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Formulation and evaluation of inclusion complexed repaglinide with β-cyclodextrin transdermal patches

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***Abstract*---**Chronic diseases such as diabetes mellitus have high prevalence all over the world. The purpose of the study is to prepare a transdermal patch that can be used to treat diabetes, reducing pill burden and increasing patient compliance. Based on positive results of a feasibility study, including doctor's opinion and prescription survey, repaglinide was selected as the active ingredients for developing a transdermal patch. The complexation of repaglinide and β cyclodextrin was done by grinding method. The present study was designed to develop Matrix type systems of transdermal patch containing repaglinide- β cyclodextrin complexes, using different polymeric combinations such as Hydroxy Propyl Methyl cellulose (HPMC), Ethyl Cellulose (EC), and Eudragit L100 with Poly vinyl pyrolidone (PVP) by solvent evaporation technique. The patches were subjected to physicochemical parameters, *in-vitro* drug release and *in-vitro* skin permeation studies. Good results were obtained in all the evaluated parameters. The developed transdermal delivery system containing complex of repaglinide and β cyclodextrin can further be studied for launching it in market.

***Keywords*---**Transdermal drug delivery, penetration enhancers, Diabetes Mellitus, Hypertension.

Introduction

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs [1]. The skin as a site of drug delivery has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric

irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy, provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation, the reduction of fluctuations in plasma levels of drugs, and avoid pain associated with injections. The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects [2].

Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged ill health and early death. It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency, and it is often combined with insulin resistance [3]. Repaglinide is an oral blood glucose lowering drug of the meglitinide class use to treat NIDDM (noninsulin-dependent diabetes mellitus). It lowers blood glucose by stimulating the release of insulin from the pancreas. It has an extremely short half-life of 1 h. In addition, the oral bioavailability of Repaglinide is low (56%) due to extensive hepatic first-pass effect. Dosage frequency of Repaglinide is 0.5 to 4mg in 3 to 4 times in a day. It has melting point of 130-131◦C and mol. wt. 452.58 [4–5]. It belongs to class 2 drug. Repaglinide topical preparation may be beneficial to the patient since it reduce adverse effects and avoid the hepatic first-pass metabolism. The need for transdermal delivery of Repaglinide is further justified due to the requirement of maintaining unfluctuating plasma concentrations for effective management of blood sugar for long period in diabetic patients. The purpose of the present work was to develop transdermal formulation of repaglinide which increases the patient compliance and also sustain the release of drug to increase the bioavailability.

Material and Method

Repaglinide was received as a gift sample from Torrent Pharmaceutical Ltd., Gujarat, India. B-cyclodextrin was procured from Sigma Chemical Company, St.Louis, USA. Eudragit L100 was received as gift sample from Corel Pharma, Ahmedabad. HPMC, EC and PVP were purchased from SD fine—Chem. Ltd, Mumbai. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Preparation of inclusion complexes

The complexation of repaglinide-β-cyclodextrin (1:1, 1:2, 1:3, molar ratio, respectively) was prepared by the grinding method as described by Mura et. Al [6]. In detail, repaglinide and β –cyclodextrin with different molar ratios were grinded with 50% (v/v) ethanol for 0.5 h. The inclusion complexes were washed with methanol three times to remove free repaglinide and then dried at 50°C to obtain a dry powder.

Preparation of Transdermal Patch.

Drug-inclusion complex loaded matrix- type transdermal patches of Repaglinide were prepared by using solvent casting method. Di-butylphthalate was

incorporated as a plasticizer at a concentration of 20% w/w of dry weight of polymers. Backing membrane was casted by pouring and then evaporating 4% aqueous solution of polyvinyl alcohol in a petridish containing glycerin at 60°C for 6h. The drug matrix was prepared by dissolving the different polymer (PVP with HPMC or EC or Eudragit L100) in different ratio with drug complexes in dimethylformamide solvent. The homogeneous dispersion was prepared by slow stirring with a magnetic stirrer. Prepared homogeneous dispersion with plasticizer poured on the prepared backing membrane. The dispersion was evaporated slowly at 40°C for 2 hours to achieve a drug polymer matrix patch. After complete drying, patch were removed from the petridish and kept in desiccators until use [7]. The ingredients and their quantities are shown in Table No. 1.

