www.ijrps.pharmascope.org

ISSN: 0975-7538
Research Article

Formulation and evaluation of glipizide pellets by using fluid bed coating method

Gaikwad Abhijit[1]*, Pathade Parag[2], and Pawar Amol[3]

[1]Department of Pharmaceutics, AISSMS College of Pharmacy, Kennedy Road, Near RTO, Pune -411001, Maharashtra, India
[2]Department of Pharmaceutical Analysis, KBHSSTS Institute of Pharmacy, Malegaon-423105, Dist Nasik, Maharashtra, India
[3]Department of Pharmaceutics, D.Y. Patil Institute of Pharmaceutical Science and research center, Pimpri, Pune, Maharashtra, India

ABSTRACT

The present invention embodies formulation and evaluation of controlled release pellets of glipizide. The objective of the work was to decrease the dosage regimen and to maintain the necessary blood concentration for the treatment of non insulin dependent diabetes mellitus (NIDDM). For this purpose, solution layering technique was utilized. Fluid bed coater with wurster insert (bottom spray) was used for the coating of Non pareils with drug solution. Then, drug loaded pellets were coated with dispersion of Eudragit NE 30 D: Eudragit L 30 D 55 (80:20) upto 30% weight gains. The shape and surface morphology of prepared pellet were characterized by scanning electron microscopy and it shows the uniformity in the coating process. The prepared pellets exhibited prolonged drug release (> 12h) by altering the theoretical weight gain of pellets. In vivo testing of the pellets to albino Wistar rats demonstrated significant hypoglycemic effect of glipizide.

Keywords: Pellets; Glipizide; Scanning electron microscopy; *in vivo* study.

INTRODUCTION

Glipizide, belonging to the sulfonylurea group, is one of the major drugs used for the treatment of non insulin dependent diabetes mellitus (NIDDM). It is a white odourless powder which is water insoluble. On the other hand, it is sparingly soluble in acetone and soluble in methylene chloride and chloroform (Stamm A, 1989; EP, 200; BP, 1993). It is also bound to the plasma proteins with a ratio of 98% having a pKa value of 5.9 (Moffat AC, 1986; Kivisto KT, 1991). Glipizide was administered once or twice daily in doses of 5 to 20mg (Lebovitz HE, 1985). Pelletization is a term used to define agglomeration of drug substances in either powder or granule form resulting in the form of semi-spherical and spherical agglomerates having good flow properties. Generally, the particle sizes of the resulting pellets are between 0.5 and 1.5 mm depending on the preparation technique (Ghebre Sellassie, 1989).

Pellets provide a reduction in the dosage regimen and gastrointestinal irritation moreover controlling the drug release and increasing the absorption of the active ingredient. Also one of the advantageous properties of the pellet formulations is being good candidates for the delivery of the drug substances due to minimizing the dose dumping effect. The reproducibility of the release characteristics from pellet formulations is also much better with respect to the single-unit dosage forms. (Palsson BO et al., 1990; Wu XY et al., 1998; Zhon Y and Wu XY, 2003). They are suitable systems for film coating with respect to the low surface area-volume ratios. Also, resistance to external factors such as moisture, air and light are the most advantageous properties of these dosage forms (Iyer RM et al., 1993; Heng PWS, 1996; Govender T et al., 1995; Govender T et al., 1997; Boles MG et al., 1994; Sellassie IG et al., 1985; Wang DP et al., 1997; Lin SY, 1993; Mehta AM et al., 1986).

Fluid bed coating is a method for the preparation of the coated pellets. In fluid bed coating method; a core material is coated with the drug substance following a secondary coating process in which the release controlling polymer material is introduced. Pellets are pushed through the coating column by hot drying air. As beads circulate through the bed the coating suspension dries and leaves the thin layer of solids on the pellets. While moving through the coating column, beads are spread with the coating suspension.

In this study, the pellet formulations are prepared fluid bed coating method. Formulations were prepared to control the release of glipizide from the pellets to

* Corresponding Author
Email: paragpathade01@gmail.com
Contact: +91-9960063169
Received on: 28-01-2011
Revised on: 11-03-2011
Accepted on: 21-05-2011

maintain the necessary blood glipizide concentration for the treatment. The in vitro characterization of the pellet formulation as well as in vivo study was investigated.

