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Development, Optimization and *In-Vitro* Evaluation of Aceclofenac Dry Emulsion Tablets by Carrier Based Technique

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ABSTRACT

Dry emulsion tablet (DET) is a solid dosage form that is prepared from emulsion system. The objective of this project was to formulate a dried emulsified tablet of aceclofenac which on contact with the aqueous phase transforms quickly into emulsion with better release behavior and improved physical and microbiological stability. A physically stable emulsion was prepared with the help of HPMC(E15) and blends of Tween 80 and Span 80 as emulsifier and capric acid as oil phase by studying the stability parameters. Thus prepared stable emulsions were adsorbed by adding aerosil till free flowing powder was obtained. The micromeretic properties like flow and powder density was studied. Then the powder was dried at low temperature (50^{o}C) to remove the remaining moisture in the hot air oven. Thus devised dry emulsion powder was then compressed into tablets and was compared with marketed products. The formulation containing oil in the proportion 50%, emulsifier as HPMC 30% (HPMC 3% w/w) and water 20% showed the highest drug release (96%) as compared to other formulation and also compared to the marketed product. Dried Emulsion tablets thus produced by the current method have improved dissolution profile and fast onset of actions.

INTRODUCTION

Dry emulsions are lipid based powders from which an o/w emulsion can easily be reconstituted when exposed to an aqueous solution, and thus they present a potential for an oral drug delivery system (1). The water part of emulsion is removed by heating (spray drying) or by sublimation (by freeze drying) and solidified by structural additives. This way emulsion can be stored and carried as tablets thus increasing shelf life and portability while upon administration they turn back into emulsion and hence bypassing disintegration step, and providing the emulsion advantage of improved absorption and taste masking and suitability for hydrophobic drugs (2). Different methods of preparation like lyophilization, spray drying, rotary evaporation and adsoption method are chiefly used for the preparation of dry emulsion tablets (3). Dry emulsion can be further utilized for the processing of tablets and capsules. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary vaporation (4), freeze-drying (5) or spray drying (6-8) and an insoluble carrier such as colloidal silica (9). Dried emulsion has also been prepared by spreading liquid O/W emulsions on a flat glass, then dried and triturated to powders (10) . Another method of development of dried emulsion which is also used in the current study is the adsorption method. Basically Colloidal Sillicon Dioxide can be used as a good adsorbant due to the fact that it can readily adsorb the emulsion and can later be devised into dosage forms such as tablets.The addition of the hydrophobic silica changes the creamy liquid into a fluid powder that is the “dry adsorbed emulsion” (11). Thus prepared dry adsorbed emulsion offer several advantages over the conventional dosage form such as improvement in the biovailability of the drug, reduction in side effects, physical and microbiological stability, potentiality of serving as delivery system for the lipophilic and low soluble drugs and use as prolong release devices (12) .

MATERIALS AND METHODS

Aceclofenac was provided as gift sample from National Health Care Pvt. Ltd., Birgunj, Nepal. The other chemicals used were of analytical grades. Other Excipients were purchased from Central Drug House (P) Ltd. New Delhi and Hydroxypropyl Methyl Cellulose E15 was obtained as a gift sample from Omnica Laboratories, Bhaktapur, Nepal.

(i) Selection of Drug:

In the present study Aceclofenac was selected as a model drug for the preparation of dry emulsion. Aceclofenac is the drug belonging to class II of the biopharmaceutical classification system (BCS). These classes of drugs have low solubility and high permeability. The development of a tablet dosage form which can be developed as a self emulsifying drug upon its contact with the fluids in stomach can help to improve the solubility profile of aceclofenac.

(ii) Solubility of Drug in Oil:

0.5 gm of drug was added to 20 ml of capric acid (oil) and agitated for 24 hrs in an orbital shaker. After that it was centrifuged at 4000rpm for 15 min. Solution were diluted to 500 times with an ethanol. Then absorbance of the resulting solution was measured spectrophotometrically at 545nm.

