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Research Article

Design and *in vitro* evaluation of mucoadhesive drug delivery of Nateglinide

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ABSTRACT

The aim of the present work was to design and evaluate mucoadhesive drug delivery system of nateglinide. The novel mucoadhesive tablets were involves the three preparation process may include adhesive cups, core material and tablets. FTIR and DSC analysis is performed for drug-polymer interaction studies there is no interaction between drug and polymers. Nateglinide core material in adhesive cups are influenced by the many number of physical and chemical parameters. Adhesive cup formulations MAC2, MAC4, MAC8, MAC9 and MAC10 that showed superior qualities in the adhesive strengths and hence they were selected for further studies. Drug release from various mucoadhesive tablets was slow and prolong the release rate up to 12 hr and depended on composition, polymers ratio with drug.

Keywords: Mucoadhesive strength; kinetic models; swelling index; diffusion coefficient.

INTRODUCTION

Nateglinide was utilized as a model drug for the mucoadhesive drug delivery system, as it shows the good absorption through oral route. The polymers are having the ability to interaction with mucus in oral cavity. Mostly oral route for drug delivery is preferred than all other routes (Patel VF *et al.,* 2011). The preparation and utilization of mucoadhesive polymer has been accepted as a promised strategy for prolonging resident time and to improve the specific localization of drug delivery systems (Jain NK *et al.,* 1997). The drug release pattern of the drug in mucosal membrane in a controlled release manner to achieve in a therapeutic response (Kaelbe DH *et al.,* 1977). It is also focused on the selection of bioadhesive polymers and its activity in various combinations and ratios.

MATERIALS & METHODS

Nateglinide was obtained as a gift sample from Yarrow Chemical Private limited, Mumbai, India. carboxy methyl cellulose sodium. Hydroxy ethyl cellulose were obtained from SD Fine Chemical Ltd., Carbopol, Hydroxy propyl methyl cellulose (K15), Sodium alginate, Microcrystalline cellulose were obtained from Merck India Pvt Ltd. All other chemicals were of analytical grade purchased from local suppliers.

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Drug-Polymer Compatibility studies

FT-IR Spectra

In this research, FTIR study (Singh B et al., 2002) was performed for the Drug, polymers and drug and polymer mixture characteristic peaks were shown from figure 1 to figure 4.

DSC

The selective drug, polymer and optimized formulation thermal peaks were reported from figure 5 to figure 8 and in which thermal peaks indicate as melting point of the selective material.

Preparation of Mucoadhesive cups

Tablet Rotary Press is the mechanical device having a multiple punches on which a lots of tooling upper punches and dies. The lower and upper punch come close together to compress the granule material. The die volume and compression force was so adjusted in the rotary press tablet machine was designed by MAC1-MAC20.

The Granules were compressed by using a 10 station rotary tablet top mini press with a specially designed fabricated projected upper punch of having dimensions, 4.4 mm outer diameter and 2.8 mm inner diameter. The die volume and compression force was so adjusted to get thickness (1.2 mm) and hardness (4 kg/cm^2) for all the batches. (MAC1-MAC20).

Nateglinide core Material

The core Material was prepared by direct compression method. (Kulkarni RV *et al.,* 2014) Accurately weighed

Table 1: Fabrication of Nateglinide core Material

Code	Mucoadhesive Polymer (%)						MCC	Talc
	Nateglinide	Carbopol	HEC	CMCS	HPMCK15	Sod.Alg		
CL1	60	05	-	-	-	-	18.5	1.5
CL2	60	10	-	-	-	-	13.5	1.5
CL3	60	15	-	-	-	-	8.5	1.5
CL4	60	20	-	-	-	-	3.5	1.5
HE1	60	-	05	-	-	-	18.5	1.5
HE2	60	-	10	-	-	-	13.5	1.5
HE3	60	-	15	-	-	-	8.5	1.5
HE4	60	-	20	-	-	-	3.5	1.5
CS1	60	-	-	05	-	-	18.5	1.5
CS2	60	-	-	10	-	-	13.5	1.5
CS3	60	-	-	15	-	-	8.5	1.5
CS4	60	-	-	20	-	-	3.5	1.5
HK1	60	-	-	-	05	-	18.5	1.5
HK2	60	-	-	-	10	-	13.5	1.5
HK3	60	-	-	-	15	-	8.5	1.5
HK4	60	-	-	-	20	-	3.5	1.5
SA1	60	-	-	-	-	10	18.5	1.5
SA2	60	-	-	-	-	15	13.5	1.5
SA3	60	-	-	-	-	20	8.5	1.5
SA4	60	-	-	-	-	25	3.5	1.5

