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RESEARCH ARTICLE

DEVELOPMENT AND PHYSICO-CHEMICAL EVALUATION OF MONOLITHIC MATRIX TYPE TRANSDERMAL FILMS OF AMMONIA METHACRYLATE COPOLYMER-METHOCEL AND METHACRYLIC ACID COPOLYMER-METHOCEL OF A MODEL ANTI-HYPERTENSIVE DRUG

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ABSTRACT

The main challenge of the present study is to effectively design a Monolithic Matrix type of transdermal films with the use of binary blends of polymers (Methacrylic Acid Copolymer: Acrylcoat S100 & Acrylcoat L100-Methocel K15M and Ammonia Methacrylate Copolymer: Eudragit RSPO & Eudragit RLPO-MK15M and use of most appropriate plasticizer: hydrophilic such as Polyethylene glycol 400 & Propylene Glycol or hydrophobic such as Dibutyl phthalate (DBT) & Dibutyl sebacate for that particular combination of polymers so that a good film can be obtained. In this research work, 2 different permeation enhancers of Terpene class such as d- limonene and 1,8 cineole in combination were used. The Physico-chemical properties of patches determined for the suitability and acceptability of the prepared patches. The thickness, weight, tensile strength, % elongation, folding endurance and flatness were determined for the prepared patches. We found good and acceptable Physicochemical parameters of the matrix films regarding properties and performance.

Keywords: Transdermal, Monolithic, Matrix films, Physico-chemical properties

INTRODUCTION

It was planned to design the formulation in such a way that it provides the delivery of drug at a controlled rate across intact human skin to achieve a therapeutic effective drug level for a longer period of time. The polymeric monolithic matrix type transdermal films are widely used to provide controlled delivery of drug substances because of their versatility, effectiveness, and low cost. These types of systems are also suitable for in-house development because they are usually manufactured using conventional equipment and processing. The benefits of using transdermal drug delivery include improved systemic bioavailability resulting from bypassing the first hepatic metabolism. Variables due to oral administration, such as pH, the presence of food or enzymes, and transit times can all be eliminated. The aim in the development of new transdermal drug delivery device is to obtain a controlled, predictable, and reproducible release of the drug into the blood stream of the patient.[1,2]

The first and most important parameter for the development of a polymeric film is the choice of polymer. Besides having good film-forming properties and being a non-skin-irritant, the polymer must be soluble in a skin-tolerant solvent. The investigated polymers comprised combination of polymers - Ammonio Methacrylate Copolymers such as Eudragit RLPO (ERLPO) and Eudragit RSPO (ERSPO) with hydrophilic polymer Methocel K15M (MK15M) and combination of polymers such as Methacrylic acid co-polymers Acrylcoat L100 (AL100) and Acrylcoat S100 (AS100) with hydrophilic polymer MK15M. A great effort has been devoted to optimize the innovated films as far as possible. However, optimal properties cannot be achieved for a single polymer. Therefore, blending of polymers is necessary to attain more suitable transdermal devices regarding properties and performance. These transdermal delivery systems are neither extremely hydrophobic nor extremely hydrophilic. Binary blends of MK15M and the different types of Ammonio Methacrylate Copolymers & Methacrylic acid co-polymers in different concentration were done to ameliorate physicochemical properties and to optimize performance. Beside the other components of transdermal patches, plasticizers also significantly change the viscoelastic properties of the polymers by the improvement of film forming properties and the appearance of the film, preventing film cracking, increasing film flexibility and obtaining desirable mechanical properties. The plasticizers tried in optimization trials were lipophilic plasticizers Dibutyl Phathalate (DBP) & Dibutyl Sebacate (DBS) and hydrophilic plasticizers Polyethylene glycol 400 (PEG 400) & Propylene Glycol (PG). In this research work, 2 different permeation enhancers of Terpene class such as d- limonene and 1,8 cineole were used. They were used in combinations so that more effective and enhanced transdermal drug transport can be obtained by synergism and it's also safe as the strength of individual enhancers can be reduced without compromising on drug release.

