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Original Research Article

Formulation, development and evaluation of paracetamol tablet by moisture activated dry granulation (MADG) process

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ABSTRACT

Background: Paracetamol, also known as acetaminophen, is a painkiller that is popular throughout the world because it does not irritate the stomach. Paracetamol was first discovered to have both analgesic and antipyretic properties in the late nineteenth century. The aim of present work was to Formulate, develop and evaluate Paracetamol Tablets by Moisture Activated Dry Granulation (MADG) process to short manufacturing time and process variables as compared with convention process.

Materials and Methods: Colloidal anhydrous silica is used in the formulation to absorb the extra moisture present in the MADG process formulation. A total number of five formulations were prepared and weight of all tablets kept constant. i.e. 595 mg.

Result: All the formulations resulted in acceptable limit. The final batch F3 (contained PVPK 3% and Kollidon 90F 4%) considered as optimized batch which gives the release up to 95.38 % in 30 min. All Pre-compression parameters like Carr's Index, Hausner's Ratio and Angle of Repose met the standard values indicating good flow properties. The average weight, friability and hardness were within compendia limits. Drug content uniformity was within acceptable limits. The result of stability study of the batch F3 showed that there was no significant change in Hardness, Friability, In-vitro Disintegration time, The optimized formulation batch F3 showed better drug release profile with other formulations.

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

1. Introduction

is a unit solid dosage form containing active ingredient with or without suitable excipients. These are the most widely used dosage form. The main objective of the design and manufacture of the compressed tablet is to deliver orally correct amount of drug in the properform over proper time and at desired location, so as to have suitable chemical integrity protected at the point of its action. The physical design, manufacturing process, and complete chemical makeup of the tablet can have a profound effect on the efficiency of the drug being administered. MADG is a process in which moisture is used to activate granule formation, without the need to apply heat to dry the granules. During this process, the generation of moist agglomerates is followed by the stepwise addition and blending of common pharmaceutical ingredients that absorb and distribute the moisture, which results in a uniform, free-flowing and compactable granulation. Comparison of MADG process with conventional granulation methods The MADG method produced granules with excellent flowability.[1–6] The tablets prepared using the MADG

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method had better content uniformity MADG is a simple, economical, clean, lean and robust process that creates granulation with very good physical properties and finished products with satisfactory quality attributes In the MADG process, only a small amount of water is used to create agglomeration. Moisture distribution and absorption steps follow, and neither heat drying nor milling is needed. [7–14]

2. The Objectives of the Research Work:

1. To prepare, optimize, characterize immediate release tablets by MADG process and set parameters that can serve as quality control tool.
2. To overcome the difficulties experienced with wet granulation, in terms of endpoint, drying and milling.
3. To perform Preformulation studies of selected API.
4. To shorten the processing time
5. To improve the efficacy of drug and minimize endpoint sensitivity.
6. To optimize the developed formulation.
7. Physicochemical, in-vitro evaluation of optimized formulation.
8. To study stability of optimized formulation.
9. To improve the solubility of drug.

3. Materials and Methods

3.1. Preformulation studies

Identification test for Paracetamol: The sample was observed visually**.**

3.2. Melting point

Melting point analysis is also useful for identification of compound. The melting point range can be indicated and recorded with the help of a digital thermometer. Small amount of crystals of sample was fetched into the melting point capillary tube. The capillary tube contained the sample was placed into the melting point apparatus. . Hence, both initial and final melting point of the samples was observed and recorded. This experiment was repeated twice to obtain the ranges of the melting point. The melting point of Paracetamol ranges from 167 to174 degree Celsius.

3.3. Solubility

Solubility of Paracetamol is determined in ethanol (95%) and acetone. Solubility studies were performed by taking excess amount of Paracetamol in different beakers containing the solvents. The mixture was shaken for 24 hrs. at regular intervals. The solution was filtered by using whattmann's filter paper grade no.41. The filtered solutions were analyzed spectrophotometric ally at 243 nm.

3.4. Infrared absorption spectrophotometry

The experiment was conducted for all samples.0.1g of each samples were measured with macro spatula and 1ml of concentrated hydrochloric acid was added to it. The solution was gently shake and heated to boil for about three minutes. 1ml of water was added to the boiling solution. After boiling, the solution was then placed in an ice bath to cool. Observation was made and there was no precipitation form. Therefore, 0.05m of 4.9/L solution of potassium dichromate was added to it and the colour developed for sample was violet without changing into red.

