



Original Article

Solubility Enhancement of an Inadequately Water Soluble Drug (Ketorolac Tromethamine) by using different Vehicles

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Abstract

For poorly soluble, highly permeable drugs, such as ketorolac tromethamine, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. The object of the present study is to increase dissolution rate of ketorolac tromethamine using different polymer to prepare liquisolid mixture. Several formulations of liquisolid compacts containing various ratios of drug: propylene glycol (ranging from 1:1 to 1:4) was prepared. In this study the ratio of microcrystalline cellulose (carrier) to silica (coating powder material) was 20:1 in all formulations. The dissolution behavior of ketorolac tromethamine from liquisolid mixture and conventional formulation was investigated by distilled water and phosphate buffer. To enhance the solubility and efficacy of ketorolac tromethamine, we used PG, tween 80, PEG 400, PEG 1500, PEG 6000 polymers in different concentrations. In this study the release pattern was examined of ketorolac tromethamine loaded capsules by using dissolution medium in (water) and phosphate buffer. This work examines the influence of polymers such as Propylene Glycol (PG), tween 80, PEG 400, PEG 1500, and PEG 6000 in different amounts. The experiment provides an acceptable result to predict the solubility of ketorolac tromethamine which has been successfully improved dissolution rate without compromising the physical stability of the systems. These results suggested that, by using propylene glycol, tween 80, PEG 400, PEG 1500 and PEG 6000 the release of ketorolac increased up to 76%, 66%, 81%, 59% and 75% respectively by phosphate buffer where as released of Conventional formulation (DCC) was 27.93%.

Keywords: Ketorolac tromethamine, Solid Dispersion, Surfactants and Carriers.

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1. Introduction

Ketorolac tromethamine is a novel Non-steroidal anti-inflammatory drug (NSAID) with potent analgesic & modest anti-inflammatory activity. In postoperative pain it has the same efficacy of morphine, but does not interact with opioid receptors & is free of respiratory depressant, dependence producing, hypertensive & constipating side effects. In short lasting pain, it has compared favorably with aspirin. Ketorolac tromethamine is dihydroazine carboxylic acid derivatives structure related to indomethacin [1]. Ketorolac has a chiral center and is used as a racemate marketed under the name Toradol the (-)-S isomer has many times greater analgesic potency than the (+)-R-isomer [2]. Ketorolac tromethamine is off-white crystalline powder and has a pK value of 3.49. Ketorolac is quite lipophilic with a partition coefficient (logPC) value of 2.72 [3]. Ketorolac tromethamine is extremely soluble in aqueous solution at pH 4-8, with a very long self-life at 25°C. However it is light sensitive with decarboxylation, especially in the presence of oxygen [4].

Poorly soluble drugs are associated with slow drug absorption leading to inadequate and variable bioavailability [5, 6]. Most formulation strategies for such drugs are targeted at enhancing their dissolution rate and / or solubility *in vivo* by achieving their fine dispersion at absorption level [6, 7, 8].

Definition of solid dispersion:

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [9].

Advantages of solid dispersion:

Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the

drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability [10].

Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects [11, 12].

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form [12]. For drugs with low crystal energy (low melting temperature or heat

of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

2. Materials and Methods:

Materials: Ketorolac tromethamine (Divis Pharma Pvt. Limited, India), Avicel, Colloidal Anhydrous Silica (Evonic Degussa GmbH, Germany), Sodium Starch Glycolate (DMV-Fonterra Excipient, Netherlands), Propylene glycol (BASF, Germany), PEG 400 (Loba Chemicals, India), PEG 1500 (Loba Chemicals, India), PEG 6000 (Loba Chemicals, India), Tween 80 (Ester Chem. SDN, Malaysia), *Distilled Water (University Laboratory)*.

Methods:

Preparation of Conventional Capsule

Ketorolac tromethamine conventional capsules were produced by mixing the drug with microcrystalline cellulose-silica (ratio of microcrystalline cellulose: silica was 20:1) for a period of 10 min in a mortar and pestle. The mixture was mixed with sodium starch glycolate for 10 min.

