How to Cite:
Rajan, J., Rajan, V., & Kaur, B. (2022). Alcohol induced dose dumping in modified release formulations in vivo and in vitro studies: Comprehensive review. *International Journal of Health Sciences*, *6*(S3), 9633–9650. https://doi.org/10.53730/ijhs.v6nS3.8295

Alcohol induced dose dumping in modified release formulations in vivo and in vitro studies: Comprehensive review

Jasu Rajan
University Institute of Pharma Sciences, Chandigarh University, Mohali, 140301, India

Vasu Rajan
University Institute of Pharma Sciences, Chandigarh University, Mohali, 140301, India

Bhupinder Kaur*
University Institute of Pharma Sciences, Chandigarh University, Mohali, 140301, India

***Abstract*---**Various case studies based on alcohol-induced dose dumping in modified release dosage forms both in vivo and in vitro have been studied in this review, as well as a study of numerous factors impacting it, polymers that can be used to prevent it, and a perspective of regulatory authorities. The drug from various modified release dosage forms is released in such a way that the release of the drug is tailored or delayed especially for drugs that are having a therapeutic index in a very narrow range or are opioids. These types of drugs possess a very high risk of dose dumping if co-administered with alcohol. Since the problem of alcohol-induced dose dumping (AIDD) has been caught by the regulatory agencies some of the formulations come with black box warnings and some are even withdrawn from the market. It's been set as a benchmark by the regulatory agencies that if the formulation withstands 0-40% alcoholic condition under in-vitro release tests then the modified release formulations can be classified rugged against the dose duping. Delayed-release oral dosage forms when administered together with alcoholic beverages can have a fatal effect on the health of the patients as alcohol can alter the release mechanism of the dosage form

***Keywords*---**alcohol induced dose, modified release, in vivo, in vitro studies.

Key points

- Iv vivo testing is not of much significance to the regulatory agencies.
- Various polymers (cellulose ethers, carbomers, polyethylene oxide and sodium alginate) can be used to prevent alcohol induced dose dumping.
- Modification in different physico-chemical parameters (solubility, wettability, swell-ability and mechanical properties) can be done to prevent dose dumping caused due to ethanol.
- There is a need for in vivo testing to be done on modified release formulations to be sure about the safety when co-administered with alcohol.

Introduction

In recent years 'Alcohol-Induced Dose Dumping' has escalated the attention of regulatory authorities worldwide. Unintended, uncontrolled release of the whole or half of the complete drug amount present in a modified release dosage form is called dose dumping and when it occurs due to concomitant administration of the dosage form with alcohol then it is called alcohol-induced dose dumping. And this can have dangerous and fatal effects. As in the case of PalladoneTM (modified release hydromorphone formulation) withdrawn by FDA in 2005 from the US market, because when it was co-administered with alcohol hydromorphone's peak plasma concentrations were lethally intensified which could cause serious effects like change in heart rate which could lead to heart attack, tremors, double visions, involuntary movement of eyes, hallucinations, disorientation, etc... and rather than being helpful the medicine would itself become poison for the patient [1]. So, assessing the seriousness of the situation FDA recommended specific guidelines to assess the risk of alcohol-induced dose dumping in opioid as well as non-opioid drugs present in modified release dosage forms. Especially the dosage forms which provide prolonged therapeutic effects and reduced dosage frequency are of specific interest. As opioid formulation (even though being risky) is considered to be the first choice of medical practitioners in the treatment of chronic pain.

And in conditions of chronic pain a patient usually or generally to bear up the pain is attracted towards alcohol. It has been proved in a study conducted on the problem and non-problem drinkers to assess the relationship between pain and it's been observed that both categories of patients have a very high chance of developing a drinking problem to cope with the pain and emotional traumas of life they are going through the life due to the disease they are suffering from. If a being treated with analgesics will show fatal effects on patients' body like rapid dose upsurge, leading to respiratory depression, effect on kidneys by urinary retention, fatal effect on body nervous system, hypoxia or even can cause the death of the patient [2]. Even in the case of non-opioid drugs alcohol can be fatal for patients if administered along with dosage forms as it may magnify sedation effects (due to synergistic effects), orthostatic hypotension, and reduction in motor skills, etc... In the case of drugs that are not acid labile but are intended to be absorbed from the intestine, alcohol-induced dose dumping may still be fatal as when an oral dosage form may cause a complete or partial release of a large number of drugs in the stomach and when after gastric retention the whole is shifted to intestine the dosage form may start to show its release as designed but

now alongside with already present amount (which was released due to ethanol in the stomach) and may cause increased plasma concentrations of the drug in the body [3]. Also, the drug may cause side effects in the stomach like ulcers, acidity, etc… and if the drug is acid-labile it will get degraded in the stomach much before it was intended to be released and may cause economical as well as a medical issue for the patient. In healthy individuals, the rate of gastric emptying ranges from 120 to 180 minutes which depends on the absorption of the drug in the intestine. To screen for possible effects of alcohol-induced dose dumping gastric physiology (emptying) must be mimicked (especially for 2h) by in-vitro studies by [3].

