Recent Advanced of Multiple Unite Pellet System (MUPS) Technology in Formulation of Pharmaceutical Products: A Review

1V. K. Chatap*, 2Deshbandhu Joshi

1Department of Pharmaceutics, H. R. Patel Institute of Pharmaceutical Education and Research, Karwand Naka, Shirpur, Dhule-425405, Maharashtra.
2 Department of pharmaceutical chemistry, Shrinathji Institute of Pharmacy, Nathdwara-313301 (Rajasthan)

Abstracts:
The oral route of drug administration is the most important and most user-friendly route of administration. In recent years, Multiple Unit Pellet Systems (MUPS) tablets are widely used in solid dosage form design. MUPS is considered to provide pharmacokinetic advantages compared to monolithic dosage forms. Combination of drug substances and release profiles can be provided by formulating the MUPS tablets with different pellet qualities or combining pellets with drugs in powder or granulated form. MUPS tablet contains several hundred of coated pellets of active pharmaceutical ingredients which delivered the drug at predetermined rate and absorption to provide constant blood profile. MUPS are easily administered as disintegratable tablet which disperse into their subunits across the stomach and the small intestine, leading to predictable oral transition and constant bioavailability.

Keywords: Pellets, MUPS, Pelletization, Sustained Release, Spheronization, matrix pellets

1. Introduction:
The oral route of drug administration is the most important and most user-friendly route of administration [1-5]. In recent years, Multiple Unit Pellet Systems (MUPS) tablets are widely used in solid dosage form design. MUPS is considered to provide pharmacokinetic advantages compared to monolithic dosage forms [6-8]. Typically, modified release pellets are contained in MUPS tablets[9-12]. Modified release drug delivery systems have acquired very important role in pharmaceutical research and development [13]. Tablets are indeed the most popular solid dosage form for oral administration. One category of tablet formulations that has gained remarkable importance in drug therapeutics owing to various benefits it offers is controlled or modified release formulations. Controlled release capsules often containing plurality of coated pellets is yet another category of solid oral formulation that offers analogous therapeutic benefits. A relatively more recent approach that has come into existence is the one that combines the features of both controlled release tablets and modified release capsules in one dosage form. Such a system is known as MUPS tablets. MUPS is abbreviation for Multiple-Unit Pellet System. However, from pharmaceutical industry and research perspective, the term in general refers to MUPS compacted into tablets. Thus, the resulting tablets prepared by compaction
of modified release coated multiparticulates or pellets are called as MUPS. Compaction of MUPS is a challenging area. Aggressive research but by few individuals and industries is being carried out worldwide in this area [11].

Properties of an Ideal MUPS Tablet (11 Articles) (10 Articles)

A MUPS tablet should possess following characteristics:-

1. The compacted pellets should not fuse into a nondisintegrating matrix during compaction. The dosage form must disintegrate rapidly into individual pellets in gastrointestinal fluids.

2. The drug release should not be affected by the compaction process.

3. With MUPS containing reservoir-type coated pellets, the polymeric coating must be able to withstand the compression force; it may deform, but it should not rupture.

4. Pellet compacts must possess optimum physical strength to withstand the mechanical shocks encountered in their production, packaging, shipping and dispensing.

5. Surface of compacted MUPS should be smooth and elegant and devoid of pinholes and other imperfections and should facilitate ease of film coating if needed.

6. Pellets should not show any interaction like developing electrostatic charges; during compression.

7. The pellets should not show any deviation in its release even after compression.

8. The coated pellets during the process of compression should not fuse into a nondisintegrating matrix and should not lose its coating integrity either by breaking or cracking or rupturing the coating layer(s) or pinholes and other imperfections.

Advantages of Compaction of MUPS over Conventional Modified-Release Tablets and/or Pellet-Filled Capsules and Tablets (11 Article)

1. The compression of multiparticulates into tablets, unlike the hard gelatin capsule, is a tamper-proof dosage form and has greater physicochemical and microbiological stability of pellets as they are embedment in the inert matrix.

2. Tablets have less difficulty in esophageal transport than capsules.

3. Tablets containing coated subunits can be prepared at a lower cost than these subunits filled into hard gelatin capsules because of higher production rate of the tablet press.

