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DEVELOPMENT OF IMMEDIATE RELEASE LIQUID FILL FORMULATIONS FOR SOFT GELS OF PARACETAMOL

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ABSTRACT

The present investigation includes the preparation and evaluation of liquid filling formulations for soft gels using an analgesic drug Paracetamol, in order to improve its dissolution properties and there by its bioavailability. Formulations were prepared using excipients like poly ethylene glycol 400(PEG 400), propylene glycol(PG), polyvinylpyrrolidone(PVPK-30), DMSO, antioxidants, ethanol, and purified water. Prepared formulations were evaluated for appearance, pH, drug content uniformity, viscosity, stability, and *in-vitro* dissolution studies. The compatability between the drug and excipients was confirmed by FTIR spectra. The drug contents of the liquid fill formulations were found to be in the range of 60.34- 99.31 and the viscosity was in the range of 37.95-1056.46 cps. Formulations containing water/PEG/PG system gave better dissolution than other formulations. Formulation F3 is having superior release properties(100% drug release in 4min) when compared to those with different concentrations of PVPK-30(F7&F8) and those with antioxidants like BHT(F5%F6), hence F3 was selected as optimized fromulation.This confirms that water/PEG/PG system is better for Paracetamol release than Ethanol/PEG/PG and PVP/PEG/PG systems. Stability studies were conducted for all the formulations for a period of 6 months at room temperature(30^{o}C/65%RH). From these studies, it can be concluded that Paracetamol liquid formulations for soft gels were successfully prepared with in vitro dissolution properties superior when compard to Paracetamol itself.

Keywords: Butylated hydroxyl toulene, Dimethyl sulfoxide, Liquid fill formulations, Polyvinylpyrrolidone, Propylene glycol, Poly ethylene glycol, Paracetamol.

INTRODUCTION

Soft gelatin capsules are commonly known as soft gels. Soft gelatin capsules are becoming a popular dosage form for the administration of liquids, suspensions, pastes, and dry powders in the dietary supplement industry. Soft gels can be effective delivery system for oral drugs, especially poorly soluble drugs [1]. This is because the fill can contain liquid ingredients that help increase solubility or permeability of the drug across the membranes in the body. The absorption of poorly soluble compounds encapsulated in soft gels may also be higher compared to that from other conventional dosage forms not only due to the solubilisation of the compounds in the fill formulation but also due to the fill excipients induced inhibition of P-glycoprotein-mediated drug efflux and reduced enzyme-catalysed degradation of the compound in the lumen of the GIT [2]. Soft gels are easy to swallow, once swallowed, release their contents quickly. They are advantageous because of the following properties:

- Have the ability to mask odours and unpleasant tastes.
- Have an elegant appearance.
- Readily dissolved in the gastric juices of the digestive tract
- They may enhance the bioavailability of active ingredients.
- In specialised dosage form, soft gels can be into chewable, extended release cap tabs.
- Also can be used for ophthalmic preparations.
- Content uniformity of the active ingredients and dosage accuracy can be achieved. Another advantage that derives from the liquid nature of fill is rapid release of the contents with enhanced bioavailability. The proper choice of vehicle may promote rapid dispersion of capsule contents and drug dissolution. Soft gelatin capsules are available in a wide variety of sizes and shapes. Specialty packages in tube form (ophthalmic, ointments) or bead forms [3].

The pH of the liquid can be between 2.5 and 7.5. Liquids with more acidic pH would tend to leakage by hydrolysis of gelatin. Both liquids with pH > 7.5 and aldehydes decrease the shell solubility by tanning the gelatin [4].

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Paracetamol was chemically known as N-(4-hydroxyphenyl) acetamide ($C_8H_9NO_2$) [5-7]. The melting point of Paracetamol is 169 °C. It has analgesic and antipyretic properties. It is a class-III drug. It is readily soluble in water, methanol, ethylenedichloride, dimethylformide slightly soluble in ether. Although the exact site and mechanism of analgesic action is not clearly defined, acetaminophen appears to produce analgesic by elevation of the threshold [8]. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors incuding N-methyl-D-aspartate and substance P [9]. Vellani V *et al.,* studied on Effects of NSAIDs and Paracetamol (acetaminophen) on protein kinase C epsilon translocation and on substance P synthesis and release in cultured sensory neurons. Roger dobson *et al* studied on how Paracetamol can reduce stress and sharpen your memory. Pranati srivastava rishabha *et al* studied on that formulation and evaluation of Paracetamol tablets to assess binding property of orange peel pectin. David A. Perrott *et al* studied on efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever meta-analysis free, but there were no reported works found on the liquid fill formulations of Paracetamol.

