ASIAN JOURNAL OF BIOMEDICAL & PHARMACEUTICAL SCIENCES

e-ISSN: 2249-622X

RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Matrix Tablets Using Natural Gum *Limonia acidissima*as Release Modifier

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Received:
22th Aug 2013
Received in revised form:
30th Aug 2013
Accepted:
5th Sept 2013
Available online:
15th Sept 2013

OPEN ACCESS

Online ISSN 2249–622X
http://www.jbiopharm.com

ABSTRACT

The objective of this study was to design oral sustained release matrix tablets of nicorandil using different proportion of *Limonia acidissima* gum as the release retardant and to study the effect of formulation factor such asin-vitro release of drug. The gum is extracted and evaluated for physico-chemical and phyto-chemical property of the gum. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index, showed satisfactory results. Compressed tablets were evaluated for thickness, friability, hardness, drug content, weight variation and in-vitro dissolution studies. Fourier transform infrared (FTIR) study revealed that there was no chemical interaction between drug and the gum used. All the formulation showed compliance with Pharmacopoeial standards. In-vitro drug release studies were carried out using USP 35/NF30 dissolution apparatus type II at 50 rpm (rate per minute). The release kinetics was analyzed using the zero-order, first-order model, Higuchi's square-root equation and the Korsmeyer-peppas model. In-vitro release studies revealed that the release rate decreased with increase in gum proportion. The developed sustained release matrix tablets of nicorandil, with good initial release (15% in first hour) and extension of release for more than 12 h, can overcome the disadvantages of conventional tablets of nicorandil.

Keywords: Controlled release, *Limonia acidissima*, Matrix tablets, Nicorandil.

1. INTRODUCTION:

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages[1]. Sustained release tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs[2].

Different types of oral sustained release formulations have been developed to improve the efficacy and patient compliance[3]. The sustained release formulations are fabricated to release a drug at predetermined rate for prolonged time period. The most commonly used method to formulate is by conventional wet granulation method or direct compression. The formulation of sustained release tablets is very simple and cost effective. Matrix technology is used for sustaining effect or rate controlling polymer. The mechanism of drug release is due to hydration of polymer, which results in the formation of a gel layer that controls the drug release rate[5].

Nicorandil, a drug approved for the treatment of ischemic heart disease, is believed to have dual properties. The intrinsic mechanism of the drug (selective activation of K^+_{ATP}channels atthe sarcolemmal and mitochondrial level) allows coronary and peripheral vasodilatation with subsequent reduction of preload and afterload. Secondly, because of the role K^+_{ATP}channels in ischemic preconditioning, nicorandil have been attributed cardio -

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protective effects[6].

Nicorandil is soluble in water, freely soluble in acetone, methanol, and ethanol. Nicorandil is eliminated by plasma with a half-life of approximately 1 h. The total body clearance of nicorandil is less than the liver blood flow. After metabolism the nicorandil is converted primarily to the de-nitrated compound, SG-86(N-2-hydroxyethyl nicotinamide), which is pharmacologically inactive. The urinary excretion and the alcohol metabolite accounted for 1% and 4% of the dose (single 20 mg dose) in 24 h, respectively[7].

However, developing oral controlled release tablets for water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate and produce a toxic concentration of the drug on oral administration. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, cellulose derivatives such as methyl cellulose, hydroxylpropyl methylcellulose, and sodium carboxymethyl cellulose are generally considered to be stable and safe as release retardant excipients in the development of oral controlled release dosage forms. These semi-synthetic polymers are quite expensive when compared with natural gums such as *Limonia acidissima* gum (limonia gum). The natural gums are nontoxic and easily available. The objective of the present investigation was to develop oral controlled release tablets for water soluble nicorandil using a natural gum obtained from *Limonia acidissima* [8].

Limonia acidissima tree belongs to family Rutaceae.It is called by different namesWood apple, elephant apple. The wood-apple is seen all around the dry plains of India, Ceylon and Penang Island. The tree is normally seen cultivated along road edges of fields. The tree is straight tall with few upward reaching branches which bend outward towards the end. The bark is ridged, fissured scaly and contains sharp spines. The leaves are alternating deciduous with dark green in colour. The flowers are bisexual greenish in colour. The fruit is oval wide with hard woody grayish-white. The trunk and branches exude a white, transparent gumespecially following the rainy season[9].The bark, leaf, pulp, seed contains protein, carbohydrate and amino acids[10]. The carbohydrate content was high in bark, pulp and seed. Alkaloid, flavonoids, saponins, gums and mucilage, phenols and fixed oils are present.Gum and mucilage is present in all the plant parts.The plant has many medicinal actions. The fruit is used as a liver and cardiac tonic. It is effective in preventing hiccough, gum diseases. The bark and other part of the plant are used against snakebite[11]. Literature survey reveals that comprehensive physicochemical characterization and pharmaceutical application of the *Limonia acidissima*gum as a release retarding property in the tablet formulation has not been reported yet.

