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FORMULATION AND DEVELOPMENT OF SUSTAINED RELEASE PELLETS OF GLIPIZIDE

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ABSTRACT

The present work describe development a sustained release pellets of glipizide using solution layering technique. The goal of designing the sustain drug delivery was to reduce the frequency of dosing. Glipizide (BCS II) is an antidiabetic drug with short biological half life (3.4 ± 0.7 h). Hence, sustained release formulation is needed for glipizide for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficiency, to reduce G.I disturbances and to enhance patient compliance. The effect of polymer (Eudragit RL100) and binder(PVPK30) on % drug release at 2 h and % drug release at 8 h was optimized using 3^2 factorial design. The effect of the variables and behavior of the system was studied using response surface plots. The pellets were evaluated for flow properties, % drug content, % drug release, % coating efficiency, FT-IR, DSC. The drug release optimized batch was compared with marketed product that was found to be similar.

KEYWORDS: Glipizide, Solution layering technique, sustained release pellets, Eudragit RL 100.

1. INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs, because of the greater stability, smaller bulk, accurate dosage and easy production.[1] Pelletization offers various advantages over other similar techniques; such as uniformity of dose and flexibility in dosage form.[2] Glipizide (BCS II) is an antidiabetic that used for the treatment of non insulin dependent diabetes mellitus (NIDDM).[3] Glipizide is sparingly soluble in ethanol and acetone, and soluble in methylene chloride. Pellets help reduce GI irritation, controlling the drug release and increasing the absoption of active ingredients. Pan coating is commonly

used for preparation of coated pellets. Previous reports on glipizide pellets by solution layering describe use of Eudragit RS100 and Eudragit RL100 coating, which aims to extend the release by changing the coating layer composition and coating layer.[4] Present work describes formulation of SR glipzide pellets by solution layering technique. Eudragit RL100[5] is used as a polymer to retard the drug release[12] and optimization of the binder and polymer composition by a 2 factor 3 level design.

2. MATERIAL AND METHOD

2.1 Materials

Following materials was kind gifts, Glipizide from Intas Pharmaceutical Ltd. (Ahmedabad). Eudragit RL100 (Evonik industries, Mumbai), Non-pareil seed of MCC (ACG worldwide Mumbai). Other chemicals were procured from local sources and were of EP grade.

2.2 Methods

2.2.1 Drug excipient Compatiblity Studies

Compatibility of glipizide with polymer Eudragit RL100 and PVP K30 in 1:1 ratio of physical mixture were analyzed by FT-IR spectroscopic analysis and differential scanning calorimeter.

2.2.2 Preparation of glipizide coated pellets[4]

Pellets were coated with glipizide using Solution Layering Technique. The Glipizide and PVP K30 solution was sprayed onto non-pareil beads using pan coater (R&D coater INSTACOAT, IC Deluxe, Mumbai). First, Glipizide (1 g) was dissolved in 1:1 ratio solution of Dichoromethane : Ethanol (100 ml) and PVP K-30 (0.5 g, 0.75 g, 1g) was mixed with the above solvent separately, both the solutions were mixed and sprayed onto non-pareil beads using pan coater (table F1-F9) . The layered pellets were dried at 40°C. The composition of drug coating solution mentioned in Table no 1.

2.2.3 Polymer coating on drug layered pellets[4]

The polymer coating solution was prepared using ethanol. Required amount of Eudragit RL 100 was dissolved in ethanol and sonicated for 20 min. Triethyl citrate was added to the solution as plasticizer and talc as a antisticking agent. The drug layered pellets were then coated with the polymeric solutioun at a rate of 1ml/min. The composition of polymer coating solution mentioned in Table. 2 and the process parameters are listed in Table.3.

Table 1: Compostion of drug Coating Solution for Glipizide.

Sr. No	Ingrident	Quantity								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Glipizide (g)	1	1	1	1	1	1	1	1	1
2.	PVP K 30 (g)	0.5	0.75	1	0.5	0.75	1	0.5	0.75	1
3.	Dichloromethane:Ethanol(1:1) (ml)	100	100	100	100	100	100	100	100	100

Table 2: Composition of Polymer Coating Solution.

