

# SUSTAINED RELEASE FORMULATION AND IN-VITRO EVALUATION OF IBUPROFEN-HPMC MATRIX TABLETS

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## **Abstract**

Ibuprofen is one of the safest and most potent non-steroidal anti-inflammatory drug (NSAID) available in the market. To improve the bioavailability of ibuprofen, a thorough preformulation trial was undertaken. As a part of these studies, different formulations of ibuprofen containing different amounts of hydroxypropylmethylcellulose (HPMC) and microcrystalline cellulose (Avicel<sup>®</sup>) were made and evaluated. The superior formulation which released the drug at constant rate of about 60 mg/hour was chosen. Then the effect of changing particle size of granulation was studied. Two different crystal forms of ibuprofen were prepared and their release pattern were studied. Produced crystal forms of ibuprofen showed different release mechanisms in comparison with the original form. Incorporation of various proportions of tween 80 and Sodium Lauryl Sulfate (SLS) as wetting agent on the release rate of ibuprofen in the formulations were also studied. Sodium lauryl sulphate disintegrated the tablets faster than tween 80.

## **Keywords:**

Ibuprofen, HPMC, Matrix tablets, Dissolution, Sodium Luryl Sulphate, Tween 80.

## **Introduction**

Ibuprofen is one of the safest and most potent non-steroidal anti-inflammatory drugs (NSAID) available in the market (1). It may be tolerated better than other NSAIDs. Due to rapid excretion of ibuprofen in the urine, large amount of drug is required for conventional dosage form. However, it suffers from limited aqueous solubility, gastrointestinal side effects and hardening of the tablets on aging (2). Due to short half life of ibuprofen (about 2 hours), and rapid excretion from urine, for prevention of drug fluctuation in blood, ibuprofen must be administered frequently (3). Therefore, studies were done to prepare a sustained release formulation of ibuprofen to minimize these problems. Many crystalline organic compounds can exist in more than one polymorphic

structure. Different polymorphs have different physical characteristics such as: dissolution rate, density, melting point and stability (4, 5, 6). The objective of the present study was the investigation of characterization and dissolution behavior of different drugs : polymer ratios, particle size and crystal forms of ibuprofen that is practically insoluble in water. In this research, different formulations of ibuprofen containing different amounts of hydroxypropylmethylcellulose (HPMC) and Avicel<sup>®</sup> were made and evaluated.

## **Materials**

Ibuprofen BP Shasun (India), was supplied by Aria Pharmaceutical Company, Iran; hydroxypropylmethylcellulose (HPMC K100M), from Colorcon Ltd, England;

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microcrystalline cellulose (Avicel®), Merck Germany. All other chemicals (lactose, starch, polysorbate 80, sodium lauryl sulfate, magnesium stearate and talk) were of analytical grade obtained commercially and were used in the formulations.

## Methods

**Tablet Preparation:** Thirteen formulations containing 600 mg ibuprofen, were developed as shown in table 1, and the granules were prepared by the wet granulation method. The granules were made of drug and Avicel® by using 10% gels of HPMC as binder. They were dried at 40° C for 3 hours in oven. Then granules were mixed with talk, starch and then compressed (Formulation F1).

**The effect of drug : polymer on drug release:** In the formulations of F2, F3, F4 and F5 different ratios of HPMC and Avicel® were used and the tablets were prepared as mentioned previously.

**The effect of particle size of drug granules on release rate:** Formulation F5 (particle size of no.40 mesh) was chosen for further investigation. Therefore, the effect of particle size of ibuprofen granules on drug release was investigated. As it was mentioned in the footnote of table 1, formulations F6 and F7 were made with large particle size (between sieve no. 14 and 30) and small particle size (between sieve no. 50-70), respectively. Again, same procedure was done for preparation of the formulations.

**The effect of crystal form on drug release:** The method of Khan (4) with slight modification was used for preparation of crystal forms of ibuprofen. In this method, a solution of ibuprofen in alcohol was placed on hot water bath (70°C). Then, the alcoholic solution was poured in cold water and kept for 24 hours to produce crystallized form. After 24 hours, due to insolubility of ibuprofen in distilled water,

the crystals were formed and collected. The produced precipitated ibuprofen was separated by filtration using Buchner funnel, rapidly washed with cold water and dried at room temperature. In this procedure, the crystal forms were of smallest size and had circular and amorph shape which were used in the formulation F8. Since it found that the temperature and drug concentration strongly affect the crystal form of ibuprofen (4, 6), therefore, ibuprofen in the formulation F9 was made with high concentration of drug in alcohol solution poured in icy cold water, which produced flat form crystals. Formulations F8 and F9 were made using prepared ibuprofen crystals and compared with original ibuprofen (needle form) tablet (Formulation F5).

**The effect of wetting agents on drug release:** Tween 80 in the ratio of 1% w/w was used as wetting agent in the ideal formulations to produce formulation F10. In other tests, sodium lauryl sulphate in the concentrations of 1, 0.1 and 0.01% (Formulations respectively F11, F12 and F13) were used.