Preparation of Liquisolid Mixture

Several liquisolid Ketorolac tromethamine mixtures were prepared by dispersing drug in different vehicles with different ratios ranging from 1:1 to 1:4 (Drug : Vehicle). Then binary mixtures of microcrystalline cellulose-silica (microcrystalline cellulose as the carrier powder and silica as the coating material with a ratio of 20:1) were added to the mixture containing the drug and vehicle under continuous mixing by the mortar-pestle which were employed in our liquisolid preparations. Sodium starch glycolate as a disintegrant was mixed with all formulations for a period of 10 min. The final mixture was filled in a one size capsule shell.

Buffer solution preparation

The dissolution was performed in artificial intestinal fluid (pH 6.8). For preparation of pH 6.8 buffer solution Disodium hydrogen phosphate (Na_2HPO_4) & Sodium dihydrogen phosphate ($\text{Na}_2\text{H}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$) were used. At 37°C, disodium hydrogen phosphate 15.91 gm and sodium dihydrogen phosphate 13.9 gm were taken in a 1000 ml volumetric flask and adjusted it up to the mark by distilled water to prepare 1000 ml of pH 6.8 phosphate buffer solution.

In vitro Dissolution study

In vitro drug release study of capsule was conducted for a period of 1 hour using a eight station USP XXII type II apparatus equilibrated at $37 \pm 0.5^\circ\text{C}$ temperature and 50 rpm speed and the capsule was kept inside the basket in 900 ml water vessel. The dissolution studies were carried out in water medium and buffer medium. Every 10 minutes interval sample of 10 ml was withdrawn from dissolution medium and replaced with fresh medium to maintain the volume constant. After appropriate dissolution, the sample solution was analyzed at 322 nm by UV Spectrophotometer. The amount of drug release was calculated with the help of appropriate calibration curves constructed from reference standard of drug. Drug dissolution at specified period was plotted as percent release versus time curve.

Preparation of standard curve of Ketorolac tromethamine

At first 20 mg of Ketorolac tromethamine was taken in a 100 ml volumetric flask then buffer solution was added up to the mark & properly mixed by shaker. Then transfer 10 ml solution in 100 ml volumetric flask and add buffer solution up to mark. This is the stock solution. Then 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml of solution were taken in 10 ml volumetric flask & the solution was adjusted up to the mark with buffer solution. Then the absorbance of the solution was determined at 322 nm.

Formulations of Ketorolac Liquisolid Mixture:

Sr No.	Ketorolac Tromethamine (mg)	Avicel (mg)	Silica (mg)	Sodium Starch Glycolate (mg)	Propylene Glycol, PG (mg)	Tween 80 (mg)	PEG 400 (mg)	PEG 1500 (mg)	PEG 6000 (mg)
DCC	10	40	2	2	-	-	-	-	-
F1	10	40	2	2	10	-	-	-	-
F2	10	40	2	2	20	-	-	-	-
F3	10	40	2	2	30	-	-	-	-
F4	10	40	2	2	40	-	-	-	-
F5	10	40	2	2	-	10	-	-	-
F6	10	40	2	2	-	20	-	-	-
F7	10	40	2	2	-	30	-	-	-
F8	10	40	2	2	-	40	-	-	-
F9	10	40	2	2	-	-	10	-	-
F10	10	40	2	2	-	-	20	-	-
F11	10	40	2	2	-	-	30	-	-
F12	10	40	2	2	-	-	40	-	-
F13	10	40	2	2	-	-	-	10	-
F14	10	40	2	2	-	-	-	20	-
F15	10	40	2	2	-	-	-	30	-
F16	10	40	2	2	-	-	-	40	-
F17	10	40	2	2	-	-	-	-	10
F18	10	40	2	2	-	-	-	-	20
F19	10	40	2	2	-	-	-	-	30
F20	10	40	2	2	-	-	-	-	40