All ingredients were taken in mg

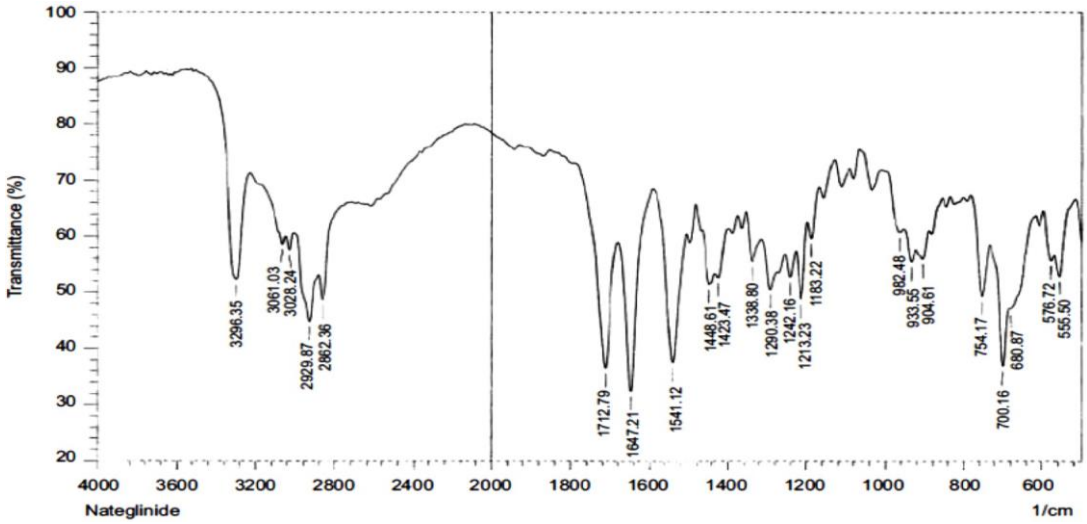

Figure 1: FTIR spectrum of Nateglinide

quantity of Nateglinide, microcrystalline cellulose, carbopol, HEC, and purified talc. Weigh accurately 30 mg of the excipients along with drug placed in a die cavity by applying compression force to lower & upper punch to get tablets. Different formulation ration of core material as shown in the Table 1.

Nateglinide core material used in mucoadhesive cups

The core material was compressed in the form of tablet placed in a respective cups. The formulation of mucoadhesive (Singh MK *et al*., 2011) Nateglinide tablets were coded as NMT1 to NMT20 depends on efficiency of mucoadhesive polymer cups.

Evaluation of mucoadhesive tablets

For all formulation were evaluated the following parameters respectively as follows

Evaluation of mucoadhesive cups

Swelling studies

Gravimetric method for measuring the swelling studies of adhesive cups. The mucoadhesive cups was placed in agar gel in a Petri dish kept in a incubator to maintain the temperature 37^{o}C and observe the swelling in time intervals of 1hr, 2hr, 3hr, 4hr, 5hr & 6 hr. (Cavalcanti O *et al.,* 2005). The swelling Index can be calculated by given below equation.

