RESEARCH ARTICLE

Formulation Designing and Evaluation of pH responsive Enteric layered preparation of Model Drug

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ABSTRACT

The aim of this study was to prevent the drug release in stomach. The pellets were prepared based on full factorial design. Independent variables were % of PVP K30 (1, 3, 5) and ratio of Eudragit S100 to Eudragit L100 (2:1, 1:1, 1:2). The evaluated response were Drug content, % Drug release in 0.1N HCL, % Drug release in phosphate buffer. Surface characteristics, Sphericity, Aspect ratio, Friability of pellet were also evaluated. Linear regression and response surface modeling was used for analysis result. It show that addition of higher amount of PVP K30 result in higher drug release in 0.1N HCL, high drug content, no effect on drug release in phosphate buffer and has complex effect on overall desirability. Addition of Eudragit S100: Eudragit L100 in ratio of 1:2 show high drug release in phosphate buffer because high amount of Eudragit L100 dissolve fast and disappear enteric coating layer and release drug faster. Eudragit S100:Eudragit L100 has complex effect on drug content and overall desirability. Desirability function was employed to select an optimized batch. The batch that had desirability value near to one was considered to be optimized. In the present work, Batch G had highest desirability value of 0.75.

Keywords: Eudragit L100, Eudragit S100, Ibuprofen, Solution layering, Sugar sphere

INTRODUCTION

The oral route of drug administration is the most common and convenient for patient use. Tablets and capsules have emerged as the most popular solid oral dosage form. But loss of single unit dosage form result in dose dumping and such single unit dosage form do not distribute uniformly throughout G.I tract. In order to overcome these problems, several multiple drug delivery systems have been developed. Multiple unit dosage form have advantage compare with single unit dosage form including more stable plasma profile and little risk of local side effects. [1] Among the various type of multiple unit dosage forms, pellets have attracted more attention due to their clinical and technical advantages. [2]

Pellets are defined as spherical, free flowing granules with narrower size distribution typically varying between 500-1500 mcg for pharmaceutical application. [3] The interest in pellet as dosage form have been increasing continuously because their multiparticulate nature offers some important pharmacological as well as technological advantages over conventional single unit dosage form.[4]

Here in the present study Ibuprofen have been selected as model drug as it is Non Steroidal Anti Inflammatory Drug (NSAIDs) that inhibit both Cyclooxygenase 1(COX1) and Cyclooxygenase 2 (COX2) completely which is used in treating various inflammatory conditions such as rheumatoid arthritis and osteoarthritis. Gastrointestinal toxicities associated with NSAIDs proved to be major drawback during long term therapy. [5]

pH in the terminal ileum and colon is higher than in any other region of the G.I tract. Thus dosage form that disintegrates at high pH level has good potential for site specific delivery into this region. [6] One of the simplest approaches for designing pH dependent multiparticulate delivery system is to formulate enteric coated pellets. Most commonly used pH dependent enteric coating polymers are Eudragit S100 and Eudragit L100 which dissolve at pH 6 and pH 7 respectively. Use of Eudragit alone is not suitable for colonic delivery. [7] Studies in human volunteers have shown that pH drops from 7 at terminal ileum to pH 6 of ascending colon. Such system fails to release drug. [8] In order to overcome this problem, a proper

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combination of Eudragit S100 and Eudragit L100 ensure that the release of the drug from the formulation will occur even when the pH value of the G.I tract does not reach more than pH 6.8. [9]

The aim of present work is to prepare enteric coating pellets using enteric coating polymer Eudragit S100 and Eudragit L100, to prevent the release of drug in stomach, to prevent dose dumping and to achieve uniform distribution of drug through G.I tract. [10-12]

MATERIALS AND METHODS

Materials

Ibuprofen was obtained from Cadila Pharmaceuticals (Ahmedabad, India); Sugar sphere were from Alembic pharmaceutical Ltd. (Baroda, India); PVP K30 and HPC were from Lincoln Pharmaceutical (Ahmedabad, India): Talc and SLS were from Cadila Pharmaceutical (Ahmedabad, India)

