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Research Article

Development, characterization of Glipizide spherical agglomerates by direct compression method

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ABSTRACT

The objective of the research is to prepare glipizide spherical agglomerates with increased solubility, flow and compression properties by novel crystallization technique. Glipizide was dissolved in 30ml dichloromethane (good solvent) and stirred. 100ml of water (poor solvent) was added and continued stirring. 5ml of chloroform (bridging liquid) was added and stirred at 1000rpm for 40minutes to precipitate glipizide. The agglomeration method was optimized for parameters like speed and agitation time and amount of bridging liquid added. The precipitated particles were filtered and dried at 40°C. Spherical agglomerates were characterized by IR spectroscopy, X-ray diffraction studies, DSC and SEM and its results showed that no physical or chemical interaction existed in the prepared agglomerates. Spherical agglomerates exhibited decreased crystallinity and improved micromeritic properties (bulk density, tapped density, compressibility index, angle of repose). The prepared agglomerates of glipizide were spherical in shape and dissolution profile was faster and exhibited improved solubility along with proper micromeritic properties than pure drug. The agglomerates can be made directly into tablets because of their excellent flowability. Directly compressed tablets of the glipizide agglomerates exhibited hardness, friability and weight variation appropriately along with improved drug release characteristics. Among the different control release polymers Caesalpinia spinosa (natural mucoadhesive polymer) showed increased drug release retarding capacity. F2 showed the satisfactory results and have better sustainability. A zero order release rate kinetics is exhibited for the best formulation i.e. because it shows correlation coefficient value of zero order is more when compared to first order. F2 formulation diffusion exponent (n) value is 0.45< n >0.89 so they follow Anomalous (Non- Fickian) diffusion. Pharmacokinetic evaluation parameters are used for determination of bioavailability, like maximum $C_{max,}$ T_{max}, AUC, Volume of distribution, half-life ($t_{1/2}$), clearance(Cl_T) and mean residence time (MRT). C_{max} of Glipizide market and test formulations were 1.285 ± 0.1 µg/mL and 01.48 ± 0.02 µg/mL respectively having significantly no difference (P<0.05). T_{max} values of Glipizide market and test were 4.65 ± 0.25 Hours, 10.05 ± 0.80 Hours respectively with significant variance (P<0.05) and a P value 0.0005. ETOVA and test $t_{½}$ values were 3.77 ± 0.645 hrs, 4.56 ± 1.71hrs respectively, with significant variance (P<0.05) and a P value is 0.0002. $AUC_{0-\infty}$ values were 118.3± 20.04 µg-hr/mL, 536.5 ± 49.44 µg-hr/mL respectively. Elimination rate constant of reference and test were0.83 ± 0.44 hr^{-1}, 6.36 ± 1.586 hr^{-1} respectively with significantly variant and P value is 0.0001.

Keywords: Spherical agglomerates, caesalpinia spinosa, HPMC, ethyl cellulose, sodium alginate, crystallization technique.

INTRODUCTION

Direct compression is one of the preferred method for preparation of tablets. It offers numerous advantages like, it is economical when compared to that of wet granulation since it requires fewer unit operations, it is more suitable for moisture and heat sensitive API, the changes in dissolution profile are less likely to occur in tablets made by direct compression method (Sunil Kumar et al., 2014).

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Spherical crystallization technique is the current innovation in particle engineering in which crystallized drug particles are tailored to spherical agglomerates, which can be utilized for direct compression to save money and time for tabletting. In direct tabletting technique, in order to obtain a steady supply of powder mixture to the tabletting machine and sufficient mechanical strength of the compressed tablets it is important to increase the flowability and compressibility of the bulk powder along with increased bioavailability of the drug by improving the solubility pattern of bulk drug. Spherical agglomeration is such a technique to improvise the micromeritic properties and dissolution profile of the drug (P.Kulkarni et al., 2011). Spherical agglomeration is the process of formation of aggregates of crystal particles held together by liquid

bridges. These agglomerates are formed by agitating the crystals in a liquid suspension medium in the presence of binding agent (Mudit Dixit et al., 2010). It is the novel method for enlargement of smaller particles of solid into large size by inter-particle bonding (Pavitra Solanki et al., 2012; Martino DP e al., 1999) .This agglomeration technique can be utilised to increase solubility of the drug, dissolution characteristics and bioavailability of poorly soluble drugs (Sano A et al., 1987; Sano A et al 1990). Direct tabletting is utmost desirable and simplest technique of manufacturing tablet. Such manufacturing process of tablets involve normal mixing and compression of powder, which result in number of benefits including time, cost and energy.

Glipizide is a second generation sulfonyl urea class, oral rapid short acting anti diabetic drug. It is more potent and is having shorter half life than first generation sulfonyl ureas. Polymers like sodium alginate, ethyl cellulose, caesalpinea spinosa (natural polymer) were used with different viscosity grades.

MATERIALS AND METHODS

Glipizide drug was obtained as a gift sample from Dr. Reddys laboratories, Hyderabad. Ethyl cellulose and sodium alginate was obtained as a gift sample from Astra Zeneca Bangalore, India. All other chemicals used were of pharmacopeial grade. All solvents employed in this research were of analytical grade and utilized as it was procured.

Extraction of natural mucoadhesive material from Caesalpinea Spinosa

Collection and authentication of plant

The seeds of caesalpinea spinosa were collected from in and around areas of Nellore disctrict. The plants were authenticated by Prof. K. Madhava Chetty, Department of Botany, SV University, Tirupathi, Chittoor District, Andhra Pradesh and seeds specimen samples were kept in the laboratory for further use.

Caesalpinia spinosa, a small tree belonging to the family Leguminosae. Commonly known as Tara, which is a gum obtained from the seed(endosperm) of Caesalpinia spinosa. The Tara gum is an odorless, white powder. It is obtained by removing and grinding the endosperm of the mature black colored seeds of Tara plant. The primary component of the gum is a galactomannan polymer similar to the main constituents of guar and locust bean gums. In various pharmaceutical and food industries, Tara gum is used as a thickening agent and a stabilizer around the world. Further studies also gave an idea about its applications in various patents like; the use of tara gum as a controlled release formulations includes a gastro retentive controlled drug delivery systems and used as emulsions for various drug products (Saurabh Dilip Bhandare et al., 2015; Pritam Dinesh Choudhary et al., 2014; D. Mahidhar Reddy et al., 2013).