(iii) Preparation of calibration curve:

This method was proposed by N. M. EI Kousy (13), Linearity of an analytical method can be defined as its ability to produce results which are directly proportional to the concentration of analyte in the sample. Into series of 10 ml volumetric flasks, aliquot amounts of stock solution equivalent to 8-55 mcg/ml of aceclofenac was transferred subsequently. Then, 8 ml of 0.2% (w/v) p-dimethylaminobenzaldehyde (PDAB) solution reagent was added. To each flask, 0.2 ml of 2.5% (w/v) ferric chloride solution was added and heated on a water bath at 65°C for 20 min. Finally the solution was cooled and volume was made up using 50% (v/v) sulfuric acid (H_2SO_4) and the absorbance was measured at 545nm. Then the calibration curve was constructed. This is based on colorimetric reaction, where the reaction of PDAB with Aceclofenac in presence of $FeCl_3$ and H_2SO_4 gives pink colour.

(iv) Analytical method Validation:

The analytical method validation was done using the guidelines as per International Conference on Harmonisation (ICH). The different validation characteristics considered during validation are linearity, range, accuracy, precision, detection limit and limit of quantitation.

(v) Preparation of Dry Adsorbed Emulsion (DAE) by Kneading Method:

DAE was prepared by the method by kneading method as described by Chambling et.al (14). Initially, the required quantity of drug was dispersed in oil. The aqueous phase was prepared by dissolving the required amount of emulsifier in water. Then the oil phase was added to the aqueous phase and was stirred for about 20 minutes manually in order to prepare a physically stable emulsion. Thus prepared emulsions were adsorbed by adding aerosil till free flowing powder was obtained. Then the powder was dried at low temperature ($50^{o}C$) to remove the remaining moisture in the hot air oven.

(vi) Preparation of Dry Adsorbed Emulsion (DAE) Tablets:

The dried emulsion powder were passed through the sieve of 24 mesh screen and then weighed. Microcrystalline cellulose was added to the dry powder at 5% (w/w) then super-disintegrant was added in the concentration of 10% (w/w) and talc 1% (w/w). The super-disintegrant of choice was sodium starch glycollate. The powders were mixed for 30 minutes to ensure the homogenous powder mixture. The powder was then subjected to compression in a 10 station rotatory punching machine and dry emulsion tablets were obtained.

(vii) Study of Derived Properties of DAE System Powder:

Flow Analysis Micro particle were characterized for their micromeritic properties such as particle size, bulk density, tapped density, Hausner's ratio, % Carr's index and angle of repose. The particle possess should an adequate level of flowability when blending with ingredients in formulation.

(viii) Evaluation of dry emulsion tablets:

Weight variation

Twenty tablets from each batch were randomly taken and the weights of each tablet were measured. The result was expressed as average weight ± standard deviation.

Hardness test

Ten tablets were selected randomly from each batch and the hardness of each tablet was taken. The result was expressed in terms of average hardness± standard deviation.

Friability test

The tablets placed in the Roche Friabiliator and were rotated at speed of 25 rpm for 4min.Those tablets whose percentage friability less than 1% was accepted.

Disintegration Test

Six tablets were taken in random order and then placed in 6 tubes of the USP disintegration test apparatus with 10 mesh screen. Phosphate buffer was selected as the media for disintegration test; the temperature was maintained at 37±2^{o}C. The time when all the residues of the 6 tablets in the tubes of apparatus were passed through the mesh screen was noted.

(ix) Assay:

Ten tablets from each batch were taken at random and were crushed into powder. The powder equivalent to 50mg of active ingredient was taken and dissolved in 100ml ethanol and filtered. Then 0.6ml of the sample was prepared with PDAB reagent solution and ferric chloride, then volume was made upto 10ml and heated at 65^{o}C for 20min, cooled and volume was made with 50% sulphuric acid then analyzed spectrophotometrically at 545nm.

(x) Dissolution test:

Dissolution testing of dry emulsion tablets was performed in USP Type II apparatus (paddle apparatus) at a rotational speed of 50 rpm in 450 ml distilled water at 37±0.5^{0}C in the phosphate buffer of pH6.5. Samples were withdrawn at time interval (5, 15, 25, 35 and 45min) and replaced by fresh medium at the same time. The withdrawn sample was passed through the filter paper, and the sample was diluted and prepared with the PDAB solution reagent in presence of ferric chloride and were heated at 65^{o}C for 20min, cooled and were spectrophotometrically analyzed at 545nm.

