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SUSTAINED RELEASE TABLETS OF GLIPIZIDE: COMPRESSION OF COATED, FORMULATION, DISSOLUTION AND CONVOLUTION

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Abstarct

The current study's goal was to create a sustained release (SR) tablet formulation of glipizide by combining two hydrophobic polymers with two naturally occurring hydrophilic gum resins. The preparation of several batches of glipizide sustained release tablets moist granulation with lactose and dicalcium phosphate as diluents. The produced pills were assessed based on a number of factors. The commercial Glynase XL pills were compared with the results of an in vitro drug release research. An ideal formulation (SR F3) that contains olibanum resin and lactose as a diluent was discovered to have dissolving profiles that were comparable to those of the reference product. The Korsmeyer and Peppas model provided the best explanation for the kinetics of drug release, and a non-fickian diffusion mechanism was used to release the medication from these tablets. In conclusion, an SR formulation of Glipizide might be created using lactose as a diluent and olibanum resin as a matrix forming that regulates rate.

Key words: Glipizide, Lactose, Olibanum resin, Modified release, extended release, Release Kinetics.

Introduction

Pharmaceuticals have made a major contribution to improving the health status of patients over a past few decades. At the same time, its expenditure has increased rapidly, with spending on medicines outpacing economic growth in many countries. Many economists have speculated that, if spending on healthcare continues to increase at the current rate, the economies of most countries will be severely affected. Most governments have, therefore, begun to implement cost-containment measures to slow the rate of healthcare spending and have concentrated to a larger degree on pharmaceutical spending. Since generics are usually marketed at substantially lower prices than the original brand-name products and, with the rising cost of healthcare; thishas made them an attractive option to healthcare providers and governments.

Glipizide

Glipizide lowers blood sugar by encouraging the pancreas to create insulin, a hormone that the body naturally needs to break down sugar. It also facilitates the body's effective utilization of insulin. This drug only lowers blood sugar in those whose bodies naturally manufacture insulin. Glipizide is a second-generation sulfonylurea that is FDA-approved for the treatment of adults with diabetes mellitus type 2. It is administered as an adjunct to diet and exercise.

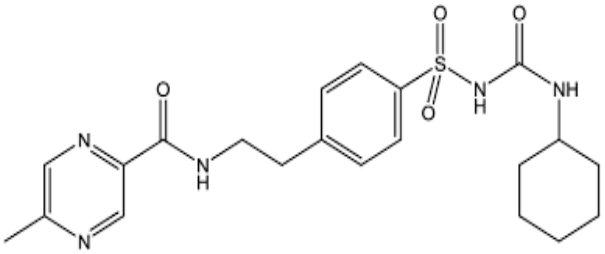

Fig. No. 1 Structure of Glipizide

Material and Method

The following drug, excipients and chemicals were selected for the formulation and evaluation of Sustained release tablet.

Sr. No.	Ingredients Names	Source
1	Drug	MSN Lab
2	Sugar beads	DFE Chem.
3	HPMC	Avantor
4	Surelease solids content	BASF
5	Surelease solid content: Lactose	Fischer
6	Lactose: Explotab	Grace

Table 1: List of materials used

Sr. No.	Instruments	Manufactures
1	Disintegration test apparatus	Electrolab, India.
2	Rapid Mixture Granulator	Saral, India
3	Glatt Fluid Bed Dryer	Glatt Pharma Technology
4	Weighing Balance (Range 10 mg-400 gm)	Sartorius, Germany.
5	Weighing Balance (Range 100 mg-6000gm)	Sartorius, Germany.
6	Cone blender	Mitutoyo, Japan.
7	Mechanical Stirrer	Sartorius, Germany.
8	Automated Tap & Bulk Density Tester	Electrolab, India.
9	Hardness Tester	Erweka, Germany.
10	Fluid Bed Processor	Acumen Tech Solution Pvt ltd Electrolab
11	Friability Tester (USP)	Electrolab, India.
12	Vernier Caliper scale	Mitutoyo, Japan.
13	Mechanical Stirrer	Sartorius, Germany.

14	Dissolution Test Apparatus TDT 8L	Electrolab, India.
15	Coating Machine	Neo Cota, Kolkata (India)
16	HPLC	Shimadzu, Japan.
17	UV visible Spectrophotometer 1800	Shimadzu, Japan.
18	FTIR	Shimadzu, Japan.

