RESEARCH ARTICLE

Standarization and optimization of micromeretic properties of nimesulide for processing into a tablet dosage form by crystalo-co-agglomeration technology

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The present study was undertaken to prepare direct compressible tablets of nimesulide by altering its physical properties with the help of the method crystallo-co-agglomeration technology. Nimesulide is a widely used nonsteroidal anti-inflammatory drugs type of drug and is very useful in the treatment of arthritis. Because of its poor flowability character, tablets of nimesulide cannot be prepared by direct compression. An attempt has been taken to improve the tableting property by altering the micromeretic properties, like flow rate, Carr index, Hausner ratio and angle of repose. Conformation of improvement of compressibility and other processing problems was studied by Heckel analysis and Kawakita constant using a hydraulic press under a pressure of 0.5, 1, 2 and 4 tonnes for 10 s. The tablets were prepared by direct compression of nimesulide agglomerates using two different types of polymers, polyethelene glycol (PEG6000) and ethyl cellulose (EC) in different ratios (50, 100 and 200 mg). The drug release shows different patterns for the various percentages of PEG and EC.

Key words: *Crytallo-co-agglomarates, Heckel analysis, Kawakita constant, micromeretic properties*

INTRODUCTION

Nimesulide, 4-nitro-2-phenoxy methane sulfonaanilide, is a highly effective nonsteroidal anti-inflammatory and analgesic drug with a high gastrointestinal tolerability and minimum drug-related side-effects.[1] It can also be used in retard Alzheimer disease.[2] Its plasma half-life is just 2-5h, which calls for frequent administration. The dose of nimesulide is 100 mg/bd. In view of the easy availability of the drug, nimesulide has been selected for the present research work. The same can be done by other drugs also, dependent on the formation of agglomerates.[3-4] Tablets prepared by a direct compressional method are always preferable in industry by the point of profitability. Nimesulide has a poor flow property and unsatisfactory micromeretic properties. Here, an attempted has been taken to alter the physical characteristics of nimesulide by a novel crystallo-co-agglomeration technology.[5] Dichloromethane (DCM) is used to prepare the agglomerates as a bridging liquid.[6-7] Polyethylene glycol (PEG) and ethyl cellulose (EC) in different ratios were used to sustain the drug release for prolonged therapy and to minimize the frequency of the doses. All the micromeretic properties, like flow rate, Carr index, Hausner ratio and angle of repose, were found to be satisfactory with the nimesulide agglomerates. Heckel analysis[8-9] and Kawakita constant[10] proves the better compressibility.

MATERIALS AND METHODS

Nimesulide was obtained as a gift sample from Dr. Reddys Lab, Hyderabad, India; PEG and EC were obtained from Ranbaxy Fine Chemicals Ltd., New Delhi, India. All other chemicals used were of analytical reagent grade.

Preparation of agglomerates

Pure nimesulide (6 g) is dissolved using DCM as a solvent. DCM is used as a bridging liquid also. The two selected polymers are PEG 6000 and EC, which were added in three different ratios. Then, the mixture was stirred under a mechanical stirrer (Remy) for 15 min at 100 rpm at room temperature. After evaporation of DCM, a specific amount of 10% dextrose solution was

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added to the mixture and then stirred for 800 rpm for 30-40 min. After formation of agglomerates, it was kept for drying under room temperature for 24 h.

Micromeritic study

Dried agglomerates were sieved through a 16-number mesh and were evaluated for their flow properties through a funnel using the glass funnel specified in the European Pharmacopoeia-III. The flow rate (g/s) was calculated from the time needed for the entire sample (40 g) to empty from the funnel. Bulk density was calculated from the amount of agglomerates poured into a 100 ml graduated cylinder up to a total volume of 50 ml, whereas for the tap density determination, the cylinder was tapped 20-25 times with a standard tapped density apparatus. The number of attempts for each experiment was 10. The mean value has taken for the calculation. Based on bulk and tapped density, both the Carr Index (%) {(tapped-bulk) $\times$100/tapped} and the Hausner ratio (tapped/bulk) were calculated. Angle of repose was determined by the fixed funnel method. The materials were carefully poured through the funnel until the apex of the conical pile so formed just touched the tip of the funnel. The mean diameter (2R) of the base of the powder cone was determined and the tangent of the angle of repose is given by tan θ = H/R, where θ is the angle of repose.

