SUMMARY

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Dissolution of drugs in biophase plays an important role to increase bioavailability. Poorly water soluble drugs always pose a challenge for the dissolution and ultimately leads to low bioavailability. The increase in dissolution is reflected in increased bioavailability of poorly water soluble drugs.

The above problem can be solved by a number of approaches for increasing the dissolution. In the present investigation, it was attempted to achieve this goal by way of preparing solid dispersions of poorly soluble Ampicillin trihydrate, Chlorpropamide and Prednisolone. Solid dispersions of these drugs were formulated with mannitol, polyethylene glycol 6000, polyvinyl pyrrolidone and urea with 20, 40, 60 and 80 percent of these materials. Two different methods viz. solvent method and melting solvent method were attempted.

All the three drugs and carriers were standardized for various parameters like identification, melting point, freezing point, thin layer chromatography, loss on drying, UV Spectroscopy, IR Spectroscopy, X-Ray diffraction and test for heavy metals; before the preparation of these solid dispersions.

Standard curve for Ampicillin trihydrate was
prepared in 5N sodium hydroxide at 264 nm over Backman DBG Spectrophotometer. Likewise the standard curve for Chlorpropamide and prednisolone were prepared by observing absorbances at 232 and 240 nm respectively. For chlorpropamide the solutions were made in 0.1N HCl, whereas for prednisolone methanol was the solvent.

The solid dispersions were prepared by two different methods. In the first method the drug and carrier with the respective percentages were dissolved in the common solvent and the solvent was evaporated off by vacuum evaporation. Dried solid dispersions obtained were then pulverized and kept in the sealed containers. In the second method the solutions of the drug were added to the melting carriers with respective percentages. This mixture was then subjected to vacuum evaporation. Vacuum dried products were pulverized and stored in sealed containers.

All the prepared solid dispersions were then characterized by Infra red spectroscopy, X-Ray Diffraction and melting point determinations for each product.

Dissolution rate studies were performed for each solid dispersion thus prepared and the products were screened for best solubility behaviour amongst their group. These selected products and the pure drug were tested for blood plasma level study in the dog.
The data obtained in the dissolution rate studies were then transformed for percent dissolution, Log percent to be dissolved, Higuchi's square root plot, dissolution rate constants and Higuchi's proportionality constants. The blood plasma level data were used for the calculation of area under the curve.

The data obtained in dissolution rate and biopharmaceutical studies were subjected for F-test, ANOVA and regressed for their statistical fitness. On the basis of result obtained in various experiments and the transformed data, it can be concluded that:

Drug and carrier standardization:

Drugs and carriers were standardized according to compendial / available standards. All the drugs and the carriers were found to comply with pharmacopeial standards.

Standard Curves:

Lambert and Beer's plots of all three drugs were prepared in the ranges, Ampicillin trihydrate (0 to 400 μg/ml), Chlorpropamide (0 to 10 μg/ml) and Prednisolone (0 to 10 μg/ml) respectively.

The plots have a good degree of linearity within the range and acceptable linearity (correlation coefficient > 0.99).
Dissolution Studies

Dissolution behaviour of solid dispersion is one of the most powerful theoretical tool to understand their behaviour which provide the insight into their physicochemical features. Briefly dissolution features are as follow:

Ampicillin trihydrate solid dispersion have shown a consistent increase in drug dissolution. Increase in mannitol concentration increases the dissolution by 1.54 times at 80% level. In case of PEG 6000 as carrier, around 2.15 fold dissolution enhancement is observed. In case of PVP and urea the dissolution enhancement at 80% carrier were around 1.82 and 1.49 fold respectively. Change in the method of preparation have slightly lowered the dissolution enhancement effect, the values are 1.5, 2.24, 1.89 and 1.55 for Mannitol, PEG 6000, PVP and Urea respectively.

Chlorpropamide: In this case, Mannitol has enhanced the drug dissolution by 1.35, 1.76, 4.56 and 4.9 times for 20, 40, 60 and 80% carrier respectively. PEG 6000 has increased the drug dissolution by 1.9, 2.27, 2.772 and 5.57 times, 1.59, 1.91, 2.32 and 4.67 folds for PVP while Urea has the values 1.33, 1.61, 1.77 and 2.57 folds for various percentages of carriers. The alternative melting solvent has the maximum dissolution enhancement as 4.20, 4.82, 4.00 and 2.2 respectively at 80% carrier level of
Mannitol, PEG 6000, PVP and Urea.

