Nat. Volatiles & Essent. Oils, 2022; 9(1): 1958-1969

NVEO
Natural Volatiles &
Essential Oils

In-Vivo And In-Vitro Modified Release Drug Resistant Into The Alcohol Dose Dumping Formulation: A Review

[1]Lalit Garg* , [2]Dr. Amul Mishra

[1]Faculty of Pharmacy, BN Institute of Pharmaceutical Sciences, BN University, Udaipur, Rajasthan, India.

[2]Associate Professor & Head department of Pharmaceutics, BN Institute of Pharmaceutical Sciences, Faculty of Pharmacy, BN University, Udaipur, Rajasthan, India.

Abstract

AIDD in modified release dosage formulation has been extensively investigated in both animals and humans. This review summarizes the findings. These drugs, which can be engineered to release their active ingredients at specific or delayed timings, are at significant risk of dose dumping. After learning about AIDD, regulators recalled certain products and issued "black box" warnings on others. Since then, much effort has gone into testing a formulation's resistance to alcohol. The patient risk is negligible if the preparation and its function are unaffected by 0–40 percent alcohol in vivo and in vitro.

Keywords: AIDDS, In-vitro, In-vivo, Narrow therapeutic index, Dosage form

Introduction

Prescription medicines taken with alcohol can have unwanted side effects and produce rapid drug release, resulting in deadly overdoses and significant health hazards for the patient[1]. Dose dumping happens when a medicine is released into the body too early or too quickly. Slowing the drug's release reduces dosage requirements, improving patient compliance. Moreover, modifying drug release can lower peak effects and boost therapeutic effectiveness over time. For new or updated treatments, formulators are concerned about alcohol-induced dosage dumping[2-5]. The FDA and the European Medicines Agency currently have two sets of guidelines for the formulation of modified release drugs to address alcohol-induced dose dumping (EMA). Formulating for a global audience might be tough for global pharmaceutical companies. According to the technical service/development leader in North America and EMEA, a worldwide standard is required. IPEC and GPA endorsed a study titled "Regulatory Considerations for Alcohol-Induced Dose Dumping of Oral Modified-Release Formulations" (GPh A). The updated guidance allows Dow's ETHOCEL product to be used to produce safer drugs. Immediate release oral medications such as tablets and capsules are designed to release the active substance immediately after oral administration. Typical drugs do not modify the rate at which a medicament reaches the bloodstream [6-9]. Immediate-release formulations often provide faster absorption and onset of

pharmacological effects. Typical oral medications containing prodrugs may have slow pharmaco-dynamic activity due to hepatic or intestinal metabolism or chemical hydrolysis. Lipophilic medications, which are poorly soluble in water, may have a delayed onset time due to slow dissolution or selective absorption. Environmental factors might cause premature or excessive drug release[10]. Increasing a medicine's concentration in the body might cause undesired side effects or even drug poisoning, so be cautious. Dosage dumping is the most common problem with oral drugs. Patients can eat fatty foods or drink alcohol while taking their medication, which increases absorption. These chemicals can speed up medication release in two ways: by affecting the drug's capsule or by activating the body's absorption surfaces. "Dose dumping" occurs when too much medication is taken at once in extended-release dosage formulations. Pharma companies often avoid dose-dumping drugs. Safety concerns frequently force the recall of such drugs[11-14]. The narcotic Palladone was one example. Because alcohol dose-dumping, this is a once-daily formulation.

The delayed-release or extended-release dosage mechanisms of modified-release dosage distribute the medication over time or to a specific place in the body (targeted-release dosage).

