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RESEARCH ARTICLE

Formulation and *in-vitro* Evaluation of Mefanemic acid Solid Dispersion

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ABSTRACT:

The objective of the research work to enhance the solubility of mefanemic acid by formulating solid dispersion with hydrophilic polymers such as poly ethylene glycol (PEG 4000) and ethyl cellulose as carrier and solid dispersions were prepared by the method of conventional and physical mixture technique. Further formulated as tablet and capsular dosage forms and were evaluated for drug content, In-vitro dissolution studies and differential scanning calorimetry. Results showed that formulations F1-F5 varied from 58.41-96.91% of drug content, release 20-70% of drug in 60 minutes and follows Hixson crowell dissolution release kinetics. DSC Studies shows that there is no evidence of interaction between drug-excipient and as the solid dispersion exhibited no endothermic peak. During the stability study it was found that at low temperature the capsule shell breakdown and does not able to maintain its physical integrity and at high temperature and RH conditions therefore storage preferably below 30^0C will make stable formulations.

Keywords: Solubility enhancement, poly ethylene glycol, solid dispersions, differential scanning calorimetry, Hixsoncrowell.

INTRODUCTION:

A drug may be defined "as 'poorly soluble' when its dissolution rate is so slow that dissolution takes longer than the transit time past its absorptive sites, resulting in incomplete bioavailability". Approximately 40% of all newly discovered drugs display limited solubility in water and therefore poor and often greatly variable oral bioavailability. Drugs can also be classed as poorly soluble if they exhibit solubility in water below 100µg/ml.[1] Among these

methods, preparation of solid dispersion has become one of the most active areas of research in the pharmaceutical field to improve the bioavailability of poorly water-soluble drugs. This method involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixture, which resulted in solubility enhancement.[2]

The solid dispersion can be defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melt, solvent or solvent-melt method. The definition has now been extended to include certain nanoparticles, microspheres, microcapsules and other dispersions of drugs in polymers.[3]

Mefenemic acid is marketed in the form of conventional tablet and capsule only; but both oral solid dosage form has limited solubility and dissolution profile i.e. approx 25%; to overcome this problem manufacturer incorporate high amount of disintegrant (10-80%) which was hazardous to patient and also inflate overall cost of product. Another limitation of the existed dosage form is that they are very porous and thus not very hard as a consequence they cannot be broken in two or more pieces, this porous tablets tends to be very sensitive to humidity therefore they cannot be stored for some day's once the blister is opened.[4] The poor stability and low oral bioavailability with poor aqueous solubility warrants the administration of large dosage of mefenemic acid to maintain desired therapeutic concentration in blood.[5-7]

The main aim of the present study is to prepare an improved oral mefenemic acid formulation for once a daily dose i.e. 'solid dispersion' that delivers the drug in both solublize form and in a predictable manner which is independent of pH in gastro intestinal tract. By preparing its solid dispersion we can reduce the amount of disintegrant in formulation in contrast to present dosage form. Thus it reduces overall cost of the product and prevent the patient form exposure of such a high concentration of disintegrant. By preparing its solid dispersion we can improve its flow property and it can be either compressed in tablet form or it can be suitably dispensed in capsule.

MATERIAL AND METHOD:

Material:

Mefenemic acid was kind gift sample from Pfizer ltd. Ethyl cellulose, micro crystalline cellulose was purchased from Himedia Chemical private ltd. Mumbai. PEG 600, Sodium Lourayl sulphate, Talc was purchased in local market.

Method:

Preparation of solid dispersions:

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method.

Physical mixture method: All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixture of drug with carrier Ethylcellose (EC) was prepared in different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: EC ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 60 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to dissolution study.[8]

Table 1: Percentage cumulative drug release of physical mixture

S. No.	Time interval (mins)	Percentage cumulative drug release of physical mixture *		
		1:1	1:2	1:3
1)	0	0	0	0
2)	30	54.15 ± 0.11	47.46 ± 0.28	30.12 ± 0.18
3)	60	63.64 ± 0.19	71.64 ± 0.74	58.67 ± 0.33
4)	120	78.56 ± 0.34	73.12 ± 0.19	62.72 ± 0.45
5)	240	84.14 ± 0.42	74.34 ± 0.45	65.87 ± 0.61
6)	360	86.66 ± 1.08	74.76 ± 0.89	66.62 ± 0.59
7)	480	86.72 ± 1.11	77.12 ± 0.71	67.14 ± 0.72

