INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

FORMULATION AND EVALUATION OF IBUPROFEN GRANULES WITH PEG 6000 CARRIER

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ABSTRACT

Ibuprofen granules were prepared with the objective of solubility and dissolution improvement using PEG 6000 carrier by wet granulation technique[1]. The flow ability and *in vitro* dissolution studies showed remarkable improvement in solubility and drug dissolution of these ibuprofen with PEG 6000 granules and physical mixtures over pure ibuprofen with starch granules.[2,3] This study concluded that the improved flow ability as well as drug dissolution of these ibuprofen granules using PEG 6000 may be attributed to improved wettability and reduction in drug crystallinity, which can be modulated by appropriate level of hydrophilic carriers.[3] The properties of ibuprofen related to the biopharmaceutics classification system (BCS), Ibuprofen were assessed to be a BCS class II drug. Differences in composition and/or manufacturing procedures were reported to have an effect on the rate, but not the extent of absorption; such differences are likely to be detectable by comparative in vitro dissolution test.[4]

Keywords: Ibuprofen, flow ability, wettability, dissolution, polyethylene glycol.

1. INTRODUCTION

Wet granulation is the most widely used granulation method. It is almost suitable for all drugs except moisture or heat sensitive drugs, because this technique requires liquid binder and drying step.[5] In roll compaction process the powder is fed between two counter rotating rolls and compacted to dense ribbons. The produced ribbons are subsequently broken into granules. In most cases roll compaction is performed prior to tableting.[5] There are several process factors affecting the properties of produced granules by wet granulation and the Resulting tablets for example: tablet strength[3], friability[4], dissolution[4], solubility[2], wettability[2] etc.

1.1 In Vitro Dissolution Studies[5,6]

In vitro dissolution studies are done to find out dissolution behavior. The in-vitro dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through in vitro – in vivo correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed in-vivo dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately.

1.2 Solubility Studies

Solubility studies are done for the finding out the solubility behavior shown by the solid dispersion system in different types of solvent system and body fluids.[7, 8]

1.3 PREFORMULATION STUDIES OF IBUPROFEN

The preformulation studies include the physicochemical characterization of the drug and excipients which are useful in formulation or dosage form[9].

1.3.1 GENERAL CHARACTERISTICS [10, 11]

Ibuprofens chemical name is (RS)-2-(4-Isobutylphenyl) propionic acid and its structure

shown in Figure 1. The drug is usually administered as the racemic compound, but preparations containing only the S-enantiomer (dexibuprofen) are available in some countries, for instance in Finland (FI). Ibuprofen is usually given as the free acid but various salts, esters, and other complexes are also used. These include lysine and sodium salts, guaiacol and pyridoxine esters, isobutanolammonium and meglumine derivatives. In this monograph, ibuprofen is understood to be the free acid in the racemic form, unless otherwise indicated.

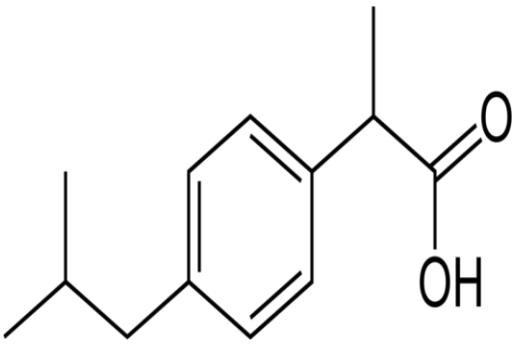


Fig. 1: Structure of ibuprofen

1.3.2. Therapeutic Indication and therapeutic Index

Ibuprofen is a well-known and widely used non steroidal anti-inflammatory drug (NSAID). Theracemic compound is regarded a nonselective cyclooxygenase (COX)-inhibitor.[11] The S- enantiomer was found to be a selective COX-1 inhibitor while R-ibuprofen has little pharmacodynamic efficacy. Racemic ibuprofen and the S-enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhoea, headache, migraine, postoperative, and dental pain and in the management of spondylitis, osteo-arthritis, rheumatoid arthritis, and soft tissue disorders.[11, 12] Ibuprofen has also antipyretic properties. Ibuprofen is regarded one of the safest NSAIDs available.[13]

