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Polyox (Polyethylene Oxide) Multifunctional Polymer in Novel Drug Delivery System

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ABSTRACT
Polymers are tools used in novel drug delivery system to modify the drug release of pharmaceutical dosage form. Polyox is hydrophilic polymer made of non-ionic homopolymer of ethylene oxide. Polyox is popular for its film forming, binding, lubricating, mucoadhesive, viscosity imparting property in pharmaceuticals. Polyox are available in various grades based on its molecular weight. Lower molecular weight Polyox are widely used for immediate drug release based on erosion properties of the polymer like quick dissolving film and high molecular weight Polyox are used to retard the drug release based on swelling and erosion properties of the polymer in controlled release, sustained release, extended release, buccal films, ocular inserts, ocular gels, osmotic tablets and so on. Polyox plays an important role in design of a novel drug delivery system for both highly and poorly soluble drug due to its multifunctional property. This review is detailed on Polyox its advantages, disadvantages, salient feature, mechanism, stability and application in pharmaceutical dosage form.

Keywords: Polymers, Polyox, swelling, erosion, novel drug delivery system.

INTRODUCTION

Conventional oral dosage form is most old and common in formulation. Most conventional (immediate release) oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration. In the formulation of conventional drug products, no deliberate effort is made to modify the drug release rate. Immediate-release products generally result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. In the case of conventional oral products containing prodrugs, the pharmacodynamic activity may be slow due to conversion to the active drug by hepatic or intestinal metabolism or by chemical hydrolysis. Alternatively, conventional oral products containing poorly soluble (lipophilic drugs), drug absorption may be gradual due to slow dissolution in or selective absorption across the GI tract, also resulting in a delayed onset time. The pharmaceutical industry uses various terms to describe modified-release drug products. New and novel drug delivery systems are being developed by the pharmaceutical industry to alter the drug release profile, which in turn, results in a unique plasma drug concentration versus time profile and pharmacodynamic effect. Modified release dosage form has various advantages over conventional like

- Less fluctuation in drug blood levels by controlling rate of release eliminates peaks and valleys of blood levels.
- Reducing the frequency of dosing which enhanced convenience and compliance as extended–release products frequently deliver more than a single dose.
- Reduction in adverse side effects
- Reduction in overall health care cost.

To modify the release of drug in dosage form, polymers with different molecular weight are introduced. The introduction of polymers has resulted in development of dosage form with unique properties. Initially polymers were used as solubilisers, stabilizers and mechanical supports for sustained release of drugs. But over a period of time, the functionalities of polymers have changed. The polymers have been synthesized to suit specific needs or rather solve specific problems associated with development of drug delivery systems. So there is need to understand the role of polymers. Polymers can be classified based on any of the following categories in Table 1: (1) source; (2) type of polymerization; (3) Chain growth polymerization; (4) degradability.(5) Nature of Polymer and Water Interaction. Water soluble polymers have a wide range of industrial applications like food, pharmaceuticals, paint, textiles, paper, constructions, adhesives, coatings, water treatment, *etc.* [1]

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Table 1: Examples of polymers used in modified release dosage form [1]

Based on Source	
Natural	Chitosan, Alginate, Gelatin, Albumin, Collagen, Dextran, Cyclodextrin, Polyethylene glycol (PEG).
Semi Synthetic	Hydroxy Propyl Cellulose (HPC), Methyl Cellulose (MC), Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Ethyl Cellulose (HEC), Sodium Carboxy Methyl Cellulose (Na CMC).
Synthetic	Polyethylene, Polylactic acid, Polypropylene, Polyglycolic acid, Polyhydroxy Butyrate, Polyanhydride, Polyacrylamide
Type of Polymerization	
Addition Polymer	Polyethylene, Polypropylene, Polyvinyl Chloride
Condensation Polymer	Polyester, Polyurethane
Chain Growth Polymerization	
	Polyethylene, Polystyrene, Polyacrylates
Degradability	
Biodegradable	Polylactic acid, Polyglycolic acid, Polycaprolactone, Polyanhydrides,
Non-Biodegradable	Polydimethyl Siloxane, Polyether Urethane, Ethyl Cellulose
Nature of Polymer Water Interaction	
Hydrophobic Polymer and Water Soluble Polymer	Ethyl Cellulose, Polydimethyl Siloxane.
Hydrophilic Polymer	Cellulosic: MC, HPMC, HPC, HEC, NaCMC. Non-cellulosic: Sodium Alginate, Xanthum Gum, Carrageenan, Ceratonia (Locust Bean Gum), Chitosan, Guar Gum, Pectin, Polyethylene Oxide (Polyox)
Hydrogel Material	Cross-linked Polyvinyl Alcohol, Polyethylene Oxide, Polyacrylamide