**Dissolution studies:** Dissolution was determined using an Erweka dissolution tester. The USP XXII(Apparatus I) was used, rotating at 150 rev min<sup>-1</sup> in 900 ml buffer phosphate solution pH 7.2 maintained at 37 °C. Ibuprofen concentration was measured using UV spectroscopy at 221 nm. The mean results of 3 tablets was used to characterize the drug release for each formulation (7)

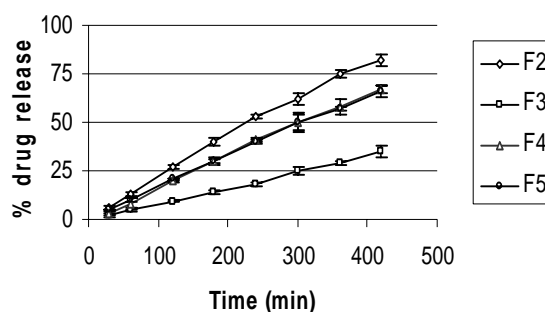
**Analysis of drug release:** In order to investigate the mode of drug release from matrices, the obtained data were fitted to equation ( $Q=Kt^n$ ), where Q is % drug released, K is dissolution rate constant, t is the release time and n is a release exponent (8).

**Results and discussion**

**The effect of drug : polymer ratio on drug release:** In the first formulation, starch was used as filler and starch paste at concentration of 25% w/w was used as binder. The prepared tablets had low hardness of about 1 kg (not shown in table 1). Therefore, the granules were made of drug, Avicel® by using 10% gels of HPMC as binder.

The obtained tablets had hardness of about 6 or 7 kg (Formulation F1). When the starch

was omitted from the formulation F1, the obtained tablets had the hardness of 10-11 kg (Formulation F2). Different formulations of ibuprofen, HPMC and Avicel (formulations F2, F3, F4 and F5) were made and tested. Figure 1 shows the effect of drug : polymer ratio on the release of ibuprofen. The release kinetics from matrices composed of varying amounts of HPMC and Avicel were analyzed using equation  $Q = Kt^n$  as shown in the table 2.



**Fig. 1:** The effect of drug: polymer ratio on drug release

**Table 1:** Different formulations of ibuprofen (600 mg)

Formulation	HPMC (mg)	Avicel® (mg)	Dried Starch (mg)	Tween 80 (%)	SLS (%)
F1	60	40	20	-	-
F2	80	20	-	-	-
F3	100	-	-	-	-
F4	60	40	-	-	-
F5	40	60	-	-	-
F6 (L) <sup>+</sup>	40	60	-	-	-
F7(S) <sup>++</sup>	40	60	-	-	-
F8(Amorph)	40	60	-	-	-
F9(Flat)	40	60	-	-	-
F10	40	60	-	1	-
F11	40	60	-	-	1
F12	40	60	-	-	0.1
F13	40	60	-	-	0.01

<sup>+</sup> Large particle size of granules, between sieve No. 14 and 30.

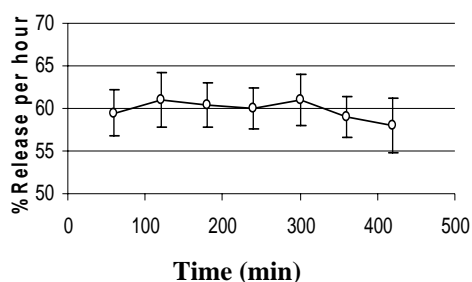
<sup>++</sup> Small particle size of granules, between sieve No. 50 and 70.

**Table 2:** The effect of polymer content of HPMC and Avicel on the dissolution constant and release exponent from matrices containing 600 mg ibuprofen.

Formulation	K (min) <sup>-n</sup>	n	r ( $\sqrt{t}$ )	r (t)
F1	*	*	*	*
F2	0.299	0.938	0.9960	0.9991
F3	0.063	1.050	0.9878	0.9996
F4	0.164	1.000	0.9965	0.9988
F5	0.218	0.950	0.9960	0.9986

\*Drug released very fast and therefore the data not calculated.

Although, no significant difference was observed between formulations 4 and 5, formulation 5 consisted of HPMC and Avicel was chosen as the ideal formulation. The reason for this similarity, may be due to the similarity of the amount of polymers used. Perhaps, in high content of the polymers, the release kinetic will change. Formulation 5, could release the drug at zero order mechanism with constant rate of about 60 mg/h. In order to ascertain the zero-order release from matrices containing 600 mg ibuprofen and 100 mg of the mixture of HPMC and Advice, the release rate was alternatively evaluated by calculating the instantaneous release rate and plotting it as a function of time (figure 2). Colombo et al (9), using similar plots, interpreted the kinetics of drug release from matrices of different surface areas. They suggested that the least variable release rate



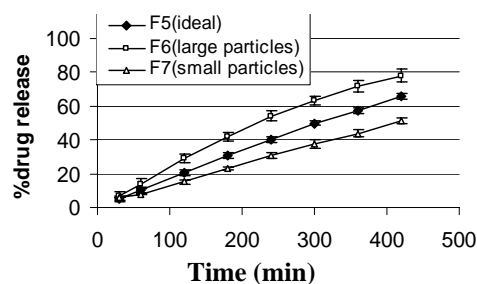
**Fig. 2:** Instantaneous ibuprofen release rates versus time from matrices containing 600 mg drug and 100 mg mixture of HPMC and Avicel (Formulation F5).