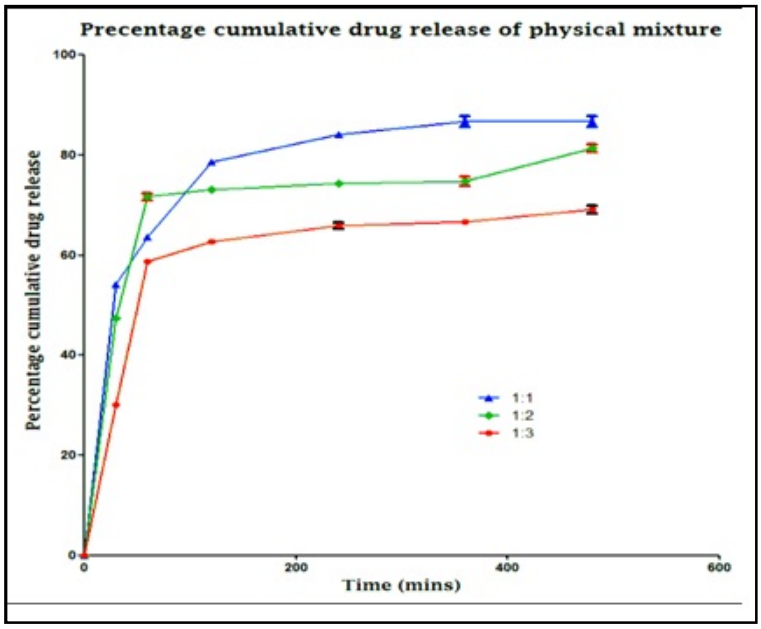

Fig. 1: Percentage cumulative drug release of physical mixture

On the basis of percentage cumulative drug release study it was concluded that solid dispersion is better option in spite of physical mixture. The study revealed that physical mixture shows a sudden bursting effect and erratic pattern in their release mechanism therefore the solid dispersion was best alternate. In solid dispersion it was found that in 1:1 and 1:2 ratio there was also a bursting effect and at higher polymer ratio i.e. at 1:3 the drug release was truly delayed which can further optimized to get better results. Therefore 1:3 ratios were found to be superior and were used for further evaluation purpose.

Preparation of solid dispersion of mefanamic acid

For the preparation of a mefanamic acid -PEG 4000 solid dispersion by conventional method, PEG 4000 was weighed and melted at 58 °C (± 1 °C) and a measured amount of mefanamic acid was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 60 mg of MEF-PEG 4000 powder (containing 15 mg of mefanamic acid and 45 mg of PEG 4000) was filled into a hard gelatin capsule (size no 2) for further investigations.

Preparation of physical mixture

For the preparation of a MEF-PEG 4000 physical mixture, MEF and PEG 4000 were weighed and mixed for 5 min with use of a pestle and mortar and sieved through a 400- mm mesh. 60 mg of MEF - PEG 4000 powder mixture (containing 15 mg of MEF and 45 mg of PEG 4000) was filled into a hard gelatin capsule (size no 2) for further investigations.

Tablet-making

MEF - PEG 4000 tablets were prepared with a Korsch EKO eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany). The compression tools were single, flat punches 10 mm in diameter, furnished with strain gauges. The physical mixture of MEF - PEG 4000 was compressed at a pressure of 10 ± 1 kN at an air temperature of 24 °C and an air relative humidity of 45%. The crushing strength of the tablets was investigated with a Heberlein apparatus (Flisa, Le Locle, Switzerland). The geometrical parameters were measured with a screw micrometer (Mitutoyo, Japan). The weight of the tablets was calibrated to 60 mg. Each tablet contained 15 mg of MEF and 45 mg of PEG 4000.

