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Important Characterization of Nicorandil Buccal Tablets

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ABSTRACT

The controlled release gastroretentive drug delivery system which gives prolonged & continuous input of the drug to the upper parts of the gastrointestinal tract (GIT) and improves the bioavailability of medications that are characterized by narrow therapeutics window. The aim of this project was to formulate sustained delivery of buccal matrix tablet for Nicorandil by using natural polymers and semisynthetic polymers like polycarbophils and carbomers. Also objective of the work was to evaluate the impact of granulation on the release profile of the tablets by wet granulation and direct compression. In one of the articles, the behavior of the granules made using wet and dry granulation was described. In the present article, the most important characteristics of buccal matrix tablets like surface pH, swelling index, floating capacity, mucoadhesive strength and *ex vivo* permeation in two different skins were studied. From the important characterization studies, it was concluded that the some of the formulations made of wet granulation has met the required criteria for buccal matrix tablets and the *ex vivo* permeation was good in sheep buccal mucosa.

INTRODUCTION

The development of gastrointestinal bioadhesive drug delivery systems gastrointestinal retention of dosage forms through adhesion to the mucosa has been studied for over a decade now, mainly *in vitro* or *ex vivo* with few in situ or *in vivo* studies and even fewer trials in man. The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation, etc. It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the gastrointestinal tract (GIT) for a prolonged and predictable period of time exists today[1].

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. Although nicorandil is one of the emerging molecules in the case of hypertension and angina, successful treatment means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired.[2,3]. Nicorandil has a short half-life, and the usual oral dosage regimen is 5 to 40 mg taken 2 to 4 times a day. To reduce the frequency of administration and to improve patient compliance, once daily sustained release formulation of nicorandil is desirable. The drug is freely soluble in water, and hence judicious selection of release retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug.

MATERIALS AND METHODS

Experimental

Chemicals and Reagents

Nicorandil was procured from Taj Pharma Limited, Mumbai. The polymers were received as gift sample from different companies like Atlas Ind. Sidhpur for psyllium Husk, hakea gum from Green Earth Products Pvt. Ltd., New Delhi. All the other chemicals used were of standard grade.

IMPORTANT EVALUATION OF BUCCAL TABLETS

Surface pH

The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. The method

used to determine the surface pH of the formulation was similar to that used by Bottenberg et al[4]. A combined glass electrode was used for the purpose. The tablets were allowed to swell by keeping them in contact with 1 mL of distilled water for 2 hrs and pH was noted by bringing the electrode in contact with the surface of tablet and allowing it to equilibrate for 1 min.

Swelling index

Swelling is a vital factor to ensure floating. To obtain floating, the balance between the swelling and water must be reported.

This test was carried out by using Petri dishes having 10 ml of phosphate buffer of pH 6.8 and tablet was placed in Petri dish. The initial weights of the drug loaded tablets in each batch were determined (W0) using an electronic balance. Tablets from each batch were removed at different time intervals (1, 2, 3, 4, 6 and 8 hrs), wiped with filter paper to remove excess water from the tablet surface, and then reweighed (W1). The swelling index (% w/w) was determined from the following relationship and plotted against time[5].

The experiment was performed in triplicate. (Eq.1)

$$\text{Swelling index} = \left[\frac{W_1 - W_0}{W_0}\right] \times 100$$

Mucoadhesive Strength

The mucoadhesive strength of prepared buccal tablet was studied using sheep buccal mucosa and the mucoadhesive parameters are represented in Table 4.

Mucoadhesive strength of the tablet was measured on a modified physical balance employing the method as described by Gupta et al[6] using sheep buccal mucosa as model mucosal membrane.

The force of adhesion was calculated as;

Force of Adhesion (N) = Mucoadhesive strength × 9.8 / 1000

Floating Capacity

Three individual tablets from each formulation were put in an individual flask containing 900 ml of 0.1N HCl solutions. Then note time in minutes for each tablet to go from the bottom to the top

of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated[7].

