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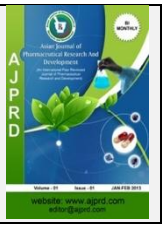

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Research Article

Formulation and Evaluation of Nicorandil Floating Tablets Using Natural Polymers

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A B S T R A C T

The present work described the pre-formulation and formulation development that led to the production of Nicorandil (NDL) floating tablets by direct compression of a homogeneous powder blend/ granules. In order to achieve the drug (NDL) release up to 24 hrs, rafting approach was selected. Studies have been carried out on rafting method by the use of natural polymers (sodium alginate, xanthan gum and guar gum) alone and their combination to get maximum rafting properties with superior drug release retarding activity. The results obtained in the rafting approach indicated that the polymer combination showed significant influence on rafting properties with maximum drug release retarding ability than individual polymers. In addition, the polymer combination of xanthan gum and guar gum resulted with maximum drug release retarding ability with poor rafting properties, whereas, the polymer combination of sodium alginate and guar gum resulted with predictable release behaviour (i.e. slightly lower retarding ability than the combination of xanthan gum and guar gum) with maximum rafting properties. As such the floating tablets prepared with rafting approach were recommended for oral controlled delivery of NDL.

Key words: Nicorandil, floating tablets, xanthan gum, sodium alginate.

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INTRODUCTION:

The oral route is a privileged route of administration and increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 80 % of the drug delivery systems available in the market are oral drug delivery systems [1]. Solid oral dosage forms like tablets play important role and the range of different types of tablet could be produced, including those to be swallowed intact, sucked, held within the buccal pouch or under the tongue, dissolved or dispersed in water before ingestion, or so formulated that the active ingredient is released in a controlled manner [2] for many disease for effective management of therapy with an ideal dosage regimen [3].

Conventional dosage forms, the rate of absorption and elimination for most of drugs follow first order kinetics. The rate of drug absorption for pharmacological effect increase with expanded dose, for further dose increments have minimal additional effect with the plasma concentration [4]. Conventional dosage forms release the entire dose of drug into accessible biological fluids immediately after administration (immediate release) and for such a type of systems, the rate-determining step (also called as rate-limiting step.

If any doses are missed, periods of sub-therapeutic drug blood levels or those underneath the minimum effective concentration may result, with no advantage to the patient [5]. The conventional dosage forms neither control the rate of drug delivery nor maintain the drug plasma concentration within the therapeutic range for an extended period of time to restore the health. Oral bioavailability of drug is directly related to physicochemical properties of drug, dosage form factors, and biophysicochemical properties of gastro intestine tract (hereafter, GIT or simply GI) barrier membrane [6]. GRDDS can increases the duration of drug release there by improve the bioavailability of drug that exhibit site specific absorption.

Various mechanisms [7] have been proposed to increase the gastric retention that includes (i) floating systems [8] (or low

density dosage form) that causes floating or buoyancy above gastric fluid; (ii) high density dosage form (or sedimentation or sinking systems) that sinks in the bottom of the stomach; (iii) mucoadhesive (or bioadhesive) systems that causes bioadhesion to the stomach mucosa; (iv) expanding (or swelling) systems that causes a limited emptying of the dosage form through the pyloric sphincter by swelling or unfolding to a larger size; and magnetic systems that contains a small internal magnet, and a magnet is placed on the abdomen over the position of stomach with a great precision.

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach.

This results in an increased gastric retention time and control of the fluctuation in plasma drug concentration [9]. Nicorandil (NDL), was selected as model drug to develop gastroretentive floating tablets using direct compression method. NDL was common choice of drug in cardiovascular diseases like hypertension and angina pectoris, which require constant monitoring. It has a short steady state half-life (1.33 hr), and necessitating the administration 2 to 4 times daily so as to maintain adequate plasma levels of drug.

Therefore, patients were directed to adhere a strict routine medication of several times a day and may chance of missing dose. In such case, the formulation releasing the drug in sustained/ controlled manner for prolonged period of time (preferably once daily) will aid the patient's convenience way by avoiding the need to take the dosage form 2 to 4 times daily. Controlled release gastroretentive dosage form was one of the choice and most feasible approach which were capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue by prolong the gastric retention time (GRT) and delay the gastric emptying time (GET).

In general, swellable and hydrophilic polymers were selected to develop gastroretentive formulation. Therefore, this study was aimed to investigate the effect of different hydrophilic and/or hydrophobic polymers to retard the drug release up to 24 hrs. NDL is a freely soluble drug, judicious selection of release-retarding excipients is necessary to achieve a constant in-vivo input rate of NDL. The most commonly used method of modulating the drug release is to include it in a matrix system using combination of hydrophilic and hydrophobic gel forming polymers [10-11].

MATERIALS AND METHODS:

Organoleptic properties:

The selected drug, Nicorandil (NDL) was characterized for organoleptic characteristics such as colour, odour and taste.