MATERIALS AND METHODS

MATERIALS

The active substance glipizide gifted from (Sidmak Laboratoties), non-pareils starch pellets were gifted from Murli Krishna Pharmaceuticals, Pune. Eudragit NE 30D and Eudragit L30D-55was gifted from (Degussa Mumbai. India), polyvinyl pyrrolidone K-30 (PVP-K 30) from (Signet Chemical Corporation, Mumbai, India), potassium dihydrogen orthophosphate was procured from S.D. Fine Chem. Ltd; India. All other chemicals/reagents used were of analytical grade.

METHODS

Preparation of drug solution layer

Fluid bed coating method was used in order to prepare spherical pellets. Glipizide was incorporated into non-pareils seeds by spraying glipizide in a solution in methylene chloride containing polyvinyl pyrrolidone (PVP 30K) as a binder and talc as antisticking agent. The composition of glipizide solution for non perils are stated in Table 1.

The stated amounts of glipizide and PVP 30 K were dissolved in methylene chloride solution separately. After mixing each solution for a certain period of time, these two solutions were mixed together and volume was made up to the 100ml by using methylene chloride. Pellets were coated by using fluid bed coater (Umang Pharmatech Pvt. Ltd.) The pellets were dried at room temperature up to a constant weight. Drug solution layering parameters for non pareils is given in Table 2.

Polymer coating

The dispersion used to deposit on a drug loaded pellets constituted of Eudragit NE 30 D and Eudragit L 30 D55 at the ratio 80:20. Eudragit L 30 D55 was previously plasticized with 10% triethyl citrate based on dry polymer weight. Talc, at 50% of total polymer weight, was homogenized with purified water for 10 minutes using a high speed stirrer and then added to the polymer blend. The solid content of coating dispersion was adjusted by diluting with purified water. The coating composition and parameters are mentioned in the Table 1 and 2 respectively. Coating process was performed to the desired theoretical weight gain of 5, 10, 20, 30, and 40%. At the end of the coating process, the beads were collected and cured at 40°C for 12 h. No sticking was observed at the end of this period (Malah YE et al., 2008).

Table 1: Composition of glipizide solution and Eudragit coating solution of NE 30 D: Eudragit L 30 D55 for non pareils

Sr. No.	Ingredients	Quantities	Ingredients	Quantities (%)
1	Glipizide	0.5 g	Eudragit NE 30 D	80
2	Polyvinylpyrolidone (PVP) 30K	3.5 g	Eudragit L 30 D 55	20
3	Talc	1.5 g	Triethyl citrate	10
4	Methylene Chloride q.s.	100 ml	Talc	50

Table 2: Coating parameters for Drug solution layering and Eudragit NE 30 D: Eudragit L 30 D55 non pareils

Sr. No.	Process Parameters	Conditions	
		Drug solution layering	Eudragit NE 30 D: Eudragit L 30 D55
1	Non - pareils	500 gms	200 gms
2	Spray rate	5 ml/min	3 ml/min
3	Atomizing air pressure	1.2 kg/cm^2	1.2 kg/cm^2
4	Product bed temperature	30°C	43°C
5	Wurster insert	Bottom spray	Bottom spray
6	Preheating of time	10 min at 80°C	10 min at 80°C
7	Coating efficiency	70.86%	72.33%
8	Inlet temperature	40°C	56°C
9	Pump RPM	1	1

Evaluation of pellets

Friability Test

Friability of all pellets (Eudragit coated pellet formulations, glipizide coated non-pareils seeds, and uncoated non-pareils seeds) were determined by using USP friability test apparatus. Friability of the pellet formulations was evaluated over 10 g of samples in Roche Friabilator at 25 rpm for 4 minutes (USP, 2004). Prior to and following the test, the weights of the formulations were accurately recorded and the friability ratios were calculated with Equation where w_0 is the initial weight and w_t final weight of the formulation. The results are

expressed in terms of the percentage of weight lost during the process.

$$F = 100 (1 - W_t / W_0)$$

Where, Wo = wt. of pellets before friability test.

W_t = wt. of pellets after friability test.

