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Original Article

PROCESS DEVELOPMENT AND OPTIMIZATION FOR MOISTURE ACTIVATED DRY GRANULATION METHOD FOR LOSARTAN POTASSIUM TABLETS

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ABSTRACT

Objective: The present study deals with the formulation and process development of Losartan potassium tablets by moisture activated dry granulation (MADG) process and optimization of granulating fluid uptake concentration.

Methods: Losartan potassium was selected as a model drug and Micro crystalline cellulose (MCC) as a binder. Losartan potassium tablets prepared by MADG process were found to be a simple, clean and robust process. Losartan potassium tablets were manufactured for the Seven batches **F-I to F-VII** using different concentrations of granulating fluid, keeping the total weight (75 mg) of the tablet constant in all the formulations.

Results: The results from the evaluation of the effects of the granulating binder level, binder type suggest that the MADG process is robust and creates granulation with good physical properties and finished products with satisfactory quality attributes. The process is applicable for accomplishing most of the granulation need for solid dosage-form development as practiced in the pharmaceutical industry. It is essentially a one-step granulation process. It is also an economical, energy-saving and efficient manufacturing process.

Conclusion: The losartan potassium tablets prepared by MADG process had advantages such as short manufacturing time and process variables when compared with convention wet granulation process.

Keywords: Moisture activated, Optimization, Robust, Quality attributes, Pharmaceutical industry.

INTRODUCTION

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are most preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. Tablets are safe and convenient dosage form for administration of active pharmaceutical ingredients (API) with excellent physicochemical stability by comparison to some other dosage forms and also provide means of accurate dosing. However the process of manufacturing of tablets is complex. Hence, careful consideration has to be given to selection of right process and right excipients ultimately give a robust, high productivity and regulatory complaint product of good quality [1].

Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms like tablets [2].

Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. Granulation process is defined as ‘‘any process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified.’’ The term ‘‘granulated’’ material is derived from the Latin word ‘‘**granulatum**’’ meaning ‘grained’. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use [3]. In modern times, granulation technology has been widely used by a wide range of industries such as coal, mining and agrochemical. These industries employ agglomeration techniques to reduce dust, provide ease of handling and enhance the material’s ultimate utility [4].

Granulation methods can be divided into two major types: wet methods which utilize some form of liquid to bind the primary particles and dry methods which do not utilize any liquid. The classical granulation process using either wet or dry methods is employed in the process industries [5]. Pharmaceutical granulation process is used for tablet and sometimes capsule dosage forms; however, in some applications the process is used to produce spherical granules for the modified release indications or to prepare granules as sprinkles to be used by pediatric patients. In some countries like Japan, having granulated product in a ‘‘sachet’’ is acceptable where a large dose of the drug product is not suitable for swallowing [6].

A simple and novel granulation process called moisture-activated dry granulation (MADG) is that granulation process, in which a small amount of water is used to activate the granule formation (i.e., perform agglomeration) without requiring hot air drying of the granules [7]. After creating the moist agglomerates, this process uses stepwise addition and blending of common pharmaceutical ingredients that absorb and distribute moisture, thus resulting in a uniform, free-flowing and compatible granulation [8].

MADG is a very simple and innovative process where granules are created with water and a granulating binder, as in wet granulation but are not heat dried or milled. This process helps to minimize endpoint sensitivity [9].

MADG also offers energy savings, a short manufacturing time, and fewer critical formulation and process variables which makes it an easier candidate than conventional wet or dry granulation processes with which to implement the FDA's Quality by Design concepts [10,11].

MADG also offers energy savings short manufacturing time, fewer critical formulation and process variables which make it an easier candidate than conventional wet or dry granulation processes with which to implement the FDA's Quality by Design concepts [12]. Applicable to more than 90% of the granulation needs for pharmaceutical, food and nutritional industry, very few variables, resulting in less need for expensive process analytical technology (PAT), applicable to a number of formulations including high and low drug load formulations [13]. Polymer matrix type controlled release formulations, water soluble and insoluble drug formulations suitable for continuous processing. It uses very little energy so it is a green process, reproducible and scalable.