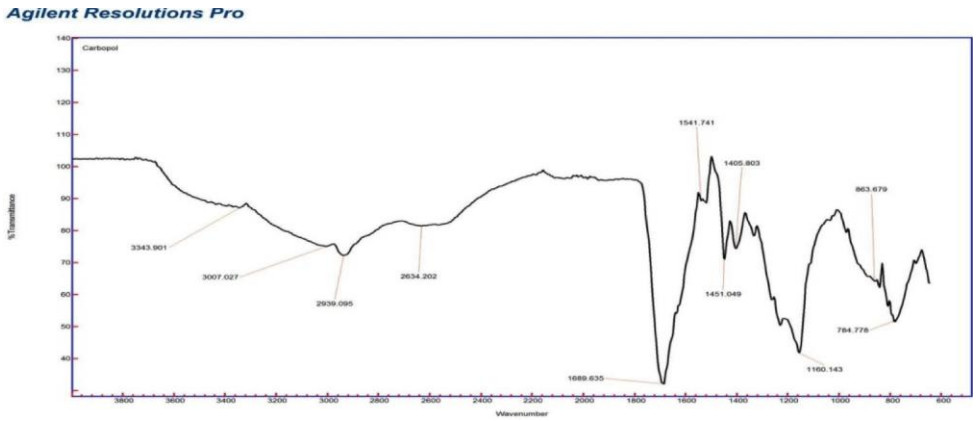

Figure 2: FTIR spectrum of Carbopol

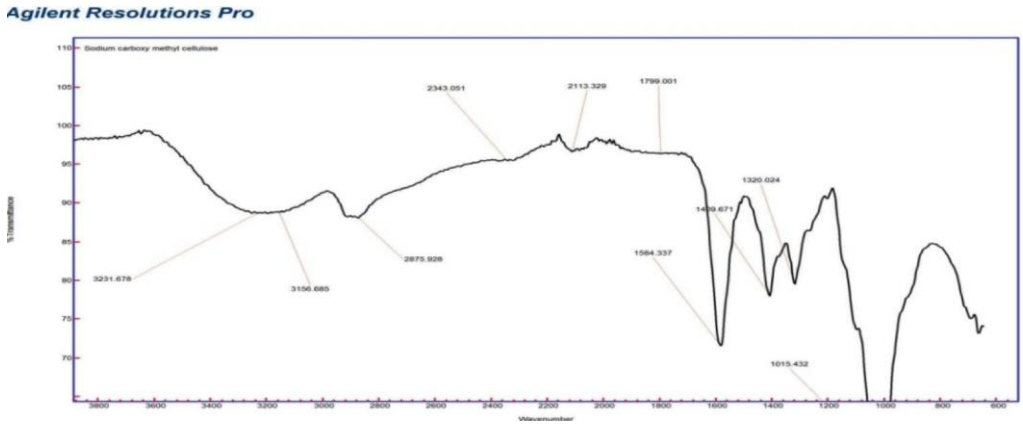

Figure 3: FTIR spectrum of Carboxy Methyl Cellulose Sodium

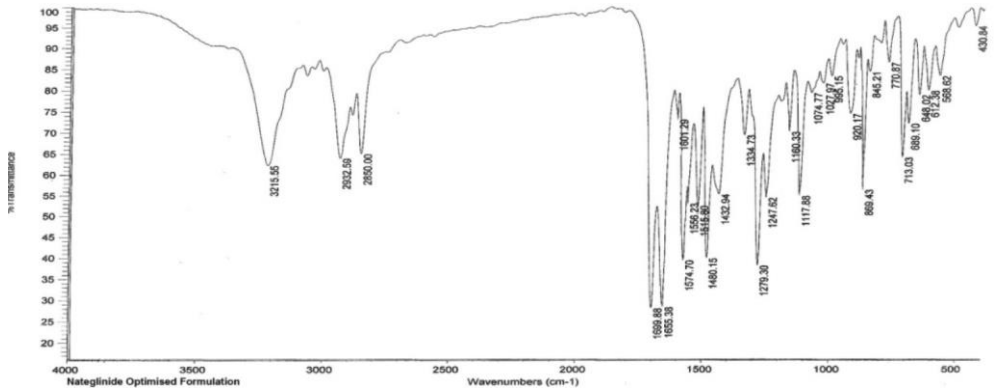

Figure 4: FTIR spectrum of drug and polymer mixture

$$Index\ of\ swelling\ (S.I) = \left[\frac{(W_2 - W_1)}{W_1}\right] \times 100$$

Where

W1= Actually weight of mucoadhesive cups

W2= After swelling of mucoadhesive cups

Mucoadhesive strength

The mucoadhesive strength of the tablets was measured on a modified two arm physical balance. The sheep gastric mucosa was used as biological membrane for the studies. The membrane was washed with distilled water and then with pH 6.8 at 37°C. The sheep gastric mucosa was cut into pieces and washed with buffer pH 6.8 the left pan of physical balance was removed. To the left arm of balance a thick thread of sutiable length was hung. To the free end of thread attach a glass stopper of circular base. A clean 250 ml beaker was placed below the glass stopper. (Nayak RK et al., 2011) A piece of gastric mucoasa was tied to the glass vial which was fitted with buffer pH 6.8 buffer. The Mucoadhesive cups was suck to the lower side of a rubber stopper. The two sides of the balance were made equal before the study. By keeping a 5gm was removed from the right hand pan which lowered the pan along with the cup over the mucosa. The mucoadhesive strength was assessed in terms of weight (gm) required to detach the cup from the membrane. The following formula was used and the results as shown in figure 11 & 12.

