FORMULATION DEVELOPMENT AND OPTIMIZATION OF IBUPROFEN TABLETS BY DIRECT COMPRESSION METHOD

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ABSTRACT

Ibuprofen is widely used as a prescription and non-prescription medicine. The aim of study is to prepare Ibuprofen tablets (200mg) using direct compression technique which is now days considered a cost effective and simple method of manufacturing. It is considered as an appropriate method for hygroscopic and thermolabile substances. In order to obtain the best, optimized product, nine different formulations were developed. Diluent (X1), disintegrant (X2) and lubricant (X3) were taken as independent variables. Weight variation (Y1), thickness (Y2), length and width (Y3), hardness (Y4), friability (Y5), disintegration (Y6), dissolution (Y7) and pharmaceutical assay (Y8) were studied as response variables. The results of all nine formulations were found within the acceptable limits conforming to those given in official compendia. However, F-6 was selected as an optimized product on the basis of high dissolution (99.05%) and Assay (100.04%). The variation of weight among the tablets of F-6 was least which showed best ratio of excipients in the formulation. Optimization has proven as an effective tool in product development. This is because no clear relationship exists between the variables.

Keywords: Ibuprofen, direct compression, optimization, independent variables, response variables.

INTRODUCTION

Ibuprofen is a commonly used NSAID (Abraham *et al*., 2005). Low-dose Ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with over-the-counter (OTC) medications (Moore, 2003). Ibuprofen is used as an analgesic, anti-inflammatory agent and anti-pyretic agent (Wood *et al*., 2006). Recemic Ibuprofen and the S (+)-enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhoea, headache, migrane, post operative and in the management of spondylitis, Osteo-arthritis, rheumatoid arthritis, and soft tissue disorders (Potthast, 2005 and Tan *et al*., 1999). Ibuprofen also studied for the closure of the ductus arteriosus. Results indicate that Ibuprofen is as effective as Indomethacin (Kravs and Pharm, 2005). Dental practitioners have relied on Ibuprofen and other nonsteroidal anti-inflammatory drugs to manage acute and chronic orofacial pain (Moore and Hersh, 2001).

The common analgesic drug Ibuprofen ($C_{13}H_{18}O_2$) shows bad dissolution and tableting behavior due to its hydrophobic structure. Additionally its high cohesivity results in low flowability. Another problem in its manufacturing is its high tendency of sticking to the punches (Rasenack and Muller, 2002). There are three methods of tablet manufacturing with the choice depending upon the dose and the drug's physical properties, such as, compressibility and flow of the blend (Halbert, 1993). Direct compression is a process by which tablets are compressed directly from mixtures of the drug and excipients, without any preliminary treatment (British Pharamaceutical Codex, 1994). A simple formula is considered to be composed of an active ingredient, a diluent and a lubricant (Martino *et al*., 2004).

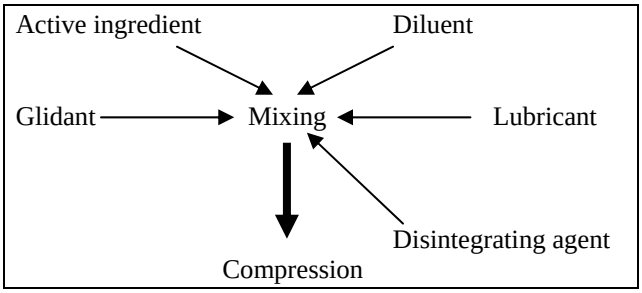

Fig. 1: The direct compression process of tablet manufacturing (Armstrong, 2002).

Tablet manufacturing by direct compression has increased steadily over the years. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency (Zhang *et al*., 2003). As direct compression is more economic, reducing the cycle time and straight forward in terms of good manufacturing practice requirements. On the other hand wet granulation not only increases the cycle time, but also has certain limits imposed by thermolability and moisture sensitivity of the active. So pharmaceutical industry is

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now focusing increasingly on this process (Yasmeen *et al*., 2005 and Beyer *et al*., 2001). The unnecessary exposure of any drug to moisture and heat can never be justified (Shangraw, 1989). Tablets produced by direct compression method give lower microbial levels than those prepared by the wet granulation method. The compaction process exerts lethal effect on the survival of microorganisms (Ibrahim and Olurinola, 1991). The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with the dissolution fluid and exhibit a comparatively faster dissolution (Gohel, 2005). The serious limitation of direct compression is the use of more than 30% of the drug in the formulation, mainly for drugs that present low flowability and segregation (Jivraj *et al*., 2000).

