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Review

A world of low molecular weight heparins (LMWHs) enoxaparin as a promising moiety—A review

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ABSTRACT

Anti-coagulants are one of the most important categories in healthcare therapeutics. For healthcare professionals dealing in cases of in-vivo blood clotting problems. Heparin and low molecular weight heparins (LMWHs) would be the first choice of drugs. This review represents an overview of the LMWHs, their importance over heparin and enlightens the advancements. In addition to these, different methods used for preparation and purification are discuss in terms of production and synthesis. Worldwide availability in pre-filled syringe, market, manufacturers and suppliers drug interactions, adverse drug reactions, in-vitro study, freezing/thawing process and structural differences of LMWHs are also focused upon in this review.

Contents

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1. Introduction

A novel approach for the development of specific low molecular weight heparins (LMWHs) as a better therapeutic agent than heparin with reduced side effects, smaller risk of bleeding, less frequent subcutaneous dosing in post-operative prophylaxis is a therapeutic challenge which is the rationale for LMWHs synthesis. The LMWHs successfully entered as new, effective and better anticoagulant agents. Now-a-days by virtue of increase in demand of this class all over the world; we are furnishing some methods of preparation and purification for LMWHs (Barrowcliffe, 1995; Donayre, 1996; Green & Hirsh, 1994; Linhardt & Gunay, 1999). They are sulphated salts of heparin having molecular weight less than 8000 Da which are obtained by fractionation or depolymerization of heparin. It should have a potency of greater than 70 Units/mg of antifactor Xa and ratio of antifactor Xa activity to antifactor IIa activity of >1.5 (European Pharmacopoeia, 1991).

In addition to heparin, numbers of LMWHs are commercially available like dalteparin by deaminative process, enoxaparin by beta eliminative cleavage, tinzaparin by enzymatic cleavage, parnaparin by oxidative depolymerization and so on. Literature concludes that by using controlled condition we get better yield, appropriate chemical and biological properties of LMWHs.

LMWHs are analyzed by different techniques like antifactor Xa and antifactor IIa activities for assay; nuclear magnetic resonance (NMR), fast atom bombardment (MS/MS-FAB), matrix assisted laser desorption ionization (MALDI), electro spray ionization (ESI) techniques for structural elucidation. The chromatographic analysis of LMWHs involves high performance liquid chromatography (HPLC), gel permeation chromatography (GPC), size exclusion chromatography (SEC) and capillary electrophoresis (CE) to determine polydispersity and molecular weight of LMWHs. Structural differences affect the clinical properties of LMWHs which is of main concern while working on these costly molecule (Linhardt & Gunay, 1999).

There are eight clinically approved LMWHs, prepared by depolymerization techniques. They show little differences in their structural forms which was analyzed by H NMR/C NMR in the end group residues. Those LMWHs prepared by deaminative depolymerization method show anhydromannitol residue at reducing end. LMWHs prepared by nitrous acid depolymerization method show a tetrasaccharide containing reducing end residue and the same prepared by chemical beta elimination method show both 2-O-sulfo unsaturated uronate residue and unsulfated residue. Therefore, all these heparin family structurally differentiated by using spectroscopic data. Some worldwide commercially available LMWHs have been summarized here (Table 1) (Linhardt & Gunay, 1999).

2. Methods of preparation of LMWHs

All the methods of preparation were selected to give LMWHs with appropriate average molecular weight, low polydispersity and antifactor Xa/antifactor IIa activity (>1). The following methods describe about cost effective fractionation/depolymerization process to prepare LMWHs (Branellee, Espego, & Picart, 1997).

2.1. Ultrasonic assisted preparation of LMWHs

This method comprises the use of hydrogen peroxide catalyzed radical hydrolysis assisted by ultrasonic waves which have strong penetrating power. LMWHs that are produced using this method have an average molecular weight and anticoagulant properties that are comparable to some commercial LMWHs. This method provides product with low polydispersity index, lower degree of sulphation and similar chromatographic profile compared to other commercial methods (Achour, Bridian, & Godhbani, 2013).

2.2. Photochemical preparation of novel LMWHs

This method has the advantage to avoid the strong reaction conditions or harsh chemicals, side reactions which give the better quality and better yield of product. Here, photolysis of unfractionated heparin can be performed by using titanium dioxide in distilled water. The characterization data show the anticoagulant activity of pLMWHs is comparable to commercially available LMWHs like dalteparin, enoxaparin. In this method, titanium dioxide is used as a photocatalyst which will get removed by centrifugation or filtration technique readily. A specially designed photoreactor is essential to carry out fractionation of LMWHs (Higashi, Hosoyama, & Ohno, 2012).