Extraction of natural mucoadhesive materials

The collected seeds were washed thoroughly with water to remove the adhering materials. 500gm of dried seeds were soaked in distilled water (2500ml) separately for 24 hr and later boiled for one hour with continuous stirring at 2000rpm and then kept aside for the release of natural gum into water. The soaked seeds were then squeezed using multiple folds of muslin cloth to separate the marc from the filtrate. The marc was not discarded but it was used for multiple or several extractions. All the extractions were pooled and concentrated under vacuum at 60C to half of the volume. Then to the filtrate equal quantity of acetone was added to precipitate the natural mucoadhesive material, which was later separated by filtration. The precipitated mucilage was dried at 60C in a hot air oven. The dried mucoadhesive agent was powdered, passes through the sieve no.100 and is stored in an airtight container at room temperature for further use. This natural mucoadhesive material is used for different formulations.

Physical characterization of spherical agglomerates

Differential scanning calorimetry (DSC) study

A DSC study was carried out to determine possible polymorphic transitions during the crystallization procedure. DSC measurements were performed with a thermal analyser (A.R.Tapas et al., 2009; Sarfaraz Md et al., 2011; Sachin Kumar Patil et al., 2013; D.Saritha et al., 2012; A.Saritha et al., 2012).

FT-IR Spectroscopy

The FT-IR spectral data were measured at ambient temperature using a Shimadzu, model 8033(USA). Samples were dispersed in KBr powder and pellets were made by applying 5 ton pressure (A.R.Tapas et al., 2009; Sarfaraz Md et al., 2011; Sachin Kumar Patil et al., 2013; D.Saritha et al., 2012; A.Saritha et al., 2012).

X-RAY Analysis

X-Ray powder diffraction studies were obtained at room temperature using Bruker diffractometer, with Cu acting as anode material and graphite monochromator, operated at an voltage of 40mA, 45kV (A.R.Tapas et al., 2009; Sarfaraz Md et al., 2011; Sachin Kumar Patil et al., 2013; D.Saritha et al., 2012; A.Saritha et al., 2012).

Scanning Electron Microscopy (SEM)

SEM (Shimadzu-LV-5600, USA) photographs were obtained inorder identify and confirm spherical character and surface topography of the crystals (A.R.Tapas et al., 2009; Sarfaraz Md et al., 2011; Sachin Kumar Patil et al., 2013; D.Saritha et al., 2012; A.Saritha et al., 2012).

Preparation of glipizide spherical agglomerates

Glipizide was dissolved in 30ml dichloromethane and stirred 100ml water was added and continued stirring. 5ml of chloroform was added and stirred at 1000rpm for 40min to precipitate glipizide. The precipitated recrystallized agglomerates were collected by vaccum filtration and dried in oven at 40°C for 6hr. The dried crystals

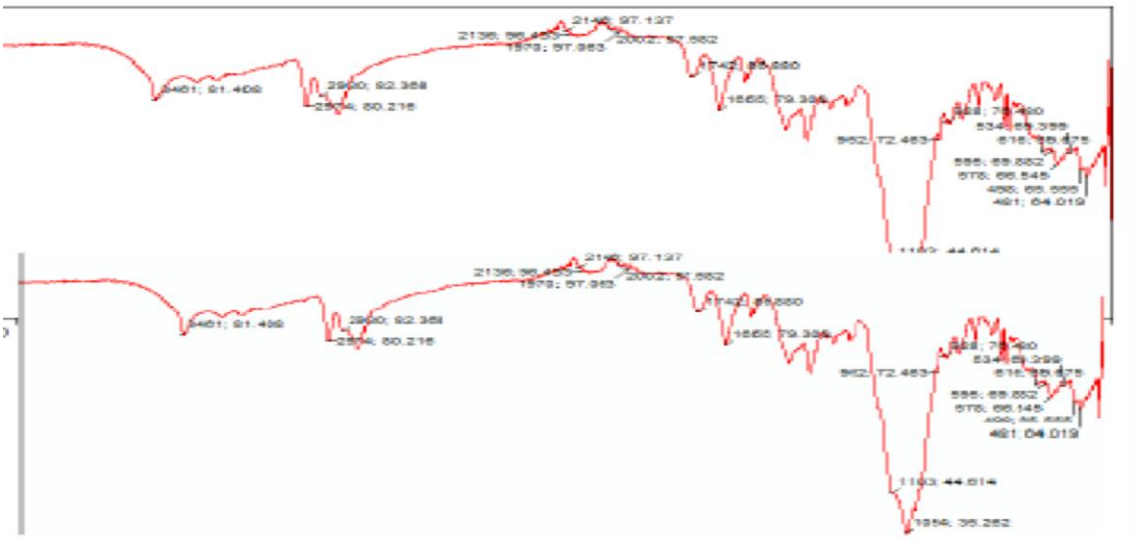

Figure 1: FTIR Spectra of glipizide pure drug and Glipizide spherical agglomerates