Current-day pharmaceutical formulation may be trial and error in nature due to the absence of a clear relationship between the formulation characteristics (output variables) and the material and process variables (input variables) (Kesavan and Peck, 1996). Experimental design studies (EDS) are widely used in pharmaceutical industry for drug formulation or process optimization (Goutte *et al*., 2002). Now days, most of experimentation of tablet formulation development is still performed by changing the levels of each variable (factor) at a time, in an unsystematic way, keeping all other variables constant in order to study the effects of that specific variable on the formulation (Martinello *et al*., 2006).

The plan of present research is to develop a cost effective Ibuprofen 200mg tablet by direct compression method. The aim is to cut down the time required for disintegration of the tablets in small intestine. Secondarily, direct compression is being studied for its simplicity, cost effectiveness and for its comparatively shorter process. Thus nine different formulations were designed to obtain best optimized product.

MATERIALS AND METHODS

Materials

Ibuprofen ($C_{13}H_{18}O_2$) pure was kindly gifted by Deluxe Pharma, Pakistan, Microcrystalline Cellulose (Avicel PH-101; FMC Corporation, USA), Crospovidone (ISP Technologies, Inc. Wayne, NJ) and Magnesium Stearate (FMC Corporation, USA) were used as directly compressible excipients. Sodium hydroxide (Merck, Kga A, and Darmstadt, Germany) monobasic potassium phosphate (Merck, Kga A, and Darmstadt, Germany) Methanol HPLC grade (RDH, Sigma-Aldrich GmbH, Seelze, Germany), ortho phosphoric acid (Merck, Kga A, Demarst, Germany) and all other chemicals used were of analytical grade and procured from commercial sources.

Preparation of Ibuprofen tablets

Tablets ingredients were accurately weighed (Mettler Toledo B204-S) as mentioned in table 1. These powders were then passed through 20 mesh sieve.

Ibuprofen, Microcrystalline cellulose (X1) and Crospovidone (X2) were mixed in a large size poly bag using tumbling action. Finally magnesium stearate (X3) was added and again mixed for 5 minutes so that particle surface was coated by lubricant evenly. The blend was compressed using single punch tablet machine (KORSCH Erweka, Frankfurt Germany), having caplet shaped concave punches.

Optimization of Ibuprofen formulation (200 mg)

In order to obtain "best" or an "optimized product" nine different formulations were generated using factorial design. Microcrystalline cellulose (X1) and Crospovidone (X2) and magnesium stearate (X3) were taken as independent formulation variables while weight variations (Y1), thickness (Y2), length and width (Y3), hardness (Y4), friability (Y5), disintegration (Y6), dissolution (Y7) and pharmaceutical assay (Y8) were considered as dependent or response variables. The percentage composition and low and high levels of variables are shown in tables 2 and 3.

Evaluation of tablet properties

After compression a number of different pharmacopoeial and non-pharmacopoeial physico-chemical tests were performed on all nine formulations, which are as follow:

Weight variation test

The variation of the weight of individual tablets is a valid indication of the corresponding variation in the drug content (Rawlins, 1995). The average tablet weight was determined by weighing 20 units or tablets individually using an analytical balance ((Mettler Toledo B204-S, Germany). The mean ± S.D. of each formulation is mention in table 4.

Thickness, length and width measurement

The thickness of a tablet was determined by the amount of fill permitted to enter the die and the amount of pressure applied during compression (Allen *et al*., 2005). 20 tablets were taken and their thickness, length and width were determined individually by vernier caliper. Mean and standard deviation were calculated.

Crushing strength or hardness determination

20 tablets were taken randomly and hardness was measured using Hardness Tester (Fujiwara, Seisukusho Corporation, Japan). The mean ± S.D of 20 tablets of each formulation is shown in table 4.