4. The expensive control of capsule integrity after filling is also eliminated.

5. In addition, tablets containing multiparticulates without losing the controlled-release properties could be scored, which allow a more flexible dosage regimen.

6. Composing the tablet with equal or different kinds of particles can be combined and so that very specific release profiles can be generated.

7. Once the coated subunits have been developed different dose strengths can be prepared just by varying the tablet size keeping the same composition – no additional development efforts need to be taken.

8. Another option for dose strength variation is the development of dividable multi-unit tablets. Since the release characteristics are related to the single subunits, dividing the tablet does not affect the release characteristics as it is true for monolithic tablets.

9. Rapid and uniform transit of subunits contained in tablets from the stomach into small intestine owing to their small size, drug release is more uniform and possibility of dose dumping is avoided with minimized tendency for inter-subject variations.

[10. Rapid but uniform transit of micro pellets contained in MUPS from the stomach into small intestine owing to their small size and thus lesser possibility of localized irritation, better and more
Uniform drug absorption and greater bioavailability.

11. Uniform emptying of micro pellets from stomach into small intestine facilitates rapid dissolution of enteric coating and drug release resulting in early tmax and Cmax (peak time and peak plasma concentration) in case of delayed-release formulations. In case of controlled-release preparations, drug release is more uniform and possibility of dose dumping is avoided with minimized tendency for inter-subject variations.[10]

**Pharmacodynamic advantages:** [11]

Owing to rapid and uniform gastric emptying and subsequently uniform drug dissolution of pellets in the gastrointestinal tract due to their small size and larger surface, uniform drug absorption is facilitated which results in consistent and controlled pharmacological action.

A further reduction in inter- and intra-subject variability in drug absorption and clinical response is facilitated since the number of pellets per MUPS dosage form is much more than a conventional pellet-filled capsule and possibility of dose dumping (in stomach) and incomplete drug release is further minimized.

**Disadvantages of MUPS:**

1. Dosing by volume rather than number and splitting into single dose units as required.
2. Involves capsule filling which can increase the costs or tabletting which destroy film coatings on the pellets.
3. The size of pellets varies from formulation to formulation but usually lies between 1 to 2 mm.

**Methods of pelletization** [13, 16-18]

Compaction and drug layering are the most widely used pelletization techniques. Other methods such as globulation, balling are also used in development of pellets in a limited scale. Some of the desirable properties of the pellets include pellets shape should be near spherical and have a smooth surface; both considered important characteristics for subsequent film coating. Additionally, the particle size of pellets should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 0.5 and 1mm.

**Powder layering:**

Powder layering involves the deposition of dry powders of drugs and excipients on neutral spheres with the help of binding liquids. Powder layering involves simultaneous addition of binding agents and dry powders; hence it requires specialized equipments like spheronizer. If the process is set-up properly, hourly weight gains up to 300% are possible, which indicates the processing option is very fast and efficient.

**Solution / suspension layering:**

Solution/suspension layering involves the deposition of solution or suspensions of drug substances and binder over the neutral spheres. Consequently conventional coating pans, fluid bed processor, centrifugal granulators, wurster coaters have been used successfully to manufacture pellets by this method. To achieve uniform layers the bottom spray method should be the processing option of choice. Average weight gain per processing hour is about 15-20%, because 80 – 85% liquid vehicle have to be evaporated.

**Extrusion and Spheronization:** This processing option is the oldest known industrial pelletizing technique. First all ingredients are blended, then by adding liquid a wet dough is formed, which is passed through an extruder with defined dye sizes.

Other pelletization methods such as globulation, cryopelletization, spray drying, spray congealing, balling, and compression are used, although on a limited scale in the preparation of pharmaceutical pellets.

**Desirable Properties of Pellets:** [16]

1. **Uncoated pellets:**
   a) Uniform spherical shape,
   b) Uniform size,
V. K. Chatap / Recent Advanced of Multiple Unite Pellet System (MUPS) Technology in Formulation of Pharmaceutical Products: A Review

- Good flow properties,
- Reproducible packing,
- High strength,
- Low friability, Low dust,
- Smooth surface,
- Ease of coating.

2. Once coated:
- Maintain all of the above properties,
- Have desired drug release characteristics.

Figure 1: (a) Pellets, (b) Perfect pellet, (c) Coated pellet.

