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Research

Formulation development and invitro evaluation of quinethazone sustained release oral dry syrup (ds)

Dr. Nansri saha*

Associate Professor, Department of Pharmaceutics, SSJ College of Pharmacy, V.N Pally, Hyderabad, Telangana, India

*Author for Correspondence: Nansri saha
Email: nansrisaha@gmail.com

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Abstract

The aim of this present investigation was to develop Quinethazone sustained release dry syrup formulation. The formulations were evaluated for different parameters like taste evaluation, Micromeritic properties and % of drug release. It was concluded that the taste was completely masked and acceptable for patients. The taste masked syrup was prepared using three different suspending agents namely Ghatti gum, Eudragit EPO and Eudragit RLPO. The final formulation contained three different concentrations of each suspending agents. Then it was evaluated for different parameters like colour, odour, flow properties, % drug content, sedimentation volume, pH, redispersibility, viscosity and in-vitro drug release. From the results it was concluded that the formulation with suspending agent Eudragit EPO with 3% concentration showed highest sedimentation volume and better redispersibility which were very important parameter when once have to deal with syrup. The other parameters were also showed better results for the same suspending agent. So it was selected as an optimized suspending agent amongst three.

Keywords: Dry syrup (DS), Quinethazone, Eudragit EPO etc

INTRODUCTION

"A finely divided insoluble particle with a diameter of 0.5 to 5 μ that is to be distributed in an appropriate vehicle is what is commonly referred to as dry pharmaceutical syrup." For oral administration, dry syrups are solid dose forms that may be reconstituted by adding water. Dry syrup is mostly used for antibiotics, while several pediatric and moisture-sensitive medications are also available.[1]

Liquid dose forms are necessary because many patients, particularly young and elderly patients, have trouble swallowing solid dosage forms1. Drugs that are only marginally soluble in water are therefore best suited for suspension formulation; nonetheless, the final product may not be chemically and physically stable. The current study

focuses on creating a dry syrup-based reconstitutable suspension dosage form[2,3]. Commercial dry combinations that need water added when dispensed are known as dry syrups. In order to improve the stability of the formulation, the dry syrup is commercially made utilizing drugs, colorants, flavors, sweeteners, stabilizing agents, and preservation agents. Many commercial and governmental remedies are offered as granules or dry powder combinations that are meant to be suspended in water or another medium before being taken orally.[4]. Antibiotics make up the majority of medications that are formulated as dry suspensions for oral use. The medicine, colorants, tastes, sweeteners, stabilizing agents, suspending agents, and preservation agents that may be required to improve the formulation's stability are all included in the commercially manufactured dry mix of oral suspension. It is necessary to take the granules in the sachets as a suspension in a glass filled with the recommended quantity of an edible liquid, primarily water. It is advised that the dry oral suspension be swallowed right away after production, even though research has shown that it remains stable for 24 hours after being constituted in a liquid [5]. One of the most crucial factors influencing patient compliance is taste. One of the many significant formulation issues with some medications is their undesirable taste [8]. A major concern for medical professionals is the oral delivery of bitter medications with a tolerable level of palatability, particularly for young patients. There are unpleasant, bitter-tasting ingredients in many food and beverage items, bulking agents, and some oral medications. Therefore, any pharmaceutical formulation that tastes good will undoubtedly be chosen over a product from a rival company. This would result in improved patient compliance and therapeutic value as well as increased sales and profits for the business. Many formulations with enhanced performance and acceptability have been developed in response to the quest for increased palatability in these goods[9-14].

METHODOLOGY

Analytical method development

Determination of absorption maxima

A solution of containing the concentration 10 µg/ ml was prepared in 0.1N. HCl, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200–400.