Table No. 1: Formulation Table of transdermal patch

S. No.	Formulation code	Polymer (mg)				Drug complex (mg)
		PVP	HPMC	EUD.L 100	EC	
1	F1	300	200	-	-	200
2	F2	200	300	-	-	200
3	F3	100	400	-	-	200
4	F4	300	-	-	200	200
5	F5	200	-	-	300	200
6	F6	100	-	-	400	200
7	F7	300	-	200	-	200
8	F8	200	-	300	-	200
9	F9	100	-	400	-	200

Physicochemical evaluation of transdermal patch
Thickness of the patch

For evaluation of patch thickness three patches of each formulation were taken and the film thickness was measured using micrometer screw gauge at three different places and the mean value was calculated.

Uniformity of weight
Each film was weighed individually and average weight of three films was found out [8].

Drug content determination

The patch were taken into a 100 ml volumetric flask containing phosphate buffer and the flask was sonicated for 2 h. A blank was prepared in the same manner using a drug-free placebo patch. The solution was then filtered using a 0.45- µm filter and the drug content was analyzed at 281 nm [9]

Moisture content

The patches were weighed individually and kept in a desiccator containing 10g calcium chloride at 40^{o} C for 24 hr. The final weight was noted when there was no

further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to initial weight [10]

$$\%\ Moisture\ content = \frac{Initial\ weight - final\ weight}{final\ weight} \times 100$$

Uptake Moisture

The films were weighed accurately and placed in a desiccators containing 100 ml of saturated solution of aluminium chloride (79.50% RH). After 3 days, the films were taken out and weighed, the percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [11]

$$\%\ Moisture\ uptake = \frac{final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

Water absorption capacity

To determine the water absorption capacity of the patches, three weighed patches of the same composition were kept at room temperature for 24 h and exposed to two relative humidity's of 75% (a saturated solution of sodium chloride) and 93% (a saturated solution of ammonium hydrogen phosphate) in different desiccators at room temperature. The water absorption capacity of the patches was determined as the percentage increase in the weight of the patch divided by its initial weight. The weights were periodically recorded until a constant weight was obtained. An average was recorded.

Water vapor transmission rate

The film was fixed over the brim of a glass vial of 5ml capacity, containing 3 g of fused calcium chloride as desiccant and polymer film of 2.26 cm^2. The vial was weighed and kept in desiccator containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed after 24 hrs. The water vapor transmission rate was calculated from the plots of amount of water vapor transmitted versus time.

$$\text{Waer vapour transmission rate} = \frac{final\ weight - Initial\ weight}{Time \times Area} \times 100$$

Water vapour transmission rate usually expressed as the number of grams of moisture/hr/sq cm from the data obtained water vapour transmission calculated [12]

Swellability

The patches of 33.15 cm^2 was weighed and put in a petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed. The degree of swelling (% S) was calculated using the formula

$$\% \text{ Swelling } = \frac{Wt - Wo}{Wo} \times 100$$

Where S is percent swelling, Wt is the weight of patch at time t and Wo is the weight of patch at time zero.

Surface pH

Surface pH was determine by the patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute

Flatness

A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, Three longitudinal strips were cut out from each film: 1 from the center, 1 from the left side, and 1 from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

$$\% \text{ Constriction } = \frac{L1 - L2}{L2} \times 100$$

Where L_1 = initial length of each strip, L_2 = final length of each strip.[102,119]

Folding Endurance

It was determined by repeatedly folding a patch at the same place till it broke. The number of times, the patch could be folded at the same place without breaking gave the value of folding endurance.

Tensile Strength

The tensile strength was determined by the apparatus designed in lab. The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds transdermal patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three patch were having 33.15 cm^2.The rate of change of stress was kept constant with the increment of 0.5g per 2 minutes. The elongation was observed and the total weights taken were used for calculation. The tensile strength was calculated by using following formula.

$$\text{Tenstile stress} = \frac{apllied\ force}{Lcross\ section\ area} = \frac{m \times g}{b \times t}$$

Where, S = tensile stress in 980 dynes/cm2, m = mass in grams

g = acceleration due to gravity (980 dynes/cm^2), b = breadth of strip in centimeters
t = thickness of strip in centimeters
The strain is change resulting in size of strip after the force was applied to its original size. Therefore, the strain can be given as, see from above eq.(elongation).

