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COMPARITIVE STUDY OF THE EFFECT OF DIFFERENT POLYMERS ON THE FORMULATION OF MUCOADHESIVE DRUG DELIVERY SYSTEM OF REPAGLINIDE

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ABSRTACT

The aim of proposed research work is to isolate the natural mucoadhesive polymer from natural source (Date Palm) & formulation and evaluation of gastro mucoadhesive Sustained release matrix tablet. The maximum utilisation of Mucoadhesive drug delivery system of drug which enables reduction in total amount of dose administered in fluctuation and therefore better control of diseased condition. Mucoadhesive drug delivery system of repaglinide is indicated only for type 2 Diabetes Mellitus. It should be avoided in liver disease. The aim is to drug residence time in stomach by development and evaluation of *In vitro* performances of gastro mucoadhesive sustained release (GMSR) of Repaglinide. Gastro mucoadhesive sustained release formulations (GMSR) of Repaglinide were developed by the direct compression method and these were measured by 'modified balance method'.

KEY WORDS:

Adhesion time, Diabetes mellitus**,** Mucoadhesive strength, Mucous membrane, Sustained release, Repaglinide.

INTRODUCTION

Repaglinide is a drug used for the treatment of type II Diabetes Mellitus. Repaglinide belongs to the meglitinide class of blood glucose-lowering drugs. Repaglinide lowers blood glucose by stimulating the release of insulin from the pancreas. It achieves this by closing ATP dependent potassium in the membrane of the beta cells. This depolarizes the beta cells, opening the cells' calcium channels, and the resulting calcium influx induces insulin secretion. Oral sustained release (SR) systems continue to be the most popular ones amongst all the drug delivery systems (Ahuja A *et al.*, 1993).

Oral sustained release (SR) systems continue to be the most popular ones amongst all the drug delivery systems (Bernkop-Schnurch A *et al.*, 2009). Mucoadhesive delivery systems offer several advantages over other oral SR systems by virtue of prolongation of residence time of drug in gastrointestinal (G.I.) tract, and targeting and localization of the dosage form at specific site (Ali J *et al.*, 2002; Asane GS *et al.*, 2008). Also, these mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in high drug flux through the absorbing tissue (Chein Y, 1992; Chowdary KPR *et al.*, 2000). Repaglinide, bind to sulfonyl urea receptor as well as to other distinct site. Administration of conventional tablets of Repaglinide has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects of receptor which leads to closure of ATP dependent K^+ channels which leads to reduction in drug concentration at the receptor site (Semalty M *et al.*, 2000). Response surface methodology (RSM) is a widely practiced approach in the development and optimization

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of drug delivery devices. Based on the principal of design of experiments (DoE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation(s) (Harding SE *et al.*, 1989). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms.

The current study aims at developing and optimizing an oral mucoadshesive drug delivery system of repaglinide which is indicated only for type II Diabetes Mellitus. As an alternative, it may prove to be more productive SR systems by virtue native to sulfonylurea. These formulations should be avoided in liver disease. Prolongation of drug residence time in stomach of G.I. tract (Sanders LM *et al.*, 1990). Repaglinide is required for long period of time so that mucoadhesive sustained release formulation was developed (Asane GS *et al.*, 2008). It improves the effectiveness of a drug by helping to maintain the drug concentration between the effective and toxic levels. Inhibition of the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site (Yamsani VV *et al.*, 2008) . A drug can be incorporated into a across linked polymeric devices that would adhere to a mucous substrate in the body and then drug can diffuse from the device directly into the tissue. Mucoadhesive nature of the device can increase the residence time of the contact between a drug containing polymer and a mucous surface (Ghandhi RB *et al.*, 1998). The term 'bio adhesion' is defined as the attachment of a synthetic or natural macromolecule to a biological tissue for an extended period of time. The biological tissue can be epithelial tissue, or it can be the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as 'mucoadhesion' (Ahuja A *et al.*, 1993).

The date palm (Phoenix dactylifera L.) is a tropical and subtropical tree that belongs to the plamae (Arecaceae) family and plays an essential ecological role in Arabian countries. It is extremely useful in controlling desertification by creating a microclimate which prevents long-term degradation of ecologically weak environments (Ali J *et al.*, 2002). Considering the food importance of date fruits, numerous studies have been carried out on the characterization of its chemical composition particularly, polysaccharides (heteroxylan & glucomannan) (Omar I *et al.*, 2003).