Evaluation:

Percentage drug content:

For the determination of MEF content, dispersion granules equivalent to 120 mg of MEF, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5 min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for MEF at 245 nm using a validated UV spectrophotometric method.[9]

In vitro dissolution studies

Samples of conventional, direct capsule filling and dropping method containing Mefanamic acid were prepared for dissolution studies. Samples were filled into hard gelatin capsules (size no. 2). Each capsule contained 15 mg of Mefanamic acid and 45 mg of PEG 4000. Dissolution tests were performed with a Pharmatest (Hainburg, Germany) dissolution tester, set with a paddle speed of 100 rpm. Artificial enteric juice (900 ml) with a pH of 7.5 (± 0.1) at 37 °C (± 0.5 °C) was used. Samples were withdrawn at 5, 10, 30 20, 30 and 60 minutes, and were assayed spectrophotometrically at 280 nm (Helios a, Spectronic Unicam, Cambridge, UK) after filtering. Dissolution studies for samples containing MEF were carried out as follow: Samples of tablets, physical mixture, pure MEF and round particles were prepared for dissolution studies. The physical mixture, round particles and pure MEF as reference sample were filled into hard gelatin capsules (size no. 2). Each capsule contained 15 mg of MEF and 45 mg of PEG 4000. Dissolution tests were performed with a Pharmatest (Hainburg, Germany) dissolution tester, set with a paddle speed of 100 rpm. Artificial enteric juice (900 ml) with a pH of 7.5 (± 0.1) at 37 °C (± 0.5 °C) was used. Samples were

withdrawn at 5, 10, 20, 30, 60 and 90 min, and were assayed spectrophotometrically at 245 nm (Helios a, Spectronic Unicam, Cambridge, UK) after filtering.[10,11]

Differential scanning calorimetry (DSC)

Thermal analysis was carried out with a DSC instrument (Mettler-Toledo GmbH, Switzerland). Sample was weighed into a non-hermetically sealed aluminum pan. The samples were heated from 25 to 400 °C at a heating rate of 5 °C/min for Mefanamic acid. In case of MEF the samples were heated from 25 to 300 °C at a heating rate of 5 °C/min and 30 °C/min. The instrument was calibrated by using indium.[12]

Result and discussion:

Percentage drug content

Table 2 : Result of five batches produced by central composite design

S. No.	Formulation batches	Observed parameters	
		Angle of repose *	Percentage drug content *
1)	F-1	43.52 ± 0.44	58.41 ± 0.97 %
2)	F-2	39.65 ± 0.72	68.95 ± 0.86 %
3)	F-3	44.84 ± 0.17	76.54 ± 0.61%
4)	F-4	41.65 ± 0.28	81.49 ± 1.03 %
5)	F-5	27.36 ± 0.12	96.91 ± 0.43 %

Drug content and % drug content was found to be within the limit which shows that the drug was uniformly distributed throughout the product and it also indicate that both impeller speed and kneading time has its significant impact on the quality of final solid dispersion.

