ORIGINAL ARTICLE

Optimization of Ibuprofen Hydrogel-based Matrix Tablet Formulation for Oral Delivery

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ABSTRACT

Objective. Ibuprofen, a nonsteroidal anti-inflammatory drug, is poorly soluble leading to its slow systemic absorption. This study aimed to optimize the formulation of an ibuprofen hydrogel-based matrix tablet to improve its dissolution for better oral bioavailability.

Methods. Raw material of ibuprofen was subjected to quality control test and compatibility test with the excipients. Six trial formulations were performed, with polyethylene glycol (PEG) 6000 as the matrix for the first three trial formulations and carbopol for the remaining trial formulations. Finished product quality control (FPQC) tests were conducted to choose the best formulations to be compared against the marketed products using comparative dissolution and stability studies.

Results. Among the trial formulations, Formulation 3 and Formulation 4 displayed highly satisfactory results from FPQC. The results of disintegration tests, comparative dissolution, and stability studies suggested carbopol as the better polymer over PEG 6000 which made Formulation 4 as the best.

Conclusion. Based on the percent drug release and similarity factor, it was concluded that the formulation optimized in this study was considered to be similar with the standard liquigel.

Key Words: hydrogel, ibuprofen, solubility

INTRODUCTION

Acute pain is the most common type of pain experienced worldwide. Despite extensive advances in pain research and management, millions of people continue to suffer because of inadequate pain control. Pain management faces difficulties that restrict therapeutic success, such as the limited efficiency of analgesics, adverse systemic effects, and cognitive impairment of drugs due to central effects.[1]

Ibuprofen, a poor water soluble drug, is a first-line non-steroidal anti-inflammatory drug for mild to moderate acute pain based on effectiveness, adverse effect profile, cost, and over-the-counter availability.[2] The poor water solubility (log P value 3.6) of ibuprofen limits its entry into the systemic circulation before gastric emptying occurs.[3] Poor solubility is a major challenge to developing formulations using such active ingredient.[4] In order to exhibit fast therapeutic action against pain, an optimized dosage form with quick drug release and good bioavailability must be formulated. [5]

To address the poor solubility of ibuprofen, different techniques have been proposed to improve the systemic absorption of ibuprofen such as mechanical micronization, neutralization, and soft gel capsule formulation. However,

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these dosage forms pose handling difficulties and safety risks. In formulating a new dosage form, physicochemical characteristics of the ingredients and an ideal drug development involving simple and productive manufacturing parameters must be considered.

Recent studies reported that incorporation of poor water soluble drugs into hydrogels enhance their aqueous solubility thereby improving their systemic delivery.[6] Hydrogel, also known as hydrophilic gel, is a polymer network extensively swollen with water which is sometimes found as colloidal gel wherein water is the dispersion medium.[7] Synthetic water soluble polymers may be used as matrix to improve the solubility of a hydrophobic drug since these are substances that dissolve, disperse, or swell in water.[8]

Polyethylene glycol and carbopol are among the synthetic polymers used as matrix in formulating hydrogels. According to Shailendra and Priti, the PEG 6000 in the formulation improves the dissolution rate of a drug. The enhanced solubility of the hydrophobic drug may be due to the high hydrophilic nature of PEG and the increased wettability of the drug since PEG 6000 decreases the interfacial tension between the drug and dissolution medium.[9] Carbopol is also used as water soluble polymer and provide very low viscosity and excellent yield value at low usage level.[10, 11]

In this study, the polymer matrix was directly compressed with the drug substance and other excipients into a tablet which will release the drug when the matrix swells through diffusion and degradation. Therefore, this study aimed to optimize the formulation of ibuprofen hydrogel-based matrix tablet to improve its dissolution for better oral bioavailability.

MATERIALS AND METHODS

Pre-formulation

For the pre-formulation study, the compatibility of ibuprofen with the selected excipients were evaluated by mixing (1:1) a small amount of the ibuprofen and the excipient. The mixtures were placed in 10 mL vials, covered with rubber stopper and was stored at 5°C, 30°C, and 40°C for 3 weeks. The organoleptic characteristics of the mixture was observed.

Formulation Preparation of ibuprofen hydrogel based-matrix tablets

Six formulations of ibuprofen hydrogel-based matrix tablet were prepared with three formulations in each series for PEG 6000 and for carbopol as matrix. PEG 6000 was used as polymer for Formulation 1, Formulation 2, and Formulation 3 while carbopol was the polymer used for Formulation 4, Formulation 5, and Formulation 6. Ibuprofen and the excipients were weighed as shown in Table 1, passed through sieve no. 40, and were mixed. Then, the tablet blends were subjected to in-process quality control tests such as angle of repose (Θ), bulk density, tapped density, Carr's index (CI), Hausner's ratio (HR), and moisture content.