Table 2: List of Instruments used

Results and Discussion

Pre formulation Studies:

Evaluation of API

Sr.No.	Test	Limit	Observation
1	Appearance	White to off white crystalline powder	Complies
2	Infra-red spectra	Sample IR spectrum should comply with standard IR spectrum	Sample IR spectrum complies with standard IR spectrum
3	Melting Point	208 to 209 °C	208°C
4	Water content (by KF %w/w)	1.2-1.3 %	1.25%
5	Assay	98.0-102.0%	100.1%

Table No- 3 Evaluation of API

UV Scanning: The λ_{max} of glipizide citrate was found to be 270 nm. This complies with specified λ max.

Preparation of standard calibration curve:

The max of this solution was found to be 270 nm. Absorbance of all solutions was measured at 270 nm against diluent as a blank. The calibration curve was prepared by plotting absorbance versus concentration of Drug.

Sr. No.	Concentration (ppm)	Absorbance
1	0	0
2	10	0.1123
3	20	0.221
4	30	0.3464
5	40	0.4678
6	50	0.5789

Table No. 4 Determination of calibration curve Glipizide

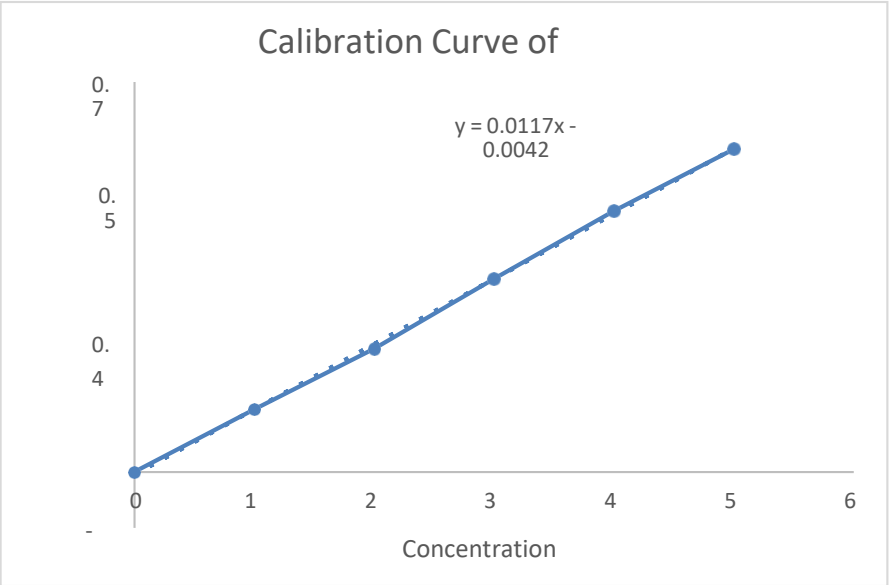

Fig No. 2 - Standard calibration curve of Glipizide Citrate.

The linear regression analysis for standard curve:

The linear regression analysis was done on Absorbance data points. The results are asfollows: For standard curve in: pH 7.4 buffer medium

The slope =0.0007 the intercept = 0.0087

The correlation coefficient = 0.9999

Solubility study of Drug

Solubility study of drug was carried out in various pH conditions and media at 37^0 Cthe result is shown in Table.

Sr. No	Solvent Used	Solubility (mg/ml)	Descriptive term
1.	Dichloromethane	>100	Freely soluble
2.	Acetone	0.87	sparingly soluble
3.	Ethanol	0.45	Very slightly soluble
4.	H_2O (Water)	0.002	insoluble
5.	0.1 N HCL	1.41	Slightly soluble
6.	Citrate Buffer pH 4.5	2.79	Slightly soluble
7.	Phosphate buffer pH 6.8	6.35	Slightly soluble
8.	Phosphate buffer pH 7.5	4.98	soluble

Table No 5 - API Solubility in different pH media

The results showed that glipizide citrate is freely soluble in dichloromethane, slightly soluble in 0.1 N HCL, and very slightly soluble in ethanol. To prepare the desired concentration of glipizide formulation. It also showed that the solubility of glipizide is pH-dependent. The aqueous solubility of glipizide decreases as pH increases from 1 to 3, slightly increases at pH 4.5 also increases above pH 6.8.