Table 1: Composition of Ibuprofen 200mg tablets

Ingredients	Batch Code								
(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibuprofen	200	200	200	200	200	200	200	200	200
Avicel PH101	150	150	150	175	200	200	200	175	175
Magnesium Stearate	05	7.5	2.5	05	05	05	05	05	05
Crospovidone	10	10	10	10	10	05	2.5	05	2.5
Quantity per Tablet (mg)	365	367.5	362.5	390	415	410	407.5	385	382.5

Table 2: Percentage Composition of Ibuprofen 200mg tablets

Ingredients (%/tablet)	Batch Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibuprofen	54.79	54.42	55.17	51.28	48.19	48.78	49.07	51.94	52.28
Avicel PH101	41.09	40.81	41.37	44.87	48.19	48.78	49.07	45.45	45.75
Magnesium Stearate	1.36	2.04	0.68	1.28	1.20	1.21	1.22	1.29	1.30
Crospovidone	2.73	2.72	2.75	2.56	2.40	1.21	0.61	1.29	0.65
Quantity Tablet (%)	99.97	99.99	99.97	99.99	99.99	99.98	99.97	99.97	99.98

Table 3: Variables selected to perform optimization

	Variables	Low Level	High Level
(X1)	Quantity of MCC (Avicel PH 101)	150mg	200mg
(X2)	Quantity of Crospovidone	2.5mg	10mg
(X3)	Quantity of Magnesium stearate	2.5mg	7.5mg

The amount of Ibuprofen was fixed at 200mg. While the quantities of excipients were not constant.

Table 4: Physico-chemical tests

Formulation	Weight(mg) Mean ± S.D	Thickness (mm) Mean ± S.D	Length (mm) Mean ± S.D	Width (mm) Mean ± S.D	Hardness (kg)
Pharmacopoeial Limits	±5 %	-	-	-	At least 5 kg
F-1	365.85 ± 3.468	4.855 ± 0.035	15.18 ± 0.034	6.605± 0.053	6.189±0.57
F-2	363.20 ± 2.894	4.525± 0.061	15.025 ± 0.035	6.587± 0.222	5.881± 0.463
F-3	360.35 ± 1.631	4.482 ± 0.049	15.205 ± 0.035	6.587 ± 0.074	6.04 ± 0.381
F-4	390.40 ± 2.909	4.790 ± 0.047	15.207 ± 0.037	6.597 ± 0.049	6.989 ± 0.77
F-5	412.50 ± 1.849	5.142 ± 0.051	15.215 ± 0.070	6.57 ± 0.063	7.745 ± 0.428
F-6	409.75 ± 1.831	5.112 ± 0.035	15.192 ± 0.046	6.573 ± 0.063	7.955 ± 0.395
F-7	405.65 ± 2.109	4.742 ± 0.037	15.175 ± 0.057	6.552 ± 0.071	6.83 ± 0.300
F-8	384.8 ± 3.270	4.650 ± 0.039	15.177 ± 0.049	6.547 ± 0.067	5.123 ± 0.299
F-9	381.80 ± 2.627	4.632 ± 0.040	15.185 ± 0.04	6.567 ± 0.059	4.637 ± 0.326

Friability testing

20 tablets were taken randomly and placed on a sieve. Loose dust was removed with the aid of air pressure or a soft brush. Tablet samples were weighed accurately and placed in Friabilator **(**H.Jurgens and Co- GmbH and Co-D2800, Bermen, Germany). After the given number of rotations (100 rotations/4 min) loose dust was removed from the tablets as before. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear (British Pharmacopoeia, 2004).

The percent friability was determined by using following formula:

$$\% \text{ friability} = \frac{(\text{initial weight} - \text{final weight})}{\text{Initial weight}} \times 100$$

Disintegration test

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract (Block and Yu, 2001). Disintegration time was measured for 6 tablets by inserting disks using 900ml purified water at 37±2ºC in

Table 5: Physico-chemical tests

Formulation	Percent Friability	Disintegration Time (sec)	Average Percent Dissolution	Average Percent Assay
Pharmacopeial limits	Not more than 1%	Within 30 minutes	Not less than 80%	95-105%
F-1	0.28	22	87.563	98.448
F-2	0.54	210	81.145	98.214
F-3	0.29	30	95.222	97.681
F-4	0.30	40	95.596	97.432
F-5	0.25	100	92.997	98.190
F-6	0.27	120	99.051	100.042
F-7	0.12	135	92.523	98.465
F-8	0.26	30	84.901	98.135
F-9	0.27	225	90.226	98.393

Table 6: Weight of randomly selected 20 tablets of optimized product (F-6)

No. of tab	1	2	3	4	5	6	7	8	9	10
weight (mg)	408	410	410	409	408	412	408	410	411	410
No. of tab	11	12	13	14	15	16	17	18	19	20
weight (mg)	413	411	407	409	413	410	411	409	406	410

Table 7: Hardness of randomly selected 20 tablets of optimized product (F-6)

No. of tab	1	2	3	4	5	6	7	8	9	10
hardness (kg)	7.8	8.8	8.1	7.85	7.45	7.85	7.9	8.25	8.15	8.8
No. of tab	11	12	13	14	15	16	17	18	19	20
hardness (kg)	7.75	7.85	7.45	7.85	7.35	7.6	8.25	8.35	7.15	7.95

Disintegration Apparatus (Erweka ZT-2, Huesnstanm, Germany).

