Available Online at www.jddt.in

ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 2 (21) 2014, 30-37

REVIEW ARTICLE

Formulation and evaluation of tramadol, and diclofenac sofium multimodel tablet dosage form: an overview

Rajesh Asija[1]*, Shalendra Bhatt[1], Sampat Lal Sharma[1], Prem Chand Dhaker[1]

[1]Maharishi Arvind Institute of Pharmacy, Jaipur-302020, Rajasthan, India

Accepted 03 September 2014; Published 12 September 2014

ABSTRACT

The current article has been focused on the unimodal pain management which are based on either central analgesic drug mechanism or non steroidal anti-inflammatory drug. These drugs control the pain by central nervous system or peripheral nervous system.

But in body both system involve for the pain so for moderate to severe pain unimodal approach is not sufficient to address multimodal mechanism of the pain. In the analgesic drug combination when we add peripheral anti-inflammatory drug then this multimodal drug combination provide pure pain relief. The ascending and descending modulation pain pathway message is inhibited by the opioid analgesics and at the site of injury where peripheral nocicepter and peripheral nerve present there NSAID require to relive the pain.

Keywords: Multimodal tablet solid dosage form.

INTRODUCTION:

Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parental routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe [in respect to Parenteral route] due to its ease of administration, patient acceptance, and cost-effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1) Drug with short half-life requires frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits[39].

A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tabletting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets visually attractive. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending shelf life), or to enhance the tablet's appearance address the multi model mechanism of the pain a unimodal pain killer is no sufficient so for moderate to severe pain multimodal drug combination is require The tramadol is central analgesic drug which is use for chronic pain. To reduce the side effect paracetamol is add for reduce the dose of tramadol and increase the therapeutic effect that produce synergic effect [5].

A multimodal (or balanced) approach to anaesthesia is a familiar concept that offers important benefits in the management of both acute and chronic pain. Rational combinations of analgesic agents with different mechanisms of action can achieve improved efficacy

*Corresponding author: Dr. Rajesh Asija || E-mail: sampatsharma851@gmail.com

and/or tolerability and safety compared with analgesic doses of the individual drugs. Combining different agents also enhances efficacy in complex pain states that involve multiple causes. Combinations of paracetamol plus a weak opioid agent are widely used. One such combination, paracetamol plus tramadol, exploits the well-established complementary pharmacokinetics and mechanisms of action of these two drugs. This combination has demonstrated genuine synergy in animal studies and also combines paracetamol's rapid onset of efficacy with tramadol's prolonged analgesic effect. Numerous studies have confirmed the efficacy and tolerability of paracetamol plus tramadol in both acute and chronic pain. As a single-dose treatment for acute post-operative pain, this combination delivers rapid and sustained pain relief that is greater than either agent alone. There is also extensive evidence for efficacy in the long-term management of chronic pain conditions, including osteoarthritis, low back pain and fibromyalgia. In the setting of chronic pain, paracetamol plus tramadol has shown sustained efficacy, safety and tolerability for up to 2 years without the development of tolerance. The efficacy of this combination has been demonstrated as well in respect to reduction of pain intensity and, more importantly, with regard to improvement of function and quality of life and the reduction of disability. Comparative trials have shown that paracetamol plus tramadol has comparable efficacy to paracetamol plus codeine, but with reduced somnolence and constipation compared with the codeine combination. The paracetamol plus tramadol combination is also free of organ toxicity associated with selective and non-selective non-steroidal anti-inflammatory drugs. Hence, paracetamol plus tramadol offers an effective and well-tolerated alternative to anti-inflammatory drugs or other paracetamol plus weak opioid combinations. [3]

Contents

1. Types

- **Pill**

"The Pill", a general nickname for the combined oral contraceptive pill (COCP) Today, pills include tablets, capsules, and variants thereof like caplets—essentially anything with medication that can be digested, minus the liquid forms, colloquially falls into the pill category.