Sustained-release medication is designed to release a drug over time with minimum side effects, allowing the medicine's concentration to remain constant. Liposomes and drug-polymer conjugates are two examples of such formulations (an example being hydrogels). "Sustained release" is more closely related to "controlled release" than "sustained". Extended-release doses come in two flavours: sustained and regulated[15,16]. The SR's release is not continuous, despite the substance's long-term release. Continuous release is designed to keep medicine release rates nearly constant over time (CR)[17]. Although these and other terms are frequently used interchangeably, the FDA considers them different intellectual conceptions that should not be misconstrued. Non-native English speakers occasionally use the termdepot tablet, which is a straight translation of the word used in Swedish and other languages. Modified-release dose and its variants are techniques used in tablets (pills) and capsules to release a medicine more slowly into the bloodstream[18]. This allows for less frequent dosing than immediate-release formulations. For persistent pain, one or two extended-release morphine tablets per day is sufficient. The most common are oral dose forms with time-dependent release[19-24]. Timed releases include sustained, pulsed, and delayed (e.g. targeting distinct regions of the GI tract). Controlled release tries to keep medication concentrations within therapeutic ranges, reducing the danger of hazardous drug concentration peaks and increasing therapeutic efficacy following administration[25]. It also applies to gels, implants, and devices (such the vaginal ring and contraceptive implant), as well as transdermal patches and capsules. These data show that alcohol and drug delivery systems have varied impacts on drug release. New guidelines for designing MR dosage forms emphasise risk assessment for ADD[26]. MR formulations that can survive the effects of alcohol are encouraged, even when sufficient warnings regarding the dangers of alcohol consumption are provided on product labels. For example, in the management of chronic pain, MR opioid dosage formulations are preferred. Despite adequate warnings on the product labeling[27-30], chronic pain sufferers frequently turn to alcohol to cope with stress and reduce pain perception. Alcohol's physiological effects are akin to anaesthetics. Researchers studied 401 elderly people with chronic pain and classified them as problem or non-problem drinkers. This study found that both problem and non-

problem drinkers utilise alcohol as a painkiller. Unintentional ADD can emerge due to extensive alcohol intake. Worldwide, more than half of individuals drink alcohol (WHO database). In reality, spirits account for 44.8% of all alcohol consumed globally, followed by beer (34.3%) and wine (11.7%). Also, alcohol remained in the stomach from prior drinks may create unintentional ADD[30,31].

Regulatory Consideration

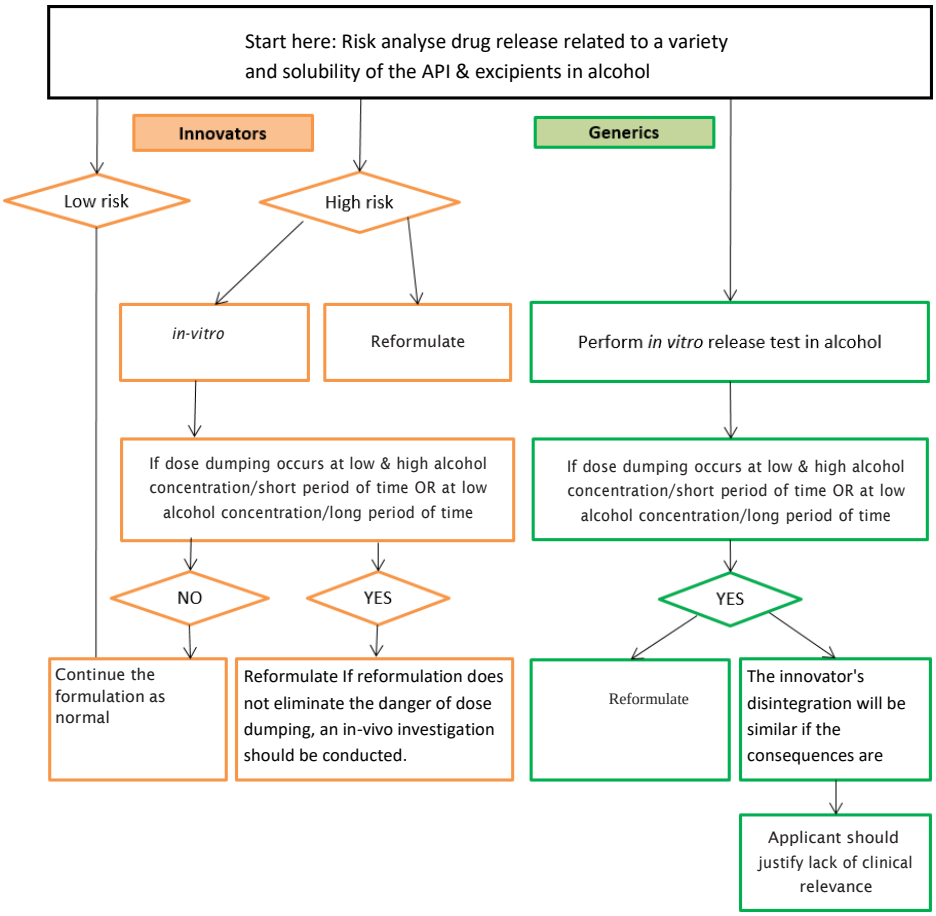
Regulations in the EU, united States, and other countries have provided recommendations on ADD. It is typically advised that appropriate in-vitro dissolving assays be tested in the presence of ethanol to rule out ADD. Nobody knows if the International Conference on Harmonization will release guidelines or a single document containing everything. The FDA only studied APIs with a restricted therapeutic window for ADD risk. (Fig.1) These two government agencies have their own set of rules (Table 1)[32,33]. As demonstrated in the chart below, the ADD requirements differ in three key areas: methodological requirements, test items, and approval criteria. The FDA requires testing in media containing up to 40% (v/v) ethanol, however the EMA only allows up to 20% (v/v). Two presentations were scheduled to educate the committee about the dangers of rapid drug release from a modified release dosage form due to concomitant alcohol consumption. Patients may be hazarded if a formulation's Dosing dumping can reduce the efficacy of various medications. The drug's therapeutic use and therapeutic index determine these risks[34-36].

