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FORMULATION AND EVALUATION OF MULTIPARTICULATE PELLETS CONTAINING GLIBENCLAMIDE SOLID DISPERSION

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Abstract

The present study was aimed to develop a novel multiparticulate delivery system by using solid dispersion method. Multiparticulate pellets are particularly useful in paediatric, geriatric, psychiatric and bedridden patients who have difficulty in swallowing. Glibenclamide is an anti diabetic drug belonging to BCS Class II , which is a poorly water-soluble drug which leads to decrease in bioavailability. In this study Solid dispersion method is used for increasing the solubility of the drug by using carriers like PEG-6000 and PVP-K30. The aim of the present study was to develop the multiparticulate pellets of Glibenclamide to increase the patient compliance and to reduce the risk of dose dumping. Multiparticulate pellets were prepared by using Extrusion-Spheronization method using different grades of crosspovidone and sodium starch glycolate. The multiparticulate pellets were evaluated for compatibility, drug content, friability pellet size, sphericity, disintegration, dissolution studies. FTIR results indicated that there was no incompatibility between the drug and the excipients.

Keywords: Multiparticulate pellets, Glibenclamide, Solid dispersion.

Introduction

Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water.

Poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs[1]. Different techniques are used to enhance the solubility of the drug. The improvement of drug solubility thereby its oral bio-availability remains

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one of the most challenging aspects of drug development process especially for oral-drug delivery system.

Oral bioavailability of a drug depends on its solubility and dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility is often needed. Improvement in the dissolution rate of the poorly soluble drugs after oral administration is one of the most crucial challenges in modern pharmaceutics. Many methods are available to improve these characteristics including salt formation, Micronization and addition of solvent or surface-active agents and solid dispersion method[2,3].

Glibenclamide[4] is an anti-diabetic drug belonging to class II which has poor water solubility there by posing problems in their formulations in absorption leads to poor bioavailability. Therefore enhancement of the solubility of drug is very important in those cases. Usually Initial dose of Glibenclamide is 2.5 to 5mg once daily. Glibenclamide appears to lower the blood glucose acutely in healthy individuals and patients with type 2 diabetes by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells. Glibenclamide is nearly completely absorbed (84 ± 9%) after oral administration and is extensively bound (99%) to serum proteins. The peak serum concentration is reached in 2-6 hours after taking a 5 mg tablet of drug and falls within 24 hours to less than 5% of the peak value. Multiple-dose studies with glibenclamide[5] in diabetic patients demonstrate drug level concentration-time curves similar to single-dose studies, indicating no build-up of drug in tissue depots. In non-fasting diabetic patients, the hypoglycaemic action of a single morning dose of glibenclamide persists for 24 hours.

Solid dispersion[6] refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Different carriers like PEG 6000 and PVP K 30 can be used to enhance the bioavailability. Both polymers show excellent water solubility and vary significantly in molecular weight, ranging from 200 to >300,000 for polyethylene glycol and from 10,000 to 700,000 for polyvinylpyrrolidone. Both polymers are often employed as vehicles due to their low toxicity, low melting point, rapid solidification rate, high aqueous solubility, availability in various molecular weights, economic cost, and physiological tolerance.

Pellets are spherical or nearly spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 μm for pharmaceutical applications[7]. They are generally produced via a pelletization process, whereby a powder blend consisting of an API and excipient particles is agglomerated into spherical granules. After being produced, pellets are usually filled into hard gelatin capsules or compressed into tablets. Furthermore, they can be formulated as immediate-release dosage forms or coated in order to sustain drug release over a longer period of time or to deliver a drug to a specific site of action in the gastrointestinal tract.

Multiparticulate solid dosage forms derives from several important advantages of those multi-unit forms over conventional, single-unit solid dosage forms (tablets)[8]. Extrusion/ Spheronisation is one of the most established techniques for production of pellets with high quality.