Sr. No	Ingridents	Quantity								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Eudragit RL 100 (g)	0.15	0.15	0.15	0.2	0.2	0.2	0.25	0.25	0.25
2.	Talc (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
3.	Triethyl citrate (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
4.	Ethanol(ml)	50	50	50	50	50	50	50	50	50

Table 3: Process Parameters Used for coating drug and Polymer.

Parameters	Glipizide Layering	Sustained release polymer coating
Inlet temperature (^{o}C)	42-50	37-40
Outlet temperature (^{o}C)	30-40	25-30
Bed temperature (^{o}C)	32-38	30-35
Nozzle diameter (mm)	1	1
Spray Rate (ml/min)	1	1
Atomization Pressure (bar)	2.0	2.0

2.2.4 % coating efficiency[6]

The % coating efficiency of coated pellets was calculated by using the formula:

$$\% \text{ Coating efficiency} = \frac{a-b}{c} \times 100$$

Where,

a= Final weight of coated pellets in grams; b= Initial weight of pellets (Blank pellets in grams); c= Total amount of coating material (grams).

3. Experimental design and statistical analysis

A 3^2 full factorial design was employed to optimize the formulation of pellets in this study. The target was to obtain the drug release for 8 h. In order to optimize the formulations, the amount of Eudragit RL100 and the amount of PVP K-30, were chosen as independent variables. The combination of PVP K30 and Eudragit RL100 was used for release sustaining of glipizide. The response variables selected for evaluation of sustained release were percent drug release at 2 h hour and 8 h and was selected as dependent variables.

3.1 Analysis of data[11,12]

Using Design Expert 11.0 software optimization of batch was done. 3-D response surfaces curves were constructed to study the effect of two independent variables alone and in combination on % drug release at 2 h and 8 h. All the responses were fitted to Quadratic model and were evaluated in terms of statistical parameters. According to the given solution the optimized batch was found.

Table 4: Independent variables and their selected levels for pellet formulation.

Coded Factor	Level	Factor 1 Concentration of PVP K30(gm)	Factor 2 Concentration of Eudragit RL 100(gm)
-1	Low	0.5	0.15
0	Medium	0.75	0.2
+1	High	1	0.25

4. Evaluation of Pellets

4.1 Flow properties of pellets

The flow properties of coated pellets were determined which included angle of repose, bulk density, tap density, Hausner's ratio, carr's index, compressibility index.[7,8]

4.2 Determination of % drug content

To determine percent content of Glipizide in the pellets, accurately weighed crushed pellets (100 mg) were dissolved in 10 ml methanol, solution was filtered and analyzed spectrophotometrically at 276 nm after suitable dilution.

4.3 *In-vitro* drug release[4]

USP dissolution apparatus Type II was used to study the drug release from various formulations prepared. Accurately weighed quantity of drug loaded pellets equivalent to 10 mg glipizide were taken in 900 ml 0.1N HCl at 37±0.5^{o}C and drug release was studied at 50 rpm. 5 ml of dissolution medium was withdrawn periodically at regular interval of 1 hour and was replaced with the same volume of fresh medium. The withdrawn sample were filtered through whattmann filter and analyzed spectrophotometrically at 275 nm for drug release. The marketed formulation was analyzed similarly.

4.4 Similarity factor

The similarity factor was calculated for the marketed formulation and the optimized batch using the formula,

F2= 50log {[1+/N) ∑ (Ri-Ti) 2-0.5X100}

Where, N is the number of time points, Ri and Ti are dissolution of reference and test products at time respectively. F2 values greater than 50 considered as two products are similar and showed similar drug release profile.[9],[10]

4.5. Differntial Scanning Calorimetry

Differential scanning calorimetry (DSC) studies were carried out using DSC *e software. Samples were accurately weighed and heated in sealed aluminium pans at a rate 10°C/min between 30- 300°C temperature range under nitrogen atmosphere. Empty aluminium pan was used as a reference.

4.6. SEM studies

Scanning Electron Microscopy was done to determine the surface Morphology of the Pellets. Using the Instrument:FEI, Model: Nova nano SEM 450 photographs were taken and recorded at suitable magnification.