Drug content

100 mg of glipizide loaded pellets were triturated to get fine powder, and then it was transferred into 100 ml volumetric flask and dissolved in 100 ml phosphate buffer pH 7.4. The resulting mixture was agitated on an orbital shaker (Remi instruments, Mumbai) for 24 h. Quantity of samples equivalent to 10 mg of glipizide were taken, filtered through 0.45 µm whatman filter paper, diluted suitably and anlysed at 276 nm (Behera BC et al., 2008) using spectrophotometer. The experiment was performed in triplicate and mean values were taken.

Scanning electron microscopy (SEM)

The morphology of pellet were studied by scanning electron microscopy (SEM) (JEOL JSM 6360A, Physics Department, Pune University, Pune) was performed to characterize the surface of formed pellets. SEM photographs of the Eudragit NE 30 D and Eudragit L 30 D 55 coated nonpareil pellets of glipizide were taken before and after coating using. The coated pellets were loaded on studs and applied fine gold coating with gold for 5min at 10mA ion current under a pressure of 0.1 Torr using ion sputter. The coated pellets were scanned and the micrographs were examined.

***In vitro* Drug release studies**

A USP basket apparatus has been used to study *in-vitro* drug release from pellets. The dissolution test for coated pellets equivalent to 10mg was performed in triplicate using dissolution test apparatus (Veego DA-6D USP Standard). The dissolution test was performed using 900 ml pH 7.4 buffer, at 37 ± 0.5°C and 100 rpm. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. Withdrawn samples (10 mL) were analyzed spectrophotometrically at 276 nm (JASCO, V-530, Japan). Cumulative percentage drug release was calculated using PCP Disso v2.08 software (Poona College of Pharmacy, Pune).

***In-vivo* study**

Before starting the experiments on animals, the experimental protocol was cleared by the Institutional Animal Ethical Committee (CPCSEA/IAEC/PT-02/07-2K2). The study was conducted in accordance with standard institutional guidelines. Three groups of Wistar rats of either sex weighing 250 to 300 g each (4 in each group) with no prior drug treatment, that were fasted with water at 24 hours before the experiments were used for the study. An in vivo evaluation study for best found formulation was performed on normal healthy Wistar rats (Shukla NR, 2007).

Induction of diabetes mellitus

Diabetes was induced in the rats by administering alloxan monohydrate (120mg/kg) intraperitoneally into the 24 hr fasted rats. The rats had free access to standard laboratory feed and water and were kept under standard laboratory conditions. Blood samples were collected after 48 h. and blood glucose levels were estimated. Albino rats which have shown more than 200 mg/dl blood glucose levels were considered as diabetic. These animals were used for further studies.

The diabetic rats were marked conveniently and distributed randomly into three groups of 4 animals. All the animals were over night fasted with water. The animals in group-1 received A dose of 800 µg/kg of glipizide was administrated in a suspension form (freshly prepared) for each rat. Group-2 animals received the pellets of glipizide were administered orally to each group using stomach intubation tube. Group-3 animals marked as control received only saline water only. A blood sample as a control was taken from each rat from behind the eyeball through the angle of ocular cavity using small capillary tubes. The blood glucose level for the control and test samples was determined using the glucose-measuring instrument. The instrument was self-calibrated, and the samples were al-

Table 3: Friability and drug content results of formulations

Formulations	Friability[a] (%)	Drug Content[a] (%)
F_1	0.1	97.47±0.25
F_2	0.04	96.58±0.15
F_3	0.03	97.48±0.19
F_4	0.5	95.84±0.30
F_5	0.7	94.89±0.21
Glipizide coated non- pareils	0.1	97.8±0.15
Uncoated non- pareils	0.2	--

F-formulation [a]Mean ± SD; n = 3.

For friability, Formulations F_1 - 5% weight gain, F_2 - 10% weight gain.

F_3 - 20% weight gain, F_4 - 30% weight gain. F_5 - 40% weight gain.

lowed to dry before the results were read to avoid contamination of the lens. Blood samples were collected at predetermined time at 1 h. up to 12 h, and the blood glucose level was performed as per method described earlier. The percentage reduction in blood glucose level was measured. The percentage reduction in glucose level was calculated as follow (Igboasoiyi AC et al., 2007),

$$\text{Percent change} = G_T / G_o \times 100$$

Where G_T = blood glucose concentration at time t

G_o = blood glucose concentration at time zero

RESULTS AND DISCUSSION

Friability Test

Friability results for all pellet formulations (Eudragit coated pellet formulations, glipizide coated non-pareil seeds and uncoated non-pareil seeds) as a characterization parameter were evaluated and the results were in a range between ratios of 0.03-0.7 %. Detailed results for all pellet formulations are expressed in Table 3.

