

Formulation and Characterization of Ketoprofen Emulgels

Ramakanth Ambala, Sateesh Kumar Vemula

¹Department of Pharmaceutics, Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda, Warangal, Andhra Pradesh, India.

²College of Medical and Health Sciences, Wollega University, Post Box No: 395, Nekemte, Ethiopia.

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ABSTRACT

The present study was intended to formulate the ketoprofen emulgels using different viscosity grades of hydroxypropyl methylcellulose and carbopol as gelling agents. All the prepared emulgels were shown acceptable physical properties concerning colour, homogeneity, consistency, and pH value. Emulgels containing hydroxypropyl methylcellulose were poor in clarity when compared to carbopol formulations. The influence of the type of gelling agent on the drug release from the prepared emulgels was investigated and carbopol 934 showed good results not only in the drug release but also in physical evaluation parameters. From the drug release studies, F3 formulation showed $98.46 \pm 2.05\%$ drug release in 8 h with good clarity and physical appearance. The T10% and T80% values of best formulation F3 was found to be 0.9 h and 6.6 h respectively. The T10% and T80% was higher for formulations with carbopol in low concentration when compared to hydroxypropyl methylcellulose K 4M and K 15M in high concentrations, indicating better controlled release. FTIR studies proved the compatibility between drug and carbopol. From the stability studies, similarity index value between dissolution profiles of F3 formulation before and after storage was found to be 87.16. Hence the development of ketoprofen emulgels is a suitable way for topical administration.

INTRODUCTION

Topical administration facilitates safe and effective delivery of drug molecules with lower doses when compared with that of oral dosage forms. Another potential advantage topical dosage forms is the optimization of drug concentration at the desirable sites, reducing the chances of side effects. Topical preparation is used for the localized effect at the site of their application by virtue of drug penetration into the underlying layer of skin or mucous membrane (Chien, 1992). Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations (Vyas *et al.*, 2002). In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and

creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. As the name suggests, emulgels are the combination of emulsion and gel. When gels and emulsions are used in combined form the dosage forms are referred as emulgel (Khullar *et al.*, 2011; Mohamed, 2004a). Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin (Rieger *et al.*, 1986). The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel (Khullar *et al.*, 2012). Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. Use of topical agents requires an appreciation of the factors that influence percutaneous absorption (Stanos, 2007). Many widely used topical agents like ointments, creams lotions have many disadvantages. They have very sticky causing uneasiness to the patient when applied. Moreover they also have lesser spreading coefficient and need to apply with rubbing. And they exhibit the problem of stability also (Cecv, 2008). Due to all these factors within the major group of semisolid preparations, the use of transparent gels and emulgels has expanded both in cosmetics and in pharmaceutical preparations.

* Corresponding Author

Sateesh Kumar Vemula, Department of Pharmaceutics, Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda, Warangal, Andhra Pradesh, India-506001

Email: vemulasatish15@gmail.com

Some of the recent research examples for emulgels are diclofenac acid and its salts (Wang *et al.*, 2008), Chlorphenesin (Mohamed, 2004b), Clotrimazole (Mostafa *et al.*, 2011), Rofecoxib (Desai, 2004), Fluconazole (Bachhav *et al.*, 2009) and Piroxicam (Khunt *et al.*, 2012).

Ketoprofen is a member of non-steroidal anti-inflammatory drugs and shows strong analgesic and anti-pyretic effect. Ketoprofen causes gastrointestinal disturbances, peptic ulceration with bleeding, if present in large doses in gastrointestinal tract upon oral administration (Singh *et al.*, 2009; Patil *et al.*, 2004). The topical application allows for a higher local concentration of the drug at the site of initiation of the pain and lower or negligible systemic drug levels producing fewer or no adverse drug effects (Nikumbh *et al.*, 2013; Hosny *et al.*, 2013). Emulgels have emerged as a promising drug delivery system for the delivery of hydrophobic drugs. By considering the above factors, the present study is intended to develop the ketoprofen emulgel using carbapol 940 and hydroxypropyl methylcellulose (HPMC K4M & K15M) as a gelling agent to overcome the gastric side effects and achieve the therapeutic benefit.

MATERIALS AND METHODS

Materials

Ketoprofen and Carbapol 934, HPMC K4M and HPMC K15M are obtained as a gift sample from MSN Laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

Preparation of ketoprofen emulgels

Ketoprofen emulgel was prepared using carbapol 940, HPMC K4M and HPMC K15M as gelling agents (Table 1). The gels in formulations were prepared by dispersing carbapol or HPMC in purified water with constant stirring at a moderate speed and then the pH are adjusted to around 6 using tri ethanol amine. The oil phase of the emulsion was prepared by dissolving span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl and propyl parabens were dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. Finally the emulgel was prepared by mixing the both gel and emulsion in 1:1 ratio (Baibhav *et al.*, 2011; Sabri *et al.*, 2009).

