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Research Article

Development of immediate release liquid fill formulations for soft gels of sumatriptan succinate

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ABSTRACT

The present investigation includes the preparation of liquid filling formulations for soft gels using an anti-migraine drug Sumatriptan Succinate (SMT), in order to improve its rate of absorption and thereby its bioavailability. Formulations were prepared using excipients like polyethylene glycol (PEG-400), propylene glycol (PG), Polyvinylpyrrolidone (PVP K-30), antioxidants, tween-80, SLS, ethanol and purified water. Prepared formulations were evaluated for appearance, pH, drug content uniformity, drug- excipients compatibility, viscosity, and stability and *in-vitro* dissolution studies. The compatibility between the drug and excipients in the formulations was confirmed by FTIR spectra and DSC thermograms. The drug contents were in the range of 97.65 to 99.62 and the viscosity was in the range of 37.95 to 452.93 cps for all the developed formulations. Formulation F1 containing PEG-400 (20%)/PG (20%)/water (52%) system gave superior drug release when compared to other liquid filling formulations and complete drug release (100%) was observed at the end of 90 seconds. Stability studies were conducted for all formulations (F1-F10) over a period of 6 months at room temperature (30ºC/65%RH). From these studies, it can be concluded that SMT liquid fill formulations for soft gels were successfully prepared. The *in-vitro* dissolution properties of SMT liquid fill formulations for soft gels were superior when compared to pure SMT and marketed SMT.

Keywords: Anti-migraine; Liquid fill formulations; Polyethylene glycol (PEG-400); Propylene glycol (PG); Polyvinylpyrrolidone (PVP K-30); Sumatriptan Succinate; Soft gels; Tween 80

INTRODUCTION

New chemical entities (NCEs) coming out of the current drug discovery process have poor biopharmaceutical properties, such as low aqueous solubility and/or permeability (BCS class II or class IV) (G.L.Amidon et al., 1995; S. James., 2007). They show extremely low aqueous solubility throughout the physiological pH range, resulting in low and inconsistent bioavailability when administered as solid oral dosage forms. Liquids, in contrast, generally have better bioavailability and one such liquid dosage form is soft gel (S.James, 2007). The soft gel dosage form offers several advantages over other oral solid dosage forms, such as delivering a liquid matrix designed to solubilise and improve the oral bioavailability of a poorly soluble compound as a unit dose solid dosage form, delivering low and ultralow doses of a compound (R.P.Gullapalli, 2010). In contrast with other dosage forms soft gelatin capsules require much less supplementary substances, most of which are herbal in origin. The feasibility to regulate the shell ingredients enables the adaptation of its parameters to specify requirements of storage conditions and especially to chemical as well as pharmacological properties of a medication (A. Markham et al., 1997).

The extensive research on bioavailability of various medication forms has reportedly demonstrated that the rate, extent of absorption and bioavailability was much better in the form of soft gelatin capsules. This is mainly the consequence of one of the best properties – the exact suspension or solution of therapeutic substance in the liquid medium. Owing to that, absorption of medicament starts at the moment of capsule disintegration in the elimentary tract and is more effective because of small size of suspended or dissolved particles of the medicament.

In soft gelatin capsules the powdered active ingredients are dissolved in a liquid vehicle, or a suspension of drug in a liquid which is limited to those that do not have any harmful effects on the gelatin walls. 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 (Banker S et al., 2002).

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Table 1: Composition of different Liquid Fill Formulations containing SMT

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DRUG	20	20	20	20	20	20	20	20	20	20
PEG-400	50	50	50	50	50	50	50	50	50	50
PG	50	50	50	50	50	50	50	50	50	50
PVPK-30	--	--	10	20	--	--	10	--	--	--
TWEEN 80	--	--	--	--	10	20	--	--	--	--
SLS	--	--	--	--	--	--	--	1	2	1
BHT	--	--	--	--	--	--	1	--	--	1
ETHANOL	--	70	50	50	50	50	50	29	28	28
DISTILLED WATER	130	60	70	60	70	60	69	100	100	100
TOTAL	250	250	250	250	250	250	250	250	250	250

Sumatriptan Succinate (SMT) is a potent, highly selective and orally administered anti-migraine drug, with poor bioavailability ranging from 10-20% be. The drug is rapidly absorbed after oral administration and median Tmax values of 2.75 and 3 hours have been reported after the oral absorption of tablet and capsule formulations, respectively. The reported absolute bioavailability is 15%-21% for tablet formulation for a buffer solution and injectables (Fox et al., 2004).

