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Research Article

Formulation and Evaluation of Immediate Release Pellets By Using Co-Processed Polymer

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ABSTRACT

The present study was intended towards the formulation and evaluation of immediate release pellets of irbesartan (Irbesartan as model drug has low solubility). Pellets were prepared by the extrusion-spheronization method using co-processed excipient to improve the disintegration time and faster drug release from the pellets. Immediate release pellets were prepared by using co-processed excipient consisting silicon dioxide and calcium stearate. The prepared pellets were evaluated by the flow parameters, friability, disintegration time, FTIR, DSC, SEM and *in-vitro* dissolution study. It was found that pellet prepared by using co-processed excipient were mechanically stable, good flowability and sphericity. FTIR and DSC study shows that there is no drug excipient interaction; SEM Images shows that co-processed excipient gives spherical pellets. Formulation containing 40% co-processed excipient and 20% MCC shows higher drug release and faster disintegration. Hence, study concludes that co-processed excipient which shows improved disintegration time and faster drug release may be suitable for immediate release pellets.

INTRODUCTION

Oral drug delivery has been most widely utilized route of administration, among all other routes [1, 2]. Today, a variety of techniques have been utilized for development and preparation of solid oral dosage form such as powder, tablet, capsule and pellet [3, 4]. Among the solid oral dosage form pellets have various advantages as compared to other oral solid dosage form [5-7]. Pellets having spherical shape are gaining attention in designing solid dosage form [8, 9]. The extrusion-spheronisation method is mostly appropriate method for production of pellets and MCC is most widely used as pelletizing aid or excipient for the production of pellet [10, 11]. Universal MCC accepted as pelletizing aid due to certain reasons such as cohesiveness, plasticity and rheological properties, and but it have certain disadvantage such as drug absorption onto the surface of MCC fibres, prolong drug release of poorly water soluble drug and lack of disintegration of pellets [12, 13].

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Co-processing of excipients is a combination of two or more excipients by appropriate process, which is used as excipients because it produces better properties as compared to simple physical mixture of their components or with individual components [14, 15]. Co-processing is based on the novel concept of two or more excipients interacting at sub-particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients [16, 17]. Various co-processed excipients have allowed the number stages and the number of excipients needed in the process of developing different formulation to be reduced and, thus have simplified the production processes, reduced costs and improved the dosage form properties [14-16]. They have been developed primarily to address the issues of flowability, compressibility, content uniformity, dilution potential, lubricant sensitivity, or improved performance such as the disintegration and dissolution profile [14-16].

The choice of silicon dioxide was based upon its unique high water absorption capacity and

surface modification when being co-processed with polymers [18]. In practice, silicon dioxide was proven to be an efficient additive for the processing of microcrystalline cellulose and carboxymethyl cellulose [18, 19]. Thus colloidal silicon dioxide could be a useful candidate for the development and modification of highly compressible, highly compactable, and disintegrable excipients [18, 19].

The aim of this work is to formulate and evaluate immediate release pellet by using co-processed excipients of silicon dioxide and calcium stearate, with suitable properties for improving release of drug, disintegration and accelerating the dissolution of low solubility drugs in pellets produced by extrusion-spheronization. For this study, we have selected Irbesartan (IRB) as the low solubility model drug. In addition, we have incorporated Croscarmellose sodium as super-disintegrant and lactose as filler in order to assess the presence of any possible synergistic effect, between co-process excipient and crosscarmellose sodium as well as lactose, which could affect the drug dissolution process. Novelty of the work is that, we developed a new multiple unit immediate release pellets using novel co-processed silicon dioxide and calcium stearate (as excipient) as pelletization aid which is having promising potential for the faster release of drug and immediate disintegration of the pellets.

MATERIALS AND METHOD

Materials

Irbesartan was supplied as a gift sample from IPCA laboratories ltd, Mumbai, India. Microcrystalline cellulose (Avicel pH101) provided by signet chemical corporation. Croscarmellose sodium (CCS), Lactose Monohydrate (LM), Calcium Stearate, Silicon dioxide was purchased from Merk Pvt Ltd (Mumbai).All other chemicals and reagents used in the study were of analytical grade.