Micrometric Properties of API

Sr. No.	API	Glipizide
1	Bulk Density* (g/ml)	0.225±0.003
2	Tapped Density* (g/ml)	0.401±0.004
3	Compressibility Index (%) *	20.80±0.48
4	Hausner's Ratio*	1.31±0.009
5	Angle of Repose* (Degree)	50.09±0.26
6	Moisture content (%)	1.25%

Table No: 6 - Micrometric Properties of API

Inference:

The Bulk density of the powder was found to be 0.225gm/ml. The Tapped density of the powder was found to be 0.401gm/ml. The Compressibility Index was found to be 20.80 indicating poor flow properties. The Hausner's ratio was found to be 1.31 and the value was indicating poor flow property. The Angle of repose was obtained as 50.09°, indicating poor flow of powder drug. Based on the above results it was concluded that the drug is not suitable for direct compression method due to fine particle size and poor flow characteristics.

Drug-Excipient compatibility studies

a) Physical studies:

Sr. No	Drug and excipients	Ratio	Observations on appearance	Assay
1	Drug alone	1	White to off white crystalline powder	99.7%
2	Drug + Sugar beads	1:05	White to off white crystalline powder	99.4%
3	Drug + HPMC	1:05	White to off white crystalline powder	99.8%
5	Drug + Surelease solids content	1:05	White to off white crystalline powder	99.8%
6	Drug + Surelease solid content: Lactose	1:05	White to off white crystalline powder	99.9%
7	Drug + Lactose: Explotab = 2:1	1:05	White to off white crystalline powder	99.2%
8	Drug + Placebo	1:05	White to off white crystalline powder	100.0%

Table No: 7 - Drug-Excipient Compatibility Study

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added in the formulation. The drug and excipients must be compatible with one another to produce a product that is stable, Efficacious and easy to administer and safe. The physical compatibility evaluation was performed in visual basis. The study complies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description.

Evaluation of Post-compression Parameters for sustained release tablets

Formulation Code	Average Weight(mg)	Thickness (mm)	Friability (%)	Hardness (Kg/Cm2)	Moisture Content	Assay
F 1	110	4.86	0.52	3.68	1.86	99.5
F 2	102	3.86	0.61	3.28	2.01	100.1
F 3	100	3.80	0.58	4.25	1.84	99.8
F 4	110	4.85	0.68	4.84	2.08	100.3
F 5	110	4.86	0.71	5.10	1.68	100.8
F 6	107	4.12	0.70	4.36	2.05	99.8
F 7	108	4.34	0.68	4.98	1.95	99.3
F8	107	4.28	0.63	4.86	1.63	100.3
F9	107	4.29	0.73	4.74	1.84	99.6
F10	115	5.10	0.74	4.6	1.26	100.1

Table No: 8 - Evaluation of sustained release tablets

The sustained given to the tablet to protect drug from acidic condition The accepted percentage deviation ±5% for more than 115 mg weight tablets since weight variation of tablet was within range the thickness of the tablets was found to be in the range. The result showed that the thickness of all formulates tablets is found to be uniform. The hardness of the all tablet formulation was found to be in range. It indicates all the tablets have adequate mechanical strength. In friability test the maximum weight loss should not be more than 1%. The result revealed that the tablets passed the friability test.

Inference:

- All the tablets hardness was found to be in the range of 3-5 kg/cm² in all the formulations indicating good mechanical strength.
- In all the formulations the friability value is less than 1 % giving an indication that tabletsformulated are mechanically stable during handling & transporting.
- The percentage weight variation was within the USP limits.
- The drug content was known by performing assay and it was found to be 95-105% and it was withinthe limits.
- The moisture content of tablet with in specification limit.

In-vitro drug release

The in-vitro drug release characteristics were studied of different trial batches F1, F2,F3, F4, F5, F6, F7, F8, F9, F10 With media For Dissolution method.

Dissolution parameter as follow:

Medium	pH 7.4 Phosphate buffer
Apparatus	USP Type I (Basket)
Speed	50 rpm
Temperature	37°C
Time point	0.5, 1, 2, 4, 6, 8, 12, 16, 24 hr

Dissolution profile of different trial batches F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 WithpH 7.4 media.

