EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 8
01-09
Year: 2019

ENHANCEMENT OF IRBESARTAN DISSOLUTION VIA CONTROLLED PRECIPITATION: PREPARATION OF ORALLY DISPERSIBLE COMPACTS

Khaleel M. Abuleid*, Ebtessam A. Essa and Gamal M. El Maghraby

Department of Pharmaceutical Technology, College of Pharmacy, Tanta University, Tanta, Egypt.

***Corresponding Author: Khaleel M. Abuleid**
Department of Pharmaceutical Technology, College of Pharmacy, Tanta University, Tanta, Egypt.

Article Received on 24/05/2019 **Article Revised on 15/06/2019** **Article Accepted on 04/07/2019**

ABSTRACT
Irbesartan is an antihypertensive angiotensin II receptor antagonist. It suffers poor aqueous solubility. Therefore, the aim of this work was to investigate the potential use of controlled precipitation over solid carrier technique to enhance irbesartan dissolution rate. Hydrophilic polymers were used to increase the hydrophilicity of the prepared crystals. The selected polymers were polyvinylpyrrolidone 40T (PVP), hydroxypropylmethyl cellulose E5 (HPMC) and polyethylene glycol 4000 (PEG). The work was extended to develop fast disintegrated compacts. Aerosil 200 was dispersed in ethanolic solution of irbesartan in presence hydrophilic polymers. Distilled water was added as antisolvent to precipitate the drug over Aerosil 200. Unprocessed and drug liberated from its ethanolic solution were used as negative and positive control, respectively. The resultant precipitate were centrifuged and dried at ambient temperature. The recovered microparticles were subjected to FTIR spectroscopic, X-ray diffraction, thermal analyses and dissolution studies. The FTIR spectroscopy excluded any interaction between irbesartan and excipients. The thermal analysis reflected possible reduction in crystal size after controlled precipitation in the presence of hydrophilic polymers. This was further confirmed by X-ray diffraction. These changes was associated with a significant enhancement irbesartan dissolution rate. The recovered microcrystals were successfully formulated as rapidly disintegrating compacts with subsequent fast drug liberation. Precipitation over large solid surface area in presence of hydrophilic polymers during precipitation process is a simple promising technique for improving dissolution of slowly dissolving drugs with high scaling up potential.

KEYWORDS: Irbesartan, controlled precipitation, Aerosil, fast disintegrating tablets.

INTRODUCTION
Oral route of drug administration is the most convenient route for self-administration with tablets being the most commonly used dosage form for this route. Advancement in this field resulted in development of fast disintegrating tablets (FDTs). This type of tablet provides greater chance for eliminating the effect of disintegration step with a possibility for intraoral administration. In addition, rapidly disintegrating tablets can open the way for delivering drugs to children and elderly while maintaining the dosage form in solid state avoiding the stability problems of liquid dosage forms.[1] However, for maximum advantage, the loaded drug must undergo fast dissolution immediately after disintegration.[2] This can ensure rapid absorption of significant amount of the loaded drug from the buccal cavity avoiding the problems associated with oral administration.[3]

According to European Pharmacopoeia, fast disintegration tablets (FDTs) should undergo disintegration in less than 3 minutes in thebuccal cavity before oral swallowing. This objectives, development of a new forms of tablets known as fast disintegration tablets (FDTs), superdisintegrant can be employed with other authors utilizing fast melting or mouth dissolving formulations.[2,4] These systemswill provide an advantage where peak plasma concentration is required for prompt rapid response to achieve desired pharmacological response at a specified time.[5]

Irbesartan is an antihypertensive angiotensin II receptor antagonist. It acts by selective binding to the AT1 angiotensin II receptor without affecting the receptor of AT2.[6,7] It is mainly eliminated via the liver with minimal amount being excreted through the kidney.[8] Irbesartan is classified as class II drug based on the Biopharmaceutical Classification System. This means that the drug is of high permeability but suffers from low aqueous solubility.[2,9] This is responsible for the variable oral bioavailability of irbesartan.[10] Accordingly, enhancing the dissolution rate of the drug will improve its oral bioavailability.

The objective of this study was to investigate the effect of controlled antisolvent recrystallization on the dissolution rate of irbesartan with the aim of producing fast disintegrating tablets.

MATERIALS AND METHODS

Materials

Irbesartan, croscarmellose, magnesium stearate, sucralose, Aerosil 200 and crosspovidone were obtained from Sigma Pharmaceutical Chemical Company, Qwesna, Egypt. Polyvinylpyrrolidone 40T (PVP) was purchased from Sigma Chemical Co, St. Louis, USA. Hydroxypropylmethyl cellulose E5 (HPMC) obtained from SAS. Co for medica, polyethylene glycol 4000 (PEG) obtained from laboratory Rasayan, Gujarat, India. (Avicel PH 101) were obtained from ISO Chem, Cairo, Egypt. Ethanol was purchased from Eljomhoreia Chemicals Co. (Tanta, Egypt).

Methods

Controlled antisolvent recrystallization

Table 1 presents the composition of the tested formulations. Irbesartan and the polymer (if any) were dissolved in the least amount of ethanol. Aerosil 200was then dispersed in the obtained ethanolic solution. Distilled water was added to the ethanolic solution while stirring to liberate the drug crystals. The volume of water was five times that of ethanol. For comparative reason, positive control was prepared by precipitating the drug from its ethanolic solution, in absence of both polymer and Aerosil 200. The later was chosen due to its extremely low bulk density and high surface area. The resulting suspension was centrifuged for 15 minutes at 2000 rpm to separate the deposited crystals. The recovered solids were left to dry at ambient temperature and stored in tightly closed containers till use.