Method

Preparation of Co-processed Silicon Dioxide-Calcium Stearate Excipient

The method described by El-Barghouthi et al. for the preparation of the co-precipitated chitosan-silica was followed to prepare the co-processed calcium stearate –silicon dioxide. 500 g of calcium stearate was suspended in 1L of 2 M HCl, and 500g of silicon dioxide in 1L of 2 M NaOH. To the latter suspension, under stirring, 1L of distilled was added over 1h, followed by the calcium stearate suspension and, simultaneously, concentrated HCl solution (to keep the pH below 6.5). The resulting co-processed was filtered out, washed with distilled water, dried in an oven at 90°C and passed through a sieve with 0.5 mm mesh.

Characterization of Co-processed Silicon Dioxide-Calcium Stearate Excipient

FTIR and XRD

Infrared spectroscopy was used to follow the molecular interaction between silicon dioxide and calcium stearate. Samples of silicon dioxide, calcium stearate and co-processed silicon dioxide-calcium stearate at the mass ratio of 100:1 were mixed with dried KBr. Then small portion of the mixture was compressed by hydraulic pressure. Prepared KBr pellet was analysed over scanning range 4000-400 cm^{-1} with a 4 cm^{-1} resolution using FTIR (8400 S, Shimadzu, Tokyo, Japan). The XRD patterns of silicon dioxide and co-processed silicon dioxide-calcium stearate was measured using X-ray diffractometer (X-pert PRO, Panalytical, Netherland) with glass tubing Cu anode and graphite monochromator at 30 mA and 40 kV sample was placed on a glass slide. The rate employed was 10 $^{min-1}$ over a 10-30º diffraction angle (2θ) range.

SEM

The surface morphology of silicon dioxide and co-processed silicon dioxide- calcium stearate was observed by the scanning electron microscopy (SEM) (S-4800, Type-II, Hitachi High Technologies Corp. Tokyo, Japan). The dried samples were mounted on aluminum stubs and then coated with gold by sputtering at 1200 V, 20 Ma for 105 s using vacuum coater and photograph were captured.

Preparation of Pellets

For the preparation pellets, all the accurately weighed ingredients were mixed intimately, and the dry powder mixture was blended for 10 minutes in laboratory scale blender ((LM40, Bohle, Ennigerloh, Germany). Granulating liquid (Distilled water) was then added drop wise and mixed until wet mass obtained. The wet mass was extruded (1.0 mm pore size) at 75 rpm for 20 min using extruder and these extrudate was spheronized for 10 minutes at 1200 rpm in spheronizer(Innovative UICE, Umang Pharmatech Pvt Ltd, Mumbai, India) fitted with a cross-hatched rotor plate of 150 mm and 3 mm thickness. Resulting pellets were dried in hot air oven at 40°C for removing moisture from pellets.

These dried pellets were then screened by using sieve. Formulations of batches are shown in Table 1.

Table 1: Formulation of Batches

Batches	Drug (gm)	Crosscarmellose sodium (mg)	Lactose (gm)	MCC (pH101) (gm)	CO-Processed (gm)
F1	2	800	1.2	3	3
F2	2	800	1.2	3	2
F3	2	800	1.2	3	4
F4	2	800	1.2	2	3
F5	2	800	1.2	2	4
F6	2	800	1.2	2	2
F7	2	800	1.2	4	4
F8	2	800	1.2	4	3
F9	2	800	1.2	4	2
F10	2	800	1.2	2	-

Characterization of Pellet

FTIR and DSC

Drug-Excipients interaction study was carried out by using FTIR spectroscopy and Differential scanning calorimetry (DSC).

FTIR spectra of individual drugs and mixture of drugs and excipients were recorded with FTIR spectrophotometer (IR IFFINITY-1 CE, Shimadzu crops, Japan) equipped with pyroelectric detector using dispersion method. The FTIR measurements were performed in the scanning range of 4000-400 cm^{-1} at ambient temperature. The spectra were saved using IR solution software. The mixture spectra compared with spectra of drug respectively for their bands.DSC study of formulation was carried out to find out the melting point. The thermogram of formulation was obtained using DSC analysis system. Scanning was carried out up to 300 °C at heating rate 10°C/min with 30 ml/min nitrogen flow.