Table 1: FDA and EMA standards for in vitro testing of ADD-prone formulations.

Required metho d	0.1N HCl 0%, 5%, 20%, and 40% alcohol 15 min intervals until 2 hrs DA	Medium of dissolution: same as for regular tests Alcohol content: 5%, 10%, and 20% Time: unknown MA
Items to be tested	At least all (generic) opioid medicine products; preferably all opioid drug products with risk of alcohol-induced dose dumping	Any and all applications of oral modified release

An unsuitable dosage form could result in dose dumping, posing a safety risk to study participants. These studies' findings could be put to better use in clinical study design and dosing regimen suggestions if they were explicitly designed to assess dose-dumping. The FDA recommends reliable alternatives to in vivo testing to reduce human risk. Risk reduction assumes that undesirable outcomes must be avoided at all costs[37]. Based on regulatory experience, tough modified-release dosage forms impermeable to alcohol should be developed to prevent the risk of dose-dumping induced by alcohol.

Fig 1: ADD risk assessment using EMA guidelines



An in vitro test for alcohol-induced dose dumping potential confirms class membership and identifies product and process failure modes. In some cases, a valid categorization system based on drug release mechanism may be sufficient, whereas in others, an in vitro test may be required. A range of MR drug product strengths were tested in vitro for drug release using various alcohol concentrations[38]. Keep in mind the following when assessing in vitro alcohol-induced dose dumping of MR medicines:

Factor influencing AID

Direct compression is the process of compressing tablet formulations straight from a powdered excipient and API combination. No need to granulate the powdered mixture. Faster manufacturing requires less machinery, fewer personnel, fewer unit activities, and less processing time. Several factors, such as dosage form quality, etha- nol absorption and metabolism, stomach content dilution, and gastric emptying, influence the likelihood of AIDD[39]. While studies have compared fed and fasted gastric emptying In ethanol-sensitive formulations, delayed stomach emptying increases the risk of dose-dumping. Even ethanol doses of 4% and 10% have been demonstrated to slow stomach emptying. These are new enhanced oral products entering the market, and there is definitely room for more in this expanding market area. A third of patients seek fast therapeutic activity from their medicines, resulting in poor adherence and treatment efficacy[40]. Instant release (IR) pharmaceutical formulations combine

convenience and efficacy in a new dosing form. They are meant to speed up drug release. Due to current technological limitations, there is an unmet demand for improved manufacturing techniques for fast release medications. This would enable for improved packing and manufacturing using the above super disintegrants and technologies. To satisfy these medical needs, efforts have been made to develop a new type of oral tablet dose that disintegrates and dissolves quickly with enhanced solubility[41,42]. An instant release dosage form extension of market exclusivity can target an underserved and under-treated patent population. A polymeric matrix commonly surrounds the drug in oral MR dosage forms such as tablets or capsules. The rate of liquid diffusion into the polymer and then drug diffusion out of the matrix determines the rate of drug release from an MR tablet. MR capsules, which include an inert bead wrapped in a polymer matrix and an adsorbed medicine, use similar methods. These factors should be considered before developing and testing dose forms in vitro or in vivo[43,44].