In the present work, we have isolated and characterized *Limonia acidissima*gum and evaluated its sustained-release properties employing nicorandil as a model drug. The matrix tablet ofnicorandil was formulated and evaluated for Pre and Post compression parameters.

2. MATERIALS AND METHODS

Nicorandil was obtained as a gift sample from Gayatri Pharmachem, Rankanpur. Limoniagum was collected from the incised trunk of *Limonia acidissima*tree in Tumkur region. PVP K 30,Talc and Magnesium stearate from LobaChem(Mumbai, India). All other chemicals and ingredients were used for study are of Analytical grade.

Extraction of *Limonia acidissima*Gum

The limonia gum was collected from *Limonia acidissima*trees (injured trunk site). It was dried, milled and passed through sieve no 80. Dried gum was stirred in distilled water for 6-8 h at room temperature. The supernatant was obtained by centrifugation. The residue was washed with water and the washings were added to separate supernatant. The procedure was repeated four more times. Finally the supernatant was made up to 500 ml and treated with twice the volume of acetone by continuous stirring. The precipitated material was washed with acetone and dried at 50-60°C under vacuum. The dried gum was pulverized and stored in tightly closed container[12-13].

Physicochemical properties of Limonia gum

The physicochemical properties such as visual identification, solubility, pH, Ash value, and loss on drying, pre-compression parameters and microbial load of the limonia gum were determined according to official Procedures[14-17]. The following evaluation parameters were presented, see Table 2.

Phytochemical properties of Limonia gum

Preliminary tests were performed to confirm the nature of gum obtained. The chemical tests are conducted for carbohydrates, tannins, alkaloids, proteins, glycosides, flavanoids, reducing sugars[18]. The result of the phytochemical examination were presented, see Table 3.

Characterization of Drug and Excipients using Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of pure Nicorandil, limonia gum and physical mixture of drug and excipients were recorded on Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC.The Fourier transform-infrared (FT-IR) spectrum of the sample was recorded in an IR spectrometer using potassium bromide (KBr) discs prepared from powdered samples

mixed with dry KBr in the ratio 1:200. Triplicate measurements were made, and the spectrum with the clearest identifiable peaks was chosen.

Preparation of Nicorandil Matrix Tablets

Matrix tablets were prepared by wet granulation method. The composition of various formulations is given, see Table 1. Nicorandil, limonia gum and Lactose were mixed in a polybag and the mixture was passed through mesh (No.60). Granulation was done using a solution of PVP- K-30 in sufficient isopropyl alcohol. The wet mass passed though mesh No.16. The wet granules were air dried for 2 hours. The granules were then sized by mesh No.22 and mixed with magnesium stearate and talc. Tablets were compressed using rotary tablet machine with concave punch. Tablet weight was (150 mg) kept constant as shown in Table. Five different formulae, having different concentrations of limonia gum (30, 35, 40, 45 and 50 mg per tablet), were developed to evaluate the drug release and to study the effect of limonia gum concentration on drug release.

Ingredients (mg)	F1	F2	F3	F4	F5
Nicorandil	20	20	20	20	20
Limonia acidissima	30	35	40	45	50
PVP K 30	5	5	5	5	5
Talc	6	6	6	6	6
Magnesium stearate	3	3	3	3	3
Lactosemonohydrate	91	86	81	76	71

Total weight per tablet: 150 mg

Table 1: Composition of different formulations

Pre compression parameters

The prepared powder blend was evaluated for various parameters like angle of repose, loose bulk density, tapped bulk density, compressibility index[19-21].

Post compression parameters

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester. Friability was determined by testing 20 tablets in a friability tester for 4 minutes at 25 rpm/min. The weight variation was determined by taking 20 tablets using an electronic balance[22].