Table 1: The composition of the prepared formulations together with dissolution parameters represented as percentage amount released after 5 minutes (Q5) and dissolution efficiency (DE).

Formula	Drug (gm)	Aerosil (gm)	PVP (gm)	HPMC (gm)	PEG 4000 (gm)	Q5	DE%
Control	0.5	_	_	_	_	8.2±0.8	16.16±1.4
Positive control	0.5	_	_	_	_	12.16±1.78	22.39±1.5
F1	0.5	0.25	0.15	_	_	63.86±2.33	87.6±7.3
F2	0.5	0.25	_	0.15		60.16±2.8	77.3±4.6
F3	0.5	0.25	_	_	0.15	52.26±1.83	81.0±8.5

Drug content

The drug content in each formulation was determined by taking a weight equivalent to 50mg of irbesartan and dissolving in a 50ml of ethanol. Solubilization was hastened by sonication. The resulting liquid was centrifuged for 10minutes at 2000 rpm. The clear supernatant was suitably diluted with ethanol and the concentration of the drug was determined by spectrophotometric analysis at 244 nm. The drug content was determined using the following equation.[11]

Drug content (%) = (amount of drug recovered/theoretical amount) x 100

Solid state characterization of the prepared crystals

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of unprocessed irbesartan, HPMC E5, PEG 4000, PVP40K, Aerosil 200 and the precipitated crystal microparticles were obtained using FTIR system (Bruker Tensor 27, Ettlingen, Germany). The solid material was blended with potassium bromide (spectroscopic grade) and the blend was compressed into thin disc before mounting in the sample holder. The spectrum was recorded in the range of 4000 to 400cm^{-1}, using DLaTGS detector adjusted to potassium bromide diffuse reflectance mode. The collected data were analyzed using Opus IR, FTIR spectroscopy Software.

Differential thermal analysis (DTA)

The thermal behavior of irbesartan, HPMC E5, PEG 4000, PVP40K, Aerosil 200 and recrystallized microparticle formulations was investigated using differential thermal analyzer (PerkinElmer STA 6000 module, USA). The dry sample (2-4 mg) was loaded into aluminum pan which was crimped using Shimadzu crimper. Thermal analysis was conducted in the temperature range of 30 to 400^{o}C. This was conducted at a heating rate of 10°C/minute under continuous flow of nitrogen gas. The experimental conditions and the whole system was controlled by a computer utilizing Pyris software.

Powder diffraction X- ray (XRPD)

The diffraction pattern of irbesartan, HPMC E5, PEG 4000, PVP40K, aerosil 200 and recrystallized formulations was monitored using a GNR APD 2000 pro-X-ray diffractometer which depends on Cu Ka radiation (1.54 Å) (Agrate, Conturbia, Italy). Powdered samples were loaded into the sampling port and were subjected to continuous scanning in the range of 3–60˚ with the equipment being adjusted to step size of 0.03^{o}.

Pre-formulation studies of the prepared formulations

Bulk Density (D_b): It is estimated by pouring a known weight of powder into a measuring cylinder. The initial volume is called the bulk volume. The bulk density is calculated according to the following formula:

$D_b = M/ V_b$

Where, M is the mass of powder, and Vb is the bulk volume of the powder.[13]

Tapped Density (D_t): The volume occupied by the powder after tapping for 100 times is identified as tapped

volume (Vt). The tapped density was calculated from the equation mentioned below.[12-14] It is expressed in g/ml and is given by:

$D_t = M / V_t$

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by following formula.[15,16]

Hausner's ratio = Dt / Db

Where, Dt is tapped density and Db is bulk density.

The compressibility index (Carr's Index) was determined by using following equation.[15,16]

Carr's Index (%) = $[(D_t - D_b) \times 100] / D_t$

Preparation of fast disintegrating tablets (FDTs)

FDTs were prepared according to the master formulae presented in Table 2. In a clean dry bottle, 150mg of pure drug or its equivalent amount of the prepared crystals was mixed geometrically with used excipients. Crosscarmelose sodium and crosspovidone were used as super disintegrants, while sucralose was used as sweetening agent. Tablets were prepared by compression technique of amount equivalent to of drug in each prepared tablet. This process used single punch tablet machine (Royal Artist, Mumbai, India) using 10mm punch. The compression force was adjusted to produce tablets having a hardness of about 4-5 Kp.

Table 2: Compositions of the prepared fast disintegrating compacts.

Content (mg/tablet).	Cont Tab	HPMC Tab	PVP Tab	PEG Tab
Irbesartan or itsequivalent formulation	150	306	249	360
Avicel PH101	364	208	265	154
Crosscarmellose sodium	30	30	30	30
Crosspovidone	30	30	30	30
Sucralose	20	20	20	20
Magnesium stearate	6	6	6	6

Evaluation of fast disintegration tablets

Uniformity of weight was performed by random selection of 20 tablets and weight each tablet individually and the average weight was calculated and the deviation from the average weight was calculated. The batch should be complying with USP standards.[17]

Tablet friability**:** The weight of 10 tablets was recorded before being placed in friabilator (Erweka, Heusenstamm, Germany). The tablets were subjected to 100 revolutions and the intact tablets were dedusted and the final weight was recorded. The percent friability is calculated from the difference in weight relative to the initial weight and should not exceed 1% according to the USP standards.[17]

Drug content uniformity: To ensure the consistency of dosage units, each tablet in a given batch should contain the active drug within a narrow range around the labeled amount. The drug content was determined by random selection of 10 tablets, each tablet was individually subjected to drug content determination. The tablet batch complies if the content of not more than one was outside the limits of 90–110% of the labeled content and none is outside the limits of 75–125% of the labeled content.[17]

Tablet disintegration tester (Copley scientific NE4-cop, Nottingham, UK) was used to evaluate the disintegration time of the prepared tablets. The media used was distilled water maintained at 37ºC. The time taken for complete disintegration of all tablet was recorded and compared to the required specification.[17,18] The tablet hardness was conducted using 6 tablets and the test was performed using hardness tester (DR. Schleuniger Pharmatron tablet tester 8M).