Route of elimination of only 3% of the dose is excreted in the urine as unchanged, sumatriptan 42% of the dose is excreted as major metabolite, the indole acetic acid analogue of sumatriptan. From the literature review, it is clearly evident that most of the works were published with formulation and evaluation of various dosage forms to enhance the bioavailability and to study the pharmacokinetic properties of SMT.

M.Suvarchala *et al* carried out works on immediate release tablets (M.Suvarchala et al., 2012). Several works were carried out on mouth dissolving films (Buchi N.Nalluri et al., 2013) and Mucoadhesive microspheres for Nasal Delivery of Sumatriptan, development of thermoreversible mucoadhesive microemulsion for delivery (Twarita.Deshpande et al., 2011; RS Bhanushali et al., 2007) for increasing the bioavailability of sumatriptan. So far no reports were published on the liquid fill formulations for soft gel dosage forms in order to improve the *in-vitro* dissolution properties and thereby rate of absorption of SMT. Hence the present investigation was aimed at developing oral administrable soft gels (liquid fills) of SMT with improved rate of bioavailability.

MATERIALS AND METHODS

Materials

SMT was supplied by Aurobindo Pharma Ltd., Hyderabad, as a gift sample, PVP K-30 (Sisco Research Laboratories, Mumbai), PEG 400 (Central Drug House, Mumbai), Propylene glycol (SD Fine Chemicals, Mumbai), Butylated Hydroxy Toluene (Loba Chemie, Mumbai). All the chemicals and reagents used in the study were of analytical grade.

Preparation of Liquid Fill Formulations

Liquid fill formulations were prepared as per the formulae given in Table.1 to a batch size of 250mg. Initially Propylene glycol and PEG-400 were taken into a small beaker and PVP K-30 was added and dissolved.SMT succinate which was equivalent to 20 mg of SMT base was weighed and transferred into this beaker and mixed thoroughly followed by the addition of ethyl alcohol and distilled water to dissolve the drug completely (10 mg of SMT base is equivalent to 17.97 mg of SMT succinate). 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 the liquid ingredients like Ethyl alcohol, Propylene glycol, Poly ethylene glycol-400, Tween 80 was converted to volume from density values and taken accordingly.

The volume of the above ingredients derived from the available values of density reported in standard literature (density of ethyl alcohol is 1gm/cm^3, propylene glycol is1.038gm/cm^3, PEG-400 is 1.12gm/cm^3, Tween-80 is1.06gm/cm^3). Empty soft gelatin capsules were incubated at 40ºC for 10 minutes with an objective of removing moisture taken up by the capsules during storage. Each oval shaped soft gelatine capsule of size 20 equivalent to 1.232ml was taken for filling. Each capsule was filled by injection with 1.0ml 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 gelatine capsules filled with liquid fill formulations of SMT were then subjected to different tests to evaluate for various parameters.

Evaluation parameters for SMT Liquid fill formulations

SMT 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.

Table 2: Evaluation Parameters for Liquid Fill Formulations of SMT (n =3)

Formulation	Appearance	pH (mean±sd)	Drug content (%) (mean±sd)	Viscosity (cps)
F1	Clear	5.19±0.015	99.066±0.20	37.95
F2	Clear	5.25±0.026	99.433±0.17	79.46
F3	Clear	5.30±0.015	97.31±0.01	219.78
F4	Clear	5.11±0.02	99.276±0.18	452.93
F5	Clear	5.23±0.01	99.456±0.04	129.24
F6	Clear	5.35±0.15	99.436±0.20	196.56
F7	Clear	5.08±0.02	98.543±0.06	230.53
F8	Clear	5.27±0.01	98.896±0.55	61.24
F9	Clear	5.15±0.015	98.246±0.03	59.24
F10	Clear	5.36±0.20	99.75±0.10	67.35