Now-a-days among all granulating techniques, MADG technology is widely employed in granulation of moisture sensitive active pharmaceutical ingredients.

The present study will be carried out with the Losartan potassium as ideal drug candidate for the preparation of granules by innovative MADG technology & optimization of water content, concentration of granulating binder and moisture absorbents along with other excipients.

Losartan potassium, an orally active non-peptide molecule, belongs to the group angiotensin II receptor antagonist, used in the treatment of hypertension. This active substance is selected with the attributes of freely solubility in water, less bioavailability (33 %) and terminal half-life of Losartan and its active metabolite is approximately 2 and 6–9 hours, respectively.

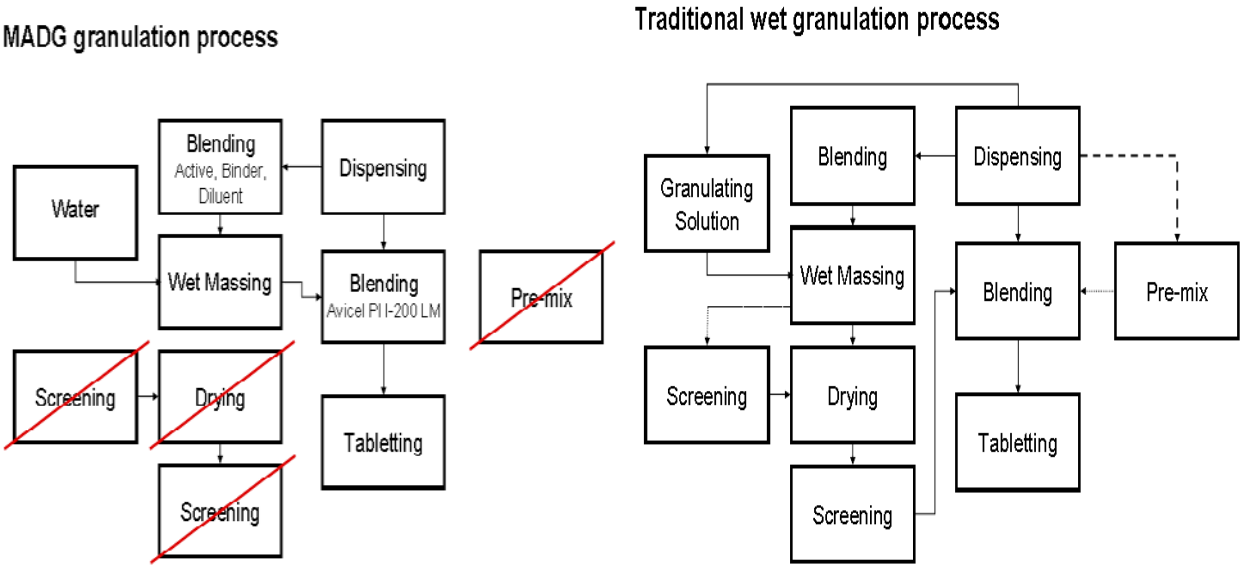

Fig. 1: Processing steps involved in MADG and WG

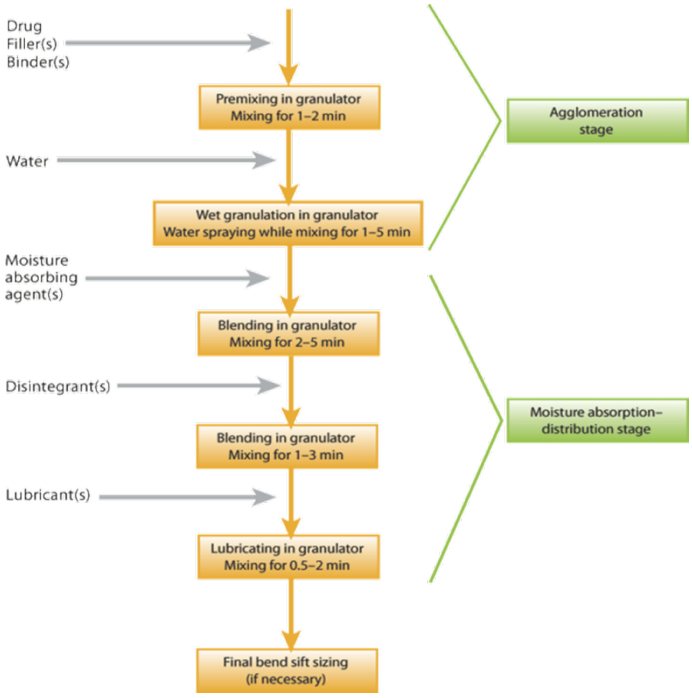

Fig. 2: Flow diagram of the moisture-activated dry-granulation process

MATERIALS AND METHODS

Losartan potassium was received as a gift sample from Aurobindo Pharma, Hyderabad. Microcrystalline Cellulose was obtained from FMC bio polymers, Lactose monohydrate from DMV international, Pregelatinized starch from Colorcon Asia Pvt Ltd, Low substituted hydroxyl propyl cellulose from Shin-Etsu Chemical Co. Ltd and Magnesium Stearate from Ferro international. All other ingredients, reagents and solvents were of analytical grade.

Experimental Design

Manufacture of Losartan potassium immediate release tablets by MADG method

Manufacturing of Losartan potassium tablets involves two major steps they are

1. Preparation of Losartan potassium granules by MADG.

2. Production of Losartan potassium tablets by compressing the granules.

Losartan potassium tablets were manufactured for the Seven batches **F-I to F-VII** using different concentrations of granulating fluid, keeping the total weight (75 mg) of the tablet constant in all the formulations.

Table 1: Formulations of Losartan potassium

Ingredients in (mgs)	Formulation code						
	F1	F2	F3	F4	F5	F6	WG