Physical evaluation of emulgels

The prepared ketoprofen emulgel formulations were inspected visually for their colour, clarity, homogeneity, pH and viscosity. All developed gels were tested for colour, clarity and homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance to identify the presence of any aggregates. The pH values of 1% aqueous solutions of the prepared emulgel were measured by a pH meter

(Digital pH meter, Systronics). The pH of emulgels is adjusting to avoid the risk of irritation upon application to the skin and the acceptable pH is around 5.5 (Panwar *et al.*, 2011). Viscosity measurements were carried out at room temperature (25- 27°C) using a Brookfield viscometer (Model RVTDV II).

Determination of drug content

The prepared emulgels were tested for the drug content uniformity. Accurately weighed quantity of formulation was transferred to a 100 ml volumetric flask containing 50 ml of methanol and allowed to stand for 5 h with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with methanol. The solution was suitably diluted and the absorption was determined by UV-Visible spectrophotometer at 260nm.

Spreadability

Spreadability is used to express the extent of area to which gel readily spread on application to skin or affected part and the therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability was determined by wooden block and glass slide apparatus. Weights about 20g were added to the pan and the time were noted for upper slide (movable) to separate completely from the fixed slides. Spreadability was then calculated by using the formula:

$$S = M \times L / T$$

Where, S = Spreadability; M = Weight tide to upper slide; L = Length of glass slide; T = Time taken to separate the slide completely from each other (Jain *et al.*, 2010).

Swelling index

To determine the swelling index of prepared emulgels, 1 gm of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N sodium hydroxide. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed. Swelling index is calculated as follows:

$$\text{Swelling Index (SW) \%} = [(Wt-W_0)/W_0] \times 100$$

Where (SW) % = Equilibrium percent swelling, Wt = Weight of swollen emulgel after time t, W₀ = Original weight of emulgel at zero time (Khalil *et al.*, 2011).

In vitro drug release studies

Franz diffusion cell (with effective diffusion area 3.14 cm² and 15 ml cell volume) was used for the drug release studies. Emulgel (200 mg) was applied onto the surface of cellophane membrane evenly. The membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared buffer pH 5.5 solutions to solublize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer at 260 nm after appropriate dilutions.

Table 1: Formulation of ketoprofen emulgels.

Ingredients (% w/w)	F1	F2	F3	F4	F5	F6	F7	F8
Ketoprofen	1	1	1	1	1	1	1	1
Carbopol 934	0.25	0.5	0.75	1	-	-	-	-
HPMC K4M	-	-	-	-	2.5	5	-	-
HPMC K15M	-	-	-	-	-	-	2.5	5
Liquid paraffin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Tween 20	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Span 80	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Propylene glycol	5	5	5	5	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methyl paraben	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
Propyl paraben	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Water	Q.S.							

Table 2: Physical evaluation of ketoprofen emulgels (Mean±SD, n=3)

Formulations	Clarity	Colour	Homogeneity	pH	Viscosity (cps)	% Drug content
F1	+++	Off white	Good	5.8±0.26	9495±12	99.83±1.68
F2	+++	Off white	Good	5.4±0.16	9512±16	98.56±0.78
F3	+++	Off white	Good	5.5±0.31	9756±11	99.86±0.52
F4	+++	Off white	Good	5.4±0.24	9634±17	98.47±1.12
F5	++	White	Good	5.3±0.28	9326±14	99.46±0.92
F6	++	White	Good	5.7±0.62	9394±18	98.63±0.68
F7	+	White	Good	5.4±0.45	9687±11	99.12±0.23
F8	+	White	Good	5.8±0.12	9512±13	98.33±0.45

Table 3: Drug release kinetics parameters of selected emulgel formulations.

Formulation Code	Zero order (R ²)	First order (R ²)	Higuchi (R ²)	T10% (h)	T80% (h)
F3	0.9163	0.8911	0.9724	0.9	6.6
F6	0.9292	0.8591	0.9512	0.7	6.1
F8	0.9254	0.8856	0.9538	0.8	6.4

R2- Correlation coefficient, T10%-Time to release 10% drug release and T80%-Time to release 80% drug release.

Table 4: Stability studies of F3 emulgel formulation-physical evaluation.