Preparation calibration curve

10mg of drug was accurately weighed and dissolved in 10ml of 0.1N HCl in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20µg/ml with 0.1N HCl. The absorbance of standard solution was determined using UV/VIS spectrophotometer at 271nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Drug –- Excipient compatibility studies Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of Repose

The frictional force within the powders can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powders are added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The angle of repose (θ) was calculated using the following formula

$$\mathbf{Tan\ \theta = h/r}$$

Bulk Density

Density is defined as weight per unit volume. Bulk density (Db), is defined as the mass of the powders divided by the bulk volume and is expressed as gm/cm3. The bulk density of the powders primarily depends on particle size

distribution, particle shape and the tendency of particles to adhere together. The bulk volume (Vb) and weight of the granules (M) was determined. The bulk density was calculated using the formula.

$$Db = M/Vb$$

Where, M is the mass of the powders and Vb is bulk volume of the granules.

Tapped Density

The measuring cylinder containing a known mass of powders was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the powders was measured. The tapped density was calculated using the formula.

$$Dt = M/Vt$$

Where, M is the mass of the powders Vtis tapped volume of the powders

Compressibility Index

The compressibility Index (Carr's Index) could be a live of the propensity of a powder/ granules to be compressed. it's determined from the majority and broached densities. In theory, the less compressible a fabric the additional flowable it's. during a free-flowing powder/ granules, such interactions ar typically diminished, and also the bulk and broached densities are going to be nearer in price. For poor flowing materials, there ar oftentimes bigger interparticulate interactions, and a bigger distinction between the majority and broached densities are going to be ascertained. These variations ar mirrored within the squeezability Index that is calculated exploitation the subsequent formulas.

$$CI\ (\%) = [(\text{Tapped density} - \text{Bulk density}) / \text{Tapped density}] \times 100$$

Preparation of dry syrup of quinethazone

Table 1: formulations of quinethazone dry syrup mixture

Ingredients (%w/v)	Batch code								
	QF1	QF2	QF3	QF4	QF5	QF6	QF7	QF8	QF9
Quinethazone	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86
Ghatti gum	1	2	3	-	-	-	-	-	-
Eudragit EPO	-	-	-	1	2	3	-	-	-
Eudragit RLPO	-	-	-	-	-	-	1	2	3
SSG	1	1	1	1	1	1	1	1	1
Sodium benzoate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sodium citrate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sucrose	23.13	23.13	23.13	23.13	23.13	23.13	23.13	23.13	23.13
Sodium laurel sulfate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Indian vanilla flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Sunset yellow	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total(gm)	10gm	10gm	10gm	10gm	10gm	10gm	10gm	10gm	10gm

- The dose of dry syrup was selected 37.5 mg/5 ml
- So total 30 ml of dry syrup was prepared which contained total amount of 187.5 mg of Linezolid.
- Dry syrup of Quinethazone (QTZ) (37.5 mg/5ml) was prepared using suspending agents, wetting agent, preservative, flocculating agent, superdisintegrant, buffer, anticaking agent, sweetener, flavours by granulation technique.
- All ingredients were passed through 200# before mixing.
- The complex of drug and resin equivalent to 187.5 mg Quinethazone (QTZ) was blended with the other ingredients by geometric mixing.
- The solid ingredients were blended and massed using water.
- Granulation was carried out by means of wet granulation using water as granulating fluid.

- The wet mass was formed into granules using 30 mesh sieve. The formed granules were dried in the oven and passed through 32 mesh after drying.
- Final Linezolid dry syrup formulation were diluted upto 30 ml for final formulation.

Evaluation parameter of dry syrup

Colour, odour and appearance

All the developed batches of syrup from QF1 to QF9 were evaluated for organoleptic properties such as colour, odour and appearance.

Drug content

Dry syrup equivalent to 100 mg of linezolid was taken in 100 ml volumetric flask and dissolved in 10 ml methanol and volume was made up to 100 ml by adding sufficient 0.1 N HCl. The solution was analyzed at 243.6 nm to found out drug content

Determination of pH

The pH value conventionally represents the acidity or alkalinity of an aqueous solution. The pH value of a solution was determined potentiometrically by means of the glass electrode. A digital pH meter was allowed to stabilize. Then the pH meter was standardized using buffer tablets. The suspension formulation was placed in the pH meter. The reading was noted when there is no fluctuation in the pH meter. (22)

Sedimentation Volume (F)

Sedimentation volume (F) is a ratio of the final or ultimate volume of sediment (Vu) to the original volume of sediment (Vo) before settling. It can be calculated by following equation.

