Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

PREPARATION AND CHARACTERIZATION OF POLYMERIC MATRIX DIFFUSIONAL RECTAL PATCHES OF DILTIAZEM

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ABSTRACT

The present work deals with the development of Diltiazem base loaded polymeric matrix using different polymers. The preliminary screening was carried out for the selection of best polymer. A diffusion mediated matrix controlled rectal drug delivery system for Diltiazem base was successfully prepared using different polymers like EVA(VA 40%), EC, ERS 100 and combination polymer ratios of ERL 100: ERS 100 in the ratios of 1: 4 using mercury substrate method and all matrices were evaluated using different physiochemical parameters. Out of four formulations, F1 was the optimized formulation with maximum Q/square root of T release rate.

KEY WORDS

Diltiazem base, Diffusion, Polymers and Mercury substrate method.

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INTRODUCTION

Conventional systems of medication that require multi dose therapy are having many problems. The controlled drug delivery is a newer approach is to deliver drug in to systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only by passes hepatic ‘first pass’ elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug in to systemic circulation. Following skin

permeation, the drugs first reach the systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action.

Rectal drug delivery offers the following potential advantages[1-3]

- Avoid the risks and inconveniences of intravenous therapy and of varied conditions of absorption and metabolism associated with the oral therapy.
- Continuity of drug administration in CDDS permits the use of a drug with short biological half-life.
- Rectal drug delivery improves the bioavailability that reduces the total daily dose.
- Avoids first-pass hepatic metabolism.
- Less chances of over or under dosing as the result of prolonged preprogrammed delivery of drug at the required therapeutic rate.
- Decrease gastrointestinal side effects.
- Elimination drug food interactions.
- Increased patient compliance in following manner
  - Provisions of simplified therapeutic regimen.
  - Painless delivery of drug.
  - Eliminates swallowing.
  - No chances of forgetting the dose.
  - Easy to carry a patch in wallet.
- Patches offer less friability problems of wear and tear than the tablets.
- In a multi-drug regimen RDDS avoids drug interaction in GIT.
- It is easy to terminate the medication simply by removing the drug delivery device from the skin surface.
- RDDS system can be taken without any aid, which makes it most suitable formulation; for instance, tablet and capsule need little water. Liquid oral preparation needs teaspoon and parentaral delivery needs specialized person whereas if a patient is told to apply RDDS patch, he/she can do it anywhere e.g. in office, in theatre, in club, in house without any aid.
- Chance of toxicity due to additives e.g. preservatives, stabilizing agent antioxidants etc. are less as compared to other dosage forms.
- Problem of dose dumping is least in RDDS, because stratum corneum is more resistant than the inner membranes (i.e. mucous membrane in case of oral controlled release delivery systems) and stratum corneum itself is a rate limiting factor.
- Need not to be sterile, obviates processing problem.

Disadvantages of rectal drug delivery system[4]

The limitation of rectal drug delivery is principally associated with skins barrier function, which severely constrains the absolute amount of drug that can be absorbed across reasonable area of skin during the dosing period. Thus, the major disadvantage of the method is that it is limited to potent drug molecule typically those requiring a daily dose on the order of 20 mg or less.

Even if the drug is sufficiently potent, it must yet satisfy other criteria to be considered a viable candidate for rectal drug delivery. For example its physiochemical properties must allow to be absorbed percutaneously. This mean that its molecular weight should ideally be less than 500 Daltons and it should have adequate solubility in both lipophillic and aqueous environments since, to reach dermal micro circulation and gain access to systemic circulation, the molecule must cross that stratum corneum (a lipid barrier) and then transfer through the much-more-aqueous-in-nature viable epidermis and upper dermis. Absence of either oil or water solubility altogether, will preclude permeation at a useful rate.

The pharmacokinetic and pharmacodynamic characteristic of the drug must be such that relatively sustained and slow input provided by rectal delivery makes sense. Tolerance inducing compounds are not intelligent choice for this mode of administration unless until an appropriate “wash out” period is programmed into the dosing regimen.

Drugs that can be given once a day orally, with reproducible bioavailability and which are well

tolerated by patient do not really need a patch formulation.

