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AN *IN-VITRO* STUDY FOR MUCOADHESION AND CONTROL RELEASE PROPERTIES OF GUAR GUM AND CHITOSAN IN ITRACONAZOLE MUCOADHESIVE TABLETS

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ABSTRACT

This study describes the effect of Guar gum and chitosan on formulation of mucoadhesive drug delivery system of itraconazole. Mucoadhesive strength, Drug content, Hardness, Friability, Weight variation, Moisture content and accelerated stability studies were performed to study the effect of polymers on prepared mucoadhesive tablets. Results of the present study clarified the potential of guar gum and chitosan in mucoadhesion and control release of itraconazole tablets. Both polymers i.e. Chitosan and guar gum were helpful for controlling the drug release in better way when used in proper combinations. When result of mucoadhesion was checked guar gum gives more mucoadhesive strength to the prepared tablets as compared to chitosan. Accelerated stability studies were performed on prepared formulations, results indicates that the formulations were stable that mince excipients used in the formulations were stable and are not causing major changes in drug release pattern after a period of 6 months. From above mentioned work it can be concluded that combination of Chitosan and guar gum is better and effective approach to have controlled mucoadhesive drug delivery system of Itraconazole.

INTRODUCTION: In recent years the interest in bioadhesion has been inspired by the development of novel bioadhesive polymers for mucosal delivery [1,2]. Bioadhesive, or more precise mucoadhesive drug delivery systems are aimed to adhere to various mucosal tissues [3]. The localisation of mucoadhesive delivery systems within a certain GI-segment, ideally where the drug has its absorption window, would lead to a tremendous improvement in the oral bio-availability of these drugs [4].

The absorption of riboflavin, for instance, which has its absorption window in the stomach, as well as the small intestine, could be strongly improved in human volunteers by oral administration of mucoadhesive microspheres versus non-adhesive microspheres [5].

Gastrointestinal retention depends on many factors such as density of the dosage form, size of the dosage form, fasting and fed condition, nature of the meal taken, sleep, posture, etc. It also depends strongly on a complicated and unpredictable gastric emptying with migrating myoelectric complex motility of the stomach [6]. Various delivery systems like floating, swellable, mucoadhesive, high density formulations, etc., have been developed to achieve gastroretention [7].

Itraconazole, being triazole antifungal, is used to contol the prophylaxis of fungal infections in immuno-compromised patients with doses of 100-200 mg administered 2 to 3 times a day. Itraconazole is practically insoluble in water, very slightly soluble in alcohol and freely soluble in dichloromethane [8].

MATERIALS AND METHODS:

Materials: The drug Itraconazole was procured as gift sample from (Loba Chemicals, Mumbai, India), Guar gum and Chitosan were procured from (Loba Chemicals, Munbai ,India), All other chemicals purchased were of analytical grade.

Determination of solubility of Itraconazole: Drug solubility was determined by adding excess amounts of Itraconazole to 0.1M HCl at 37°C ± 0.5°C, respectively. The suspensions formed were equilibrated under continuous agitation for 48 hrs and filter to obtain a clear solution. The absorption of the samples was measured in a UV spectrophotometer (JASCO – V530) at 254 nm and the concentrations in µg/ml were determined. Each sample was determined in triplicate.

Moisture Content: Moisture content of drug was determined by Karl Fischer titrator (Matic D, Veego).

Preparation of Mucoadhesive Tablet of Itraconazole: Mucoadhesive formulations were prepared using Itraconazole, chitosan and Guar gum and were mixed in various combinations **(Table 1)**. Powdered mass was then passed through 40-mesh screen. The tablets were compressed by direct compression method by using tablet Punching Machine – Karnavati - Minipress D-II Link.

