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Directly Compressible Sustained Release Matrix Tablets of Losartan Potassium via Crystallo-co-agglomeration

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ABSTRACT: Background: Losartan potassium possesses poor bioavailability due to low elimination half-life and so requires to be developed as sustained release dosage form. Objectives: The present study was intended to prepare directly compressible sustained release matrix tablets of losartan potassium using hydrophilic polymer. Methods: Directly compressible agglomerates of drug were prepared by crystallo-co-agglomeration technique employing HPMC K100M as release retardant polymer. Prepared agglomerates were subjected for evaluation of flow, packing and compaction properties. Morphology of spherical agglomerates was studied by photomicrography and DSC and FTIR were performed to study drug-excipient compatibility. Optimized formulations of crystallo-co-agglomerates were then compressed into matrix tablets. Tablets were evaluated for various pharmacopeial and non-pharmacopeial tests. In-vitro dissolution study performed to evaluate drug release. Results: Results for agglomerates indicated superior flow; packing and compaction properties compared to pure drug and suggested utilization of agglomerates for direct compression tableting. DSC and FTIR proved that drug did not undergo structural and/or polymorphic changes in presence of polymer. Photomicrography images confirmed spherical shape of agglomerates. Results observed for evaluation of tablets were within the compendia limits. In-vitro dissolution study revealed extension of drug release for significantly prolonged period of time. Conclusion: Crystallo-co-agglomeration method can be successfully utilized for preparation of directly compressible sustained release matrix tablets.

INTRODUCTION

Over the several methods available for tablet manufacturing, direct compression tableting hold several advantages like less and easy processing steps, efficient manufacturing output due to decreased cost and reduced time of production [1]. So, it remains as the method of choice for tablet manufacturing but majority of drugs are not suitable for direct compression on account of their inferior flow, packing, compression and compaction qualities. Inclusion of directly compressible diluents can make it possible to process such drugs by direct compression [2] but this cannot be helpful for drugs with larger dose as they increase the bulk of tablet causing difficulty in swallowing. In such cases, spherical crystallization is one of the best alternatives to convert drug into directly compressible spherical agglomerates having excellent flow, packing, compression and compaction properties [3,4]. So far, various techniques of spherical crystallization were employed to improve processibility of drugs through fortification of flow, packing, compression and compression qualities [5]. Techniques were also used to mask the unpleasant taste of drugs [6], to increase solubility and dissolution rate of poorly soluble drugs [7,8], to prepare solid dispersions [9] as well as to produce functional drug devices like microspheres and microsponges [10,11]. Further, inclusion of suitable rate retarding polymers during the spherical crystallization process makes it possible to control the rate of drug release from the tablets or compacts prepared from such agglomerates. In association with direct compression, the method has been proved to be of great importance to modify drug release [12,13]. Amongst the several techniques of spherical crystallization, crystallo-co-agglomeration (CCA) technique is utilized for preparing spherical agglomerates of large dose drugs with or without additives. It has been also used for the preparation of modified

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release dosage forms with proper selection of polymers [14,15].

Various studies have proved utilization of CCA for development of spherical crystal agglomerates with tremendous improvement in processibility by enhancement of flow, compaction and compression characteristics with satisfactory mechanical strength [16-18]. Types and amount of polymers used during crystallo-co-agglomeration have profound effect on release pattern of drug [19]. So far, a few studies have been performed to apply the technique of CCA for preparation of directly compressible sustained release dosage forms [20,21].

Losartan potassium possesses poor flow and compression properties which make it unsuitable for direct compression. It has low bioavailability due to extensive first pass metabolism and low elimination half-life which instigate to develop sustained release preparation with extended clinical effects and reduce dosing frequency [22].

The present study was aimed to prepare directly compressible sustained release matrix tablets of losartan potassium from spherical agglomerates prepared by crystallo-co-agglomeration. Prepared agglomerates were evaluated for flow, packing, compaction and compression properties as well as compatibility study. Agglomerates were compressed into tablets and evaluated for various official and non-official tests and in-vitro dissolution study.