$$\text{Force of adhesion(n)} = \text{mucoadhesive strength}/100\ \text{X}9.81$$

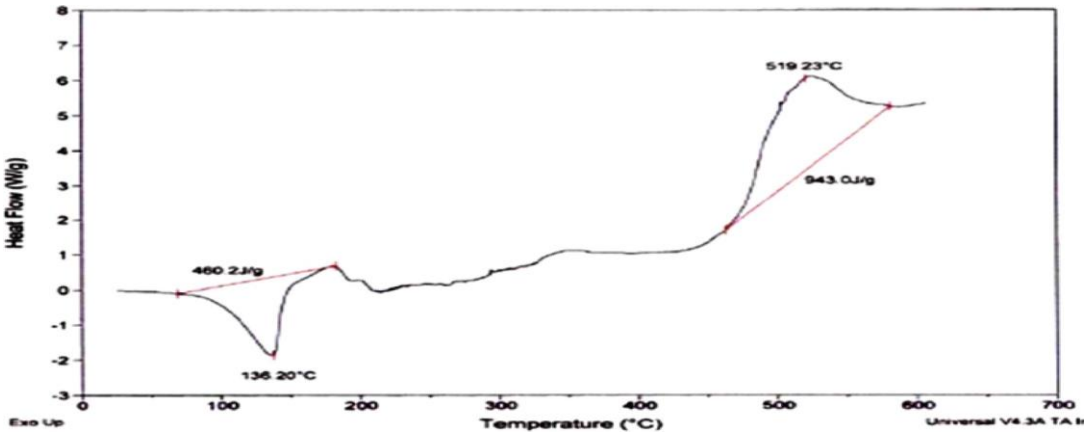

Figure 5: DSC thermogram of Nateglinide

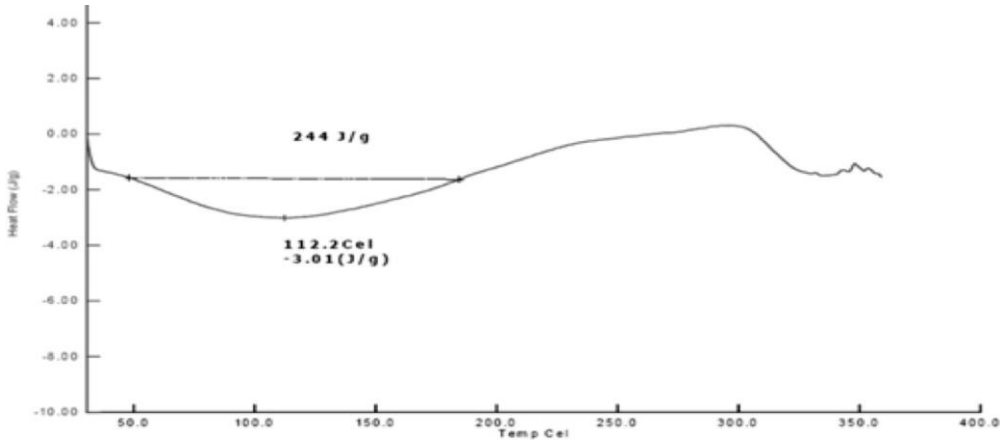

Figure 6: DSC Thermogram of HPMCK15

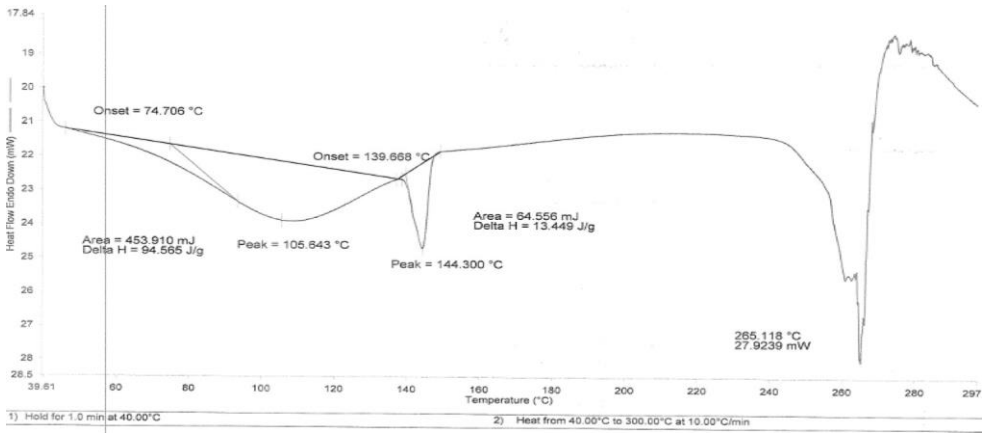

Figure 7: DSC Thermograms of drug-polymer mixture

***In-vitro* mucoadhesive strengths**

This is determined by measuring the following parameters.

Shear strength

The backside of mucoadhesive cup was attached to a movable plastic strip having a synthetic adhesive. On the other hand side cup containing mucosa for 30 sec by applying constant pressure. (Basani G *et al.,* 2010) How much amount of force is required to detach the adhesive cup parallelly from mucosa was recorded.

Peel strength

The experiment was conducted similarly to determine the detachment force required to remove the adhesive cup tangentially from mucosal membrane (Gazzi S *et al.,* 2009).

Tensile strength

This method is based on the measurement of the strength required to detach from adhesive cup in a mucosal membrane (Bhanja S *et al.,* 2010).

