



## PHARMACEUTICAL ASPECTS OF NICORANDIL

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## ABSTRACT

Nicorandil (N-[2-hydroxyethyl] nicotinamide nitrate [ester]) is one of the most emerging molecule for the treatment of hypertension and angina pectoris. Nicorandil is highly hydrophilic and having a short elimination half-life. It has various side effects such as headache, dizziness and one of the major side effect is ulceration. To reduce the dosing frequency of administration and to improve patient compliance, a once daily sustain or control release formulation of nicorandil is desirable. The current approaches are mainly focused on to minimize the major side effects in the treatment of angina pectoris as well as hypertension. Therefore this review is the first comprehensive account of the pharmaceutical features of nicorandil with special emphasis on its delivery.

**Keywords:** Nicorandil, Drug delivery, Transdermal therapeutic system, Controlled oral delivery system.

## INTRODUCTION

Angina pectoris, the primary symptom of ischemic heart disease, is caused by transient episodes of myocardial ischemia that are due to an imbalance in myocardial oxygen supply and demand relationship. Imbalance may be caused by an increase in myocardial oxygen supply and demand or by a decrease in myocardial oxygen supply or sometimes by both. According to this, angina has classified as, stable angina and unstable angina. Stable angina is the most common type of angina. Unstable angina is less common. The associated symptoms are unpredictable and often occur at rest. The symptoms are worse in unstable angina; the pain is more frequent, more severe, long lasting, occurs at rest and are not relieved by nitroglycerin under the tongue<sup>1</sup>. Angina pectoris is the most common form of cardiovascular diseases that require constant monitoring and therapy.

Potassium channel openers are presently considered as an important class of drugs for hypertension and angina pectoris. Nicorandil is the first therapeutic molecule has an ability to hyperpolarize muscle cell membranes and a potent coronary vasodilator<sup>2</sup>. Nicorandil appears to be effective in all types of angina pectoris, including advanced coronary artery lesion. Nicorandil may be of having particular effect in patients with impaired cardiac function, since it produces very few hemodynamic reactions and improve heart function. Since nicorandil does not produce a significant prolonged sinoatrial and atrioventricular conduction, it can be administered in patients with bradycardia and/or atrioventricular conduction disturbances<sup>3,4&5</sup>.

**Table 1: Physicochemical and pharmacokinetic parameters of nicorandil<sup>10</sup>**

Chemical Data	
Mol. Formula	C8H9-N3O4
Mol. Mass	211.75g/mol
Pharmacokinetics Data	
Bioavailability	75 to 80%
Cmax	64±19 ng/ml (5mg)
Area under curve (AUC)	98±2 (after dose of 5 mg)
Protein Binding	25%
Volume of Distribution	1.4 lit/kg (after IV dose of 5mg)
Metabolism	Hepatic
Half- life	1 hour
Total body Clearance	52±18 lit/hr
Excretion	Renal (21%)
Therapeutic Considerations	
Routes	Oral, Parenteral
Dosage Forms	Tablet, Injection, Transdermal Patch

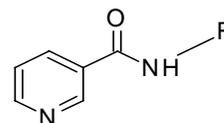
In 1982 clinical investigation on nicorandil provided the beneficial effects in myocardia and regional wall motion pace induced ischemia, because it allows comparison of reproducible interventional conditions<sup>6,7,8&9</sup>. Nicorandil has become a widely used in antianginal therapy since its first launch in Japan in 1984 and in Europe in 1994. Following 17 years of clinical experience in the world, nicorandil safety record continues to give physicians confidence when treating this important patient group<sup>9</sup>. The physicochemical and pharmacokinetic parameters of nicorandil are mentioned in Table 1.

The advances achieved during the last decades have resulted in the successful treatment of hypertension and angina pectoris. The objective of this review is to focus attention on various physicochemical characteristics and pharmaceutical aspects of nicorandil with major emphasis on its novel drug delivery.