MATERIALS AND METHODS

Materials

Paracetamol, Polyvinylpyrolidone k-30 Polyethylene glycol-400, Propylene glycol, Ethyl alcohol, Butylated Hydroxy toluene ,Hydrochloric acid ,Sodium hydroxide.

Method used in present research work

An UV-VIS Spectrophotometric method based on the measurement of absorbance at 249 nm in methanol stock solution was used in the present research work for the estimation of Paracetamol.

For the estimation of Paracetamol in different aqueous fluids the stock solution was subsequently diluted to get a series of dilutions 2, 4, 6, 8 and 10 µg/mL of solution and the absorbance was measured at 249 nm (UV-VIS spectrophotometer, SL-150, Elico) against the same dilution as blank.

Preparation of liquid filling formulations

Liquid filling formulations were prepared as per the formulae given in Table 1 to a batch size of 6g. Initially propylene glycol and PEG-400 were taken into a small beaker. Now accurate amount of Paracetamol was weighed and transferred into this beaker and mixed thoroughly followed by the addition of pvpk-30 to dissolve the drug completely. BHT was then added and mixed thoroughly. The prepared formulation was sonicated for 3 minutes in order to remove any entrapped air. The weight of liquid ingredients like ethyl alchohol, propylene glycol (PG), polyethylene glycol – 400, DMSO was converted to volume from density values and taken accordingly. The volume of the above liquid ingredients was derived from the available values of density reported in standard literature (density of ethyl alchohol is 1 gm/cm^3, propylene glycol is 1.038 gm/cm^3, PEG -400 is 1.12 gm/cm^3, DMSO is 1.1004 gm/cm^3. Empty soft gelatine capsules were incubated at 40° C for 10 minutes with an objective of removing moisture taken up by the capsules during storage. Each oval shaped soft gelatin capsule of size 20 equivalent to 1.232 ml was taken for filling. Each capsule was filled by injection with 1.0 ml of each of the formulation. Each capsule should be filled up to 75 percent of its total volume. Using a glass syringe the liquid fill was injected into the capsule, which was then sealed by heat. The soft gelatin capsules filled with liquid fill formulations of Paracetamol were then subjected to different tests to evaluate for various parameters.

Evaluation parameters for Paracetamol Liquid filling formulations

Paracetamol liquid filling formulations were evaluated for appearance, viscosity, pH and drug content uniformity.

Appearance

Appearance is one of the most important parameter of liquid filling formulations. All the formulations were evaluated for clarity by visual appearance.

pH

The developed formulations were evaluated for pH by using Elico LI 120 pH meter and estimations carried out in triplicate.

Drug content uniformity

Drug content was estimated in the liquid filling formulation by weighing approximately 250mg of the fill formulation into a 5 mL volumetric flask. Few ml Methanol was added and dissolved the paracetamol and the volume was made up to 5 mL with remaining methanol. Samples were suitably diluted with 0.1N HCL and the samples were analysed for paracetamol content by measuring absorbance at 249nm. The estimations were carried out in triplicate.

Rheological studies

Viscosity of all formulations was measured using a Brookfield DV-II + PRO viscometer. The formulations were taken in cup of Brookfield DV-II + PRO viscometer rotated with CP52 spindle. The angular velocity was fixed at 10-100 rpm. The viscosity measurements were made in triplicate using fresh samples each time at room temperature.

FTIR studies

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000–500 cm−1 at a resolution of 1.0 cm^{-1}. The powder or film sample is simply placed onto the ATR crystal and the sample spectrum is collected. ATR analysis is less complicated than

using KBr pellets is fast and a very small amount of the sample is needed.