3.5. Determination of λmax

A solution of Paracetamol containing the concentration 10 μg/ml was prepared in acetone and UV spectrum was taken using Shimadzu 1800, Japan UV/ Visible Double beam Spectrophotometer. The solution was scanned in the range of 200 - 400 nm. a. Preparation of standard calibration curve of Paracetamol: 100 mg of Paracetamol was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and made up to the volume with 0.1 N HCl to gine stock solution containing 1000 μg/ml. From the standard stock solution, 10 ml solution was diluted with 100 ml 0.1 N HCl (100 μg/ml). Appropriate aliquots were taken in different volumetric flasks and made up to 10 ml with 0.1 N HCl so as to get 6 different concentrations (2, 4, 6, 8, and 10) μg/ml. The UV absorbance readings were taken at 243 nm using UV- Visible spectrophotometer. 0.1 N HCl was used as a blank. The Beer- Lambert curve was drawn and correlation coefficients calculated.

4. Compatibility Studies

Fourier Transform Infra-red (FT-IR) Spectrophotometer of pure crystalline drug and granules were obtained. The samples were diluted with pure crystalline KBr. The pellets were prepared on a KBr-press (Spectra lab, India). The spectra were scanned at range from 4000 cm-400 cm-1. 6.2.8 Loss on drying: Loss on drying is the loss of weight expressed as percentage w/w resulting from volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

4.1. Drug - excipients compatibility studies

Drug excipients studies holds great importance in designing a formulation. In drug formulation it is essential to evaluate the possible interactions between the active principle and the excipients, as the choice of the excipients should be performed in relation to the drug delivery, to their compatibility with the same drug and to the stability of the final product. 1.3. Preparation and evaluation of granules:

4.1.1. Preparation of granules

There are two major stages in MADG

Agglomeration and moisture distribution / absorption. All ingredients were weighed and passed through mesh #40. During agglomeration, Paracetamol was mixed with agglomerating binders such as PVP K30 and Kollidon 90F to obtain a uniform mixture. While mixing, a small amount of water was sprayed onto the powder blend, which moistened the binder and makes it tacky. The binder facilitates the binding of the drug and excipients as they move in a circular motion forced by the mixer impellers or blades. The resulting agglomerates were small and spherical because the amount of water used in MADG is much lower than in conventional wet granulation; thus preventing the agglomerates from forming large wet lumps. The particle size of the agglomerates generally falls in the range of 150–500 μm. In moisture distribution/absorption, moisture absorbents, such as microcrystalline cellulose or colloidal anhydrous silica, were added while mixing continues. When they came into contact, the moisture absorbents pick up moisture from the moist agglomerates resulted in moisture redistribution within the mixture. When this happens, the entire mixture becomes relatively dry. While some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact and some - usually the larger particles -may break up. This process results in granulation with more uniform particle size distribution. The process continues with the addition of a disintegrant, such as crospovidone, to the mixture followed by blending for a few minutes. Then, while mixing, lubricant(s), such as magnesium stearate are added and blended for sufficient time to achieve adequate lubricity. Different formulations were prepared by MADG technique.

4.1.2. Evaluation of micromeritic properties of granules

Before tablet preparation, the mixture blend of all the formulation were subjected for compatibility studies, IR. and pre-compressible parameters like Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio.

The tablets prepared were subjected to post compression parameters like Hardness, Friability, Weight variation, Wetting time, Water absorption ratio, in-vitro dissolution and in-vitro disintegration. Tablet compression was carried out in Rotary compression machine. Compression force was kept constant throughout the study. Compression was carried out using 12.5 mm flat beveled edge punches Rotary Press Tablet , Rimek Tablet Compression Machine according to the 1, 2, 3, 4 ,5... a total number of five formulations were prepared along with one with conventional wet granulation process and weight of all tablets kept constant. i.e 595 mg.

5. Result and Discussion

5.1. Preformulation studies of paracetamol

The Preformulation studies of drug were carried out by conducting various parameters i.e. solubility, melting point, pH determination and spectral analysis.

5.1.1. Solubility

The solubility of pure drug in solvent was carried out and found to be soluble in acetone and ethanol, and insoluble in water.

5.1.2. Melting point

Melting point of Paracetamol was found to be 170oC. From this it was concluded that drug sample is pure.

6. Estimation of Paracetamol by UV Spectroscopy

Determination of λ max for Paracetamol: The λ max for Paracetamol was found to be 243 nm.