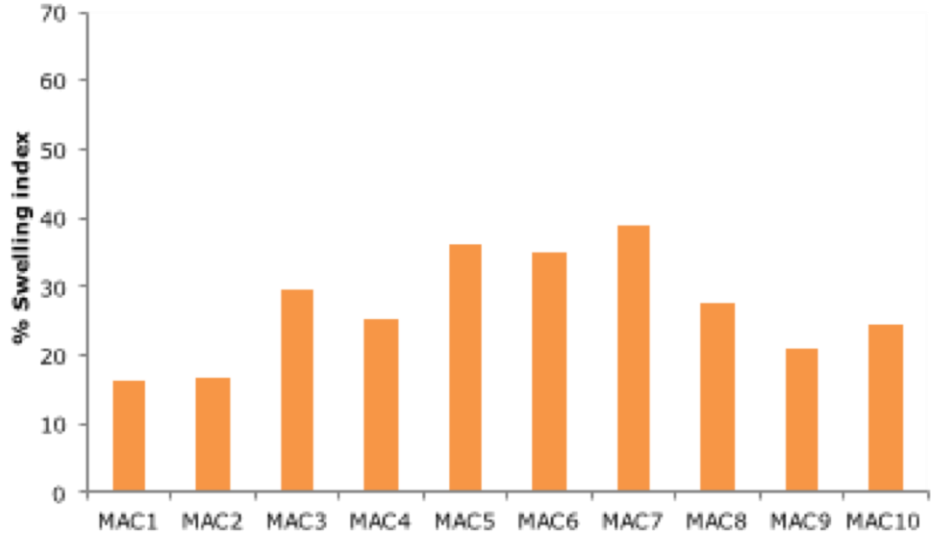

Figure 8: Swelling percentage of mucoadhesive cups (MAC1-MAC10)

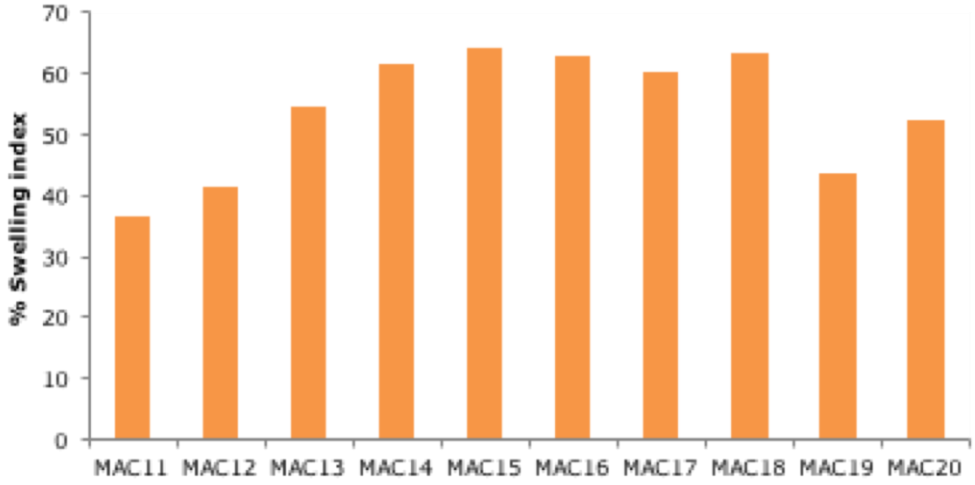

Figure 9: Swelling percentage of mucoadhesive cups (MAC11-MAC20)

***In-vitro* residence time**

The mucoadhesive cups was performed by disintegration apparatus. In this apparatus containing 700 ml of phosphate buffer pH 6.8 to maintained temperature at 37°C. The sheep mucosa was placed on the surface of a glass portion, perpendicularly attached to the apparatus (Umarji B *et al.,* 2012). The surface of one side cup was placed with 0.5 ml of phosphate buffer, after few minutes moist surface contact with the mucosal surface membrane. The time taken for completing detachment of the cup from the surface of mucosa was recorded.

Evaluation of mucoadhesive tablets

Thickness

From the prepared formulation, selected 3 tablets randomly and thickness was measured with Vernier calipers.

Uniformity of Weight

It is desirable that every individual tablet in a batch should be uniform in weight, but a small variation in the weight of the individual table is liable to occur. weight 20 tablets selected at random and determine their average weight. Not more than 2 of the individual weights may deviate from the average weight by more than the percentage deviation and none should deviate by more than twice that percentage.

Hardness

The prepared Nateglinide Tablet hardness was determined by using Monsanto apparatus to test the hardness of a tablet. It has a graduated scale which gives the reading in Kg/cm^2.