TABLE 1: BATCHES PREPARED BY DIRECT COMPRESSION METHOD OF ITRACONAZOLE

Ingredients	Formulation Code							
	G1	G2	G3	G4	G5	G6	G7	G8
Guar gum(mg)	60	60	50	50	40	40	30	25
Chitosan (mg)	10	05	10	05	10	05	10	05
Drug (mg)	100	100	100	100	100	100	100	100
Total Weight (mg)	170	165	160	155	150	145	140	130

Evaluation of Itraconazole Mucoadhesive Tablets: The tablets were evaluated as per IP1996 for weight variation (n=20), hardness (n=6), thickness (n=20), and friability. Hardness was determined by using a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test was conducted using Roche friabilator (F. Hoffmann-La Roche Ltd, Basel, Switzerland). Thickness of the tablets was measured by digital Vernier calipers (Mitutoyo Corp, Kawasaki, Japan).

Determination of Drug Content: Ten tablets were selected randomly and powdered [9]. Accurately weighed powder equivalent to weight of one tablet was stirred using magnetic stirrer in 100 ml phosphate buffer saline pH 1.2 for a period of 2 hours. Sample was analyzed after appropriate dilutions by UV spectrophotometer at 254 nm.

***In-Vitro* Drug Release Studies:** The release rates of Itraconazole mucoadhesive tablets were determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of phosphate buffer pH 1.2, temperature and speed of the apparatus was maintained at 37°c ± 0.50°C and 100 rpm respectively. A 5ml aliquot of dissolution medium was withdrawn from the dissolution apparatus hourly for 8 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper no. 41. Absorbance of these solutions was measured at 254 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Determination of Mucoadhesive strength:

Instrument: The apparatus was locally assembled and was a modification of the apparatus applied by Parodi *et al*., [10]. The device was mainly composed of a two-arm balance [11]. The left arm of the balance was replaced by small copper lamina plate vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane.

***Ex vivo* mucoadhesion studies:** The instrument described above was used with sheep intestinal mucosa as model membrane [12]. The mucosal membrane was excised in pH 1.2 phosphate buffer before the bioadhesion evaluation study by removing the underlying connective and adipose tissue, and equilibrated at 37°C± 1°C for 30min. The tablet was lowered on to the mucosa under a constant weight of 5g for a total contact period of 1 min. Bioadhesive strength was assessed in terms of the weight in grams required to detach the tablet from the membrane.

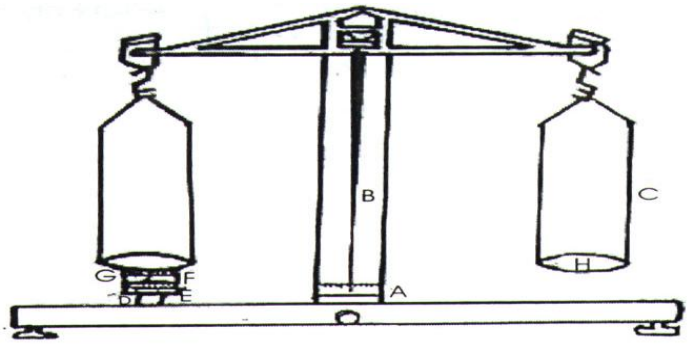

FIGURE 1: ASSEMBLY FOR MEASUREMENT OF ADHESION FORCE

A- Scale; B- Pointer; C- Pan; D- Protrusion for tying Mucosal tissue; E- Sheep Intestinal Mucosa; F- Muco-adhesive tablet; G- Double layered adhesive tape; H- Weight

Stability Studies: Stability studies were conducted on mucoadhesive tablets to assess their stability with respect to their physical appearance, drug content, mucoadhesion and drug release characteristics. Stability studies were done at a temperature of 40 ºC ± 2°C and humidity 75% ± 5%RH. The formulation was evaluated for a period of 6 months [13].

RESULT AND DISCUSSION:

Determination of Solubility: The solubility of Itraconazole in water and 0.1 M HCL at 37°C was found to be 48 ng/ml and 1.3 µg/ml respectively.

Moisture Content: Moisture content of Itraconazole was found to be 3.55% and it is within the limit that Itraconazole should contain less than 5% of moisture.

Determination of Drug Content: The drug contents of Itraconazole tablets were depicted in **Table 2**. The results obtained are in accordance with the specifications given in official pharmacopoeia that the Itraconazole powder should contains 98.5% to 102.5% of Itraconazole.

