IJPSR (2015), Vol. 6, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 24 May, 2014; received in revised form, 26 July, 2014; accepted, 16 September, 2014; published 01 January, 2015

A NOVEL SUSTAINED RELEASE ROBUST MATRIX PELLETS OF GLIPIZIDE

P. K. Puranik*, S. D. Pol, S. B. Patil, N. G. Ransing, P. S. Ramteke, B. A. Patil, P. K. Khobragade and R. G. Palaskar.

Department of pharmaceutics, Government College of pharmacy, Aurangabad-431005, MH, India.

Keywords:

Robust, Matrix pellets, Glipizide, Extrusion –Spheronization, sustain release.

Correspondence to Author:

Shankar D. Pol

Research Associate, Intellectual property Rights (IPR-Formulation), Getz Pharma Research Pvt. Ltd. Plot PL -11, M.I.D.C. Anandnagar Addl, Ambernath, Dist. Thane-421506, India

E-mail: polshankar01@yahoo.com

ABSTRACT: Multiparticulate drug delivery system are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some amount desired characteristics such as pellets.The purpose of present study was to prepare sustained release robust matrix pellets of Glipizide. The study revealed successful application of factorial design, optimization of extrusion spheronization process, and sustaining release of Glipizide for formulating uniform, spherical Glipizide pellets. Speed and time of spheronization is critical parameter for optimum sphericity. The Optimum speed and time of operating spheronization is 1350 rpm and 15 min. The results of this study showed that combination of HPMC K100M LVCR as hydrophilic matrix polymer and PEG 400 as potential plasticizer is effective and useful for sustaining the Glipizide release to treat diabetes mellitus. The in-vitro studies showed Q16 at approximately 80% cumulative release in case of F4, F5, F6, It indicates that this system can sustain the release upto 24 h which is desirable for sustained release specificity. Although, the hydrophilic matrix polymer optimization is critical for drug release, this study suggests the promising approach for formulation of sustained release robust matrix pellets of Glipizide.

INTRODUCTION: Recent trend in pharmaceutical research is to design and develop new formulations, thereby enhancing the therapeutic efficacy of existing drugs. Invariably, new drug discovery and patenting new drug which is time and money consuming process. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some amount desired characteristics. Together, these characteristic units provide the overall desired sustained release (SR) of the dose.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(1).333-44

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(1).333-44

These multiple units are also referred as pellets, spherical granules or spheroids[1]. Though there are many approaches to prepare pellets, such as extrusion and spheronization, fluid bed granulation, centrifugal granulation. Extrusion-spheronization is one of common strategies to prepare pellets for acquiring modified release systems in pharmaceutical industry since 1970, and the method consist of two basic processes of extrusion and spheronization.

Pellets prepared by the method of extrusion-spheronization have some advantages, such as high sphericity, compact structure, low hygroscopicity, narrow particle size distribution and smooth surface[1]. If there is dose dumping occur with sustained release monolithic tablet which result in dramatic side effects. By contrast, in multiparticulate formulation, reduced the toxicity and risk dose dumping[2]. Sustained release from

pellets is conventionally achieved by polymeric coating. There is growing interest in the development of matrix pellet formulations because, in practice, polymeric coating is associated with various problems. 1) The process is time consuming and expensive 2) Film thickness is variable 3) There may be cracks in the film or aging of the polymer coating which leads to dose dumping. Hence, we aimed to develop sustained release matrix pellets by extrusion- spheronization method[3].

Many acute and chronic diseases require frequent medication. The problem can be solved by developing sustained release dosage form with similar therapeutic response as that of conventional dosage forms and longer duration of action without fluctuations in drug levels in plasma. The sustained drug delivery includes application of physical and polymer chemistry. These polymers slowly release the drug in biosystem and maintain blood drug level within therapeutic range for longer duration[4,5].

Diabetes mellitus is one of the major causes of death and disability in the world. Although the prevalence of both Type-I and Type-II diabetes is increasing worldwide, the prevalence of Type- II diabetes is expected to rise more rapidly in future because of sedentary lifestyle, increasing obesity and reduced activity levels. Glipizide is a second generation sulfonylurea and is one of the most widely used agents against Type II diabetes. It is a weak acid (pKa = 5.9), practically insoluble in water and acidic environment but highly permeable drug belonging to BCS class 2.

It has a short biological half life (3.4± 0.7 h) and requires 2–3 doses per day for treatment. This drug is usually intended to be taken for a long period of time, which often leads to non-compliance.

Thus, there is a strong clinical, Industrial, social need and market potential for sustained delivery system for Glipizide, as follows- **A) Medical:** For utilization of optimum dose, at the right time, and in the right location. **B) Industrial**: For efficient use of expansive ingredients and reduction in production costs. **C) Social:** Beneficial to patients, better therapy and improved comfort. Thereby resulting in better patient compliance[6].

MATERIALS AND METHODS

Glipizide was obtained as a gift sample from Wockhardt research center, Aurangabad, India. HPMC K100 LVCR, HPMC K4M was provided by Colorcon Asia Pvt. Ltd., Goa, India. Eudragit L100 was obtained from Evonik. MCC PH 101 was provided by Signet chemical corporation Pvt. Ltd., Mumbai, India. PEG 400 was provided by Degussa Pvt. Ltd. Other excipients used to prepare pellets were of standard pharmaceutical grade and all chemical reagents of analytical grade.

EXPERIMENTAL

Optimization of Extrusion Spheronization Process

Pellets prepared by Extrusion and spheronization technique. To reduce the computational complexities, above mentioned components were eased to (2) two independent variables namely,

Speed of spheronization (X1) = 1200, 1350, 1500 rpm

Time of spheronization (X2) = 10, 15, 20 min

The approximate appropriate levels of these independent variables were chosen from the data available from literature as well as the initial experimentation while Aspect ratio, Roundness, Carr's index of pellets as dependent factor.

It becomes essential to use a factorial design with 3 levels to estimate curvature in response (i.e. 3^2 factorial with total no. of experiments = 9). To save time, single block design with zero (0) replication has been preferred. The experimental grid was coded for ease of representation in **Table 1** and **2**.

TABLE 1: TRANSLATION OF EXPERIMENTAL CONDITIONS INTO PHYSICAL UNITS FOR EXTRUSION SPHERONIZATION

Coded Values	Actual Values (%)		Response		
	X_1 (Speed)	X_2 (Process time)	Y_1	Y_2	Y3
-1	1200	10	Aspect	Roundness	Carr's
0	1350	15	ratio		index
+1	1500	20			

TABLE 2: FACTOR COMBINATION AS PER THE EXPERIMENTAL DESIGN FOR EXTRUSION SPHERONIZATION

Variable level	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
X1	-1	-1	-1	0	0	0	1	1	1
X2	-1	0	1	-1	0	1	-1	0	1

Following parameters were kept constant for extrusion spheronization process, Extrusion Sieve: 1 mm, Extruder speed: 45 rpm, Radial plate of Spheronizer: 4.2 mm. Optimized Formula for Non-Drug Loaded Pellets is shown in **Table 3**.