- Variations on a common tablet design, which can be distinguished by both color and shape A smooth, coated, oval-shaped medicinal tablet in the shape of a capsules, and are called "caplets".

- **Orally disintegrating tablet (ODT)**

Olanzapine ODT blister pack with "wafer" tablets that which rapidly dissolves in saliva. An orally disintegrating tablet or orodispersible tablet (ODT), is a drug dosage form available for a limited range of over-the-counter (OTC) and prescription medications.

2. Tabletting formulations

In the tablet-pressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size, and freely flowing. Mixed particle sized powders segregate during manufacturing operations due to different densities, which can result in tablets with poor drug or active pharmaceutical ingredient (API) content uniformity but granulation should prevent this. Content uniformity ensures that the same API dose is delivered with each tablet. Some APIs may be tableted as pure substances, but this is rarely the case; most formulations include excipients. Normally, a pharmacologically inactive ingredient (excipient) termed a binder is added to help hold the tablet together and give it strength. A wide variety of binders may be used, some common ones including lactose, dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, povidonepolyvinylpyrrolidone and modified cellulose (for example hydroxypropyl methylcellulose and hydroxyethylcellulose). [24]

3. Advantages and disadvantages

Tablets are simple and convenient to use. They provide an accurately measured dosage of the active ingredient in a convenient portable package, and can be designed to protect unstable medications or disguise unpalatable ingredients. Colored coatings, embossed markings and printing can be used to aid tablet recognition. Manufacturing processes and techniques can provide tablets special properties, for example, sustained release or fast dissolving formulations.

Some drugs may be unsuitable for administration by the oral route. For example, protein drugs such as insulin may be denatured by stomach acids. Such drugs cannot be made into tablets. Some drugs may be deactivated by the liver when they are carried there from the gastrointestinal tract by the hepatic portal vein (the "first pass effect"), making them unsuitable for oral use. Drugs which can be taken sublingually are absorbed through the oral mucosae, so that they bypass the liver and are less susceptible to the first pass effect. The oral bioavailability of some drugs may be low due to poor absorption from the gastrointestinal tract. Such drugs may need to be given in very high doses or by injection. For drugs that need to have rapid onset, or that have severe side effects, the oral route may not be suitable. For example salbutamol, used to treat problems in the pulmonary system, can have effects on the heart and circulation if taken orally; these effects are greatly reduced by inhaling smaller doses direct to the required site of action. A proportion of the population have difficulties swallowing tablets either because they just don't like taking them or because their medical condition makes it difficult for them (dysphagia, vomiting). In such instances it may be better to consider alternative dosage form or administration route. [21]

4. Tablet properties

Tablets can be made in virtually any shape, although requirements of patients and tableting machines mean that most are round, oval or capsule shaped. More unusual shapes have been manufactured but patients find these harder to swallow, and they are more vulnerable to chipping or manufacturing problems. Tablet diameter and shape are determined by the machine tooling used to produce them - a die plus an upper and a lower punch are required. This is called a station of tooling. The thickness is determined by the amount of tablet material and the position of the punches in relation to each other during compression. Once this is done, we can measure the corresponding pressure applied during compression. The shorter the distance between the punches, thickness, and the greater the pressure applied during compression, and sometimes the harder the tablet. Tablets need to be hard enough that they don't break up in the bottle, yet friable enough that they disintegrate in the gastric tract. [9]

5. Manufacturing

- **Manufacture of the tableting blend**

In the tablet pressing process, the main guideline is to ensure that the appropriate amount of active ingredient is in each tablet. Hence, all the ingredients should be well-mixed. If a sufficiently homogenous mix of the components cannot be obtained with simple blending processes, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet. Two basic techniques are used to granulate powders for compression into a tablet: wet granulation and dry granulation. Powders that can be mixed well do not require granulation and can be compressed into tablets through direct compression.