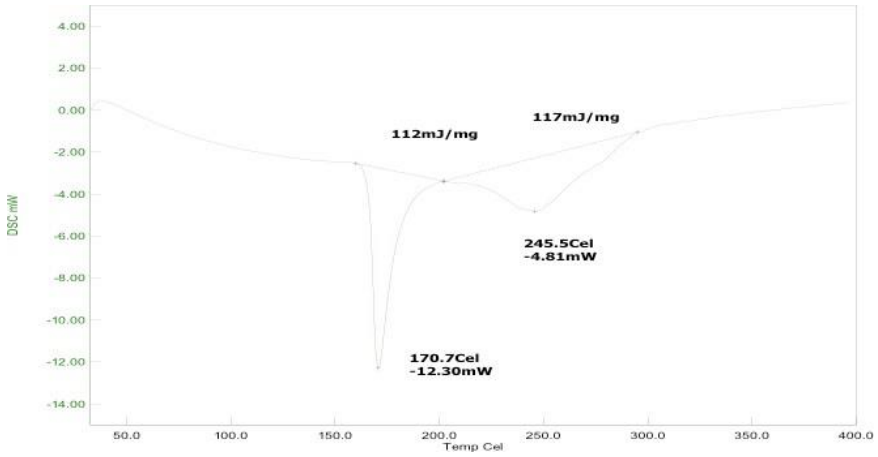

Figure 1: DSC Thermogram of Pure SMT

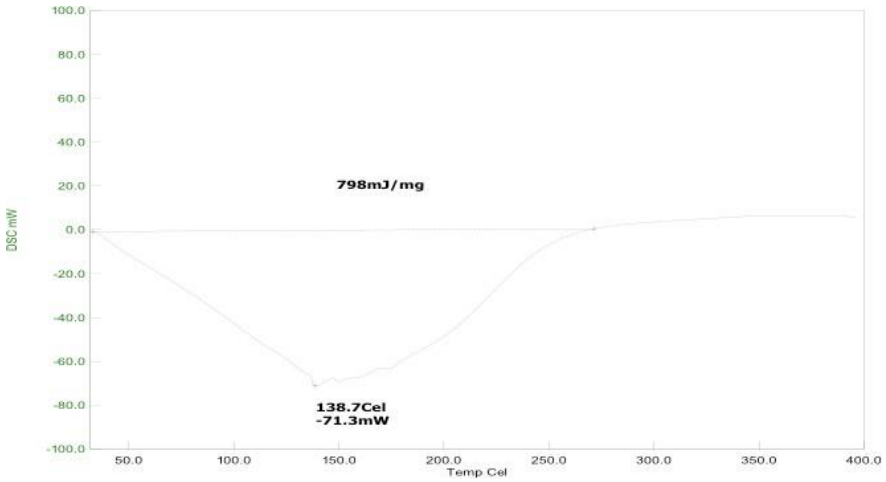

Figure 2: DSC Thermogram of SMT Liquid Fill Formulation F1

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 20mg of the fill formulation into a 5 mL volumetric flask. Few mL of methanol was added to dissolve the SMT 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 SMT content by measuring absorbance at 225nm. 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.