MATERIALS AND METHODS

Materials

Losartan Potassium was procured from Balaji Drugs, Gujarat (India). Polymer (HPMC K100M) was purchased from Astron Chemicals (India), Ahmedabad. Acetone and DCM were purchased from Loba Chemie Pvt. Ltd. Mumbai, India. All other solvents and materials used were of analytical grade.

Formulation of spherical agglomerates

Selection of solvent system: For the preparation of the spherical agglomerates of the drug, three solvents have to be selected, i.e., good solvent, poor solvent and bridging liquid. The selection of the solvent system was based on the solubility profile of the drug. The solubility of losartan potassium in different solvents was determined by the 'shake flask method' as suggested by E. Baka et al. [23] where an excess amount of losartan potassium was added in the 25 ml volumetric flask containing 10 ml of solvent. After keeping the flask in rotary shaker bath for 72 h, the equilibrated samples were removed from and centrifuged at 3000 RPM for 15 min. After filtration and suitable dilution with methanol, the supernatant was analyzed for drug content by UV spectrophotometer. Results for solubility are depicted in **Table 1**. The solvent which has good solubility for the losartan potassium was selected as a good solvent and which has least solubility was selected as a poor solvent. The bridging liquid was selected on the basis of the immiscibility with the poor solvent and the solubility for the drug. Preliminary batches were prepared with different solvent composition for selection of proper solvent system.

Table 1: Solubility of losartan potassium

Sr. No.	Solvent	Solubility* (mg/ml)
1	Acetone	531.33 ± 9.504
2	Methanol	599 ± 9.643
3	Distilled water	431 ± 22.51
4	Dichloromethane	16.66 ± 3.511
5	n-hexane	31.66 ± 4.509
6	Liquid paraffin	17.66 ± 4.725
7	Isopropyl alcohol	74 ± 16.37
8	Chloroform	16.60 ± 3.05
9	Ethanol	237 ± 25.23
10	Toluene	5 ± 2.645

* Results are mean ± SD of n=3 observations

Table 2: Formulation of Agglomerates

Batch	Drug: Polymer ratio	% of Polymer
F1	5:1	16.67
F2	4:1	20.00
F3	3:1	25.00
F4	2:1	33.33
F5	2:1.5	42.86
F6	1:1	50.00

Preparation of agglomerates: Crystallo-co-agglomeration is a promising technique for the preparation of spherical agglomerates with or without additives. Agglomerates of losartan potassium were prepared by CCA using water-acetone-DCM solvent system. HPMC K100M in varying concentration was utilized as rate retardant polymer. Polymer, according to ratio (**Table 2**), was dissolved along with the

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drug in good solvent. This solution was added into poor solvent with continuous agitation by mechanical stirrer. Speed of agitation was optimized for preparation of agglomerates of desired properties. After formation of fine crystals, bridging liquid was added in it and allowed to stir for around 1 h. This resulted into agglomeration of crystals by formation of liquid bridges which on evaporation forms solid agglomerates of crystals. So formed agglomerates were allowed to settle and clear supernatant was decanted prior to filtration through filter paper. Crystallo-co-agglomerates were then washed with the distilled water and dried at room temperature for 24 h and stored in desiccators till further analysis.

Evaluation of agglomerates

Loading efficiency and yield of agglomerates: Loading efficiency is percentage (%) of drug loaded and was calculated from experimentally measured drug content and the theoretical quantity of drug used to prepare agglomerates. Agglomerates equivalent to 50 mg were dissolved into 50 ml of phosphate buffer pH 7.4 and absorbance was measured after appropriate dilution using UV spectrophotometer at 233.0 nm [24]. Experimental drug content was calculated using calibration equation. % drug loading was calculated using following formula:

$$\%\ drug\ loading = \frac{Experimental\ drug\ content}{Theoretical\ drug\ content} \times 100$$

The yield of crystallo-co-agglomerates was determined from weight of formed agglomerates and total weight of raw materials (drug and polymer) used [25]. The % yield of agglomerates was calculated using following equation.