All other pellet formulations achieved friability values less than 1%. Thus all pellets passed the USP friability test.

Drug content

Drug content of pellet formulations (F1 to F5) was found out to be 97.88 to 101.89%. So the drug content was found out be within the limit (Table 3).

Scanning electron microscopy (SEM)

Morphology of non pareils was examined by scanning electron microscopy. The view of the pellets showed a spherical structure with a rough surface morphology Fig I (i).

Coated pellets have smooth surface and porous in nature and the polymers was uniformly distributed onto the pellet which allows penetration of dissolution media and allow passage of drug which may responsible for controlled drug release Fig I (ii).

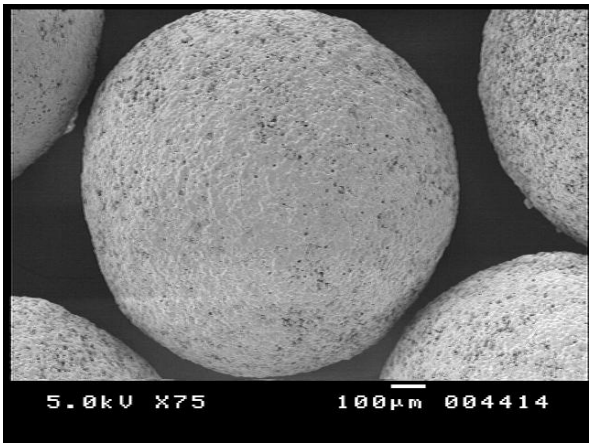
***In vitro* drug release**

In vitro dissolution studies of glipizide from different pellets were performed in phosphate buffer pH 7.4 for 12 h using USP Type I dissolution test apparatus. The in vitro release experiments were evaluated in order to investigate the effect of the type of coating polymer and the amount of the polymer regardless from the type. Glipizide pellets coated with this blend revealed a drug release in a control manner, as indicated by dissolution profile and also the time required to release 50% of the drug release delayed. This could explain by the fact that the 80:20 blend was a homogeneous mixture of the two polymers (Min-Soo K et al., 2007). This was implication of the molecular structure of the film and its ability to control the drug release. At this ratio during coating and curing process, water evaporation generates surface tension effects and capillary forces between the polymer particles. This results in the coalescence of the individual colloidal particles and the inter diffusion of polymeric particles to form a continuous film (Fukumori Y, 1994). Therefore pellets were cured at 40°c for 12 hrs to produce a densely packed homogeneous film in which Eudragit L30D 55 was molecularly distributed. Curing leads to a complete fusion of the polymer particles to form a continuous film, which is facilitated by the evaporation of the residual water. During dissolution process in dissolution medium with pH ≥ 5.5, Eudragit L30 D-55 dissolved slowly creating microscopic pores through which drug diffused into the dissolution medium. Glipizide loaded pellets were coated with an 80:20 Eudragit blend to a theoretical weight gain ranging from 5 to 30%, based on dry polymer weight. A linear correlation was observed between T_{50}, which is the time required for 50% drug release, and theoretical polymer content. T_{50} increased with an increase in the theoretical weight gain of both polymer blends. This is due to the time required for the drug to diffuse through the coating membrane. The formulation F_1 shows 86.82% and 91.41% drug release whereas formulation F_2 shows 81.89% and 91.6% drug released in 9 and 10 h respectively. Formulation F3, F4 and F5 showed the glipizide release 82.93%, 87.75% and 88.73% in 10, 11 and 11 h. respectively which is shown in Table 4.