2.3. Depolymerization by enzyme

Depolymerization of heparin is carried out by using bacterial enzyme like heparinase-I (heparin lyase), which cleaves heparin into LMWH enzymatically by beta elimination mechanism. The commercially available tinzaparin sodium is the LMWH produced by enzymatic cleavage which shows the different properties than other LMWHs (Linhardt & Gunay, 1999).

2.4. Alkaline depolymerization

This is the most suitable method of preparation for enoxaparin sodium which has gained maximum market of LMWHs globally. Alkaline depolymerization is carried out by direct treatment of heparin or its heparin benzyl ester sodium salt with base (NaOH) under certain reaction conditions. LMWHs are produced by chemical beta cleavage of heparin salt. Alternatively, the benzyl ester salt of heparin can be prepared by reacting benzethonium salt of heparin with benzyl chloride and base followed by heating. The depolymerization of heparin into LMWHs is done by an inert organic solvent, such as dichloromethane, tetrahydrofuran, anisole and N,N-dimethyl formamide (Linhardt & Gunay, 1999).

2.5. Oxidative depolymerization

Heparin can be oxidatively broken down using various reagents like hydrogen peroxide or by using ionizing gamma radiation for LMWHs. The oxygen species generate the oxygen radicals which act by oxidizing sensitive saccharide residues within heparin polymer. Generally, hydrogen peroxide is used commercially to prepare ardeparin sodium and parnaparin sodium which are available in the market as an anticoagulant (Linhardt & Gunay, 1999).

2.6. Deaminative degradation

Heparin is depolymerized by using nitrous acid or isoamyl nitrite which yields LMWHs by deaminative process. The LMWHs prepared by controlled deamination gives better yield with better chemical and biological properties. Available marketed products like certoparin sodium, dalteparin sodium, nadroparin sodium and reviparin sodium are produced by this method (Linhardt & Gunay, 1999).

2.7. By aq. 2-hydroxypyridine

Heparin is partially depolymerized by heating at 115 °C with aqueous 2-hydroxypyridine. As compared to heparin, no significant loss of anticoagulant activity was observed by this method. So, it

Table 1
World-wide available LMWHs.

Sr. no.	LMWHs	Trade name	Manufacturer	Method of preparation	Factor Xa:IIa ratio (daltons)	Average molecular weight (U)	Approved market
1	Enoxaparin sodium	Lovenox, Clexane	Rhone-Poulenc Rorer, Avantis, Eurofarma lab ltda, Aspen pharma	Alkaline depolymerization	2.7:1	4500	USA, Germany, Spain
2	Ardeparin sodium	Normiflo	Wyeth-Ayerst	Oxidative depolymerization with H_2O_2	2.0:1	5600–6500	USA
3	Certoparin sodium	Sandoparin	Novartis	Deaminative clevage with isoamyl nitrite	2.4:1	5400	Germany
4	Dalteparin sodium	Fragmin	Pharmacia-Upjohn Kissei	Deaminative clevage with nitrous acid	2.0:1	4000–6000	USA, japan, Germany, UK
5	Nadroparin sodium	Fraxiparin	Sanofi-Winthrop	Deaminative clevage with nitrous acid	2.4:1	4500	Germany, France
6	Parnaparin sodium	Fluxum	Alfa Wassermann	Oxidative depolymerization with Cu^+ & H_2O_2	3:1	4500–5000	Italy
7	Reviparin sodium	Clivarin	Knoll	Deaminative clevage with nitrous acid	3.5:1	4300	Germany, Canada
8	Tinzaparin sodium	Innohep, Logiparin	Braun, Novo/Leo/Dupont	Beta eliminative cleavage by heparinase	2:1	4900	Germany, Denmark
9	Gammaprin sodium	NA	Corcon Pharmaceutical	Gamma irradiation	NA	NA	NA
10	Bioparin	NA	Bioberica	NA	NA	NA	U.S.
11	Miniparin	NA	Syntex	NA	NA	NA	U.S.
12	Sandoparin	Clivarine, Embolex	Sandoz, Novartis, Biochemie	Deaminative cleavage with isoamyl nitrite	NA	NA	U.S., Austria, Switzerland
13	Fondaparinux	Arixtra	GSK, Dr. Reddy's lab	Synthetic pentasaccharide	NA	NA	U.S.
14	Idraparinux	Xarelto®	Sanofi-aventis	Synthetic pentasaccharide	NA	NA	NA

is less significant as compared to other methods (Berry, Parmar, Hatton, & Chan, 2006).