Materials and methods Preparation of polymeric matrix device

Matrix – type rectal patches containing Diltiazem were prepared using different ratios of drug to polymers (Table No.1). The polymers were weighed in required ratios keeping the total polymer weight 800mg, and dissolved in a given solvent. Diethyl Phathalate (2% w/w of polymer composition), Di-n-butyl Phalate (30% w/w of polymer composition) and glycerin (40% w/w of polymer composition) were used as a plasticizer for EVA, ERL100, ERS100 and EC respectively. Diltiazem (533.33mg) was added and mixed using a mechanical stirrer. The uniform dispersion of polymeric solution of drug (10 ml) was poured on the mercury surface (73.86 cm^2), and dried at room temperature. After 24h, the films were cut into a 3.14 cm^2 area and backing membrane (biaxial oriented polyethylene film) was then glued. A glossy paper having a smooth surface was used as a release liner. The devices were stored in desiccators until used (Figure No.1).

PHYSIOCHEMICAL EVALUATION OF POLYMERIC MATRIX DEVICE

Thickness

The thickness of the laminate was assessed at six different points of the prepared medicated film using thickness gauge micrometer (0.001mm, Mitutoyo, Japan). For each formulation, three randomly selected laminated were used.

Weight Variation

The weight variation for each batch was determined using Sartorius electronic balance (Model CP-224 S), Shimadzu, Japan. Six patch from each batch (3.14 cm^2), were weighed individually and the average weight was calculated.

Drug Content

The Diltiazem content of each prepared film was measured in triplicate and analyzed by UV-VIS spectrophotometer and expressed as the percentage of nominal lode**.** Patches (n=3) of specified area (3.14 cm^2), were cut and weighed accurately. The pieces were taken into 100 ml volumetric flask and dissolved in respective solvent. The solution was filtered through whatman filter paper (Nyulge Nune, UK). This stock solution was diluted 100 times using respective solvent and the absorbance of the resulting solution was measured at specific wavelength. The content of Diltiazem was calculated at 281.5 nm for toluene and 259 nm for chloroform using calibration curve prepared using respective solvent system[3,4].

Flatness

The flatness was measured manually for the prepared films. Longitudinal strips were cut out from each film, one from the center and two from either side. The length of each strip was measured and the variation in the length because of non-uniformity in flatness was measured by determining percentage constriction, considering 0% constriction is equivalent to 100 % flatness[5]. Flatness was determined using below given formula:

$$\% \text{ Constriction} = [(l1 - l2)/ l2] * 100$$

Where,

l_1 = Initial length of each strip

l_2 = Final length of each strip

The flatness for Diltiazem matrices was measured in triplicate and average reading was considered.

Folding Endurance

The folding endurance was measured manually for the prepared films. The folding endurance of the films was determined by repeatedly folding a strip measuring 2x2 cm size at same place till it break[6]. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Moisture Content (Loss on Drying)[7]

The inherent moisture presents in material may influence the stability of dosage forms, especially if it contains a drug that is sensitive to water. The absolute method is employed to determine the moisture content which gives a weight loss registered during process.

Three patch from each batch (3.14 cm^2), were weighed individually and the average weight was calculated. This weight was considered as an Initial weight. Then all the patches were kept in a

desiccators containing activated Silica at normal room temperature for 24hr. The final weight was noted when there was no further change in the weight of individual patch. The percentage moisture absorption was calculated as a difference between initial and final weight with respect to final weight.

% Moisture content = [(Initial weight – Final weight)/ Final weight]* 100

Moisture Absorption[8]

Moisture uptake also influences the stability of dosage form. Low moisture uptake protects the material from microbial contamination. So for Rectal drug delivery system it is necessary to determine % Moisture absorption of matrices.

Three patch from each batch (3.14 cm^2), were weighed individually and the average weight was calculated. This weight was considered as an Initial weight. Then all the patches were kept in a desiccators containing 200 ml saturated solution of Sodium chloride (Relative humidity of 75%) at normal room temperature for 72h. The final weight was noted when there was no further change in the weight of individual patch. The percentage moisture absorption was calculated as a difference between final and initial weight with respect to initial weight. The % Moisture absorption was determined using below formula:

% Moisture absorption = [(Final weight – Initial weight)/ Initial weight]* 100

Water Vapor Transmission Rate (%WVTR)[9]

For this study vials of equal diameters were used as transmission cells. These cells were washed thoroughly and dried in oven, about 1 gm of activated silica was taken in cells and the polymeric films measuring 3.14cm^2 were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccators containing 200 ml saturated solution of potassium chloride. The cells were taken out and weighed after 6, 12, 24, 36, 48 and 72 hr of storage. The amount and rate of water vapor transmitted was calculated by the difference in weight using below given formula:

% Water vapor transmission rate = (Final weight-Initial weight)/ time * Area

RESULTS AND DISCUSSION

The present investigation deals with the development of Diltiazem base loaded polymeric matrix using different polymers. The preliminary screening was carried out for the selection of best polymer.