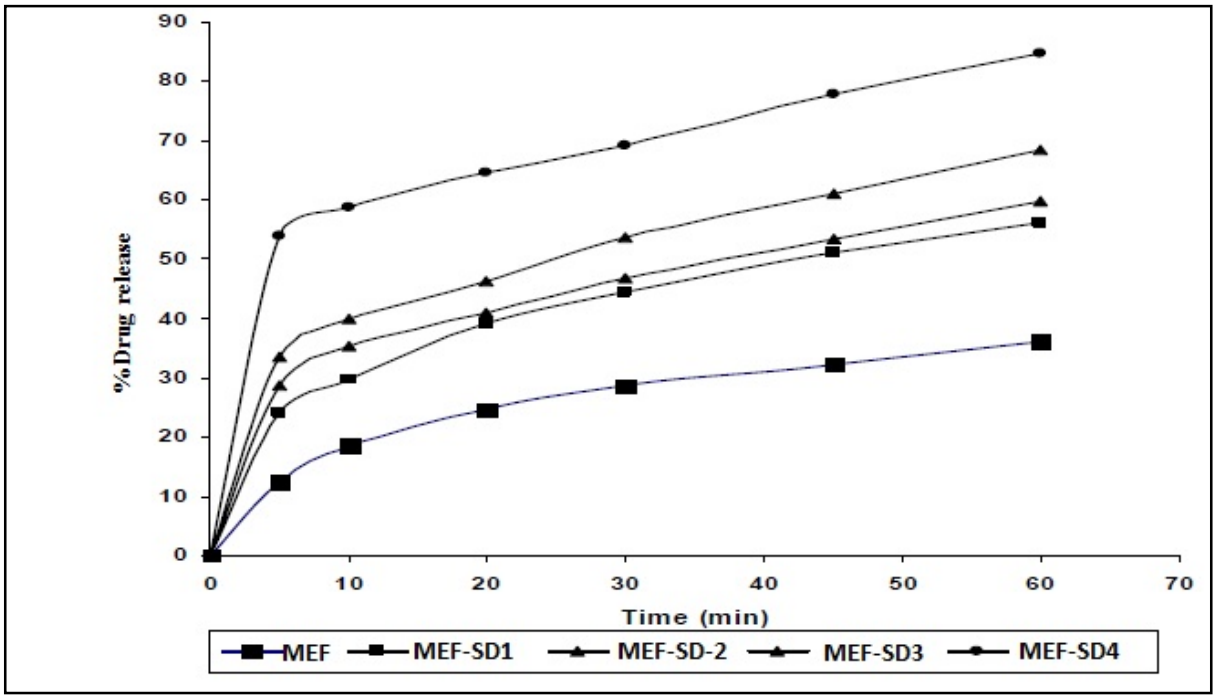

Fig. 2. In vitro dissolution studies

To further analyze the in-vitro release rate it was further evaluated for the specific release mechanism with the help of 'Kinetic- DS 0.3 rev. 2010 version software by comparing their respective 'regression coefficient'.