Elongation

The percent elongation at break was measured by formula given below

$$\%\ \text{Elongation at break} = \frac{L - Lo}{Lo} \times 100$$

Where, L = length after force was applied Lo = original length [10]

Drug excipients compatibility study

Compatibility of the drug with formulation excipients was determined by FT-IR spectral analysis. The spectra were recorded in the wavelength region between 4000 cm^{-1} and 400cm^{-1}. The spectra obtained for repaglidine and physical mixtures of drug with polymers were compared to study any possible drug polymer interactions [14-17].

***In-vitro* release studies**

The *In vitro* release studies were carried out in a Franz diffusion cell. A piece of matrix patch (circular, 3.5 cm diameter) was mounted carefully on the donor compartment. The donor compartment was empty and the backing membrane side of the matrix patch was open to the atmosphere while the receptor compartment was filled with freshly prepared phosphate buffer pH 7.4. Outside the receptor compartment, water from a constant temperature bath flowed continuously through the jacket at 37±0.5°C. The receptor liquid was slowly stirred by magnetic stirrer at 40-50 rpm. The temperature in the release/permeation area was maintained at 37±0.5°C. The volume of the receptor liquid (90 ml) was such that the piece of the matrix patch (drug side) just touches the receptor liquid surface horizontally for molecular diffusion. Samples (2 ml) were withdrawn at 1 hr intervals up to 24 h and replaced immediately with the same volume of 7.4 Phosphate Buffer solutions. Samples were analyzed by UV at 281 nm after suitable dilution.

Result and Discussion

Transdermal drug delivery systems can act on the topical skin. It can also deliver drugs to the blood circulation through skin. TDDS enjoys numerous advantages over the conventional dosage forms. Enhancement of the patient compliance by decreasing the dose frequency, lesser adverse effects and noninvasive delivery of drugs are a few amongst many advantages [18].

All the transdermal patches containing HPMC, EC and EUDRAGIT L100 with drug complexes were prepared by solvent casting method. Dimethylformamide

was used to dissolve all the polymer and drugs. The patches with higher percentage of EC and EUDRAGIT L100 could not be prepared easily because they could not be removed easily from the petridish in which they were cast. The patches which containing HPMC were produced smooth and flexible. Where those prepared from EC and EUDRAGIT L100 were slightly rough in texture. The prepared patches were slightly pale yellow in appearance and possessed uniform surface. Drug complex was uniformly distribution through the matrix patch. There were no observable particles of drug in the matrix patch.

Prepared transdermal patches were evaluated for thickness at various points. The thickness of the patches varied from 0.30mm±0.005 to 0.33±0.01 showed in table 2. The thickness of all batches with low SD values indicates the physical uniformity of prepared patches. Formulation F_3 (containing HPMC), formulation F_4 and F_6 (containing EC) having the highest thickness 0.33±0.01 because of these formulation having highest mass among all formulation. The average weight of all the patches was found in the range between 970.2±0.11to 990.8±0.05 reported in table 2. Three patches from all the formulations were used for standard deviation, which indicates that the patches from all the batches were found uniform in their weight. Result indicated that the formulation F_5 having the least weight among the different formulation. All the formulation show uniform drug content as seen in the table 2. The low value of SD indicated that the drug was uniformly distributed through the patches. The drug content was in the range of 81.14±1.09 to 98.34±0.49%.

Moisture content of the formulation exhibit that with the increase in the concentration of hydrophilic polymer the percentage of moisture content was increased. The moisture content was found to be greater with the increase of HPMC and Eudragit L100 as compare to hydrophobic polymer EC. The moisture content of the prepared formulation was low 1.29±0.054 to 2.87±0.016 which could help the formulation remain stable and reduce brittleness during long term storage.

Table 2: Physicochemical evaluations of transdermal patches (Thickness, Uniformity of weight and drug content)

Formulation Code	Thickness (mm±SD)	Uniformity of weight (mg±SD)	Drug content (%±SD)
F_1	0.30±0.005	990.8±0.05	97.35±0.51
F_2	0.31±0.005	990.5±0.32	90.88±2.33
F_3	0.33±0.010	990.6±0.37	98.34±0.49
F_4	0.33±0.005	980.7±0.05	88.20±0.35
F_5	0.30±0.005	980.8±0.11	81.14±1.09
F_6	0.33±0.010	970.2±0.11	81.27±1.36
F_7	0.30±0.005	980.2±0.05	96.09±0.97
F_8	0.31±0.005	980.6±-.050	84.22±1.04
F_9	0.30±0.005	980.7±0.20	92.16±0.75

SD = Mean Standard Deviation, n = 3.