Hydromorphone: A Extended release Tablet

The difference in VAS score changes between groups from baseline through completion or termination of treatment was 0.4 millimetres (95 % confidence interval 5.9 to 5 millimetres). The noninferiority threshold was chosen at 95 percent CI less than 10 mm. This study revealed that hydromorphone pills were as effective and tolerable as oxycodone tablets. The hydromorphone group experienced 80.7 percent (71 of 88) adverse events, while the oxycodone group had 83.7 percent (77 of 93) [45]. The most prevalent side effects were nausea, vomiting, drowsiness, diarrhoea, and constipation. Hydromorphone extended-release tablets were not superior to oxycodone extended-release tablets in opioid-nave Japanese cancer patients. Hydromorphone extended-release tablets are absolutely safe[46-48].

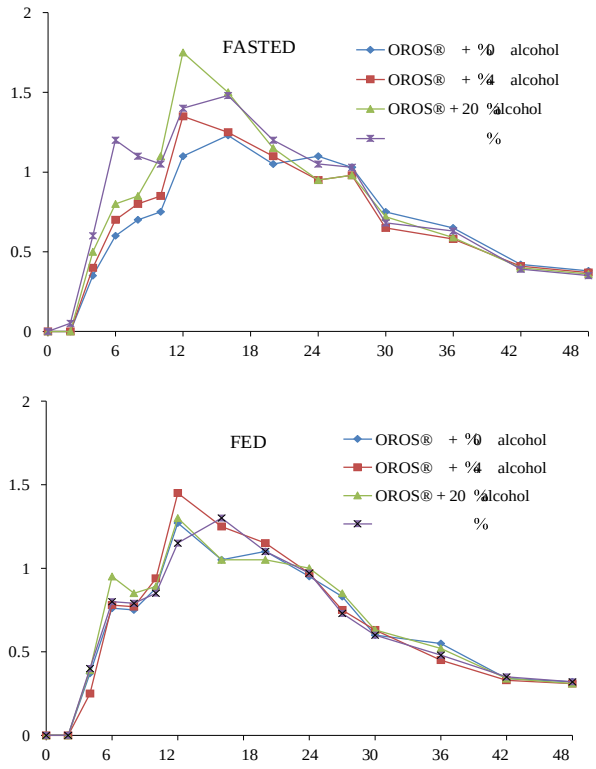


Fig.2: MHC plasma concentration profiles

Effect of ethanol on morphine sulfate SR

Oramorph SR tablets (15, 30, 60, and 100 mg; Xanodyne Pharmaceuticals, Inc. Newport, KY) were cultured in vitro in medium without ethanol or with ethanol concentrations ranging from 4% to 40% (v/v). The release of morphine sulphate was measured using HPLC during a period of 1 to 24 hours (United States Pharmacopeia). The active drug dosage of morphine sulphate tablets was proven[49]. The body's ethanol content had no effect on morphine sulphate release. On average, 20% to 25% of morphine sulphate dose was released in an hour, depending on ethanol dose and concentration. The release of morphine sulphate from the 60 and 100 mg tablets exposed to greater ethanol concentrations was delayed by around an hour (20 percent and 40 percent). This in vitro study found that ethanol concentrations up to 40% had no effect on the sustained-release properties of morphine sulphate tablets[50-53].

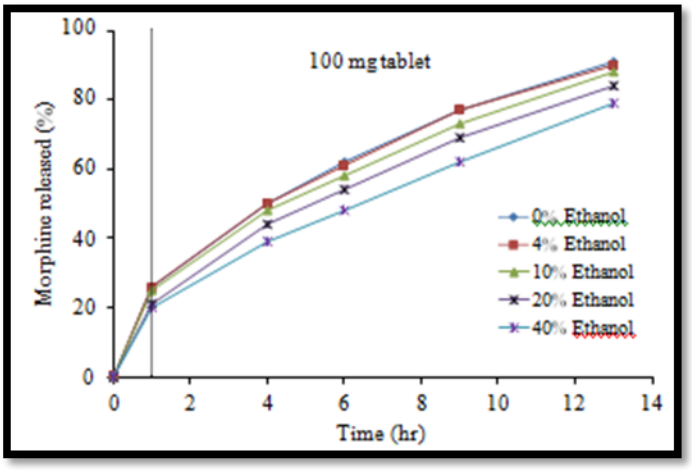


Fig 3: SR tablet release morphine sulphate into ethanol

Hydro-alcoholic media and the ethanol resistant excipient polyacrylic acid polymer (Carbopol 971G)