Also, ethanol has a lag effect on the duration of the gastric emptying rate as it may prolong the gastric emptying rate and so the onset of a drug would also be prolonged. The low content ethanolic beverages like Wines and beers have a stronger effect in prolonging the gastric emptying as compared to Whiskey and Scotch with high contents of ethanol [4]. Mostly for alcohol-induced dose dumping in-vivo studies are not performed because of ethical issues so from the limited number of studies present on this problem majority are in-vitro studies [5]. For in-vitro studies, the conditions are very specific as they should be conducted in acidic media (0.1 N HCL) with ethanolic concentrations of 5%, 20%, and 40% v/v for a duration of 2h. The purpose behind setting up different ethanolic concentrations is that it mimics the different alcoholic beverages like beer with 5% ethanol, mixed drinks with 20% ethanol, and hard liquor at 40% ethanolic concentrations. Assessment of a drug formulation's alcohol-induced dose dumping effect is still an issue for the regulatory authorities because it does not have any specific regulatory framework. A suggestion for the regulatory authorities is to classify the formulations based on in-vitro data into either a vulnerable class or a rugged class [6]. The formulation's drug release is observed and analyzed in acidic media with and without the ethanolic concentrations and then an F2 similarity test must be done to classify the formulations into these categories. When the F2 value exceeds 50 dissolution profiles are considered to be similar.

Formulations should be considered non-resistant to alcohol-induced dose dumping when the F2 value is less than 50. Secondly other that F2 value relative change in the amount of dissolution (DA/n) media as compared to pure media should be calculated [7]. Another challenge to alcohol-induced dose dumping prevention is preventing the abuse of dosage forms by drug addicts. The development of such types of dosage forms is called abuse-resistant formulations. The formulations which are containing opioid drugs can be manipulated by drug addicts by breaking or milling and to stop/prevent it an opioid antagonist is present in them which will antagonize the effects of opioids and prevent the abuse is called abuse-deterrent formulation. Whereas another type (abuse-resistant) used more common strategies like physical and mechanical barriers like to prevent the crushing and milling of tablets increased hardness can be used. In this review, a study is done on all the available parameters, methods, techniques, and materials (Physico-chemical) which can be used to develop a formulation that could prevent alcohol-induced dose dumping. In today's world majority of the pharmaceutical industry tries to formulate formulations with prolonged and sustained therapeutic blood levels with time intervals ranging from (12-24h) as

this is observed as a popular approach for treating the patients among the doctors and even among the patients as modified release dosage forms limit the need to keep a tight track on the interval and frequency of dosage administration. Thus, there are many benefits to enjoy with the modified-release (MR) dosage forms like patient errors caused in dosage administration getting eliminated or problem of sudden pain while treatment with immediate-release (IR) pain medications also get rectified [8].

In modified release dosage forms the drug is released in such a way that its release is modulated to be slow and contain large quantities of therapeutic agents for that purpose, with this stands a big risk that as the quantity of drug present is too large in a single dose of any sort of disruption occurs in the release mechanism whole of the drug or large quantities of a drug could get released immediately. Modified release formulations of theophylline when co-administered with alcohol showed higher serum levels [9]. So, it's very obvious that adverse events, toxicity, high exposure levels, and safety issues will get raised even with a single bolus dose in case of dose dumping conditions. Clinical efficacy is the worst affected by the dumping conditions and it is assumable that drugs that are centrally acting or the drugs that are having a narrow therapeutic index are of high concern. Effects of food on the release of the drug can be assessed by the set of guidelines provided by the Centre for Drug Evaluation and Research) CDER guides on how to conduct clinical studies. Matrix coating of the drugs with a suitable hydrophilic/hydrophobic polymer is one of the commonly used methods to control the drug release and prevent dose dumping. In-Vivo food studies must be done to analyze the effects of food on the release rate and also ensure that the release is in the intended fashion and that content uniformity is present in every batch, in-vitro studies must also be done.

The changes in the release of drugs from the modified-release (MR) dosage forms can also be by food and food can also lead to dose dumping but in this review paper, we will only focus on the dose dumping caused by the interaction of the formulation with alcohol [10]. Drugs used to treat severe pain in treatment of diseases like cancer are usually the drugs of (opioid class oxycodone, morphine, tramadol, hydromorphone, dihydrocodeine, etc..) and are usually the last resort for patients suffering from severe pain and the formulation for these drugs is usually modified-release (MR) dosage forms due to several reasons like cost of treatment, the prolonged need of pain relief, etc. and in diseases like cancer where drug therapy is required for a prolonged period of times the drugs with short half-lives are globally preferred to be formulated as modified release (MR) dosage forms [11]. The pharmacodynamic, in-vivo absorption, as well as the kinetic properties of the formulations, can be modified depending upon the technology and the excipients used to formulate the modified release (MR) formulation. Globally the regulatory agencies are concerned about the dose dumping for modified release (MR) formulations with opioid drugs. A prominent example of such a situation was observed by FDA in 2005 when a modified release dosage form containing (hydromorphone hydrochloride) Palladone XL was found to be showing 6 times higher levels in the blood when co-administered with alcohol. The co-administration of ethanol with a modified-release (MR) dosage form causes the mechanism designed to control the release of drug from the dosage form to be disrupted and leads to the release of a large amount of drug or

even the whole amount of drug to be released at once [12]. Thus, unintended rapid release due to interaction of alcohol with the release mechanisms of the formulations leading to a large number of drugs to be released or even a whole amount of drug can be defined as alcohol-induced dose dumping (AIDD).