## CHEMISTRY

Nicorandil is a nicotinamide derivative, efficacious in the treatment of hypertension and angina pectoris. It is a potassium channel opener providing vasodilatation of arterioles and large coronary arteries. Its nitrate component produced venous vasodilatation<sup>10</sup>. Nicorandil (N-[2-hydroxyethyl] nicotinamide nitrate [ester]), (molecular formula {C8H9N3O4}, molecular weight {211.175}). Chemically nicorandil belongs to the organic nitrate groups, on the basis of the fact that nicorandil has a nitrate moiety, which has been reported to be essential for its pharmacologic activities. Organic nitrate produced a vasodilatation effect by stimulating the formation of cyclic GMP in smooth muscle cells<sup>11,12&13</sup>. It opens the ATP-sensitive K<sup>+</sup> channels, thereby causing dilatation of peripheral and coronary resistant arterioles. In addition, it contains a NO<sub>2</sub>-moiety, which dilates systemic veins and epicardial coronary arteries<sup>14</sup>.

N-nicotinylethanolamine is widely used as the active moiety in the synthesis of nicorandil which is a new and higher efficient for antianginal therapy. The nicorandil has two nitrate groups in the structure which is shown in Figure 1. Nicorandil is a white to off, white needle crystalline powder. The drug is freely water soluble and melting point approximately 92°C.



R = (CH<sub>2</sub>)<sub>2</sub>ONO<sub>2</sub>: Nicorandil      R = (CH<sub>2</sub>)<sub>3</sub>ONO<sub>2</sub>: Internal standard

**Fig.1: Structure of nicorandil and an n-propyl homologue used as internal standards**

## MODE OF ACTION

Nicorandil has dual mechanism of action and its action differs significantly from currently available vasodilators by causing sustained dilation of both the venous capacitance and arterial resistant vessels, thus reducing preload and afterload. The vasodilating agent nicorandil produces marked coronary artery dilatation by a number of mechanisms including an increase in cyclic guanosine monophosphate (c-GMP), an effect, which is common to all organic nitrates and a novel potassium channel opening effect. Nicorandil has been shown to produce beneficial hemodynamic effects in patients with stable angina pectoris without significant deleterious effects on pulse rate, the cardiac conducting system, myocardial contractility or myocardial oxygen consumption<sup>15</sup>. It has shown improvement in both functional and mechanism during recurrent myocardial ischemia which are independent of hemodynamic effects, as noted by the improvement in myocardial segment shortening during reperfusion, the reversal of a significant increase in free fatty acid uptake, an attenuation of increase in oxygen and CO<sub>2</sub> production in the ischemic zone and the preservation of endocardial adenosine triphosphate (ATP) and total adenine nucleotides<sup>16</sup>. It has definite cardioprotective properties in acute myocardial ischemia. At higher concentrations, nicorandil appears to act through the NO group-activated guanylate cyclase. While both pathways contribute to these effects, which are independent<sup>17</sup>. Investigation of nicorandil in angina (IONA) studies have classified the unique pharmacological effect of nicorandil not only improves symptoms but also reduces ischemia related cardiac events, e.g. death, non-fatal myocardial infarction and angina pectoris<sup>18</sup>.

## PHARMACOKINETICS AND PHARMACODYNAMICS

### Absorption

Nicorandil is well absorbed from the gastrointestinal tract and maximum plasma concentration of nicorandil is linearly related to the administered dose. The urinary recovery data following oral administration of the drug indicated that more than 90% of the oral dose (20 mg) was absorbed. There is some evidence that consumption of food concurrently with the administration of nicorandil can prolong drug absorption resulting in a delayed and decreased maximum plasma concentration. The absolute bioavailability of nicorandil is 75±23%, indicating that no significant first pass effect exists<sup>2</sup>. The different doses and its pharmacokinetic parameters of nicorandil shown in Table 2.