Flow Properties of Pellets

For the flow properties of prepared pellet initially were characterized by Bulk density (BD) and Tapped density (TD) of the pellets were determine by digital density apparatus (Innovative XCN 77). 10 gm of pellets was introduced into a 100 ml calibrated measuring cylinder in density apparatus. After noting down the initial volume, cylinder was allowed to fall under its own weight on to a hard surface from the height. The tapping was continued for 100 tapping complete and further change in volume after 100 tapping was noted. BD and TD were calculated using following equations 1 and 2 respectively. Then actually go for the determination of flow properties such as Hausner's ratio and Compressibility index (Carr's index) by following formulas.

$$\text{Bulk density (BD)} = \frac{\text{Weight of pellets}}{\text{Bulk volume}} \ldots\ldots \text{ Eq 1}$$

$$\text{Tapped density (TD)} = \frac{\text{Weight of pellets}}{\text{Tapped volume}} \ldots \text{ Eq 2}$$

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \ldots\ldots\ldots\ldots \text{Eq 3}$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \ldots\ldots\ldots \text{Eq 4}$$

The angle of repose was determined by the fixed funnel method. The accurately weighed pellet was taken in funnel. The height of the funnel was adjusted in such a way that the tip of funnel just touched the apex of heap of the pellets. The pellet was allowed to flow through the funnel freely on to the surface. Finally the diameter of pellets cone was measured. The angle of repose was calculated using following formula.

$$\text{Angle of repose } (\theta) = \tan^{-1}\frac{h}{r} \ldots\ldots\ldots \text{ Eq 5}$$

Where, 'h' and 'r' are the height and radius of the powder cone.

Pellet Size and Shape

The pellet size and shape of the prepared pellets batches were performed using motic microscopy. Formulated 3 selected pellets of each batch were observed in Motic DMWB 2-223 digital microscopes fitted with 1/3 CCD camera imaging accessory and using Motic images 2000 (1.3 version) image analysis software (Motic Instruments, Toronto, Canada).

Aspect Ratio

Aspect ratio is defined as the ratio of the length of a pellet divided by the width, with pellets being considered round (spherical) if the aspect ratio lies between 1.0 and 1.20. The length and width of pellets were measured by using digimatic caliper (Absolute Digimatic Caliper, Mitutoyo Corporation, Japan) and their ratio was determined and calculated by the following formula.

$$\text{Aspect ratio} = \frac{\text{Length of pellets}}{\text{Width of pellets}} \quad \ldots\ldots\ldots\ldots \text{Eq 6}$$

Friability

Friability of the pellets was performed by using Roche friabilator (FE2, Electrolab, Mumbai, India.) normally pre-weighed 5 gm pellets were placed in the plastic chamber of friabilator. It was then operated for 100 revolutions. Pellets were dropping from a distance of six inches with each revolution, after completion of desired cycles; pellets were removed from friabilator, dusted and reweighed.

$$\%\ \text{Friability} = \frac{\text{Initialweight of pellets} - \text{Finalweiht of pellets}}{\text{Initialweight of pellets}} x100 \quad \ldots\ldots\ldots\ldots \text{Eq 7}$$

Disintegration Test

Disintegration test was performed in water using disintegration tester (USP) (Innovative Pathak Electicals Works, Mumbai, India.). The disintegration test was performed at 37 ± 1° C in distilled water for pellets from each formulations using the disintegration unit. The pellets were considered completely disintegrated as no residue remains on the screen.

Drug Content and Percent Production Yield

The drug content of pellet formulation was determined in accurately weighed 100 mg pellets. The pellets were powdered in mortar, and the powder is dissolved in methanol using ultra sonication. After filtration, the UV absorbance of the suitably diluted filtrate through 0.45 lm filter (Millipore) was measured at 244 nm to determine the drug content. The content uniformity test was carried out three times for each formulation, and the results were expressed with the standard deviations.