TABLE 3: OPTIMIZED FORMULA FOR NON-DRUG LOADED PELLETS

Sr.no	Ingredients	Quantities
1	MCC PH101	28gm
2	HPMC K100M LVCR (powder form)	1.5gm
3	HPMC K4M (2% w/v solution in water)	Approximate 22 gm
4	PEG 400 (2% v/v solution in 2% HPMC K4M)	
5	Water	q.s.

To optimize spheronization speed, to optimize spheronization time, to get aspect ratio nearer to 1, to get maximum roundness.

Evaluation of dummy pellets

The objective of present investigation was to optimize process of extrusion spheronization for pelletization.

All the factorial batches were evaluated for physical, morphological, flow properties and friability. Results of all factorial batches are mentioned in **Table 4** and **Table 5**.

TABLE 4: FLOW PROPERTY OF PELLETS

Flow property	Angle of Repose (θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's Index (%)	Hausner's Ratio
F1	34.90±2.51	0.65±0.028	0.81±0.04	19.75±0.52	1.24±0.04
F2	32.88±1.33	0.71±0.02	0.84±0.02	15.71±0.31	1.18±0.02
F3	31.30±1.17	0.73±0.01	0.87±0.01	16.09±0.20	1.19±0.02
F4	26.29±2.37	0.74±0.01	0.85±0.02	12.94±0.25	1.14±0.02
F5	23.72±1.06	0.87±0.01	0.94±0.02	7.79±0.07	1.08±0.01
F6	25.39±1.45	0.75±0.008	0.84±0.009	10.71±0.19	1.12±0.02
F7	33.29±1.67	0.82±0.04	0.95±0.05	15.71±0.31	1.16±0.03
F8	29.75±3.26	0.75±0.01	0.83±0.02	9.63±0.28	1.11±0.02
F9	30.2±2.62	0.79±0.02	0.90±0.05	12.22±0.27	1.14±0.03

TABLE 5: MORPHOLOGICAL CHARACTERISTICS OF PELLETS

Batches	Shape	Aspect ratio	Roundness (%)
F1	Cylindrical /Rod	1.19-2.49	38.394 – 46.691
F2	Cylindrical /Rod	1.17 – 2.01	70.296 - 78.768
F3	Cylindrical + Dumbbell	1.15-1.18	62.514 - 73.641
F4	Dumbbell + Oval	1.11-1.14	81.623 -85.152
F5	Sphere	1 – 1.07	91.85-99.106
F6	Oval + Sphere	1.09-1.12	87.128 - 93.125
F7	Dumbbell +Ellipsoid	1.18 - 1.19	41.667 - 48.077
F8	Oval + Sphere	1.13 – 1.16	87.072 – 98.07
F9	Ellipsoid + Oval	1.15 - 1.17	63.763 - 67.473

The Photomicrographic study also confirmed that batch F5 has more spherical and uniform pellets with smooth surface compared to other batches. The comparative studies of photomicrograph of all batches are as shown in **Figure 1**. Thus, Batch F5 was selected as a final optimized batch and used for further studies. On the basis of dummy pellets evaluation (F1 to F9 batches) optimized Parameters for Extrusion Spheronization as shown in **Table 6**.

TABLE 6: OPTIMIZED PARAMETERS FOR EXTRUSION SPHERONIZATION

Parameter	Value
Extrusion speed	45 rpm
Extrusion sieve	1 mm
Spheronization plate	4.2 mm
Spheronization speed	1350 rpm
Spheronization time	15 min

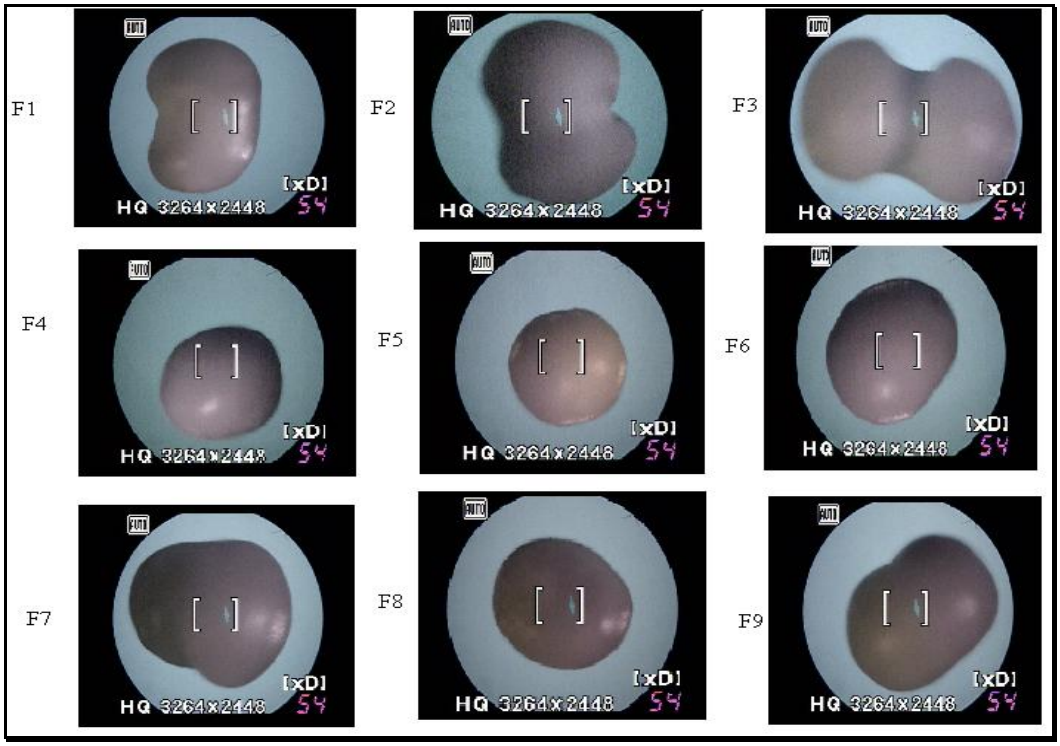

FIGURE 1: PHOTOMICROGRAPHS OF ALL BATCHES (F1 TO F9)

Particle Size Analysis of Final Batch (F5)

Particle size was determined by optical microscopy for pellets. Average particle size was found to be 945.595±015 mm. Roundness of the pellets was found to be 94.079 %. Hence it was concluded that the pellets were spherical. Particle size analysis parameters of pellets are shown in **Table 7**.