3. Results

The rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract for poorly soluble drug, highly permeable drugs, such as Ketorolac tromethamine. Therefore together with permeability, solubility and dissolution

behavior of a drug are key determinants of the oral bioavailability. The target of the present study is to increase dissolution rate of Ketorolac tromethamine using different polymer to prepare liquid mixture. To investigate the effect of vehicle type on the rate of Ketorolac tromethamine dissolution

from liquisolid mixture, several formulations were prepared with Propylene glycol, Tween 80, PEG 400, PEG 1500 and PEG 6000 containing 10 mg of Ketorolac tromethamine in liquid medication. The dissolution profiles of capsule were conducted using water media and buffer media. The study was undertaken to evaluate the dissolution rate of Ketorolac tromethamine from liquisolid mixture in comparison with the conventional capsule formulations.

It is interesting that DCC released near about 5.96% and 27.93% drug after 10 minutes and 1 hour of dissolution period respectively (Figure-2). On the other hand after using vehicle the rate of drug released was increased gradually (Figure-1 to Figure-5).

As it has been seen from formulation F1 after near about 2.5% and 47% drug was released after 10 mins and 1 hr of dissolution period respectively. According to the formulation F2, we have got 6% drug released after 10 mins and 57% released occur after 1 hour. It was also seen that F3 and F4 released drug 63% and 76% after completion of dissolution period using PG in 1:3 and 1:4. So it is observed that capsule contains PG in higher concentration exhibit higher release than lower concentration (Figure-1).

From formulation F5 we have observed that, about 20% of drug liberated after 10 minutes and 51% of drug was revealed after 1 hour of dissolution period using the ratio of 1:1. In the same way the formulation F6 released 58% drug after completion of dissolution study. It was also evident that F7 and F8 released 61% and 66% drug after completion of dissolution period. So it is observed that capsule contains Tween 80 in higher concentration exhibit higher

release than lower concentration (Figure-2). Serajuddin and co-worker demonstrated that a commonly used surfactant, polysorbate 80, could be used in solid dispersion by mixing it with solid PEG or any other carrier. Although polysorbate 80 is liquid at room temperature, it forms a solid matrix when it is mixed with PEG because it's incorporated within the amorphous region of PEG solid structure.

However, 3.5% of drug by 10 minutes & 69% of drug by 1 hour has been liberated from formulation F9. Similarly, F10 released 5% and 75% drug after 10 minutes and 1 hour respectively. It was also seen from F11 and F12 which have released 79% and 81% of drug after completion of dissolution period. So it is observed that capsules containing PEG 400 in higher concentration exhibit lower release than lower concentration (Figure-3). Lower molecular weight of PEG 400 is liquid in nature and liquid form of polymer, releases the drug in higher amount. When we used the polymer in liquid form drug easily merged with the liquid vehicle and solubility of drug was increased.

Conversely, F13 released approximately 10% drug after 10 minutes and 38% drug exposed after 1 hour. At the same rate formulation F14 released 14% drug after 10 minutes and 40% drug after 1 hour. It is also observed that F15 and F16 drug released 57% and 59% after completion of dissolution period. So it is experimented that capsule contains PEG 1500 in higher concentration exhibit lower release than lower concentration (Figure-4). Other investigators also reported that enhanced dissolution and bioavailability of drugs from PEG 1500 and avicel as carrier increases the dissolution rate of nifedipine from a PEG based solid dispersion. PEG 1500 loaded

mixture can be attributed to the higher solubility profile of low molecular weight of PEG in aqueous media. PEGs, being highly soluble in water, act as channeling agent and is preferentially liberated from the gelatin capsule shell.

Correspondingly formulation F17 liberated 10% of drug after 10 minutes and about 50% of drug released after 1 hr. At the same extent F18 released 14% of drug after 10 minutes and 55% of drug after 1 hour. It is also seen from F19 and F20 released 59% and 75% of drug after completion of dissolution period. So it is observed that capsule contains PEG 6000 in higher concentration exhibit higher release than lower concentration (Ffigure-5). Higher molecular weight of PEG decreases greater releases of drug because higher solubility of drug in phosphate buffer.