$$\%\ Yield = \frac{total\ weight\ of\ formed\ agglomerates}{total\ weight\ of\ drug\ and\ polymer} \times 100$$

Particle Size: The process of crystallo-co-agglomeration has profound effect on particle size and size distribution as it involves particle growth through process of agglomeration of crystals. Size analysis of agglomerates was performed by optical microscopy where eye-piece micrometer, calibrated with stage micrometer, was utilized to determine size of particles. The samples of agglomerates were placed on clean glass slide and sizes of 100 randomly selected particles were measured to calculate appropriate mean diameter [17,18].

Flow and packability parameters: Flow characteristic of agglomerated particles was determined through measurement of angle of repose, Carr's index and Hausner's ratio [17]. Angle of repose was measured using fixed funnel method. In this method, samples were allowed to pass through the funnel fixed at specified height until the tip of the so formed powder cone touched the funnel tip. The diameter of the formed powder pile was measured and used to calculate angle of repose. Carr's Index and Hausner's ratio were calculated from values of poured bulk density and tapped bulk density. The fixed amount of agglomerates were placed into cylinder and volume of sample immediately after pouring into cylinder and volume after 100 tapping were measured using Electrolab tap density tester and appropriate bulk densities were calculated [18].

Compactibility parameters: Crystallo-co-agglomeration is one of the most effective techniques used to improve compaction properties of the powder making them suitable for direct compression. Heckel plot analysis was performed to study deformation behavior of agglomerates under pressure. Samples were compressed into compacts at varied pressures using a 6-mm flat-faced punch and steady compression speed [16]. The compaction qualities of agglomerates were articulated as parameters of Heckel equation [26,27].

$$ln\left(\frac{1}{E}\right) = KP + A$$

Where, E is the % porosity of the tablet; P is the applied pressure; K is the slope of Heckel plot; Py, reciprocal of K, is the mean yield pressure. The constant A expresses the densification at low pressure.

Tensile strength and elastic recovery test were performed by preparing compacts of agglomerates. The compacts of samples were utilized to determine elastic recovery of pure drug and their agglomerates. Thickness of the compacts was measured immediately after ejection (Hc) as well as after 24 h relaxation (He). Elastic recovery was calculated using following equation [28].

$$\%\ ER = \frac{(H_e - H_c)}{H_c} \times 100$$

After determination of elastic recovery, compacts were utilised to determine tensile strength. The force required to break compacts (F) were measured and tensile strengths were calculated using following equation [29].

$$T = \frac{2F}{\pi d t}$$

Where, $\boldsymbol{d}$ is the diameter and $\boldsymbol{t}$ is the thickness of the compacts.

Morphology: The optical microscope was used to observe for the morphology, surface smoothness and sphericity of the shape. Photomicrographs of prepared agglomerates were taken using CCD camera and examined for surface morphology and sphericity of shape [30]. Further, morphology of agglomerates were studied by taking SEM photographs [30] using Scanning Electron Microscope (Make: ZEISS; Model No. : EVO-18-13-04). Samples were kept in sputter coater (Make: Emitech, model no. SR7620) for 4 min and process current was 10 mA. Surface morphology, agglomeration efficiency and packing of agglomerated crystals were observed through SEM photographs.

Differential Scanning Calorimetry (DSC): Compatibility study was performed using DSC analysis. Thermograms of drug and agglomerates were obtained using DSC-60 (Shimadzu, Japan) in which samples were placed in aluminum

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crucible while empty aluminum pans were used as a reference. Samples were heated at the temperature between 45°C to 300°C at the rate of 10°C /min.

Fourier Transform Infra-red (FT-IR) Spectroscopy: The drug-polymer compatibility and any possible structural modifications in the drug during process were analyzed by FT-IR study. IR spectra of drug and agglomerates were recorded using FTIR-8400 Spectrophotometer (Shimadzu, Japan). The samples were uniformly mixed with KBr and compressed into disc or pellet by applying pressure. The pellets were placed in light path to record IR Spectra.