3. Purification techniques for LMWHs

Recently, a contaminant was found in some clinically used unfractionated heparin (UFH) preparations. Generally contaminated heparins may have been used as starting material in the production of LMWHs. A major contaminant found was oversulfated chondroitin sulfate (OSCS). Varying degrees of high-molecular weight dermatan sulfate and other minor impurities were detected, in which OSCS is the major one. The process involved in the production of enoxaparin does not significantly degrade OSCS (Viskov et al., 2009).

Enoxaparin sodium, a widely used LMWH, has a unique and reproducible oligosaccharide profile which is determined by the origin of the starting material and a tightly controlled manufacturing process (Houiste et al., 2009). To ensure their safety, quality, purity and immunologic profile, we require to purify the crude material into pure LMWHs by using techniques as described here.

3.1. Purification by reduction

LMWHs especially enoxaparin sodium should be purified using reducing agent like sodium borohydride which yield pure enoxaparin sodium. This may bring controlled purification with lessen effects on chemical properties of enoxaparin sodium (Linhardt & Gunay, 1999).

3.2. Purification by demineralized water

LMWHs should be purified by taking appropriate quantity of LMWHs in demineralized water and with maintained pH up to 8.4 by addition of 1 N NaOH. Then heat the mixture at about 50 °C for 30 min and cool the reaction mixture at room temperature followed by adjustment of pH up to 12 with addition of 1 N NaOH and dry the product.

3.3. Purification by hydrogen peroxide

Here, LMWHs are treated with sufficient quantity of demineralized water with pH range of 9–11 by adding sodium hydroxide solution at 60 °C. Then filter the reaction mixture and add 1–3% solution of hydrogen peroxide which acts as an amphiphile. Finally, maintain pH near about 6–8 followed by addition of 10% sodium chloride solution and keep the reaction mixture for 3 h. After completion of reaction filter it properly, wash with methanol and dry the final purified product (MCCULL Pharma Nantong INC, 2012).

3.4. Purification by microwave

Microwave technique gained a lot of importance in the chemical synthesis and its purification because of its precise and time saving properties. Here, LMWHs should be purified by using microwave technique so the case with enoxaparin. In this technique crude enoxaparin treated with demineralized water and seed crystal in the microwave, finally filter the product and dry. This technique serves the higher yield of product and low production cost (Yulong, 2012).

4. Disaccharide composition of LMWHs

LMWHs are basically polysaccharides which show the different compositions of sulfated disaccharides. Following data shows the disaccharide analysis of LMWHs and their compositions (Table 2). It reveals how they are different in their trisulfated, disulfated and monosulfated disaccharides by their method of preparation (Fussi, 1981).

Table 2
Disaccharide composition of LMWHs.

Sr. no.	Name of LMWHs	Trisulfated disaccharides		Disulfated disaccharides		Monosulfated disaccharides
Sample		2SNS6S	NS3S6S	NS6S	2SNS	6S
01	Enoxaparin sodium	71.3	1.9	11.4	2.5	1.4
02	Ardeparin sodium	86.1	1.7	7.0	6.1	1.3
03	Dalteparin sodium	49.3	2.6	3.2	3.1	2.0
04	Nadroparin calcium	17.2	0.8	1.2	1.8	0.7
05	Parnaparin sodium	48.4	0.4	3.6	4.4	0.3
06	Tinzaparin sodium	88.9	1.9	7.5	5.4	1.4

5. Enoxaparin as an emerging LMWH

Enoxaparin is a globally emerging LMWH which belongs to the category B pregnancy drug. Generally, it is administered by subcutaneous route. Enoxaparin shows approximately 100% bioavailability with 80% albumin protein binding. Enoxaparin is metabolized by liver and kidney with half-life of 4.5 h. In case of enoxaparin the molecular weight distribution include 9–20% of polysaccharide chains having molecular weight less than 2000 Da and from 5% to 20% of polysaccharide chains having molecular weight greater than 8000 Da, the ratio between the weight average molecular weight and the number average molecular weight ranging from 1.3 to 1.6 (Debrie, 2005). This is prepared by alkaline depolymerization and beta elimination process ranging molecular weight from 3800 to 5000 Da or as an average of 4500 Da. Advantages of LMWHs, like enoxaparin, over heparin are better bioavailability and higher anifactor Xa/antifactor IIa activity ratio (Lima, De Farias, Rudd, Ebner, & Gesteira, 2011).

