Design and in-vitro characterization of orally disintegrating modified release tablets of naproxen sodium

Amjad Hussain¹, Maham Misbah¹, Nasir Abbas¹, Muhammad Irfan², Muhammad Sohail Arshad³, Rahat Shamim¹, Nadeem Irfan Bukhari¹, Faisal Mahmood¹

¹University College of Pharmacy, University of the Punjab, Lahore, 54590, Pakistan

²College of Pharmacy, Government College University, Faisalabad (38000)

³Department of Pharmacy, Bahauddin Zakariya University, Multan (60800, Pakistan)

INTRODUCTION: The aim of this study was to prepare orally disintegrating, slow release tablets of naproxen sodium for prompt onset and sustained action required in many types of acute pains.

METHODS: Tablet formulations containing varying concentration of croscarmellose sodium (a super-disintegrant) and Soluplus® (as release modifier), were prepared by wet granulation method using a single punch tablet machine. The prepared granules were evaluated for their bulk properties and the tablets were evaluated for hardness, disintegration time and drug release profiles.

RESULTS: The results showed that the granules so prepared have good flow and compressional properties. The disintegration time (DT) of tablets <30 seconds was achieved by selecting an optimum concentration of croscarmellose sodium. The drug release from the tablets was sustained for 2 hrs by incorporating suitable amount of soluplus.

DISCUSSION AND CONCLUSION: This study depicts the use soluplus (a novel solubilizer) for the first time as release modifier of API from the tablets.

Keywords: Orally disintegrating tablets, modified release tablets, naproxen sodium, soluplus

INTRODUCTION

The design and manufacturing of solid oral dosage forms (tablets and capsules) are widespread as the oral route is preferred by both healthcare professionals¹ and patients as well²⁻³. The main advantages include: easy for self-administration⁴, cost-effective⁵ highly stable dosage forms and dispensing in more ready to administer forms⁴. On the other hand; some problems are also associated with the use of solid oral dosage forms in conventional or immediate release tablets is the frequent administration and small residence time of the drug in the plasma due to short half-life, leading to fluctuation in plasma level and non-compliance by the patients due to frequent administration. The development of modified release tablets is an advancement in the design of tablets which overcomes these problems associated with the conventional tablet design and promotes a constant plasma level and improves the patient compliance⁶⁻⁷.

Where these modified release tablets overcome several problems associated with conventional tablets; these also possess the drawback of being bigger in size than the immediate release tablets of the same drug. This makes them difficult to swallow, particularly for geriatric patients and those suffering from dysphagia, a condition marked by difficulty in swallowing which is reported in about 35 % of the general population, 30–40 % of elderly in-patients and 18–22 % of all people in long-term care facilities. This difficulty reduces patient compliance and can be overcome⁴ by producing an orally disintegrating tablets (ODTs). An orally disintegrating tablet is one that disintegrates into small granules within 30 secs after its placement in the oral cavity⁸. The small granules produced thereby can easily be swallowed as compared to swallowing the whole tablet⁹. ODTs are also advantageous for travelers who can take their medicine without the requirement of water. According to a survey, the majority of patients prefer to have an orally disintegrating tablet than conventional forms of tablets⁸. Therefore, an orally disintegrating tablet improves patient compliance.

Recently, researchers have become increasingly interested in developing modified release orally disintegrating tablets which combine the above-mentioned benefits of both modified release dosage forms and orally disintegrating tablets¹⁰⁻¹¹.

Naproxen sodium is the drug of choice in rheumatoid arthritis-associated joint pain and early morning stiffness. Hence, a modified release preparation of naproxen sodium would be useful in maintaining a sustained level of naproxen sodium at the required time. The half-life of naproxen sodium is 14 hours, therefore, its effect is long lasting but repeated administration of an immediate release formulation will lead to spikes in plasma concentration of the drug thus making the pain relieving effect erratic and remitting. Besides leading to gastro-intestinal irritation due to high drug concentration at one time. In order to maintain a sustained level of drug plasma concentration with minimum variations, a sustained release formulation is required which will lead to sustained pain relief action and a

more optimal therapeutic response with minimal side effects. Moreover, due to the high protein binding of naproxen sodium (99.7 %), it may be more efficient to deliver this drug as a sustained release dosage form ¹².