Table 2: Grades of Polyox based on molecular weight and viscosity

Polyox(tm) Water-Soluble Resin NF Product	Approximate Molecular Weight	Viscosity Range at 25degC, cP		
		5% Solution	2% Solution	1% Solution
WSR N-10	100,000	30 - 50		
WSR N-80	200,000	55- 90		
WSR N-750	300,000	600 - 1,200		
WSR N-205	600,000	4,500 - 8,800		
WSR N-1105	900,000	8,800 - 17,600		
WSR N-12K	1,000,000		400 - 800	
WSR N-60K	2,000,000		2,000 - 4,000	
WSR-301	4,000,000			1,650 - 5,500
WSR Coagulant	5,000,000			5,500 - 7,500
WSR-303	7,000,000			7,500 - 10,000

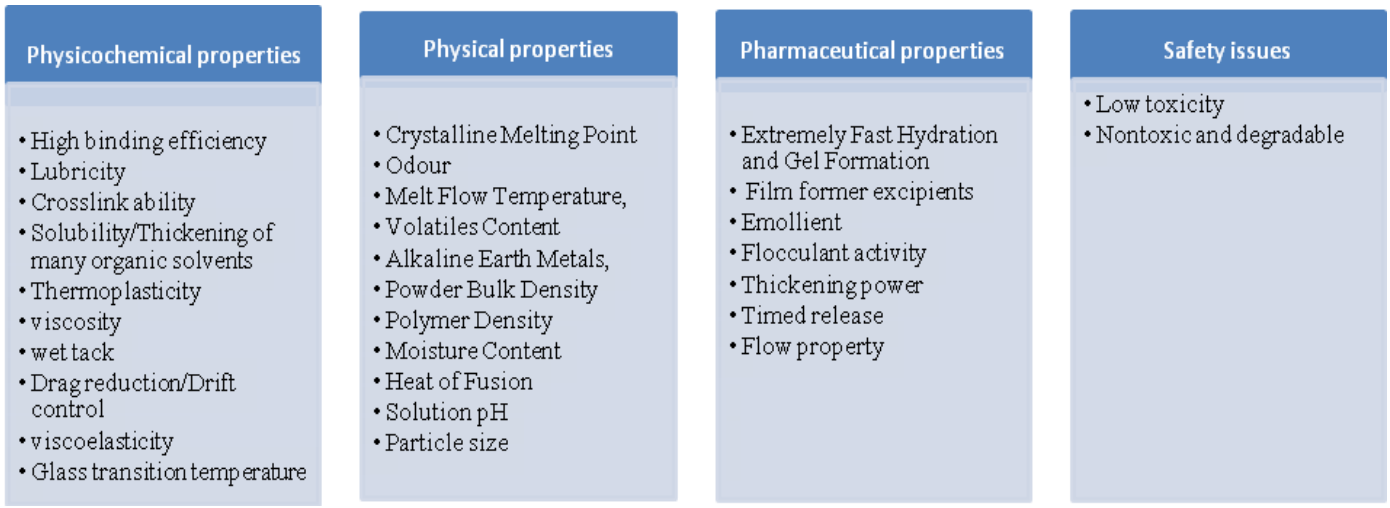

Fig. 1: Salient features of Polyox

Amongst all above polymer Polyox is becoming most famous polymer for immediate and controlled release of drug. So the present review elaborates the complete details on Polyox as polymer for modifying the release of drug.