Experimental design

A 3^2 full factorial design was used for the preparation of pellets. The independent variables studied ($X1$, $X2$) and their levels are shown in Table 1. The chosen dependent variables or responses ($Y1$, $Y2$ and $Y3$) were % Drug release in 0.1N HCL, % Drug release in phosphate buffer, Drug content. [13]

Table 1: Independent variables: factors and levels for full factorial design

Factors	Level		
	-1	0	1
Amount of PVP K30	1%	3%	5%
Polymer ratio (RS/RL)	1/2	1/1	2/1

Table 2: Composition of different formulation

Batch	Ibuprofen (%)	Eudragit ratio % (RS/RL)	PVP K30 (%)	SLS (%)	IPA (%)
A	53.28	5:10	1	0.6	30
B	53.28	4.5:9	3	0.6	30
C	53.28	3.5:7	5	0.6	30
D	53.28	7.5:7.5	1	0.6	30
E	53.28	6.5:6.5	3	0.6	30
F	53.28	5.5:5.5	5	0.6	30
G	53.28	10:5	1	0.6	30
H	53.28	9:4.5	3	0.6	30
I	53.28	7:3.5	5	0.6	30

Powder Layering Technique

Sugar spheres were poured into the coating pan; the drug was sieved through a 200 mm mesh sieve and then mixed with the excipients. Afterwards, the obtained mixture was dissolved in sprayed binder solution. Sugar spheres were treated with a nebulized binder solution applied by spray guns. Sphere bed was dried to remove the solvent completely, in this way forming the intraparticular solid bridges between the spheres.

Image analysis

Shape and area of pellets were investigated by optical microscopic image analysis. Fifty pellets from each batch were placed on black background. The image analyzer consisted of a computer system linked to a stereomicroscope. The digitalized image was analyzed by scion image analyzing software. [14]

The areas (A), perimeter (Pm), Feret diameter were measured and two shaped factor were measured as follow:

Aspect ratio = d_{max}/d_{min}

Sphericity = $4 \pi A / P_m^2$

Area: Amount of surface the 2D shape cover. It is measured in square unit.

Perimeter: It is a total distance around the outside of 2D shape.

Feret diameter: It is a distance between two parallel tangents of the particles

For pellet:

Area = πr^2

Perimeter = $2 \pi r$

Particle Morphology

The shape and surface characteristics of the Ibuprofen-containing pellets were evaluated by Scanning electron microscopy using a Stereoscan 360 microscope (PHILIPS XL 360 series).

Pellet Friability Test

Resistance to abrasion was determined using Roche friabilator. The sample was subjected to falling shocks for 4 min at a rotation speed of 25 rpm. Weigh pellets and measure % friability by the following equation

% Friability = [(Fs-Fa)/Fa]*100

Determination of Pellet Ibuprofen Content

Ibuprofen content was determined by titrimetric method as per IP 1996. Weigh accurately about 0.4gm of pellets, dissolve in 100ml ethanol and titrate with 0.1M sodium hydroxide using 0.2ml phenolphthalein as indicator. Carry out a blank titration.

1ml 0.1N Sodium Hydroxide = 0.02063 gm of Ibuprofen

Drug Release Test

Dissolution study was carry out using USP basket type apparatus at 37˚C ± 0.5˚C using 0.1N HCl of pH 1.2 as dissolution medium for 2 hr and in phosphate buffer solution of pH 7.2 for 1 hr or until 80% drug release. [15]

Drug-Excipients Compatibility Studies:

Fourier transform infrared spectroscopy was carried out for solid samples to detect if any interactions were present between the drug and polymers. The samples were prepared by the potassium bromide disc method (3 mg sample in 297mg KBr). Powders were triturated in a small size glass mortar and pestle until the powder mixture was fine and uniform. Pure KBr powder was used as background, and for baseline correction. Samples were placed in a sample holder. Afterwards, the sample was transferred to sample compartment. Samples were scanned in the region of 4000-400 cm-1 using a brucker FTIR spectrometer. [16]

Statistical Analysis Of Data

The effect of independent variable on each experimental response Y were modeled using following equation

$$Y = b_o + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2$$

RESULTS AND DISCUSSION

Preformulation Study

Sugar spheres consisting of sugar and starch, with a mean diameter of 600 mm, were chosen as inert seeds in order to obtain final pellets having dimensions compatible with the filling of hard gelatin capsules of intermediate size such as size no. 1. In order to maximize the interactions between drug and inert cores, a micronized Ibuprofen powder with a mean diameter (by number) of 6 mm was chosen, resulting in a size-ratio of 1:100 between the drug particles and the inert cores.