TABLE 7: PARTICLE SIZE ANALYSIS PARAMETER OF PELLETS

Length	Width	Area	Asp. Ratio	Roundness	Shape	Sphere volume
1001.789	962.81	795694.4	1.04	95.293	0.01	61524192

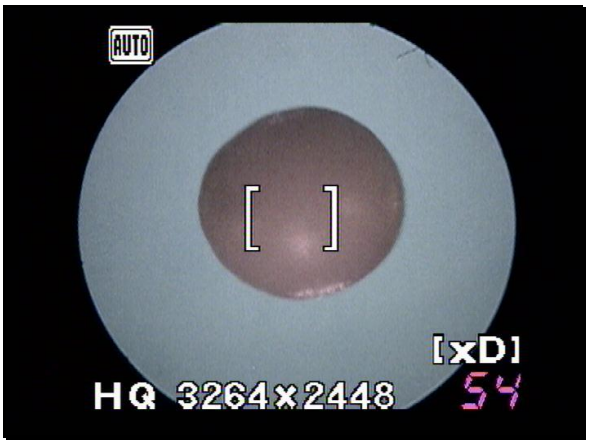

FIGURE 2: OPTICAL PHOTOMICROGRAPH OF OPTIMIZED BATCH (F5) PELLET

Statistical Analysis of Extrusion Spheronitzation Data

The 3^2 full factorial design was selected to study the effect of independent variables Spheronization speed (X1) and spheronization time (X2) on parameter Optimization for Extrusion Spheronization. The response data was analyzed by using Stat Ease Design Expert 8.0.1 software (Minneapolis, MN, USA). Summary of statistical design and responses shown in **Table 8** and **9** respectively. The results were shown in the **Table10, 11** and **12**. The final equations in terms of coded values of factors and actual values of factor obtained from software Design Expert are given below-

Final equations for Aspect Ratio in terms of coded factors:

Aspect Ratio = 1.02 - 0.28 (A) - 0.18 (B) + 0.16 (AB) + 0.40 (A) 2 + 0.12 (B) 2

Final Equation for Roundness in Terms of Coded Factors

Roundness = 90.30244959 + 13.85631809(A) + 4.410158605(B) + 3.117693182(AB) - 22.80882411(A) ^{2} - 4.136619895 (B) ^{2}

Final Equation for Carr's Index in Terms of Coded Factors

Carr's Index = 8.13 - 2.33(A) - 1.56 (B) + 0.042 (AB) + 4.37(A) 2 + 3.53(B) 2

P-value less than 0.05 indicated significance of the model terms. Analysis of variance (ANOVA) indicated that the developed models were significant for each considered response. The large Model F-values imply that the model is significant. Smaller the P value, more significant is the corresponding coefficient. Positive and negative sign in front of the terms indicate synergistic and antagonistic effect upon the factors respectively. The regression coefficient (r2) was high indicating the adequate fitting of the quadratic model for response Aspect Ratio, Roundness and Carr's Index.

The analysis of variance study of the data also showed same results revealing the spheronization speed and spheronization time as significant variable (P value <0.05) at all response point. It indicates the significance of spheronization speed and spheronization time in the evaluation of pellets for optimization of extrusion spheronization.

The 3D response plots were constructed from quadratic model obtained through Design Expert software in which the responses were represented by bars as a function of independent variables as shown in the **Figures 3, 4** and **5**. The relationship between the response and independent variables can be directly visualized from the response plots[7].

TABLE 8: SUMMARY OF STATISTICAL DESIGN

Factor	Name	Unit	Type	Actual values		Coded Values	
				Lowest	Highest	Lowest	Highest
A	Spheronization speed	rpm	Numerical	1200	1500	-1	+1
B	Spheronization Time	Min	Numerical	10	20	-1	+1

TABLE 9: SUMMARY OF RESPONSES

Response	Description	Units	Obs.	Analysis	Min	Max	Mean
Y1	Aspect Ratio	-	9	polynomial	1	2.49	1.74
Y2	Roundness	%	9	polynomial	38.394	99.106	68.250
Y3	Carr's Index	-	9	polynomial	7.79	19.75	13.77

TABLE 10: ANALYSIS OF VARIANCE FOR ASPECT RATIO

Source	F Value	p-value, Prob > F
Model	10.95	0.0040
A-Spheronization speed	22.89	0.0009
B-Spheronization time	9.10	0.0541
AB	5.13	0.0577
A^2	16.13	0.0043
B^2	1.48	0.8831

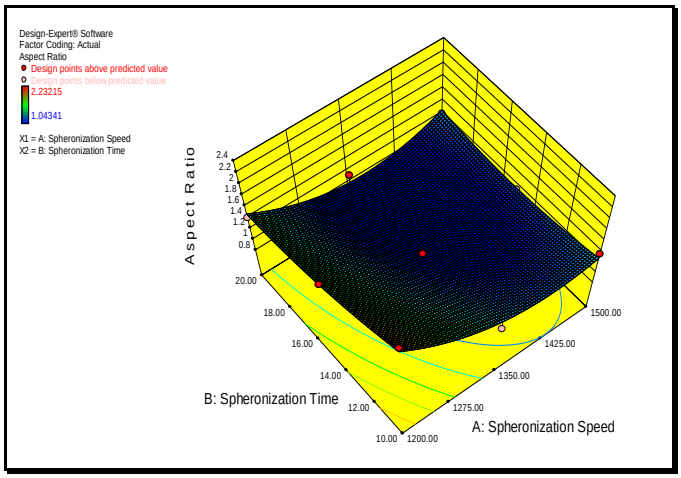

FIGURE 3: 3D PLOT FOR ASPECT RATIO

TABLE 11: ANALYSIS OF VARIANCE FOR ROUNDNESS

Source	F Value	p-value Prob > F
Model	12.70	0.0312
A-Spheronization speed	30.72	0.0116
B-Spheronization time	3.11	0.1759
AB	1.03	0.3835
A2	27.75	0.0133
B2	0.91	0.4098

TABLE 12: ANALYSIS OF VARIANCE FOR CARR'S INDEX

Source	F Value	p-value, Prob > F
Model	27.99	0.0101
A-Spheronization speed	41.35	0.0076
B-Spheronization time	18.59	0.0230
AB	9.159	0.9298
A2	48.45	0.0061
B2	31.53	0.0112