Wetting time: The test was performed by placing a filter paper on a petri-dish containing a 6ml of distilled water. Small amount of Allura red powder was spread on the tablet surface. Tablets were then placed on the wet filter paper. The wetting time is recorded as the time required to develop the red color on the surface of tablet.[19]

In vitro drug dissolution studies

The dissolution rate of irbesartan from different controlled precipitated crystals and fast disintegration tablets was investigated. Unprocessed pure drug was used as a control for the drug microcrystals. The study employed USP type II dissolution apparatus (Copley, NG 42 JY, Nottingham, UK) using0.01N HCL (pH value 1.2) maintained at of 37ºC ± 0.5ºC as dissolution media. The paddle rotation rate adjusted on 50 rpm. The release study was conducted for 60 minutes through which aliquots of 5 ml each were taken at predetermined time intervals (5, 10, 15, 30, 45, and 60min), and replaced with fresh dissolution medium. The samples were immediately filtered through 0.45 mm Whatman membrane filter. The filtrate was suitably diluted with the fresh dissolution medium before spectrophotometric analysis for drug content at 244 nm.[20]

Statistical Analysis

All experiments were conducted in at least in triplicates and statistical analysis was performed using Student *t*-test. Results were quoted as significant when $P < 0.05$.

RESULTS AND DISCUSSION

Characterization of the prepared formulations

The drug content of the prepared formulations was in the acceptable range. The drug content values were in the range of 96.6–98%w/w, indicating good recovery of the drug after controlled precipitation.

Differential thermal analysis

The thermograms of pure irbesartan, pure polymers, Aerosil 200 and different formulations are shown in Figure 1. The onset, endset and transition midpoint (T_m) of each peak were extracted from each thermogram were determined and are presented in Table 3. The thermogram of unprocessed irbesartan showed two endothermic peaks, the first of which was sharp peak having an onset of 179.46ºC, endset of 194.84ºC and a T_m of 183.8ºC. This sharp peak can be attributed to the melting transition of the drug and reflects its crystalline nature. The second peak was very broad and had a T_m of 241.24 ºC and could be due to drug decomposition. This thermal behavior of the drug is in good agreement with published data.[21] For pure PVP, the thermogramshowed a broad endothermic peak with *Tm* of 75ºC due to the release of the adsorbed moisture. The thermal behavior of pure HPMC revealed similar broad endothermic peak which can be similarly explained. Additionally, a broad peak was observed at higher temperature with *Tm* of about 320.8ºC that could be attributed to decomposition of the polymer.

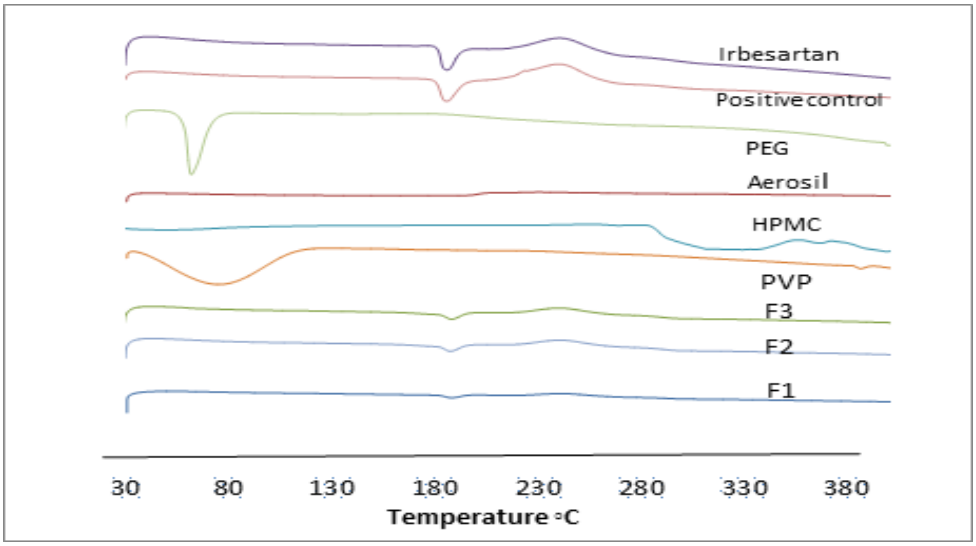

Figure 1: Differential thermal traces of pure irbesartan, polymers, Aerosil 200 and different formulations. For detailed formulation refer to Table 1.

The thermogram of pure PEG 4000 showed the characteristic sharp endothermic peak at about 62.31ºC. For Aerosil 200, the thermogram showed no endothermic or exothermic peak indicating its amorphous nature. The thermal behavior of the pure polymers and Aerosil 200 is in good agreement with previously published data.[2,22]

For positive control, liberated drug from its ethanolic solution absence of polymer and Aerosil, the thermal behavior showed slight shift to lower *Tm* of about 182.2 ºC (Figure 1). The exothermic peak showed slight broadening with a shoulder appearing at 211.2 ºC.

Table 3: The thermal parameters calculated for the main peaks of drug and the polymers.