***In vitro* residence time**

A buccal tablet was pressed over the excised goat buccal mucosa for 30 sec after previously being secured on a glass slide and was immersed in a beaker containing 500 ml of pH 6.8 isotonic phosphate buffer, at 37±0.2°C. One stirrer was fitted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time for complete erosion or detachment of the tablet from the mucosa was recorded[8].

***Ex vivo* permeation study by Franz-diffusion apparatus[9] using two animal skin membranes**

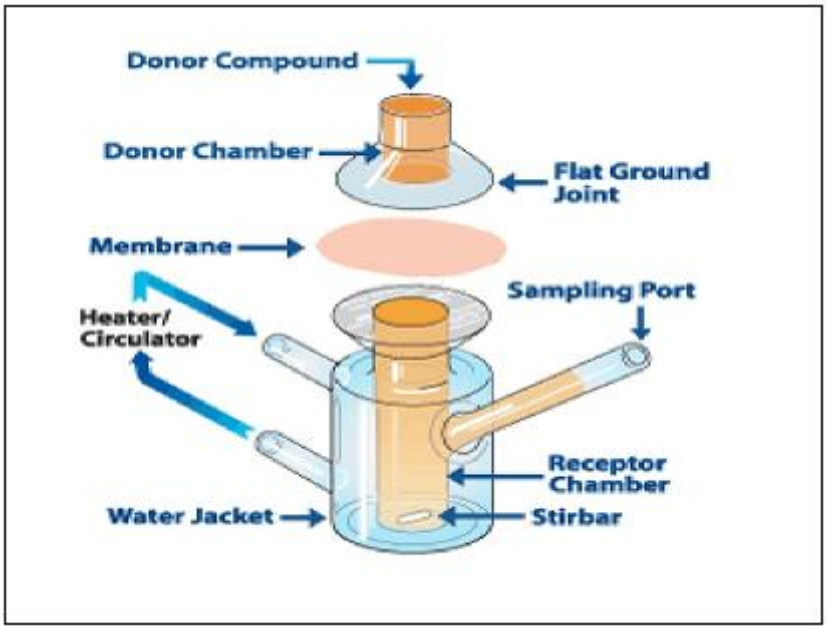

Figure. 1. *Ex vivo* permeation study by Franz-diffusion apparatus

The fresh goat buccal mucosal membrane was obtained from slaughter house. It was then excised by removing the underlying connective and adipose tissue and was equilibrated at 37 ± 1.0^{o} C for 30 min in pH 6.8 isotonic phosphate buffer. The buccal epithelium was carefully mounted in between the two compartments of Franz Diffusion Cell. Tablets were stuck to the mucosa in the donor side containing pH 6.8 phosphate buffer. Receiver medium was 20 ml of pH 6.8 phosphate buffer maintained at 37±0.5^{o} C under gentle stirring. From the receiver compartment, 5 ml aliquots were collected at predetermined time intervals and replaced by an

amount of fresh buffer. The samples removed were filtered, diluted and analyzed at λ_{max} value of 272 nm. The schematic representation of Franz diffusion apparatus was displayed in the Figure 1. Only 4 optimized formulations were selected [NWTF6, NWTF4, NWTF2 and NWTF8] for understanding the *ex vivo* permeation behavior through fresh goat skin.

RESULTS AND DISCUSSION

Surface pH

Surface pH of all formulations was found to be in the range of 5.3 to 6.5 as shown in. Hence it is assumed that these formulations do not cause any irritation in the oral cavity.

Swelling index

The formulation made using wet granulation took about 8 hrs to complete swell about 80% as compared to the formulation prepared by direct compression that took 4-5 hrs to swell about 80%. Swelling index is calculated with respect to time.

The probable reason for difference in the swelling index is because of the psyllium husk/Hakea gum is a natural agent took more time to hydrate as compared to synthetic agent like Carbomer and polycarbophil.

The swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of the polymer. The outermost hydrophilic polymer layer hydrates/swells first and as the hydrated layer progressively dissolves or disperse, the hydration swelling process will continuous towards new expose surfaces thus maintaining the integrity of dosage form. Refer the table 1 and 2 for swelling index behavior.

