IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
November 2016 Vol.:7, Issue:4

Crystallo-Co-Agglomeration: An Effective Tool to Change the Powder Characteristics of Indomethacin IP

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

[1]Dr. Sarath Chandran C*, [2]Theju John Thomas, [1]Vipin K V, [1]Amitha S

[1] Academy of Pharmaceutical Sciences, Pariyaram Medical College, India.

[2]College of Pharmacy, Gulf Medical University, Ajman, United Arab Emirates.

Submission: 10 November 2016
Accepted: 15 November 2016
Published: 25 November 2016

Keywords: Indomethacin IP, Spherical, Agglomerates, Compression, Crystallo-co-agglomeration

ABSTRACT

The low dose Indomethacin IP is having poor flow and compressibility making it a least suitable candidate for direct compression. Crystallo-co-agglomeration technique was effectively utilized to change the powder character of Indomethacin IP into spherical agglomerate. The polymers PEG 6000 and PVP K30, used for the investigation are found to be effective in developing spherical agglomerates. The developed spherical agglomerates were subjected for characterisation studies and are directly compressed to tablets. The formulation SG2 and TSG2 were considered to be the best formulation during the investigation. The tablets developed from spherical agglomerates of Indomethacin IP showed good in-vitro drug release profile as well as stability. The Crystallo-co-agglomeration may be suggested as s suitable method to prepare compressed tablets of Indomethacin IP.

HUMAN JOURNALS

www.ijppr.humanjournals.com

INTRODUCTION

The oral route is the most preferred option to administer drugs for systemic as well as local effects in the human body. Solid dosage forms such as tablets and capsules are the preferred class of products administered through the oral route. There are several advantages available for solid dosage forms such as good therapeutic effects, cost, ease of packing and shipment, product identification through monogram or engraving, stability, modification in release properties and patient compliance.[1] Tablets may be having slight advantage above capsule as a preferred solid dosage form for oral administration. The objective behind the design and development of compressed tablet is to deliver orally the correct dose of drug in proper form, at proper time and in the desired location with the ability to protect the chemical integrity. The formulation and manufacturing of tablets consist of critical steps such as granulation and compression. The properties of powder material involved in the formulation play a critical role in effective granulation and then onwards in compression into tablets. The tablets may be formulated by wet granulation, compression granulation and direct compression. The process such as wet granulation and compression granulation involves more steps and time to finish. The materials which are not stable under heat and moisture may not be suitable to process through more popular technique of wet granulation.[1,2] Until the late 1950's, the majority of tablets were produced in the world by means of granulation techniques and subsequent compression. The primary objective of granulation is to produce free flowing and highly compressible mixture of ingredients.

The excipients should show good flow, cohesion and lubricating properties under pressure to make such compacts. The availability of new forms of excipients and modified machineries as well as technologies allowed the possibilities to produce tablets by direct compression. The direct compression was long used to for the compression of single crystalline compound into a compact without the addition of other substances. The direct compression process has advantages such as lesser processing time and steps, reduced labor, lesser process validation, fewer chemical stability issues etc.[3, 4]

Crystallo-co-agglomeration (CCA) is an innovative technique developed with the intention to provide the drugs with good micromeritic and mechanical characteristics. The process of CCA involves crystallization followed by simultaneous agglomeration of the drug with the aid of a good solvent and/or a bridging liquid and a bad solvent. This process enables designing of spherical agglomerates containing low dose drugs which are poorly flowable

and compressible. The CCA require less processing time and may reduce the manufacturing as well as processing time during compression. The crystallo-co-agglomeration technique may be utilized to improve the micromeritic properties of powder materials utilized in direct compression. The resultant tablets may show improved crushing, compression, disintegration and dissolution profile when compared with the tablet utilizing other conventional methods.[5,6]

Non-steroidal anti-inflammatory drugs (NSAID) are the category of drugs used to treat inflammation, pain and related symptoms. Some of the low dose NSAID's exhibit poor compressibility and flow properties, hence may not be suitable candidate for direct compression process.[7] But by applying the crystallo-co-agglomeration technique, the attempt may be made to change the properties of these molecules to make them suitable candidates for direct compression. This investigation was aimed to utilize CCA process to develop spherical agglomerates of Indomethacin IP in selected polymers in different ratio. The developed spherical agglomerates of Indomethacin IP may exhibit improved micrometric and dissolution properties hence may be suitable for direct compression process.