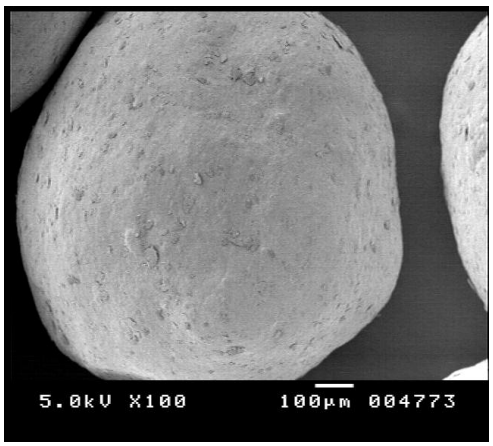
From the dissolution profile (Figure II) it is understood that as the coating thickness increased drug release is retarded.

***In Vivo* Studies**

In vivo efficiency of the best found formulation F5 was performed in healthy normal Wistar rats by measuring the hypoglycemic effect produced after oral administration. The drug was administered at a dose equivalent to 800 mg/ kg pure glipizide, and glipizide pellets were used for the study. Pure glipizide drug was administered in a suspension form at the same dose. When pure glipizide suspension was administered, a rapid reduction in blood glucose levels was observed and maximum reduction of 54.3% was observed within 2 h after oral administration. In the case of glipizide pellets, the reduction in blood glucose levels was slow and reached maximum reduction within 4 h after oral administration. This reduction in blood glucose levels was sustained over longer periods of time (12 h). Kahn and Shechter have suggested that a 25% reduction in blood glucose levels is considered a significant hypoglycemic effect (Kahn CR, 1991). Significant hypoglycemic effect (25%) was maintained only from 0.5 to 5 h after oral administration of glipizide, whereas in the case of glipizide pellets, significant hypoglycemic effect (25%) was maintained for a period of 2 to 12 h. Whereas blood glucose level during the study was shown in Figure III.



[i] – Non pareils



[ii] – Coated pellets

Figure 1: SEM of pellets

Table 4: Dissolution study of Eudragit NE 30D: Eudragit L30D coated glipizide loaded pellets

Time (Hrs)	Cumulative % drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	22.43	18.13	14.73	6.97	1.38
2	30.63	27.8	22.18	13.84	8.45
3	38.46	33.1	28.67	20.75	16.45
4	46.98	38.17	36.43	32.76	25.75
5	53.33	47.03	43.62	41.39	38.34
6	64.26	56.59	50.77	50.24	46.15
7	75.05	64.39	58.66	57.62	55.17
8	83.8	72.58	66.89	66.78	63.08
9	86.82	81.89	73.72	73.27	69.34
10	91.41	91.6	82.93	80.11	78.81
11	97.48	95.2	90.5	87.75	84.16
12	-	98.7	97.74	92.43	88.73

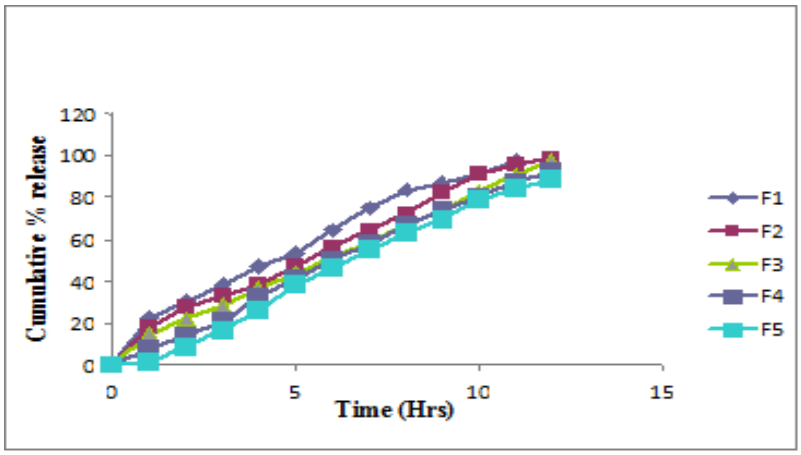


Figure 2: Dissolution profiles of formulations F1to F5

The sustained hypoglycemic effect observed over a longer period of time in the case of pellets is due to the slow release and absorption of glipizide over longer periods of time. The percentage reduction in glucose level is given in Table 5.