Time Period	Clarity	Homogeneity	pH	Spreadability	Viscosity (cps)	% Drug content
Before storage	+++	Good	5.5±0.31	52±0.68	9756±11	99.86±0.52
After 3 months	++	Good	5.4±0.18	51±0.48	9742±11	98.91±0.72

Table 5: Stability studies of F3 emulgel formulation-drug release studies.

Time (h)	Before storage	After 3 months	t-test at 0.05 LS	Similarity Factor (F2)
0	0.00±0.00	0.00±0.00		
0.5	3.89±0.41	3.12±0.32		
1	12.18±0.76	11.54±0.56		
2	27.18±1.35	25.95±0.98		
3	31.72±1.18	30.26±0.85	Not Significant	87.16
4	38.90±1.62	37.67±1.24		
5	47.81±2.01	46.92±0.76		
6	75.93±2.32	74.84±1.18		
8	98.46±2.05	97.51±0.45		

In vitro drug release kinetics

To elucidate the drug release pattern and mechanism from the prepared formulations, the data obtained from the *in vitro* dissolution studies was integrated to zero order, first order and Higuchi models (Valluru *et al.*, 2008). Then the dissolution data was also used to calculate the T10% and T80% (time in hours to take 10% and 80% drug release, respectively) to elucidate the drug release from emulgels (Vemula *et al.*, 2013a; Vemula *et al.*, 2014a).

FTIR study

The infrared spectra of ketoprofen, physical mixture of drug and polymers were recorded between 400 to 4000 cm⁻¹ on

FTIR to detect the drug-excipients interactions. The FTIR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer. The resultant spectra were compared for any possible changes in the peaks of the spectra.

Stability studies

With the help of ICH guidelines, the stability studies were planned to assess the stability of ketoprofen in emulgels. Three replicates of F3 formulation was sealed in aluminum coated inside with polyethylene pack and stored at 40±2 °C and 75±5% RH in the humidity chamber for three months (Chaudhary *et al.*, 2011). Specimens were gathered following three months of storage and estimated for the all physical evaluation parameters and *in*

vitro dissolution rate (Mathews, 1999). Then to prove the stability of dosage form, the similarity index was calculated between dissolution rates of optimized tablets before and after storage. The similarity factor (F_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves. It is calculated using the following formula. At this point, the data was statistically analyzed using paired *t*-test to test the significance of difference at level of significance 0.05 (Vemula *et al.*, 2013b; Vemula *et al.*, 2014b).

$$F_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

RESULTS AND DISCUSSION

Evaluation of ketoprofen emulgel

The prepared ketoprofen emulgels (F1-F8) were evaluated for clarity, colour, pH, spreadability, viscosity, homogeneity and drug content. F3 has shown better results in pH, spreadability, homogeneity, high viscosity and drug content. The prepared ketoprofen emulgel formulations were white viscous creamy preparation with a smooth and homogeneous appearance. The pH values of all prepared formulation ranged from 5.3 to 5.8, which are considered acceptable to avoid the risk of irritation upon application to the skin because adult skin pH is 5.5. Spreadability values were shown in Figure 1.

The viscosity of prepared formulations was found in the range of 9326±14 to 9756.±11 cps. In all the formulations, formulations with carbopol showed high viscosity that indicates carbopol as the better gelling agent in low concentration when compared to HPMC formulations. The drug content of all emulgel formulations was found above 98%. All the above physical parameters of F1-F8 formulations were given in below Table 2.

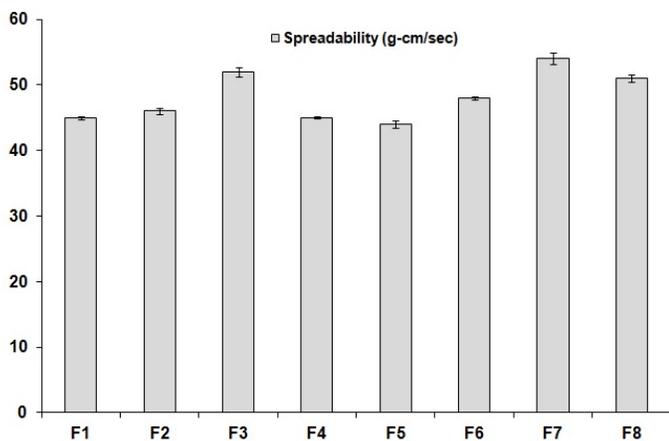


Fig. 1: Spreadability of ketoprofen emulgels (F1-F8).