In-vitro dissolution studies

The release rate of Nicorandil from sustained matrix tablets were determined using USP dissolution testing apparatus II (paddle type) at 50 rpm. The dissolution test was performed using750 ml of 0.1N HCl (pH 1.2) for 2 h at 37±0.5°C and then 250 ml of 0.2M trisodium phosphate ($Na_3PO_4.12H_2O$) was added and pH is adjusted to 6.8 as described in the USP 35/NF 30general monograph.Dissolution test was carried out for a period of 12 h using, 0.1N HCl (pH 1.2) for first 2 h and then the pH is adjusted to 6.8 for the rest of the period. The temperature of the dissolution medium is maintained at 37±0.5°C. 10 ml of the sample was withdrawn at regular intervals and replaced with the same volume of fresh pre-warmed dissolution medium. After filtration, the drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Labindia, Mumbai, India) at 262 nm. The study was performed in triplicate[23].

Drug release kinetics

To study the release kinetics, data obtained from in-vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug release vs time, first order (Equation 2) as log cumulative percentage of drug remaining vs time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs square root of time.

$$C=K0\ t \quad \ldots\ldots (1)$$

Where K0 is the zero order rate constant expressed in units of concentration / time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes[24].

$$\text{Log } C = \log C0 - Kt/2.303 \quad \ldots\ldots (2)$$

Where C0 is theinitial concentration of drug, K is the first order constant, and t is the time[25].

$$Q = kt½ \quad \ldots\ldots (3)$$

Where k is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time[26].

Mechanism of drug release:

To evaluate the mechanism of drug release from nicorandil sustained release tablets, data of drug release were plotted in korsmeyer et al's equation (Equation 4) as log cumulative percentage of drug release vs log time and the exponent n was calculated through the slope of the straight line.

$$Mt/ M\infty = ktn \quad \ldots\ldots (4)$$

Where Mt/ M∞ are the fractional solute release, t is the release time, k is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent n=0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 <n <0.89, then it is non-Fickian or anomalous diffusion. An exponent's value of 0.89 is indicative of case-II Transport or typical zero-order release[27-28].

Stability Studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The optimized formulation was subjected to stability study at

40±2ºC and 75±5% RHfor 90days. The samples were evaluated for physical changes, hardness, friability, drug content and percentage drug release during the stability studies[29-30].

3. RESULTS and DISCUSSION

Physico-chemical properties Limonia gum

The physicochemical parametersof limonia gum were evaluated. The limonia gum issoluble in water and practically insoluble in alcohol, acetoneand chloroform. The moisture content of limonia gum was low, suggesting itssuitability in formulations containing moisture sensitivedrugs. A 1% w/v solution of limonia gum in water gave a pH of 6.9. Knowledge of the pH ofexcipients is an importantparameter in determining its suitability in formulations sincethe stability and physiological activity of most preparationsdepends on pH.

The total ash and acid insoluble ash value of limonia gum wasfound to be 2.41% and 0.41%w/w respectively. Ash valuesreflect the level of adulteration or handling of the drug.Adulteration by sand or earth is immediately detected as thetotal ash is normally composed of inorganic mixtures ofcarbonates, phosphates, silicates and silica. Therefore, thelow values of total ash and acid insoluble ash obtained in thisstudy indicate low levels of contamination during gatheringand handling of crude *Limonia acidissima*.The bulk and tapped densities give an insight on thepacking and arrangement of the particles and the compactionprofile of a material. The compressibility index and angle ofrepose of limonia gum was 11.76% and 23.53° respectively,implying that the limonia gum has a good compressibility with moderate flow. The loss ondrying, ash value and microbial count were well within official limits.

The limonia gum physicochemical properties are presented in Table 2.

Parameters	*Limonia acidissima*
Solubility	Soluble in water, practically insoluble in alcohol, chloroform and acetone.
Odor	No characteristic odor
Taste	Tasteless
Color	Cream color
State	Amorphous
pH (1% w/v solution)	6.9
Loss on drying	1.60%
Ash value	2.41%
Water soluble ash	1.35%
Acid insoluble ash	0.40%
Sulphated ash	1.25%
Swelling ratio	
In water	20
In 0.1 N HCl	15
In phosphate Buffer 6.8	12
Bulk density (g/ml)	0.34
Tapped density (g/ml)	0.38
Compressibity index (%)	11.76
Angle of repose	23.53
Total bacterial count	
E.coli	Not detected
Salmonella typhi	Not detected
S.aureus	Not detected
Yield (%)	30

Table 2: Physico-chemical properties of *Limonia acidissima*.

