Original Research Article

International Journal of Bioassays
ISSN: 2278-778X
www.ijbio.com
OPEN ACCESS

DESIGN AND EVALUATION OF ROSIGLITAZONE LOADED BIO LIP STRIPS FOR TRANSLABIAL DRUG DELIVERY

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Received for publication: January 11, 2014; **Revised:** March 13, 2014; **Accepted:** May 17, 2014

Abstract: Rosiglitazone is an oral hypoglycemic agent which undergoes extensive first pass metabolism and having extremely short half-life which make it a possible candidate for delivery through skin. The aim of this study was to explore the potentiality of lip skin as a novelistic platform due to its unique histology by formulating Rosiglitazone loaded lip strip using a novel bio material which was isolated from pulp of artocarpus heterophyllus by simplified economical process. Rosiglitazone loaded bio lip strips were formulated by using artocarpus heterophyllus biomaterial as a strip former and dextrose as a flexicizer. The formulated strip was subjected for various evaluation parameters like moisture content, folding endurance, swelling index, stability studies, *in-vitro* and *in-vivo* release. Our results revealed that the Rosiglitazone release was extended over a period of 24 hrs. This was confirmed by the *in-vitro* release data. Release kinetics of bio strips followed Higuchi model and the mechanism of the drug release was diffusion and anomalous type. The results are expressed as mean ± SEM values. Statistical significances were evaluated using t test. A value of $p<0.05$ was considered significant. The best formulation was selected on the basis of various evaluated parameters, linearity of drug diffusion rate and used concentration of biomaterial in the formulation. The formulated strips are feasible for delivering Rosiglitazone through Translabial route.

Key Words: Translabial, Rosiglitazone, Artocarpus heterophyllus, Strips, Release Kinetics.

INTRODUCTION

Lip skin is very unique. Lips are two fleshy folds surrounds the orifice of mouth consisting of three to five cellular layers of flat and scale like cells. Lip composed of skin and mucosa and devoid of hair follicles, sweat glands, sebaceous glands and melanin [1]. Unlike other skin the stratum corneum of lip skin is extremely thin or completely absent in most people. Translabial drug delivery can be used for both; local therapeutic effects on diseased lip skin as well as for systemic delivery of drugs. Translabial route avoids problems of gastric irritation, hepatic first pass metabolism, reduce the risk of systemic side effects and sustained the release of drug at the site of application [2-5]. The skin forms an excellent barrier against drug permeation, due to the rigid lamellar structure of the stratum corneum lipids. Our novel lip drug delivery sidesteps this barrier due to very less layers of stratum corneum. Rosiglitazone belongs to thiazolidinedione class. It is used in the management of type II diabetes mellitus particularly for overweight patients and for whom metformin is contraindicated [6, 7]. It is selective agonist for paroxisome proliferator-activated receptor gamma (ppar-γ) [8]. Rosiglitazone reduces fasting and postprandial glucose levels and effectively lowers plasma insulin and triglyceride levels [9]. It regulates the transcription of certain insulin-responsive genes and improves insulin sensitivity. It controls glucose production, transport and utilization. The drug has a log P value of 2.1, which contributes to its lipid solubility and hydrophilicity. However, Rosiglitazone is metabolized extensively with an elimination half-life of 3 to 5 hr, i.e. the drug needs frequent administration. The bio strip of Rosiglitazone may be beneficial to the patients since it enhance the bioavailability due to avoidance of hepatic first pass metabolism, reduce dose frequency and adverse effects and maintaining un-fluctuating plasma concentration of Rosiglitazone. *Artocarpus heterophyllus* belong to family moraceae. The pulps are exceptionally rich in iron, magnesium, manganese, copper, calcium and contain vitamin B_1 and vitamin E. The aim of our research work was the formulation and evaluation of bio lip strip of Rosiglitazone using natural biomaterial (JB) for lip skin as a site for drug delivery.

MATERIALS AND METHODS

Rosiglitazone maleate (assigned purity, 99.8%) was a gift sample from Sun Pharma (Mumbai), India. *Artocarpus heterophyllus* were purchased from market of Dehradun, Uttarakhand, India, Sodium carboxy methylcellulose (Na-CMC) and Hydroxy propyl methyl cellulose (HPMC) were purchased from Merck Specialties Private Limited, Mumbai, India. All other chemicals and solvents were of analytical grade.

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Isolation of Artocarpus heterophyllus bio material

Artocarpus heterophyllus were procured from the local market. Novel biomaterial from *Artocarpus heterophyllus* was isolated by simplified economical process using acetone and purified by hot dialysis method using ORCHID scientific dialysis apparatus for complete removal of impurities like Chlorides and sulfates. The purified bio material was screened through 200# and stored for further research work.