Mucoadhesive Strength

Mucoadhesion is considered to occur in four major stages wetting, interpenetration, adsorption and formation of secondary chemical bonds between mucus membrane and polymers. The mucoadhesive strength is affected by molecular weight of polymer, contact time with membrane and degree of swelling of the polymer. Refer the table 3 and 4 for Mucoadhesive strength results.

Floating Capacity

The fasted state is associated with various cyclic movement commonly referred as migrating motor complex (MMC). The third phase of MMC (burst phase) is characterized by the large, intense and regular contraction termed as housekeeper waves that swept out the particulate matter (undigested food particles) from the stomach and lasts to 10 to 20 minutes. To prevent the formulation from the effect of this phase, tablet should be float as fast as possible after reaching in the stomach. In similar way floating duration is important in case of once daily formulation to obtain the continuous and constant drug release up to the 24 hrs. If physical integrity of the formulation is not maintained, the tablet could break down in to the small fragments and escape from the upper part of GIT.

In fact, buoyancy of the tablet is governed by both the swelling the outer surface of the tablets when it comes in the contact with the gastric fluids and the presence of the internal void (Porosity) in the dry centre of the tablet. These two factors are essential for the tablet to acquire bulk density less than that of the gastric fluid i.e. 1.04 gm/cm3 that helps it to remain buoyant on gastric fluids.

Compression force of these tablets to high degree hardness may result in reduction of porosity of the tablet and moreover, the compressed hydrocolloids particle on the surface of the tablet fail to hydrate rapidly when it come in contact with the gastric fluid and as a result, the capability of the tablets to float is significantly reduced. Refer the table 5 and 6 for Floating capacity results.

***In vitro* residence time**

The *in vitro* residence time is one of the most important physical parameters of buccal tablet. The *in vitro* residence time is the time necessary for complete detachment or erosion of tablet from mucosal surface without losing integrity. This test reflects the adhesive capacity of polymer used in formulation. All the formulations showed residence time of 200 to 450 minutes. Only the wet granulation based tablets were evaluated for *in vitro* residence time. As all the polymers used were hydrogel forming hydrophilic matrix and get swelled to adhere to the mucus surface and hence *in vitro* residence time directly relates to the swelling index. Refer the table 7 for *in vitro* residence timing results.

***Ex vivo* permeation**

The 4 optimized formulations of wet granulation based like NWTF6, NWTF4, NWTF2 and NWTF8 showed good mucoadhesive strength, *In vitro* residence time, swelling index as well as promising drug release pattern. On the basis of above results, all formulations were studied for *ex vivo* drug permeation using sheep buccal mucosa. The buccal mucosa of sheep resembles that of humans in terms of structure and composition and therefore sheep buccal mucosa was selected for drug permeation studies. The optimized formulation was analyzed by HPLC method at 262 nm till 10 hrs release through sheep buccal mucosa.

CONCLUSION

The buccal delivery tablets of nicorandil could be prepared using the above mentioned polymers however the most important factor observed is the impact of granulation. The tablets made using wet granulation has required behavior when compared to the tablets made using direct compression technique. Also the incorporation of hydrophobic polymer in the hydrophilic polymers is helping to control the rate of release which is very much essential for prolonged release profile.