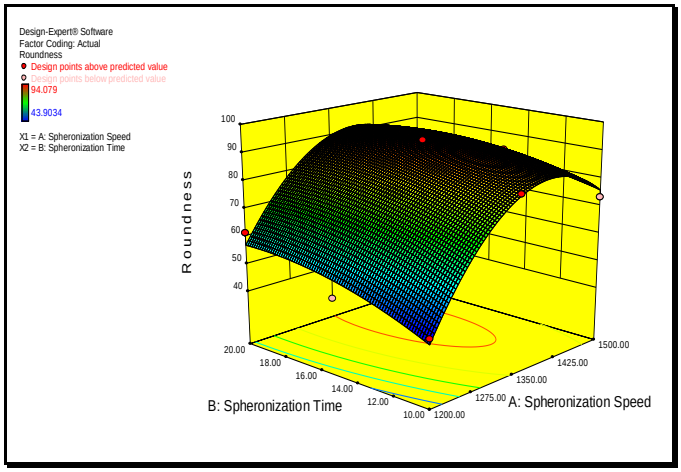

FIGURE 4: 3D PLOT FOR ROUNDNESS

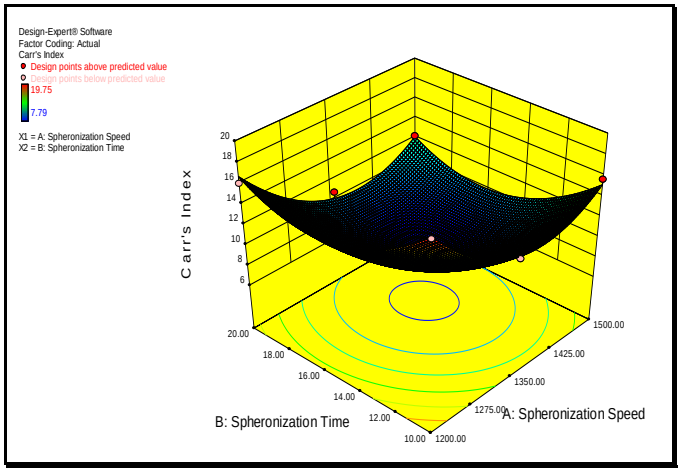

FIG 5: 3D PLOT FOR CARR'S INDEX

Preparation of drug loaded pellets

Preparation of Preliminary Drug Loaded Pellets

Preliminary batches (P1 to P6) of drug loaded pellets were prepared as per composition of preliminary batches mentioned in **Table 13** at optimized parameter of Extrusion and Spheronization process which is mentioned in **Table 6**. After preparation of Preliminary batches (P1 to P6), pellets are dried at 60°C for 3 Hrs and pellets are passed through sieve no. 20 and retained pellets are used for further in vitro drug release study.

TABLE 13: COMPOSITION OF PRELIMINARY BATCHES

Ingredients	P1	P2	P3	P4	P5	P6
Glipizide	10%	10%	10%	10%	10%	10%
MCC 101	84.6%	83%	84.%	83%	81%	82%
HPMCK100 LVCR (1gm and 1.5gm)	3.4%	5%	-	-	-	5%
HPMC E15 (1gm and1.5gm)	-	-	3.4%	5%	-	-
HPMCK100 LVCR (1gm) + Eudragit L100 (1gm)	-	-	-	-	7%	-
HPMC K4M (2%w/v solution in water)	(Approximate 22 gm) 2%PEG					3% PEG
PEG 400 (% v/v solution in 2% HPMC K4M)						
Deionised Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation of Preliminary Drug Loaded Pellets

In Vitro Drug Release Study

Preliminary batches were evaluated by studying the release profile for 12 hr, in 900ml dissolution medium (0.1N HCL for 2hr and PH 6.8 phosphate buffer for remaining 10 hr) using USP type I (Basket) dissolution apparatus with 100 rpm. The drug release from pellets ranges from 46.04% to 69.95%. With respect to weight gain of matrix polymer, % PEG and % drug release, the optimum polymer combination selected was HPMC K100M LVCR and plasticizer PEG 400. Total drug releases in 12 hr from all factorial batches are shown in **Table 14**.

TABLE 14: DRUG RELEASE STUDY OF PRELIMINARY BATCHES AT PH 6.8

Batch code	HPMC E15	HPMC K100M LVCR	HPMC K100M LVCR and Eudragit L100
P1	49.09	-	-
P2	57.64	-	-
P3	-	63.789	-
P4	-	68.81	-
P5	-	-	46.04
P6	-	69.95	-

Optimization of Sustained Release Polymer and Plasticizer Level by Using 3^2 Factorial Design

The objective of present investigation is to observe the combine effect of sustained release polymer as well as plasticizer on the drug release pattern for attaining the sustained release of Glipizide (Dependent Responses /objective functions) to maximize drug release upto 24 hr.

To achieve this objective Glipizide was used as drug and pellets were prepared by using HPMC K100M LVCR as sustaining polymer and PEG 400 as plasticizer. To reduce the computational complexities, above mentioned polymers were eased to 2 independent variables namely

HPMC K100 LVCR as sustaining polymer level(X1) = 0.5gm, 1gm, 1.5gm.
PEG 400 as plasticizer level (X2) = 1%, 2%, 3%.
The approximate levels of these independent variables were chosen from drug release profile of preliminary batches.
It becomes essential to use a factorial design with 3 levels to estimate curvature in response (i.e. 3^2 factorial with total no. of experiments = 9). To save time, single block design with zero (0) replication has been preferred. The experimental grid was coded for ease of representation in **Table 15** and **16**.

TABLE 15: TRANSLATION OF EXPERIMENTAL CONDITIONS INTO PHYSICAL UNIT FOR SUSTAINED RELEASE

Coded Values	Actual Values (%)		Response	
	X1 (HPMC K100 LVCR as sustaining polymer level)	X2 (PEG 400 asplasticizer)	Y1	Y3
-1	0.5	1	T30%	T80%
0	1	2		
+1	1.5	3		

TABLE 16: FACTOR COMBINATION AS PER EXPERIMENTAL DESIGN FOR SUSTAINED RELEASE POLYMER

Variable level	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
X1	-1	-1	-1	0	0	0	1	1	1
X2	-1	0	1	-1	0	1	-1	0	1

RESULT AND DISCUSSION:

Evaluation of Pellets

Optimization of Sustained Release Polymer and Plasticizer Polymer Ratio The matrix pellets were evaluated for drug release profile upto 24 hr, dissolution efficiency, flow, and morphological properties of pellets. Particle size analysis was studied for optimized batch.

Evaluation of Flow Properties of Matrix Pellets

The flow properties of pellets were most important parameter for filling pellets into the capsule shell.