Friability

Friability test performed to evaluate the ability of the tablet to withstand wear and tear in packing, handling and transporting. Twenty tablets are weighed and placed in the plastic chamber. The chamber revolves at a speed of 25 rpm. During each revolution the tablet falls from a distance of 6 inch. The tablets are removed from the chamber after 100 revolutions and

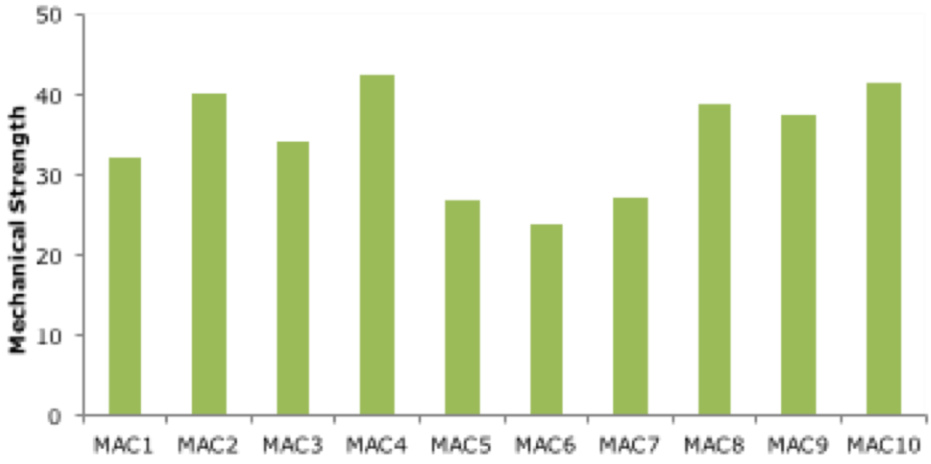

Figure 10: Mucoadhesive strength of mucoadhesive cups (MAC1-MAC10)

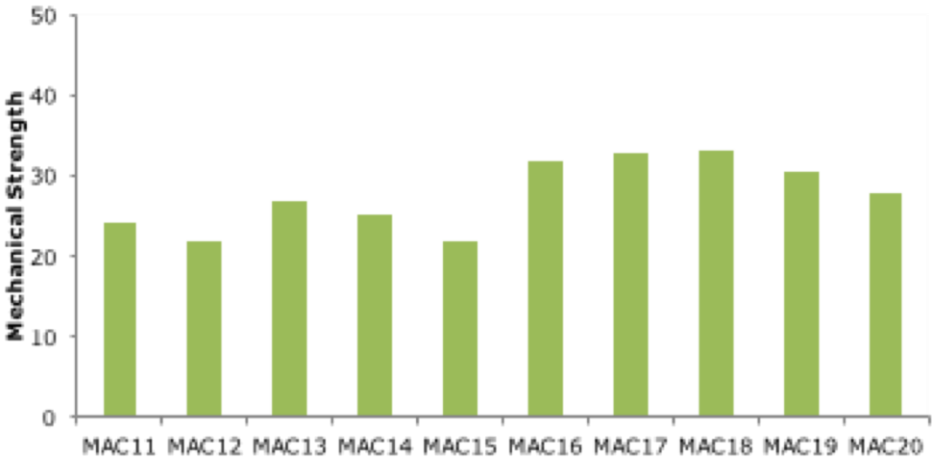

Figure 11: Mucoadhesive strength of mucoadhesive cups (MAC11-MAC20)

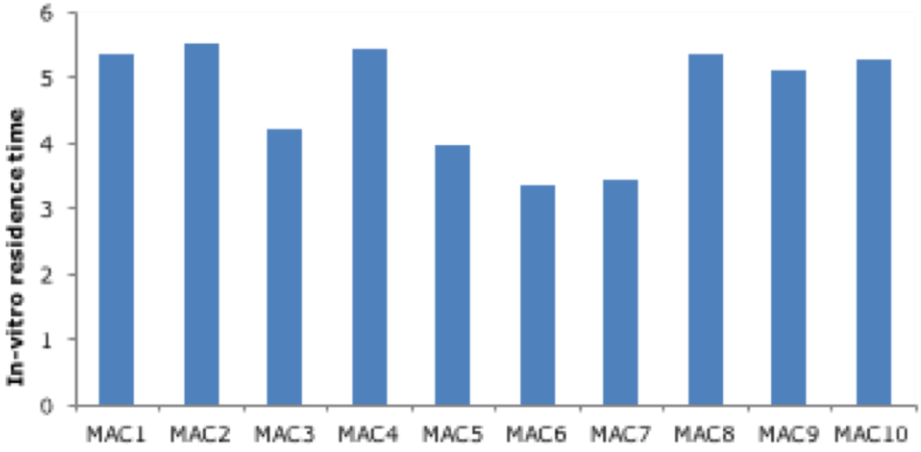

Figure 12: In-vitro residence time of mucoadhesive cups (MAC1-MAC10)

weighed. Loss in weight indicates the friability. The tablets are considered to be of good quality if the loss in weight is less than 0.8%.