Flow properties:

The drug, NDL was tested for various flow properties like Carr's index, Hausner's' ratio and angle of repose.

Determination of moisture content:

Weigh accurately about 5 g of drug in a tarred china dish (W1). Dry in an oven repeatedly at 100±2°C until the difference in two successive weighing was less than 1mg and record the lowest weight (W2). The study was carried out in triplicate.

Moisture percentage = W1 / W2 × 100

Melting point:

The melting point was determined by "Open Capillary Tube Method" in melting point apparatus. The capillary tube was sealed with gentle heating from one end. A small quantity of drug was filled into the sealed capillary, placed into the slot of the melting point apparatus and the temperature was noted at which the drug melt. The study was carried out in triplicate.

Particle size determination:

A drop of drug suspension was mounted on glass slide and observed under microscope, where the eye piece micrometer was previously calibrated using stage micrometer (on stage micrometer, one mm was divided into 100 equal divisions and hence each division was equals to 10 µm.). About 300 particles were measured with the help of eye piece micrometer and average particle size was calculated.

Solubility studies: Saturated solution (Aulton, 2002) of NCRD was prepared using different solvents in iodine flask. To facilitate maximum solubilisation, it was kept in orbital shaker for 24 hr at 25 oC and kept aside for 12 hr to achieve equilibrium. The solution was filtered and estimated the drug content using UV-visible spectrophotometer at 262 nm. The study was carried out in triplicate.

Partition coefficient:

An excess of drug was added to iodine flask containing 25 mL of aqueous phase (water or 0.1 N HCl) and 25 mL of organic phase (n-Octanol). The iodine flask was shaken for 2 hrs in orbital shaker and allowed to stand for 24 hrs with intermittent shaking. The contents were transferred into separating funnel, allowed to stand for 1 hr to separate both the phases. The solutions were filtered separately and estimated the drug content using UV- visible spectrophotometer at 262 nm. The study was carried out in triplicate. The partition coefficient was calculated using formula,

Drug-Excipients Compatibility Studies:

Compatibility study of drug and excipients was done by physical observation. The binary mixture of drug and excipients were ground in a mortar, screened. The mixture was filled in a light resistant glass vial and sealed with teflon-lined screwcap. All samples were stored at 40±2 oC /75±5 % RH for four weeks. Sampling was done at particular time interval and observed for any colour change with naked eye. The change in colour in any mixture was basis for discarding from study.

Compatibility studies with FTIR:

The physical compatibility between drug and excipients was tested by Fourier- transformed infrared (hereafter, FTIR)

spectrophotometer. The FTIR instrument was recorded from an upper wave length region of 4000 (by convention) to 400 cm-1 by potassium bromide (as a blank) based pellets prepared by establishing pressure of 10 kg/cm2 for about 30 sec and the band/peak positions were recorded.

Compatibility studies with DSC:

Differential scanning calorimetric (DSC) thermogram were recorded using sealed 40 µL aluminium pans containing drug and/ or excipients, at heating rate 10°C/min over a temperature range of 0 to 350°C. About 5 mg of sample was hermetically sealed in a aluminium crucibles and heated. The heat flows as a function of temperature was measured for drug-polymer mixture and spectrum was recorded.

Calibration curve:

Standard stock solution of NDL was prepared by dissolving 100 mg of the drug in 30 mL of 0.1 N HCl using 100 mL volumetric flask, sonicated for about 10 min and adjusted the volume with 0.1 N HCl to get a concentration of 1000 µg/mL. This solution was used to prepare different aliquots of standard working solutions by diluting with 0.1 N HCl. The absorbance of each solution was measured at 262 nm using UV-visible spectrophotometer. The assay was performed in triplicate.

Preparation of GRDDS of Nicorandil by Raft Forming Approach:

The aim of this section was to formulate controlled release gastroretentive matrix tablet of NDL using raft forming approach prepared by direct compression method. Different natural raft forming agents like sodium alginate (SA), guar gum (GG) and xanthan gum (XA) were used along with sodium bicarbonate as effervescent and microcrystalline cellulose as directly compressible vehicle. Various steps involved in the tablet preparation by direct compression method. All the ingredients accurately weighed, passed through sieve number 40 (#40). After sieving, all the ingredients (including API) except lubricant and glidant were geometrically blended in poly bag with about half empty space by tumbling to provide enough space for the powder bed for five minutes.Add magnesium stearate (as lubricant) and talc (as glidant) into a poly bag and mix for five minutes to get a uniform blend. Finally, the homogeneous blend was compressed into a tablet.