Formulation	T_m (ºC)	Onset (ºC)	Endset (ºC)
Pure irbesartan			
1st Peak	185.85	179.46	194.84
2nd Peak	241.24	216.91	263.86
Positive Control			
1st Peak	185.74	178.74	196.31
2nd peak	240.34	213.08	262.15
PVP	75.44	38.97	112.09
HPMC	63.62	31.18	99.31
PEG	62.31	56.54	73.59
F1			
1st Peak	187.40	179.31	196.03
2nd peak	241.89	220.47	263.20
F2			
1st Peak	187.44	178.94	196.02
2nd peak	241.26	219.44	262.72
F3			
1st Peak	187.28	179.48	195.54
2nd peak	241.44	219.56	263.47

Preparation of the drug by controlled precipitation over carrier in presence of hydrophilic polymer produced drug crystals with a thermal behavior depending on the additives used in the process. Usually peak broadening or shifting to a lower T_m were taken as an indication of reduced crystallinity.[23] Controlled precipitation of irbesartan in presence of PVP, PEG 4000 and HPMC resulted in peak broadening and reduced peak sharpening. The midpoint transition values for crystals prepared in presence of PVP, PEG 4000 and HPMC were found to be 180.7ºC, 178.2ºC, 181.9ºC, respectively. Such reduced midpoint transition peaks. It is important to highlight that the recorded endothermic peaks of the drug after controlled precipitation reflect a trend of reduced enthalpy especially in the presence of polymer. This recorded changes in the main endothermic peak suggests partial conversion to amorphous form. The decomposition peak of the drug was also broadened for all formulations further and was shifted to slightly higher T_m. This again suggests some surface adsorption, formation of different crystalline species or hydrogen bonding.

X-ray powder diffraction

The diffractograms of the unprocessed irbesartan, polymers, Aerosil 200 and prepared formulations are shown in Figure 2. The diffraction pattern of unprocessed drug revealed its crystalline nature which was indicated by numerous distinctive peaks at a diffraction angular range of 4.75°, 12.49°, 19.45°, 23.18° that confirms the crystalline nature of Irbesartan.[24]

The diffraction pattern of pure PEG showed its two main distinct peaks at about 23.1° and 19.1° reflecting its crystalline nature. The diffractograms of PVP and HPMC showed diffuse pattern with no distinct diffraction peak being recorded.[2] Aerosil 200 diffractogram showed no peaks indicating its amorphous nature. For positive control, drug liberated from its ethanolic solution in absence of polymer and Aerosil 200, showed diffractogram similar to the unprocessed drug. However, microcrystal formulations prepared in presence of polymer (F1, F2 and F3) as well as.

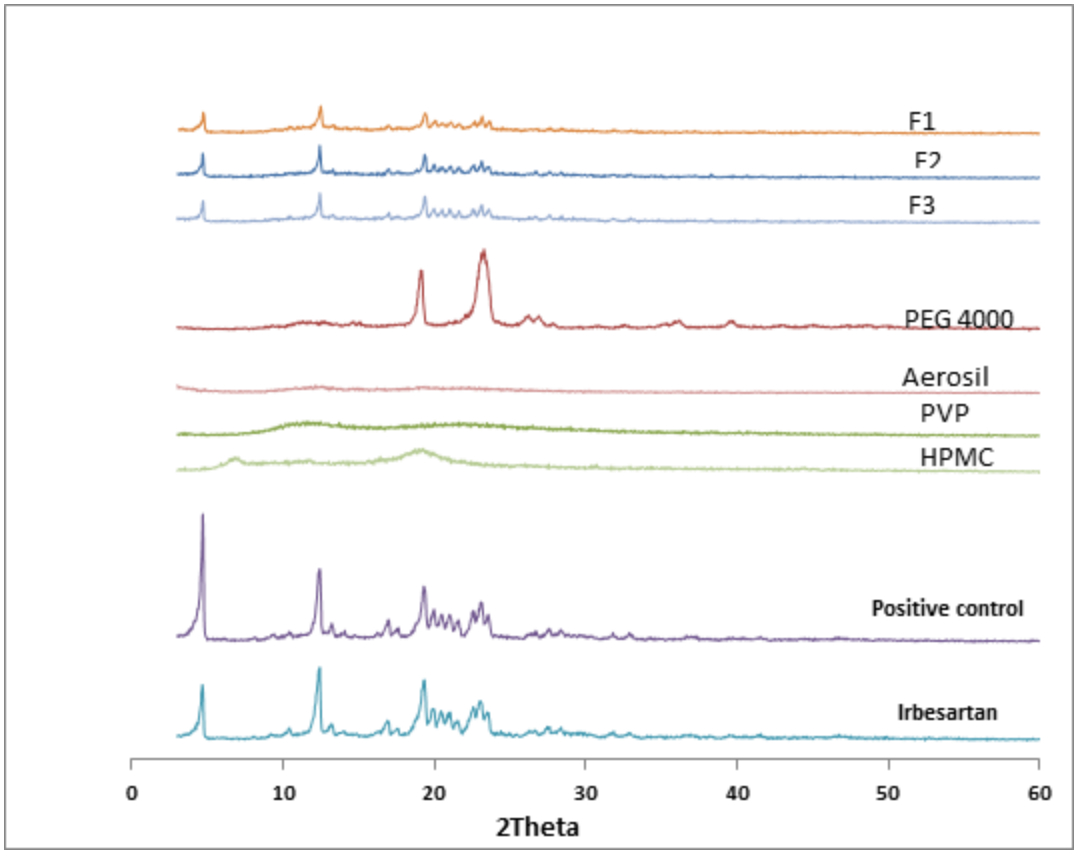

Figure 2: X-ray diffractograms of pure irbesartan, pure polymers, Aerosil 200 and different formulations. For detailed formulation refer to Table 1.