Enoxaparin sodium, which contains an average eight disaccharide units, are analyzed by chromatographic techniques like ion exchange chromatography, size exclusion chromatography, capillary electrophoresis and counter current chromatography for the separation of all disaccharides (Intes, Renault, Singuin, Hanrot, & Nuzillard, 2001). A structural analysis of enoxaparin can be performed by combination of ultraperformance size exclusion chromatography (UPSEC), electrospray quadrupole time-of-flight-mass spectrometry (Q-TOF-MS) with capillary zone electrophoresis (CZE). On the basis of obtained high resolution mass spectra, 70 components of enoxaparin were identified (Zhang et al., 2013).

In case of dosage form design of this blockbuster advantageous molecule, pre-filled syringes are becoming an increasingly popular format for delivering biotherapeutics conveniently and cost effectively. The device design and stable liquid formulations required to enable this pre-filled syringe format are technically challenging. In choosing the materials and process conditions to fabricate the syringe units, their compatibility with the biotherapeutic need to be carefully assessed. The biotherapeutic stability demanded for the production of syringe-compatible low-viscosity liquid solutions require critical excipient choice to be made (Jezek, Darton, Derham, Royle, & Simpson, 2013).

In Germany, after training the nursing and medical staff in guideline-compliant implementation of thromboembolism prophylaxis with pre-filled certoparin safety syringes (03/09-05/09) or nadroparin (06/09-08/09) and enoxaparin (02/10-04/10) from multi-dose vials, they calculated the total cost on the basis of procedure and technical application. Furthermore, the satisfaction of the nursing staff was interrogated. Final result gives total cost for nadroparin are 1.16 €/0.3 mL, 1.30 €/0.4 mL and 1.58 €/0.6 mL, for enoxaparin 1.04 €/20 and 1.42 €/40, and for certoparin 1.25 €/pre-filled safety syringe. The pre-filled certoparin safety syringe made a very good overall impression on the nursing staff (Seidl & Trouillier, 2013).

Now-a-days, enoxaparin has become the treatment of choice for various thromboembolic diseases. In most patients with end-stage renal disease (ESRD), prophylactic dosage of enoxaparin does not appear to be associated with an increased bleeding risk and can be used without the need for monitoring and adjustment of regimens (Lai & Coppola, 2013). In another case of patients with localized lung adenocarcinoma, hypercoagulability is characterized by high thrombin generation. Tumour mass resection is related with attenuation of thrombin generation, which is inhibited by postoperative thromboprophylaxis with enoxaparin. The response to enoxaparin is not predicted by the concentration of the anti-Xa activity in plasma. The assessment of thrombin generation during prophylaxis with enoxaparin allows to identify patients with high residual plasma hypercoagulability (Papageorgiou, Vandreden, Marret, Bonnet, & Robert, 2013).

The use of enoxaparin sodium immediately after a surgery may confer valuable thromboprophylaxis beneficial for urologic laparoscopic surgery (Nomura, Takahashi, Iwasaki, Oribe, & Shinohara, 2013). Literature also reveals that enoxaparin sodium treatment is cost saving in unstable angina (Detournay, Huet, Fragnani, & Montalescot, 2000).

Those patients having history of hypersensitivity to enoxaparin, heparin, benzyl alcohol (multidose formulation only) or pork, administration of enoxaparin is contraindicated. Following data (Table 3) gives the idea about availability of enoxaparin sodium in pre-filled syringe in various concentrations.

5.1. Availability of enoxaparin sodium in pre-filled syringe (PFS)

To avoid needle stick injuries and to grab the numerous advantages of pre-filled syringes, industries have changed their vision for both healthcare and business point of view. There are numbers of life-saving drugs are being available in PFS. Enoxaparin is not an exception (Table 4). Many Pharmaceuticals giants along with other manufacturers are in market with their product in ready-to-use format with same efficacy and more safety.

Table 3
Availability of enoxaparin sodium.