Characterization of Powder Blend/ Granules:

Evaluation was performed to assess the flow and consolidation characteristics of the powder/ granules for the developed formulations. Five determinations were made for each batch and the mean value was computed. The bulk density (g/cc, mass per unit volume of untapped material), tapped density (g/cc, mass per tapped volume) and bulkiness (cc/g, reciprocal of bulk density) were determined using standard procedure stipulated in Manavalan & Ramaswamy, 2004. An automated tap density tester was used for tapping the powder/ granules. The final volume of the powder/ granules after sufficient tapping was noted where there was no further volume changes occur (up to 1200 taps). Carr's index (also called as compressibility index, determined from the ratio of difference in tapped and bulk density to that of tapped density), Hausner's ratio (determined from the ratio of tapped density to bulk density) and angle of repose (determined by fixed funnel method, the tangent of the ratio of the height and diameter of the symmetrical cone of powder) were calculated using the method stipulated in Rishikesh et al., 2014 and Liebermann et al., 1990. Five determinations were made for each batch and the mean value was computed.

Characterization of floating tablets:

Compressed tablets were characterized for tablet dimensions like thickness and diameter, hardness using Monsanto hardness, weight variation calculated from the mean weight of 20 tablets (USP official limits of percentage deviation, friability (determined by Roche friabilator apparatus, a maximum weight loss of not greater than 1.0 per cent of their weight were considered acceptable, drug content uniformity and tablet apparent density (mass per unit volume). As per USP, the acceptance criteria for drug content uniformity follow as, 30 tablets were randomly selected from the prepared tablets and at least 10 of them were assayed individually. The tablets comply with USP for this test if not more than one of the individual values thus obtained was outside the limits 85 - 115 % and none was outside the limits 75 - 125 % of the labelled content. If this condition was not meet (i.e. if two or three individual values were outside the limits of 85 - 115 %) repeat the determination using another 20 tablets (remaining from 30 tablets), assayed individually and none of the tablet may fall outside of the 85 to 115 %. In vitro buoyancy was determined at 37±0.5°C by observing floating lag time (FLT, time required for dosage form to rise to the surface and float) and in vitro floating time (IFT, total duration of time by which dosage form remain buoyant in medium) stipulated. Further, swelling characteristic like water uptake study and matrix erosion study (weight loss study) were also tested as per the procedure respectively. Disintegration test also conducted as per the standard procedure.

Raft strength measurement:

Raft strength was determined using self-fabricated apparatus (modified double beam physical balance) assembled in the laboratory (see the model Fig. 4.1). Briefly, to left lever arm of balance, 250 mL glass beaker was placed and the right lever armof balance was removed. L-shaped stainless steel wire probe (having diameter of 1.2 mm, height of 90 mm and bottom length of 20 mm) was hooked to the right lever arm of balance, finally, the lever arms were balanced with the help of additional weights tothe right side of the lever until the beam return to the horizontal position. A tablet powder equivalent to unit dose (maximum dose) was transferred to 150 mL of 0.1 N HCl previously equilibrated at 37 oC in a 250 mL transparent glass beaker. Immediately, the wire probe was held upright in the beaker throughout the whole period (approximately 30 min) of raft development. After 30 min, water was added drop wise to the pan and the weight of water required to break the raft was recorded. The test was conducted in triplicate and the mean values were calculated.

Raft volume, raft weight and raft thickness:

Raft volume was determined, as above, but without the inclusion of a wire probe. Briefly, transfer 150 mL of 0.1 N

HCl previously equilibrated at 37°C into a 250 mL pre-weighed (W1) transparent beaker. A tablet powder equivalent to unit dose (maximum dose) was added to the above beaker and remains for 30 min undisturbed for complete raft development. The position to which the top of raft reached was marked (both upper and lower limits of their thickness) on the outside of the beaker. The total weight of the beaker and contents after raft developing was note down (W2). The raft was then removed from the beaker by carefully decanting off the subnatant liquid and dry the raft using towel paper to remove the excess subnatant liquid and the raft was weighed (W3). Remaining liquid was removed from the beaker and refilled with water to the marked position and weighed (W4). The volume of raft was then calculated from the formula,

$$\text{Raft volume: } W_4 - W_1 - W_2 - W_1 - W_3$$

The dry weight of the raft (W3) was considered as raft weight which was measured in mg, whereas the raft volume was measured in mL. The thickness (Johnson et al., 1997) of the raft was measured at three places around the cylinder after completion of raft (30 min). In order to get accurate value, three measurements were made for each raft and three rafts were studied from each formulation.

Raft resilience:

Raft resilience test was conducted in USP type-II (Paddle) dissolution test apparatus. Briefly, transfer 250 mL of 0.1 N HCl previously equilibrated at 37 oC into a transparent basket. A tablet powder equivalent to unit dose (maximum dose) was added to the above beaker and remains for 30 min undisturbed for complete raft development. The paddle was rotated at 20 RPM, to simulate gastric agitation. The rafts were carefully assessed for gel size and coherence after total period of time that a raft could no longer be detected. A raft was defined, for visual assessment, as two or more floating gels at least 15 mm in diameter. Raft resilience was defined as the last time point at which a raft was observed.