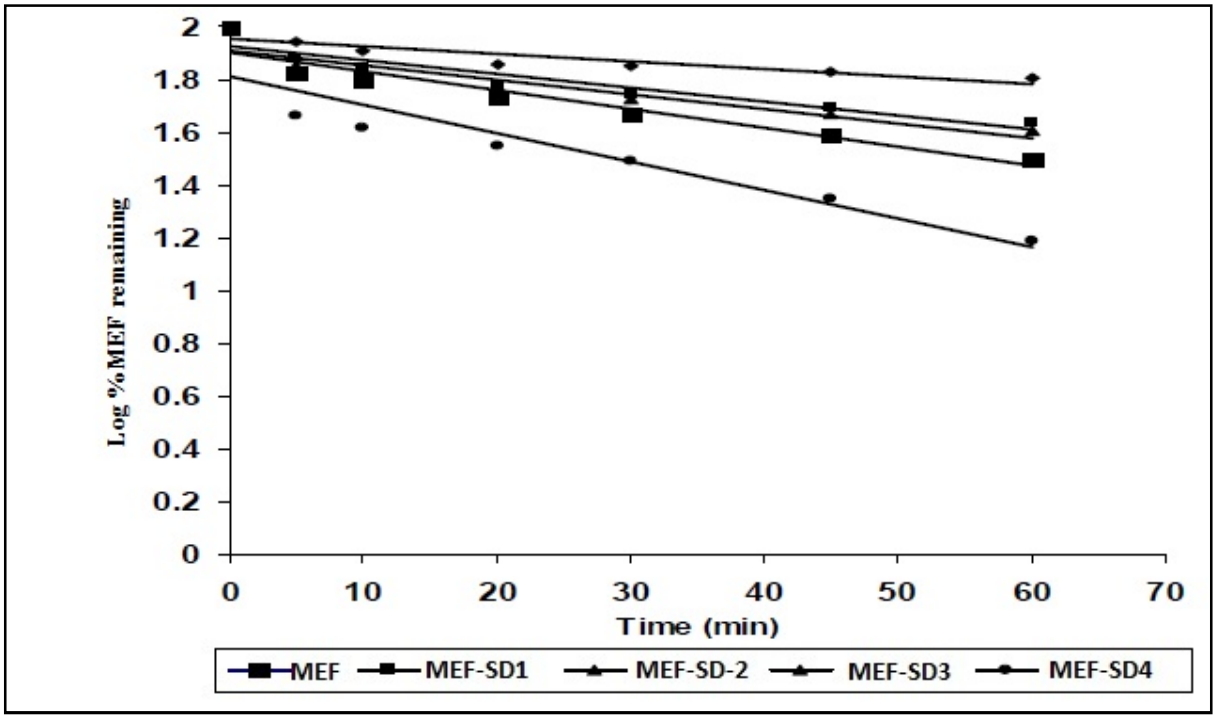

Fig.3: First order dissolution plots of Mefenamic acid and its solid dispersions

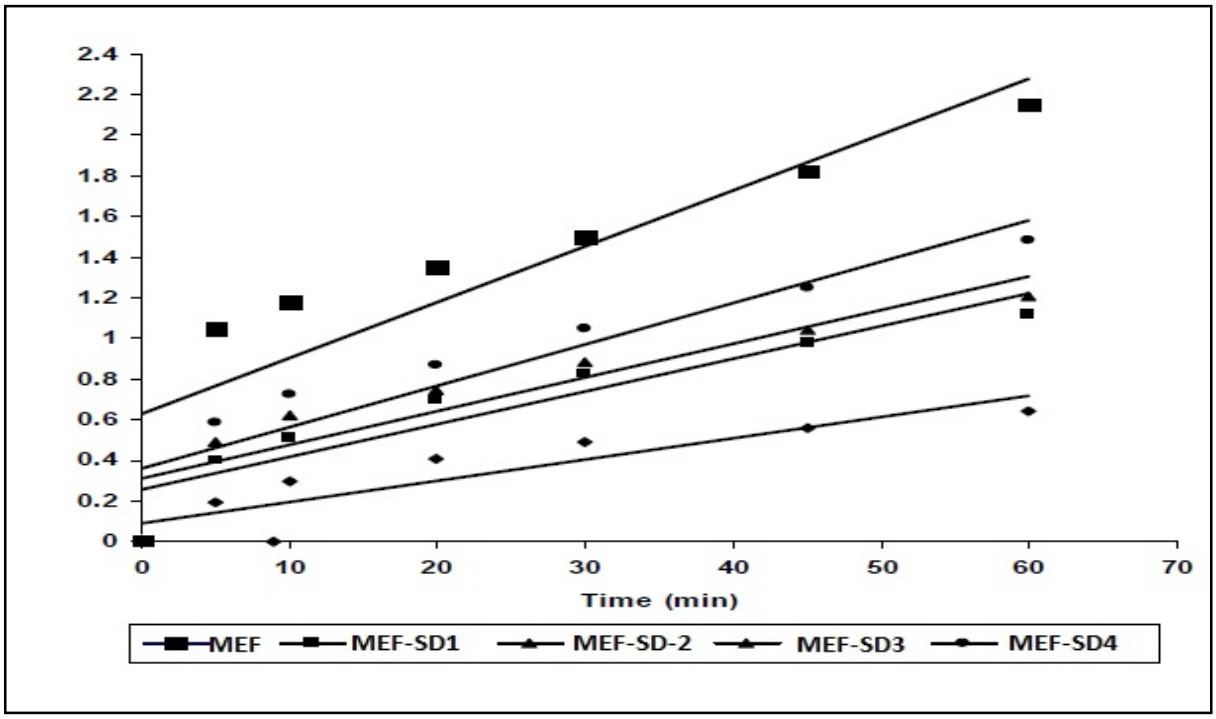

Fig.4: Hixsoncrowell dissolution plots of Mefenamic acid and its solid dispersions

In-vitro release shows that it follows delayed Hixson Crowell with lag period in release drug kinetics with the regression coefficient value up to 0.9929 and able to maintain release rate for a longer period of time (> 8 hrs).

Differential scanning calorimetry (DSC)

Thermal analysis was carried out with a DSC instrument (Mettler-Toledo GmbH, Switzerland). Sample was weighed into a non-hermetically sealed aluminum pan. The samples were heated from 25 to 400 °C at a heating rate of 5 °C/min for Mefanamic acid. In case of MEF the samples were heated from 25 to 300 °C at a heating rate of 5 °C/min and 30 °C/min. The instrument was calibrated by using indium.