To determine production yield, pellets were passed through 16/25 mesh sieves of Tylor's standard using a sieve shaker (Electromagnetic sieve shaker, EMS-8, Electrolab, Mumbai, India) at a frequency of 50 Hz with amplitude of 1 mm for 5 min. A fraction of pellets between 710 and 1,190 µm sizes were selected as the final product. The percent production yield was calculated by using following formula.

$$\text{Production yield of pellets}(\%) = \frac{\text{Practical weight of pellets}}{\text{Therotical weight of pellets}} x100 \quad \ldots\ldots\ldots\ldots \text{Eq 8}$$

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) is used to examine the surface morphology and cross section of the pellets. The sampling pellets were coated with thin layer of gold and these gold coated pellets were placed in SEM apparatus(S-4800, Type-II, Hitachi High Technolugies Corp. Tokyo, Japan) in front of camera and pellets were analyzed at 10 kv acceleration voltages using scanning electron microscope.

***In- vitro* Dissolution Study of Formulation**

In-vitro drug release was performed, Equivalent amount of dose of drug containing pellets of Irbesartan using DT – 6 USP 29 type II apparatus (Dissolution Tester EDT 08Lx, Electrolab, Mumbai, India) stirred at paddle speed of 50 rpm in 900 ml of 0.1 N HCl at 37± 0.5°C, A 5 millilitre sample was withdrawn at predetermined time intervals and it was replaced with fresh dissolution media to maintain the sink condition. The withdrawn sample were filtered through 0.45 µm membrane filter and analyzed using UV spectrophotometer (UV1700, Shimadzu, Japan) Periodically measuring absorbance at 244 nm.

RESULT AND DISCUSSION

Characterization of Co-Processed Excipient FTIR and XRPD

To characterize the co-processed excipients, the IR spectroscopy and X-ray powder diffraction techniques were employed. The observation of IR spectra shows that the process does not induce any kind of chemical reaction, since the IR spectra of those co-processed Silicon dioxide-calcium stearate are predictable on the basis of the IR spectra of silicon dioxide and calcium stearate, as an example co-processed-calcium stearate IR spectrum is shown (Fig 1).

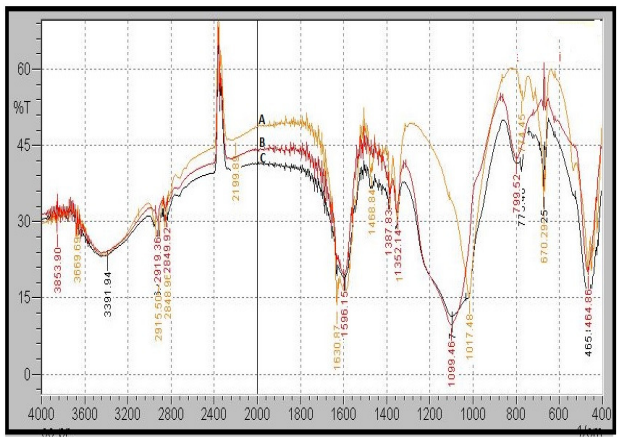

Figure 1: FTIR spectra of A) calcium stearate B) silicon dioxide C) co-processed calcium stearate – silicon dioxide.

Table 2: Flow properties of prepared pellets

Batch	Flow properties				
	Angle of Repose (Θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner'sratio (%)
F1	29.32± 0.5	0.76 ± 0.1	0.86 ± 0.1	11.62 ± 0.7	1.13 ± 0.03
F2	29.74± 0.8	0.75 ± 0.1	0.82 ± 0.1	3.65 ± 0.8	1.09 ± 0.02
F3	30.46± 0.9	0.77 ± 0.1	0.80 ± 0.1	3.75 ± 0.9	1.03 ± 0.04
F4	29.81± 0.6	0.76 ± 0.2	0.81 ± 0.1	6.17 ± 0.7	1.00 ± 0.02
F5	29.05± 0.5	0.78 ± 0.1	0.84 ± 0.1	7.14 ± 0.8	1.03 ± 0.05
F6	28.39± 0.6	0.74 ± 0.1	0.82 ± 0.1	9.75 ± 0.8	1.10 ± 0.04
F7	27.14± 0.9	0.70 ± 0.1	0.75 ± 0.1	6.66 ± 0.9	1.00 ± 0.03
F8	27.25± 0.7	0.72 ± 0.1	0.77 ± 0.1	6.49 ± 0.7	1.06 ± 0.02
F9	28.00± 0.9	0.74 ± 0.2	0.82 ± 0.1	9.75 ± 0.8	1.10 ± 0.02
F10	28.05± 0.5	0.77 ± 0.1	0.85 ± 0.1	7.44 ± 0.8	1.03 ± 0.05