Figure 4 shows the solubility of HCTZ in each of the six dissolving fluids. It shows that the drug's solubility in the media does not explain the observed dissolving discrepancies. Aspirin's release is attributable to its increased solubility in ethanolic environments[54-56]. The different release behaviours identified in various dissolution media and the quick release reported in the 30% ethanol medium imply that variables other than solubility influence HCTZ release from carbopol 971G matrices[57].

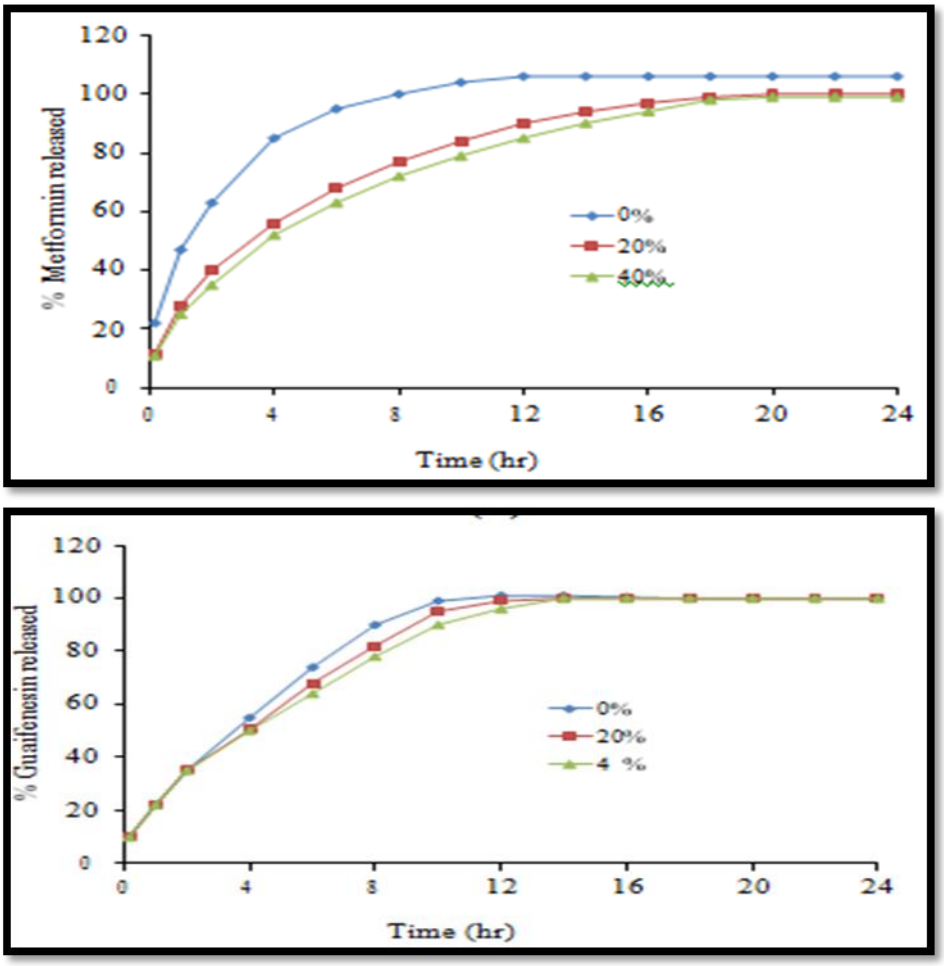


FIG 4: Caffeine, metformin, and guaifenesin release from Carbopol 971G based tablets, Lubrizol Technical Data Sheet