The values of angle of repose, Carr's index and Hausnar's ratio indicate excellent flow properties of pellets. All the factorial batches were evaluated for flow property. Results of all factorial batches are shown in **Table 17**.

TABLE 17: EVALUATION PARAMETER OF MATRIX PELLETS

Batch	Angle of repose (θ)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner's ratio
F1	24.43±0.42	0.80±0.004	0.85±0.003	5.88±0.15	1.06±0.001
F2	22.13±0.28	0.74±0.004	0.78±0.003	5.12±0.27	1.05±0.001
F3	23.97±1.09	0.82±0.004	0.85±0.002	3.52±0.69	1.03±0.003
F4	25.73±0.34	0.81±0.004	0.90±0.006	10.12±0.42	1.11±0.004
F5	23.39±0.56	0.82±0.004	0.87±0.009	5.80±0.72	1.06±0.006
F6	22.65±0.30	0.78±0.009	0.88±0.01	6.81±0.49	1.07±0.005
F7	23.19±0.31	0.74±0.003	0.86±0.004	13.95±0.47	1.16±0.004
F8	22.65±0.30	0.72±0.005	0.80±0.007	10.01±0.42	1.11±0.004
F9	22.13±0.28	0.75±0.003	0.83±0.004	9.63±0.32	1.10±0.203

Morphological Characteristics of All Factorial Batches Aspect ratio and roundness are important parameters for characterization of pellets. Aspect ratio nearer to 1 and roundness nearer to 100% shows spherical pellets. The morphological characteristics of all factorial batches are as shown in **Table 18**.

TABLE 18: MORPHOLOGICAL CHARACTERISTICS OF PELLETS

Batch	Shape	Aspect ratio	Roundness (%)
F1	Dumbbell+ Sphere	1.11-1.15	80.17
F2	Sphere	1.02-1.12	86.78
F3	Sphere	1.02 – 1.11	89.63
F4	Dumbbell + Oval	1.12-1.17	79.98
F5	Sphere	1.07-1.12	85.76
F6	Sphere	1.04-1.12	85.70
F7	Dumbbell +Ellipsoid	1.13 - 1.19	77.72
F8	Oval + Sphere	1.11 – 1.14	80.46
F9	Sphere	1.11 - 1.13	83.23

Particle Size Analysis

Particle size was determined by optical microscopy for drug loaded matrix pellets. On the basis of roundness, batches F2, F3, F5, F6, and F9 have shown good result with respect to HPMC K100 LVCR and plasticizer ratio. Average particle size was found in range 945.595mm to 1076mm. Particle size analysis of batches F2, F3, F5, F6, and F9 have shown in **Table 19**.

TABLE 19: PARTICLE SIZE ANALYSIS OF BATCHES (F2, F3, F5, F6, F9)

Batch	Length	Width	Area	Asp. Ratio	Roundness	Shape	Sphere volume
F2	1004.406	904.38	751944.4	1.111	87.266	0.011	56520379
F3	1093.103	998.102	914097.2	1.095	90.955	0.011	75755633
F5	1051.075	943.87	814375	1.114	86.101	0.012	63703467
F6	1193.557	1076.617	1009306	1.109	86.101	0.012	87894233
F9	1146.422	1015.892	963194.4	1.128	83.173	0.012	81940258

Friability

The preliminary aim to produce mechanically strong pellets was thereby achieved. Friability (%) of all factorial batches is as shown in **Table 20**.

Drug Content

The drug loaded pellets of Glipizide prepared with optimized formula exhibited drug loading capacity in range of 92.97- 105.98%. Drug content of all factorial batches are as shown in **Table 20**. All values expressed as mean± SD, n=3.

TABLE 20: FRIABILITY (%) AND CONTENT UNIFORMITY

Batch	(%)Friability	Drug content
F1	0.18±0.053	92.97±0.29
F2	0.15±0.03	98.72±1.06
F3	0.14±0.026	105.98±0.65
F4	0.15±0.01	95.25±1.46
F5	0.13±0.015	99.32±0.54
F6	0.18±0.053	95.85±0.95
F7	0.13±0.03	94.89±1.08
F8	0.14±0.026	95.66±0.84
F9	0.15±0.01	100.51±0.95

Scanning Electron Microscopy

The scanning electron microscopic (SEM) evaluation is important for determining the surface morphology, size, shape[8]. Surface of pellets as shown in (**Figure 6**) SEM photograph was smooth and spherocity was also good and size of pellets was found to be 968µm to 1003µm and ratio of length to width (Aspect ratio) is 1.03 which indicates pellets are spherical in shape.

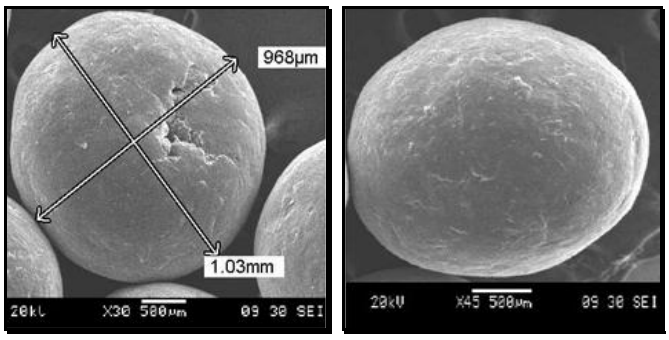

FIGURE 6: SEM ANALYSIS OF OPTIMIZED F5 BATCH

In-Vitro Drug Release Study

In-vitro drug release study of all formulation batches (F1-F9) were performed in triplicate using USP apparatus Type-I (Basket). The batch F1 showed 85.972±0.23% drug release in 12 hr, batch F2 released 84.366±0.60 % in 12 hr and F3 released 92.248±0.09 % in 12 hr. F1, F2, F3 batches sustained the drug release only upto 12hr.

These batches could not sustain the drug release upto 24 hr due to low weight gain of HPMC K100MLVCR. The batches F4, F7, F8 and F9 retarded drug release upto 78.336±0.49 % 73.294±0.43% 73.35±0.69% and 78.819±0.69 % respectively in 16 hr, which can release the drug upto 24 hr. but unable meet the criteria of 80% drug in release 16 hrs due to more weight gain of HPMC K100MLVCR as compare to F1, F2, F3 and low level of PEG 400 in case F4 and in case of F7, F8 and F9 due to more weight gain of HPMC K100MLVCR as compare to F1 to F6.