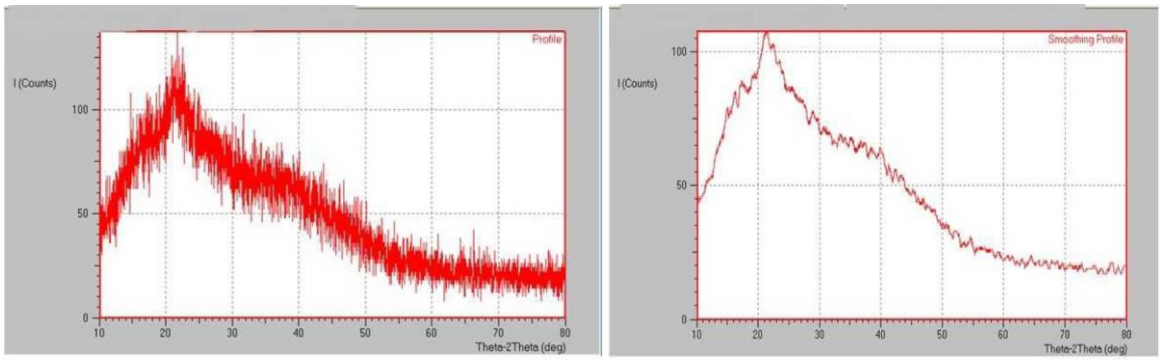

Figure 2: X-Ray diffraction spectra of glipizide

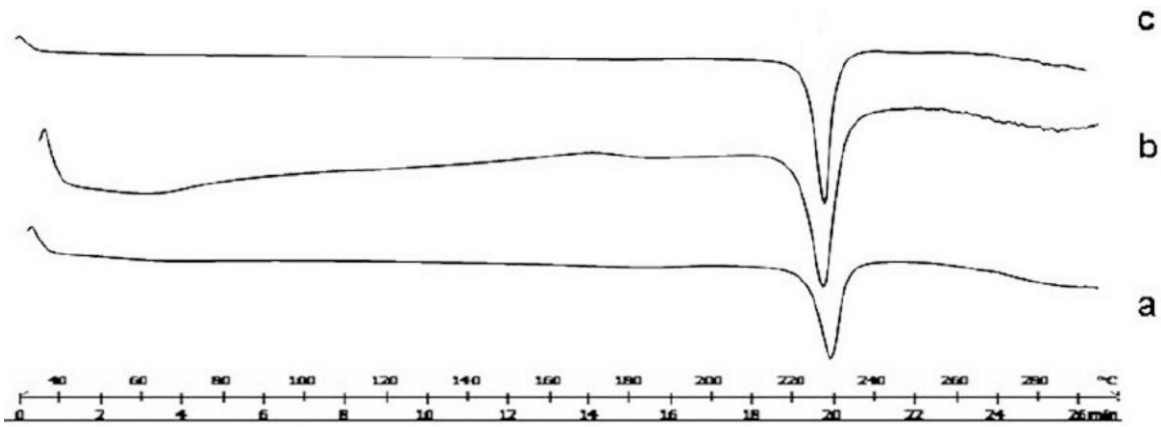

Figure 3: DSC Spectra of glipizide a) Pure drug; b) Recrystallized product; c) Spherical agglomerate

were stored in desiccators at room temperature prior to use. The above procedure was repeated several times to obtain enough materials for characterization and to observe repeatability. Formulation codes were given for spherical agglomerates with polymers (ceasalpinea spinosa, ethyl cellulose and sodium alginate) from F1 to F9 and for pure drug with polymers from F10 to F18 respectively.

Drug content

Drug content was determined by taking spherical agglomerates of glipizide equivalent to 100mg glipizide were triturated and dissolved in a solvent mixture containing dichloromethane: water: chloroform (30:100:5 v/v). Diluted samples were filtered from 0.45µ injection filter and the drug content was determined spectrophotometrically at 276nm using UV-Visible spectrophotometer (Lab India, UV 3000+)

Yield and Micromeritic properties

The yield of prepared agglomerates were determined by the weight of agglomerates after drying. Bulk density (sisco), tapped density was determined by tap density

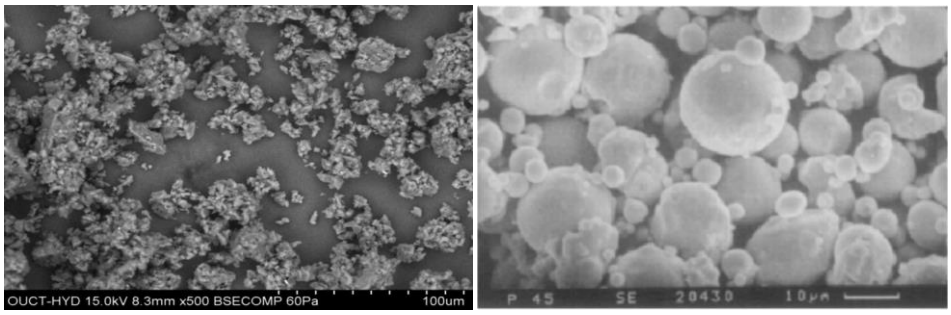

Figure 4: Scanning Electron Microscopy of Glipizide

Table 1: Composition of the formulation

	Spherical Agglomerates of Glipizide												Glipizide API											
Ingredients(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**	**F22**	**F23**	**F24**
Drug	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
mccph112	158	148	138	158	148	138	158	148	138	158	148	138	158	148	138	158	148	138	158	148	138	158	148	138
caesalpinia spinosa	30	40	50	-	-	-	-	-	-	-	-	-	30	40	50	-	-	-	-	-	-	-	-	-
HPMC	-	-	-	30	40	50	-	-	-	-	-	-	--	-	-	30	40	50	-	-	-	-	-	-
sodium alginate	-	-	-	-	-	-	30	40	50	-	-	-	-	-	-	-	-	-	30	40	50	-	-	-
ethyl cellulose	-	-	-	-	-	-	-	-	-	30	40	50	-	-	-	-	-	-	-	-	-	30	40	50
mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

tester and Carr´s index and Hausners ratio were determined. The flow behaviour of raw crystals and spherical agglomerates was characterized by angle of repose by using fixed funnel method.

Preparation of glipizide tablets

Glipizide agglomerates equivalent to 10mg of glipizide were mixed manually with directly compressible microcrystalline cellulose and the blend was finally mixed with magnesium stearate for 2 min. Final blend (200mg per tablet) was compressed by using rotary tablet machine with 6mm standard concave punch. Hardness, thickness, friability of tablets were studied by Monsanto Hardness tester, vernier calipers (Cd 6"Cs), Roche friabilator (ELECTRO LAB) respectively. The weight variation of the tablets was determined taking weight of 20 tablets using electronic balance.

Evaluation of glipizide tablets *In Vitro* dissolution study

The dissolution profile of raw crystals and spherical agglomerates of glipizide were performed by using USP 26 type II dissolution test apparatus (electro lab 08L) in 900ml of pH 7.5 phosphate buffer. Temperature was maintained at 37±2°C and 50rpm stirring was provided for every dissolution study. At predetermined time intervals, 5ml of samples were withdrawn and analysed spectrophotometrically. At each time of withdrawal, 5ml of fresh corresponding medium was replaced into the dissolution flask. Upon filtration through Whattman filter paper, concentration of glipizide was determined spectrophotometrically at 276nm. (A.R.Tapas et al., 2009; Sarfaraz Md et al., 2011; Sachin Kumar Patil et al., 2013; D.Saritha et al., 2012; A.Saritha et al., 2012; Soni Varinder et al., 2013; Rajesh Parid 2010).