A diffusion mediated matrix controlled Rectal drug delivery system for Diltiazem base was successfully prepared using different polymers using mercury subtract method and all matrices were evaluated using different physiochemical parameters.

Thickness

With the help of micrometer (0.001mm), Mitutoyo, Japan, the thickness of film was measured at six different points and the average thickness was noted. The thickness results are given in Table No.2. The results indicate that there was no much difference in the thickness with in the formulations. Thickness in the different formulations was in the range of 173.33 ± 1.443 μm to 85 ± 2.5 μm. Maximum thickness was found in formulation F1, while minimum found in formulation F4. These results revealed that thickness was found to increase as hydrophobic portion of polymer increases. The results of thickness also indicate uniform distribution of the drug and polymer over the mercury surface. The rank order of thickness of Diltiazem loaded polymeric matrices was

EVA (40% vinyl acetate)> EC> ERS 100> ERL100:ERS100 (1:4).

Weight Variation

Drug loaded films (3.14cm2) were weighed using Sartorius electronic balance (Model CP-224 S), Shimadzu, Japan and the results of weight variation are given in Table No.3. The weight of 3.14 cm^2 film ranged from 50.30 ± 0.100 mg to 58 ± 0.500 mg. The weight of the patches was found to be uniform among different batches.

*Standard deviation, n=3

In a weight variation test, the pharmacopoeial limit for the percentage deviation of all the films of less than mg is ± 10%. The average percentage deviation of all formulations was found to be within the limit, and hence all the formulation passed the test for

weight variation as per official requirements. All the formulations showed acceptable pharmaco-technincal properties. From the results obtained, it was clear that there was proper distribution of Diltiazem in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation, with acceptable deviation.

Drug Content

Drug content of the matrices was carried out to ascertain that the loading of drug is uniform in the formulation. The results obtained are represented in Table No.4.

The films were found to contain 97.87% - 101.23% of the labeled amount of Diltiazem indicating uniformity of drug content. The average percentage deviation of all formulations was found to be within the limit, and hence all the formulation passed the test for content uniformity as per official requirements. All the formulations showed acceptable pharmaco-technincal properties. From the results obtained, it was clear that there was proper distribution of Diltiazem in the film formulations. Hence it was concluded that drug was uniformly distributed in all the formulation, with acceptable deviation.

The drug content analyses of prepared formulation showed that the process employed to prepared patches was capable of giving uniform drug content, with minimum batch variability.

Flatness

The flatness was measured manually for the prepared films. An ideal patch should be formulated in such a way that it possesses a smooth surface and it should not constrict with time. Flatness studies were performed to assess the same. The results of the flatness study showed that none of the formulations had the differences in the strip length before and after their cuts. It indicates 100% flatness observed in the formulated patches. Thus, no amount of constriction was observed in the film of any formulation and it indicates smooth flat surface of the patches and thus they could maintain a smooth surface when applied on to the skin.

Folding Endurance

Folding endurance was determined manually for drug loaded polymeric matrices. The folding endurance of the films was determined by repeatedly folding a strip measuring 2x2 cm size at same place till it break. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The results of folding endurance are given in Table No.5.

Here formulation F1 and formulation F2 shows good folding endurance as compare to formulation F3 and F4.

Moisture Content (Loss on Drying)

The moisture content was determined by keeping the drug loaded polymeric matrix patches in desiccator containing activated silica for 24hr. The percentage moisture content was calculated from the weight differences relative to the final weight. The results of the moisture content studies for different formulations are shown in Figure No.2.

The moisture content in all the formulations was found to be low and ranged from 0.681 ± 0.019 to 3.181 ± 0.024%. The result revealed that the moisture content was found to increase with increasing concentration of hydrophilic polymers. The small moisture content in the formulations helps them to remain stable and from being a completely dried and brittle film. The rank order of % moisture content of Diltiazem loaded polymeric matrices was EVA (40% vinyl acetate) < EC < ERS 100 < ERL100:ERS100 (1:4)

Moisture Absorption

Moisture uptake also influences the stability of dosage form. Low moisture uptake protects the material from microbial contamination. So for Rectal drug delivery system it was necessary to determine % Moisture absorption of matrices.