Furthermore, the X-ray powder diffractograms reveal that the process remains unchanged the crystallinity characteristics of silicon dioxide (Fig 2). Therefore, one of the requirements of the co-processed excipients is fulfilled, such as the absence of chemical change.

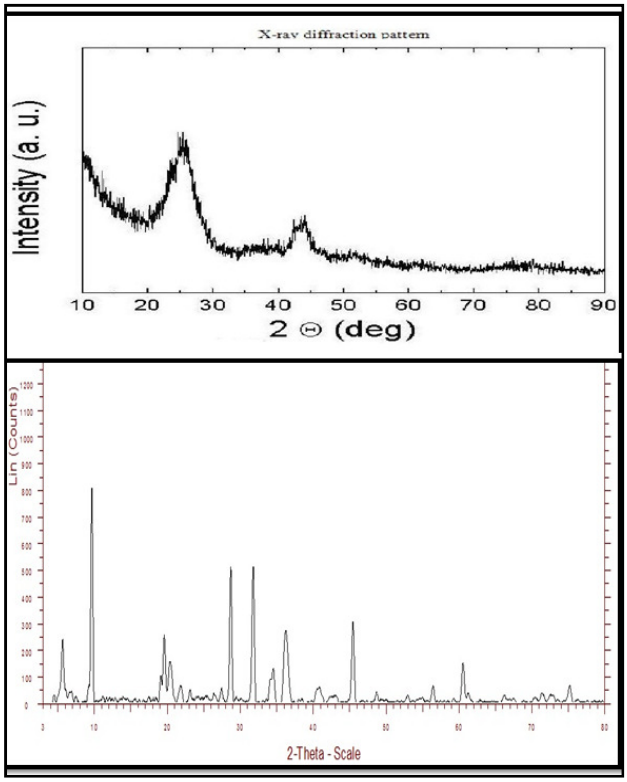

Figure 2: X-ray powder diffractions of silicon dioxide (A) and co-processed calcium stearate – silicon dioxide (B).

SEM

The photomicrographs of scanning electron microscopy (SEM) obtained for the two excipients allow observing the silicon dioxide particles and the effects produced by the presence of co-processed excipients. In the (Fig 3A) image, silicon dioxide is free and unconnected. The silicon dioxide appear thicker as calcium stearate added in the excipient, due to the presence of the copolymer on its surface, and partially agglomerated due to binding effect of calcium stearate as shown in (Fig 3B) image.

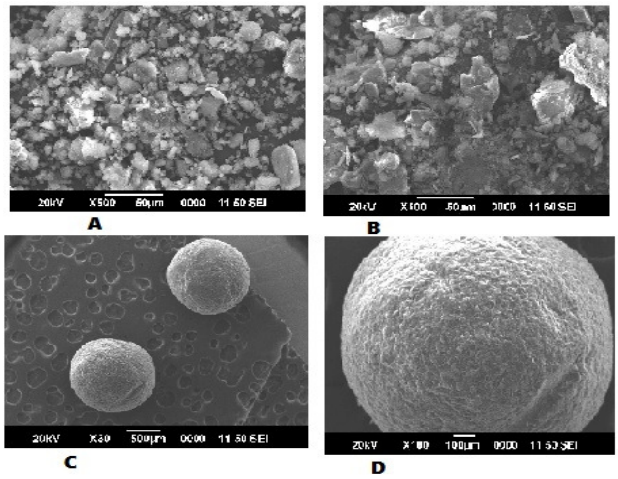

Figure 3: Scanning electron photomicrographs of the Co-processed (A), Physical mixture (B), Formulation(C) and Pellet surface