CONCLUSION

Controlled release pellets of glipizide were prepared by coating drug pellets with Eudragit NE 30 D and Eudragit L 30 D55 dispersion using fluidized bed coater. The coated pellets were found to provide desirable controlled release rates during 12 h testing interval. The results of this study indicated that coating the drug loaded pellets by polymer blends upto 30% weight gain gives controlled release of glipizide from the pellets. The in vivo study demonstrated significant hypoglycemic activity of the pellets of glipizide. Further studies are needed for determining the performances of these

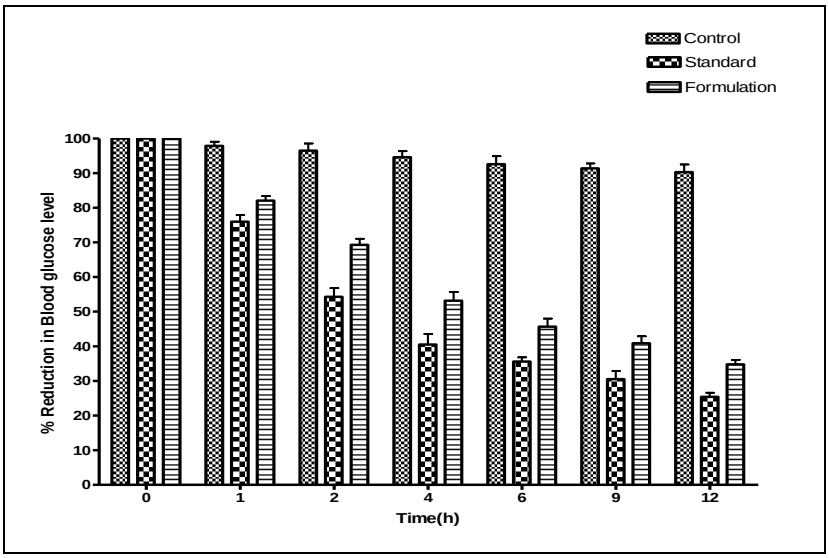


Figure 3: Blood glucose level during the study

Table 5: Change in blood glucose levels at different time intervals

Reduction in blood glucose concentration, Mean ± SEM			
Time in Hrs	**Control**	**Standard**	**Formulation**
Fasting	100	100	100
1	97.9 ±1.22	76. ± 1.9	82.10 ±1.3
2	96.5 ± 2.11	54.3 ± 2.5	69.30 ± 1.8
4	94.66 ± 1.7	40.5 ± 3.1	53.19 ± 2.5
6	92.6 ± 2.3	35.6 ± 1.2	45.70 ± 2.3
9	91.41 ± 1.4	30.5 ± 2.3	40.90 ± 2.0
12	90.33 ± 2.2	25.4 ± 1.2	34.80 ± 1.3

formulations for the aim of extending the release of glipizide.

ACKNOWLEDGEMENTS

The authors thanks to Pune University for performing SEM studies. The authors greatly acknowledge Sidmak laboratories Pvt Ltd. Gujrat, India for the supply of Glipizide as a gift sample, Murali Krishna Pharmaceutical, India for supply of nonpareil beads as gift sample.

REFERENCES

Behera, BC. Sahoo, SK. Dhal, S. Barik, BB. and Gupta, BK. 'Characterization of glipizide loaded polymethacrylate microspheres prepared by an emulsion solvent evaporation method', Tropical Journal Pharmaceutical Research, vol. 7, 2008 pp. 879-885.

Boles, MG. Deasy, PB. and Donnellan, MF. 'Microencapsulation studies on aminophylline involving spherical crystallization, spheronization and drug loading on to non-pareil seeds', Journal Microencapsulation, vol. 11, 1994 pp. 55-67.

British Phamacopoeia, London, 1993, vol 1, 306-307.

European Pharmacopoeia, 4th edition, Strasbourg, 2001, 1248-1249.

Fukumori, Y. 'Multiparticulate Oral Drug Delivery-Drugs and Pharmaceutical Science', Marcel Dekker: New York, vol. 65 1994 pp. 79-117.

Ghebre-Sellassie, I. Pharmaceutical Pelletization Technology, 1st Edition, Marcel Dekker Inc: New York, 1989 pp. 1-13.

Govender, T. Dangor, C. and Chetty, DJ. 'Drug release and surface morphology studies on salbutamol controlled release pellets', Drug Development Industrial Pharmacy. Vol. 21, 1995 pp. 1303-1322.