Drug of choice Monolithic matrix transdermal therapeutic systems is Metoprolol Tartrate. Metoprolol tartrate is prferred because of its relative β-1 selectivity, it is safe for use in patients with bronchospastic disease. Metoprolol tartrate has a oral bioavailability of only 38 % due to extensive hepatic first-pass metabolism. The half-life of the Metoprolol is about 3.2 hours, which makes frequent dosing necessary to maintain the

 ISSN: 2250-1177 CODEN (USA): JDDTAO

therapeutic blood levels of the drug for long-term treatment.[3-7]

MATERIAL AND METHODS

Materials

Metoprolol tartrate is obtained from Emcure Pharmaceuticals Pvt. Ltd., Pune. Eudragit RSPO and Eudragit RLPO are obtained from Evonik Degussa India pvt. Ltd.,Mumbai. Acrylcoat S100 and Acrylcoat L100 are obtained from Corel Pharma chem., Ahmedabad ,Methocel K15M is obtained from Colorcon Asia Pvt. Ltd, Goa. Plasticzers and permeation enhancers are obtained from Merck India Ltd. Mumbai and Himedia, Mumbai respectively. All other chemicals used are procured from S.D. Fine Chemicals, Mumbai

Methods

Dose Calculation for Monolithic Matrix type Transdermal films[8]

The dose to be incorporated in a patch was calculated using the following mathematical equation-

$$\text{Drug input (theoretical)} = C_{ss} * K_e * V_d$$

Where C_{ss} is concentration at steady state, k_e is elimination rate constant and V_d is volume of distribution

Volume of distribution (V_d) = 290 L/ 70kg

=290000 ml

Concentration at steady state (C_{ss})/target concentration

= 25 ng/ml

= 25×10^{-6} mg/ml

Half -life of MT ($t_{1/2}$) = 3.2 hr

Elimination rate constant (k_e) = $0.693 \div t_{1/2}$

= $0.693 \div 3.2$

= $0.21666\ hr^{-1}$

Drug input (theoretical) = $C_{ss} * K_e * V_d$

= $25 \times 10^{-6} \times 0.2166 \times 290000$

= 1.570 mg/hr

Maintenance dose for 24 hours (for therapeutic activity)= $1.570 \times 24 = 37.68$ mg/24 hr

Expected bioavailability of the drug from the TDDS patch (Expected drug that will reach the blood plasma after crossing the skin as a barrier) = 75%

Amount of the drug to be incorporated in each transdermal patch = $37.68 \times 100/75$

= 50.24 mg ≈ 50 mg

Internal diameter of petriplate / glass mould = 9.2 cm

Internal surface area of mould = $\pi r^2 = 22/7 \times (4.6)^2$

= 66.49 cm^2

Diameter of transdermal patch = 2 cm

Area of transdermal patch = $\pi r^2 = 22/7 \times (1)^2$

= 3.14 cm^2

Amount of drug loaded per unit area= 50mg/3.14 cm^2

= 15.92 mg/ square centimeter patch

Number of transdermal patches from one circular cast film:

=66.49/3.14 = 21.175 ≈ 21 patches

Amount of MT to be present in each TDDS patch =50 mg

Amount of MT should be loaded in one circular cast film = 50 x21 = 1050 mg

10 ml of the solution containing 1050 mg is poured in each mould of 66.49 cm^2 area

Fabrication of Drug loaded Monolithic Matrix type transdermal films:

The Drug loaded Monolithic Matrix type transdermal films were prepared by film casting technique on mercury substrate using different ratios of ERLPO:MK15M, ERSPO:MK15M, AS100:MK15M and AL100:MK15M (1:4,2:3,3:2,4:1) containing drug MT (15.92 mg/ square centimeter patch). The polymers were weighed in requisite ratios keeping the total polymer weight 500 mg constant. Hydrophilic materials i.e. MK15M was dissolved in water and hydrophobic material i.e. ERLPO or ERSPO or AS100 or AL100 was dissolved in blend of Methanol and Isopropyl alcohol (50:50). Then both the solution (MK15M solution was mixed separately with each hydrophobic polymer in different ratios) were mixed and stirred on magnetic stirrer to accomplished homogeneous mixture. The above polymeric dispersion was sonicated for 2 minutes to remove entrapped air bubbles. In this study Lipophilic plasticizers DBP & DBS or hydrophilic plasticizers such as PEG 400 & PG was added for each polymer combination. Two different permeation enhancers of Terpene class such as limonene and cineole in different percentage in combination (2.5:2.5 w/w %) was added to each polymer combination. The resulting solution (10 ml) was poured in a petri dish of 9.2 cm diameter containing mercury. The rate of evaporation of the solvent was controlled by placing an inverted funnel over the petri dish and allowed for drying over night followed by vacuum drying. The film formation was noted by observing the mercury surface after complete evaporation of the solvent. Aluminium foil was used as backing film and wax paper as release liner (which could be removed before application of the patch on the skin) were applied to complete the TDDS. The patches were cut with a circular metallic die of 2 cm internal diameter to give an area of 3.14 cm^2 and stored in a desiccator until use. [1,2,9]

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Table 1: Composition of Drug loaded transdermal films EM1-EM8

S.No.	Formulation code	Drug (mg/ square centimeter patch)	Polymer combination with ratio	Plasticizer type and Percentage (%w/w)	Permeation Enhancer (%w/w)	
					Limonene	Cineole
1.	EM1	15.92	ERSPO:MK15M (1:4)	PEG 400 (20%)	2.5	2.5
2.	EM2	15.92	ERSPO: MK15M (2:3)	PEG 400 (20%)	2.5	2.5
3.	EM3	15.92	ERSPO: MK15M (3:2)	DBS (25%)	2.5	2.5
4.	EM4	15.92	ERSPO: MK15M (4:1)	DBS (25%)	2.5	2.5
5.	EM5	15.92	ERLPO: MK15M (1:4)	PEG 400 (20%)	2.5	2.5
6.	EM6	15.92	ERLPO: MK15M (2:3)	PEG 400 (20%)	2.5	2.5
7.	EM7	15.92	ERLPO: MK15M (3:2)	DBS (25%)	2.5	2.5
8.	EM8	15.92	ERLPO: MK15M (4:1)	DBS (25%)	2.5	2.5

Table 2: Composition of Drug loaded transdermal films AM1-AM8

S.No.	Formulation code	Drug (mg/ square centimeter patch)	Polymer combination with ratio	Plasticizer type and Percentage (w/w %)	Permeation Enhancer (%w/w)	
					Limonene	Cineole
1.	AM1	15.92	AS100: MK15M (1:4)	PG (15%)	2.5	2.5
2.	AM2	15.92	AS100: MK15M (2:3)	PG (15%)	2.5	2.5
3.	AM3	15.92	AS100: K15M (3:2)	PG (15%)	2.5	2.5
4.	AM4	15.92	AS100: MK15M (4:1)	DBT (30%)	2.5	2.5
5.	AM5	15.92	AL100: MK15M (1:4)	PG (15%)	2.5	2.5
6.	AM6	15.92	AL100: MK15M (2:3)	PG (15%)	2.5	2.5
7.	AM7	15.92	AL100: MK15M (3:2)	PG (15%)	2.5	2.5
8.	AM8	15.92	AL100: MK15M (4:1)	DBT (30%)	2.5	2.5

EVALUATION OF FORMULATIONS:

Physico-chemical evaluation

The Physico-chemical properties of patches are among the factors, which determine the suitability and acceptability of the prepared patches. The thickness, weight, drug content, tensile strength, % elongation, folding endurance, flatness % absorption and % loss, swelling and pH were determined for the prepared patches. Physicochemical evaluation and appropriate quality control are essential to ensure safety and adequate performance of designed formulae.

