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FORMULATION AND EVALUATION OF LIQUID FILLED CAPSULE OF IMMEDIATE RELEASE ALPRAZOLAM

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ABSTRACT

Alprazolam is a benzodiazepine. It affects chemicals in the brain that may be unbalanced in people with anxiety. It is used to treat anxiety disorders, panic disorders and anxiety caused by depression. Its mechanism of action is by binding to the GAB receptors in the brain and enhances GABA mediated synaptic inhibition, such actions may be responsible for the efficiency of Alprazolam in anxiety and panic disorder. The major problem encountered with this drug was its poor aqueous solubility. Since dissolution is the rate determining step for hydrophobic, poor aqueous soluble drug, absorption of such drugs is often said to be dissolution rate limited. To design proper dosage regimen and to improve oral bioavailability, efforts were made to solubilise the drug. Liquid filled hard gelatine capsule is well established as a solid dosage form for convenient administration of drugs orally in a liquid form in two piece gelatine capsule. This technology is more adapted for insoluble hydrophobic and potent drugs. And there are also many advantages in giving the drug in liquid form. Hence drug compounds are solubilised inside the hard gelatine capsules such that on subsequent dissolution of LFHGC in the gastrointestinal tract, the drug remains in solution and contribute for good bioavailability of drugs.

Keywords: Dissolution rate, Bioavailability, Liquid filled hard gelatin capsule, Alprazolam, Immediate release.

INTRODUCTION

Liquid filled hard gelatine capsule is well established as a solid dosage form for convenient administration of drugs orally in a liquid form. Liquid filled capsule technology can be used for liquid and semisolid fills in two piece gelatine or HPMC capsule with or without banding. This range of liquid composition available to accommodate even the most challenging drug compounds in capsules has increased significantly in recent years. In particular, it is possible to solubilise many drug compounds in a micro emulsion pre-concentrate inside the hard gelatine capsules such that on the subsequent dispersion in the gastrointestinal tract, the drug remains in solution. It is considered that this technology can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in – house formulation when only small quantities of drug substance is available.

Liquid-fill formulations – whether in soft gelatine or hard shell capsules – offer an important oral dosing strategy for drugs with low aqueous solubility and/or permeability, and low dose drugs that can cause content homogeneity issues when formulated as powders into capsules or tablets. In addition, this technology offers an inherently safer process than powder filled capsules and tablets for highly potent or cytotoxic drugs, as dust generation does not occur with liquid-fill formulations. The liquid-fill capsule dosage form (soft and hard) has gained increased acceptance over the last 30 years in an industry that has historically been dominated by tablets; a selection of current commercial products formulated in this way is listed in Table 1.

The process involves the addition and mixing of the active substance in a liquid or molten vehicle (which could be a single excipient or a multi-component mix). The drug formulation is then filled into capsules, which can be sealed if necessary to prevent leakage

Gelatin (bovine, porcine and fish) continues to be the main capsule-forming material, with ongoing activity in developing alternatives. HPMC shells are an established alternative to gelatin where there is a market preference and for products where cross-linking or other compatibility issue is a problem with gelatin.

Advantages

1. Capsules are easier to swallow because of their shape and because their gelatin exterior becomes slippery when patients take them with water.
2. This technology potentially provides the industry with an in - house process to develop drugs which are poorly water -

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soluble, have a low melting point, are highly potent or lower dose or have a critical stability issue, into bioavailable, stable and safe dosage form.

One problem which has prevented wider acceptance of this technology was the fact that the capsules had to be bonded using a process which is difficult to operate and capital intensive. Liquid filling and sealing of hard gelatine capsules thus become a much more feasible option. It provides the formulation scientist with an in - house operation to rapidly develop products for clinical trials when drug substance is at a premium and also provides an easy route to scale - up and production

MATERIALS AND METHODS

Alprazolam was obtained as a gift sample from LAKE CHEMICALS PVT.LTD, Bangalore, India. Hard gelatine capsule was purchased from Yarrow Chem., Mumbai. Olive oil was purchased from Nice Chemicals Pvt Ltd, Cochin. All other materials used were of analytical grade.

Preparation of liquid filled capsule

As the drug Alprazolam is insoluble in water the drug is dissolved using olive oil. Olive oil has additional health benefits too. Alprazolam fast releasing liquid were prepared by using olive oil. The weighed quantity of the drug is simply mixed with olive oil using a magnetic stirrer. It will result in a colorless liquid. The prepared drug is filled in to the body of hard gelatine capsule and closed by using a cap. The capsule is sealed by using 15% w/v gelatine solution in order to prevent leakage.