Aerosil 200 showed a reduction in the intensity of the diffraction peaks compared with the unprocessed drug and positive control (Figure 2). This suggests reduction in the particle size of the drug after controlled precipitation in presence of polymer. Reduced intensity of the diffraction peaks was taken as an indication of particle size reduction by other investigators.[2,10] It is important to highlight the possible slight transformation to amorphous state upon controlled precipitation, a suggestion that can be supported by the DTA data.

Fourier-transform infrared spectroscopy

FTIR spectra of unprocessed irbesartan, polymers and that prepared formulations are shown in Figure 3. The

spectrum of the unprocessed drug showed the characteristic absorption bands of irbesartan. These included the absorption band at 1711 cm^{-1} which is due to carbonyl group, the peak range at 2950-3059 cm^{-1} for the C–N stretching vibrations. The absorption band of the OH group was recorded at 2935 cm^{-1} with a broadband being noticed in the range of 3292–3771 cm^{-1} due to hydrogen bonding.[25]

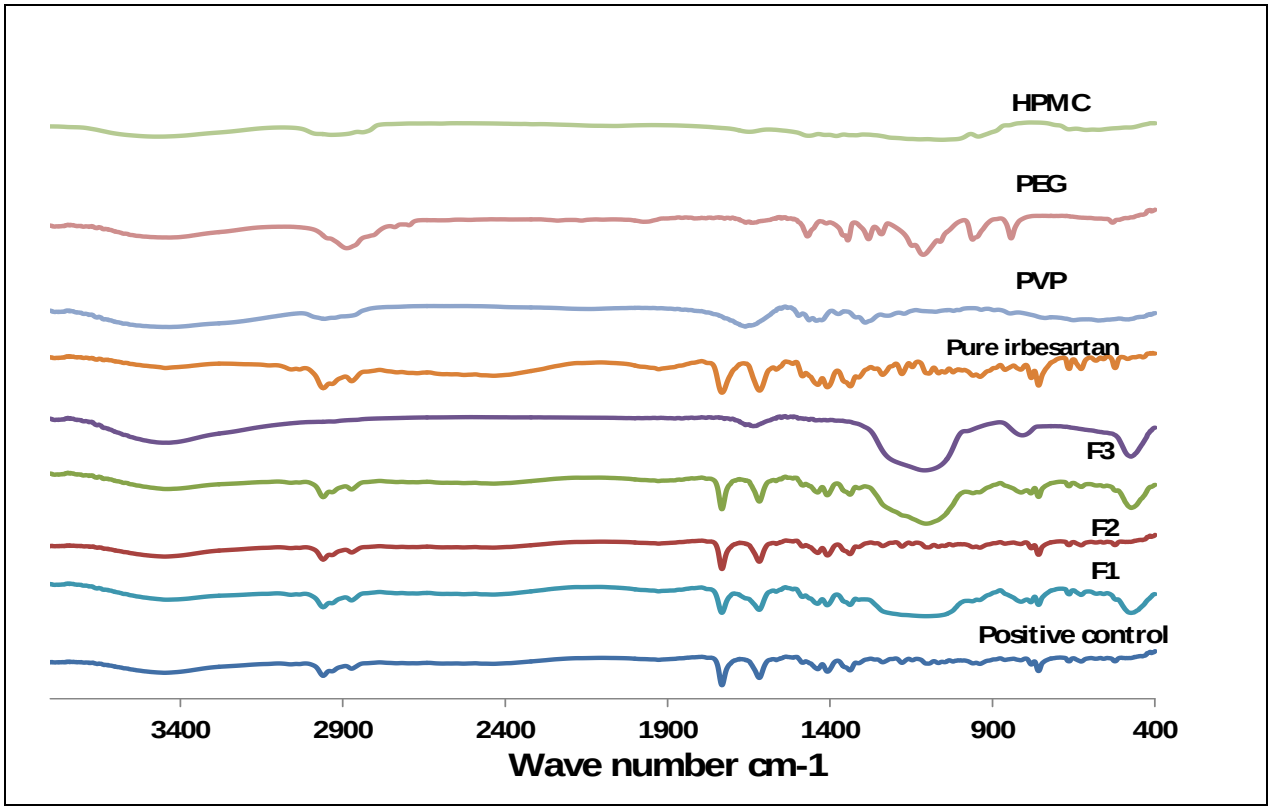

Figure 3: Samples FTIR spectra of pure irbesartan, pure polymers, Aerosil 200 and different formulations. For detailed formulation refer to Table 1.

The FTIR spectrum of pure PVP was characterized by its carbonyl group which was detected at lower frequency of 1621cm^{-1} due to hydrogen bonding with the adsorbed water. The hygroscopic property of PVP was evidenced as broadband for the hydrogen bonded OH group at 3397 cm^{-1} correlating with the published spectrum.[19] The characteristic broadband of hydroxyl group was shown in the range of 3100–3600 cm^{-1} as the main peak of pure HPMC. This correlates with a previously published spectrumof the same polymer.[19,26] The spectrum of PEG 4000 revealed broadband at 3405 cm^{1} for the OH group. The aliphatic C–H stretching was shown at 2839 $cm^{-1}$with a band appearing at 1064 cm^{-1} for C–O stretching in agreement with the previous investigations on the polymer.[26] FTIR spectrums of tested formulations (F1, F2 and F3) as well as positive control revealed the main absorption bands of irbesartan and showed no significant changes compared with the spectrum of pure drug. This suggests absence of any possible interaction between the drug and other excipients.