**Table 2: Effect of different doses and pharmacokinetic aspects of nicorandil<sup>2</sup>**

Dose (mg)	C <sub>max</sub> (ng/ml)	AUC (hr ng/ml)
5	64±19	98±2
10	107±30	202±56
20	261±86	465±113
40	492±262	977±250

### Distribution

After oral (and i.v.) administration of the drug, the apparent volume of distribution is approximately 1.0 L/kg body weight. The drug distribution in the body was reported that it follows two compartment model. Nicorandil is metabolized extensively and the major route of elimination is through kidney: Less than 2% of the dose is excreted through the biliary route. As a consequence the parent drug is excreted poorly in urine (very low renal clearance), whereas 2-nicotinamidoethanol, a pharmacologically inactive denitrated metabolite, is the major nicorandil related compound excreted in urine. The nicotinamide/nicotinic acid biotransformation pathway contributes to the accumulation of nicorandil and 2-nicotinamidoethanol (denitrated metabolite) during repeated dosing because of the saturable merging of nicotinamide/nicotinic acid derivatives (from the nicorandil metabolism) into the NAD/NADP endogenous pool of coenzymes. While it is very weakly bound to albumin (19.4%) and protein binding is found to be (23.3%)<sup>19</sup>.

## Metabolism and excretion

Nicorandil is eliminated by plasma with a half-life of approximately 1 hour. The total body clearance of nicorandil is equal to 52 ± 18 lit/hr, indicating that it is less than the liver blood flow. After metabolism the nicorandil is converted primarily to the denitrated compound, SG-86 (N-2-hydroxyethyl nicotinamide), which is pharmacologically inactive<sup>20</sup>. The urinary excretion and the alcohol metabolite accounted for 1% and 4% of the dose (single 20 mg dose) in 24 hours, respectively<sup>2</sup>.

## Dose, dosing and problems

The therapeutic response is always associated with toxic effects. Nicorandil has a shorter half life and the usual oral dosage regimen is 5 to 40 mg taken daily 2 to 4 times. Nicorandil is hydrophilic; therefore it is available commercially in the form of injections and tablets such as, Nikoran IV 2 mg (Torrent Pharma) and conventional tablet Korandil 5 mg (Sun Pharma) and sustain release (SR) tablet Nikoran 20 mg (Torrent Pharma). Sublingual nitroglycerin may be co-administered with nicorandil to stop acute anginal attacks. Table 1 summarizes the therapeutic efficacy and toxicities encountered with nicorandil therapy. Intravenous injection of nicorandil (0.03-3 mg/Kg) decreased the systemic blood pressure dose dependently and the depression response reached a peak at about 1 min and retained to the basal value after 1 hour<sup>20</sup>. The hypotension occurred in 4 of 10 patients with chest pain when 40 mg of nicorandil administered sublingually. Thus, an excessive high plasma concentration of nicorandil caused vasodilatation in the arteriolar resistant vessels, leading to general hypotension<sup>21</sup>. Adverse effects reported with nicorandil are headache, vasodilation, flushing, nausea, vomiting and weakness. An uncommon side effect includes angioneuritic oedema, photosensitivity as well as tachycardia<sup>9</sup>. Mouth ulceration has long been recognized as a major side effect of nicorandil treatment, but more recently it has been associated with ulceration of any region of the gastrointestinal tract including the perianal area. The ulceration is commonly severe, refractory to treatment and in a few patients, has led to perforation. Time of onset of ulceration may vary widely and ulcers only respond to withdrawal of nicorandil<sup>10</sup>.

**Table 3: Summary of therapeutic efficacy and toxicity of nicorandil<sup>9</sup>**

Therapeutics efficacy	Toxicities
Angina pectoris	Headache may be due to cereberovasodilation, nausea, vomiting.
Potassium channel opener	Anorexia, lassitude.
Coronary vasodilation	Sleep disorder, leg edema.
Vasospasmodic action	Mouth ulcer, tightness of the chest.