In vitro release study of liquid filled hard gelatine capsule

Dissolution studies were carried out using USP XXIII dissolution test apparatus II basket type (Electrolab TDL- 08L) at a rotation speed of 50rpm and at 37 ± 0.5° using 900 ml of 0.1N HCl (pH 1.2) for two hours. A 1 ml sample was withdrawn at 15 minutes time intervals for 2 hours and replaced by an equal volume of 0.1N HCl (pH 1.2). Samples withdrawn were filtered through whatman filter paper (0.45µm). The amount of Alprazolam was analyzed using a Shimadzu UV spectrophotometer at 260nm. The studies were carried out in triplicate and the mean values plotted verses time with standard error of mean, indicating the reproducibility of the results.

Fig 1. Reasons for Formulating Drugs As Liquid Or Semisolid Dosage Forms

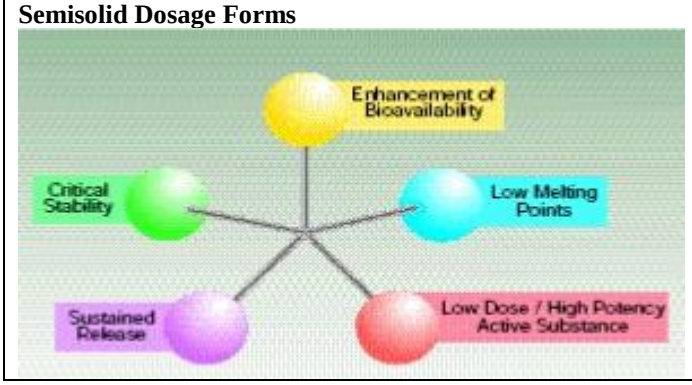

Fig 2. *in-vitro* dissolution study of liquid filled capsule

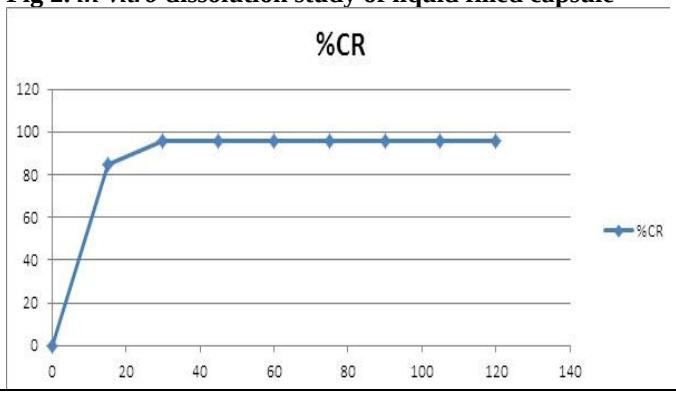

Table 1. Currently marketed products formulated as liquid fill capsules

Sl no:	Active	Brand	Dosage form	License holder
1	Danthron	Co-Danthromer	Hard capsule	Napp
2	Captopril	Captopril-R	Hard capsule	Sankyo
3	Peppermint oil	Colpermin	Hard capsule	J & J
4	Isotretinion	Claravis	Hard capsule	Teva
5	Mebeverine	Mebeverine	Hard capsule	Mylan
6	Paricalcitol	Zemplar	Soft gel	Abbott
7	Dutasteride	Avodart	Soft gel	GSK

Table 2. *In-vitro* dissolution study of liquid filled capsule

Time (min)	Absorbance	Concentration	Drug release	%CR
0	0	0	0	0
15	0.023	0.942	8.48	84.8
30	0.026	1.065	9.55	95.5
45	0.026	1.065	9.55	95.5
60	0.026	1.065	9.55	95.5

75	0.026	1.065	9.55	95.5
90	0.026	1.065	9.55	95.5
105	0.026	1.065	9.55	95.5
120	0.026	1.065	9.55	95.5

RESULTS AND DISCUSSION

The in-vitro release study of liquid filled capsule is carried out and the dosage form shows a release of 84.8% at 15 minutes and 95.5% release at the 30th minute of dissolution as indicated in the table 2 and the graph of dissolution study are indicated in the figure 2.

CONCLUSION

Alprazolam used to treat anxiety disorders; panic disorders and anxiety caused by depression are water insoluble drugs. They can be administrated by dissolving in organic solvents or fats.

In this study, Alprazolam is dissolved in olive oil and this liquid is filled into the hard gelatin capsule in order to formulate the liquid into solid oral dosage form. From the *in-vitro* release study the immediate release formulation of Alprazolam gives a release of 77.4% in 15 minutes and 95.5% in 30 minutes of dissolution time. The dosage form can be given for once daily dose in the morning.

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CONFLICT OF INTEREST

None

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