Also, AIDD is of serious concern to the regulatory agencies as this problem could be exploited intentionally by drug addicts and can lead to widespread abuse of modified-release (MR) dosage forms, especially those containing opioids or barbiturates. Excretion, absorption, and metabolism of drugs that are co-administered with alcohol are negatively influenced (12,2). Drugs acting on the central nervous system like opioids show intensified pharmacodynamics effects on co-consumption with alcohol and most of these drugs also pose the risk of drug-drug interactions which is of moderate level but could not be overlooked as may pose a serious concern in the safety of patients [13]. Although on the label most of the formulations show a warning to prevent administration with alcohol, alcohol may be co-consumed after some while, and then modified-release (MR) dosage form may still cause serious adverse interactions. These situations could be very fatal as side effects like respiratory functions depression, serious long-time sedation, etc. could occur in patients. Thus, regulatory agencies are concerned and it has become a challenge for them to cope with AIDD in modified release (MR) dosage forms, especially in pain medications containing opioids.

Prevention of Alcohol-induced dose dumping by manipulation of important physical and chemical factors

The important factors for the development of alcohol-resistant dosage forms are swell ability, solubility, wettability, properties of API, and excipients.

Use of wettability to prevent AIDD

According to chemistry the static contact angle between a liquid and a surface in contact with it is called wettability. Good wettability is when the angle is less than 90 degrees and above 90 degrees is poor wettability. The crucial solute-solvent contacts due to which release of a drug could be affected as penetration of solvent into the matrix system depend on it. The solvent to which the matrix system is exposed may be sucked into the matrix pores due to capillary forces. So, if the penetration rate is high, it means good wettability. Sometimes there may be a hindrance in the penetration of solvent into the matrix pores due to negative capillary pressure, causing a decrease in drug release. So, while designing alcohol-resistant matrix system angles should not decrease in presence of ethanol to prevent the release of drugs in ethanolic media [14].

Solubility for preventing AIDD

According to the basics of chemistry, non-polar solvents are highly soluble in non-polar molecules and vice-versa. So, in a drug, the main role of its solubility in different solvents depends upon the ratio of hydrophilic and hydrophobic groups. According to fundamentals the solubility of a drug in aqueous solvents depends upon its ability to form bonds (hydrogen) with molecules of water. Hence if in a drug the hydrophobic part is less or we can say that the hydrophilic part is more

that means it will have high aqueous solubility and will have less solubility in ethanol because its capacity to form hydrogen bonds is less than in water. If we take a look at the di-electric constants of the ethanol (20) and that of water (80) we come to know that pure water is more polar as compared to ethanol. When ethanol is added to water it also becomes less polar. Hence if a drug was less soluble in water its solubility will increase with it the addition of ethanol and vice-versa for a less soluble drug. So, to protect the drug it should be coated with an alcohol-resistant coating layer or embedding it in a matrix system. The release of drugs from the matrix system is controlled based on various factors, but generally, the medium in which the matrix system has to perform is the influencing factor. The matrix system itself should withstand the ethanol; it should remain intact during the course till drug release is required. There is a need for scholars/scientists to study more on the solubility behaviour of matrix systems in ethanolic media as very limited literature is yet available [14].

Swell-ability to prevent AIDD

There are generally 2 types of polymers, one which is insoluble in water but swells in contact with aqueous media, and the second which is also soluble in water and swells in contact with aqueous media, the first one is called hydrogel and the second is called a hydrophilic polymer. The type which is insoluble forms cross-linked polymeric 3D network in presence of water. Entanglements, hydrogen bonding, and crystallites are some of the physicochemical crosslinks that make hydrogels insoluble in water. The swelling of the polymers is due to the polymeric chains compatibility (thermodynamic) with the nearby fluid. Hydrophilic polymers are in main focus of this review for the development of alcohol-resistant dosage forms. In presence of aqueous media, a transition from a glassy state to a rubbery hydrated state is shown by the hydrophilic polymers. For swelling, the responsible phenomenon is adjacent polymeric chains entanglement in which proper crosslinking does not form. The erosion of the matrix, diffusion of drug, release rate, kinetics, and water transport into the matrix system all depends on gel layers' physical properties and composition. An alcohol-resistant formulation can be obtained with the use of hydrophilic polymers because fast diffusion of ethanol can be prevented as thermodynamic equilibrium is achieved quickly by the hydrophilic polymer in the ethanolic media. The tipping point of equilibrium is very important as if not reached fast enough the ethanolic media may diffuse into the system and rapid drug release will occur. So, to develop an alcohol-resistant layer for the formulation rapid formation of the gel layer and tipping point of equilibrium quickly is very important [15].

Use of mechanical properties to prevent AIDD

To develop an alcohol-resistant delayed-release tablet the final dosage forms mechanical strength (tablets) is very important. The factors on which it depends are production techniques used, porosity along with compactness (compressibility) of the tablet. The compactness of the final dosage form will increase with the use of polymeric matrix systems as with its use the pores decrease in number and increase compactness. Disentangled chains are formed with high shear forces, and very strong bridges (solid) between the polymer and the drug particles are formed hence in turn further increasing the compactness of

the formulation. It can also help to prevent crushing, chewing, and dissolving for IV injections and hence in turn helps to prevent abuse of the formulation [16].