Based upon the nature of polymer and water interaction Polyethylene oxide is a hydrophilic polymer. It is a non-ionic homopolymer of ethylene oxide. It is also known as Polyox. Polyox is a water soluble resins, is also referred to as poly (ethylene oxide). They are white, free-flowing hydrophilic crystalline powders supplied in a wide variety of molecular weight grades, ranging from one hundred thousand to eight million with an average particle size of around 150 mm. Polyethylene oxide is used as matrix materials. High molecular weight polyethylene oxide successfully delayed the release rate of soluble and insoluble drugs from matrix tablets prepared by direct compression. It is also used as a mucoadhesive polymer**.** Polyox water-soluble resins have applications in pharmaceutical products, tablet binding, tablet coatings, transdermal drug delivery systems, and immediate release dosage form and gastro-retentive dosage forms. [2-3] They exhibit film forming and water retention properties. It has high water solubility and low toxicity. [4]

Polyox resins can form associated compounds with many substances such as polystyrene, polycaprolactone, polyethylene, polypropylene and polylactides to produce unique blends and achieve a wide variety of additional, useful formulation properties.

Common structure

$$(\text{-O-CH2-CH2-})_n\,\text{OH}.$$

They have same chemical structure as PEG but higher molecular weights. n = average number of oxyethylene groups. [5] The ethylene oxide monomer is an epoxide ring.

Grades of Polyox

Polyox are supplied with variety of molecular weight grades and are formulated as NF and other official grade compounds. Different grades of Polyox and its pharmaceutical applications are cited in Table 2.

Advantages of Polyox

Polyox also provide a number of benefits:

- Wide range of molecular weights offers formulation flexibility
- Versatile application in direct compression and granulation
- Rapid hydration and swelling for use in osmotic pump technologies
- Fast hydration and gel formation for use in hydrophilic matrices
- Polyox films demonstrated higher bioadhesion than HPC films because Polyox hydrates faster, takes up more water and swell more than HPC.
- Polyox can be used as alternative to HPMC as tablet binder in direct compression. The swelling ratio of PEO was approximately twice as that of HPMC in acidic and neutral testing media.
- The swelling behaviour of PEO hydrogels is pH independent. While Carbopol has pH dependant swelling and bioadhesion behaviour.
- So it makes Polyox a reliable polymer for bioadhesion in stomach. [2]
- Meets requirements of the United States Pharmacopoeia (USP) and compliance with US Food Chemicals Codex. [2]

Physicochemical Properties

High binding efficiency- Polyox has high-binding efficiency for powders.

Crosslink ability- Polyox can be cross-linked to form gels that are highly water-retentive.

Lubricity- Polyox imparts a high degree of lubricity when in contact with water.

Solubility/Thickening of organic solvents- Polyox are readily soluble and will thicken wide variety of organic solvents (halogenated hydrocarbons, various ketones, alcohols, aromatic hydrocarbons and esters) at various temperatures. Polyox are not generally soluble in aliphatic hydrocarbon solvents, glycols, diols and aliphatic ethers.

Thermoplasticity- As thermoplastics, Polyox are readily extruded, injection molded, or cast. Sheets and films of this material are heat-sealable and can be oriented to develop high strength. Films are inherently flexible, tough and resistant to most oils and greases. These resins are compatible with many natural and synthetic polymers.

Wet tack- Polyox exhibit a high degree of wet tack and, thus, are useful as wet adhesives. The dried residue is non-tacky.

Drag reduction- Very low concentrations of the higher molecular weight Polyox can reduce the turbulent frictional drag of the water in which they are dissolved by as much as 80 percent.