RESULTS AND DISCUSSION

FT-IR Spectra of glipizide

Glipizide pure drug & Glipizide spherical agglomerates

All crystals have exhibited general characteristic peaks at 3030-3351cm^{-1}(3351 cm^{-1} for NH-CO-NH stretching, 3030 cm^{-1}for aromatic C-H stretching). Specific changes in IR spectra are not clear, could be due to variations in resonance structure, rotation of a part of a molecular or certain bonds.

X-RAY Diffraction spectra of glipizide

All the drug samples exhibited similar peak positions in X-ray diffraction studies. The relative abundance of the planes exposed to the X-Ray source would have been altered, producing the variations in relative intensities of the peak or may be due to difference in crystal sizes.

DSC

The DSC thermograms shows a sharp endothermic peak for all the glipizide crystals. Melting points showed slight

Table 2: Stability studies of tablets prepared from spherical agglomerates of Glipizide

Time in hrs	Initial (0 day) DR	30 day DR	60 day DR	90 day DR	120 day DR
0.5	16.12 ± 1.44	14.65 ±1.22	14.21 ± 1.32	15.01 ±1.39	16.24 ±2.14
1	22.32 ± 1.32	23.43 ±1.34	22.22 ±1.34	24.22 ±1.23	23.95 ± 2.32
2	29.01 ±1.23	30.45 ± 1.44	31.43 ±1.40	31.19 ±1.45	31.83 ± 1.37
4	44.45 ±1.35	47.09 ± 1.56	46.12 ± 1.51	45.56 ± 1.56	47.17 ±1.39
6	59.62 ±1.56	56.22 ± 1.67	57.61 ± 1.03	58.65 ±1.55	61.33 ±1.24
8	74.66 ±1.69	71.28 ± 1.32	76.66 ±1.78	74.56 ±1.71	75.51 ±1.32
10	86.67 ±1.72	86.78 ± 1.45	83.76 ±1.88	87.88 ±1.01	86.08 ±1.65
12	97.34 ±1.89	98.50 ± 1.52	97.10 ± 1.21	98.02 ±1.10	98.05 ±2.22

DR-drug release (%), values in parentheses indicates± SD

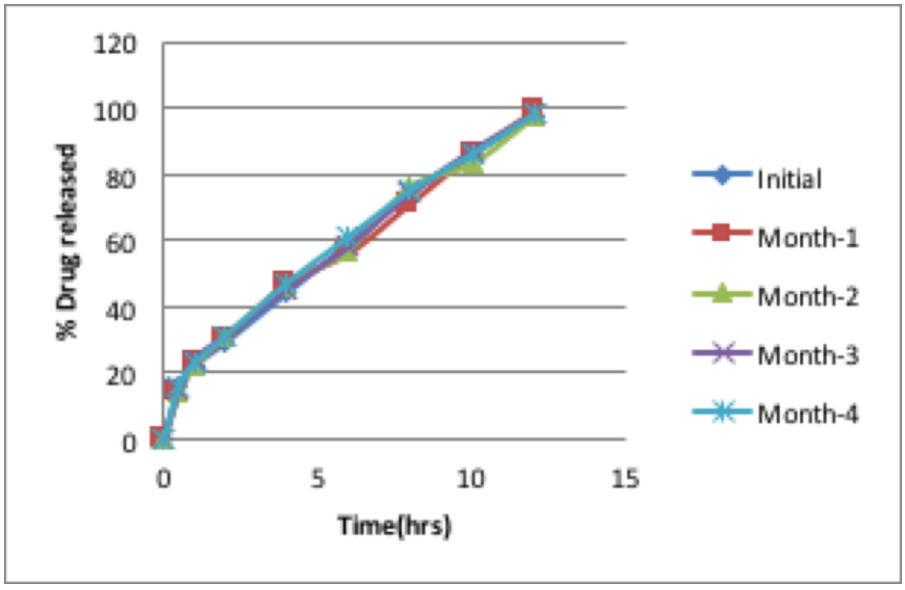

Figure 5: Accelerated stability studies for best formulation

variation as the nature of the crystals might have been affected by the solvents used.

Scanning electron microscopy of glipizide

Crystals of pure sample are of smallest size (4-10µm) and have irregular shapes. Recrystallization product crystals have intermediate size (9-15µm). The agglomerates were formed by coalescence of the microcrystalline precipitates, so the agglomerates had a rugged surface. Agglomerates obtained were spherical in its shape with size 198µm- 670µm.

Stability studies

Accelerated stability studies of tablets of Glipizide prepared from spherical agglomerates was carried out at 40±2ºC and 75±5% RH for a period of 4months in a stability testing chamber. The samples were placed in vials with bromobutyl rubber plugs and sealed with aluminium caps. The samples were withdrawn at 30, 60, 90 and 120 days and evaluated for drug content and invitro drug release.

Dissolution profiles

The dissolution profile of glipizide exhibited improved dissolution behavior for spherical agglomerates than pure sample. Prepared spherical crystals exhibited decreased crystallanity and improved micromeritic properties. Amount of bridging liquid, speed of agitation and duration of agitation had its effect on the mechanical and micromeritic properties of spherical crystals. DSC and XRD studies showed that there is no change in the crystal structure of glipizide during the crystallization process i.e. polymorphism is not present. DSC results further supported IR spectroscopy results, which indicated the absence of any interactions between drug and additives used in the preparation. Hence the spherical crystallization technique can be used for formulation of tablets of glipizide by direct compression with directly compressible excipients. On the other hand, all prepared spherical agglomerates exhibited good compressibility indicating good packability. Among the different control release polymers Caesalpinia spinosa showed highest drug release retarding capacity. F2 was showing the satisfactory results and having better sustainability. When we plot the release rate kinetics for best formulation f2 was following zero order because correlation coefficient value of zero order is more than first order value.