Raft buoyancy:

The raft buoyancy formed due to raft forming agent might be expected to contribute to the effectiveness of the product in resisting reflux since a more buoyant raft would be more likely to displace corrosive gastric contents in the upper part of the stomach and it would also be less likely to be emptied along with the meal. Raft buoyancy was most effectively obtained by trapping carbon dioxide gas in the raft asit was formed. A buoyancy index was computed for those products which formed a structured raft as opposed to a precipitate. The raft buoyancy was calculated by,

Raft buoyancy = Volume – Weight / Weight

In vitro drug release study:

In vitro drug release studies of all prepared NCRD floating tablets were conducted for a period of 24 hrs using an eight station USP type-II (paddle type) apparatus. Triplicate runs were carried out and the results were averaged. Criteria of in vitro dissolution study as follows,

Apparatus used: USP type-II (Paddle) dissolution test apparatus

Dissolution medium: 0.1 N HCl (pH 1.2)Volume of dissolution medium: 900 mL

Temperature of medium: 37 ± 0.5°C Agitation speed: 75 RPM

Sampling time intervals: 1, 2, 3, 4, 5, 6, 9, 12, 15 and

24th hr

Sample withdraw: 5 mL

Analyzed instrument: UV-visible spectrophotometer at 262 nm.

Accelerated Stability Studies:

The stability studies were performed by keeping the optimised formulation NDL4 in the amber colour bottle by laminating with aluminium foil on the upper part of the bottle and these packed formulation was stored in stability chamber maintained at 40±2°C and 75±5 % RH for 3 months as per FDA draft. The samples were withdrawn periodically and evaluated for different parameters.

Table 1: *Composition of NDL floating tablets to determine the effect of rafting polymers*

F. code	NDL	SA	GG	XA	NaHCO3	MCC	Lactose	MS	Talc
NFT1	20	100	-	-	40	80	139	10	10
NFT2	20	125	-	-	40	80	114	10	10
NFT3	20	150	-	-	40	80	89	10	10
NFT4	20	-	100	-	40	80	139	10	10
NFT5	20	-	125	-	40	80	114	10	10
NFT6	20	-	150	-	40	80	89	10	10
NFT7	20	-	-	100	40	80	139	10	10
NFT8	20	-	-	125	40	80	114	10	10
NFT9	20	-	-	150	40	80	89	10	10

(NDL, Nicorandil; SA, Sodium alginate; GG, Guar gum; XG, Xanthan gum; NaHCO3, Sodium bicarbonate; MS,Magnesium stearate)

Table 2: Physical parameters of NDL floating tablets

F. Code	BD (g/cc)	TD (g/cc)	ulkiness (cc/g)	Carr's index (%)		Hausner's ratio		Angle of repose (θ)	
				Result	INF	Result	INF	Result	INF
NFT1	0.725	0.838	1.38	13.48	Good	1.16	Good	31.28	Good
NFT2	0.671	0.769	1.49	12.74	Good	1.15	Good	31.48	Good
NFT3	0.716	0.824	1.4	13.11	Good	1.15	Good	34.53	Good
NFT4	0.679	0.801	1.47	15.23	Good	1.18	Good	32.47	Good
NFT5	0.697	0.789	1.43	11.66	Good	1.13	Good	32.66	Good
NFT6	0.657	0.745	1.4	13.02	Good	1.15	Good	34.61	Good
NFT7	0.658	0.775	1.52	15.1	Good	1.18	Good	34.55	Good
NFT8	0.682	0.788	1.47	13.45	Good	1.16	Good	33.63	Good
NFT9	0.673	0.789	1.49	14.7	Good	1.17	Good	31.63	Good

Table 3: Various characterization parameters of NDL floating tablets

F. Code	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Weight variation(mg)	Friability (%)	% Drug content	FLT (sec)	IFT (hr)
NFT1	10.2±0.11	6.31±0.14	4.3±0.13	399.35±0.63	0.542±0.15	99.44±0.13	102±3	>24
NFT2	10.1±0.17	6.65±0.15	4.6±0.14	399.16±0.72	0.645±0.11	98.14±0.08	108±3	>24
NFT3	10.2±0.15	6.49±0.12	4.9±0.06	402.48±0.14	0.357±0.07	101.21±0.15	112±2	>24
NFT4	10.2±0.21	6.68±0.16	4.6±0.14	400.46±0.86	0.526±0.12	99.53±0.11	128±2	>24
NFT5	10.1±0.14	6.34±0.11	4.1±0.11	399.37±0.64	0.643±0.14	99.34±0.06	132±2	>24
NFT6	10.1±0.12	6.92±0.16	4.7±0.13	398.74±0.47	0.468±0.12	98.73±0.08	136±1	>24
NFT7	10.1±0.19	6.64±0.08	4.3±0.15	399.42±0.35	0.365±0.06	99.49±0.12	153±2	>24
NFT8	10.2±0.13	6.64±0.15	4.2±0.17	401.62±0.55	0.536±0.05	100.35±0.11	148±2	>24
NFT9	10.2±0.12	6.91±0.13	4.5±0.13	401.48±0.68	0.395±0.08	100.64±0.14	143±2	>24