More recently, Ishurd, Zgheel, Kermagi, Flefla, and Elmabruk reported that this glucan was found to exhibit potent antitumor activity. Xylans represent the most abundant hemicellulose-type polysaccharides constituent in the plant kingdom. They are known to display several structural varieties in terrestrial plants and, even in different plant tissues within one plant. Zahid, Ahmad, and Pan (2001), Ishrud, Zahid, Zhou, and Pan (2001), Ishurd, Sun, Xiao, Ashour, and Pan (2002) have isolated and studied polysaccharides from Date Palm. They characterized galactomannose-type polysaccharides, heteroxylan, and glucomannan (Abdelkader B *et al.*, 2007).

Previous studies have shown that plant xylans form a family of polysaccharides which consist of a backbone of b-(1, 4)-D-xylopyranose residues which can be substituted in C-2 and/or C-3 by short and flexible side chains. Besides the natural ingredients majority of the products also contain some pharmaceutically useful properties, one of them is mucoadhesive property. From pulp fruit, Haq and Gomes (1977) have isolated xylan and Ishurd et al. (2002) have purified a linear glucan which shows mixing linkage, (1→3)-and (1→4)-. More recently, Ishurd and Kennedy (2005) reported that this glucan was found to exhibit potent antitumor activity and also mucoadhesive nature (Abdelkader B *et al.*, 2007). Pragati S. *et al.*, shows the evaluation of Date Palm Polysaccharide (DPP) as a bioadhesent and its comparison with various mucoadhesive polymers (Pragati S *et al.*, 2010).

MATERIALS AND METHODS

Isolation of Mucoadhesive polymer from Date Palm:

DPP was prepared following methods by Rao *et al.*, (Rao PS, 1973; Rao PS *et al.*, 1946) in three batches on a laboratory scale. To 50g of fruit pulp, 200ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 minutes under stirring condition in a water bath and filtered it. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The solution was then centrifuged. The supernatant was separated, boiled on water bath for conc.and it was dried from Lyophillizer. (Model no.–NSW-275, Company: - Narang scientific works Pvt. Ltd.) .The dried material was ground and sieved to obtain granules of different particle size range. It was stored in decsicator (Pragati S *et al.*, 2010).

MATERIALS

Repaglinide was a gift sample from Sun Pharma India Limited, Hyderabad. Carbopol 934 (Central drug house, Delhi), Hydroxy propyl methyl cellulose – 50 cps (Central drug house, Delhi) , Chitosan (high molecular wt) (Central drug house, Delhi), Date Palm (Isolated from date palm fruit), Poly Vinyl Pyruvate (Central drug house, Delhi), Magnesium stearate (Central drug house, Delhi), Aerosil (Central drug house, Delhi), Mannitol (Central drug house, Delhi) and other chemicals used were procured commercially and were used as received.

METHOD

Formulations were developed by the direct compression method after setting the individual excipient levels through preformulation studies. A series of formulations was developed as mentioned in the table 1. Different polymers in different variable Chitosan, H.P.M.C-50cps, carbopol-934 and polymer isolated from date palm were used to formulate the tablets. These were evaluated by In Vitro (Table 1).

RESULTS AND DISCUSSION

The evaluation parameters preferred for the optimization of Mucoadhesive Tablets are (Table 2)-:

1. Weight variation
2. Hardness
3. Friability test
4. In vitro mocoadhesive study
5. In vitro dissolution test by- Ultra Violet-Spectrophotometry

Optimized formulation was one which shows better combination in both adhesion time as well as percentage drug release.

IN-VITRO MUCOADHESIVE STUDY

Mucoadhesive strength

These were measured by 'modified balance method' (Fig. 2) briefly, a balance was taken and its left pan was replaced with a weight to the bottom of which a tablet was attached. Both sides were balanced with weight. Porcine gastric mucosa (obtained from local piggery) having a thick layer of mucus was fixed to a rubber cork, which was already attached to the bottom of the beaker containing corresponding medium with a level slightly above the mucosa (Rao PS *et al.,* 1946) . The weight, which was attached to the tablet, was brought into contact with the porcine mucosa, kept undisturbed for 5 minutes and then the pan was raised. The left side of the balance was made 26 gm heavier than the right side by placing a 26 gm weight on left side pan. Take the tablet & adhere the tablet to the lower side of the pan. A preload of 5 gm was placed on the clamp for 5 minutes (preload time) to establish adhesion bonding between tablet and porcine mucosa. The preload and preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp, and weight was then added into pan. The addition of weight was stopped when tablet was detached from either porcine or stomach mucosa (Pragati S *et al.,* 2010).