5. RESULT AND DISCUSSION

Eudragit polymer is used in tablet and capsule dosage forms for film coating. It is highly permeable and allows drug permeation across the film independent of pH of digestive tract. Hence it is a polymer of choice for pellets formulation.

5.1 Fourier Transform Infrared spectroscopy

To study the compatibility of drug with excipient the IR spectra with the combination of drug and excipient in 1:1 ratio was studied. The spectra was obtained at 4500-400cm^{-1}. The IR spectrum was observed and the peaks of major fuctional group in glipizide were found to be C=O amide at 1689.64, C=O urea at 1650.23, C-H stretching (aromatic) at 1528.10, C-H bending (aromatic) 1443.49, O=S=O at 1333.41,1159.98. The IR spectrum of drug and physical mixture showed no physicochemical interaction in between drug and used excipient.

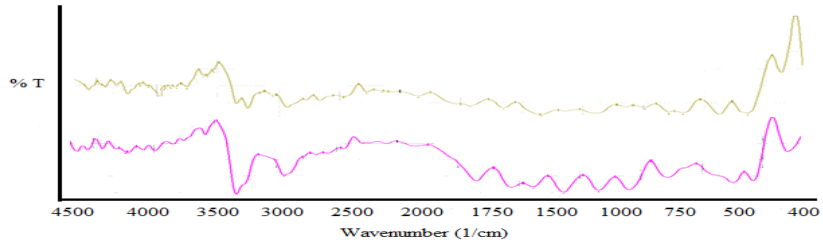

Fig. 1: FT-IR spectrum of glipizide and physical mixture.

5.2 Differential Scanning Calorimetry

The endothermic peak obtained in thermogram of venlafaxine at 216°C can be attributed to melting of Glipizide, same was reproduced in thermogram of pellets while the additional endotherm at 246°C represents peak of MCC. Thus, the thermogram showed that the Glipizide, Eudragit and PVP K-30 are compatible with each other since there is no significant difference in endothermic peak of pure drug (Fig. 2) and coated pellet.

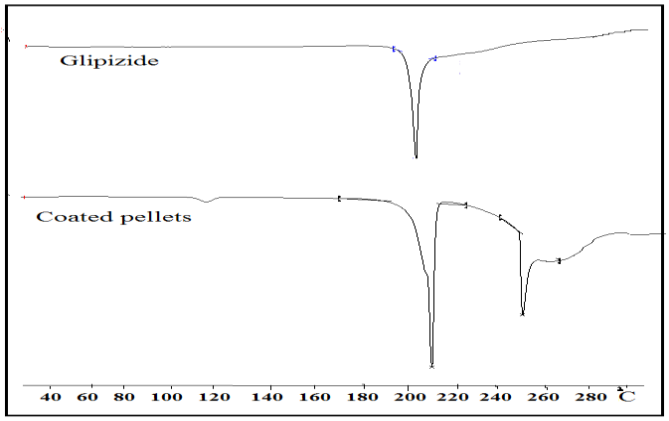

Fig. 2: DSC thermogram of Glipizide and coated pellets.

5.3 % Coating efficiency

The % coating efficiency for all batches were calculated. The limit for % coating efficiency is 90-95% for film coating. Among all the formulations F2, F3, F4, F5, F7 and F9 were in the limit. Formulation F5 has achieved highest coating efficiency.

Table 5: % coating efficiency of formulations (F1-F9).

Batch No.	% coating efficiency
F1	78.62 ±0.54
F2	92.83 ±0.25
F3	90.00 ±0.23
F4	92.47 ±0.38
F5	94.87 ±0.75
F6	83.78 ±0.40
F7	91.16 ±1.01
F8	89 .00±0.83
F9	90.97 ±0.43

5.4 Optimization

3^2 factorial design was used for the optimization, levels were selected according to the literature, 9 formulation were prepared. Two factors were taken that is binder (PVP K30) and

polymer(Eudragit RL100) which are responsible for the drug release. The % drug release at 2 h and % drug release at 8 h were taken as the dependent variables were determined. The highest drug release was achieved in F5 formulation which is similar to that of marketed product.