- **Wet granulation**

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis. [27]

Procedure

1. The active ingredient and excipients are weighed and mixed.
2. The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, cellulose derivatives such as methyl cellulose, gelatin, and povidone.
3. Screening the damp mass through a mesh to form pellets or granules.
4. Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.
5. After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

Low shear wet granulation processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state. High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process. Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process. [34]

- **Dry granulation**

Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller

compactor. Dry granulation equipment offers a wide range of pressures to attain proper densification and granule formation. Dry granulation is simpler than wet granulation, therefore the cost is reduced. However, dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules.

- **Granule lubrication**

After granulation, a final lubrication step is used to ensure that the tableting blend does not stick to the equipment during the tableting process. This usually involves low shear blending of the granules with a powdered lubricant, such as magnesium stearate or stearic acid.

- **Manufacture of the tablets**

Tablets that failed due to capping and lamination compared to a normal tablet. Whatever process is used to make the tableting blend, the process of making a tablet by powder compaction is very similar. First, the powder is filled into the die from above. The mass of powder is determined by the position of the lower punch in the die, the cross-sectional area of the die, and the powder density. At this stage, adjustments to the tablet weight are normally made by repositioning the lower punch. After die filling, the upper punch is lowered into the die and the powder is uniaxially compressed to a porosity of between 5 and 20%. The compression can take place in one or two stages (main compression, and, sometimes, pre-compression or tamping) and for commercial production occurs very fast (500–50 ms per tablet). Finally, the upper punch is pulled up and out of the die (decompression), and the tablet is ejected from the die by lifting the lower punch until its upper surface is flush with the top face of the die. This process is repeated for each tablet.

Common problems encountered during tablet manufacturing operations include:

- Fluctuations in tablet weight, usually caused by uneven powder flow into the die due to poor powder flow properties.
- Fluctuations in dosage of the Active Pharmaceutical Ingredient, caused by uneven distribution of the API in the tableting blend (either due to poor mixing or separation in process.
- Sticking of the powder blend to the tablet tooling, due to inadequate lubrication, worn or dirty tooling, or a sticky powder formulation
- Capping, lamination or chipping. This is caused by air being compressed with the tablet formulation and then expanding when the punch is released: if this breaks the tablet apart, it can be due to incorrect machine settings, or due to incorrect formulation: either because the tablet formulation is too brittle or not adhesive enough, or because the powder being fed to the tablet press contains too much air (has too low bulk density).

Capping can also occur due to high moisture content. [22]

- **Tablet compaction simulator**

Tablet formulations are designed and tested using a laboratory machine called a Tablet Compaction Simulator or Powder Compaction Simulator. This is a computer controlled device that can measure the punch positions, punch pressures, friction forces, die wall pressures, and sometimes the tablet internal temperature during the compaction event. Numerous experiments with small quantities of different mixtures can be performed to optimise a formulation. Mathematically corrected punch motions can be programmed to simulate any type and model of production tablet press. Initial quantities of active pharmaceutical ingredients are very expensive to produce, and using a Compaction Simulator reduces the amount of powder required for product development.

- **Tablet presses**

An old Cadmach rotary tablet press

Tablet presses, also called tableting machines, range from small, inexpensive bench-top models that make one tablet at a time (single-station presses), with only around a half-ton pressure, to large, computerized, industrial models (multi-station rotary presses) that can make hundreds of thousands to millions of tablets an hour with much greater pressure. The tablet press is an essential piece of machinery for any pharmaceutical and nutraceutical manufacturer. Common manufacturers of tablet presses include Stokes, Fette Compacting, Korsch, Kikusui, Manesty, B&D, IMA and Courtoy. Tablet presses must allow the operator to adjust the position of the lower and upper punches accurately, so that the tablet weight, thickness and density can each be controlled. This is achieved using a series of cams, rollers, and/or tracks that act on the tablet tooling (punches). Mechanical systems are also incorporated for die filling, and for ejecting and removing the tablets from the press after compression. Pharmaceutical tablet presses are required to be easy to clean and quick to reconfigure with different tooling, because they are usually used to manufacture many different products. There are 2 main standards of tablet tooling used in pharmaceutical industry: American standard 'TSM' and European

standard 'EU'. TSM and EU configurations are similar to each other but cannot be interchanged.

