Mouth Dissolving Delivery System: A Novel Approach for Angina

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Abstract

Aim: The study aims to see the sights of potential of mouth dissolving tablets for improving the oral delivery of nicorandil by the use of superdisintegrants. **Materials and Methods:** Fast dissolving tablets of nicorandil successfully prepared by direct compression techniques using various concentrations of sodium starch glycolate, croscarmellose sodium, and crospovidone (CP) as superdisintegrants. The optimized batch of fast dissolving tablets of nicorandil were characterized for hardness, friability, *in vitro* disintegration, dissolution, stability studies. **Results and Discussion**: In comparison to marketed immediate-release formulation, the formulation (F9) was found to be faster in drug release profile as well as short disintegration time. The formulation F9 were found to be stable in 6 months stability studies in different packing. **Conclusion:** Nicorandil tablets containing CP as a superdisintegrant show faster disintegration and dissolution rate.

Key words: *In vitro* disintegration time, *in vitro* dissolution test, nicorandil, superdisintegrants

INTRODUCTION

Oral drug delivery is one of the most common and most patients – convenient means of drug administration. It is one of the largest and the oldest segments of the total drug delivery market.[1] The popularity of the oral route is due to some reasons such as patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods, and generally improved shelf life of the product. Consequently, much effort is directed during drug discovery to identify orally active candidates that will provide reproducible and effective plasma concentration *in vivo*.[2] The fact is that majority of compounds are either incompletely or ineffectively absorbed after administering from oral route (i.e. bioavailability is an issue), or that the required dosing frequency is too short to enable once or twice daily administration (i.e. pharmacokinetic half – life is an issue). Lead optimization typically addresses such drawbacks during a discovery program; however, in many cases it is not possible to identify an ideal clinical candidate with the requisite "ideal" physicochemical and/or pharmacokinetic properties.[3] During clinical research phase, drug candidate or drug already marketed, the opportunity for enhancing their clinical pharmacology profile after oral administration through attainment of more optimal blood drug concentration – time profiles

should always be considered. Modified release formulation technologies offers an effective means to optimize the bioavailability and resulting blood concentration – time profiles of drugs that otherwise suffer from above mentioned limitations.[4]

Nicorandil is a vasodilatory drug used for the treatment of angina. It is marketed under the trade name Ikorel and commercially available in the form of plain tablets in the market. Literature reveals that after oral administration of nicorandil tablets, the decreased bioavailability is mainly due to disintegration and dissolution process. The efficacy of drug may be improved by number of techniques such as complexation, salt formation, solid dispersion, and by formulating into a dispersible tablet.

Fast dissolving tablets are formulated with an objective of improving disintegration and dissolution rate of the drug.

Orally disintegrating tablets (ODTs), also known as fast-disintegrating, fast-melt or fast dissolving tablets, are a

relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form into a solution or suspension in the mouth without the need for water. The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect.

Formulation of ODTs was originally developed to overcome swallowing difficulties of conventional solid oral dosage forms (tablets and capsules) experienced by wide range of patient population, especially children and elderly.

The disintegrants are usually added to the tablet formulations to promote the breakup of the tablet into fragments into an aqueous environment. The breakage of the tablet will convert it into small fragments. Those fragments will have bigger surface area and that will promote a more rapid release of drug substance and therefore drug absorption.[5,6]

Superdisintegrants

Use of disintegrants is the basic approach in the development of mouth dissolving tablets (MDTs). Disintegrants play a major role in the disintegration and dissolution of MDT. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates. Superdisintegrants provide quick disintegration due to the combined effect of swelling and water absorption by the formulation. Due to the swelling of superdisintegrants, the wetted surface of the carrier increases, which promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant.[7-9]

Many techniques have been reported for the formulation of fast dissolving tablets or orodispersible tablets such as:
- Freeze-drying or lyophilization
- Tablet molding
- Spray drying
- Sublimation
- Direct compression
- Cotton candy process
- Mass-extrusion.

Some of the patented technologies for formulation of MDTs are as follows:
- Zydis technology
- Durasolve technology
- Orasolve technology
- Flash dose technology
- Wow tab technology
- Flash tab technology
- Oraquick technology
- Quick-Dis technology
- Nanocrystal technology.

MATERIALS AND METHODS

Nicorandil was obtained as a gift sample from Macleods Pharmaceuticals Pvt. Ltd. and other chemicals were obtained from college source. All chemicals and reagents used were of analytical grade.

