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A Novel Approach for the Treatment of Migraine

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ABSTRACT

According to the Migraine Research Foundation, migraine ranks in the top 20 of the world's most disabling medical illnesses with more than 10 % of the population, including children, suffering from the migraine. Sumatriptan Succinate is a choice of drug used for the treatment of migraine when received at oral dose its bioavailability is approximately 14%. Considering the low bioavailability after oral and intranasal administration, due to presystemic metabolism and incomplete absorption as well as additional inconveniences associated with parenteral & oral administration, the exploitation of an alternative route of sumatriptan topical delivery, such as topical gel could sort out mentioned problem and enhance its therapeutic benefit up to possible extent. Topical delivery systems of Sumatriptan succinate gel were formulated using polymers like HPMC, Carbopol 934 & Pectin and penetration enhancers like eucalyptus oil, menthol & oleic acid. The gels were evaluated for various parameters such as homogeneity, grittiness, extrudability, *in vitro* drug release, viscosity, pH, spreadability and drug content. The release rate of gel obeyed koresmeyer peppas kinetics. It can be concluded that HPMC gel has properties similar to marketed preparation and eucalyptus oil acts as a good penetration enhancer in formulation as compare to menthol & oleic acid.

Keywords: Sumatriptan Succinate, topical gel, migraine, penetration enhancer and bioavailability

1. INTRODUCTION

Pharmaceutical gels are semisolid preparations in which there is interaction (either physical or covalent) between colloidal particles of polymers within a liquid vehicle. The vehicle is continuous and interacts with the colloidal particles of polymers within the three-dimensional network that is formed by the bonds formed between adjacent particles.[1] Migraine is an intense, often unbearable type of headache. It is a severe, throbbing vascular headache. This sort of headache is characterized by recurrent unilateral head pain combined with neurological & GI disturbances.[2] Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side, which comes in attack lasting 4-48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, vertigo, loose motions and other symptoms. Sumatriptan Succinate serotonin receptor agonist majorly used for the treatment of migraine.[3] Its topical application may be a better alternative that also reduces the side effects associated with oral and parental therapy. As per patent filed by Ronald Aung-Din *et al* (2008) it has been reported that Sumatriptan could be efficiently used in the treatment of the migraine in the topical gel formulation.[4] The study confirmed that Sumatriptan gel is an effective and safe option for the management migraine. Topical preparations avoid GI irritation, prevent the metabolism of drug in the liver, increase the bioavailability of the drugs enhance the therapeutic effect of drug and provide its action directly at the site of action. Although gel formulation of Sumatriptan appears to be highly useful, but unfortunately there is lack of literature on the formulation development of Sumatriptan topical gels. Therefore main objective of the present work was to develop topical gel of Sumatriptan and by using penetration enhancers of natural, chemical and synthetic origin to study the formulation variables affecting the release of drug and it was found that eucalyptus oil; from natural source act as a best penetration enhancer. [5]

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For a topical formulation to be effective, it must be initially penetrate the barriers of skin, only when the drug has entered the lower layers of the skin it can be absorbed by blood and available for the site of action, or penetrate deeper in areas where inflammation occurs. The stratum cornea provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption of drug from formulation. The permeation of drugs through skin can be enhanced by physical methods such as mechanical disruption, electrical disruption, and chemical modification or by the use of chemical enhancers. Some compounds may increase skin permeability by increasing the partition coefficient of the drug into the skin.[6] Chemical penetration enhancers modify barrier properties of the stratum corneum and hence increase drug permeability across skin. Ideally, the effects of the penetration enhancer on the skin should be reversible, non-toxic, non-allergenic, compatible with drugs and excipients and non-irritating. However the synthetic permeation enhancers are associated with adverse effect of producing irritation and toxicity to the skin. [7] Hence natural penetration enhancers are increasingly been used as compatible permeation enhancers due to their better safety profile.

2. MATERIAL AND METHODS

Materials

Sumatriptan succinate was a gift sample from Nosch Laboratory Pvt. Ltd. Hyderabad. Propylene glycol, triethanolamine and ethanol were obtained from Central Drug House and all other chemicals are of analytical grade.

Method of Preparation of gel

Sumatriptan succinate gel formulations were prepared using hydroxypropylmethyl cellulose, carbopol 934 and pectin as gelling agent. Gelling agent was dispersed in a small quantity of distilled water and then remaining distilled water was mixed with the mixture of ethanol and propylene glycol then weighed amount of drug was dissolved in solvent system with continuous stirring with the help of mechanical stirrer and drug solution was added slowly in the gel base. pH of the vehicle was brought near to skin by using triethanolamine. The final weight of the gel was adjusted to 50 gm with remaining solvent system. Entrapped air bubbles were removed by keeping the gels overnight at room temperature. Table 1 shows the composition of the Sumatriptan succinate gels.

Evaluation of Gel

Measurement of pH [8]

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Viscosity study [9]

The measurement of viscosity of the prepared gel was done by Brookfield Viscometer. Brookfield DV – II + Pro Viscometer. Model D220. Serial no. 6527715. Made in USA.