Evaluation of Itraconazole Mucoadhesive Tablets: Tablets were evaluated for Hardness, Friability, Weight Variation and Thickness. Result suggests that the parameters are within the specified range **(Table 2).**

***In-Vitro* Drug Release Studies**: Percent drug release of Itraconazole mucoadhesive tablets prepared by direct compression are shown in **Table 2 and Figure 2**. Result of drug release from mucoadhesive tablet shows that increasing amount of chitosan in the formulations leads to retardance in drug release. In general, the drug release from the tablet is controlled by gel formation of Chitosan in acidic environment, diffusion of drug through the gel and finally erosion of gel taking place as a result of dissolution of Chitosan [14]. Guar gum has both the abilities i.e. controlling the drug release and increasing the mucoadhesive strength.

The mechanism of drug release from guar gum is due to water penetration, gelatinization and diffusion [15]. From the *in-vitro* drug release study it can be noted that both the polymers is having ability to control the drug release. The drug release is not hundred percent in present study it is due to poor solubility of Itraconazole, but still the effect of polymers on drug release can be easily noted from the obtained results **(Table 2 and Fig. 2).**

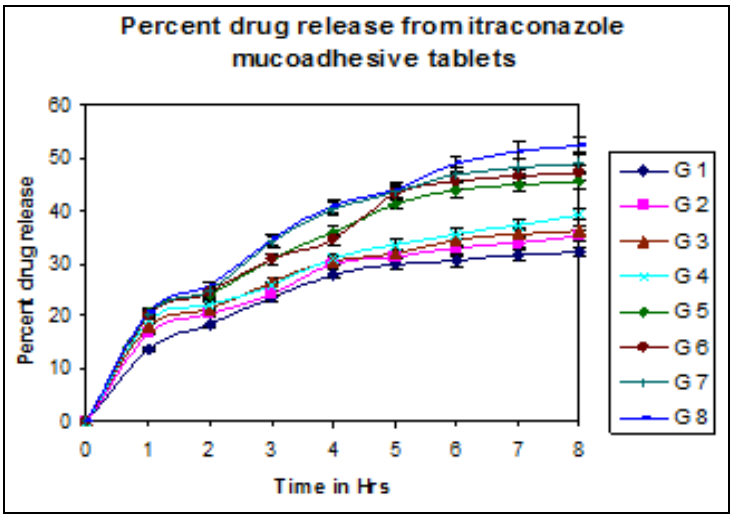

FIGURE 2: PERCENT DRUG RELEASE FROM ITRACONAZOLE MUCOADHESIVE TABLETS

Determination of Mucoadhesive strength: Effect of Guar gum and chitosan on mucoadhesive strength of itraconazole tablets is depicted in **Table 2.** From the table it is clarified that Guar gum and chitosan both are increasing the mucoadhesive strength of itraconazole tablets but the effect of mucoadhesion shown by guar gum was more proven as compared to effect of chitosan. The mechanism behind the mucoadhesion due to use of guar gum is it swells and facilitates the formation of an adhesive interaction between Guar gum and mucosa and contributes to the establishment of a more extensive cohesive layer, resulting in superior levels of mucosal retention.

TABLE 2: EVALUATION OF ITRACONAZOLE MUCOADHESIVE TABLETS

Formulation code	Percent Friability	Thickness (mm)	Hardness (Kg/Cm^2)	Weight variation	Drug content (%)	Muco-adhesive strength (gm)	% release (After 8 hrs)
G1	0.59	3.3 ± 0.05	3.7 ± 1.0	170 ± 0.36	99.6	10.5	32.311
G2	0.62	3.3 ± 0.07	3.6 ± 0.7	165 ± 0.42	98.5	10.2	35.083
G3	0.57	3.2 ± 0.01	3.4 ± 0.5	160 ± 0.51	98.3	9.7	36.172
G4	0.52	3.2 ± 0.04	3.7 ± 0.4	155 ± 0.19	99.5	9.2	39.236
G5	0.41	3.1 ± 0.09	3.5 ± 0.7	150 ± 0.18	98.4	8.5	45.630
G6	0.57	3.0 ± 0.06	3.5 ± 0.7	145 ± 0.24	99.3	8.2	47.145
G7	0.49	2.9 ± 0.02	3.7 ± 1.1	140 ± 0.36	99.5	7.7	49.046
G8	0.62	2.9 ± 0.04	3.6 ± 0.8	130 ± 0.52	99.1	7	52.451

Stability Study: At the end of the testing period, tablets were observed for changes in physical appearance, analyzed for drug content, Mucoadhesive strength and subjected to in vitro drug release studies. No visible changes in the appearance of the matrix tablets were observed and a significant change was not seen in the drug content and drug release at the end of the storage period.