The equation obtained for % drug release at 2 h and % drug release at 8 h for 3^2 factorial design are as follows,

% Drug release at 2nd hour =

- 83.0+127.21A+586.25B-173.0AB-50.74A-1070.50 …. (Equation 1)

% Drug release at 8th hour

-156087=+153.48A+1757.43B-189.60AB-69.56A-3837 …..(Equation 2)

Table 6: Adequate precision.

Responses	f- value	p- value	Predicted value	Experimental value	% Error
% Drug release at 2 hr	11.92	0.0045	32.74	32.56	0.18
% Drug release at 8th hr	5.05	0.0367	89.14	89.75	-0.61

5.5 Response surface analysis

The drug release is decreased when there is high concentration of both A(PVP K30) B(Eudragit RL100) that is A and B is increased it shows negative effect in drug release. When the concentration is in middle range it gives satisfactory drug release i.e when AB together, shows positive effect in drug release and when the concentration of A and B is low it shows small increase in drug release(Fig. 4).

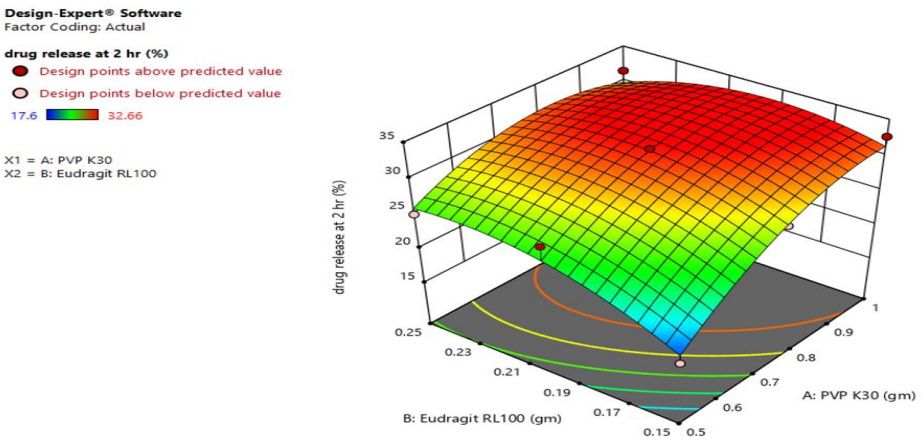

Fig. 3: Response surface plot showing the influence of amount of polymer and amount of binder on the % drug release at 2 h of glipizide.

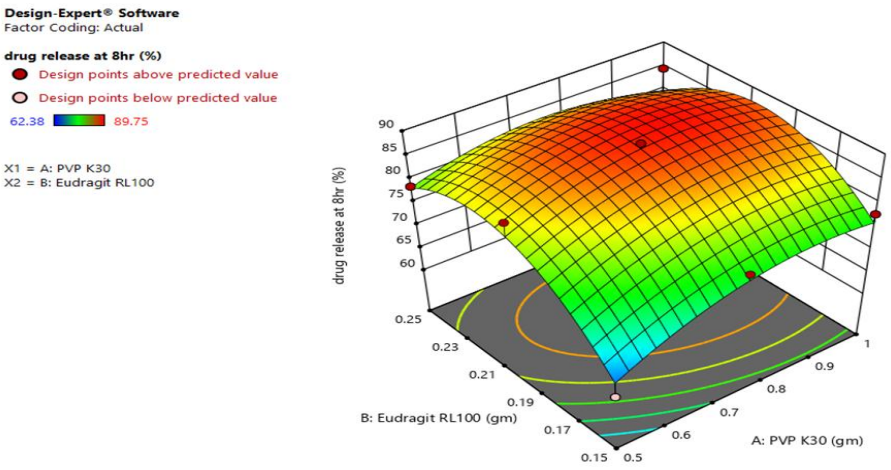

Fig. 4: Response surface plot showing the influence of amount of polymer and amount of binder on the % drug release at 8 h of glipizide.

5.6 Flow properties

Flow properties of all the 9 batches were found to be within the I.P limit and were excellent. The flow properties were found to be as follows:

Table 7: Flow properties for the coated glipizide pellets.

