



Formulation Optimization of Sustained Release Pellets of Itopride Hydrochloride using Different Polymers

*Pankaj Chhipa¹, Anil M. Pethe¹, Satish Upadhyay², Avinash Tekade³

¹Asst. Professor, Pharmaceutics, School of Pharmacy & Technology Management, NMIMS University, Mumbai (Shirpur Campus). Mumbai- Agra Highway, Savalda, Shirpur. 425405. MH.

²Director F&D, Vergo Pharma, Goa.

³Asst. Professor, Pharmaceutics, R.C. Patel College of Pharmacy, Shirpur. 425205. MH.

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ABSTRACT

Purpose: The purpose of this study was to formulate sustained release pellets formulation and to investigate release profiles by using different polymers for the coating of pellets. **Methods:** The Itopride hydrochloride loaded pellets were coated with different polymers (ethyl cellulose and kollicoat SR 30 D) at different coating levels. Drug release from pellets as well as physical parameters such as size distribution, bulk density and tapped density etc. were evaluated. **Results:** Drug release from the pellets strongly depends on type of polymers and coating variables such as coating levels etc. The various polymers show different release mechanism. The sustained-release matrix pellets with good physical, mechanical and technological properties were obtained with a ethylcellulose polymer of coating level of 10 % (w/w). A comparative kinetic study of the present pellets and commercial Ganaton OD capsules was established. The value for the similarity factor ($f = 77.6$) suggested that the dissolution profile of the present two sustained-release oral dosage forms are similar. **Conclusion :** The type of polymer coating strongly affects the film microstructure and thus, the release mechanism and rate from pellets coated with different polymer.

Keywords: Pellets, Ethyl cellulose, Kollicoat SR 30D, Coating Level, Release Kinetic

INTRODUCTION

Itopride hydrochloride, an oral prokinetic agent used in the treatment of gastric motility disorders, is a benzamide derivative, is stable in acid and is designed for oral use. It is more readily absorbed from gastrointestinal tract. Food does not interfere with absorption, perhaps because of more complete absorption. The half-life of itopride is 5-6 hr. Most of itopride is excreted through in a metabolite form in the urine. Itopride act by inhibition of dopamine receptors (D_2) thus increasing the acetylcholine secretion and by preventing the degradation of acetylcholine from acetylcholine esterase. Thus frequent administration and to minimize the peak-to-trough oscillation of the blood concentration, sustained release formulations were developed. [1, 2, 3]

Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time. Development of a successful sustained release formulation depends upon a number of factors: from the selection of potential drug candidates to the optimization of process variables involved in the preparation. There have been significant advances in the area of sustained release with the introduction of new and better polymers. [4, 5, 6, 7]

The drug release from coated pellets depends on many process and formulation variables, including polymer type, coating levels, plasti-

zation, curing treatment, and properties of the core. In this respect, a decrease Propranolol HCl release from ethyl cellulose and Eudragit coated pellets upon storage for 4 months at room temperature was reported. In contrast, Itopride pellets coated with ethyl cellulose showed an decrease in release from pellets. [8] Curing the pellets resulted in release profiles, which did not change during storage for 3 years and also had a smooth, continuous surface and a dense film structure after curing. [9,10,11]

The objective of this study was to evaluate the influence of polymers and polymer coating level conditions on the drug release from pellets coated with different polymers (ethyl cellulose and kollicoat SR 30 D). The polymers were applied for different coating levels to achieve the sustained drug release [12, 13, 14, 15]

Materials and Methods

Materials

Itopride hydrochloride (particle size: 100-200 μ m) was obtained from Cadila Healthcare ltd (Ankleshwar, India). Hydroxy propyl cellulose and Celphere CP 203 (microcrystalline cellulose spheres) were obtained from Signet Chemical Corporation Pvt Ltd (Mumbai, India). Ethyl Cellulose (EC, Ethocel 7 cps, Dow Chemical Company, Midland, MI, USA), Kollicoat SR 30 D was obtained from BASF Pharma, (Germany), Triethylcitrate (TEC) was obtained from Merck (Germany) while isopropyl alcohol (IPA) was obtained from Alkem research center (Mumbai, India). Other ingredients such as lubricants and glidants used to prepare the tablet were of standard pharmacological grade.