Viscosity- As the concentration of Polyox water-soluble resin is increased, solution viscosity increases rapidly. The pH of a Polyox solution is 8-10. Polyox solutions will be most stable at neutral to slightly alkaline pH. At pH > 12, Polyox resins will precipitate out. At pH < 2, the polymer will degrade since ethers undergo acidic hydrolysis. [2]

Viscoelasticity- The flexibility of ether linkages combined with the extremely high molecular weight of Polyox produces solutions with elastic behaviour.

Glass transition temperature- The glass transition temperature (Tg) of the family of poly (ethylene oxide) products ranges from -50 to -57°C. Molecular weight does not have a significant impact on the Tg within the family of products.

Pharmaceutical Property

Extremely Fast Hydration and Gel Formation: Polyox are among the fastest-hydrating water-soluble polymers used in pharmaceutical systems. They quickly form hydrogels that initiate and regulate release of active ingredients.

Emollient- When applied to the skin and hair, Polyox produce a soft and silky feel.

Film former excipients- Polyox can be formed into flexible films both by thermoplastic processing and casting techniques.

Flocculant activity- High molecular weight grades of Polyox effectively adsorb onto many colloidal materials and perform as efficient flocculating agents.

Thickening power (aqueous) - Polyox are nonionic and completely water-soluble at all temperatures and are extremely effective thickening agents in both fresh and salt water. Aqueous solutions are pseudoplastic (i.e. shear thinning).

Flow property - All grades of Polyox flow relatively the same. Polyox contains silica (~1.5%) to help with the flow ability.

Timed release - Unique swelling properties coupled with the controlled rate of dissolution make Polyox an ideal choice for time-release formulations. Devices that provide a time-release of fragrance, colors, surfactants, reagents, etc., can be extruded using Polyox.

Safety Issues

Low toxicity - Polyox shows very low order of toxicity in animal studies by all routes of exposure. At the maximum practical oral dose to rates of about 2 g/kg of body weight. [2] These resins are neither skin irritants nor sensitizers, nor do they cause eye irritation as the dry powder or as aqueous solutions.

Nontoxic and degradable- Polyox are nontoxic and have received FDA approvals for a number of food and drug applications. Aqueous solutions of Polyox are environmentally degradable due to oxidation and aerobic biodegradation.

Because of their many unique properties, Polyox are particularly suited for the following processes like Casting, Extrusion, Injection molding and Blown film. [2]

Physical Property

Properties of Polyox are shown in Table 3. [2]

Table 3: Physical Property of Polyox

Appearance	Off-white powder
Crystalline Melting Point	62-67 °C
Odour	Slightly smells like ammonia
Volatiles Content, (at 105degC)	<1.0 % by wt
Alkaline Earth Metals	1.0 % by wt
Powder Bulk Density	19-37 lb/ft^3
Moisture Content	<1%
Heat of Fusion	33 cal/gm
Solution Ph	8-10
Particle size, % by wt	
Average through 10-mesh (U.S. standard)	100
Average through 20-mesh	96

Mechanism of Release

Polyox is uniformly incorporated throughout the tablet. Upon contact with water, it hydrates the outer tablet surface to form a gel layer. The rate of diffusion out of the gel layer and the rate of tablet erosion control the overall dissolution rate and delivery of the active substance. [2] The Polyox should be selected based on the molecular weight (MW) needed to obtain the release profile desired. A lower MW polymer will release faster than a high MW grade. For a robust and reproducible release profile the amount of Polyox should be 20-90% of the tablet weight. [2]

The drug release from the high molecular weight Polyox tablets is governed by the swelling of the polymer rather than by the erosion of the polymer, leading to anomalous release kinetics. However, the drug release from the low molecular weight Polyox is controlled primarily by the swelling/erosion of the polymer, resulting in front synchronization and a constant release rate. It is observed that drug loading and drug solubility do not influence the release of drugs from low molecular weight Polyox tablets. The pH of the dissolution medium and the stirring rate do not affect the drug release regardless of the molecular weight of the Polyox. [2]

Also, applications of Polyox as a carrier or component of oral, mucosal and transdermal drug delivery systems are documented.