$$F = V u / Vo$$

Where, Vu = final or ultimate volume of sediment Vo = original volume of suspension before settling**.**

Redispersibility

after maintaining the suspension in undisturbed condition for 7 days, at the end of 7th day how many strokes required to redisperse the suspension

In vitro drug release studies

Dissolution parameters:

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl
RPM	--	50
Sampling intervals (min)	--	5, 10, 15, 30, 45, 60
Temperature	--	37°c + 0.5°c

As the preparation was for non effervescent floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. dry syrup was placed in the vessel and the vessel was covered the apparatus was operated for 60 min and then the medium 0.1 N HCl was taken and process was continued from 0 to 60min at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 271 nm using UV-spectrophotometer

RESULTS AND DISCUSSION

UV Scanning of Quinethazone (QTZ)

Quinethazone (QTZ) pure drug was scanned in methanol between 200 nm and 400 nm using ultraviolet spectrophotometer. Quinethazone(QTZ) was identified by its light absorption pattern which follows the absorption of light in the range 220 to 400 nm and a maximum absorbance at about 271 nm. A broad shoulder at about 271 nm was observed which confirm the presence of Quinethazone(QTZ).

Discussion: Quinethazone(QTZ) gave highest peak at 271 nm and the same was selected for further evaluations.

Calibration curve in water (make up with ph 1.2 hcl buffer)

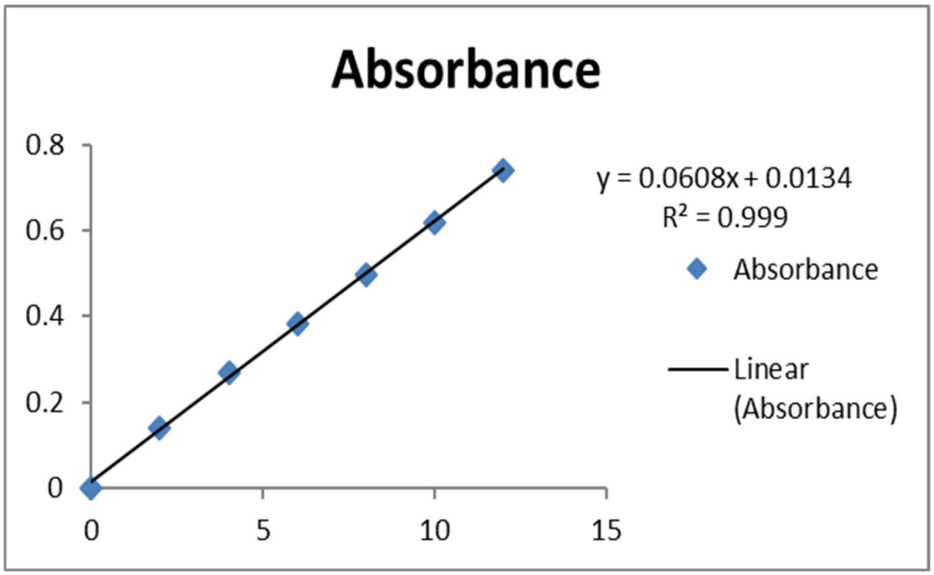

Fig 1: Standard graph of Quinethazone(QTZ)

Drug –- Excipient compatibility studies Fourier Transform Infrared (FTIR) spectroscopy