Conclusion

ADD in MR dosage formulations puts some individuals at danger. This may be a problem. AIDD in modified release dosage forms has been extensively researched in both animals and humans. All three regulatory agencies' perspectives were compared. Clinical case studies were investigated in certain opioid extended-release PK studies[58]. Finally, in vitro dissolution experiments reveal the impact of formulation excipients on drug release when subjected to varying quantities of ethanol. The case studies' sensitivity to alcohol-induced dosage dumping varied. MR formulations with significant AIDD may need to be adjusted based on regulatory information. In less severe cases, a clinical PK study may be required to assess how alcohol impacts medication release. As a result, regulators have advised formulators on how to reduce the risk of ADD-related formulations. Effective dosage forms may be challenging to produce since in-vitro testing may not adequately match actual physiological conditions. The cost of drugs for global firms is rising due to regulatory differences between countries[59,60]. The FDA and EMA recommendations for ADD in-vitro testing should be harmonised to reflect physiologically realistic alcohol concentrations and exposure times.

REFERENCES

1. World Health Organization . Cancer Pain Relief: With a Guide to Opioid Availability. 2nd ed. Geneva: WHO; 1996.

2. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995;**63**(1):65–76.

3. International Narcotics Control Board . Report of the International Narcotics Control Board for 2013. Vienna: United Nations; 2014

4. Hanks GW, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer. 2001;**84**(5):587–593.

5. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012;**13**(2):e58–e68.

6. Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol. 2012;**23**(Suppl 7):vii139–vii154.

7. National Comprehensive Cancer Network Adult cancer pain. Version 2. 2012. [Accessed July 21, 2017]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf.

8. Johnson SJ. Opioid safety in patients with renal or hepatic dysfunction. 2007. [Accessed July 21, 2017]. Available,from: http://paincommunity.org/blog/wp-content/uploads/Opioids-Renal-Hepatic-Dysfunction.pdf.

9. Lussier D, Richarz U, Finco G. Use of hydromorphone, with particular reference to the OROS formulation, in the elderly. Drugs Aging. 2010;**27**(4):327–335.

10. Davison SN, Mayo PR. Pain management in chronic kidney disease: the pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients. J Opioid Manag. 2008;**4**(6):335–336. 339–344.

11. Quigley C, Wiffen P. A systematic review of hydromorphone in acute and chronic pain. J Pain Symptom Manage. 2003;**25**(2):169–178.

12. Toyama K, Uchuda N, Ishizuka H, et al. Single-dose evaluation of safety, tolerability and pharmacokinetics of newly formulated hydromorphone immediate-release and hydrophilic matrix extended-release tablets in healthy Japanese subjects without co-administration of an opioid antagonist. J Clin Pharmacol. 2015;**55**(9):975–984

13. Fukui S, Yano H, Yada S, Mikkaichi T, Minami H. Design and evaluation of an extended-release matrix tablet formulation; the combination of hypromellose acetate succinate and hydroxypropyl lcellulose. Asian J Pharm Sci. 2017;**12**(2):149–156.

14. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain. 1997;**72**(1–2):95–97.

15. Boonstra AM, Preuper HR, Balk GA, Stewart RE. Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. Pain. 2014;**155**(12):2545–2550.

16. Moore RA, Straube S, Aldington D. Pain measures and cut-offs: 'no worse than mild pain' as a simple, universal outcome. Anaesthesia. 2013;**68**(4):400–412.

17. Dekel BG, Tomasi M, Vasarri A, et al. Opioid titration with sustained-release oxycodone and immediate-release morphine for moderate/severe cancer pain: a pilot assessment of the CoDem protocol. J Opioid Manag. 2014;**10**(1):29–38.

18. Lazzari M, Greco MT, Marcassa C, Finocchi S, Caldarulo C, Corli O. Efficacy and tolerability of oral oxycodone and oxycodone/naloxone combination in opioid-naïve cancer patients: a propensity analysis. Drug Des Devel Ther. 2015;**9**:5863–5872.

19. Koizumi W, Toma H, Watanabe K, et al. Efficacy and tolerability of cancer pain management with controlled-release oxycodone tablets in opioid-naive cancer pain patients, starting with 5 mg tablets. Jpn J Clin Oncol. 2004;**34**(10):608–614.

20. Imanaka K, Tominaga Y, Etropolski M, et al. Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain. Curr Med Res Opin. 2013;**29**(10):1399–1409.

21. Mercadante S, Porzio G, Ferrera P, et al. Tapentadol in cancer pain management: a prospective open-label study. Curr Med Res Opin. 2012;**28**(11):1775–1779.