The wettability of the drug powder was also considered. In fact, it is well known that successful interaction between the drug and the binder solution is greatly influenced by the wettability of the drug (as measured by the contact angle, which should be kept as low as possible). For instance, Ibuprofen, being a hydrophobic compound, is characterized by an unfavorable wettability expressed by a contact angle of 70°. In order to reduce this value, a surface agent (sodium lauryl sulfate, SLS) was included in the formulation to aid the wetting of the drug. **Fig. 1** reports the effect of SLS on the contact angle of Ibuprofen. The results clearly indicate that a formulation including 0.75% (W/W) SLS was able to sharply reduce the contact angle to 0°, representing complete wetting of a solid surface.

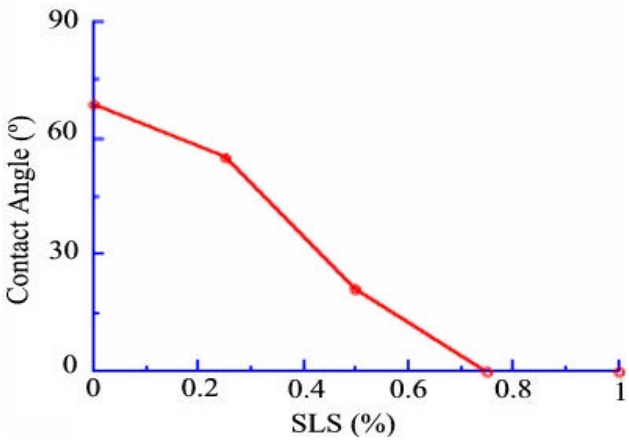

Figure 1: Effect of sodium lauryl sulfate (SLS) on the contact angle of Ibuprofen powder

Other important parameters to be considered in order to obtain optimal powder layering are the type and quantity of binder. The binder has to possess high adhesivity and an appropriate viscosity, to guarantee a good adhesion between sugar cores and drug particles, resulting in a high concentration of drug in the pellets. In the present study two different binders were assayed, namely Hydroxylpropyl cellulose (HPC) and Polyvinylpyrrolidone (PVP K30). PVP is a water-

soluble binder that allows a rapid dissolution of the final pellet. HPC, being a less water-soluble polymer, gave rise to slower dissolution rates.

Preliminary Experiments of Layered Pellet Production

Table 3: Drug and excipients used for the preparation of Ibuprofen pellets by layering technique

Batch	Sphere	Ibuprofen	SLS	Talc	HPC	PVP K30
1	250	133.3	_	-	8%	-
2	250	133.3	_	-	5%	-
3	250	133.3	_	15%	5%	-
4	250	133.3	_	-	-	8%
5	250	133.3	0.6%	-	-	5%

Pellets prepared using 8% Hydroxyl propyl cellulose (HPC) give 24% recovery (% of drug remaining on seed) and give quite uniform rough surface but are not completely free of imperfection. Pellets prepared with 8% HPC stick to a certain degree, therefore pellet with 5% HPC were prepared (Batch 2).

Pellets prepared using 5% HPC solution (Which have lower viscosity as compare to 8% HPC) produce pellets with smoother surface but give lower recovery as compare to 8% HPC. So, if increase the concentration of HPC from 5% to 8% recovery increase but pellets stick to certain degree. So, pellets with different concentration of talc were prepared (Batch 3).