Considering above result & according to Figures (1, 2, 3, 4 & 5), PEG 400 (Figure-3) and Propylene glycol (Figure-1) produced higher dissolution rates compared to other vehicles Tween 80, PEG 6000 and PEG 1500 of the same concentration. For example, the amount of the drug released from F4 and F12 after 1 hour in the presence of PG and PEG 400 were 76% and 81% respectively. This is due to higher solubility of Ketorolac tromethamine in PG and PEG 400 liquid medications. On the contrary, after 1 hour from F8, F16 and F20 drug released 66%, 59% and 75% respectively using Tween 80, PEG 1500 and PEG 6000 at the ratio of 1:4.

In this study we have seen that liquisolid formulation indicated a faster dissolution rate compared to the conventional formulations in all the way and if the concentration of the carriers are

increased the released profile of the drug are surprisingly increased. It is added that PEG 400 showed its excellence as a carrier among all by increasing the release profile of a poorly soluble drug like Ketorolac tromethamine.

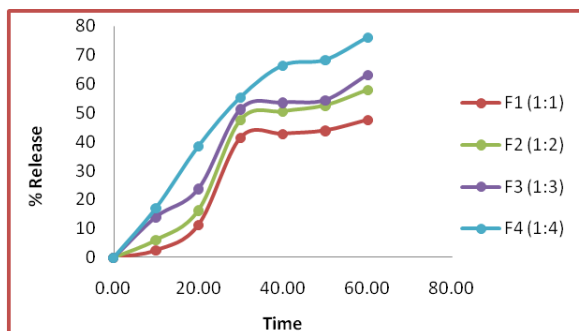


Figure-1: % of release of Ketorolac tromethamine from PG loaded liquid solid mixture

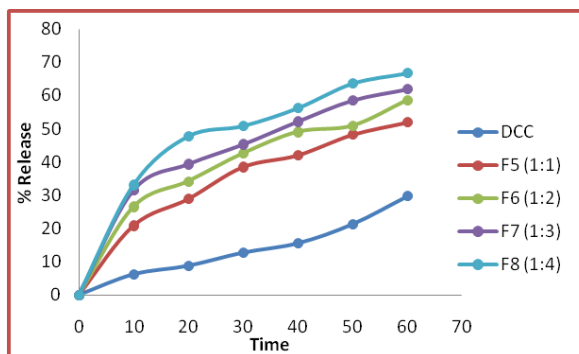


Figure-2: % of release of Ketorolac tromethamine from Tween 80 loaded liquid solid mixture

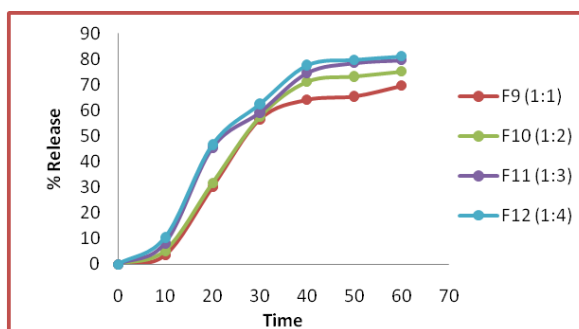


Figure-3: % of release of Ketorolac tromethamine from PEG 400 Loaded liquid solid mixture

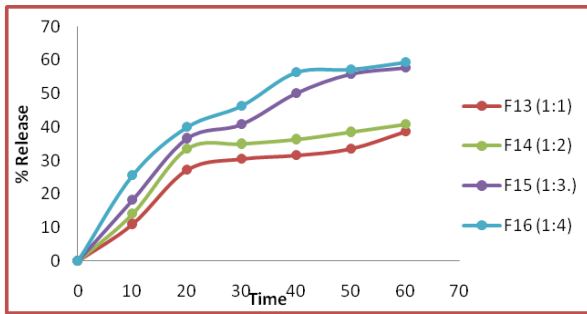


Figure-4: % of release of Ketorolac tromethamine from PEG 1500 Loaded liquid solid mixture.