Statistical tool:

The statistical tool used was STATGRAPHICS Centurion XV.II for the generation of pseudoternary diagram for stable formulations.

(xi) Stability:

The stability of the emulsion was assessed by preparing the emulsion system with varying concentration of oil, emulsifier and aqueous phase as distilled water. Total of 30 emulsion systems were prepared. Fifteen emulsion systems were prepared using blend of tween80 and span80 and the other 15 with Hydroxypropyl Methyl Cellulose (HPMC) as an emulsifier. For the formulation of emulsion, oil used was in the proportion of 10% to 70% (w/w), water in the proportion of 20% to 80% and two different emulsions blend of tween80 and span80 in the proportion of 10% to 70% and HPMC 10% (w/v) aqueous solution in the proportion 20% to 70%. The resulting systems were incubated in the incubator at 40^{o}C and were observed for phase separation at different time intervals: 1hour, 4hour and 24hour respectively. The observation was done visually for the evaluation of phase separation. Then the data were fed in the statistical tool STATGRAPHICS Centurion XV.II.

Table 1: Composition of various stable formulations

Formulation	Drug (gm)	Oil (gm)	Tween80/span80 (gm)	HPMC (gm)	Water(gm)	Weight of emulsion (gm)
F1	3.75	14.88	14.88	-	44.65	1.5632
F2	3.75	14.88	3.72	-	18.6	0.819
F3	3.75	14.88	9.92	-	24.8	1.067
F4	3.75	14.88	-	24.8	9.92	1.067
F5	3.75	14.88	-	9.92	24.8	1.067
F6	3.75	14.88	-	8.92	5.96	0.6702

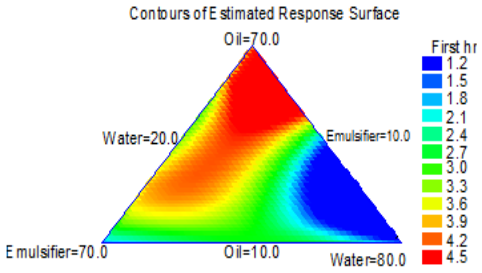

Figure 1: Pseudoternary Diagram for response for response usingween80/span80 at first hour

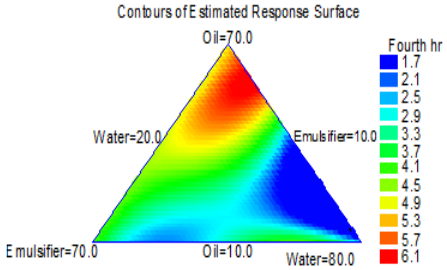

Figure 2:Pseudoternary Diagram using ween80/span80 at fourth hour

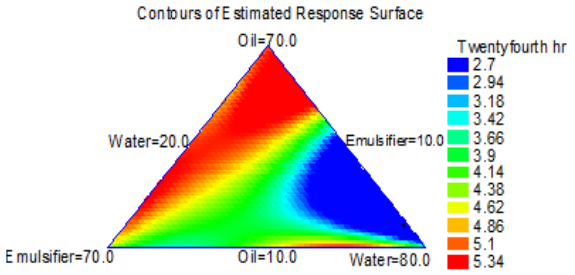

Figure 3:Pseudoternary Diagram for response response using ween80/span80 at twenty-four hour