Preparation of Bioadhesive Lipstrip

Accurately 100mg of *Artocarpus heterophyllus* biomaterial(JB) was weighed and transformed into the mortar, to this 110mg of dextrose was added and triturated the mixture for a period of 5minutes after that 5mg of Rosiglitazone was incorporated in geometrical dilution pattern. Further 10ml of double distilled water was incorporated by adding drop by drop to the mixture with constant trituration. The mixture was subjected for magnetic stirring for a period of 10 minutes and sonicated at 400 Hz for 3 cycles of 60seconds each in order to form a colloidal mixture. The colloidal mixture was poured into Petridis having 6cm diameter and subjected for evaporation at room temperature for a period of 10hrs. Dried strips were carefully removed and it was cut into 2X2cm^2 and strips were placed over the adhesive backing membrane (Table 1). F7 and F8 are standard formulations.

Table 1: Composition of various batches of Rosiglitazone loaded bio-lip strips.

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Rosiglitazone (mg)	5	5	5	5	5	5	5	5
2	*Artocarcus heterophyllus* biomaterial (mg)	100 (1%)	200 (2%)	300 (3%)	400 (4%)	500 (5%)	600 (6%)	--	--
3	Sodium carboxy methyl cellulose (mg)	--	--	--	--	--	--	400 (4%)	--
4	Sodium alginate(mg)	--	--	--	--	--	--	--	400 (4%)

Drug- Excipient interaction study

The pure drug along with other formulation excipients was subjected to interaction studies. Studies were carried out by dry as well as wet mixing of drug and excipients in the ratios 1:1, 1:3 and 3:1. Both types of mixtures were stored at room temperature and at 55°C in oven for three days. The appropriate dilutions were done with the help of methanol and phosphate buffer of pH 7.4 and samples were scanned for λmax using UV spectroscopy and result was reported.

The pure drug along with formulation excipients were subjected to interaction studies. The study was performed by using FT-IR spectroscopy. It was performed by mixing/grinding definite proportions of drug and excipients with a specially purified salt (potassium bromide) finely (to remove scattering effects from large crystals). The powder mixture was then pressed in a mechanical press to form a translucent pellet through which the beam of the spectrometer can pass. The FT-IR peaks were found and reported.

Characterization of Bio-Lip strips

Thickness: The thickness of three randomly selected bio-lip strips was assessed at five (centre and four corners) different places on a single patch of each formulation using a micrometer screw gauge and the mean value were calculated and reported [10].

Weight uniformity study: Weight uniform study for all formulated bio-lip strips was performed by taken three randomly selected bio-lip strips from each formulation with surface area 1cm^2 were used. Each strip was weighed individually on electronic balance. The study was performed thrice and average weights were calculated and registered [10, 11].

Content uniformity: All formulated bio-lip strips were evaluated for its drug content uniformity. From each formulation the randomly selected strip (1cm^2) was transferred into a 100ml volumetric flask containing 7ml of phosphate buffer of pH7.4 and 1ml of methanol. The flask was stirred for 4 hrs on magnetic stirrer. A blank was prepared by using a drug free patch treated similarly. The solutions were filtered through a 0.45micro meter membrane. The drug content was then determined after proper dilutions by using an UV spectrophotometer (Shimadzu 1800) [10, 11].

Folding endurance: Folding endurance for all bio-lip strips containing Rosiglitazone was performed by using a strip of area 4cm^2 from each formulation. The selected bio-lip strip was subjected to folding endurance by repeatedly folding a strip at the same place until it broke. The number of folding required to break or crack a strip was taken as the folding endurance. This test was repeated thrice and overcomes was noted [12, 13].

Swelling index: Swelling study of all formulated bio lip strip was calculated by taken a bio strip from each formulation of size 1 cm^2 .the bio-lip strip was weighed on a pre-weighed cover slip. It was

kept in a Petri dish and 10 ml of phosphate buffer of pH 7.4 was transferred. After one hour, the cover slip was removed and weighed. The difference in the weights gives the weight increase due to absorption of water and swelling of bio-film. The change in weight was noted after 24 hrs [14]. The procedure was repeated thrice and swelling index(S) was determined by using below formula.

$$\% S = (X_t - X_o / X_o) 100$$

Where, Xt - weight of the swollen bio strip after time t and Xo - original weight of bio strip.

Percentage moisture absorption (PMA)

Percent moisture absorption study for all formulated bio-lip strips was conducted by taking a 1cm² of Rosiglitazone loaded bio-lip strips. The bio-lip strips were transferred into a watch glass and it was placed in dessicator containing saturated solution of Aluminium chloride and kept a side for 72hrs. At the end the weight gained by the strip was determined [15]. The study was repeated thrice and percentage moisture absorption calculated by using the below mentioned formula.