Preparation and evaluation of tablets

The prepared agglomerates were compressed into tablets using rotary tablet press and subjected to various official and non-official tests.

Weight uniformity: Weight uniformity of tablets was performed as per IP 2010. Individual weights of 20 tablets from each batch were determined using electronic weighing balance and average weight was calculated for each batch. Appropriate % deviation was calculated for each tablets and compared with standard value.

Hardness and Friability: Mechanical strength of tablets is useful consideration for the integrity of tablets during handling and can be measured in terms of hardness and friability. Hardness of tablets was measured by Monsanto hardness tester [31]. Tablet to be tested for hardness was held between a fixed and a moving jaw of hardness test apparatus and reading of the indicator is adjusted to zero. The force required to break the tablet was measured by moving the screw knob forward until the tablet broke. Friability test was performed using Roche friabilator [31] using 10 tablets. The tablets were weighed (initial weight, W_0) and placed in the friabilator operated at 25 RPM for 4 min. The tablets were dedusted and reweighed (final weight, W_t) after 100 revolutions. The following formula was used to calculate percentage friability.

$$\% \, Friability = \frac{(W_0 - W_t)}{W_0} \times 100$$

Swelling Index: Swelling index is used to evaluate mechanism and rate of degeneration of a tablet. Swelling behavior was measured in terms of percentage of weight gain by tablet when placed in a Petri dish containing water for complete wetting [32]. A tablet was placed in a Petri dish containing deaerated water and weights of the tablet were recorded before placing (W_0) as well as after complete wetting of tablet (W_t). Percentage weight gain by the tablet was calculated from initial and final weights of tablet using following equation.

$$\% \, Swelling = \frac{(W_t - W_0)}{W_0} \times 100$$

Drug content: 20 tablets from each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was weighed and dissolved in phosphate buffer pH 7.4. After appropriate dilution, absorbance was measured using UV spectrophotometer at 233 nm and amount of drug was calculated using calibration equation to determine % drug content [24].

***In-vitro* dissolution study:** Dissolution studies of tablets were performed using USP apparatus-2 (paddle apparatus). The tablets were placed in each vessel containing 900 ml of phosphate buffer pH 7.4 maintained at temperature 37±0.5°C and rotated at the speed of 50 RPM. The samples of 5 ml were withdrawn at specified time intervals and fresh medium was added to replace the sampled medium. After suitable dilution with same medium, samples were analyzed at 233 nm by UV spectrophotometer to determine amount of drug released at specified time intervals. Cumulative % drug release was calculated and plotted against time to generate dissolution profile.

Table 3: Yield and drug loading efficiency of agglomerates

Batch	Yield* (%)	Drug loading* (%)
F1	70.82 ± 1.35	80.16 ± 1.44
F2	74.96 ± 0.99	82.24 ± 1.47
F3	80.31 ± 1.83	83.56 ± 2.42
F4	86.25 ± 1.18	89.39 ± 1.74
F5	91.44 ± 1.92	90.63 ± 2.64
F6	94.55 ± 0.97	93.88 ± 1.45

* Results are mean ± SD of n=3 observations

RESULTS AND DISCUSSION

Free flowing directly compressible spherical agglomerates of drug with release retardant polymer were prepared using good solvent (water)-bridging liquid (acetone)-poor solvent (DCM). Speed of rotation and time of stirring were optimized through preliminary trials at 500 RPM and 1 h respectively. The addition of solution of drug and polymer to poor solvent resulted in formation of crystals which then started to agglomerate in presence of bridging liquid and on evaporation resulted into formation of spherical agglomerates. The yield of agglomerates was found satisfactory in the range of 70 % to 95 % as shown in **Table 3**. Loading of drug was found to be more than 80 % (**Table 3**). Results confirmed that maximum amount of drug and polymer were utilized in formation of agglomerates and there was no considerable loss of drug.