Additionally, an orally disintegrating formulation with sustained release characteristics will certainly benefit the patient with quick onset of action. Naproxen sodium has been declared as an ideal candidate for development into an orally disintegrating tablet in ¹³. In the present study, an orally disintegrating modified release matrix tablet of naproxen sodium was prepared by incorporating Soluplus®, a novel amphiphilic graft co-polymer. In parallel, the potential of Soluplus® as a tablet binder as well as a release modifier for water-soluble drug has been investigated.

MATERIALS AND METHODS

Naproxen sodium was obtained as gift sample from Pacific Pharmaceuticals Pvt. Ltd, Lahore Pakistan; Soluplus was purchased from BASF, UK, Croscarmellose Sodium, starch and all other excipients (pharmaceutical grade) were purchased from local market of Lahore, Pakistan and were used as received.

Preparation of orally disintegrating tablets

The design of tablet formulations was accomplished in two phases. The target of first phase was to achieve fast disintegration of tablets i.e. within 30 sec. Eight trial tablet formulation (F1-F8) were prepared (see Table 1) by wet granulation method by varying the concentration (2-20 %) and distribution (extra-granular/intra-granular) of superdisintegrant i.e. Croscarmellose sodium. For this purpose, a dry mixture of naproxen sodium (API), starch (disintegrant) and lactose monohydrate (diluent) was prepared in a tumbler mixture. This mixture was then moistened by using 2.5 % soluplus solution as binder and the wet mass was screened through sieve 8 to produce granules. The granules were then dried in hot air oven for 24 hrs. Croscarmellose sodium as superdisintegrant ¹⁴ and magnesium stearate (1.5%) as lubricant were mixed with these granules and the mixtures was compressed in single punch tablet machine (Locally manufactured, Lahore, Pakistan).

Table 1: Composition of trial formulations F1-F8.

Formulation	Naproxen sodium (mg)	CSS (% w/w) Extra-gran	CSS (mg) Intra-gran	Starch (mg)	Magnesium stearate (mg)	Lactose Qs (mg)
F1	200	10	-	10	3	400
F2	200	20	-	10	3	400
F3	200	30	-	10	3	400
F4	200	40	-	10	3	400
F5	200	5	5	10	3	400
F6	200	10	10	10	3	400
F7	200	15	15	10	3	400
F8	200	20	20	10	3	400

In the next phase; sustaining the release of naproxen sodium was the target. For this purpose, eight test formulations (F9-F16) were prepared having same composition of API, diluent, superdisintegrant (optimum concentration) and binder, except the incorporation of varying concentrations of soluplus (5 to 50 % w/w of drug), as release modifier. A control tablet formulation of naproxen sodium (F0) was also prepared containing superdisintegrant but no release modifier for comparison purposes.

Characterization of granules

In order to determine the compaction and flowability; bulk and tapped densities and angle of repose of prepared granules of each formulation were measured. Porosity, compressibility index and hausner ratio were calculated using tapped and bulk densities data.

Characterization of tablets

The tablets of each formulation were tested for their hardness, disintegration time and drug release characteristics. Tablet hardness/crushing strength was measured by applying a force till the crushing of tablet using a digital hardness tester (Curio/ 2020+, Pakistan) in triplicate and the average value was reported for each formulation.

The disintegration of each formulation was tested by using the method described in literature ¹¹. For this purpose, tablet from each formulation was placed in a petri dish containing distilled water maintained at ~37 °C. The time taken by the tablet to disintegrate completely was recorded by stopwatch. The measurements were performed in triplicates and the average disintegration time for each test formulation was reported. The disintegration pattern of tablets was also photographed by Stereo-Zoom microscope (MODEL SZ2-ILST/Olympus Corporation, Japan).

In-vitro drug release studies

In-vitro drug release of naproxen sodium from the test formulations was carried out in a USP type II (Paddle) dissolution apparatus (Curio, Pakistan). Phosphate buffer (pH 7.4) was selected as dissolution medium and 900 mL of this was added in each flask of the test apparatus and the temperature of the medium was maintained at 37 ± 0.5 °C. One tablet was placed in each dissolution flask and the paddle was rotated at the speed of 50 rpm. Aliquots of 5 mL was withdrawn at various intervals and replaced with equal amounts of fresh dissolution medium to maintain the sink conditions. The samples were diluted adequately and analyzed spectrophotometrically for the naproxen sodium content.