In vitro drug release from prepared formulations

The cumulative amount dissolved from unprocessed irbesartan and different formulations (expressed as % of the labeled amount) was plotted as a function of time to produce the dissolution profiles shown in Figure 4A. These profiles were used to calculate the dissolution parameters represented as the percentage amount dissolved in the first 5 min (Q_5) and the dissolution efficiency (DE). The latter was calculated from the area under the dissolution profile at time *t* expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.[27] These dissolution parameters are presented in Table 1.

Unprocessed drug showed slow dissolution with Q_5 and DE of about 8.2% and 16.16%, respectively. This poor dissolution can be attributed to the hydrophobic nature of the drug.[28] For positive control, irbesartan precipitated over aerosol 200 in absence of hydrophilic polymer, significant increase in dissolution parameters over that of unprocessed drug was observed ($P<0.05$). Such enhancement could be due to increased area of the drug as it was precipitated over a carrier with huge surface area.

Preparation of irbesartan by controlled precipitated on the surface of aerosol 200, in presence of hydrophilic polymer, produced drug crystals with marked increase in dissolution rate compared with the negative (unprocessed drug) and positive control. Formula F1, prepared using PVP, showed the highest Q5 of 63.3%. Formula F2,

prepared using HPMC, showed similar results to F1 ($P < 0.05$), that was significantly higher than that of F3 (prepared using PEG4000). The overall dissolution.

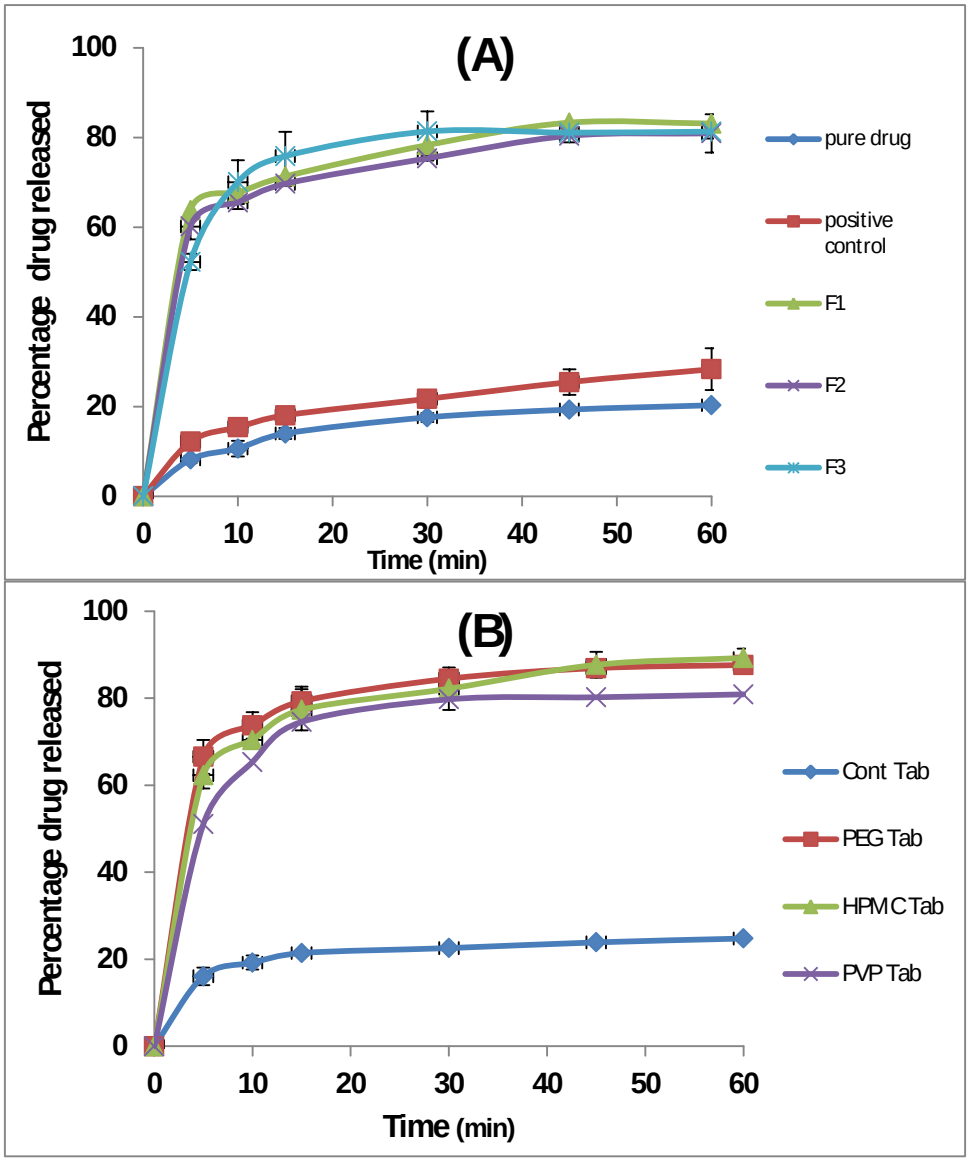

Figure 4: Dissolution profiles of irbesartan from (A) unprocessed form, positive control, Different controlled precipitated drug microparticles and (B) Fast disintegrated tablets. For detailed formulations refer to Tables 1 and 2.