MATERIALS AND METHODS

Materials

The sample of Indomethacin IP was supplied by Balaji chemicals, Ahmedabad. The polymers selected were polyethylene glycol 6000 (PEG 6000), polyvinyl pyrrolidone K30 (PVP K30). Ethyl acetate supplied by spectrum reagent and chemicals Pvt Ltd, Cochin. The distilled water was procured from distillation plant at Pariyaram Medical College, Pariyaram. All the chemicals and solvents used for the investigation were of analytical grade.

Methods

Preformulation studies

The drugs and excipients selected for the investigation were subjects for various preformulation studies such as drug- polymer interaction, melting point and loss on drying.[8,9]

Development of spherical agglomerates by CCA

The drug Indomethacin IP was dissolved in ethyl acetate and portion of the total amount of talc. This was added slowly to a solution of polymer in distilled water and talc. The resultant

mixture was stirred at 800 rpm for 20 minutes to form spherical crystals. The spherical crystals were filtered, washed and air dried.[10,11] A total of seven formulations were developed using different polymer solutions at varying concentration (Table No.1).

Table No. 1: Composition for the developed spherical agglomerates of Indomethacin IP

Ingredients	Formulation code						
	SG1	SG2	SG3	SG4	SG5	SG6	SG7
Indomethacin IP (gm)	0.025	0.025	0.025	0.025	0.025	0.025	0.025
PEG 6000 (gm)	-	0.100	0.200	-	-	-	-
PVP K30 (gm)	-	-	-	0.100	0.200	-	-
Blend at 1:1 ratio (gm)	-	-	-	-	-	0.100	0.200
Talc (gm)	0.200	0.200	0.200	0.200	0.200	0.200	0.200
Ethyl acetate (ml)	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Distilled water (ml)	qs	qs	qs	qs	qs	qs	qs

Evaluation of developed spherical agglomerates

Percentage yield of spherical agglomerates

The agglomerates were collected and weighed. The measured weight was divided by the total amount of all non-volatile compounds used for the formulation.[11]

Drug content estimation

The weighed quantity of spherical agglomerates was taken and triturated in distilled water. This solution was mixed with methanol and phosphate buffer solution (PBS) of pH 6.2 to produce 100 ml. Absorbance was measured using UV spectrophotometric method at 319 nm and drug content was estimated.[8]

Particle shape and surface morphology

Scanning electron microscopy (SEM) by Hitachi, Japan was used to determine the shape, size and surface morphology of developed spherical agglomerates.[10]

Determination of crystallinity

X-ray diffraction instruments by Philips analytical XRD with copper target was used to determine the crystallinity.[12]

Solubility analysis

The weighed quantities of spherical agglomerates were dispersed in distilled water taken in screw capped glass vials. The vials were shaken for two hours in a mechanical shaker. The concentration of drug was determined by UV spectrophotometric method at 319 nm.[8]

Determination of micromeritic properties

The bulk density, tapped density, compressibility index, Hausner ratio and angle repose were measured and calculated for the developed spherical agglomerates.[2]

In- vitro dissolution studies

The developed spherical agglomerates of Indomethacin IP (SG2 to SG7) was directly compressed as tablet and subjected for *in-vitro* dissolution studies using type-II USP dissolution apparatus. The dissolution study was carried out for 8 hours using PBS of pH 6.2 as medium.[10,12] The dissolution profile was compared against a tablet developed from spherical granules SG1.

Stability studies of developed spherical agglomerates

Accelerated stability studies for a period of 45 days were performed on best tablet formulation by using ICH guidelines with necessary modifications. The sample was tested for drug content and percentage drug released.[13]

RESULTS AND DISCUSSION

The IR spectrum of pure drug and physical mixture with excipients correspond to similar wave numbers. The study revealed that there was no interaction between drug and excipients, hence compatible to develop a safe and stable formulation. The melting point and loss on drying was measured at 156±0.5^{o}C and 0.2% respectively, which complies with IP standards.[9] The spherical agglomerates of Indomethacin IP were prepared by crystallo-co-agglomeration technique using three solvent system i.e. good solvent, bad solvent and

bridging liquid. The good solvent and bridging liquid used here was ethyl acetate and distilled water as bad solvent. The selection of these solvents depends on the miscibility of the solvents and solubility of drug in individual solvents. Talc was added to increase the bulk of the formulation. Upon addition of solution of drug to the polymer solution, the drug crystals precipitate out, resulting in the formation of spherical agglomerates. The speed of stirring may influence the size of developed spherical agglomerates. Hence optimization of speed may be essential during the investigation.[8]

The percentage yield of developed formulations was between 74.76 to 90.7 (Table No.2). The 2% talc has contributed towards the satisfactory yield of the product. The formulation SG2 with 100 mg of PEG 6000 was reported with highest percentage yield. The investigation pointed out a possibility of reduction in percentage yield with an increase in polymer concentration.[6] All the developed formulations of spherical agglomerates were reported with good percentage drug content. The highest percentage drug content of 95.01 was reported with formulation SG2 (Table No.2).