Table 3: Pre-compression parameters

Formulation code	Bulk density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (ɵ)	Diameter
F1	0.52± 0.02	11.86±1.21	1.13±0.03	32.81±0.51	7.94±1.10
F2	0.55±0.01	9.84±1.23	1.11±0.04	30.45±0.54	7.99±1.12
F3	0.49±0.02	14.04±1.22	1.16±0.06	33.64±0.53	8.02±1.23
F4	0.52±0.01	10.34±1.20	1.12±0.07	31.28±0.67	7.96±1.27
F5	0.57±0.02	12.31±1.23	1.14±0.05	32.45±0.69	9.97±1.34
F6	0.54±0.01	10.00±1.36	1.11±0.04	30.87±0.56	7.94±1.40
F7	0.51±0.03	10.53±1.22	1.12±0.03	31.73±0.76	8.06±1.41
F8	0.55±0.02	11.29±1.32	1.13±0.07	32.67±0.78	8.04±1.43
F9	0.53±0.02	11.67±1.38	1.13±0.04	33.76±0.80	7.96±1.51
F10	0.57±0.01	14.93±1.43	1.18±0.08	35.42±0.80	8.01±1.55
F11	0.53±0.03	8.62±1.23	1.09±0.06	27.83±0.65	7.94±1.61
F12	0.51±0.03	13.56±1.54	1.16±0.06	36.79±0.75	7.97±1.64
F13	0.53±0.02	13.11±1.35	1.15±0.03	32.87±0.54	7.97±1.72
F14	0.57±0.01	12.31±1.26	1.14±0.04	34.73±0.52	8.02±1.75
F15	0.51±0.02	19.05±1.24	1.24±0.07	37.25±0.63	7.98±1.23
F16	0.51±0.02	17.74±1.43	1.22±0.04	36.93±0.56	7.96±1.34
F17	0.54±0.01	14.29±1.54	1.17±0.03	34.27±0.65	8.05±1.34
F18	0.56±0.1	17.65±1.36	1.21±0.04	38.23±0.67	8.01±1.24
F19	0.53±0.02	14.52±1.54	1.17±0.03	34.26±0.54	7.99±1.45
F20	0.52±0.01	18.75±1.23	1.23±0.04	38.64±0.63	8.03±1.23
F21	0.56±0.02	12.50±1.34	1.14±0.05	33.16±0.56	7.95±1.56
F22	0.52±0.03	17.46±1.67	1.21±0.07	37.38±0.56	8.04±1.32
F23	0.55±0.01	12.70±1.43	1.15±0.03	33.62±0.80	8.02±1.65
F24	0.55±0.02	19.12±1.24	1.24±0.06	37.98±0.83	7.96±1.33

Statistical Analysis

Results are expressed as mean ± S.D for the taken samples. The results were statistically analysed and significant differences amongst the formulation parameters were determined. Statistical significant was considered at $p< 0.05$.

Pharmacokinetic Evaluation in Rabbits

Animal Ethical committee Approval

The proposed protocol of the Glipizide SR tablets in healthy New Zealand Rabbits accepted by Animal Ethical committee of Sanzyme Labs Pvt., Ltd. Telangana, India with Registered No 1688/PO/Rc/8/13/2011/CPCSEA. Proposal no.345.

Subjects

2.0 to 2.5 kg, sound healthy, 16 male New Zealand white rabbits were taken for the present preclinical study. Animals were under observation for 10 days prior to study.

Food was not provided for the rabbits before 12 hrs and after 24 hrs of administration whereas free access to water is present in the entire study period. Rabbits were placed in metabolic cages and blood samples were collected by using 27 gauge needle from the marginal ear vein into heparinized tubes at time intervals of 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 Hours. Xylene was applied to the shaved marginal ear vein, which causes blood vessel to dilate. The samples were subjected to centrifugation by adding 50µl of Acetonitrile cyclo mix at 8000 rpm for 20 mins and the supernatant was collected by using micropipette. After filtration 20 µl sample was injected into the HPLC system.

Pharmacokinetic Parameters Evaluation

The pharmacokinetic parameters are compulsory for determination of bioavailability, such as maximum concentration of serum $C_{max,}$ T_{max}, AUC, V_d, half-life ($t_{1/2}$) and clearance(Cl_T). Tables 7 and 8 shows the plasma concentration values and bioavailability levels of reference marketed formulation and test extended release formulation.

RESULTS AND DISCUSSION

The dissolution profile of glipizide exhibited efficient dissolution rate for spherical agglomerates than the pure sample. Spherical crystals exhibited decreased crystallanity and better micromeritic properties. Volume of bridging liquid added, speed and duration of agitation affects the mechanical strength and micromeritic characteristics of prepared spherical crystals. DSC and XRD studies proved that there is no significant change in the crystal nature of glipizide during the crystallization process. DSC results further supported IR spectroscopy results, indicating the absence of other interactions between drug and additives used in the formulation. Hence the spherical agglomeration technique can be

Table 4: Post-compression parameters

F. Code	Weight variation (%)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug content (%)
F1	Pass	2.94 ± 0.1	9.34 ± 1.22	0.43 ± 0.02	99.54±1.01
F2	Pass	3.12±0.3	9.83±1.41	0.21±0.04	99.62±1.21
F3	Pass	2.87±0.5	10.15±1.39	0.37±0.02	100.14±0.14
F4	Pass	3.19±0.2	10.89±1.23	0.51±0.01	100.67±0.12
F5	Pass	2.93±0.2	9.46±1.56	0.32±0.02	101.05±0.11
F6	Pass	3.08±0.1	10.07±1.42	0.27±0.03	99.85±1.19
F7	Pass	2.85±0.2	11.12±1.31	0.15±0.02	100.57±1.22
F8	Pass	3.15±0.3	9.38±1.22	0.28±0.01	100.89±1.34
F9	Pass	3.22±0.1	9.72±1.46	0.36±0.03	99.37±1.17
F10	Pass	2.97±0.2	10.48±1.16	0.38±0.04	99.92±1.03
F11	Pass	3.18±0.3	10.39±1.19	0.23±0.05	100.53±1.09
F12	Pass	3.13±0.1	11.03±1.21	0.25±0.05	101.62±1.11
F13	Pass	3.12±0.2	9.93±1.43	0.47±0.02	100.12±1.21
F14	Pass	3.27±0.1	10.02±1.32	0.28±0.04	99.93±1.04
F15	Pass	2.97±0.2	10.37±1.11	0.38±0.02	100.36±1.00
F16	Pass	2.89±0.1	9.82±1.52	0.25±0.04	100.62±1.32
F17	Pass	3.01±0.1	10.28±1.31	0.28±0.04	100.82±1.10
F18	Pass	3.07±0.2	10.42±1.24	0.41±0.01	99.59±1.21
F19	Pass	3.16±0.2	9.93±1.22	0.18±0.05	99.17±1.39
F20	Pass	2.99±0.3	10.75±1.17	0.48±0.01	100.32±1.40
F21	Pass	3.24±0.1	9.85±1.11	0.29±0.03	100.93±1.19
F22	Pass	3.19±0.2	10.51±1.21	0.32±0.02	99.27±1.11
F23	Pass	3.04±0.1	10.75±1.31	0.42±0.01	100.28±1.01
F24	Pass	2.92±0.2	9.93±1.32	0.26±0.03	99.29±1.22