Batch No.	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.78 ± 0.028	0.85 ± 0.011	28.32 ± 0.37	6.42 ± 0.03	1..059± 0.015
F2	0.76 ±0.011	0.85 ± 0.015	25.98 ± 0.49	9.23 ± 0.16	1.087± 0.023
F3	0.79 ±0.005	0.86 ±0.005	28.40 ±0.20	9.60± 0.14	1.098±0.010
F4	0.84 ±0.034	0.88 ±0.011	27.06 ±0.86	3.90± 0.79	1.043±0.014
F5	0.79 ±0.005	0.86 ±0.005	29.34 ±0.19	7.44± 0.85	1.08±0.010
F6	0.78 ±0.026	0.85 ±0.015	25.92 ±0.55	4.38± 0.80	1.067±0.029
F7	0.76 ±0.023	0.84 ±0.011	27.73 ±0.38	9.88 ±0.62	1.098±0.012
F8	0.78 ±0.023	0.85 ±0.011	26.00 ±0.48	9.32± 0.27	1.089±0.018
F9	0.79 ±0.005	0.87 ±0.015	25.68 ±0.11	6.94 ± 0.85	1.090±0.026

5.7 % Drug Content

The % drug content of all the 9 batches were determined it was found to be in between 63 to 68%. The highest % drug content was shown in F5 that is 67.13.

Table 8: % drug content for the formulations (F1-F9).

Batch No.	Drug Content (%)
F1	63.67 ± 0.38
F2	65.60 ± 0.34
F3	63.60 ± 0.36
F4	65.50 ± 0.33
F5	67.13 ± 0.10
F6	66.55 ± 0.31
F7	63.37 ± 0.17
F8	64.51 ± 0.38
F9	65.52 ± 0.21

5.8 *In – Vitro* drug release

The drug release was determined from the formulated F1 to F9 batches and marketed formulation and shown Fig 5. The in vitro percentage drug release from the pellet formulation f1-f9 using different concentration of polymer EudragitRL100 and binder PVPK-30 showed 63.46%, 76.39%, 77.74%, 84.40%, 89.75%, 80% 78.62% 77.52%, 84.62% respectively. Among all the batches F5 batch was found to be the best formulation which sustains the drug release rate of glipizide. Regression analysis of the optimized batch was determined. The best fit model for the optimized batch was found to be first order release model. The formulation F5 and marketed formulation was compared and the results were reported graphically.

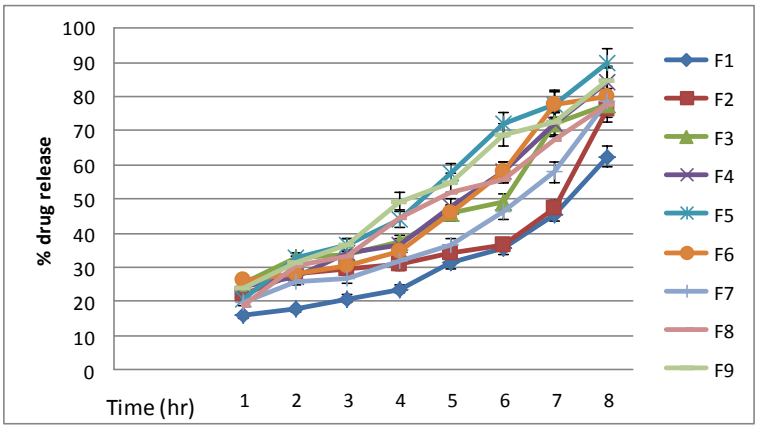

Fig. 5: In –Vitro Drug release of formulations (F1 to F9).

Comparative dissolution profile of Optimized formulation and marketed formulation

From all the 9 batches, formulation F5 was the optimized batch obtained from the in vitro release data. The optimized batch F5 of Sustained release pellets were then compared with the marketed formulation shown in fig 6.