Table No. 2: % Yield and Drug content of developed spherical agglomerates

Formulation code	Percentage yield	Percentage drug content
SGI	88.0	90.4
SG2	90.7	95.01
SG3	87.6	91.9
SG4	84.54	93.2
SG5	74.76	92.8
SG6	84.62	94.06
SG7	79.47	92.3

The SEM photographs of pure Indomethacin IP suggested the possible sharp needle like fine crystals (Fig No.1), which was converted to compact spherical agglomerates by the process of Crystallo-co-agglomeration (Fig No.2).

The smooth surface and spherical shape of the developed agglomerates may impart good flow and circularity factor ranging between 1 to 1.001. The optimized speed of stirring may increase the impact energy for collision of particle with turbulence, resulting in dense and compact agglomerates.[8]

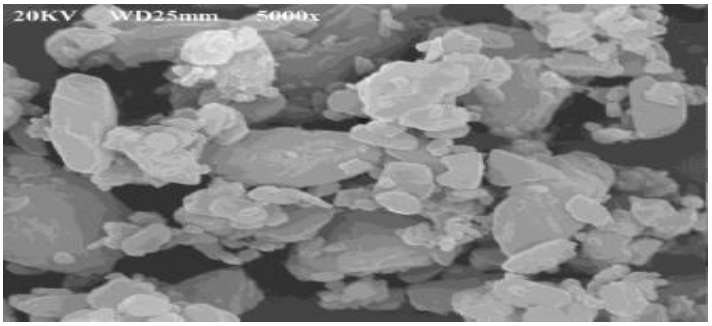

Fig No. 1: SEM for pure Indomethacin IP

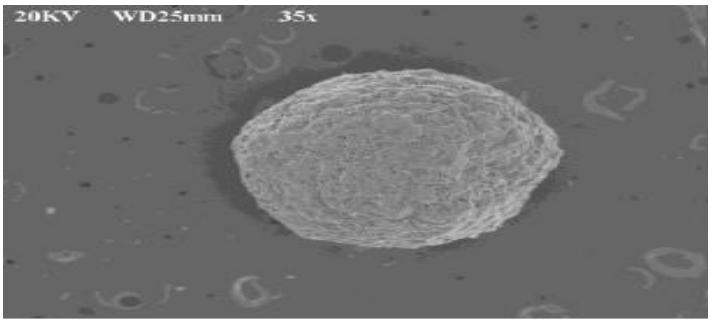

Fig No. 2: SEM for spherical agglomerate of Indomethacin IP with PEG 6000

The powder X-ray diffraction pattern (PXRD) for pure Indomethacin IP showed intense peaks, which was transformed to halo pattern with less intense and dense in case of spherical agglomerates. This suggested the possible decrease in crystalline nature or partial amorphous nature of developed spherical agglomerates.[6] The intensity of peaks found to be reduced more significantly with spherical agglomerates of PEG 6000.

As per the solubility studies, developed spherical agglomerates of Indomethacin IP had superior solubility profile than pure drug which was poorly water soluble. The solubility of developed spherical agglomerates found to differ with polymers as well as their concentration. The formulation SG3 with 0.200 gm of PEG 6000 was reported with highest solubility. As the concentration of polymer was increased, the solubility of spherical agglomerate was increased.[13] The enhanced solubility of SG3 may be because of superior wetting properties of PEG 6000.

The developed spherical agglomerates were analyzed for their micromeritic properties to confirm their flow property and compressibility. The angle of repose for pure drug was 45.012^{o}, which was reduced up to 18.133^{o} for spherical agglomerates. The reduced angle of repose confirms the improved flow property of developed spherical agglomerates. The Hauser's ratio and Carr’s index values for the developed spherical agglomerates were less

than 1.25 and 15 % respectively. These two parameters further confirmed the good flow property expected from developed spherical agglomerates of Indomethacin IP. The bulk and tapped densities of developed spherical agglomerates were lower than pure Indomethacin IP which may support for their good compressibility property.