Table 4: Micromeritic characteristics of agglomerates

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Batch	P. Size[#] (µm)	Angle of repose* (θ)	Carr's index* (%)	Hausner's ratio*
Drug	18.65 ± 3.65	46.12 ± 0.46	32.61 ± 0.3	1.43 ± 0.03
F1	583.8 ± 12.89	25.92 ± 0.81	13.11 ± 0.5	1.19 ± 0.02
F2	612.4 ± 16.36	25.67 ± 0.66	10.81 ± 0.6	1.16 ± 0.02
F3	621.7 ± 20.56	24.74 ± 0.34	10.06 ± 0.4	1.18 ± 0.01
F4	652.2 ± 19.52	23.39 ± 0.64	09.54 ± 0.5	1.17 ± 0.02
F5	671.3 ± 19.45	20.77 ± 0.77	10.04 ± 0.6	1.16 ± 0.03
F6	679.8 ± 21.09	21.36 ± 0.43	09.68 ± 0.5	1.15 ± 0.02

Results are mean ± SD of [#](n=100 particles) and *(n=3) observations

Table-5: Compaction parameters of agglomerates

Batch	Heckel Plot Analysis			Tensile strength* (kg/cm^2)	Elastic recovery* (%)
	(Py)	(σ0)	A		
Drug	27.88	8.84	0.76	1.52 ± 0.07	3.99 ± 0.7
F1	17.62	5.85	0.73	3.81 ± 0.04	1.22 ± 0.6
F2	16.64	5.65	0.64	3.25 ± 0.05	1.10 ± 0.6
F3	14.37	4.78	0.51	3.15 ± 0.06	1.10 ± 0.7
F4	13.12	4.56	0.48	3.19 ± 0.05	1.09 ± 0.4
F5	12.24	4.41	0.37	3.16 ± 0.06	1.12 ± 0.5
F6	12.02	4.22	0.32	3.21 ± 0.05	1.08 ± 0.4

* Results are mean ± SD of n=3 observations

Table 6: Physical evaluation of matrix tablets

Batch	Weight deviation[#] (%)	Hardness* (kg/cm^2)	Friability (%)	Swelling index[†] (%)	Drug content[†] (%)
F1	2.31 ± 0.36	5.22 ± 0.25	0.21	58.42 ± 2.3	97.23 ± 1.16
F2	1.42 ± 0.11	5.47 ± 0.34	0.15	60.06 ± 2.5	98.49 ± 1.51
F3	2.18 ± 0.57	6.14 ± 0.23	0.14	64.66 ± 1.9	100.06 ± 1.07
F4	1.68 ± 0.21	6.49 ± 0.41	0.11	67.43 ± 2.1	99.63 ± 0.98
F5	2.05 ± 0.10	7.47 ± 0.37	0.11	71.06 ± 1.5	100.01 ± 0.99
F6	2.17 ± 0.32	8.18 ± 0.51	0.10	75.62 ± 2.5	98.87 ± 1.02

Results are mean ± SD of [#](n=20); *(n=5) and [†](n=3) observations

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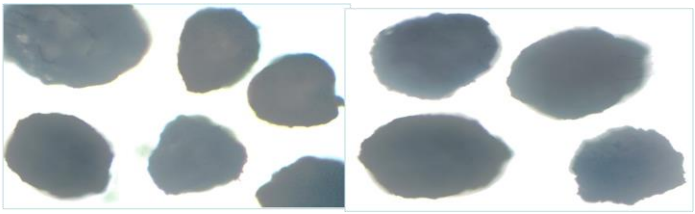
Increase in % yield with increase in polymer amount indicated role of polymer in formation of crystallo-co-agglomerates, which are in conformity with the findings reported by various researchers that polymers and other additives have substantial influence on formation of spherical agglomerates [18,33]. These can be attributed to enhanced bridging and bonding between crystals during formation of agglomerates.