The results of the moisture content studies for different formulations are shown in Figure No.3.

The moisture absorption in all the formulations was found to be low and ranged from 0.7584 ± 0.0276 to 3.2617 ± 0.05696%. The result revealed that the moisture absorption was found to increase with increasing concentration of hydrophilic polymers. The small moisture absorption in the formulations

helps them to remain stable and protects the material from microbial contamination and bulkiness of the patches. The rank order of % moisture absorption for Diltiazem loaded matrices was EVA (40% vinyl acetate) < EC < ERS 100 < ERL100:ERS100 (1:4)

Water Vapor Transmission Rate (%WVTR)

The water vapor transmission rates of different formulation were evaluated, the results are shown in Figure No.4. Diltiazem films containing ERL100 showed higher % WVTR as compared to other polymers. This may be due to the hydrophilic nature of ERL 100. Formulation F1 and F2 showed less % WVTR as compared to F3 and F4. The rank order of % water vapor transmission rate for Diltiazem loaded polymeric matrices was EVA (40% vinyl acetate) < EC < ERS 100 < ERL100:ERS100 (1:4)

***IN VITRO* DIFFUSION STUDY OF MATRIX DIFFUSIONAL RECTAL DRUG DELIVERY DEVICE OF DILTIAZEM**

The release rate determination is one of the most important studies to be conducted for all controlled release delivery systems. The diffusion studies of patches are very crucial, because one needs to maintain the drug concentration on the surface of stratum corneum consistently and substantially greater than the drug concentration in the body to achieve a constant rate of drug permeation[10].

Experimental[11,12]

In vitro diffusion studies of Diltiazem from various Rectal patches was studied using modified Keshary-Chien diffusion cell (Figure No.5). The diffusion cell consists of two parts; the upper parts i.e. the donor compartment and contains the active ingredients and the carrier adhesive/patch; the bottom part contains the receptor solution, the water jacket for temperature control, and the sampling port.

The effective permeation area of the diffusion cell and receptor cell volume was 3.14cm^2 and 40 ml, respectively. The temperature was maintained at 37±0.5^{o}C. The receptor compartment contained 40 ml of 0.01N HCl stirred by magnetic stirrer.

Samples (2 ml) were withdrawn and replaced with the same volume of fresh receptor solution, through the sampling port of the diffusion cell at different time intervals. The absorbance of the withdrawn samples were measured using UV VIS spectrophotometer at 237.8 nm using 0.01N HCl as a blank. The experiments were done in triplicate. Amount of drug released per square centimeter of patch were plotted against function of square root of time for different formulations. The release rate Q/√T was determined by simple regression analysis of steady state data.

Diffusion studies are important for ensuring the sustained release performance and the reproducibility of rate and duration of drug release. *In vitro* release profile is an important tool that predicts in advance how the drug will behave *in vivo*[13]. The results of in vitro drug diffusion studies of Rectal patches are depicted in Table No.6 and Figure No.7.

The results of diffusion study of Diltiazem loaded polymeric matrix formulated using various polymers are presented in Table No.6 and profiles are shown in Figure No.7. The release rate Q/√T **(**µg/cm2 √hr) was determined by simple regression analysis of steady state data. The release of Diltiazem from all the matrices followed square root law. The rank order of release was EVA (40% vinyl acetate) >EC > ERL100:ERS100 (1:4) > ERS 100.

Formulation F1 EVA (VA 40%) copolymer exhibited maximum Q/√T release rate 1488.10 µg/cm^2√h while Formulation F3 exhibited minimum Q/√T release rate (503.29 µg/cm^2√h). The physiochemical property of polymer plays important role in drug release characteristics, from the polymeric matrix. EVA (VA 40%) copolymer is more hydrophobic as compare to other polymers and enhanced permeation from the matrix. The solubility characteristic of Diltiazem base in EVA matrix seems to have played, the significant role in the release characteristics. The higher polymer solubility has played significant improvement in release of drug from EVA (VA 40%) copolymer matrix. EVA (VA 40%) copolymer matrix provides a good release for Diltiazem base. Based on physiochemical and *in vitro* release experiments,

formulation F1 may be chosen for further *in vitro* permeability study through human live skin[14].