REFERENCES

1. Garg, R. and Gupta G.D., Progress in controlled gastroretentive delivery systems. Trop J Pharm Res., 7(3): 1055- 1066. 2008.
2. Leonetti G, Fruscio M, Gradnik R, Chianca R, Bolla GB, Prandi P, Zanchetti A. Nicorandil, a new vasodilator drug, in patients with essential hypertension. J Hypertens. 1989;7:S292-S293.
3. Camm AJ, Maltz MB. A controlled single-dose study of the efficacy, dose response and duration of action of nicorandil in angina pectoris. Am J Cardiol. 1989; 20(63):61J-65J.
4. Bottenberg P., Cleymaet R., Muynek C.D.,Remon J.P., Coomans D., Michotte Y., and Slop P., Development and testing of bioadhesive fluoride containing slow release tablets for oral use, J. Pharm. Pharmacol.,1991, 43, 457-464
5. Tamilvanan D, Bangale GS, Ananthi JJ, Sivakumar V, Vinothapooshan G, Palanivelu M, and Viswanathan MB, "Carvedilol-loaded mucoadhesive buccal tablets: Influence of various mucoadhesive polymers on drug release behavior." PDA Journal of Pharmaceutical Science and Technology. 2009; 63(3): 196 – 206.
6. Gupta A, Garg S, Khar RK, Measurement of bioadhesive strength of mucoadhesive buccal tablets: Design of an in vitro assembly. Indian Drugs., 1993; 30: 152155.
7. Rahman Z, Khar RK. Design and Evaluation of Bilayer FloatingTablets of Captopril. ActaPharma 2006; 56:49-57.
8. John AS, Sathesh BPR, Divakar G, Jangid MK and Purohit KK. Development and evaluation of mucoadhesive drug delivery system for Atorvastatin calcium. Journal of Current Pharmaceutical Research. 2010; 1: 31-38.
9. Gavaskar B, Venkateswarlu E, Kumaraswamy D, Dooda D and Nagaraju M.Formulation and evaluation of mucoadhesive tablets of baclofen. International Journal of Pharmacy & Technology. 2010; 2(2): 396-409.

TABLES

Table: 1: Wet granulation based Swelling Index

Sl. No.	Formulation Codes	FORMULATION CODES							
		1 Hr	2 Hr	3 Hr	4 Hr	5 Hr	6 Hr	7 Hr	8 Hr
1	NWTF1	39.56	49.86	58.63	65.41	72.56	77.05	83.11	83.56
2	NWTF2	30.12	40.26	49.11	56.14	63.00	69.12	73.11	79.30
3	NWTF3	36.15	47.26	56.85	64.23	70.34	75.18	80.89	85.96
4	NWTF4	29.74	39.56	48.52	56.36	63.09	69.26	75.18	77.23
5	NWTF5	34.52	43.25	51.28	57.18	63.69	68.48	69.82	71.25
6	NWTF6	26.58	37.15	46.58	54.86	61.75	67.85	73.25	74.52
7	NWTF7	41.89	51.28	58.47	67.85	72.58	79.60	83.96	84.05
8	NWTF8	32.15	43.23	51.14	57.25	62.04	70.25	74.25	80.14

Table: 2: Direct compression based Swelling Index

Sl. No.	Formulation Codes	FORMULATION CODES			
		1 Hr	2 Hr	3 Hr	4 Hr
1	NDTF1	46.86	63.13	74.09	84.55
2	NDTF2	48.91	64.14	76.05	84.56
3	NDTF3	42.15	56.18	67.38	70.25
4	NDTF4	52.13	68.95	80.60	85.05

Table: 3: Wet granulation based Mucoadhesive Index

Sl. No.	Formulation Codes	Mucoadhesive Strength [g]	Force of adhesion [N]
1	NWTF1	20.12 ± 0.062	1.789± 0.002
2	NWTF2	26.12 ± 0.058	2.509± 0.008
3	NWTF3	20.84 ± 0.065	1.892± 0.009
4	NWTF4	25.28 ± 0.048	2.529± 0.001
5	NWTF5	21.98 ± 0.061	2.158± 0.008
6	NWTF6	25.94 ± 0.039	2.689± 0.004
7	NWTF7	19.98 ± 0.078	1.709± 0.008
8	NWTF8	23.89 ± 0.069	2.356± 0.002

Table: 4: Direct compression based Mucoadhesive Index

Sl. No.	Formulation Codes	Mucoadhesive Strength [g]	Force of adhesion [N]
1	NDTF1	19.25 ± 0.062	1.769 ± 0.002
2	NDTF2	19.68 ± 0.069	1.749 ± 0.008
3	NDTF3	20.54 ± 0.054	1.792 ± 0.007
4	NDTF4	19.05 ± 0.044	1.698 ± 0.003