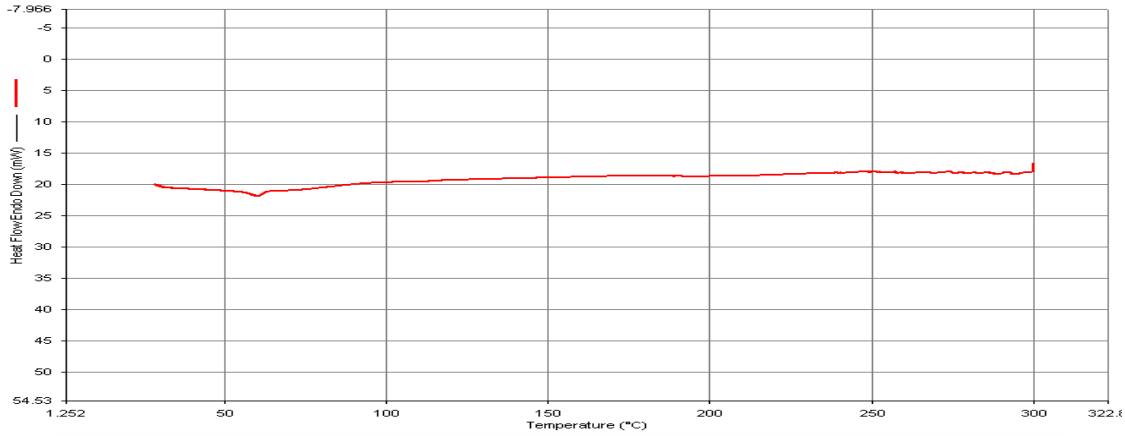

Fig.5. DSC Profile of solid dispersion formulation (MESD4)

On the basis of experimental design method it was concluded that in spite of physical mixture the solid dispersion was superior in terms of dissolution profile; they are capable of maintaining the drug release rate for a longer period of time. On the basis of same study it was found that drug: carrier ratio 1:3 is most suitable for the formation of delayed release solid dispersion.

In order to maintain the product quality, content uniformity, homogeneity and desirable flow property of SD, MEF-SD4 formulation was selected for further formulation and characterization purpose.

The optimized batch was subjected for micrometric tests which reveal that it was white amorphous powder with irregular shaped crystals. The bulk density and tapped density was found to be 0.656 ± 0.066 g/cm3and 0.969 ± 0.098 g/cm3 respectively. The H.R, % C.I, and angle of repose suggest that it posses fair flow property with a significant cohesiveness which can be improved with the help of proper addition of lubricant and glidants.

In-vitro release shows that it follows delayed Hixson crowell with lag period in release drug kinetics with the regression coefficient value upto 0.9929 and able to maintain release rate for a longer period of time (> 8 hrs).

DSC Studies shows that there is no evidence of interaction between drug-excipient and as the solid dispersion exhibited no endothermic peak corresponding to the melting point of MEF indicating that the drug is dispersed amorphously in ethyl cellulose matrix.[13]

CAPSULAR DOSAGE FORM

As both the solid dispersions were prepared and optimized, they cannot be administered as such they have to be given in suitable dosage form. The propose dosage form for the optimized granules was capsule.

Capsule can be simply defined as the ‘single unit oral dosage form’. It is one of the most popular dosage forms. It is most suitable for the dispensing of the drugs which have noxious and unpleasant odour and taste. The composition of proposed capsular dosage form can be given as follows:

Table 3 : Proposed capsular dosage form

S. No.	Ingredients	Quantity taken (mg)
1)	Optimized conventional solid dispersion (F6)	120
2)	Optimized delayed release solid dispersion (F5)	480
3)	Microcrystalline cellulose	45
4)	Talc	5
	Total quantity for 1 capsule	650

Characterization of Capsule Dosage Form:-

General physical characterization: The general physical characteristics which are taken with prime considerations are color, shape, surface texture etc. These characteristics can be suitably determined in laboratory by visual inspection only. The procedures which are used to determine the above parameter can be briefly summarized as follows:- It is usually determined with the help of visual inspection. In this dosage form is subjected to suitable bright illuminating source and colour, shape and surface texture was observed, the value was given in the Table 4.

Weight variation: The process consists of weighing 20 intact capsules, determining the average weight / capsule and finding out weight variation of each capsule. Weight of each capsule should fall within 90-110% of the average weight, thus a ± 10% weight variation was permitted. As per IP not more than 2 capsules should differ by more than ± 25%. In routine procedure, the intact capsule was weighed and then opens the capsule without losing any part of the shell and the content was removed. Then empty shell was weighed, the actual weight of content was the difference of weight of intact capsule and empty shell. The whole procedure was repeated for 19 capsules and its average weight was determined. The result was shown in Table 4.

Table 4: Showing observed characteristics of proposed capsule

S. No.	Parameter	Observation
1)	Physical characters	
	Color	Pale yellow
	Shape	Oblong
	Surface texture	Smooth
2)	Weight variation (%)	± 2.64
3)	Drug content (mg)	154.32 ± 1.87
4)	% Drug content	96.45 ± 2.93

Drug content and percentage drug content determination

This test was performed to ensure uniform distribution of medicament. The test was performed by selecting a number of capsules and followed by an assay procedure as per monograph. According to IP 20 capsules were taken; out of which 10 was assayed individually. The average drug content and percentage drug content result of 10 capsules was determined and it was reported in Table 8.2. The result of assay of 10 capsules was found to fall within the limit of 85-115%, which shows that it complies with standard.