***In Vitro* Release Kinetics**

The release data was fitted into various mathematical models using software to know which mathematical model will best fit to obtained release profiles. The obtained R values for various models are given in Table No.7. Here R is regression coefficient.

Table No.1: Composition of polymeric matrix diffusional patches of Diltiazem

S.No	Formulation code	Polymers	Plasticizers (% w/w of polymer composition)	Solvent
1	F1	EVA (VA 40%) copolymer	DEP (2 %)	Toluene
2	F2	EC	Glycerin (40 %)	Chloroform
3	F3	ERS100	DBP (30%)	Chloroform
4	F4	ERL100: ERS100 (1:4)	DBP (30 %)	Chloroform

Table No.2: Results of thickness uniformity of F1 to F4 matrix formulations

S.No	Formulation code	Average thickness (µm)			
		Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	172.5	175.0	172.5	173.33 ± 1.443
2	F2	115.0	117.5	117.5	116.66 ± 1.443
3	F3	150.0	152.5	150.0	150.83 ± 1.443
4	F4	85.0	87.5	82.5	85.00 ± 2.500

***Standard deviation, n=3**

Table No.3: Results of weight variations of F1 to F4 matrix formulations

S.No	Formulation Code	Average weight (mg)			
		Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	53.0	53.1	52.9	53.00 ± 0.100
2	F2	52.5	52.6	52.3	52.46 ± 0.152
3	F3	58.0	57.5	58.5	58.00 ± 0.500
4	F4	50.3	50.2	50.4	50.30 ± 0.100

***Standard deviation, n=3**

Table No.4: Results of % drug content of F1 to F4 matrix formulations

S.No	Formulation code	Drug content (mg)			
		Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	98.57	96.52	98.53	97.87 ± 1.172
2	F2	101.20	100.05	101.23	100.82 ± 0.672
3	F3	97.80	98.90	99.02	98.57 ± 0.672
4	F4	101.50	101.20	101.00	101.23 ± 0.251

***Standard deviation, n=3**

Table No.5: Results of folding endurance of F1 to F4 matrix formulations

S.No	Formulation Code	Folding endurance			
		Trial 1	Trial 2	Trial 3	Mean ± S.D.*
1	F1	248	250	247	248.33 ± 1.527
2	F2	245	244	247	245.33 ± 1.527
3	F3	15	17	18	16.66 ± 1.527
4	F4	19	17	18	18.00 ± 1.000

***Standard deviation, n=3**

Table No.6: *In vitro* diffusion profiles of Diltiazem from F1 to F4 formulations

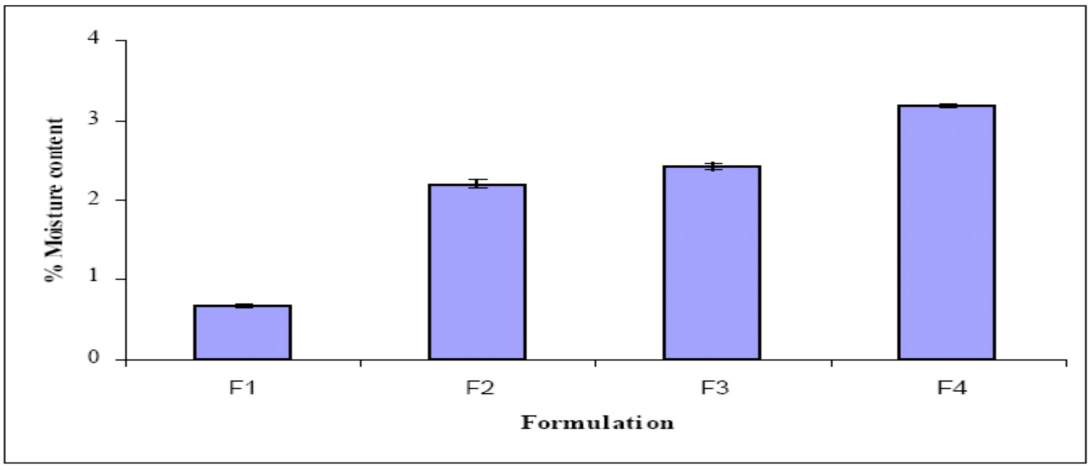
S.No	Time (hr ½)	Cumulative amount of drug release from device (µg/cm^2)			
		Formulation code			
		F1	F2	F3	F4
1	0.707	1105.51 ± 15.20	486.25 ± 5.39	180.16 ± 5.34	305.87 ± 6.32
2	1.000	1499.85 ± 20.33	750.17 ± 10.34	339.65 ± 6.40	475.53 ± 8.44
3	1.414	2099.63 ± 25.46	1164.70 ± 15.34	540.96 ± 7.35	845.80 ± 10.32
4	1.732	2470.25 ± 26.59	1520.00 ± 18.45	688.56 ± 10.49	1050.56 ± 12.53
5	2.000	2985.46 ± 32.46	1775.24 ± 20.58	830.25 ± 11.40	1295.23 ± 15.42
6	2.236	3231.56 ± 30.29	1920.56 ± 22.59	940.56 ± 17.39	1475.47 ± 18.48
7	2.449	3500.23 ± 45.38	2100.36 ± 25.79	1075.82 ± 19.84	1675.69 ± 19.32
8	**Q/√T (µg/cm2 √hr)**	**1488.10**	**946.30**	**503.29**	**794.08**
9	**Correlation coefficient**	**0.9976**	**0.9959**	**0.9990**	**0.9987**