CONCLUSION: Present study describes the effect of Chitosan and Guar gum on mucoadhesive drug delivery system of Itraconazole. Both polymers i.e. Chitosan and guar gum were helpful for controlling the drug release in better way when used in proper combinations. Result of mucoadhesion shows the significant potential of guar gum as a mucoadhesive polymer over chotosan. This drug delivery system can be a better alternative to the conventional drug delivery by virtue of its site specific absorption as we are increasing the residence time of drug at its target site. From above mentioned work it can be concluded that combination of Chitosan and guar gum is better and effective approach to have controlled mucoadhesive drug delivery system of Itraconazole

REFERENCES:

1. Alur, HH, Beal, JD, Pather, SI, Mitra, AK, Johnston, TP. Evaluation of a novel natural oligosaccharide gum as a sustained-release and mucoadhesion component of calcitonin buccal tablets, 1999, *J. Pharm. Sci*. 88, 1313–1319.
2. Lehr CM. Lectin-mediated drug delivery: the second generation of bioadhesives. 2000*J. Contr. Rel*. 65, 19–29.
3. Lehr C.M. From sticky stuff to sweet receptors-achievements, limits and novel approaches to bioadhesion. 1996, *Eur. J. Drug Met. Pharm*. 21, 139–148.
4. Andreas A, Bernkop S. Mucoadhesive polymers: strategies, achievements and future challenges, 2005, *Adv Drug Deliv. Rev*. **57**(11):1553-5.
5. Mathiowitz E, Chickering DE, Lehr CM. Bioadhesive Drug Delivery Systems, Marcel Dekker, New York, 1999, p. 177.
6. Talukder R, Fassihi R,. Gastroretentive delivery systems: a mini review. 2004, *Drug. Dev. Ind. Pharm*. 30 (10), 1019–1028.
7. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. 2000, *Int. J. Pharm*. 195, 125–135.
8. Sweetman C, Martindale, The Complete Drug Reference, The Pharmaceutical Press, London, 2002, 33rd Edition, 1084.
9. Lachman L, Lieberman HA, Kanig JL, The Theory and Practice of Industrial Pharmacy,1987, Varghese Publishing House, Third Edition.. p.182-184.
10. Desai KH, Kumar TP, Preparation and evaluation of a novel buccal adhesive system, 2004, *AAPS PharmSciTech*,5(3):1.
11. Parvez N, Ahuja A, Khar R. Development and evaluation of mucoadhesive buccal tablets of lignocaine hydrochloride, 2002, *Ind J Pharm Sci*.:563-567.
12. Accili D, Menghi G, Bonacucina G, Martin P, Palmieri G. Mucoadhesion dependence of pharmaceutical polymers on mucosa characteristics, 2004, *Eur J Pharm Sci.* 22(4):225-234.
13. Mathews BR. Regulatory aspects of stability testing in Europe, 1999, *Drug Dev Ind Pharm.* 25,831-856.
14. Sakkinen M, Tuononen T, Jurjenson H, Vesk P, Marvola M. Evaluation of microcrystalline chitosans for gastro-retentive drug delivery, 2003, *European Journal of Pharmaceutical Sciences* 19, 345–353.
15. Al-Saidan SM, Yellela SR, Patro SS, Satyanaryana V. *In Vitro* and *In Vivo* Evaluation of Guar Gum Matrix Tablets for Oral Controlled Release of Water-Soluble Diltiazem Hydrochloride, 2005, *AAPS PharmSciTech* , 6(1).

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