Polymers can be potential candidates to form an alcohol-resistant delayed-release tablet

For the modified release formulations, the hydrophilic matrix systems are very widely used and because these are insoluble in ethanol and can control the release of the drug are potential candidates for excipients to be used for the alcohol-resistant part of the formulation. Most of these polymers get transitioned to a gel layer when coming in contact with aqueous media. Erosion mechanisms and diffusion through the gel layer control the drug release. Hypromellose, Sodium Benzoate, Carbopol, Polyethylene oxide) are of special focus in this review.

Carbomers

Alkyl ethers of pentaerythritol or alkyl sucrose when cross-linked with high molecular weight acrylic acid are known as carbomers and are synthetic polymers in nature. CarbopolTM is the marketed trade name for these polymers and these come under different polymer grades depending upon the molecular weight and polymer type. Typically, carbomers find their use as increasing viscosity or as suspending agents in liquid or semi-solid pharmaceutical formulations. But these are also usable as release modifying agents, bio-adhesives, emulsifying agents, and binders in tablets. For use in wet granulation, the carbomers are mixed with water to form a binding solution [17].

Sustained release matrix beads also have the use of carbomers in peptide-containing dosage forms to inhibit the proteases present in the intestine which could be catastrophic for the peptide present in the dosage form. These polymers swell readily upon hydration and do not dissolve in polar solvents (like ethanol), thus forming a gel-like layer. The drug is dispersed in many smaller polymeric particles which come together as many discrete microgels rather than forming an entangled chain of polymers or a single hydrogel. These Carbopol matrices show slow drug release as microgels contain small water-filled interstitial spaces between the microgels from which drug diffusion occurs due to the breakup of the network due to the osmotic pressure from inside of the gel layer on complete hydration. The formation of the gel layer is pH-dependent as the pKa of the Carbopol polymer is 6. At low pH values, the polymer is not fully swollen and drug release is faster but above the limit of 6, the drug release is retarded [18]. Carbopol polymers can be used in the development of alcohol-resistant controlled release dosage forms due to their appropriate swelling behaviour in both ethanol and water and their cross-linked structure [19].

Cellulose Ethers

Derivatives of cellulose are the most widely used excipients in the pharmaceutical industry to form hydrophilic matrix systems. In specific terms hydroxypropyl methylcellulose (HPMC) with the trade name Hypromellose is one of the most famous excipients for hydrophilic matrix systems and is extensively employed in

the preparation of oral controlled release dosage forms. The drug released from it is pH-dependent and is also non-ionic. It forms a gel layer that is more viscous and is formed due to crosslinking of polymer chains and their entanglement happening after the relaxation of the polymer chains on coming in contact with the water [20]. The swollen layer gets eroded showing matric erosion and also diffusion of the drug from the swelled layer in gel form is the controlling factor for the drug release rate. The matrix system is required to show a complete swelling to prevent the early release of the drug and this could happen only with rapid hydration of the polymers.

Triple-layered HCL coated tablets using Hypromellose and water-insoluble ethyl cellulose release drug as controlled release nature to stop burst release of drug which is highly aqueous soluble [21]. on venlafaxine drug. The 10% ethanolic media was for conducting the release studies of modified release dosage forms. Authors on analysis of the in-vitro dissolution data concluded that the formulations are alcohol resistant and that the rate-controlling polymer remains intact in 10% ethanolic media which means Hypromellose remains intact in 10% ethanolic media. But as ethanol can easily dissolve ethyl cellulose due to its high solubility in it 40% ethanolic may show alcohol-induced dose dumping. Study on the matric-based controlled-release tablets containing Hypromellose matrix and aspirin as a drug to study the influence of ethanol on release rate was studies and it was observed that as concentrations of ethanol increased the release of the drug also increased significantly. The drug release was concluded to be erosion-dominated and a zero-order release profile was obtained [22,23]. Effect of 5% and 40% v/v on 3 model drugs: felodipine, metformin HCL, and gliclazide with matrix systems formed with the help of Hypromellose was studied and it was observed from the release profile that the formulation shows alcohol resistance based on F2 values but also notified that release was increased as compared to no-alcoholic media this was explained with the drug solubility in different concentrations of ethanol [24]. The matrices of Hypromellose remained intact for 6H after hydration irrespective of the ethanolic concentrations. All the above studies conclude that no dose dumping was observed, but there is a point to notice that ethanol affects the release kinetics, mechanism, and rheological properties of the formulations. But the in-vivo correlations may be difficult on the data of in-vitro studies as in-vivo physiologic conditions are not reflected accurately as conditions were not hydrodynamic and only conventional methods and media which were non-physiologic were used [25].