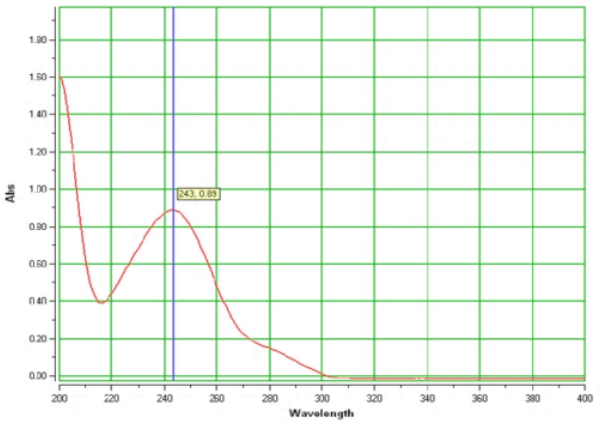

Figure 1: Determination of λ max forparacetamol

Calibration curve

Absorbance data for the calibration curve of Paracetamol at 243 nm

6.1. Pre-compression evaluation of paracetamol tablets

Five formulations were prepared along with a formulation with conventional wet granulation method was prepared. For each designed formulation, powder mixed blend of drug and excipients were prepared and evaluated for various parameters as follows:

6.1.1. Angle of repose (θ)

The angle of repose of various powders mixed blend, prepared with different quantities, was measured by cylinder method. Angle of repose was found in the range from 29.42 to 37.27. The good flow ability of powder blend was also

Table 1: Different formulations were prepared by MADG technique

Sr. No	Ingredients	Trial (F1)	Trial (F2)	Trial (F3)	Trial (F4)	Trial (F5)
1.	Paracetamol	84	84	84	84	84
2.	PVP K- 25	6	4	4	2	1
3.	Kollidon 90F	1	3	4	6	6
4.	Water	2	2	2	2	2
5.	Colloidal anhydrous silica	0.6	0.6	0.6	0.6	0.6
6.	Microcrystalline Cellulose	3	3	2	2	3
7.	Crospovidone	1.9	1.9	1.9	1.9	1.9
8.	Purified talcum	1	1	1	1	1
9.	Magnesium Stearate	0.5	0.5	0.5	0.5	0.5

Table 2: Calibration curve of paracetamol

Sr. no	Concentration (μg/ml)	Absorbance
1.	0	0.00
2.	2	0.14
3.	4	0.23
4.	6	0.35
5.	8	0.44
6.	10	0.62

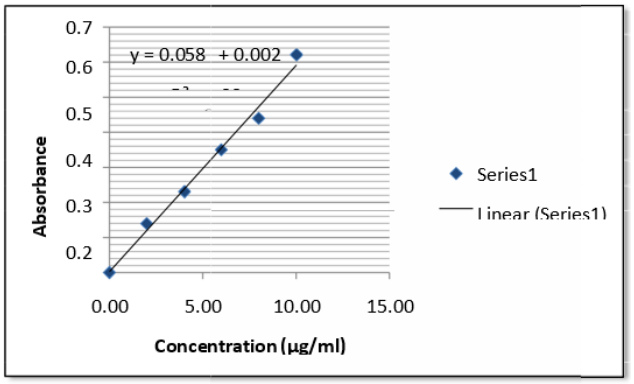

Figure 2: Calibration curve of Paracetamol

evidenced with angle of repose which is indicated a good flow ability. The result is given in Table 8:

Table 3: Angle of repose of various powder mixed blend

Batch code	Angle of repose (θ)
F1	37.27
F2	34.92
F3	32.71
F4	31.65
F5	29.42
FCWG	32.78

6.1.2. Moisture content

Moisture content of various powders mixed blend, prepared with different quantities, was determined using a moisture balance (Mettler PM 480, Switzerland) fitted with an infrared heating unit (Mettler LP 16). Moisture content was found in the range from 2.11 to 2.19

The result are given in Table 9.

Table 4: Moisture content of various powder mixed blend

Batch code	Moisture content
F1	2.1
F2	2.12
F3	2.16
F4	2.14
F5	2.19
FCWG	2.12

6.2. Tapped density

The tapped density of various powder mixed blends prepared with different quantities, was measured by measuring cylinder. The tapped density was found in the range from 0.605 to 0.621. The result is given in Table 10.