Methods

Preparation of Drug-Containing Pellets

Itopride (ITP) loaded pellets were prepared by layering a drug-binder

*Corresponding author.

Tel.: + 91-9975243375

Telefax: +91-

E-mail: sendpankaj@gmail.com, pkchgwl112@yahoo.co.in

anilpethe@gmail.com, satishupadh01@rediffmail.com,

avi.tekade@yahoo.com

solution (10 % w/w) on to celphere CP 203 beads using a fluidized bed coater (Umang coater, Wurster insert, Umang Ltd, Mumbai, India). Dispersion of ITP and polyvinyl pyrrolidone (PVP K - 30) was sprayed using the bottom spray mode. Layered beads were dried at 40 °C for 5 – 10 min. The detailed composition of drug layering and polymer coating is given in Table 1 and the process parameter of the drug layering processes and coating are given in Table 2.^[16]

Coating of the drug layered Pellets

The drug layered pellets were coated in a fluidized bed coater using the bottom spray mode (Umang coater, Wurster insert, Umang Ltd, Mumbai, India) with a plasticized non aqueous solution of polymer (ethyl cellulose EC 7 cps) and polymer (kollicoat SR 30 D) at different coating levels each respectively. The solution was plasticized with TEC (10 wt%, based on the mass of the polymer). The non aqueous solvents contain the Iso-propyl alcohol (IPA). The polymer content of the plasticized dispersion was then adjusted to 25 wt %. The final coating solution was sprayed onto a drug-loaded celphere beads to achieve weight gain of 10 %. The process parameters for the coating step are given in Table 2.^[16]

Table 1: Composition of Drug Loading and Polymer Coating

Ingredients.	Batch No	I	II	III	IV	V
Drug Layering						
Sugar Sphere (20-25 mesh) (g)		200	200	200	200	200
ITP (g)		380.5	380.5	380.5	380.5	380.5
PVP K-30 (g)		75.0	75.0	75.0	75.0	75.0
Talc (g)		8.0	8.0	8.0	8.0	8.0
Seal Coating						
HPMC E5 (g)		30.5	30.5	30.5	30.5	30.5
Polymer Coating						
Ethyl Cellulose 7 cps (g)		20.0	20.0	20.0	20.0	-
Kollicoat SR 30 D		-	-	-	-	33.54
TEC (g)		1.5	1.5	1.5	1.5	1.5
Talc (g)		qs	qs	qs	qs	qs

Table 2: Process Parameter of Dug Layering and Polymer Coating

Process Parameter	Drug Layering	Polymer Coating
Inlet temperature	42°C	42°C
Product temperature	35°C	38°C
Exhaust temperature	35°C	35°C
Atomizing air pressure	1.5 Kg/cm ²	1.5 Kg/cm ²
Spray Rate	2-15 ml/min	2-15 ml/min
Blower RPM	1850 rpm	1850 rpm

Particle Morphology Study

The particle morphology was analyzed by using Motic Digital Image Recorder (Motic 2000, Made in China). At various stages of formulation images were drawn to study the shape & size characteristics of pellets.^[17]

Determination of size distribution of pellets

Pellet size distribution was determined using the sieve analysis method. Approximately 50 g of coated pellets were placed on the top sieve in the sieve shaker (AS200 digit model, Retsch, Germany) equipped with 14, 16, 18, 25, 35, 45 and 60-mesh US standard sieves and were shaken for 10 min. Finally, the mass of each fraction was measured.^[17]

Measurement of Itopride hydrochloride Content in Pellets

About 400 mg of 14/20 mesh ITP pellets were transferred to a 50.0 ml volumetric flask. Then, 30 ml of 0.01 N hydrochloric acid was added to

the flask. The mixture was stirred for 30 min, with 0.01 N hydrochloric acid added to maintain volume, and mixed. The mixture was filtered, and the filtrate was collected. The absorbance of the filtrate was determined by spectrophotometer at 258 nm.^[17]