Physical appearance of formed films

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.[10]

Uniformity of Thickness

The thicknesses of the drug-loaded polymeric films were measured at three different points using a digital micrometer (Mitutoyo, Japan). The average and standard deviation of three readings were calculated for each batch of the drug-loaded films.[11,12]

Uniformity of weight

A specified area (1 cm^2) of patch is to be cut in different parts of the patch and is to be dried at 60°c for 4hrs before testing and Weight variation is studied by individually weighing 03 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.[13,14]

Uniformity of Drug content

An accurately weighed portion of patch was placed in 100 ml of 7.4 phosphate buffer and then the solution was shaken continuously for 24 hrs in shaker incubator. Then the whole solution was sonicated for complete extraction of drug from the patch. After incubation and subsequent filtration, drug in solution was estimated against the reference solution consisting of placebo films (contains no drug) with UV spectrophotometry at 274 nm.[15,16]

Surface pH

Surface pH of the patches was determined by the m ethod described by Bottenberg et al. The patches were allowed to swell by keeping them in co ntact with 0.5 ml of double distilled water for 1 hour i n glass tubes. The surface pH was then noted by bringing

acombined glass electrode near the surface of the patch and allowing it to equilibrate for 1 minute.[17]

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, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. 0% constriction is equivalent to 100 % flatness.[18]

$$\% \text{ constriction} = L_1 - L_2 / L_1 X\ 100$$

L2 = Final length of each strip

L1 = Initial length of each strip

Tensile Strength

Tensile strength of the film was determined with Universal Strength Testing Machine. The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size ($4\times1cm^2$) was fixed between these cell grips and force was gradually applied till the film broke. Tensile strength is expressed as follows [19,20]

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

Percentage elongation break test

The percentage elongation break is determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula [21]

$$\text{Elongation percentage} = L_1\text{-}L_2/L_2 \times 100$$

Where, $L_1$is the final length of each strip and L_2 is the initial length of each strip.

Folding endurance

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break; the number of times the films could be folded at the same place without breaking is folding endurance value.[22]

Percentage moisture absorption

Initial weight of the patch was taken and noted, then weighed patch are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 75% relative humidity using saturated solution of sodium chloride in desiccators until a constant weight is achieved. Final weight of the patch was calculated and percentage moisture uptake is calculated as given below.[23]

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} X\ 100$$

Percentage moisture loss

The prepared patch are weighed individually and kept in a desiccators containing fused calcium chloride at room temperature for 24 h. The patch is weighed again after a specified interval until they show a constant weight. The percent moisture content is calculated using following formula:[24]

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} X\ 100$$

Swelling Studies

Weight increase due to swelling was measured. The drug-loaded patch of size 1 x 1 cm^2 was weighed on a pre-weighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer (pH 7.4) solution was added. After every five min, the cover slip was removed, wiped with tissue paper, and weighed upto 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.[25,26]

The percent swelling, %S was calculated using the following equation;

$$\%S = \frac{X_t - X_o}{X_o} x\ 100$$

Where Xt is the weight of the swollen patch after time t and Xo is the original patch weight at zero time.

RESULT AND DISCUSSION

Physico-chemical Evaluation of Formulations

Physical appearance of formed films

All the patches prepared with different polymer concentration were found to be flexible, translucent, hard and homogeneous in nature.

Uniformity of Thickness

Transdermal patches were transparent, smooth, uniform and flexible. The thickness of the weights ranged between 0.179±0.0051 to 0.258±0.0063 formulations (EM1 to EM8 and AM1 to AM8). The result indicated that there was no much difference in the thickness within the formulations. Low standard deviation and % Relative standard deviation values in the film thickness measurements ensured uniformity of the films prepared by solvent evaporation method. If we compare among different polymer combination we found that as the proportion of Ammonio Methacrylate Copolymers or Methacrylic acid co-polymers was increased or as the proportion of MK15M was decreased, the thickness decreases. The uniformity of thickness of the formulation EM1-EM8 and AM1-AM8 were shown in table No.3 and table No.4 respectively.

Table 3 Uniformity of Thickness of formulations EM1-EM8

Formulation code	Thickness(mm) Mean±SD	RSD %
EM1	0.225±0.0066	2.93
EM2	0.214±0.0057	2.66
EM3	0.188±0.0049	2.61
EM4	0.179±0.0051	2.85
EM5	0.258±0.0063	2.44
EM6	0.244±0.0054	2.21
EM7	0.225±0.0067	2.98
EM8	0.214±0.0058	2.71

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Table 4: Uniformity of Thickness of formulations AM1-AM8