Phyto-chemical properties of limonia gum

Phytochemical tests carried out on limonia gum confirmed the presence of mucilage giving positive result when treated with ruthenium red, it showed red colour confirming the obtained product as gum. Molisch's test gives positive with the formation of violet ring at the junction of two liquids, confirming the presence of carbohydrates. Mucilage could not reduce Fehling's solution, sothe sugars present were non reducing sugars.

Tests Observation	*Limonia acidissima*
Test for Carbohydrates (Molisch's test)	+
Test for Tannins (Ferric chloride test)	-
Test for proteins (Ninhydrin test)	-
Test for alkaloids (Wagner's test)	-
Test for glycosides(Keller-Killaini test)	-
Test for mucilage (Ruthenium red test)	+
Test for steroids (Salkowski test)	
Test for flavonoids (Shinoda test)	-
Test for reducing sugar (Felhing's test)	-
Mounted in 95% alcohol	Transluscent angular masses under microscope
Mounting in the iodine	No blue colored particles (starch absent)
Test for chlorides (silver nitrate test)	-
Test for sulphates (barium chloride test)	-

Table 3: Phyto-chemical properties of *Limonia acidissima*.

It reduced Fehling's solution after hydrolysis for 1h with concentrated sulfuric acid under reflux. The test confirmed the absence of alkaloids, glycosides and tannins. No blue colour obtained when the gum is treated with iodine indicating the absence of starch. The results of phytochemical properties of gum were summarized, see Table 3.

Characterization of Drug and Excipients

In order to determine possible interaction between the nicorandil drug, limonia gum and other excipients used in the formulation, compatibility studies were conducted using FTIR spectroscopy. There was no significant shift in the positions of the wave numbers when compared to that of the pure drug values. Thus there was no interaction between the drug and other excipients of the formulation.

Pre compression parameters

Powder blend prepared for compression of matrix tablets were evaluated for their flow propertieslike angle of repose, loose bulk density, tapped bulk density and compressibility index. Theresults were shown, see Table 4. Angle of repose was in the range of 26.63±0.98 to 30.32±1.42. The loose bulk density of the granules was in the range of 0.2689±0.023 to 0.2875±0.021gm/ml. The tapped bulk densitywas in the range of 0.3004±0.012 to 0.3316±0.009gm/ml, which indicates that the granules were notbulky. The compressibility index was found to be in the range of 11.64to 16.96.

Parameters	F1	F2	F3	F4	F5
Angle of repose (Θ)	28.32± 1.64	26.73± 1.78	30.32± 1.42	27.63± 2.12	26.63± 0.98
Loose bulk density LBD (g/ml)	0.2783 ±0.013	0.2875 ±0.021	0.2739 ±0.008	0.2835 ±0.017	0.2689 ±0.023
Tapped bulk density TBD (g/ml)	0.3176 ±0.015	0.3261 ±0.019	0.3058 ±0.021	0.3316 ±0.009	0.3004 ±0.012
Compressibility index (%)	14.12	13.42	11.64	16.96	11.71

Table 4: Pre compression parameter of granules.

Post compression parameters

The results of physical properties of nicorandil sustained release matrix tablets are presented see Table 5.The thickness of matrix tablets was measured by vernier caliper and was ranged between 3.008±0.002 mmto 3.010±0.002mm. The diameter of matrix tablets was measured by vernier caliper and was ranged between 6.007±0.001 mm to 6.009±0.002 mm. The hardness of the matrix tablets was measured by Monsanto testerand was controlled between 3.83±0.31kg/cm^{2}to 4.46±0.18kg/cm^2. The friability was below 1% for all theformulations. The percentage of drug content for F1 to F5 was found to be in between 99.46±0.45% to100.63± 0.45% of nicorandil, it complies with official specification. Thus all the physical attributes of theprepared tablets were found be practically within control. The nicorandil matrix tablets were offwhite,smooth, and flat shaped in appearance.

Weight variations for different formulations were found to be 149.45 mg to150.19mg. The weight variation is presented, see Table 6.

Parameters	F1	F2	F3	F4	F5
Thickness (mm)	3.008±0. 002	3.009±0. 002	3.008±0. 001	3.009±0. 002	3.010±0. 002
Diameter (mm)	6.007±0. 001	6.008±0. 001	6.008±0. 002	6.009±0. 002	6.008±0. 001
Hardness (kg/cm²)	4.16±0.1 1	4.24±0.3 0	4.46±0.1 8	3.83±0.3 1	3.94±0.2 5
Friability (%)	0.165	0.208	0.241	0.317	0.329
Drug content (%)	100.63± 0.45	99.46± 0.38	99.87±0. 62	99.61±0. 34	99.78±0. 38

Table 5:Post compression parameter of tablets.