***In-vitro* dissolution studies**

In vitro dissolution studies were conducted using 900mL of 0.1N HCL, as dissolution medium using USP XXI type I/II (paddle method) dissolution apparatus (DISSO 8000, LAB INDIA). A temperature of 37 ± 0.5ºC and a rotation speed of 50 rpm were maintained. Liquid formulations containing Paracetamol were filled into empty soft gelatin capsules and dissolution studies were performed. As the capsule tends to float in the dissolution medium, sinkers were used. A 5mL samples were withdrawn at predetermined time intervals over a period 0,30,60,90,120,180,240,300 seconds and then replaced with same volume of fresh dissolution medium. The filtered samples were suitably diluted and analyzed at 249nm using UV-Visible Elico SL150 spectrophotometer. Dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSIONS

The prepared solutions were evaluated for the following properties

Appearance

The prepared formulations were visually tested for homogeneity, transparency, colour and smoothness and the results were given in Table.2 and shown in Fig.4(a),4(b),4(c). Formulations F5 and F6 were clear .This may be due to the presence of DMSO which is a good solvent for Paracetamol.

Drug content

All the liquid filling formulations were subjected to drug content estimation within the labelled claim limits and it indicates that the amount of active ingredient in all these formulations was uniformly distributed and the values were satisfactory. The results were given in Table.3. Percent dug content was found to be in the range of 60.34±1.91to 99.31±0.54.

pH

The pH of formulation is in the range of 2.5-7.5. The solutions prepared for formulations were close to 6. The results were shown in Table.4.

Rheological studies

The rheological studies for all the liquid formulations were carried out in a Brookfield DV-II PRO viscometer.

From the rheological data the formulations showed increase in viscosity as concentration of PVP K-30 increased and all prepared liquid filling formulations showed Newtonian fluid behaviour with straight line. It was clearly evident that changes in the viscosity and consistency of formulations depend on the change in concentration of PVP K-30. The viscosity of moderately concentrated solutions of PVP K-30 has been studied in PEG 400, PG, and ethanol at different shear rate conditions. The study showed that PVP K-30 solutions are Newtonian at high shear rates and non Newtonian fluid in the low shear rate region. The viscosity data for all the liquid fill formulation of paracetamol was given in Table.5.

Drug-excipients compatibility studies

The IR spectra of Paracetamol pure drug and all other formulations were obtained by KBr pellet method by ATR-FTIR spectrometer (Bruker, Germany). The characteristic spectrums were observed for all the formulations within specified I.R. ranges, indicates that there was no interaction between drug and excipients. The spectrums were shown in Figs.1-2.

***In vitro* dissolution studies**

In vitro dissolution studies were carried out to evaluate the drug release from liquid fill formulations & tablets. Dissolution studies were conducted in 900mL of 0.1 N HCl at 37 ± 0.5^0c. Totally eight different formulations of Paracetamol Liquid filled capsules were prepared and one of these containing without PVP k-30. From all liquid fill formulations pvpk-30 has greater effect on the formulation. The comparative *in-vitro* dissolution profiles for all the formulations F1-F8 were shown in fig.3(a).

The dissolution properties showed that in f1 formulation pvpk-30 was used and percent drug release was found to be 65% in 60min.Even though PEG-400 at 22% and PG at 24% were used the drug release was less. This may be due to incompatible cosolvents present.

In F2 formulation ethyl alcohol was used at 20%, PG at 29%, PEG at 22% instead of pvp k-30 then the percent drug release was found to be 100%in 15min.This may be due to compatibility of ethyl alcohol with PEG and PG.

In F3 formulation water at 20% along with PEG 22% and PG 29% were used instead of pvpk-30 and ethyl alcohol and the percent drug release was found to be100%in 4min.Hence water is the best cosolvent for PEG and PG to Paracetamol drug release.

From the dissolution profiles it was observed that F3 containing water/PEG/PG system showed better drug release (100% in 4min) when compared to formualtionF8 containing PVPK-30(100% in 6min). This may be due to increase in viscosity of the liquid fill formulation. The comparative *in-vitro* profile for F3 and F8 was shown in fig.3(b).

Similarly when formulations F5 and F6 were compared the formulation F5 containing antioxidant 1% BHT showed 100% drug release in 45min whereas F6 containing DMSO and PVPK-30 (19%) showed complete drug release within 15 min. The comparative *in-vitro* profile for F5 and F6 was shown in fig.3(c).

Formulations containing different concentrations of PVP-K30 (F7&F8) were compared to evaluate the effect of polymer concentration on drug release. Increase in polymer

concentration results in the decrease of the drug release. The comparative *in-vitro* dissolution profiles for F7 and F8 was shown in fig.3(d).