Table No 1. Different Concentration of polymers used in formulation of Gel.

Code	Conc.	Code	Conc.	Code	Conc
C1	0.5%	H1	0.5%	P1	0.5%
C2	1.0%	H2	1.0%	P2	1.0%
C3	1.5%	H3	1.5%	P3	1.5%
C4	2.0%	H4	2.0%	P4	2.0%

C = Carbopol, H = HPMC, P = Pectin

Homogeneity [10]

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Spreabability [11,12]

It was determined by spreadibility apparatus. About 1g of gel was added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load. It is calculated by using the formula:

$S = M \cdot L / T$

Where M = wt. tied to upper slide, L = length of glass slides

T = time taken to separate the slides

Extrudability study [13]

The formulations were filled in the collapsible tubes after the gels were set in the collapsible tube. The extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm ribbon of gel in 10 second.

Grittiness [14]

All the formulations were evaluated microscopically for the presence of particles no remarkable particulate matter was seen

Table No 2. Composition of Sumatriptan succinate gel

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%	1.5%
OLEIC ACID	1%	3%	5%	-----	-----	-----	-----	-----	-----
MENTHOL	-----	-----	-----	1%	3%	5%	-----	-----	-----
EUCALYPTUS OIL	-----	-----	-----	-----	-----	-----	1%	3%	5%
PROPYLENE GLYCOL	1%	1%	1%	1%	1%	1%	1%	1%	1%
ETHANOL	3%	3%	3%	3%	3%	3%	3%	3%	3%
DISTTILLED WATER	6%	6%	6%	6%	6%	6%	6%	6%	6%
DRUG	1%	1%	1%	1%	1%	1%	1%	1%	1%
TRIETHANOL AMINE	0.4ml	0.6ml	0.4ml	0.5ml	0.4ml	0.7ml	0.6ml	0.7ml	0.7ml

Table No 3. (a) Evaluation parameters of prepared gel formulations

PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8	F9
VISCOSITY (cps)	2828.00 ± 4.93	2888.66 ± 80.15	3518.00 ± 33.29	3656.66 ± 55.57	4026.66 ± 25.16	4288.33 ± 34.03	2606.6 ± 30.55	3714.33 ± 10.20	4376.00 ± 25.16
SPREADIBILITY	18.3 ± 0.18	17.90 ± 0.40	16.51 ± 0.38	13.0 ± 0.48	11.26 ± 0.36	10.85 ± 0.1	17.53 ± 0.37	15.44 ± 0.12	11.63 ± 0.70
HOMOGENITY	++	+++	++	+++	++	+++	++	++	++
pH	6.76 ± 0.18	6.76 ± 0.14	6.68 ± 0.02	7.43 ± 0.32	7.26 ± 0.208	7.4 ± 0.12	7.5 ± 0.26	7.4 ± 0.44	7.74 ± 0.028
GRITTINESS	-	-	-	-	-	-	-	-	-
DRUG CONTENT (%)	93.70 ± 1.55	93.68 ± 1.17	92.10 ± 2.15	92.34 ± 1.01	93.11 ± 2.2	92.20 ± 1.14	91.78 ± 2.9	91.19 ± 3.0	93.76 ± 2.55

under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

Drug content [15]

A specific quantity (100mg) of developed gel and marketed gel were taken and dissolved in 100ml of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 227.0 nm using phosphate buffer (pH 7.4) as blank.

In vitro diffusion studies

The diffusion studies of the prepared gels were performed in modified diffusion cell to studying the dissolution release of gels**.** Gel sample (0.5g) was taken and the diffusion studies were carried out at 37 ± 1° using 200 ml of phosphate buffer (pH 7.4) as the dissolution medium. 5 ml of each sample was withdrawn and was replaced with equal volume of fresh dissolution medium in the diffusion cell. Then the samples were analyzed for the drug content by using phosphate buffer as blank by UV spectroscopy at 227 nm.

Table No 3 (b) .Evaluation of marketed gel formulation

PARAMETERS	Marketed formulation
VISCOSITY (cps)	4410 ± 25cps
SPREADIBILITY	11.94 ± 0.36
HOMOGENITY	+++ (Excellent)
pH	7.2 ± 0.5
GRITTINESS	- (No grittiness)
DRUG CONTENT (%)	99.5 ± 6.5%

++ Good +++ Excellent

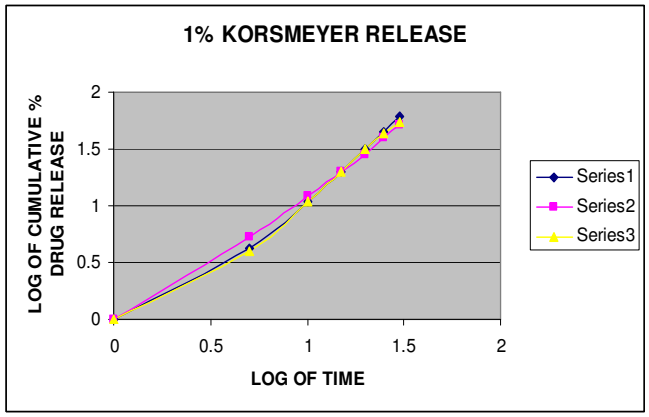

Fig.1. Korsmeyer release plot of different formulations of gel containing 1% Eucalyptus oil Series 1, Menthol Series 2 and Oleic acid Series 3