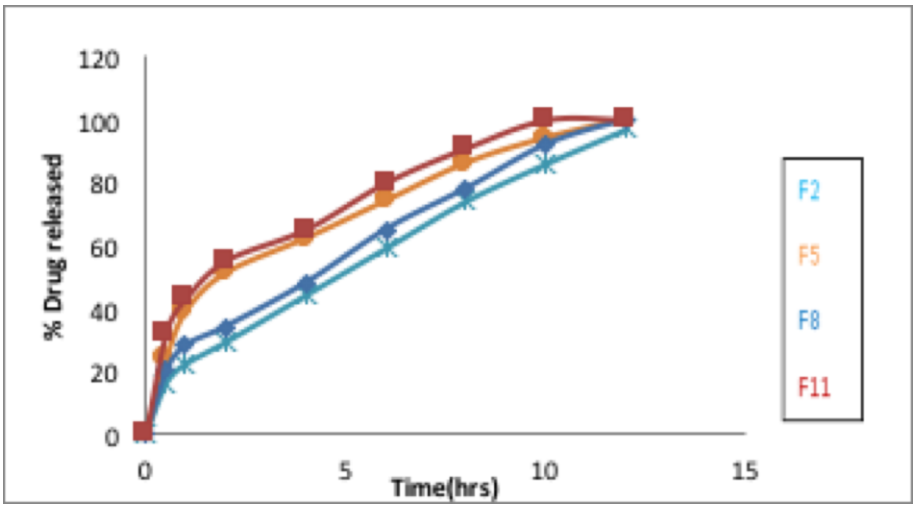

Figure 6: Comparative dissolution profile for drug:polymer (1:4) used formulations

used for formulation of glipizide tablets by direct compression technique using directly compressible excipients. On the other hand, all prepared spherical agglomerates exhibited good compressibility indicating good packability. Saturation solubility studies indicate that the pure drug have least solubility whereas the prepared formulations have higher solubility. Among the various control release polymers Caesalpinia spinosa showed highest drug release retarding capability. F2 was showing the satisfactory results and having good sustainability. When we plot the release rate kinetics for best formulation f2 was following zero order because correlation coefficient value of zero order is more than first order value. F2 formulation followed Anomalous diffusion. C_{max} of Glipizide market and test formulations were 1.285 ± 0.1 µg/mL and 01.48 ± 0.02 µg/mL respectively with significantly no difference (P<0.05) and a P value of 0.0856. T_{max} values of Glipizide market and test were 4.65 ± 0.25 Hours, 10.05 ± 0.80 Hours respectively with significant variance (P<0.05) and a P value 0.0005. ETOVA and test $t_{½}$ values were 3.77 ± 0.645 hrs, 4.56 ± 1.71hrs respectively, with significant variance (P<0.05) and a P value is 0.0002. $AUC_{0-\infty}$ values were 118.3± 20.04 µg-hr/mL, 536.5 ± 49.44 µg-hr/mL respectively for ETOVA and test with significant variance (P<0.05) and P value is <0.0001. Elimination rate constant of reference and test were0.83 ± 0.44 hr^{-1}, 6.36 ± 1.586 hr^{-1} respectively with significantly variant and P value is 0.0001.

Table 5: Drug release kinetic profile of glipizide tablets

lation code	R² Value s				'n' Valu
	Zero order	First order	Higuchi	Peppas	
F1	0.949	0.959	0.995	0.996	0.420
F2	**0.990**	**0.984**	**0.991**	**0.994**	**0.574**
F3	0.988	0.996	0.993	0.998	0.612
F4	0.864	0.990	0.963	0.974	0.370
F5	0.939	0.986	0.994	0.993	0.423
F6	0.954	0.992	0.998	0.998	0.470
F7	0.808	0.996	0.933	0.964	0.295
F8	0.848	0.988	0.956	0.980	0.320
F9	0.890	0.982	0.976	0.986	0.359
F10	0.914	0.961	0.985	0.990	0.398
F11	0.940	0.983	0.994	0.995	0.410
F12	0.953	0.980	0.995	0.993	0.428
F13	0.930	0.984	0.990	0.998	0.369
F14	0.982	0.989	0.994	0.992	0.508
F15	0.980	0.991	0.996	0.996	0.511
F16	0.834	0.990	0.948	0.967	0.332
F17	0.922	0.972	0.988	0.997	0.362
F18	0.949	0.982	0.997	0.999	0.422
F19	0.774	0.996	0.911	0.947	0.268
F20	0.815	0.977	0.937	0.975	0.282
F21	0.860	0.936	0.960	0.977	0.321
F22	0.887	0.977	0.974	0.989	0.354
F23	0.922	0.960	0.988	0.992	0.378
F24	0.943	0.950	0.992	0.992	0.396

Table 6: Composition of in vivo spherical agglomerates

Ingredients	Quantity	Quantity
	Formulation	Placebo
Spherical agglomerate of glipizide API	10	--
mccph112	148	148
Caesalpinia Spinosa	40	40
HPMCK100M	--	--
sodium alginate	--	--
ethyl cellulose	--	--
Mg stearate	2	2

Table 7: Plasma concentrations of GLIPIZIDE (Reference Marketed Formulation) at different time intervals

Rabbits	Plasma Conc. (µg/mL)	Time (Hr)												
		0.5	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**24**
1		0.25	0.32	0.42	1.3	1.1	0.82	0.8	0.53	0	NA	NA	NA	NA
2		0.26	0.32	0.45	1.32	1.2	0.83	0.78	0.55	0	NA	NA	NA	NA
3		0.27	0.36	0.45	1.25	1.15	0.81	0.82	0.56	0	NA	NA	NA	NA
4		0.23	0.33	0.47	1.26	1.17	0.82	0.81	0.54	0	NA	NA	NA	NA
N	Statistical Parameters	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean		**0.25**	**0.33**	**0.44**	**1.28**	**1.15**	**0.82**	0.80	**0.54**	**0**	*	*	*	*
SD		0.01	0.01	0.02	0.03	0.04	0.08	0.01	0.01	0	*	*	*	*
Min		0.23	0.32	0.42	1.25	1.1	0.81	0.78	0.53	0	*	*	*	*
Median		0.255	0.325	0.45	1.28	1.16	0.82	0.805	0.54	0	*	*	*	*
Max		0.27	0.36	0.47	1.32	1.2	0.83	0.82	0.56	0	*	*	*	*
%CV		6.76	5.69	4.60	3.63	3.63	0.99	2.13	2.36	0	*	*	*	*