Pelletization Techniques [9-15]: Article 16
The preparation of spherical agglomerates can be approached by several techniques which can be subdivided into the basic types of systems shown in figure 3.

![Pelletization Techniques Diagram](image)

**Figure 1: Different pelletization techniques**

Types of MUPS formulations
MUPS formulations are broadly classified into two types:

1. MUPS with matrix pellets.
2. MUPS with polymer coated pellets.

MUPS with matrix pellets used generally in controlled release formulations. These pellets are coated with swellable or erodable polymers than diffusible polymers. The main problem of matrix
pellets in compression is fusion of polymer coating of pellets with other pellets and also polymer coating with extra-granular material. This can be counteracted by coating with any non interfering coating agent. For example hydrophobic coating agent prevent fusion of pellets-pellet and pellet-tabletting excipients.

**MUPS with pellets coated** using different pelletization techniques with all the desired characteristics for compression of pellets.

**Modulation of Pellet Coating:** [28]

After compaction into MUPS, maintenance of integrity of functional coating present on the surface of drug pellet is vital for preservation of desired product characteristics, which could be taste masking, sustained-release, delayed release or drug stability. Approaches adopted to retain the characteristics of applied membrane coating include:-

**a. Use of more elastic coating composition:** - Coating films have been made more elastic to withstand pressures of compaction by use of more elastic materials such as acrylic polymers instead of cellulosic polymers, use of more quantity of plasticizers or a more efficient plasticizer, etc.9 However, there should not be tendency of coated pellets to fuse with each other. Fusion tendency of pellets during compaction can be reduced by incorporation of lubricants and pigments such as talc in the coating composition but such materials are known to reduce elasticity of coating.

**b. Increased thickness of coating:**- Thicker but elastic polymeric coat can better withstand the deformation and rupturing forces of compression in comparison to thinner coatings.19

**c. Elastic/thermoplastic layer on the outer surface of drug pellets:**- Presence of an outer coating comprising of thermoplastic material such as carbowaxes on the surface of drug pellets, on which is applied the functional polymer coating, is known to absorb the stresses that may otherwise tear or fissure the outermost surface coating.20

**d. Powder layer over the surface of polymer coated pellets:**- Application of an integral but porous powder layer on the outside of polymer coated pellets results in preferential damage to the powder shell resulting in its breakage thus preventing/reducing transmission of compaction force to polymer coated core drug pellet present beneath.

**Modulation of Core Pellet:**

Besides the role of polymer coating on the pellets, the nature of core drug pellet can dramatically influence the damage to its own structure and the coating on its surface. Following pellet-related factors influence compaction characteristics:-

**a. Composition:**- Besides the inherent nature of drug, the other excipients that comprise core pellets can influence compaction characteristics. Presence of hard and brittle materials produce rigid pellet core that resists bulk deformation while elastic/plastic materials such as microcrystalline cellulose get easily deformed.

**b. Pellet porosity:**- If the pellets being compacted are coated, during compaction, pellet deformation (change in shape of pellets) and densification (reduction in pellet porosity) occurs to a larger extent while fragmentation is seen to a lesser extent. Porous pellets get more deformed during compaction, due to the higher freedom degree of rearrangement of the powder particles within them. On the other hand, more compact pellets are more intensively buffered during compaction by powder particles, because they cannot widely rearrange.[11]

**c. Pellet size:** - Larger pellets deform more easily than smaller pellets.12

**d. Pellet elasticity:** - Findings of various researchers on elasticity of core pellets are discordant. Bodmeier et al. claimed that the bead core should possess some degree of elasticity, in order to accommodate changes in shape and deformation during tabletting.18 To sum up, pellets that are smaller in size, stronger mechanically, less porous and more uniform in size distribution are more suited for compaction without deformation than pellets with wide size distribution, greater porosity, larger size and mechanically soft. Further, the polymer coating on such core drug pellets should be thick and elastic[21-26].

Often a combination of above approaches can be employed to result in a MUPS that retains the desired drug release and product characteristics. Even if compaction of coated particles do not result in destruction of coating, there still exist two possible outcome of compaction on drug release profile of coated pellets22:-
a. **Faster drug release:** The deformation of the substrate pellet may stretch out the coating, making it thinner or more permeable, which has a negative effect on the control of the drug release. This often explains that the release rate increases with increased irregularity of the compacted reservoir pellets.

b. **Prolonged drug release:** The densification of the substrate pellet may compress the coating, making it thicker or less permeable, and consequently prolong the drug release.