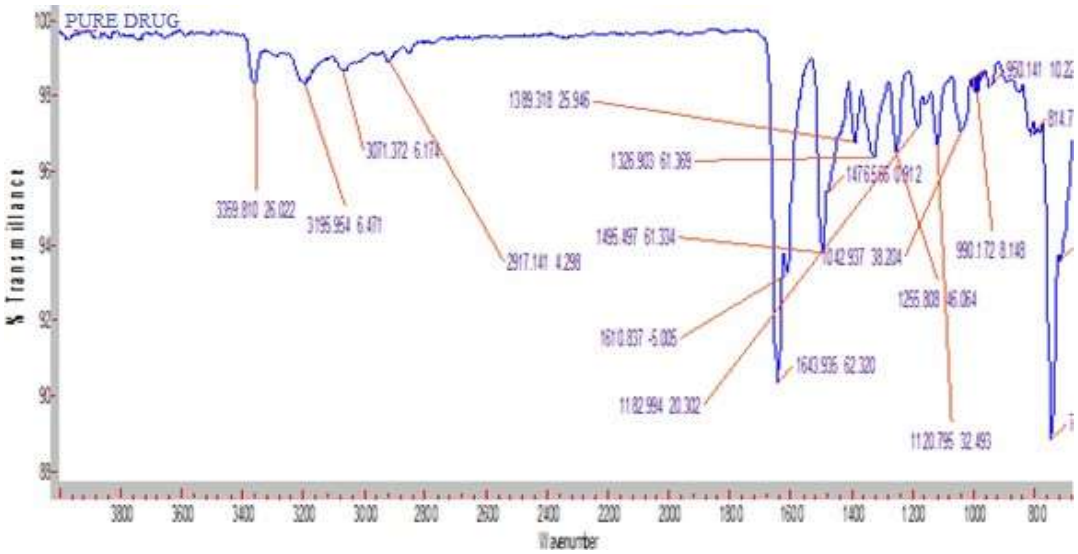

Fig 2: FTIR Spectrum Of optimized formulation

Characterization dry syrup (DS)

Table 2: Organoleptic properties of all formulations

Formulations	Colour	Odour	Appearance
QF1	Sunset yellow	Vanilla	Granular
QF2	Sunset yellow	Vanilla	Granular
QF3	Sunset yellow	Vanilla	Granular

QF4	Sunset yellow	Vanilla	Granular
QF5	Sunset yellow	Vanilla	Granular
QF6	Sunset yellow	Vanilla	Granular
QF7	Sunset yellow	Vanilla	Granular
QF8	Sunset yellow	Vanilla	Granular
QF9	Sunset yellow	Vanilla	Granular

Discussion: In all the formulation sunset yellow was used as a coloring agent and vanilla flavor was used. Dry syrup was formed by means of granulation technique. All the formulations from Q F1 to QF9 were appeared as a granular.

Drug content

Table 3: % drug content of Quinethazone (QTZ) dry syrup (DSt)

Formulations	%drug content
QF1	98.47 %
QF2	101. 84 %
QF3	99.36 %
QF4	99.27 %
QF5	100.67%
QF6	99.54 %
QF7	102.45 %
QF8	98.46 %
QF9	98. 62 %

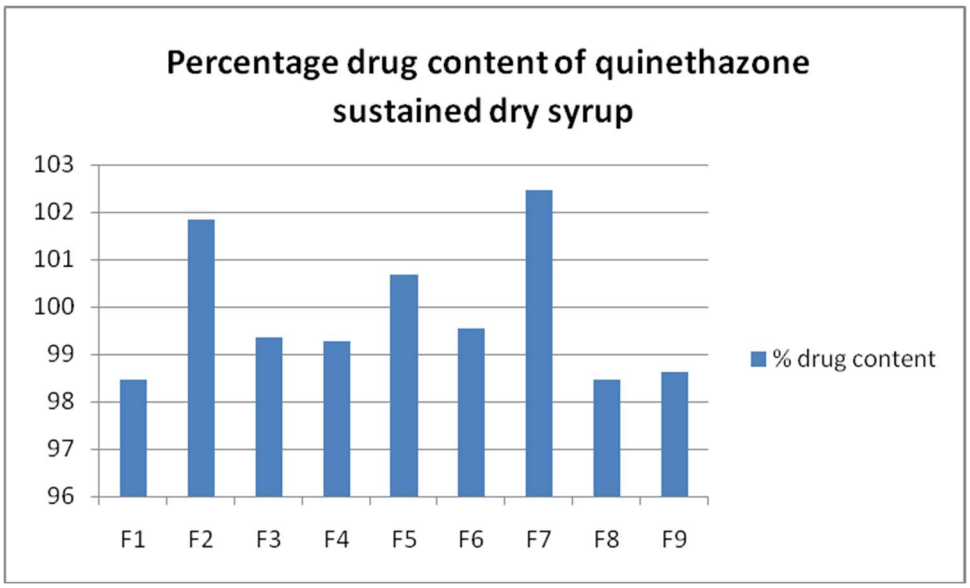

Fig 3: Percentage drug content of Quinethazone sustained dry syrup

Flow properties of sustained release dry syrup formulations of Quinethazone

Table 4: Micromeritics property of Dry syrup (DS)