Losartan potassium	25	25	25	25	25	25	25
Microcrystalline cellulose (AvicelPH102)	10.8	10.8	10.8	10.8	10.8	10.8	10.8
Lactose mono hydrate	19.25	18.5	17.0	15.5	14.75	14.0	12.5
Purified water	0.75 (1%)	1.5 (2%)	3.00 (4%)	4.5 (6%)	5.25 (7%)	6.00 (8%)	7.5 (10%)
Microcrystalline cellulose (AvicelPH200)	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Pregelatinised starch	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Low substituted hydroxyl propyl cellulose	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Magnesium stearate	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Total tablet weight	75	75	75	75	75	75	75

Table 2: Brief manufacturing process of Losartan potassium granules by MADG

S. No.	Process	Description
1	Sifting	Losartan Potassium is passed through 600µm sieve (#30), Microcrystalline cellulose (PH 102), and Lactose Monohydrate are passed through t 425µm (#40)
2	Dry mixing	Half quantity of the above sifted ingredients is loaded into Rapid Mixing Granulator and mixed for 10 min at impeller speed.
3	Granulation	
3.1	Agglomeration	Purified water is sprayed (qty equivalent to certain % of dry mix) over a period of 1-2 minutes with impeller at slow speed. Check for the granules formation.
3.2	Moisture absorption & Distribution Phase	Remaining quantity of the ingredients are added to the above step and mixed for 2 minutes.
4	Extra granular material sifting	MCC (PH 200)is passed through 600µm sieve (#30), Pre gelatinized starch, Low substituted Hydroxy propyl Cellulose are passed through 425µm (#40) and Magnesium stearate is passed through 250µm (#60)
5	Pre-Lubrication	Granules formed in the step 3.2, and the sifted extra granular materials of step 4 except Mag. Stearate are added into low shear blender and mixed for 10 min.
6	Lubrication	Mag. stearate of the step 4 is added to the above step and lubricated for 3 minutes.

Preparation of granules

Compression of granules into tablets

After granulation the lubricated blend was compressed into tablets by using 8 station mini tablet press GMP machine with required punches and compression parameters.