Table: 5: Wet granulation based Floating Capacity

Sl. No.	Formulation Codes	Floating Lag time
1	NWTF1	9 minutes
2	NWTF2	10 minutes
3	NWTF3	8 minutes
4	NWTF4	9 minutes
5	NWTF5	7 minutes
6	NWTF6	8 minutes
7	NWTF7	14 minutes
8	NWTF8	12 minutes

Table: 6: Direct Compression Based Floating Capacity

Sl. No.	Formulation Codes	Floating Lag time
1	NDTF1	13 minutes
2	NDTF2	16 minutes
3	NDTF3	10 minutes
4	NDTF4	11 minutes

Table: 7: Wet granulation based Invitro residence time

Sl. No.	Formulation Codes	Invitro Residence Time
1	NWTF1	420 minutes
2	NWTF2	255 minutes
3	NWTF3	380 minutes
4	NWTF4	220 minutes
5	NWTF5	340 minutes
6	NWTF6	200 minutes
7	NWTF7	450 minutes
8	NWTF8	280 minutes

Table: 8: Percentage Drug Permeation Details of Optimized Formulation.

Sl. No.	Formulation Codes	% Drug Permeated			
	Time Point	NWTF6	NWTF4	NWTF2	NWTF8
1	0 - 2nd Hour	11	8.5	6	5
2	3 - 5th Hour	19	15	13	12
3	6 - 8th Hour	34	31	29	25
4	9 - 10th Hour	41	37	34	31

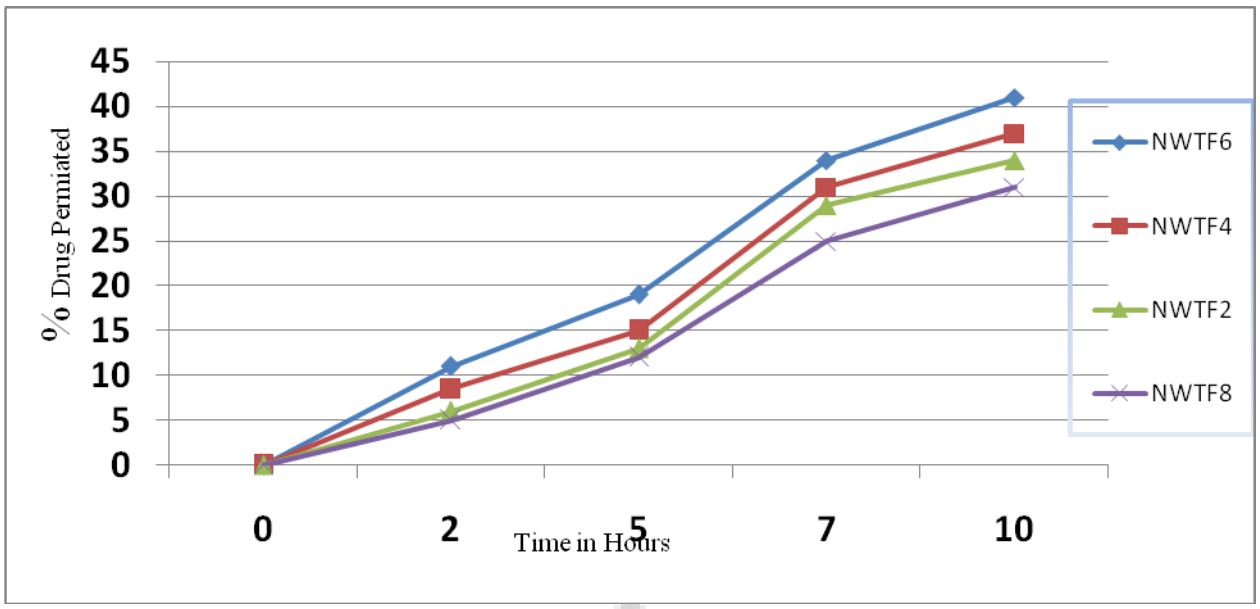

Figure 1: Graphical representation of % drug permeation across sheep mucosa