Determination of Heckel analysis and Kawakita constant

The compressibility of a powder bed could be obtained from the relationship between porosity and applied pressure.

Compact compression was performed on a hydraulic press. Four different compaction forces (from 0.5, 1, 2 and 4 tonne) were used for each material. The total time of compression (dwell time) was 1 min for all the materials. For each compact, 400 mg of pure drug powder was weighed on an analytical balance and then manually filled into the die. A flat-faced punch with a diameter of 6.5 mm was used. Cracking was observed when more than 4 tonnes of pressure was used. For each compression, the number of attempts was 20.

Each compact was weighed accurately and its dimensions (diameter and thickness) were measured with a screw gauge. This information was used for calculating the relative density, porosity and degree of volume reduction, which are essential parameters for the Heckel analysis.

All the values were taken after 24 h of the compression.

The Heckel equation is $= \text{In}\frac{1}{1-D} = KP + A$

Where "D" is the relative density of a powder compact at pressure "P."

"K" is the measure of plasticity of a compressed material.

"A" is related to the die filling and particle rearrangement before deformation of the particles.

"K" and "A" are constants obtained from the slope and intercept of the plot $\text{In}\frac{1}{1-D}$ vs. "P."

Yield strength: Yield strength (Y) can be determined from the Heckel equation.

$K = \frac{1}{3}Y$ or $Y = 3K$

Yield strength determination is important to standardize the experimental conditions, such as tablet dimensions and speed of compaction.

The Kawakita equation is $\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}$

Where "C" is the degree of volume reduction of a powder compact at pressure "P."

"a" value is the indication of the total volume reduction for the powder bed.

"b" is a constant that is inversely related to the yield strength (Y) of the particle.

"a" and "b" can be evaluated from a plot of P/C vs. P.

Yield Strength: Yield strength (Y) can be determined from the Kawakita equation:

$a = \frac{1}{3}Y$ or $Y = a3$

Preparation of the tablets

The agglomerates were lubricated with 1% w/w talc and directly compressed to tablets weighing 176 mg each [Table 1] using 6.5-mm round, flat and plain punches on a ten station (Rimek tablet punching machine, Karnavati Engg. Pvt. Ltd., Ahmedabad, India) tablet punching machine. For each formulation, the batch size was 50.

RESULTS AND DISCUSSION

Flow properties of the agglomerates determined as good flowability is as per theoretical value for the preparation of tablets with an acceptable weight variation. For all the formulations, the flow rate of the agglomerates was between 5 and 7 g/s. According to the literature, excellent flow properties are seen for powders with a Carr index between 5 and 15% and a Hausner ratio below 1.25.[11] All the formulations tested [Table 2] had a Carr index ranging between 7 and 13%, whereas the Hausner ratio was below 1.25. The angle of repose was found to be between 20 and 25.

Angle of repose, Carr index and Hausners ratio show a

remarkable improvement in flowability for nimesulide agglomerates.

For the Heckel and Kawakita analyses, the greater slopes (K) and "a" value indicated a greater degree of plasticity of the material. From the Heckel equation, the greater K value or plasticity indicates resistance toward fracturing of tablets or resistance from capping during long-term storage. For Kawakita equations, the greater value of "a" indicates a greater volume of reduction. The significance of a greater value of volume of reduction is considered to describe the satisfactory compressibility of a powder. From Tables 3 and 4, it can be observed that the "K" value for Heckel plot and the "a" value for Kawakita plot are significantly grater for nimesulide agglomerates prepared with PEG and EC, which indicates that the formulations have higher yield strength values, a major parameter for tableting properties.