- **Tablet coating**

Many tablets today are coated after being pressed. Although sugar-coating was popular in the past, the process has many drawbacks. Modern tablet coatings are polymer and polysaccharide based, with plasticizers and pigments included. Tablet coatings must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating process, and must follow the fine contours of embossed characters or logos on tablets. Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow. Tablet coatings are also useful to extend the shelf-life of components that are sensitive to moisture or oxidation. Special coatings (for example with pearlescent effects) can enhance brand recognition. [20]

There are two types of coating machines used in the pharmaceutical industry: coating pans and automatic coaters. Coating pans are used mostly for sugar coating of pellets. Automatic coaters are used for all kinds of coatings; they can be equipped with remote control panel, dehumidifier, and dust collectors. The explosion-proof design is required for alcohol containing coatings.

- **Pill-splitters**

It is sometimes necessary to split tablets into halves or quarters. Tablets are easier to break accurately if scored, but there are devices called pill-splitters which cut unscored and scored tablets. Tablets with special coatings (for example enteric coatings or controlled-release coatings) should not be broken before use, as this will expose the tablet core to the digestive juices, circumventing the intended delayed-release effect. [1]

Evaluation of Tablet

A. Preformation study

a. Bulk Density: Bulk density of a powder is defined as the ratio of the mass of the powder and its bulk volume. For bulk density determination a weigh quantity of the powder material is introduce into a graduated measuring cylinder and volume of powder is determine.

Bulk Density = Mass of the powder/ Bulk volume

b. Granule Density: Granule density is the ratio of the mass of the granular powder and the volume occupied by the granular material together with its intraparticle spaces.

Granule density = Mass of the granular powder/ Granule Volume

c. Tapped Density: For determination of the bulk density, a weigh quantity of the granular powder is introduced into a graduated measuring cylinder and is tapped mechanically either manually or using a tapping device till a constant volume is obtained.

Tapped density = Mass of the granular powder/ Tapped volume of granules

d. Compressibility Index:

C= 100(1 - ? B /? T)

Where? B is the freely settled bulk density of the granules, and? T is the tapped bulk density of the granules. A Carr's index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

e. Angle of Repose: The angle of repose is determine by allowing mass of powdered to flow freely through an orifice from a certain height and form a conical heap on the horizontal surface. The angle of repose is determined by the formula:

$\tan\theta = h/r$

Or $\theta = \tan^{-1} h/r$

Where, θ is the angle of repose, h is the height of the heap of powder and

r is the radius of the base of the heap of powder.

B. Post Compression Characterization

a. Weight Variation Test: The weight of tablet is measured to ensure that a tablet contains the proper amount of drug.

1. The weight variation test is run by weighing 20 tablets individually.
2. Calculate the average weight.
3. Comparing the individual tablet weights to the average weight.
4. The tablets pass the test if not more than 2 tablets go outside the percentage limit.

Table 1:

Average weight of tablet allowed(mg)	Maximum %difference
130 or less	10%
130-324	7.5%
More then 324	5%

b. Friability Test: This test evaluates ability of tablet to with abrasion and edge damage during packing, handling and shipping. Friability is measured by the help of Roche friabilator. A number of pre weigh tablet is placed in plastic chamber that revolves at 25 rpm for 100 revolutions. The tablet are then de-dusted and reweighed. The friability is calculated by the formula.

F = (1- w/w*) 100

Where W* is the original wt. of tablet

W is the final wt. of tablet after test.