1.3.3. Pharmacokinetic Properties[14]

1.3.3.1 Absorption and Permeability

Permeability was observed because NSAIDs promote their own transport. This observation may possibly explain the GI side effects and the damage of the GI membrane following oral administration of high doses or upon long term oral usage of ibuprofen.[14] Similar to other NSAIDs, high permeability of ibuprofen and its enantiomers has been observed in rats, where increased GI permeability was observed because NSAIDs promote their own transport.[15] This observation may possibly explain the GI side effects and the damage of the GI membrane following oral administration of high doses or upon long term oral usage of ibuprofen. High permeability of ibuprofen and its enantiomers has been also observed in Caco-2 cell cultures.[15]

1.3.4. Pharmacokinetics

Linear pharmacokinetics of ibuprofen has been reported in the dose range of 200–400 mg. At doses higher than 400 mg nonlinearity has been reported, but this is more likely due to changes of plasma protein binding than reduced absorption.[14,15] Dose linearity in the absorption of S-ibuprofen in the dose range of 200–600 mg has also been documented. Ibuprofen is extensively bound to plasma proteins (99%) R- ibuprofen, undergoes systemic unidirectional inversion to S-ibuprofen, which is known to be the main pharmacodynamically active moiety.[15] Besides the extensive enantiomeric metabolic inversion of the active S-ibuprofen, there are no known metabolites of ibuprofen, which are pharmacologically active.[16] Hepatic biotransformation results in two inactive main metabolites (2-hydroxy-2-methylpropyl) phenylpropionic acid and (2-carboxypropyl) phenylpropionic acid, which are excreted either free or as conjugates in urine.[16]

1.4. Physicochemical Characteristics

1.4.1. Solubility

In the literature only data at 208 ℃ or room temperature were found.[16] BCS classification requires data on the solubility at 378℃, these values were experimentally determined, for each media in triplicate.[17] Ibuprofen drug substance was suspended in medium and stirred for 24 hr. at 378 ℃ and then stored for a further 24 hr. without agitation.[17] In each case sediment on the bottom of the flask was observed. The ibuprofen concentration in the clear supernatant was determined by UV-analysis.[17]

1.4.2. Polymorphism

Ibuprofen does not exhibit genuine polymorphism. However, it has a tendency towards slight crystal lattice modification, which may affect also its dissolution behavior.[18]

1.4.3. pKa

The pKa of ibuprofen is in the range of 4.5-4.6[18]

1.4.4. Density

Powder flow, compressibility, dissolution and other properties may dependent on density.[19]

1.4.4.1. Bulk density

The term bulk density refers to a measure used to describe a packing of particles. It is (gm/ml) and was determine using a balance and measuring cylinder.[19] Initially the weight of the measuring cylinder was tarred. Then, 4 gm presieved (40) bulk drug were poured into the measuring cylinder using a funnel. Then volume of the powder was taken. Bulk density of the granules was calculated using following formula.[19, 20]

Bulk density = Weight of powder / Volume of powder

1.4.4.2. Tapped density

Tapped density is determined by placing a graduated cylinder containing same mass of powder used for B.D. on a mechanical tapper apparatus which is operated for a fixed number of taps (approx500) until powder bed volume has reached a minimum.[20]

Tapped density = Weight of powder / min. volume of powder

1.4.5. Carr's Index (CI)

Tapped and bulk density measurements can be used to estimate the carr's index of a material. Carr's index was determined by,[20]

Carr's index (%) = [(Tapped density – bulk density)/tapped density] * 100

1.4.6. Hausner's ratio (HR)

It is stated by Hausner. It was calculated as follows:[20]