Sr. no.	Types	Availability	
Concentrations		100 mg/ml	150 mg/ml
01	Pre-filled syringe	20 mg/0.2 ml, 30 mg/0.3 ml, 40 mg/0.4 ml, 50 mg/0.5 ml, 60 mg/0.6 ml, 80 mg/0.8 ml, 100 mg/1 ml	120 mg/0.8 ml, 150 mg/1 ml
02	Multiple dose vial	300 mg/3 ml	NA

Table 4
Availability of enoxaparin sodium in PFS.

Sr. no.	API	Trade name	Strength	Company	Country
01	Enoxaparin sodium	ROSINOX	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml	Rose Labs Ltd.	India
02	Enoxaparin sodium	LOVENOX	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml	Sanofi	France
03	Enoxaparin sodium	XAPARIN	60 mg/0.6 ml	New Medicon	India
04	Enoxaparin sodium	DYNALIX	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml	Bicon	Netherlands
05	Enoxaparin sodium	ENOXARIN	40 mg/0.4 ml, 60 mg/0.6 ml	Zuventus	India
06	Enoxaparin sodium	FLOTHIN	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml	Ranbaxy	India
07	Enoxaparin sodium	HEPANOX	40 mg/0.4 ml, 60 mg/0.6 ml	Minova Life Sc.	India
08	Enoxaparin sodium	LMWX-PFS	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml	Piramal HC	India
09	Enoxaparin sodium	MEGAPARIN	40 mg/0.4 ml, 60 mg/0.6 ml	Venus Remedies	India
10	Enoxaparin sodium	TROYNOXA	40 mg/0.4 ml 60 mg/0.6 ml	Troikaa	India
11	Enoxaparin sodium	CLEXANE	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml	Sanofi Aventis	France
12	Enoxaparin sodium	ENOCARD	40 mg/0.4 ml, 60 mg/0.6 ml	Cardium (Olcare)	India
13	Enoxaparin sodium	LOMORIN-NX	20 mg/0.2 ml, 40 mg/0.4 ml, 50 mg/0.5 ml, 60 mg/0.6 ml, 80 mg/0.8 ml	VHB Life Sc.	India
14	Enoxaparin sodium	LUPENOX	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml	Lupin	India
15	Enoxaparin sodium	MAXIPARINE	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml	Chandra Bhagat PH.	India
16	Enoxaparin sodium	PAXENO	20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml	Trigenesis Life S.	India

Table 5
Drug interactions of enoxaparin sodium.

Sr. no	Class of drugs	Significance
01	Anti-thrombin	Severe bleeding/risk of haemorrhagic reactions.
02	Oral anticoagulants (warfarin)	
03	Platelet inhibitors (dipyridamole)	
04	NSAIDs	
05	Salicylates	
06	Sulfinpyrazone	
07	Ticlopidine	
08	SSRIs (fluoxetine)	

Table 6
Adverse drug reactions of enoxaparin sodium.

Sr. no	Class	Significance
01	Cardiovascular	Atrial fibrillation, Heart failure (01%)
02	Dermatologic	Perpurea, Skin necrosis, Cutaneous vasculitis
03	Gastrointestinal	Nausea (3%), Diarrhoea (2%)
04	Respiratory	Dyspnoea (3%), Pneumonia (01%), Lung oedema

5.2. Drug interactions and adverse drug reactions of enoxaparin sodium

An enoxaparin sodium gives the vast drug interactions and adverse drug reactions with following class of drugs which generate the severe bleeding or risk of haemorrhagic reactions (Tables 5 and 6).

5.3. Lyophilization of enoxaparin

A lyophilization is a very important step in case of enoxaparin sodium which yields amorphous, lusterus and stable product. According to literature study, enoxaparin solution was frozen and thawed under various conditions, in presence or absence of dimethyl sulfoxide or 1,2-propanediol, and antifactor Xa activity was determined. An enoxaparin solution lost more than 60% of its Xa activity when thawed rapidly after freezing at −196 °C. The loss of antifactor Xa activity is less with higher freezing temperature. Literature also reveals that enoxaparin does not lose its anticoagulant activity by elimination of N-sulfonate or O-sulfonate groups. Following data in Table 7 shows the results of analyses of free sulphate, free amino groups in liquid nitrogen frozen/thawed enoxaparin solution. This research also reveals the effect of freezing and thawing process on the biological, physical and chemical properties of enoxaparin solution under different conditions. These data may provide insight for enoxaparin solution stability under different conditions (Patel, Narkowicz, & Jacobson, 2009).