Figures 1 and 2 represent the comparative plot for Heckel and Kawakita analyses between the different formulations of nimesulide. It can be observed that for both analyses, the polymer-based formulations achieved the best-fitting curve respect of their value of slopes.

A dissolution study was carried out with the prepared tablets using a USPXXIV dissolution test apparatus Type II as per the monograph on formulations F1-F5. From the dissolution profile [Figure 3], it can be seen that the F2 and F3 formulations show a similar release pattern. The F5 formulation shows slow drug release. The F6 formulation shows maximum extended drug release with EC-based

Table 1: Composition of tablets containing polyethylene glycol 6000 and ethyl cellulose as the sustained release polymer

Ingredient	F1	F2	F3	F4	F5	F6
Nimesulide (mg)	100	100	100	100	100	100
Dextrose (mg)	75	74	73	75	74	73
PEG 6000 (mg)	1	2	3	-	-	-
EC (mg)	-	-	-	1	2	3
Talc (%)	1	1	1	1	1	1
Total weight of the tablet (mg)	176	176	176	176	176	176

For F1, F2 and F3, PEG 6000 = 1, 2 and 3 mg, respectively, and for F4, F5 and F6, EC is 1, 2 and 3 mg, respectively. The total tablet weight is kept at 176 mg, PEG, EC

Table 2: Comparative studies of micromeritic parameters between nimesulide pure powders and agglomerates

Results for powder and agglomerates	Angle of repose (in degree)	Carr index (%)	Hausner ratio
Nimesulide pure powder	47–49	15–17	2.23–2.30
Nimesulide agglomerates	20–25	7–13	1.05–1.10

Table 3: Measurement of Heckel analysis using hydraulic press

Powder	Pressure in tonnes	K	a	Y
Pure nimesulide	0.5	0.0013	0.0368	0.0039
	1			
	2			
	4			
Nimesulide with PEG 6000	0.5	0.0056	0.0335	0.0168
	1			
	2			
	4			
Nimesulide with EC	0.5	0.0055	0.0355	0.0162
	1			
	2			
	4			

PEG 6000, polyethylene glycol; EC, ethyl cellulose. Heckel analysis showed an improvement in yield strength (Y) for both PEG and EC-based agglomerates

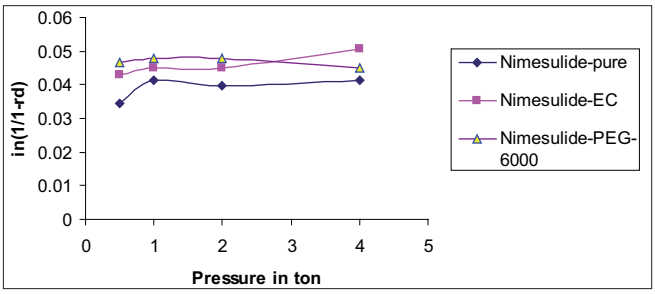


Figure 1: Comparative plot for Heckel analysis between pure nimesulide, nimesulide–ethyl cellulose agglomerates and nimesulide–polyethylene glycol 6000 agglomerates

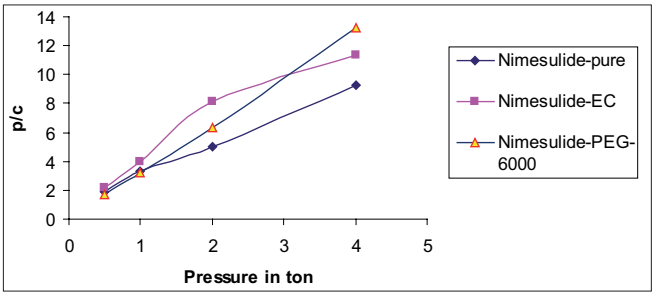
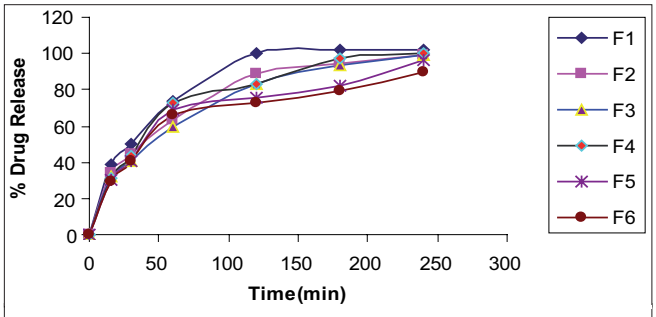