efficiencies were 87.6, 77.6 and 81 for F1, F2 and F3, respectively. This enhanced dissolution parameters can be explained by the precipitation of the drug crystals in an extremely fine state of subdivision, as evidenced by X-ray data. The presence of Aerosil 200 during the precipitation step would act as carrier upon which drug crystal would deposit. The resulting decrease in particle size and the concomitant increase in the surface area increased the dissolution rate. Other explanation is the increased hydrophilic nature of the precipitated microcrystals by the deposited hydrophilic polymer on crystal surface during the precipitation step rendering the crystals more hydrophilic. It was reported that hydrophilic polymers would adsorb to the crystals by polar interactions (such as hydrogen bonding), Van der Waals and hydrophobic interaction.[29] This would increase the wettability and consequently drug solubility. The synergic effect between reduced particle size, deposition of the microcrystals over large surface area of the carrier particle and adsorbed hydrophilic polymer chains is expected to result in such enhancement in drug dissolution.[2,30]

Characterization of fast disintegrating tablets

Formulations F1, F2 and F3 were used to prepare the fast disintegrating tablet producing PVP Tab, HPMC Tab and PEG Tab, respectively. Tablets containing unprocessed drug was used as control (Cont Tab). Tablets were prepared to contain 150 mg of unprocessed drug or an equivalent amount of the crystal formulations. Tablets were prepared by direct compression method, after

geometric mixing with suitable excipient, according to compositions represented in Table 2.

To ensure dose uniformity during the tablet manufacture, flow properties of each tablet powder blend were investigated. The results of powder flowability are presented in Table 4. The small value of Carr's Index value would indicate better flow properties, powders with values between 5 and 18 are considered to have good flow behavior. For Hausner ratio, values of less than 1.25 indicate free flowing powders, where values more than 1.25 reflects bad flowability.[14] All formulations showed good powder flow properties and were suitable for manufacture of tablets. Results of Carr's compressibility indices coincide with the Hausner ratio values. The consistency of tablet weight is a good reflection of good powder flow. All tablet batches complied with the US Pharmacopeial requirements with a deviation from average weight being less that 1%. All tablets were accepted regarding hardness and friability tests (Table 4).

Regarding disintegration time, tablets prepared using the microcrystal formulations showed faster disintegration compared to that batch prepared using unprocessed drug. This could be due to presence of the hydrophilic polymer that increased tablet wettability and disintegration. Regarding wetting time, tablets.

Table 4: Results of powder flow study, tablet quality control tests, and in vitro irbesartan dissolution parameters from different fast disintegrating tablets represented as percentage drug released after 5 minutes (Q5) and dissolution efficiency (DE).

	Flowability of powder		Hardness (kg/cm^2)	Disintegration time (min)	Friability (%)	Wetting time (sec)	Q5	DE (%)
	Carr's Index	Hausner ratio						
Control Tab	30.1±2	1.4±0.2	4.5± (0.2	2.1±2	0.1±0.1	35±5	16±2.0	24.±0.5
PVP Tab	14.3±1	1.22±0.1	5.3±0.5	1.3±1	0.2±0.08	24±2	51±4.5	86.2±5.24
HPMC Tab	16.3±2	1.26±0.1	4.8±0.5	1.4.0±3	0.3+0.1	22±3	62±3.3	80.3±3.2
PEG Tab	18.5±2	1.32±0.2	5.0±0.2	1.4±0.6	0.1±0.1	26±2	66.5±4	81.6±4.9

prepared using precipitated drug microcrystals showed rapid wetting time compared to control tablet (Table 4). This could be due to increased hydrophilicity of the drug crystals due to in the adsorbed hydrophilic polymers over drug crystals.[2]

For in vitro dissolution study, The cumulative amount of drug released from different tablet batches are presented in Figure 4B. Dissolution parameters are presented as Q5 and $dissolution values in Table 4. Cont Tab showed slow drug release with a total dissolution of 24% of the labeled dose at the end of the experiment. It worth noting that there is about 2-fold increase in Q2 compared to pure drug powder. This could be explained by the adsorption of drug particles over large surface area of the added tablet excipients. Fast disintegrating tablets prepared using the precipitated drug microparticles showed rapid initial drug release, with tablets prepared using microcrystals F3 (PEG Tab) showing the highest Q5. Reduced particle size after precipitation on the vast solid surface area can provide another explanation for enhanced dissolution rate. The developed drug particles were successfully formulated as fast disintegrating tablets with subsequent rapid dissolution.

CONCLUSION

Irbesartan microcrystals were prepared by controlled precipitation in presence of solid carrier (Aerosil 200) in presence of different hydrophilic polymer. The selected polymers were polyvinylpyrrolidone, polyethylene glycol 4000 and hydroxypropylmethyl cellulose. The adopted technique was highly effective in enhancing the dissolution of irbesartan compared to raw drug and that liberated from its ethanolic solution. Such enhancement could be attributed to the adsorption of the partially amorphous drug microparticles on the large surface of the solid carrier. Reduced particle size after precipitation on the vast solid surface area is another explanation. The prepared microcrystals were successively formulated into fast disintegrating tablets with most of the drug liberated in the first few minutes.