Micromeritics characteristics of drug and agglomerates are depicted in table 4. All the agglomerates obtained were having size around 0.5 mm. Considerable increase in particle size of agglomerates compared to pure drug was an indication of good agglomeration of individual drug particles in presence of polymer. Significant effect of polymer amount on particle size was found as indication of role of polymer in formation of liquid bridges between crystals. As shown in **Table 4**, flow properties of agglomerates were excellent as compared to pure drug. Remarkable reduction in Carr's index and Hausner's ratio as well as angle of repose indicated improvement in flow and packing ability of agglomerates as compare to pure drug. These findings can be attributed to increased particle size and sphericity of agglomerates. Surface smoothness of the agglomerates also contributed in enhancement of flow properties which are in agreement with reported literature [6,34]. The similar work reported by Maghsoodi et al [16] also indicated dramatic improvement in flow, packing and compaction properties of drug through CCA.

Heckel plot analysis for drug and prepared agglomerates was performed to study compaction behavior and deformation of agglomerates under applied pressure. Results shown in **Table 5** suggested improvement in compaction and packing properties of agglomerates compared to unprocessed drug. Plastic deformation of agglomerates was indicated by linear plots obtained using Heckel equation [35,36]. The plasticity of material is indicated by 'K' value while 'A' indicates densification of material at lower applied pressure in Heckel plot parameters. Values of 'K' for agglomerates higher than that of drug suggested better plasticity as well as lower values of 'A' for agglomerates compared to drug (**Table 5**) indicates higher densification at low applied pressure [37]. As shown in table 5, values of yield strength for agglomerates were smaller compared to drug indicating negligible resistance to compression. The results of Heckel plot analysis confirmed good compression and compaction efficiency of agglomerates which can be utilized for direct compression into tablets. These findings are in close agreement with those reported by various scientists that spherical crystallization techniques are promising for improvement of compaction and packing properties of drug making them suitable for direct compression into tablets [14,16,38]. Moreover, polymer amount also have considerable effect on compaction of agglomerates as higher concentration of polymer increased binding of particles to form compacts with good strength [18].

Improved strength of agglomerates was indicated by higher values of tensile strength as shown in **Table 5**. This could be attributed to strong bonding between particles of agglomerates generated in presence of polymer during process of crystallo-co-agglomeration. Lower values of elastic recovery, as depicted in **Table 5**, was an indication of good tabletability of agglomerates as they break easily to generate new surface during compression. Lower elastic recovery and higher tensile strength of compacts of agglomerates showed enhanced compression ability. These finding suggested utilization of agglomerates for compression into tablets having good mechanical strength as reported in various researches [3,6]. Polymer also have significant effect on strength and compaction characteristics of agglomerates as revealed in results of Heckel plot, tensile strength as well as elastic recovery. Studies performed so far have revealed that spherical agglomerates of drugs without excipients have poor compression, compaction and handling characteristics and so, addition of suitable polymers or other additives during CCA is required to improve these properties [16,39].

Figure 1. Photomicrographs of agglomerates



Photomicrographs (**Fig. 1**) showed near spherical shape of agglomerates with considerable improvements in flow and surface characteristics. The enhanced flow and compaction properties can be attributed to agglomeration with near spherical shape as well as smooth surface. The agglomeration also resulted into considerable increase in particle size which can be confirmed with results of particle size analysis and photomicrographs of agglomerates.

As depicted in SEM photographs (**Fig. 2**), prepared agglomerates possessed good agglomeration and smooth surface. The improvements in flow and compaction properties of agglomerates compared to pure drug crystals can be accredited to improved agglomeration of crystals with spherical shape as well as smooth surface.

Figure 2. SEM photographs of agglomerates

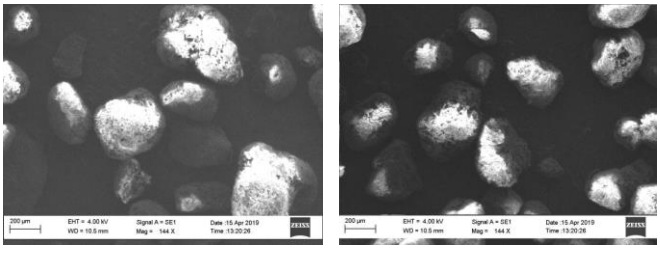


Fig. 3 shows DSC thermograms of pure drug as well as agglomerates. As revealed in DSC thermogram, sharp endothermic peak was observed for agglomerates (at 257.74

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°C) which is in close proximity to that of drug (at 259.08 °C) indicating there is no any significant change in the melting endotherms. These findings suggested that drug has not undergone any alterations in characteristic properties even after processing and there is no interaction of drug with polymer and other excipients used in process.