Percentage moisture absorption= [(final weight – initial weight)/initial weight] X 100

Percentage moisture loss (PML)

Percentage moisture loss study for all formulated bio lip strip was performed by taking three 1cm² strips from each formulation. The strips were cut out and weighed accurately and kept in dessicator containing fused anhydrous calcium chloride for 72 hrs. At the end the weight loss by the strips were determined [16]. The study was repeated thrice and percentage moisture loss calculated by using the below mentioned formula and reported.

Percentage moisture loss = [(initial weight – final weight) / Initial weight] X 100

Surface pH study

The surface pH of the bio lip strips containing Rosiglitazone was determined by using a glass electrode. The bio lip strips was allowed to swell by keeping it in contact with 0.5 ml of distilled water for 1 hour at room temperature. The pH was measured by bringing the electrode in contact with the surface of the bio strip and allowing it to equilibrate for 1 minute [16]. The experiments were performed in triplicate and average values were noted.

Water vapor transmission test (WVT)

WVT defined as quantity of moisture transmitted through unit area of strip in unit time. Glass-bottle (length= 5 cm, narrow mouth with internal diameter =0.8 cm) filled with 2g anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The bio strip was fixed over the adhesive and the assembly was placed in dessicator in which 200 ml of saturated sodium bromide and saturated potassium chloride solution were placed. The desiccator was tightly closed. The weighed bottle was then placed in dessicator and procedure was repeated [17, 18].

$$WVT = W/ST$$

W is the increase in weight in 24 h; S is area of strip exposed (cm²); T is exposure time.

Skin Irritancy

Primary skin irritation studies were conducted with best two optimized patch in four rabbits. Rabbits were divided into two groups of two animals. Blank strip were applied on the lip of rabbits of group I which served as control and rabbits of group II received medicated strips on their lip. Strips were changed after 6hrs with fresh strips. The study was carried out for a period of 7 days and application sites were graded for redness, erythematic or irritation visually [19].

In-Vitro Diffusion study

The *in-vitro* drug diffusion was carried out in the M.S. diffusion apparatus. This was the static method and employed complete replacement of the sample. Dialysis membrane was tied to the terminal portion of the cylindrical donor compartment. A 1cm² bio-lip strip was kept above the dialysis membrane in the donor compartment, and the receiver compartment was filled with 13 ml of diffusion medium. The complete sample was withdrawn at different time intervals and the receiver compartment was refilled with 13 ml of fresh medium. The amount of drug released was assessed by measuring the absorbance at 247nm using UV spectrophotometer (Shimadzu 1800).

Stability studies

Optimized bio lip strip was subjected to stability study. Bio strips were wrapped in Aluminum foil and packed them in glass vials. These strips were kept in an incubator (stability study chamber) maintained at 40±2°C and 75±5%R.H. for six months. The change in appearance, physical characteristics and release behavior of the stored strips were investigated after 1-6 months [20]. The data presented were the mean of three determinants.

RESULTS AND DISCUSSION

Drug-Excipients Interaction study

The drug interaction study revealed that there was no interaction between the drug and the excipients including the bio- material because there was no change in the λmax value which was observed to be 247 nm prior to the test and after the test, which

confirmed that there was no interaction between the drug and excipients. All the FT-IR peaks of Rosiglitazone were present as such in the spectra of grinded drug and excipients mixture. No observable signs of drug interaction were seen. It was conclude that none of the excipients had a detrimental effect on the drug and could be safely used for the formulation of the bio-films.

Evaluation parameters of Rosiglitazone loaded bio-lip strips

The formulated strips were smooth and translucent in appearance. The average thickness of all prepared bio-lip strips ranged from 0.45±0.03 to 0.73±0.07 mm. Thus the proportional gain in weight of strips was observed as the thickness of strips increased. The values were uniform for the strips within the respective group of formulation type. This depicts that the strips cast was uniform. Surface pH for all formulations was found to range from 6.34±0.30 to 6.83±0.19. Since range of the pH of strip is near to the skin pH. No skin irritation was expected. The folding endurance of strips was found in the range of 145±4.8 to 188±5.6. High folding endurance values for strips indicates high mechanical strength of strips. This is highly desirable because it would not allow easy dislocation of the strips from the site of application or breaking of strip during administration. No skin irritation, redness or erythema was observed during primary skin irritation studies with all formulations. Rest observations of evaluated parameters are shown in table 2.

Table 2: Evaluation of various batches of Rosiglitazone loaded bio-lip strips.