Applications in Pharmaceutical Industries

Polyox offers a history of successful use in extended release applications of osmotic pump technologies, hydrophilic matrices, gastro-retentive dosage forms and other drug delivery systems such as transdermal and mucoadhesive technologies. Now a day's Polyox is successfully used in development of immediate release dosage form like films.

Controlled release matrix systems: Controlled release drug delivery systems are those dosage formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to a tissue. [6]

High molecular weight linear poly (ethylene oxide) (Polyox) has shown a great potential as a material for controlled drug delivery systems. Matrix tablets based on Polyox can be manufactured readily, because of good compressibility of this polymer. [7] The polyether chains of Polyox can form strong hydrogen bonds with water; Polyox upon exposure to water or gastric juices, they hydrate and swell rapidly to form hydrogels with properties ideally suited for controlled drug-delivery vehicles. Hence, a variety of release patterns can be obtained, depending on the Polyox molecular mass and the drug physicochemical properties.

Maggi *et al.* [8] formulated hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) of two different molecular weights: Polyox WSRN 1105 (M_w=0.9×10^6) and Polyox WSRN 301 (M_w=4×10^6) for the controlled release. The results show that the higher molecular weight PEO swells to a greater extent as compared to the lower molecular weight PEO. This difference in the erosion behaviour can explain the different efficiencies of the two polymeric products in modulating the delivery rate of the water-soluble drug.

Sanjeevani *et al.* [9] developed sustained release tablet of Mebeverine hydrochloride using Methocel K15M, K100M and Polyox 303 in the concentration of 10%, 20%, 30% and 40% of the tablet weight and mixed with necessary excipients and then compressed by direct compression technique. The formulations containing Methocel K15M (20% w/w), Methocel K100M (10% w/w) and PEO-303 (20% w/w) could retard drug release upto 12 hrs.

Vidhyadhara *et al.* [10] formulated controlled release matrix tablets of verapamil hydrochloride using Polyox WSR 303 by direct compression method. It was found that higher polymeric content in the matrix decreased the release rate of drug. *In-vivo* pharmacokinetic study proves that the verapamil hydrochloride from matrix tablets showed prolonged release and were be able to sustain the therapeutic effect up to 24 h.

Direct compression tablet binding: Polyox acts as binders in direct compression systems. They often provide better flow and compaction properties than other binders and their lubricity also assists tableting operations.

Dimitrov *et al.* [11] studied verapamil hydrochloride release from tablets based on high molecular weight Polyox. The drug release proceeds as a controlled diffusion which rate is dependent on the molecular weight of PEO. The introduction of hydrophilic polymers with pH dependent solubility (Eudragit L, Eudisperthv and Carbopol 934) at concentrations of 10-50% with respect to PEO ensures relatively complete release both in alkali medium. At lower drug concentrations on the matrix from a typical abnormal diffusion it turns into a relaxation controlled diffusion.

Kim *et al.* [12] studied the drug release from compressed tablets manufactured with a powder mixture of Polyox, a drug, and magnesium stearate. The drug release from the high molecular weight PEO tablets (MW= 2×10^6 and 4×10^6) is governed by the swelling of the polymer rather than by the erosion of the polymer, leading to anomalous release kinetics. However, the drug release from the low molecular weight PEO (MW=0.9×10^6) is controlled primarily by the swelling/erosion of the polymer, resulting in front synchronization and a constant release rate. The pH of the dissolution medium and the stirring rate do not affect the drug release regardless of the molecular weight of the PEO.

Mucosal bioadhesives: Polyox offers number of important properties for mucoadhesion- water solubility, hydrophilicity, high molecular weight, hydrogen bonding functionality and good biocompatibility. These resins have a long linear chain structure which allows them to form a strong interpenetrating network with mucus. Data indicates that molecular weights of 4,000,000 and higher have the highest level of adhesion.