Formulation F3 is having superior release properties, hence F3 was selected as optimized formulation. This confirms that water/PEG/PG system is better for Paracetamol release than Ethanol/PEG/PG and PVP/PEG/PG systems.

Drug release kinetics

To analyze the *in-vitro* drug release data, various kinetic models were used to describe the release kinetics for both liquid filling and tablet formulations. Both liquid filling and tablet formulations followed the First order release kinetics.First order kinetics data for liquid filling formulations was given in Table.6 and shown in fig.3(e).The 'k' values were significantly higher for 10% PVP K-30 containing liquid filling formulation when compared with 0 and 5% PVP K-30 containing formulations.

In the case of tablet formulation, first order kinetics values significantly higher for F5 which was prepared under wet granulation method.

The order of regression coefficient (R^2) values for all the formulations were F8>F7>F6>F2>F5>F3 >F4>F1. In F8 formulation higher the r^2 value and it indicates that F7 has superior release characteristics at 50 rpm speed among all the liquid fill formulations. Finally, the release kinetic was studied and showed that F3 better fits the first order release kinetics among all formulations. The viscosity modifier, PVP k-30 was added in this formulation as per the specified limits and better release of Paracetamol compared to remaining formulations

Stability Studies

Stability studies for liquid filling formulations were conducted at room temperature for a period of 6 months. The results were shown in Table.7 and shown in figs.4(a),4(b),4(c) and 5(a),5(b),5(c).

The results indicated that F1 and F8 have no significant changes all formulations were stable at room temperature without undergoing any degradation. Stability studies were conducted for evaluation of various parameters such as drug content, viscosity, and pH were remains constant for a period of 6 months.

- No change was observed in drug content, pH and viscosity for 3months at room temperature in liquid filling formulations.
- Formulations were stable with respect to colour, clarity, homogeneity and precipitation for a period of 3 months and 6 months
- After six months also same results were observed for F1 and F8.

All formulations showed good physicochemical properties.

Table 1. Formulae of all the liquid fill formulation for soft gels of Paracetamol

Ingredients (mg/cap)	F1	F2	F3	F4	F5	F6	F7	F8
Paracetamol	250	250	250	250	250	250	250	250
PVP k-30	290	-	-	100	190	139	100	150
Ethyl alcohol	-	200	-	-	-	-	150	150
PG	240	290	290	300	200	250	200	-
PEG-400	221	220	220	250	250	250	200	150
BHT	-	-	-	-	10	10	-	-
DMSO	-	-	-	-	100	100	-	-
Water	-	-	200	100	-	-	150	150
Total wt	1000	1000	1000	1000	1000	1000	1000	1000

Table 2. Morphological characters of liquid filling formulations

Formulations	Morphological character
F1	Homogeneous, viscous, no color change
F2	Homogeneous, viscous, no color change
F3	Homogeneous, viscous, no color change
F4	Homogeneous, viscous, no color change
F5	Homogeneous, clear, no color change
F6	Homogeneous, clear, no color change
F7	Homogeneous, viscous, no color change
F8	Homogeneous, viscous, no color change
F9(placebo)	Homogeneous, clear, no color change

Table 3. Percent drug content for Paracetamol liquid filling formulations (0-6Months)

Formulae	Percent Paracetamol content		
	0-M	3-M	6-M
F1	60.34±1.19	60.56±1.52	60.39±1.89
F2	99.31±0.54	99.15±0.69	99.45±0.21
F3	98.24±0.55	98.51±0.45	98.45±0.29

F4	80.55±1.411	80.63±1.26	80.23±1.52
F5	63.41±2.57	63.56±2.67	63.37±2.45
F6	82.73±2.25	82.56±2.13	82.49±2.39
F7	96.46±1.40	96.52±1.32	96.69±1.26
F8	94.15±3.22	94.19±3.52	94.14±3.49

Table 4. pH values for Paracetamol liquid filling formulations (0-6Months)

Formulae	pH		
	0-M	3-M	6-M
F1	6	6	6
F2	6	6	6
F3	6	6	6
F4	6	6	6
F5	6	6	6
F6	6	6	6
F7	6	6	6
F8	6	6	6
Placebo	5	5	5

Table 5. Viscosity data for liquid filling formulations (0-6Months)