Formulation	Content uniformity (%)	Moisture uptake (%)	VTR	Weight uniformity (mg)	Moisture content (%)	Swelling index
F1	95.25±0.59	3.76±0.48	6.63±0.52	23.29±0.21	1.43±0.25	148.58±0.32
F2	96.32±0.41	3.82±0.46	6.69±0.63	26.13±0.27	0.78±0.36	117.48±0.53
F3	93.15±0.45	3.78±0.38	7.71±0.69	28.34±0.25	0.65±0.085	136.76±0.63
F4	95.73±0.52	3.45±0.42	7.26±0.74	22.75±0.35	1.25±0.092	123.37±0.66
F5	90.81±0.50	4.25±0.44	7.53±0.71	21.82±0.37	1.36±0.46	142.44±0.68
F6	96.42±0.48	4.75±0.49	7.61±0.76	27.35±0.31	1.48±0.48	109.76±0.71
F7	95.25±0.59	3.76±0.48	6.63±0.52	23.29±0.21	1.43±0.25	148.58±0.32
F8	96.32±0.41	3.82±0.46	6.69±0.63	26.13±0.27	0.78±0.36	117.48±0.53

In-vitro release

In-vitro release of Rosiglitazone from different strips is shown in fig. no. 01. Formulations F1 to F8 showed drug release in a controlled manner. Formulation F2 showed the maximum release of 92.06% at the end of 24hrs. The results showed that initially drug release decreases with increasing the concentration of biomaterial and further drug release increased. We could not detect any exact relationship between the drug release profile and polymer composition may be due to release mechanism which governed by diffusion as well as erosion controlled, since our biomaterial is slightly soluble in water. The release data of the tested strips were analyzed on the basis of Krosmeyer-Peppas equation and Higuchi kinetics (by BIT-SOFT 1.12: drug release kinetics with model fitting). Coefficients of correlation (R^2) were used to evaluate the accuracy of fit. The R^2 value for Higuchi and Peppas kinetic models were calculated and compared. All the tested formulations gave good fit to the Krosmeyer-Peppas model (fig. no. 02). All formulations showed non-Fickian drug release ($0.5<n<1$). The in-vitro release obtained by Translabial strip were significantly ($p<0.05$) different from standard formulations. On the basis of above parameters and used concentration of biomaterial F3 was selected as the best formulation. The *in vitro* studies have shown that this is a potential drug delivery system for Rosiglitazone with considerable good stability and release profile.

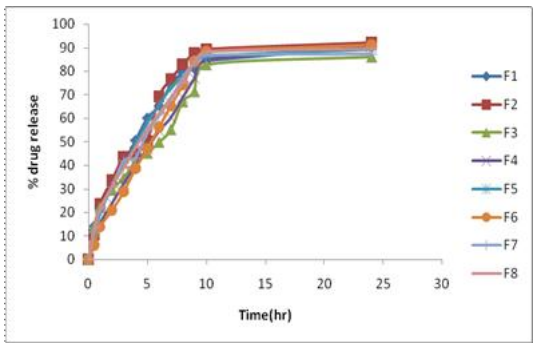

Figure 01: In-Vitro drug release profile for batch F1-F8

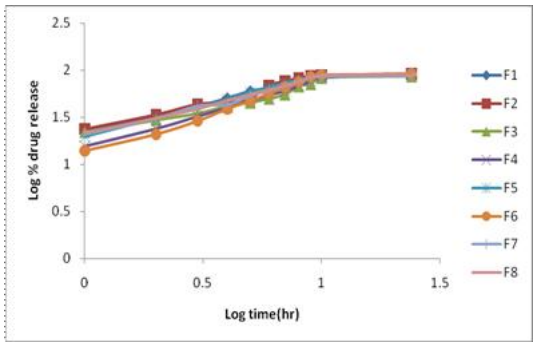

Figure 02: Korsmeyer-Peppas model for Rosiglitazone loaded biolip-strips.

Stability study

At the end of stability study, the tested strips showed similar drug content as observed at the beginning of the study. They also showed insignificant difference for in-vitro drug release. All optimized strips showed satisfactory flexibility and elastic properties during and at the end of the accelerated stability period. These all indicated that there were no influences on the chemical and physical stability of the formulation during the test period.

CONCLUSION

In the present study bioadhesive bio-lip strips based on *Artocarpus heterophyllus* biomaterial was developed, which released the drug over the required period of time which would prevent first-pass metabolism. Thus, an attempt of formulating a stable bio adhesive bio-lip strip of Rosiglitazone for treatment of diabetes using novel biomaterial was made by optimization technique. Thus, this natural biomaterial could be a promising excipient for systemic delivery of drugs through labial route and other transdermal route.

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Source of support: Nil
Conflict of interest: None Declared