For the purpose of UV assay, absorbance of each sample was recorded in triplicate at 271 nm (i.e. $\lambda_{\max}$ of naproxen sodium determined in this study). From the average value of this absorbance, the corresponding value of concentration was calculated from the calibration curve. The calibration curve (absorbance vs concentration) was plotted by measuring the absorbance of stock solution and its dilutions. The plot was linear between the concentration range of 10 µg/mL and 50 µg/mL of naproxen sodium with coefficient of regression approaching to unity i.e. 0.998. The value of intercept and gradient is 0.0093 and 0.0131, respectively. Drug release are presented as mean $\pm$ standard deviation (SD) and were analyzed by one-way ANOVA, the Statistical differences were set at $p < 0.05$.

RESULTS AND DISCUSSION

Bulk properties of granules

The values of bulk and tapped density of the granules of all formulation have been summarized in Table 2. The values of bulk density ranged between 0.234 to 0.341 g/mL and of tapped density between 0.250 to 0.357 g/mL. From these values the respective Carr's index and Hausner's ratio were obtained.

The values of Carr's index lies in the range of 3.23 to 12.5 % whereas values of Hausner's ratio lie between 1.03 and 1.13 that shows excellent flow properties of all formulation (F1-F16) except one (F3) formulation that showed good flow properties. Carr's index corresponds to powder bridge strength and stability, and the Hausner's ratio depicts the inter-particulate friction. Therefore, given the low values of both these parameters for all formulations, one can expect good die fill and proper compressible tablets from all formulations¹⁵.

Table 2: Values of bulk density, tapped density, Hausner's ratio, Porosity and Carr's index and corresponding flow properties of granules of different formulations.

Formulation	Bulk volume	Tapped volume	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index	Hausner Ratio	Porosity	Flow properties
F1	5.2	5.0	0.288	0.300	4.0	1.04	3.8	Excellent
F2	5.4	5.2	0.278	0.288	3.85	1.04	3.7	Excellent
F3	5.4	4.8	0.278	0.313	12.5	1.13	11.11	Good
F4	6.2	5.6	0.242	0.268	10.7	1.11	9.6	Excellent
F5	6.0	5.4	0.250	0.278	11.1	1.11	10	Excellent
F6	6.4	6.2	0.234	0.242	3.23	1.03	3.12	Excellent
F7	6.2	5.6	0.241	0.268	10.7	1.11	9.6	Excellent
F8	6.4	5.8	0.234	0.259	10.3	1.1	9.37	Excellent
F9	4.8	4.6	0.313	0.326	4.3	1.04	4.16	Excellent
F10	4.4	4.2	0.341	0.357	4.8	1.05	4.54	Excellent
F11	5.2	5.0	0.288	0.3	4	1.04	3.84	Excellent
F12	5.4	5.0	0.277	0.3	8	1.08	7.40	Excellent
F13	6.2	6.0	0.242	0.25	3.3	1.03	3.22	Excellent
F14	6.4	6.0	0.234	0.25	6.7	1.06	6.25	Excellent
F15	6.0	5.4	0.25	0.278	11.1	1.11	10	Excellent
F16	6.0	5.6	0.25	0.268	7.1	1.07	6.66	Excellent

Hardness of prepared tablets

The tablet hardness of trial formulations F1-F4 between 2.9 to 3.3 Kg/cm² (Table 3). However, incorporation of disintegrant into the granules (formulation F5-F8) increases the overall hardness of the tablets (average hardness ~3.4 Kg/cm²). The test formulations F9-F16 also show the hardness of ~3.4 Kg/cm². These hardness values are relatively lower than that of regular tablets i.e. 4-6 Kg/cm²¹⁶, however; these are still sufficient to tolerate any stress during manufacturing and processing¹⁷.

Table 3: Values of Hardness and disintegration of trial and test tablets formulations.

Trial formulation			Test formulation		
Formulation	Hardness Kg/cm ²	Disintegration time (min)	Formulation	Hardness (Kg/cm ²)	Disintegration time (Sec)
F1	2.87±0.06	68.0±1.0	F9	3.4±0.1	27.1±0.1
F2	3.30±0.20	49.5±0.5	F10	3.2±0.1	27.3±0.1
F3	3.07±0.06	36.5±0.5	F11	3.4±0.1	27.3±0.1
F4	3.1±0.1	7.5±0.5	F12	3.3±0.1	27.5±0.1
F5	3.6±0.2	2.4±0.4	F13	3.4±0.1	27.1±0.1
F6	3.5±0.25	0.45±0.06	F14	3.2±0.1	28.2±0.1
F7	3.4±0.15	0.85±0.06	F15	3.1±0.1	27.5±0.1
F8	3.4±0.2	0.73±0.08	F16	3.1±0.1	28.2±0.1
			F0	3.3±0.1	26.3±0.1