***Standard deviation, n=3**

Table No.7: Data of various parameters of model fitting of formulation F1 to F4

S.No	Formulation code	Zero order equation	First order Equation	Higuchi's equation
1	F1	0.9774	0.9326	0.9960
2	F2	0.9604	0.8915	0.9930
3	F3	0.9907	0.9309	0.9984
4	F4	0.9851	0.9074	0.9981

Figure No.1: Matrix diffusional rectal patch of Diltiazem



*** Standard deviation, n=3**

Figure No.2: % Moisture content of F1 to F4 matrix formulations

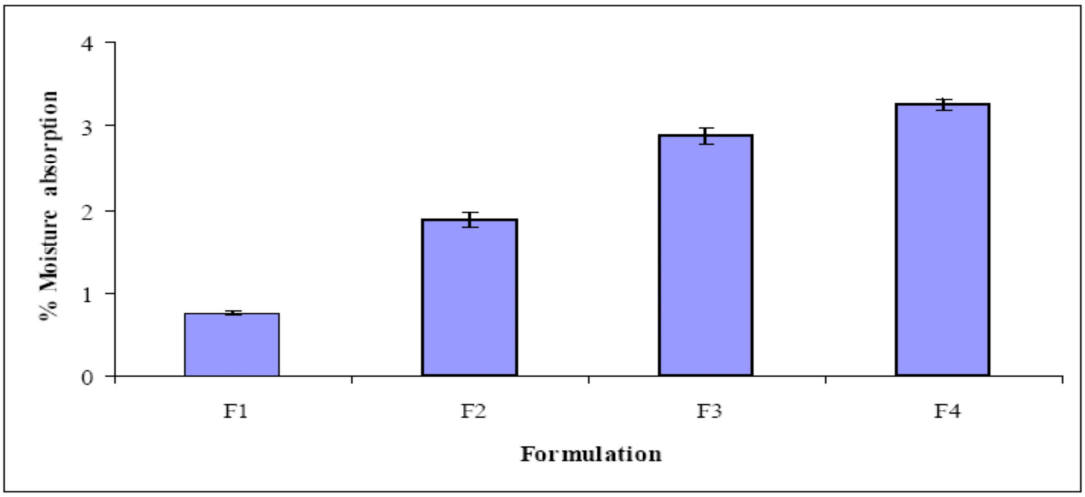
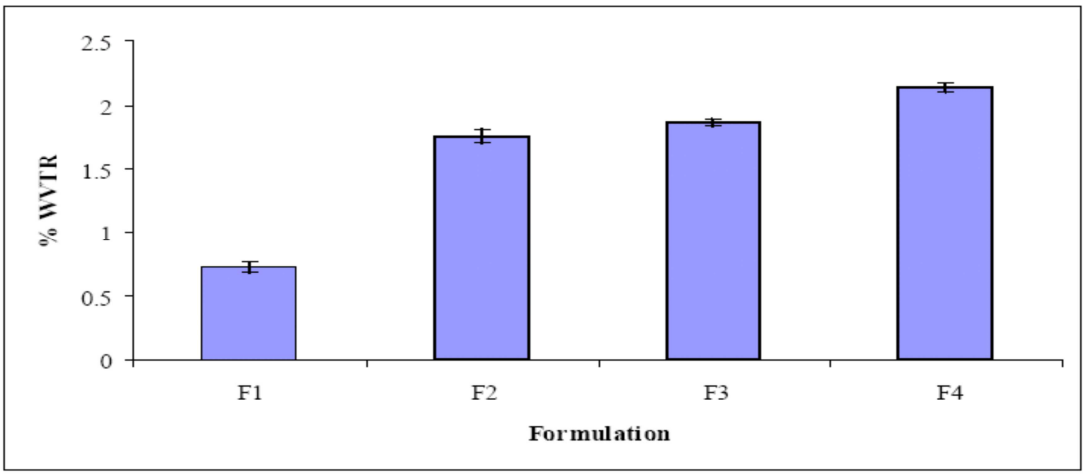