**Matrix pellets:** Pellets which inherently contain excipients that retard drug release by being contained within the matrix of pellet structure, for example matrix pellets of swellable polymers or waxes, retain their controlled release characteristics to a larger extent even on compression since the release of drug from such pellets depend upon swelling or erosion of matrix rather than by diffusion through the membrane.23,24 However, an important point that needs consideration in the design of MUPS of such matrix pellets is fusion of pellets with each other during compaction which may not be obvious during compression of coated pellets. Fusion of matrix pellets as a result of compaction can be avoided by application of film coating on such pellets or excessive blending with a hydrophobic agent separately prior to mixing them other extra granular materials before compression into tablets.[27-30]

*Figure 1:* Illustrates the MUPS comprising of reservoir and matrix pellets, figure 2 represents the approaches adopted for preparation of MUPS without damaging the membrane coating while figure 3 portrays the impact of compaction on pellet deformation and drug release.

*Figure 2:* Types of MUPS – (a) MUPS Figure 2. Schematic representation of containing polymer coated pellets, and the various approaches to prepare (b) MUPS containing matrix pellets MUPS of coated pellets formulation.
Table 1: Factors to be considered in the Design of MUPS Tablets

| Formulation Variables | Composition – hard brittle e.g. sucrose or plastic, e.g. MCC |
|-----------------------|-------------------------------------------------------------|
| Pellet core           | Size                                                        |
| Type – matrix or reservoir[31-33] | Shape                                                     |
|                       | Porosity                                                    |
Elasticity – is directly related to pellet composition
Thermoplastic layer on surface of drug pellet

**Membrane coating**
Type of polymer – cellulosic or acrylic, etc.
Coating thickness
Type and amount of plasticizer[34]
Presence of pigments
Additional outer coat on polymer surface – plastic layer or powder layer

**Cushioning excipients**
Nature – deformable (plastic) or fracturable (brittle)
Size – powder or pellets
Amount – ideally 50 to 75%

**Process variables**
Compression force
Compression speed

**Equipment variables**
Design of tabletting machine, powder feeding mechanism, etc.

---

**Mechanisms involved in Compression of MUPS:**

Four stages are considered in compression into MUPS includes:
1. Deformation of functional coating layer,
2. Densification of polymeric coating layer,
3. Fragmentation.
4. Attrition of pellets.

Owing to the irregular shape and to the surface roughness of granules, it is rather difficult to determine the degree of incidence of the suggested mechanisms. Recently, the use of nearly spherical units, here defined as pellets, brought new light into the mechanistic knowledge of the compaction process of porous particles and justified the use of these units as an alternative model system. It has been suggested that permanent deformation and densification are the major mechanisms involved in

---

**Figure 3: Impact of compaction on pellet deformation and drug release**
the compression of spherical units while fragmentation and attrition seem to be inexistent or to occur to a minute extent.

**Disintegration and Dissolution Behavior of MUPS:**

Since MUPS are often designed to possess particulates having modified release characteristics, they are expected to disintegrate in one of the following ways –

1. Rapid disintegration in the oral cavity, if the MUPS contains taste-masked coated particles or modified release coated particles but designed as a compact in an or dispersible base (orally disintegrating tablets) e.g. Prevacid SoluTab.
2. Rapid disintegration in the gastrointestinal tract after oral administration or swallowing, e.g. Losec MUPS[35-38].
3. Slow and gradual erosion of MUPS in the GIT to release polymer-coated particles slowly, e.g. Toprol XL. The dissolution behavior of individual coated multiparticulates that separate out as a result of disintegration of MUPS follow the one that is expected of such particles and is often dictated by the type of coating or matrix design of such pellets.