***In-vitro* drug release studies**

In dissolution apparatus tablets were taken in a basket immersed in 900 ml of pH 6.8 medium to maintain temperature of 37±0.5^{0}C, with 50 rpm. The tablets were placed in basket immersed in 900 ml of medium of pH 6.8 which serves as a medium for dissolution. The Dissolution studies were performed in three Time ranging from. Take 5 ml sample was taken at every 1 hour interval up to 12 hr. At the time intervals withdrawal of sample freshly prepared sample 5ml was replaced into the medium. These samples containing any dust particles were filtered and diluted with the buffer. The drug release was seen in the UV-Visible spectrophotometer. (Karavana SY et al., 2009).

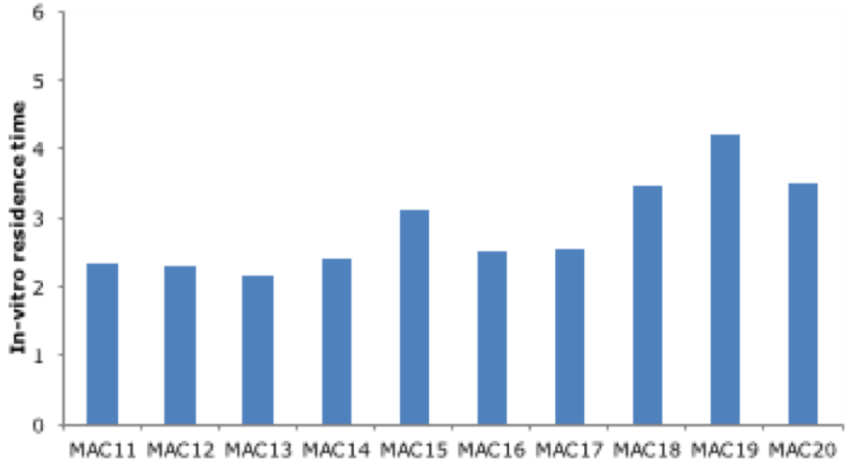

Figure 13: In-vitro residence time of mucoadhesive cups (MAC11-MAC20)

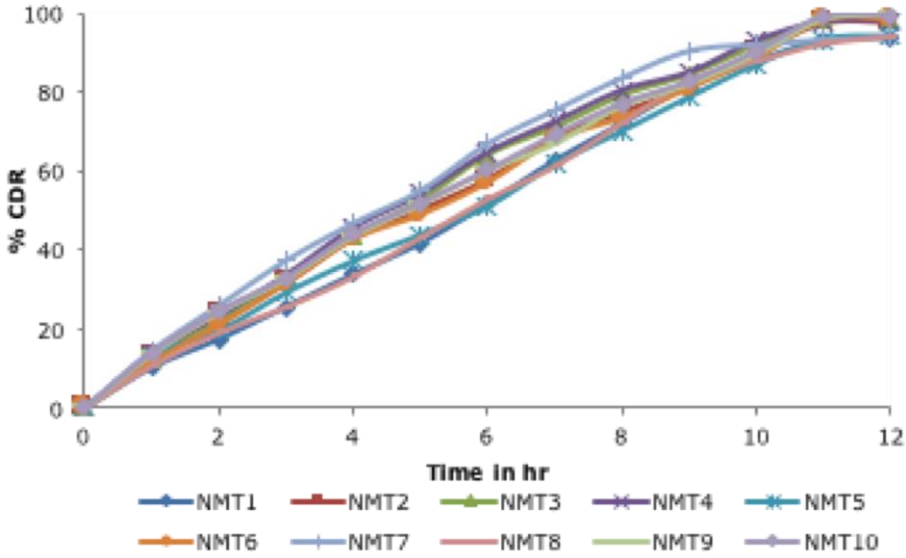

Figure 14: In-vitro drug release profile of NMT1 - NMT10

RESULTS AND DISCUSSION

Compatibility Studies by FTIR

In the IR spectral analysis of Nateglinide exhibits characteristic peaks at 1712 (C=O), 3061 (CH Stretching) 3299 (NH), 1448, 1647 (Aromatic CH Str) and physical mixture of Nateglinide and their admixture with polymers the characteristic absorption peaks at 3215 (CH-S), 1699 & 1655 (C=O), 1574 (CH Stretching Aromatic) were recorded by FT-IR spectrometer is shown from Figure 1 to 4. Differential Scanning Colorimetry thermograms were reported from figure 5 to figure 7. Thermal peaks were observed at respective peak areas which describes compatibility between drug and polymer.