Bulk Density and Friability

A weighed amount (50 g) was introduced into a 100 ml graduated cylinder. The cylinder was fixed on the Bulk Density Apparatus and the timber knob is set (regulator) for 100 tapings & volume occupied by the pellets noted. After tapping, the final volume was noted. Bulk density is calculated by using formula.^[17]

Bulk Density = Mass of pellets / Bulk volume, Tapped Density = Mass of pellets/ Final volume

Friability of the pellet formulations was evaluated over 10 g of samples in Roche Friabilator (Hoffman-la Roche, Basel) at 25 rpm for 4 minutes. Prior to and following the test, the weights of the formulations were accurately recorded and the friability ratios were calculated with below equation where w1 is the initial weight and w2 is the final weight of the formulation. The results are expressed in terms of the percentage of weight lost during the process.^[18]

$$F = \frac{W_1 - W_2}{W_1} * 100$$

Drug Release Study

The U.S. Pharmacopeia (USP) 24, apparatus 2 (Vankel VK6010; Cary, NC, USA) was used to investigate the dissolution properties of coated pellets over a 16-hr period. The dissolution medium (500mL) was 0.1N hydrochloric acid solution, and was maintained at 37± 0.2 °C and agitated at a paddle speed of 100 rpm. Coated pellets containing 150 mg ITP HCl were introduced into the dissolution medium, and 5-mL samples were with drawn by an autosampler (Vankel VK 8000; Cary, NC, USA) at 2-, 4-, 8-, 12-, 16-, 20-, 24-hr time points. Sample concentrations were determined by UV spectroscopy (Model Shimadzu UV 1700, Japan) at 258 nm wavelength. Dissolution tests were performed in triplicate.^[19]

Similarity factor

The dissolution data was subjected for determining f 2 values by using the formula, $f_2 = 50 \times \log \{ 1 + (1/n)E \delta = 1n (Rt - Tt) 2 \} - 0.5 \times 100$.

Release Kinetic study of Pellet

The rate and the mechanism of release of amoxicillin trihydrate from the prepared matrix tablets were analyzed by fitting the dissolution data^[20, 21, 22]. The various models such as Zero order, first order, Higuchi Kinetic and Korsmeyer – Peppas were studied for release form Itopride hydrochloride pellets (Table 4).^[23, 24, 25]

Results and Discussion

An Umang coater was an appropriate machine for powder layering and polymer coating. Keeping the balance between the feeding rate of the layering powder and the binder solution is very important for powder coating using a Umang Coater. The feeding rate of powder and binder was optimized in order to prevent agglomeration and powder loss.

Morphology of Several Coating Process Pellets

Micro-scopic evaluation of pellets was performed. Figure 1a, 1b and 1c shows optical photographs of drug loaded pellets, seal coated and polymer coated pellets respectively. According to visual observations, the surfaces of pellets are all smooth, indicating that the bal-

ance of powder feeding and the binder addition were in good conditions in this study.



Figure 1: a) Drug loaded, b) seal coated, c) polymer coated ITP Pellet Morphology

Particle Size Distribution

Particle Size distribution of the coated pellets (formulation) was determined by the sieve analysis method. Approximately 77 % (m/m) of the pellets were retained on 20 mesh sieve and in size range of 710–1000 μm, and about 23 % (m/m) were retained on 25 mesh sieve and in size range between 1000 to 1410μm, all pellets were passed through 16 and 18 mesh sieve.

Table 3 shows the various physical properties of pellets such as sieve analysis, bulk density, tapped density and friability. All physical parameters are within limit.

Table 3: Physical Properties of Itopride Hydrochloride Pellets

Physical Properties

Sieve Analysis

Percentage Wiegth retained on

Sieve 16	-
Sieve 20	77 .0
Sieve 24	20.0
Sieve 28	3.0
Sieve 40	-
Sieve 60	-

Percentage sieve fraction on 18/25 mesh pellet 77.0

Bulk Density (g/ml, ±SD) 0.83 (0.001)

Tapped density (g/ml, ±SD) 0.86 (0.001)

Percent Friability 0.3

Drug release

The release profiles of itopride hydrochloride from pellet coated with ethyl cellulose and kollicoat SR 30 D are shown in Figure 3 respectively. The entire pellet disintegrates during the dissolution test, and no gel like structure remained, indicating complete dissolution at different coating levels. As the coating level increased, the drug release decreased. The reduction in the release rate with increasing coating level may be due to the increased diffusional path length with increase in the thickness of the coat (Figure 3).