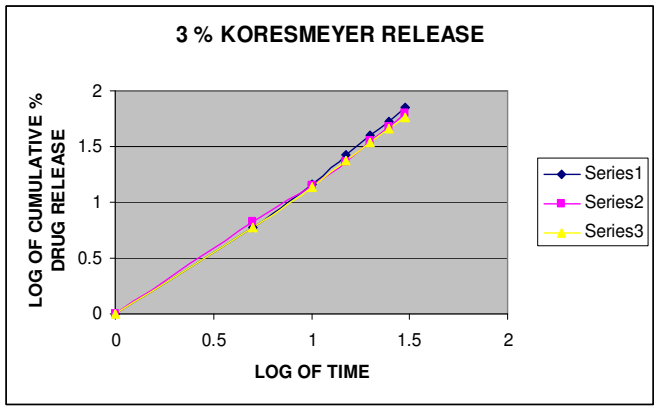

Fig. 2. Koresmeyer plot of different formulations of gel containing 3% Eucalyptus oil Series 1, Menthol Series 2 and Oleic acid Series 3

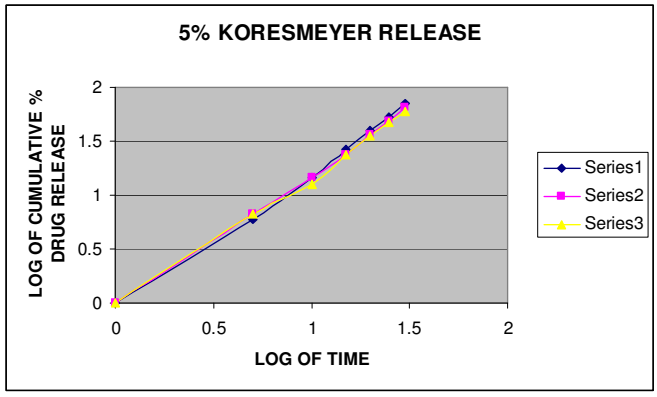

Fig.3. Koresmeyer Release of different formulations of gel containing 5% Eucalyptus oil Series 1, Menthol Series 2 and Oleic acid Series 3

3. RESULTS AND DISCUSSION

Topical gel of Sumatriptan succinate was prepared by using different polymers (synthetic, semi synthetic and natural) such as HPMC, Corbopol and Pectin. It was found that Carbopol and pectin were precipitated during the preparation of gel and HPMC didn't show any sign of unstability or any variation in their consistency during formulation.

The prepared Gel was evaluated for their suitability as a perfect formulation as compare to marketed formulation. Prepared HPMC gel was transparent, good in appearance and consistency. The evaluation studies of all the formulations were performed by standard methods.

The pH, grittiness, homogeneity, viscosity, spreadibility, extrudability and *in vitro* diffusion studies of the formulation were performed and they all were found to be satisfactory. We also compared gel with standard marketed gel and the result obtained was similar to marketed gel preparation which was shown in table no. 3 (a) and 3 (b).

Comparative studies were performed between different polymers and penetration enhancers and it revealed that gel containing HPMC as a gelling agent were shown satisfactory results as compare to gel formulations containing different gelling agents such as carbopol and pectin. The results of the *in vitro* release study from HPMC gel by using different concentration of different penetration enhancers across the biological membrane was performed and 5% eucalyptus oil was found to be better penetration enhancer as compare to menthol and oleic acid because its penetrability was best among the other enhancers and it showed good release rate also.

To establish the order and mechanism of drug release, dissolution data of all the formulations were fitted to four different kinetic models named as zero order model, first order model, higuchi model and koresmeyer peppas model. [16] The model for best fit was predicted from the value of r^2. The value which was closer to 1 was selected as the best fit model for the drug release. [17] The *in vitro* drug release was found to follow Korsmeyer-Peppas kinetics as correlation coefficient r^2 =0.9983 which was closer to 1.

The aim of this project was to formulate the topical gel using different polymers and penetration enhancers which may deliver the drug better than conventional dosage form of Sumatriptan on site of action and avoid the first pass metabolism as well as other gastric side effects of drug. Above mentioned aim was fulfilled by formulation of different formulations having combination of different gelling agent as well as penetration enhancers. An Optimized formulation was formulated showed good, spreadibility, viscosity, extrutability, consistency, appearance, penetrability and *in vitro* release. In the present study results showed that natural penetration enhancers may also used satisfactory as compare to chemical ones. It is also considerable that by developing such sort of promising formulations may open the doors for drugs having bioavailability problems and are not able to give efficient therapeutic effect which is a soul for the development of perfect, potent and therapeutic efficient drug delivery system.

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