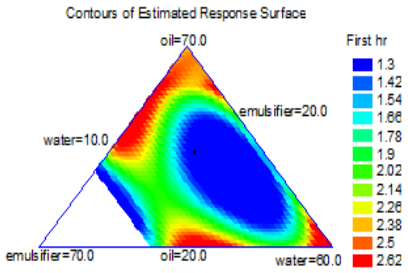

Figure 4: Pseudoternary Diagram for using HPMC at first hour

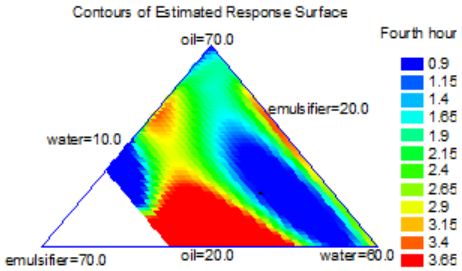

Figure 5:Pseudoternary Diagram for response response using HPMC at fourth hour

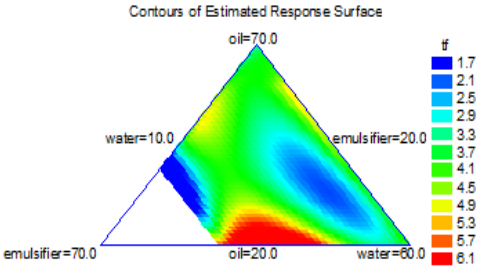

Figure 6:Pseudoternary Diagram for using HPMC at twenty-four hour

(xii) Analytical method validation

The analytical method was validated following the International conference on Harmonization (ICH) Guidelines. Linearity, range precision, detection limit and limit of quantitation were considered for the validation of the analytical method.

Linearity:

Linearity was evaluated on the basis of coefficient of regression (r^2) of a plot of signals (absorbance) as the function of analyze concentration. The value of coefficient of regression obtained from the graph was 0.9963 which signifies that the method is linear and can be performed in the concentration rang used in the study. The equation of line determined from the graph is given in equation 3.1.

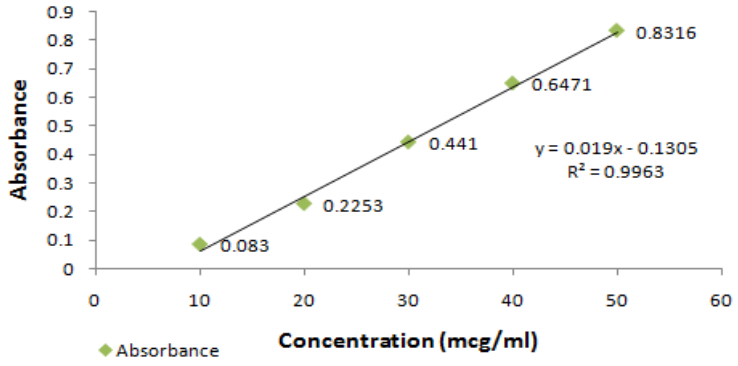

Figure 7: Calibration curve for Aceclofenac in p-dimethylaminobenzaldehyde (PDAB)

Y= 0.0192X - 0.1305

Where; Y= absorbance at 545nm and

X= concentration (mcg/ml)

Precision:

In repeatability assessment, nine determinations were made with three different concentrations ranging from 30mcg/ml to 50mcg/ml (n=3). The results obtained from the repeatability test are shown in the Table 2.

Table 2: Precision determination

S.no	Test concentration (mcg/ml)	Absorbance	Determined concentration (mcg/ml)	RSD
1.	30	0.4863	32.125	
		0.4953	32.593	1.16
		0.4816	31.880	
2.	40	0.6428	40.276	
		0.6521	40.76	0.01
		0.6564	40.9843	
3.	50	0.7950	48.203	
		0.7976	48.3385	0.41
		0.7896	47.921	

Since from the data it was found that the Relative standard deviation value to be less than 2% the method selected is precised.

Detection limit:

The detection limit was determined on the basis of standard deviation (σ) of the response and the slope (S) of the linearity curve. The standard deviation of the response was found to be 0.00974 and the slope of the line 0.01867; hence the detection limit was calculated to be 1.5655mcg/ml.

Limit of Quantitation:

The limit of quantitation was determined on the basis of standard deviation of the response and the slope of the calibration curve. The standard deviation of the response was found to be 0.00974 and the slope of the line to be 0.018667; hence the limit of quantitation was calculated to be 5.2177mcg/ml.

Stability:

Three systems were found to be stable when observed visually. These systems showed no signs of phase separation till fourth hour. There was no phase separation for 24 hours where HPMC was used as an emulsifier. There was initiation of phase separation for the emulsion systems where blend of tween80 and span80 was used as an emulsifier during 24th hours. The visually inspected data were fed in the statistical tool STATGRAPHICS Centurion XV.II.