The effect of coating level on release of itopride hydrochloride from pellets coated with ethyl cellulose and kollicoat SR 30 D is shown in Figure 3 respectively. Uncoated itopride hydrochloride pellets disintegrate rapidly in dissolution medium and release their drug content within 10 min. For instant at higher coating level such as 20 % coating, only about 10% of itopride hydrochloride was released in 2 hr, whereas those pellets coated to weight increases of 15%, 10% and 5% released 20%, 35% and 80% of drug, respectively. For Itopride hydrochloride pellets coated with 10% kollicoat SR 30 D, about 20% drug was released in 2 hr. As the coating levels increases pellets shows a biphasic release pattern, initially a low slope was observed (lag time) and a steep slope as the coating level increases. It is observed from the results that the coating levels had a major effect on the ultimate rate of drug release and the duration of the release. The entire pellet remained intact during the dissolution test, indicating

that the ethyl cellulose coating layer controlled the drug release. These results are in agreement with the finding of Ghebre – Shellassie et al. and porter, who showed that the release of drug (Diphenhydramine Hydrochloride and Chlorpheniramine Maleate) from pellets coated with surelease was related to weight of coating polymer. Generally, in dosage forms that have a water – insoluble polymer as the rate – controlling membrane, since diffusion through the membrane controls the overall release rate of the drug, the layer properties and geometry, such as coating porosity, internal structure (tortuosity), and coating thickness, may be critical factors in determining the release rate of drug .The dissolution data was subjected for determining f 2 values by using the formula, $f_2 = 50 \times \log \left\{ 1 + \frac{1}{n} \right\} E \delta = 1n (Rt - Tt) 2 \} - 0.5 \times 100$.

Similarity factor (f2) for EC 5%, EC 10%, EC 15 %, EC 20% and KL 10 % was found to be 27.39, 77.56, 46.76, 29.32 and 32.31 respectively.

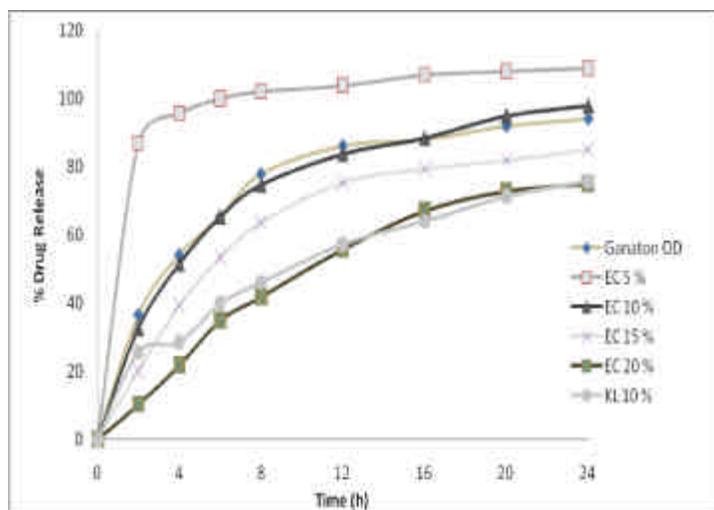


Figure 3: Dissolution profile of ITP with different polymers and coating levels

Release Kinetic Study

The release curve of the drug showed poor fit for zero order kinetics (Table 4, Figure 4a, 4b, 4c and figure 5a, 5b,5c). The regression coefficient values ($r^2 = 0.718$) increased gradually with increasing ethyl cellulose content in coating. It implies the release may follow zero order kinetics at higher amount of ethyl cellulose. On the other hand, the delivery system showed better linearity for first order kinetic ($r^2 = 0.9856$) then Higuchi release kinetics ($r^2 = 0.9567$). It indicates that drug release was a diffusion process. Equation 1, the zero order Equation; and Equation 2 Higuchi's square root equation; and equation 3 Korsmeyer and Peppas equation.