The conversion of sharp needle like crystal structure of pure indomethacin IP into more compact as well as dense spherical agglomerates was the reason behind improved micromeritic properties, which may contribute towards effective direct compression process with low dose, poorly water soluble and sharp crystalline drug like Indomethacin IP.[13]All the developed formulations of spherical agglomerates were subjected for direct compression to prepare tablets. The formulation SG1 was the only exception since it was not a spherical agglomerate by crystallo-co-agglomeration technology, hence it was compressed using compression granulation technology. The prepared tablets were subjected to *in-vitro* dissolution study for 8 hours using PBS of pH 6.2 as medium.[13] The *in-vitro* drug release profile of the directly compressed tablets containing spherical agglomerates of Indomethacin IP was analyzed (Table No.3 & Fig No.3).

Table No. 3: % Drug release from compressed tablets from developed formulations

Time (Minutes)	Percentage drug release					
	TSG2	TSG3	TSG4	TSG5	TSG6	TSG7
0	0.00	0.00	0.00	0.00	0.00	0.00
5	20.20	18.00	15.60	13.40	17.00	14.80
15	31.98	29.04	27.38	24.44	28.78	25.84
30	40.70	38.50	36.10	33.90	37.50	35.30
45	48.54	46.80	43.94	42.20	45.34	43.60
60	53.30	51.64	48.70	47.04	50.10	48.44
120	57.01	55.34	52.41	50.74	53.81	52.14
180	61.30	59.70	56.70	55.10	58.10	56.50
240	65.79	62.90	61.19	58.30	62.59	59.70
300	69.86	66.56	65.26	61.96	66.66	63.36
360	72.75	69.25	68.15	64.65	69.55	66.05
420	75.70	72.35	71.10	67.75	72.50	69.15
480	77.39	74.96	72.76	70.36	74.19	71.76

The tablet TSG2 with PEG 6000 released maximum percentage of drug. The highest percentage of drug released from TSG2 was 77.39 at the end of 8 hours. The formulation TSG4 and TSG6 with PVP K30 and 1:1 blend of polymers respectively showed 72.76 % and 74.19 % of drug release in 8-hour duration .[13] The drug release profile of directly compressible tablets were compared against the percentage drug release obtained from Indomethacin IP tablets developed using compression granulation technology (TSG1).The formulation TSG1 was able to release 61.89% of drug after the completion of 8-hour dissolution study. As per the findings from *in-vitro* dissolution study, it was evident that optimization of the concentration of polymer is required to avail maximum percentage drug release.[13]

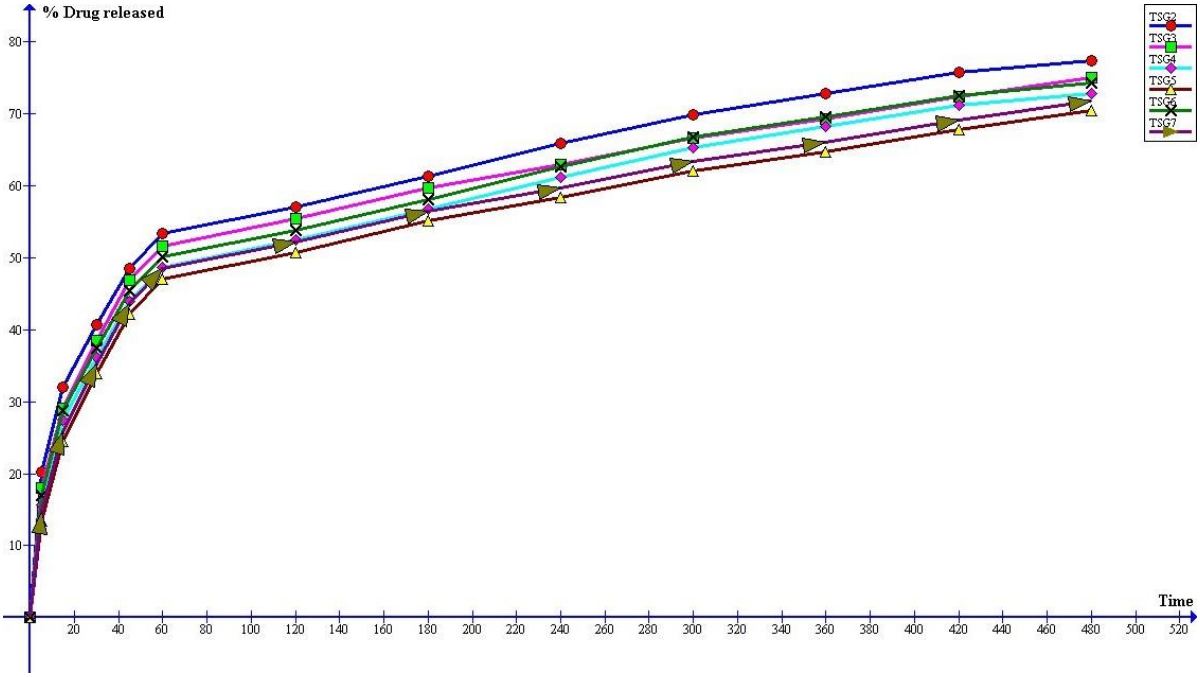

Fig No. 3: Drug release profile from tablets prepared from spherical agglomerates