Formulations	Bulk density	Tapped density	Hausner ratio	Carr's index	Angle of repose
QF1	0.426	0.512	1.20	16.79	20.70
QF2	0.486	0.571	1.17	14.88	21.27
QF3	0.468	0.562	1.20	16.72	20.33
QF4	0.482	0.556	1.15	13.30	21.46

QF5	0.458	0.539	1.17	15.02	19.86
QF6	0.477	0.562	1.17	15.12	19.37
QF7	0.438	0.530	1.22	17.35	21.67
QF8	0.470	0.563	1.19	16.51	22.27
QF9	0.450	0.525	1.16	14.28	22.84

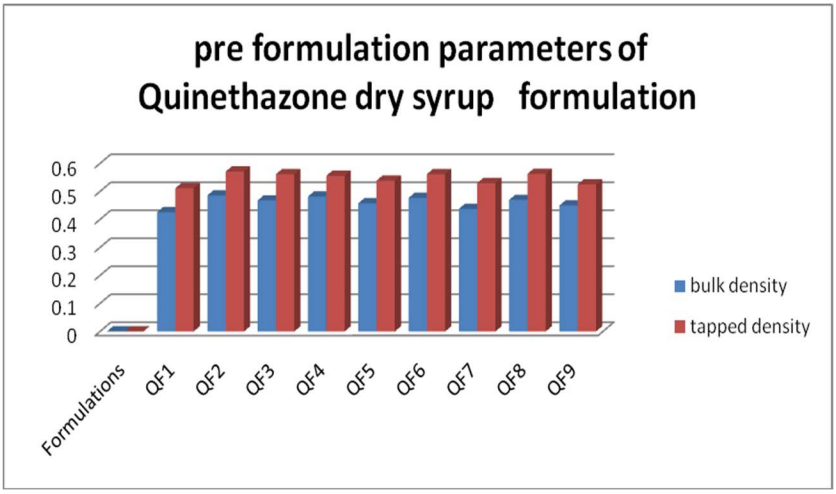

Fig 4: Preformulation parameters of Quinethazone dry syrup formulation

Discussion: Micromeritics property of the dry syrup was carried out and it was found that all the batches of formulation were have all the parameter in the good to excellent range. As the dry syrup were in the form of granules they were free flowing having good flow property

Viscosity

Table 5: Viscosity of QF1 to QF9 formulations of Quinethazone dry syrup

Formulations	Viscosity (cps)
QF1	347 cps
QF2	451 cps
QF3	566 cps
QF4	1033 cps
QF5	1296 cps
QF6	1563 cps
QF7	426 cps
QF8	510 cps
QF9	762 cps