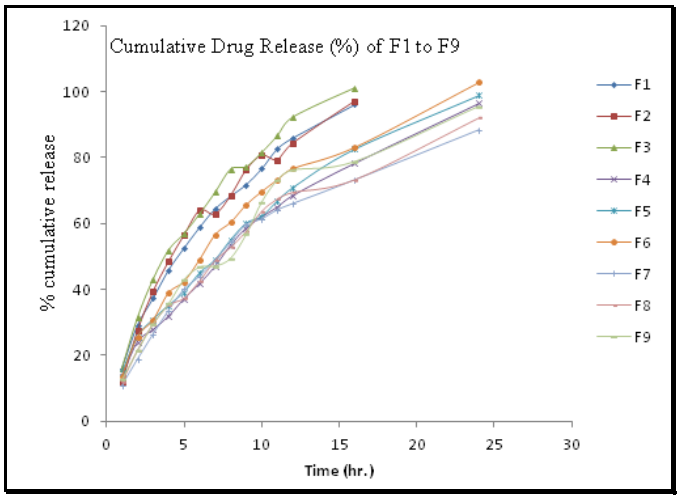

FIGURE 7: CUMULATIVE DRUG RELEASE OF ALL FORMULATION BATCHES

The batches F5 and F6 retarded drug release upto 82.601±0.43% and 83.155±0.69 % respectively in

16 hr, which also sustained drug release upto 24 hr. Only the batches F5 and F6 showed desirable release profile suitable for sustained release system. The PEG 400 increases drug release as increasing the level from 1% to 3%. These drug release increase may be due to PEG 400 as it is hydrophilic and solubility enhancing agent.

The result of cumulative drug release (%) of all formulation batches are shown in **Table 21, Table 22 and Figure 7**.

TABLE 21: CUMULATIVE DRUG RELEASE (%) OF F1 TO F5

Time[Hr]	F1	F2	F3	F4	F5
	16.11±0.77	11.917±1.03	16.092±0.69	13.599±1.18	14.778±1.58
2	29.074±1.25	27.584±0.63	31.413±1.56	23.971±0.31	25.535±1.74
3	37.226±1.32	39.404±0.58	42.977±0.59	27.687±1.21	30.829±1.9
4	45.844±1.74	48.55±0.54	51.869±0.15	31.807±1.23	35.081±.67
5	52.548±0.66	56.533±0.66	56.926± 0.93	37.086±1.73	39.162±1.57
6	58.849±1.73	64.007±1.02	62.884±0.69	41.708±1.2	44.976±0.94
7	64.443±1.23	62.884±0.77	69.447±0.74	47.009±0.3	48.944±1.27
8	68.309±0.79	68.517±0.08	76.449±0.93	53.474±1.39	55.074±0.8
9	71.812±1.07	76.291±1.01	77.196±1.09	58.628±0.4	60.035±1.37
10	76.632±1.07	80.636±0.68	81.489±1.2	62.003±1.07	62.206±1.61
11	82.686±0.99	79.296±1.61	86.545±0.73	64.999±0.32	66.799±1.33
12	85.972±1.14	84.366±1.48	92.248±0.59	68.479±0.54	70.888±1.28
16	96.125±0.9	97.124±0.85	101.147±0.92	78.336±1.27	82.601±1.42
24	-	-	-	96.531±0.46	98.922±0.28

TABLE 22: CUMULATIVE DRUG RELEASE (%) OF F6 TO F9

Time[Hr]	F6	F7	F8	F9
1	13.581±0.84	10.845±1.45	11.898±0.70	12.726±0.58
2	25.506±0.02	18.742±1.33	21.631±0.53	21.398±0.54
3	30.603±0.15	26.334±0.85	29.549±1.41	29.623±1.46
4	38.865±1.96	33.592±1.16	35.243±1.15	35.741±0.35
5	42.306±1.51	40.039±1.39	37.398±0.48	43.086±0.48
6	48.984±1.41	43.944±1.6	42.668±0.54	46.842±1.53
7	56.583±1.15	48.812±0.7	48.81±0.21	47.156±1.87
8	60.326±0.88	54.402±0.36	52.892±0.77	49.540±0.95
9	65.673±1.86	59.663±0.71	57.655±0.91	56.787±1.32
10	69.704±1.05	61.396±0.98	63.789±1.06	62.082±1.26
11	73.247±1.02	64.141±0.95	67.489±1.19	67.241±0.49
12	76.658±1.25	66.04±1.03	69.497±1.06	74.338±0.53
16	83.155±0.39	73.294±0.66	73.35±0.70	78.819±1.03
24	102.901±2.1	88.483±1.16	92.129±1.39	95.591±1.74

Kinetics of Drug Release The kinetics of the drug release from the matrix pellets, release data was evaluated by model-dependent (curve fitting) method using PCP Disso v3 software and model with the higher correlation coefficient was considered to be the best model. The results showed that the most factorial batches F1, F2, F3, F4, F5, F6, F7, F8, F9 followed matrix order kinetics. The observations are summarized in **Table 23.**

TABLE 23: DRUG RELEASE KINETICS OF ALL FACTORIAL BATCHES

Batch Code	r2					N	K
	Zero order	First order	Matrix	Korsmeyer peppas	Hixon crowell		
F1	0.729	0.729	0.983	0.969	0.729	0.434	0.017
F2	0.643	0.643	0.988	0.987	0.643	0.478	0.018
F3	0.633	0.634	0.990	0.986	0.634	0.452	0.019
F4	0.798	0.962	0.983	0.943	0.928	0.416	15.800
F5	0.810	0.969	0.984	0.945	0.937	0.430	15.718
F6	0.778	0.967	0.987	0.950	0.930	0.437	16.739
F7	0.707	0.917	0.985	0.944	0.867	0.404	15.934
F8	0.751	0.941	0.979	0.928	0.900	0.398	16.390
F9	0.749	0.943	0.972	0.924	0.901	0.407	17.349

Statistical Analysis of Dissolution Data

The 3^2 full factorial design was selected to study the effect of independent variables HPMC K100M LVCR as sustaining polymer and PEG 400 as plasticizer for sustaining the release of Glipizide and forming spherical pellets. The response data was analyzed by using Stat Ease Design Expert 8.0.1 software (Minneapolis, MN, USA). Summary of statistical design and responses shown in **Table 24 and 25** respectively. The results were shown in the **Table 26** and **27**.