Table 5: Tapped density of various powder mixed blends

Batch code	Tapped density (gm/cm3)
F1	0.605
F2	0.609
F3	0.612
F4	0.612
F5	0.621
FCWG	0.601

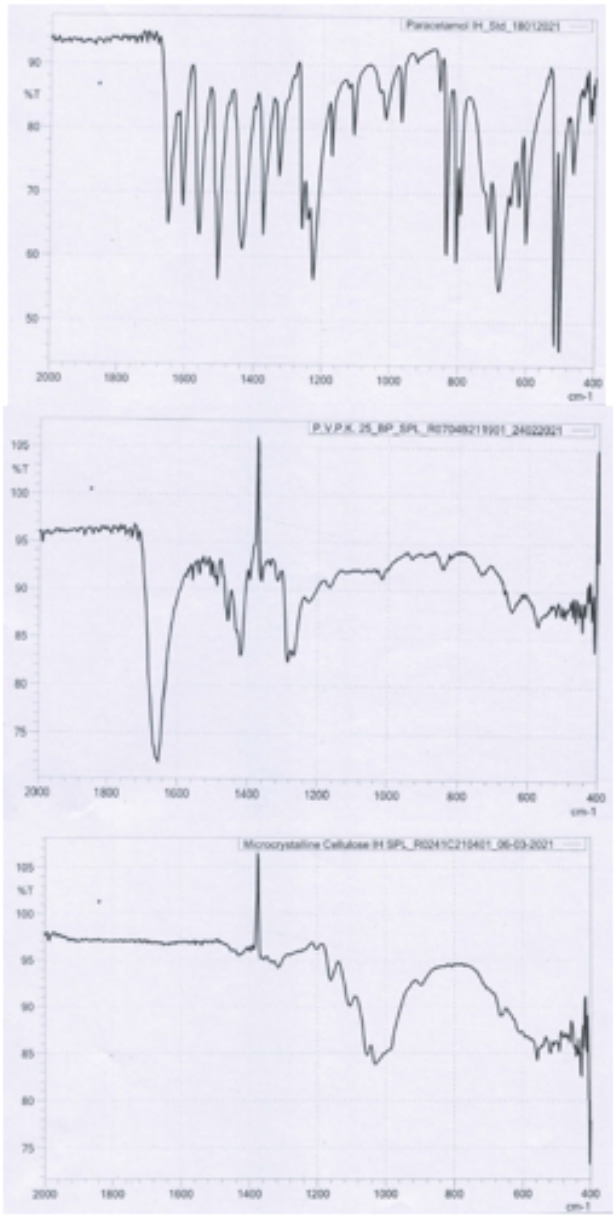

Figure 3: FTIR spectra of paracetamol, PVPK-25 and microcrystalline cellulose

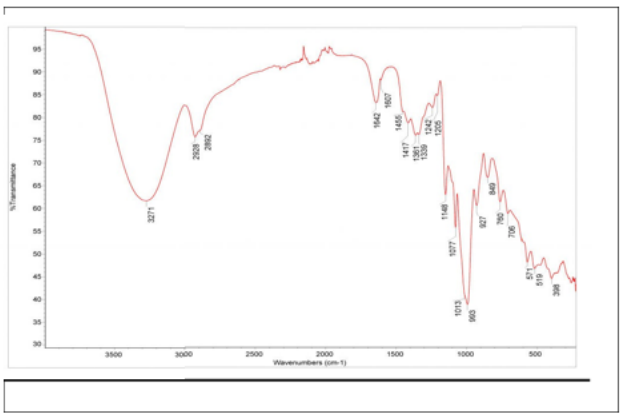

Figure 4: IR Spectrum of starch

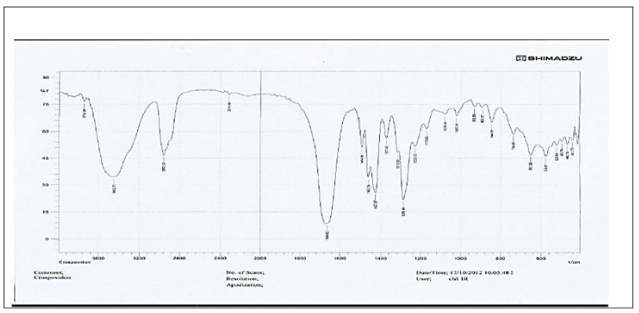

Figure 5: IR Spectrum of Crospovidone

Table 6: Compressibility index of various powder mixed blends

Batch code	Compressibility Index(%)
F1	17.34
F2	16.86
F3	14.57
F4	12.43
F5	9.06
FCWG	16.65

6.3. Compressibility index

The compressibility index of various powder mixed blends prepared with different quantities using bulk density and tapped density data, compressibility index was calculated. It was found in the range 9.06 to 17.34 indicates better flow. The results are given in Table **??**.