Dissolution test

Dissolution of Ibuprofen from tablets was measured according to the USP 27 NF 22, 28th edition (United State Pharmacopoeia 2005). Paddle method, at a paddle speed of 50 rpm, in 900 mL of pH 7.2 phosphate buffer solution at 37 ± 0.5˚C, using UV-VIS Spectrophotometer (Heliosa UV VIS spectrophotometer 150, England). The Ibuprofen concentration of each sample (n=6) was spectrophotometrically determined at 241nm using following formula:

$$\%Absorbance = \frac{Absrbance\ of\ sample}{Absorbance\ of\ s\tan dard} \times 100$$

Pharmaceutical assay

Assay was performed on HPLC (LC-10A, SPD-2A) according to B.P 2005. The chromatographic procedure was carried out by using a stainless steel column (25 cm x 4.6 mm). A mixture of 3 volumes of ortho phosphoric acid (Merck, KgA, Demarst, Germany), 247 volumes of water and 750 volumes of methanol (Merck, KgA, Demarst, Germany) was used as mobile phase and peak was detected at a wave-length of 264 nm

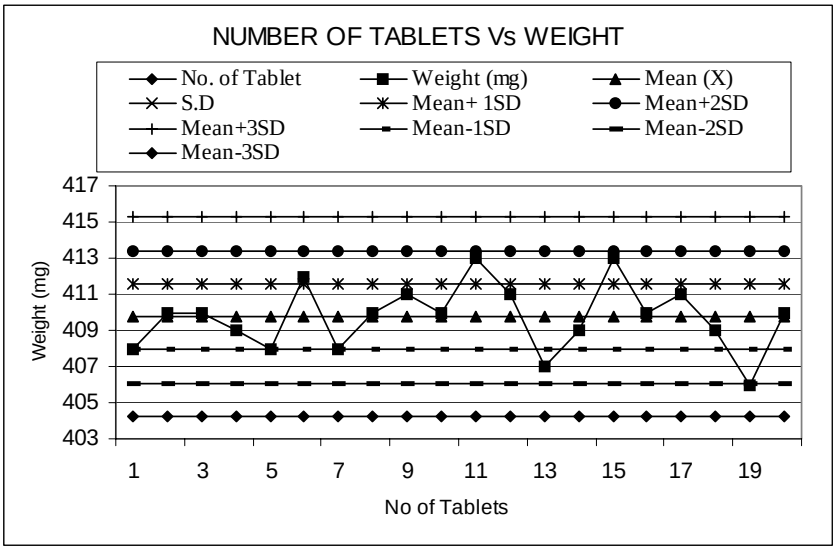
Potency of Active Drug was calculated by the following equation:

$$\%\ Assay = \frac{Average\ Peak\ Area\ Of\ Sample \times Conc.\ Of\ S\tan dard}{Average\ Peak\ Area\ Of\ S\tan dard \times Conc.\ Of\ Sample} \times 100$$