Table 3: Physicochemical evaluations of transversal patches (Moisture content, moisture uptake, water absorption capacity)

Formulation Code	Moisture Content % ± SD	Moisture Uptake %± SD	Water absorption capacity %± SD	
			75%RH	93%RH
F1	2.44±0.097	4.57±0.015	4.52±0.408	5.35±0.035
F2	2.65±0.004	4.64±0.026	5.98±0.010	6.97±0.005
F3	2.87±0.016	4.87±0.015	4.84±0.051	5.84±0.055
F4	1.29±0.054	2.52±0.015	1.14±0.043	1.13±0.049
F5	1.42±0.012	2.43±0.020	1.23±0.015	1.27±0.020
F6	1.48±0.009	2.32±0.020	1.35±0.036	1.37±0.020
F7	1.85±0.030	3.32±0.015	2.42±0.020	2.41±0.010
F8	1.88±0.016	3.42±0.015	2.98±0.010	2.98±0.005
F9	1.98±0.004	3.68±0.005	2.26±0.026	2.36±0.026

SD = Mean Standard Deviation, n = 3.

The formulation F_6 showed lowest percent moisture uptake than other formulations. This might be because of the low water permeability of ethyl cellulose polymer. Formulation F_3 showed highest moisture uptake due to hydrophilic polymer. The low moisture uptake protects the patches from microbial contamination and bulkiness. The values for the moisture uptake have been given in the table 3. The high water absorption capacity was found in F_2 formulation as 5.84±0.055 and the formulation F_4 has shown minimum water absorption as 1.14±0.043 at 75% RH. The high water absorption capacity was found in F_2 formulation 6.97±0.005 and the formulation F_4 has shown minimum water absorption as 1.13±0.049 at 93% RH. The hydrophilic nature of PVP and HPMC has to be taken into account with regard to their higher water absorption capacity. Water absorption capacity of all formulation has shown in table 3.

Table 4: Physicochemical evaluations of transdermal patches

Formulation Code	Water vapor transmission rate % ± SD	Surface pH	Swellability % ± SD	
			5 Mint	10Mint
F_1	3.88±0.010	6.2±0.05	5.28±0.060	6.86±0.036
F_2	3.86±0.020	6.2±0.10	5.95±0.005	7.24±0.055
F_3	4.12±0.011	6.2±0.11	6.25±0.050	9.45±0,040
F_4	1.88±0.010	6.0±0.55	2.74±0.045	3.87±0.020
F_5	1.77±0.020	6.1±0.20	2.61±0.055	3.77±0.015
F_6	1.23±0.020	6.0±0.57	2.44±0.035	3.35±0.051
F_7	2.76±0.020	6.2±0.34	3.78±0.010	6.27±0.057
F_8	3.97±0.005	6.0±0.17	3.54±0.030	5.64±0.064
F_9	2.87±0.015	6.1±0.30	3.28±0.060	4.98±0.014

SD = Mean Standard Deviation, n = 3.

Table 5: Physicochemical evaluations of transdermal patches

Formulation Code	Flatness (%)	Folding endurance	Tensile Strength gm/cm^2	Elongation % ± SD
F_1	100	310±1.52	294.64±0.451	23.02±0.723
F_2	100	307±2.08	293.85±0.782	21.96±0.632
F_3	100	299±2.64	291.48±1.065	23.50±0.040
F_4	100	287±1.52	260.84±0.743	18.70±0.365
F_5	100	286±1.73	262.51±0.295	19.36±0.185
F_6	100	287±1.52	261.23±0.451	16.43±0.100
F_7	100	291±1.52	287.64±0.782	19.69±0.304
F_8	100	295±1.52	288.72±0.615	18.64±0.574
F_9	100	297±1.52	288.23±0.886	19.43±0.850

SD = Mean Standard Deviation, n = 3.