Swelling index

From the swelling studies, the formulations with carbopol showed maximum swelling index in comparison of HPMC formulations. Among the all formulations, F3 emulgel formulation showed highest swelling index properties in comparison of other it means emulgel formulating having greater

swelling tendency i.e. tendency to from wound. Similar type of observation was found in a study by Ghodekar *et al.*, 2011. The swelling index values of all formulations were given in Figure 2.

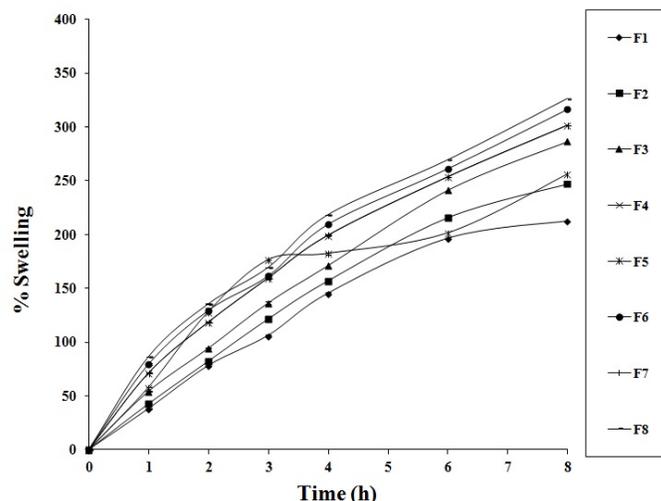


Fig. 2: Percent swelling of ketoprofen emulgels (F1-F8)

In vitro drug release study

The *in vitro* drug release studies carried out for all the formulations and Figure 3 and 4 represents the drug release from carbopol and HPMC. The study showed the release of the drugs from its emulsified carbopol gel formulation can be ranked in the following descending order: F1 > F2 > F3 > F4 where the F3 formulation showed highest drug release after 8h (98.46±2.05%). Similar type of results were observed in a study by Khullar *et al.*, 2012 i.e., mefenamic acid emulgel using carbopol.

To give similar type of drug release in case of HPMC based emulgel preparations, they required high concentration of polymer than carbopol. Thus the F3 formulation containing carbopol is considered as the better formulation among all other formulations.

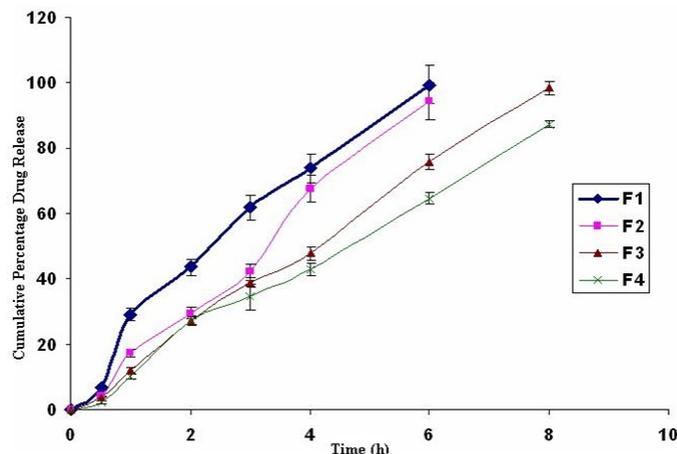


Fig. 3: Percent drug release of ketoprofen from carbopol emulgels.

In vitro drug release kinetics

The drug release mechanism and kinetics was determined by the application of Higuchi's model, zero order and first order kinetics. Most of the emulgel formulations showed high r^2 values for Higuchi's model as their r^2 values were between 0.9724 and 0.9538.

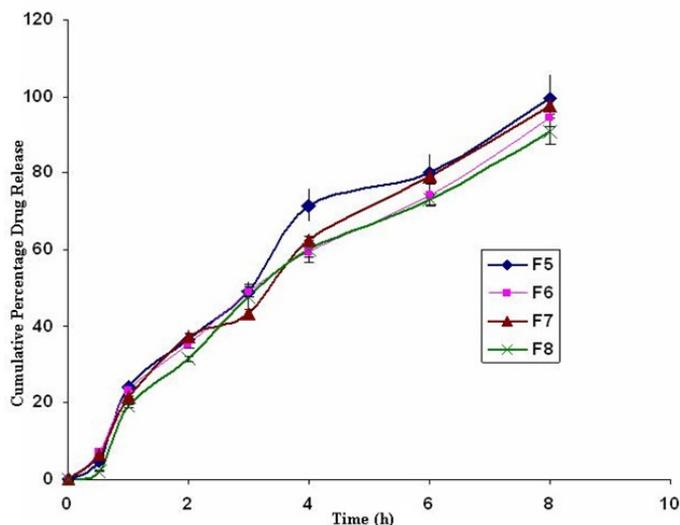


Fig. 4: Percent drug release of ketoprofen from HPMC emulgels.