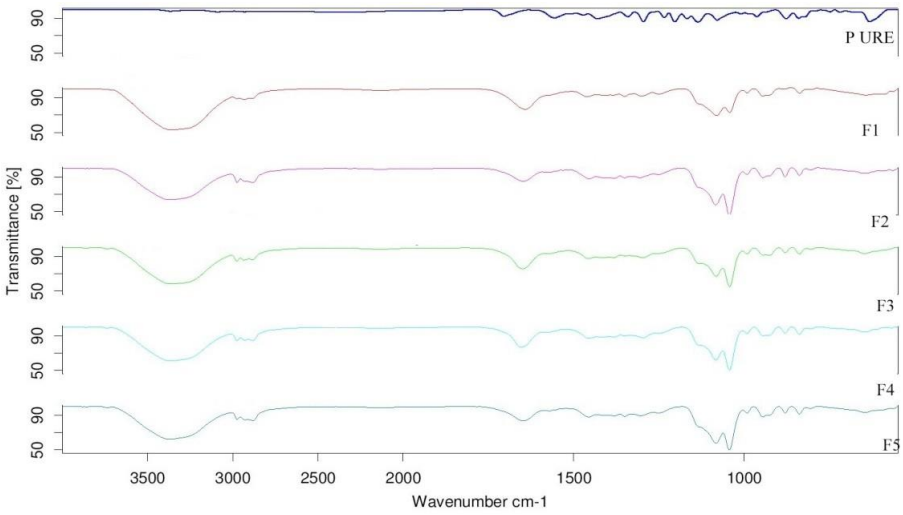

Figure 3: FTIR spectrum of pure SMT and F1, F2, F3, F4, F5

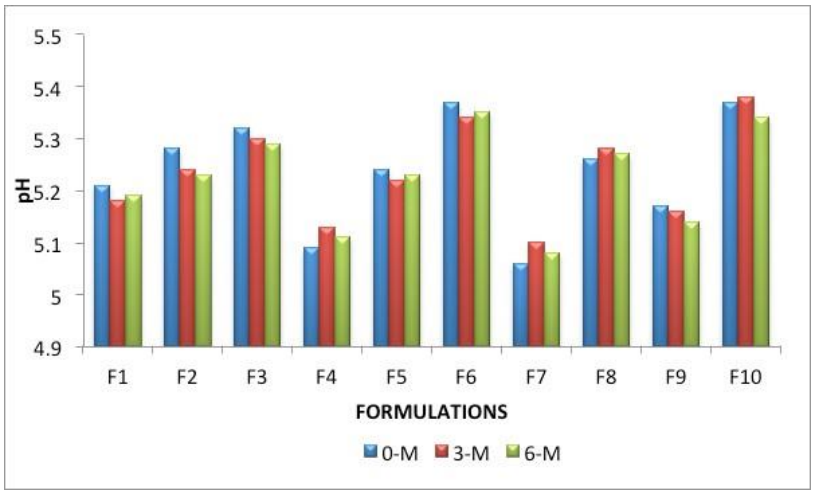

Figure 4: pH values of all the formulations (0-6M)

DSC Studies

Thermograms of SMT and SMT Liquid fill formulations for soft gels were recorded using Differential Scanning Calorimeter (Schimadzu, DSC-60, Japan). Samples weighing 2.611 mg were sealed in aluminium pans and heated to 400˚C at a rate of 10˚C per minute. The equipment was calibrated using indium. Samples were heated from 50-400˚C.

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 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 20mg of SMT 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 225nm using UV-Visible Elico SL150 spectrophotometer. Dissolution experiments were conducted in triplicate.

Stability studies

Stability studies for liquid filling formulations were conducted at room temperature for a period of 6 months.

RESULTS AND DISCUSSION

Appearance

All liquid filling formulations of SMT were visually tested for clarity, colour and precipitation of drug if

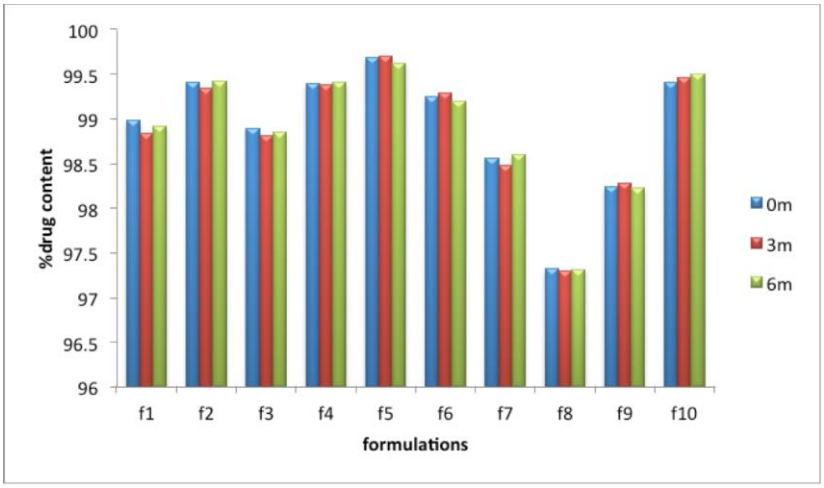

Figure 5: Drug content profiles for all the liquid fill formulations (F1-F10)

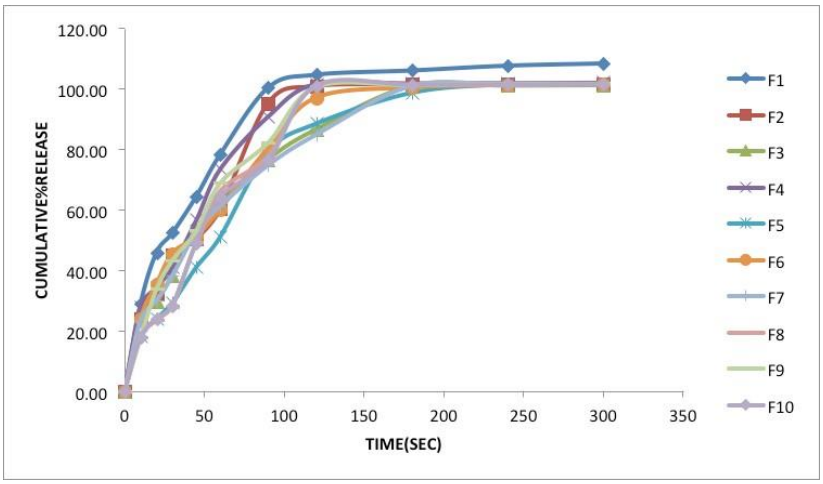

Figure 6: Comparative *in-vitro* dissolution profiles of all the liquid fill formulations (F1-F10)

