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Fabrication and characterization of a matrix-type transdermal patch containing microspheres of risperidone

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ABSTRACT

One of the important problems in the case of psychotic patients is that of compliance with the therapy. Since the routes of administration are invasive, patients resist adhering to the treatment which reduces the efficacy. In the present study, an attempt was made to develop a non-invasive dosage form for the treatment of psychosis. Hence, microspheres of an atypical antipsychotic drug, Risperidone were prepared using HPMC as the polymer by ionic gelation method. Out of the 4 batches of microspheres prepared, Batch F2 (Drug: Polymer ratio 1:2) was found to give better release (about 81%) for 12 hours. SEM studies revealed that the particles were spherical with a smooth surface. Also, it showed satisfactory results for other tests like particle size, micromeritic properties, percentage yield. Hence this batch was further selected to be dispersed in the EC matrix. The matrix was prepared using EC by solvent evaporation method after incorporating the calculated amount of microspheres. Films were evaluated for physicochemical parameters such as thickness, % moisture loss, % moisture absorption, % water vapour transmission and such other tests. Drug content and weight uniformity analysis indicated that the films had relatively uniform weights and Risperidone content with minimum intra-batch variability. The films were stable during the stability studies carried out for one month. Formulation T3 (Drug: Polymer ratio 1:18) gave the highest release, i.e. up to 84% for a duration of up to 24hrs. And hence it was selected to be the best amongst all.

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INTRODUCTION

The administration of conventional oral dosage forms like tablets, capsules, liquids orals of drugs suffers a setback due to the problems such as gastrointestinal tract absorption, local irritation, dilution of drug strength, Liver first pass metabolism, degradation of the drug by gastrointestinal tract enzymes, the protein binding of the drug at an absorption surface, reduction of bioavailability and poor patient compliance with the therapy (Bhargava A. *et al.,* 2013).

About 74% of drugs are taken orally and are found not to be as effective as desired. To improve effectiveness, transdermal drug delivery system emerged (Ratnaparkhi M. P. *et al.,* 2013). Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery (Chien Y. *et al.,* 2009). Transdermal drug delivery systems (TDDS) are dosage forms involving drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation (Allen L. *et al.,*

1999). The adhesive used in the transdermal drug

delivery system is critical to the safety, efficacy and quality of the product (Gaikwad. *et al.,* 2013). Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery (Lachman L. *et al.,* 1999).

Advantages of Transdermal Drug Delivery System (TDDS) (Ueda C. *et al.,* 2009).

1. Avoidance of the first-pass metabolism of drugs.
2. Reduced plasma concentration levels of drugs, with decreased side effects.
3. Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with a short half-life and low therapeutic index.
4. Easy elimination of drug delivery in case of toxicity.
5. Reduction of dosing frequency an enhancement of patient compliance.
6. Transdermal medications deliver a steady infusion of a drug over an extended period. Adverse effects or therapeutic failure frequently associated with intermittent dosing can also be avoided (Shingade M. *et al.,* 2009).
7. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug. Example-GI irritation, reduced absorption, decomposition due to 'hepatic first pass' effect.
8. Due to high advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than if the drug is given orally.
9. The simplified medication regimen led to improved patient compliance and reduced inter and intra-patient variability.

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable and ideally having a particle size in the range of 1-1000µm (Rolland A. *et al.,* 1993). A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are various approaches to delivering a therapeutic substance to the target site in a sustained, controlled release fashion. One such approach is using microspheres as carriers for drugs. It is the reliable means to deliver the drug to the target site with specificity if modified and to maintain the desired concentration at the site of interest without untoward effects (Sahil K. *et al.,* 2011).

MATERIALS AND METHODS

Risperidone was obtained as gift sample from Cadila Ltd. Goa. Pharma grade Sodium Alginate was obtained as a gift sample from Snap Natural and Alginate Products Pvt Ltd. Calcium Chloride (Pharma Grade), Potassium Chloride and Ethanol were obtained from Loba Chemie. Methocel K 4M and Ethocel E50 were obtained as gift samples from Colorcon Pvt Ltd. Sodium Hydroxide Pellets was obtained from Nice Chemicals Pvt Ltd., and Potassium Dihydrogen Phosphate was obtained from Chemport (India) Pvt Ltd.