Materials and methods

Glibenclamide was obtained as a gift sample from Hetero drugs limited, Hyderabad, India. PVP-K30 and PEG-6000, Microcrystalline cellulose, Crosspovidone, Mannitol, Lactose and all other chemicals and solvents used were of analytical grade.

Preparation of solid dispersions by solvent evaporation method

Drug and carrier was taken in a ratio of 1:9. In case of Glibenclamide solid dispersion (G-SD1), the drug and the polymer was dissolved in adequate quantity of solvent (chloroform) and stirred continuously for about 30 mins at room temperature to obtain a clear solution .To this solution, 10 mg of aerosil was added and stirred at room temperature until two thirds of the solvent has evaporated. The stirring was stopped and the balance solvent was removed by drying under vaccum at room temperature. In case of Glibenclamide solid dispersion (G-SD2) containing a combination of PVP K-30 was first melted with

the aid of heat and the drug dissolved in chloroform was added. The rest of the preparation of solid dispersion was same as that of G-SD1. The dried powder was collected and passed through mesh no.60 and stored for further use[2].

Table No. 01: Composition of solid dispersion

Ingredients	G-SD1	G-SD2
Glibenclamide	05 mg	05 mg
PEG-6000	45 mg	-
PVP-K30	-	45 mg
Chloroform	Q.S	Q.S

Table No. 02: Formulation chart for preparation of pellets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
G-SD1	50	50	50	50	-	-	-	-
G-SD2	-	-	-	-	50	50	50	50
MCC	81	79	81	79	81	79	81	79
Cross povidone	06	08	-	-	06	08	-	-
SSG	-	-	06	08	-	-	06	08
Lactose	50	50	50	50	50	50	50	50
Mannitol	07	07	07	07	07	07	07	07
Aerosil	02	02	02	02	02	02	02	02
Talc	02	02	02	02	02	02	02	02
Magnesium stearate	02	02	02	02	02	02	02	02

Preparation and Characterization of pellets

Glibenclamide solid dispersions in PEG-6000 and PVP K-30 at a drug to carrier ratio of 1:9 were formulated into pellets. The pellets containing 5mg of Glibenclamide equivalent solid dispersion in each formula was prepared by extrusion-spheronization pelletization technique. Required amount of solid dispersion equivalent to 5mg of drug, MCC, lactose, crosspovidone and mannitol in 4 formulations F1-F8 were passed through sieve no.40 prior to pelletization and mixed uniformly in a double cone blender[9]. Double distilled water of required quantity was used to bind the mass to obtain a dove mass which was extruded using a piston extruder (1mm orifice), Kalweka,(Karnavati, Banglore) India. The extrudates were immediately spheronized at varying time of 2,4,10 min. with varying rotation speed of 400, 700, 1000 rpm with an air velocity of 1kg/cm^2. The pellets were dried at 40^{O}C for 2hrs.in the hot air oven[10] (BIO:26, Biotechnics India).

Evaluation parameters of pellets

Particle size analysis[11]

The particle size of drug loaded formulations was measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The Olympus model (SZX-12) having resolution of 40x was used for this purpose. The instrument was calibrated at 1 unit of eyepiece micrometer was equal to 1/30 mm (33.33µm).

Drug content Estimation[12]

Accurately weighed 200mg of pellets dissolved in acetone and suspended in 100ml of phosphate buffer (6.8pH).The resulting solution was kept for 24hrs after it was stirred for 15-20 min. The solution was filtered, Glibenclamide content in filtrate was analyzed at 227nm using Shimatzu UV Spectrophotometer (UV-1800 Shimadzu corporation, Japan). The experiments were carried out in triplicate for the pellets of all formulations and average values were recorded.