Formulae	Viscosity		
	0-M	3-M	6-M
F1	-	-	-
F2	79.46 ± 3.15	79.66 ± 3.05	73.26 ± 3.05
F3	37.95± 2.01	34.95± 2.61	31.95± 2.31
F4	59.24± 1.07	61.24± 1.37	58.24± 1.27
F5	1056.46 ± 3.42	1016.6 ± 3.12	1026.6 ± 3.02
F6 Placebo	219.78± 3.56	209.78± 2.56	229.78± 2.36
F7	216.92± 2.76	205.92± 2.16	215.92± 2.36
F8	138.65± 2.14	128.65± 2.34	124.65± 2.04

Table 6. First order kinetics data for Paracetamol and liquid filling formulations

Formula	K value	R2
F1	0.011	0.442
F2	0.340	0.955
F3	0.06	0.971
F4	0.027	0.659
F5	0.154	0.914
F6	0.340	0.936
F7	0.879	0.9
F8	1.077	0.79

Table 7. Comparative stability data for PARA liquid filling formulations (0-6 M)

Formulations	Appearance			Precipitation			Viscosity			pH			Drug content		
	0	3	6	0	3	6	0	3	6	0	3	6	0	3	6
F1	*X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
F8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*X - No change

Fig 1. FTIR spectrum of Paracetamol

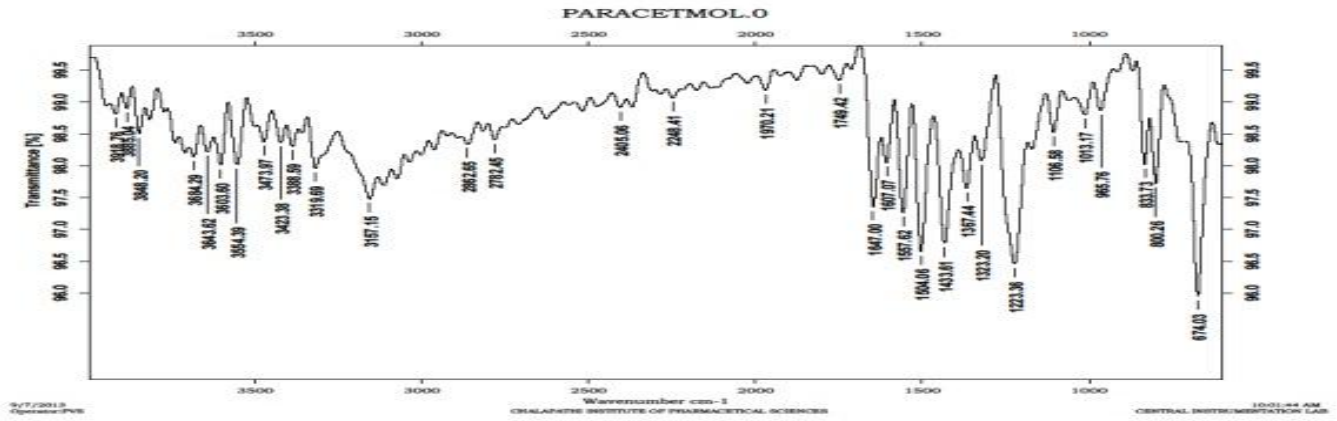


Fig 2. FTIR spectrum of F3

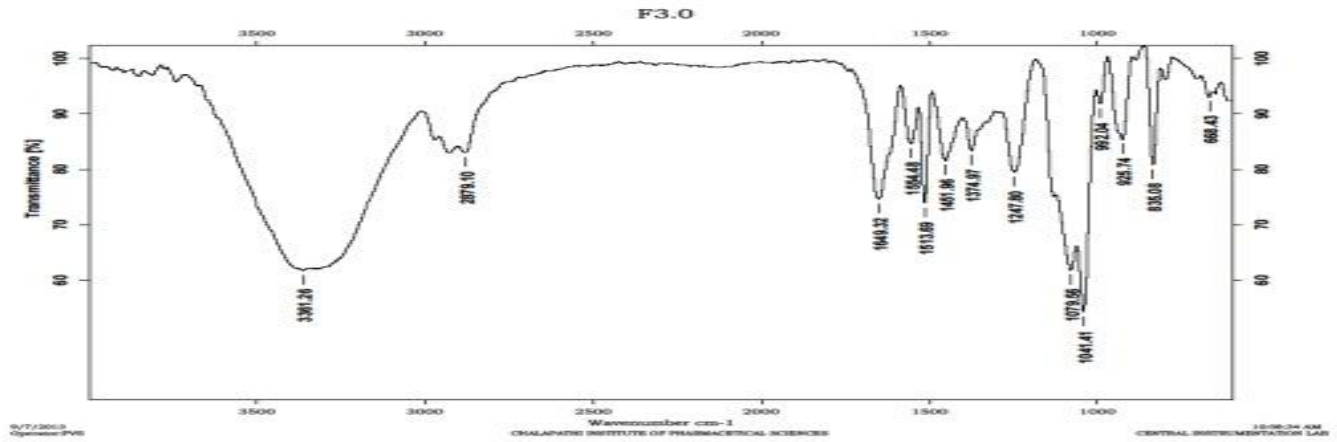


Fig 3(a). Comparative *in-vitro* dissolution profiles for F1 to f8

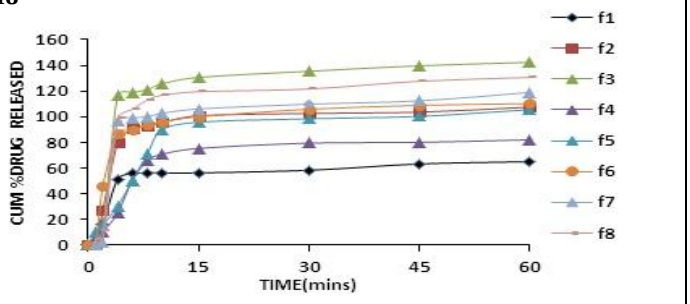


Fig 3(b). Comparative *in-vitro* dissolution profiles for F3 and f8

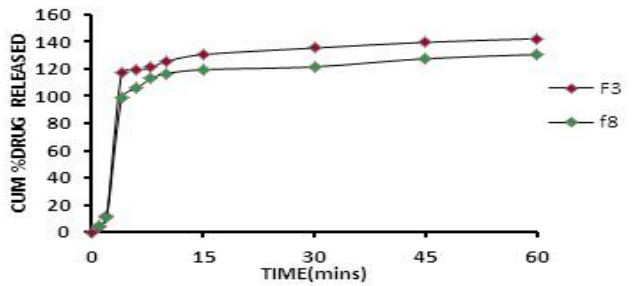


Fig 3(c). Comparative *in-vitro* dissolution profiles for F5and f6

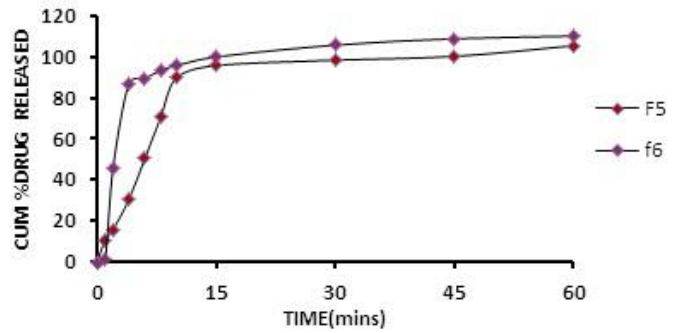


Fig 3(d). Comparative *in-vitro* dissolution profiles for F3 F7and F8

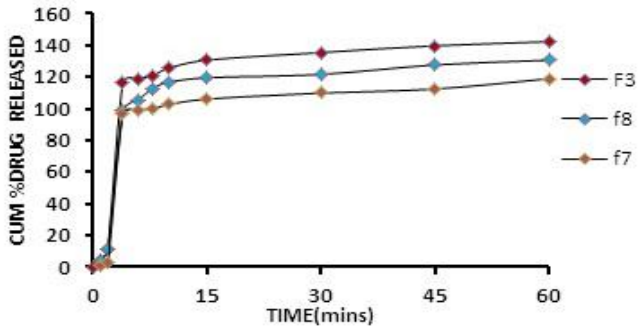


Fig 3(e). Comparative first order plots of f2 , f3, f5, f6, f7

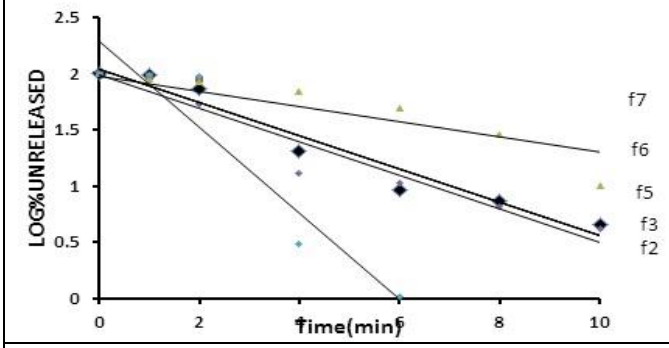


Fig 4(a). Appearance at 0 months

Fig 4(b). Appearance at 3 months

Fig 4(c). Appearance at 6 months

Fig 5(a). Comparative profiles of pH at 0, 3 and 6 months