Time point	**Cumulative % drug release in pH 7.4 different trials**									
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10
0	0	0	0	0	0	0	0	0	0	0
0.5	10	15	31	20	8	10	10	12	16	10
1	21	22	35	28	21	22	21	27	28	25
2	29	30	55	48	43	32	30	47	44	35
4	34	37	62	55	51	53	47	54	56	54
6	48	51	70	62	61	63	52	66	61	66
8	52	58	78	73	66	72	65	79	72	80
12	61	63	82	80	71	76	71	85	77	88
16	65	70	85	86	78	82	86	90	89	95
24	72	76	89	92	83	86	90	93	95	101

Table No: 9- *In-Vitro* Dissolution Profile of sustained release tablets

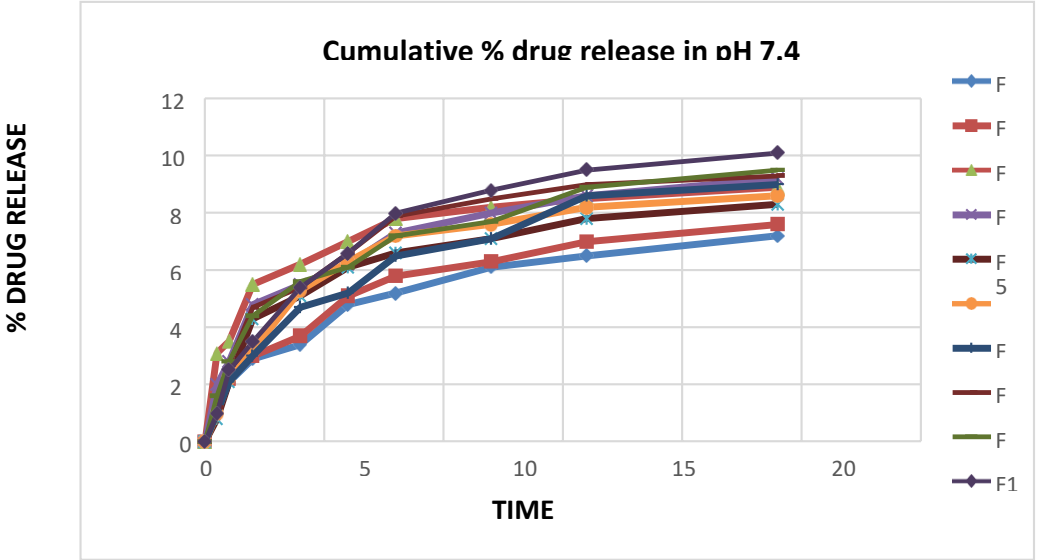

Fig No: 3- *In-Vitro* Dissolution Profile of sustained release tablets

In-Vitro Dissolution Profile of Enteric Coated Tablets in 0.1 N HCL, pH 4.5 Acetate Buffer and pH 6.8 phosphate buffer.

Media	**0.1 N HCL**	**pH 4.5 acetate buffer**	**pH 6.8 Phosphate buffer**
Time (hrs)	**F10**	**F10**	**F10**
0	0	0	0
0.5	0	2	7
1	0	8	23
2	0	21	32
4	1	33	49
6	3	45	60
8	5	52	72
12	6	64	79
16	8	69	85
24	9	76	92

Table 10 - Dissolution profile of F10 trial batch with Innovator in 0.1 N HCL, pH 4.5 Acetate Buffer and pH 6.8 phosphate buffer

