of the nuclei (%)	25.305		

Table No. 1: Composition of nuclei and seal coated pellets (Weights are expressed in g)

Materials	Formulation codes			
	F-1	F-2	F-3	F-4
Seal Coated Pellets	200.000	200.000	200.000	200.000
Sodium Hydroxide Pellets	0.590	0.708	0.826	0.944
Titanium dioxide	2.520	3.024	3.528	4.032
*Methacrylic acid copolymer dispersion (Type C)	166.667	200.000	233.333	266.667
Purified Talc	1.889	2.267	2.645	3.023
Triethyl citrate	8.062	9.675	11.287	12.900
Weight of enteric-coated pellets (12/20)	237.000	249.000	260.000	272.000
Potency of enteric coated pellets (%)	17.521	16.725	15.756	15.230

Table No. 2: Codes and formulation of Duloxetine enteric coated pellets (Weights are expressed in g)

Parameters	Fluid bed coater (Wurster, Umang Pharmatech Ltd.)	
	Seal coating	Enteric coating
Batch Size	800 g	200 g
Inlet air temperature	40-45 ^{0}C	40-45 ^{0}C
Outlet air temperature	30-35 ^{0}C	30-35 ^{0}C
Product temperature	37-40 ^{0}C	37-40 ^{0}C
Chamber Humidity	55%-60%	55%-60%
Air flow	90 m^3/hour	90 m^3/hour
Spraying pressure	1.20 bar	1.20 bar
Spraying rate	2.0 g/minutes	3.0 g/minutes
Secondary drying	60^{0}C for 180 minutes	60^{0}C for 300 minutes

Table No. 3: Machine parameters during fluid bed coating

PHYSICAL CHARACTERIZATION OF COATED PELLETS:

Friability of nuclei was tested with friabilator (Erweka, Germany) at 25 rpm for 10 minutes along with glass spheres of 5 µm diameter. Moisture content of coated pellets was determined by loss on drying (LOD) of the pellet under vaccum at 60^{0}C for 4 hours. Bulk density of coated pellets was measured using a 100 ml graduated cylinder.

IN VITRO DISSOLUTION STUDY:

The dissolution of duloxetine hydrochloride enteric coated pellets was studied by dissolution tester (Erweka ,Germany) using USP apparatus II (Paddle method). An appropriate amount of duloxetine Enteric coated pellets containing 20 mg of duloxetine in total was used in 900 ml of dissolution medium (0.1 N hydrochloric acid) at 37^0C and 100 rpm for 2 hours. After 1 hour 25 ml sample was withdrawn from each vessel and replaced with fresh medium so that the volume remain constant. At the end of 2^{nd} hour 25 ml sample was withdrawn from each vessel. Drug content of the sample solution i.e. the quantity of drug release was determined by high-performance liquid chromatography (HPLC) method. Then by replacing the acid media after 2^{nd} hour, 900 ml dissolution media (KH_2PO_4 buffer, pH 6.8) was added in each vessel. Then again the machine was operated at a rotation of 100 rpm at 37^0C for next 1 hour. After 1 hour 25 ml sample was withdrawn from each vessel. After appropriate dilution, the drug content of the collected samples i.e. the quantity of the drug release was determined by HPLC method. The HPLC system consisted of a pump (Waters, USA), an auto sampler (Waters, USA), and a UV detector (Waters,USA). The reverse-phase column (C18) (Xterra, 5µm, 4.6 mm x 25 cm, Waters) was used at ambient temperature. The mobile phase consisted of acetonitrile (40%) and the flow rate was 1 ml/min. The injection volume was 20 µl and the signal was observed at 218 nm.

RESULTS AND DISCUSSION:

The appearance of the nuclei (drug-loaded pellets) was found white to off-white. The moisture content was 0.67%. The friability of nuclei was 0.29%. The surface of coated pellets was found smooth. Bulk density of the pellets was found 0.75-0.79 g/cm^3, which is suitable for filling pellets in empty hard gelatin capsule shell. The pellets size distribution before coating was 850 micron-1.18 mm but after seal coating and enteric coating it was slightly increased (850 micron – 1.40 mm). A narrow size distribution of pellets is a prerequisite for acceptable film coating because it affects both the release rate of the drug and the performance of the coating. So, the physical characteristics of the nuclei and coated pellets were satisfactory. The dissolution profiles of drug release from Eudragit L30 D55 coated pellets are presented in Figure 1, Figure 2 and Figure 3.