**Patient friendly dosage form**

Better patient compliance is expected from MUPS for following reasons:-

a. Mouth disintegrating MUPS dosage form having a palatable taste is suitable for pediatric and geriatric patients who cannot swallow tablet or capsule, e.g. Prevacid SoluTab[39].

b. The orodispersible MUPS medication can be taken without water, especially while travelling since the dosage form can be designed as orally disintegrating preparation that contains flavors and sweeteners that stimulate salivation and swallowing, e.g. Prevacid SoluTab.

c. Being tablets, quite unlike a capsule formulation, MUPS can be also designed into a divisible dosage form, without compromising the drug release characteristics of coated particles contained therein[40-42].

d. The MUPS have lesser tendency of adhering to esophagus during swallowing.

e. Smaller volume/size of tablet leads to better patient compliance than capsules.

**Marketed Products OF MUPS** (13 article)

Losec MUPS is the second highest selling pharmaceutical drug product in Sweden in the year 2002[43]. Another patent is of European Patent Office by Astrazeneca EP 723437 for Nexium and Losec for compression of proton pump inhibitor to tablets for MUPS into the market. Various marketed products are tabulated in Table I.

**Table 1: Marketed Products of MUPS**

| Product         | Company       | Drug          | Therapeutic category | Formulation                  |
|-----------------|---------------|---------------|----------------------|------------------------------|
| Losec MUPS      | Astra Zeneca  | Omeprazole    | Antiulcer            | Antiulcer [44]              |
|                 |               | Magnesium     |                      |                              |
| Esomeprazole    | Astra Zeneca  | Esomeprazole  | Antiulcer            | Antiulcer[45]               |
|                 |               | Magnesium     |                      |                              |
| Tropol XL       | Astra Zeneca  | Metoprolol    | Antihypertensive     | Extended release[46]        |
|                 |               | Tartrate      |                      |                              |
| Prevacid SoluTab| Takeda        | Lansoprazole  | Antiulcer            | Delayed release Orodispersible tablet[47] |
| Theodur         | Key           | Theophyllin   | Antiasthmatic        | Extend release[48]          |

International Journal of Contemporary Research and Review, Vol. 9, Issue. 10, Page no: 20202-20214
DOI: https://doi.org/10.15520/ijcrr.v9i10.879
Application of MUPS:
1. To protect drugs that are unstable in acid from disintegrating in the gastric juice e.g. antibiotics enzymes, peptides proton pump inhibitors[49].
2. pH Dependent controlled release of drugs for optimal absorption
3. GI targeting of different sections of small intestine or of the colon (absorption window, targeting localized effects).
4. Colon targeting for local treatment and systemic therapies. The key to controlling the release of the drug is the pH dependent dissolution of the film coating, which takes advantage of the different pH values that exist along the gastrointestinal tract. Since the coatings dissolution is controlled by pH, or by gradually permeability, the drug is release in a precise manner in specific sections of the digestive tract, or at specific times after intake.
5. Combination of drug substances and release profiles can be provided by formulating the MUPS tablets with different pellet qualities or combining pellets with APIs in powder or granulated form[50-52].

References:
1. Warden SJ (April 2010). "Prophylactic Use of NSAIDs by Athletes: A Risk/Benefit Assessment". The Physician and Sports Medicine 38 (1): 132–138.
2. Hinz B, Cheremina O, Brune K (2008). "Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man." The FASEB journal: official publication of the Federation of American Societies for Experimental Biology 22 (2): 383–390
3. Clive P. Page, Michael J. Curtis, Morley Sutter, Michael Walker, Brian Hoffman. Farmacología integrada (in Spanish). Published by Elsevier Espana, 1998.
4. Simone Rossi, ed. (2006). Australian medicines handbook 2006. Adelaide: Australian Medicines Handbook Pty Ltd.
5. Consumer Reports Health Best Buy Drugs (July 2013). "The Nonsteroidal Anti-Inflammatory Drugs: Treating Osteoarthritis and Pain. Comparing effectiveness, safety, and price." NSAIDs. Yonkers, New York: Consumer Reports. Retrieved 12 February 2014
6. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G (2006). "Acetaminophen for osteoarthritis". Cochrane Database Syst Rev (1): CD004257.
7. Gotzsche PC (March 1989). "Methodology and overt and hidden bias in reports of 196 double-blind trials of nonsteroidal anti-inflammatory drugs in rheumatoid arthritis". Controlled clinical trials 10 (1): 31–56.
8. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW (2008). "Non-steroidal anti-inflammatory drugs for low back pain". Cochrane Database of Systematic Reviews (1). pp. CD000396.
9. Pattanittum P, Turner T, Green S, Buchbinder R (2013). "Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults". Cochrane Database of Systematic Reviews 5. pp. CD003686.
10. Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, McGowan J (2002). "Prevention of NSAID-induced gastro duodenal ulcers". Cochrane Database Syst Rev (4): CD002296.
11. Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP (2007). "Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function". Cochrane Database Syst Rev (2): CD002765.
12. Green GA (2001). "Understanding NSAIDs: from aspirin to COX-2". Clinical cornerstone 3 (5): 50–60.
13. Bayer HealthCare Pharmaceuticals Inc (September 2008). "CIPRO (ciprofloxacin hydrochloride) TABLETS CIPRO,
14. Royal Pharmaceutical Society of Great Britain (2009). "5 Infections". British National Formulary (BNF 57). BMJ Group and RPS Publishing.