Figure 3. DSC thermograms of [A] pure drug; [B] agglomerates

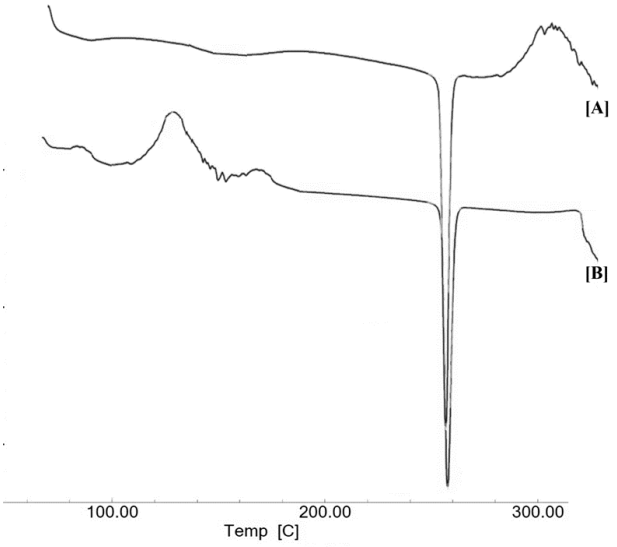
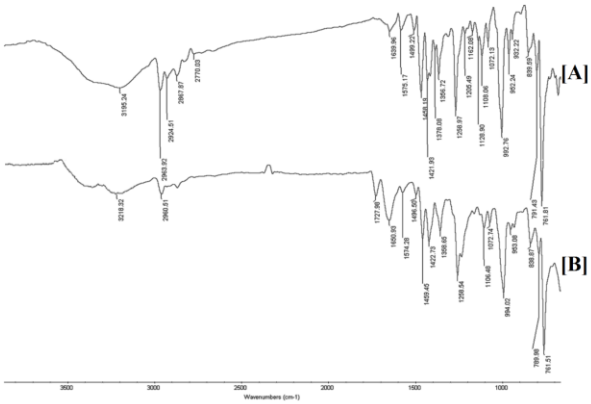


Fig. 4 shows FT-IR spectra of drug and agglomerates. Peaks observed in FT-IR spectra of the agglomerates were compared with the FT-IR spectra of pure drug and the characteristic peaks corresponding to specific functional groups and bonds of the molecules were observed. As shown in Fig.-4, FT-IR spectra of agglomerates shows all the peaks corresponding to peaks present in the spectra of drug indicating no structural changes in drug during crystallo-co-agglomeration in presence of polymer and there is no interaction between drug and polymer. The results of DSC and FT-IR proved compatibility of drug with polymer and other ingredients used during the process of CCA.

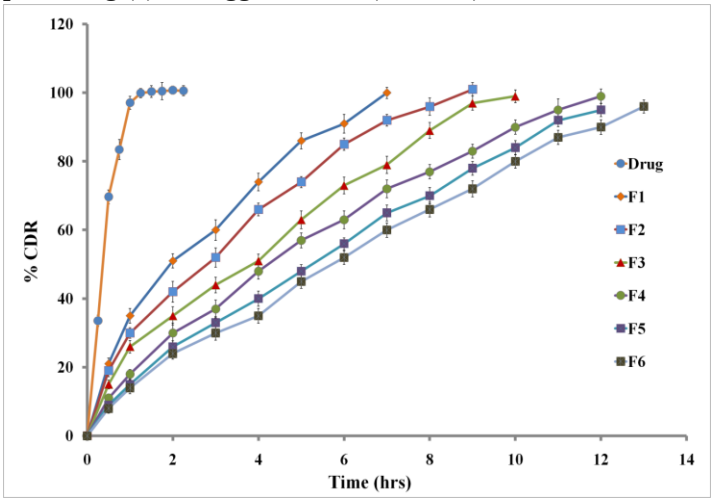
Figure 4. FTIR spectra of [A] pure drug; [B] agglomerates