Cappello *et al.* [13] investigated matrix properties and release behaviour of monolithic devices. Polyethylene oxides of different molecular weights have been blended in order to tune the release mechanism. In particular the developments of the external swollen layer of the tablet as well as the kinetic of dissolution have been monitored. The different drug delivery behaviours observed were related to the different matrix properties. Viscoelastic properties of the matrices have been also investigated. The best results of good release, viscoelatic and mucoadhesive properties was obtained in the case of 50% by weight blend of the two adopted polymer fractions (600,000 and 4,000,000 molecular weight).

Cappello *et al.* [14] developed a tablet for the buccal delivery of the poorly soluble drug carvedilol (CAR), based on poly (ethyleneoxide) (PEO) as bioadhesive sustained-release

platform and hydroxypropyl-beta-cyclodextrin (HPbetaCD) as modulator of drug release. As first, PEO tablets loaded with CAR/HPbetaCD binary systems with different dissolution properties were tested for CAR and HPbetaCD release features and compared to PEO tablets containing only CAR. The feasibility of buccal administration of CAR was assessed by permeation experiments on pig excised mucosa. The amount of CAR permeated from PEO tablet was higher in the case of HPbetaCD-containing tablets, the maximum value being obtained for CAR/HPbetaCD freeze-dried system.

Rama Bukka *et al.* [15] formulated buccal mucoadhesive films of Felodipine by casting method using polyethylene oxide with hydroxy propyl cellulose (HPC) or Ethyl Cellulose using 2^3factorial design. The solvent was ethanol and dichloromethane (1:1 ratio). The films were evaluated for ex-vivo mucoadhesive strength and in-vitro residence time, drug release and percentage swelling. All the formulations were following the zero order release and non Fickian model of kinetic release.

Ocular drug delivery

Di Colo *et al.* [16] studied new application of high molecular weight (400 kDa) linear poly (ethylene oxide) (PEO) in gel-forming erodible inserts for ocular controlled delivery of ofloxacin (OFX) by powder compression. The erosion time scale was varied by compounding PEO with Eudragit L100 (EUD) 17% neutralized (EUDNa17) or 71% neutralized (EUDNa71). Immediately after application in the lower conjunctival sac of the rabbit eyes, the inserts based on plain PEO, PEO-EUDNa17 or PEO-EUDNa71 formed mucoadhesive gels, well tolerated by the animals; then the gels spread over the corneal surface and eroded. The gel residence time in the precorneal area was in the order PEO-EUDNa71 < PEO < PEO-EUDNa17.

Osmotic drug delivery

Patel *et al.* [17] developed push-pull osmotic pumps (PPOP) of a practically insoluble model drug which deliver at a constant rate (zero order release) over a long period of time using Polyox. To evaluate the effect of Polyox, various grades were examined, i.e. Polyox WSR N-80 NF or N-750 NF for the pull layer and Polyox WSR-301 NF, Coagulant NF or 303 NF for the push layer formulations. Evaluation of various Polyox grades in the push layer showed that drug release was not significantly affected by the grade of Polyox used (*f2* >70). For the pull layer, using the higher viscosity grade (N-750) prolonged the lag time and slowed down the drug release (*f2* =32-34) when compared to the control formulation.

Kenneth *et al.* [18] prepared an osmotic, oral, controlled-release capsule which provides drug delivery at fixed delivery rates (T80%= 6 or 14 h) independent of drug properties (e.g., solubility) or drug loading. The osmotic capsule consists of active tablet and push tablet. Active tablet consist of drug admixed with polyethylene oxide. A "push" tablet consisting of high molecular weight polyethylene oxide, microcrystalline cellulose, and sodium chloride is also inserted into the capsule body. The result shows and the dissolution of the API is independent of drug loading between 65 and 375 mg of the active being used. The dissolution rate was independent of pH in the biorelevant range (2 to 6.8)