Preformulation studies

Preformulation testing is the first step in the development of dosage forms of a drug substance by any of technique. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined excipients. The overall objective of preformulation studies is to generate information useful to the formulator in developing stable and bioavailable dosage forms.

Drug–excipients compatibility studies

Excipients were integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage forms depends on the selection of excipients, which are added to facilitate administration of the drug and protect it from degradation.

FT- IR Studies

FT- IR spectroscopy was employed to ascertain the compatibility between Losartan potassium and the selected excipients. The pure drug, drug-excipient combinations, and formulations were subjected to FT- IR studies. Potassium bromide, pure drug, and the excipients were heated to 105 ^{0}C for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and/or excipient in 1:1 ratio. Grinding in smooth mortar can effect mixing. The mixtures were then placed in the sample holder of the instrument and the spectra were taken. The spectra were run from 4000 cm-1 to 500 cm-1 wave number. FT-IR spectrum of Losartan potassium was compared with FT-IR spectra of Losartan potassium with excipients. The pure drug and drug with excipients were scanned separately. Disappearance of Losartan potassium peaks or shifting of peak in any of the spectra was studied.

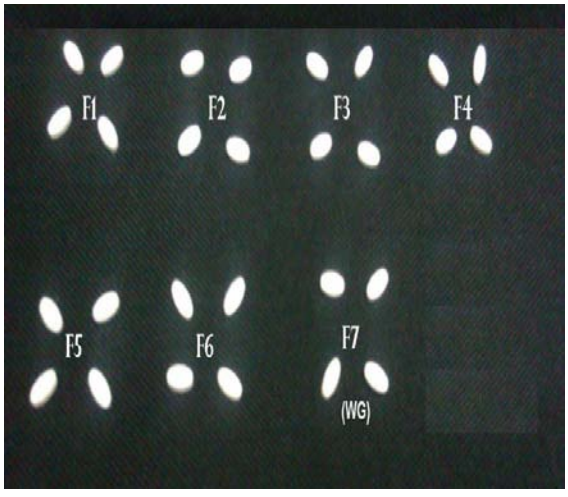

Fig. 3: Tablets prepared Formulation F 1 – F 7

Physical Properties [14]

The powder of excipients and drugs were characterized by angle of repose, bulk density, tapped density, % compressibility, and Hausner's ratio. The flow properties of powders have a great impact on tableting because non-uniform flow will result in variation in

weight of the tablets. It also creates problem of hardness during compression of tablets.

Post formulation studies

Evaluation of Losartan potassium Tablets [15]

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight Uniformity test, hardness, friability, drug content, in- vitro drug release.

Appearance, Shape and Color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and color was observed by keeping the tablets in light. The tablets were checked for presence of cracks, depressions, pinholes etc. if any, uniformity of the color, and the polish of the tablet

Thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using digimatic calipers (Mitutoyo Campbell Electronics, Japan).

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the same tablets from each formulation was determined. The mean and standard deviation values were also calculated.

Friability Test

Roche friabilator (Electro lab, Mumbai) was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches within the chamber of the friabilator). It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively and the percent friability was determined.

Drug content

It was determined for 10 tablets from each batch. The prior calculated average weight for 10 tablets was powdered using mortar and pestle and 25 mg equivalent to Losartan potassium in tablet triturate was accurately weighed and transferred to 100 ml volumetric flask. The volume was equilibrated with 0.1 N Hcl & sonicated (Bandelin Electronics, Berlin) for 15 minutes. Subsequently stock solution was filtered and 5 ml filtrate was diluted suitably in 50 ml volumetric flask with 0.1 N Hcl The assay was carried out at 234 nm using UV-visible spectrophotometer (Shimadzu UV-1800, Japan) against 0.1 N Hcl as blank.

Weight Variation Test

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%).