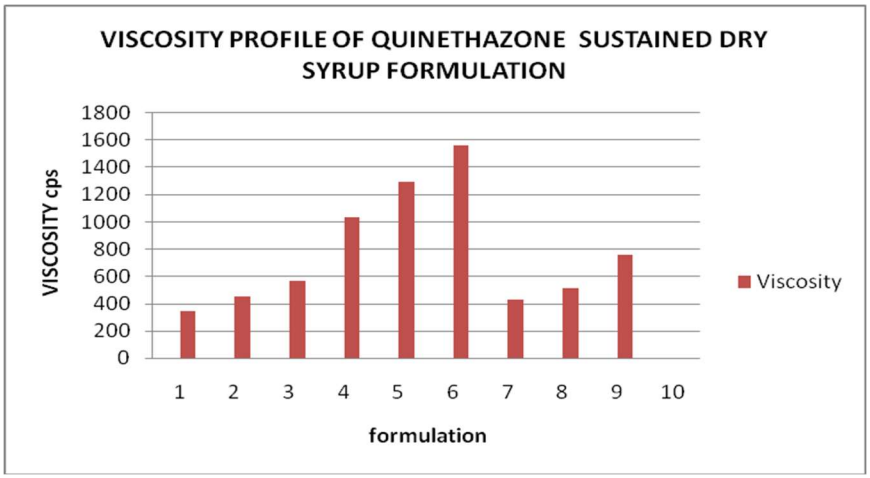

Fig 5: Viscosity profile of Quinethazone sustained dry syrup formulation

Discussion: Viscosity of the QF1 to QF9 formulations is shown in table 6 the Eudragit EPO had the highest viscosity than two other suspending agents. So it was concluded that the high sedimentation volume and the better Redispersibility was because of high viscosity of the suspending agent Eudragit EPO.

As the viscosity of syrup of QF8q was higher the particles or the solid contents present in the syrup will not sediment for a long time. So they will remain suspended in the syrup. Due to this effect the sedimentation volume of syrup was higher and the sedimentation rate was slow.

Redispersibility of higher viscous syrup is also better. This was because of that as the lowest sediments of particles occur it will easily redisperse again. So in present work it was shown that due to high viscosity of Eudragit EPO (3%), its the sedimentation volume was highest and Redispersibility was better than any other batch.

Sedimentation volume

Table 6: Sedimentation volume of formulations

	Height of Sediment (cm) after								
Formulations	**3 min Ho**	**1 day**	**2 day**	**3 day**	**4 day**	**5 day**	**6 day**	**7 day**	**Sedimentation volume F= Hu/Ho**
QF1	7.0	6.2	5.0	4.5	4.1	3.6	3.4	3.2	0.45
QF2	7.0	6.3	5.2	4.6	4.2	3.7	3.6	3.6	0.51
QF3	7.0	6.7	5.5	5.2	4.5	4.1	3.9	3.9	0.55
QF4	7.0	6.7	6.4	6.6	6.2	6.1	6.0	5.9	0.84
QF5	7.0	6.8	6.7	6.6	6.4	6.3	6.2	6.1	0.87
QF6	7.0	7.0	7.0	6.8	6.8	6.5	6.4	6.4	0.91
QF7	7.0	6.2	5.6	5.1	4.8	4.5	4.2	4.1	0.58
QF8	7.0	6.5	5.9	5.4	5.1	4.6	4.4	4.4	0.62
QF9	7.0	6.6	6.0	5.5	5.3	4.8	4.7	4.6	0.65

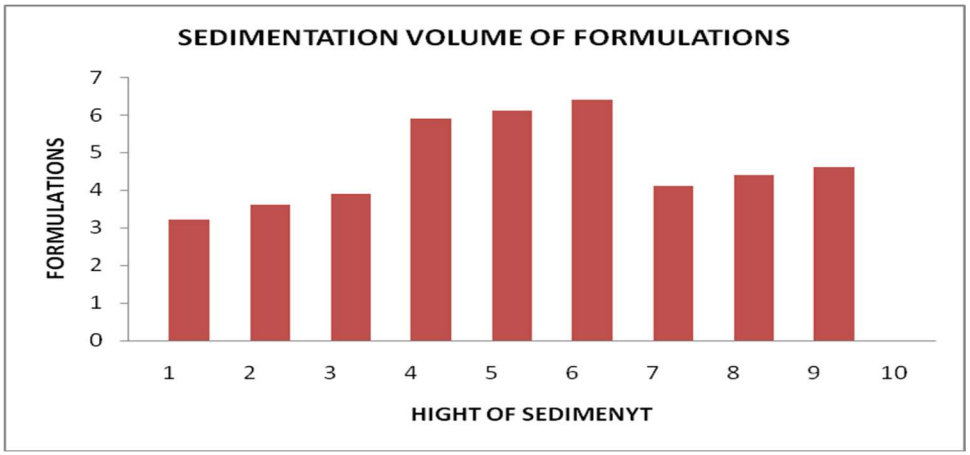

Fig 6: Sedimentation volume of formulation

Discussion: From results it was proved that Eudragit EPO 3 % was the optimum concentration of suspending agent required to make a good quality Quinethazone syrup. So the formulation of batch QF6 was better than all other formulation as they all had sedimentation volume less than batch QF6.