Gastroretentive drug delivery

Swati *et al.* [19] designed and optimized compression coated floating pulsatile drug delivery systems of bisoprolol composed of a core tablet containing the active ingredient and an erodible outer shell with gas generating agent. Press coating of optimized RRCT was done by Polyox WSR205 and PolyoxWSR N12K. A 3^2 full factorial design was done using the amount of Polyox WSR205 and PolyoxWSR N12K was selected as independent variables. Lag period, drug release, and swelling index were selected as dependent variables. Floating pulsatile release formulation (FPRT) F13 at level 0 (55mg) for PolyoxWSR205 and level +1 (65mg) for Polyox WSR N12K showed lag time of 4 h with >90% drug release. Release kinetics of the optimized formulation best fitted the zero order models. *In-vivo* study confirms burst effect at 4 h in indicating the optimization of the dosage form.

Ramesh *et al.* [20] investigated the cefuroxime axetil sustained-release floating tablets using polymers like HPMC K4M and HPMC K100M alone, and polymer combination of HPMC K4M and Polyox WSR 303 by effervescent technique. All the formulations could sustain drug release for 12 h. The dissolution profiles were subjected to various kinetic release models and it was found that the mechanism of drug release followed Peppas model. The *in vivo* radiographic studies revealed that the tablets remained in stomach for 225±30 min.

Yang *et al.* [21] proposed asymmetric triple layer tablet for the triple drug treatment (tetracycline, metronidazole and bismuth salt) of *Helicobacter* using Hydroxypropylmethylcellulose and poly (ethylene oxide) as the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt could be included in one of the outer layers for instant release. Results demonstrated that sustained delivery of tetracycline and metronidazole over 6-8 h.

Mahalingam *et al.* [22] prepared compacts containing selected bioadhesive polymers, fillers, and binders bioadhesive gastroretentive delivery system to deliver water soluble and water insoluble compounds in the stomach. Compacts with 90:10, 75:25, and 60:40 of polyvinylpyrrolidone (PVP) and polyethylene oxide (PEO) were evaluated for swelling, dissolution, bioadhesion, and in vitro gastric retention. Compacts containing higher PEO showed higher swelling (111.13%) and bioadhesion (0.62±0.03 N/cm^2), and retained their integrity and adherence onto gastric mucosa for about 9 h under in vitro conditions. Compacts containing 58% PVP, 40% PEO and 2% of water soluble or water insoluble marker compounds showed gastroadhesive and retentive properties in vivo. It is concluded that PEO in combination with PVP yields a non disintegrating type bioadhesive dosage form which is suitable for gastroretentive applications.

Immediate release film

Low molecular weight linear poly (ethylene oxide) (Polyox) has shown a great potential as a material for immediate release drug delivery especially in rapid dissolving film formation.

Film based on Polyox can be manufactured readily, because of its good film forming capacity. When film of Polyox comes in contact with aqueous media, it immediately dissolves giving rapid disintegration due to high water absorbing nature of Polyox. Several studies on low molecular

weight Polyox based rapid dissolving film for oral application have been reported.

Sunita *et al.* [23] prepared quick dissolving film by various grades of Polyox like Polyox N10, N80, N750 and N205. Film is optimized for concentration of polymer and plasticizer using CCD design. The tensile Strength, folding Endurance, % drug released at 10 min (Y10) and disintegration time were selected as dependent variables. The data revealed that 2% of Polyox N 750 and 15% of PEG 400 showed excellent film forming property and drug release of 100% n 15 minutes.

Extended release

Hiroyuki *et al.* [24] evaluated the feasibility of using a counter polymer in polyethylene oxide (PEO)/polyethylene glycol (PEG) polymeric matrices for the sustained release of a large amount of highly water-soluble drug. PEO/PEG matrix tablets (CR-A) containing four drugs with different water solubilities. Cross-linked carboxyvinyl polymer (CVP)/PEO/PEG matrix tablets (CR-B) containing a water-soluble drug, diltiazem hydrochloride (DTZ), were also prepared, and their *in-vitro* characteristics were compared with CR-A. In an attempt to control the drug release of higher water soluble drugs, a polymer bearing a charge opposite to that of the drug was used to effectively decrease the diffusion of DTZ, resulting in sustained release for 24 h or longer.