The water vapour transmission rate was accelerated due to presence of hydrophilic nature of polymer. Incorporation of hydrophobic polymer in patches such as EC and Eudragit RL 100, they were reduces the value of water vapor transmission. Formulation F6 shown less water transmission of vapor. Formulation F_3 and formulation F_8 showed good water vapor permeation than that of EC containing patches. All the formulations were permeable to water vapor. Water vapour transmission rate of all formulation has shown in table 4. The study of the swelling of polymers used in sustained release applications has been an area of interest because it is believed that it affects drug release from controlled release matrix. The consequence of water uptake could be the formation of empty spaces within the patch that could make its structure less resistant to mechanical stresses. The HPMC: PVP and Euragit RL100: PVP patches showed more pronounced swelling as compared to EC: PVP patches. The high swellability was found in F_3 formulation as 6.25±0.050% at 5mint and 9.45±0.040% at 10mint. The formulation F_6 has shown minimum swellability as 2.44±0.035% at 5mint and 3.35±0.051% at 10mint. The swellability varied with nature and composition of patches. Hydrophilic polymer showed considerable swelling, as it increased the surface wettability and consequently water penetration within the matrix. Swellability of all formulation has shown in table 4. An acidic or alkaline pH of administered dosage forms can irritate the skin. The measured surface pH was found to be close to neutral in all the formulations which means that they have less potential to irritate the skin and therefore they should be fairly comfortable. The surface pH of all the formulation exhibited almost uniformity in their values and they were found between 6.2±0.05 to 6.0±0.57. The surface pH of all formulation has shown in table 4.

Flatness was calculated by measuring constriction of patch. A 100% flatness of all the formulation indicates no amount of constriction in formulated transdermal patches. All patches had a smooth, flat surface, and that smooth surface could be maintained when the patch was applied to the skin. The flatness of all formulation has shown in table 5. The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The result indicated that the patches would not break and would maintain their integrity with general

skin than patches containing EC. Patches did not show any crack even after folding for more than 300 times. The folding endurance of all formulation has shown in table 5. Tensile strength of the prepared patches was measured using instrument designed at laboratory. The tensile strength of prepared patch was fond in the ranged between 260.84±0.743 to 294.64±0.451 gm/ cm^2. The tensile strength of the patches was found to vary with the nature of polymer and plasticizer. Polymer combination PVP: HPMC possed high tensile strength than PVP:EC and PVP: Eudragit L100 patches. In the formulation increased HPMC proportion the tensile strength of patch was increased. It reflects that hydrophilic polymer develops cross linking better than hydrophobic polymer. The tensile strength of all formulation has shown in table 5. The percentage elongation value of fresh patches whose were directly proportional to the value of tensile strength. Formulation contain HPMC (F_1, F_3, F_4) shown increased percentage elongation. Because HPMC is soft and tough polymer which shows a high tensile strength and percentage elongation. Formulation F3 shown 23.50±0.160 maximum elongation and F_6 shown 16.43±0.100 minimum elongation. The percentage elongation value of all formulation has shown in table 5.

Compatibility studies of pure drug repaglidine and formulation were carried out. IR spectra of pure drug and that of with polymers were obtained. All the characteristic peaks of drug were present in spectra of physical mixture, thus indicating compatibility between drug and polymer. It shows that there was no significant change in the chemical integrity of the drugs.