TABLE 24: SUMMARY OF STATISTICAL DESIGN

Factor	Name	Unit	Type	Actual values		Coded Values	
				Lowest	Highest	Lowest	Highest
A	HPMC K100M LVCR	gm	Numerical	0.5	1.	-1	+1
B	PEG 400	%	Numerical	1	3	-1	+1

TABLE 25: SUMMARY OF RESPONSES

Response	Description	Units	Obs.	Analysis	Min	Max	Mean
Y1	Q3	%	9	polynomial			
Y2	Q16	%	9	polynomial			

The final equations in terms of coded values of factors and actual values of factor obtained from software Design Expert are given below-

Final equation for Q3 in terms of coded factors

$Q3 = 47.10 - 42.34(A) + 7.83(B) - 1.68(AB) + 17.32(A)^2 - 1.00(B)^2$

Final Equation for Q16 in Terms of Coded Factors

$Q16 = 123.46 - 65.71(A) - 0.84(B) + 0.25(AB) + 21.12(A)^2 + 0.79(B)^2$

Analysis of variance for Q3

TABLE 26: ANALYSIS OF VARIANCE FOR Q3

Source	F Value	p-value Prob > F
Model	51.18	0.0042
A-Spheronization speed	49.34	0.0059
B-Spheronization time	6.75	0.0804
AB	2.85	0.1899
A2	37.83	0.0086
B2	2.03	0.2496

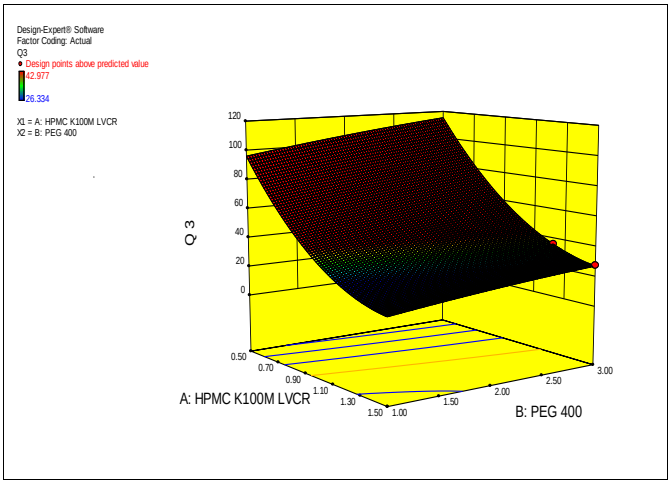

FIGURE 8: 3D PLOT FOR Q3

TABLE 27: ANALYSIS OF VARIANCE FOR Q16

Source	F Value	p-value Prob > F
Model	70.77	0.0026
A-Spheronization speed	46.91	0.0064
B-Spheronization time	0.03	0.8720
AB	0.02	0.8840
A2	22.20	0.0181
B2	0.49	0.5327

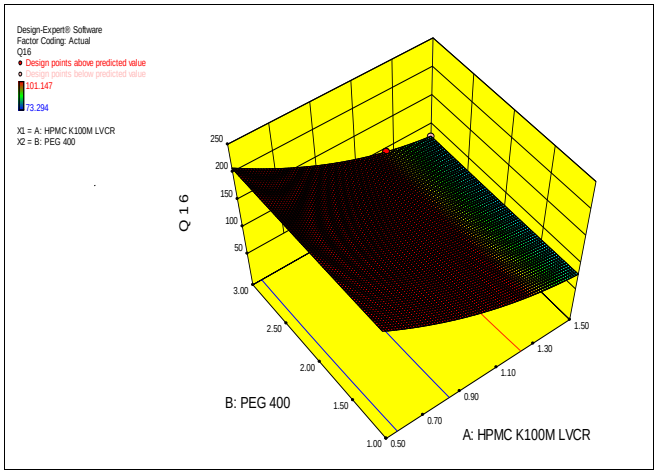

FIGURE 9: 3D PLOT FOR Q16

Influence of Robustness on Release Profile of Glipizide Pellets

Influence of robustness on release profile of Glipizide pellets was studied by testing matrix pellets at different agitation speed (rpm i.e. 100 and 150) in dissolution media (0.1N HCL for 2hr and PH 6.8 phosphate buffer for remaining 24 hr) using USP type (Basket) dissolution apparatus as shown in **Table 28**. This matrix system shows the improved physical characteristics that exhibited similar dissolution profile. It means these matrix system not only modulated the release profile but also produced more robust matrix system.

TABLE 28: INFLUENCE OF ROBUSTNESS ON RELEASE PROFILE OF GLIPIZIDE PELLETS

Time	RPM 100	RPM 150
1	17.912	15.78
2	29.031	28.621
3	34.629	32.389
4	36.426	35.313
5	42.256	40.295
6	46.756	49.492
7	51.284	53.101
8	55.596	56.646
9	64.25	66.548
10	67.473	68.14
11	69.255	69.259
12	75.257	71.77
16	84.298	84.028
24	99.177	101.447

Effect of Plasticizer on Pellets Roundness and Drug Release

The ease in pellets production process and changes in mechanical properties of pellets would be the advantages of using plasticizer in production of pellets containing HPMC in their formulation. The PEG 400 increases drug release as increasing the level from 1% to 3%. These drug release increase may be due to as PEG 400 is hydrophilic agent and solubility enhancing agent[9].

Overall PEG400 is a potential plasticizer in production of pellets based on HPMC K100M LVCR and Glipizide. The ease in process of extrusion-spheronization and change in mechanical properties of pellets from brittle to plastic behavior were advantages of using PEG400.

PEG 400 as plasticizer above 2%, increases the plasticity of damp mass which is suitable for ease in process of extrusion-spheronization and change in mechanical properties of pellets from brittle to plastic behavior leads to spherical and more uniform pellets but PEG 400 as plasticizer at 1% unable change in mechanical properties of pellets from brittle to plastic behavior leads to oval and some Dumbbell +Ellipsoid pellets as shown in **Figure 10**. Batches F2 F3, F5, F6, F9 are good spherical pellets as the effect of conc. of PEG 400 as plasticizer on shape of pellets with respect to different concentration of HPMC K100M LVCR.