DISADVANTAGES

- They have property to impart lubricity and water solubility to the end product. But when relatively small constant stress is applied to Polyox products crazing and tensile failure can occur. [2]
- Crystallization is also observed with polymer and especially more and faster in lower molecular weight Polyox, because water absorbing capacity is increased with decreased molecular weight.
- Due to high water absorption by LMW Polyox, a glassy rubbery transition can be observed on SEM photomicrographs and so it must be more in case of Polyox LMW.
- These structural changes occur due to physical aging not only effect pure substance but also dosage form.
- Mechanical and drug release property can change which might result in stability problem in long term. In order to avoid problem, it is advisable to monitor possible structural changes. [25]

Regulatory Aspects of Polyox

Compliance with FDA and Other Regulatory Requirements: Polyox Water-Soluble Resins, NF Grade comply with the USP polyethylene oxide NF monograph. These products meet the requirements of the Food Chemicals Codex, the International Codex Alimentarius, and the U.S. National Formulary (NF). These products have also been approved in drug products sold in all major European countries. Approval for use in Japan is under way and anticipated. [3]

Stability of Polyox

Polyox polymers are prone to degradation that occurs due to oxidation, leading to chain cleavage and reduction of viscosity during storage. Accordingly all Polyox polymers intended for pharmaceutical use contain 300-500 ppm butylated hydroxyl toluene (BHT) as an antioxidant. The mechanism of Polyox degradation is quite similar to that of hydrocarbon chains, but the presence of oxygen in the molecules strongly activates the process by increasing the labile nature of protons on α-carbon atoms.

The decomposition of Polyox can be catalyzed by several metal ions, such as ferrous, cuprous, cupric and silver. Typically, lower valent ions are more effective catalysts.

One approach to improve polymer stability is to apply an oxygen barrier film coat onto the final dosage form.

The most popular antioxidants used with Polyox are BHT and Vitamin E. While Polyox polymers intended for pharmaceutical use contain about 300-500 ppm (0.03-0.05% w/w) of BHT, it is also recommended to add approximately 100-1000 ppm (0.01-0.10%) of BHT to the Polyox tablet formulation.

Vitamin E is also used in pharmaceutical applications as an oxidative stabilizer. Typical use level is 500-1000 ppm. To achieve good mixing of vitamin E into the Polyox powder, vitamin E is dissolved in a small amount of isopropyl alcohol before mixing it with the Polyox (tm) powder. [2]

In industrial applications, sodium thiosulphate (0.1%w/v) can be used as a solid stabilizer. Sodium thiosulphate acts as a chlorine scavenger and is most useful for processes using municipal (treated) water. [3]

Polyox do not have a shelf-life per se; however, it is recommended that it is good to retest the material periodically to ensure suitability in any application. Retesting of batches of material is done to ensure viscosity specification compliance. [2]

To check the stability of Polyox retest frequency or different grades of Polyox are as follows:

- Mid to high molecular weight grades- 6 months [WSR N-3000, 205, 1105, 12K, 60K, 301, Coagulant, 303, and N-750]
- Low molecular weight grades-2 years [WSR N-10 and N-80]

Poly (ethylene oxide) is a biocompatible eroding polymer available in a number of molecular weights, which is receiving growing attention as sustained-release and immediate platform due to its safety, ease of processing (direct compression is feasible) and possibility to regulate drug release. HMW Polyox shows release by swelling instead of erosion, leads to anomalous release kinetics. LMW Polyox hydrates faster and erosion is faster. Based on the varying molecular weight and release rate produced by Polyox, it has been used in oral sustained-release tablets, gasteroretentive tablet, extended release, buccal films, ocular inserts, colon targeted tablet, osmotic tablets and quick dissolving film. As per current status, it is very helpful polymer in novel drug delivery system for both highly soluble and poorly soluble drug.

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