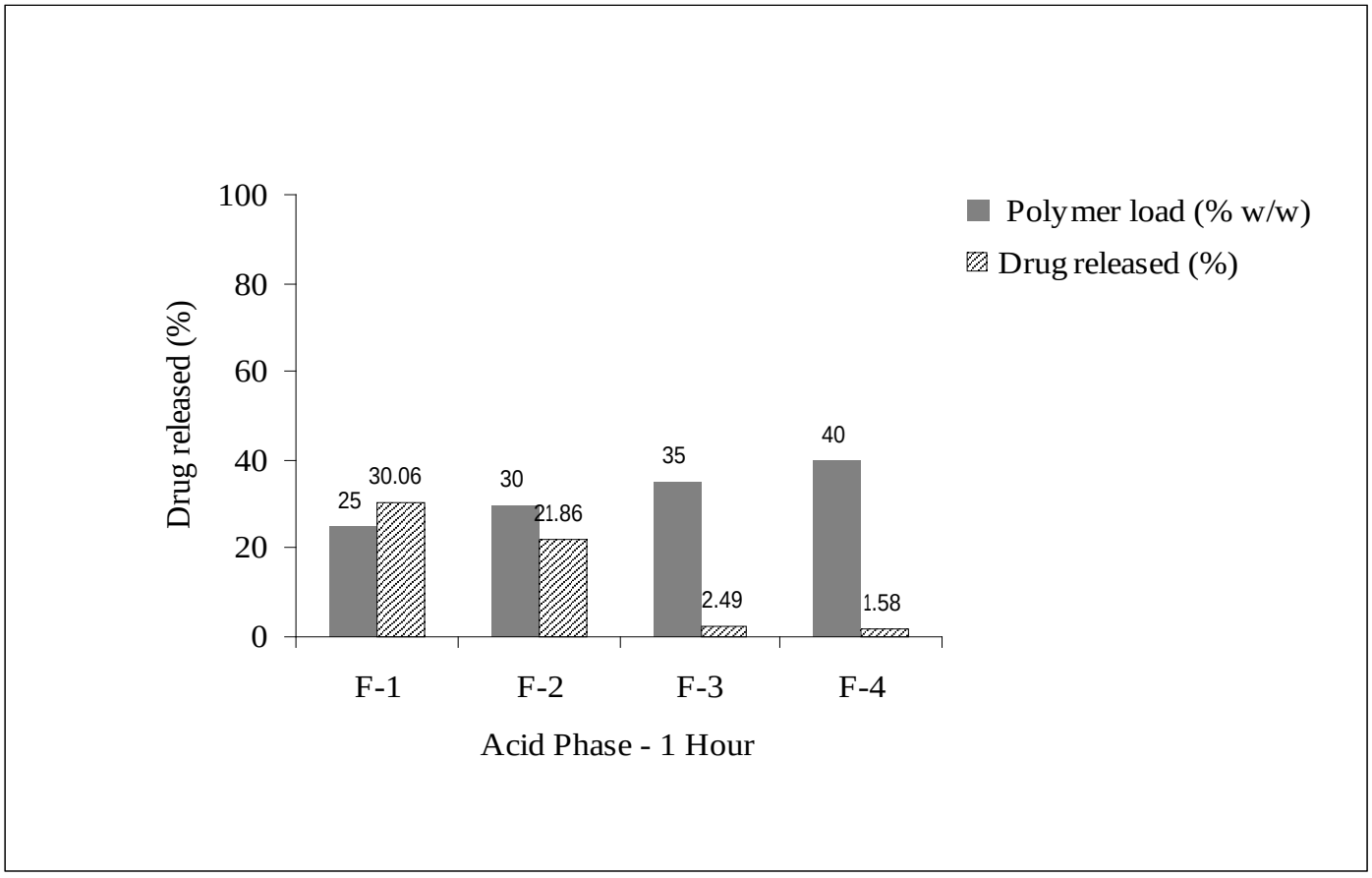

Figure No. 1: Drug released from Duloxetine hydrochloride enteric-coated pellets at different coating loads (Acid Phase-1 hour)