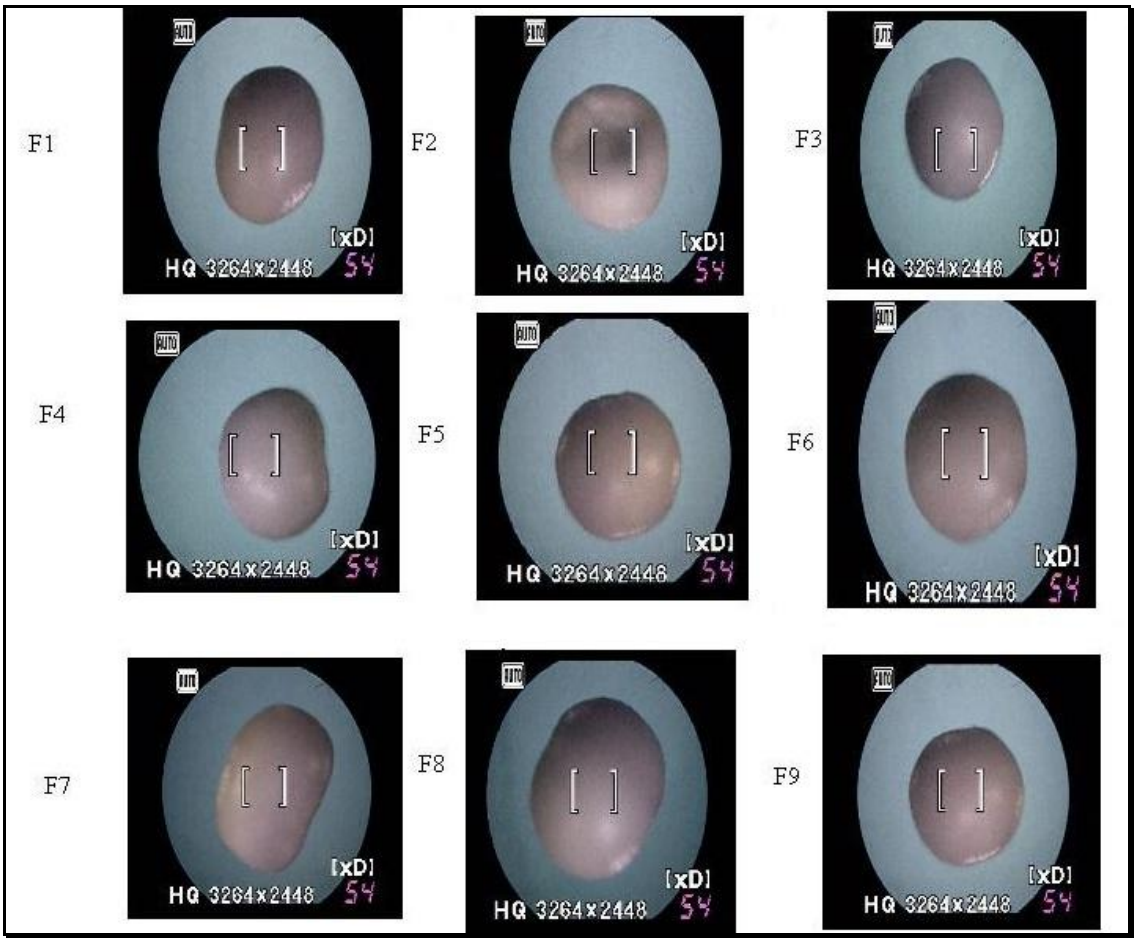

FIGURE 10: EFFECT OF PLASTICIZER ON PELLETS ROUNDNESS

CONCLUSIONS: The Glipizide sustained release matrix pellets were successfully prepared. In present investigation, industrially applied extrusion spheronization technique was used to prepare matrix Glipizide pellets. MCC PH101 was used as a spheronization aid and HPMC K4M (2.5% w/w) as binder. The matrix pellets achieved good sphericity, low friability, narrow particle size distribution and smooth surface.

These formulated pellets sustained Glipizide release upto 24 hrs by using HPMC K100M LVCR as hydrophilic matrix polymer and PEG 400 as potential plasticizer. The study revealed successful application of factorial design, optimization of extrusion spheronization process.

The investigation carried out far has been encouraging and leading to summarization:

- Formula of robust matrix pellets was developed with proper and compatible excipients.
- Speed and time of spheronization is critical parameter for optimum sphericity. The Optimum speed and time of operating spheronization is 1350 rpm and 15 min.
- The results of this study showed that combination of HPMC K100M LVCR as hydrophilic matrix polymer and PEG 400 as potential plasticizer is effective and useful for sustaining the Glipizide release to treat diabetes mellitus.
- The resultant optimum formulation was the one with HPMC K100M LVCR as hydrophilic matrix polymer. The in-vitro studies showed Q16 at approximately 80% cumulative release in case of F4, F5, F6, It indicates that this system can sustain the release upto 24 h which is desirable for sustained release specificity.
- Although, the hydrophilic matrix polymer optimization is critical for drug release, this study suggests the promising approach for formulation of sustained release matrix pellets of Glipizide.

ACKNOWLEDGEMENTS: Authors are thankful to Wockhardt research centre for providing gift sample of Glipizide.

DECLARATION OF INTEREST: The authors report no conflicts of interest. The authors are responsible for the content and writing of this paper.

REFERENCES:

1. Singh S, Pai RS: Respone surface methodology and process optimization of sustained release pellets using Taguchi orthogonal array design and central composite design. Journal of Advanced Pharmaceutical Technology and Research. 2012; 3:30-40.
2. Dey NS, Majumdar S, Rao MEB: Multiparticulate drug delivery systems for controlled release. Trop Journal of Pharmaceutical Res. 2008; 7:1067-1075.
3. Zhou F, Vervaet C, Remon JP: Matrix pellets based on the combination of waxes, starches and maltodextrins. International Journal of Pharmaceutics. 1996; 133:155-160.
4. Masazumi K, Hiroaki N: Development of controlled release matrix pellets by annealing with micronized water-insoluble or enteric polymers. Journal of Controlled Release 2002; 82:335–343.
5. Wah HH: Design and fabrication of oral controlled release drug delivery systems; In Robinson JR, Lee VHL, (eds), Controlled Drug Delivery: Fundamentals and Applications, 2nd ed., New York: Marcel Dekker Inc. 2005; 375-421.
6. Yadav D. Survase S. Kumar K: Dual coating of swellable and rupturable polymers on Glipizide loaded MCC pellets for pulsatile delivery: Formulation design and in vitro evaluation. International Journal of Pharmaceutics 2011; 419:121– 130.
7. Lewis GA, Mathieu D, Phan-Tan-Luu R: Pharmaceutical experimental design, Marcel Dekker Inc. 1999; 1-86.
8. Alonso L, Pacheco M, Gómez AR: SEM image analysis as a tool for the surface characterization of pharmaceutical pellets obtained by extrusion-spheronization. Microscopy: Science, Technology, Applications and Education. 2010; 293-299.
9. Kibria G, Monzurul AR: Effect of Plasticizer on Release Kinetics of Diclofenac Sodium Pellets Coated with Eudragit RS 30 D. AAPS PharmSciTech 2008; 9:1240-1246.

How to cite this article:
Puranik PK, Pol SD, Patil SB, Ransing NG, Ramteke PS, Patil BA, Khobragade PK and Palaskar RG: A Novel Sustained Release Robust Matrix Pellets of Glipizide. Int J Pharm Sci Res 2015; 6(1): 333-44.doi: 10.13040/IJPSR.0975-8232.6 (1).333-44.