The excess weight on the right pan i.e., total minus 5 gm was taken as a measure of mucoadhesive strength and from the mucoadhesive strength, the force of adhesion was calculated using the following formula

$$\text{Force of adhesion} = \frac{\text{Mucoadhesive strength}}{100} * 9.81$$

Weights were continuously added on the right side pan in small increments and the weight at which the tablet detached from the mucosa was recorded (Fig. 1 and Table 3).

IN VITRO STUDY OF ADHESION TIME AND DISSOLUTION PROFILE

Apparatus use: Basket type dissolution apparatus

Media: 1.2 pH Phosphate buffer

Speed: 50 Rpm

Temperature: 37^0C

Procedure: - The albino rat stomach mucosa membrane was wrapped outside from the basket and adhered the formulation to the mucous membrane. Dissolution was started and sample times were taken (As shown in the Fig. 3 and Fig. 4) and note the adhesion of formulation from stomach mucous membrane and calculated the % drug release (Table 4). The tablet is most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. Mucoadhesive delivery systems offer several advantages over other oral SR systems by virtue of its prolongation of residence time in stomach of gastrointestinal (G.I.) tract, and targeting and localization of the dosage form at a specific site. Also, these mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, thereby resulting in high drug flux through the absorbing tissue.

Formulation aspects

Mucoadhesion

The current study aims at developing and optimizing an oral mucoadhesive drug delivery system of repaglinide which is indicated only for type 2 Diabetes Mellitus. The A_3, B_3, C_2, D_2 were optimized on the basis of their adhesion and retention time in stomach. It was found that formulation C_2 is optimized formulation of mucoadhesive tablet because of good adhesion & retention time. C_2 Formulation release 89.6% drug in 23 hrs. in sustained manner and shown adhesion for 23 hrs.

Dissolution (In Vitro Release Profile)

In-Vitro drug release of formulation A_3, B_3, C_2, & D_2 were determined on the basis of their mucoadhesion study; it was found that formulation C_2 is the optimized formulation because of their mucoadhesion time and shows better release profile that of other formulation. C_2 formulation release 42.45% drug in 6 hrs in a sustained manner and release almost 91.43% drug in 24 hrs. Formulation C_2 shows sustained release pattern from the beginning and as 31.52% drug release in 4 hrs. and 42.45% drug releases in 6hrs. and in 11 hrs. 79.54% and up to 23 hrs. 89.65% drug is released. Therefore, formulation C_2 is found to be the optimized formulations which can be used as a gastro mucoadhesive formulation provide sustained release of Repaglinide in stomach. After stability study there is no significant difference found in the mucoadhesion, drug degradation and percentage cumulative drug release in optimized formulation is C_2 (As shown in the Fig. 4, Fig. 5 and Fig. 6).

Stability studies

In Accelerated condition Stability study at 40 ± 2^0C/ 75±5% RH after 1, 3, & 6 months of storage the formulations were characterized for *in vitro* drug release, drug content, hardness, friability, adhesion time and description. After 1 month the drug release was found to be, in 89.46 % and adhesion time is 23 hrs. for both the drugs and hardness was also with in limit.

Table No. 1: Formulation of Mucoadhesive tablets

Batch	A			B			C			D		
Formulation	A_1 (mg)	A_2 (mg)	A_3 (mg)	B_1 (mg)	B_2 (mg)	B_3 (mg)	C_1 (mg)	C_2 (mg)	C_3 (mg)	D_1 (mg)	D_2 (mg)	D_2 (mg)
Drug	8	8	8	8	8	8	8	8	8	8	8	8
Chitosan	36 (30%)	60 (50%)	84 (70%)	----	----	----	----	----	----	----	----	----
H.P.M.C.-50cps	----	----	----	36 (30%)	62.5 (50%)	84 (70%)	----	----	---	---	----	----
Carbopol-934	----	----	----	----	----	----	36 (30%)	62.5 (50%)	84 (70%)	----	----	----
Date Palm	--	--	--	--	--	--	--	--	--	36 (30%)	62.5 (50%)	84 (70%)
PVP	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	4	4	4	4	4	4	4	4	4	4	4	4
Mannitol	67.2	43.2	19.2	67.2	43.2	19.2	67.2	43.2	19.20	67.2	43.2	19.2

Table No. 2: Physical parameter results of formulation

Batch / Parameters	A			B			C			D		
	A_1	A_2	A_3	B_1	B_2	B_3	C_1	C_2	C_3	D_1	D_2	D_2
Weight Variation	2.46%	3.5%	0.054%	3.52%	2.36%	0.54%	3.05%	0.74%	2.43%	1.56%	0.52 %	1.78 %
Tablet Hardness	5.8	5.5	4.8	5.2	5.6	5.9	5.5	5.9	8	5.4	5.8	6.9
Friability	0.5%	0.51 %	0.42%	0.54%	0.49%	0.55%	0.57%	0.54%	0.73%	0.53%	0.51%	0.59 %