**Prednisolone:** Dissolution enhancement of Prednisolone by 80% of carrier level were found to have the order of 1.28, 1.56 1.56 and 1.27 for solvent method and 1.26, 1.62, 1.54 and 1.23 respectively for melting solvent method. The above observation upon gross inspection indicates the relative effect of carriers upon drug dissolution which can be broadly summarised as increase in the fraction of the carrier increases drug dissolution, PEG 6000 is most effective among all other carriers under investigation and solvent method is more effective than melting solvent method.

**Percentage Dissolution Plot:** These plots were prepared with the view to assess the release efficacy of carriers. Overview of percent dissolution data has indicated the enhancement of Ampicillin trihydrate dissolution from 28 to 44.8%, 62.72% 53.06% and 43.51% using Mannitol, PEG 6000, PVP, and Urea respectively upto 80% carrier level, for melting solvent method these values are slightly lower. In the case of Chlorpropamide the dissolution was increased from 9.62% to 47.16%, 53.67%, 45.08% and 24.79% for Mannitol, PEG 6000, PVP and Urea respectively. While in melting solvent method although increase is their but less in comparision to solvent method. The percent dissolution data for Prednisolone shows a marked increase in dissolution from
53.77% to 69.25%, 88.44%, 84.16% and 68.32% using 80%
Mannitol, PEG 6000, PVP and Urea respectively. Similarly
the melting solvent method shows slightly low values than
the solvent method.

Log Transformation of Dissolution Data:

. In an attempt to fit the dissolution data in
standard kinetic fashion, most common first order
release kinetics was investigated in which the logarithm
of percentage of drug remaining to be dissolved was
plotted against time. None of the logarithmically
transformed curve has shown the linearity, specially in
the first region. The curvature encountered indicates,
the other operating parameter than the concentration
gradient but these curves successfully indicate the
efficacy of PEG 6000 as the powerful hydrophilic agent.
These curves also indicate the superiority of solvent
method over melting solvent method.

Higuchi's Plot:

Failure of the first order kinetics to explain, the
dissolution behaviour of solid dispersion, Higuchi's
time plot was attempted to fit the dissolution data, as
in its development it indicates the drug dissolution from
solid-liquid interfaces. Almost all plots have indicated
a good degree of linearity and the fitness of the data is
monitored by preparing linear regression analysis.
Interestingly these plots have shown a very high degree
of linearity of the order of 0.99 with the estimated error of Y, maximum 0.16, which indicated the suitability of the model to explain quantitatively, the drug dissolution through solid dispersion. After observing the linearity of Higuchi's plot, crude proportionality between the amount dissolved and square root of time is established to facilitate the computation of proportionality constant as the indicator of the effectiveness of system. The result obtained from these three dimensional graphics were in conformity with dissolution data.

Following important conclusions are easily drawn through these dissolution data.

1. Solvent method is superior method over melting solvent method in drug dissolution enhancement.

2. Carriers are more effective in the initial dissolution phase than the end phase.

3. Effectiveness of carriers has the order Polyethelene glycol 6000 > PVP > mannitol > urea.

4. In case of chlorpropamide urea possesses the optimum efficacy at around 60% level, which warrants the use of carrier percentage in a well defined range.

**BLOOD PLASMA LEVEL CURVE**

The in vivo efficacy of solid dispersion were estimated by administering the drug orally and monitoring
the plasma level and comparing it with the selected solid
dispersion, which have shown the significant dissolution
enhancement in comparison to the plain drug. In case of
ampicillin trihydrate the maximum level of drug is
observed at around 2 hrs. (4 μG/mL), while solid
dispersion using 80% of Polyethylene glycol 6000 has
aided 5.6 μG/mL blood level. For chlorpropamide, the
blood level of plain drug and solid dispersions are 30
and 36 μG/mL correspondingly, for Prednisolone and its
dispersion with 80% PEG these values are 1.3 and 1.6
μG/mL respectively. The plasma level data were confirmed
by the corresponding values of elimination, constant
determinated from the end segment of plasma level curves
and comparing then with the reference values obtained
from literature.