Table 3: Avg. weight of tablet and % deviation allowed

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

7. *In-vitro* Disintegration Test

Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH1.2 maintained at 37^0±2^{0}C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 1.2 maintained at 37^0±2^{0}C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

8. *In-Vitro* Drug Release

In-vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of 0.1N HCl solution, was placed into the dissolution flask maintaining the temperature of 37 ± 0.5^{0}C and rpm of 50. One Losartan potassium tablet placed in each flask of dissolution apparatus. The apparatus was allowed to run for 60 min. Samples measuring 5 ml were withdrawn at predetermined time interval. Samples were filtered through 10 µm filters. The fresh dissolution medium was replaced every time with the same quantity of the sample. The collected samples were analyzed at 234 nm using dissolution medium as blank. The cumulative percentage drug release was calculated.

The various parameters related to dissolution which are evaluated in the present work are as follows:

Drug release

Cumulative percentage drug release

Cumulative percentage drug retained

Model fitting of the release profiles using different models.

The following procedure was employed throughout the study to determine the *in-vitro* dissolution rate for all the formulations.

RESULTS AND DISCUSSION

Drug–excipients compatibility studies

Compatibility studies were performed using IR interpretation for pure drug and for pure drug and excipients physical mixture and it were found that there were no interactions between the pure drug and the excipients so the further formulation was carried out.

Evaluation of Tablets

I) Pre compression Parameters

Pre compression parameters such as bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio which are evaluated for prepared tablets are given in following table: The results of pre compression studies are shown in the table 4. All formulations showed the angle of repose within 30^0. The values were found to be in the range of 25.22±0.598to 30.17±0.633. Both loose bulk density (LBD) and tapped bulk density results are shown in Table 5.3. The loose bulk density and tapped bulk density for all the formulations varied from 0.56±0.014gm/cm^3 to 0.62±0.012gm/cm^3 and 0.67±0.008gm/cm^3 to 0.73±0.018gm/cm^3 respectively.

The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. This result helps in calculating the % compressibility of the powder. The percent compressibility for all the formulations lies within the range of 13.432±1.978 to 17.808±1.297. All formulations are showing good compressibility. Hausner's ratio of the prepared blends/granules fall in the range of 1.154±0.012-1.289±0.029 indicated that the blends/granules have the required flow property and strength for compression.

Table 4: Pre compression Parameters for the granules

Formulation code	Angle of Repose (θ)	Loose Bulk Density(gm/cm³)	Tapped Density(gm/cm³)	% Compressibility	Hausner's Ratio
F1	29.23±0.173	0.58±0.005	0.71±0.007	15.492±1.784	1.289±0.029
F2	27.31±0.643	0.57±0.008	0.70±0.008	14.285±1.043	1.220±0.015
F3	25.22±0.598	0.56±0.014	0.67±0.008	13.432±1.978	1.177±0.012
F4	27.37±0.527	0.60±0.018	0.72±0.013	15.666±1.120	1.232±0.021
F5	26.22±0.449	0.61±0.006	0.72±0.016	17.289±1.321	1.172±0.017
F6	29.37±0.565	0.59±0.009	0.69±0.023	14.205±1.201	1.281±0.019
F7(WG)	26.17±0.633	0.62±0.012	0.73±0.018	17.808±1.297	1.154±0.012

*Values are mean±SD, n=3.

Table 5: Post-compression Parameters for the developed formulation

Formulation Code	Physical appearance	Thickness (mm)	Hardness (KP)	Friability %	Weight variation(mg)	Drug Content (%)	*In-vitro* Disintegration Time (min.)
F1	Clear, white	2.45±0.12	4.6±0.3	0.622	68.5±1.34	97.6±1.1	7.2 ±0.5
F2	Clear, white	2.52±0.10	4.8±0.2	0.557	70.6±1.1	97.3±1.6	7.3±0.6
F3	Clear, white	2.55±0.05	5.9±0.3	0.601	74.3±1.3	97.5±1.2	7.3±0.8
F4	Clear, white	2.50±0.15	7.0±0.2	0.479	75.2±1.5	97.8±1.0	7.2±0.3
F5	Clear, white	**2.57±0.19**	**7.4±0.3**	**0.352**	**75.7±1.3**	**98.5±0.6**	**7.6±0.2**
F6	Clear, white	2.53±0.12	6.9±0.5	0.371	76.3±1.2	98.1±1.1	8.1±0.5
F7(WG)	Clear, white	2.60±0.05	7.6±0.4	0.384	76.0±1.1	98.2±1.3	8.8±0.6

*Values are mean±SD, n=3.