22. Fallon M, Cherny NI, Hanks G. Opioid analgesic therapy. In: Smith HS, editor. Opioid Therapy in the 21st Century. 2nd ed. New York: Oxford University Press; 2014. pp. 661–698

23. Vignaroli E, Bennett MI, Nekolaichuk C, et al. Strategic pain management: the identification and development of the IAHPC opioid essential prescription package. J Palliat Med. 2012;**15**(2):186–191.

24. Aditya, S.T., K.A. Mehta, L.L. Augsburger and S.W. Hoag, 2004. Influence of methacrylic and acrylic acid polymers on the release performance of weakly basic drugs from sustained release hydrophilic matrices. J. Pharmaceut. Sci., 939: 2319-2331.

25. Hendeles L, Wubbena P, Wein berger M. Food-induced dose dumping of once-aday theophylline. Lancet. 22: 1471 (1984).

26. Guidance for Industry: Food effect guidance Food-Effect Bioavailability and Fed Bioequivalence Studies (Issued 12/2002, Posted 1/30/2003). http://www.fda.gov/cder/guidance/5194fnl.pdf

27. kalická, B.; Matzick, K.; Komersová, A.; Svoboda, R.; Bartoš, M.; Hromádko, L. 3D-Printed Coating of Extended-Release Matrix Tablets: Effective Tool for Prevention of Alcohol-Induced Dose Dumping Effect. Pharmaceutics 2021, 13, 2123 https://doi.org/10.3390/pharmaceutics13122123

28. Baertschi SW, Alsante KM, Tønnesen HH. A critical assessment of the ICH guideline on photostability testing of new drug substances and products (Q1B): recommendation for revision. J Pharm Sci. 2010;99(7):2934–2940. doi:10.1002/jps.22076

29. Mukharya A, Patel PU, Chaudhary S. Effect assessment of "film coating and packaging" on the photo-stability of highly photo-labile antihypertensive products. Int J Pharm Investig. 2013;3(2):77. doi:10.4103/2230-973X.114903

30. Felton LA, Porter SC. An update on pharmaceutical film coating for drug delivery. Expert Opin Drug Deliv. 2013;10(4):421–435.

31. Ashton P, Chen J, Guo H, Polymer-based, sustained release drug delivery system. Google Patents. 2009.

32. Zaid AN, Qaddomi A. Development and stability evaluation of enteric coated Diclofenac sodium tablets using Sureteric. Pak J Pharm Sci. 2012;25:1.

33. Zaid AN, Natour S, Ghoush A, et al. Formulation and in vitro and in vivo evaluation of film-coated montelukast sodium tablets using Opadry® yellow 20A82938 on an industrial scale. Drug Des Devel Ther. 2013;7:83. doi:10.2147/DDDT.S37369

34. Zaid A, Fadda AM, Nator S, et al. Development and stability evaluation of enteric coated diclofenac sodium tablets using AquaPolish E. J Pharm Invest. 2011;41(4):211–215. doi:10.4333/KPS.2011.41. 4.211
35. Flößer A, Kolter K, Reich H-B, et al. Variation of composition of an enteric formulation based on Kollicoat MAE 30 D. Drug Dev Ind Pharm. 2000;26(2):177–187. doi:10.1081/DDC-100100342

36. Felton L, Haase MM, Shah NH, et al. Physical and enteric properties of soft gelatin capsules coated with eudragit ® L 30 D-55. Int J Pharm. 1995;113(1):17–24. doi:10.1016/0378-5173(94)001 69-6

37. Park HJ, Jung HJ, Ho MJ, et al. Colon-targeted delivery of solubilized bisacodyl by doubly enteric-coated multiple-unit tablet. Eur J Pharm Sci. 2017;102:172–179. doi:10.1016/j.ejps.2017.03.006

38. Howden CW. Update on dual delayed-release PPI formulations. Gastroenterol Hepatol (N Y). 2010;6(7):417.

39. Maroni A, Moutaharrik S, Zema L, Gazzaniga A. Enteric Coatings for Colonic Drug Delivery: State of the Art. Taylor & Francis; 2017.

40. Ibekwe V, Khela MK, Evans DF, Basit AW. A new concept in colonic drug targeting: a combined pH-responsive and bacterially-triggered drug delivery technology. 2008;28(7):911–916.