Table 4: Rafting performance of the formulations of NDL floating tablets

F. Code	Raft strength (g)	Raft volume (ml)	Raft weight (g)	Raft thickness (cm)	Raft resilience(min)	Raft buoyancy
NFT1	4.83	11.24	9.42	0.67	10-Dec	0.292
NFT2	5.12	13.43	10.55	0.82	Nov-13	0.335
NFT3	5.66	15.49	13.46	0.95	Dec-15	0.318
NFT4	3.16	6.72	6.45	0.58	Nov-15	0.364
NFT5	4.12	8.46	7.14	0.62	Oct-15	0.272
NFT6	4.65	10.26	7.86	0.75	Oct-13	0.391
NFT7	2.14	5.43	5.23	0.41	04-Aug	0.332
NFT8	2.63	7.19	5.96	0.46	02-Aug	0.352
NFT9	3.25	7.93	6.78	0.53	02-May	0.407

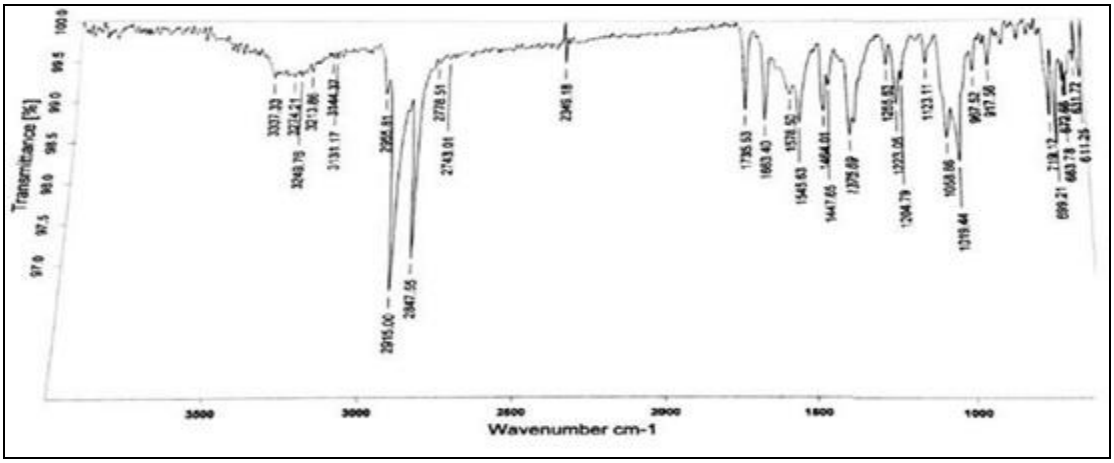

Figure 1: FTIR of pure drug Nicorandil

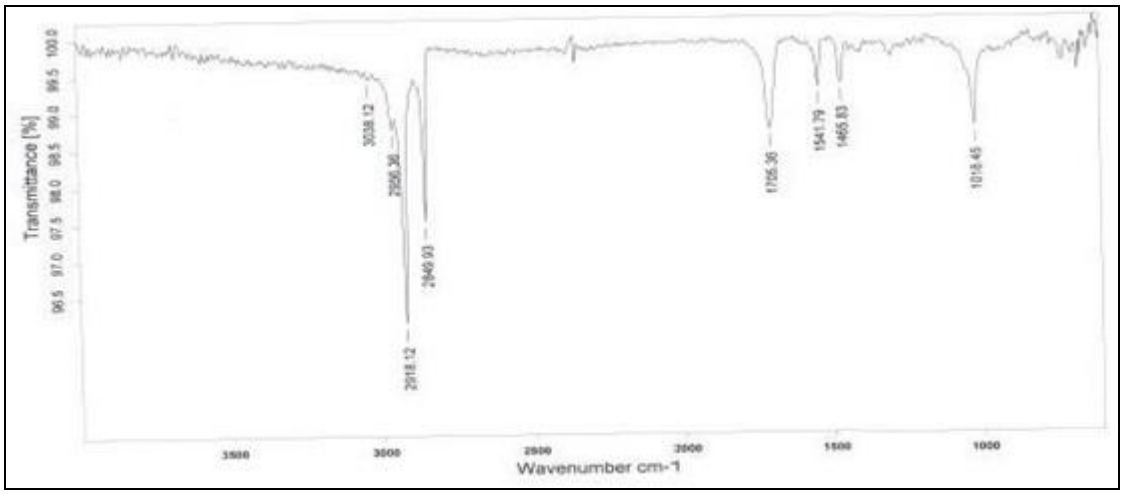

Figure 2: FTIR of pure drug Nicorandil and excipients

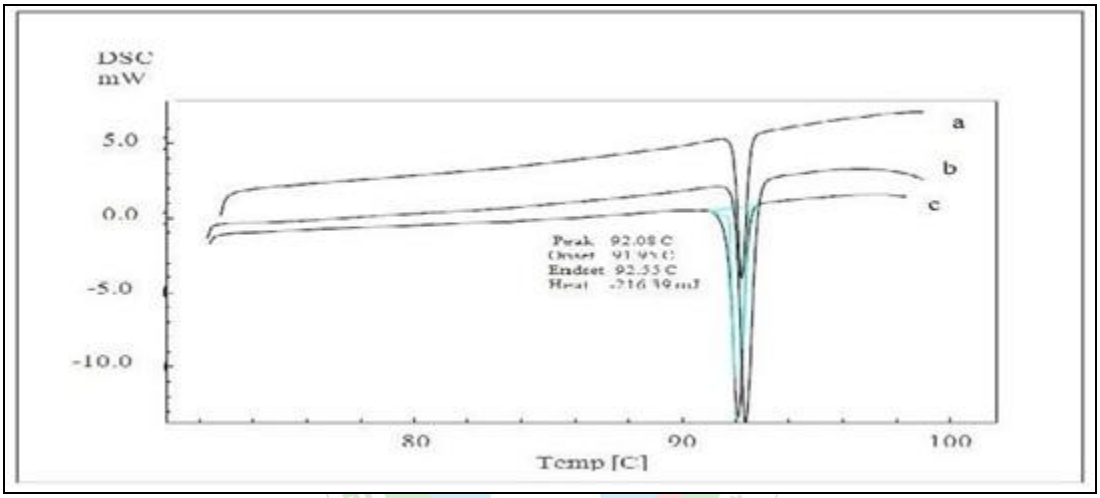

Figure 3: DSC thermogram of pure drug Nicorandil and excipients

RESULT AND DISCUSSION:

The drug was a white to off white crystalline solid powder, faint characteristic odour and foul taste. The flow property of the powder play an important role in pharmaceuticals, especially in tablet formulation prepared by direct compression because improper flow may cause more weight variation. The flow properties values of NDL presented in Table 2. Bulk density (hereafter, BD), tapped density (hereafter, TD) and bulkiness of NDL was found at 0.628 g/cc, 0.775 g/cc, and 1.592 cc/g, respectively. Based on micromeritics of pure drug (NDL) exhibited fair to excellent type of flow properties. Without aid of mechanical aids to API, it might be difficult to get good flow of powder for direct compression. So, for the preparation of NDL tablets by direct compression, slightly excess concentration glidant has to be added to achieve good flow of powder blend.

The moisture content was found to be 7.6 % with low standard deviation of ±0.305. The melting point of NDL was found to be 92±0.5°C. The average particle size of NDL was analysed by laboratory microscope and the value was found to be 153 µm. The solubility of drug was important in pharmaceutical research and support formulation development, including product optimization. Solubility of NDL was estimated with various solvents and at various pH. The solubility of NCRD in distilled water and 0.1 N HCl were found to be 3.8 mg/mL and 3.7 mg/mL, respectively, indicates that the drug was freely soluble in water. Considering the economic factor, the drug was stable in 0.1 N HCl and selected as dissolution media.