RESULT AND DISCUSSION

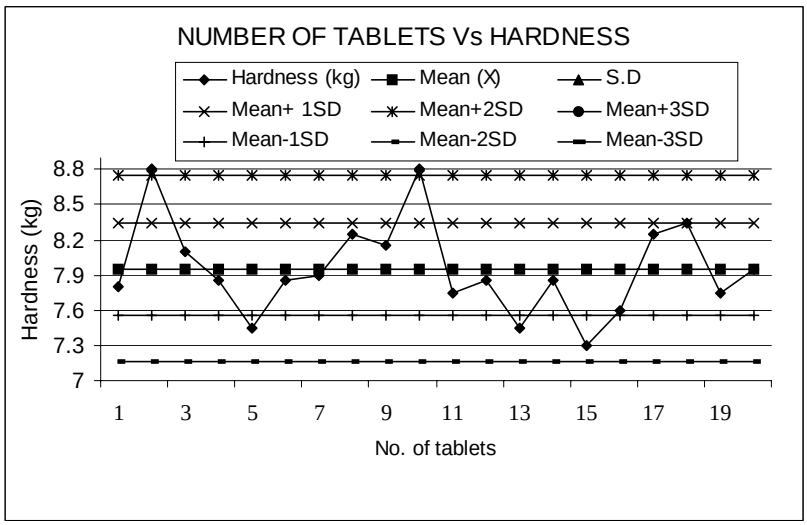
Blend of all nine formulations were individually compressed, with out any problem, by direct compression method. A typical tablet formulation consists of the active pharmaceutical ingredient(s), fillers, disintegrants, lubricant and other inactive ingredients (e.g., binder, glidant and colors etc.). When formulating direct compression tablets, the choice of binder is extremely critical since a slight variation in the binder ratio can lead to capping, lamination, chipping and friable tablets and all of these are common defects experienced with direct compressible formulations. Here, microcrystalline cellulose (Avicel PH 101) was used as filler and is it, which showed excellent compressibility of the Ibuprofen tablets. It is self-lubricating (Omray and Omray, 1986) and adds compact and strength into the tablets considerably (Hernier and Teleman, 1997). Since the Ibuprofen does not possess excellent fluidity and flow so magnesium stearate was selected as lubricant, because of

it, a uniform flow from hopper to die was possible. It prevents the adhesion of tablet material to the machine parts such as punches and dies, reduce inter particle friction and facilitates the ejection of tablets from the die-cavity. Past studies show that the addition of magnesium stearate dramatically improved the blending characteristics of the milled batches (Mackin *et al*., 2002). It is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations (Hussain *et al*., 1992; Caldwell, 1974). Magnesium stearate was found to be the most effective lubricant based on LPEF-lubricant (low punch ejection force) concentration profile (Turkoglu *et al*., 2005). However, formulations with Magnesium Stearate had the worst results on tests of friability and tensile strength (Garcia-Marquez *et al*., 1992).



Mean (X) = 409.75 S.D = 1.831 Mean + 1 S.D = 411.581 Mean – 1 S.D = 407.919
Mean + 2 S.D = 413.412 Mean – 2 S.D = 406.088 Mean + 3 S.D = 415.243 Mean – 3 S.D = 404.257
Upper Limit (+5%) = 430.237 Lower Limit (-5%) = 438.263

Fig. 2: Uniformity of weight of 20 tablets (F-6).



Mean (X) = 7.955 S.D = 0.395 Mean + 1 S.D = 8.35 Mean – 1 S.D = 7.56
Mean + 2 S.D = 8.745 Mean – 2 S.D = 7.165 Mean + 3 S.D = 9.14 Mean – 3 S.D = 6.77
Upper Limit (+5%) = 8.352 Lower Limit (-5%) = 7.558

Fig. 3: Hardness of 20 tablets (F-6).

Crospovidone was used as a disintegrant. It is water-insoluble and belongs to the class superdisintegrants. About 2-5 % concentration of it is generally recommended in tablets prepared by direct compression (He and Kibbe, 2003). Here it was utilized in a concentration ranging between 0.61 to 2.75%, because the presence of crospovidone, tablets from each batch disintegrated rapidly. Khairuzzaman *et al*., in 2006 compacted aspirin, theophylline and atenolol tablets using the wet granulation method. Disintegration times of tablets were reduced from 18 mins to 6 mins when 6% crospovidone was added to the formulaton (Khairuzzaman *et al*., 2006). Studies suggest that the particle size of crospovidone strongly influences the disintegration of analgesic tablets. Larger particle size provides a faster disintegration as compared to smaller particle size (He and Kibbe, 2003).

The physical and chemical tests of all formulations were found to confirm with the limits given in British and United State Pharmacopoeias (tables 4 and 5).

The most obvious advantage of direct compression is economy. Savings can occur in number of areas, including reduced processing time and thus reduced labor costs, fewer manufacturing steps and pieces of equipment, less space and lower consumption of power.

Wet granulation is laborious, involving considerable material handling, as well as several processing steps. It is expensive because of equipment, energy and space requirements.

Although directly compressible excipients are more costly than excipients used in wet granulation but the over all method is very cheap and cost effective.

The technique of optimization is well reported in the literature for the development of tablet formulations (Bos *et al*., 1991; Ceshel *et al*., 1999; Rhodes *et al*., 1991). The purpose of carrying out optimization is to select the best possible formulation from pharmaceutical as well as consumer point of view. In this study effects on response variables (Y) were observed by changing one variable (X) at most of the time. Optimization is considered as an efficient and economical method to understand the relationship between independent and dependent variables. Optimization has gaining popularity in pharmaceutical research, day by day, since the best results are obtained in a limited number of experiments. Among these nine formulations, formulation 6 (F-6) was selected as an optimized product on the basis of different pharmaceutically significant parameters as hardness, dissolution and assay.