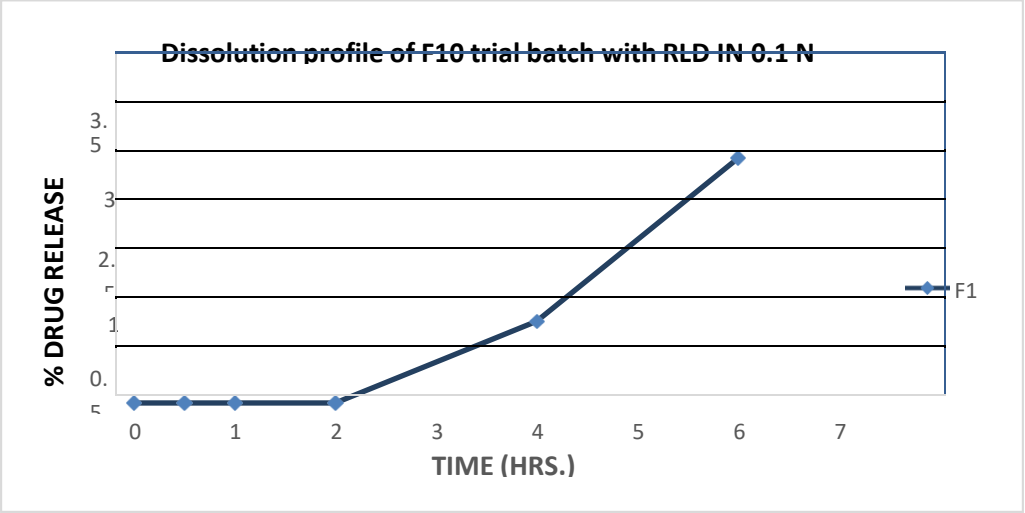

Fig No 4 – Dissolution profile of F10 trial batch with IN 0.1 N HCl

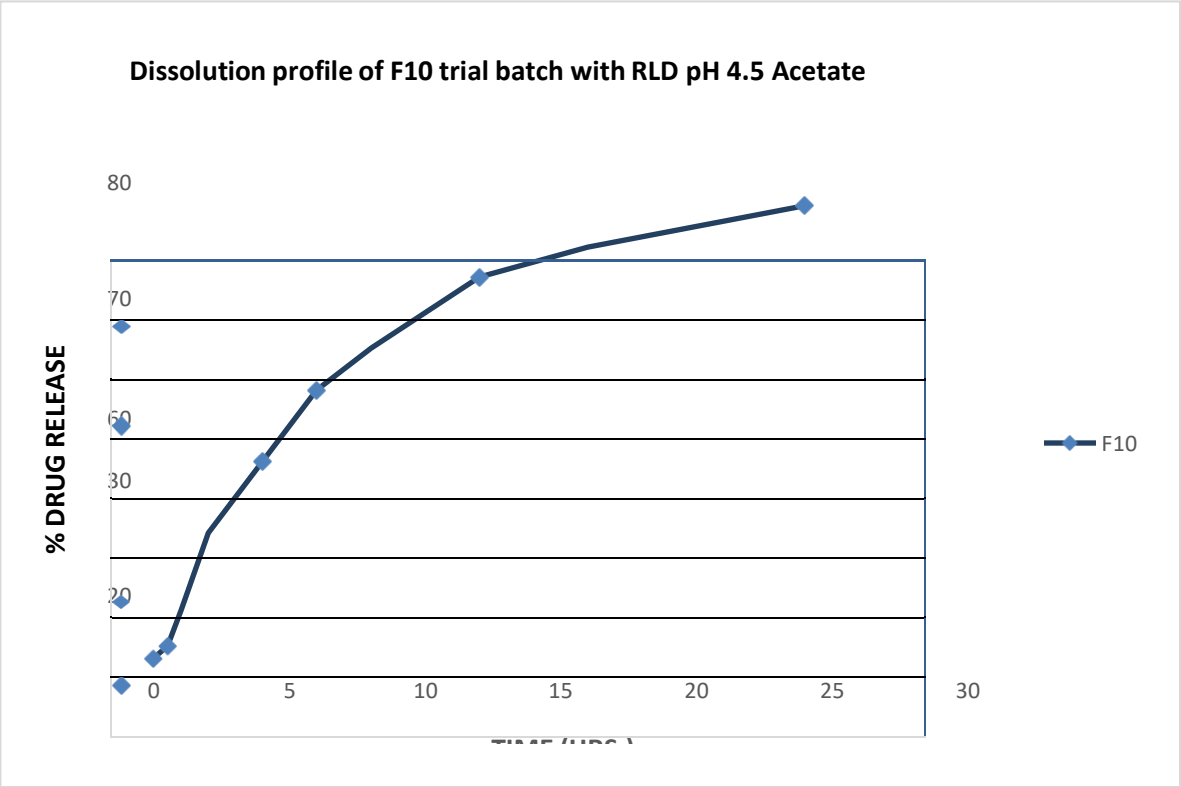

Fig No 5 – Dissolution profile of F10 trial batch pH 4.5 Acetate Buffer

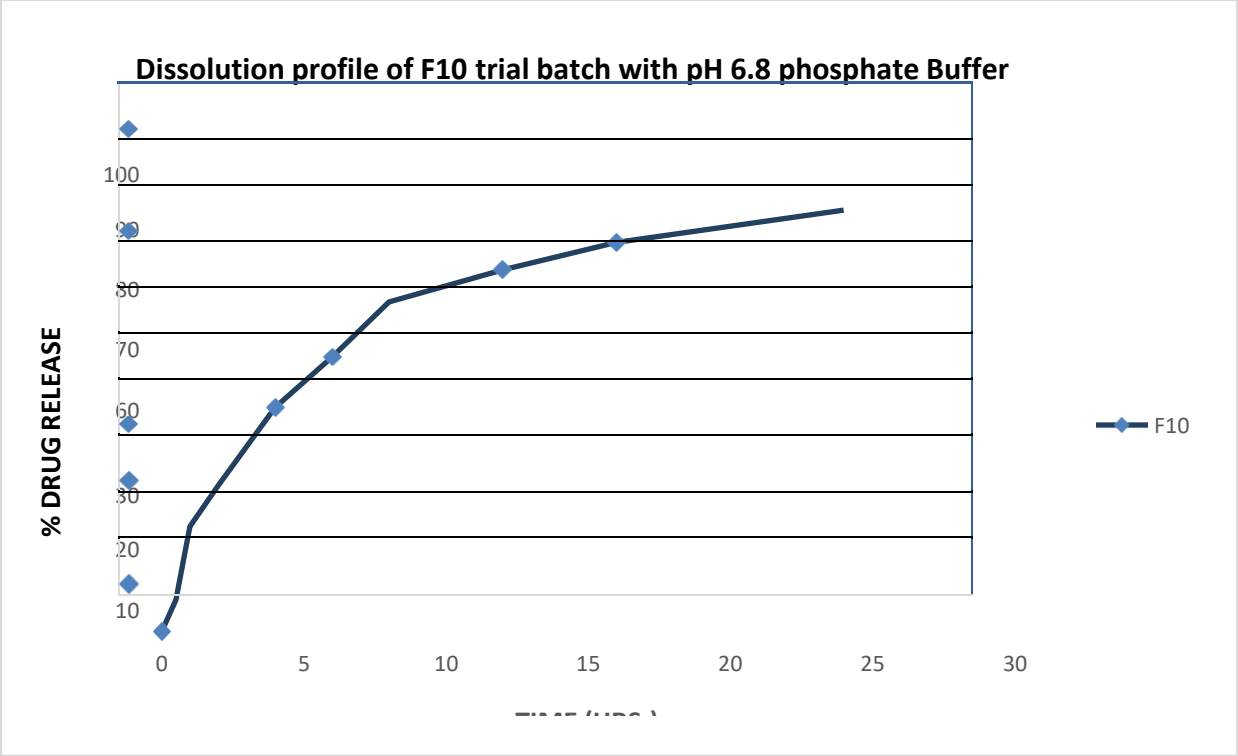

Fig. No. 6 – Dissolution profile of F10 trial batch with pH 6.8 Phosphate Buffer

Conclusion

Novel formulation of glipizide was developed comprising compression of four layer coated beads into tablets that has advantages of keeping sustained-release characteristics and proper lag time, and providing approximately zero-order drug release, and drug release that is nearly independent of basket speeds 100 rpm. The amount of binding and disintegrate ingredients can be adjusted to produce appropriate disintegration time for tablets. With 22.22% weight gain of binder: disintegrant (lactose:Explotab) = 2:1, beads-compressed into tablets disintegrated within 3 hours, and individual coated particulates controlled drug release. The inclusion of HPMC in the formulation as a bead hardening agent plays a role in manufacturing as well as keeping and facilitating desirable drug release with appropriate weight gain of 6.54%. There are two Surelease layers and both are important for controlling release, with the predominate sensitivity being in a Surelease-drug layer. Tablet compression pressures between 1000 and 3000 pounds have a little effect on drug release at the dissolution paddle speed of 