Formulation code	Thickness(mm) Mean±SD	RSD %
AM1	0.234±0.0052	2.22
AM2	0.223±0.0063	2.83
AM3	0.216±0.0060	2.78
AM4	0.194±0.0057	2.93
AM5	0.227±0.0059	2.59
AM6	0.217±0.0053	2.44
AM7	0.201±0.0051	2.53
AM8	0.189±0.0055	2.91

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Uniformity of weight

The weight of all the formulation varies between 70.61±0.218-79.81±79.81±0.222 (EM1 to EM8 and AM1 to AM8). The result indicated that there was no much difference in the thickness within the formulations. Low standard deviation and % Relative standard deviation values in the weight of film measurements ensured uniformity of the films prepared by solvent evaporation method. we found that as the proportion of Ammonio Methacrylate Copolymers or Methacrylic acid co-polymers was increased or as the proportion of Methocel K15M was decreased, the weight decreases. Patches were favourable because these were thinner and less heavier and do not affect quality of life of patients and giving feel of bulkiness. The uniformity of weight of the formulation EM1-EM8 are shown in table No.5 and table No.6 respectively.

Table 5 Uniformity of Weight of formulations EM1-EM8

Formulation code	Weight (mg) Mean±SD	RSD %
EM1	77.21±0.225	0.291
EM2	75.03±0.221	0.294
EM3	72.29±0.215	0.297
EM4	70.61±0.218	0.308
EM5	79.81±0.222	0.278
EM6	77.24±0.211	0.273
EM7	74.54±0.212	0.284
EM8	72.37±0.215	0.297

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Table 6 Uniformity of Weight of formulations AM1-AM8

Formulation code	Drug content(%) Mean±SD	RSD %
EM1	94.64±1.22	1.28
EM2	95.13±1.31	1.37
EM3	95.63±1.15	1.20
EM4	94.71±1.05	1.11
EM5	95.36±1.48	1.55
EM6	95.77±0.83	0.86
EM7	95.37±0.96	1.01
EM8	94.43±1.33	1.41

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Uniformity of Drug content

Homogeneous uniform drug distribution is one of the important characteristics of a transdermal patch that ensures the uniform reproducible sustained release of the drug from the patch. The drug content **(%)** of all the formulations was found to be more than 90%. The results of content uniformity indicated that the drug was uniformly dispersed. The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 94.43±1.33 to 95.77±0.83 for formulations EM1 to EM8 and 94.20±1.25 to 96.33±±1.14 for formulations AM1 to AM8. The uniformity of drug content of the formulation EM1-EM8 are shown in table No.7 and table No.8 respectively.

Table 7: Uniformity of Drug content of formulations EM1-EM8

Formulation code	Weight (mg) Mean±SD	RSD %
AM1	78.36±0.213	0.271
AM2	75.56±0.219	0.289
AM3	73.40±0.215	0.292
AM4	71.50±0.222	0.310
AM5	77.91±0.224	0.287
AM6	75.37±0.212	0.281
AM7	72.58±0.216	0.297
AM8	70.66±0.218	0.308

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 8: Uniformity of Drug content of formulations AM1-AM8

Formulation code	Drug content (%) Mean±SD	RSD %
AM1	95.36±1.16	1.22
AM2	95.52±1.03	1.08
AM3	94.20±1.25	1.32
AM4	95.44±1.19	1.24
AM5	95.23±1.28	1.34
AM6	95.61±0.97	1.05
AM7	96.33±1.14	1.19
AM8	95.54±1.29	1.36

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Surface pH

The surface pH of all the formulations was in th e range of 5.2±0.154 to 5.90±0.145 (EM1 to EM8 and AM1 to AM8), these values are close to the pH range of skin (4.5-5.5)[1] and hence no skin irritation was expected. The surface pH of the formulations EM1-EM8 and AM1 to AM8) are shown in table No.8 and table No.9 respectively.