Formulation of Sodium Alginate Microspheres containing Risperidone

Microspheres containing Risperidone were prepared by *Ionotropic Gelation technique.* The required quantities of Sodium Alginate and polymer HPMC were dissolved in 25 ml of purified water to form a homogenous polymer solution. The drug, Risperidone (5 mg) was added to the polymer solution and mixed homogeneously to get a smooth, viscous dispersion. The resulting solution was then added to calcium chloride (5% w/v in water) solution through a syringe using a 21G needle with continuous stirring at 400-500 rpm. The stirring was continued for continued for 1 hr to complete the curing reaction and to produce the spherical rigid microspheres. The microspheres were prepared by decantation, and the product thus obtained was separated and dried at 30-40°C for 4 hrs. 4 formulations of Risperidone were prepared.

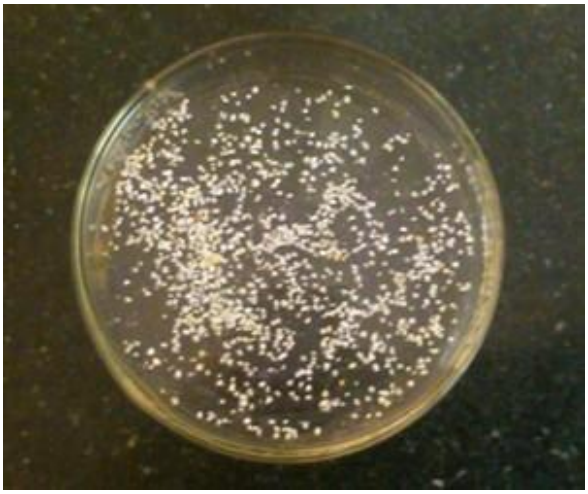

Figure 1: Prepared Microspheres

Formulation of TDDS matrix containing microspheres

Matrix type transdermal patch containing Risperidone microspheres was prepared by a solvent evaporation method. The polymer (EC) was dissolved in 10ml of ethanol to a homogenous polymer solution. Dibutyl phthalate was used as the plasticiser. And Span 80 was added as a permeation enhancer. The microspheres were added to the polymer solution with continuous agitation. The resultant solution was poured into the petri plate covered with aluminium foil. Controlled solvent evaporation was achieved by inverting a fun-

Table 1: Composition of Microspheres

Formulation code	Drug: Polymer ratio	HPMC: Sodium Alginate	Calcium Chloride solution
F1	1:1	1:2	5% w/v Solution in water
F2	1:2		
F3	1:3		
F4	1:4		

Table 2: Composition of TDDS Patch

Formulation code	EC (mg)	Ethanol	Plasticiser	Microspheres (mg)
T1	125	10 % of the polymer weight	30 % of the polymer weight	50
T2	250			45
T3	375			42
T4	500			38

Drug incorporated = 5mg of Risperidone (Area =2×2 cm^2)

Table 3: Physio-chemical properties of prepared formulations

Formulation code	Weight variation (mg) ± s.d	Thickness (mm) ± s.d	Folding Endurance ± s.d	Tensile Strength (%) ± s.d
T1	130 ± 4.15	0.203 ± 0.0021	49 ± 2.9	75.02 ± 8.36
T2	145 ± 6.51	0.170 ± 0.0090	52 ± 5.1	92.57 ± 6.18
T3	151 ± 3.07	0.211 ± 0.0038	65 ± 4.9	103.4 ± 9.24
T4	163 ± 4.13	0.235 ± 0.0079	34 ± 3.8	84.96 ± 5.34