Acceptance limit of friability is: 0.5 – 1%.

c. Hardness Test: Tablet requires a certain amount of hardness to with stand mechanical shock of handling in manufacture, packaging, and shipping. Hardness is measured with the help of hardness tester like:

Monsanto tester

Pfizer tester

Strong cob tester

Hardness is measured with the help of Monsanto tester. The tester consists of a barrel containing a compressed spring held between two plungers. The lower plunger is then forced against a spring by turning a threaded boltuntil the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is record and the zero force reading is deducted from it .Hardness is measured in kg/ cm sq.

d. In Vitro Drug Release profile:

In vitro drug release profile of matrix tablet is determined with the help of USP dissolution apparatus type 2. In general, a single matrix tablet is placed in dissolution flask which contain 900 ml dissolution medium. The flask is maintained at 37º ± 0.5º C by a constant temperature bath. The motor is adjusted to turn at the specified speed (50 rpm), and sample of the fluid are withdrawn at intervals to determine the amount of drug in the solution. Matrix tablet slowly release the drug for a prolong period of time as compare to conventional tablet. [29]

CONCLUSION:

As per the above discussion, it can be easily concluded that multimodal tablet formulation are helpful in pure pain relief and the efficiency of the dose as well as they are also improving the patient's compatibility. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the number of other drug use of the same time.

REFERENCES:

1. Brayfield, A, ed. (13 December 2013). "Tramadol Hydrochloride". Martindale: The Complete Drug Reference. Pharmaceutical Press. Retrieved 5 April 2014.
2. "Ultram, Ultram ER (tramadol) dosing, indications, interactions, adverse effects, and more". Medscape Reference. WebMD. Retrieved 28 November 2013.
3. "PRODUCT INFORMATION Tramadol SANDOZ 50 mg capsules" (PDF). TGA eBusiness Services. Sandoz Pty Ltd. 4 November 2011. Retrieved 6 April 2014.
4. Leppert, W (November–December 2009). "Tramadol as an analgesic for mild to moderate cancer pain." (PDF). Pharmacological reports 61 (6): 978–92. doi:10.1016/s1734-1140(09)70159-8. PMID 20081232.
5. Reimann W, Schneider F (1998). "Induction of 5-hydroxytryptamine release by tramadol, fenfluramine and reserpine". European Journal of Pharmacology 349 (2–3): 199–203. doi:10.1016/S0014-2999(98) 00195-2. PMID 9671098.
6. Gobbi M, Moia M, Pirona L, Ceglia I, Reyes-Parada M, Scorza C, Mennini T (September 2002). "p-Methyl-thioamphetamine and 1-(m-chlorophenyl)piperazine, two non-neurotoxic 5-HT releasers in vivo, differ from neurotoxic amphetamine derivatives in their mode of action at 5-HT nerve endings in vitro". Journal of Neurochemistry 82 (6): 1435–43. doi:10.1046/j.1471-4159.2002.01073.x. PMID 12354291.
7. Raffa RB, Buschmann H, Christoph T, Eichenbaum G, Englberger W, Flores CM, Hertrampf T, Kögel B, Schiene K, Straßburger W, Terlinden R, Tzschentke TM (2012). "Mechanistic and functional differen-tiation of tapentadol and tramadol". Expert Opinion on Pharmacotherapy 13 (10): 1437–49. doi:10.1517/14656566.2012.696097. PMID 22698264.
8. Katz WA (1996). "Pharmacology and clinical experience with tramadol in osteoarthritis". Drugs. 52 Suppl 3: 39–47. doi:10.2165/00003495-199600523-00007. PMID 8911798.
9. Boumendjel A, Sotoing Taïwe G, Ngo Bum E, Chabrol T, Beney C, Sinniger V, Haudecoeur R, Marcourt L, Challal S, Ferreira Queiroz E, Souard F, Le Borgne M, Lomberget T, Depaulis A, Lavaud C, Robins R, Wolfender JL, Bonaz B, De Waard M (November 2013). "Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant". Angewandte Chemie International Edition 52 (45): 11780–11784. doi:10.1002/anie.201305697.
10. Rossi, S, ed. (2013). Australian Medicines Handbook (2013 ed.). Adelaide: The Australian Medicines Handbook Unit Trust. ISBN 978-0-9805790-9-3. edit11. Patel VM, Prajapati BG, Patel MM. Design and

characterization of chitosan-containing muco-adhesivebuccal patches of propranolol hydr-ochloride. Acta Pharm 2007;57:61-72.