Disintegration time

The results show that the disintegration time is inversely proportional to the concentration of superdisintegrant as it decreases from 68 min of F1 containing 5% of disintegrant to 7.5 min of F4 containing 20% of the disintegrant. The mode of addition of disintegrant also influences the disintegration time. The formulations containing only extra-granular disintegrants (F1-F4) have shown the disintegration time >35 min. However, in formulations where the disintegrant was also added intra-granularly (F5-F8), the disintegration time was much lower and lies between 0.45 to 7.5 min (Table 3). Out of these formulations, F6 has shown rapid disintegration i.e. 0.45 min (27.3 sec) that satisfies the limits set for ODTs. This indicated that it is not only the addition of superdisintegrant, but also the mode addition (intra-granular or extra-granular or both) affects the disintegration time¹⁸. The formulation F6 depicted fastest dissolution rate as it contains both intra and extra granular disintegrant and the optimum concentration of super-disintegrants was 10 % each.

The disintegration time of all orally disintegrating test formulations (F9-F16) and blank formulation F0 was almost the same as trial formulations i.e. <30 sec as shown in Table 3. This indicates that the different concentrations of Soluplus® have no influence on disintegration time, probably due to its highly water soluble nature¹⁹.

The rapid disintegration of tablets can be attributed to wicking and swelling capability of starch and croscarmellose sodium²⁰. This was witnessed by microscopic images of tablets taken during disintegration test. Figure 1 shows that the tablets were swollen at 15 secs as the water was taken up by the disintegrants, which ultimately leads to the erosion of tablets after 20 sec.

Figure 1: Stages of tablet disintegration, showing swelling and erosion of a tablet of formulation F12 at 0 sec, 5 sec, 10 sec, 15 sec, 20 sec and 25 sec.

In-vitro drug release

The release profiles of naproxen sodium from test formulations F9-F16 have been shown in Figure 2. It is evident that in first 10 min the drug release was almost complete (100 %) from F0 and F9, while it was ~ 95 % from F10, ~90 % from F11, ~90 % from F12, ~75 % from F13, ~50% from F14, ~40% from F15 and ~ 20% from F16. This trend remained similar after 30 min, where the drug release was almost complete from formulations F10-F12 while F13, showed ~90%, F14 ~80%, F15 ~ 70% and F16 ~30 % drug release. The results indicate that drug release was sustained with the incorporation of Soluplus® in ODTs and increasing the concentration of Soluplus® in the formulations from F9 (containing 5 % w/w) to F16 (50 % w/w with drug) enhanced this release modifying effect of this co-polymer. Statistical analysis has shown a significant difference in drug release ($p < 0.05$) from all nine formulations. This indicated the significant role of Soluplus in the drug release.

Figure 2: Dissolution profiles of orally disintegrating tablet formulations (F0 and F9-F16) having no soluplus OR containing different concentrations of soluplus as release modifier.

This shows that Soluplus® has the ability to retard drug release of naproxen sodium, a water-soluble drug. This effect of Soluplus® has been shown in some previous studies²¹. In order to find the pattern of drug release from the tablets formulation, the release data was subjected different release models. It was shown from the results that Korsmeyer-Peppas model best fitted with the release profile with R² values 0.971. The value of release coefficient 'n' was 0.748 i.e. >0.5 indicating the non-Fickian or anomalous from the tablet formulations²².

CONCLUSION

This study concludes that the orally disintegrating sustained release tablets of naproxen sodium, a water-soluble drug were successfully prepared using an optimum concentration of croscarmellose sodium as disintegrant and Soluplus® as release modifier. The study highlighted the drug release modifier role of Soluplus for the first time from the tablet formulations.

Acknowledgement

Authors would like to thank university of the Punjab, Lahore, Pakistan for funding this project.

REFERENCES

- (1) Shojaei, A. H. Buccal mucosa as a route for systemic drug delivery: a review. *J. Pharm. Pharm. Sci.* 1998; 1(1): 15-30.
- (2) Abdelbary, G., Prinderre, P., Eouani, C., Joachim, J., Reynier, J. P., Piccerelle, P. The preparation of orally disintegrating tablets using a hydrophilic waxy binder *Int. J. Pharm.* 2004;278(2): 423-433.
- (3) Hirani, J. J., Rathod, D. A., Vadalia, K. R. Orally disintegrating tablets: A Review. *Trop.J. Pharm Res.* 2009 8(2): 61-172.
- (4) Mahal, R. K., Dr. Samein, L. H., Dr. Shehab, M. Formulation and In-vitro Evaluation of Orodispersible Tablet. *Int.J.Pharm.Sci.Res.* 2015;4: 689-696.