Preparation of fast dissolving tablets

Fast dissolving tablets of nicorandil were prepared using direct compression method incorporating superdisintegrants such as crospovidone (CP), croscarmellose sodium (CCS), and sodium starch glycolate (SSG). The nicorandil equivalent to 5 mg, mannitol and microcrystalline cellulose were mixed thoroughly in glass mortar using a pestle. Superdisintegrants were incorporated in the powder mixture according to each formulation in the tablets and finally aspartame and magnesium stearate were added. The whole mixture was passed through Sieve No. 60 twice. Tablets were prepared using 8 mm round flat-faced punch of the rotary tablet machine (Kambert Machinery). Compression force was constant for all formulations.[10]

Evaluation of tablet[11-14]

Pre-compression parameter

Angle of repose
Angle of repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is determined by using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured as angle of repose (θ) was calculated using the formula:

$$\theta = \tan^{-1}(h/r)$$

Bulk density
Apparent bulk density (P_b) was determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula:

$$P_b = M/V_b$$

Tapped density
The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (P_t) was calculated by using formula:

$$P_t = M/V_t$$

Compressibility index
The simplest way for measuring of free flow of powder was compressibility, an indication of the ease with which a material can be induced to flow was given by compressibility index:

$$I = (V_0 - V_t/V_0) \times 100$$

Where, V_0 is the bulk volume and V_t is tapped volume.

Hausner's ratio
Hausner's ratio was an indirect index of ease of powder flow. It was calculated by

Hausner ratio = P_t/P_d

Where, P_t is tapped density and P_d is bulk density lower Hausner's ratio (1.25).

Post-compression parameters[11,13,15]

All the batches of tablets were evaluated for various parameters such as weight variation, friability, hardness, drug content, disintegration, and dissolution and results reported in Table 3.

Uniformity of weight
This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random

Table 1: Formulation of nicorandil fast dissolving tablets

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicorandil	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose	25	25	25	25	25	25	25	25	25
CP	-	-	-	-	-	-	2	4	6
CCS	-	-	-	2	4	6	-	-	-
SSG	2	4	6	-	-	-	-	-	-
Polyvinyl pyrrolidone K30	3	3	3	3	3	3	3	3	3
Aspartame	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1
Mannitol (q.s.)	100	100	100	100	100	100	100	100	100

CP: Crospovidone, CCS: Croscarmellose sodium, SSG: Sodium starch glycolate

and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in Table 3 and none deviate by more than twice the percentage. The mean and standard deviation were determined.

Thickness
The thickness and diameter of the tablets was determined using a micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

Hardness test
The hardness of the tablet was determined using Monsanto Hardness tester.

Friability test
Six tablets from each batch were examined for friability using Roche Fribilator, and the equipment was run for 4 min at 25 revolutions per minute. The tablets were taken out, dedusted, and reweighted and % friability was calculated

Percent firability = Initial Weight – Final Weight/Initial weight × 100

Wetting time
A piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a small Petri dish (ID = 9 cm) containing 6 ml pH 6.8 phosphate buffer. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

In vitro disintegration time

Initially, the disintegration time for fast dissolving tablets was measured using the conventional test for tablets as described in the Pharmacopeia. Tablets were placed in the disintegration tubes and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time.

Table 2: Pre-compression parameters

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility (%)	Hausner ratio	Angle of repose (θ)
F1	0.478	0.522	8.42	1.09	26°
F2	0.502	0.554	9.39	1.10	27°
F3	0.486	0.526	7.61	1.08	25°
F4	0.430	0.508	12.35	1.18	31°
F5	0.482	0.528	10.71	1.10	26°
F6	0.465	0.516	9.88	1.11	32°
F7	0.442	0.502	11.95	1.14	30°
F8	0.445	0.516	11.01	1.05	27°
F9	0.405	0.526	11.06	1.04	28°

In vitro dissolution testing

Dissolution study was conducted for all the formulation using USP type-II apparatus (Electrolab TDT-08L). The dissolution test was performed using 900 ml of phosphate buffer (pH 6.8) was taken as the dissolution medium at 50 rpm and 37°C ± 0.5°C. About 10 ml of aliquots were periodically withdrawn, and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 260 nm.

Content uniformity test

About 20 tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 5 mg of Nicorandil was weighed and dissolved in 100 ml of pH 6.8 phosphate buffer. From the stock solution, 1 ml sample was withdrawn and diluted to 10 ml with pH 6.8 phosphate buffer, The absorbance was measured at wavelength 260 nm using double beam ultraviolet-visible spectrophotometer (IP, 2007).

Content uniformity was calculated using formula:

% Purity = 10C Absorbance of unknown (Au)/Absorbance of Standard (As)

Where, C - Concentration.

RESULT AND DISCUSSION

Nicorandil fast dissolving tablets were prepared by direct compression method using superdisintegrants such as CP, CCS, and SSG in varying concentrations such as 2%, 4%, and 6% as shown in Table 1. Angle of repose: Range from 25° to 32° show good flow. Bulk density and tapped density: Range from 0.430 to 0.50 (g/ml) and 0.51 to 0.55 (g/

ml), respectively. The values for compressibility index and Hausner ratio ranges from 7.61 to 12.35 and 1.08 to 1.14, respectively. The results for pre-compressed parameters are shown in Table 2.