6.3.1. Hausner ratio

The Hausner ratio of various powder mixed blends prepared with different quantities, it was calculated by using bulk density and tapped density data. It was found in the range of 1.1 to 1.19. As the results are in range of <1.25 indicates better flow. The results are given in Table no.

Table 7: Hausner ratio of various powder mixed blends

Batch code	Hausner ratio
F1	1.1
F2	1.14
F3	1.16
F4	1.14
F5	1.19
FCWG	1.12

6.4. Evaluation of paracetamol tablets

6.4.1. Weight variation

s were prepared using Moisture activated dry granulation technique and was compared with those of prepared with Conventional wet Granulation technique. The tablets were obtained in the range with acceptable weight variations as per pharmacopoeia specifications i.e. less than 5%. The results are given in Table 12.

Table 8: Weight variations

Batch code	Weight (mg)	Variation (5%)
F1	598.4	Passes
F2	598.4	Passes
F3	598.3	Passes
F4	599.5	Passes
F5	597.6	Passes
FCWG	597.5	Passes

6.4.2. Thickness

s were evaluated by using vernier caliper. The thickness of tablets was found to be 2.1 uniform thicknesses was obtained due to uniform die fill. The results are given in Table 13 **.**

Table 9: Thickness of various tablets

Batch code	Thickness (mm)
F1	2.12
F2	2.13
F3	2.10
F4	2.13
F5	2.04
FCWG	2.16

Tablets were evaluated by using hardness tester. Hardness of the tablets was found in the range 1.91 to 2.02. The results are given in Table 14.

6.4.3. Hardness

Table 10: Hardness of various tablets

Batch code	Hardness (kg/cm2)
F1	3.4
F2	3.6
F3	4.5
F4	5.1
F5	5.6
FCWG	3.1

6.4.4. Friability

s were evaluated by using RocheFriabilator and Friability of tablets was observed in acceptable range 0.21 to 0.73 (Less than 1%).The results are given in Disintegration.

Times were evaluated for disintegration time in the disintegration test apparatus (I.P) The disintegration time was found in the range 2.2 min to 14.32 min for all the batches. The result is given in.

Table 11: s were evaluated for disintegration time in the disintegration test apparatus (I.P) The disintegration time was found in the range 2.2 min to 14.32 min for all the batches.

Batch code	Disintegration time (min)
F1	2.25
F2	4.54
F3	6.82
F4	13.54
F5	16.32
FCWG	2.16

6.4.5. Content uniformity

The results for content uniformity are presented in table no. The results showed drug content were lying within the limits. The assay limit of Paracetamol tablets as per IP is 99-110%. The assays of the tablets were carried out as a process given in IP and data table are as follows.

Table 12: Content uniformity

Batch code	Content uniformity (%)
F1	102.27%,
F2	100.43%
F3	101.32%
F4	99.89%
F5	97.35%
FCWG	104.63 %

6.4.6. In-vitro release studies

The Comparative analysis of each formulation was based on in vitro kinetic parameters, which elucidated the release profile. The time taken for 80% drug release was taken as a response for comparative interpretation of binder quantities.. The in-vitro drug release of tablets of Paracetamol for all formulation are given as follows.

6.4.7. In vitro drug release studies details:

Apparatus used: USP Dissolution Apparatus 2 - Paddle (37°C)

Dissolution medium : 0 1N HCL Dissolution medium volume : 900 ml Temperature: 37±0 5℃

Table 13: In vitro drug release

Time (min)	F1	F2	F3	F4	F5	FCWG(Conventional Wet Granulation)
0	0	0	0	0	0	0
5	24.78	26.32	25.12	21.63	7.43	28.59
10	43.93	45.38	43.95	38.77	10.69	48.78
15	67.37	68.82	63.08	56.18	17.68	68.75
20	73.78	72.96	72.02	62.90	25.74	78.62
25	85.27	89.28	84.51	68.97	31.12	87.59
30	97.89	96.70	95.38	78.40	34.09	95.15