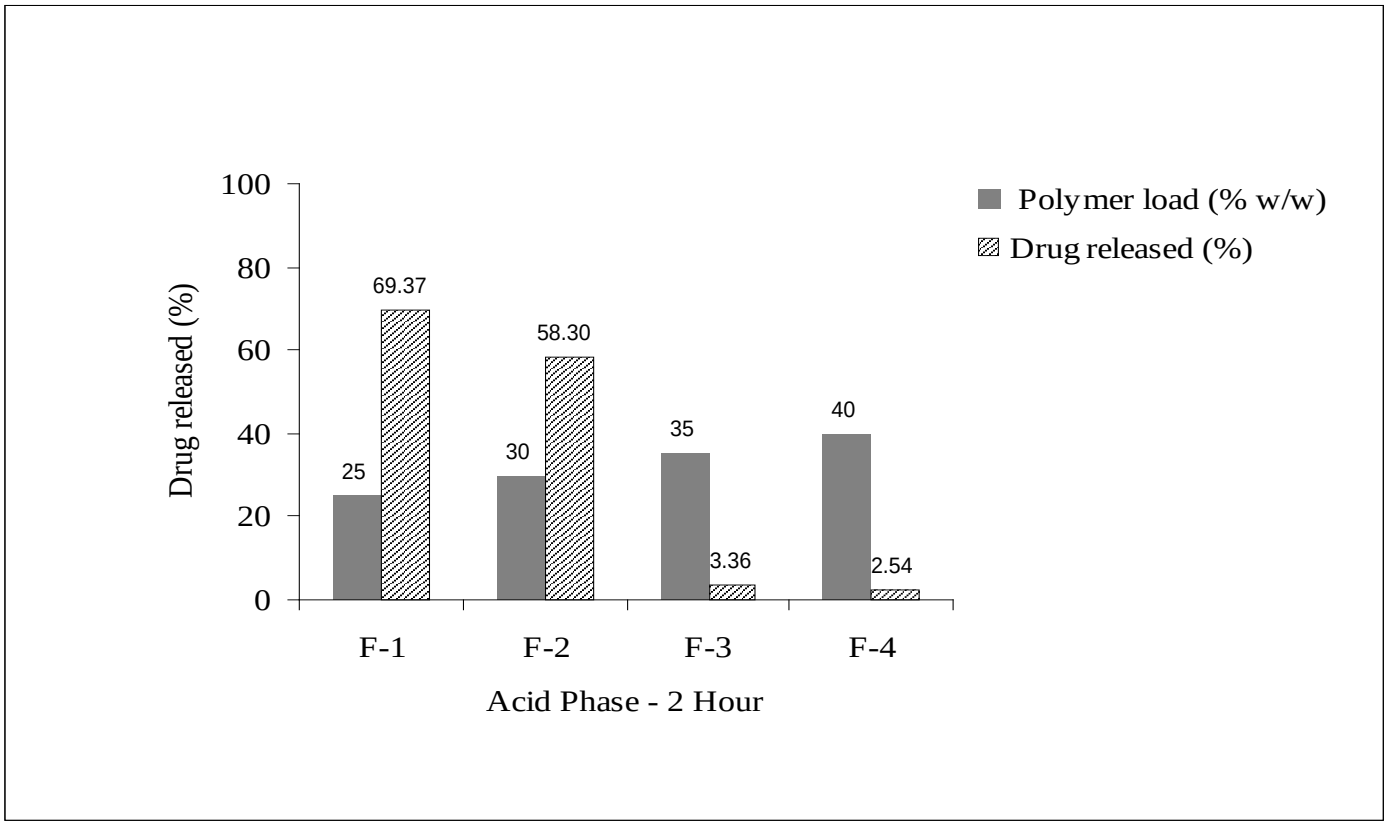

Figure No. 2: Drug released from Duloxetine hydrochloride enteric-coated pellets at different coating loads (Acid Phase-2 hour)