## Drug interaction

A comparative study of nicorandil with nitroglycerin, nifedipine and propranolol in patients with coronary artery disease. Their investigated results showed that an increase in coronary sinus flow from 117 to 148 ml/min after intravenous (IV) administration 2 mg of nicorandil, but no change during the pacing stress, while nitroglycerine increased coronary sinus flow during pacing. Nifedipine showed a response similar to that of nicorandil. Propranolol did not changed coronary sinus flow. Since coronary sinus drains blood through the ischemic and nonischemic regions, the increase in the coronary sinus flow does not necessarily indicates an increase in the ischemic region<sup>22</sup>. Nicorandil revealed better results in case of vasospastic angina that was resistant to nifedipine therapy. Nicorandil showed decreased heart rate in patients those treated from last four to fifth weeks, but did not produce any change in blood pressure. In contrast, propranolol significantly decreased heart rate as well as blood pressure in patients and some adverse reactions like headache and gastrointestinal symptoms<sup>23</sup>. In another study, the possibility of drug interaction leading to decreased activity of Gliclazide<sup>24</sup>. The

administration of diltiazem hydrochloride in combination with nicorandil especially during therapy with beta blocking agents or other calcium antagonists affected atrioventricular nodal conduction and cardiac contractility. Moreover nicorandil does not produce an adverse reaction, even in combination with calcium antagonists or beta-blocking agents<sup>25</sup>.

#### Nicorandil delivery

A drug delivery system is defined as 'one' in which a drug (one component of the system) is integrated with another chemical or drug administration process to control rate, release site, or both. The impetus for the development of newer or novel drug delivery systems apart from therapeutic efficacy. Many parameters are considered for the development of new dosage forms such as the relationship among physiologic barriers, disease characteristics, physicochemical properties, pharmacokinetics and pharmacodynamics of the drug as well as material science. Nicorandil is soluble in water and oral drug delivery is effective and also given by intravenous administration. Now days, the current approaches are mainly focused on developing formulations on controlled release tablets and also several attempts have been made to deliver nicorandil by newer methods such as transdermal drug delivery systems (TDDS).

#### TDDS

The conventional therapy may result in higher fluctuation in plasma concentration of the drug resulting in unwanted side effects. Hence, the development of a transdermal therapeutic system for nicorandil that could provide the desired constant drug delivery for a predetermined period is beneficial for an effective and safe therapy of angina pectoris. The various approaches for achieving transdermal drug delivery are reservoir type membrane moderated, matrix diffusion controlled and microreservoir systems. The reservoir type membrane moderated transdermal delivery is

considered advantage in providing desired plasma concentration of the drug for the predetermined time with minimal fluctuations. Nicorandil is a potential drug candidate to develop as transdermal therapeutic system after predicting its permeation across human skin based on its *in vitro* permeation through animal skin model<sup>26, 27</sup>.

Development of membrane-moderated transdermal therapeutic system using terpenes as penetration enhancers. The terpenes containing HPMC based gel drug reservoir showed controlled drug release *in vivo* with minimal or no adverse effects on skin. Hydroxypropyl methylcellulose (HPMC) gel drug reservoir system prepared with 70% v/v ethanol water solvent system containing 6% w/w of limonene was effective in promoting the *in vitro* transdermal delivery of nicorandil<sup>28</sup>. The hydroxypropyl methylcellulose (HPMC) gel drug reservoir was sandwiched between a drug impermeable backing laminate and a rate controlling polymeric membrane. The rate controlling membranes can be either a microporous or non-microporous polymer. Ethylene vinyl acetate (EVA) copolymer with 28% vinyl acetate content (EVA2825) was chosen as the rate controlling membrane because of its excellent film forming properties, good water vapor transmission and appreciable tensile strength<sup>29</sup>. A pressure sensitive adhesive coat on the rate controlling membrane is necessary to provide an intimate contact of the membrane-moderated transdermal therapeutic system to the skin, such that the drug permeation takes place through the skin from the drug reservoir system. Three types of pressure sensitive adhesives are commonly used in the design of TDDS are polyisobutylenes, polyisoxanes, and polyacrylic copolymers. The acrylic polymers gained much commercial acceptance<sup>30</sup>. A water based acrylic adhesive emulsion (TACK-WHITE A 4MED®) as pressure sensitive adhesive in the design of membrane moderated transdermal therapeutic system of nicorandil. The different concentrations of polymer and penetration enhancers with their respective flux of above described TDDS formulations are mentioned in Table 4.