The drug was found to be very soluble in ethanol, chloroform, 0.1 N sodium hydroxide and soluble in ether. The effect of pH on the solubility of NDL in different buffers was also conducted. It was observed that as the solubility of NDL increased with increase in the buffer pH up to 7.4 and then decreased. The pH of 1 % aqueous solution of NDL in water was identified as 5.7±0.1. The partition coefficient (Ko/w) of dru was carried out to determine the extent of drug transfer in the non aqueous layer (n-Octanol) and aqueous layer. This phenomenon usually done to obtain the drug concentration in both the layer. Partition coefficient of drug in the Octanol/ water and Octanol/ 0.1 N HCl system was found to be 0.713 and 0.711, respectively. The value of Ko/w less than one indicates that, drug was more soluble in aqueous phase than organic phase. Drug-Excipient compatibility studies were observed by physical observation and the change in colour of drug and any mixture of drug plus polymer/ excipients was obtained.

There was no significant change in the colour of drug and polymer/ excipients observed and by visual evaluations like liquefaction and cake formation not observed. NDL and excipients interaction was studied by comparing the Fourier-

transformed infrared spectrum of pure drug with excipients and the optimized blend (NFT4). Thus the comparison shows that there was no interaction between drug and other ingredients of formulation such as guar gum, sodium bicarbonate, citric acid, stearic acid and lactose. The interaction studies between the NDL and excipient(s) was carried out by differential scanning calorimetric study. The thermogram of NDL with physical mixture of polymers include GG, showed an endothermic peak of drug at 92.4°C, indicating a slight change in terms of shifting towards the lower temperature. In addition, the final blend of optimised formulation, NFT4 (include NDL, GG, NaHCo3, sodium bicarbonate, citric acid, stearic acid, lactose and talc) showed an endothermic peak of drug at 92.0°C, indicating insignificant change in melting endotherm of drug and drug with excipients.