Characterisation of Pellets

FTIR and DSC

The drug-excipients compatibility study was carried out using FTIR method and was given in Figure 4. The spectrum of pure irbesartan depicts the characteristic peaks at 1616.40 cm-1 (C=N amide), 3055.35 cm-1 (C-H aromatic), 1732.13 cm-1 (C=O ketone), 1550 cm-1 (NH), 1600 cm-1 (C=C aromatic), respectively. Wave numbers of principle peaks observed in the IR spectrum of pure IRB, and excipients are present in the FTIR spectra of physical mixture.

Table 3: Percentage friability, aspect ratio, disintegration time, drug content and *In-vitro* dissolution of all formulations

Batch	Aspect Ratio	(%)Friability	Disintegration Time(min)	%Drug content	*In-vitro* Dissolution (%)
F1	1.01 ± 0.02	0.34±0.02	11.20±0.5	101.4±0.2	96.70±0.01
F2	1.03 ± 0.01	0.66±0.015	13.10±0.6	100.2±0.4	81.36±0.04
F3	1.02 ± 0.02	0.24±0.034	11.20±0.8	100.52±0.2	95.78±0.09
F4	1.01 ± 0.01	0.65±0.012	9.40±0.4	99.96±0.3	91.43±0.06
F5	0.98 ± 0.02	0.27±0.014	9.50±0.9	100.26±0.4	100.11±0.06
F6	1.02 ± 0.01	0.51±0.022	12.00±0.5	98.23±0.2	84.56±0.04
F7	0.97 ± 0.01	0.67±0.012	11.40±0.5	100.39±0.4	98.76±0.06
F8	1.10 ± 0.01	0.48±0.025	11.60±0.2	98.86±0.2	89.83±0.04
F9	1.02 ± 0.02	0.32±0.021	13.50±0.4	99.50±0.3	76.55±0.03
F10	0.99 ± 0.02	0.26±0.014	9.90±0.9	98.23±0.2	98.23±0.2

Thus, there observed no interaction between drug and polymer. Therefore, it can be concluded that there is no major effects or changes in the properties of functional groups which affects the stability of IRB in these mixtures. Hence irbesartan is compatible with all the excipients used in the formulation. The DSC thermogram of pure Irbesartan (Figure 5A) and Irbesartan containing pellet formulation are indicated in (Figure 5B). Irbesartan showed an endothermic peak at 186.10 °C corresponding to its melting point. The Irbesartan and pellet formulation also show melting point at 186.10 °C indicating no interaction between drug and excipients.

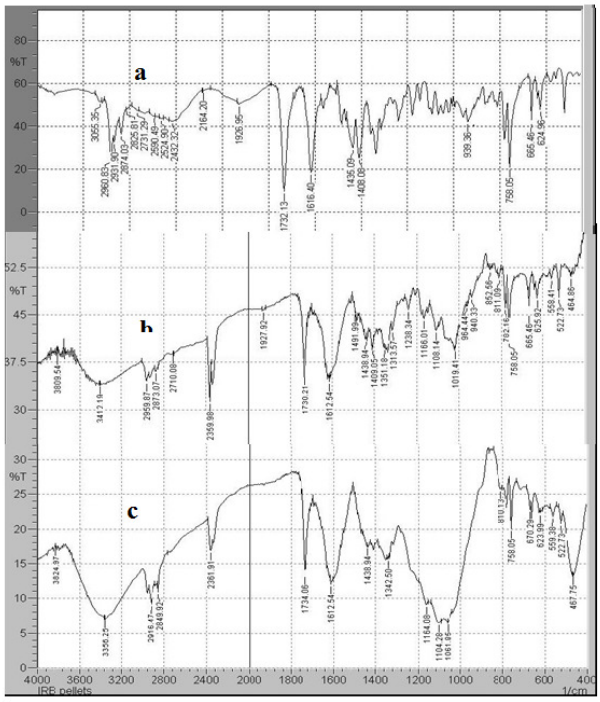

Figure 4: FTIR spectra of a) Pure Irbesartan b) physical mixture c) Formulation

The DSC Thermogram of pellet formulation was slightly shifted to lower temperature as compare to Irbesartan indicating that uniform distribution of drug in the formulation.