Table 6: *In vitro* drug release profile for prepared formulations

Time (min)	Cumulative % drug released						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
0	0	0	0	0	0	0	0
10	28.161±1.21	29.732±1.09	32.517±1.32	40.588±1.14	44.588±0.35	44.945±1.07	45.371±1.43
20	45.011±1.13	42.887±0.76	52.325±1.08	57.045±0.76	58.402±0.94	59.761±1.14	58.868±1.24
30	52.372±0.98	54.122±0.98	57.854±1.12	61.292±0.67	68.365±0.65	66.726±1.17	65.481±0.76
40	62.365±1.23	65.118±0.79	62.854±0.97	72.943±0.71	80.308±1.53	81.028±1.65	78.003±0.43
50	78.298±1.34	84.484±0.97	80.224±0.95	89.962±0.86	92.043±0.58	92.767±0.96	89.593±0.98
60	90.130±1.10	91.899±1.23	88.286±0.76	95.385±0.59	98.115±0.64	96.772±0.87	95.136±0.78

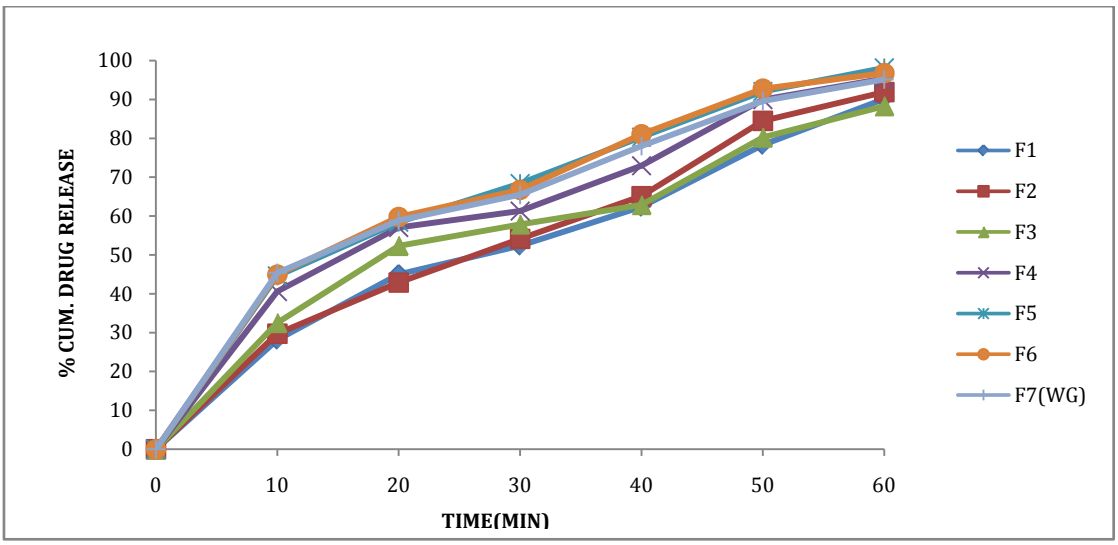

Fig. 11: Dissolution profile of Formulation F1-F6 and F7 (WG)