REFERENCES

1. Savita B, Vandana S. Formulation and evaluation of fast dissolving tablets of metoclopramide hydrochloride using natural sweetening agent of stevia leaf powder. IJRDPL, 2014; 3: 833-8.
2. Essa E, Elmarakby A, Donia A, ElMaghraby G. Controlled precipitation for enhanced dissolution rate of flurbiprofen: development of rapidly disintegrating tablets. Drug Dev Ind Pharm, 2017; 43(9): 1430-9.
3. Laitinen R, Suihko E, Toukola K, Björkqvist M, Riikonen J, Lehto VP, Järvinen K, Ketolainen J. Intraorally fast-dissolving particles of a poorly soluble drug: Preparation and in vitro characterization. Eur J Pharm Biopharm, 2009; 71(2): 271-81.
4. Masih A, Kumar A, Singh S, Tiwari KA. Fast dissolving tablets: A Review. School of Pharmaceutical Science, Jaipur National University, 2017; 23.
5. Awasthi R, Sharma G, Dua K, Kulkarni GT. Fast disintegrating drug delivery systems: A review with

special emphasis on fast disintegrating tablets. J Chronoth Drug Deliv, 2013; 4(1): 15-30.
6. Waeber B. Irbesartan in antihypertensive therapy: comparison with other antihypertensive agents. Curr ther Res, 2001; 62(7): 505-23.
7. Johnston CI, Risvanis J. Preclinical pharmacology of angiotensin II receptor antagonists: update and outstanding issues. Amer J hyper, 1997; 10: 306S-10S.
8. Coronel F, García-Mena M, Herrero JA, Calvo N, Pérez-Flores I, Cigarrán S. Irbesartan in hypertensive non-diabetic advanced chronic kidney disease. Comparative study with ACEI. Nefrología (English Edition), 2008 1; 28(1): 56-60.
9. Borghi C, Cicero AF. The role of irbesartan in the treatment of patients with hypertension. High Blood Pressure and Cardiovascular Prevention, 2012; 19(1): 19-31.
10. Zhang Z, Le Y, Wang J, Zhao H, Chen J. Irbesartan drug formulated as nanocomposite particles for the enhancement of the dissolution rate. Particuology, 2012; 10(4): 462-7.
11. De Muth JE. Basic statistics and pharmaceutical statistical applications. Chapman and Hall/CRC. 2014 Apr 28.
12. Gupta MM, Srivastava B, Sharma M, Arya V. Spherical crystallization: A tool of particle engineering for making drug powder suitable for direct compression. Int J Pharm Res Dev, 2010; 1: 1-9.
13. Lucas P, Anderson K, Potter UJ, Staniforth JN. Enhancement of small particle size dry powder aerosol formulations using an ultra low density additive. Pharm Res, 1999; 16(10): 1643-7.
14. Sinko PJ. Martin's physical pharmacy and pharmaceutical tablets of valsartan. The United States Pharmacopoeia National Formulary USP28 NF23. The United States Pharmacopoeial Convention, Canada, 2005; 342-3.
15. Lamešić D, Planinšek O, Lavrič Z, Ilić I. Spherical agglomerates of lactose with enhanced mechanical properties. Int J Pharm, 2017; 10: 516(1-2): 247-57.
16. Fassihi AR, Kanfer I. Effect of compressibility and powder flow properties on tablet weight variation. Drug Dev Ind Pharm, 1986; 12(11-13): 1947-66.
17. United States Pharmacopeia National Formulary 24. (2000) Rockville (MD): United States Pharmacopeial Convention.
18. Jain CP, Naruka PS. Formulation and evaluation of fast dissolving tablets of valsartan. Int J Pharm Pharm Sci, 2009; 1(1): 219-26.
19. El Maghraby G, Elsergany R. Fast disintegrating tablets of nisoldipine for intra-oral administration. Pharm Devel Tech, 2014; 19(6): 641-50.
20. Chowdary KP, Ravi Shankar K, Ramesh Babu CH. Formulation Development of Irbesartan Tablets: Selection of Diluent-Binder-Disintegrant Combination by 23 Factorial Designs. J Glob Trends Pharm Sci, 2014; 5(1): 1399-404.
21. Soma D, Attari Z, Reddy MS, Damodaram A, Koteshwara KBG Solid lipid nanoparticles of irbesartan: preparation, characterization, optimization and pharmacokinetic studies. Braz. J. Pharm. Sci, 2017; 53(1): 1-10.
22. Dengale SJ, Grohganz H, Rades T, Löbmann K. Recent advances in co-amorphous drug formulations. Adv drug deliv Rev, 2016; 100: 116-26.
23. Kour P, Kataria MK, Bilandi A. Dissolution Rate Enhancement of Pioglitazone by Solid Dispersion. IAJPR, 2015; 7: 2664-81.
24. Khanfar M, Fares MM, Qandil AM. Mesoporous silica based macromolecules for dissolution enhancement of Irbesartan drug using pre-adjusted pH method. Microporous and Mesoporous Materials, 2013 Jun 1; 173: 22-8.
25. Ganesh K, Balraj C, Elango KP. Spectroscopic and spectrofluorimetric studies on the interaction of irbesartan with 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone and iodine. Spectro Acta Part A: Mol Biom Spec, 2011; 5: 1621-9.
26. Maghraby G, Almorani A. Synergistic enhancement of itraconazole dissolution by ternary system formation with pluronic F68 and hydroxypropylmethylcellulose. Sci Pharm, 2009; 77(2): 401-18.
27. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol, 1975; 27(1), 48-9.
28. Chawla G, Bansal A. Improved dissolution of a poorly water soluble drug in solid dispersions with polymeric and non-polymeric hydrophilic additives. Acta Pharm, 2008; 58(3): 257-74.
29. Wen H, Morris KR, Park K. Study on the interactions between polyvinylpyrrolidone (PVP) and acetaminophen crystals: Partial dissolution pattern change. J Pharm Sci, 2005; 94(10): 2166-74.
30. Singh Y. Martin's physical pharmacy and pharmaceutical sciences. New Jersey: Department of Pharmaceutics Ernest Mario School of Pharmacy Rutgers, The State University of New Jersey, 2006.