Table 14: 20 Stability studies

Sr .no	Evaluation Parameter	Observation F3
1.	Physical Appearance	**
2.	Weight Variation (mg)	**
3.	Hardness(kg/cm2)	3.9
4.	Friability (%)	0.5
5.	Disintegration time	5.44
6.	Drug content(mg/tablet)	101.13

Speed of basket paddle: 50 rpm
Sampling intervals: 5 min
Sample withdrawn: 10 ml
Absorbance measured: 257nm

6.5. Dissolution profile of Paracetamol tablets

6.5.1. Stability studies of paracetamol tablets

On the basis of drug release profile along with other parameters, it was concluded that the batch F3 was an optimized batch, as it had all desirable properties. A stability study was carried out to check the stability of rapid disintegrating tablets of the Optimized batch at 40±2°C and 75±5% RH for three month. After time period of 03 month Hardness, Weight Variation, Friability, Disintegration time, Drug content study was carried out. From results of stability study as shown it can be concluded that there is no significant difference in the Hardness, Weight Variation, Friability, Disintegration time, Drug content parameters. So, it was concluded that selected formulation is stable for longer time period.

40 °C ± 2°C /75% RH ± 5% RH and At Room Temperature.

7. Conclusion

1. The MADG process to prepare PCM tablets was found to be a simple, clean, lean, and robust process for particle-size enlargement.
2. 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.
3. The process is applicable for accomplishing most of the granulation need for solid dosage- form development as practiced in the pharmaceutical industry.
4. It is essentially a one- step granulation process. It is also an economical, energy-saving, green, and efficient manufacturing process.
5. The PCM tablets prepared by MADG process had advantages such as short manufacturing time and few critical formulation and process variables when compared with convention wet granulation process.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

1. Sharma A, Sethi P, Pawar D. Granulation techniques and technologies: recent progresses. *Bioimpacts*. 2011;5(1):55–63.
2. Aniruddha MR, Joseph BS. Use of a moist granulation technique to develop controlled release dosage formsof acetaminophen. *Drug Dev Ind Pharm*. 2001;27(4):337–80.
3. Reddy B, Navaneetha K, Sandeep P. Improved tablet production by modified granulation techniques. *Int J Res Pharm life Sci*. 2014;2(2):224–35.
4. Chen CM, Dhananjaya A, Michael RI, Jeffrey LC. Comparison of moisture-activated dry granulation processes with conventional granulation methods for sematilide hydrochloride tablets. *Drug Dev Ind Pharm*. 1990;16(3):379–94.
5. Christensen LH, Johansen HE, Schaefer T. Moisture-activated dry granulation in a high shear mixer. *Drug Dev Ind Pharm*. 2009;20(14):2195–213.
6. Sharma D, Lanjewar A. Formulation and evaluation on water poorly soluble drug tablets by MADG method. 2017;p. 1523–37.

7. Kashyap SD, Kokhra S. Development of enteric coated tablets of ibuprofen using methacrylic acid copolymer. *Int J Inst Pharm life Sci*. 2017;2:2249.
8. Sharma DK, Joshi SB. Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: A Review. *Asian J Pharm*. 2022;1(1):7161660.
9. Li YKDX, Oh SJ, Lim JO, Kim HJ. Novel gelatin microcapsule with bioavailability enhancement of ibuprofen using spray-drying technique. *Int J Pharm*. 2008;355(1-2):277–84.
10. Himanshu K, Solanki T, Jalaram H. Recent advances in granulation technology. *Int J Pharm Sci Rev Res*. 2010;5(3):48–54.
11. Liang LH, Hsis OH, Chia C, Ta-Shuong C. Process and formulation characterizations of the thermal adhesion granulation (TAG) process for improving granular properties. *Int J Pharm*. 2008;357(1-2):206–12.
12. Sheskey P. The Development of a Novel Technique for the Delivery of Aqueous Binder Systems in High-Shear and Fluid- Bed Wet-Granulation Applications. *Powder Technol*. 2003;5(4):26–30.
13. Kaur H. Manufacturing method of tablet by Mukesh Gohel, www pharmainfo.net/tablet-ruling- dosage-form and Pharmaceutical Sciences. *Int J Pharm Pharm Sci*. 2014;6(6):3–7.
14. Ullah I, Wang J. Moisture activated dry granulation: The 'one-pot' process. *Pharm Tech Europe*. 2010;22(3):40–4.

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