**Table 4: Different formulations composition of nicorindil TDDS**

Ingredients	Device (EPA)	Device (HPMC)
Polymer	2-ethylhexy acrylate(EHA), methyl methacrylate (MMA) acrylate acid (AA), vinyl acetate (VA),	HPMC (2 % w/w)
Penetration enhancers	-	Limonene(6% w/v)
Solvent system	Ethyl acetate, acetone.	Ethanol-water
Device	Matrix diffusion controlled	Reservoir type membrane moderate
<i>In vitro</i> studies and its flux	10.418 ± 2.09 µg/cm <sup>2</sup> /hr	384.0 ± 4.6 µg/cm <sup>2</sup> /hr (on rat skin)
<i>In vivo</i> studies and its flux	-	164.8 ± 1.8 µg/cm <sup>2</sup>
References	Dnyanesh, Pradeep, 2003 <sup>30</sup> .	Krishnaiah YSR, 2005 <sup>29</sup> .

However in another study, matrix type transdermal patches of nicorandil were prepared by using three different grades of HPMC (6 cps, 15cps, and K4M). All the polymers used for the fabrication of the transdermal system showed good film forming properties. HPMC films were thin, flexible, smooth, and transparent. All the patches showed good folding endurance properties. The permeability of the drug through the skin was less than the required flux. Thus, flux studies were performed again by the addition of permeation

enhancer, dimethyl sulfoxide (DMSO), at different concentrations. 6% w/v DMSO showed a maximum flux of 93.972 mcg/cm<sup>2</sup>/hour. *In vitro* and *in vivo* evaluation parameters of nicorandil TDDS were mentioned in the Table 5. Among the six different HPMC formulations, transdermal patch with 6 cps and 6% w/v DMSO as permeation enhancer showed maximum release and offered least resistance to the movement of the drug molecule due to its high hydrophilic in nature and high water permeability value<sup>30,31</sup>.

**Table 5: *In vitro* and *in vivo* evaluation parameters of nicorandil TDDS<sup>30</sup>**

Polymers (2% w/v)	ST <sup>1</sup>	Plasticizer <sup>2</sup>	PE <sup>3</sup>	<i>In-vitro</i> release	<i>In-vitro</i> permeation	Flux (µg/cm <sup>2</sup> )
HPMC 6cps	8:2	30	-	58.30%	14.50%	-
HPMC 15cps	8:2	30	-	43.20%	7.50%	-
HPMC K4M	8:2	30	-	38.50%	7.10%	-
HPMC 6cps	8:2	30	(6%w/v)	92.59%	44.70%	37.93
HPMC 15cps	8:2	30	(6%w/v)	84.91%	23.80%	18.92
HPMC K4M	8:2	30	(6%w/v)	79.20%	20.00%	17.85

ST<sup>1</sup>: Solvent system (water: ethanol), concentration of plasticizer<sup>2</sup>: (PEG-400 %w/v), PE<sup>3</sup>: penetration enhancer (DMSO).

### Controlled oral delivery systems

Oral dosage forms are most popular and commonly used are tablets and capsules, etc. Tablet is most preferred choice by the physicians and patients. Nicorandil is also available in tablet form having dose 5 to 40 mg twice daily, hence to reduce the frequency of administration and to improve patient compliance, once daily sustained release formulation of nicorandil is desirable. Nicorandil with all evident advantages shows a suitable candidate for development of controlled release dosage form.

The drug is freely water soluble and selection of release retarding excipient is necessary to mimic the *in vivo* input rate of the drug. The one of the most commonly used methods of modulating the drug release is to include in matrix system. Hydrophilic gel forming polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance<sup>32,33,34</sup>. Hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (CMC) and sodium alginate (SA) are the hydrophilic polymers gaining the

importance in the development of nicorandil controlled release delivery systems. HPMC matrix tablet with different granulating agent using different concentrations achieve the controlled release of nicorandil.