It has been observed that the quantity of material used effects the peak shape and enthalpy. Thus these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipients which lower the purity of each component in the mixture and may not necessarily indicate potential incompatibility. These results indicates, drug with polymers and other excipients used were compatible with each other.

At first, the preliminary screening was carried out to determine the effect of raft forming agent on NDL gastroretentive tablets using different natural raft forming cum retarding polymers like sodium alginate (SA) a sodium salt of alginic acid, guar gum (GG) and xanthan gum (XG). Direct compression was employed for the preparation of NDL floating tablets, in which the powder mixture of all the ingredients had to possess good flow properties. In the study of effect of raft forming agent, nine formulations were prepared using SA (NFT1, NFT2 and NFT3), GG (NFT4, NFT5 and NFT6) and XG (NFT7, NFT8 and NFT9) as raft forming agents at the concentrations of 100 mg, 125 mg, and 150 mg per tablet. Before tabletting, the powder blend of each formulation was evaluated for their flow properties like: bulk density (BD), tapped density (TD), compressibility index (or Carr's index), Hausner's ratio, and angle of repose of the formulations NFT1 to NFT9 were found in the range between 0.657 to 0.725 g/cc and 0.745 to 0.838 g/cc, respectively. The bulkiness of the entire prepared blend found in the range of 1.38 to 1.52 cc/g. In accordance with literature (Mangesh et al., 2013), powders or granules with Carr's index values below 16 % were ideal for producing tablets via direct compression and those with Hausner's ratio values below 1.18 and angle of repose below 35o indicate good flow properties of powders or granules. The limiting values of flow properties as per USP, the Carr's index value of pre-compressed blend of the formulations NFT1 to NFT9 were in the range of 11.66 to 15.23 %, indicating that the powder blend showed good flow properties.

In addition, Hausner's ratio of these formulations were in the range of 1.13 to 1.18, indicating that the powder blend showed good flow properties i.e. the granules present with low inter-particle friction. Nevertheless, the nature of good powder flow property of the formulations NFT1 to NFT9 were further supported by angle of repose having the value ranged from 31.28 to 34.61o, indicates good flowability i.e. the powder was not too cohesive to flow through the funnel. Among these formulations, the granules prepared with calcium carbonate showed better flowability than sodium bicarbonate indicated by lower flow property values. Overall, these formulation blends were suitable for direct compression into matrix tablets. The general appearance of tablets, its visual identity and overall 'elegance' was essential for acceptability of dosage form by the patient. Microscopic examination of tablets from each formulation code NFT1 to NFT9 presented with circular shape with no cracks. The diameter and thickness of the formulations NFT1 to NFT9 were in a range of 10.1±0.12 to 10.2±0.21 mm and 6.31±0.14 to 6.92±0.16 mm with less standard deviation, respectively.

The measured hardness of the formulations NFT1 to NFT9 ranged between 4.1±0.11 to 4.9±0.06 kg/cm2 with less standard deviation. All the formulated (NFT1 to NFT9) tablets passed weight variation test as the percent weight variation was found in range of 398.42 to 402.48 mg and found within the USP limits (as per USP, the maximum percentage difference allowed was 5.0 % having tablet weight of greater than 324 mg. As per USP, conventional compressed tablets that lose less than 1 % of their weight were generally considered acceptable. The percentage friability of the formulations NFT1 to NFT9 was found in range of 0.357 to 0.645 % (i.e. below 1 % W/W), indicating that the friability was within the prescribed limits according to USP, ensuring that the tablets were mechanically stable and also suitable to prepare floating tables. The drug content estimations showed the values in the range of 98.14 to 101.21 % which reflects good uniformity in drug content among the formulations NFT1 to NFT9 and indicates these values were within specified range as per USP (±15 % of label claim was acceptable). Floating characteristics of the prepared formulations were determined in 0.1 N HCl. All the formulations were found to exhibit different FLT, even the same amount of sodium bicarbonate presented in the formulation. Among these, the formulations prepared with SA presented with shorter FLT than gums. The reason may be expected that, faster penetration of fluid into the core tablet prepared with SA to expel carbon dioxide gas than gums.