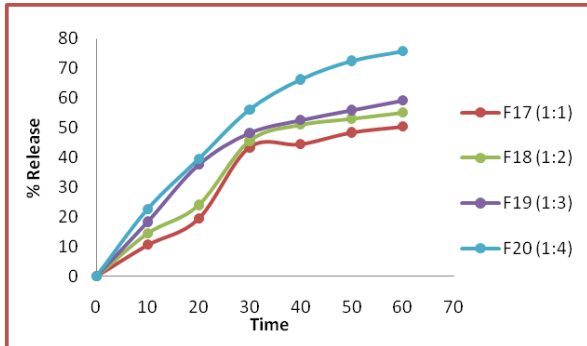
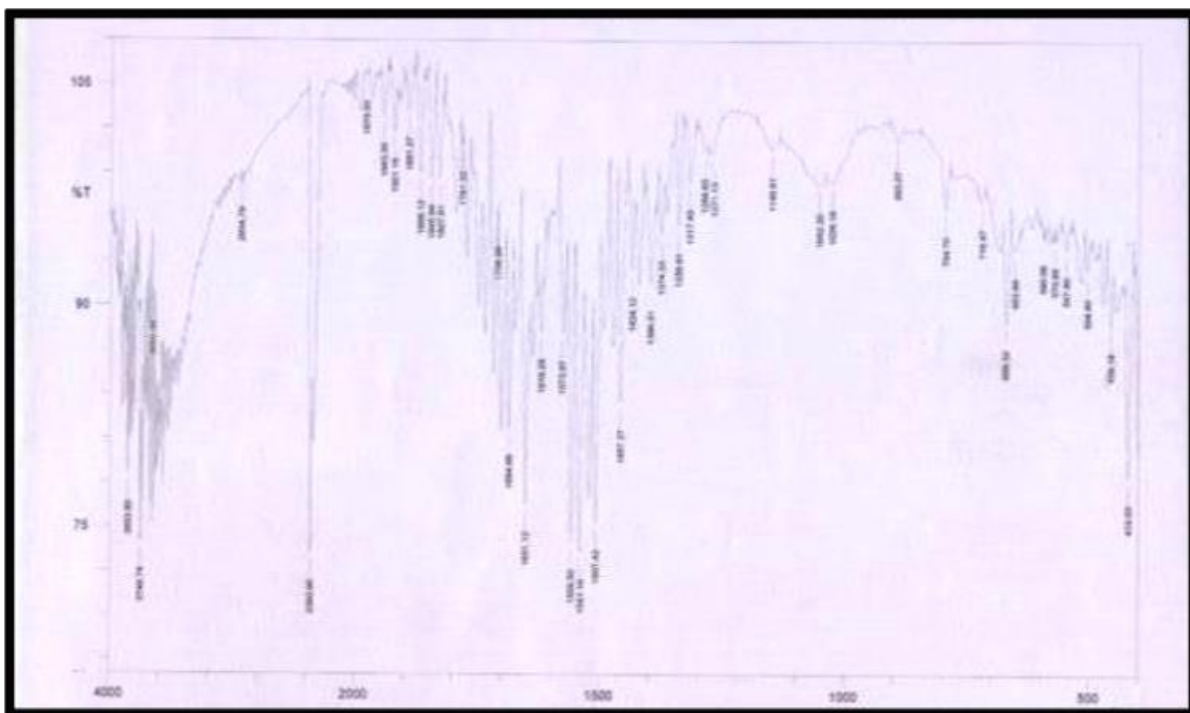


Figure-5: % of release of Ketorolac tromethamine from PEG 6000 Loaded liquid solid mixture

Figure-6: IR spectroscopy of pure Ketorolac tromethamine



The IR study was carried out to know the compatibility of the excipients with ketorolac, the active constituents of the formulation. The above study confirms that the drug and excipients in the formulation are compatible with each other (Fig. 6 & 7).

Discussion and Conclusions

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical, and commercial use has been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drugs in melted carriers and the filling of the hot solutions into hard gelatin capsules.