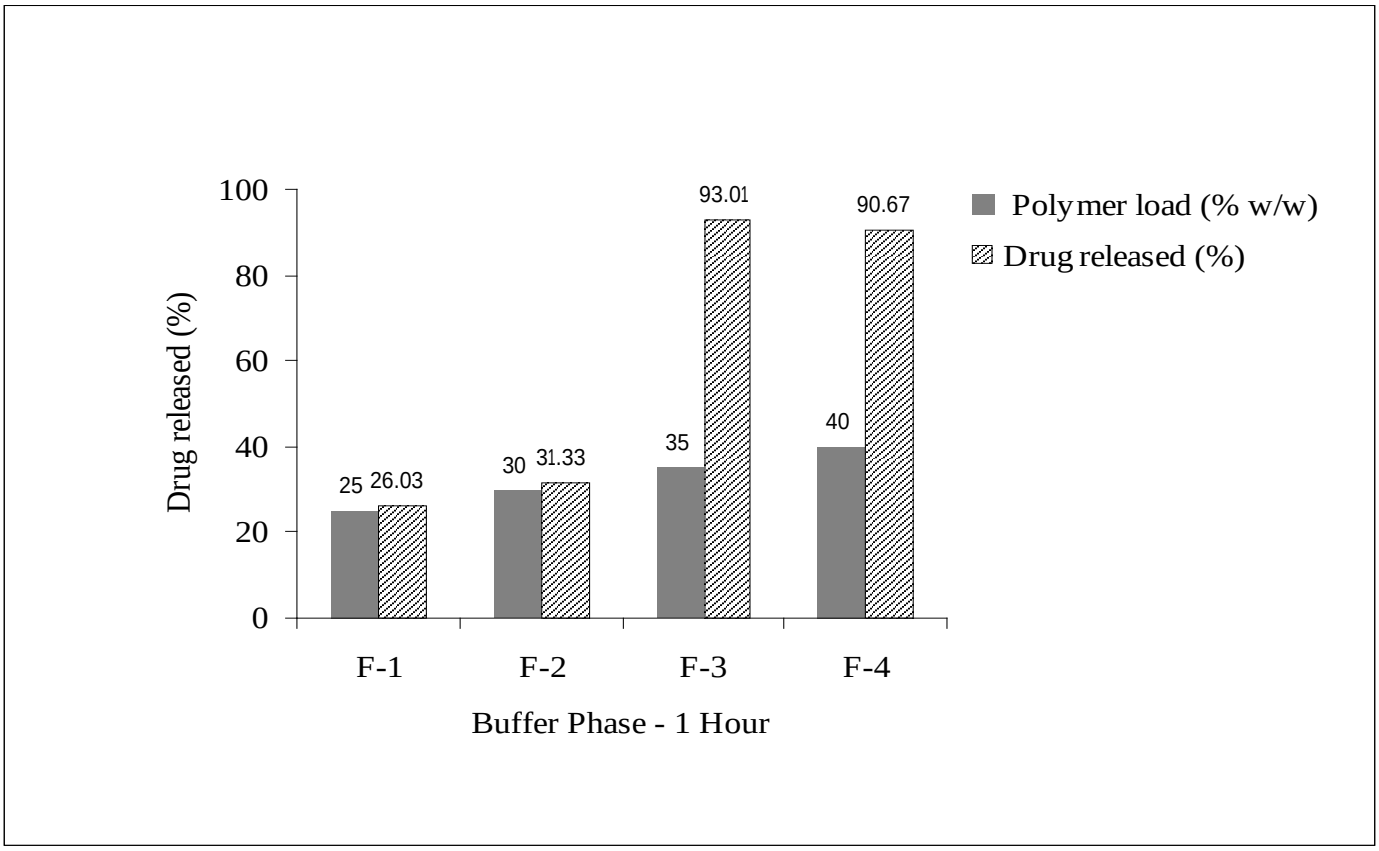

Figure No. 3: Drug released from Duloxetine hydrochloride enteric-coated pellets at different coating loads (Buffer Phase-1 hour)

Uncoated pellets disintegrated in dissolution medium and released 100% drug within 1 hour. The dissolution data showed that 30.06% and 21.86% duloxetine was released in acid phase after 1 hour from the coated pellets of F-1 and F-2 respectively whereas only 2.49% and 1.58% drug was released in acid phase after 1 hour from the coated pellets of F-3 and F-4 respectively. After 2nd hour cumulative release of drug from coated pellets was 69.37%, 58.30%, 3.36% and 2.54% for F-1, F-2, F-3 and F-4 respectively. On the other hand, 26.03%, 31.33%, 93.01% and 90.67% drug was released in buffer phase (pH≈6.8) after 1 hour from the coated pellets of F-1, F-2, F-3 and F-4 respectively. In order to perform adequately, an enteric-coated dosage form should not allow significant release of drug in the stomach, yet must provide rapid dissolution of the polymer and complete release of the active material once in the environment of intestine. From this viewpoint coated pellets of F-3 and F-4 showed adequate performance to be regarded as successful delayed release multiparticulate dosage form of duloxetine hydrochloride. It was also observed that the enteric coating polymer (Eudragit L30 D55) in the hydrated state in the acidic environment would be permeable to some degree to the active material. Formulation measures such as coating load played an important part in keeping this permeability within acceptable limits. Variation of this parameter might play such a powerful role that there was a temptation to place almost total reliance upon it in the development of an enteric-coated dosage form.

CONCLUSION:

Duloxetine hydrochloride loaded pellets were prepared by powder-layering technology. Acid resistant coating with acrylic polymer was done using fluid bed coater at different coating loads and the *in vitro* release of drug was investigated. The release of drug was found to be a function of polymer load. The results indicated that it is possible to prevent the release of drug in the upper GI tract where the environment is acidic and release the drug in the intestinal region, by developing of multiparticulate system coated with suitable pH dependent polymer.

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