Figure No.3: % Moisture absorption of F1 to F4 matrix formulations



*** Standard deviation, n=3**

Figure No.4: % water vapor transmission rate of F1 to F4 matrix formulations

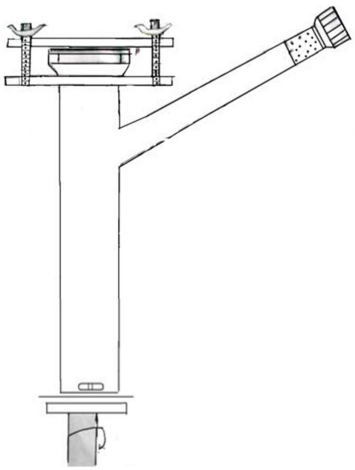


Figure No.5: Modified Keshary-Chien diffusion cell

Figure No.6: Experimental setup

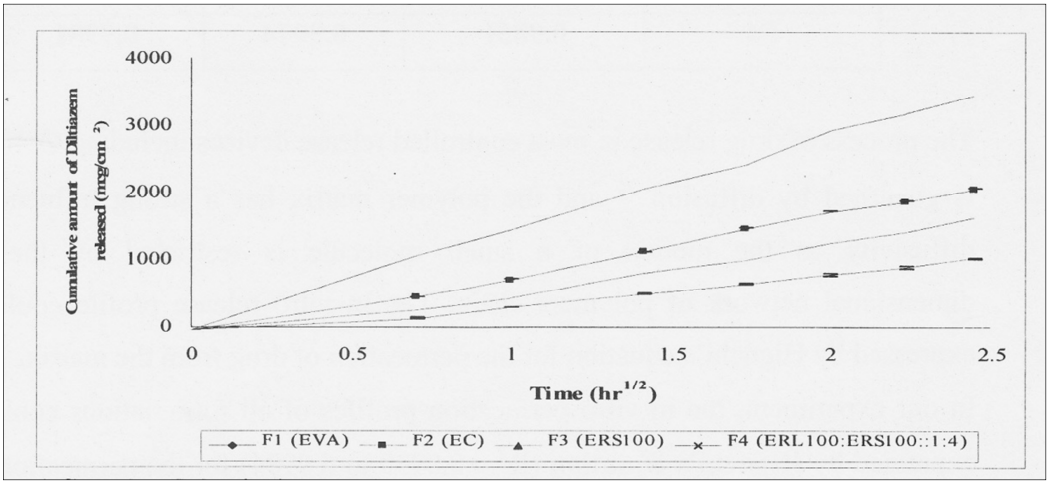


Figure No.7: *In vitro* diffusion profiles of Diltiazem from F1 to F4 formulations

CONCLUSION

The process of drug release in most controlled release devices including Rectal patches is governed by diffusion and the polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by the three – dimensional network of polymers chain. The in vitro release profile could be best expressed by Higuchi's equation for the permeation of drug from the matrix. In our experiment, the in vitro permeation profiles of all formulations could be best expressed by Higuchi's equation (R^2 = 0.9930 to 0.9984) for the permeation of drug from a homogeneous- polymer matrix type delivery system that depends mostly on diffusion characteristics[9].

ACKNOWLEDGEMENT

The authors gratefully acknowledges to Department of Pharmaceutics, Bhagwant University, Ajmer, Rajasthan, India, they gave valuable suggestions and support to finish this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Vijayasankar G R and Anurag Bhargava. Preparation and characterization of polymeric matrix diffusional rectal patches of Diltiazem, *International Journal of Research in Pharmaceutical and Nano Sciences*, 4(5), 2015, 319 - 329.