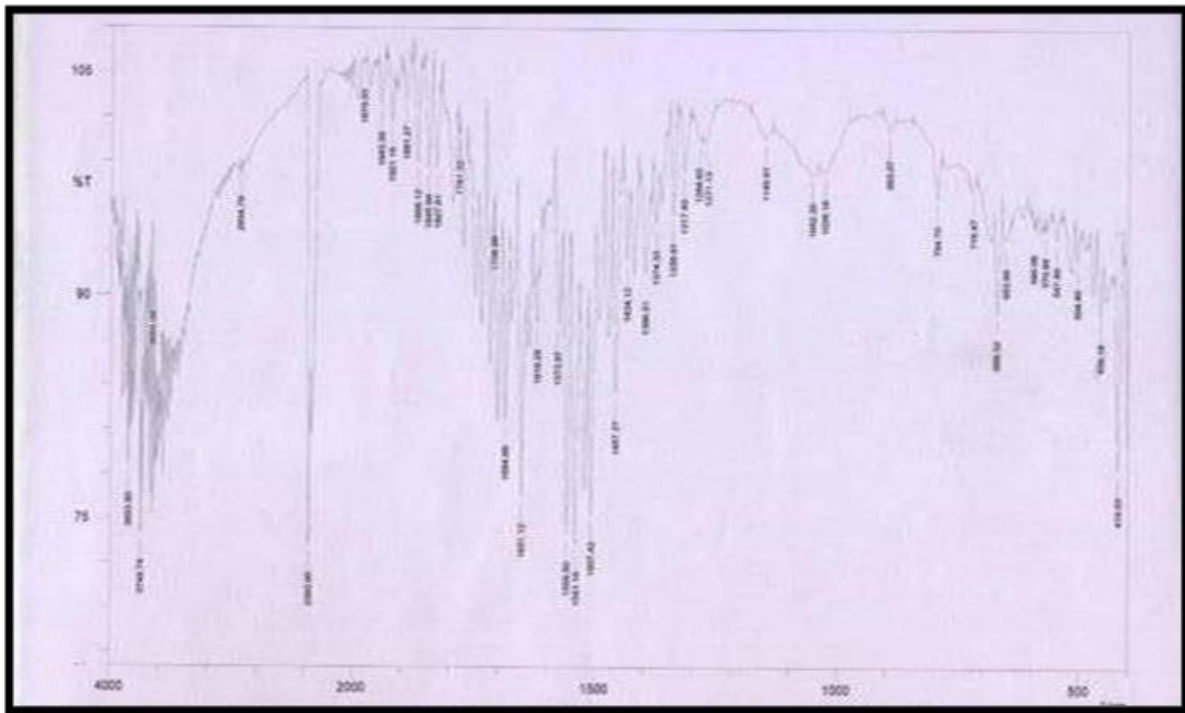


Figure-7: IR spectroscopy of formulation (Ketorolac tromethamine + excipients).

Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and, as a result, the bioavailability of solid dispersions is not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly

water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation.

Ketorolac tromethamine is poorly water soluble drug and is not soluble in the water easily. In this experiment different

vehicle has been use along with the drug (Ketorolac tromethamine). Here different vehicles (Propylene glycol, Tween 80, PEG 400, PEG 1500, PEG 6000) which have been used as carriers and did effect on the solubility of Ketorolac tromethamine. As a result the dissolution curves follow the zero order release pattern. This similarity of the curve indicates that the solubility of poorly water soluble drug increases by the use of such kind of polymers. Although, the direct filling of solid dispersion into hard gelatin capsules is a relatively simple process, there are very limited reports on the scale up of the technology.

Further studies on scale up and validation of the process will be essential. Many problems and challenges still remain with solid dispersion systems. Nevertheless, as a result of recent breakthroughs, it will continue to be one of the exciting frontiers of drug development.

Acknowledgement

The authors would like to acknowledge the support received from the Pharmaceutical Technology Research Laboratory of the Department of Pharmacy, University of Asia Pacific.

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