Evaluation of mucoadhesive cups

Swelling studies

The higher swelling index may be due to the presence of water soluble polymers in the formulation. The swelling studies at 6 hrs shows the higher rate, followed by eroding of polymer in the medium. The results of swelling studies at different time intervals were graphically represented in figures 8 & 9.

Mucoadhesive strength

The Tensile strengths of the prepared mucoadhesive cups and evaluate their mucoadhesiveness. sheep mucosa was used as a substrate to measure the mucoadhesive strength. The bond strength as showed in the adhesive cups was formulated with carbopol, sodium alginate slightly shows the other polymers. The formulation codes of MAC2, MAC4, MAC8, MAC9, MAC10 showed better mucoadhesive strength compared with other formulations were shown in figures 10&11. Adhesive cup formulations MAC2, MAC4, MAC8, MAC9, MAC10 that showed superior qualities in the adhesive strengths were selected for further studies.

In-vitro residence time

The formulated mucoadhesive cups were performed by In-vitro residence time by using sheep mucosa. Residence time means specific time for complete removal or erosion from the cup through mucosal surface without

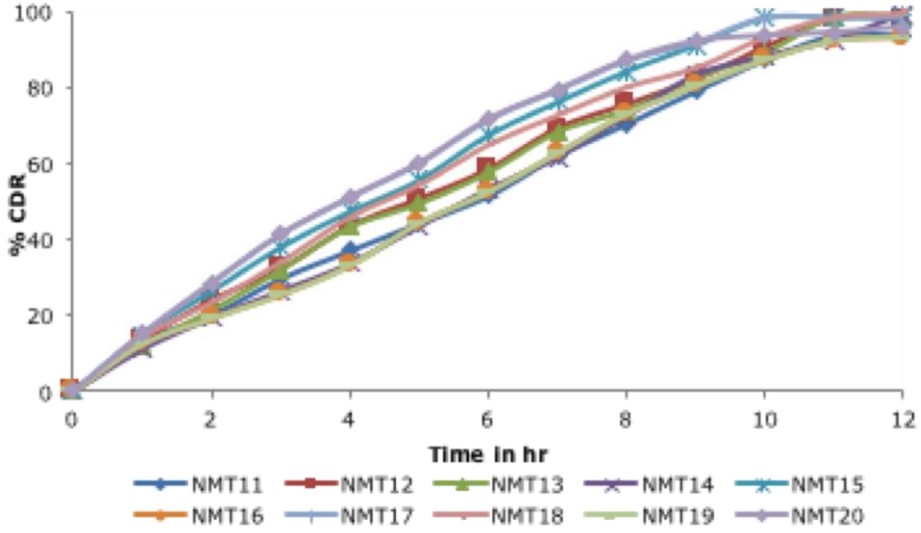

Figure 15: In-vitro drug release profile of NMT11 - NMT20

the loss of integrity. All Adhesive cups the residence time of 2.16 to 5.50 hr. The MAC2, MAC4, MAC8, MAC9, MAC10 exhibited maximum residence time in figure 12.

Evaluation of Nateglinide mucoadhesive tablets

It represents the results of various evaluation parameters adopted for the evaluation of physicochemical properties of mucoadhesive Nateglinide tablets. The ranges of tablets uniformity of weight between 29.8 to 30.8 mg. Studying of evaluation parameters like Uniformity of weight suggests the individual tablet in a batch should be uniform in weight, but small variation in the weight of the individual tablet may occur. Results such as physical parameters little variation is allowed in the weight of a tablets by the pharmacopoeia.

***In-vitro* dissolution studies**

The dissolution studies containing dissolution medium pH 6.8 and the obtained results were presented figure 14 & 15. The Hydroxy propyl cellulose K15, carbopol, carboxy methyl cellulose sodium, hydroxy ethyl cellulose, sodium alginate is a hydrophilic nature it can easily swell. Among all these formulations, NMT9 was shows the highest percentage release of drug. The *In-vitro* dissolution st udies was correlated with release order kinetics performed by zero order, first order, Higuchi and Korsemeyer Peppa's equation.

CONCLUSION

From the total research, mucoadhesive drug delivery of Nateglinide have been successfully designed and developed. Drug release from mucoadhesive Nateglinide tablets was release for a period of 12 hr. The polymers like Sodium Carboxymethyl Cellulose has less viscosity as compared to the HPMCK15 and low binding forces between the molecules of Carbopol. It might be concluded that release order kinetic of mucoadhesive tablets was best fit with peppa's plot indicate the non-fickian release of drug may occurred in diffusion and erosion of the polymer.

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