(Conc.= Concentration; CV= Coefficient of variation; SD=Standard deviation)

Table 8: Plasma concentrations tablet (T) of Optimized GLIPIZIDE spherical agglomerates at different Time intervals

Sub-jects	Plasma Conc. (µg/mL)	Time (Hr)												
		0.5	1	2	4	6	8	10	12	14	16	18	20	24
1		0.29	0.35	0.48	0.63	0.92	1.29	1.48	0.98	0.8	0	NA	NA	NA
2		0.26	0.36	0.52	0.66	1.01	1.31	1.47	0.95	0.82	0	NA	NA	NA
3		0.27	0.38	0.51	0.67	1.0	1.26	1.48	0.89	0.83	0	NA	NA	NA
4		0.28	0.36	0.53	0.65	1.03	1.32	1.49	0.93	0.81	0	NA	NA	NA
N	Statistical Parameters	4	4	4	4	4	4	4	4	4	4	*	*	*
Mean		0.28	0.36	0.51	0.65	0.99	1.30	1.48	0.94	0.82	0	*	*	*
SD		0.01	0.01	0.02	0.01	0.04	0.02	0.01	0.03	0.01	0	*	*	*
Min		0.26	0.35	0.48	0.63	0.92	1.26	1.47	0.89	0.8	0	*	*	*
Median		0.27	0.36	0.51	0.65	1.00	1.3	1.48	0.94	0.81	0	*	*	*
Max		0.29	0.38	0.53	0.67	1.03	1.32	1.49	0.98	0.83	0	*	*	*
%CV		4.69	3.47	4.24	2.62	4.88	2.04	0.55	4.03	1.58	0	*	*	*

(Conc.= Concentration; CV= Coefficient of variation; SD=Standard deviation)

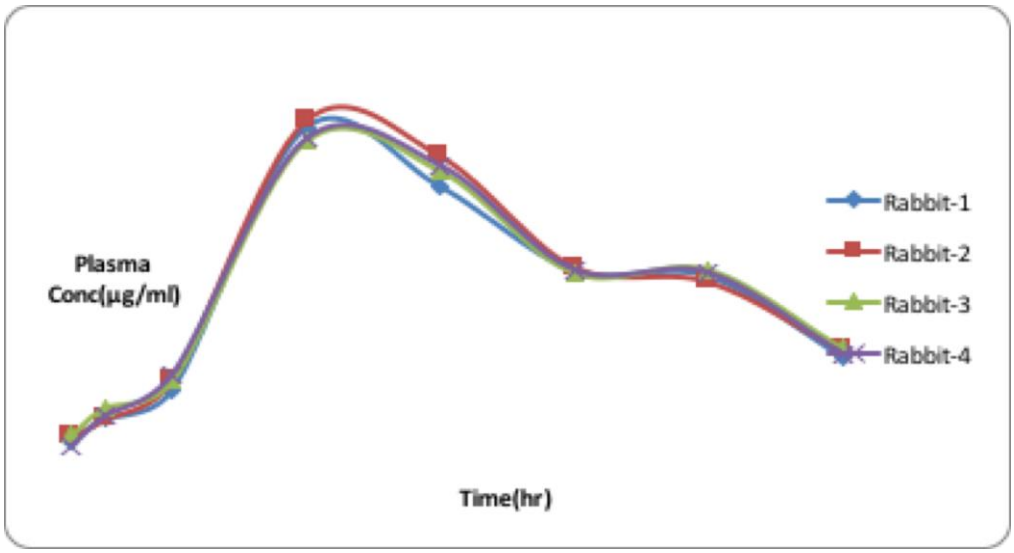

Figure 7: Plasma concentration vs. time profile of Marketed Glipizide in Rabbit plasma levels

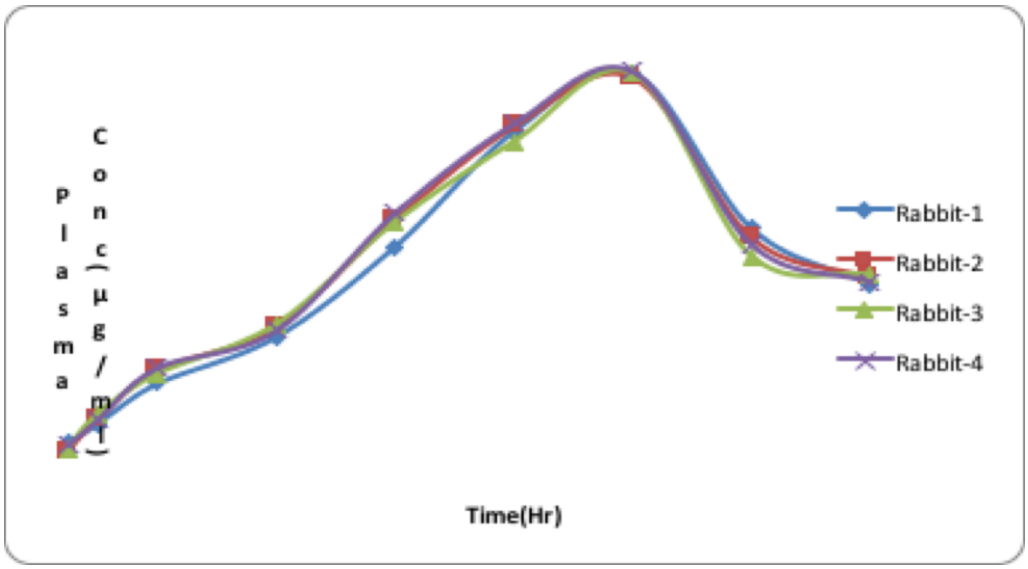

Figure 8: Plasma concentration vs. time profile of test Glipizide spherical agglomerates in rabbit plasma levels

Table 9: Comparative bioavailability parameters of reference and Test formulations

PK parameter	Reference Tablet	Spherical agglomerates	't' test at 0.05
C_{max} (µg/mL)	1.285	1.48	Not significant
T_{max} (Hours)	4.65	10.08	Significant
$t_{1/2}$ (hrs)	3.77	4.56	Significant
Total AUC (µg-hr/mL)	118.33	536.42	Significant
Total AUMC (µg-hr/mL)	330.17	3710.5	Significant
Cl (mL/min)	557.0	162.13	Significant
K_{el} (hrs^{-1})	0.83	6.36	Significant

Owing to the subjective variability there was variance in individual T_{max} and C_{max} values. This is applicable in marketed and test samples also. The reports of pharmacokinetic characteristics showed that the marketed formulation and test formulation were purely different showing that the prepared tablets exhibits extended release.