Polyethylene oxide

Homopolymers that are non-ionic like polyethylene oxide are present with a diverse variety of grades in the market based on molecular weight differences. These polymers are insoluble in alcohol and are water-soluble. Controlled release of drugs can be achieved by PEO grades which have high molecular weight. The hot-melt extrusion method is the best suited to develop sustain release matrix tablets using these polymers. The hydrogel layer due to hydration from water is formed on the matrix surface. A rotary tablet press was put in use to formulate the robust matrix tablets and we can say robust as gliclazide tablets had 2.3 MPa strength and Metformin HCL tablets were 0.70 Mpa. After analysis of in-vitro drug release data, the authors concluded that no dose dumping was shown by the

formulations and matrices are intact even in the presence of ethanolic concentrations. The F2 values were acceptable for all the formulations when a comparison was made between hydroalcoholic media release profiles and non-alcoholic media release profiles. With exception of metformin HCL tablets which show F2 values less than 50 after exposure to hydroalcoholic media for 12H. Authors after the analysis observed a great difference in release profiles of metformin HCL matrix tablets in alcoholic and non-alcoholic media. F2 value is not an appropriate method to check the alcohol-induced dose dumping. Matrix systems with PEO for multiple unit dosage forms are not studied by anyone for the influence of ethanol on alcohol-induced dose dumping [26].

Sodium alginate

It is inodorous in nature and also appears to be tasteless. Its physical characteristics are that its coloured powder (pale yellowish-brown). Mostly it is used as a tablet binder, solubilizing agent, capsule disintegrant, and suspending agent. As sodium alginate can delay the drug dissolution from tablets it is used in sustained-release formulations. Sodium alginate forms a gel layer on coming in contact with aqueous media, especially in low pH conditions and drug release is shown by dissolution. It is completely insoluble on organic solvents like ethanol and sodium alginates gel layer upon pH above its PKA value starts to disintegrate. So appropriately sodium alginate can be used in the development of alcohol-resistant delayed-release tablets that will prevent the drug release in the stomach even in ethanolic concentrations and will release a drug in intestinal conditions. To use it in delayed-release conditions its seal coating could be done interior to the enteric coat as sodium alginate alone could not be a very good enteric coat but can be used to prevent alcohol-induced dose dumping as a protective coating inside the enteric coat which on failure in ethanolic concentrations will get solubilized and then the alcohol-resistant seal coating could prevent the drug release from the formulations and will release the drug in the intestine [27]. Various grades of sodium alginate are available in the market with different use for different types of modified release dosage forms. The 3 main grades that can be used in delayed-release formulations as an alcohol-resistant seal coat are Protanal CR8113, Protanal CR 8223, and Manucol LKX. On further search, no studies were found on the effect of ethanolic concentrations on sodium alginate seal coats. It is found to be incompatible with a few other excipients like phenylmercuric acetate and nitrate, acridine derivatives, calcium salts, and heavy metals. High electrolyte concentrations cause salting out of sodium alginate. Eventually, sodium alginate can be used as a very effective seal coat in the development of alcohol-resistant delayed-release tablets as all the properties that are appropriate to prevent the drug release in ethanolic concentrations in the stomach are available in the sodium alginate [28].

The perspective of regulatory agencies on AIDD
Position of US FDA on AIDD

(CDER/FDA 2002; CDER/FDA 2014) for (AIDD) only a draft has been issued whereas formal guidance has been issued for food consumption caused dose dumping related problems. A set of tests has been advised that must be conducted in 0.1N HCL media containing different ethanolic concentrations 0f

0,5,20 and 40% v/v ethanol in the media. For drugs with media other than 0.1N HCL for testing stability and release of drug product the testing with different concentrations of ethanol must be done in the specific media. The US FDA currently is believed to be thinking that when the release studies i-vitro for the drug product with ethanolic concentrations up to 40% which is equivalent to scotch in real-world would show appropriate release behavior then there is no or very little need for in-vivo studies in ethanolic concentrations. For the modified release (MR) dosage forms especially for opioids, now it's made mandatory to provide information regarding the in-vitro release studies with different ethanolic concentrations in a review of ANDA by the DBE (Division of Bioequivalence) of FDA. For drug products that mandated similar in-vitro studies for NDA application for those drug products, the generics will also require similar in-vitro studies. Complete details about FDA's position on AIDD can be found in Individual Products Bioequivalence Recommendations Guidelines and FDA's guidelines for the industry [29].

Position Of Health Canada on AIDD

The therapeutic products Directorate (TPD) of Health Canada has a very similar stance on AIDD as that of the US FDA and Pose immense focus on in-vitro release testing in different ethanolic concentrations to assess the risk of AIDD for modified release (MR) dosage forms on patients. This is all done mainly with one purpose in mind which is to reduce the number of patients that will be put at risk due to dangerous clinical studies.

European Union

European medicines agency has mandated that modified-release (MR) dosage forms tests of dissolution profiles must be capable of projecting consistency between routine batches production and pivotal batches for clinical studies and modified-release formulation on analysis of the data must be formed to be robust in ethanolic conditions. In the guidelines on clinical and pharmacokinetic evaluation of modified release (MR) dosage forms, it was mandated that the product should be sent for reformulation on observation of AIDD in in-vitro studies in 0, 5 and 20% ethanolic concentrations. As the EMEA has not mandated 40% ethanolic concentrations for in-vitro studies clear communication and harmonization gap can be seen in the EMEA and the rest of the global regulatory agencies. The drug products containing polymethacrylate triethyl citrate are ordered to be removed from markets of the EU and are advised to be re-formulated with more robustness against AIDD.