Results are the means  $\pm$  SD of 3 determinations

indicated zero-order or near zero-order release.

**The effect of particle size on drug release:**

Figure 3 shows the effect of particle size of ibuprofen on drug release. Changing the particle size of ibuprofen granules changed the release rate (table 3), while did not affect the release mechanism (the values of “n” from the formulations did not change significantly). Large particle size between 14-30 mesh, reduced the release rate and small particle size between 30-70 mesh, increased the release rate in comparison with ideal formulation (F5). Similar finding was observed by Dabbagh (8) using propranolol hydrochloride and HPMC.



**Fig. 3:** The effect of particle size of ibuprofen granule on drug release

**Table 3:** The effect of granule particle size on the dissolution constants and release exponent from matrices containing 600 mg ibuprofen.

Formulation	K (min) <sup>-n</sup>	n	r ( $\sqrt{t}$ )	r (t)
F5	0.218	0.950	0.9960	0.9986
F6	0.223	0.897	0.9879	0.9988
F7	0.398	0.893	0.9963	0.9986

**The effect of crystal forms of ibuprofen on drug release:** Using alcohol as solvent at 2 different temperature and procedures, produced two kinds of ibuprofen crystals. While the commercial ibuprofen powder had needle like crystal, the shapes of the crystals were either flat or a mixture of amorphous and spherical. Figure 4 shows the release of drug from different crystal forms and the data obtained are presented in the table 4. It can be seen that the value of n in the formulation F8 (amorph crystal) was significantly different from that of formulation F9 (flat form). Janjkhel (10) reported similar findings of ibuprofen crystals.

**The effect of wetting agents on drug release:** Using wetting agents such as Tween 80 and sodium lauryl sulfate in the formulations, led to rapid disintegration of the tablets. Figure 5 shows the effect of adding wetting agents on the release rate of the formulations. Sodium lauryl sulfate in the formulations was more effective than tween 80. Data obtained are presented in the table 5. Figure 5 shows that as the concentration of SLS decreased, the release rate decreased or the fast release was observed when the high concentration of SLS was used.

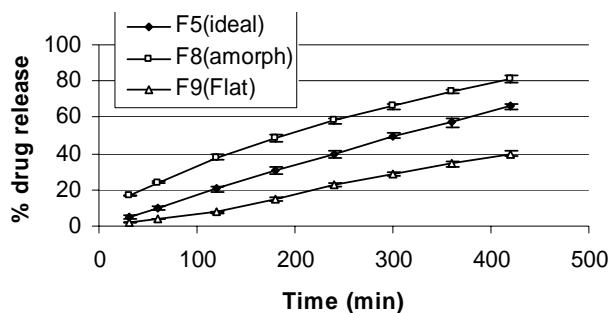
**Table 4:** The effect of crystal form of ibuprofen on the dissolution constants and release exponent from matrices containing 600 mg ibuprofen.

Formulation	K (min) <sup>-n</sup>	n	r ( $\sqrt{t}$ )	r (t)
F5 (needle)	0.218	0.950	0.9960	0.9986
F8 (Amorph)	2.140	0.604	0.9957	0.9959
F9 (flat)	0.040	1.150	0.9887	0.9983

**Table 5:** The effect of wetting agents on the dissolution constants and release exponent from matrices containing 600 mg ibuprofen.

Formulation	K (min) <sup>-n</sup>	n	r ( $\sqrt{t}$ )	r (t)
F10 (Tween 80)	4.3	0.626	0.964	0.917
F11 (SLS 1%) *	-	-	-	-
F12 (SLS 0.1%)	44	0.164	0.860	0.802
F13 (SLS 0.01%)	14.6	0.274	0.999	0.983

\* Drug released very fast and therefore the data not calculated



**Fig. 5:** The effect of adding surfactant (Tween and SLS) in different amounts on drug release

### Conclusion

It can be concluded that appropriate crystal forms of ibuprofen could modify drug release mechanism. A formulation which could release drug at constant rate of about 60 mg/hour was chosen as the ideal formulation. More investigation were done on this formulation. Changing the particle size of drug granules caused change in drug release but did not affect the mechanism of drug release. Also, the effect of different crystal forms of ibuprofen on drug release was investigated. Finally adding wetting agents such as tween 80 and Sodium Lauryl Sulphate (SLS), caused rapid disintegration of the tablets. SLS was more effective than Tween 80 in disintegration of the tablets (5).

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