Hausner's ratio = Tapped density / Bulk density

1.4.7. Angle of repose (Tan θ)

Angle of repose is the tan inverse of angle between height (h) of pile of powder and the radius (r) of the base of conical pile.[19,20] It can be obtained between the freestanding surface of the powder heap and the horizontal plane. The fixed funnel that is secured with its tip at a given height h, above graph paper, placed on the flat horizontal surface.[20] Powder is carefully poured through funnel until the apex of conical pile just touches the tip of funnel.[20]

02. AIM

2.1 To enhance the flowability properties of Ibuprofen granules by wet granulation.

2.2 To improve the dissolution of Ibuprofen granules by increasing its wettability.

2.3 To compare the flowability and dissolution characters of pure drug, physical mixtures and prepared granules.

03. EXPERIMENTAL WORK[19,20]

3.1. Procedure for Bulk Density and Tapped Density [19, 20]

Approximately 100 ml of powder (Vb) was gently poured into a tarred graduated measuring cylinder and the initial volume (bulk density db) and weight of the material (M) was recorded. The graduated cylinder was placed on a tap density tester and the final volume was recorded after 200 taps (Vt). The data obtained were used to calculate bulk density and tap density of the powders which were used to determine the percent compressibility index (I). Lower compressibility values represent better flow.

3.2. Procedure for Dissolution Study[19,20] :

Dissolution study was carried out by dissolution apparatus (VEEGO VDA-8DR paddle method) dissolution study was carried out at a rotation speed of 100 rpm in 900 ml phosphate buffer (pH 6.8 with 0.2 M) maintained at 37°C. Sample of 5 ml ware taken at 15 min. intervals. The concentration of Ibuprofen was determined using UV spectroscopy at 221 nm[21].

3.3. Procedure for Physical Mixture [19,20]

For physical mixture of Ibuprofen and polymer (PEG 6000) in powder form were triturated and mixed in mortar and pestle. Then they were passed through sieve mesh no.35. The prepared physical mixtures were in the ratios Ibuprofen: PEG 6000- 1:1, 1:2, 1:4. Determination of Dissolution studies for physical mixtures are reported in Table no.5

3.4. Procedure for Granules [19,20]

The granules were prepared by Wet Granulation and kept at 50-60°C for 2 hrs and then cooled at room temperature to dry out totally. The prepared granules were milled to pass through sieve mesh no.35. Determination of dissolution studies for granules are reported in Table no.5 [22]

3.5. Procedure for Angle of Repose [19,20]

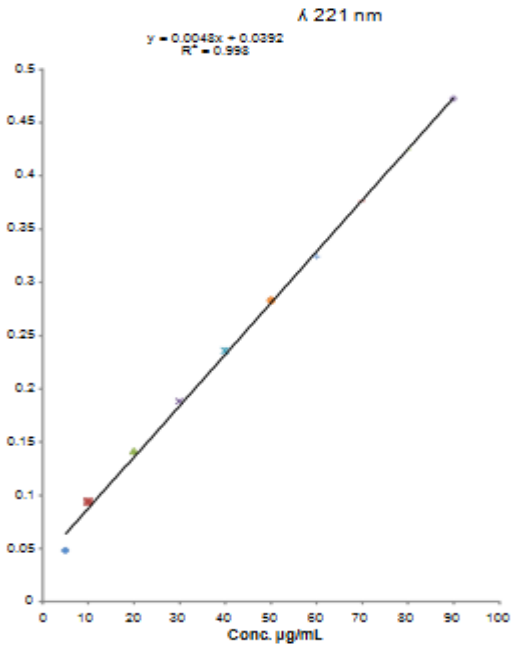
Approximately 15 g of powder was poured through a stainless steel funnel from a height of 6 centimeters onto a level bench top. The angle that the side of the conical heap made with the horizontal plane was recorded as the angle of repose. Lower angle of repose values represented better flow.