$$Mt/M8 = K_0t \dots \dots \dots (1)$$

$$Mt/M8 = KHt^{1/2} \dots \dots \dots (2)$$

$$Mt/M8 = Ktn \dots \dots \dots (3)$$

Where Mt/M8 is the fraction of drug released at any time t and K_0, K_H, K are release rate constants for Equation 1, 2, and 3, respectively. In equation 1, n is the diffusional exponent indicative of drug release. The values of K, KH, Ko, n, t50% (time required for 50% of drug release), and r (correlation coefficient) were determined.

Table 4: Correlation Coefficient (r²) value of optimized formulation and marketed formulation

Parameter	First Order	Zero Order	Higuchi Plot	Korsmeyer-Peppas Plot
r ² (Ganaton OD)	0.954	0.718	0.927	0.652
r ² (EC 10%)	0.985	0.776	0.956	0.679

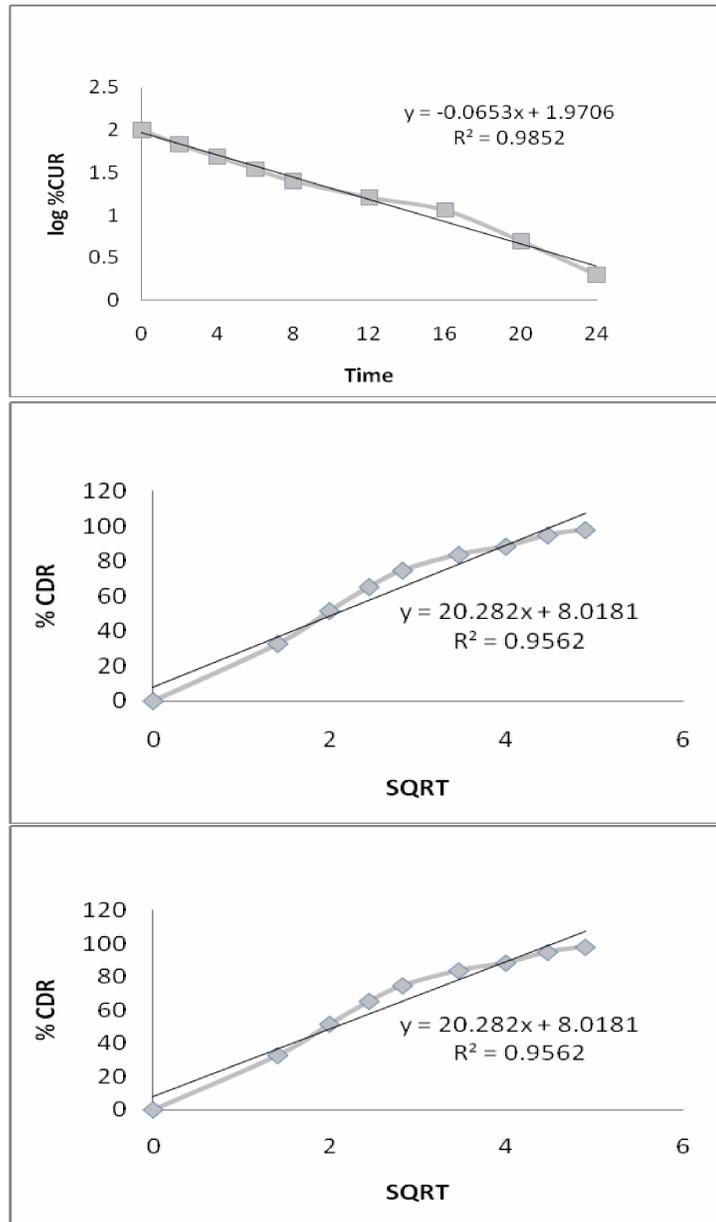


Figure 4 : Release kinetic plots of Ethyl Cellulose coated pellets ; a) First order, b) Higuchi plot, c) Korsmeyer peppas