In vitro case studies

Various in vitro case studies on AIDD have been selected systematically and discussed for the readers. In those studies, retrospective tests were done in which existing items on the market were assessed for their ability to dosage dump at various amounts of alcohol. Other studies compared formulations and discovered that some extended-release excipients are more sensitive to dumping of dose as compared to others. Some studies have been summarized in this article.

A hot-melt extruded pellets of codeine phosphate and paracetamol

Dose dumping in different formulations consisting of codeine phosphate in alcoholic media was tested by Jedinger et al. [30]. Codeine phosphate itself has reduced solubility in ethanol. The dosage form used for the study was hot-melt extruded pellets. 0% ethanol in 0.1 N HCl, 20% ethanol in 0.1 N HCl, and 40% ethanol in 0.1 N HCl was used to test solubility. Three formulations were developed, each with a 20% active ingredient. The overview of ingredients according to percentage in these formulations. (Fig. 1) shows the dissolving of codeine phosphate in media containing 0.1 N HCl with 0% ethanol and 40% v/v ethanol in acidic media. After 2 hours in 0.1 N HCl, codeine phosphate releases more. With only a modest increase in 40% ethanol. The data for the 20% N HCl the formulation that consisted of CaSt has the highest amount of release, ethanol has been omitted because the in 0% ethanol the dissolution results of paracetamol in 0.1 N HCl and 20% ethanol were similar, as shown in (Fig. 1). In 0.1 N HCl, paracetamol does not have a substantial release after 2 hours, while dosage dumping is detected in a medium containing 40% ethanol. After 2 hours, the formulation containing Precirol releases the highest dose. The formulation incorporating Precirol, like the codeine trial, has the highest dose released after 2 hours.

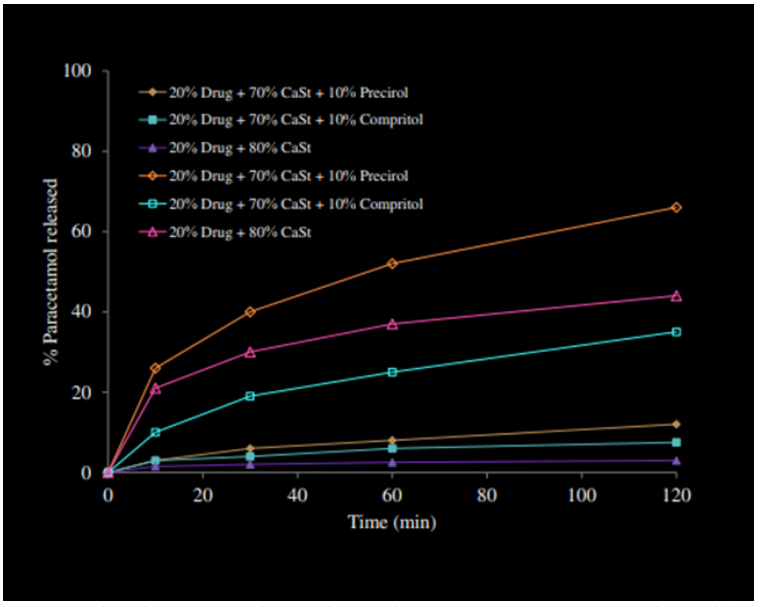

Fig. 1. Paracetamol release under ethanolic concentrations (closed legends = 0% ethanol, open legends = 40% ethanol.

The 3 formulations containing Tramadol

Traynor et al. [31] used 0, 20, and 40% v/v ethanolic media to evaluate three commercially available tramadol formulations for AIDD. The sensitivity to alcohol in the three formulations varied depending on the solubility of the excipient in ethanol. The principal excipient in the 3 chosen formulations (T-long® capsules, Eudragit® NE30D), is found to be soluble in organic solvents and has shown dose dumping in alcoholic dissolution medium containing 20% and 40% ethanol. Povidone and ethyl cellulose are both found to be soluble in organic solvents. This formulation exhibits a greater main after release profile in

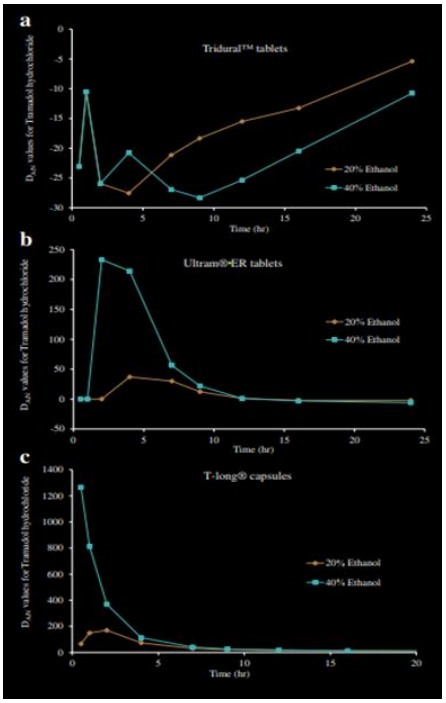

Fig. 2. For three different tramadol hydrochloride formulations, the influence of ethanol concentration on the DA/N values

40% alcohol than the control (0% alcohol) medium. Kollidon SR is also included in the Tridural® Tablet. An insoluble physical combination of polyvinyl acetate makes up this excipient (80%). This excipient is a physical mixture of insoluble in ethanol polyvinyl acetate (80%) and soluble in alcohol povidone (20%). In both 20% and 40% ethanol media, the product's release rate decreases, as shown in (Fig. 2) (Traynor *et al.*, 2008).