Friability[13]

The friability test was performed on the pellets to ensure their mechanical strength. Lower friability values indicate good mechanical strength. Pellets of known mass (200mg) were placed in a Roche Friability tester (Electro lab Friability tester, EF -2) and subjected to impact testing at 25 RPM for 5 min. Fines were removed using a suitable sieve and the pellets were weighed and percentage friability was calculated using the following formula.

$$Percent\ Friability = \frac{1 - Initial\ weight}{Weight\ retained} \times 100$$

Pellet sphericity[14]

Pellet shape was also determined using an image analysis system. The magnification was set such that 1 pixel corresponding to 5.7µm and pellets for all the batches were analyzed. Each individual pellet was characterized by mean feret diameter

(FD) (average of calliper measurements with an angle of rotation of 1°). Next to the mean feret diameter, each individual pellet was characterized by aspect ratio (AR) (ratio of the longest feret diameter and its longest perpendicular diameter) and two dimensional shape factor, as described by following equation.

$$e_r = \frac{2.\pi.r}{P_m} - \sqrt{1-\left(\frac{b}{l}\right)^2}$$

Where *r* is the pellet radius, *Pm* is the perimeter; *l* is the pellet length (longest Feret Diameter) and *b* is the pellet width (longest diameter perpendicular to the longest Feret Diameter).

Scanning electron microscopy (SEM)[15,16]

Morphology and surface topography of the core and the coated pellets were studied by scanning electron Microscopy. (SEM-JEOL, JSM-840A, Japan). The samples were mounted on the SEM sample stab, using a double-sided sticking tape and coated with gold (200A0) under reduced pressure (0.001 torr) for 5 min using an Ion sputtering device (JEOL, JFC-1100 E, Japan).

Fourier transform- infrared spectroscopic analysis (FT- IR)[17,18]

Drug-excipient compatability study was performed by Fourier transform infrared (FTIR) Spectroscopy. In the preparation of formulation, the drug and polymers were in close contact with each other, which could leads to instability of drug. Thus preformulation studies regarding drug-polymer interaction is very important in selecting appropriate polymers. Thus FTIR spectroscopy study was performed to determine the compatibility between the selected drug and polymer.

***In vitro* Disintegration time Studies[19]**

The disintegration time is the time when a film starts to break or disintegrate. The *in vitro* disintegration time of pellets was determined visually in a glass dish of 25 ml distilled water with swirling every 10 sec.

***In-vitro* drug release studies[20,21]**

The release profile of Glibenclamide from prepared pellets in phosphate buffer pH 6.8. The media of pH 6.8 simulates the pH of the oral salivary secretions. The dissolution process was carried out by USP Type II (Electro lab TDT-08L USP, Mumbai, India) rotating paddle apparatus. The drug loaded pellets (equivalent to 5mg of Glibenclamide) were placed into the dissolution media (900ml) and the paddle was kept at a constant speed 50rpm and temperature 37±0.5°C. The test was carried out for 1hr at regular intervals of 5, 10, 15, 30min. The sample 5ml was withdrawn and replaced with same volume of fresh media. The withdrawn samples were filtered through a 0.4µm membrane filter. Glibenclamide concentration was estimated spectrophotometrically using UV Spectrophotometer at λmax 227nm.

Stability studies of pellets

The drug loaded pellets equivalent to 5mg of Glibenclamide were taken in a glass vial and it was sealed using aluminium packaging coated inside with polyethylene. The study was carried out as per ICH guidelines at 40°C and 75% RH for three months. The pellets were withdrawn periodically and evaluated for the friability, disintegration, drug content and *in-vitro* drug release studies. The values for *in vitro* drug release from the pellets were calculated and were compared for change in the dissolution profile.