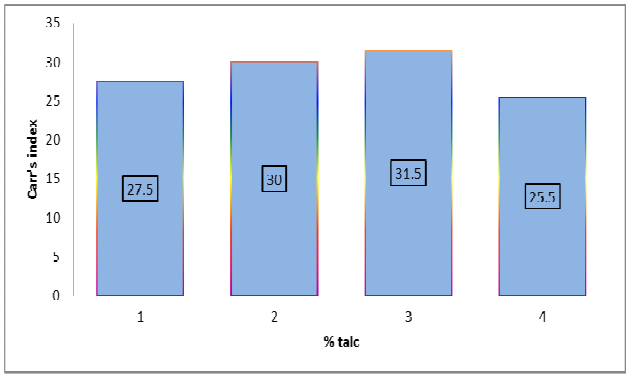

Figure 2: Effect of talc on Ibuprofen flowability measured by means of the Carr's index

In order to promote the pellets separation into distinct unit 15% talc was added but pellets with talc give delay in disintegration because HPC being less water soluble polymer give rise to slower dissolution rate. So, pellets with different concentration of PVP K30 were prepared (Batch 4).

Pellets prepared using 8% PVP K30 produced relatively smooth surface and homogenous morphological characteristics but caused seedless drug particle and low recovery as compared to 3% PVP K30. For increase recovery of pellets prepared with PVP K30, Sodium luaryl sulphate (SLS) was used (Batch 5).

Successful interaction between drug and binder solution is influenced by wettability of drug. Ibuprofen, a hydrophobic compound, is characterized by wettability expressed by contact angle 70°. To reduced this value SLS included in formulation. Results indicate that formulation including 0.6% SLS was able to reduce the contact angle to 0° representing complete wetting of drug.

Table 4 indicates that there is no significant relation between the sphericity of pellets and drug load, binder concentration and also the type of Eudragit used. Overall results showed that the drug loading, binder concentration and type of Eudragit did not affect the shape and sphericity of pellets.

Table 4: Result of image analysis

BATCH	ASPECT RATIO (d_{max}/d_{min})	SPHERICITY
A	1.17±0.06	0.87±0.05
B	1.13±0.08	0.85±0.01
C	1.17±0.04	0.86±0.02
D	1.15±0.10	0.87±0.01
E	1.12±0.12	0.84±0.03
F	1.10±0.04	0.87±0.02
G	1.10±0.06	0.86±0.01
H	1.19±0.03	0.87±0.06
I	1.15±0.02	0.84±0.02

Table 5 shows the results of % drug release in HCl, % Drug release in phosphate buffer, Drug content as experimental responses (*Y*1, *Y*2 and *Y*3).

Table 5: Experimental responses for different formulations

Batch	Variables		Response values		
	X_1	X_2	% Drug release in 0.1N HCl	% Drug release in phosphate buffer	Drug content (%)
A	-1	-1	0.84±0.211	83.47±0.435	86.44±0.425
B	0	0	2.87±0.575	80.30±0.534	78±0.643
C	1	1	4.36±0.427	82.45±0.710	85.55±0.168
D	0	1	3.72±0.566	89.14±0.368	85±0.276
E	1	0	4.05±0.278	78.29±0.513	84.26±0.316
F	0	-1	1.06±0.244	80.96±0.378	90.76±0.156
G	1	-1	1.49±0.311	86.43±0.157	98±0.128
H	-1	0	2.09±0.138	86.47±0.245	79±0.756
I	-1	1	2.44±0.457	93.95±0.124	82.52±0.249

By regression of these results against *X*1, *X*2 we can obtain following models for % Drug release in HCl (Y_1), % Drug release in buffer (Y_2), Drug content (Y_3)

$Y_1 = 3.0067 + 0.755\ X_1 + 1.1833\ X_2 - 0.685\ X_2^2$ ..... (1)

$Y_2 = 80.5466 - 2.7866\ X_1 + 2.4466 X_2 - 3.615\ X1X_2$..... (2)

$Y_3 = 79.5033 + 3.3083\ X_1 - 3.6883\ X_2 + 7.625\ X_2^2$ ..... (3)

Coefficients with one factor represent the effect of that particular factor, while the coefficients with more than one factor and those with second-order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. A positive sign in front of the terms indicates a positive effect, while a negative sign indicates a negative effect of the factors. From the equations 1 to 3, it can be concluded that PVP K30 has a positive effect on drug release in 0.1N HCL, Drug content, while it has negative effect on % drug release in phosphate buffer. Ratio of Eudragit S100: Eudragit L100 has positive effect on % Drug release in phosphate buffer and Drug release in 0.1N HCl, while it has negative effect on Drug content