11. Grond S, Sablotzki A (2004). "Clinical pharmacology of tramadol". Clinical Pharmacokinetics 43 (13): 879–923. doi:10.2165/ 00003088-200443130-00004. PMID 15509185.

12. Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, Da Silva JA, Danneskiold-Samsøe B, Dincer F, Henriksson C, Henriksson KG, Kosek E, Longley K, McCarthy GM, Perrot S, Puszczewicz M, Sarzi-Puttini P, Silman A, Späth M, Choy EH (2008). "EULAR evidence-based recommendations for the management of fibromyalgia syndrome". Annals of the Rheumatic Diseases 67 (4): 536–41. doi:10.1136/ard.2007.071522. PMID 17644548.

13. Lee CR, McTavish D, Sorkin EM (1993). "Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states". Drugs 46 (2): 313–40. doi:10.2165/00003495-199346020-00008. PMID 7691519.

14. Micó JA, Ardid D, Berrocoso E, Eschalier A (2006). "Antidepressants and pain". Trends in Pharmacological Sciences 27 (7): 348–54. doi:10.1016/j.tips.2006.05.004. PMID 16762426.

15. Harati Y, Gooch C, Swenson M, Edelman S, Greene D, Raskin P, Donofrio P, Cornblath D, Sachdeo R, Siu CO, Kamin M (1998). "Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy". Neurology 50 (6): 1842–6. doi:10.1212/WNL.50.6.1842. PMID 9633738.

16. Harati Y, Gooch C, Swenson M, Edelman SV, Greene D, Raskin P, Donofrio P, Cornblath D, Olson WH, Kamin M (2000). "Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy". Journal of diabetes and its complications 14 (2): 65–70. doi:10.1016/S1056-8727(00)00060-X. PMID 10959067.

17. Barber J (2011). "Examining the use of tramadol hydrochloride as an antidepressant". Experimental and Clinical Psychopharmacology 19 (2): 123–30. doi:10.1037/a0022721. PMID 21463069.

18. Göbel H, Stadler T (1997). "[Treatment of post-herpes zoster pain with tramadol. Results of an open pilot study versus clomipramine with or without levomepromazine]". Drugs (in French). 53 Suppl 2: 34–9. doi:10.2165/00003495-199700532-00008. PMID 9190323.

19. Boureau F, Legallicier P, Kabir-Ahmadi M (July 2003). "Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial". Pain 104 (1-2): 323–31. doi:10.1016/S0304-3959(03)00020-4. PMID 12855342.

20. Sobey PW, Parran TV, Grey SF, Adelman CL, Yu J (2003). "The use of tramadol for acute heroin withdrawal: a comparison to clonidine". Journal of Addictive Diseases 22 (4): 13–25. doi:10.1300/J069v22n04_03. PMID 14723475.

21. Mazumdar K, Dutta NK, Dastidar SG, Motohashi N, Shirataki Y (2006). "Diclofenac in the management of E. coli urinary tract infections". In Vivo 20 (5): 613–619. PMID 17091768.

22. Dutta NK, Annadurai S, Mazumdar K, Dastidar SG, Kristiansen JE, Molnar J, Martins M, Amaral L. (2007). "Potential management of resistant microbial infections with a novel non-antibiotic: the anti-inflammatory drug diclofenac sodium". Int. J. Antimicrob. Agents 30 (3): 242–249. doi:10.1016/j.ijantimicag.2007.04.018. PMID 17644318.