Formulation considerations

Choice of analytical method:

As the drug's normal analytical method at wavelength 274nm was interfered by the selected oil, in order to nullify the effect colorimetric method namely: oxidation of aceclofenac in acidic medium in presence of ferric chloride and potassium ferricyanide (at 612nm), using Folin-Ciocalteu phenol reageant (at 642.6nm), and method using PDAB solution reagent in presence of ferric chloride and sulphuric acid (at 545nm) were performed. The use of PDAB solution reagent in presence of ferric chloride and sulphuric acid was the method of choice.

Choice of oil and emulsifier:

Two different oils were chosen for the experiment on the basis of solubility of drug in the oil. Those two oils were oleic acid and capric acid. Since it was found that the solubility of Aceclofenac was higher in capric acid (23.876mcg/ml) than compared to that of oleic acid (16mcg/ml), thus only capric acid was selected for the further experiment.

Two different emulsifiers were chosen and formulations were prepared using the emulsifiers in varying concentration range. The chosen emulsifiers were tween80, span80 and HPMC . Tween-80 and Span-80 were used in the combination of 6.3:3:7 to maintain the required HLB value of the system. The combination system of tween and span were tried in various concentration range, however the concentration range from 10-20% system were found to be best as emulsifier in the formulation. Similarly, HPMC as emulsifier was tried in various concentration range and it acts as best emulsifier in the concentration range of 20-50% of the 10% w/v solution of HPMC in purified water.

RESULTS AND DISCUSSION

Physico-chemical properties of Dry Emulsion Tablets:

HPMC is a cellulosic derivative. Since all cellulose ethers are hygroscopic, they will absorb moisture from surroundings if left exposed from original packaging. The tiny spikes seen on the surface of the tablets may be because of the absorption of the moisture. When the tablets were stored in the controlled condition (in the vial heated prior to remove the moisture and closed effectively) in the desiccator or stored in the freeze no problems of formation such spike were seen. The hardness of the tablets follows the order: F4>F6>F5>F2>F1>F3.

HPMC is a cross linked polymer which accounts for the rigid structure and hardness of the tablets. Thus, the formulations of HPMC have higher hardness than the tween span formulations. HPMC moisture content is positively related to the tensile strength of the tablets. The formulations of the HPMC which have shown greater aqueous content (i.e. Formulation F4 is the hardest one. Other with lower aqueous content has lower degree of hardness.

The disintegration of the HPMC formulation based tablets follows the order: F5>F4>F6.

Table 3: Characterization of dry emulsion tablet

Formulation	Hardness (kg/cm^2)	Friability(%)	Disintegration time(sec)	Thickness (mm)	Diameter (mm)	Weight (mg)	Assay
F1	3±1.50	0.435	65	6.2±0.03	13.08±0.07	1090±0.0	100.6
F2	1.4±0.98	0.297	69	4.43±0.03	13.08±0.05	672±0.00	98.9
F3	2.8±0.372	0.224	40	6.07±0.02	13.06±0.02	877±0.01	91.13
F4	3.1±1.54	0.284	187	3.82±0.02	13.25±0.03	579±0.01	96.45
F5	2.6±0.316	0.149	327	3.56±0.03	13.2±0.03	557±0.01	96.45
F6	2.84±1.02	0.845	69	3.82±0.02	13.17±0.07	569±0.01	100.1

The amount of HPMC is the highest in the formulation F5. Since HPMC primarily functions as binder the increase in disintegration time most is probably due to its concentration. Similarly accounting for the total disintegration time of the tablets, the disintegration follows the order, F5>F4>F6=F2>F1>F3

This may be due to the rigidity provided by the HPMC polymer.

Dissolution Profile:

The samples of the DETs were subjected to the phosphate buffer pH 6.5 in the type II (paddle apparatus at 50rpm and 450ml dissolution medium. The samples were withdrawn at different time interval for 45 min and observed spectrophotometrically at 545nm by adding necessary.