The release profile also fitted well with first order kinetics suggesting release was drug concentration dependant (Table 4). The dissolution data was fitted to the Korsmeyer equation , which is often used to describe the drug release behavior from polymeric systems. Marketd product was observed to follow Fickian release because release exponent value (n = 0.4023) is between 0-0.45 i.e n < 0.45, so it was showing fickian or diffusion release mechanism. Ethyl cellulose (EC 10%) was showing Fickian release because release exponent value (n = 0.4205)

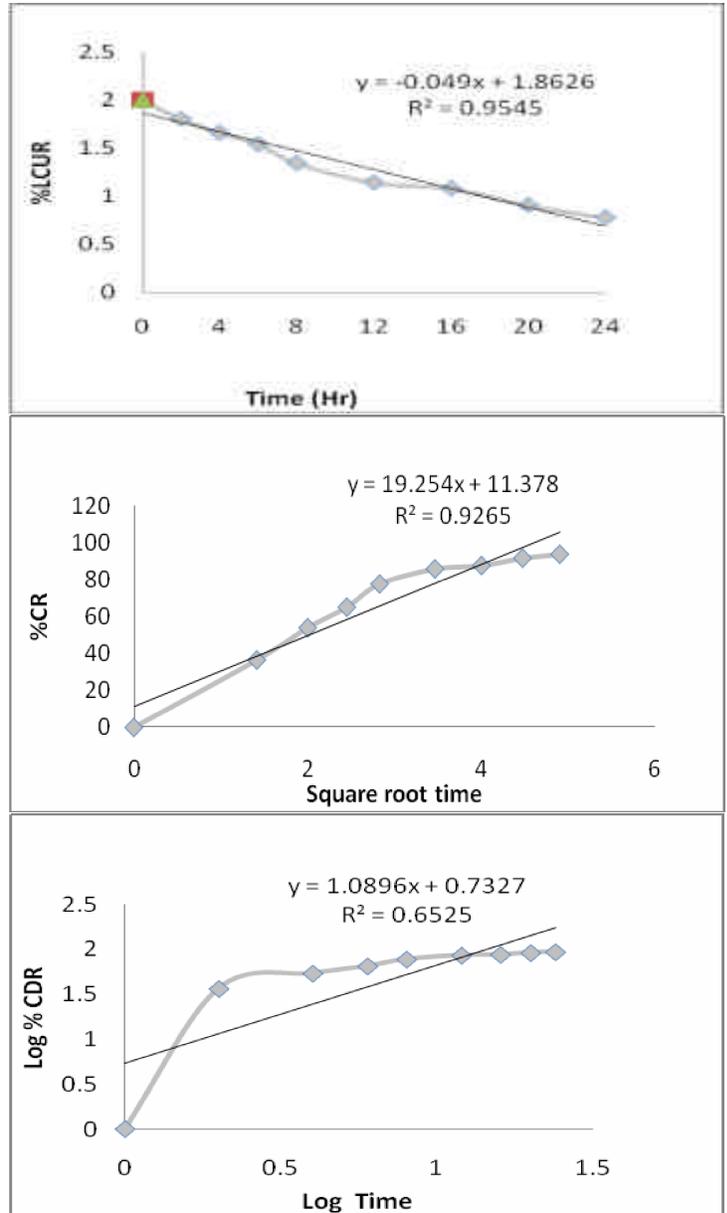


Figure 5: Release kinetic plots of Ganaton OD; a) first order, b) Higuchi plot, c) Korsmeyer Peppas

is between 0 – 0.45 i.e n < 0.45 , so it was showing diffusion release mechanism

Conclusion

Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time. Itopride hydrochloride is an prokinetic and antiemetic agent was chosen as drug having high solubility. The Ethyl cellulose 7 cps was the polymer and 10% coating level was found to be very successful to achieve desired release profile. Pellets were tested for various physical and chemical properties, such as particle size distribution, friability, Bulk density, tapped density and dissolution studies. Pellets was found to be following First order kinetic and then highuchi kinetic. Hence, the pellets formulation (EC 10 %) was found to be having same retardant release profile as marketed product (Ganaton OD).

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