Table 4: Physio-chemical properties of prepared formulations

Formulation code	Wvtr (%) ± s.d	Moisture Content (%)± s.d	Moisture uptake (%) ± s.d
T1	0.90± 0.027	2.01± 0.013	2.41 ± 0.87
T2	0.84 ± 0.038	2.60 ± 0.038	1.70 ± 0.40
T3	0.63 ± 0.051	1.83 ± 0.074	1.36 ± 0.53
T4	0.59± 0.064	1.72 ± 0.095	1.21 ± 0.24

nel, and the patch was allowed to dry at room temperature for 24 hrs. The film was removed using sharp blades and stored in a desiccator in a cool, dry place. 4 formulations of Risperidone TDDS patch were prepared. The composition of films is given in tables 1 and 2.

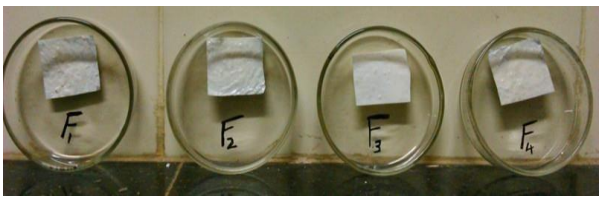

Figure 2: Formulations of TDDS matrix

RESULTS AND DISCUSSION

Evaluation of microspheres: Particles of microspheres were white in colour, spherical in shape and free flowing in nature. The particle size of microspheres ranges from 1-1000µm. In the present study, the average particle the size of the microspheres was found to be in the range of 426-528µm. The percentage yield was found in the range of 79% to 93%. The drug loading was found to be in the range of 42% to 63%, and entrapment efficiency was found to be 84% to 95%. Inter-particulate interaction is one of the most important parameters that affect the bulk and flow characteristics of the powder. The studies of flow characteristics, i.e. bulk density, tap density suggested that the microspheres had good packability and enhanced flowability. The value of Carr's index if greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability. In this study, Carr's index of most of the formulations was found to be below 15 which indicates good flowability.

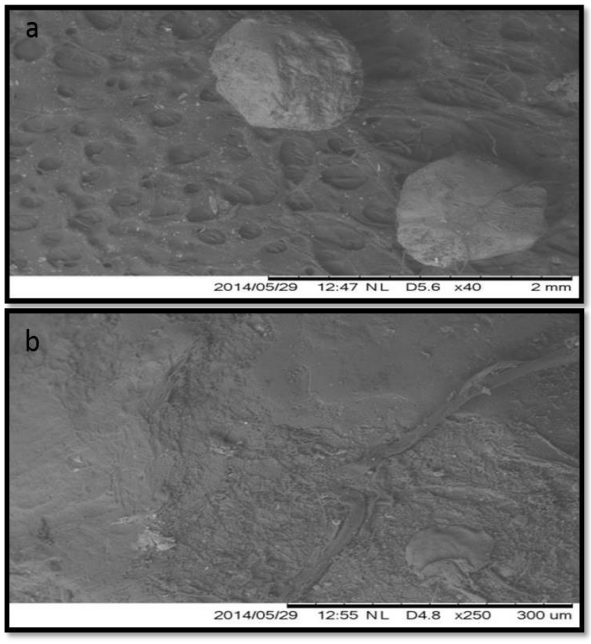

Figure 3: SEM photographs of Microspheres; a-Under 40x; b-Under 250x

The morphological evaluation of the microsphere formulations was done by Scanning Electron Microscopy. SEM study revealed that the HPMC and Sodium Alginate microspheres were almost spherical. Also, they had a smooth surface. The cumulative percent drug release of drug ranged from 55% to 81%. Out of the 4 batches, the release was found to be the highest in Formulation F2, i.e. about 81% and for about 12 hours. The proportion of Drug: Polymer in case of Formulation F2 was 1:2. This may be due to the fact that the dissolution of aqueous soluble fraction (HPMC) of the microsphere matrix leads to the formation of gelanous pores. The formation of such pores leads to decrease in the path length between the drug molecules and the dissolution medium causing a higher release rate. Since HPMC is hydrophilic in nature, it tends to swell in *in-vitro* medium, and thus the drug diffuses out.