The evaluation parameters for tablets are shown in **Table 6**. As shown in **Table 6**, weight deviations for various batches of the tablets (1.42 to 2.31) were within the prescribed compendial limit. The results for drug content were found between 97-100 % which is also within pharmacopeial limit and indicated uniformity of drug content within and between various batches. These findings suggested efficiency of CCA technique to produce agglomerates which can be utilized for direct compression into tablets of desired qualities. Swelling behavior of tablets was revealed in results of swelling index. As revealed in results, swelling index increased with increase in polymer concentration. This can be attributed to hydrophilic nature of polymer. The swelling of tablets will result in the formation of matrix which in turn causes retarding effect on drug release from the tablet. These can be further confirmed with the results of dissolution study.

Hardness values for tablets (**Table 6**) were ranging between 5 to 8.5 kg/cm^2 which indicated sufficient strength to provide good matrix forming potential as well as dissolution profiles and prevent friability losses. Friability values for tablets (table 6) were found between 0.10 and 0.21%, which are less than the compendial limit of 0.8%. Results obtained from hardness and friability indicated superior binding and mechanical strength of tablets prepared from spherical agglomerates of drug and polymer. These findings were comparable to those of tensile strength indicating role of polymer in bonding and adhesion between particles and improvement in mechanical strength.

Figure 5. Dissolution profiles matrix tablets prepared from pure drug (•) and agglomerates (F1 to F6).



As shown in **Fig. 5**, the dissolution rate of drug from tablet prepared from untreated drug is fast, indicating necessity of frequent dosing to maintain plasma concentration owing to short biological half life of drug. *In vitro* dissolution profile (Fig. 5) of tablets prepared form agglomerates shows release retardant and matrix development properties of polymer depending upon its concentration. The rate of drug release decreased with increase in polymer concentration, which demonstrated concentration-dependent matrix formation. The

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retarding effect of polymer on drug from tablets can be attributed to matrix formation ability and swellability of the polymer. In-vitro dissolution study showed extended release of drug from tablets compressed from agglomerates compare to tablets prepared from pure drug. The results also indicated uniform dispersion of drug within matrix of polymer generated during process of agglomeration which resulted into sustained release of drug. The utilization of release retardant polymer during spherical crystallization is thus proved as an alternative technique to formulate sustained release matrix tablets with polymer dependent drug release. Similar polymer dependent drug release was also reported in various studies [20,40,41] indicating utilization of technique with optimum concentration to fabricate dosage form with desired rate of drug release.

CONCLUSION

Directly compressible agglomerated crystals of losartan potassium has been successfully prepared using crystallo-co-agglomeration technique. The agglomerates prepared with release retardant polymer possessed properties that can be utilized for direct compression into sustained release matrix tablets. The characteristics of agglomerates and tablets were evaluated through various parameters. The excellent flow and compaction properties of agglomerates can be attributed to spherical shape and plastic deformation behavior under pressure. The DSC and FT-IR confirmed compatibility of drug with polymer and other processing reagents. The results for evaluation of tablets were within compendia limits. Extended release of drug, depending on concentration of polymer, was found for sufficiently longer duration. Thus, crystallo-co-agglomeration technique can be successfully utilized as an alternative to conventional granulation process to obtain directly compressible agglomerates of drug with enhanced flow and compression properties. Technique can also be utilized to form agglomerates with release retardant polymer to prepare sustained release matrix tablets.

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CONFLICT OF INTEREST

Authors do not have any conflict of interest.

FUNDING SOURCE

None

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

DATA AVAILABILITY

The data used in the current study is available from the corresponding author on reasonable request.

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