Table 8
Enoxaparin sodium API suppliers (regulatory market and non-regulatory market).

Sr. no.	Name of suppliers
Regulatory market	
01	Dongying Tiandong Biochemical Industry Co., Ltd. – China.
02	Shenzhen techdow pharmaceutical co. Ltd. – China.
03	Yantai Dongcheng Bioschemicals Co. Ltd. – China.
04	OPOCRIN SPA, Italy.
05	Chemos GmbH, Germany.
06	BOC Sciences, USA.
07	LGM Pharma, USA.
08	AK Scientific Inc., USA.
Non-regulatory market	
09	Enoray Biopharmaceutical Co., Ltd.
10	Hebei Changshan Biochemical Pharmaceutical Co., Ltd.
11	Haihang Industry Co., Ltd.
12	Hebei Lead Bio-Chemicals Co., Ltd.
13	Hangzhou Jiuyuan Gene Engineering Co., Ltd.
14	Zaozhuang Sinock Biochemical Pharmaceutical Co., Ltd.
15	TianJin Chilite Chem Co., Ltd.
16	Shijiazhuang xiehe pharmaceutical Co., Ltd
17	Xiamen Forever Green Source Biochem Tech. Co., Ltd.
18	Shaanxi New Leader Enterprise Co., Ltd.
19	Sichuan Neijiang Huixin Pharmaceutical Co., Ltd.
20	Yikang pharmaceutical Co., Ltd.
21	Hangzhou ICH Biopharm Co., Ltd.
22	Lanzhou Jianxing Commercial and Trading Co., Ltd. – China
23	Afine Chemicals Ltd. – China
24	Shaanxi TOP Pharm Chemical Co., Ltd.
25	Changzhou Dahua Imp. And Exp. (Group) Corp., Ltd.
26	Quzhou Newchem Trade Co., Ltd.
27	Shanghai SIPI Pharmaceutical Co., Ltd.

5.4. In vitro study of enoxaparin

The purpose of in vitro study was to determine whether the activated clotting time (ACT) or the activated partial

Table 7
Enoxaparin solution lyophilization data.

Sr. no.	Enoxaparin sample	Free sulfate groups (mmol/L)		Free amino groups (mmol/L)		Reducing ends (mol/L)	
		Mean	% RSD	Mean	% RSD	Mean	% RSD
01	Unfrozen	0.0181	1.52	0.011	3.57	0.019	5.93
02	Frozen	0.0189	1.75	0.013	5.74	0.022	6.92

thromboplastin time (aPTT) can be used to monitor the anticoagulant effect of LMWHs like enoxaparin. After the test results, it is concluded that enoxaparin produces significantly less prolongation time of ACT and the aPTT than heparin. Therefore, ACT and aPTT cannot be used to monitor LMWHs which creates the need for studying and understanding of antifactor Xa activity assay of LMWHs (Linkins, Julian, Rischke, Hirsh, & Weitz, 2002).

5.5. Enoxaparin sodium API suppliers

A growing market of enoxaparin also leads to rise in the suppliers throughout the world. Here, the focus is on the approved enoxaparin sodium API suppliers of the regulatory market and non-regulatory market (Table 8). All these suppliers provide enoxaparin sodium API having potency in the range of 100–115 IU according to the standard of European Pharmacopoeia (Enoxaparin, 2013).

6. Conclusion

The various methods of preparation and purification of LMWHs show promise for new era of research in polysaccharides. It is noteworthy that significance of this review is that all worldwide enoxaparin sodium API suppliers and lyophilization study of enoxaparin solution are mentioned in suitable manner.

Future advances in this field may be based on a better understanding of methods of preparation of LMWHs, drug interactions, adverse drug reactions, in vitro study, worldwide availability and a better control of the cost for the routine use of such exciting moiety over conventional anticoagulants. This review also reveals that how enoxaparin sodium pre filled syringe is better than other multi dose vials and how enoxaparin sodium becomes drug of choice for various critical thromboembolic diseases, which is beneficial immediately after surgery. Future research on LMWHs should embrace a more systematic approach taking into account of data not only from synthesis but also from the advancement in worldwide? and which opens the new doors for global market of LMWHs and enoxaparin sodium.

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