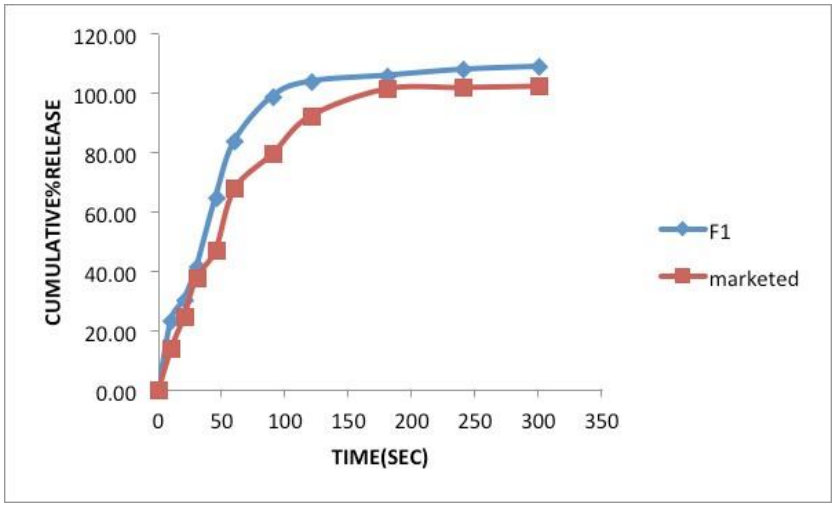

Figure 7: Comparitive i*n-vitro* dissolution profiles for F1 and Marketed Formulation

any. The formulations (F1-F10) were homogeneous and colourless and no precipitation of drug was observed. The results are given in Table. 2.

pH

pH is another important parameter for liquid filling formulations. The two areas of critical importance are the effect of pH on solubility and stability. Liquid filling formulations should have a pH in the range of 2.5 to 7.5. At pH values below 2.5, gelatin is hydrolysed causing leakage of the soft gel, whereas at pH values above 7.5, gelatin may be either hydrolysed or tanned (i.e., crossslinked) resulting in decreased solubility of the gelatin shell. The pH of all the formulations was close to 7.2. The pH of the soft gelatin fill formulation without drug was found to be at 5.4 and therefore, all

