Two-drug Controlled Release Solid, Oral Formulations for Combination Pain Relief and Anti-platelet Therapy

Corbett, J.T.[1], Shalaby, M.[2], Gray, K.D.[1], and Shalaby, S.W.[1]
[1]Poly-Med, Inc., Anderson, South Carolina
[2]Lehigh Valley Hospital, Allentown, Pennsylvania

Statement of Purpose: A recent report by the present investigators dealt with solid, oral pharmaceutical formulations for combination therapy comprised of extended release acetaminophen as an analgesic agent admixed with a second compound as an anti-inflammatory agent (with concomitant antipyretic and analgesic properties), plus a third component to reduce gastric acid secretion.[1] Additionally, a novel bilayer tablet (Theraprene-I®) for the controlled release of three active agents has been described.[2] This tablet is comprised of acetaminophen in one disc (or layer) adjoined with a second disc comprised of the non-steroidal anti-inflammatory drug (NSAID) naproxen and ranitidine, an agent that reduces gastric acid secretion. The present investigators are now extending combination therapy beyond those agents that contain acetaminophen. Aspirin is the most widely-used anti-platelet agent for the prevention of cardiovascular disease. Naproxen is a popular anti-inflammatory/analgesic. Unfortunately, both agents indirectly inhibit the production of the protective layer in the stomach that shields the gastric mucosa from the acidic environment. As such, both agents are known to increase the risk of gastrointestinal bleeding. Recognizing the therapeutic importance of such agents and recognizing the clinical importance of co-administration of these drugs with agents that suppress gastric acid secretion, the present investigators have pursued the development of different mixed formulations for combined therapy using conventional and novel methods for tablet preparation. The present study provides preliminary results on the release of the different components of the subject formulations.

Methods: To prepare the first type of combination therapy tablet, a single layer tablet, PEG 20,000 (75mg), aspirin (325 mg) Ranitidine HCl (37.5 mg), and microcrystalline cellulose (MCC) (325 mg) were all mixed thoroughly and pressed using 10,000 pounds. The amounts of drug were chosen based on the therapeutic amounts needed for each. For coating, the tablets were dipped in an isopropyl alcohol solution of hydroxypropyl cellulose until the desired add weight on was achieved after drying. The coated tablet is denoted Theraprene-II®. In order to monitor the release profile, the tablet was placed in a simulated gastric fluid (low pH) for one hour and then removed and placed in distilled water. This is to simulate the aqueous environment in the stomach and then intestine. At selected time points, the water was removed and distilled water was placed on the tablet. All tablet incubation was performed at 37ºC. The simulated gastric fluid and water media that had contact with the tablet were evaluated for drug content using reverse phase HPLC. The amount of drug released compared to the original amount in the tablet was calculated from the assay and reported as a percentage of the total versus time for each drug contained in the tablet.

To prepare a second type of combination therapy tablet (Theraprene-III®) comprising naproxen sodium (110 mg) and ranitidine HCl (37.5 mg), protocols similar to those described above for the preparation and characterization of Theraprene-II were used.

Results: The release data for Theraprene-II in Table I indicate that about 20 to 30% of the ranitidine and less than 2 to 10% of aspirin are released in the first two hours. This release profile would allow for feasible, timely, and effective protection of the gastric mucosa by ranitidine against the effects of aspirin. The therapeutic and protective effects of the ranitidine (reduced gastric acid secretion) will begin before a significant amount of aspirin is absorbed. Similarly, for Theraprene-III, within the first two hours, about 35% of the ranitidine and about 5% of naproxen are released, respectively. These data prompt the suggestion to use Theraprene-II or –III as anti-platelet and anti-inflammatory formulations, respectively.

Table I. Release Data of Two-drug Component, Single-layer Theraprene-II Tablet*

Drug	Aspirin	Ranitidine
Initial Weight, mg	325	27.5
% Release at hours:		
1	1.86	18.27
2	4.35	31.30
4	9.48	50.98
6	15.39	69.41
8	21.76	84.67

*Coated with 1.03% hydroxypropyl cellulose

Table II. Release Data of Two-drug Component, Single-layer Theraprene-III Tablet*

Drug	Naproxen Na	Ranitidine HCl
Initial Weight, mg	110	37.5
% Release at hours:		
1	0.32	15.46
2	5.35	34.91
4	52.18	95.04
6	56.02	99.09
8	56.75	99.31

*Coated with 1.66% hydroxypropyl cellulose

Conclusions: Bifunctional, coated tablet combination formulations of ranitidine and aspirin (Theraprene-II) or naproxen (Theraprene-III) can be prepared as controlled release systems for anti-platelet therapy and pain relief.

References:

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