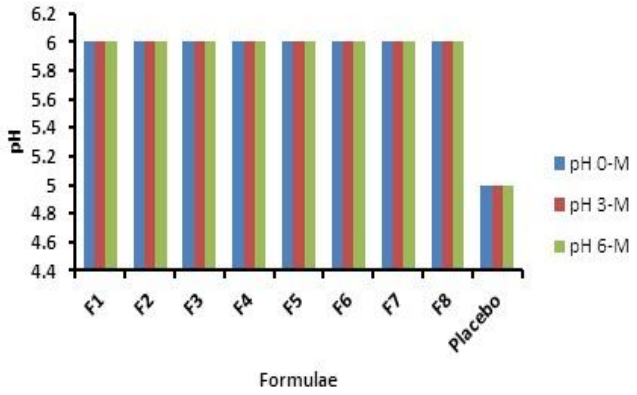


Fig 5(b). Comparative profiles of drug content at 0, 3 and 6 months

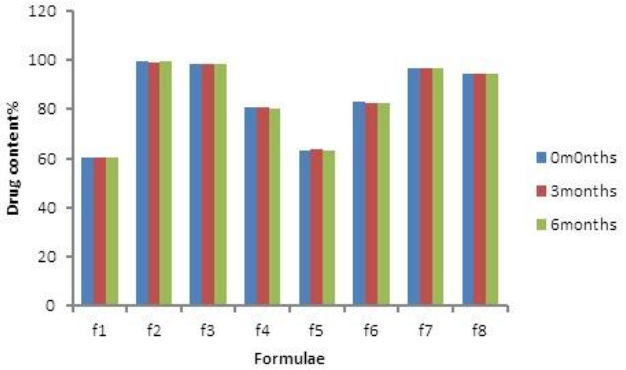
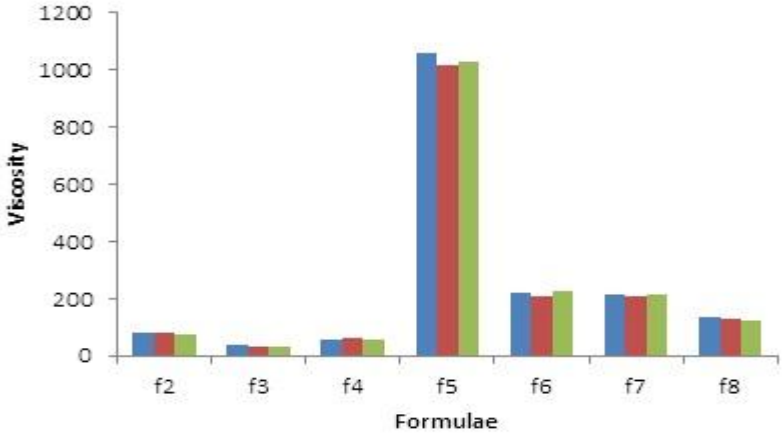


Fig 5(c). Comparative profiles of Viscosity at 0, 3 and 6 months



CONCLUSION

Paracetamol can be solubilised by the use of a co solvent system (PEG/PG/water, PEG/PG/ethanol) in liquid fill formulations and showed improved dissolution properties when compared to the Paracetamol alone in powder form and marketed formulation. Liquid filling formulations with PEG/PG/water gave the superior results when compared to formulations containing PEG/PG/water/ethanol. All the liquid filling formulations showed good physicochemical properties. The formulations were stable up to 6 months without undergoing any degradation.

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