All the formulation were found to float for longer duration of greater than 12 hrs. Raft performance of the three polymers was determined and the in order to fully verify the rafting performance of raft forming agent, raft strength was calculated. Raft strength was directly proportional to the amount of polymer present in the tablet which was in agreement with literature. From these results it was also observed that, the formulations prepared with SA presented with superior raft strength and raft volume than the formulations prepared with gums. Also, the raft weight along with their thickness were found to be higher for the formulations prepared by SA than gums. Superior raft resilience values were observed with the formulation having SA than gums. All these parameters were predominant in the formulations prepared with SA, while the formulations of XG showed predominant effect on raft buoyancy. In vitro dissolution studies were conducted for the formulations NFT1 to NFT9 to determine the effect raft forming agent on drug release In vitro release rate studies showed that the

maximum retard in drug release was observed with NFT6 formulation prepared by GG (up to 7 hrs). Among these polymers, the order of retard in drug release was as follows, GG > XG > SA. The formulations prepared with SA had predominant effect on raft performance, while the formulations prepared with GG had predominant effect on drug release characters. Moreover, the rate of drug release was retarded with concentration increased among all these polymers.

The kinetic data of all formulations NFT1 to NFT9 were best expressed by zero order equation as the plots showed highest linearity (R: 0.9756 to 0.9930 and R2: 0.9518 to 0.9861, than first order release kinetics (R: 0.9063 to 0.9550 and R2: 0.8213 to 0.9121). Overall, it was demonstrated that, the three polymers showed raft forming property, but different in extent to form raft. Among these polymers, SA showed maximum rafting performance with poor drug release retarding ability, whereas, the polymer GG showed greater drug release retarding ability with poor rafting performance. Hence, the combination of these polymers was studied to get maximum rafting performance with greater drug release retarding ability.

Table 5: In vitro drug release profile of the formulations of NDL floating tablets

Time (h)	Cumulative percentage of drug release								
	NFT1	NFT2	NFT3	NFT4	NFT5	NFT6	NFT7	NFT8	NFT9
0	0	0	0	0	0	0	0	0	0
1	35.46	32.14	30.71	28.35	25.46	23.41	29.75	28.14	26.24
2	48.21	45.37	42.17	39.72	35.34	33.66	40.16	39.43	37.22
4	63.75	59.71	56.72	53.82	50.49	46.27	58.23	55.17	52.42
6	76.48	72.58	70.43	67.16	65.44	62.85	70.41	68.82	66.14
8	85.37	83.25	80.44	76.43	72.42	69.42	79.34	77.33	75.43
10	98.43	96.47	95.14	92.11	89.65	85.26	95.27	93.14	90.17
12	-	-	-	97.86	95.62	93.47	99.14	97.54	96.48

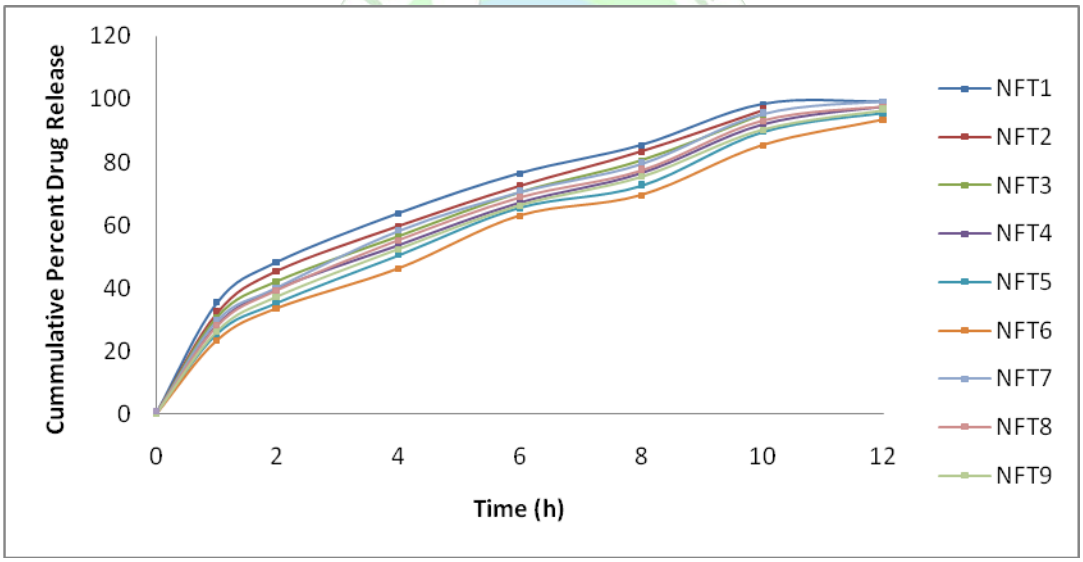

Figure 4: In vitro drug release profile of the formulations of NDL floating tablets

CONCLUSION:

It was concluded that, the floating tablet of NDL was prepared by direct compression method. The polymers used for proposed work was showed raft forming property, whereas the formulation prepared with SA showed maximum rafting performance with poor drug release retarding ability. The other formulations with the polymer GG showed greater drug release retarding ability with poor rafting performance than the prepared with XG. Hence, the combination of these polymers was studied to get maximum rafting performance with greater drug release retarding ability. The tablets showed acceptable pharmacotechnical properties and complied with compendial requirements with Non-Fickian diffusion mechanism drug release mechanism from these tablets.

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