The matrix tablet of sodium carboxymethyl cellulose (CMC) and sodium alginate (SA) were compared with release profile of HPMC matrix tablet at the end of 2 hrs and 24 hrs was tabulated in the Table 6. The hydrophilic matrix of HPMC alone could not control the nicorandil release effectively for 24 hrs. It is evident from results that a matrix tablet prepared with HPMC and a granulating agent of a hydrophobic polymer (ethyl cellulose 4% w/v) is a better system for once daily sustained release of highly water soluble drug nicorandil, but this formulation exhibits diffusion coupled with erosion mechanism have been reported. HPMC based formulation showed that 32.55% drug release in 2 hrs and 84.53% at the end of 12 hrs, but this formulation when used with EC (4% w/v) as granulating agent, resulted that 15.35% of drug release at the end of 2 hrs and 94.68% at the end of 24 hrs, respectively<sup>35</sup>.

**Table 6: The effect of polymers, solvent system for granulation and *in-vitro* release profile of nicorandil matrix tablets<sup>35</sup>**

Drug: Polymers	Granulating agents	At the end of 2 hrs.	Up to 24 hrs.
HPMC (1:4)	Ethanol (95%)	32.55%	84.53% for 12 hrs.
CMC (1:4)	Ethanol (95%)	48.75%	100% for 8 hrs.
SA (1:4)	Ethanol (95%)	62.55%	100% for 6 hrs.
HPMC (1:4)	PVP (100%w/v)	30.46%	99.50% for 24 hrs.
HPMC (1:4)	ERL (10% w/v)	26.13%	99.36% for 24 hrs
HPMC (1:4)	ERS (4% w/v)	23.63%	98.92% for 24 hrs
HPMC (1:4)	EC (2% w/v)	20.15%	97.61% for 24 hrs
HPMC (1:4)	ERS (8% w/v)	22.54%	95.58% for 24 hrs
HPMC (1:4)	EC (4% w/v)	15.35%	94.68% for 24 hrs

In another study, hydrophilic polymers such as xanthan gum, guar gum and HPMC are used in the preparation of matrix tablet of nicorandil. They have standardized and optimized the hardness of the developed formulations and effect on dissolution studies. The dissolution study indicated that in xanthan gum and guar gum based formulations the drug release was 9.3% and 5.7% at the end of 2 hrs and 84.56% and 73.82% at the end of 24 hrs respectively. The formulation containing only HPMC based formulation the drug release was 23.48% at the end of 2 hrs and 99.97% at the end of 24 hrs this could indicate that the drug-polymer 1:4 ratio released the drug continuously in controlled manner from the matrix, the overall phenomenon is due to the hardness of the compressed tablet. Different polymers, binders and their effect on hardness and drug

release profile were tabulated in Table 7. Xanthan gum, guar gum, HPMC combination polymers and 10% (20 mg) polyvinyl pyrrolidone (PVP) based formulations the drug release was 7.33%, 9.21%, 7.81% at the end of 2 hrs and 76.87%, 86.18%, 90.97% at the end 24 hrs respectively. Xanthan gum, guar gum, HPMC combination and 10% (20 mg) ethyl cellulose (EC) based formulations the drug release was at the end of 2 hrs are 2.13%, 3.18%, 3.12% and release at the end of 24 hrs are 69.55%, 70.10%, 71.13% respectively. Xanthan gum, guar gum, HPMC combination polymers and 10% (20 mg) ethyl cellulose (EC) formulations showed the drug release was slow as compared to xanthan gum, guar gum, HPMC based formulations which are also generally responsible for the hardness and amorphous nature of the polymers<sup>36</sup>.