INFRA-RED SPECTROSCOPY:

The infrared spectroscopy of the drugs, carriers and
selected solid dispersions of drugs and carriers were
carried out. The spectra for all those represent no
chemical change before and after preparations of solid
dispersions.

1 Increase in the carrier fraction in solid
dispersion matrix increases the drug dissolution.

2 Impact of polyethylene glycol 6000 is maximum on
dissolution enhancement. Out of chosen carrier they exhibited the efficacy order PEG 6000 > PVP mannitol > urea.

3 Solvent method was found to be little superior than the melting solvent method.

The above mentioned hypothesis were tested for their authenticity by performing rigorous statistical treatment over the dissolution data. Fischer's F-test have been performed on the dissolution data grouped in three format having null hypothesis for: Change in the percentage of carrier has no significant effect over drug dissolution. To prove the validity of the statement "Change in the percentage of carrier has no significant effect over drug dissolution ", F-values were calculated for the solid dispersion having same carrier in different percentages and prepared by same method.

a) Change in the method of preparation has no significant effect over dry dissolution. In an attempt to establish the influence of method of preparation over drug dissolution. Similar composition dispersions were prepared by two methods, were subjected to analysis of variance. None of the pair has exhibited the value more than the tabulated value at (5% level for 10 degrees of freedom - 4.17). Which reflects the statistically
insignificance between the drug dissolution obtained from matrix prepared by two different methods.

b) Except for chlorpropamide change in the carrier has no significant effect over drug dissolution. The influence of nature of carrier was established by determining F-values among the dissolution data of solid dispersions having the same percentages of different carriers for the similar degree of freedom.

At 5% level tabulated values for 30 degree of freedom for residual corresponds to 2.92. Using this yardstick statistically significant difference exists among the solid dispersions of ampicillin trihydrate prepared by polyethylene glycol 6000 by both methods and solid dispersion of chlorpropamide prepared by all investigated using carriers (F-values were greater than 2.92). F-values for prednisolone carrier system were statistically insignificant.

On the basis of comparison of cal-F values it can be said:

1. Ampicillin trihydrate dissolution can be significantly altered using various percentages of PEG 6000.

2. Chlorpropamide dissolution can easily be altered by changing the carrier percentage and
3. Prednisolone dissolution is relatively insensitive to the change in carrier percentage.

4. Maximum dissolution is encountered in the early dissolution phase than the post dissolution phase.

5. On the basis of analysis of variance performed following conclusions can be drawn affirmatively.
   a) Successful dissolution enhancement can be achieved in case of ampicillin trihydrate using PEG 6000.
   b) Chlorpropamide dissolution can be easily increased using solid dispersion having hydrophilic carrier.
   c) Prednisolone is relatively insensitive drug for dissolution modification using carriers under investigation.

6. The following factor may have contributed to improve dissolution observed in the studies:
a) Generation of very small crystalline particle after dissolving highly water soluble carrier in G.I. fluid.

b) Solubilization effect by the carrier in the micro environment, immediately surrounding the drug particles in early stages of diffusion.

c) Absence of agglomeration between fine crystals of hydrophobic drug.

d) Excellent wettability and dispersibility of a drug generated in situ which is free from non-polar air envelopes.

e) Formation of metastable crystal form due to sudden solidification from solution.

f) Formation of amorphous fraction of dispersed drug due to difficulty in drug molecule movement in polymer matrix.

g) Formation of weak complexes having high aqueous solubility.

7) It is evident from the studies that the bioavailability of drug is increased as clearly seen by the plasma levels of drug in dogs. The improved bioavailability of fabricated solid dispersions are clearly reflected by area under the curve, from 13.74 uG-hr/mL to 19.14, from 241.915 to 284.2 & from 4.0735 to 5.0335 uG-hr/mL for ampicillin trihydrate, chlorpropamide and prednisolone respectively.
Differential Scanning Calorimetry and more number of biopharmaceutical trials would have placed the studies in better perspectives.

Further tablet formulations would be better appriliated by pharmaceutical manufacturer.