Theophylline-containing polymeric films

Guar gums (low-medium-high viscosity grades) and ethyl cellulose present in extended-release formulations of theophylline were subjected to 40% ethanolic concentration media for analyzing any possible dose dumping that may be caused due to ethanol. The first step is to run 900 mL of 0.1 N HCl dissolving solution for 2h in USP Apparatus II. The phosphate buffer pH 7.4 was used as the media for

the 2nd stage, and the experiment was repeated for an additional 6 hours. A fluidized bed coater was used to coat theophylline matrix cores with various ethyl cellulose: guar gum mixes throughout the formulation process. Film properties, anti-tacking agent additions, curing, and stability studies were all included in the formulation testing. On analysis of the results, the experimenters concluded that in 40% v/v ethanolic media both the medium and high viscosity coatings of guar gum were released at similar rates when compared to the tests without alcohol. The results of analysis have shown that in 40% ethanolic media the 2 coatings of guar gum that have shown faster release rates are both the lower viscosity grade coatings. But these issues are not found in the coatings that are done with higher viscosity grade polymers.

The Hydro-alcoholic media effects on the Hypromellose (HPMC) matrix systems

Three formulations (felodipine, gliclazide, and metformin) were studied by Levina et al [24]. for analyzing the effect of alcohol on matrix formulations consisting of HPMC. Multiple time points were employed to perform dissolution profiles in ethanol media containing 0, 5, and 40% ethanol for 12 hours (26 per profile). The participants were given alcohol for one hour and the entire 12-hour period. In-vivo exposures were deemed to be more realistic than a one-hour exposure. For two of the three medicines, there was no substantial change in drug release characteristics after 12-hour alcohol exposure. The drug release profile of the metformin formulation did decrease in a 40% ethanol medium, which was due to metformin's decreased solubility in alcohol. At both 5 and 40% ethanol media. No major change in the release of drug was found after exposure to ethanolic media for 1h which was followed by 11h of specific dissolution media (specific according to the pharmacopeia). In an acetate buffer media, dissolution profiles were carried out with 0, 10%, 20%, 30%, and 40% v/v ethanol incorporated. The release of a drug increases as the alcohol concentration rise, but there is no evidence of dose dumping in the dissolution profiles after 6 hours. According to the findings, at greater alcohol concentrations, the release mechanism governing the drug release from the HPMC matrix is affected mainly by 2 factors the matrix swelling decrease and the increase in solubility of aspirin, shown in (Fig. 3).

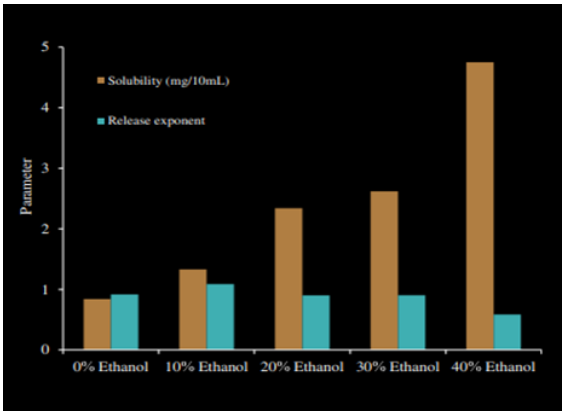

Fig. 3. Ethanol's effect on aspirin solubility and exponent of release from Hypromellose matrices

In vivo case studies

The opioid class of medications has been studied in case studies of modified-release (MR) drug formulations. This study looked at studies with ethanolic concentrations of 4%, 20%, and 40% alcohol, with single-dose, open-label, and cross-over studies being the most common.

Hydromorphone capsules (extended-release)

Palladone XL was tested in healthy volunteers in a four-arm, open-label, cross-over trial in both fasted and fed (n=24) settings. To reduce opioid-related side effects, healthy volunteers were given naltrexone, an opioid antagonist. To create the ethanolic circumstances, the water that the patients used to administer the capsules (240ml of water) had varied amounts of ethanol in it, such as 4%, 20%, and 40%, and some were given plain water in both fasted and fed states. The hydromorphone plasma concentration is shown in (fig. 4). The mean Cmax value was 3.5 for 40 ratios, with 6 as the maximum value, indicating that co-ingestion of drug with alcohol had a more visible effect in a fasting state [32].