41. Liu F, Moreno P, Basit AW. A novel double-coating approach for improved pH-triggered delivery to the ileo-colonic region of the gastrointestinal tract. Eur J Pharm Biopharm. 2010;74(2):311–315. doi:10.1016/j.ejpb.2009.11.008

42. Varum F, Hatton GB, Freire AC, et al. A novel coating concept for ileo-colonic drug targeting: proof of concept in humans using scintigraphy. Eur J Pharm Biopharm. 2013;84(3):573–577. doi:10.1016/j.ejpb.2013.01.002

43. Y. Qiu, Chapter 20 - Rational design of oral modified-release drug delivery systems, in: Y. Qiu, Y. Chen, G.G.Z. Zhang, L. Liu, W.R. Porter (Eds.) Developing solid oral dosage forms, Academic Press, San Diego, 2009, pp. 469-499

44. S. Missaghi, K.A. Fegely, A.R. Rajabi-Siahboomi, Investigation of the effects of hydroalcoholic solutions on textural and rheological properties of various controlled release grades of hypromellose, AAPS PharmSciTech, 10 (2009) 77-80.

45 C. Maderuelo, A. Zarzuelo, J.M. Lanao, Critical factors in the release of drugs from sustained release hydrophilic matrices, Journal of Controlled Release, 154 (2011) 2-19.

46. M.V.S. Varma, A.M. Kaushal, A. Garg, S. Garg, Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems, American Journal of Drug Delivery, 2 (2004) 43-57.

47. Y.-E. Zhang, R. Tchao, J.B. Schwartz, Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release, Pharmaceutical Development and Technology, 6 (2001) 131-144.

48. R. Chokshi, B. Leclercq, M. Sestrick, M. Butt, J. Lee, Aqueous ethyl cellulose coating with alcohol resistant properties: formulation and process considerations, https://www.controlledreleasesociety.org/meetings/Documents/2013Abstracts/100712.pdf

49. M.J. Traynor, M.B. Brown, A. Pannala, P. Beck, G.P. Martin, Influence of alcohol on the release of tramadol from 24-h controlled-release formulations during in vitro dissolution experiments, Drug Development and Industrial Pharmacy, 34 (2008) 885-889.

50. P. Tripura Sundari, R.S. Gaud, Formulation and evaluation of alcohol resistant dosage forms of diclofenac sodium, International Journal of Pharmacy and Pharmaceutical Sciences, 5 (2013) 854-857.

51. M. Levina, H. Vuong, A.R. Rajabi-Siahboomi, The influence of hydro-alcoholic media on hypromellose matrix systems, Drug Development and Industrial Pharmacy, 33 (2007) 1125-1134.

52. M. Roberts, M. Cespi, J.L. Ford, A.M. Dyas, J. Downing, L.G. Martini, P.J. Crowley, Influence of ethanol on aspirin release from hypromellose matrices, International Journal of Pharmaceutics, 332 (2007) 31-37.

53. J.H. Bartholomaeus, E. Arkenau-Maric, E. Galia, Opioid extended-release tablets with improved tamper-resistant properties, Expert Opinion on Drug Delivery, 9 (2012) 879-891.

53. H.K. J. Bartholomaus, E. Arkenau-Maric, Dosage form that is safeguarded from abuse, EP1658054B1, 2007.

54. G. Sathyan, K. Sivakumar, J. Thipphawong, Pharmacokinetic profile of a 24-hour controlled release OROS formulation of hydromorphone in the presence of alcohol, Current Medical Research and Opinion, 24 (2008) 297-305.

55. S.J. Koziara J., Agarwal N., The effect of ethanol on semipermeable cellulose acetate-based membranes, poster presentation, AAPS Annual Meeting and Exposition, San Antonio, TX, USA, 2006.

56. CimaLabs, OraGuard™ Abuse-deterrent, alcohol-resistant extended release technology, http://www.cimalabs.com/technology/oraguard.aspx (accessed November 2018).

60.M.V. Velasco, J.L. Ford, P. Rowe, A.R. Rajabi-Siahboomi, Influence of drug: hydroxy propylmethy lcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets, Journal of Controlled Release, 57 (1999) 75-85.