Sl. No	F-1	F-2	F-3	F-4	F-5
1	152.2	151.8	153	151.2	151.3
2	151.5	150.3	150.8	150.3	148.5
3	150.6	150.3	151.4	149.4	148.6
4	150.3	150.8	150.3	150.6	149.4
5	150.9	151.1	149.9	150.8	149.9
6	151.8	150.2	150.3	150.3	150.5
7	148.5	150.7	151.7	151.3	150.8
8	149.6	149.5	150.3	150.8	150.7
9	149.3	149.2	149.2	151.2	149.8
10	151.3	149.5	151.3	150.2	150.9
Average Weight (mg)	150.6	150.34	150.82	150.61	150.04
% Maximum Positive deviation	1.06	0.97	1.45	0.46	0.84
% Minimum Negative deviation	1.34	0.76	0.89	0.8	1.03

Table 6: Weight variation of tablets.

In-vitro dissolution studies

The cumulative percentage drug release for F-1, F-2, F-3, F-4 and F-5 was (97.62%, 97.98%, 96.48%, 95.485%, and 98.49%) at the end of 12 h respectively. Formulation F1 failed to sustain release beyond 6 h. Among all the formulation, F5 shows 98.49%release at the end of 12 h. It was found cumulative percentage of drug release decreases with increase in the limonia gum concentration. The in-vitro release of the formulation is presented, see Figure 1.

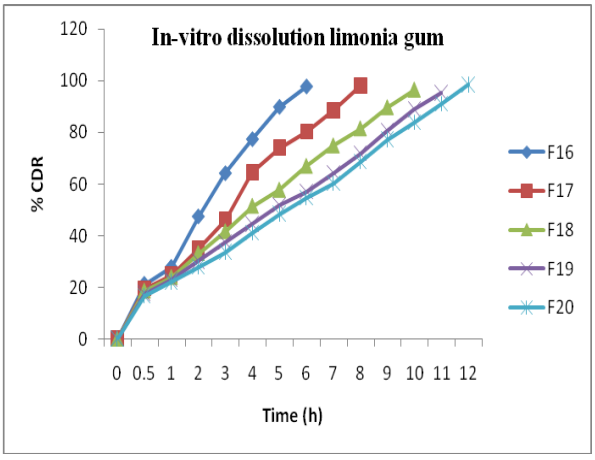

Figure 1: ***In-vitro*** **dissolution profile of sustained release tablets**

Drug release kinetics

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of the drug release, see Table 7.The regression coefficient obtained for zero order kinetics were found to be higher (R^2:0.987 to 0.994) when compared with those of the first order kinetics (R^2: 0.772 to 0.864), indicating that drug release from all the formulations followed zero order kinetics. In this experiment, the in-vitro release profiles of drug from all these formulation could be best expressed by Higuchi's equation as the plots showed the highest linearity (R^2: 0.987 to 0.994). To confirm the diffusion mechanism the data was fitted into Korsemeyer-Peppas equation. All the formulation showed good linearity (R^2:0.936 to 0.964) with slope (n) values ranging from 0.55 to 0.647. The mechanism of release from formulation F1 to F5 showed behaviors of anomalous (non-Fickian) diffusion. The n value increases as the drug gum ratio of the tablet increases. This n value appears to indicate a coupling of diffusion and erosion mechanism (known anomalous non-Fickian diffusion). Hence, diffusion coupled with erosion might be mechanism for the drug release from limonia gum sustained release based matrix tablets.

Formulations	Zero order plots◘	First order plots▪	Higuchi's plots●	Korsmeyer et al's plots□	
				Slope(n)	R^2
F1	0.989	0.863	0.989	0.647	0.936
F2	0.987	0.824	0.987	0.612	0.942
F3	0.992	0.864	0.992	0.564	0.944
F4	0.992	0.849	0.992	0.55	0.959
F5	0.994	0.772	0.994	0.565	0.964

Table 7: Release kinetics parameters of designed sustained release matrix tablets of Nicorandil

◘Zero order equation, C=K0 t.

▪First order equation, LogC=logC□-Kt/2.303.

●Higuchi's equation, Q= Kt½.

□Korsmeyer et al's equation, Mt/Mα= Ktn.