After physical evaluation, the tablet blends were compressed into tablets using 7/16" flat, scored punches of Stokes® single punch tablet compression machine. Then, the finished ibuprofen hydrogel-based matrix tablets were evaluated for organoleptic properties, weight variation, friability, thickness, hardness, friability, swelling index, wetting time, and disintegration time according to the specifications of United States Pharmacopoeia (USP).[12] The drug content of the formulations were analyzed through

Table 1. Trial formulation of ibuprofen hydrogel-based matrix tablets

Ingredient	Trial formulation					
	F1	F2	F3	F4	F5	F6
Ibuprofen	54.81%	56.02%	52.16%	46.57%	60.20%	51.38%
PEG 6000	13.71%	14.01%	11.74%	-	-	-
Carbopol	-	-	-	10.48%	15.05%	12.85%
Talc	2.06%	2.10%	1.96%	0.58%	0.75%	0.64%
Microcrystalline cellulose	-	-	0.33%	-	0.38%	-
Sodium bicarbonate	4.12%	4.20%	3.92%	13.97%	-	-
Sodium alginate	4.12%	2.10%	1.95%	3.49%	-	-
Lactose	18.11%	19.49%	17.22%	15.37%	-	-
Magnesium stearate	2.74%	2.80%	2.61%	2.33%	3.01%	2.57%
Maltodextrin	-	-	3.91%	3.49%	-	-
Microcrystalline cellulose	-	-	-	-	19.86%	0.32%
Colloidal silicone dioxide	-	-	-	-	0.45%	-
Crospovidone	-	-	-	-	-	1.54%
Polyvinyl Pyrrolidone	-	-	3.91%	3.49%	-	-
Croscarmellose	-	-	-	-	-	0.39%
Silicified microcrystalline Cellulose	-	-	-	-	-	30.06%
Propylparaben	0.14%	0.14%	0.13%	0.12%	0.15%	0.13%
Methylparaben	0.14%	0.14%	0.13%	0.12%	0.15%	0.13%
Weight per tablet	729 mg	714 mg	767 mg	859 mg	665 mg	779 mg

Genesys 10S UV-Visible spectrophotometer at 221 nm with the acceptance criteria of 90-110% of the labelled ibuprofen. Based on the FPQC results, the best formulation from each series of carbopol and PEG 6000 were chosen to be compared against the marketed formulations of ibuprofen.

Since the dissolution rate is the one being addressed in this formulation, the dissolution tests of the two best trial formulations, standard tablet, and standard liquigel was conducted based on the United States Pharmacopoeia with the acceptance criteria that not less than 80% of the labelled ibuprofen should be dissolved in 60 min.[12] Six tablets were placed in each vessel of USP apparatus 2 containing pH 7.2 phosphate buffer, equilibrated at dissolution medium to 37 ± 0.5°C then operated at 50 revolutions per minute for 60 min. Five mL of the sample was withdrawn and analyzed using a UV-Vis spectrophotometer at 221 nm. The absorbance of liquigel was measured at 226 nm which was subtracted from its absorbance at 280 nm.

Then, the stability test modified from International Conference of Harmonisation (ICH) was conducted on the two best trial formulations.[13] The optimized formulations were wrapped with aluminum foil then stored in a dry hot oven at accelerated temperature of 40°C and relative humidity of 75% for four weeks. Quality control tests including observation of physical changes and assay were performed every week.

Statistical analyses

All tests were done in triplicate and data were recorded as mean. The percent drug released from the comparative dissolution test conducted was compared by calculating the similarity factor and p-value using paired t-test.

RESULTS AND DISCUSSION

Pre-formulation

For the pre-formulation study, there was no incompatibility observed between ibuprofen and excipients as there was no change in their organoleptic characteristics.

Formulation Preparation of ibuprofen hydrogel based-matrix tablets

As shown in Table 2, the tablet blends for all trial formulations show acceptable results and passed all the IPQC tests.

Evaluation of hydrogel-based matrix tablet

The FPQC results of ibuprofen hydrogel based-matrix tablet formulations are shown in Table 3. For organoleptic properties, all finished tablets appeared to be white and uniform in color except for Formulation 1 which manifested an off-white color. All formulations exhibited acceptable organoleptic properties as they showed no signs of cracks or capping, chipping in the tablet surfaces or coating, swelling, mottling, discoloration, fusion between tablets, or presence of excessive powder.