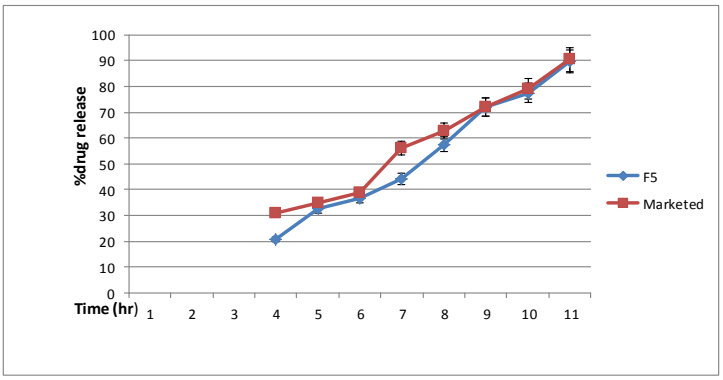

Fig. 6: Comparative dissolution profile of optimized and marketed formulation.

5.9 Similarity Factor

The Similarity factor was calculated between the marketed formulation and formulation F5, it was found to be 84.6. Therefore optimized batch and marketed formulation showed similar drug release profile.

5.10 Scanning Electron Microscopy

The surface morphology of Glipizide coated pellets and uncoated pellets was studied by Scanning electron microscopy. It was observed that the morphology of the pellets was spherical in shape and smooth in surface. It was also observed that the coating of the pellets was uniform as shown in the Fig. 7.

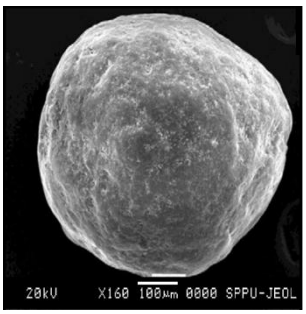

Fig. 7: Coated pellet.

CONCLUSION

The pellets loaded with glipizide was coated with Eudragit RL 100 optimized with respect to binder and coating agent concentration to achieve desired drug release. The pellets succeeded in sustaining the release of the drug for 8 h. Thus, the glipizide pellets that were prepared were found to be similar to marketed product.

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REFERENCES

1. Gedar Shushma, Mahesh Kumar Kataria, Ajay Bilandi. Formulation and Evaluation of Sustained Release Matrix Tablet of Glipizide. International Journal of Pharmaceutical Sciences Letters, 2014; 4(3): 376-383.
2. Deb Ratul, Ahmed Abdul Baquee A. Pellets and pelletization techniques:a review. International Research Journal of Pharmacy, 2013; 4(4): 90-95.
3. Kambham Venkateswarlu, A Shanthi. Formulation and Evaluation of Sustained Release Glipizide Matrix. IOSR Journal of Pharmacy and Biological Sciences, 2012; 2(5): 17-23.
4. Mustafa Sinan Kaynak, H. Suheyla Kas, Levent Oner. Formulation of Controlled Release Glipizide Pellets Using Pan Coating Method. Hacettepe University Journal of the Faculty of Pharmacy, 2007; 27(2): 93-106.
5. Niranjan PC, Goutam KJ, Panigrahi KC. Pharmaceutical significance of Eudragit : A review. Future journal of pharmaceutical sciences, 2017; 1-9.
6. Mangesh R Bhalekar, Ashwini R Madgulkar, Sumedha S Andure. Formulation and Evaluation of sustained release pellets of venlaflaxine hydrochloride. Inernational Journal of Applied Research, 2017; 3(5): 793-799.
7. Lachman L, Libberman HA. Theory and practice of industrial pharmacy. 3rd edition, 2009; 183-185.
8. Indian Pharmacopoeia. ministry of health and family welfare, volume 3, 7th edition: 2607-2608.
9. Kamlesh J Wadher, Rajendra B Kakde, Milind J Umekar. Study on sustained-release metformin hydrochloride from matrix tablet: Influence of hydrophilic polymers and in vitro evaluation, International Journal of Pharmaceutical Investigation, 2011; (1): 157-163.
10. Ehab Hamed, Adel Sakr. Application of multiple response optimization technique to extended release formulations design. Journal of Controlled Release, 2001; 329–338.

11. Kramar A, Turk S, Vercer F. Statistical optimization of diclofenac sustained release pellets coated with polymethacrylic films. International Journal of Pharmaceutics, 2003; 256: 43-52.
12. A. Akhgari, H. Afrasiabi Garekani, F. Sadeghi, M. Azimaie. Statistical optimization of indomethacin pellets coated with pH-dependent methacrylic polymers for possible colonic drug delivery. International Journal of Pharmaceutics, 2005; 22-30.