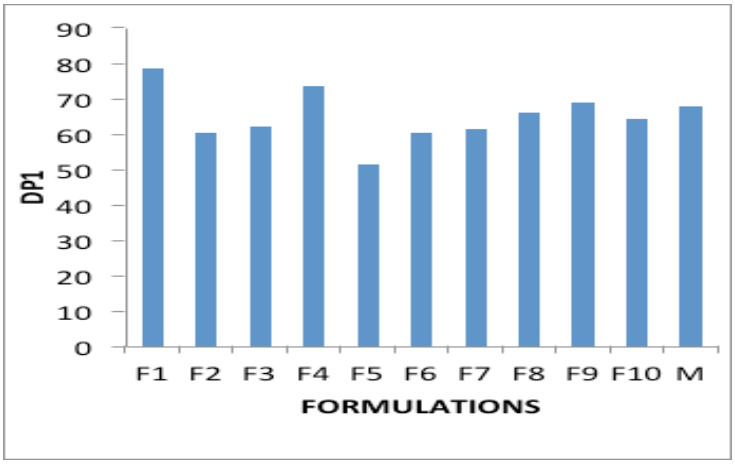

Figure 8: Comparative DP1 values

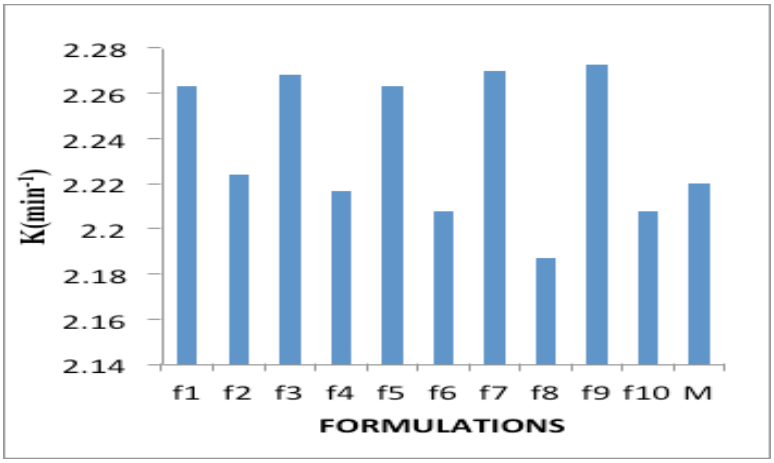

Figure 9: Comparative K (min^{-1}) values

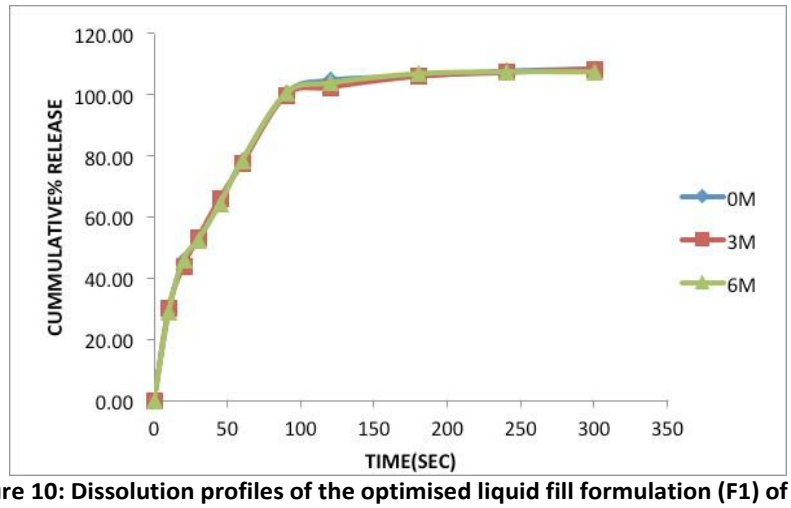

Figure 10: Dissolution profiles of the optimised liquid fill formulation (F1) of SMT

the batches of formulation pH are suitable for capsule filling. The results were given in Table.2 and shown in Figure 4.

Drug content uniformity

The drug content of all the liquid fill formulations for soft gels of SMT were estimated at 225 nm and the values were found to be in the range of 97.31±0.01 to 99.75±0.10. The results were shown in the Table.2 and Figure 5.

Rheological studies

Viscosity is one of the important parameters which provide vital information during the optimization of the liquid filling formulation for soft gels. In general, the viscosity of liquid filling formulations for soft gels is in the range of 0.222–3000 cps.

Formulations F1, F2, F5, F6, F8 and F9 had fluid like consistency, whereas F6 had thicker consistency. But formulation F1 had very less viscosity and was like a

very clear solution. The viscosity was measured by plotting the shear stress on x-axis, and shear rate on y-axis which gave a straight line. From the slope values viscosity was calculated for each formulation. The consistency and viscosity of the filling formulations were related to each other because both are dependent on concentration of PVP K-30/SLS/TWEEN-80.All the formulations showed the Newtonian fluid behaviour. Significant increase in viscosity was observed with increasing PVP K-30 concentration as the system offers more resistance to flow. The decrease in shear viscosity with increasing shear rate is due to tendency of PVP K-30 molecules to orient more in the direction of shear. It is clearly evident that changes in the viscosity and consistency of liquid filling formulations are because of change in concentration of PVPk-30 and slightly because of change in concentration of PEG-400, tween-80.

The viscosity of all formulations was studied. The viscosity of moderately concentrated solutions of PVP K- 30 has been studied in PEG 400, PG, and ethanol at different shear rate conditions in concentration range of 5-10%w/w. 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 rheological data for the formulations (F1- F10) were given in Table. 2

DSC Studies

DSC thermogram obtained for SMT and SMT liquid fill formulations for soft gels were shown in Figure 1 and Figure 2. SMT showed melting endotherm at 170.2°C. SMT Liquid fills formulations showed no or weak peaks compared to SMT. It may be due to molecular dispersion of SMT within liquid fill formulations. Overall DSC curves indicate that there is no interaction observed between drug and excipients.