In Formulation 1, sodium alginate was used as the tablet disintegrant to facilitate the water absorption of the tablet and to achieve faster disintegration time. Generally, sodium alginate with the amount of 2.5-10% in formulations is used as tablet disintegrant.[14] In this formulation, 4% of sodium alginate was added yet slower disintegration times were observed. This result corroborated the study of Richardson et al., (2005) that sodium alginate may provide a barrier against gastric reflux or site-specific delivery of the therapeutic agent.[15]

Table 2. In process quality control test results

Trial formulation	Angle of repose	Compressibility index	Hausner's ratio	Tapped density	Bulk density	Flow character	Moisture content
1	23.20	1.16	13.51	0.63	0.54	Good	2.98 %
2	29.46	1.06	5.71	0.60	0.57	Excellent	2.66 %
3	26.57	1.09	8.33	0.60	0.56	Excellent	2.87 %
4	26.56	1.16	13.51	0.63	0.54	Good	1.85 %
5	26.57	1.08	6.97	0.50	0.47	Excellent	2.01 %
6	26.56	1.125	11.11	0.48	0.44	Good	1.96 %

All tests were done in triplicate and data were recorded as mean.

Table 3. Finished product quality control results

Finished product quality control test	Trial formulation						Standard	
	1	2	3	4	5	6	Tablet	Liquigel
Tablet hardness (kg)	4.2	3.85	4.1	2.95	2.95	3.35	-	-
Tablet thickness (mm)	1.37	1.40	1.36	1.35	1.33	1.35	-	-
Friability (%)	0.65	0.56	0.63	0.31	0.33	0.46	-	-
Wetting time (sec)	64	46	59	36	32	43	-	-
Swelling index (%)	86.67	85.19	79.63	96.72	98.36	92.73	53.85	-
Disintegration time (sec)	223	136	76	43	59	57	720	-
Weight of 20 tablets (g)	14.670	14.246	13.714	17.042	13.056	15.554	12.270	12.076
Percent Label claim	91.93	100.40	95.97	109.35	89.63	92.04	93.62	99.76

All tests were done in triplicate and data were recorded as mean.

Therefore, sodium may delay the disintegration time of this formulation. In the Formulation 2, less amount of sodium alginate was used (2 %) which led to faster disintegration time compared to Formulation 1. However, it did not pass the acceptable disintegration time for a fast dissolving tablet which is 60 sec. Hence, disintegrants such as microcrystalline cellulose, polyvinylpyrrolidone, and maltodextrin were added for Formulation 3 which led to faster disintegration time. For PEG 6000 series, all formulations failed to meet the acceptance criteria for disintegration time but Formulation 3 was selected as the best formulation since it exhibited the fastest disintegration time.

For Formulation 4, Formulation 5, and Formulation 6, carbopol was used as the polymer for the hydrogel-based matrix tablet and faster disintegration times were observed. While carbopol is generally used as a controlled release agent (5-30 %), the results were supported by the study made by Abbasi et al,[11] where they used carbopol (10 %) in fast disintegrating captopril formulation. A slight increase in the amount of carbopol was used in Formulation 5 and Formulation 6 which slowed disintegration time. For Formulation 6, a pre-mix powder of microcrystalline cellulose and anhydrous dibasic calcium phosphate replaced lactose as tablet binder which resulted to enhanced tableting performance and fewer rejected tablets. Silicified microcrystalline cellulose was added since it is a water-soluble cellulose derivative which aids the fast hydration of drug, dilution of the gel layer, and faster drug release.[16] Based on the results, the higher polymer content accompanied with slower disintegration time can be attributed to smaller micropores and increased tortuosity.[17]

As presented in Table 3, the formulations that exhibited the fastest disintegration time were Formulation 3 for the PEG 6000 series and Formulation 4 for the carbopol series. Therefore, Formulation 3 and Formulation 4 were chosen to be the best formulations to proceed to comparative dissolution test and stability test.

In vitro comparative dissolution test of Formulation 3, Formulation 4, standard tablet, and standard liquigel were conducted since *in vivo* measurement of the active pharmaceutical ingredient (API) in blood and urine is prone to error due to matrix complications. Therefore, *in vitro* dissolution measurement of the active pharmaceutical ingredient from the oral dosage forms are recognized by regulatory agencies as an important consideration in the formulation process. From the dissolution test results, the similarity factor (f2), measurement of the similarity in the percentage (%) dissolution between the two curves, can be calculated. If f2 ≥ 50, the drugs are considered to be similar and no further *in vivo* studies are necessary.[18]

Based on comparative dissolution test results as shown in Figures 1 and 2, only the standard tablet for ibuprofen did not pass the acceptance criteria for dissolution tests which is to release 80% of labelled ibuprofen after 60 minutes. Based on the percent drug release, similarity factor and p-values were calculated. As shown on Table 4 and Table 5, the similarity factor of f2 > 50 indicates that both Formulation 3 and Formulation 4 were similar to both standards. Based on the