Table 6: Overall desirability value of 32 Factorial batches of Ibuprofen pellet

Batch	Individual Desirability Value of each Response			Overall Desirability $D = (d_1 d_2 d_3)^{1/3}$
	% Drug release in 0.1N HCL (d_1)	% Drug release in Phosphate buffer (d_2)	Drug content (d_3)	
A	0.00	0.33	0.42	0.00
B	0.42	0.13	0.00	0.00
C	1.00	0.26	0.38	0.46
D	0.18	0.69	0.35	0.35
E	0.08	0.00	0.31	0.00
F	0.94	0.17	0.64	0.47
G	0.81	0.52	1.00	0.75
H	0.64	0.52	0.05	0.25
I	0.54	1.00	0.23	0.50

The results shown in Table 6 reveal that pellet of batch G is the best since it showed highest overall desirability of 0.75. The values of the independent variables of batch G was considered as optimum values for the preparation of the pellet.

Surface Plot for each Response and Overall Desirability

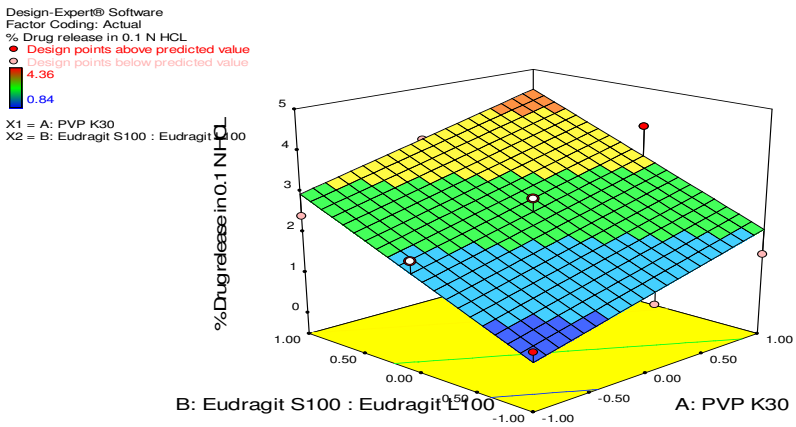

Figure 3: Surface plot showing relationship between Drug release in 0.1N HCL and factor X_1 (amount of PVP K30) and X_2 (Eudragit S100 : Eudragit L100)

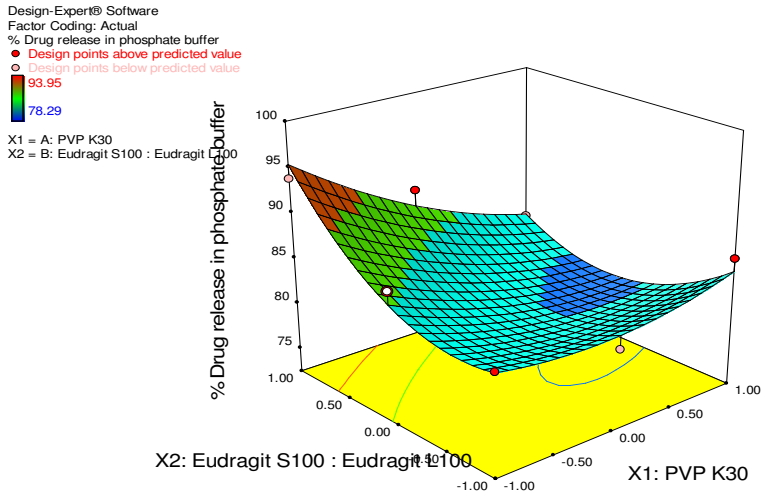

Figure 4: Surface plot showing relationship between Drug release in phosphate buffer and factor X_1 (amount of PVP K30) and X_2 (Eudragit S100 : Eudragit L100)