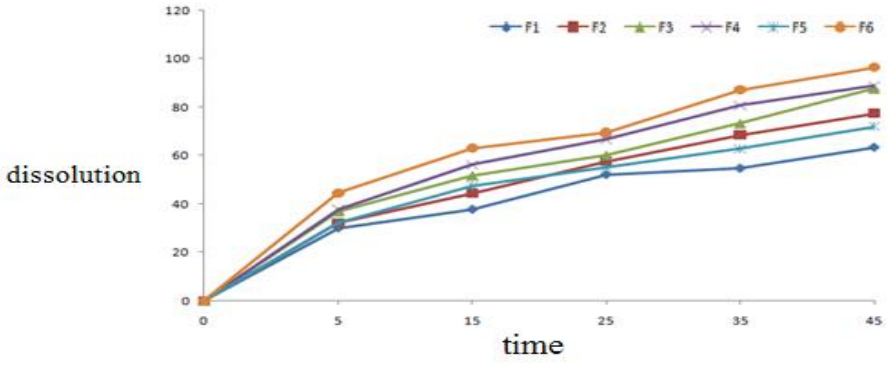

Figure 8: Dissolution profile of various formulations of dry emulsion tablets (DETs).

DISCUSSION

Formulation F6 containing oil 50%, 30% emulsifier (HPMC 10% solution) and 20% water had the maximum drug release 96% in 24th hour compared to other formulation. This formulation had been prepared from the HPMC as the emulsifying system. The dissolution of the formulation F1 had the least dissolution (63% in 45 min). This formulation had been prepared using the blend of tween80 and span 80 as emulsifier in the ratio 6.3:3.7.

There is no clear distinction between the drug release profile in the formulation containing 50% (w/v) and the blend of tween80 and span80 as an emulsifier in the concentration 20% (w/v). The drug released in the formulation F3 (containing tween80/span80 20%) showed the total drug release of 87% in 45min and the formulation F4 (containing HPMC 5%) showed the total drug release of 88% in 45min. Since the amount of oil in both of these formulations is same it may be the probable reason for the similar drug release pattern.

The onset of drug release on comparison showed no clear distinction; however the difference is seen in between formulation F1 and F6. The release in F1 was 30% and that of F6 was 44.5% in 5thmins. But the cumulative drug release for F1 is 63% and that of F6 is 96% in the 45thmins. This gives the clear distinction between F1 and F6. The probable reason for this may be the amount of oil where, the amount of oil in F1 is less (20%) than compared to the formulation F6 (50% oil). Also the other reason may be because since the emulsifier used in F6 (HPMC) has the aqueous solubility than the tween80 and span80 the rate of dispersion of oil globules in the dissolution medium is enhanced due to the hydrophilic nature of HPMC.

Out of the 3 formulation prepared form the blend of tween80 and span 80 as an emulsifier formulation F3 had the maximum drug release (87% in 45min) and the formulation F1 had the least drug release (63% in 45min). There is distinctive feature in drug release pattern in using the blend as emulsifier. The higher drug release is seen in the formulation containing the higher concentration of the emulsifier. Also in this formulation the amount of water used is slightly lower than the formulation with least drug releasing capacity. Since the emulsifier in these systems had lipophilic nature, higher proportion of oil globules may have dispersed in the medium in the formulation F3 so the drug release may have increased noticeably.

Since, the hydrophilic property of HPMC which facilitates the easy wetting of the tablet and the dry emulsion tablet system based on this emulsifier easily disperses in the dissolution media, the HPMC based system showed the better dissolution profile than tween/span based system. The dissolution profile follows the order, F6>F4>F3>F2>F5>F1.

As there is relation between drug release rate and polymer concentration used as emulsifier, the drug release from tablet is dependent on the HPMC concentration. The fast release rate was found to be in that formulation with low HPMC concentration, as the emulsifier concentration increases the swelling and gel formation tendency of the HPMC causes the slowing of release rate from the formulation. Thus the formulation F6 with 3% HPMC concentration was found to have higher drug release profile. Hence the formulation F6 can be considered as the best formulation.

CONCLUSION

The formulation F6 containing oil in the proportion 50%, emulsifier as HPMC 30% (HPMC 3% w/w) and water 20% showed the highest drug release (96%) as compared to other formulation which shows that the formulated dry emulsion tablets (DETs) can have fast onset of action in comparison to other formulations. Thus formulation F6 can be considered as the best dry emulsion tablets.

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CONFLICT OF INTEREST

The authors declare no conflict of interest on the manuscript

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