15. http://orthoinfo.aaos.org/fact/thr_report.cfm?Thread_ID=398&topcategory=About

16. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ (November 2000). "Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis". New England Journal of Medicine 343 (21): 1520–8, 2 p following 1528.

17. Baron JA, Sandler RS, Bresalier RS, Lanas A, Morton DG, Riddell R, Iverson ER, Demets DL (15 November 2008). "Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial". Lancet 372 (9651): 1756–64.

18. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C (June 2006). "Do selective cyclo-oxygenase-2 inhibitors and traditional nonsteroidal anti-inflammatory drugs original nsaid reference.docx increase the risk of atherothrombosis? Meta-analysis of randomised trials" BMJ (Clinical research ed.) 332 (7553): 769–79.

21. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Farkouh ME, FitzGerald GA, Goss P, Halls H, Hawk E, Hawkey C, Hennekens C, Hochberg M, Holland LE, Kearney PM, Laine L, Lanas A, Lance P, Laupacis A, Oates J, Patrono C, Schnitzer TJ, Solomon S, Tugwell P, Wilson K, Wittes J, Baigent C (Aug 31, 2013). "Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials." Lancet 382 (9894): 769–79.

22. Page J, Henry D (March 2000). "Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an under recognized public health problem" Archives of Internal Medicine 160 (6): 777–84.

23. Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Fosbol EL, Sørensen R, Folke F, Buch P, Gadsboll N, Rasmussen S, Poulsen HE, Kober L, Madsen M, Torp-Pedersen C (2009). "Increased Mortality and Cardiovascular Morbidity Associated with Use of Nonsteroidal Anti-inflammatory Drugs in Chronic Heart Failure". Archives of Internal Medicine 169 (2): 141–149.

24. Traversa G, Walker AM, Ippolito FM, Caffari B, Capurso L, Dezi A, Koch M, Maggini M, Alegiani SS, Rascetti R (January 1995). "Gastro duodenal toxicity of different nonsteroidal anti-inflammatory drugs". Epidemiology (Cambridge, Mass.) 6 (1): 49–54.

25. Textbook of Gastroenterology, Tadataka Yamada, 2008, Ch.40, Peptic Ulcer Disease, page 941
26. Higuchi K, Umegaki E, Watanabe T, Yoda Y, Morita E, Murano M, Tokioka S, Arakawa T (July 2009). "Present status and strategy of NSAIDs-induced small bowel injury". Journal of Gastroenterology 44 (9): 879–888.

27. Thomas MC (February 2000). "Diuretics, ACE inhibitors and NSAIDs—the triple whammy". The Medical journal of Australia 172 (4): 184–5.

28. De Broe ME, Elseviers MM (February 1998). "Analgesic nephropathy". New England Journal of Medicine 338 (7): 446–52.

29. Ostensen ME, Skomsvoll JF (March 2004). "Anti-inflammatory pharmacotherapy during pregnancy". Expert opinion on pharmacotherapy 5 (3): 571–80.

30. Nakhai-Pour HR, Broy P, Sheehy O, Berard A (September 2011). "Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion". Canadian Medical Association Journal 183 (15): 1713–20.

31. Reza Nakhai-Pour MD PhD., Hamid. "Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion". Canadian Medical Association Journal. Retrieved 7 September 2011.

32. Cervera R, Balasch J (2004). "The management of pregnant patients with antiphospholipid syndrome". Lupus 13 (9): 683–7.