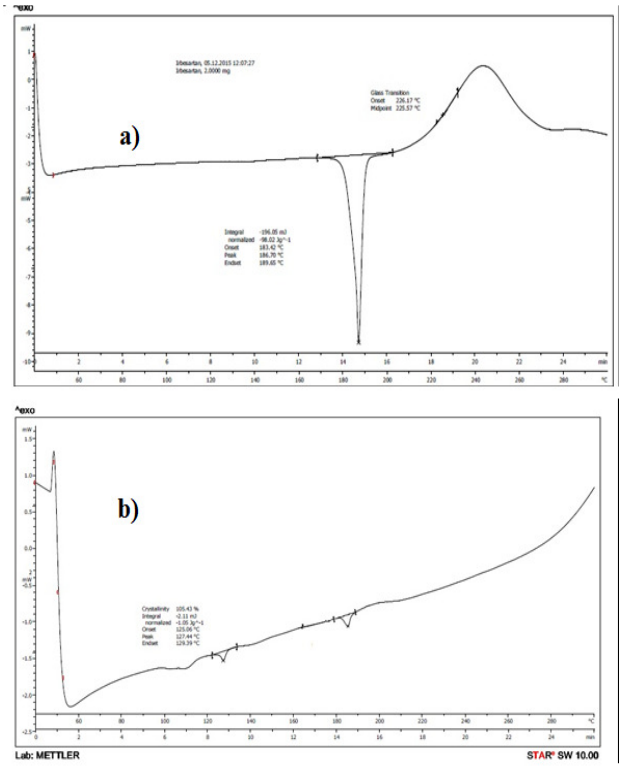

Figure 5: DSC thermograms of Pure irbesartan (a) and Pellet formulation (b).

Flow Properties of Prepared Pellets

The pellets were tested for bulk density, tapped density, carr's index, hausner ratio and angle of repose and all the values indicate excellent and free flowing nature of pellets and the results were given in table 20. The normal range for angle of repose is 25-30 i.e gives excellent flowing ability, angle of repose of all formulation batches renges from 27.14±0.9 to 30.46±09 i.e in

the normal range. Bulk density and tapped density ranges from 0.70 ± 0.1 to 0.78 ± 0.1 (g/ml), which is in normal range show good flow ability. Carr's index ranges from 3.65±0.8 to 11.62±0.7 i.e lower than the 10, shows excellent flow. Hausnerratio of all batches are in normal range i.e 1.00-1.11, shows excellent flowing ability. The resulting values shows good flowability by comparing with their standard values. The values were shown in Table no 2.

Pellet Size and Shape

Visual inspection of pellet formulation was done by using motic microscope and results for all formulation batches shows good sphericity. Formulation conaining MCC (20%) and co-processed excipient(40%)shows good sphericity of pellets.

Aspect Ratio

All formulation batches were evaluated for aspect ratio in triplicates and there values of aspect ratio lies between 1.0 to 1.20, therefore all these formulation batches passes the limit of aspect ratio. The results of aspect ratio shown in Table 3 indicated that the pellets formulations were spherical (round).

Friability

All formulation batches pass the pharmacopoeial limits. All formulation batches were evaluated for friability testing triplicates. The percentage friability of all the formulations was found to be not more than 0.7 % which is well within the 1% limit. The results of friability indicated that the pellets formulations were mechanically stable shown in Table 3.

Disintegration Time

Disintegration time of all formulations was performed using disintegration test apparatus at 37±1°C in distilled water. Disintegration is depends up on the concentration of co-processed excipient as concentration increased decreased the disintegration time. Formulation containing co-processed excipient were disintegrate faster than the without co-processed excipient. Formulation F5 were disintegrate within 9 min and formulation without co-processed excipient disintegrate within 13 min respectively.The values of disintegration time were shown in Table no 3.