FTIR studies

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). The overlay spectra of Pure SMT and that of liquid fill formulations F1, F2, F3, F4, and F5 were shown in Figure 3. FTIR spectrum of pure Sumatriptan succinate showed Aromatic C = C stretch at 1471.34cm^{-1}, Aliphatic C –H stretch at 2931cm^{-1}, Aliphatic C –C stretch at 840.21cm^{-1}, Aliphatic C –N stretch at 1079.27cm^{-1}, Aromatic C –N stretch at 1339.77cm^{-1}, N – H (secondary amine) stretch at 3366.67cm^{-1}, C – S stretch at 633.15^{-1}, S=o stretch at 1350.76cm^{-1}. It indicates there is no interaction between drug and excipients. The spectra showed that there are no interactions observed between the drug and excipients.

***In-vitro* dissolution studies**

The comparative *in-vitro* dissolution profiles of all the liquid fill formulations of SMT were shown in Figure 6.1 and the DP1 values of all the liquid fill formulations were shown in Figure 6.3.

Formulation F1 prepared using water/PEG/PG system showed superior drug release (99.00 % at 90 seconds) when compared to formulation F2 prepared using ethanol/water/PEG/PG system (95.34% at the end of 90 seconds). This may attributed to the higher solubility of SMT in water when compared to ethanol.

Formulations F3 and F4 were prepared using different concentrations of PVPk-30 to study the effect of polymer on SMT drug release. The dissolution profiles indicated that F4 (20% PVP K-30) showed faster drug release (73.67% at the end of 60 seconds) compared to F3 (which showed 62.02% at the end of 60 seconds). This may be attributed to the higher concentration of PVPk30 in F4 when compared to that of F3.

Formulations F8 and F9 were prepared using different concentrations of SLS to study the effect of wetting agents on drug release. The dissolution profiles indicated that F9 showed faster drug release (69.03%) compared to F8 (66.24%). This may be attributed to the higher concentration of SLS in F9 when compared to that of F8.

Formulations F5&F6 were prepared using different concentrations of Tween-80 to study the effect of wetting agents on the drug release. The dissolution profiles indicated that F6 (60.211%) showed better drug release when compared to F5 (51.38%).This may be attributed to the higher concentration of Tween-80 in F6. Higher the concentration of wetting agent, higher the drug release of SMT.

Compared to formulations prepared with SLS (F8, F9), those prepared with PVPk-30 (F3, F4) showed rapid drug release.

Comparative dissolution studies showed that formulations F3, F4 containing PVPK-30 showed less drug release when compared to F1 formulation without PVPK-30.

When compared to marketed formulations, F1 formulation showed better drug release profile, i.e, F1 showed 100% drug release in 90 seconds whereas Marketed formulation, Suminat-25mg showed 100% release at the end of 4 minutes). The comparative dissolution profiles were shown in Figure 6.2.

Formulation F1 is having superior release properties; hence F1 was selected as optimized formulation. This confirms that water/PEG/PG system is better for SMT release than Ethanol/PEG/PG and PVP/PEG/PG systems. Finally, the release kinetic was studied and showed that F1 better fits the first order release kinetics among all formulations.

First order kinetics

The dissolution data were analyzed as per zero order and first order kinetics for each formulation. The r^2

values were higher in the first order model than in zero order models indicating that the release of SMT from these liquid fill formulations first order kinetics. The first order rate constant 'K' (min^{-1}) values for liquid fill formulation were calculated from dissolution data by fitting the data into first order equation. The results were given in Table. The comparative plot of 'K' values for SMT and its formulations F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10 was shown in Figure 7. The 0.980, 1.001, 1.021, 1.019, 1.022, 1.023 fold increases in "k" values were observed for formulations F1, F2, F3, F5 and F9 when compared to marketed SMT. A 1.020 fold increase was observed in formulation without PVP-K30 F1 when compared to formulation with PVP-K30 F4. Similarly, 0.975, 1.304 fold increase in "k" values were observed in F1 when compared to formulation containing Tween-80 (F6) and SLS (F8).

Stability studies

The results indicated that all the liquid fill formulationsF1 to F10 showed no significant changes in drug content, pH and viscosity for 6months at room temperature in liquid filling formulations. The results were shown in Table. 3.

CONCLUSION

SMT 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 SMT 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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