Weight variation test range from 98.69 to 104.50 mg as per IP specification. Friability: Less than 0.59%, the results indicate that the percentage losses were not more than 1.0% (complies IP specifications). Thickness: Range from 2.30 to 2.58 mm; the results indicate that the tablets are suitable for packing. Content uniformity was found in between 98.92% and 103.16%. Hardness of the tablet was found to be between 5.33 and 6.0 kg/cm². The results indicate that the tablets are mechanically strong and are in limit. Disintegration time which was in-between 36.6 and 52.0 s, the results indicate that disintegration time of tablets is within 1 min. Wetting time: In between 37.66 and 58.00 s and water absorption ratio was found to be 83.69-109.34. The results of post-compression parameters are shown in Table 3. Dissolution study was carried out in 6.8 pH phosphate buffer for formulations F1, F2, F3, F4, F5, F6, F7, F8, and F9 from time 0 to 30 min, the results are shown in Table 4. Content uniformity was found in between 98.92% to 103.16% and % assay for optimized batch was found to be between 99.12% to 101.53% as shown in Table 5. Storage condition: Tablets were stored at 45°C ± 2°C/75% for a storage period of 0, 30, 60, and 90 days, Hardness was increased with time but in all cases, hardness was within the limit. Disintegration time: At various storage conditions increases but maximum 40 s which is <1 min (specification of IP). Dissolution studies shows there was no significant change in dissolution data of formulations at initial and after specified storage period.

CONCLUSION

Fast dissolving tablets of nicorandil can be successfully prepared by direct compression techniques using CP and CCS as an superdisintegrants for the better patient compliance and

Table 3: Post-compression parameters							
Formulation code	Diameter (mm) 6.35±0.2 mm	Thickness (mm) 2.45±0.3 mm	Hardness (kg/cm²) NLT 4.0 kg/cm²	Weight variation (mg) 100 mg±10%	Friability (%) NMT 1%	Disintegration time (s)	Wetting time (s)
F1	6.40	2.49	5.5	101.23	0.39	43.66	37.66
F2	6.45	2.42	6.0	104.50	0.42	40.66	40.66
F3	6.32	2.30	5.5	99.56	0.45	36.60	41.33
F4	6.39	2.34	5.5	98.69	0.56	47.33	45.33
F5	6.50	2.39	5.5	100.67	0.40	52.00	53.00
F6	6.52	2.56	6.0	101.89	0.59	51.33	47.67
F7	6.31	2.58	5.5	103.15	0.55	46.33	47.67
F8	6.25	2.57	5.3	100.12	0.45	50.33	57.67
F9	6.34	2.56	5.5	100.34	0.48	50.66	56.77

Diameter: NMT 6.55 mm and NLT 6.15 mm, Thickness: NMT 2.75 mm and NLT 2.15 mm, Hardness : NLT 4.0 kg/cm²,
Weight Variation: NMT 110 mg and NLT 90 mg, Friability: NMT 1%, Disintegration time: NMT 3 min, Wetting time: NMT 3 min

Time (min)	Cumulative percent nicorandil released formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	24.57	29.58	31.70	13.83	15.22	15.53	21.74	22.47	42.06
4	37.67	41.16	42.67	19.71	23.21	21.67	32.16	31.76	52.74
6	41.03	52.16	54.13	23.06	29.49	41.19	38.24	58.80	64.74
8	55.02	65.32	66.17	28.72	35.36	59.67	44.81	67.03	75.64
10	60.88	70.44	70.99	31.26	49.71	66.55	67.68	74.91	83.12
15	67.84	77.88	79.86	40.44	56.64	70.02	72.85	84.08	94.57
20	70.44	80.54	80.97	53.56	62.71	77.85	88.87	92.21	100.24
25	79.60	85.99	86.55	60.94	79.11	82.14	91.06	98.24	-
30	85.21	88.85	90.42	70.98	86.82	92.64	97.80	99.80	-

Table 4: *In vitro* drug release study for nicorandil fast dissolving tablets

Table 5: Results of content uniformity and cummulative % assay

Formulation code	Content uniformity	% Assay
F1	101.34	100.02
F2	100.59	99.56
F3	98.92	101.02
F4	99.96	99.12
F5	103.16	99.89
F6	102.87	101.53
F7	100.05	100.54
F8	100.21	100.52
F9	100.15	100.45

effective therapy. Nicorandil tablets containing CP show faster disintegration and dissolution rate and the relative efficiency of CP as an superdisintegrant was found to be better than CCS and SSG.

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