Results and discussion

Fourier Transform Infrared (FTIR) Spectroscopy

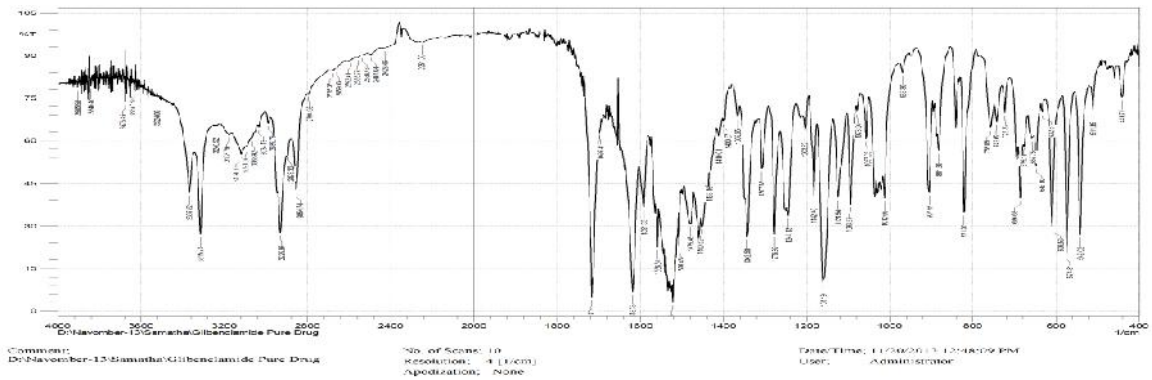

Fig. No. 01: FTIR spectra of pure drug Glibenclamide

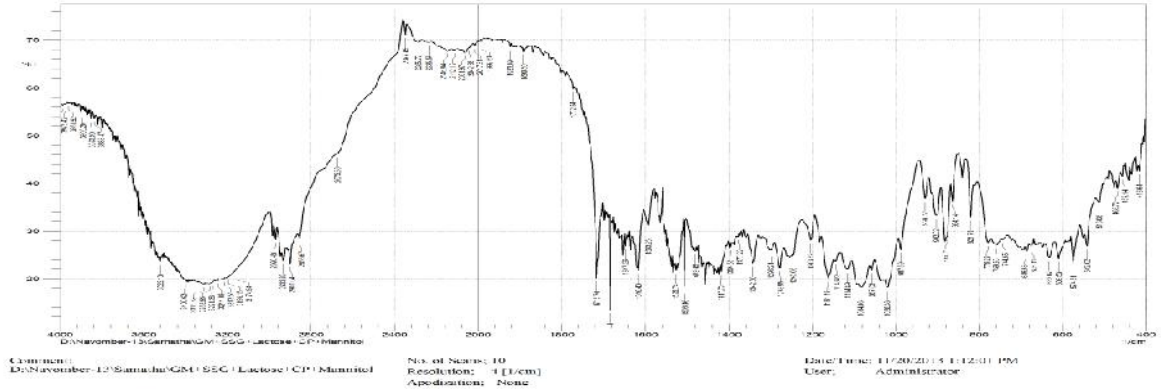

Fig. No. 02: FTIR spectra of optimum formulation F2

FTIR studies was carried out for the pure drug – Glibenclamide, optimum formulation F2 and their spectra are as shown in fig 1& fig 2 respectively

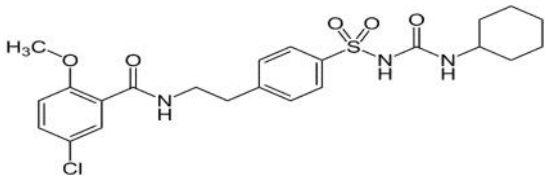

Fig. No. 03: Structure of Glibenclamide

The characteristic peaks of the pure drug – Glibenclamide was assigned from standard literature. These included N-H stretching (hydrogen-bonded), C-N stretching in primary aromatic amine, C-Cl stretching, symmetric SO_2 stretching and are as shown below.

1. 3178.79: N-H stretching(hydrogen-bonded)
2. 1697.41: C=O stretching
3. 1307.78: C-N stretching in primary aromatic amine
4. 1182.40: symmetric SO2 stretching
5. 742.62: C-Cl stretching

As seen in fig 1, the spectra for Glibenclamide exhibits a peak at 3178.79 due to primary and secondary amine (N-H) stretching vibration, 1697.41 due to C=O stretching vibration, 1307.78 due to C-N stretching in primary aromatic amine.