Table 8: Surface pH of formulations EM1-EM8

Formulation code	Surface pH Mean±SD	RSD %
EM1	5.83±0.163	2.79
EM2	5.35±0.158	2.95
EM3	5.20±0.154	2.96
EM4	5.66±0.159	2.80
EM5	5.44±0.142	2.61
EM6	5.31±0.122	2.29
EM7	5.25±0.149	2.83
EM8	5.75±0.121	2.10

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Table 9: Surface pH of formulations AM1-AM8

Formulation code	Surface pH Mean±SD	RSD %
AM1	5.85±0.169	2.88
AM2	5.42±0.151	2.78
AM3	5.55±0.161	2.91
AM4	5.74±0.154	2.68
AM5	5.32±0.159	2.98
AM6	5.42±0.146	2.69
AM7	5.90±0.145	2.45
AM8	5.44±0.153	2.81

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Flatness (%)

An idyllic 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 judge the same.

The %Flatness of all the formulations was in the range of 99.12±1.01 to 99.68±1.11 (EM1 to EM8 and AM1 to AM8). The flatness study showed that all the formulations had the nearly same strip length before and after their cuts, indicating nearly 100% flatness, which indicates negligible amount of constriction of the prepared transdermal patches. The % Flatness of the formulations EM1-EM8 and AM1-AM8 are shown in table No.10 and table No.11 respectively.

Table 10: Flatness of formulations EM1-EM8

Formulation code	Flatness (%) Mean±SD	RSD %
EM1	99.62±1.12	1.12
EM2	99.26±1.44	1.45
EM3	99.68±1.11	1.11
EM4	99.55±1.65	1.65
EM5	99.33±1.53	1.54
EM6	99.50±1.05	1.05
EM7	99.12±1.01	1.01
EM8	99.63±1.45	1.45

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Table 11: Flatness of formulations AM1-AM8

Formulation code	Flatness(%) Mean±SD	RSD %
AM1	99.40±1.66	1.67
AM2	99.59±1.15	1.15
AM3	99.47±1.49	1.49
AM4	99.38±1.71	1.72
AM5	99.56±1.43	1.43
AM6	99.37±1.19	1.19
AM7	99.31±1.53	1.54
AM8	99.65±1.44	1.45

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Tensile strength

Strength of the film and the risk of film cracking were indicated by its tensile strength. The Tensile strength of all the formulations was in the range of 0.442 ±0.0132 to 0.538±0.0121 (EM1 to EM8 and AM1 to AM8). The prepared transdermal films were shown good tensile strength and there was no sign of cracking in prepared transdermal film. Tensile strength test results showed that the patch contains Methocel K15M in lower amount were more strengthens. There is increase in tensile strength with increase in Ammonio Methacrylate Copolymers or Methacrylic acid co-polymers in the polymer blend. The Tensile strength of the formulation EM1-EM8 and AM1-AM8 are shown in table No.12 and table No.13 respectively.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 12: Tensile strength of formulations EM1-EM8

Formulation code	Tensile strength (Kg/cm^2) Mean±SD	RSD %
EM1	0.467±0.0115	2.46
EM2	0.497±0.0129	2.59
EM3	0.514±0.0133	2.58
EM4	0.538±0.0121	2.24
EM5	0.465±0.0127	2.73
EM6	0.474±0.0115	2.42
EM7	0.501±0.0119	2.37
EM8	0.518±0.0131	2.52

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Table 13: Tensile strength of formulations AM1-AM8

Formulation code	Tensile strength (Kg/cm^2) Mean±SD	RSD %
AM1	0.453±0.0121	2.67
AM2	0.467±0.0116	2.48
AM3	0.475±0.0122	2.56
AM4	0.488±0.0111	2.27
AM5	0.442±0.0132	2.98
AM6	0.458±0.0114	2.48
AM7	0.471±0.0125	2.65
AM8	0.483±0.0050	2.67

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Percentage Elongation at break

The % elongation at break gives an indication of the elasticity of the film. An inverse relation was observed between tensile strength and elongation at break. The % Elongation at break of all the formulations was in the range of 71.22±1.44 % to 86.31±1.82 % (EM1 to EM8 and AM1 to AM8). Elongation at break test (%) results showed that the patch contains Methocel K15M in higher amount were more strengthens. There is increase in % elongation at break with decrease in Ammonio Methacrylate Copolymers or Methacrylic acid co-polymers in the polymer blend. The % elongation at break of the formulation EM1-EM8 and AM1-AM8 are shown in table No.14 and table No.15 respectively.