CONCLUSION

Glipizide spherical agglomerates were prepared which showed improved flowability, solubility, packability and compactability resulting in effective direct tabletting. The important criteria in the improvement of the flowability and packability was a significant reduction in interparticle friction, due to spherical shape of the tabletted particles. Agglomerates were tableted directly by compression with quick disintegration time and produced higher dissolution rate. In vitro and in vivo studies depicts the effectiveness of spherical agglomeration technique in many parameters like improved bioavailability and other compression parameters. The extended or increased bioavailability achieved with spherical agglomeration of glipizide may reduce the total dose of drug, beneficial for the cost effectiveness and better patient compliance. It concludes that direct compression of spherical crystallization of glipizide with selective polymers is an efficient method to improve compressibility and also dissolution profile of glipizide.

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REFERENCES

A.R.Tapas, P.S.Kawtikwar, D.M. Sarkar. Enhanced dissolution rate of felodipine using spherical agglomeration with inutec SP by quasi emulsion solvent diffusion method. Research in pharmaceutical sciences. 2009 Jul-Dec; 4(2): 77–84.

A.Saritha, Nalini Shastri, Sadanandam, Anantha Laxmi. Enhancement of dissolution and anti-inflammatory activity of meloxicam by spherical agglomeration technique. J. of pharmaceutical Sciences and Research. Vol. 4(1). 2012. Pg-1657-1661.

D. Mahidhar Reddy, Sk. Razia Begum, K. Jyothirmai, G.V. Dileep Kumar, S. Jayasree, J. Jeevankumar, A.V.S. Gita Samira. A Novel Review on Natural Polymers Used In Formulation of Pharmaceutical Dosage Forms. International Journal of Pharmacy and Natural Medicines. 2013, Vol.1 (1): 71-78.

D.Saritha, P.Subhash Chandra Bose, P. Srikanrth Reddy, G.Madhuri, R.Nagaraju. Improved dissolution and micromeritic properties of naproxen from spherical agglomerates: preparation, invitro and invivo characterization. Brajilian J of Pharmaceutical Sciences. Vol-48.2012. Pg-667-676.

Martino DP, Barthelemy C, Piva F, Joiris E, Palmieri GF and Martelli S. improved dissolution behavior of Fenbrufen by spherical crystallization. Drug Dev Ind Pharm 1999; 25(10): 1073-1081.

Mudit Dixit, Dr.K.Kulkarni, Shahnanwaz Anis and Ashwini G Kini. Preparation and characterization of spherical agglomerates of ketoprofen by neutralization method. International Journal of Pharma and Bio Sciences, Vol-1, Issue-4, Oct-Dec.2010, Pg:395-406).

P.Kulkarni K, Mudit Dixit, Ashwini G Kini, Akash Johri. Spherical agglomerates of mefanic acid by solvent change method. International Journal of Pharm.Sciences, Vol-2, Issue-2, 2011. Pg-111-125.

Pavitra Solanki, Anoop Kumar, Abinav Garg, Pankaj Sharma, Satyavir Singh. Designing and development of spherical agglomerates of ibuprofen-paracetamol blend for improved tableting and dissolution. International /journal of therapeutic Applications.Vol-8, 2012, Pg-8-13.

Pritam Dinesh Choudhary and Harshal Ashok Pawar Recently Investigated Natural Gums and Mucilages as Pharmaceutical Excipients: An Overview. Journal of pharmaceutics. 2014; 2014: 204849.

Rajesh Parid. Evaluation parameters for spherical agglomerates formed by spherical crystallization technique. Int.J. of Pharma & Bio Sci. Vol.1(3). 2010. Pg.1-10.

Sachin Kumar Patil, Atul Kadam, Shital Kumar Patil, Sunit Kumar Sahoo. Directly compressible glibenclamide tablet prepared from spherical agglomerates: A comparative evaluation with marketed tablet. J.of Pharm.Sci.Tech. vol-3.Issue-1.2013. Pg:31-36.

Sano A, Kuriki T, Handa T, Takeuchi H, Kawashima Y. particle design of tolbutamide in the presence of soluble polymer or surfactant by the spherical crystallization technique: improvement of dissolution rate. J Pharm Sci 1987; 76:471-474.

Sano A, Kuriki T, Handa T, Takeuchi H, Kawashima Y. particle design of tolbutamide in the presence of soluble polymer or surfactant by the spherical crystallization technique: improvement of dissolution and bioavailability of direct compressed tablets prepared using tolbutamide agglomerated crystals. Chem Pharm Bull 1990; (11): 3030-3035.

Sarfaraz Md, Arshad Ahmed Khan, Doddayya H, Reddy, SR, Udupi R.H. Particle design of aceclofenac-disintegrant agglomerates for direct compression by crystallo-co-agglomeration technique. Asian J.of Pharamaceutical Technology. 2011, vol-1, issue-2.Pg- 40-48.

Saurabh Dilip Bhandare, Ekta Kavade and Sunita Surse. natural polymers: as pharmaceutical excipients and their applications in different pharmaceutical formulations - a review. World Journal of Pharmaceutical Research. Volume 4, Issue 6, 2015, 626-644.

Soni Varinder, Rathore MS. Spherical agglomeration techniques and their evaluation parameters.Int.J.Drug Dev.&.Res. vol.5(3).2013. Pg.67-76.

Sunil kumar, K. P. R. Chowdary, P. Suresh A comparative evaluation of direct compression and wet granulation methods for formulation of stavudine tablets JGTPS Vol 5(3), 2014Pg. 2000-2003.