- (5) Sharma, D., Kumar, D., Singh, M., Singh, G., Rathore, M. Fast disintegrating tablets: a new era in novel drug delivery system and new market opportunities. *JDDT*. 2012;1(2): 74-86.
- (6) Reddy, K. R., Mutalik, S., Reddy, S. Once-daily sustained-release matrix tablets of nicorandil: formulation and in vitro evaluation. *AAPS PharmSciTech*. 2003;4(4): 480-488.
- (7) Tiwari, S. B., Murthy, T. K., Pai, M. R., Mehta, P. R., Chowdary, P. B. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. *AAPS PharmSciTech*. 2003;4(3): 18-23.
- (8) Sagar, N., Goswami, L., Kothiyal, P. Orally disintegrating tablets: A review. *Int.J.Apl Res*. 2012;3(10): 1222-1228.
- (9) Chang, R.-K., Xiaodi, G., Burnside, B. A., Couch, R. A. Fast-dissolving tablets. *Pharm tech*. 2000;24(6): 52-58.
- (10) Fini, A., Bergamante, V., Ceschel, G. C., Ronchi, C., de Moraes, C. A. F. Fast dispersible/slow releasing ibuprofen tablets. *Eur. J. Pharm. Biopharm*. 2008;69(1): 335-341.
- (11) Wei, Q., Yang, F., Luan, L. Preparation and in vitro/in vivo evaluation of a Ketoprofen orally disintegrating/sustained release tablet. *Drug Dev. Ind. Pharm*. 2013;39(6): 928-934.
- (12) Amaral, M. H., Lobo, J. S., Ferreira, D. Effect of Hydroxypropyl Methylcellulose and Hydrogenated castor oil on naproxen release from sustained-release tablets *AAPS PharmSciTech*. 2001;2(2): 14-21.
- (13) Badgujar, B., Mundada, The technologies used for developing orally disintegrating tablets: A review. *Acta Pharm*. 2011;61(2): 117-39.
- (14) Setty, C. M., Prasad, D. V. K., Gupta, V. R. M., & Sa, B. Development of fast dispersible aceclofenac tablets: effect of functionality of superdisintegrants. *Ind. J. of pharm. Sci*. 2008;70(2): 180.
- (15) Shah, R. B., Tawakkul, M. A., & Khan, M. A. Comparative evaluation of flow for pharmaceutical powders and granules. *AAPS PharmSciTech*. 2008;9(1): 250-258.
- (16) Elkhodairy, K. A., Hassan, M. A., & Afifi, S. A. Formulation and optimization of orodispersible tablets of flutamide. *Saudi Pharma. J*. 2014;22(1): 53-61.
- (17) Siddiqui, M. N., Garg, G., Sharma, P. K. Fast dissolving tablets: preparation, characterization and evaluation: an overview. *IJPSRR*. 2010: 4(2): 87-96.
- (18) Gohel, M. C., Parikh, R. K., Brahmabhatt, B. K., & Shah, A. R. Preparation and assessment of novel coprocessed superdisintegrant consisting of crospovidone and sodium starch glycolate: a technical note. *AAPS PharmSciTech*. 2007;8(1), E63-E69.
- (19) Djuric, D. *Solubility enhancement with BASF pharma polymers: Solubilizer compendium*. BASF SE Pharma Ingredients & Services, Germany 2011: (pp. 67-72).
- (20) Khairnar, D. A., Anantwar, S. P., Chaudhari, C. S., & Shelke, P. A. Superdisintegrants: An emerging paradigm in orodispersible tablets. *Int J Biopharm*. 2014;5(2), 119-28.
- (21) Naelapää, K., Boetker, J. P., Müllertz, A., Rades, T., Rantanen, J., and Bar-Shalom, D. Soluplus® for modifying the release of highly water soluble APIs. *AAPS Annual meeting and exposition, Chicago, USA 2012*.
- (22) Ford, J. L., Rubinstein, M. H., McCaul, F., Hogan, J. E., & Edgar, P. J. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. *Int. J pharm*. 1987;40(3): 223-234.