The high regression value of Higuchi model ensured that the release of drug from emulgels followed diffusion mechanism. The T10% and T80% values of best formulation F3 was found to be 0.9 h and 6.6 h respectively. The T10% and T80% was higher for formulations with carbopol in low concentration when compared to HPMC K 4M and K 15M in high concentrations, indicating better controlled release. Time in hours to take 10% and 80% drug release (T10% and T80%) explained the ability of prolonged release. All these results were given in Table 3.

FTIR study

The infrared spectra of ketoprofen, physical mixture of drug and polymers were recorded and shown in Figure 5. From the results, FTIR spectra showed that there were no interactions identified between drug and polymers. From the FTIR spectral analysis all the principal peaks observed in pure drug were present in the FTIR spectra of the F3 formulation and some additional peaks were observed with physical mixtures, which could be due to the presence of polymer. No drug-polymer interaction was observed in the FTIR spectra of the powder mixture of best formulation since the absorption peaks of the drug still could be detected in the mixture.

Stability studies

The stability studies data was represented in Table 4 and 5. All the prepared emulgel formulations were found to be stable upon storage for three months, no change was observed in their physical appearance, clarity, pH, viscosity, spreadability and drug content. After storage of six months, the formulation was

subjected to *in vitro* drug release studies (Table 5) and from the statistical analysis there was no significant difference between before and after storage ($P < 0.05$). The similarity index value between dissolution profiles of optimized formulation before and after storage was found to be 87.16. The similarity index value was found as more than 50 indicate similarity between the dissolution profile before and after storage.

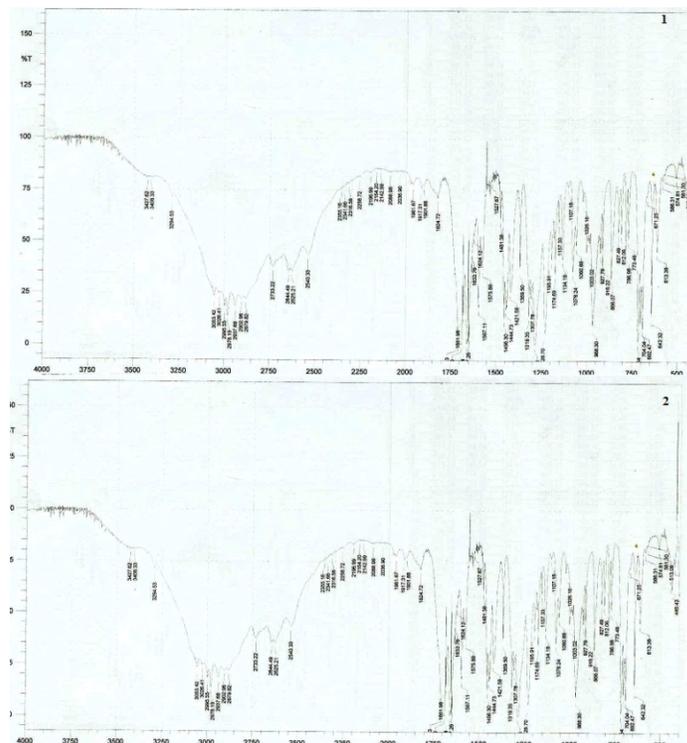


Fig. 5: FTIR spectra of 1) pure ketoprofen and 2) physical mixture of drug and carbopol.

CONCLUSION

Emulgels, considered as the recent technique for the topical drug delivery, are better suitable for the delivery of hydrophobic drugs and combination of both hydrophilic and hydrophobic drugs. Mainly the hydrophobic drug formulation can be developed with Emulgel technique because it contain both oil and aqueous (i.e. gel phase) on the other hand hydrogel are not suitable for hydrophobic drugs. In the present study ketoprofen emulgels were prepared using carbopol and HPMC as gelling agents. All the formulations were characterized for different parameters and formulations with carbopol shown better results when compared to HPMC as gelling agent. From the *in vitro* drug release studies, formulation F3 showed maximum drug release of $98.46 \pm 2.05\%$ in 8 h with good physical properties. FTIR studies proved that there were no possible interactions between ketoprofen and carbopol. From the stability studies, after storage the F3 formulation was observed in stable form. Thus the formulation of carbopol emulgels was considered as the good approach for topical delivery of drugs like ketoprofen.

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