Table No. 3: In-vitro mucoadhesive strength study of the prepared Mucoadhesive tablets

Batch no	Mucoadhesive strength (Gm.)	Mucoadhesion ($Gm.cm/sec^2$)
A_1	13.67	1.86
A_2	15.41	2.11
A_3	14.15	5.35
B_1	15.35	3.97
B_2	24.52	6.12
B_3	25.73	9.43
C_1	23.18	6.19
C_2	25.77	10.86
C_3	26.04	15.96
D_1	22.14	6.15
D_2	26.92	10.02
D_3	27.72	15.14

Table No. 4: In-vitro mucoadhesion time and % release study of the prepared mucoadhesive tablets

Batch no	Mucoadhesion Time(Hrs)	% Drug Release
A_1	4	58.512
A_2	5	40.512
A_3	7	57.608
B_1	5.30	50.608
B_2	6.0	50.608
B_3	7.30	62.984
C_1	7	62.985
C_2	23	89.658
C_3	27.30	52.658
D_1	6.0	49.225
D_2	22.35	85.456
D_3	25.30	53.235

Fig.-1: Mucoadhesive strength of formulation (On the basis of mucoadhesive formulation A_3, B_3, C_2 & D_2 were optimized).

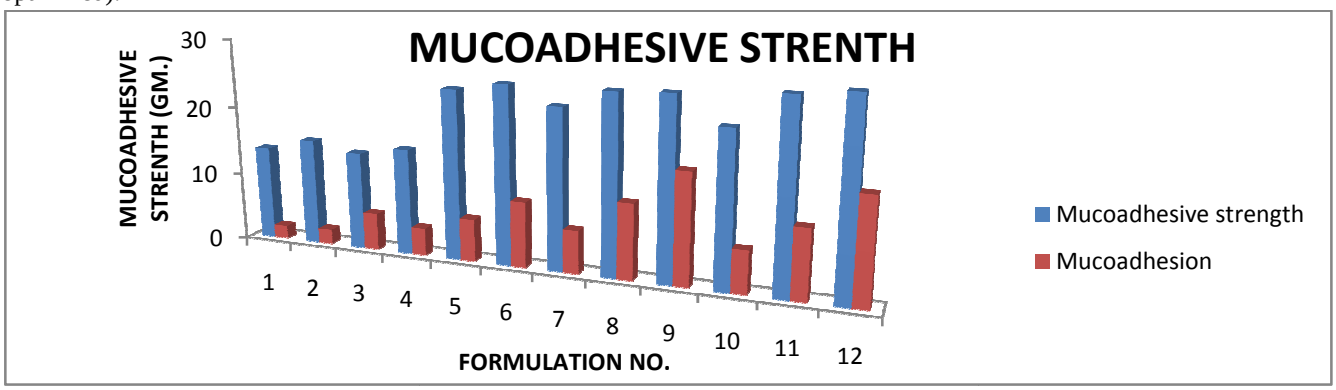


Fig-2: Modified physical balance system showing mucoadhesive strength of formulation