Redispersibility

Table 7: Redispersibility of formulations QF1 to QF9

Formulations	Redispersibility (no. of strokes)
QF1	13
QF2	10
QF3	8
QF4	9
QF5	7
QF6	5
QF7	13
QF8	11
QF9	9

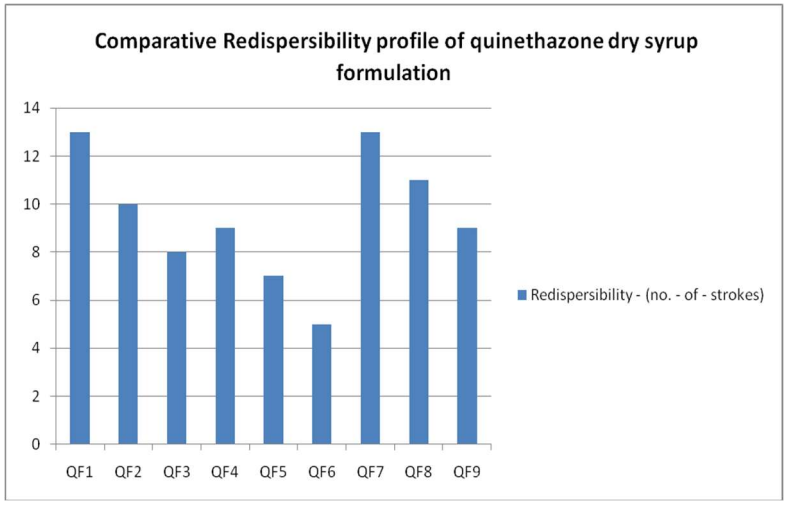

Fig 7: Comparative redispersibility profile of Quinethazone dry syrup formulation

Discussion: From the results it was concluded that the formulation batch F6 (Eudragit EPO 3 %) had the minimum number (5) of strokes as compared to all the other formulation. So results concluded that the formulation with Eudragit EPO (3%) was easily redispersable this was because the sedimentation volume was also higher for the same formulation than any other formulation.

In-vitro drug release

Table 8: In vitro- drug release in 0.1 N HCl

Time(min)	%drug release								
	QF1	QF2	QF3	QF4	QF5	QF6	QF7	QF8	QF9
0	0	0	0	0	0	0	0	0	0
0.5	84.9	78.9	45.69	78.99	78.9	65.98	87.9	65.09	64.9
1	87.09	89	89	96.99	94.9	89.09	97.46	89.09	85.09
1.5	96.87	97.59	89.67	99.29	99.55	97.86	99.48	99.55	97.65
2	98.64	99.59	98.79	99.55	99.87	99.69	99.82	99.76	99.77
4	99.09	99.87	99.79	99.88	99.92	99.84	99.98	99.91	99.89
6	99.85	99.94	99.87	99.98	99.98	99.89	99.98	99.91	99.98