Table 14: % Elongation at break of formulations EM1-EM8

Formulation code	% Elongation at break Mean±SD	RSD %
EM1	76.180±1.51	1.98
EM2	74.783±1.77	2.36
EM3	73.163±1.59	2.17
EM4	71.220±1.44	2.02
EM5	79.403±1.79	2.25
EM6	77.253±1.43	1.85
EM7	74.380±1.62	2.17
EM8	73.483±1.71	2.32

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Table 15: % Elongation at break of formulations AM1-AM8

Formulation code	% Elongation at break Mean±SD	RSD %
AM1	82.73±1.65	1.99
AM2	80.51±1.52	1.88
AM3	77.60±1.56	2.01
AM4	75.60±1.62	2.14
AM5	86.31±1.82	2.11
AM6	83.58±1.49	1.78
AM7	81.22±1.65	2.03
AM8	78.04±1.77	2.27

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Folding endurance

The folding endurance was measured manually and it lies in the range of 121±2.89 to 154±2.29 (EM1 to EM8 and AM1 to AM8). It was found to be high in patches containing higher amount of the Eudragit and acrylcoat. T Folding endurance test results indicates that all the patches will withstand to rupture and would maintain their integrity with general skin folding, when used. There is increase in folding endurance with increase in Ammonio Methacrylate Copolymers or Methacrylic acid co-polymers in the polymer blend with Methocel K15M. The folding endurance of the formulation EM1-EM8 and AM1-AM8 are shown in table No.16 and table No.17 respectively.

Table 16: Folding endurance of formulations EM1-EM8

Formulation code	Folding endurance Mean±SD	RSD %
EM1	135.66±2.61	1.92
EM2	144.33±2.93	2.03
EM3	146.66±2.22	1.51
EM4	154.00±2.29	1.48
EM5	131.66±2.64	2.01
EM6	138.00±2.25	1.63
EM7	143.33±2.81	1.96
EM8	145.33±2.77	1.91

Table 17: Folding endurance of formulations AM1-AM8

Formulation code	Folding endurance Mean±SD	RSD %
AM1	126.66±2.23	1.76
AM2	132.66±2.27	1.71
AM3	137.33±2.55	1.85
AM4	142.66±2.21	1.54
AM5	121.00±2.89	2.38
AM6	127.33±2.69	2.11
AM7	131.33±2.56	1.94
AM8	139.00±2.81	2.02

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Percentage moisture absorption

The physicochemical studies like moisture loss and moisture uptake provide the information regarding the stability of the formulation. The % moisture uptake of the transdermal formulations was also low, which protect the film from microbial contamination as well as bulkiness of transdermal patch. The moisture absorption of all the formulations was in the range of 4.6 ±0.109 % to 6.70±0.125 % (EM1 to EM8 and AM1 to AM8). The % Moisture absorption of the formulation EM1-EM8 and AM1-AM8 are shown in table No.18 and table No.19 respectively.

Table 18: % Moisture absorption of formulations EM1-EM8

Formulation code	% Moisture absorption Mean±SD	RSD %
EM1	5.65±0.161	2.84
EM2	5.17±0.083	1.61
EM3	4.85±0.121	2.49
EM4	4.60±0.109	2.36
EM5	6.70±0.125	1.86
EM6	5.95±0.115	1.93
EM7	5.56±0.149	2.67
EM8	5.15±0.133	2.58

SD: Standard deviation; n=3; RSD %: % Relative Standard deviation

Table 19: % Moisture absorption of formulations AM1-AM8

Formulation code	%Moisture absorption Mean±SD	RSD %
AM1	5.84±0.146	2.50
AM2	5.34±0.132	2.47
AM3	5.05±0.091	1.80
AM4	4.74±0.112	2.36
AM5	6.13±0.157	2.56
AM6	5.63±0.105	1.86
AM7	5.24±0.151	2.88
AM8	4.93±0.111	2.25