The results suggested that polymer quantity at 0.100 gm was able to provide best overall performance for the spherical agglomerates as well as compressed tablets. The evaluation of all available data from this investigation suggested that formulation TSG2 with spherical agglomerates from 0.100 gm of PEG 6000 may be the best formulation developed. Hence was subjected for stability studies. The stability studies were performed to determine the shelf life and suitable storage conditions for a product. The best formulation TSG2 was subjected for accelerated stability studies in accordance with ICH guidelines with necessary modifications. The studies were carried out under 40±2^{o} C and 75±2 % RH for a period of 45

days. The percentage drug content and percentage drug release (after 8 hours) remained unchanged after the period of 45 days. Hence, the directly compressible tablet from spherical agglomerates of Indomethacin IP may be recommended as a stable product.

CONCLUSION

The crystallo-co-agglomeration technique to develop the spherical agglomerates of Indomethacin IP may be possible. The developed spherical agglomerates were having good yield, percentage drug content, excellent micromeritic properties enabling them to be compressed directly as a stable tablet. The tablets developed from spherical agglomerates of Indomethacin IP proved to be a successful product in terms of good *in-vitro* drug release profile as well as stability. Hence crystallo-co-agglomeration may be suggested as a suitable method to develop stable and effective directly compressed tablets of Indomethacin IP. The possibilities of utilizing this technology develop sustained and controlled release solid dosage forms may be wide open.

REFERENCES

1. Leom L, Herbert L. The Theory and Practice of Industrial Pharmacy.4th ed. New Delhi: CBS Publishers and Distributers; 2013.
2. Shangraw R F. Compressed Tablets by Direct Compression Granulation Pharmaceutical Dosage Forms: Tablets Vol-1. 2nd ed. USA: Marcel Dekker; 1989.
3. Ankita C, Pramod Kumar S, Mayank B. A review on recent advancement in crystallo-co-agglomeration, Advances in biological research. 2011; 5(6):273-281.
4. Christy MJ, Lekshmi P, Licey C, Bijin. Crystallo– Co-Agglomeration: An Innovative Technique for Size Enlargement and Improved Flow Properties of Powders. RRJMS. 2013; 1(2).
5. Pawar AP, Paradkar AR, Kadam SS, Mahadik KR. Agglomeration of Ibuprofen with Talc By Novel Crystallo Co-Agglomeration Technique. AAPS Pharm Sci Tech. 2004 ;5:30-35
6. Pawar AP, Paradkar AR, Kadam SS, Mahadik KR. Crystallo Co-Agglomeration: A Novel Technique To Obtain Ibuprofen-Paracetamol Agglomerates. AAPS Pharm Sci Tech. 2004; 5 : 57-64
7. Johnson JL, Wimsatt J, Buckel SD, Dyer RD, Maddipati KR. Purification and characterization of prostaglandin H synthase-2 from sheep placental cotyledons. Arch Biochem Biophys. 1995;324(1):26-34.
8. Bose PC, Saritha D, Varma VK, DathrikaSK. Influence of various bridging liquid on spherical agglomerates of Indomethacin. International Journal of Research in Pharmaceutical Sciences. 2011; 2(2):147-157.
9. Indian Pharmacopeia. Vol 2. New Delhi: Controller of Publications Ministry of health and family well fare Government of India; 2007.
10. Khan AA, Sarfaraz MD, Doddayya H. Design and evaluation of Aceclofenac fast dissolving tablets prepared by crystallo-co-agglomeration technique. IJPPS. 2011; 3(4):116-123.
11. Mudit D, Keshavarao KP, Krishna NV, Lavanya D, Anil G. Enhancing solubility and dissolution of Indomethacin by freeze drying. IRJP. 2011; 2(6):69-74.
12. Kulkarni PK, Dixit M, Jain A. Spherical agglomeration of Naproxen by solvent change method. S J Pharm Sci. 2011;4(1):1-8.

13. Sarfaraz, MD, Khan AA, Doddayya H,Reddy SR,Udupi RH. Particle design of Aceclofenac disintegrant agglomerates for direct compression by crystallo-co-agglomeration technique. Asian J. Pharm. Tech. 2011;1(2):40-48.