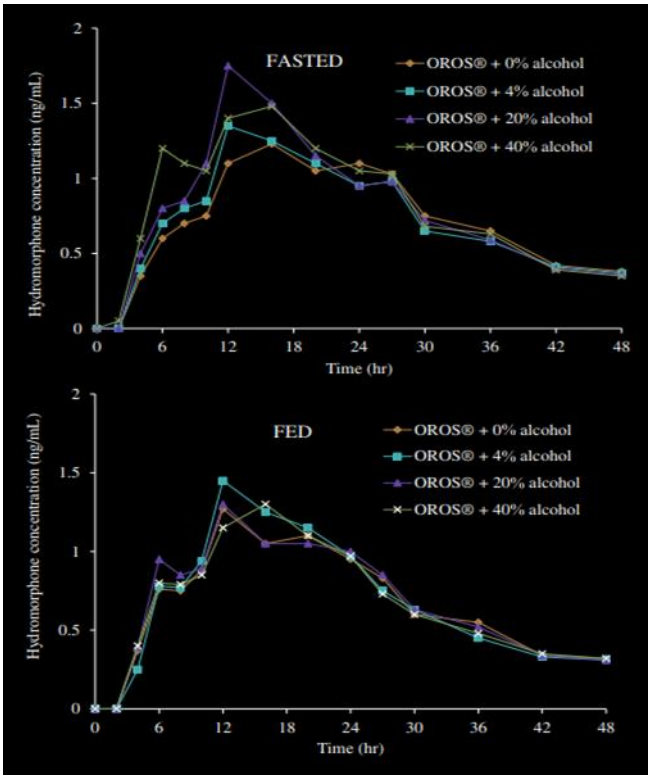

Fig. 4. Profiles of mean hydromorphone plasma concentrations

OROS push-pull

Sathyan et al [27] conducted a study with hydromorphone hydrochloride on healthy volunteers with a release mechanism that was osmotically controlled and

is called OROS push-pull. The condition chosen for testing of patients was both (fed and non-fed states). There were 2 groups. Group 1 consisted of the volunteers' hat were fed and group 2 consisted of non-fed volunteers. The subjects were given a 16mg of dose of hydromorphone hydrochloride (OROS push-pull) with 240ml orange juice or with 240mL with different ethanolic concentrations (4,20 and 40% v/v). While the fed and fasted groups had the same Tmax and AUC in f values, the fed and fasted groups had higher Cmax values after consuming alcohol. The authors on analysis of results found higher Cmax values for alcohol consumed in 20-30 minutes, a relatively short time, and concluded that the OROS technology had little impact on hydromorphone bioavailability.

Morphine Sulphate Capsules (Extended Release*)*

Healthy individuals were examined with EMBEDA (60 mg) capsules in a 4-way crossover, open-label, 4-sequence drug interaction, randomized, single-dose trial. EMBEDA can be used to treat both acute and chronic pain. Patients were instructed to administer (240 mL water) with various ethanolic concentrations of 0, 4, 20, and 40 in shots every 5 minutes, with the first shot serving as the medication administration. After analyzing the data, the authors found that the value of Tmax decreased from 9 to 4 hours, and the value of Cmax increased 2-fold in the 40% alcoholic condition, whereas there was no change in the extent of exposure or rate of absorption in the 4 to 20% alcoholic condition [33].

Oxycodone capsules (Controlled Release)

Kater et al. [34] conducted a four-way cross-over, randomized research on controlled release capsules of OXYCODONE. To separate four treatment sequences, a 96-hour washout time was used.

- Treatment 1 - plain water+ 40mg capsules
- Treatment 2 - 4% ethanol+ 40mg capsules (low concentration)
- Treatment 3 - 20% ethanol+ 40mg capsules (medium concentration)
- Treatment 4 - 40% ethanol + 40mg capsules (high concentration)

The authors of the study determined that 4% alcohol did not influence pharmacokinetic effects. In the 20% and 40% circumstances, only a modest increase in the effect of pharmacokinetic parameters was seen, leading the authors to conclude that the formulation retained regulated release characteristics.

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Conclusion

A comprehensive review of alcohol-induced dose dumping, with a focus on regulatory agencies' perspectives, factors affecting, polymers that can be used to prevent alcohol-induced dose dumping, and studies (both in vitro-Vivo), revealed that the regulatory agencies of the US, Europe, and Canada are all concerned about the effects of dose dumping caused by concomitant intake of ethanol and modified release formulations. Alcohol-induced dosed dumping is a significant barrier to the currently available modified release dosage forms, and it impedes

the development of new formulations as well as the safety and efficacy of existing formulations, particularly for medicines with a narrow therapeutic range and opioids. A rigorous evaluation of physicochemical parameters such as wettability, mechanical qualities, solubility, swell ability, properties of excipients, and final dosage form should be done to create a robust alcohol-resistant dosage form. Finally, in vitro dissolution tests are carried out to show how formulation excipients in modified release dosage forms affect drug release when exposed to different levels of ethanol. In a variety of ways, the formulations in the case studies were vulnerable to alcohol-induced dose dumping. MR formulations that demonstrate high AIDD may need to be modified, according to regulatory information. Less severe cases, on the other hand, may necessitate a clinical pharmacokinetic investigation.

Declarations

Funding No funding was received for publication of this review.
Conflicts of interest Vasu Rajan and Jasu Rajan declare no competing/conflict of interests.
Ethics approval Not applicable.
Consent to participate Not applicable.
Consent for publication Not applicable.
Availability of data and material Not applicable.
Code availability Not applicable.

Authors' contributions

Both Vasu Rajan and Jasu Rajan have equal contributions in drafting and concept building of the manuscript. Both the authors have read the final form of manuscript and take complete responsibility of the presented work.

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