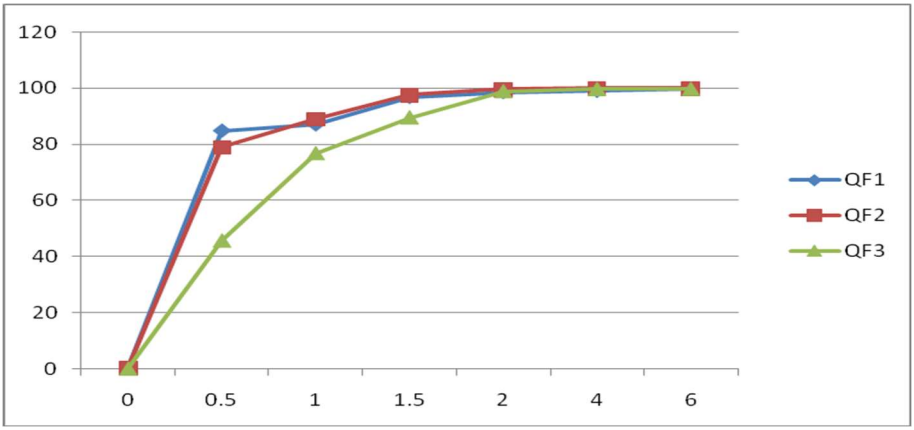

Fig 8: % drug release of formulations prepared with Ghatti gum

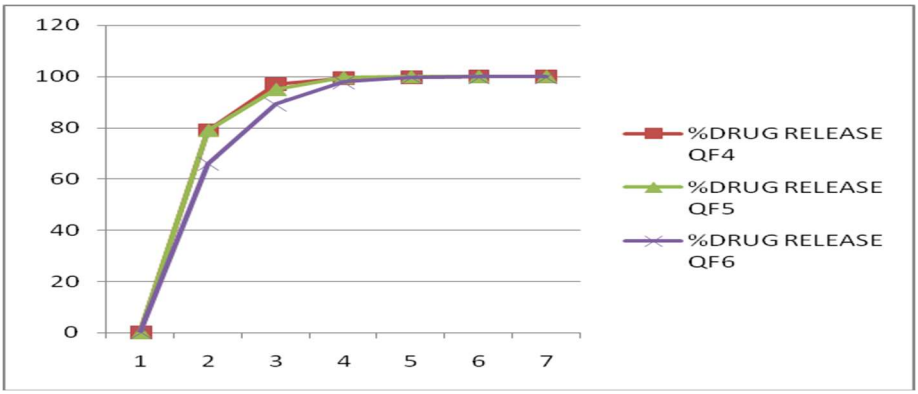

Fig 9: % drug release of formulations prepared with Eudragit EPO

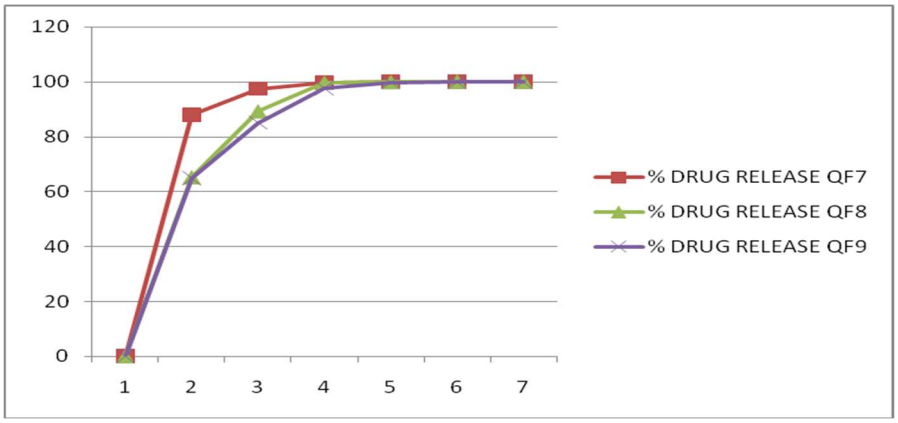

Fig 10: % drug release of formulations prepared with Eudragit RLPO

pH of reconstitutable syrup

Table 9: pH of reconstitutable syrup

Formulations	pH
QF1	6.5
QF2	6.3
QF3	6.2
QF4	6.6
QF5	6.7
QF6	6.4
QF7	6.8
QF8	6.7
QF9	6.6

SUMMARY& CONCLUSION

The aim of this present investigation was to develop taste masked Quinethazone dry syrup. The formulations were evaluated for different parameters like taste evaluation, Micromeritic properties and %drug content. It was concluded that the taste was completely masked and acceptable for patients. The taste masked syrup was prepared using three different suspending agents namely Ghatti gum, Eudragit EPO and Eudragit RLPO.

The final formulation contained three different concentrations of each suspending agents. Then it was evaluated for different parameters like colour, odour, % drug content, flow properties, sedimentation volume, pH, redispersibility, viscosity and in- vitro drug release.
Among all the 9 formulations F4 F5 F6 formulations which contain Eudragit Epo showed highest sedimentation volueme and better redispersibility which were very important parameter when once have to deal with syrup. The other parameters were also showed better results for the same suspending agent. So it was selected as an optimized suspending agent amongst three.

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