100 rpm. The tablet compression pressures between 1500 and 3000 pounds the more sensitive drug release was to basket speeds. At 100 basket speeds significantly increased drug release rate occurred from CH20 tablets compacted at 1500 pounds pressure compared with 50 and 100 rpm. There is convincing statistical evidence that the interaction between tablet compression pressure and paddle speed was associated with %release and drug release rate (P-values < 0.01). CH20 is a novel formulation of glipizide developed comprising compression of four-layer coated beads into tablets. It is possible to obtain essentially nearly zero-order drug release in pH 7.4 media at stirring speeds of 100 rpm with the USP basket method. The final formulation in this study contains four layer beads: the drug layer of 71.25 g of sugar beads over coated with 2.5 g of glipizide and 3.75 g of solid

Surelease; the hardening layer of 5 g of HPMC; the controlled release layer of 7.5 g of ratio solid content of Surelease:lactose = 100:7; and outmost layer of 20 g of lactose:Explotab = 2:1 Then beads were compressed into tablets containing 11mg of glipizide with 1500 pounds of compression pressure. The release rate and %release at 24 hours of CH20 did not differ from that of Glucotrol XL at all basket speeds (P-values > 0.05). CH20 tablet is predicted by convolution simulation to be bioequivalent to Glucotrol-XL *in vivo*.

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