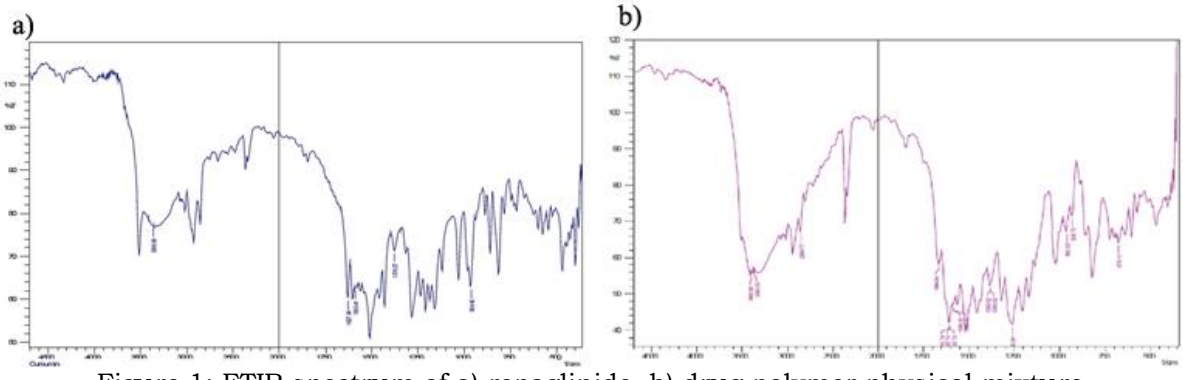

Figure 1: FTIR spectrum of a) repaglinide, b) drug polymer physical mixture

In vitro drug release studies in phosphate buffer show more than 50% release of repaglinide from all formulations. This could be attributed to the higher rate and extent of swelling of the larger proportion of the hydrophilic polymer, HPMC. The higher percentage of the retardant polymers EC and Eudragit L 100 was responsible for the comparatively slower drug release from HPMC containing patches.

Increasing the proportion of hydrophilic polymer (HPMC) concentration in the polymer matrix increases the % cumulative drug release because of highly hydrophilic nature of HPMC, which has very less interactions with drug. Due to its high hydrophilicity it absorbs water, dissolution of aqueous soluble fraction of polymer matrix leads to the swelling of polymer which results into more release of

drug from gelaneous pores of the films because of adequate porosity & diffusivity. The formation of such pores leads to decrease the mean diffusion path length of the drug molecules to release and permeates into the diffusion medium & hence, to cause higher release rate. EC and Eudragit L100 attributed to the relatively hydrophobic nature of polymer which were having less affinity for water, results in decrease in thermodynamic activity of the drug in the film & decreased drug release and permeation was obtained. Eudragit L100 and EC can be used as 'better release retardant' at higher concentration as compared to the HPMC. *In - vitro* release studies data of all formulation are shown in figure 2.

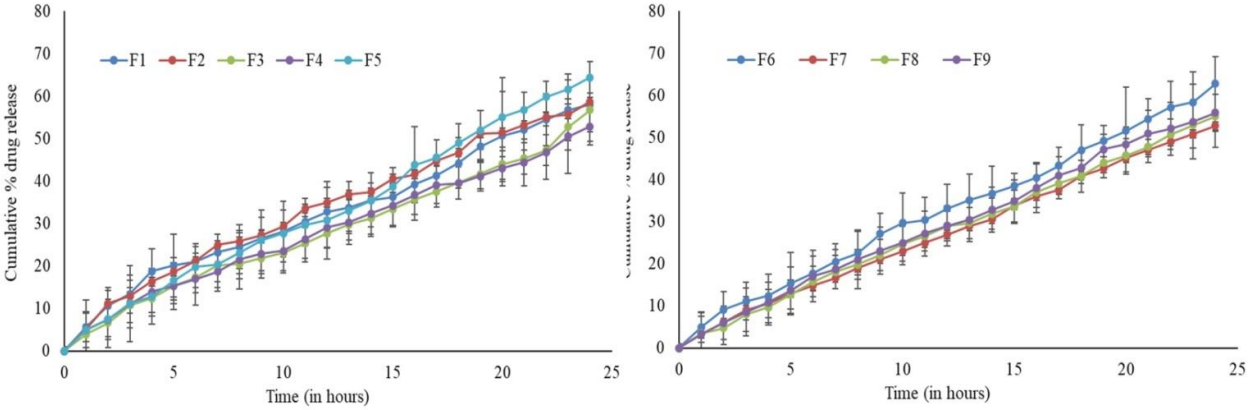

Fig 2: In vitro drug release of formulation F1 – F9

Conclusion

Transdermal route is an attractive alternative route for drugs exhibiting low bioavailability due to extensive first-pass metabolism. This investigation shows that the transdermal patch of repaglinide can be formulated with the intention of obtaining better therapeutic efficiency by controlling drug release thereby improving patient compliance and increasing bioavailability with decreased dosing and fewer side effects. Based on physicochemical evaluation of patch and in vitro release studies, formulation F_3, shows better result. On the basis of these *in- vitro* evaluation of the transdermal formulations it can reasonably be concluded that repaglinide can be formulated into trasdermal polymeric patches for development of a transdermal drug delivery system

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