The FTIR results from optimum formulation (F2) exhibited peaks at 3174.94 due to primary and secondary amine(N-H) stretching vibration, 1663.66 due to C=O stretching vibration, 1417.73 due to C-N stretching in primary aromatic amine. The intensity and position of these characteristic peaks permits easy interpretation of any possible interaction between the drug and the excipients in the formulation. The results clearly showed that there was no interaction between the drug and the excipients in the prepared formulation F2. The drug Glibenclamide was intact and there was no sign of any degradation due to preparative processes adopted during the loading of the drug into oral fast disintegrating pellets.

Pellet size analysis

The pellet size of the drug loaded formulations was measured by optical microscope which showed for formulations (F1-F8) of 3 different sizes of pellets of which the minimum size ranges from 1.01-1.16mm and of the maximum size ranges from 1.20-1.41mm. The maximum size of the pellet of 1.41mm for the formulation F2 was considered as the optimum required size of the pellets.

Friability

Friability of the pellet formulations was in the range 0.606 to 0.848 and it lies in the expected range less than 1% as per FDA specifications. Friability is measure to assess the mechanical strength of the pellets interms of fragmentation or powder during handling and transit. From the data it was concluded that amount of MCC found to influences the friability. Less moisture content helps to produce pellets with good mechanical strength. As the curing temperature was increased (45^{o}C for 24hrs), friability of the pellets was found to decrease and pellets having shrunken porosities due to loss of moisture. When the pellets were cured below 40^{o}C dumbbell shaped pellets were obtained with protruding surfaces. Due to presence of more moisture content, these pellets were considered not suitable for pharmaceutical purpose.

Content Uniformity

The content uniformity test was performed to ensure uniform distribution of drug. The content uniformity was performed for all the formulations and was tabulated in table no. 3. Obtained results indicate that in the all the formulations drug content was uniform and ranged between 92.82 % to 96.08 %. The cumulative percent drug released by each film in the *in vitro* release studies was based on the mean content of drug present in the respective pellets.

Table no. 03: Evaluation parameters of Glibenclamide pellets

Formulation	Particle size(mm)	Drug content(%)	Friability(%)
F1	1.35	94.56	0.66
F2	1.41	96.08	0.60
F3	1.20	93.06	0.90
F4	1.29	94.06	0.78
F5	1.36	94.42	0.84
F6	1.39	95.86	0.72
F7	1.32	92.82	0.75
F8	1.32	94.56	0.80

Pellet sphericity

The results of the sphericity (aspect ratio) showed a reduction of pellet sphericity when using the higher spheronization load. This might be due to higher pellet agglomeration incase of higher spheronization load. The influence of spheronization load on the sphericity of MCC based pellets and concluded that a longer spheronization load. In our case prolonged spheronization was not possible. Since it would lead to excessive agglomeration. The calculated sphericity value of the optimized pellets F2 was found nearer to 1 which confirms the pellets of F2 were spherical in nature.

Table no. 04: Process parameters of solid dispersion pellets with super disintegrants (F1-F4)

Formulation code	SD Code	Parameters	Parametric values	Description of pellets
F1	PEG	Drug SD:CP	5:45:6	Spherical
F2	PEG	Drug SD:CP	5:45:8	Spherical and hard
F3	PEG	Drug SD: SSG	5:45:6	Dumbbell
F4	PEG	Drug SD:SSG	5:45:8	Rod shape and brittle
Spheronization speed(rpm)	F2	400	400	Rod shape
		700	700	Dumbbell shape
		1000	1000	Spherical
Spheronization speed(time in min)	F2		2	Rod shape
			4	Dumbbell shape
			10	Spherical
Yield(%)	F1		97	Spherical and brittle
	F2		99.2	Spherical and hard
	F3		95	Dumbbell and brittle
	F4		92	Rod shape and brittle