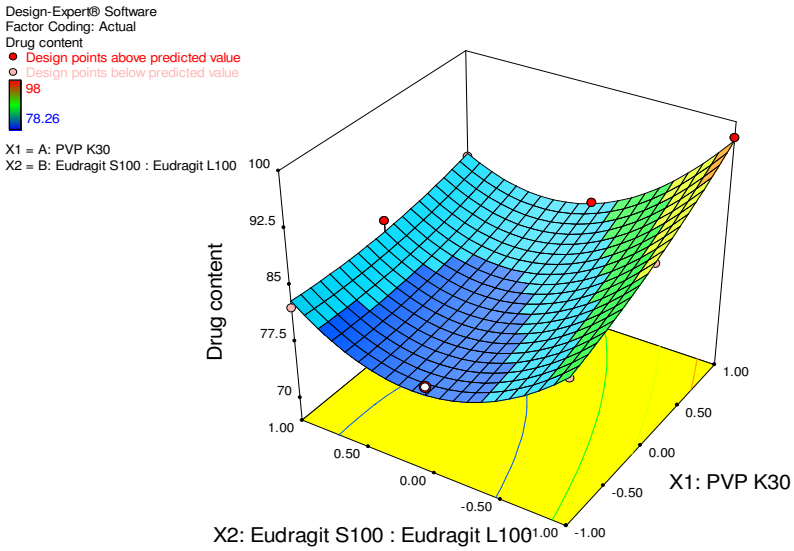

Figure 5: Surface plot showing relationship between Drug content and factor X_1 (amount of PVP K30) and X_2 (Eudragit S100 : Eudragit L100)

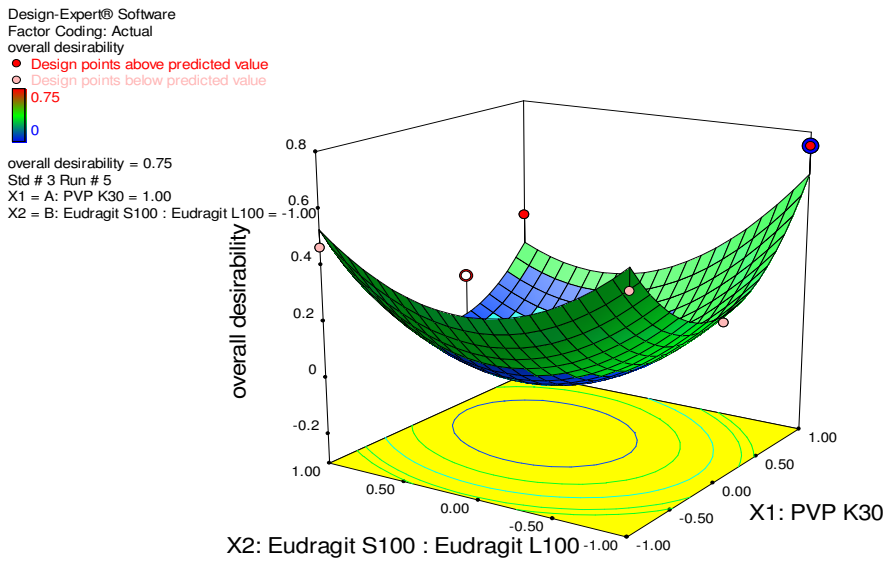

Figure 6: Surface plot showing relationship between overall desirability factor X_1 (amount of PVP K30) and X_2 (Eudragit S100 : Eudragit L100)

Surface plot indicate that addition of higher amount of PVP K30 result in higher drug release in 0.1N HCl, high drug content, no effect on drug release in phosphate buffer and has complex effect on overall desirability. Addition of Eudragit S100 : Eudragit L100 in ratio of 1:2 show high drug release in phosphate buffer because high amount of Eudragit L100 dissolve fast and disappear enteric coating layer and release drug faster. Eudragit S100 : Eudragit L100 has complex effect on drug content and overall desirability. Increase amount of PVP K30 result in increase drug content because PVP K30 act as binder but increase amount of PVP K30 result in increase drug release in 0.1N HCL which is not desired.

CONCLUSION

The Ibuprofen pellets based on Eudragit L100 and Eudragit S100 combination were produced successfully using solution layering technique. All the characteristic peaks of groups of pure drug were also appear in physical mixture of drug with excipients. So, FTIR gave conformation about their purity and showed no interaction between drug and polymer. It demonstrates that Eudragit ratio of RS100: RL100 in 1:2 had adequate effect on drug release. Amount of PVP K30 show effect on drug release in HCl and has no effect on drug release in buffer.

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