33. Knights, Kathleen. "Defining the COX Inhibitor Selectivity of NSAIDs: Implications for Understanding Toxicity". Web MD LLC. Retrieved 17 February 2013.

34. "Inhibit Ors Of Cyclooxygenases: Mechanisms, Selectivity And Uses". Journal of Physiology and Pharmacology. Retrieved 2014-03-16.

35. "Inflammation page 5". Pharmacology2000.com. Retrieved 2012-11-30.

36. Brayfield, A. ed. (14 January 2014). "Aspirin" Martindale: The Complete Drug Reference. Pharmaceutical Press. Retrieved 3 April 2014.

37. Lewis, H. D.; Davis, J. W.; Archibald, D. G.; Steinke, W. E.; Smitherman, T. C.; Doherty Je, J. E.; Schnaper, H. W.; Lewinter, M. M.; Linares, E.; Pouget, J. M.; Sabharwal, S. C.; Chesler, E.; Demots, H. (1983). "Protective Effects of Aspirin against Acute Myocardial Infarction and Death in Men with Unstable Angina". New England Journal of Medicine 309 (7): 396–403.

38. Julian, D G; D A Chamberlain; S J Pocock (24 September 1996). "A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): a multicentre unblinded randomised clinical trial". BMJ (British Medical Journal) 313 (7070): 1429–1431.

39. Krumholz, H. M.; Radford, M. J.; Ellerbeck, E. F.; Hennen, J.; Meehan, T. P.; Petrillo, M.; Wang, Y.; Kresowik, T. F. et al. (1995). "Aspirin in the treatment of acute myocardial infarction in elderly Medicare beneficiaries. Patterns of use and outcomes". Circulation 92 (10): 2841–2847.

40. Algra, Annemijn M; Rothwell, Peter M (2012). "Effects of regular aspirin on long-term cancer incidence and metastasis: A systematic comparison of evidence from observational studies versus randomised trials". The Lancet Oncology 13 (5): 518–27.

41. Rothwell, Peter M; Price, Jacqueline F; Fowkes, F Gerald R; Zanchetti, Alberto; Roncaglioni, Maria Carla; Tognoni, Gianni; Lee, Robert; Belch, Jill FF; Wilson, Michelle; Mehta, Ziyah; Meade, Tom W (2012). "Short-term effects of daily aspirin
on cancer incidence, mortality, and non-vascular death: Analysis of the time course of risks and benefits in 51 randomised controlled trials”. The Lancet 379 (9826): 1602.

42. Rothwell, Peter M; Wilson, Michelle; Price, Jacqueline F; Belch, Jill FF; Meade, Tom W; Mehta, Ziyah (2012). "Effect of daily aspirin on risk of cancer metastasis: A study of incident cancers during randomised controlled trials”. The Lancet 379 (9826): 1591.

43. Macdonald S (2002). "Aspirin use to be banned in under 16-year olds". BMJ 325 (7371): 988.

44. "Aspirin". The American Society of Health-System Pharmacists. Retrieved 3 April 2011.

45. "Aspirin for Reducing Your Risk of Heart Attack and Stroke: Know the Facts". U.S. Food and Drug Administration. Retrieved 26 July 2012.

46. "Aspirin for the Prevention of Cardiovascular Disease". U.S. Preventive Services Task Force. Retrieved 26 July 2012.

47. Seshasai, SR; Wijesuriya, S; Sivakumaran, R; Nethercott, S; Erqou, S; Sattar, N; Ray, KK (13 February 2012). "Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials”. Archives of Internal Medicine 172 (3): 209–16.

48. Algra, AM; Rothwell, PM (May 2012). "Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials". The lancet oncology 13 (5): 518–27.

49. Sachs, C. J. (2005). "Oral analgesics for acute nonspecific pain". American family physician 71 (5): 913–918.

50. Gaciong (2003). "The real dimension of analgesic activity of aspirin". Thrombosis research 110 (5–6): 361–364.

51. Derry, C.J.; Derry, S.; Moore, R. A. (2012). Caffeine as an analgesic adjuvant for acute pain in adults. In Derry, Sheena. "Cochrane Database of Systematic Reviews". Cochrane database of systematic reviews (Online) 3: CD009281.

52. management of acute salicylate (aspirin) overdose". Emerg Med J 19 (3): 206–9.