Table 4. Similarity factor and p-value of Formulation 3 and Formulation 4 vs. standard liquigel

	Similarity factor (f2)	Remarks	t-value	p-value	Remarks
Standard liquigel vs. Formulation 3	50.67	Similar	1.4101	0.1839	Not significantly different
Standard liquigel vs. Formulation 4	51.36	Similar	-0.0366	0.9714	Not significantly different

Table 5. Similarity factor and p-value of Formulation 3 and Formulation 4 vs. standard tablet

	Similarity factor (f2)	Remarks	t-value	p-value	Remarks
Standard tablet vs. Formulation 3	50.62	Similar	-1.4718	0.1668	Not significantly different
Standard tablet vs. Formulation 4	50.38	Similar	-3.2707	0.0067	Significantly different

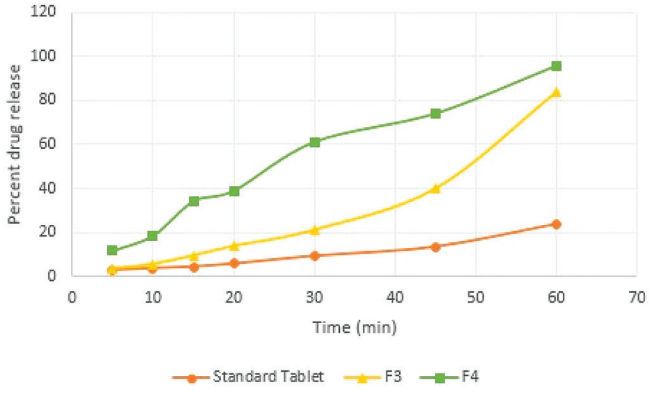

Figure 1. Percent drug release of standard tablet, Formulation 3 (F3), and Formulation 4 (F4).

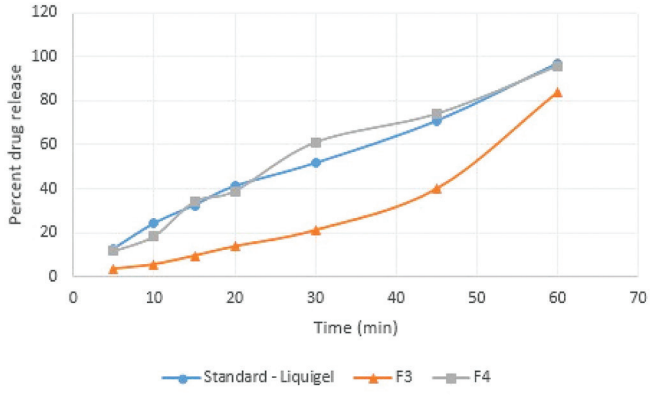

Figure 2. Percent drug release of standard liquigel, Formulation 3 (F3), and Formulation 4 (F4).

p-values, there is a significant difference between the standard tablets and Formulation 4 (p-value < 0.05) however there was no significant difference between Formulation 3 against both standards and Formulation 4 against the standard liquigel (p-value > 0.05).

For the stability test, Formulation 3 showed yellow coloration on the third week and swelling, fusion of tablets, and characteristic pungent odor on the fourth week. The assay for last three characteristics failed to meet the acceptance criteria. Hence, Formulation 3 failed the stability test. Formulation 4 passed the stability tests as there was no sign of cracking, capping, chipping, coating, swelling, mottling, discoloration, fusion of tablets, or presence of excessive powder up to the fourth week. No characteristic odor was observed. Thus, the tablets were able to meet the acceptance criteria.

The results of the stability test may be due to the fact that polyethylene glycol compounds are very hygroscopic[9] which was evident when the tablets were subjected to a humid environment. Furthermore, in a stability study made by Hampton Research,[19] the aging of polyethylene glycols can alter the chemical properties of common polyethylene glycols which could result in increased levels of aldehydes, carboxylates, and peroxides. It was found that aging of polyethylene containing compounds can be accelerated by various factors such as warm temperature, light, and presence of oxygen. Polyethylene compounds are more stable when stored in frozen or refrigerated state compared to room temperature. Although carbopol is also hygroscopic, it is stable even at temperatures up to 104°C for two hours without affecting their efficiency.[14] Therefore, carbopol is more preferred as the potential polymer for hydrogel-based matrix formulation than PEG in terms of stability.

CONCLUSION

Based on the results of quality control tests, comparative dissolution test, and stability test, it is concluded that carbopol was the superior polymer over polyethylene glycol 6000. The optimized formulation of ibuprofen hydrogel-based matrix tablet was found to be similar with the standard liquigel based on the percent drug release and similarity factor. In this study, an optimized ibuprofen hydrogel-based matrix tablet formulation improved the dissolution rate of ibuprofen.

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Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

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