Govender, T. Dangor, C. and Chetty, DJ. 'Microencapsulated Eudragit RS30D-coated controlled-release pellets: the influence of dissolution variables and topographical evaluation', Journal Microencapsulation, vol. 14, 1997 pp. 1-13.

Heng, PWS. Wan, LSC. and Tan, YTF. 'Relationship between aggregation of HPMC coated spheroids and tackiness/viscosity/additives of the coating formulations', International Journal Pharmaceutics, vol. 138, 1996 pp. 57-66.

Igboasoiyi, AC. Essien, EE. Eseyin, OA. and Ubam, G. 'Screening of the seed of picralima nitida for hypoglycemic activity', Pakistan Journal Biological Sciences, vol. 10, 2007 pp. 828-836.

Iyer, RM. Augsburger, LL. and Parikh, DM. 'Evaluation of drug layering and coating: effect of process mode and binder level', Drug Development Industrial Pharmacy, vol. 19, 1993 pp. 981-998.

Kahn, CR. and Shechter, Y. Goodman and Gilman's the Pharmacological Basis of Therapeutics, 8th edition, McGraw-Hill: New York, 1991, pp. 1461-1495.

Kivisto, KT. and Neuvonen, PJ. 'Enhancement of absorption and effect of glipizide by magnesium hydroxide', Clinical Pharmacology Therapeutics, vol. 49, 1991 pp. 39-43.

Lebovitz, HE. 'Glipizide: A second-generation sulfonylurea hypoglycemic agent', Pharmacotherapy. Vol. 5, 1985 pp. 63-77.

Lin, SY. 'Release kinetics of drug from different combined ratios of micropellets', Journal Microencapsulation, vol. 10, 1993 pp. 319-322.

Malah, YE. and Nazzal, S. 'Novel use of Eudragit NE 30D/Eudragit L 30D-55 blends as a functional coating material in time-delayed drug release applications', International Journal Pharmaceutics, vol. 357, 2008 pp. 219-227.

Mehta, AM. Valazza, MJ. and Abele, SE. 'Evaluation of fluidized-bed processes for enteric coating systems', Pharmaceutical Technology, vol. 12, 1986 pp. 46-56.

Min-Soo, K. Jeong-Soo, K. Yeon-Hee, Y. Hee Jun, P. Lee, S. Jeong-Sook, P. Jong-Soo, W. and Sung-Joo, H. 'Development and optimization of a novel oral controlled delivery system for tamsulosin hydrochloride using response surface methodology'. International Journal Pharmaceutics, vol. 341, 2007 pp. 97-100.

Moffat, AC. (ed.) Clarke's Isolation and Identification of Drugs, 20th edition, The Pharmaceutical Press: Great Britain, 1986.

Palsson, BO. Wheatley, TA. and Dressman JB. 'Mechanism of release from pellets coated with an ethylcellulose based film', Journal Controlled Release, vol. 14, 1990 pp. 203-213.

Sellassie, IG. Gordon, RH. Fawzi, MB. Nesbitt, RU. and Davis, WLP. 'Evaluation of a high speed pelletization process and equipment', Drug Development Industrial Pharmacy, vol. 11, 1985 pp. 623-631.

Shukla, NR. and Chanda, S. 'Assessment of polyalthia longifolia var. pendula for hypoglycemic and antihyperglycemic activity', Journal Clinical and Diagnostic Research, vol. 1, 2007 pp. 116-121.

Stamm, A. 'Process and dosage form controls: Formulation factors', Drug Dev Indian Pharmacy, vol. 15, 1989 pp. 965-974.

The United States Pharmacopeia (USP 27), Toronto: Webcom Limited, 2004.

Wang, DP. Yang, MC. and Wong, CY. 'Formulation development of oral controlled-release pellets of diclofenac sodium', Drug Development Industrial Pharmacy, Vol. 23, 1997 pp. 1013-1017.

Wu, XY. Eshun, G. and Zhou, Y. 'Effect of interparticulate interaction on release kinetics of microsphere ensembles', Journal Pharmaceutical Sciences, vol. 87, 1998 pp. 586-593.

Zhon, Y. and Wu, XY. 'Modeling and analysis of dispersed-drug release into a finite medium from sphere ensembles with a boundary layer', Journal Controlled Release, vol. 90, 2003 pp. 23-36.