3.6. UV SPECTROPHOTOMETRIC ANALYSIS[22,23]

100 mg drug was dissolved in 100ml of ethanol. 1 ml of this stock solution (A) was added to 100 mL volumetric flask and volume made up with PBS pH 6.8, it was then analyzed for λmax. Standard dilutions and observed absorbances are reported below in Table 4.

Table 4: Standard Dilutions and Absorbance

Conc. (µg/mL)	Abs @ 221 nm
5	0.0481
10	0.0939
20	0.1416
30	0.1881
40	0.2357
50	0.2829
60	0.3242
70	0.3763
80	0.4244
90	0.4725



Graph of Abs v/s conc

04. RESULT AND DISCUSSION

Table 5: For Physical Mixture (IBU:PEG 6000)

Conc.	Abs	Drug Release
1:1	0.0629	15.686 µg/mL
1:2	0.0697	15.686 µg/mL
1:4	0.0739	18.436 µg/mL

Table 6: For Granules

Conc.	Abs	Drug Release
1:1	0.1747	43.636µg/mL
1:2	0.2398	59.911µg/mL
1:4	0.3692	91.910µg/Ml

Table 7: Bulk density, tapped density, Carr's index, Hausner's ratio, Angle of Repose determination from physical mixture of Ibuprofen and PEG 6000.

4.1 FOR PHYSICAL MIXTURES

Table 7:

Parameters	units	1:1	1:2	1:4
Bulk Density	g/cm^3	0.365	0.390	0.440
Tapped Density	g/cm^3	0.549	0.588	0.631
Carr's Index	%	33.5	33.67	30.26
		(23-35) poor	(23-35) poor	(23-35) poor
		flow	flow	flow
Hausner's Ratio	---	1.5	1.50	1.43
		(1.4-1.5) fair flow	(1.4-1.5) fair	(1.4-1.5) fair
			flow	flow
Angle of Repose	θ	41°32'	38°41'	35°55
		(40-45) poor	(35-40) fair	(35-40) fair
		flow	flow	flow

Table 8: Bulk density, tapped density, Carr's index, Hausner's ratio, Angle of Repose determination from Granules of Ibuprofen and PEG 6000.

4.2 FOR GRANULES

Table 8:

Parameters	Units	1:1	1:2	1:4
Bulk Density	g/cm^3	0.480	0.500	0.510
Tapped Density	g/cm^3	0.631	0.666	0.675
Carr's Index	%	30.26	24.92	24.44
		(23-35) poor flow	(23-35) poor flow	(23-35) poor flow
Hausner's Ratio	----	1.36	1.33	1.32
		(1.3-1.4) good flow	(1.3-1.4) good flow	(1.3-1.4) good flow
Angle Of Repose	θ	33°12'	32°24'	32°24'
		(30-35) good flow	(30-35) good flow	(30-35) good flow

Preliminary test for Drug

Test	Result
Colour	White Powder
Odour	Not

5. CONCLUSION

1. Ibuprofen granules were prepared using PEG 6000 as a carrier to improve physicochemical characteristics and dissolution profile of Ibuprofen.
2. Wet Granulation technique was found to be effective in increasing the aqueous solubility of Ibuprofen.
3. In vitro dissolution studies showed that in the granules by Wet Granulation containing PEG 6000 as a carrier gave faster dissolution rate than physical mixtures
4. The granules were dissolving at faster rate (85% in less than 30mins) in Phosphate Buffer of pH 6.8.
5. The studies indicated No physical or chemical interactions between the drug and carrier.
6. The studies indicated increased dissolution rate with the formation of granules
7. The granules performed better than the corresponding physical mixtures while the physical mixtures performed better than the pure drug.
8. The drug was completely soluble in water miscible carrier and hence the possible mechanism for improvement could be Solubilization Effect of carrier.

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