Stability study of capsule dosage form

In order to determine the stability of prepared capsules, it was subjected to stability studies. In our stability study; all capsules was sealed in aluminium foils and then those packs was subject to three different conditions i.e. 5 ± 3^0C; 25 ± 2^0C / 60 ± 5% RH; 40 ± 2^0C / 75 ± 5 % RH for 4 weeks. The stability study initially was determined with the help of drug content determination weekly. The result was shown in Table 5 and corresponding graph was shown in Fig 6.

Table 5 : Stability study of capsule

S. No.	Formula tion	Storage condition	Initial drug concentration (%)	Observation % drug content determination for weeks			
				First*	Second*	Third*	Fourth*
1)	Capsule	5 ± 30C	100	98.66 ± 0.45	98.23 ± 0.18	97.98 ± 0.29	97.41 ± 0.31
2)	Capsule	25 ± 20C / 60% RH	100	98.45 ± 0.78	98.12 ± 0.63	97.63 ± 0.26	97.12 ± 0.65
3)	Capsule	40 ± 20C / 75% RH	100	98.12 ± 0.77	82.02 ± 0.59	77.32 ± 0.11	73.58 ± 0.39

* All values are mean ± Std. dev.; where n=3

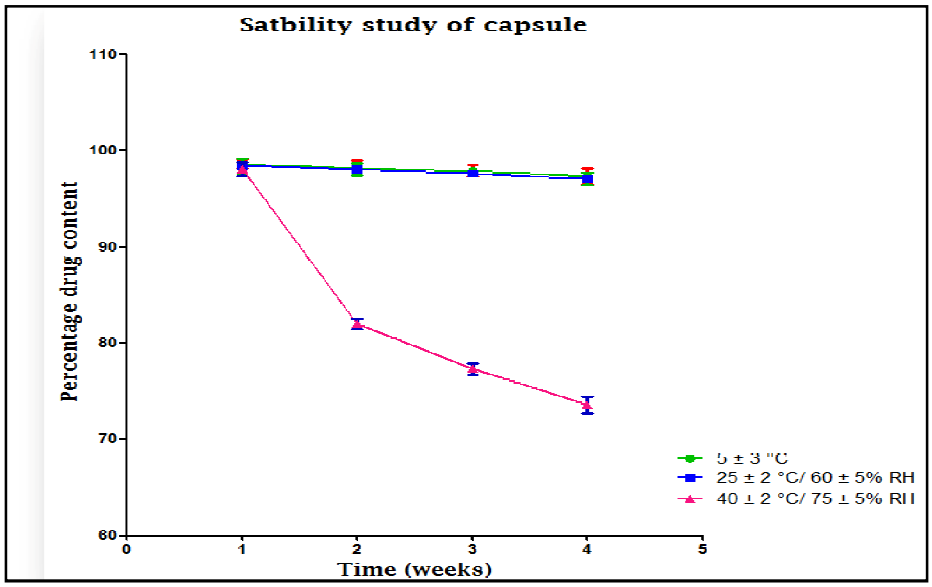

Fig 6: Stability study of capsule

Conclusion:

The proposed capsular dosage form was evaluated for following test: On basis of physical characterization it was concluded that the dosage form was up to the mark and can be used to dispense the optimum dose of drug as it poses a smooth surface texture it was proposed that it will be free from the leakage problem and hence can be cat as suitable

and stable dosage form. The weight variation was found to be ± 2.64% which shows that the result was obtained within the specified limit as prescribed in I.P and it shows minimum loss during filling procedure and minimum chances of leakage (or) hygroscopic character of capsule. The result of assay of 10 capsules was found to fall within the limit of 85-115%, which shows that it complies with standard. It shows that the dosage forms maintain its homogeneity.

During the stability study it was found that at low temperature the capsule shell breakdown and does not able to maintain its physical integrity and at high temperature and RH conditions they are found to loss it plasticity and get melt down; therefore in both the above stated cases there are possible chances of drug deterioration and leakage. Therefore one should store the capsule at room temperature preferably below 30^0C.

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