SD: Standard deviation; n=3; RSD %: % Relative Standard deviation

Percentage moisture loss

The % moisture loss of the prepared transdermal film was low, which maintains suppleness, thus preventing drying and brittleness. The moisture content of all the formulations was in the range of 2.50±0.081 % to 3.80±0.088% (EM1 to EM8 and AM1 to AM8). Generally, the moisture uptake capacity of films increases with increasing hydrophilicity of the polymer or plasticizer. The formulations containing higher proportion of hydrophilic polymer Methocel K15M shows significant moisture absorption and moisture loss when compare to other patches having lower proportion of Methocel K15M. The moisture content of the Eudragit RLPO and Methocel K15M combination patches was higher compared to Eudragit RSPO and Methocel K15M combination patches due to relatively more hydrophobic nature of Eudragit RSPO than Eudragit RLPO. The % Moisture loss of the formulation EM1-EM8 and AM1-AM8 are shown in table No.20 and table No.21 respectively.

Table 20: % Moisture Loss of formulations EM1-EM8

Formulation code	% Moisture loss Mean±SD	RSD %
EM1	2.95±0.058	1.96
EM2	2.75±0.069	2.51
EM3	2.62±0.052	1.98
EM4	2.50±0.081	3.24
EM5	3.80±0.088	2.31
EM6	3.64±0.049	1.34
EM7	3.35±0.064	1.91
EM8	3.15±0.085	2.69

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Table 21: % Moisture Loss of formulations AM1-AM8

Formulation code	% Moisture loss Mean±SD	RSD %
AM1	3.14±0.052	1.65
AM2	2.95±0.045	1.52
AM3	2.74±0.057	2.08
AM4	2.58±0.086	3.33
AM5	3.44±0.079	2.29
AM6	3.24±0.058	1.79
AM7	3.07±0.042	1.36
AM8	2.94±0.083	2.82

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

Swelling Studies

Percentage swelling varied between 11.15±0.31 to 20.65±0.56 % (EM1 to EM8 and AM1 to AM8) for different polymeric patches. Hydrophilic polymers showed considerable swelling, as it increased the surface wettability and consequently water penetration within the matrix. The formulations containing higher proportion of hydrophilic polymer MK15M shows significant swellability when compare to other patches having lower proportion of MK15M.

Table 22: % Swelling of formulations EM1-EM8

Formulation code	% Swelling Mean±SD	RSD %
EM1	14.68±0.41	2.79
EM2	13.31±0.39	2.93
EM3	12.61±0.32	2.53
EM4	11.15±0.31	2.70
EM5	20.65±0.56	2.71
EM6	18.51±0.36	1.94
EM7	17.55±0.46	2.62
EM8	16.5±0.31	1.87

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

The % swellability of the ERLPO and MK15M combination patches was higher compared to ERSPO and MK15M combination patches due to relatively more hydrophobic nature of ERSPO than ERLPO. The % Swelling of the formulation EM1-EM8 and AM1-AM8 are shown in table No.22 and table No.23 respectively.

Table 23:% Swelling of formulations AM1-AM8

Formulation code	% Swelling Mean±SD	RSD %
AM1	16.47±0.48	2.91
AM2	15.42±0.31	2.01
AM3	14.58±0.36	2.46
AM4	13.44±0.38	2.82
AM5	18.57±0.32	1.72
AM6	16.52±0.35	2.11
AM7	15.41±0.46	2.98
AM8	14.36±0.41	2.85

SD: Standard deviation; n=3; RSD %: Percentage Relative Standard deviation

CONCLUSION

From the above experimental results it can be reasonably concluded that The Monolithic Matrix type of transdermal films of Metoprolol tartrate developed in this study have great utility and are a viable option for effective and controlled management of hypertension. The monolithic matrix type transdermal patches were prepared by film casting technique on mercury substrate using different ratios of ERSPO: MK15M, ELSPO: MK15M, AS100: MK15M and AL100: MK15M (1:4,2:3,3:2,4:1) and evaluated for physico-chemical properties for suitability and acceptability of the prepared patches. The thickness, weight, drug content, tensile strength, % elongation, folding endurance, flatness % absorption and % loss, swelling and pH were determined for the prepared patches. Physicochemical evaluation and appropriate quality control are essential to ensure safety and adequate performance of designed formulae.

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 ISSN: 2250-1177 CODEN (USA): JDDTAO