Drug Content Determination

It gives the percentage of drug present per unit dosage form. The drug loaded pellets of Irbesartan prepared with optimized formula exhibited drug loading capacity in range of 98.23-101.4 % and it complies with the reported range of drug content of irbesartan. Hence, pellets prepared showed good drug content for all formulations shown in Table 3.

Scanning Electron Microscopy (SEM)

The scanning electron microscopy (SEM) evaluation is important for determining the surface morphology, size, and shape. SEM images of the formulated pellets at different magnification were shown in Figure 3C and 3D. Surface morphology of pellets studied by SEM indicated that the pellets give spherical and somewhat rod shaped pellets with rigid surface.

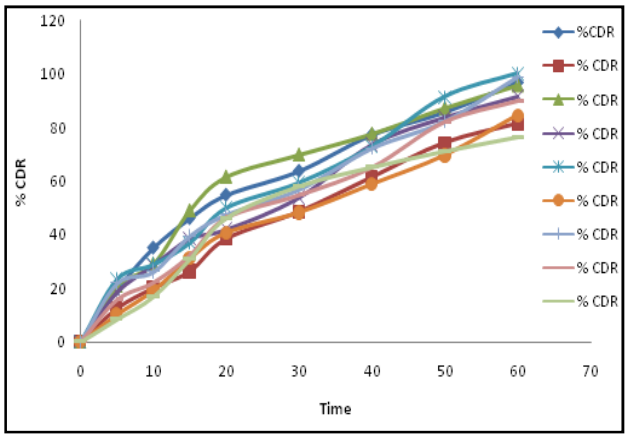

Figure 6: In-vitro dissolution of F1 – F9.

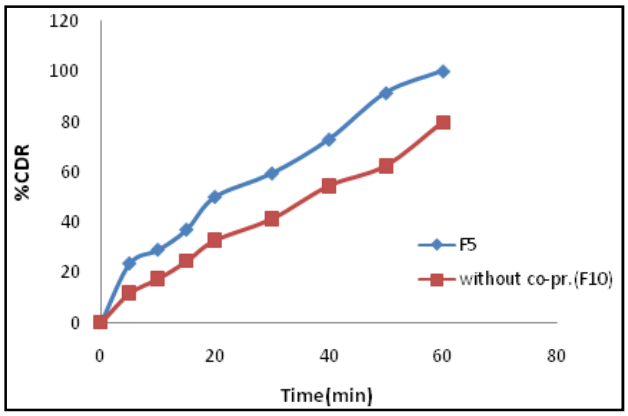

Figure 7: In-vitro dissolution of F5 & F10 (formulation without co-processed excipient).

***In-vitro* Dissolution Study of Formulation**

With the consideration to the dissolution rate, there are marked differences in the average cumulative curves of irbesartan dissolution for the evaluated formulation (Figure 6) which are reflected in the values of 0 – 60 min dissolution rate. From the dissolution study data, it should be noted, First that formulation (F9) containing

20% co-processed excipient & 40% MCC shows less drug release than (F5) containing 40 % co-processed excipient & 20% MCC i.e. 100.11% drug release compared with the formulation F9 having drug release only 76.55% after 60 min. The co-processed excipient & crosscarmellose sodium shows synergetic effect which significantly increases the values of dissolution rate. About all batches (F5) shows drug release up to 100.11% over a period of time 60 min. In comparison of formulation F5 with formulation F10 (i.e. formulation without co-processed excipient), F5 shows a higher drug release than the F10, i.e. F5 shows 100.11% drug release in 60 min and F10 shows 79.66% drug release in 60 min. Comparison drug release profile of formulation F5 & F10 were shown in following figure 7.

CONCLUSION

In conclusion, we can say that, the formulated immediate release pellets by using co-processed excipient, promising the approach, which is utilized for improving disintegration time and faster drug release. The use of co-processed excipient shows a better immediate drug release. There was formation of pellet with suitable size and shape, with high mechanical stability and very good flow properties. There was no drug polymer interaction observed in FTIR and DSC. Among all batches F5 showed better immediate drug release over the time period of 60 min. Hence it can be conclude that, the co-processed excipient improves the disintegration time and faster the drug release from immediate release pellets.

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