Powders intended for compression into tablets must possess good compressibility and fluidity. Problems in fluidity cause variations in the die filling and consequently variation in the tablet weight and strength (Prescott and Hossfield, 1994). Results of all developed formulations were within the acceptable ranges of values as given in official compendia but it was observed that the weight variation was lowest with tablets developed by formulation, F-6 (table 6). It is a well-known fact that the weight variation has a direct impact on the assay of the tablets. Moreover, it also indicates that the distribution of excipients is not right or homogenous.

Fig. 2 shows that the proportions of all excipients in F-6 were just right and this showed least variation in tablet weight so much so that even no tablet crossed the 2nd line of control at upper or lower limits, and also with in the range of ±5%.

Assay of the drug was carried out by HPLC technique using a stainless steel column (15 cm x 4.6 mm). In this study the average percentage of assay of all formulations ranged from 97.432 to 100.042. The chromatograms of standard Ibuprofen (200mg) and the optimized product are given in figs. 3 and 4.

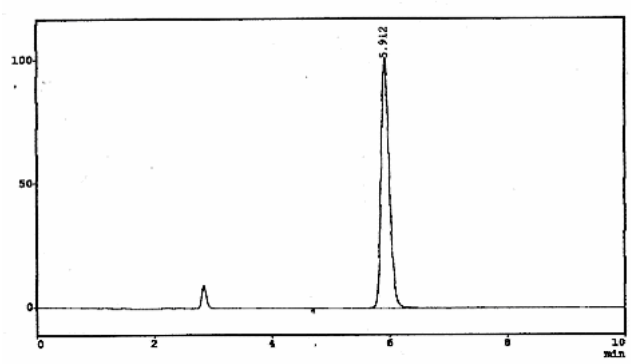


Fig. 4: Ibuprofen standard (200mg)

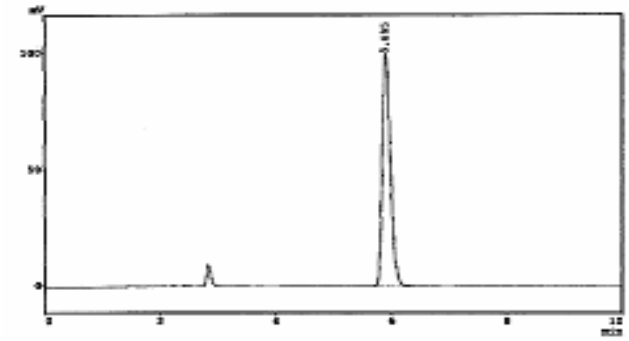


Fig. 5: Ibuprofen (200mg) formulation 6

All formulations disintegrated very rapidly and were well within official limits. The time of disintegration ranged from 22 sec to 225 sec. while the USP and BP have official limits of not more than a time period of 15 mins disintegration time for uncoated tablets. This rapid

disintegration is most probably due to the presence of a superior class of disintegrant, i.e. Crospovidone, which is synthetic cross -linked poly-vinylpyrrolidone NF.

Terashita and Imamura in 2002 suggested that Direct compression is able to produce tablets at a lower cost than wet granulation and tableting method, due to a fewer items of process validation. Acetaminophen was used to formulate tablets by direct compression, and evaluating their physical properties. Consequently, direct compression was found effective in formulating tablets with excellent physical properties. It was confirmed that tablets produced by direct compression were similar in physical properties in tablets produced by wet granulation and tableting method.

Gazikolovie *et al*., in 1999 presented the test results of Lithium carbonate tablets made by direct compression. The content of lithium carbonate, tablets weight variation, hardness, friability, disintegration, as well as the lithium carbonate dissolution rate were determined. The best properties were observed in tablets made with microcrystalline cellulose (Avicel PH 101), spray dried lactose and corn starch.

CONCLUSION

Direct compression methods can be used alternatively for wet granulation, because it is an easier, simplified and economical method of manufacturing of tablets. A number of research articles are available which are evident that the direct compression is a preferred method of tableting. Optimization technique is a good tool for preparing better quality of dosage forms. This is widely used developing optimal dosage forms and a better process of manufacture.

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