When the drug is released from the matrix in such a way that the rate of release of the drug remains constant, the release kinetics of the drug is believed to follow zero-order kinetics. The *in-vitro* drug analysis data showed that the drug release followed zero order kinetics as correlation coefficients (R^2=0.86 to 0.98) of Zero orders were better than that of the First order (R^2=0.78 to 0.97).

The Higuchi's Plot showed the regression coefficient of 0.9104 to 0.9631, which indicated that diffusion was the mechanism of drug release. In order to confirm this fact, Peppa's plot was drawn which showed the R^2 value 0.9078 to 0.9807 which confirmed that the diffusion mechanism involved in the drug release was of non-fickian type. Since microspheres of Batch F2 showed better release (81%) than the rest; they were selected to be incorporated in the patch made up of EC.

Evaluation of transdermal patch

The transdermal films were smooth, uniform and flexible. The films were found to be satisfactory. The weight of the films ranged between 130 to 163 mg, which indicates that different batches showed relatively similar weights. The thickness of the films varied from 0.170 to 0.235. The minimum standard deviation values assumed that the process used for preparing the drug delivery system is capable of giving reproducible results. The folding endurance was measured manually for the prepared films. Results indicated that Formulation T3 showed better folding endurance than the rest of the films. i.e.65 numbers of folds. This revealed that the prepared films had good flexibility and would maintain their integrity with the skin folding when used. 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 indicated 100% flatness observed in the formulated patches. Thus, no amount of constriction was observed in the film of any formulation, and it indicated that they could maintain a smooth surface when applied on to the skin. The tensile strength measures the ability of a film to withstand rupture. Tensile strength was seen in the range of 0.65 to 0.73. Transdermal films containing a lower amount of EC showed better results. Formulation T1 and T2 showed less % WVTR as compared to T3 and T4. The % moisture loss was found to be between 1.83% to 2.60%. This value helps to indicate stability and brittleness of the patches. The moisture absorption in all the formulations was found to be low and ranged from 1.21 to 2.24%. The result revealed that the moisture absorption was found to decrease with increase in the concentration of hydrophobic polymers.

Batch F2 of the Risperidone microspheres was found to give desirable release and hence was selected to be incorporated in the EC matrix. Out of the 4 batches of the patches formed using different proportions of EC batch T3 showed the release of 84.90% which could be sustained for a duration of 24hours. With further increase in the EC polymer concentration, the release was found to decrease. This may be attributed to the fact that, with an increase in the concentration of hydrophobic polymer, the release of the drug is retarded and reduced. When the drug is released from the matrix in such a way that the rate of release of the drug decreases with time, the release kinetics of the drug is believed to follow First-order kinetics. The *In-vitro* drug analysis data showed that the drug release followed First order kinetics as correlation coefficients (R^2=0.91 to 0.97) of First-order were better than that of the Zero order (R^2=0.86 to 0.95).

The Higuchi's Plot showed the regression coefficient of 0.7374 to 0.9491, which indicated that diffusion was the mechanism of drug release. In order to confirm this fact, Peppa's plot was drawn which showed the R^2 value of 0.911 to 0.978 which confirmed that the diffusion mechanism involved in the drug release was of non-fickian type. The samples did not show any alteration in the physical appearance to an extent. There were no visible signs of physical or chemical degradation. The content uniformity did not show any significant changes. The results indicated that the drug remained stable during the period of stability studies.

SUMMARY AND CONCLUSIONS

The main aim of the study was to sustain the release of the formulation for at least 24 hours. Microspheres of Risperidone were prepared using HPMC as the polymer by ionic gelation method. And that such patch can be formulated by prepara-

tion of microspheres of the anti-psychotic drug using HPMC and incorporation of the microspheres thus formed, in a matrix of EC polymer. Further research on this dosage form is definitely desirable.

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