Figure 2: Comparative plot for Kawakita analysis between pure nimesulide, nimesulide–ethyl cellulose agglomerates and nimesulide–polyethylene glycol 6000 agglomerates



F1 – Nimesulide with 1 mg PEG 6000; F2 – Nimesulide with 2 mg PEG 6000;
F3 – Nimesulide with 3 mg PEG 6000; F4 – Nimesulide with 1 mg EC;
F5 – Nimesulide with 2 mg EC; F6 – Nimesulide with 3 mg EC.

Figure 3: Comparative *in vitro* release profiles of pure nimesulide with different formulations of agglomerates of nimesulide

Table 4: Measurement of Kawakita constant using a hydraulic press

Powder	Pressure in tonnes	a	b	Y
Nimesulide	0.5	2.0584	0.0989	6.1752
	1			
	2			
	4			
Nimesulide with PEG 6000	0.5	2.7937	0.1562	8.3811
	1			
	2			
	4			
Nimesulide with EC	0.5	2.7835	0.1569	8.3833
	1			
	2			
	4			

PEG 6000, polyethylene glycol; EC, ethyl cellulose. Kawakita analysis showed an improvement in yield strength (Y) for both PEG and EC-based agglomerates

agglomerates. Among other formulations, F1 and F4 show relatively faster drug release. It has been observed that the cumulative percentage drug release decreased with increasing the proportion of polymer ratio. The testing was carried out in triplicate.

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REFERENCES

1. Singla AK, Chawla M, Singh A. Nimesulide: Some pharmaceutical and pharmacological aspects and update. J Pharm Pharmacol 2000;52: 467-86.
2. Lipsky PE. The clinical potential of cyclooxygenase-2-specific inhibitors. Am J Med 1999;106:51-7.
3. Kawashima Y, Takeuchi H, Niwa T, Hino T, Kihara K. Development of a emulsion-solvent-diffusion preparation method of agglomerated crystals for direct tableting and evaluation of their compressibility's. J Soc Powder Technol 1989;26:659-65.
4. Kawashima Y, Aoki S, Takenama H, Miyake Y. Preparation of spherically agglomerated crystals of aminophylline. J Pharm Sci 1984;73:1407-9.
5. Pawar AP, Paradkar AR, Kadam SS, Mahadik KR. Crystallo-co-agglomeration: A Novel Technique to Obtain Ibuprofen-Paracetamol Agglomerates. AAPS PharmSciTech 2004;5:e44.
6. Kawashima Y, Okumara M, Takenaka H. The effect of temperature on the Spherical crystallization of salicylic acid. Powder Technol 1984;39: 41-7.
7. Paradkar AR, Pawar AP, Chordiya JK, Patil VB, Ketkar AR. Spherical crystallization of celecoxib. Drug Develop Ind Pharm 2002;28:1213-20.
8. Sun CC. A material sparing method for simultaneous determination of true density and powder compaction properties: Aspartame as an example. Int J Pharm 2006;326:94-9.
9. Gonnissen Y, Remon JP, Vervaet C. Development of directly compressible powders via co-spray drying. Eur J Pharm Biopharm 2007;67:220-6.
10. Zhang Y, Law Y, Chakrabarti S. Physical properties and compact analysis of commonly used direct compression binders. AAPS PharmSciTech 2003;4:e62.
11. Wells JI, Swarbrick J, Boylan JC. Encyclopedia of pharmaceutical technology. Vol-14, New York: Marcel Dekker; 1997. p. 401-18.

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