II) Post-compression Parameters

Post compression parameters such as colour, thickness, hardness, friability, weight variation, disintegration, drug content and % cumulative drug release are given in following tables. The results of post compression studies for formulated tablets were tabulated in Table-5. Randomly picked tablets from each formulation batch examined under lens for shape and in presence of light for color. Tablets showed flat, oval shape in white color. Tablets mean thickness in all the formulations were found to be in the range of 2.45 mm-2.60 mm. All the results are found to be within the limits (2.60 mm to 2.71 mm). The results showed that the hardness of the

tablets was in the range of 4.6±0.3 to 7.6±0.4KP. Hardness of all the formulations are found to be within the limits except the F-1 & F-2which shown the low hardness because of the less moisture. The results showed that the friability of the tablets was in the range of 0.352% to 0.622%. The friability of the formulations are within the limits except F-1, F-2 & F-3which are showing the values out of limits due to less binding activity. Weight of the tablet is 75 mg; so the permissible limit is ±7.5%. The results of the test showed that, the tablet weight was within pharmacopeial limit. The formulations F-1 and F-2 shown weight variation during compression, to avoid this, the compression machine speed is reduced.

The content uniformity of all the formulations was found to be in the range of 97.3±1.6% to 98.5±0.6% which showed that there was uniform distribution of the drug throughout the batch. The IP standard says that Losartan tablets must contain not less than 95.0% and not more than 105.0% of the stated amount of Losartan potassium.

Thus all the formulations of Losartan potassium complies with IP limit for assay. The results showed that the disintegration time of prepared tablets were in the range of 7-9 minutes. All the results are within the pharmacopeial limits.

Table 7: Kinetic modeling and comparative kinetic values of Losartan Potassium formulations

Formulation code	First order		Hixson Crowels	
	R	K1	R	KHC
F-1	0.9247	0.035	0.9681	0.0877
F-2	0.9291	0.039	0.9711	0.0967
F-3	0.9496	0.033	0.9663	0.0834
F-4	0.9246	0.047	0.9653	0.1062
F-5	0.908	0.059	0.977	0.1202
F-6	0.9481	0.054	0.9805	0.1152
F-7(WG)	0.9484	0.045	0.9769	0.1018

In- vitro dissolution profile of the formulations

Finally, the tablets were evaluated for *in vitro* dissolution studies in0.1N HCl buffer of pH-1.2and the results were shown in the table-6. Graph is plotted and is shown in Figure-11. Among all the 6 formulations prepared by MADG process the F-5formulation shows the highest dissolution rate and drug release. The results shows that the drug release pattern of F-5 and F-7(WG) are similar. The dissolution data of Losartan potassium formulations were analyzed as per first order & Hixson-Crowell's cube root equation. Kinetic modeling and comparative kinetic values of Losartan Potassium formulations are showed in table 7. In all the cases, the first order plots were found to be fairly linear with the correlation coefficient values in the range of 0.9-1. Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the "cube-root law" to nullify the effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell's cube root law is given by the following equation. $(W_o)^{1/3}-(W_t)^{1/3}= Kt$, where $W_o$is initial mass and W_t is the mass remained at time '*t*'. A plot of $(W_o)^{1/3}-(W_t)^{1/3}$ versus time will be linear. Hixson-Crowell plots were plotted based on the dissolution data of all the formulations were found to be linear indicating that the drug dissolution, occurring discretely from surface. Hence the release of drug from the formulations followed first order kinetics and Hixson-Crowell cube root law.

CONCLUSION

In the present study, we have successfully prepared and developed Losartan potassium tablets by moisture activated dry granulation technique. The formulations of Losartan potassium were prepared by using two techniques i.e., moisture activated dry granulation technique and wet granulation technique. A total of 7 formulations were prepared out of them one formulation is prepared by using wet granulation technique. In the present study we have successfully developed the process for preparation of Losartan potassium tablets by moisture activated dry granulation technique. The Precompression parameters of all formulations have shown good flow properties. The post compression parameters of all formulations were determined and the values were found to be within pharmacopeial limits. Out of all the six formulations, F-5 formulation prepared by moisture activated dry granulation technique is predicted to be the best formulation by comparing all the six formulations F-1 to F-6 with F-7. Water percentage to be used in the preparation of Losartan potassium tablets by using moisture activated dry granulation technique is optimized by various trails and it found to be 7%.

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