Table no. 05: Process parameters of solid dispersion pellets with super disintegrants (F5-F8)

Formulation code	SD Code	Parameters	Parametric values	Description of pellets
F5	PVP K-30	Drug SD:CP	5:45:6	Spherical
F6	PVP K-30	Drug SD:CP	5:45:8	Spherical and hard
F7	PVP K-30	Drug SD:SSG	5:45:6	Dumbbell
F8	PVP K-30	Drug SD:SSG	5:45:8	Rod shape and brittle
Spheronization speed(rpm)	F6	400	400	Rod shape
		700	700	Dumbbell shape
		1000	1000	Spherical
Spheronization speed(time in min)	F6		2	Rod shape
			4	Dumbbell shape
			10	Spherical
Yield(%)	F5		96	Spherical and brittle
	F6		99	Spherical and hard
	F7		94	Dumbbell and brittle
	F8		93	Rod shape and brittle

Scanning electron microscopy (SEM)

SEM photograph of the pellets (optimized formulation F2) showed spherical nature and smooth surface of pellets as they were cured at 2hrs at 40°C. SEM photo micrograph of the pellets revealed. The uniform distribution of the drug in the pellets.

***In-vitro* disintegration study**

Disintegration test of the pellets were performed by dissolving the pellets in a glass beaker containing 25 ml of water with occasional gentle swirling and shaking for every 10 sec. The disintegration time is the time when the pellets start to break or disintegrate and time was noted. Results of disintegration time of all the formulations were tabulated in table no6. The disintegration time of all the formulations were in a range of 194 ± 2 sec to 655 ± 1.9 sec.

***In-vitro* dissolution study**

The dissolution profile of prepared pellets for the formulations (F1-F4) which contains PEG 6000 SD (solid dispersion) with two different concentrations of crosspovidone and sodium starch glycolate. The minimum drug release of (91.9%) at the end of 30min.for the formulation F4 was obtained which contains Sodium starch glycolate as the super disintegrant. The release (99.7%) for more in case of pellets (F2) loaded with PEG 6000 SD (solid dispersion) along with crosspovidone as superdisintegrant. The dissolution profile of prepared pellets for the formulations (F5-F8) which contains PVP K-30 with two different concentrations of crosspovidone and sodium starch glycolate. The minimum drug release of (93.39%) at the end of 30min. For the formulation F7 was obtained which contains Sodium starch glycolate as the super disintegrant. The release (96.76%) for more in case of pellets (F6) loaded with PVP K-30 SD (solid dispersion) along with crosspovidone as superdisintegrant.

The optimised formulation (F2) was selected based on the highest drug release of 99.7% at the end of 30min.Which was considered as desired drug release from the pellet formulation. This highest drug release was obtained due to the solid dispersion formulation of the drug with PEG 6000 which ultimately enhanced the poorly soluble Glibenclamide. Further loading of this Solid dispersion into the pellet formulation along with crosspovidone provided maximum drug release with in 30min. This in-vitro drug release profile of optimized formulation F2 was compared with the marketed formulation of Glibenclamide tablet (5mg) which showed 56.5% of drug release at the end of the 30min.