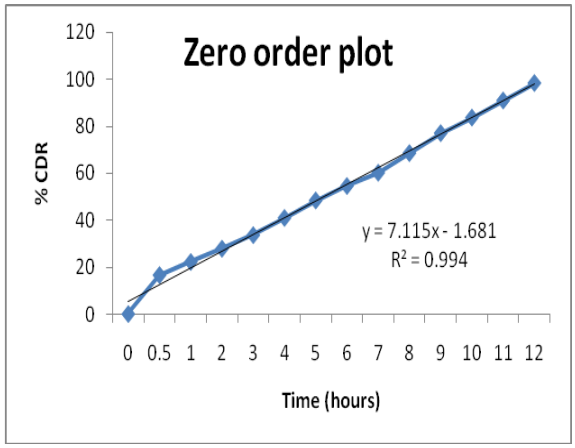

Figure 2: Zero order release kinetics of optimized formulation F5

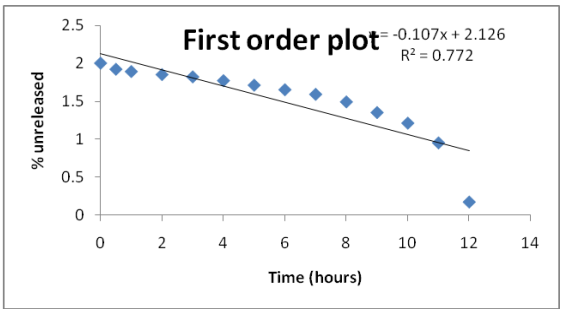

Figure 3: First order release kinetics of optimized formulation F5

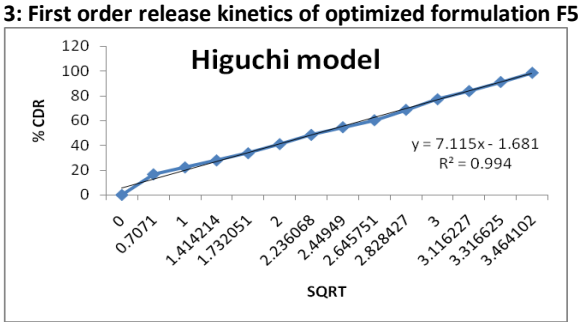

Figure 4: Higuchi model release kinetics of optimized formulation F5

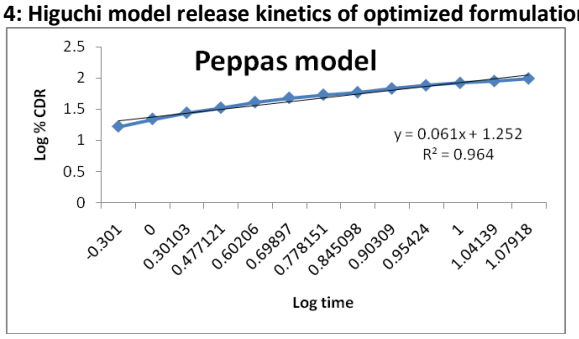

Figure 5: Korsmeyer and Peppas release kinetics of optimized formulation F5

Stability study

The optimized formulation F5 was kept at controlledstorage conditions. After stability test period, tablets were analyzed for drug content, hardness,friability and in-vitro release. Stability studies result showed that there was no significant change inhardness, friability, drug content and dissolution profile of formulation F5. The formulation wasstable under accelerated condition.

4. CONCLUSION

It may be concluded from the present study that slow and sustained release of nicorandil over a period of 12 h was obtained (F1 to F5) by the using limonia gum was successful in the formulation of matrix tablet and at the same time it is effective in retarding the drug release. Among all the formulation F5shows that 98.49% release at the end of 12 h. The cumulative percentage of drug release was decreased by increase in limonia gum concentration. The mechanism of the drug release from formulation F1 to F5 was anomalous (non-Fickian) diffusion. Stability studies shown that there was no significant changes in hardness, friability, drug content and in-vitro dissolution of selected formulation F5. The sustained effect and efficient drug delivery system was developed in the present study will maintain plasma

nicorandil levels better, which will overcome the drawbacks associated with the conventional therapy.

5. ACKNOWLEDGEMENT

We would like to thank ICMR for the financial support for this research (21/12/17/09/HSR, dated: 24/06/2010).

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Conflict of Interest: None Declared

Cite this article as:
Vinod R., Formulation and Evaluation of Sustained Release Matrix Tablets Using Natural Gum *Limonia Acidissima*as Release Modifier. Asian Journal of Biomedical and Pharmaceutical Sciences, 2013, 3: (23), 38-44.