Fig-3: In Vitro study of Adhesion Time and Dissolution profile

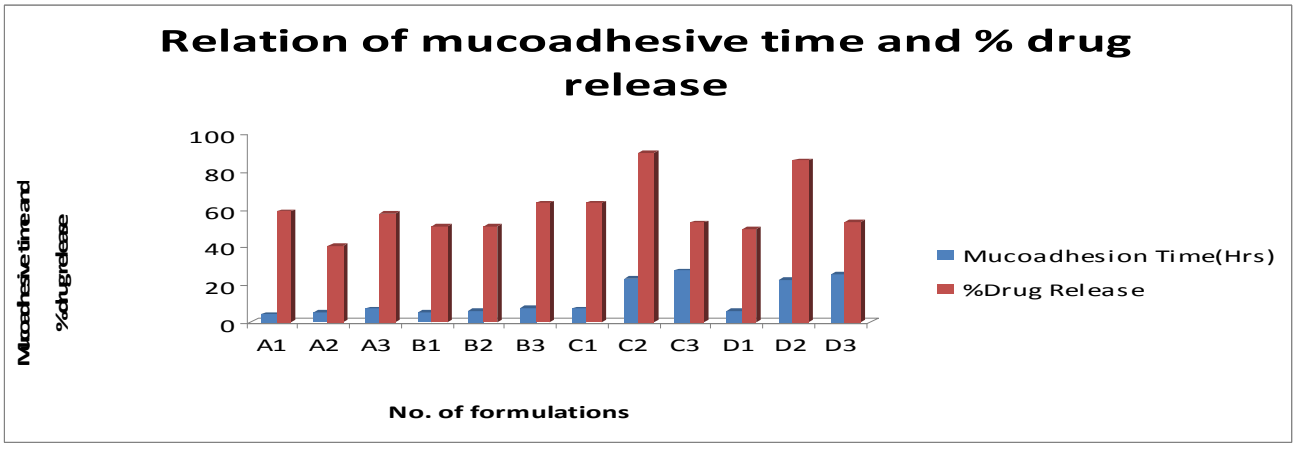
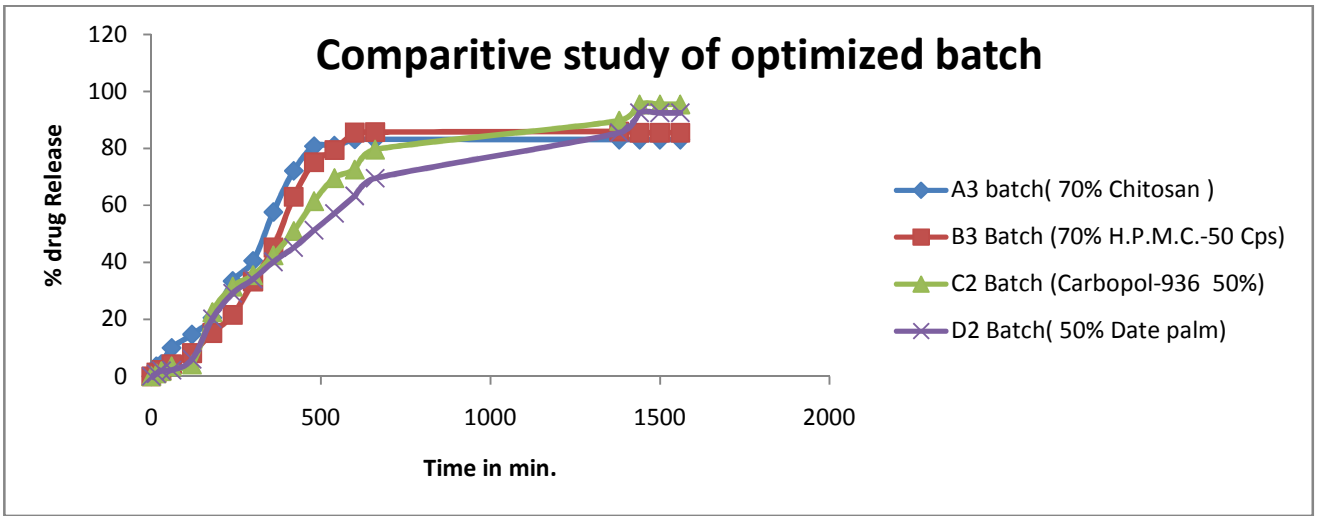


Fig-4: Adhesion of Tablet on mucous membrane of Albino rat stomach stage of starting of dissolution of Optimized Batch of using different Polymer(These batches were optimized & dissolution studies were performed as shown in fig -6).

Fig-5: Adhesion of Tablet on mucous membrane of Albino rat stomach after Dissolution. Optimized Batch Result (Adhesion time and Drug release)

Fig-6: Comparative study of optimized batch



CONCLUSION

In Vitro Mucoadhesive study of formulation was determined on the basis of their adhesion and retention time in stomach. The formulation was optimized on the basis of its good adhesion & retention on stomach. Mucoadhesive nature of the device can increase the residence time of the drug in the body because of increased intimacy and the duration of the contact between a drug containing polymer and a mucous surface (Kumar s *et al.*, 2004)**.** The aims of above project are-:

1. Advantage of patient convenience & compliance drug administration.

2. Reduction in fluctuation in steady state levels and therefore better controlled of diseased condition and reduced intensity of local or systemic side effect.

3. Increase safety margin of high potency drug due to better control of Plasma levels.

4. Maximum utilization of drug enabling reduction in total amount of dose administered.

Conclusions drawn from the project work are,

- As A_3, B_3, C_2 & D_2 were optimized batches on the basis of *in vitro* performances of Physical modified balance and dissolution performances.
- It was reported that the polymer isolated from Date Palm in the formulation D_2 gave almost same result

as that of formulation C_2 that was formulate from carbopol.

- Date Palm polymers were used further in the place of carbopol-934 as a mucoadhesive polymer.

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