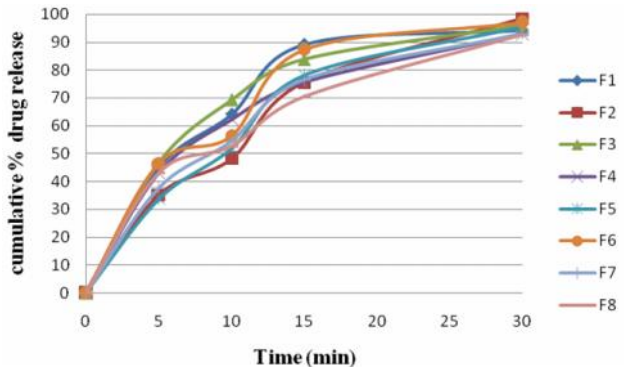

Fig. No. 04: *In-vitro* Dissolution profile of formulations F1-F8

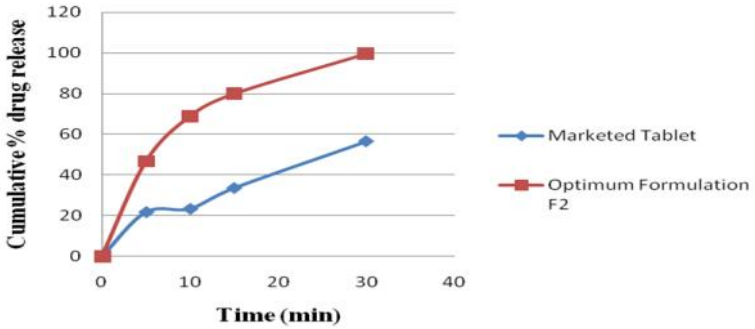

Fig. No. 05: Comparative drug release study for marketed tablet and optimized formulation

Table no. 06: Evaluation parameters of Glibenclamide pellets:

Properties	F1	F2	F3	F4	F5	F6	F7	F8
Pellet size	1.352	1.417	1.202	1.293	1.361	1.395	1.329	1.324
Friability	0.666±0.31	0.606±0.12	0.709±0.13	0.787±0.33	0.848±0.14	0.727±0.17	0.757±0.11	0.703±0.09
Drug Content[a] (%)	94.56±0.05	96.08±0.26	93.06±0.16	94.09±0.13	94.42±0.07	95.86±0.10	92.82±0.04	94.56±0.06
Disintegration time[a] (sec)	426±1.318	194±1.00	630±1.90	646±1.00	465±2.20	223±1.80	642±2.10	655±1.50
% Cumulative drug release (90 min)	94.91±0.27	98.5±0.42	96.2±0.29	92.9±0.46	95.6±0.25	97.1±0.17	93.1±0.66	92.71±0.40

Table no. 07: Stability studies of Glibenclamide pellets

Properties	F1	F2	F3	F4	F5	F6	F7	F8
Pellet size	1.315	1.395	1.168	1.283	1.359	1.382	1.309	1.318
Friability	0.659±0.25	0.607±0.1	0.698±0.25	0.783±0.56	0.839±0.29	0.716±0.13	0.746±0.35	0.695±0.06
Drug Content[a] (%)	93.9±0.09	96.05±0.15	92.90±0.26	93.68±0.15	94.05±0.09	94.92±0.09	92.85±0.02	93.95±0.05
Disintegration time[a] (sec)	428±1.08	205±3.00	642±2.00	656±1.50	468±2.38	238±2.95	659±3.06	659±3.28
% Cumulative drug release (90 min)	93.85±0.19	97.98±0.39	95.7±0.45	92.09±0.27	93.87±0.38	96.8±0.29	92.7±0.29	91.5±0.26

Conclusion

Glibenclamide pellets were formulated by Extrusion- spheronization method by using solid dispersion drug, microcrystalline cellulose as spheronization aid, crosspovidone and sodium starch glycolate as super disintegrants. The drug excipient compatibility studies were performed by using IR spectroscopy and found that they were compatible. All formulations were prepared into the pellets and analysed for the parameters such as % friability, pellet size, pellet sphericity, drug content, SEM and % drug release. Drug loaded pellets exhibited spherical nature as evidenced by SEM photomicrographs and sphericity studies. In-vitro dissolution studies for all formulations were carried out and % drug release was calculated. Stability studies were conducted for optimized formulation (F2) as per ICH guidelines at 40oC and 75%RH for three months and no changes were observed. Finally it was concluded that the optimised formulation F2 pellets had maximum drug release within a shorter period of time rather than the marketed formulation. Hence better absorption and bioavailability of the drug can be achieved.

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