**Table 7: Different polymers, binders and their effect on hardness and drug release profile<sup>36</sup>**

Drug: Polymers	Binders	At the end of 2 hrs.	Up to 24 hrs.	Hardness (Kg/cm <sup>2</sup> )
Xanthan gum (1:4)	-	9.30%	84.56%	4.8
Guar gum (1:4)	-	5.71%	73.82%	4.7
HPMC (1:4)	-	23.48%	99.97%	4.2
Xanthan. gum: Guar gum (1:2:2)	PVP (10%)	7.33%	76.87%	5.2
Guar gum:HPMC (1:2:2)	PVP (10%)	9.21%	86.18%	5.1
Xanthan. gum : HPMC (1:2:2)	PVP (10%)	7.81%	90.97%	5
Xanthan. gum: Guar gum (1:2:2)	EC (10%)	2.13%	69.55%	5.7
Guar gum:HPMC (1:2:2)	EC (10%)	3.18%	70.10%	5.8
Xanthan. gum; HPMC (1:2:2)	EC (10%)	3.12%	71.13%	5.7

### Formulation aspects on nicorandil patents

Novel technology is patented by Ishihara<sup>37</sup>. Non-liquid type preparation for injection that has improved stability contains nicorandil and an inorganic or organic acid and/or an alkaline metal salt thereof. Freeze drying and powder packing methods were developed. These ingredients, together with an excipient that is pharmaceutically acceptable, may be dissolved in a solvent,

sterilized by filtration and freeze-dried to obtain a freeze-dried preparation, or may be dissolved in a solvent under an aseptic condition and recrystallized to obtain an injectable powder. Nicorandil preparations according to the present invention are very stable and useful in clinical applications.

Novel technology is patented by Iida<sup>38</sup>. A method for producing a stable preparation containing nicorandil, a saturated higher

aliphatic acid or a saturated higher alcohol which is solid at ordinary temperatures and optionally an organic acid such as fumaric acid, oxalic acid, salicylic acid, tartaric acid or glutaric acid is disclosed. The inventors conducted intensive studies in order to develop a method for providing a nicorandil preparation which is stable not only in humid conditions but also under the compressive pressure exerted by punching operations in tablet making. Their overall opinion was nicorandil is useful as a curative for various types of angina pectoris. However, it is unstable in humid conditions and under the compressive pressure exerted by punching operations in tablets preparations and therefore, the development of a stable nicorandil preparation has been desired.

This is patented by Sato<sup>39</sup>. The transdermal penetration of nicorandil is useful for the treatment of angina pectoris is improved by the use of a solvent comprising an alcohol of 2 to 7 carbon atom and an aliphatic ester having molecular weight of at least 180 in the formulation of external preparation. The application of such drugs by transdermal administration can produce the advantages of ease of administration and discontinuation, sustained release properties and alleviation of adverse effects etc., and thus it is especially useful for the treatment of angina pectoris which is the disease with unpredictable spasm.

Novel technology is patented by Veronesi<sup>40</sup>. A pharmaceutically stable composition comprising a suspension or dispersion of nicorandil in polydimethyl siloxanes optionally the composition also includes colloidal silica and/ or lecithin. The composition may be used for coronary vasodilation and suppression of coronary vasoconstriction. Nicorandil is stable in solid state in extreme dry condition, but degrades when exposed to moisture even if only for short period at low humidity levels and at room temperature. Various factors influencing hydrolysis of nicorandil are the increase in the percentage of moisture to which the product is exposed, temperature and storage period.

This is patented by Veronesi<sup>41</sup>. Pharmaceutically/storage-stable, water resistant formulations of nicorandil comprise unit dosage coronary vasodilating amounts thereof in association, e.g. in suspension or in dispersion, with a pharmaceutically acceptable, characteristically low density dimethyl polysiloxane chemically compatible therewith, e.g., dimethicone or simethicone, are well suited for encapsulation within hard or soft gelatin capsules for oral/sublingual administration.

## CONCLUSION

The development of new dosage form like capsule, nanoparticle with improved patient compliance and improve drug action with minimum side effects as well as pharmaceutical properties of formulation appears to be an important aspects of cardiovascular therapy. Nanoparticle formulation of nicorandil is another approach which has maximum potential for systemic therapy. Nanoparticle formulation can be developed with different technology like spray drying, FBD, etc. current adverse effects such as ulceration can be over come by using nanoparticle formulation. The mouth dissolving tablet of nicorandil has one of the approach for development of immediate action therapy, because some times need the quick action of drug is required and to maintained the imbalance of oxygen supply and demand in the angina pectoris.

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