23. Dutta NK, Mazumdar K, Dastidar SG, Park JH (2007). "Activity of diclofenac used alone and in combination with streptomycin against Mycobacterium tuberculosis in mice". Int. J. Antimicrob. Agents 30 (4): 336–340. doi:10.1016/j.ijantimicag.2007.04.016. PMID 17644321.

24. Naidoo V, Swan GE (August 2008). "Diclofenac toxicity in Gyps vulture is associated with decreased uric acid excretion and not renal portal vasoconstriction". Comp. Biochem. Physiol. C Toxicol. Pharmacol. 149 (3): 269–74. doi:10.1016/ j.cbpc. 2008.07.014. PMID 18727958.

25. Kearney P, Baigent C, Godwin J, H, Emberson J, Patrono C (2006). "Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials". BMJ 332 (7553): 1302–8. doi:10.1136 /bmj.332.7553.1302. PMC 1473048. PMID 16740558.

26. Solomon D, Avorn J, Stürmer T, Glynn R, Mogun H, Schneeweiss S (2006). "Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: high-risk subgroups and time course of risk". Arthritis Rheum 54 (5): 1378–89. doi:10.1002/art.21887. PMID 16645966.

27. Perry GF, John M, Fang X, James R. Long-Term Safety and Tolerability of Fentanyl Buccal Tablet for the Treatment of Breakthrough Pain in Opoid-Tolerant Patients with Chronic Pain: An 18-Month Study. J of Pain and Symptom Management 2010;40:747-60.

28. David MS, John M, Fang X, Martin H. Fentanyl Buccal Tablet for the Relief of Breakthrough Pain in Opoid-Tolerant Adult Patients with Chronic Neuropathic Pain: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study, Clinical Therapeutics 2007;29:588-601.

29. Libero IG, Viviana DC, Giulia G, Maria GS, Claudio T, Ada MF, Giuseppina C, Release of naltrexone on buccal mucosa: Permeation studies, histological aspects and matrix system design. Eur J of Pharm and Biopharm 2007;67:425–33.

30. Luana P, Valeria A, Daniela R, Stefano G, Maurizio R, Paolo B, Carlo R. Novel mucoadhesivebuccal formulation containing metronidazole for the treatment of periodontal disease. J of Controlled Release 2004;95:521–33.

31. Ìkinci G, Senel S, Wilson CG, Sumnu M, Development of a buccalbioadhesive nicotine tablet formulation for smoking cessation, Int J of Pharm 2004;277:173–78.

32. Varshosaz J, Dehghan Z. Development and characterization of buccoadhesivenifedipine tablets. Eur J of Pharm and Biopharm 2002;54:135–41.

33. Han-Gon C, Jac-Hee J, Chul SY, Chong-Dal R, Mi-Kyung L, Jeong-Hee H, Kyung-MP, Chong-KK. Formulation and in vivo evaluation of omeprazole buccal adhesive tablet. Journal of Controlled Release 2000;68:405–12.

34. Khanna R, Agarwal SP, Ahuja A. Preparation and evaluation of bioerodiblebuccal tablet containing clotrimazole. Int J of Pharm 1996;138:67-73.

35. RaghavendraRao NG, Kulkarni GS.Formulation and Evaluation of MucoadhesiveBuccalBilayered Tablets of Salbutamol.Int J Drug Dev& Res 2012;4:375-84.

36. Chaudhary AL, Jagtap LS, Mahajan AG, Swami SP, Mali PR. Formulation and Evaluation of Buccal Tablet of Salbutamol Sulphate. Int Res J Pharm 2011;2:238-42.

37. Arya RK, Garud A, Jain NK, Garud N. Development and evaluation of mucoadhesivebuccal tablet of Salbutamol sulphate. Int J of Pharm and Pharma-ceuticSci 2010;2:40-42.

38. Wenli Y, Sihem BA, Zheng Z, Taicheng A, Danny Z, Weihua S. Photochemical transformation of Terbutaline (pharmaceutical) in simulated natural waters: Degradation kinetics and mechanisms. Water Research 2013;47:6558-65.

